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# Adherence of Newborn-Specific Antibiotic Stewardship Programs to CDC Recommendations

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## Abstract

**BACKGROUND:** The Centers for Disease Control and Prevention (CDC) published the Core Elements of Hospital Antibiotic Stewardship Programs (ASPs), while the Choosing Wisely for Newborn Medicine Top 5 list identified antibiotic therapy as an area of overuse. We identify the baseline prevalence and makeup of newborn-specific ASPs and assess the variability of NICU antibiotic use rates (AURs).

**METHODS:** Data were collected using a cross-sectional audit of Vermont Oxford Network members in February 2016. Unit measures were derived from the 7 domains of the CDC's Core

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Drs Ho and Buus-Frank substantially contributed to the conception and design of the work, analyzed and interpreted the data, drafted the initial manuscript, created the tables and figures, and critically revised the manuscript for important intellectual content; Dr Edwards, Ms Morrow, and Ms Ferrelli substantially contributed to the analysis and interpretation of the data, assisted in the creation of the tables and figures, and critically revised the manuscript for important intellectual content; Drs Srinivasan, Pollock, Dukhovny, Zupancic, Pursley, Soll, and Horbar substantially contributed to the conception and design of the work and critically revised the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Elements of Hospital ASPs, including leadership commitment, accountability, drug expertise, action, tracking, reporting, and education. Patient-level measures included patient demographics, indications, and reasons for therapy. An AUR, defined as the number of infants who are on antibiotic therapy divided by the census that day, was calculated for each unit.

**RESULTS:** Overall, 143 centers completed structured self-assessments. No center addressed all 7 core elements. Of the 7, only accountability (55%) and drug expertise (62%) had compliance >50%. Centers audited 4127 infants for current antibiotic exposure. There were 725 infants who received antibiotics, for a hospital median AUR of 17% (interquartile range 10%−26%). Of the 412 patients on >48 hours of antibiotics, only 26% (107 out of 412) had positive culture results.

**CONCLUSIONS:** Significant gaps exist between CDC recommendations to improve antibiotic use and antibiotic practices during the newborn period. There is wide variation in point prevalence AURs. Three-quarters of infants who received antibiotics for >48 hours did not have infections proven by using cultures.

Antibiotics are the most commonly prescribed medications in the NICU.[1] Infants who require intensive care are prescribed antibiotics at high rates,[2] but it has been estimated that 20% to 50% of the antibiotics prescribed in NICUs are inappropriate.[3] Although no more recent researchers have characterized the appropriateness of antibiotic use in the NICU, common reasons for inappropriate use included “failure to narrow antibiotic coverage after microbiologic results were known and prolonged antibiotic prophylaxis after surgery with chest tube placement.”[3] The overuse of antibiotics in all medical specialties is 1 of the most important factors underlying the worsening global threat of antibiotic resistance.[4]

In September 2013, the Centers for Disease Control and Prevention (CDC) released its report, “Antibiotic Resistance Threats in the United States,” in which national summary data as well as 4 actions to prevent antibiotic resistance are described.[5] The following year, as the evidence base for antibiotic stewardship programs (ASPs) grew,[6] the CDC recommended that all acute care hospitals implement ASPs in its summary, Core Elements of Hospital ASPs, including leadership commitment, accountability, drug expertise, action, tracking, reporting, and education.[7] The CDC defined “drug expertise” as a single pharmacy leader who would colead the program. Although these core elements were developed for use in the United States, many hospitals in other countries have either implemented them directly or adapted them for local use.

More recently, the American Academy of Pediatrics Section on Neonatal Perinatal Medicine joined the Choosing Wisely campaign. An initiative of the American Board of Internal Medicine Foundation, the Choosing Wisely campaign charges medical societies with identifying tests or procedures that are commonly used in their fields whose use should be discussed. The administrators of a national survey, with the help of an expert panel, identified the Choosing Wisely top 5 tests and treatments in newborn medicine. The second item on the top 5 list of potentially overused tests and treatments was the “routine continuation of antibiotic therapy beyond 48 hours for initially asymptomatic infants without evidence of bacterial infection,” further underscoring the importance of antibiotic stewardship in the newborn period.[8]

In May 2015, the California Children's Services and California Perinatal Quality Care Collaborative reported a 40-fold variation in antibiotic use rates (AURs), ranging from 2.4% to 97.1% of patient-days, in a combined California Perinatal Quality Care Collaborative-California Children's Services data set for 2013, highlighting significant variations in practice and the almost certain overuse of antibiotic therapy. This 40-fold variation could not be attributable to clinical differences in the NICUs, including the rate of positive culture results.[9]

In 2016, the Vermont Oxford Network (VON) partnered with the CDC to incorporate the core elements in its Internet-based quality improvement collaborative (iNICQ), which is focused on decreasing antibiotic overuse in the newborn period. The VON is a not-for-profit organization that aims to improve the quality, safety, and value of medical care delivered to infants and their families through research, education, and quality improvement.[10] In this article, we establish the baseline from which units began their improvement efforts and underscore the elements that are missing from ASPs of the quality collaborative. This cross-sectional examination of neonatal antibiotic usage among 143 centers and 725 infants who are on antibiotics is the largest of its kind.

## METHODS

This descriptive baseline assessment was performed by using the first of a series of cross-sectional audits of centers that were enrolled in the VON iNICQ. Each year, the VON chooses an area of focus that the neonatology community considers to be a high-priority topic in need of improvement.[11] For 2016, the VON partnered with the CDC to launch the VON iNICQ 2016: Choosing Antibiotics Wisely, with an aim to decrease newborn antibiotic overuse among participating centers.

To determine organizational engagement in antibiotic stewardship for enrolled centers, the VON arranged a series of preplanned quality audits, the first of which occurred in February 2016. Similar to previous VON initiatives around neonatal abstinence[12] and alarm safety,[13] the audits included both unit-level and patient-level measures. Unit-level measures were derived from the 7 key domains of the CDC Core Elements of Hospital ASPs: leadership commitment, accountability, drug expertise, action, tracking, reporting, and education (Supplemental Table 6).

For patient-level measures, auditors were instructed to review the records of all infants present in their units on the day of the audit during a 2-week window in February 2016. Infants were included in the cohort if they were receiving antibiotics at the time of the audit. Patient-level measures included demographic information, the indication for starting antibiotic therapy, what appropriate cultures were obtained before therapy, and the reasons for continuing antibiotics beyond 48 hours. These measures were descriptive in nature. When appropriate, measures are presented as medians with interquartile ranges.

In addition to unit-level and patient-level measures, results from the baseline audit were used to calculate an AUR, defined as the number of infants who were on antibiotic therapy divided by the total census for the day, for each participating center.

Hospital characteristics were derived from the VON Annual Membership Survey. The type of NICU was derived on the basis of responses to whether the hospital was required by state regulation to transfer infants to another hospital for assisted ventilation on the basis of the infants' characteristics, duration of ventilation required, or whether any of 10 surgical procedures was performed at the hospital (eg, omphalocele repair, ventriculoperitoneal shunt, tracheoesophageal fistula or esophageal atresia repair, bowel resection or reanastomosis, meningomyelocele repair, patent ductus arteriosus ligation, cardiac catheterization, or cardiac surgery requiring bypass). Teaching hospitals were defined as those with neonatal fellows, pediatric residents, or other residents participating in direct patient care in the NICU. Results were stratified both by location (within the United States versus outside of the United States) as well as NICU type.

Auditors received a manual of operations with standardized definitions for each measure. This project was classified as non-human subjects research and was considered exempt by the Institutional Review Board of the University of Vermont. Each participating center was provided with institutional review board sample materials and instructions to obtain the necessary determinations required at their local sites. Audit data were collected by each center and reported to the VON through the use of an online data portal, with all patient data being deidentified. Local data were reported back to the centers at the completion of data entry. The aggregate data were reported back to centers and, in some participating states, used to compare their processes and patient-level outcomes with those of their peers.[12–14]

## RESULTS

Of the 158 centers participating in the VON iNICQ 2016: Choosing Antibiotics Wisely, 143 (92% of which were in the United States) participated in the first quality audit (Supplemental Table 7). Of these centers, 27% had restrictions on ventilation or did not perform surgery, 52% had no ventilation restrictions and performed neonatal surgery (except cardiac surgery requiring bypass), and 21% had no ventilation restrictions and performed neonatal surgery (including cardiac surgery requiring bypass). Sixty percent were teaching hospitals, and 73% were nonprofit hospitals (Table 1).

Of the key items linked to the CDC's Core Elements of Hospital ASPs, all centers reported their capacity for leadership commitment, accountability, drug expertise, action, tracking, reporting, and education (Fig 1). Figure 1 includes the percentage of participating units that were compliant with each of the 7 CDC core elements. Importantly, no center addressed all 7 CDC core elements. There were no differences in compliance when stratified by NICU type. Twelve centers from countries outside the United States participated in the audit. International centers were more likely to report leadership commitment and accountability and were less likely to report education and reporting (data not shown).

There were 143 centers in which 4127 infants were audited for current antibiotic exposure. Ten of the centers had no infants on antibiotics at the time of the audit. A total of 725 infants were receiving antibiotics on the day of the audit. Among these 725 infants, 279 (38%) had birth weights >2500 g, and 261 (36%) were between 1 and 3 days of chronological age (Table 2). The median hospital AUR was 17% (interquartile range 10%−26%; Fig 2). There

was no difference between AURs when stratified by NICU type. Parents were aware of antibiotic use for 80% of infants and were aware when the antibiotics would be discontinued for 62% of infants.

Of the 725 infants receiving antibiotics, 632 (87%) had blood cultures obtained before starting antibiotic therapy. Few had urine cultures (110 of 725; 15%) or cerebrospinal fluid cultures (57 of 725; 8%) obtained before initiating antibiotics. Ultimately, 540 of 632 (85%) of the blood cultures did not reveal an organism (Table 3).

Of the 412 patients >48 hours of age and on >48 hours of antibiotics, only 26% ($n$ = 107) had positive culture results, 17% had no culture obtained, and 69% had at least 1 negative culture result.

Among the 725 infants receiving antibiotics, a majority were on ampicillin ($n$ = 431; 60%) and/or gentamicin ($n$ = 461; 64%). Vancomycin represented the third most used antibiotic at 14% ($n$ = 100). The antifungal medication fluconazole was close behind at 11% ($n$ = 81; Table 4). Among those same 725 infants, the indication or indications for antibiotic initiation were asked about in the audit. More than one-third ($n$ = 254; 35%) received antibiotics because of maternal risk factors. Just less than half ($n$ = 319; 44%) received antibiotics because of suspected early-onset sepsis (Table 5).

## DISCUSSION

Among 143 centers planning to participate in an iNICQ centered on decreasing antibiotic overuse, initial compliance with the CDC's Core Elements of Hospital ASPs was low. Although a majority of centers had a physician leader responsible for the stewardship activities (accountability) as well as pharmacist leader involvement (drug expertise), few tracked AURs, and even fewer reported them.

This baseline audit exposes the gap between CDC recommendations for ASPs and the current state of ASPs among a sample of NICUs. The core elements were initially described for hospital-level, not unit-level, ASPs. Of note, this iNICQ operated independently of hospital-level ASPs and adapted the core elements to unit-level ASPs. However, there remains no other rubric or guideline for neonatal antibiotic stewardship teams to follow besides the CDC's Core Elements of Hospital ASPs.

This, the largest 1-day cross-sectional examination of neonatal antibiotic usage among 143 units, resulted in the auditing of >4000 infants, 725 of whom were on antibiotics. Although our approach did not show the same magnitude in variation compared with previous studies,[9] we nonetheless emphasize the wide difference in antibiotic use between centers. Most importantly, the significant majority of patients who were on antibiotics for >48 hours despite the absence of positive culture results highlights some potential for improvement in antibiotic overuse. Certainly, some infants may have false-negative culture results or reasons to continue antibiotics despite negative culture results (such as confirmed necrotizing enterocolitis on radiograph findings, wound infection, etc), but these patients likely comprise a minority of infants with negative culture results.[15] The utility of clinical biomarkers, such

as C-reactive protein, procalcitonin, and a low white blood cell count (especially with a left shift), for decision-making in infants with negative culture results remains to be determined.

This 1-day cross-sectional structured self-assessment, although the largest of its nature, is subject to day-to-day variability in census, severity of illness, and prescribing patterns. We sought to minimize day-to-day variability by including a large number of participating centers. Similarly, reliance on self-assessment and self-reporting may distort the true nature of ASPs in newborn centers, but given the low compliance with the CDC's core elements across the board, this baseline assessment is likely a close approximation of the true state of neonatal ASPs.

Additionally, this study was limited to a self-selected group of centers participating in a quality improvement collaborative. It is not known whether these centers are different from nonparticipating centers (eg, participating centers may start with lower compliance with the CDC's Core Elements of Hospital ASPs). However, participating centers have dedicated time and resources toward improving the appropriate use of antibiotics.

Lastly, all centers participating in the quality improvement collaborative were NICUs, decreasing the overall generalizability to all newborns, such as those who were admitted to the postpartum unit. These infants who require a higher level of care may be sicker than those in the postpartum unit. The 725 infants who received antibiotics were fairly evenly distributed with respect to birth weight, gestational age, and chronological age. Whether centers admit well-appearing infants undergoing sepsis rule outs to the NICU may also drastically alter the AUR for that center; centers that admit well-appearing asymptomatic sepsis rule outs to the NICU would have higher-than-expected NICU AURs. One could argue that caring for these infants in the ICU as opposed to in the postpartum unit constitutes a different kind of overuse, 1 that not only increases cost to the system with little potential benefit but also potentially causes harm by separating the infant from the mother.

Since 2016, the VON has worked with centers participating in iNICQ 2016: Choosing Antibiotics Wisely to decrease antibiotic overuse through education around improvement techniques using a quality improvement toolkit and a series of webinars. Now in its third year, antibiotic stewardship improvement teams continue to apply the Model for Improvement,[16] change ideas, and plot data over time using annotated run charts. Additional audits conducted during the collaborative will be used to assess the impact of the collaborative.

## CONCLUSIONS

There are significant gaps between the CDC recommendations and current antibiotic stewardship capacity and practices in the newborn period. In addition, there is wide variation in AURs among participating centers and a high rate of continued antibiotic treatment in the absence of positive culture results. Inadequate organizational infrastructure and capacity may contribute to the overuse and misuse of antibiotics. Systematic quality improvement efforts can be used to address these deficiencies and should be tested for their ability to be

used to promote adherence to the CDC core elements and the appropriate use of antibiotics in the newborn period.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## ABBREVIATIONS

| | |
|---|---|
| **ASP** | antibiotic stewardship program |
| **AUR** | antibiotic use rate |
| **CDC** | Centers for Disease Control and Prevention |
| **iNICQ** | Internet-based quality improvement collaborative |
| **VON** | Vermont Oxford Network |

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**WHAT'S KNOWN ON THIS SUBJECT:**

Infants requiring intensive care often need antibiotic therapy, with some qualifying as overuse. The Centers for Disease Control and Prevention recommends following the Core Elements of Hospital Antibiotic Stewardship Programs to combat antibiotic resistance. Variation exists in antibiotic prescribing practices in newborn care.

**WHAT THIS STUDY ADDS:**

In this study, we identify the baseline prevalence of antibiotic stewardship programs in the newborn setting and assess the variability in antibiotic use rates among NICUs.

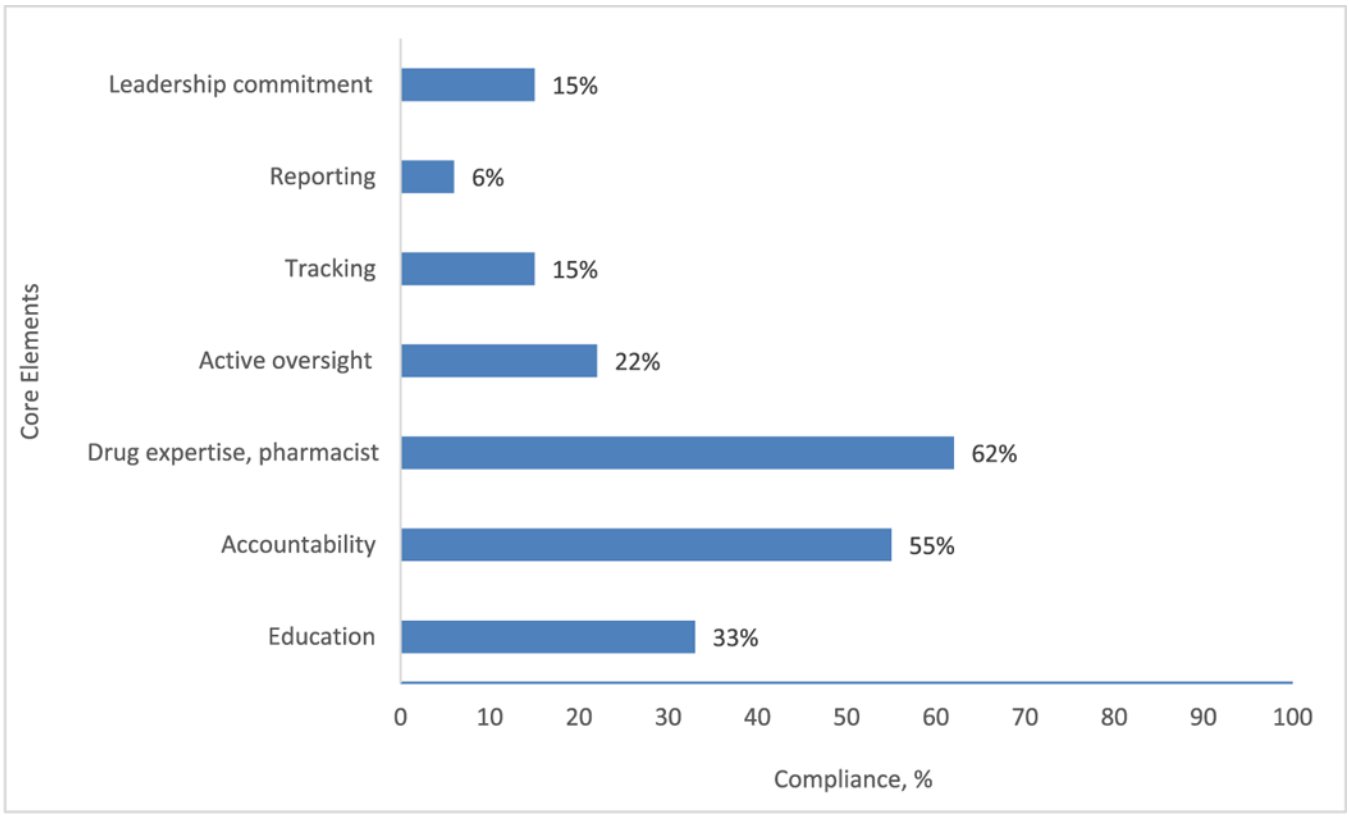


**FIGURE 1.**
Percent compliance with the CDC's Core Elements of Hospital ASPs among 143 NICUs.

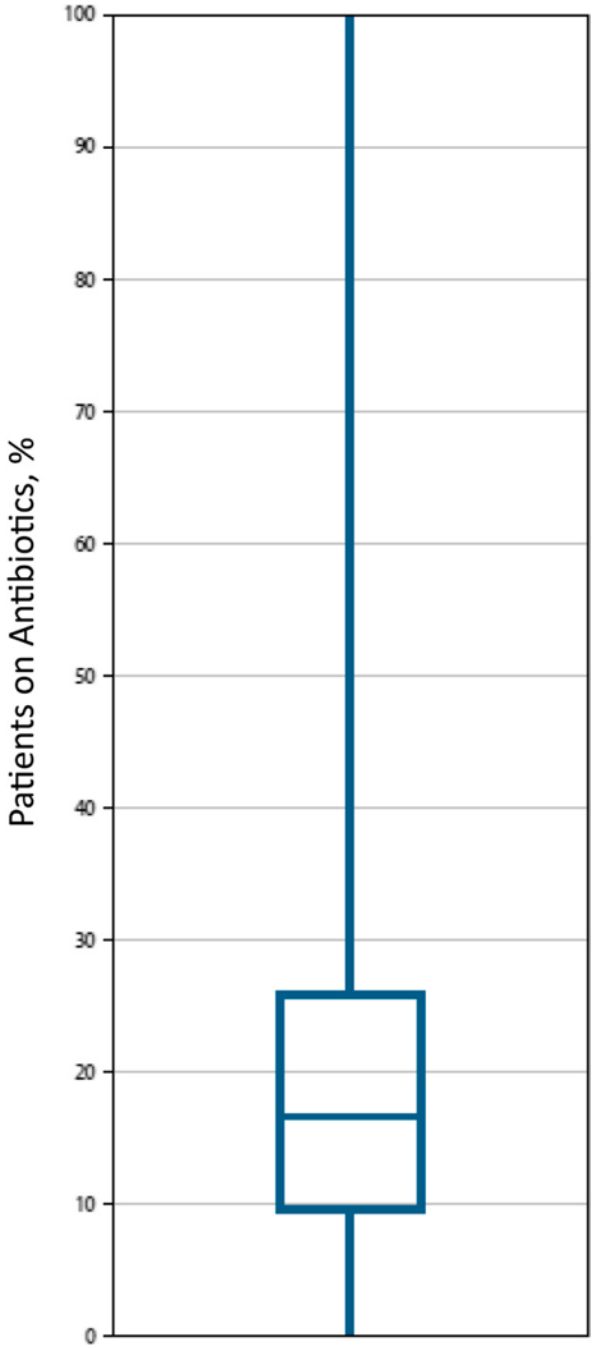


**FIGURE 2.**

AURs for 133 NICUs. The box and whisker plot displays the rates for centers. The top vertical line reaches to the maximum value. The top of the box represents the upper quartile. The line within the box represents the median. The bottom of the box represents the lower quartiles. The lower vertical line reaches to the minimum value.

**TABLE 1**

Characteristics of 143 NICUs Participating in the Audit for ASP Quality Improvement Collaborative

| Characteristic | Result |
|---|---|
| NICU beds, median (Q1, Q3) | 24 (15, 39) |
| NICU type, % | |
| A (restrictions on ventilation or did not perform surgery) | 27 |
| B (no ventilation restrictions and performed neonatal surgery [except cardiac surgery requiring bypass]) | 52 |
| C (no ventilation restrictions and performed neonatal surgery, including cardiac surgery requiring bypass) | 21 |
| Teaching hospital, % | 60 |
| Hospital ownership, % | |
| Nonprofit | 73 |
| For profit | 14 |
| Government or other | 13 |

Q1, quartile 1; Q3, quartile 3.

**TABLE 2**

Characteristics of 725 Infants Receiving Antibiotics

| Characteristic | No. (*N* = 725) | % |
|---|---|---|
| Birth wt, g | | |
| <1501 | 290 | 40 |
| 1501–2500 | 156 | 22 |
| >2500 | 279 | 39 |
| Gestational age, wk | | |
| <31 | 250 | 35 |
| 31–36 | 227 | 31 |
| >36 | 248 | 34 |
| Chronological age, d | | |
| 1 −3 | 261 | 36 |
| 4–28 | 282 | 39 |
| >28 | 182 | 25 |
| Current respiratory support | | |
| Assisted ventilation via endotracheal tube | 180 | 25 |
| Nasal ventilation or CPAP | 140 | 19 |
| High-flow nasal cannula | 73 | 10 |
| Oxygen only | 25 | 3 |
| No support | 307 | 42 |

CPAP, continuous positive airway pressure.

**TABLE 3**

Blood Culture Results for 725 Infants Receiving Antibiotics

| | No. (*N* = 725) | % |
|---|---|---|
| No culture obtained | 93 | 13 |
| Culture obtained, no organism identified | 540 | 74 |
| Organism identified | 92 | 13 |
| Known nonresistant organism | 45 | 49[a] |
| Coagulase-negative *Staphylococcus* | 20 | 22[a] |
| Methicillin-resistant *Staphylococcus aureus* | 3 | 3[a] |
| Vancomycin-resistant *Enterococcus* | 0 | 0[a] |
| Gram-negative bacilli resistant to third-generation cephalosporin | 5 | 5[a] |
| Fungal pathogen | 12 | 13[a] |
| Other | 18 | 20[a] |

[a]Percentage calculated among those with an identified organism.

**TABLE 4**

Distribution of Antibiotics Among 725 Infants

| Antibiotic or Antiviral | No. (*N* = 725) | % |
|---|---|---|
| Aminoglycoside (including gentamicin) | 461 | 64 |
| Ampicillin | 431 | 60 |
| Vancomycin | 100 | 14 |
| Fluconazole | 81 | 11 |

Infants could be on >1 antibiotic. Percentages add to >100%.

**TABLE 5**

Indications for Antibiotic Use for 725 Infants Receiving Antibiotics

| | No. (*N* = 725) | % |
|---|---|---|
| Maternal risk factors | 254 | 35.0 |
| Early-onset sepsis or meningitis[a] | 319 | 44.0 |
| Late-onset sepsis or meningitis[a] | 133 | 18.3 |
| Ventilator-associated pneumonia[a] | 22 | 3.0 |
| Central venous line infection[a] | 27 | 3.7 |
| Urinary tract infection[a] | 44 | 6.1 |
| Necrotizing enterocolitis[a] | 51 | 7.0 |
| Surgical site infection[a] | 18 | 2.5 |
| Urinary tract infection[b] | 29 | 4.0 |
| Surgery[b] | 30 | 4.1 |
| Fungal sepsis[b] | 55 | 7.6 |
| Methicillin-resistant *S aureus* colonization | 4 | 0.6 |
| Other | 114 | 15.7 |

Infants could have had >1 indication.

[a]Suspected or proven.

[b]Prophylaxis.