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Surgical Site Infections in a Longitudinal Cohort of Neonatal Intensive Care Unit Patients

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Abstract

Objective—To estimate the incidence and identify risk factors for surgical site infections (SSIs) among infants in the neonatal ICU (NICU).

Study Design—A prospective cohort study of infants undergoing surgical procedures May 2009–April 2012 in three NICUs was performed. SSI was identified if documented by an attending neonatologist and treated with intravenous (IV) antibiotics. Independent risk factors were identified using logistic regression, adjusting for NICU.

Result—A total of 902 infants underwent 1,346 procedures and experienced 60 SSIs (incidence: 4.46/100 surgeries). Risk factors for SSIs included younger chronologic age (OR 1.03/day decrease, 95% CI 1.01, 1.04), lower gestational age (OR 1.09/week decrease, CI 1.02, 1.18), male sex (OR 1.18, CI 1.04, 1.34), and use of central venous catheter (OR 4.40, CI 1.89, 10.24). Only 43% had surgical site cultures obtained and *Staphylococcus aureus* was most commonly isolated.

Conclusion—SSIs complicated 4.46% of procedures performed in the NICU. Although few modifiable risk factors for SSIs were identified, future efforts should focus on evaluating the impact of current prevention strategies on the incidence of neonatal SSI.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

Keywords

neonate; cardiac surgery; gastrointestinal tract surgery

INTRODUCTION

Surgical site infections (SSI) account for a considerable proportion (20%–31%) of healthcare-associated infections (HAIs)^{1, 2, 3} and lead to increased morbidity, mortality, healthcare costs, and length of hospital stay⁴. As reported to the National Healthcare Safety Network and the International Nosocomial Infection Control Consortium, the overall rate of SSI in adult patients is approximately 2%^{1, 5}, but far greater following high-risk surgeries such as exploratory abdominal surgery^{5, 6}. Risk factors for SSI have been identified in predominantly adult populations and include hyperglycemia, prior infections, malnutrition, increased operative time, and increased blood loss during surgery^{7, 8, 9}.

Neonates admitted to tertiary care neonatal intensive care units (NICU) often require surgery for complex congenital anomalies, particularly cardiac or gastrointestinal anomalies, and for complications of prematurity such as necrotizing enterocolitis (NEC) or intraventricular hemorrhage^{10, 11}. Infants may be at increased risk of SSI given their intrinsic immunodeficiency, immature skin, frequent need for medical devices, comorbid conditions and prolonged hospitalization. However, little is known about the incidence of and risk factors for SSI in the NICU population.

We performed a multicenter prospective cohort study to describe the epidemiology of SSI in the NICU population. In addition, we assessed potential factors associated with an increased risk of SSI, the perioperative antimicrobial prophylaxis regimens used, and management of SSI.

SUBJECTS AND METHODS

Study design, study sites and study population

We used data collected from a multicenter prospective cohort study conducted from May 1, 2009 through April 30, 2012 at three academically affiliated Level III NICUs at The Children's Hospital of Philadelphia (CHOP), the New York-Presbyterian (NYP) Hospital Komansky Center for Children's Health at Weill-Cornell Medical Center, and NYP Morgan Stanley Children's Hospital at Columbia University Medical Center. Infants were included in the current analysis if they were admitted to one of the study sites at less than 7 days of age, remained hospitalized for at least 4 days, and underwent one or more surgical procedures. Data from a subset of this cohort have been previously published¹². Human subjects approval was obtained at each study site with a waiver of documentation of written informed consent. Parents at all study sites were provided an information sheet detailing the study.

During the study period, in fall 2010, a multidisciplinary committee to prevent SSIs throughout the hospital was formed at CHOP. At the two NYPH sites, a committee was

formed in winter 2010 to reduce SSIs associated with cardiac surgery. Improvement efforts at all three sites focused on standardizing skin disinfection and perioperative prophylaxis.

Study Definitions

SSI—The outcome of interest was an SSI documented by an attending neonatologist in the medical record and treated with intravenous (IV) antibiotics. If more than one SSI occurred in the same infant, only the first SSI was included in the analysis.

Type of Surgery—Surgical notes were reviewed to determine the type of surgery performed and procedures were categorized as cardiac, neurosurgery, gastrointestinal, congenital diaphragmatic hernia repair, ear-nose-throat, ophthalmologic, genitourinary, orthopedic, pulmonary, or other (e.g., resection of lymphangioma, sternal cleft repair). If an infant had more than one surgical procedure, all were included and considered independently in the analysis; however, surgical procedures performed to treat an SSI (e.g., debridement) and other surgeries occurring after an SSI were excluded.

Data collection

A structured data collection instrument was used to capture demographic data, including gestational age, chronologic age at surgery, sex, race, ethnicity; length of stay; and crude mortality from the medical record. Use of a central venous catheter (CVC) and chest tubes following cardiac surgery were collected.

The indications for the use of IV antimicrobial agents that were documented by attending neonatologists in the electronic medical record (EMR) and the duration of use (calendar-days) were collected, including peri-operative administration for presumed surgical prophylaxis or to treat an SSI. Antimicrobial prophylaxis administered in the operating room was not collected as intraoperative dosing was not reliably captured in the EMR. When multiple surgeries were performed within 2 calendar days (e.g., repeated reductions of a silo for gastroschisis), antimicrobial prophylaxis for subsequent surgeries was excluded from the analysis. For infants diagnosed with SSIs, surgical site and blood culture results as well as antimicrobial susceptibility data were collected.

Statistical analysis

All analyses were conducted using standard programs in Stata 13 (College Station, TX). Categorical variables were summarized with frequencies and percentages. Continuous variables were summarized with medians and interquartile ranges (IQR). Chi-squared tests were used to identify differences in proportions for categorical variables. Mann-Whitney rank-sum and Kruskal-Wallis tests were used to identify significant differences for continuous variables. To calculate lengths of stay (total and post-operative) only subjects who underwent one surgical procedure were included. Exact 95% confidence intervals (CI) were calculated for the rate of SSI by surgery type. Bivariate analyses were conducted to identify risk factors that were associated with SSI using logistic regression, adjusting by study site. Multivariate models were constructed to identify independent risk factors for SSI using all variables with a bivariate p-value < 0.20, and were adjusted for clustering by NICU site. The effect of decreasing gestational age and younger chronologic age at surgery was

explored in the multivariate analyses by using the oldest gestational age and oldest chronological age in the dataset as the reference value.

RESULTS

Surgical Procedures and SSI rate

During the study period, 902 study subjects underwent 1,346 surgical procedures that were included in this analysis. Forty-four procedures occurred after an SSI was diagnosed and were excluded. Gastrointestinal (GI) and cardiac procedures were the most common (46% and 28%, respectively) types of surgery (Table 1). Differences in the types of surgery were noted among the sites. Cardiac surgeries were performed over twice as often as GI procedures at Site 1, while the number of cardiac and GI procedures was similar at Site 2. At Site 3, GI procedures were the most common type of surgeries performed and cardiac procedures were relatively rare.

Overall, 60 (6.7%) of 902 subjects developed an SSI, for an overall incidence of 4.46 infections per 100 surgical procedures. The rate of SSIs did not differ significantly by type of surgery (Table 1). The average time from surgery to diagnosis of an SSI was significantly longer for cardiac surgery (mean 16.2 days, median 14.0 days, IQR 3.0 to 27.0 days) than for GI surgery (mean 5.0 days, median 2.0 days, IQR 1.0 to 5.0 days) and neurosurgery (mean 3.0 days, median 2.5 days, IQR 1.5 to 5.0 days), but time to SSI was similar between cardiac surgery and CDH repair (mean 22.3 days, median 2.0 days, IQR 2.0 to 62.0 days).

Of the 360 infants who had GI surgery, 86 underwent multiple GI procedures. The rate of SSI did not differ between initial and subsequent procedures (4.4 per 100 procedures (16/360) and 5.8 per 100 procedures (15/257), respectively; $p=0.44$). The rate of SSI was 30.0% (6/20) among the subjects with silos placed for gastroschisis repair and 4.1% (3/74) for infants with NEC.

Preterm infants (<37 weeks gestation) were more likely than term infants to develop an SSI after cardiac surgery (8.4% v. 2.9%, $p=0.03$). The rate of SSI among preterm vs. term infants was similar after neurosurgery (0% (0/34) vs. 4.8% (4/84), respectively, $p=0.21$).

Risk factors for SSIs

Multivariate analysis, adjusted for clustering by site, revealed the following independent risk factors for SSI: the use of a CVC, male sex, lower gestational age, and younger chronological age at time of first surgery (Table 2). In bivariate analysis, lower birth weight was also associated with an increased risk of SSI ($p=0.02$), but was not included in the multivariate model due to its collinearity with gestational age.

Impact of SSI on length of NICU hospitalization and crude mortality

Among infants who underwent cardiac surgery, infants with an SSI had a longer overall NICU length of stay (LOS) (median 121.5 days vs. 20 days, $p<0.0001$) and post-operative LOS (median 98.5 days vs. 13 days, $p<0.0001$) than infants who did not develop an SSI. Similarly, among infants who underwent GI surgery, those with an SSI had a longer post-operative LOS than infants who did not develop an SSI (median 67.5 days vs. 13 days, $p<0.0001$).

0001). For other types of surgery, the overall and post-operative LOS was similar among those with and without SSI (data not shown). Among all infants undergoing surgery, the crude mortality rate was similar in infants with and without an SSI (6.7% vs. 4.2%, $p=0.32$).

Prophylactic antimicrobial agents for cardiac and GI surgical procedures

Cefazolin was the most common agent used for both cardiac (80%, 271/ 339) (Figure 1A) and GI procedures (60%, 258/ 431) (Figure 1B). The most common alternative regimens for cardiac procedures included vancomycin alone or with other agents and the most common alternative regimen for GI procedures was piperacillin-tazobactam.

The duration of peri-operative prophylaxis varied among study sites for both cardiac and GI surgery (Table 3). Infants undergoing cardiac procedures with a post-operative chest tube received a longer duration of prophylaxis when compared to infants without a chest tube (2 days, IQR, 2–4 days vs. 1 day, IQR, 0–2 days, $p<0.0001$).

Pathogens associated with SSI

Fewer than half (43%, 26/60) of the infants with SSI had a culture obtained from the infected surgical site, although most cultures obtained were positive (77%, 20/26) (Figure 2). The most commonly isolated organism was *Staphylococcus aureus* (50%, 10/20) and three infants had polymicrobial infection. Over half (60%, 36/60) had at least one blood culture obtained at the time of SSI diagnosis and all were negative.

Antibiotic Management of SSI

The average duration of IV antimicrobial treatment for SSI was 9.3 days (median 8, IQR 6 to 10.5 days) and was similar across the study sites (Kruskall-Wallis $p=0.39$). Among the 20 infants with positive cultures, 5% (1/20) received vancomycin for treatment of MRSA and 5% (1/20) received meropenem for treatment of *Enterobacter cloacae* resistant to third generation cephalosporin agents. Among the 40 infants without pathogens identified, broad spectrum agents were commonly used; 62.5% (25/40) received vancomycin, 22.5% (9/40) received third generation cephalosporin agents, and 2.5% (1/40) received meropenem.

DISCUSSION

In this multicenter study, 902 infants hospitalized in the NICU underwent 1,346 surgical procedures and nearly one-quarter of infants underwent more than one procedure. The rate of SSI was 4.46 per 100 surgical procedures and overall, 7% of infants developed an SSI. We identified multiple risk factors for SSI including younger chronologic and lower gestational age, male sex, and use of a CVC. Although SSIs did not appear to increase the rate of mortality, they were associated with prolonged length of stay. Finally we identified opportunities for improvement and standardization of the use of perioperative antibiotics and diagnostic evaluation of neonates with suspected SSI as discussed further below.

Benchmarking data for SSI following surgical procedures in the NICU population are rare as previous reports usually included all pediatric patients or preceded recent efforts to reduce SSI using bundle strategies. The National Surgical Quality Improvement Program reported

an SSI rate of 1.8% in 2011 following all pediatric surgical procedures including those performed in infants¹³. The NICU at the Children's & Women's Health Centre of British Columbia reported an SSI rate of 4.3% from 2004 to 2009 for surgical procedures of the central nervous system, airway/ear nose and throat, chest, abdominal cavity, pelvic, and other body sites¹⁴. Furthermore, analysis of the Surgeons Congenital Heart Surgery Database and the Pediatric Health Information System found that the overall unadjusted rates of postoperative infections, including sepsis, wound infection, mediastinitis, endocarditis, and pneumonia were 3.7%, but after adjustment for hospital-level patient characteristics and case-mix, the rate ranged from 0.9% to 9.8%¹⁵.

The SSI rate in our cohort was similar for initial and subsequent gastrointestinal tract procedures, but substantially higher among those who required multiple procedures to manage gastroschisis and had silos placed (30%). The Canadian Pediatric Surgery Network also demonstrated an elevated SSI rate of 14.2% among neonates with gastroschisis managed with silos¹⁶. We speculate that the complex management associated with reduction of gastroschisis which includes exposed bowel and large wounds puts these infants at high risk of SSI¹⁴. However, these surgical characteristics also make precise diagnosis of SSI difficult.

In our study cohort, each week decrease in gestational age increased the risk of developing an SSI by 14%. This increased risk could be due to the immunologic immaturity of preterm infants and immature skin structure^{17, 18}. Similarly, younger chronologic age could reflect these factors¹⁹. We also found that use of a CVC during hospitalization was associated with increased risk of SSI. We speculate that CVC is a marker for severity of underlying illness rather than part of the pathogenesis of SSI, but given that studies in neonates have shown an increase in risk of central line associated bloodstream infection with catheter dwell times greater than 2 weeks²⁰, additional work should be done to determine if more prompt removal of a catheter may lead to a decreased risk of SSI as well. Within our cohort, the mean time from first insertion to last removal of a CVC was significantly longer among those with SSI (70 days v. 32 days, $p < 0.00001$), though this is not a classical calculation of catheter dwell time as we only collected first insertion and last removal of CVC.

In this study, we did not find that infants with SSI had higher mortality rates, but they did have significantly longer overall and post-operative LOS compared with infants who underwent surgery without developing a SSI. While we were unable to determine if the increase in LOS is *attributable* to SSI, it is feasible that infants with SSI do require treatment with IV antibiotics and/ or surgical debridement, may need longer durations of parenteral therapy due to associated feeding intolerance, and may be at increased risk of adverse drug reactions from treatment^{21, 22, 23, 24}. Similar findings were noted by investigators in British Columbia; NICU patients with SSI were more likely to require further surgical procedures (median 2 procedures v. 1 procedure, respectively, $p < 0.001$) and had an increased length of hospitalization (median 79 days v. 25 days, respectively, $p < 0.001$) when compared to infants who did not experience an SSI¹⁴. In centers with high rates of post-operative infections following congenital heart surgery, patients with SSI experienced significantly higher adjusted LOS than those without SSI (25.5 days v. 11.2 days) and higher hospital costs (\$115,000 v. \$63,330)¹⁵. Data from the Agency for Healthcare Research and Quality's

National Inpatient Sample revealed that, in 2005, SSIs were responsible for approximately 1 million additional days of hospitalization and \$1.6 billion in attributable costs¹.

In the current study, only 43% of infants diagnosed with an SSI had a culture taken from the surgical site. Not having a positive culture from the infected site to guide therapy had an adverse clinical impact, as reflected in the increased use of broad spectrum antimicrobial agents in those with negative cultures or no cultures obtained. Among those infants with positive cultures, the most common organism isolated was methicillin-susceptible *S. aureus* (MSSA). Thus, it is likely that many SSI without cultures were caused by MSSA, but treated with vancomycin which is a less effective agent for methicillin-susceptible strains²⁵. Surgical teams should be educated about the benefits of obtaining cultures from a patient with a suspected post-operative wound infection. SSI were frequently caused by MSSA despite the common use of cefazolin as perioperative prophylaxis. We note that we did not evaluate appropriate timing and dosing of perioperative prophylaxis. Future studies should continue to assess SSI preventive strategies in infants including skin disinfection and the potential use of nasal and skin decolonization among infants colonized with *S. aureus* undergoing high risk surgical procedures²⁶.

There are no evidence-based perioperative prophylaxis guidelines for infants and as a result, guidelines developed for adult populations are often used. Current guidelines for adult populations from the American Society of Health-System Pharmacists, the Infectious Disease Society of America, and the Society of Hospital Epidemiology of America recommend cefazolin or cefuroxime for cardiac procedures unless there is a beta-lactam allergy, in which case vancomycin or clindamycin are recommended. Cefazolin is recommended for GI procedures without entry into the lumen, while other agents including cefotetan, ceftiofex, and cefazolin+metronidazole are recommended for more complex procedures. These guidelines also suggest a maximum of 24 hours of post-operative prophylaxis for non-cardiac procedures and 48 hours for cardiac procedures²⁷.

Our findings suggest potential opportunities for standardizing perioperative prophylaxis and antimicrobial stewardship in the NICU population. While cefazolin was the most commonly prescribed perioperative prophylactic agent used in the current study, many regimens were used, particularly for GI procedures. There were significant differences in length of perioperative prophylaxis; Site 1 prescribed a longer duration of prophylaxis for cardiac procedures and Site 3 prescribed a longer duration for GI procedures. Perioperative prophylaxis was significantly longer for cardiac procedures with post-operative chest tubes than procedures without chest tubes ($p < 0.00001$). A recent double-blind placebo-controlled trial performed among patients undergoing elective thoracic surgery that required a chest tube demonstrated no difference in infectious complications among those who did and did not receive antibiotic prophylaxis for chest tubes²⁸. Furthermore, there is a risk of becoming colonized or infected with antibiotic resistant organisms from prolonged prophylaxis²⁹ and fewer infections with organisms such as *Candida spp.* and *Pseudomonas spp.* have been reported with shorter courses of antibiotic prophylaxis^{30, 31}. Current surgical prophylaxis guidelines do not recommend continuing antibiotic prophylaxis until drains and chest tubes are removed²⁷. Thus, our findings highlight the need for development of evidence-based practices for the NICU population.

There are limitations to our study. Our definition of SSI was somewhat subjective, relying on physician documentation in the EMR instead of culture-confirmed infection or adjudication by infection prevention and control staff. Data were only gathered on antibiotics received in the NICU; therefore, we did not evaluate the pre- and intra-operative regimens. We did not collect the surgical wound class nor distinguish between superficial, deep, and organ space infections. In addition, we did not collect information on the use of prosthetic material.

In conclusion, we found that SSI occurred after 4.46% of surgical procedures in the NICU population and that younger chronologic age and lower gestational age were significant predictors of SSI. Our findings suggest several opportunities for improving antimicrobial stewardship including the need for developing evidence-based perioperative prophylaxis guidelines and SSI management in the NICU population.

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Figure 1A

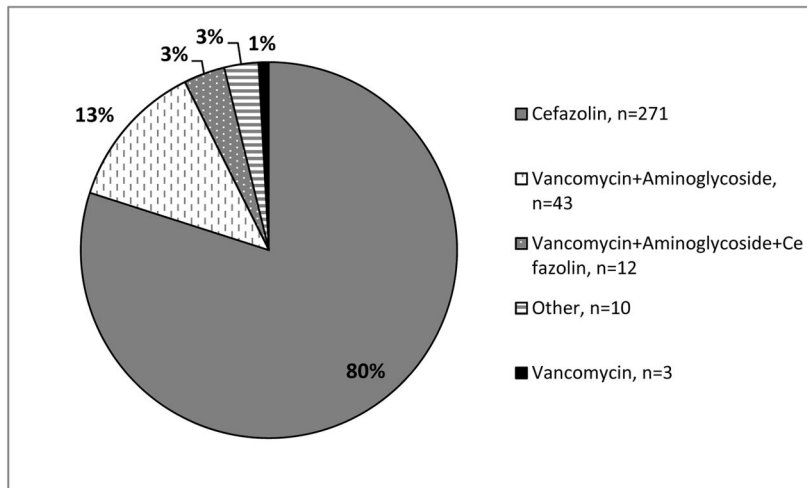


Figure 1B

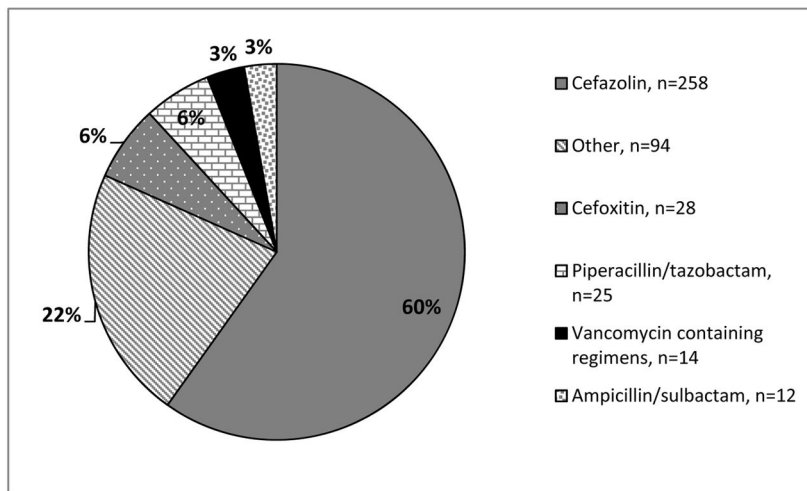


Figure 1. Prophylaxis regimens used for cardiac surgery (A) and for gastrointestinal tract surgery (B)

Count and percentage by category are displayed in the figure. For cardiac surgery the “Other” regimens included ampicillin/gentamicin/cefazolin (3), ampicillin/gentamicin/vancomycin (2), ampicillin (1), and doxycycline (1); for gastrointestinal surgery the most common ‘other’ regimens included ampicillin/gentamicin (31), cefazolin/metronidazole (11), and ampicillin (11).

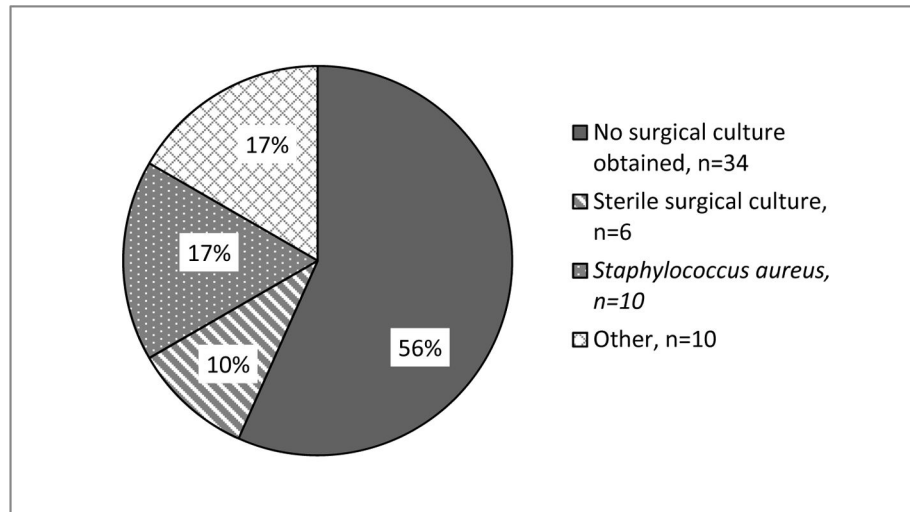


Figure 2. Cultures from 60 infants with surgical site infections

One-third of infants had positive cultures, one-third had negative cultures and one-third had no cultures obtained. Other pathogens causing the 10 SSIs included *Enterobacter spp.* (2), yeast (2), *Escherichia coli* (1), *Enterococcus faecalis* (1), non-speciated coagulase negative *Staphylococcus* (1), and polymicrobial infection (1 *S. epidermidis* + *Enterococcus faecalis*, 1 non-speciated coagulase negative *Staphylococcus* + *Enterococcal spp.*, and 1 *E. asburiae* + *Enterococcal spp.*)

Table 1

Rates of surgical site infections by type of procedure among infants in the neonatal ICU

Type of surgical procedure	Site 1	Site 2	Site 3	Total	SSIs (n)	SSI rate per 100 procedures Rate (Exact CI)
	n (%)					
Gastrointestinal	147 (26%)	52 (35%)	418 (67%)	617 (46%)	31	5.02 (3.44, 7.06)
Cardiac	323 (56%)	51 (34%)	8 (1%)	382 (28%)	15	3.93 (2.21, 6.39)
Neurosurgery	38 (7%)	23 (15%)	88 (14%)	149 (11%)	4	2.68 (0.74, 6.73)
Repair of congenital diaphragmatic hernia	41 (7%)	1 (1%)	54 (9%)	96 (7%)	6	6.25 (2.33, 13.11)
Ear/nose/throat	7 (1%)	14 (9%)	16 (3%)	37 (3%)	2	5.41 (0.66, 18.19)
Pulmonary	2 (<1%)	1 (1%)	22 (4%)	25 (2%)	1	4.00 (0.10, 20.35)
Genitourinary tract	8 (1%)	7 (5%)	9 (1%)	24 (2%)	0	0
Other [†]	9 (2%)	1 (1%)	6 (1%)	16 (1%)	1	6.25 (0.16, 30.23)
Overall	575	150	621	1,346	60	4.46 (3.48, 5.70)

[†] Includes eye, orthopedic, and other

Table 2

Demographic and clinical characteristics associated with surgical site infections among infants in the neonatal ICU

Characteristic	Subjects without SSI (n=842)	Subjects with SSI (n=60)	Unadjusted OR (CI); ¹ p-value	Adjusted OR (CI); p-value ²
Age at first surgery, days, (IQ range)	5 (2, 11)	5.5 (2, 14.5)	1.01 (1.01, 1.02) <0.0001	³ 1.03 (1.01, 1.04) 0.001
Male	471 (56%)	35 (58%)	1.10 (1.00, 1.22) 0.058	1.18 (1.04, 1.34) 0.011
Race				
White	368 (44%)	28 (47%)	REFERENCE	
Black	74 (9%)	5 (8%)	0.89 (0.58, 1.36); 0.588	-
Other	400 (48%)	27 (45%)	0.89 (0.40, 1.99); 0.771	-
Birth weight, grams (IQ range)	2945 (2365, 3400)	2537 (1955, 3265)	1.00 (1.00, 1.00); 0.022	-
Gestational age, weeks (IQ range)	38 (36, 39)	37 (34, 38)	1.07 (1.04, 1.10) <0.0001	⁴ 1.09 (1.02, 1.17) 0.013
Use of CVC	632 (75%)	56 (93%)	4.65 (2.53, 8.56); <0.0001	4.40 (1.19, 9.62); 0.001

¹ Abbreviations used in table: OR: odds ratio; CI: 95% confidence interval; IQ: Interquartile range; CVC: central venous catheter

² Model adjusted for clustering by study site.

³ Decreasing chronological age was modeled in the multivariate analysis

⁴ Decreasing gestational age was modeled in the multivariate analysis

Table 3

Duration of perioperative prophylaxis in days by type of surgical procedure and site among infants in the neonatal ICU

Type of Surgery	Site 1	Site 2	Site 3	Overall
	n			
	Median in days, Interquartile Range in days			
Cardiac procedure with chest tube	246 2 (2, 4)	12 2 (1, 2)	2 0.5 (0, 1)	260 2 (2, 4) ¹
Cardiac procedure without chest tube	40 1.5 (1, 3.5)	33 0 (0, 1)	6 1 (0, 1)	79 1 (0, 2) ²
Gastrointestinal tract procedure	109 2 (1, 4)	37 2 (1, 3)	28 3 (1, 10)	431 2 (1, 8) ³

¹Differences between sites, p=0.0047

²Differences between sites, p=0.0001

³Differences between sites, p=0.0002