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Efficacy of Non-Beta-lactam Antibiotics for Prevention of Cesarean Delivery Surgical Site Infections

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Abstract

Objective To examine the association between perioperative Beta (β))-lactam versus non-β-lactam antibiotics and cesarean delivery surgical site infection (SSI).

Study Design Retrospective cohort of women undergoing cesarean delivery from January 1 to December 31, 2014. All women undergoing cesarean after 34 weeks with a postpartum visit were included. Prevalence of SSI was compared between women receiving β-lactam versus non-β-lactam antibiotics. Bivariate analyses were performed using Pearson's Chi-square, Fisher's exact, or Wilcoxon's rank-sum tests. Logistic regression models were fit controlling for possible confounders.

Results Of the 929 women included, 826 (89%) received β-lactam prophylaxis and 103 (11%) received a non-β-lactam. Among the 893 women who reported a non-type I (low risk) allergy, 819 (92%) received β-lactam prophylaxis. SSI occurred in 7% of women who received β-lactam antibiotics versus 15% of women who received a non-β-lactam ($p = 0.004$). β-Lactam prophylaxis was associated with lower odds of SSI compared with non-β-lactam antibiotics (odds ratio [OR] = 0.43; 95% confidence interval [CI] = 0.22–0.83; $p = 0.01$) after controlling for chorioamnionitis in labor, postlabor cesarean, endometritis, tobacco use, and body mass index (BMI).

Conclusion β-Lactam perioperative prophylaxis is associated with lower odds of a cesarean delivery surgical site infection compared with non-β-lactam antibiotics.

Keywords
- antibiotics
- penicillin allergy
- cesarean delivery
- surgical site infection

Over one-third of women in the United States delivered via cesarean delivery (CD) in 2015 and approximately 2 to 18% of CDs are complicated by surgical site infections (SSI).[1–5] SSI leads to significant morbidity and higher cost including increased outpatient visits, emergency room visits, treatment with antibiotics, use of home health services, and hospital readmission.[6–8]

CD SSIs can be prevented by adherence to establish perioperative interventions including prophylactic antibiotic administration prior to skin incision.[9] The effectiveness of perioperative antibiotic administration is contingent on appropriate antibiotic selection, dose, and timing of administration. The American College of Obstetricians and Gynecologists (ACOG) recommends a single dose of perioperative antibiotics within 60 minutes prior to skin incision.[10] β-Lactam containing regimens, specifically cephalosporin, are preferred for their gram positive and selective gram negative bacterial coverage.[11] While the estimated prevalence of penicillin allergy in hospitalized patients is 10 to 20%,[12,13] only 12% of patients who report penicillin allergies are found to be truly allergic.[10,12–16] A

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true penicillin allergy is a type I hypersensitivity reaction which is characterized by immediate onset and mediation by IgE (immunoglobulin E) and mast cells and/or basophils (e.g., hives, angioedema, and anaphylaxis).[17] Of patients with a true penicillin allergy, the cross reactivity to cephalosporin antibiotics is estimated to be 0.17 to 8.5%.[12,14,15] Given the low rate of cross reactivity, cephalosporins are considered appropriate perioperative prophylaxis in the absence of a type I hypersensitivity to penicillin.

The current recommendation for CD prophylaxis is a first-generation cephalosporin cefazolin. In patients with a type I penicillin allergy, gentamicin and clindamycin are the recommended agents. The purpose of this study was to examine the association between perioperative antibiotic class (β-lactam versus non-β-lactam) and prevalence of CD surgical site infection. In addition, we aimed to assess whether women with penicillin allergies received appropriate perioperative antibiotics when undergoing CD. We hypothesize that women who receive β-lactam antibiotics, such as cefazolin, prior to CD will have lower odds of SSI compared with those who receive non-β-lactam antibiotics, such as gentamicin and clindamycin.

Materials and Methods

The Duke University Health System Institutional Review Board (IRB) approved this retrospective cohort study of women who underwent CD at Duke University Hospital from January 1, 2014 to December 31, 2014.

Women were included in the study if they delivered at $\geq$ 34 weeks of gestation and had a documented postpartum visit. Women undergoing CD received standard preoperative surgical prophylaxis of cefazolin 2 g intravenously for body mass index (BMI) $<$ 40 and 3 g intravenously for BMI $\geq$ 40 with the exception of women with a self-reported penicillin allergy. Penicillin allergy type was defined by medical record allergic event documentation. Women with a penicillin allergy received clindamycin 900 mg intravenously and gentamicin 80 mg intravenously. Subcutaneous closure with absorbable suture was standard practice for women with adipose tissue $\geq$ 2cm in depth. Subcuticular closure with absorbable suture was typically used for skin closure.

Baseline demographic information, medical comorbidities, pregnancy complications, CD indications, and antibiotic use were collected via electronic health record review. Gestational age was determined by best obstetrical estimate using ACOG dating criteria. Pregestational diabetes included patients who had a diagnosis of either type 1 or type 2 diabetes at their obstetric intake visit. Chronic and gestational hypertensions were recorded separately.

The primary outcome of interest was SSI defined by the Centers for Disease Control and Prevention (CDC) as an infection occurring at the surgical site within 30 days of surgery.[18] All the cases of SSI were confirmed with individual chart review. SSIs include superficial incisional, deep incisional, and organ space infections. For the purposes of our analysis, we categorized postpartum endometritis as a uterine organ space infection diagnosed after hospital discharge and a component of the primary outcome. Endometritis (as opposed to postpartum endometritis) was defined as uterine infection that occurred during the delivery hospitalization and was diagnosed prior to discharge from delivery admission. Due to CDC classification of postpartum as a deep organ space infection, endometritis diagnosed prior to hospital discharge was not included in the primary outcome.

Patients who reported rash or characterized their allergic reaction as "other" were considered low risk. Anaphylaxis, swelling, or an unknown reaction was considered a type I reaction. A woman was considered to receive appropriate antibiotics if she had no or a low-risk reaction to penicillin and was administered a β-lactam. Similarly, women with a type I reaction to penicillin were considered to receive appropriate antibiotics if they were given a non-β-lactam.

Summary statistics were calculated for patient and surgery characteristics stratified by antibiotic class. Differences between the two antibiotic groups were tested with Wilcoxon's rank-sum test for continuous variables and either Pearson's Chi-square or Fisher's exact test for categorical variables, as appropriate.

To assess the association between antibiotic class and surgical site infection a logistic regression model was fit controlling for chorioamnionitis in labor, cesarean during labor, endometritis prior to discharge, tobacco use, and delivery BMI. These were clinical factors thought to be related to the treatment assigned and/or surgical site infection. Patients who had missing information for the previously mentioned covariates or penicillin allergy were removed, and a complete case analysis was done due to the low number of missing values. Fisher's exact test was used to assess if the proportion of patients with a type I penicillin allergy that received appropriate antibiotics was different from the proportion in the nonallergic or low-risk group. All statistical analyses were performed in SAS 9.4 (SAS Institute, Cary, NC) at a significance level of 0.05 two-tailed.

Results

Maternal demographic, clinical, and delivery characteristics are shown in ►**Table 1**.

Among the 929 women who delivered by CD, 826 (89%) received perioperative β-lactam prophylaxis and 103 (11%) received prophylaxis with a non-β-lactam. Of women who received a β-lactam, 6.7% developed an SSI compared with 14.6% of women who received a non-β-lactam ($p = 0.004$). Patients in the non-β-lactam group tended to have chronic hypertension and chorioamnionitis more often than the β-lactam group. The use of Pfannenstiel's skin incision, low transverse uterine incision, subcutaneous sutures, skin closure with suture rather than staples, and negative pressure wound therapy (NPWT) did not differ significantly between the two treatment groups.

In the multivariable logistic regression model, β-lactam antibiotic prophylaxis was associated with a 57% reduction in the odds of SSI (odds ratio [OR] = 0.43; 95% confidence interval [CI] = 0.22–0.83; $p = 0.01$) compared with non-β-lactam prophylaxis (►**Table 2**). Variables significantly associated with

Table 1 Patient and surgery characteristics by antibiotic class

	β-Lactam ($n = 826$)	Nonβ-lactam ($n = 103$)	Total ($n = 929$)	p-Value
Age (y), median (Q1, Q3)	31.0 (26.0, 35.0)	30.0 (27.0, 35.0)	31.0 (26.0, 35.0)	0.79[a]
Race				0.85[b]
Non-white	393 (47.6%)	50 (48.5%)	443 (47.7%)	
White	433 (52.4%)	53 (51.5%)	486 (52.3%)	
Delivery BMI, median (Q1, Q3)	33.2 (28.6, 38.9)	34.6 (28.0, 41.5)	33.4 (28.5, 39.1)	0.36[a]
Private insurance	423 (51.2%)	49 (47.6%)	472 (50.8%)	0.49[b]
Gestational age (wk), median (Q1, Q3)	39.0 (37.0, 39.0)	39.0 (37.0, 39.0)	39.0 (37.0, 39.0)	0.64[a]
Tobacco use	70 (8.5%)	9 (8.7%)	79 (8.5%)	0.93[b]
Diabetes	63 (7.6%)	5 (4.9%)	68 (7.3%)	0.31[b]
Missing	1	0	1	
Chronic hypertension	64 (7.7%)	15 (14.6%)	79 (8.5%)	0.02[b]
Gestational hypertension	141 (17.1%)	17 (16.5%)	158 (17.0%)	0.88[b]
Missing	1	0	1	
Cesarean performed in labor	385 (46.6%)	54 (52.4%)	439 (47.3%)	0.26[b]
Chorioamnionitis in labor	24 (2.9%)	22 (21.4%)	46 (5.0%)	< 0.0001[b]
Pfannenstiel incision	793 (96.0%)	101 (98.1%)	894 (96.2%)	0.42[c]
Hysterotomy incision				0.93[c]
Low transverse	783 (94.8%)	99 (96.1%)	882 (94.9%)	
Classical	16 (1.9%)	1 (1.0%)	17 (1.8%)	
Other	27 (3.3%)	3 (2.9%)	30 (3.2%)	
Subcutaneous closure	734 (88.9%)	88 (85.4%)	822 (88.5%)	0.30[b]
Type of closure				0.57[c]
Subcuticular suture	797 (96.5%)	101 (98.1%)	898 (96.7%)	
Staples	29 (3.5%)	2 (1.9%)	31 (3.3%)	
Negative pressure wound therapy used	53 (6.4%)	5 (4.9%)	58 (6.2%)	0.54[b]
NPWT type				1.00[c]
NPWT not used	773	98	871	
Pico	46 (86.8%)	5 (100.0%)	51 (87.9%)	
Prevena	7 (13.2%)	0 (0.0%)	7 (12.1%)	
Endometritis prior to discharge	5 (0.6%)	1 (1.0%)	6 (0.6%)	0.51[c]
Penicillin allergy				< 0.0001[b]
Nonallergic	791 (95.8%)	21 (20.4%)	812 (87.4%)	
Allergic	35 (4.2%)	82 (79.6%)	117 (12.6%)	
Type I penicillin allergy reaction				< 0.0001[c]
No- or low-risk penicillin allergy	819 (99.2%)	74 (71.8%)	893 (96.1%)	
Type I penicillin allergy	7 (0.8%)	29 (28.2%)	36 (3.9%)	

Abbreviations: BMI, body mass index; NPWT, negative pressure wound therapy; SSI, surgical site infection; Q1, 1st quartile; Q3, 3rd quartile.
[a]Wilcoxon's rank-sum test.
[b]Chi-square test.
[c]Fisher's exact test.

increased odds of SSI included delivery BMI (OR = 1.03; 95% CI = 1.01–1.06; $p = 0.01$), and CD during labor (OR = 1.86; 95% CI = 1.10–3.12; $p = 0.02$).

The overall prevalence of self-reported allergies was 12.6%. Among the penicillin-allergic population, 69.2% of individuals reported a low-risk allergy. In the non-β-lactam group, 79.6% reported being allergic to penicillin. Patients with a non-type I penicillin allergy tended to receive appropriate antibiotics more often than those with a type I allergy (91.7 vs. 80.6%; $p = 0.03$).

Table 2 Association between β-lactam and surgical site infection controlling for potential confounders

Covariate	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	*p*-Value[a]
Beta-lactam	0.42 (0.23, 0.77)	0.43 (0.22, 0.83)	0.01
Chorioamnionitis	1.54 (0.59, 4.02)	0.82 (0.28, 2.34)	0.70
Cesarean during labor	1.75 (1.06, 2.87)	1.86 (1.10, 3.12)	0.02
Endometritis	6.29 (1.13, 34.9)	5.33 (0.93, 30.8)	0.06
Tobacco use	1.22 (0.54, 2.75)	1.06 (0.46, 2.48)	0.89
Delivery BMI	1.03 (1.01, 1.06)	1.03 (1.01, 1.06)	0.01

Abbreviations: BMI, body mass index; CI, confidence interval.
[a]From multivariable logistic regression model.

Discussion

Our study shows that receiving β-lactam antibiotics is associated with lower odds of CD SSI compared with non-β-lactams.

Our findings are consistent with recent gynecologic literature, which suggests that β-lactam perioperative antibiotics are associated with the lowest risk of SSI compared with alternative regimens.[16] To date, only one study has investigated the effectiveness of β-lactam perioperative prophylaxis in obstetric populations. Hopkins et al retrospectively evaluated 22,875 women that delivered via prelabor cesarean and received perioperative antibiotics. The composite primary outcome included wound infection, seroma, hematoma, endometritis, maternal hospital readmission due to a wound complication, and need for wound debridement. In this study, patients who received non-β-lactam antibiotics were more likely to have a wound complication, including infection, compared with those who received β-lactam antibiotics (14.6% vs. 6.7%; $p = 0.02$).[1] Findings from that study are not truly generalizable to present day cesarean surgical practices given the use of staples rather than subcuticular suture for skin closure and antibiotic prophylaxis given after cord clamping rather than preoperatively.[1]

ACOG recommends a single dose of first generation cephalosporin for perioperative prophylaxis at time of cesarean. Cefazolin is a bactericidal antibiotic that provides coverage against common gram positive organisms found in skin flora and many gram negative organisms, such as *Escherichia coli*.[19] Gentamicin is also bactericidal and covers gram negative organisms, while clindamycin is bacteriostatic and covers gram positive organisms. As gram positive bacteria are the most common organisms isolated from cesarean wound infection,[20] the bactericidal nature of cefazolin may help to explain the lower infectious morbidity associated with its use. Another potential contributing factor could be the decreased antibacterial activity of gentamicin and clindamycin[21,22] that occurs with decreasing tissue pH and acidic environment that occurs normally at a surgical incision site.[23]

In patients with a type I sensitivity to β-lactam antibiotics, consideration may be given to penicillin allergy testing to confirm the presence of a true allergy. In women with a confirmed allergy to penicillin, alternative antibiotics must be used, but women receiving the currently recommended antibiotics are at higher risk for postoperative infection than women receiving a first-generation cephalosporin.

The strengths of this study include uniform surgical practice within one institution, perioperative antibiotics prior to skin incision, and documented postpartum follow-up. These results are generalizable to tertiary care academic medical centers. The limitations of this study include its retrospective design and reliance on self-reported penicillin allergy. In addition, the dose of 80 mg gentamicin is likely suboptimal in a population with a median BMI above 30 and could have contributed to the increased risk of infection seen in the non-β-lactam group.

Our findings demonstrate the need for educational initiatives regarding appropriate use of antibiotic prophylaxis in patients with a documented β-lactam allergy. Women with a documented β-lactam allergy should receive a cephalosporin if the penicillin allergy is not a type I reaction. In addition, allergy testing for women with reported penicillin allergy would greatly increase access to the appropriate perioperative antibiotic for cesarean prophylaxis. In patients that do require non-β-lactams antibiotics, optimal dosing of both the gentamicin and clindamycin is an important consideration. Further research into alternative non-β-lactam antibiotic regimens is also warranted.

Paper Presentation
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Disclosure
The authors report no conflicts of interest to declare.

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