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Original Research Article

Duration of perioperative antibiotic prophylaxis in neonatal surgery: Less is more

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ABSTRACT

Background: The ideal duration of neonatal antibiotic prophylaxis is not determined with wide variance in practice. This study aims to evaluate the association between duration of antibiotics and surgical site infection (SSI) in neonatal surgery.
Methods: A retrospective review regarding antibiotic prophylaxis was performed on <30-day-old surgical patients at a children's hospital from 2014 to 2019. The patients were analyzed based on demographics, presence of SSI, and antibiotic duration. The primary outcome was the development of SSI with ANOVA, chi-square, and recursive partitioning used for statistical analysis.
Results: 19/155 patients developed an SSI (12.26 %). Those with an SSI had a lower weight at surgery ($p = 0.03$). Additionally, wound classification ($p = 0.17$) and antibiotic duration >48hrs ($p = 0.94$) made no statistical difference in SSI rate. The two variables most closely linked to SSI development were gestational age (100 %) and weight at time of procedure (80.76 %).
Conclusions: Antibiotic prophylaxis >48 h did not decrease the incidence of SSI. Risk factors for SSI development in neonatal surgery were lower gestational age, decreased weight at time of procedure and total length of procedure.

1. Introduction

Surgical site infections (SSI) are the most common healthcare associated infection worldwide carrying significant cost, prolonged hospital length of stay and tremendous morbidity to patients.[1] Neonates are particularly susceptible to SSIs due to immature immune systems, which add to the associated risk.[2]

Perioperative antibiotic prophylaxis is a proven strategy to prevent SSIs and their associated morbidity, thereby reducing healthcare cost.[3,4] However, current guidelines for antibiotic prophylaxis in neonatal surgery are limited and based on extrapolated adult data or expert opinion.[5] Specifically, a paucity of data exist regarding appropriate neonatal antibiotic prophylaxis following clean-contaminated vs. contaminated surgery.[4,6] Without evidence-based guidelines, there is a wide variance of prescribing patterns in this population (especially with regards to duration), potentially contributing to increased morbidity, antibiotic resistance, and cost.[3,4,7]

Our primary aim was to determine if there is a correlation between duration of perioperative antibiotic prophylaxis and the incidence of SSIs in neonates undergoing clean, clean-contaminated and contaminated surgical procedures. Additionally, we aimed to identify factors that influence the development of SSIs in this population. By addressing this critical knowledge gap, we hope to guide clinical decision making and improve the care of neonates undergoing surgical procedures.

2. Methods

2.1. Study design

After IRB approval, a retrospective case control study was performed of two Level III neonatal intensive care units (NICU), which combined contain 80 NICU beds. The review included all neonatal surgeries performed between 2014 and 2019. Patients were excluded from analysis if they were deemed to have a dirty wound classification, mortality on the

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day of surgery, required multiple operations on the same day, or had an additional co-morbid condition requiring antibiotic use.

2.2. Outcomes

Patient demographics, medical history, as well as perioperative management were all recorded including antibiotic administration and documentation of an infection. Our primary outcome was the development of SSI, which is, "an infection that occurs after surgery in the part of the body where the surgery took place," as defined by the Center of Disease Control.[8] However, not all infections are explicitly described in the medical record. For the purpose of this study, any additional antibiotic administration or clinical signs of an infection following the procedure, was considered an SSI. The patient population was then stratified based on duration of antibiotics into those that received no perioperative antibiotics (n = 55), 0–48 h (n = 42), and >48 h (n = 58) of post-operative antibiotics. Secondary analysis compared SSI rates with duration of antibiotics and specific patient characteristics.

Wound classification was determined at the time of the operation by operating room staff. For this study, we combined the wound class of clean-contaminated and contaminated prior to data analysis. This was done as prior publications have noted poor differentiation between these two wound classifications amongst pediatric surgeons.[9]

2.3. Statistical analysis

The study data were evaluated utilizing five distinct analyses: 1.) descriptive statistics of the total population, 2.) descriptive statistics of the antibiotic regimen utilized, 3.) univariate analysis based on the presence of SSI, 4.) univariate analysis based on antibiotic duration, and 5.) variable importance index to rank factors linked to SSI.

When comparing SSIs and perioperative antibiotic administration t-tests, Fischer's exact tests, and Chi-Square tests were used as needed for continuous and categorical variables. When comparing duration of antibiotics with continuous predictors, Pearson Correlation analysis was used.

Duration of antibiotics (0 h, 0–48 h, and >48 h) was compared with a one-way analysis of variance (ANOVA). Categorical variables are displayed in terms of frequencies with percentages in parentheses and are compared between the three groups using Chi-Square tests. Pairwise comparisons were done to see where the significance lies when comparing three groups. Pairwise p-values <0.0167 indicate a significant association between the pairwise comparisons. This is because the Bonferroni correction is used for multiple comparisons so pairwise $p = 0.05$ divided by 3 comparisons.

A variable importance index was generated via recursive partitioning to create a rank order of which variables were most closely linked to a SSI. Recursive partitioning is a machine learning technique that divides a dataset into smaller and smaller groups based on their characteristics, to create a decision tree that can predict outcomes. Variable importance indices measure how much each variable contributes to the accuracy of the decision tree model. Unlike p-values in frequentist statistics, which test for the significance of individual predictors, variable importance indices consider the joint effect of all predictors in the model and can identify non-linear and interactive relationships between variables.[10]

3. Results

3.1. Descriptive analysis

Out of the initial 198 patients identified, 43 were excluded, resulting in a final analysis that included 155 patients. Among these patients who met the inclusion and exclusion criteria, a total of 19 (12.26 %) ultimately developed SSI (Fig. 1).

The average age of all patients was 37.77 weeks (±2.83 weeks) with birth weight of 2.96 kgs (±0.75 kgs). The patients underwent surgery at 11.33 days (±9.54 days), and had an average weight of 3.06 kgs (±0.80 kgs) at the time of surgery. Mean surgery length was 2.02 h (±0.94 h). Patient wound classification was broken down into either clean wounds (80, 51.61 %) or clean-contaminated and contaminated wounds (75, 48.39 %). The average length of perioperative antibiotics was 2.25 days (±2.54 days). Additionally, 55 patients (35.5 %) received no antibiotics, 42 patients (27.1 %) received between 0 and 48 h of post-operative antibiotics, and 58 (37.4 %) received >48 h of post-operative antibiotics (Fig. 2).

3.2. Antibiotic regimen

In total, 17 different antibiotic combinations were given to 100 patients. No individual antibiotic regimen was statistically more or less likely to develop an SSI. The most common combination was ampicillin and gentamycin, which was administered to 47 patients (7 with an SSI and 40 without an SSI, p = 0.509). This was followed by cefazolin with 20 patients (3 with SSI and 17 without an SSI, p = 0.689) and piperacillin/tazobactam which was administered to 11 patients (all without an SSI, p = 0.198). The remaining 14 antibiotic combinations were

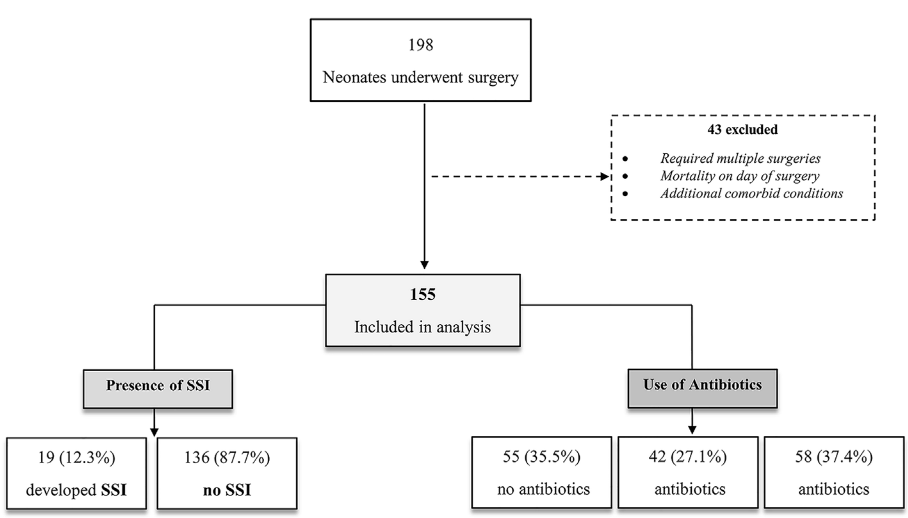

Fig. 1. Study population.

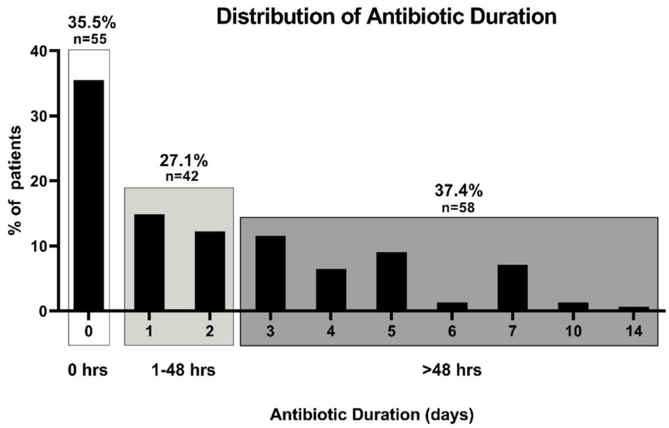

Fig. 2. Distribution of antibiotic duration.

prescribed to the final 22 patients (7 with SSI and 15 without an SSI).

3.3. SSI vs no SSI

A univariate analysis was used to compare those with a SSI to those without a SSI (Table 1). No statistically significant difference was found between groups with respect to gestational age, birth weight, age at surgery, length of procedure, or sex. Those with a SSI had a lower weight at the time of procedure, were more likely to have received perioperative antibiotics, and were prescribed antibiotics for a longer period of time (Table 1).

Table 1
Univariate analysis of patient and procedural characteristics stratified by SSI development.

Characteristic	SSI n = 19	No SSI n = 136	P value
Gestational age, weeks			
mean (SD)	36.15 (4.46)	37.99 (2.47)	0.09
Birth weight, kg			
mean (SD)	2.60 (1.04)	3.01 (0.69)	0.11
Age at surgery, days			
mean (SD)	10.71 (8.66)	11.41 (9.68)	0.76
Sex, n (%)			
male	10 (52.63)	94 (69.12)	0.15
female	9 (47.37)	42 (30.88)	
Weight at procedure, kg			
mean (SD)	2.70 (0.97)	3.11 (0.76)	**0.03**
Type of procedure[a], n (%)			
Laparoscopic	2 (10.53)	51 (37.50)	
Laparotomy	12 (63.16)	44 (32.35)	
Abdominal wall defect	0 (0)	9 (6.62)	
Thoracic	0 (0)	5 (3.68)	
ENT	1 (5.26)	1 (0.74)	
Skin and soft tissue	2 (10.53)	10 (7.35)	
Urology	2 (10.53)	10 (7.35)	
Other	0 (0)	6 (4.41)	
Length of procedure, hours			
mean (SD)	2.43 (1.35)	1.97 (0.86)	0.16
Length of perioperative antibiotics, days			
mean (SD)	3.47 (2.67)	2.07 (2.49)	**0.02**
Length of perioperative antibiotics, hours, n (%)			
0	2	53	0.05
0-48	7	35	
>48	10	48	
Perioperative antibiotics given, n (%)	17 (89.47)	83 (61.02)	**0.02**
Contamination status, n (%)			
clean	7 (36.84)	73 (53.68)	0.17
clean-contaminated/contaminated	12 (63.16)	63 (46.32)	

Abbreviations.
ENT, ear, nose, throat.
kg, kilogram.
[a] Chi square not valid for Type of Procedure due to expected frequencies <5.

3.4. Antibiotic duration (0hrs, <48hrs, >48hrs)

We then compared duration of perioperative antibiotics into the three aforementioned groups: no perioperative antibiotics, 0–48 h of post-operative antibiotics, and >48 h of postoperative antibiotics (Table 2). The groups were different with regards to each patient characteristic measured: gestational age, birth weight, age at surgery, weight at procedure, length of procedure, and sex.

Specific pairwise comparisons determined that patients who received a longer duration of antibiotics were found to be younger, both in terms of gestational age and age at surgery. Similarly, patients who received extended antibiotic regimens were smaller, both in terms of birth weight and weight at time of surgery. Finally, irrespective of age or weight, extended antibiotic use was associated with longer operations.

Patients who received a longer duration of antibiotics were more likely to have clean-contaminated and contaminated surgeries. Likewise, patients without peri-operative antibiotics were more likely to have undergone clean procedures.

3.5. Variable importance index

With the use of recursive partitioning, an analysis of the risk factors most likely to be associated with a SSI was performed (Table 3). These variables were then ranked in terms of relative importance. Gestational age was the most important risk factor linked to the development of a SSI. Second most important was weight at time of procedure, which was 80.76 % as important as gestational age for the development of a SSI. This was followed by sex, length of procedure, type of procedure, length of antibiotics, and birth weight.

4. Discussion

Great differences are seen in the prescribing patterns for antibiotics in the neonatal population.[3,11] Significant practice variability was seen in our study, with average duration of antibiotics prescribed 2.26 days with a standard deviation of 2.54. The longevity of antibiotic use has been shown to increase rates of drug resistance, however the risk of creating these multidrug resistant organisms needs to be weighed against prevention of adverse outcomes.[12] In our study, the SSI rate was 12.26 %. This rate is similar to other reported data.[13,14] In one study of 1094 neonates that underwent surgery, there was an overall SSI rate of 16.6 %, which increased to 20.2 % in contaminated cases.[15] In our population, clean contaminated and contaminated cases contributed to 48.39 % of cases while clean cases made up 51.61 % of procedures. Research has shown that surgical patients with SSI have a significantly higher risk of death, compared to patients without SSI.[16] Additionally, it has been found that both following evidence-based strategies could prevent up to half of all SSIs and implementation of antimicrobial stewardship programs limits overall antibiotic duration.[17,18]

High variability in antibiotic prophylaxis is seen in clinical practice with high percentages of inappropriate prescribing.[3,7] Even though several retrospective studies and a multicenter prospective study have identified age at surgery, sex, length of surgery, and contamination at operation as risk factors for SSI in the general pediatric population, only one study has addressed the issue of perioperative antibiotic duration in neonates prior to our study.[19,20] We found no evidence of decreased SSI rate or decreased complications in patients where antibiotics were continued for longer durations (>48 h). This is similar to recent data for all pediatric patients (<18 years old) demonstrating no correlation between postoperative antibiotic prophylaxis and SSI rates.[6] Due to the lack of consensus guidelines, pediatric and neonatal recommendations are largely based on expert opinion and from data extrapolated from adult patients.[5] While extrapolating data can improve outcomes in certain situations, there are well documented differences between neonatal and adult immune systems. Specifically, impaired chemotaxis and phagocytosis, as well as a relative deficiency of immunoglobulins, place neonates

Table 2
Univariate analysis of patient and procedural characteristics stratified by antibiotic duration.

	(1) 0 Hours (n = 55)	(2) 1–48 Hours (n = 42)	(3) > 48 Hours (n = 58)	Overall P-Value	Pairwise P-Values		
					(1) vs. (2)	(1) vs. (3)	(2) vs. (3)
Gestational Age, weeks							
mean (SD)	38.98 (1.49)	37.96 (2.63)	36.48 (3.39)	**< 0.0001**	0.03	**< 0.0001**	0.02
Birth Weight, kg							
mean (SD)	3.23 (0.58)	3.04 (0.78)	2.64 (0.77)	**< 0.0001**	0.19	**< 0.0001**	**0.01**
Age at Surgery, days							
mean (SD)	17.50 (8.32)	11.37 (9.59)	5.44 (6.49)	**< 0.0001**	**0.001**	**< 0.0001**	**0.0009**
Weight at Procedure, kg							
mean (SD)	3.44 (0.61)	3.12 (0.81)	2.67 (0.77)	**< 0.0001**	0.04	**< 0.0001**	**0.006**
Length of Procedure, hours							
mean (SD)	1.47 (0.36)	2.15 (1.15)	2.46 (0.91)	**< 0.0001**	**0.0006**	**< 0.0001**	0.13
Sex, n (%)							
male	47 (85.45)	27 (64.29)	30 (51.72)				
female	8 (14.55)	15 (35.71)	28 (48.28 %)	**0.0006**	0.02	**0.0001**	0.21
Development of SSI, n (%)							
Yes	2 (3.64)	7 (16.67)	10 (17.24)				
No	53 (96.36)	35 (83.33)	48 (82.76)	0.0524	0.0284	0.0190	0.9398
Contamination Status, n (%)							
clean	45 (81.82)	21 (50)	14 (24.14)				
clean-contaminated/contaminated	10 (18.18)	21 (50)	44 (75.86 %)	**<0.0001**	**0.0009**	**<0.0001**	**0.0074**

Abbreviations.
kg, kilogram.

Table 3
Variable importance indices.

Variable	Relative Importance
Gestational Age, weeks	100.00 %
Weight at Procedure, kg	80.76 %
Sex	59.97 %
Length of Procedure, hours	54.73 %
Type of Procedure	45.39 %
Length of Antibiotics, days	38.45 %
Birth Weight, kg	28.71 %

Abbreviations.
kg, kilogram.

at an increased rate of SSI.[19]

In our study, those patients that had greater than 48 h of antibiotics were more likely to have undergone a longer surgery, had younger gestational age, lower birth rate, lower weight at procedure, and more likely to have clean-contaminated or contaminated cases as opposed to clean procedures. This may be due to implicit bias within the practitioners who prescribe antibiotics more aggressively to seemingly more vulnerable patients. There were multiple pediatric surgeons trained in different programs, different eras and had different beliefs/reasoning for length of antibiotic prophylactic use. Additionally, a strong influence from a number of neonatologists with whom we share decision making, were involved in antibiotic prescribing.

There are limitations to our study, including the retrospective nature of this study, the differing prescribing patterns of physicians, and the long time period of the chart review. The retrospective nature of this study does not allow for randomization or control of the characteristics of the different groups. The extended duration of this chart review allows for certain changes of practice between individual providers in this time frame, which may not be accurately reflected in this study.

5. Conclusions

According to our variable importance index, potentially modifiable risk factors associated with SSI development in neonates were low gestational age, lower weight at time of procedure and total length of procedure. Most importantly, antibiotic prophylaxis greater than 48 h was not associated with a decreased rate of SSI. Going forward, these findings could aid in the development of guidelines for peri-operative antibiotics in this special patient population.

CRediT authorship contribution statement

Spencer Wilhelm: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation. **Michael Tolkacz:** Writing – review & editing, Writing – original draft. **Lior Kopel:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Anthony Stallion:** Writing – review & editing, Supervision, Investigation. **Nathan M. Novotny:** Writing – review & editing, Supervision, Investigation. **Begum Akay:** Writing – review & editing, Supervision, Investigation. **Pavan Brahmamdam:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare no financial or professional conflicts of interest related to the content of the manuscript. All authors have disclosed any affiliations or financial involvement, direct or indirect, or other possible conflicts of interest that might be perceived to influence the results or interpretation of the manuscript.

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