Evaluation and Treatment of Neonates With Suspected Late-Onset Sepsis: A Survey of Neonatologists’ Practices

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ABSTRACT. Objective. To ascertain current diagnostic and treatment practices for suspected late-onset sepsis in infants in neonatal intensive care units (NICUs) and identify areas that may benefit from clinical practice guidelines.

Methods. During June 2000, we conducted a multicenter survey of neonatologists and infection control professionals regarding practices related to late-onset sepsis in NICUs at children’s hospitals participating in the Pediatric Prevention Network.

Results. Personnel at 35 hospitals with NICUs completed surveys; 34 were infection control professionals, and 278 were neonatology clinicians, primarily attending neonatologists or neonatology fellows. At these facilities, coagulase-negative staphylococci (CoNS) were the most frequent blood culture isolate from infants with late-onset sepsis accounting for 54% of bloodstream infections. When late-onset sepsis was suspected, 83% of clinicians drew only 1 blood culture when no central venous catheter was present or when a central vascular was present with no blood return. Thirty-two percent obtained 1 or more C-reactive protein concentration determinations. Sixty percent of clinicians prescribed vancomycin-containing regimen for a 900 g, 3-week-old infant with suspected late-onset sepsis. The presence of a central venous catheter or shock increased empiric vancomycin use. The presence of methicillin-resistant Staphylococcus aureus in the NICU did not increase vancomycin use, but a vancomycin restriction policy decreased empiric vancomycin use. Clinicians at an individual NICU tended to have similar empiric antibiotic-prescribing practices: in 29 (83%) of 35 centers ≥75% of respondents had similar practice with regard to prescribing a vancomycin-containing regimen for empiric therapy. Forty-seven percent to 85% completed a full course of antimicrobials when a single blood culture was obtained and grew CoNS, but a significantly lower percentage of respondents (22%;47%) completed a full course when 1 of 2 blood cultures obtained grew CoNS. Eleven percent of respondents removed an umbilical catheter at the time of suspected sepsis, but fewer than 5% removed a non-umbilical venous catheter for suspected sepsis.

Most (≥61%) retained a nonumbilical catheter despite documentation of CoNS bacteremia.

Conclusions. Neonatologists varied in management of suspected late-onset sepsis, particularly that caused by CoNS. Procedures to prevent CoNS-positive blood cultures and to differentiate CoNS contaminants from pathogens are needed. For safely decreasing vancomycin use in NICUs, clinical practice guidelines should be developed, implemented, and evaluated. The guidelines should include optimal skin antisepsis and catheter disinfection before obtaining blood for culture, obtaining 2 blood cultures and using adjunctive tests and information to help differentiate contaminants from pathogens, and restriction on empiric vancomycin use. Pediatrics 2002;110(4). URL: http://www.pediatrics.org/cgi/content/full/110/4/e42; sepsis, neonatal intensive care, vancomycin.

ABBREVIATIONS. NICU, neonatal intensive care unit; CoNS, coagulase-negative staphylococci; CRP, C-reactive protein; CVC, central venous catheter; ICP, infection control professional; NNIS, National Nosocomial Infections Surveillance; BSI, bloodstream infection; MRSA, methicillin-resistant Staphylococcus aureus.

Late-onset sepsis—invasive infection occurring in neonates older than 3 days—occurs in approximately 10% of all neonates and in >25% of very low birth weight infants (≤1500 g) who are hospitalized in neonatal intensive care units (NICUs).1 In NICUs, these infections are often associated with vascular catheters, and coagulase-negative staphylococci (CoNS) are the most commonly reported pathogens, accounting for >50% of bloodstream infections.2,3 In this setting, the vast majority of CoNS are resistant to methicillin. NICU infants with suspected late-onset sepsis are typically treated with empiric antimicrobial therapy that often includes vancomycin. However, there are national recommendations that vancomycin use in hospitals be restricted because exposure of patients to vancomycin is a risk factor for emergence of vancomycin-resistant enterococci4–6 or vancomycin-intermediate Staphylococcus aureus.7 CoNS also are the most common blood culture contaminants in patients in NICUs.8 Currently, there is a lack of consensus among neonatologists on several aspects of diagnosis and treatment of hospitalized neonates with suspected late-onset sepsis. No consensus guidelines exist for the following: 1) the number of blood cultures obtained before initiation of empiric antimicrobial therapy (1 vs >1); 2) the choice of empiric antimicrobials, specifically use of vancomycin; 3) the use of C-reactive protein (CRP) to differentiate true
CoNS sepsis from contamination; 4) the duration of antimicrobial therapy; 5) the classification of a CoNS isolate from a single blood culture as a pathogen or contaminant; and 6) the indications for removal of central venous catheters (CVCs) in neonates with suspected late-onset sepsis. We surveyed neonatologists and infection control professionals (ICPs) to determine their diagnostic and treatment practices for suspected or proven late-onset sepsis as a basis for development of clinical practice guidelines for management of late-onset sepsis. The results of this survey can be used to define practice areas in which there is lack of consensus and to highlight the need for clinical practice guidelines for management of late-onset sepsis.

METHODS

Survey

During June 2000, ICPs at 61 children’s hospitals that had a level 3 to 4 NICU and participated in the National Association of Children’s Hospitals and Related Institutions and the Centers for Disease Control and Prevention Pediatric Prevention Network were contacted to determine their interest and that of their NICU director in participating in a survey about diagnosis and management of late-onset sepsis in patients in NICUs. A NICU was designated level 3 to 4 when it served as a regional perinatal center. A survey was sent to interested centers. Part 1 was to be completed by the ICP or hospital epidemiologist and inquired about the 1999 NICU census and birth weight distribution, categories and numbers of clinicians that staff the NICU (attending neonatologists, neonatology fellows, resident physicians, neonatal nurse practitioners), the rate and pathogens associated with late-onset sepsis in 1999, vancomycin use restriction policy in the NICU, procedures for obtaining blood cultures, and guidelines used by the ICP to classify blood culture isolates of CoNS as pathogens or contaminants. Part 2 was to be completed by each staff neonatologist, neonatology fellow, and neonatal nurse practitioner and inquired about their current clinical approach to evaluation of infants with possible sepsis. Items included the number of blood cultures obtained before initiation of empiric antimicrobial therapy, other tests routinely obtained to evaluate for late-onset sepsis, indications and practices for CVC removal in patients with possible or proven sepsis, choice of empiric antimicrobial therapy, classification of a CoNS isolate as a pathogen or contaminant under varying clinical circumstances, and duration of antimicrobial therapy when blood cultures were negative or when CoNS were isolated.

Data Analyses

Completed surveys were entered into Microsoft Excel (Microsoft, Inc, Redmond, WA) and tabulated. In 39 (14%) of 278 responses by clinicians, the status of the respondent as an attending neonatologist, fellow, or neonatal nurse practitioner was unavailable. Because most (75%) of the identified responders were attending neonatologists, there was only 1 neonatal nurse practitioner, and there was a high concordance of responses between fellows and attending neonatologists at individual institutions, all responses were combined for analysis. The data in the tables summarized the responses by individual clinicians. The Fisher exact test was used for comparison of proportions.

RESULTS

Characteristics of Participating NICUs

Completed part 1 surveys were received from ICPs at 34 hospitals. During 1999, NICUs at these hospitals admitted 24 595 infants, including 4256 infants (17.3%) with a birth weight <1500 g, 2002 infants (8.1%) with a birth weight <1000 g, and 1011 infants (4.1%) with a birth weight ≤750 g. The NICUs employed a median of 6 neonatologists (range: 3–21). Pediatric residents, neonatal nurse practitioners, and neonatology fellows provided care for patients in 74%, 79%, and 56% of the NICUs, respectively. Nineteen NICUs had fellowship programs and employed a median of 6 fellows (range: 1–16) per NICU. Completed part 2 surveys were received from 278 clinicians, including 277 attending neonatologists or fellows—72% of eligible clinicians at the 35 hospitals. There was a median of 6 respondents per NICU (range: 3–19). Thirteen NICUs (38%) also participated in the Vermont Oxford Neonatal Network, and 9 (26%) participated in the National Nosocomial Infections Surveillance (NNIS) system high-risk nursery component.

Distribution of Pathogens

Thirty-one ICPs (91%) reported that CoNS were the most frequent blood culture isolate associated with bloodstream infection (BSI) in infants older than 3 days (late-onset sepsis) in their NICU in 1999. Enterococci or Enterobacter species was the most common genera associated with CoNS in 1 NICU each. CoNS accounted for a median of 54% (range: 24%–95%) of BSIs in these NICUs, and overall resistance of CoNS to oxacillin was 84% (range: 0%–100%). Ten NICUs (30%) reported infections caused by methicillin-resistant S aureus (MRSA) with a median of 2 episodes annually (range: 1–24). None reported infections caused by vancomycin-resistant enterococci, but 2 NICUs (7%) reported infections caused by ampicillin-resistant enterococci (number of cases in these NICUs: 1 and unknown, respectively).

General NICU and Laboratory Practices

Most ICPs (76%) and laboratory reported that there was no vancomycin restriction policy in the NICU at their institution. The preparation of skin or catheter before obtaining blood for culture varied by NICU. Preparations for skin included povidone-iodine with or without alcohol in 27 NICUs (79%), chlorhexidine alone in 4 (12%), alcohol alone in 2 (6%), and both chlorhexidine and alcohol in 1 (3%). In contrast, catheter disinfection before attaching a syringe to obtain blood for culture included povidone-iodine with or without alcohol in 13 (38%), alcohol in 10 (29%), no preparation in 5 (15%), chlorhexidine in 2 (6%), and both chlorhexidine and alcohol in 1 (3%). All 34 institutions used a continuous-monitoring blood culture system, including BACTEC (Becton Dickinson Microbiology Systems, Sparks, MD) in 18, BacT/Alert (Organon Teknika Corp, Durham, NC) in 15, and Trekdiagnostico ESP (Accumed International, Inc, Westlake, OH) in 1; 17 (52%) NICUs used a single aerobic bottle, and 16 (48%) used a 2-bottle (aerobic and anaerobic) system. Seven NICUs also used the Isolator 1.5 Microbial Tube with direct plating. Twenty (59%) of 34 hospital laboratories routinely identified CoNS to species level. Thirty-one (91%) of 34 laboratories cultured segments of submitted vascular catheters; 90% of these laboratories used the roll technique.
Clinical Practices for Diagnosis and Treatment of Infants With Suspected Late-Onset Sepsis

Neonatal clinicians were presented with a series of clinical scenarios and asked how many blood cultures they would obtain from infants with suspected late-onset sepsis before initiating empiric antimicrobial therapy. Of the 275 respondents, 230 (84%) said that they would obtain a single blood culture if no CVC was present and 225 (83%) of 272 would do so if a CVC had no blood return. If a CVC had a blood return, 224 (80%) of 279 said that they would obtain at least 2 blood cultures, including at least 1 from a peripheral vein; 37 (13%) of 279 would obtain a single blood culture through the CVC; and 18 (6%) of 279 would obtain a single blood culture from a peripheral vein. Additional laboratory tests obtained during evaluations for suspected sepsis included a complete blood count and differential (275 [99%] of 278), CRP at initial evaluation (85 [31%] of 278), CRP ≥12 hours after initial evaluation or serially (88 [32%] of 278), or erythrocyte sedimentation rate (12 [4.3%] of 278). In 8 NICUs (23%), the majority of the clinicians would obtain ≥1 CRP at least 12 hours after initial evaluation. Two clinicians would obtain procalcitonin levels; none would obtain cytokine levels (ie, interleukin-6 or interleukin-8).

Clinicians were asked to choose antimicrobials for a 3-week-old infant who had a birth weight of 900 g and developed apnea and bradycardia requiring reintubation. The majority of clinicians at 20 (57%) of 35 NICUs prescribed a vancomycin-containing regimen. Clinicians at an individual NICU tended to have similar prescribing practices; in 29 (83%) of 35 centers, ≥75% of respondents had a similar practice with regard to prescribing a vancomycin-containing regimen. Considering the 278 individual respondents, 60% prescribed a vancomycin-containing regimen. For assessing the classification of a blood culture isolate of CoNS as pathogen or contaminant, clinicians were asked whether they prescribe a “full” course of antimicrobial therapy after recovery of CoNS from blood culture (ie, interpret as a pathogen) under a number of scenarios (Table 2). Approximately one half of respondents prescribe a full course of antimicrobials when a single blood culture is obtained patients with MRSA infection (50 [65%] of 77 vs 108 [58%] of 185, respectively; P = .98). In contrast, the presence of a vancomycin restriction policy was associated with decreased use of vancomycin for suspected late-onset sepsis (16 [24%] of 67 vs 138 [70%] of 196, respectively; P < .0001). Next, the clinical scenario was modified to assess the effect of additional factors on the choice of empiric antimicrobials (Table 1). Eighty-nine percent of respondents would prescribe the same regimens when the infant’s birth weight was <750 g. When the scenario was modified to include the presence of a CVC or shock, the proportion of respondents who would prescribe vancomycin increased by 18% and 11%, respectively (P < .0001). In the presence of a CVC, 42 (72%) of 58 respondents who usually prescribed ampicillin changed to vancomycin and 7 (12%) changed to oxacillin. In contrast, 22 (96%) of 23 respondents who usually prescribe oxacillin and an aminoglycoside would prescribe the same regimen in the presence of a CVC.

If blood cultures remained sterile, then 56% of clinicians would discontinue antimicrobials after 2 days, 42% would discontinue antimicrobials after 3 days, and 2% would continue antimicrobials for >3 days. Almost identical results were obtained when time to discontinuation of antibiotics was analyzed by NICU in the 90% ofNICUs in which a majority of clinicians had a uniform practice.

Treatment of Infants With Suspected Late-Onset Sepsis and a CVC and/or CoNS Bacteremia

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### Table 1. Neonologists’ Usual Choice of Empiric Antimicrobial Therapy for Suspected Late-Onset Sepsis in a 3-Week-Old Infant With a Birth Weight of 900 g Who Develops Apnea/Bradycardia Episodes Requiring Reintubation

<table>
<thead>
<tr>
<th>Empiric Antimicrobial Regimen</th>
<th>Unmodified Clinical Scenario (n = 262)*</th>
<th>Modification: CVC Is Present (n = 220)</th>
<th>Modification: Birth Weight &lt;750 g (n = 216)</th>
<th>Modification: Shock Present (n = 216)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin and Aminoglycoside</td>
<td>23†</td>
<td>4 (P &lt; .0001)‡</td>
<td>14 (P = .026)</td>
<td>9 (P &lt; .0001)</td>
</tr>
<tr>
<td>Cephalosporin§</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Oxacillin (or nafcillin) and</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>11</td>
<td>13</td>
<td>&lt;1</td>
<td>10</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>1</td>
<td>13</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Vancomycin and Aminoglycoside</td>
<td>40</td>
<td>51</td>
<td>43</td>
<td>38</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>19</td>
<td>27</td>
<td>21</td>
<td>33</td>
</tr>
<tr>
<td>Cephalosporin alone</td>
<td>&lt;1</td>
<td>0</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Other‡</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

* Number of respondents to each scenario. Sample size varied because not all respondents answered every question and 9, 5, 6, and 5 responses were not included in data columns 1 through 4, respectively, because ≥1 regimen was chosen.
† Numbers are given as percentage of respondents choosing a particular regimen.
‡ P value reflects significant differences compared with the unmodified clinical scenario.
§ Cefuroxime, cefotaxime, cefazidime, or cefepime.
|| Most of the regimens included 3 antimicrobials; approximately one third of the regimens included vancomycin.
tained and grows CoNS either peripherally in the absence of a CVC or from a single blood culture obtained via a CVC. When 2 blood cultures are obtained and only 1 grows CoNS, the percentage of respondents who prescribe a full course decreased significantly in 2 of the 3 scenarios posed (Table 2). Thus, in the presence or absence of a vascular catheter, obtaining 2 blood cultures resulted in a decrease in the number of infants treated for a single CoNS-positive blood culture.

The decision to remove an intravenous catheter from infants with suspected late-onset sepsis varied by clinical scenario and catheter type (Table 3). Thirty-one (11%) of 274 clinicians would remove an umbilical catheter present at the time of evaluation of suspected sepsis, but 5% would remove a nonumbilical CVC. Sixty-nine percent (188 of 274) of neonatologists would not remove a nonumbilical CVC for CoNS bacteremia unless the patient failed to improve clinically or bacteremia persisted despite appropriate therapy.

There was a limited consensus concerning the duration of treatment for CoNS bacteremia with no intravascular catheter present or with intravascular catheter removal: 5% of the respondents would prescribe an antimicrobial course of ≤5 days; 59%, 7 days; 31%, 10 days; and 5%, ≥14 days. In the presence of a CVC that was not removed, 1% would prescribe ≤5 days; 31%, 7 days; 48%, 10 days; and 19%, ≥14 days.

### ICP Assessments and Practices

Eighty percent of ICPs estimated that infants with a single blood culture growing CoNS were treated with a full course of antimicrobials in >50% of occurrences, and 60% estimated that such infants were treated in >75% of occurrences. These estimates are similar to the clinical treatment decisions made by neonatologists (Table 2). ICPs from 28 of 33 centers reported nosocomial infections using NNIS criteria. On the basis of these criteria, an infant who had an intravascular catheter and fever, hypothermia, or apnea or bradycardia and had CoNS isolation from a single blood culture and was treated with a course of an appropriate antimicrobial is classified as having a laboratory-confirmed BSI. For an infant who did not have a CVC and fulfilled this scenario, 61% of ICPs classified the infant as having a BSI. If the same patient had a CVC, 90% classified the infant as having a BSI, regardless of whether the blood culture was obtained through a peripheral blood vessel or through the catheter. If the same patient had a CVC and only 1 of 2 blood cultures obtained was positive, 71% or 82% classified the infant as having a BSI when the positive culture was obtained via the CVC or from a venipuncture, respectively (P = .08 comparing combined data for 1 of 1 blood culture positive vs 1 of 2 blood cultures positive). In contrast, <50% of clinicians classified isolation of CoNS from only 1 of 2 blood cultures obtained as indicative of BSI (Table 2).

### TABLE 2. Decision to Treat Neonate With a Full Course of Antimicrobials for a CoNS Blood Culture Isolate in the Following Circumstances

<table>
<thead>
<tr>
<th>CVC Present?</th>
<th>Peripheral Blood Culture</th>
<th>Catheter Blood Culture</th>
<th>No. Positive/Total No.</th>
<th>Treatment With Full Antibiotic Course (%)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>One blood culture obtained (n = 273)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. No</td>
<td>Positive</td>
<td>NA</td>
<td>1 of 1</td>
<td>47</td>
<td>&lt;.0001 (vs 4)</td>
</tr>
<tr>
<td>2. Yes</td>
<td>Not obtained</td>
<td>Positive</td>
<td>1 of 1</td>
<td>53</td>
<td>.087 (vs 5)</td>
</tr>
<tr>
<td>3. Yes</td>
<td>Positive</td>
<td>Not obtained</td>
<td>1 of 1</td>
<td>85</td>
<td>&lt;.0001 (vs 6)</td>
</tr>
<tr>
<td>Two blood cultures obtained (n = 251)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. No</td>
<td>Positive</td>
<td>NA</td>
<td>1 of 2</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>5. Yes</td>
<td>Negative</td>
<td>Positive</td>
<td>1 of 2</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>6. Yes</td>
<td>Positive</td>
<td>Negative</td>
<td>1 of 2</td>
<td>47</td>
<td>&lt;.0001 (vs 8)</td>
</tr>
<tr>
<td>7. No</td>
<td>Positive</td>
<td>NA</td>
<td>2 of 2</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>8. Yes</td>
<td>Positive</td>
<td>Positive</td>
<td>2 of 2</td>
<td>94</td>
<td></td>
</tr>
</tbody>
</table>

NA indicates not applicable

* Number reflects percentage of neonatologists who would treat.

### TABLE 3. Clinical Practice Regarding Removal of Vascular Catheters in Patients With Suspected Late-Onset Sepsis

<table>
<thead>
<tr>
<th>Catheter Type</th>
<th>Removal Time</th>
<th>At Initial Evaluation for Sepsis/Antimicrobial Initiation</th>
<th>When Gram-Positive Cocci Detected in Blood Culture, Infant Stable/Improved</th>
<th>At Identification of Blood Culture Isolate as CoNS</th>
<th>Not Routinely Removed, Although CoNS in Blood Culture*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbilical catheter</td>
<td>11%†</td>
<td>35%</td>
<td>21%</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>Peripheral inserted central catheter</td>
<td>4%</td>
<td>22%</td>
<td>20%</td>
<td>62%</td>
<td></td>
</tr>
<tr>
<td>Tunneled CVC (eg, Broviac)</td>
<td>1%</td>
<td>13%</td>
<td>11%</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Nontunneled CVC</td>
<td>3%</td>
<td>22%</td>
<td>17%</td>
<td>61%</td>
<td></td>
</tr>
</tbody>
</table>

* Unless failure to improve or sterilize cultures.

† N = 274 (total excludes 4 who did not answer affirmatively to any of the queries).
DISCUSSION

This is the first survey of neonatologists and ICPs to assess current clinical, laboratory, and surveillance practices relevant to late-onset sepsis in neonates and the use of vancomycin and other antimicrobials. We cannot fully exclude the possibility that the results are not representative of the practices studied because only 35 of 61 hospitals chose to participate and only 72% of attending neonatologists and neonatology fellows completed the survey. Late-onset sepsis is important because BSIs are the most common nosocomial infection in NICU patients, and CoNS are the most common blood culture isolates.\(^1\)–\(^3\) This has led to an increase in usage of vancomycin and other antimicrobials. Sinkowitz-Cochran et al\(^12\) studied vancomycin use in children’s hospitals and found that the most common category of use was for clinical sepsis in infants in NICUs. Surveys such as the one we performed are critical to the development of clinical practice guidelines to limit vancomycin use safely and minimize the selective pressure for antibiotic-resistant pathogens in NICUs resulting from use of vancomycin and other antimicrobials. We noted numerous practices that contributed to potentially unnecessary vancomycin use.

We found that vancomycin was frequently prescribed for empiric treatment of neonates with suspected late-onset sepsis. The most likely reason for this choice was to provide an antimicrobial with activity against CoNS. The ICPs reported that CoNS were the most common NICU nosocomial BSI pathogen, as has been observed by others,\(^2\),\(^3\) and the majority of CoNS in the reporting hospitals were oxacillin resistant. In contrast, the occurrence of infection with MRSA or ampicillin-resistant enterococci, additional pathogens treated with vancomycin, were unlikely to be the impetus for empiric vancomycin use because these pathogens were uncommon in the surveyed NICUs. Furthermore, there was no significant difference in the use of empiric vancomycin in NICUs with or without MRSA infections. As CoNS BSI in neonates is fulminant in only 1% of cases\(^13\),\(^14\) and with the observed rarity of MRSA infections in most NICUs (absent from 70% of the NICUs surveyed), the empiric use of vancomycin for suspected sepsis may be unnecessary in most NICUs. This is supported by our observation that the majority of clinicians at 41% of surveyed NICUs and 40% of all of the clinicians did not prescribe empiric vancomycin for empiric therapy of suspected sepsis in a typical very low birth weight infant in the NICU.

Other data support restricted use of empiric vancomycin for suspected late-onset sepsis.\(^14\),\(^15\) Karlowicz et al\(^14\) reviewed their 10-year experience with late-onset sepsis and compared the outcome of sepsis episodes before and after empiric vancomycin was discontinued. They found no difference in the number of episodes of fulminant sepsis or the mean duration of sepsis during periods when vancomycin (and cefotaxime) or oxacillin (and cefotaxime) was prescribed for empiric therapy of suspected late-onset sepsis. Sánchez et al\(^15\) compared the use of vancomycin and the outcome of CoNS BSI after a change in the prescribing practice in their NICU from empiric usage of vancomycin for suspected late-onset sepsis to restricted use of vancomycin and institution of the practice of obtaining 2 blood cultures before instituting antimicrobial therapy. Although CoNS remained the predominant pathogen, there was a 53% reduction in vancomycin use and no change in the overall mortality or in the number of deaths as a result of CoNS sepsis during the period of restricted use of vancomycin. Furthermore, with modern blood culturing techniques, including the common use of automated, continuous monitoring blood culture systems, the clinician is typically notified of a positive blood culture within 24 hours of incubation and clinically significant isolates are almost always noted within 48 hours.\(^16\)–\(^18\) For example, Pauli et al\(^18\) found that of positive blood cultures taken from infants not on antimicrobials, 71% of positive cultures were detected by 24 hours and 100% were detected by 30 hours. CoNS were detected after a mean of 21.7 hours.\(^18\) This allows the clinician who has not prescribed empiric vancomycin to prescribe vancomycin in a timely manner for patients with Gram-positive cocci in clusters recovered in their blood cultures. Thus, vancomycin may be unnecessary for empiric treatment of most infants with suspected late-onset sepsis. Furthermore, with the rapidity of detection of pathogens by continuously monitored blood culture systems, empiric antimicrobial therapy can be safely discontinued after 48 hours, a practice used by only 57% of clinicians in our survey.

The interpretation of a CoNS blood culture isolate as a pathogen or contaminant is problematic. In an adult with suspected sepsis, 2 blood cultures routinely are obtained. Isolation of CoNS from a single blood culture often is regarded as indicative of a contaminant; isolation of the same CoNS species with a similar antimicrobial susceptibility profile from 2 blood cultures is regarded as indicative of true BSI.\(^19\) However, in the current survey, only 20 of 34 hospital laboratories (59%) routinely identified CoNS to species level, making comparison of 2 isolates from the same patient difficult. In the current study, 83% of neonatologists obtained only a single blood culture from an infant with suspected sepsis without a CVC and a similar percentage obtained a single blood culture from an infant with a CVC without blood return. Approximately half of clinicians routinely interpreted isolation of CoNS from a single blood culture as indicative of sepsis and completed a course of antimicrobial therapy. It is likely that many of these isolates are contaminants and that many infants who receive a full course of vancomycin do so unnecessarily. In the presence of a CVC, 84% of clinicians considered isolation of CoNS from a single peripheral blood culture to be indicative of sepsis and completed a course of antimicrobial therapy. In this circumstance, the ICPs surveyed considered this patient to have a BSI for surveillance purposes, consistent with NNIS classification criteria.\(^11\) However, in these situations, a substantial proportion of isolates are likely to be blood culture contaminants, and published reports of rates of CoNS sepsis in NICU patients likely are overestimates. When 2 blood cul-
tures were obtained and only 1 grew CoNS, a smaller percentage of neonatologists completed a full course of antimicrobial therapy. This indicates that a practice of routinely obtaining 2 blood cultures as part of the evaluation for suspected late-onset sepsis is likely to result in classification of fewer CoNS blood culture isolates as pathogens, thereby reducing vancomycin use and improving accuracy of surveillance data.

Adjunctive laboratory data may assist the clinician in determining whether the CoNS isolate is a pathogen or a contaminant. Data indicating a pathogen include an elevated serum CRP \(>25\) optimally obtained at least 12 hours after the onset of symptoms, and a quantitative blood culture with \(>50\) colony-forming units/mL (or a short incubation time to positive, eg, \(<15\) hours, using an automated continuously monitored blood culture system).\(^2\) Conversely, a normal 12-hour CRP and a quantitative blood culture with \(<10\) colony-forming units/mL or an incubation time to positive of \(>20\) hours may suggest that the isolate is a contaminant. Serum CRP determinations routinely were obtained at 23% of NICUs and by 30% of clinicians. Because all of the microbiology laboratories that serve the NICUs in our survey use an automated continuously monitoring blood culture system, determination and reporting of the incubation time to detection could be provided to clinicians to facilitate this assessment. It is likely that use of incubation time to detection and a 12-hour CRP would aid interpretation of the significance of a CoNS isolate and result in classification of many isolates as contaminants.

The vast majority of clinicians surveyed do not remove CVCs at the time of suspected sepsis or when notified of a blood culture growing Gram-positive cocci. In fact, in this study and in a study at Duke University Medical Center, most neonatologists did not remove a CVC even after a blood culture isolate was identified as CoNS. Neonatologists may retain the catheter because of the difficulty of replacing the vascular catheter, because of the ability to sterilize the blood culture and resolve clinical sepsis with antimicrobial therapy alone without removing the catheter, and because they do not frequently observe a catastrophic outcome as a result of retaining the catheter. The last may be observed because CoNS sepsis in general rarely and vascular catheter-related CoNS sepsis in particular rarely are fulminant. Furthermore, with the common practice of obtaining a single blood culture, many CoNS isolates may be contaminants.

Twenty-one percent of neonatologists prescribed a cephalosporin-containing regimen (rather than an aminoglycoside) for suspected late-onset sepsis. Emergence of colonization and infections with cephalosporin-resistant Gram-negative bacilli has been observed in NICUs in which cephalosporins are routinely prescribed for infants with suspected sepsis.\(^2\) For this reason, it is generally recommended to avoid routine empiric therapy with third-generation cephalosporins in NICUs.

The variations in practices documented in this survey indicate a need for studies that define optimal methods for prevention of late-onset sepsis and for evaluation and treatment of infants with suspected late-onset sepsis and a consensus guideline. Such a statement undoubtedly would recommend enhanced diagnostics to differentiate true CoNS infection from contamination and minimize overall vancomycin use in NICUs. An encouraging finding of our study is that clinical practices commonly were uniform within a particular NICU and that vancomycin restriction correlated inversely with empiric vancomycin use for suspected sepsis. These observations suggest that most clinicians accept recommendations of the leadership of their NICU and that neonatologists may be receptive to consensus guidelines. Practices that may decrease late-onset sepsis and limit vancomycin use include 1) use of full barrier precautions when placing central venous catheters, 2) use of optimal skin and catheter surface disinfection before obtaining blood for culture and changing tubing, 3) routinely obtaining 2 blood cultures from neonates with suspected sepsis and generally interpreting isolation of CoNS from a single culture as a contaminant, 4) restricting the prescribing of vancomycin for empiric therapy of neonates with suspected sepsis, 5) routine use of tests (eg, CRP and semiquantitative blood cultures and/or the time to culture positivity) and identification of CoNS to the species level to aid in interpretation of the significance of a CoNS blood culture isolate, 6) discontinuation of empiric antimicrobials after 48 hours when cultures remain negative, and 7) limitation of the duration of antibiotic treatment of CoNS sepsis to \(\leq 10\) days. Use of such measures is likely to have an important impact on decreasing the use of vancomycin and other antimicrobials in neonates and in improving patient outcomes.

ACKNOWLEDGMENTS

This work has been published in part in abstract form: Sanchez PJ, Rubin LG, Siegel JD, Levine GL, Jarvis WR. Pediatric Prevention Network (PPN). Late-onset sepsis (LOS): a survey of neonatal intensive care unit (NICU) practices. Pediatr Res. 2001;49:228A.

We thank the infection control professionals and neonatologists of the hospitals that participated in the survey: Children’s Hospital Los Angeles, Los Angeles, CA; Lucile Packard Children’s Hospital at Stanford, Stanford, CA; Children’s Hospital, Denver, CO; Wilson Children’s Hospital, Jacksonville, FL; Sacred Heart Children’s Hospital, Pensacola, FL; Children’s Health Care of Atlanta, GA; Blank Children’s Hospital, Des Moines, Iowa; St. Luke’s Regional Medical Center, Boise, ID; Children’s Memorial Hospital, Chicago, IL; Rockford Health System Children’s Medical Center, Rockford, IL; Kosair Children’s Hospital–Norton Health Care, Inc, Louisville, KY; Children’s Hospital, Boston, MA; Barbara Bush Children’s Hospital at Maine Medical Center, Portland, ME; Children’s Hospital of Michigan, Detroit, MI; DeVos Children’s Hospital, Grand Rapids, MI; Bronson Methodist Hospital, Kalamazoo, MI; Children’s Hospital and Clinics, St. Paul and Minneapolis, MN; Children’s Mercy Hospital, Kansas City, MO; St. Louis Children’s Hospital, St. Louis, MO; Children’s Hospital–University Health System of Eastern Carolina, Greenville, NC; Schneider Children’s Hospital, New Hyde Park, NY; Children’s Hospital, Columbus, OH; Children’s Medical Center, Cincinnati, OH; Eastern Tennessee Children’s Hospital, Knoxville, TN; Methodist Children’s Hospital of South Texas, San Antonio, TX; Inova Fairfax Hospital, Fairfax, VA; Children’s Hospital of The King’s Daughters Health System, Norfolk, VA; Fletcher Allen Health Care, Burlington, VT; Children’s Hospital of West Virginia University Hospitals, Morgantown, WV; Royal Children’s Hospital, Melbourne, Australia; Hospital for Sick Children, Toronto, Canada; Schneider Children’s Medical Center of Israel, Petch- Tikva, Israel; and Hospital des Enfants, Geneva, Switzerland.
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Lorry G. Rubin, Pablo J. Sánchez, Jane Siegel, Gail Levine, Lisa Saiman and William R. Jarvis

*Pediatrics* 2002;110;e42
DOI: 10.1542/peds.110.4.e42

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