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HAL Id: hal-02566589

https://hal.univ-lille.fr/hal-02566589v1

Submitted on 7 May 2020

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Short title: Classification of penicillin allergies in pregnant women (56 characters)

Word count = 2280 words

Word count = 233 words

ABSTRACT

Background: Most pregnant women self-reporting penicillin allergy are not truly penicillin-allergic, and this misunderstanding often leads to administration of inappropriate antibiotic therapy. Decision algorithms have been developed to guide antibiotic selection, but major discrepancies have been reported between guidelines and clinical practice. We aimed to optimize the prescription of antibiotics for pregnant women who self-reported penicillin allergy, using an educational intervention about classification of penicillin allergies that targeting gynecologists, anesthesiologists and midwives.

Methods: This quasi-experimental study intended to assess the effect of an educational intervention about penicillin allergy classification. For 6 months, a combination of two strategies were used: dissemination of printed educational materials and group education. The principal endpoint was the appropriateness of the antibiotic therapy, defined in advance for each level of allergic risk.

Results: The preintervention portion of the study included 903 women; one year after its conclusion, the postintervention portion began and included 892 women. The prevalence of self-reported penicillin allergies was stable over the two periods (6.8% before vs. 5.4% after, $P$=0.24). The clinical classification of penicillin allergies was more often used after the educational intervention (68.0 vs. 100.0%, $P$<0.001). The appropriateness of the antibiotic therapy prescribed for self-reported penicillin allergic-women increased significantly between the two periods (5/29 (17.2%) vs. 18/27 (66.7%), $P$<0.001).

Conclusion: An educational intervention about penicillin allergy classification was associated with an improvement in choice of appropriate antibiotic therapy in women who reported penicillin allergy.

## INTRODUCTION

Worldwide, infection is one of the leading causes of both maternal and neonatal mortality[1]. Antibiotics have made maternal sepsis related mortality a rare event, and the frequency of maternal-fetal infections has fallen substantially[2]. Overall, 15% of pregnant women receive antibiotics during pregnancy[3] and 55% at delivery[4]. β-lactams are among the most useful antibiotics, because of their efficacy, tolerability, and safety for use during pregnancy. *Streptococcus agalactiae* is responsible for more than half of maternal-fetal infections[5], and almost all isolates are highly susceptible to penicillins[6].

Around 5 to 10% of adults report a history of penicillin allergy[7]; the frequency among pregnant women is similar[8, 9]. Penicillin-allergic patients often receive macrolides, which can result in lower efficacy, especially as resistance is present in 20 to 30% of cases for *S. agalactiae*[10]. However, between 80 and 90% of women who self-report a history of penicillin allergy able are actually able to tolerate penicillin and could be treated with a β-lactam[11]. Decision algorithms have been developed to guide selection of appropriate antibiotic in patients with suspected penicillin allergy[12, 13].

In pregnant women, specific guidelines were issued for the prevention of *S. agalactiae* perinatal infection[14]. According to these guidelines, women are at high risk of anaphylaxis if they report at least one of the following four clinical responses following administration of a penicillin or a cephalosporin: anaphylaxis, angioedema, respiratory distress, or urticaria. Among those who self-reported penicillin allergy but did not present these symptoms, treatment by cefazolin (a first-generation cephalosporin) is recommended. However, in clinical practice, only 14% to 44% of the women at low risk for anaphylaxis received cefazolin for the prevention of *S. agalactiae* perinatal infection[8, 15].

Another frequent cause of antibiotic prescription during pregnancy is prophylaxis for cesarean delivery. First-line treatment is cefazolin, except for women at high risk of anaphylaxis following administration of penicillins or cephalosporins[16]. However, in a recent study more than 50% of the women that received alternative antibiotics were not at high risk of anaphylaxis and should have received cefazoline[17]. Thus, there can be major discrepancies between guidelines and clinical practice in pregnant women.

The objective of our study was to optimize the prescription of antibiotics for pregnant women self-reporting penicillin allergy, through an educational intervention about classification of penicillin allergies targeting gynecologists, anesthesiologists and midwives.

METHODS

This quasi-experimental study intended to assess the effect of an educational intervention about penicillin allergy classification. The target population of the intervention was the hospital staff potentially prescribing antibiotics for pregnant women (gynecologists, anesthesiologists, midwives). It took place in a single university hospital.  Approval of the study was obtained from the French Data Protection Authority (CNIL) under number DEC2015-86.

One year before the beginning of the study, we proposed a standardized protocol of penicillin allergy classification based on allergy history. This classification was validated by interdisciplinary consensus between the allergy, anesthesiology, bacteriology, infectious diseases, gynecology and obstetrics teams of our hospital. Three levels of risk were defined, associated with recommendations of antibiotic therapy (Table 1). Level 0 is defined by symptoms not usually associated with penicillin allergies. In this situation, treatment by penicillin is recommended if indicated. At level 1, the existence of a severe allergic reaction is considered improbable; penicillins are contraindicated but cefazolin is recommended. At level 2, the probability of a severe allergic reaction is judged high and all β-lactams are contraindicated. The penicillin allergy classification was available in local prescribing resources from June 2014.

We conducted an educational intervention to bring this classification to the staff's attention. For 6 months (from July 2015 to December 2015), a combination of two strategies were used: dissemination of printed educational materials and group education. Posters of the classification were displayed in the prenatal and anesthesia examining rooms as well as in the delivery rooms. It was included in the pocketbook given to medical residents on their first day of arrival. The classification was formally presented to all the hospital staff potentially prescribing antibiotics for pregnant women. During weekdays morning reports, on which complicated deliveries from the last 24 hours are discussed, each time penicillin allergy was reported the penicillin allergy classification was reminded and feedback was provided. After the intervention period, the penicillin allergy classification continued to be presented to the new staff joining (mainly medical residents), but there was no specific focus during weekday morning reports.

To measure the effect of the educational intervention, two periods were studied. The preintervention period took place from March 1 to May 29, 2015. The postintervention period began from August 1 to October 26, 2016. Consecutive women having given birth during these periods were eligible to inclusion, even if the pregnancy had resulted in termination or an in-utero death. Only women with multiple pregnancies were excluded. Maternal and neonatal data were collected from the medical files: social and demographic characteristics, obstetric history, data related to pregnancy, delivery, and the newborn. All the antibiotic prescriptions during pregnancy or delivery were also collected for all women who reported penicillin allergy.

The antibiotic therapy was considered appropriate when the allergy was classified according to the three predefined levels of risk, and the recommended antibiotic therapy was prescribed; it was considered incorrect in all other cases, including when the allergic risk level was not reported in the medical file. When penicillin was indicated as a first-line treatment (e.g. prevention of *S. agalactiae* neonatal disease), the recommended antibiotic therapy was penicillin for risk level 0, cefazolin for risk level 1, non-β-lactams for risk level 2. When cefazolin was indicated as a first-line treatment (e.g. antibiotic prophylaxis for cesarean section), the recommended antibiotic therapy was cefazolin for risk level 0 and 1, non-β-lactams for risk level 2.

The statistical analysis was performed with R Software[18]. Qualitative variables were compared with Fisher's exact test or the Chi-2 test, and continuous variables with Student's t-test. Percentages are reported in parentheses, and means are reported with the standard deviation of the distribution. The principal endpoint was the appropriateness of the antibiotic therapy prescribed to women having given birth, defined in advance for each level of allergic risk. Secondary study outcome was the percentage of self-reported penicillin allergies correctly classified in the medical records. A *P*-value less than 0.05 was considered statistically significant.

RESULTS

There were 998 deliveries during the preintervention period and 971 deliveries in the postintervention period (Figure 1). After exclusion of multiple pregnancies and of records that could not be located, 903 and 893 women, respectively, were included.

The women in both study periods were representative of the hospital's patient population. The two groups were comparable for almost all their general and obstetric characteristics (Table 2), except for a slight increase in body mass index (BMI) and a reduction in the preterm delivery rate. Reported allergies to penicillin were stable (6.8 vs. 5.4%, $P= 0.24$).

Among the women who reported penicillin allergy, the penicillin allergy classification was more frequently used in the postintervention period (68.9 vs. 100%, $P<0.001$) (Table 3). Around half the women who reported penicillin allergy received at least one antibiotic during pregnancy or delivery, this percentage did not vary significantly between the study periods (47.5 vs. 56.3%, $P=0.44$).

Following the educational intervention, the rate of appropriate antibiotic treatment increased from 17.2 to 66.7% ($P<0.001$) (Table 4). In particular, the rate of cefazolin prescription increased from 7.1 to 38.5% for the women at a low-risk level, though it was not statistically significant ($P=0.07$). Antibiotics were prescribed principally at delivery. No anaphylactic reactions were reported.

Table 5 presents the classes of antibiotics administered during each period, according to the women's allergy risk level. In women for whom a serious allergy was considered improbable (risk level 1), cefazolin use increased between the two periods but this was not significant (7.1% before vs. 38.5% after, $P=0.07$).

DISCUSSION

We investigated the impact of an educational intervention on selection of appropriate antibiotic therapy among women who reported penicillin allergy. Selection of appropriate of antibiotic therapy increased significantly between the two periods (from 17.2% to 66.7%). Our study suggests that an educational intervention could increase the use of a penicillin allergy classification among gynecologists, anesthesiologists, and midwives.

Educational interventions about penicillin allergy have been previously described in the literature[19, 20]. An electronic survey of 323 inpatient providers showed baseline knowledge deficiencies, as 42% reported no prior education in penicillin allergy[20]. After a 10-min educational presentation introducing a penicillin allergy clinical guideline, preparedness to determine if an allergy was severe improved from 77% to 92% ($P$=0.03). Preparedness to prescribe antibiotics to patients with penicillin allergy slightly improved from 66% to 76%, but this was not statistically significant ($P$=0.13)[20]. Another study proposed the use of a computerized algorithm to help healthcare professionals to identify low-risk patients with an inaccurate label of penicillin allergy[19]. However, as this study only demonstrated the feasibility of implementing a computerized algorithm, its effect in clinical practice remains unknown.

The proportion of pregnant women in our study who reported penicillin allergy was around 6% during both periods. This proportion is similar to the general adult population, ranging from 5 to 10%[21-23]. The prevalence of penicillin allergies reported among pregnant women was recently assessed at 8.4% among 170,000 women in California[4]. The prevalence of anaphylaxis during pregnancy is much lower, estimated at 1.6 per 100 000 maternities, and is caused by antibiotics in 49% of cases[24]. In the UK, the primary antibiotics associated with perioperative anaphylaxis were co-amoxiclav (a β-lactam) and teicoplanin[25]. In particular, teicoplanin was 17-fold more likely to cause anaphylaxis than other antibiotics. Therefore, avoiding penicillin in patients who are not truly penicillin-allergic can paradoxically cause more anaphylactic reactions if teicoplanin is used as an alternative.

Among pregnant women, antibiotics are often prescribed during delivery, especially to prevent perinatal *S. agalactiae*[4]. The Centers for Disease Control (CDC) issued specific guidelines in 1996, and updated them in 2002 and 2010[14]. The current guidelines call for pregnant women who are colonized by *S. agalactiae* at the end of the third trimester to be questioned about the specific types of allergic reaction. The use of penicillin or cephalosporins is contraindicated among women who reported severe reactions such as anaphylaxis, angioedema, respiratory distress, or urticaria following administration of penicillins or cephalosporins. These women should receive clindamycin or vancomycin during labor, depending on the antimicrobial susceptibility of the *S. agalactiae* strain. Among pregnant women self-reporting penicillin allergy but without these severe symptoms, treatment by cefazolin (a first-generation cephalosporin) is recommended.

Compared with the CDC classification, our local policy classification was used for this study and covers a broader range of indications for antibiotic therapy during pregnancy and delivery. It also introduces a level 0 of risk for women with symptoms not associated with penicillin allergy (mycosis, fever, vertigo, diarrhea). Isolated diarrhea following β-lactams administration was not considered to be associated with allergy in our classification. Diarrhea might be observed in allergies, but is rarely the only presenting sign[26]. Moreover, diarrhea occurs in 10% of patients treated by amoxicillin-clavulanic acid[27], leading us to include it in risk level 0 (probably not an allergy)[13]. Risk level 0 covered 12.5% of the women during our postintervention period. Such women should be able to receive penicillin, as recommended during labor for colonization by *S. agalactiae*.

We selected cefazolin for women who presented with delayed urticaria after penicillin administration, although the CDC guidelines from 2010 recommend not using β-lactams in this situation. A recent decision algorithm for presumed β-lactam allergy recommended cefazolin for mild symptoms after exposure to penicillin, that included: delayed urticaria and any skin rash occurring > 2h after exposure[13]. Indeed, the most common reaction is the type IV allergic reaction, which is T-cell-mediated and occurs from 2h to several days after the last drug administration.

These nonimmediate reactions usually include skin reactions like delayed urticaria or maculopapular exanthema[28] and pose no risk of anaphylaxis[13].

Cross-reactions between penicillins and cephalosporins are rare[29], and 90% of them are due to a similarity in the R1 side chain, target of an IgE-mediated immune-allergic reaction[30]. Cefazolin does not share this side chain with the penicillins, nor do the third and fourth generation cephalosporins[31]. In two retrospective studies of penicillin-allergic patients treated by cefazolin (n=128 and n=413), only one patient presented an anaphylactic reaction[32, 33]. In another study based on electronic health records, out of 65,915 patients with a history of penicillin allergy, only 3 cases of cephalosporin-associated anaphylaxis (0.004%) were documented [34]. Therefore, cefazolin can be safely administered to most of the patients with a history of penicillin allergy, in case of mild symptoms occurring > 2h after exposure to penicillin.

The quasi-experimental design of our study is one of its limitations. Indeed, the improved appropriateness of antibiotic therapy observed over the two periods might be associated with other factors than the educational intervention. This hypothesis nonetheless appears improbable given the short interval between the two periods and the extent of the difference observed (a year apart and an increase in the appropriateness of antibiotic therapy from 17.2 to 66.7%). Moreover, no major modification of our management protocols took place between the two periods. Patients characteristics were similar, except for a moderate rise in BMI and a reduction in the preterm delivery rate. An increase in BMI was observed among pregnant women throughout France during the same period[35]. However, the pre-term birth rate slightly increased in France between 2010 (6.5%) and 2016 (7.5%)[35]. Another limitation of this study is its monocentric design. This may limit the generalization of our findings.

In conclusion, this study showed that an educational intervention about penicillin allergy classification was associated with an improvement in the selection of appropriate antibiotic therapy in women who reported penicillin allergy. Further studies are warranted to identify the most effective educational strategies to improve the management of patients with suspected penicillin-allergy.

Figure Legend:

Figure 1: Flow chart of the study.

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Table 1. Clinical classification of penicillin allergy depending on the allergy history.

| Self-reported symptoms of penicillin allergy | Risk level |
|---|---|
| Diarrhea, nausea, vomiting, abdominal pain<br>Vertigo<br>Fever<br>Mycosis | **Level 0. Probably no allergy**<br>- No contraindication to penicillins<br>- Use of penicillin desirable if indicated |
| Cutaneous eruption<br>Delayed urticaria<br>Doesn't know | **Level 1. Severe allergy improbable**<br>- Contraindication to penicillins<br>- Cephalosporins desirable<br>      if β-lactams are indicated[a] |
| Hospitalization for allergies<br>Anaphylactic shock<br>Malaise with loss of consciousness<br>Facial edema, angioedema<br>Asthma, respiratory problems, feeling of suffocation | **Level 2. High risk of serious allergy**<br>- Contraindication to all β-lactams |

[a] Prefer cefazolin or third- or fourth-generation cephalosporins.

Table 2. Women's general and obstetric characteristics before or after the educational intervention.

| | Preintervention n= 903 | Postintervention n= 892 | P |
|---|---|---|---|
| Age (years)[a] | 30.7 ± 5.4 | 30.8 ± 5.2 | 0.69 |
| Nulliparous | 351 (38.9%) | 380 (42.6%) | 0.11 |
| Smokers | 123/812 (15.1%) | 102/823 (12.4%) | 0.11 |
| Body mass index (kg/m²)[a] | 24.1 ± 5.3 | 24.7 ± 5.7 | 0.02 |
| Reported allergy to penicillin | 61 (6.8%) | 48 (5.4%) | 0.24 |
| Gestational age at delivery (weeks)[a] | 38.8 ± 2.6 | 38.8 ± 2.7 | >0.99 |
| Preterm birth (Birth < 37 weeks) | 97 (10.7%) | 68 (7.6%) | 0.02 |
| In utero death | 13 (1.4%) | 10 (1.1%) | 0.59 |
| Mode of labor onset | | | |
| - Spontaneous | 9 (67.4%) | 9 (64.9%) | |
| - Induction of labor | 7 (25.1%) | 5 (25.2%) | 0.28 |
| - Cesarean before labor | (7.3%) | (9.3%) | |
| Cesarean delivery | 146 (16.2%) | 173 (19.4%) | 0.07 |
| Birth weight (g)[a] | 3260 ± 650 | 3250 ± 670 | 0.90 |
| Transfer to NICU[b] | 37 (4.0%) | 44 (4.9%) | 0.73 |

[a] Values for age, body mass index, gestational age at delivery and birth weight are mean ± standard deviation.
[b] NICU = Neonatal Intensive Care Unit.

Table 3. Classification of allergies according to allergy history and prescription of antibiotic therapy.

|  | Preintervention n= 61 | Postintervention n= 48 | P |
|---|---|---|---|
| Classification of allergies by history | 42 (68.9%) | 48 (100.0%) | < 0.001 |
| Risk level |  |  |  |
| - 0: Probably no allergy | 2 (3.3%) | 6 (12.5%) |  |
| - 1: Severe allergy improbable | 31 (50.8%) | 27 (56.3%) | 0.18 |
| - 2: High risk of serious allergy | 9 (14.8%) | 15 (31.3%) |  |
| Antibiotic therapy during pregnancy or delivery | 29 (47.5%) | 27 (56.3%) | 0.44 |

Table 4. Antibiotic therapy during pregnancy or delivery among women who self-reported penicillin allergy.

| | Preintervention n= 29 | Postintervention n= 27 | *P* |
|---|---|---|---|
| Appropriateness of the antibiotic therapy | 5 (17.2%) | 18 (66.7%) | < 0.001 |
| | | | |
| Antibiotic therapy | | | |
| - Only during pregnancy | 2 (6.9%) | 3 (11.1%) | |
| - Only during delivery | 22 (75.9%) | 23 (85.2%) | 0.24 |
| - Both | 5 (17.2%) | 1 (3.7%) | |

Table 5. Type of the antibiotics administered depending on the risk level of penicillin allergy.

| Risk level | Preintervention n= 29 | Antibiotic therapy | Postintervention n=27 | p |
|---|---|---|---|---|
| 0<br>Probably no allergy | n=2<br>**1 (50.0%)**<br>-<br>1 (50.0%) | **Penicillins**<br>Cephalosporin<br>Macrolides | n=3<br>**2 (66.7%)**<br>1 (33.3%)<br>- | **>0.99** |
| 1<br>Severe allergy improbable | n=15<br>**1 (7.1%)**<br>3 (14.3%)<br>11 (78.6%)<br>- | **Cephalosporin**<br>Penicillins<br>Macrolides<br>Other* | n=13<br>**5 (38.5%)**<br>-<br>6 (46.2%)<br>2 (15.4%) | **0.07** |
| 2<br>High risk of serious allergy | n=3<br>**3 (100%)**<br>-<br>- | **Macrolides**<br>Penicillins<br>Cephalosporin | n=11<br>**11 (100%)**<br>-<br>- | **> 0.99** |
| Unclassified | n=9<br>1 (11.1%)<br>1 (11.1%)<br>7 (77.8%) | Penicillins<br>Cephalosporin<br>Macrolides | n=0<br>-<br>-<br>- | - |
| Total | 7 (24.1%)<br>*5 (17.2%)*<br>*2 (6.9%)*<br>22 (75.9%)<br>- | β-lactams<br>*- Penicillins*<br>*- Cephalosporins*<br>Macrolides<br>Other[a] | 8 (29.6%)<br>*2 (7.4%)*<br>*6 (22.2%)*<br>17 (63.0%)<br>2 (7.4%) | 0.56[b] |

The antibiotic class in **bold** is recommended for the corresponding risk level.
[a] 2 women received fluoroquinolones, which were more appropriate for the infection (according to the antibiotic susceptibility testing); this antibiotic therapy was considered correct.
[b] β-lactams *vs.* other.