Antibiotic stewardship in the newborn surgical patient: A quality improvement project in the neonatal intensive care unit

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Background. *There is significant diversity in the utilization of antibiotics for neonates undergoing surgical procedures. Our institution standardized antibiotic administration for surgical neonates, in which no empiric antibiotics were given to infants with surgical conditions postnatally, and antibiotics are given no more than 72 hours perioperatively.*
Methods. *We compared the time periods before and after implementation of antibiotic protocol in an institution review board–approved, retrospective review of neonates with congenital surgical conditions who underwent surgical correction within 30 days after birth. Surgical site infection at 30 days was the primary outcome, and development of hospital-acquired infections or multidrug-resistant organism were secondary outcomes.*
Results. *One hundred forty-eight infants underwent surgical procedures pre-protocol, and 127 underwent procedures post-protocol implementation. Surgical site infection rates were similar pre- and post-protocol, 14% and 9% respectively, (*P = *.21.) The incidence of hospital-acquired infections (13.7% vs 8.7%,* P = *.205) and multidrug-resistant organism (4.7% vs 1.6%,* P = *.143) was similar between the 2 periods.*
Conclusion. *Elimination of empiric postnatal antibiotics did not statistically change rates of surgical site infection, hospital-acquired infections, or multidrug-resistant organisms. Limiting the duration of perioperative antibiotic prophylaxis to no more than 72 hours after surgery did not increase the rate of surgical site infection, hospital-acquired infections, or multidrug-resistant organism. Median antibiotic days were decreased with antibiotic standardization for surgical neonates. (Surgery 2017;162:1295-303.)*

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NEONATES BORN WITH CONGENITAL ANOMALIES of the gastrointestinal (GI) tract or abdominal wall often are diagnosed prenatally, receive care in the neonatal intensive care unit (NICU) after birth, and require corrective surgery before discharge. The timing of surgery differs based on the type of congenital anomaly, the presence of comorbid conditions, and other variables such as surgeon preference and resource availability. A common practice in infants born with anomalies of the GI tract requiring surgery is the routine administration of broad-spectrum antibiotics, such as ampicillin and gentamicin from birth until surgical correction.[1] Because surgical intervention is not emergent in most conditions, many newborn infants will receive antibiotics for several days before their surgical procedures. Furthermore, the duration of antibiotic administration after surgery varies widely. Thus, many surgical neonates receive several days of antibiotics.

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AVAILABLE KNOWLEDGE

Guidelines have been published previously regarding preoperative antibiotic prophylaxis by the Centers for Medicare & Medicaid Services, the Joint Commission, the Centers for Disease Control and Prevention, and the Surgical Care Improvement Project (SCIP) to aid in decreasing rates of surgical site infection (SSI) in other patient populations.[2,3] These guidelines give recommendations on when to administer preoperative parenteral antibiotics, which preoperative antibiotics to administer, and when to discontinue perioperative antibiotics. However, they do not apply to patients younger than 1 year of age. A recent study documents wide variability of practice in perioperative antibiotic therapy in the pediatric population.[4]

Perioperative antibiotic usage in the neonatal population, specifically in the setting of elective surgery, is usually institution or provider specific. Currently, no consensus exists regarding prophylactic perinatal antibiotic administration to these neonates. Without guidelines, practices that encourage the development of multidrug-resistant organisms (MDRO), such as prolonged routine antibiotic administration, may occur. Antibiotics can alter the GI flora of neonates and may have long-lasting effect on the overall health of patients.[5,6]

In 2012, the Children's Hospital of Wisconsin adopted an antibiotic stewardship policy. Antibiotic stewardship refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration.[7] As part of this initiative, the Children's Hospital of Wisconsin standardized the antibiotic usage guidelines for babies in the NICU who were born with congenital thoracic, GI, and abdominal wall anomalies with regard to postnatal group B streptococcal (GBS) prophylaxis and perioperative antibiotic administration.

RATIONALE

With regard to postnatal antibiotic administration, we used the 2011 guidelines put forth by the American Academy of Pediatrics regarding GBS prophylaxis.[8] We also referred to general guidelines put forth by SCIP in terms of perioperative antibiotic protocols.[9] We recognized that SCIP guideline recommendations do not cover patients younger than 1 year of age. In the neonate literature, no one antimicrobial option has been proven better than another for empiric perioperative coverage. Therefore, we used our hospital antibiogram and chose piperacillin-tazobactam as a single agent for perioperative prophylaxis because it covers more than 80% of the common gram-negative organisms and anaerobic bacteria. However, if resistant organisms are suspected based on prematurity, duration of hospitalization, or known colonization or infection of resistant organisms, the antibiotic used was changed as deemed appropriate by the physicians caring for the neonate.

SPECIFIC AIMS

Our specific aims were to create a standardized antibiotic practice in the NICU commensurate with the antibiotic stewardship guidelines by administering postnatal antibiotics only when a specific need exists and standardizing the type and duration of antibiotics given to surgical neonates in the perioperative setting.

METHODS

Context. Children's Hospital of Wisconsin is a 298-bed tertiary children's hospital affiliated with the Medical College of Wisconsin with a 70-bed level IV NICU, with 750 admissions per year. Approximately 50 to 60 index surgical procedures are on the diagnoses of interest annually. A single group of surgeons and a single group of neonatologists care for patients. Both groups were engaged in the development of this quality improvement project. The number of NICU admissions and surgical cases did not vary significantly before and after implementation of the intervention.

We wanted to assess the safety and efficacy of the newly implemented practice changes. We selected the development of SSIs within 30 days of the surgical procedure as the primary outcome to assess the safety and efficacy of the new practice. We also evaluated the occurrence of other hospital-acquired infections (HAI), such as pneumonia, bacteremia, sepsis, and urinary tract infections. We specifically looked for colonization and/or infections associated with MDRO that were acquired during the infant's hospitalization. We also looked for development of necrotizing enterocolitis (NEC) and sepsis in this population before and after implementation of the practice change.

Intervention. To create changes in practice that would ensure the safety of our patients, we engaged several disciplines, including pediatric surgery, neonatology, infectious disease, pharmacy, and neonatal nursing. There were 4 main components of the protocol, with the first 2 focusing on postnatal antibiotics and the last 2 on perioperative antibiotics:

(1) Postnatal antibiotics will only be given when there are signs and symptoms of neonatal infections (ie, respiratory distress, temperature instability, hypotension) or perinatal risk factors for sepsis (ie, maternal fever, chorioamnionitis).
(2) If postnatal antibiotics are given and active infection is not borne out by cultures, laboratory values, or progressive symptoms, then antibiotics should be discontinued within 48 hours.
(3) Preoperative antibiotic prophylaxis will consist of a preoperative weight-based dose of a single antibiotic within 1 hour before incision. A single-drug regimen reduces the risk for adverse effects and, in general, is more cost-effective.
(4) Perioperative antibiotics will be promptly discontinued within 72 hours after surgery. We used 72 hours because it would give the surgical team the ability to have thoughtful input into what was an appropriate antibiotic duration based on patient status and operative findings. Perioperative antibiotics can certainly be discontinued sooner than 72 hours.

Study of the interventions. Institutional review board approval was obtained for a retrospective chart review with a full waiver of informed consent because of minimal risk; data were accessed and maintained in accordance with HIPAA standards with applicable waiver. We surveyed the charts of all neonates (<30 days of age) who underwent surgical repair for the following diagnoses from January 1, 2009 to March 31, 2016: esophageal atresia with or without tracheoesophageal fistula, congenital diaphragmatic hernia, intestinal atresia (duodenal, small bowel, and colonic), anorectal malformation, cloacal extrophy, and covered omphalocele. The patients were divided into 2 time periods relative to the implementation of the standardized neonatal antibiotic protocol: pre-protocol (January 1, 2009 to June 30, 2012) and post-protocol (July 1, 2012 to March 31, 2016). Patients were excluded if they had previously received antibiotics for established infections. Infants with gastroschisis or ruptured omphalocele were excluded because providers felt intravenous antibiotics in these conditions were not prophylactic, but instead were required for an open abdomen. Infants whose surgery was deemed emergent for any reason also were excluded.

Data were collected from the patients' electronic medical record and confirmed separately by the authors. All complications, including those collected in this study, were adjudicated weekly by members of surgical faculty during discussion at a weekly morbidity and mortality conference and were recorded in a Pediatric Infant Case Log and Infant Database, maintained by the Division of Pediatric Surgery.[10]

Measures. There were 2 distinct time points when antibiotics were given to patients: postnatally (protocol components 1 and 2) and perioperatively (protocol components 3 and 4). We looked at the compliance with process measures involving these 2 time points separately. Compliance was manually extracted from patients' electronic health records. The American College of Surgeons National Safety and Quality Improvement Project—Pediatrics definitions for SSI were used.[11,12] Patients were followed for SSI for 30 days after the surgical procedure and for all other infections until discharge. If a patient underwent more than one surgical procedure, the SSI was attributed to the most recent procedure unless the procedure was performed to treat an infection, such as a wound debridement. The presence of other types of infections were recorded if there was documentation of the diagnosis by the providers in the chart or if there were positive cultures and the patient was treated with the appropriate duration of antibiotics. Although NEC and sepsis are not considered HAIs, we collected data on these 2 conditions.

Analysis. The patient populations between the pre- and postintervention periods were compared using Wilcoxon rank sum test for continuous characteristics and χ^2 analysis for categorical variables. Rates of SSI and other infections were compared using χ^2 analysis. Statistical analyses were conducted using SAS (SAS Institute, Cary, NC) or STATA 10. (State Corporation, College Station, TX). A control g-chart was constructed for each of the outcomes measures: SSI, HAI, and MDRO.

Ethical considerations. We followed the existing national guideline and used institutional-specific antibiotics. We included all provider stakeholder representatives when we formulated the change in practice. All neonatologists and surgeons were able to weigh in before implementation. Each infectious complication in a surgical neonate was discussed weekly in morbidity and mortality conference, including the appropriate use and duration of antibiotics, thus providing timely review of each case.

RESULTS

The timeline of the development and implementation in the protocol is outlined in Fig 1. It took approximately 6 months to formulate the

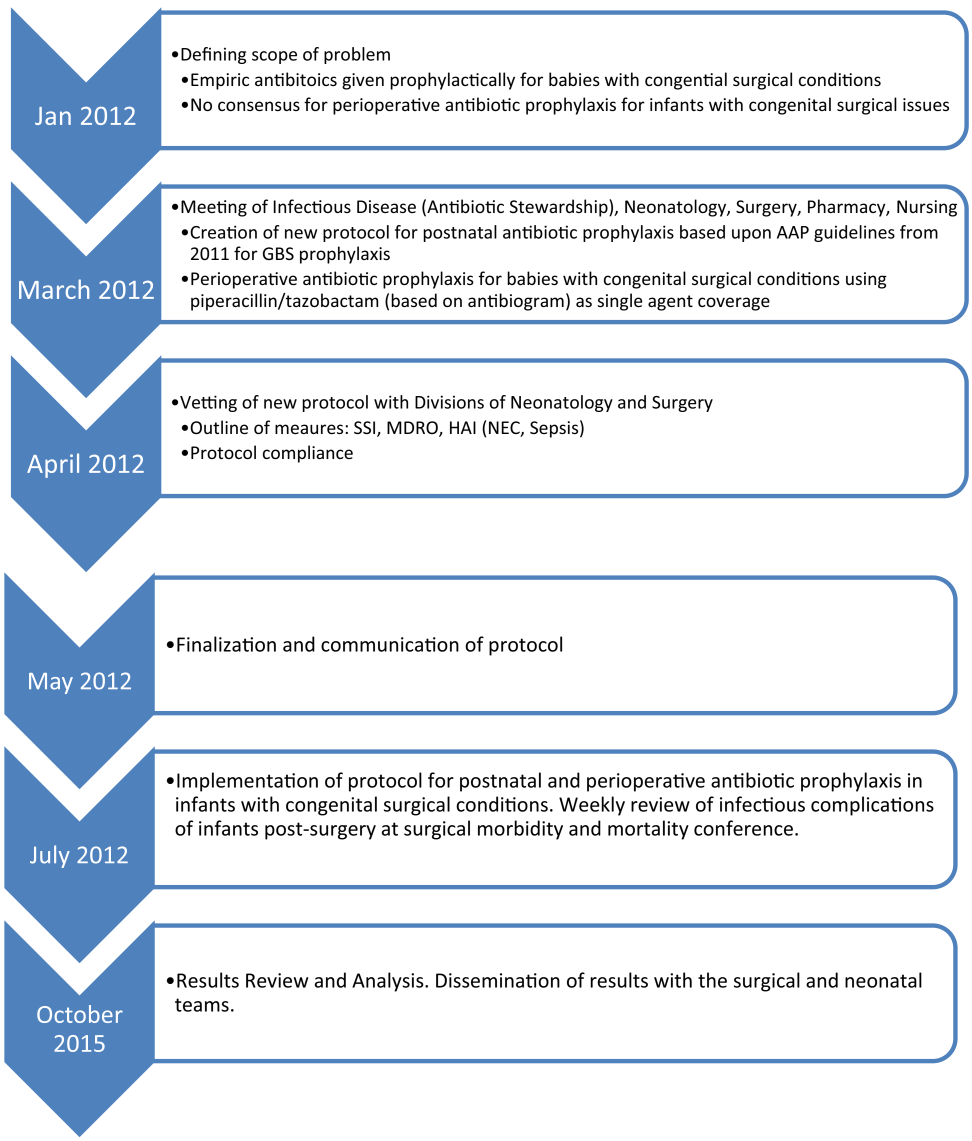

Fig 1. Timeline of development and implementation of postnatal and perioperative antibiotic quality improvement protocol in neonates with congenital surgical conditions.

intervention and present it to all stakeholder groups before implementation.

Clinical characteristics. During the study period, 275 neonates met the inclusion criteria. Table I contains the demographic characteristics, diagnoses, and American Society of Anesthesiologists (ASA) Physiologic Status of the pre- and postprotocol groups. There were 148 infants in the preprotocol group and 127 in the postprotocol group. Overall, the study population was similar between the 2 periods.

Compliance with process measures. Compliance with the first 2 steps (postnatal antibiotics) was 90%, and compliance with the last 2 steps (perioperative antibiotics) was 97%. Compliance with all 4 steps of the recommendations was 89% (Table II).

Antibiotic administration. *Postnatal antibiotics.* Before protocol implementation, 53% of patients received postnatal antibiotics, with 34% treated for inappropriate indications and/or duration. After protocol implementation, 38% of infants received postnatal antibiotics, with only 11% of patients being treated for inappropriate indications or duration. Seven patients who received postnatal antibiotics for inappropriate indications had the antibiotics administered at the referring hospital. Preprotocol, the median duration of postnatal antibiotics administered was 2 days (interquartile range [IQR] = 0–2) compared with 0 (IQR = 0–2;

Table I. Demographic characteristics, diagnosis, ASA status of patients pre- and postimplementation of antibiotic standards*

Characteristic median (IQR)	*Preprotocol* (n = *148)*	*Postprotocol* (n = *127)*	P *value*†
Birth weight (kg)	2.72 (2.28–3.24)	2.84 (2.3–3.27)	.75
Gestational or postmenstrual age (weeks)	37 (35–38)	38 (35–39)	.096
Weight at surgery (kg)	2.7 (2.2–3.24)	2.8 (2.25–3.21)	.66
Day of life at operation	2 (1–3.5)	2 (1–4)	.677
Male, %	59	59	.98
Diagnoses *n*, (%)			.259
EA with TEF	22 (14.9)	31 (24.4)	
Pure EA	7 (4.7)	3 (2.4)	
H-type TEF	2 (1.4)	1 (0.8)	
Duodenal atresia/web	27 (18.2)	20 (15.7)	
Intestinal atresia	23 (15.5)	19 (15)	
Colon atresia	2 (1.4)	2 (1.6)	
Anorectal malformation	29 (19.6)	30 (23.6)	
Cloacal extrophy	3 (2)	0	
Omphalocele	9 (6.1)	10 (7.9)	
Congenital diaphragmatic hernia	24 (16.2)	11 (8.7)	
ASA *n*, (%)			.320
ASA 1	0	1 (0.8)	
ASA 2	14 (9.5)	17 (13.4)	
ASA 3	95 (64.6)	70 (55.1)	
ASA 4	37 (25.2)	39 (30.7)	
ASA 5	1 (0.7)	0	

*The 2 populations are equal in terms of demographic characteristics, diagnoses, and ASA.
†T test was used for continuous variables and Chi-square for categorical variables. $P < .05$ was considered statistically significant..
ASA, American Society of Anesthesiologists; *EA*, esophageal atresia; *TEF*, tracheoesophageal fistula.

Table II. Compliance with standardized antibiotic practice

	Preprotocol n = *148*	*Postprotocol* n = *127*	P *value*
Postnatal antibiotic administration			
Antibiotics given at birth, *n* (%)	79 (53)	49 (38)	.01*
Patients with inappropriate indication or duration of postnatal antibiotics, *n* (%)	27 (18.2)	12 (9.4)	.04*
Median duration of postnatal antibiotics, days (IQR)	2 (0–2)	0 (0–2)	.001
Perioperative antibiotic administration			
Antibiotics given at operation, *n* (%)	147 (99.3)	126 (99.2)	.91
Patients with inappropriate indication or duration, *n* (%)	2 (1.4)	0 (0)	.19
Median duration of antibiotics, days (IQR)	1 (1–2)	1 (1–1)	.0043

*T test, where $P < .05$ statistically significant.
The first section of the table compares compliance with protocol components 1 and 2, which pertain to postnatal antibiotic administration. Postprotocol, there was 90% compliance, with a statistically significant decrease in patients who received postnatal antibiotics for inappropriate indications or duration of time. Median duration of postnatal antibiotics decreased significantly. The second section compares compliance with protocol components 3 and 4, which pertain to perioperative antibiotic administration. There was significant compliance with perioperative components even before protocol implementation. Fewer patients received prolonged postoperative therapy after implementation of the protocol.
IQR, Interquartile ratio.

P = .001). There was a statistically significant decrease in the number of patients who received postnatal antibiotics (P = .01) and the number of patients who received antibiotics for inappropriate indication or duration (P = .04) between the 2 time periods.

Perioperative antibiotics. In the preprotocol time period, 3 of 148 patients did not receive preoperative antibiotics. Review of the charts showed that the attending surgeon made a conscious decision not to give antibiotics. Postprotocol, only 1 of 127 patients did not receive preoperative antibiotics, again with a

Table III. Comparison of SSI 30 days after surgery, HAI, and MDRO in patients pre- and postprotocol implementation

	Preprotocol n = *148*	*Postprotocol* n = *127*	P *value*
SSI within 30 days, *n* (%)	21 (14)	12 (9)	.21
HAI, *n* (%)	20 (13.5)	11 (8.7)	.205
MDRO, *n* (%)	7 (4.7)	2 (1.6)	.143

conscious decision to withhold. The median duration of perioperative antibiotics was 1 day both pre- and postprotocol with an IQR of 1–2 and 1–1, respectively ($P = .0043$). Two patients received antibiotics beyond 3 days postsurgery without documented reason before protocol implementation compared with no patients after protocol implementation ($P = .338$).

Total antibiotics. Before protocol implementation, the median duration of antibiotic therapy was 2 days (IQR = 1–3). After protocol implementation, the median duration of antibiotic therapy was 1 dat (IQR = 1–3; $P = .0001$).

Incidence of SSI. SSIs occurring within 30 days of surgical procedure are detailed in Table III. Before antibiotic protocol adaptation, there were 206 surgical interventions in 148 unique patients. There were 16 superficial SSIs, 5 deep SSIs, 1 organ-space SSI, and 2 wound dehiscences. Five patients required operative interventions to manage SSI. After implementation of the protocol, there were 164 operations in 127 patients with 11 superficial SSIs and 1 dehiscence. Only one case required reoperation to manage SSI. The overall incidence of SSI was 14% preprotocol, which was not statistically different from the 9% SSI incidence postprotocol ($P = .21$). The control chart (Fig 2) illustrates that there is no difference in the mean number of cases between each SSI occurrence and there is no evidence of special cause variation.

HAI and MDRO. The incidence of HAI preprotocol was 13.5% compared with 8.7% postprotocol. There was a preprotocol incidence of 4.7% MDRO infection or colonization compared with 1.6% postprotocol. The decrease in HAI and MDRO before and after protocol did not reach statistical significance (Table III, Fig 2).

The incidence of NEC preprotocol implementation was 1.5%, with none after. Sepsis rates were 3.3% preprotocol and 3.1% postprotocol implementation.

Postnatal antibiotics and SSI. We compared all surgical infants who received postnatal antibiotics with those who did not receive postnatal antibiotics from both time periods. There were no statistically significant differences between those who received antibiotics and those who did not in terms of SSI at 30 days (11% vs 13%, $P = .64$), HAI (14% vs 8.8%, $P = .16$) and MDRO (3% vs 3, $P = .9$).

Perioperative antibiotics and SSI. One patient preprotocol did not receive preoperative antibiotics. One patient postprotocol had a covered omphalocele closure, did not receive antibiotics, and subsequently developed a superficial SSI. There was no difference in SSI with respect to the number of days of postoperative antibiotics received: 0 days, 17%; 1 day, 6.9%; 2 days, 10.9%; 3 days, 41.7%; and 4 or more days, 6%.

DISCUSSION

Neonatal infections and sepsis may present insidiously, yet cause a significant morbidity and mortality.[10,13-15] Thus, physicians and providers are obliged to treat neonates with antimicrobial agents at the first suspected signs of sepsis, making antimicrobials the most commonly used medications in NICUs.[16] A review of antibiotic usage in 29 NICUs in the United States from 1999 to 2000 found that each patient received a median of 2 antibiotics at any one time.[17] A study by Schulman et al. looked at 52,061 infants from 127 NICUs across California and found that "a considerable portion of antibiotic use lack[ed] clear warrant" and that antibiotic usage in NICUs often is excessive.[18] Patel et al used a set of clinical vignettes of NICU patients to survey providers and ascertain appropriate usage.[19] They found correct responses regarding type of antimicrobial and duration of therapy ranged from 53% to 97% among providers.[19]

A similar trend in overutilization of antibiotics has been found for antibiotics intended for perioperative prophylaxis to decrease SSIs in the pediatric population.[4] Particularly in newborn infants, there is a lack of data regarding the use of antibiotics.[20] Our institutional incidence of neonatal SSI is about 14%, similar to that quoted the literature.[9] Before 2012, our practice had reflected the variability in antibiotic practices that is seen the literature. We identified 2 areas of significant variability: postnatal and perioperative therapy. The practice of postnatal antibiotic administration in surgical infants has been ingrained in some physicians—surgeons and neonatologists alike—who were taught the surgical

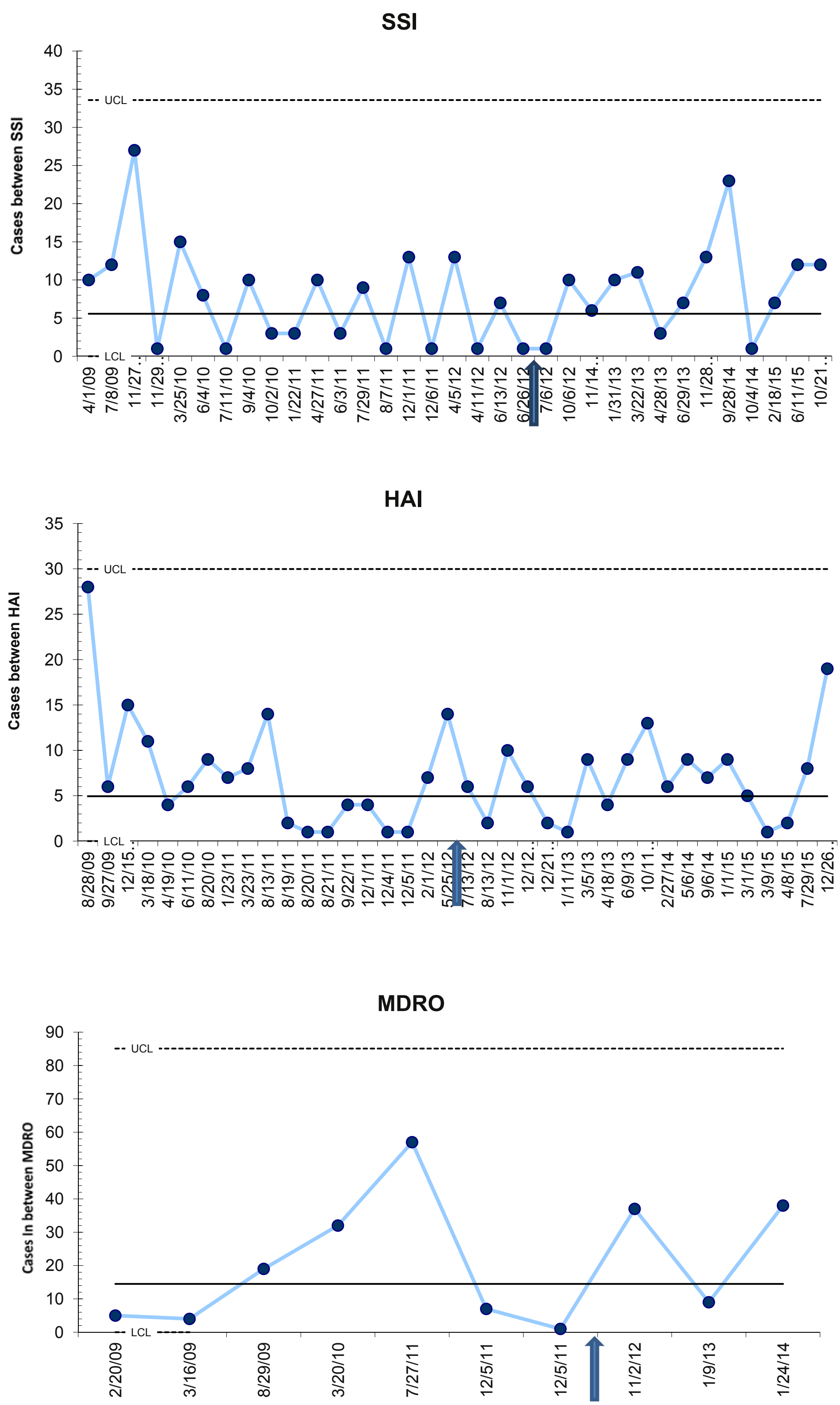

Fig 2. Control charts for number of cases between each occurrence (SSI, HAI, and MDRO). The *blue arrow* in each chart denotes the point when the antibiotic protocol was implemented. For each of the occurrences, there was no significant difference between the mean pre- and postprotocol implementation. There is no special cause variation observed. Ultimately, there is no difference in the pre- and postprotocol time periods in the number of cases between each SSI, HAI, and MDRO. (Color version of figure is available online.)

dogma that babies born with known surgical diagnoses undergo a "rule-out sepsis" workup and receive intravenous antibiotics for 48 hours or longer until blood and urine cultures show no infection. Another source of postnatal antibiotic practice variability lies in prophylaxis for maternal GBS status, possibility of meconium aspiration, or prolonged rupture of membranes. The current guidelines for postnatal antibiotic administration were published in 2012, but old practices may still prevail. Regarding perioperative antibiotic therapy, there are significant differences among providers ranging from what antibiotic to give, when to give it relative to the incision, and when to stop the antibiotic if it is being given for prophylaxis indications.

To effect any meaningful and measurable change in outcomes, our practice needed to be standardized. The hospital had been actively participating in Solutions for Patient Safety SSI bundle, but antibiotic administration in newborn infants is not specified in these recommendations. When multidisciplinary input is sought and concerted effort is spent, we proved that compliance with standardization of practice can be achieved in this patient population, with a resultant decrease in antibiotic use. We demonstrated that decrease in antibiotic use without increasing SSIs, HAIs, and MDROs. Between the two time periods, there was significant change in the SSI ($P = .21$), HAI (0.205) and MDRO (0.143). Statistical significance may not have been reached because of the low number of patients with these occurrences. We performed a post hoc power analysis, using these incidences of each occurrence in the group. We would need about 550 patients in each arm to detect a significant difference. Unfortunately, adding more patients would not be feasible because it would require historical controls before 2009. Since 2009, we have implemented practices within our institution such as central line bundles and Solutions for Patient Safety initiatives among others that may change and affect outcomes of SSIs, HAIs, and MDROs.

Because we created standards in 2 different time periods (postnatal and perioperative), we analyzed the possible effects of changing antibiotic practices with regard to our primary and secondary outcomes. Because the components of our practice change may affect the singular outcome of SSI differently, we decided to assess the primary and secondary outcomes with respect to the entire antibiotic protocol, as well as the separate components of postnatal antibiotics and perioperative antibiotics. We found that empiric administration of postnatal antibiotics did not confer any advantage to surgical infants with regard to SSIs, HAIs, and MDROs. Control charts were constructed to elucidate a difference but found none, which indicates that no untoward events resulted from this protocol. Of note, the MDRO charts did have fewer than 12 data points due to low number of events and thus might have changed with a longer collection time. When we looked at the number of days that postoperative antibiotics were given, giving antibiotics for 1 day had the least incidence of SSI. Statistical analysis for this aspect of the present study is not possible given the small number of patients who received longer courses of antibiotics.

Limitations. Limitations of this study include its retrospective nature and the use of historical controls. As knowledge is gained about the possible effects of longer antibiotic therapy, we believe that a randomized control trial would be difficult and potentially unethical. Our assumption that one antibacterial agent for antibiotic prophylaxis is sufficient is based on adult data for different surgical indications. We used piperacillin-tazobactam in our protocol based on the institution's antibiogram; there may be a more optimal alternative in other nurseries, or in our own neonatal unit as well. This is a study based on only one institutional experience. Replication of our results in other children's centers would be desirable.

In conclusion, the present study challenges the surgical dogma that postnatal antibiotics are required in uncomplicated neonates with known surgical diagnoses. The results also suggest that limitation of postoperative antibiotic prophylaxis may be beneficial. Moving forward, we have further limited our postoperative antibiotics to less than 24 hours in appropriate circumstances. Finally, we demonstrated that compliance with a thoughtful, evidence-based standard of antibiotic administration can be accomplished in neonates. We hope that the present study may be the first step in creating standard antibiotic practices in surgical neonates.

REFERENCES

1. Rowe MI, Rowe SA. The last fifty years of neonatal surgical management. Am J Surg 2000;180:345-52.
2. Centers for Disease Control and Prevention. 12-step program to prevent antimicrobial resistance in health care settings. MMWR 2002;51:343.
3. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Surg Infect (Larchmt) 2013;14:73-156.
4. Sandora TJ, Fung M, Melvin P, Graham DA, Rangel SJ. National variability and appropriateness of surgical antibiotic

prophylaxis in US children's hospitals. JAMA Pediatr 2016; 170:570-6.
5. Arboleya S, Sanchez B, Milani C, Duranti S, Solis G, Fernandez N, et al. Intestinal microbiota development in preterm neonates and effect of perinatal antibiotics. J Pediatr 2015;166:538-44.
6. Hartz LE, Bradshaw W, Brandon DH. Potential NICU environmental influences on the neonate's microbiome: a systematic review. Adv Neonatal Care 2015;15:324-35.
7. Infectious Diseases Society of America. Promoting antimicrobial stewardship in human medicine [cited]. Available from: http://www.idsociety.org/Stewardship_Policy/.
8. Baker CJ, Byington CL, Polin RA. Committee on Fetus and Newborn, Committee on Infectious Diseases. Ameican Academy of Pediatrics policy statement – recommendations for the prevention of perinatal group B streptococcal (GBS) disease. Pediatrics 2011;128:611-6.
9. Clements KE, Fisher M, Quaye K, O'Donnell R, Whyte C, Horgan MJ. Surgical site infections in the NICU. J Pediatr Surg 2016;51:1405-8.
10. Arca MJ, Enters J, Christensen M, Jeziorczak P, Sato TT, Thielke R, et al. Operationalizing quality improvement in a pediatric surgical practice. J Pediatr Surg 2014;49:202-5; discussion 5-6.
11. Bruny JL, Hall BL, Barnhart DC, Billmire DF, Dias MS, Dillon PW, et al. American College of Surgeons National Surgical Quality Improvement Program Pediatric: a beta phase report. J Pediatr Surg 2013;48:74-80.
12. Saito JM, Chen LE, Hall BL, Kraemer K, Barnhart DC, Byrd C, et al. Risk-adjusted hospital outcomes for children's surgery. Pediatrics 2013;132:e677-88.
13. Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA 2004;292:2357-65.
14. Klinger G, Levy I, Sirota L, Boyko V, Lerner-Geva L, Reichman B, et al. Outcome of early-onset sepsis in a national cohort of very low birth weight infants. Pediatrics 2010;125:e736-40.
15. Benjamin DK, DeLong E, Cotten CM, Garges HP, Steinbach WJ, Clark RH. Mortality following blood culture in premature infants: increased with gram-negative bacteremia and candidemia, but not gram-positive bacteremia. J Perinatol 2004;24:175-80.
16. Clark RH, Bloom BT, Spitzer AR, Gerstmann DR. Reported medication use in the neonatal intensive care unit: data from a large national data set. Pediatrics 2006;117: 1979-87.
17. Grohskopf LA, Huskins WC, Sinkowitz-Cochran RL, Levine GL, Goldmann DA, Jarvis WR, et al. Use of antimicrobial agents in United States neonatal and pediatric intensive care patients. Pediatr Infect Dis J 2005;24:766-73.
18. Schulman J, Dimand RJ, Lee HC, Duenas GV, Bennett MV, Gould JB. Neonatal intensive care unit antibiotic use. Pediatrics 2015;135:826-33.
19. Patel S, Landers T, Larson E, Zaoutis T, Delamora P, Paul DA, et al. Clinical vignettes provide an understanding of antibiotic prescribing practices in neonatal intensive care units. Infect Control Hosp Epidemiol 2011;32:597-602.
20. Fernandez Ibieta M, Giron Vallejo O, Martinez Castano I, Reyes Rios P, Cabrejos Perotti K, Rojas Ticona J, et al. [Neonatal surgical site infection: multicentric survey on prophylactic measures]. Cir Pediatr 2015;28:21-8.