Safety of Cefazolin in Pregnant Patients with Documented Penicillin Allergy: A Retrospective Cohort Study

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ABSTRACT

Background: The antibiotic cefazolin is commonly used in pregnancy, as first-line prophylaxis for cesarean section wounds or as an alternative to penicillin for prophylaxis against group B *Streptococcus*. About 10% of people report a penicillin allergy, and clinicians have historically avoided the use of β-lactams (including cefazolin) in these individuals. Instead, they have used non-β-lactams, which can lead to poorer maternal outcomes.

Objective: To evaluate the safety of cefazolin in pregnant patients with a documented history of penicillin allergy.

Methods: This retrospective cohort study included all pregnant patients with a documented penicillin allergy at the time of receiving their first dose of cefazolin at a large tertiary care hospital (January 2016 to August 2021). Descriptive statistics were calculated.

Results: A total of 179 patients were included in the analysis. Most (175 [97.8%]) had no allergic adverse event after receiving cefazolin. Two patients (1.1%) experienced immunoglobulin E (IgE)–mediated hives, and 2 patients (1.1%) experienced non–IgE-mediated rashes. No patients experienced anaphylaxis, and no patients with a documented history of anaphylaxis to penicillins experienced an allergic adverse event related to cefazolin. All 4 patients who experienced an allergic adverse event were discharged with no readmission to the study institution associated with the allergic adverse event.

Conclusion: No patients with a documented history of anaphylaxis to penicillin experienced an allergic adverse event upon receiving cefazolin. Cefazolin was safely given to pregnant people with a history of penicillin allergy.

Keywords: cefazolin, obstetrics, pregnancy, penicillin allergy, β-lactam allergy

RÉSUMÉ

Contexte : La céfazoline est un antibiotique couramment utilisé pendant la grossesse comme prophylaxie de première intention pour les plaies opératoires de césarienne ou comme solution de rechange à la pénicilline pour la prophylaxie contre le streptocoque du groupe B. Environ 10 % des personnes déclarent être allergiques à la pénicilline et les cliniciens ont par le passé évité l'utilisation des β-lactamines (y compris la céfazoline) chez ces patients, préférant des antibiotiques non β-lactamines, ce qui peut entraîner des résultats maternels moins favorables.

Objectif : Évaluer l'innocuité de la céfazoline chez les patientes enceintes ayant des antécédents attestés d'allergie à la pénicilline.

Méthodologie : Cette étude de cohorte rétrospective incluait toutes les patientes enceintes ayant une allergie attestée à la pénicilline au moment de recevoir la première administration de céfazoline dans un grand hôpital tertiaire (de janvier 2016 à août 2021). Des statistiques descriptives ont été calculées.

Résultats : Un total de 179 patientes ont été incluses dans l'analyse. La plupart (175 [97,8 %]) n'avaient connu aucun antécédent d'événement indésirable allergique lié à la céfazoline. Deux patientes (1,1 %) ont eu de l'urticaire médiée par les immunoglobulines E (IgE), et des éruptions non médiées par les IgE se sont produites chez deux autres (1,1 %). Aucune patiente n'a connu d'anaphylaxie, et aucune ayant des antécédents attestés d'anaphylaxie aux pénicillines n'a connu d'événement allergique lié à la céfazoline. Les 4 patientes ayant connu un événement indésirable allergique ont quitté l'établissement étudié lié à cet événement sans y être réadmises.

Conclusion : Aucune patiente ayant des antécédents attestés d'anaphylaxie à la pénicilline n'a vécu d'événement indésirable allergique après avoir reçu de la céfazoline. La céfazoline a été administrée en toute sécurité aux personnes enceintes ayant une allergie à la pénicilline.

Mots-clés : céfazoline, obstétrique, grossesse, allergie à la pénicilline, allergie aux β-lactamines

INTRODUCTION

Cefazolin is commonly prescribed during pregnancy for the treatment of infections, for surgical prophylaxis related to cesarean section, and as an alternative to penicillin for prophylaxis against group B *Streptococcus* (GBS). Penicillin allergy is one of the most commonly reported drug allergies, with up to 10% of individuals, including pregnant people, reporting a history of an allergic reaction.[1-3] Historically, clinicians have avoided β-lactam antibiotics, including cefazolin, in penicillin-allergic patients and instead have used non-β-lactam antibiotics (e.g., clindamycin, vancomycin,

or erythromycin) because of concerns regarding cross-reactivity. The use of non-β-lactam alternatives, such as clindamycin, has been associated with poorer maternal outcomes, including increased frequency of wound infections, increased length of hospital stay, and more adverse events.[4,5]

Historically, cross-reactivity between penicillins and cephalosporins, involving type I allergies (immunoglobulin E [IgE]–mediated), was attributed to the β-lactam ring; however, more recent data have suggested that cross-reactivity is associated with similarities in the side chains of the drug molecules.[6,7] Cefazolin does not share any similar side chains with penicillins (or any β-lactam antibiotic); therefore, even patients with severe type I penicillin allergies (e.g., anaphylaxis) can safely receive cefazolin.[7-12]

A growing body of literature reports the safe use of cefazolin in patients with type I penicillin allergies. However, despite the data available from the nonpregnant population, there is a dearth of evidence describing the safe use of cefazolin in the pregnant population.[13,14] Although there is no literature suggesting a difference in safety for the pregnant population, current guidelines from both the Society of Obstetricians and Gynaecologists of Canada and the American College of Obstetricians and Gynecologists recommend against the use of cefazolin in high-risk penicillin-allergic patients—defined as patients with a history of anaphylaxis, angioedema, respiratory distress, or significant urticaria—recommending instead the use of less effective non-β-lactam antibiotics.[15-18]

Extrapolating from the literature pertaining to nonpregnant patients (and anticipating no difference in safety due to pregnancy), our institution, a large tertiary care hospital in British Columbia, decided in November 2018 to use cefazolin in pregnant patients with documented penicillin allergies (including anaphylaxis) when it was indicated as first-line therapy or as an alternative to penicillin. At the time of our study, the impact of this practice change had not yet been assessed.

In this study, we aimed to assess this practice change and also address the gap in the literature by contributing relevant data from the pregnant population. The primary objective was to describe the safety of cefazolin in pregnant patients with a documented history of penicillin allergy. The secondary objectives were to describe the prevalence of allergic adverse events related to cefazolin in penicillin-allergic patients, to describe the outcomes for any patients who experienced an allergic adverse event after receiving cefazolin, and to describe nonallergic adverse drug events (ADEs) associated with cefazolin.

METHODS

Study Design

A retrospective cohort study was conducted. All pregnant patients with a documented penicillin allergy at the time of receiving their first dose of cefazolin at the study hospital, from January 1, 2016, to August 31, 2021, were included in the analysis. Patients were identified from the pharmacy database on the basis of documented allergy history and a prescription for cefazolin. Data were collected by a single investigator (C.C.) using a standardized electronic data collection form within the Research Electronic Data Capture (REDCap) tool.[19] Quality assurance, to ensure the accuracy and integrity of data collection, was based on duplicate data extraction by a second investigator, working independently, for 10% of the health records. The association between cefazolin and nonallergic ADEs was assessed with the Naranjo scoring tool, where a score of 0 or below indicates a doubtful association, a score of 1 to 4 indicates a possible association, a score of 5 to 8 indicates a probable association, and a score of 9 or above indicates a definite association.[20] All events with a Naranjo score of 1 or above were reported.

This study was approved by the institution's research ethics board. The research was conducted in accordance with the ethical standards of the research ethics board and the Helsinki Declaration.

Definitions

The following definitions were applied in this study.

Penicillin allergy was defined as an immunologically mediated response to a penicillin in a sensitized person.[1] Signs and symptoms that characterize a penicillin allergy include the following[21,22]:

- IgE-mediated hypersensitivity reaction, specifically anaphylaxis, skin or mucosal reaction (e.g., generalized hives, pruritus, flushing, and/or swelling of the lips, tongue, or uvula), respiratory symptoms (e.g., shortness of breath, wheeze, cough, or stridor), and gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting).
- Non–IgE-mediated hypersensitivity reaction, specifically antibody-dependent cytotoxic reaction (e.g., hemolytic anemia, thrombocytopenia, neutropenia), antibody complex–mediated reaction (e.g., glomerulonephritis, vasculitis, serum sickness, drug fever), or delayed-onset hypersensitivity reaction (e.g., Stevens–Johnson syndrome, toxic epidermal necrolysis).

Anaphylaxis was defined by the occurrence of any one of the following 3 sets of criteria[21]:

- Sudden onset of illness, with involvement of skin and/or mucosal tissue (e.g., hives, pruritus, flushing, or swelling of lips, tongue, or uvula) and either sudden respiratory symptoms (e.g., shortness of breath, cough, wheeze) or sudden hypotension, and/or associated symptoms of end-organ dysfunction (e.g., hypotonia, incontinence).
- Two or more of the following symptoms occurring suddenly after exposure to penicillin: skin or mucosal symptoms (e.g., hives, pruritus, flushing, or swelling of lips, tongue, or uvula), respiratory symptoms (e.g., shortness of breath,

cough, wheeze), sudden hypotension and/or associated symptoms of end-organ dysfunction, or sudden gastrointestinal symptoms (e.g., abdominal pain, vomiting).
- Hypotension after exposure to penicillin, defined as systolic blood pressure below 90 mm Hg or a decrease of 30% or more from baseline after exposure.

Length of stay was defined as the time from administration of cefazolin to discharge (in hours). If the patient experienced a hypersensitivity reaction to cefazolin, the time from reaction to discharge was also collected.

Safe tolerability of cefazolin was defined, in the context of this study, as administration of cefazolin to pregnant people with documented penicillin allergy and no subsequent documented allergic adverse event.

Statistical Analysis

Descriptive statistics were calculated, including the mean and standard deviation or median and range for continuous variables. Statistical analysis was performed using Excel spreadsheet software, version 16.82 (Microsoft Corporation).

RESULTS

In total, 179 patients were included in the analysis (Table 1). Of the documented histories of penicillin allergy, most patients had a non–IgE-mediated, nonsevere/unspecified rash (43.0%). Nineteen patients (10.6%) had a documented history of anaphylaxis to penicillin, and 9 patients (5.0%) had a documented history of a positive skin test with penicillin. For most patients (73.2%), the timing of their penicillin allergic reaction was not documented; however, of the 48 patients with documentation of timing, most (n = 45, 93.8%) reported a childhood penicillin allergy.

Most patients (175 [97.8%]) had no allergic adverse event after receiving cefazolin (Figure 1). No patients experienced anaphylaxis to cefazolin. Two patients experienced IgE-mediated hives, which were managed with a first-generation antihistamine. Two patients experienced mild non–IgE-mediated rashes. One of these patients experienced a delayed-onset (> 72 hours) rash after a single dose of cefazolin, which resolved with no drug therapy. The other patient experienced a red rash on one arm approximately 36 hours after receiving a single dose of cefazolin, which resolved without drug therapy. Of these 4 patients who experienced an allergic adverse event after receiving cefazolin, 2 patients (50%) had an unknown history of penicillin allergy, 1 patient (25%) had a documented history of hives after receiving penicillin, and 1 patient (25%) had a documented history of non–IgE-mediated rash. No patients with a documented history of anaphylaxis to penicillin experienced an allergic adverse event after receiving cefazolin. All 4 patients were discharged with no readmission to our institution associated with the allergic adverse event (Table 2).

TABLE 1. Characteristics of Patients, Prior Reactions, and Cefazolin Therapy

Characteristic	No. (%) of Patients[a] (n = 179)
Patients	
Age (mean ± SD)	
Maternal (years)	33.7 ± 5.3
Gestational (weeks)	37.0 ± 4.4
Medications received before cefazolin	
H_2 receptor antagonist	76 (42.5)
Systemic corticosteroids	17 (9.5)
First-generation antihistamine	16 (8.9)
Second-generation antihistamine	1 (0.6)
Medical conditions	
Asthma	12 (6.7)
Autoimmune disease	9 (5.0)
Atopic dermatitis	1 (0.6)
Penicillin allergy history	
IgE-mediated reaction[b]	87 (48.6)
Skin or mucosal reaction	59 (33.0)
Anaphylaxis	19 (10.6)
Respiratory symptoms	2 (1.1)
Other: positive skin test	9 (5.0)
Non–IgE-mediated reaction[b]	79 (44.1)
Antibody complex–mediated reaction	1 (0.6)
Delayed maculopapular rash	1 (0.6)
Nonsevere/unspecified rash	77 (43.0)
Other	1 (0.6)
Unknown reaction	19 (10.6)
Time between documented reaction to penicillin and current care	
< 3 months	1 (0.6)
3–12 months	0
13–59 months	1 (0.6)
5–10 years	1 (0.6)
> 10 years	45 (25.1)
Unknown	131 (73.2)
Cefazolin use	
Indication[c]	
Surgical prophylaxis for cesarean section	102 (57.0)
Group B *Streptococcus* prophylaxis	83 (46.4)
Chorioamnionitis	36 (20.1)
Skin and soft-tissue infection	2 (1.1)
Other (bacteremia, dilation and curettage)	3 (1.7)
Unknown	1 (0.6)
Frequency of administration	
Once	89 (49.7)
Every 8 hours	77 (43.0)
Once daily	1 (0.6)
Other	12 (6.7)
Cefazolin dosing information (mean ± SD)	
Initial dose (g)	2 ± 0.5
Total no. of doses	2 ± 3

IgE = immunoglobulin E, SD = standard deviation.
[a]Except where indicated otherwise.
[b]There is overlap in the characteristics of penicillin allergy, and an individual patient could have more than one documented allergy symptom.
[c]An individual patient could have more than one indication for cefazolin use.

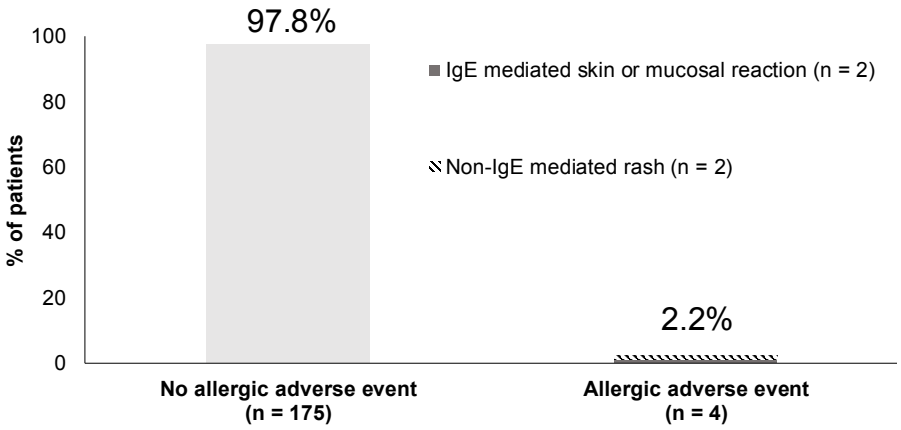

FIGURE 1. Cefazolin safety outcomes (n = 179), presented as the proportion of pregnant patients with a history of penicillin allergy who safely tolerated cefazolin versus the proportion who experienced an allergic adverse event related to cefazolin. Among those who experienced an allergic adverse event, 2 (1.1%) experienced hives mediated by immunoglobulin E (IgE), and 2 (1.1%) experienced non–IgE-mediated rashes.

Nonallergic ADEs associated with cefazolin were frequent (Table 3). For all of the reported nonallergic ADEs, the associated Naranjo score was 3 or below, indicating a possible association between cefazolin and the adverse event. Of the 80 patients who experienced nonallergic ADEs, 7 (8.8%) reported isolated subjective pruritus during their admission, and the median Naranjo score for the association between subjective pruritus and cefazolin was 1. Of these 7 patients, 6 had received an epidural during their admission. A Naranjo score to characterize the association between the epidural and subjective pruritus was also calculated; the median Naranjo score for this association was 2 (range 2–3).

TABLE 2. Outcomes of Allergic Adverse Events Related to Cefazolin

Outcome	No. (%) of Cases[a] (n = 4)
No. of cefazolin doses before reaction (median and range)	1 (1–3)
Length of stay (hours) (median and IQR)	
First dose to discharge	128.5 (47)
Allergic adverse event to discharge	70.9 (36)
Drug management of allergic adverse event	
First-generation antihistamine	2 (50)
Epinephrine	0
Inhaled β_2 agonist	0
Corticosteroid	0
None	2 (50)
Hospital ward where reaction took place	
Antepartum	1 (25)
Postpartum	2 (50)
Labour and delivery	1 (25)
Transfer of care to a higher-acuity ward	0
Delivery required	0
Discharged with no readmission associated with reaction	4 (100)

IQR = interquartile range.
[a]Except where indicated otherwise.

DISCUSSION

Most pregnant people with a documented history of penicillin allergy, including anaphylaxis, safely tolerated cefazolin with no allergic adverse event. Four patients experienced allergic adverse events after receiving cefazolin, all of which were mild reactions requiring minimal intervention. No patients experienced anaphylaxis secondary to cefazolin. There is an abundance of research characterizing the safe use of cefazolin in penicillin-allergic patients, specifically in the nonpregnant population. There are no data to suggest

TABLE 3. Nonallergic Adverse Events Associated with Cefazolin (n = 179)

Nonallergic Adverse Event[a]	No. (%) of Patients	Median Naranjo Score (Range)[b]
Any	80 (44.7)	–
Nausea and/or vomiting	43 (24.0)	3 (2–3)
Dizziness	18 (10.1)	2
Abdominal pain	8 (4.5)	2
Headache	8 (4.5)	2
Diarrhea	6 (3.4)	3

[a]Patients could report more than one adverse event.
[b]Where the median Naranjo score is reported with no range, all patients had the same score for the specified nonallergic adverse event.

any differences in safety of cefazolin in the pregnant population. However, to our knowledge, this is the first study to characterize the safe use of cefazolin in the pregnant population regardless of the severity of the previously documented penicillin allergy.[7,9,10,12]

In this study, we included all patients with a documented history of any penicillin allergy, including a history of positive skin test or anaphylaxis. In a previous retrospective cohort study, published in 2011, Critchfield and others[13] reported that non-β-lactam antibiotics were prescribed for GBS prophylaxis in 76% of patients with high-risk penicillin allergy, in accordance with national guidelines. However, the study sample included no patients with a history of anaphylaxis who received cefazolin. Another retrospective cohort study, published in 2016, described the safety of cefazolin for GBS prophylaxis in non-anaphylactic penicillin-allergic pregnant patients.[14] Although the authors concluded that cephalosporins were underutilized in this population, with 44.2% of their patient population receiving cefazolin or penicillin, they did not describe the rate of allergic adverse events within this population or the safety of cefazolin in high-risk penicillin-allergic patients.[14] Current guidelines of the Society of Obstetricians and Gynaecologists of Canada and the American College of Obstetricians and Gynecologists recommend against the use of cefazolin for high-risk penicillin-allergic pregnant patients.[15-18] In our study, 10.6% of patients had a documented history of anaphylaxis and 5.0% had a documented history of a positive skin test with penicillin, all of whom were able to safely tolerate cefazolin. No patients with a documented history of anaphylaxis to penicillin had an allergic adverse event after receiving cefazolin.

Almost half of the patients received an H_2 receptor antagonist before cefazolin, and others received first- or second-generation antihistamines or systemic corticosteroids. These medications were given as part of standard antenatal care, not as premedication or for the prevention of allergic adverse events. There is a lack of data to support the use of these drug therapies as premedications to prevent severe allergic adverse events, because they are not effective in preventing anaphylaxis and would not have masked the onset of a severe allergic adverse event in our study.[21,23] Although these medications may be used to alleviate symptoms of urticaria or pruritus during an allergic adverse event or for the management of mild cutaneous symptoms, they are likely to contribute to delay of first-line therapies and are ineffective for the acute management of anaphylaxis or severe adverse allergic events.[21,24,25]

This study also described nonallergic ADEs and their association with cefazolin. In particular, we found that 44.7% of patients may have had nonallergic ADEs related to cefazolin. Previous retrospective studies examining cefazolin exposure in penicillin-allergic pregnant patients did not report nonallergic ADEs or their association with cefazolin exposure.[13,14] For all events reported in our study, the associated Naranjo score was 3 or below, indicating a possible association between the event and exposure to cefazolin. A possible association is present when the reaction follows a temporal sequence after administration of a drug and may follow a recognized pattern for the suspected drug; however, there could be another equally likely explanation for the event and/or there is uncertainty or lack of information.[20] We took a conservative approach and reported any adverse event; however, in doing so, we may have reported some adverse events with low probability of being associated with cefazolin. In general, cefazolin is a well-tolerated antibiotic with minimal adverse effects.[26] The high proportion of nonallergic ADEs reported in our study could also be secondary to the patients' labour and delivery. Nausea and/or vomiting, dizziness, abdominal pain, headache, and diarrhea are commonly reported events that may be associated with labour and delivery, postpartum complications, and other concomitant medications given antepartum.[27,28]

Among the 80 patients in this study who experienced nonallergic ADEs, almost 10% also experienced subjective pruritus during their admission. Subjective pruritus or neuraxial opioid-induced pruritus is a commonly reported adverse event that occurs secondary to an epidural and is reported in 60% to 100% of patients.[27] Of the 7 patients in our study who experienced subjective pruritus, 6 had received an epidural during their admission. All 6 of these patients were treated effectively with nalbuphine, an opioid antagonist used for the management of epidural-induced subjective pruritus.[29] The median Naranjo score for the association between subjective pruritus and epidural was higher than the Naranjo score for the association between subjective pruritus and cefazolin (2 vs. 1). It is unlikely that these cases of subjective pruritus were allergic adverse events related to cefazolin because they were characterized by pruritus alone, with no associated skin, mucosal, respiratory, gastrointestinal, or systemic allergic signs and symptoms. Nalbuphine is ineffective for the management of an allergic adverse event.

The limitations of our study include its retrospective nature and the small sample size. More specifically, the study population included only a limited number of patients with documented history of anaphylaxis to penicillin. Additionally, the nature of the penicillin allergy and detailed allergy histories were not consistently documented in patients' medical records, and those that were documented were likely based on patient reporting and hence were not verifiable. We included all patients with unknown reactions to penicillin, as well as patients with documented nonspecific, unspecified rashes related to penicillin. This approach may have led to an overestimation of the number of true penicillin allergies captured within this patient population. Patients with unknown or childhood penicillin allergies were also included. By 5 years after the occurrence

of an allergic event, approximately 50% of people will outgrow their penicillin allergy, and at 10 years, this proportion increases to 80%.[1,30,31] Despite these limitations, we demonstrated the safe use of cefazolin among patients with a documented history of anaphylaxis to penicillin.

Another limitation was that this study captured only encounters at our own institution. Patients may have already been exposed to and tolerated cefazolin at other sites before admission to our institution. Also, we reviewed only readmissions to our institution related to allergic adverse events to cefazolin; patients who experienced delayed allergic adverse events related to cefazolin after discharge from our institution and were admitted to another institution would not have been captured in this study. Lastly, we were unable to assess neonatal outcomes for patients who had an allergic adverse event related to cefazolin; however, none of the allergic adverse events resulted in delivery, and all were considered mild, requiring minimal to no intervention.

CONCLUSION

Most pregnant people with a documented history of penicillin allergy who received cefazolin tolerated the drug with no subsequent allergic adverse event. None of the patients with a documented history of anaphylaxis to penicillin experienced an allergic adverse event related to cefazolin. Cefazolin may safely be given to pregnant people with a history of penicillin allergy.

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