Neonatal Intensive Care Unit Antibiotic Use

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abstract

BACKGROUND AND OBJECTIVES: Treatment of suspected infection is a mainstay of the daily work in the NICU. We hypothesized that NICU antibiotic prescribing practice variation correlates with rates of proven infection, necrotizing enterocolitis (NEC), mortality, inborn admission, and with NICU surgical volume and average length of stay.

METHODS: In a retrospective cohort study of 52 061 infants in 127 NICUs across California during 2013, we compared sample means and explored linear and nonparametric correlations, stratified by NICU level of care and lowest/highest antibiotic use rate quartiles.

RESULTS: Overall antibiotic use varied 40-fold, from 2.4% to 97.1% of patient-days; median = 24.5%. At all levels of care, it was independent of proven infection, NEC, surgical volume, or mortality. Fifty percent of intermediate level NICUs were in the highest antibiotic use quartile, yet most of these units reported infection rates of zero. Regional NICUs in the highest antibiotic quartile reported inborn admission rate 218% higher (0.24 vs 0.11, P = .03), and length of stay 35% longer (90.2 days vs 66.9 days, P = .03) than regional NICUs in the lowest quartile.

CONCLUSIONS: Forty-fold variation in NICU antibiotic prescribing practice across 127 NICUs with similar burdens of proven infection, NEC, surgical volume, and mortality indicates that a considerable portion of antibiotic use lacks clear warrant; in some NICUs, antibiotics are overused. Additional study is needed to establish appropriate use ranges and elucidate the determinants and directionality of relationships between antibiotic and other resource use.

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WHAT'S KNOWN ON THIS SUBJECT: Although treatment of infection is a mainstay of neonatal intensive care, little attention has focused on the proportion of patient antibiotic exposures validated by clinical indications that are unambiguous.

WHAT THIS STUDY ADDS: Septic workups in 127 California NICUs reveal similar burdens of proven infection, yet patient antibiotic exposures in those NICUs vary 40-fold. Because antibiotic stewardship principles dictate that antibiotic use should correlate with burden of infection, some NICUs overuse antibiotics.

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www.pediatrics.org/cgi/doi/10.1542/peds.2014-3409

DOI: 10.1542/peds.2014-3409

Accepted for publication Jan 29, 2015

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding. This study is a product of core evaluative and quality improvement work performed by the California Department of Health Care Services and the California Perinatal Quality Care Collaborative.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found on page 928, and online at www.pediatrics.org/cgi/doi/10.1542/peds.2015-0707.

Wide variation in hospital resource use with little connection to patient outcomes has been reported for diverse care contexts.[1] These patterns challenge the belief that directing incrementally more resources at certain health care problems necessarily produces incrementally better results. For instance, the Centers for Disease Control and Prevention estimates that as much as 50% of prescribed antibiotics are either unnecessary or suboptimally effective as prescribed.[2]

Wide variation in outcomes has also been documented among NICUs.[3,4] However, relatively little information is available connecting NICU resource use with patient outcomes. Prevention of central line associated bloodstream infection (CLABSI) and other hospital-acquired infection in the NICU has been a recent target of quality improvement efforts.[5–7] Such efforts share the broader strategic objective of reducing health care misuse (1 of 3 categories of quality problems, along with underuse and overuse).[8] In 2012, more than 60% of NICUs in California reported a CLABSI rate of zero.[9] It is unclear whether reported success of such infection prevention efforts affects the perceived overall burden of NICU infection and consequent use of antibiotics. Antibiotics used in circumstances where patient benefits are not clearly demonstrable would constitute overuse.[10] Eliminating overuse is considered perhaps the most effective way to improve quality and reduce cost,[10] yet the strategy has largely been neglected in quality improvement research and interventions.[11]

Antibiotics are commonly used drugs in NICUs.[12] If overuse is occurring in the NICU, the consequences extend beyond unwarranted resource use and increased financial cost of care. Neonatal antibiotic exposure is associated with increased risk of necrotizing enterocolitis (NEC), nosocomial infection (NI), and mortality,[13–15] as well as with asthma later in life.[16] Additionally, antimicrobial use is associated with the selection of multidrug-resistant pathogens, themselves associated with increased morbidity, mortality, cost, and length of stay.[17] To explore the possibility of overuse of antibiotics for neonates, we measured NICU antibiotic practice variation and examined relationships with proven infection and other factors unambiguously connected with antibiotic exposure.

METHODS

California Children's Services (CCS), within the California Department of Health Care Services, confers state approval for 3 levels of NICU care: regional, community, and intermediate,[18] generally corresponding to American Academy of Pediatrics levels IV, III, and II, respectively.[19] CCS standards include a requirement for annual data reporting of specific variables. Beginning in 2013, CCS required NICUs to report annual antibiotic use rate (AUR). All 116 CCS-approved NICUs submit their data to the California Perinatal Quality Care Collaborative (CPQCC),[4] which prepares an annual report for each NICU and submits an aggregate data set to CCS. Of 136 NICUs in California,[20] 132 participate in the CPQCC. Thus, the combined CPQCC/CCS data set approximates a population-based database describing NICU care and outcomes for most of the 503 738 total live births in California in 2013.[21] The authors conducted the study analysis by using the CPQCC/CCS data set for calendar year 2013. This study was approved by the Stanford University Institutional Review Board.

Study Variable Definitions

AUR is the total number of patient-days that infants were exposed to 1 or more antibacterial or antifungal agents administered intravenously or intramuscularly per 100 patient-days in the reporting NICU, expressed as a percentage. With increasing adoption by hospitals of computerized provider order entry systems,[22] NICUs were encouraged to obtain this information via a specifically designed database query, although not all units had this capability. Early onset sepsis (EOS) rate is the percentage of infants with bacterial or fungal infection diagnosed by blood culture within 2 days of birth. CLABSI rate is the number of laboratory confirmed bloodstream infections where a central line (including an umbilical catheter) was in place for >2 days on the date of the event per 1000 central-line days.[23] Inborn admission rate is the proportion of all live births at a hospital who were admitted to the NICU. Number of surgical cases counts the number of patients undergoing a surgical procedure, excluding circumcision, cannulation/decannulation for extracorporeal membrane oxygenation, placement/removal of peritoneal dialysis catheters, chest tube placement, or central line placement. NICU mortality rate is the ratio of all NICU deaths to the total number of NICU admissions.

Certain CCS/CPQCC variables are restricted to infants who were 401 to 1500 g or 22 to 29 weeks' gestation at birth. NI rate is the percentage of infants with bacterial or fungal infection diagnosed by blood culture on or after 3 days after birth; fungal infection rate is the percentage of infants with a fungal infection diagnosed by blood culture on or after 3 days after birth; NEC rate is the percentage of infants diagnosed with NEC; and average length of stay (AvLOS) is the average NICU length of stay in days for patients discharged from the hospital.

Statistical Methods

The unit of observation and unit of analysis was the individual NICU. We stratified the overall analysis by NICU

levels of care and lowest/highest AUR quartiles (quartile 1/quartile 4). Sample means were compared by analysis of variance; unequal variances were assessed by Bartlett's test for equal variances. *P* values reflect 2-tailed distributions. We estimated the magnitude of linear correlation by Pearson's correlation coefficient, unless extreme outlier values or unmet distributional assumptions warranted Spearman's rank correlation. We used Stata 13[24] (Stata Corp, College Station, TX) for all computations and graphical displays.

RESULTS

Among 132 CPQCC NICUs, 5 reported either missing AUR or fewer than 1 of 100 patient-days (values considered clinically implausible), and were dropped from the analysis. The remaining 127 NICUs admitted 52 061 infants and provided care for 746 051 patient-days, of which 214 323 entailed antibiotic exposure.

AUR variation is detailed in Fig 1 and Table 1. Overall, AUR varied 40-fold, from 2.4% of patient-days to 97.1% of patient-days (median = 24.5%; quartile 1 ≤17.5%, quartile 4 ≥33.5%). Regional NICU AUR varied almost sevenfold; community NICU AUR varied 12-fold; intermediate NICU AUR varied almost 31-fold; non-CCS NICU AUR varied almost fivefold.

In either the overall or stratified analysis, there were no statistically significant correlations between AUR and proven infection, NEC, surgical case volume, or NICU mortality (Table 2). Comparing NICUs in the lowest quartile of AUR values with NICUs in the highest quartile revealed no significant difference in burden of proven infection, NEC, surgical case volume, or mortality rate (Table 2). Figure 2 illustrates no correlation between AUR and NI among NICUs in either the lowest or highest AUR quartile (Spearman's correlation coefficient = 0.12, *P* = .51; and Pearson's correlation coefficient = −0.02, *P* = .93, respectively). Table 3 describes the percentage of NICUs reporting specific proven infection rates of zero among providers in the lowest and highest AUR quartiles. The proportion of high quartile AUR NICUs with specific infection rates of zero is noteworthy, especially among intermediate NICUs.

Examining AUR and other NICU resource use revealed no correlation between AUR and AvLOS overall, but they were positively correlated among regional-level NICUs (Fig 2; Pearson's correlation coefficient = 0.78; *P* < .001). Compared with regional NICUs in the lowest AUR

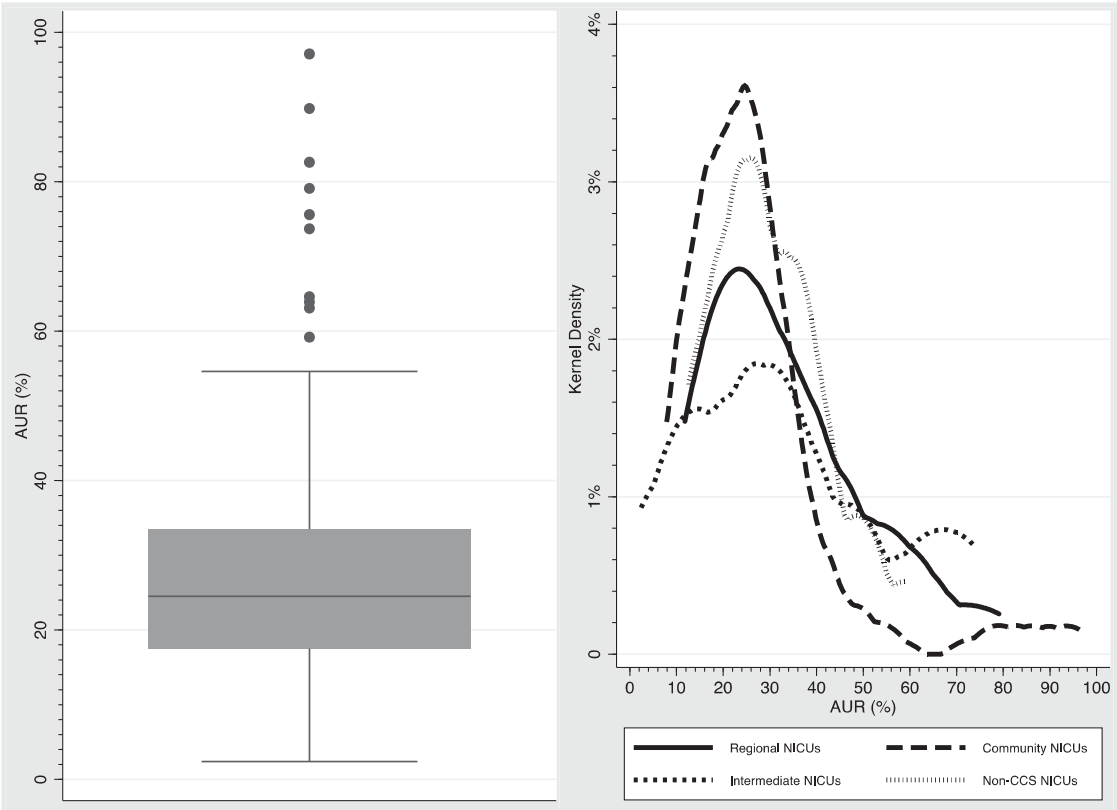

FIGURE 1
Range of AUR values and distribution of AUR values by level of care. Left, Interquartile range and median AUR across all NICUs; lines above or below the box extend further by 1.5 times the interquartile range; dots mark extreme outliers. Right, AUR stratified by NICU level of care. Kernel density is essentially a smoothed frequency distribution histogram.

TABLE 1 NICU Patient Volume and AUR

NICU Level of Care	Total Number of NICUs	Number of NICUs AUR Quartile 1	Number of NICUs AUR Quartile 4	Number of NICU Admissions			Number of NICU Patient-Days			Antibiotic Patient-Days (Overall AUR Value)			Lowest AUR Value	Highest AUR Value	Range of AUR Variation (Multiples of Lowest to Highest Value)	AUR Median/Mean (SD)
				Total	AUR Quartile 1	AUR Quartile 4	Total	AUR Quartile 1	AUR Quartile 4	Total	AUR Quartile 1	AUR Quartile 4				
All NICUs	127	32	31	52 061	11 916	12 363	746 051	157 853	161 050	214 323 (29.7)	21 296 (13.5)	85 568 (53.1)	2.4	97.1	40	24.5/28.9 (17.4)
Regional	21	4	7	14 044	2362	3718	274 689	39 563	75 716	87 853 (32.0)	6121 (15.5)	41 642 (55.0)	11.8	79.1	7	30.2/32.9 (17.6)
Community	79	23	14	31 206	8401	5787	419 435	109 059	69 756	110 688 (26.4)	14 087 (12.9)	36 179 (51.9)	7.9	97.1	12	23.7/26.9 (16.7)
Intermediate	14	3	7	3285	500	2206	21 073	3147	12 723	7677 (36.4)	196 (6.2)	6402 (50.3)	2.4	73.7	31	30.1/32.3 (22.4)
Non-CCS	13	2	3	3526	653	652	30 854	6084	2855	8105 (26.3)	892 (14.7)	1345 (47.1)	12.6	59.2	5	29.1/30.1 (12.9)

quartile, regional NICUs in the highest AUR quartile reported AvLOS 35% longer (Table 2; 90.2 days vs 66.9 days, P = .03). There was no correlation between AUR and inborn admission rate overall, but as shown in Fig 2, they were positively correlated among both regional-level (Pearson's and Spearman's correlation coefficient = 0.61; P = .01) and intermediate-level NICUs (Pearson's correlation coefficient = 0.68; P = .008). Compared with regional NICUs in the lowest AUR quartile, the inborn admission rate among regional NICUs in the highest AUR quartile was 218% higher (Table 2; 0.24 vs 0.11, P = .03).

DISCUSSION

This study of the largest and most diverse NICU antibiotic use cohort to date (127 NICUs, 52 061 infants, and 746 051 patient-days) revealed the widest known scale of antibiotic prescribing practice variation. This variation is independent of proven infection burden, NEC, surgical volume, or mortality rate. Even when the focus is restricted to NICUs in the highest and lowest AUR quartiles, NICUs do not differ in proven infection burden, NEC, surgical volume, or mortality rates. Rather, they appear to differ only in their burden of suspected but unproven infection. Variation in antibiotic prescribing practice appears to hinge on variation in how practitioners frame, interpret, and respond to clinical situations ultimately considered unproven infection. Thus, a considerable portion of the observed variation in antibiotic use appears unwarranted; in some NICUs, antibiotics are overused.

Within a particular NICU level of care, the widest variation in AUR, 31-fold, occurred among intermediate level NICUs. Although these NICUs care for infants in the lower end of the severity of illness range, their median AUR was 27% greater than for community level NICUs, and the same as for regional NICUs (Table 1). In addition, 50% of all intermediate level NICUs are in AUR quartile 4 (Table 1), yet all those NICUs reported CLABSI, NI, and fungal infection rates of zero, and 57% reported EOS of zero (Table 3).

Earlier reports of antibiotic use are less comprehensive or specific, but their findings are consistent with our observations. Among 40 children's hospitals, antibiotic-days ranged between 36.8% and 60.1% of patient-days; the variation was unexplained by patient- or hospital-level factors associated with antibiotic treatment.[25] Among 29 NICUs, the point-prevalence of antibiotic use ranged between 15.2% and 85.7% of patients (median = 45.8%).[12] Among 323 acute care hospitals, almost 56% of patients received antibiotics during their hospitalization.[26] Finally, among 19 hospitals that reported antibiotic use to the National Healthcare Safety Network in 2012, critical care units reported a median of 937 days/1000 patient-days; ward locations, a median of 549 days/1000 patient-days; the widest variation between the 10th and 90th percentiles was threefold, among the ward locations.[26] The consistency of our data with these earlier reports also mitigates concern over possible estimation errors in data reported by NICUs unable to obtain antibiotic use values via a specifically designed pharmacy database query; such NICUs instead depend upon manual abstraction of data from each medical record. Additionally to this point, if such potential errors were inaccurate in a systematic way, the effect on data patterns would tend to make it even more unlikely to find the observed absence of correlation detailed in Table 2.

Our data set accounts for almost all proven microbial infection. Although incidence of NI only reflects infants who were 401 to 1500 g or 22 to 29 weeks' gestation at birth, most NI occurs in this subpopulation.[27]

TABLE 2 Estimated Correlations With AUR and Correlate Variable Sample Means for Quartiles 1 and 4

	Correlation Coefficient (Pearson's Except Where Noted)	*P*	AUR Quartile 1, Mean (95% CI)	AUR Quartile 4, Mean (95% CI)	*P*
EOS					
All NICUs	−0.06[a]	.53	2.00 (1.33–2.68)	2.01 (1.14–2.88)	.99
Regional	−0.12[a]	.62	1.12 (0–2.45)	1.41 (0.58–2.24)	.61
Community	−0.12[a]	.28	2.45 (1.62–3.29)	2.09 (0.74–3.44)	.61
Intermediate	0.32[a]	.26	0	2.77 (0–6.02)	.22
Non-CCS	−0.26[a]	.39	1.6 (0–21.93)	1.23 (0–6.54)	.86
CLABSI					
All NICUs	−0.033	.72	0.91 (0.13–1.68)	0.45 (0.0–0.93)	.31
Regional	−0.15	.50	0.99 (0–3.6)	0.89 (0.13–1.6)	.89
Community	0.008	.94	0.56 (0–1.6)	1.0 (0.03–2.1)	.52
Intermediate	[b]	NA	0	0	NA
Non-CCS	−0.22	.48	0	0	NA
NI					
All NICUs	0.006	.95	6.5 (4.1–8.9)	6.8 (3.6–9.9)	.89
Regional	0.21	.35	5 (0–10.7)	9.5 (5.1–13.9)	.13
Community	0.05	.65	7.2 (4.3–10.1)	10.2 (4.3–16.1)	.28
Intermediate	−0.15	.64	0	0	NA
Non-CCS	−0.22	.46	8.0 (0–110)	0	.27
Fungal infection					
All NICUs	0.02	.83	0.12 (0.0–0.29)	0.34 (0.056–0.63)	.17
Regional	0.07	.77	0.3 (0–1.2)	0.79 (0.08–1.5)	.30
Community	−0.02	.82	0.10 (0–0.3)	0.37 (0–0.9)	.28
Intermediate	[b]	NA	0	0	NA
Non-CCS	[b]	NA	0	0	NA
NEC					
All NICUs	0.02	.86	3.1 (1.5–4.6)	2.6 (1.1–4.0)	.65
Regional	0.16	.49	7.0 (1.0–12.9)	6.2 (3.1–9.2)	.72
Community	−0.005	.97	2.9 (1.1–4.7)	2.7 (0.1–5.2)	.86
Intermediate	[b]	NA	0	0	NA
Non-CCS	−0.18	.56	0	0	NA
Number of surgical cases					
All NICUs	0.12	.16	13.8 (0–27.7)	47.5 (7.5–87.4)	.10
Regional	0.17	.47	82.2 (0–218.8)	193.1 (41.6–344.7)	.25
Community	0.05	.67	5.0 (0.6–9.3)	7.9 (0–16.1)	.46
Intermediate	0.07	.81	0	1.3 (0–4.0)	.49
Non-CCS	−0.17	.57	0	0	NA
NICU mortality rate					
All NICUs	0.09	.31	11.8 (8.5–15.2)	13.5 (5.6–21.4)	.69
Regional	0.22[a]	.34	16.2 (3.1–29.2)	39.7 (8.9–70.5)	.21
Community	−0.10	.39	13.1 (9.1–17.2)	9.8 (5.8–13.8)	.25
Intermediate	−0.07	.81	0.4 (0–1.6)	1.5 (0–8.1)	.38
Non-CCS	−0.30	.31	3.9 (0–54.2)	0	.27
Inborn admission rate					
All NICUs	0.15[a]	.10	0.11 (0.10–0.13)	0.14 (0.11–0.17)	.10
Regional	0.61	.01	0.11 (0.06–0.17)	0.24 (0.13–0.35)	.03
Community	−0.005[a]	.97	0.12 (0.10–0.14)	0.11 (0.09–0.14)	.77
Intermediate	0.68	.008	0.10 (0–0.25)	0.14 (0.07–0.20)	.44
Non-CCS	0.10	.75	0.09 (0–0.34)	0.11 (0–0.25)	.66
AvLOS					
All NICUs	0.06	.50	57.9 (53.6–62.2)	57.9 (49.0–66.8)	.99
Regional	0.78	<.001	66.9 (60.1–73.7)	90.2 (73.5–106.8)	.03
Community	−0.12	.28	58.8 (54.0–63.6)	56.4 (49.7–63.0)	.53
Intermediate	−0.16	.64	40.4 (0–124.9)	36.2 (28–44.3)	.55
Non-CCS	−0.04	.90	46.5 (0–104.4)	32.9 (0–71.2)	.34

CI, confidence interval; NA, not available.

[a] Distribution of values warrants nonparametric analysis: Spearman's rank correlation computed.

[b] All NICUs reported a rate of 0.

Moreover, CLABSI (a substantial subset of NI) was reported for all infants. The overall incidence of EOS is <1/1000 live births[28,29]; the median inborn admission rate in our study was 113/1000 live births. Thus, our findings are consistent with previous reports that revealed most NICU antibiotic use is empirical; in those studies the ultimate diagnosis is suspected infection, not proven infection.[12,30] A study of antibiotic use in 2 large NICUs in California revealed almost ninefold greater use of antibiotics for unproven infection than for proven infection as measured by CLABSI.[30] It should be noted, however, that our data do not enable us to estimate such practice variation as treatment duration for proven infection, perioperative prophylaxis, or contaminating/colonizing organisms.

Current knowledge indicates that some clinical thresholds for initiating and/or continuing antibiotic courses for suspected infection can be raised without harm. Recent studies reveal that well-appearing term infants with negative blood cultures can have antibiotics discontinued after 48 to 72 hours even when their mothers were treated for chorioamnionitis.[31–33] In 1 study, 24% of infants born to mothers with chorioamnionitis were treated with prolonged (>48 hours) antibiotics, but 84% of these infants received prolonged treatment solely on the basis of abnormal laboratory data.[34] A new Bayesian approach to identifying EOS in infants ≥34 weeks' gestation results in empirical antibiotic treatment of a much smaller proportion of this population (only 4%) and relies on evolving objective clinical findings to guide management of all lower risk infants.[33] These authors estimate that their approach could decrease antibiotic treatment in as many as 240 000 newborns nationwide.[33]

In contrast to other reports,[13–15] we did not find a relationship between

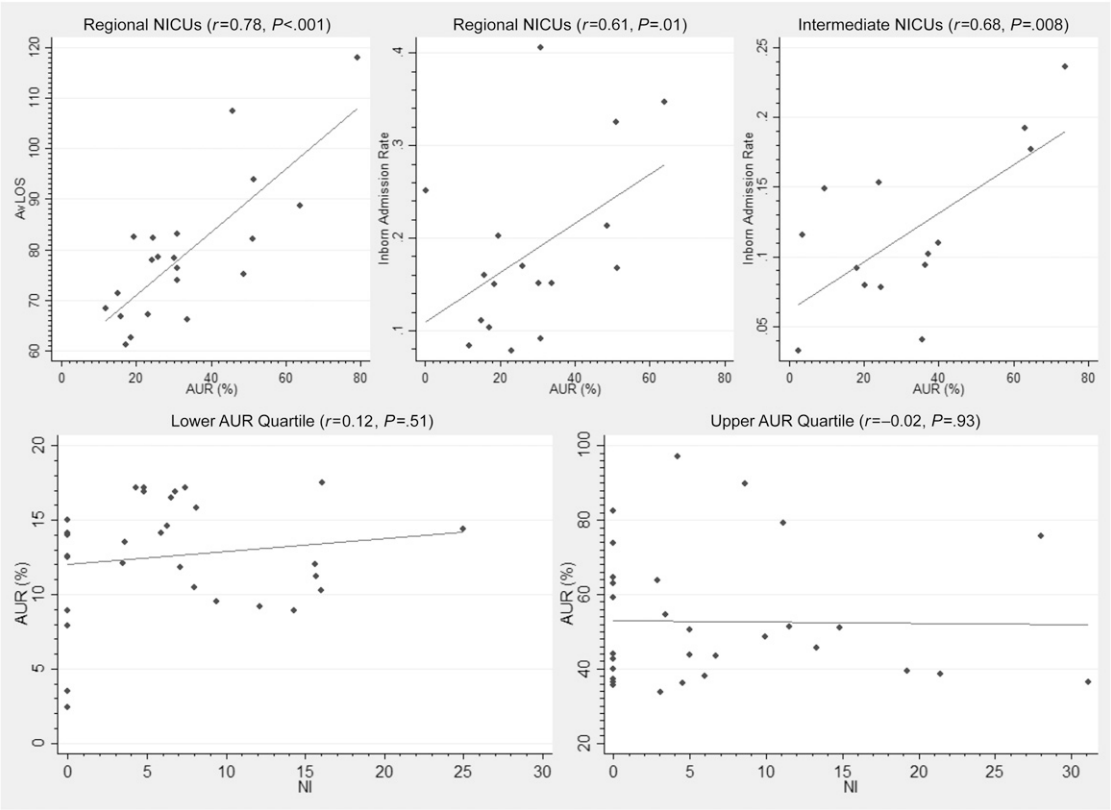

FIGURE 2
Illustrative clinical and resource use correlates with AUR. Upper left, Strong positive correlation among regional-level NICUs between AUR and AvLOS. Upper center, right, Among regional- and intermediate-level NICUs AUR and inborn admission rate are positively correlated. Lower, No correlation with NI among NICUs in either the lowest or highest AUR quartiles. Straight lines = fitted values.

AUR and NEC, NI, or mortality. Each of these previous studies analyzed duration of antibiotic exposure in individual patients during particular portions of the NICU hospitalization, such as the first week of life.[13–15] Because the unit of observation and analysis in our study is the NICU, the previously reported associations could still be operating, but may be obscured by averaging exposure across all patients in an entire NICU and across entire hospital courses for all patients. The NICU-level unit of observation and analysis also precludes adjusting outcomes for differences in baseline characteristics among patients. For example, EOS incidence and case fatality are substantially higher in African American preterm infants compared with non-African American term infants.[28] We mitigated this limitation to some degree by stratifying our analysis by NICU level, with large numbers of patients in each level. Analytical limitations notwithstanding, the available evidence does not support the current range of practice in treating unproven infection.

Case-mix adjustment is useful if study goals include a comparison among NICUs of proven infection and other factors unambiguously connected with antibiotic exposure. However, our primary study objective was to examine how NICU antibiotic practice variation relates with proven infection and other factors unambiguously connected with antibiotic exposure. Whether

TABLE 3 Percent of NICUs in the Lowest and Highest AUR Quartiles Reporting Proven Infection Rates of Zero

	EOS = 0, %	NI = 0, %	CLABSI = 0, %	Fungal Infection = 0, %
AUR quartile 1				
All NICUs, *n* = 32	31	32	68	93
Regional, *n* = 4	25	25	50	75
Community, *n* = 23	22	26.1	65.2	95.6
Intermediate, *n* = 3	100	100	100	100
Non-CCS, *n* = 2	50	50	100	100
AUR quartile 4				
All NICUs, *n* = 31	39	39	73	81
Regional, *n* = 7	14	0	14.3	42.9
Community, *n* = 14	36	14.3	84.6	85.7
Intermediate, *n* = 7	57	100	100	100
Non-CCS, *n* = 3	67	100	100	100

a relationship exists between those indications for antibiotic treatment and observed antibiotic use is independent of case-mix; providers generally agree that conditions like proven infection or NEC warrant antibiotic treatment (independent of the particular local burden of illness and case-mix).

During the past decade, some NICUs caring for extremely low birth weight neonates have been prescribing fluconazole to prevent invasive candidiasis.[35–37] Our data are unable to account for the practice, which is not uniform across NICUs, and where applied, would contribute to higher AURs. This practice would not be appropriate in intermediate level NICUs, where AUR variation is greatest.

Although AUR was independent of clinical correlates, it sometimes was correlated with resource use. At regional-level NICUs, higher AUR was correlated with both higher inborn admission rates and higher AvLOS. At intermediate-level NICUs, higher AUR was correlated with higher inborn admission rates. Elucidating the determinants and directionality of these relationships requires additional investigation.

CONCLUSIONS

The 40-fold variation in antibiotic use across California NICUs is unsupported by the burden of proven infection, other factors unambiguously warranting antibiotic exposure, or the peer-reviewed literature. Currently measured rates of proven infection provide an incomplete and possibly misleading depiction of NICU care relating to imputed microbial disease. Therefore, it is reasonable for other organizations that track NICU performance to add AUR to their arrays of evaluative variables. The goal of such benchmarking efforts should be to identify warranted ranges of AUR for NICUs providing different levels of care.[38] Additional study is also needed to elucidate the determinants and directionality of relationships between AUR and other resource use.

REFERENCES

1. Wennberg J. *Tracking Medicine*. New York, NY: Oxford University Press; 2010
2. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013 report. Available at: www.cdc.gov/drugresistance/threat-report-2013/. Accessed February 13, 2015
3. Vermont Oxford Network. Available at: https://public.vtoxford.org/research/database-qi-research/. Accessed February 13, 2015
4. California Perinatal Quality Care Collaborative. California Perinatal Quality Care Collaborative (CPQCC). Available at: www.cpqcc.org/research/publications. Accessed February 13, 2015
5. Wirtschafter DD, Powers RJ, Pettit JS, et al. Nosocomial infection reduction in VLBW infants with a statewide quality-improvement model. *Pediatrics*. 2011; 127(3):419–426
6. Kaplan HC, Lannon C, Walsh MC, Donovan EF; Ohio Perinatal Quality Collaborative. Ohio statewide quality-improvement collaborative to reduce late-onset sepsis in preterm infants. *Pediatrics*. 2011; 127(3):427–435
7. Schulman J, Stricof R, Stevens TP, et al; New York State Regional Perinatal Care Centers. Statewide NICU central-line-associated bloodstream infection rates decline after bundles and checklists. *Pediatrics*. 2011;127(3):436–444
8. Chassin MR. Quality of care. Time to act. *JAMA*. 1991;266(24):3472–3473
9. California Department of Public Health. Central line-associated bloodstream infections (CLABSI) and central line insertion practices (CLIP) in California hospitals, 2012. Available at: www.cdph.ca.gov/programs/hai/Pages/CentralLineAssociatedBloodstreamInfections-CLABSI-Reports.aspx. Accessed July 17, 2014
10. Chassin MR. Improving the quality of health care: what's taking so long? *Health Aff (Millwood)*. 2013;32(10): 1761–1765
11. Korenstein D, Falk R, Howell EA, Bishop T, Keyhani S. Overuse of health care services in the United States: an understudied problem. *Arch Intern Med*. 2012;172(2):171–178
12. Grohskopf LA, Huskins WC, Sinkowitz-Cochran RL, Levine GL, Goldmann DA, Jarvis WR; Pediatric Prevention Network. Use of antimicrobial agents in United States neonatal and pediatric intensive care patients. *Pediatr Infect Dis J*. 2005; 24(9):766–773
13. Cotten CM, Taylor S, Stoll B, et al; NICHD Neonatal Research Network. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. *Pediatrics*. 2009;123(1):58–66
14. Alexander VN, Northrup V, Bizzarro MJ. Antibiotic exposure in the newborn intensive care unit and the risk of necrotizing enterocolitis. *J Pediatr*. 2011; 159(3):392–397
15. Kuppala VS, Meinzen-Derr J, Morrow AL, Schibler KR. Prolonged initial empirical antibiotic treatment is associated with adverse outcomes in premature infants. *J Pediatr*. 2011;159(5):720–725
16. Alm B, Erdes L, Möllborg P, et al. Neonatal antibiotic treatment is a risk factor for early wheezing. *Pediatrics*. 2008;121(4): 697–702
17. Patel SJ, Saiman L. Antibiotic resistance in neonatal intensive care unit pathogens: mechanisms, clinical impact, and prevention including antibiotic stewardship. *Clin Perinatol*. 2010;37(3): 547–563
18. California Department of Health Care Services. Provider standards. Available at: www.dhcs.ca.gov/services/ccs/Pages/ProviderStandards.aspx#nicu. Accessed July 17, 2014
19. American Academy of Pediatrics Committee on Fetus and Newborn. Levels of neonatal care. *Pediatrics*. 2012;130(3): 587–597
20. Bhatt DR, Lee S, Pursley DM, et al. *Newborn Intensive Care Units (NICUs) and Neonatologists of the USA and Canada*. Elk Grove Village, IL: Section on Perinatal Pediatrics, American Academy of Pediatrics; 2011
21. Hamilton BE, Martin JA, Osterman M, Curtin SC. *Births: Preliminary Data for*

2013. Washington, DC: US Department of Health and Human Services; 2014

22. Agency for Healthcare Research and Quality. Computerized provider order entry. Available at: http://psnet.ahrq.gov/primer.aspx?primerID=6. Accessed July 30, 2014
23. Centers for Disease Control and Prevention. Bloodstream infection event (central line-associated bloodstream infection and non-central line-associated bloodstream infection). Available at: www.cdc.gov/nhsn/PDFs/pscManual/4PSC_CLABScurrent.pdf. Accessed July 30, 2014
24. *Stata Statistical Software* [computer program]. Version 13. College Station, TX: Stata Press; 2013
25. Gerber JS, Newland JG, Coffin SE, et al. Variability in antibiotic use at children's hospitals. *Pediatrics*. 2010;126(6):1067–1073
26. Fridkin SK, Baggs J, Fagan R, et al. *Vital Signs: Improving Antibiotic Use Among Hospitalized Patients*. Atlanta, GA: Centers for Disease Control and Prevention; 2014
27. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics*. 2002;110(2 pt 1):285–291
28. Weston EJ, Pondo T, Lewis MM, et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005-2008. *Pediatr Infect Dis J*. 2011;30(11):937–941
29. Stoll BJ, Hansen NI, Sánchez PJ, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. *Pediatrics*. 2011;127(5):817–826
30. Wirtschafter DD, Padilla G, Suh O, Wan K, Trupp D, Fayard EE. Antibiotic use for presumed neonatally acquired infections far exceeds that for central line-associated blood stream infections: an exploratory critique. *J Perinatol*. 2011;31(8):514–518
31. Brady MT, Polin RA. Prevention and management of infants with suspected or proven neonatal sepsis. *Pediatrics*. 2013;132(1):166–168
32. Polin RA, Watterberg K, Benitz W, Eichenwald E. The conundrum of early-onset sepsis. *Pediatrics*. 2014;133(6):1122–1123
33. Escobar GJ, Puopolo KM, Wi S, et al. Stratification of risk of early-onset sepsis in newborns ≥34 weeks' gestation. *Pediatrics*. 2014;133(1):30–36
34. Kiser C, Nawab U, McKenna K, Aghai ZH. Role of guidelines on length of therapy in chorioamnionitis and neonatal sepsis. *Pediatrics*. 2014;133(6):992–998
35. Manzoni P, Stolfi I, Pugni L, et al; Italian Task Force for the Study and Prevention of Neonatal Fungal Infections; Italian Society of Neonatology. A multicenter, randomized trial of prophylactic fluconazole in preterm neonates. *N Engl J Med*. 2007;356(24):2483–2495
36. Aziz M, Patel AL, Losavio J, et al. Efficacy of fluconazole prophylaxis for prevention of invasive fungal infection in extremely low birth weight infants. *Pediatr Infect Dis J*. 2010;29(4):352–356
37. Healy CM, Campbell JR, Zaccaria E, Baker CJ. Fluconazole prophylaxis in extremely low birth weight neonates reduces invasive candidiasis mortality rates without emergence of fluconazole-resistant Candida species. *Pediatrics*. 2008;121(4):703–710
38. Schulman J, Saiman L. Metrics for NICU antibiotic use: which rate is right? *J Perinatol*. 2011;31(8):511–513

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Pediatrics 2015;135;826; originally published online April 20, 2015;
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