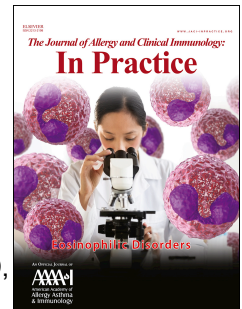


# Journal Pre-proof

## Penicillin Allergy Assessment in Pregnancy: Safety and Impact on Antibiotic Use

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PII: S2213-2198(20)31219-8

DOI: <https://doi.org/10.1016/j.jaip.2020.10.063>

Reference: JAIP 3242

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 5 August 2020

Revised Date: 27 October 2020

Accepted Date: 29 October 2020

Please cite this article as: Wolfson AR, Mancini CM, Banerji A, Fu X, Bryant AS, Phadke NA, Shenoy ES, Arman W, Zhang Y, Blumenthal KG, Penicillin Allergy Assessment in Pregnancy: Safety and Impact on Antibiotic Use, *The Journal of Allergy and Clinical Immunology: In Practice* (2020), doi: <https://doi.org/10.1016/j.jaip.2020.10.063>.

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**Contents:**

Abstract Word count: 253

Text Word count: 3672

Tables: 2

Figures: 3

References: 45

**Funding:**

This work was supported by National Institutes of Health K01AI125631, the American Academy of Allergy Asthma and Immunology Foundation (AAAAI), and the Massachusetts General Hospital Claflin Distinguished Scholars Award. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, AAAAI Foundation, nor the MGH.

**Conflict of Interest:**

KGB and ESS report a licensed clinical decision support tool for inpatient beta-lactam allergy evaluation. NAP reports spousal employment by Chiesi Farmaceutici. ARW, CM, WA, XF, ASB, and AB have nothing to disclose.

**Key words:** C-section; Group B *Streptococcus*; stewardship; antibiotic; hypersensitivity; immunologic; penicillin; cephalosporin; skin test; drug challenge; e-consult; telemedicine

**Abbreviations:**

Group B *Streptococcus*, GBS  
United States, US  
Caesarean section, C-section  
American College of Obstetrics and Gynecology, ACOG  
Massachusetts General Hospital, MGH  
electronic consultations, e-consults  
Allergy/Immunology, AI  
electronic health record, EHR  
immunoglobulin, Ig  
body mass index, BMI  
standard deviation, SD  
interquartile range, IQR  
adjusted odds ratio, aOR  
confidence interval, CI

**ABSTRACT**

**Background:** Penicillin and other beta-lactam antibiotics are recommended for Group B *Streptococcus* (GBS) and Caesarian section prophylaxis, but approximately 10% of pregnant patients report a penicillin allergy.

**Objective:** To assess the safety and impact of proactive penicillin allergy evaluation in pregnant patients.

**Methods:** This was a retrospective electronic health record review of obstetrician-ordered Allergy/Immunology (AI) electronic consultations (e-consults) from September 20, 2017 through December 31, 2019. For patients whose e-consult recommended an in-person AI evaluation, testing outcomes were determined, and multivariable logistic regression models were used to compare antibiotic use between patients who did and did not receive an in-person AI evaluation.

**Results:** Of 389 obstetrician-ordered e-consults, 363 (93%) recommended an in-person AI evaluation; of these, 222 (61%) patients received an in-person AI evaluation. Of 220 (99%) patients skin tested, 209 (94%) had their penicillin allergy label safely removed. Compared to patients who did not receive an in-person AI evaluation despite it being recommended (n=141), patients with in-person AI evaluation had reduced peripartum vancomycin (aOR 0.07 [95% CI 0.01, 0.33]), clindamycin (aOR 0.17 [95% CI 0.08, 0.34]), and gentamicin (aOR 0.39 [95% CI 0.19, 0.78]) use and increased penicillin (aOR 17.95 [95% CI 6.30, 51.16]) use. The fully AI evaluated patients had increased first-line antibiotic prophylaxis for GBS (aOR 26.87 [95% CI 6.32, 114.33]) and Cesarean section (aOR 1.94 [95% CI 1.06, 3.52]).

**Conclusion:** In a sample of 220 pregnant patients with penicillin allergy histories and in-person AI evaluation, penicillin allergy testing was safe and associated with significantly reduced broad-spectrum antibiotic use and increased first-line beta-lactam antibiotic use.

**HIGHLIGHTS BOX****What is already known about this topic?**

First-line treatments for many infections in pregnancy are beta-lactam antibiotics, particularly penicillin.

Although 10% of patients have a reported penicillin allergy, >90% of them are not allergic.

**What does this article add to our knowledge?**

Following 389 electronic-consults, 222 (57%) pregnant patients with a penicillin allergy history had an in-person Allergy/Immunology evaluation, and 209 (94%) had their penicillin allergy label removed.

Compared to patients who did not receive an in-person Allergy/Immunology evaluation despite it being recommended by electronic-consult, fully evaluated patients had reduced broad-spectrum antibiotic use and a 27-fold increased first-line penicillin prophylaxis for Group B *Streptococcus*.

**How does this study impact current management guidelines?**

Penicillin allergy evaluation was safe in the third trimester of pregnancy and was associated with an increased use of recommended antibiotics.

## INTRODUCTION

Although 32 million Americans report penicillin allergy, less than 0.1% of these patients see an allergist for penicillin allergy evaluation.<sup>1,2</sup> Penicillin allergy evaluation, which includes history-appropriate penicillin skin testing and/or oral amoxicillin challenge, is safe in the general population; removal of the penicillin allergy label (“delabeling”) is possible in up to 95% of patients with unconfirmed penicillin allergy histories and is associated with shifts in antibiotic use towards penicillins and other beta-lactam antibiotics.<sup>3,4</sup> Previously, concerns about the safety of penicillin skin testing,<sup>5</sup> anaphylaxis,<sup>6</sup> and epinephrine use<sup>7</sup> in pregnancy precluded allergy testing in pregnant women. However, severe allergic reactions, such as anaphylaxis, are rare,<sup>8</sup> and initial studies demonstrated tolerance of penicillin skin testing and subsequent penicillin use in pregnant women.<sup>9,10</sup> However, the safety of penicillin skin testing followed by oral challenge in pregnant patients has only been evaluated in small cohorts to date.

A history of penicillin allergy in pregnant patients is associated with increased exposure to broad-spectrum antibiotics, increased cost of care, and higher rates of adverse outcomes, such as new adverse drug reactions and longer hospitalizations.<sup>11</sup> Beta-lactam antibiotics are first-line agents for antibiotic prophylaxis and treatment during the peripartum period. Group B *Streptococcus* (GBS) is the leading cause of infection in newborns;<sup>12</sup> the primary risk factor for GBS infection is colonization of the genitourinary tract of the mother, which occurs in 10% to 30% of women.<sup>13,14</sup> Since guidelines were introduced to use penicillin antibiotics to treat GBS in the mother, neonatal infection rates declined by 80%.<sup>12</sup> Similarly, in 2018, approximately one-third of deliveries in the United States (US) were by Caesarian section (C-section),<sup>15</sup> for which cefazolin is recommended to prevent surgical site infections because of its safety<sup>16,17</sup> and effectiveness.<sup>18,19</sup> Because the use of penicillin and other beta-lactams is important for pregnant patients,<sup>20-22</sup> the American College of Obstetricians and Gynecologists (ACOG) encourages penicillin allergy testing in pregnant patients with a reported penicillin allergy.<sup>23</sup>

The Massachusetts General Hospital (MGH) Department of Obstetrics and Gynecology delivers more than 3,500 babies per year, and 12.8% of patients in our hospital system have a reported penicillin

allergy.<sup>24</sup> As such, we designed a feasible program to routinely and proactively evaluate obstetric patients with a reported penicillin allergy. In this study, we present our electronic consultation (e-consult) program design and assess the safety and effectiveness of in-person Allergy/Immunology (AI) assessment on peripartum antibiotic utilization.

## METHODS

### *MGH AI Program for Penicillin Allergy Assessment in Obstetrics*

E-consults are asynchronous, clinician-to-clinician exchanges that rely exclusively on information in the patient's electronic health record (EHR); they are designed to provide focused, patient-specific clinical guidance for non-urgent questions. The referring provider enters an order in the EHR, which is transmitted directly to the "In basket" of the specialist. The specialist reviews the clinical question in the order as well as relevant information in the patient's EHR and provides recommendations in the form of an EHR note. The referring provider is ultimately responsible for the patient's care, including incorporating e-consult recommendations.

MGH AI began e-consults in August 2016;<sup>25</sup> in September 2017, a new e-consult template was established to launch a new program evaluating obstetric patients with reported penicillin allergies. All pregnant patients with a reported penicillin allergy were eligible to receive an e-consult, which had to be requested by their obstetrician. E-consults were completed by a board-certified allergist (ARW, AB, KGB) who, based on the patient's allergy history available in the EHR, determined eligibility for in-person AI evaluation and conveyed antibiotic recommendations. The e-consult system was the only system for MGH Obstetrics to refer to MGH AI.

E-consult recommendations for obstetric patients with a reported penicillin allergy followed a structured approach. Referring obstetricians were advised that penicillin could be used, if indicated, without need for AI assessment for patients with a history of penicillin intolerances, such as gastrointestinal side effects, headaches, or fatigue. Referring obstetricians were advised to avoid all beta-lactams for patients who experienced a severe reaction, such as Stevens-Johnsons Syndrome or drug

reaction with eosinophilia and systemic symptoms, or recurrent reactions to penicillins/beta-lactams. For patients with a potentially immunoglobulin (Ig)E-mediated reaction, such as hives, angioedema, anaphylaxis, respiratory complaints, or any type of rash, within the last 5 years, referring obstetricians were advised to avoid penicillin. Patients with a potentially IgE-mediated reaction greater than 5 years ago were advised to proceed with in-person AI evaluation for history-appropriate penicillin skin testing and drug challenge in the third trimester. Patients with unknown reactions that occurred 5 or more years ago were also advised to come for in-person AI evaluation. Regardless of whether patients presented for the recommended in-person AI evaluation, the e-consult recommendation for patients with potentially IgE-mediated reactions more than 5 years ago encouraged cefazolin use, if needed, by direct challenge/test dose procedure.<sup>26</sup> Five years was chosen as the time period worth re-investigation of the allergy history given: 1) the waning natural history of penicillin allergy,<sup>27,28</sup> 2) lack of minor determinants available for penicillin skin testing<sup>29</sup> and 3) the goal to improve quality and safety in pregnant women given that testing was offered and performed in advance of antibiotic need. The e-consult note was posted in the EHR and routed to the patient's obstetrician; if an in-person AI evaluation was recommended, the e-consult note was routed to the AI front desk pool to facilitate direct patient scheduling during the recommended time-frame.

The in-person AI evaluation included history-appropriate skin testing, percutaneous followed by intradermal (if negative), with penicilloyl-polylysine and diluted Penicillin G;<sup>1,30</sup> ampicillin 20 mg/mL was added as an additional skin test reagent in August 2019.<sup>29,31</sup> Patients with negative skin tests completed an amoxicillin challenge (500 mg PO amoxicillin x 1, 60 minutes of observation). Following in-person AI assessment, the detailed consultation note with updated penicillin allergy label in the EHR was routed to the patient's referring obstetrician.

### *Data Collection and Definitions*

We performed a retrospective study of all Obstetric penicillin allergy e-consults from September 20, 2017 through December 31, 2019. Data were gathered from manual EHR review performed by

trained research assistants (CMM, WA) with allergist oversight (ARW). Study data were collected and managed using REDCap electronic data capture tools.<sup>32,33</sup>

Demographics included age, race, and body mass index (BMI, related to risk of pre-eclampsia and gestational diabetes). Advanced maternal age was defined as 35 years or greater. Obstetric history (i.e., gravidity, parity) was obtained from obstetric encounters.

The exposure was a patients' in-person AI evaluation status, comparing patients who received an in-person AI evaluation after their e-consult to those for whom the e-consult recommended an in-person AI evaluation but who did not receive a formal evaluation.

Our primary outcome was use of antibiotics prescribed (outpatient) and/or administered (inpatient) in the peripartum period, defined as from the first obstetrician visit through 6 weeks post-partum. We assessed use of beta-lactam alternative antibiotics (vancomycin, clindamycin, and gentamicin) and narrow-spectrum beta-lactam antibiotics (penicillin, cefazolin, and cephalexin). We also assessed first-line antibiotic use: penicillin for GBS and cefazolin for C-section prophylaxis. We also divided the peripartum period into three distinct time periods: during pregnancy (from first obstetrician visit to admission for labor and delivery), during labor and delivery, and post-partum (from labor and delivery encounter through 6 weeks post-partum).

We assessed secondary safety-related outcomes that included allergic reactions, term delivery (37 weeks or more), and C-section delivery, determined from labor and delivery records.

This project was approved by the Partners Institutional Review Board protocol number 2012P002458.

#### *Data Analysis*

Data are presented as numbers with frequencies for categorical data and means with standard deviation (SD) or medians with interquartile ranges (IQR) for continuous variables, as indicated. We compared patients' demographics by exposure status of in-person AI evaluation using chi-squared tests.

We examined the relation of patients' in-person AI evaluation status to the prevalence of each of the outcome variables (i.e., antibiotic use, term delivery, C-section delivery) using logistic regression models. In the multivariable logistic regression model, we adjusted for age, race, BMI, parity, and reaction to penicillin of angioedema, shortness of breath, or anaphylaxis. All analyses were performed in SAS (version 9.4, Cary, NC, USA).

## RESULTS

### *Allergy Evaluation and Outcomes*

Of 389 obstetric patients with a history of penicillin allergy, 363 (93%) recommended in-person AI evaluation and 222 (62%) patients received in-person AI evaluation (**Figure 1**). There were 141 patients who were only evaluated with an e-consult although an in-person evaluation was recommended. The reasons in-person evaluation was not completed were largely unknown (52%), although 24 (17%) patients delivered before their scheduled appointment and 21(15%) canceled their appointments. There were 26 (7%) patients for whom e-consult did not recommend an in-person AI evaluation: 12 (46%) patients who had a penicillin intolerance only, 12 (46%) who had a recent, severe, or recurrent penicillin reactions, 1 (4%) who had selective aminopenicillin allergy, and 1 (4%) who was delabeled based on history alone.

Of 222 patients receiving an in-person AI evaluation, 220 patients (99%) underwent penicillin skin testing: 217 patients (99%) had a negative skin test, 2 patients had a positive penicillin skin test, and 1 patient described subjective throat and tongue swelling during skin testing. 210 of the 217 (97%) skin test negative patients had negative oral amoxicillin challenge. There was 1 patient with a non-urticarial rash within 1-hour and 2 patients with delayed maculopapular exanthema after oral amoxicillin challenge; 4 patients did not undergo oral challenge. Of the 222 patients who presented for in-person AI evaluation, 209 (94%) ultimately had their penicillin allergy label removed at their visit.

### *Demographic Characteristics*

Obstetric patients had mean age 33y [SD 4y] and were largely white (75%), without differences by in-person AI evaluation status (**Table 1**). The median gravity was 2 [IQR 1,3] and median parity was 1 [IQR 0,2], without notable differences between evaluation status.

Penicillin reaction histories included: rash (47%), urticaria (39%), angioedema/swelling (9%), and gastrointestinal symptoms (4%). 306 (84%) reactions occurred 5 or more years ago; in-person AI evaluated patients had remote (>5 years ago) reactions more frequently when compared to patients not evaluated in-person (94% vs 70%). 332 patients (91%) had a reported allergy to penicillin only; 26 patients (7%) had one other reported drug allergy, 5 patients (1%) had two or more other drug allergies; 23 (6%) reported a concomitant cephalosporin allergy. Other drug allergies were not different by in-person AI evaluation status.

#### *Primary Outcome: Antibiotic Utilization*

Peripartum antibiotics were used for 133 (60%) patients who received in-person AI evaluation compared to 86 patients (61%) who were not evaluated in-person after e-consult (**Figure 2**). Compared to patients who were not evaluated in-person by AI, patients who were evaluated in-person were less likely to receive beta-lactam alternatives (15% vs 36%) including peripartum vancomycin (1% vs 11%), clindamycin (6% vs 27%), but were more likely to receive narrow beta-lactams specifically peripartum penicillin (34% vs 3%, **Table 2**).

After adjusting for potential confounders, compared to patients who were not evaluated in-person by AI, patients who received in-person AI evaluation had decreased beta-lactam alternative antibiotic use (multivariable adjusted odds ratio (aOR) 0.29 [95% CI 0.17, 0.50]) and increased narrow beta-lactams (aOR 2.42 [95% CI 1.52, 3.84]). Specifically, compared to patients who were not evaluated in-person, patients who received in-person AI evaluation had decreased vancomycin (aOR 0.07 [95% CI 0.01, 0.33]) clindamycin (aOR 0.17 [95% CI 0.08, 0.34]), and gentamycin (aOR 0.39 [95% CI 0.19, 0.78]) use. Fully evaluated patients had increased penicillin use (aOR 17.95 [95% CI 6.30, 51.16]).

GBS was present in 60 (27%) of patients who completed in-person AI evaluation compared to 30 (21%) patients who did not complete in-person AI evaluation (**Figure 3**). C-section delivery was performed for 57 (26%) of patients who completed in-person AI evaluation compared to 37 (26%) who did not complete in-person AI evaluation. First-line GBS prophylaxis (penicillin) and C-section prophylaxis (cefazolin) was higher in evaluated patients (46% vs 16%, **Table 2**). After adjusting for potential confounders, compared to patients who were not evaluated in-person, in-person AI evaluation was associated with an increased use of first-line antibiotic prophylaxis (aOR 5.36 [95% CI 3.05, 9.41]). Specifically, there was an increased first-line antibiotic prophylaxis for GBS (penicillin) (aOR 26.87 [95% CI 6.32, 114.33]) and C-section prophylaxis (cefazolin) (aOR 1.94 [95% CI 1.06, 3.52]) (**Table 2**).

One patient who had been evaluated in-person by AI after e-consult and who had negative testing experienced a delayed rash after amoxicillin treatment for a urinary tract infection during pregnancy; no other reports of drug allergy were identified.

#### *Secondary Outcomes: Allergy Assessment Safety for Pregnant Women*

No treatment except for antihistamines was required for any patient who received an in-person AI evaluation. Compared to patients not evaluated in-person (and excluding the 24 patients who delivered before appointment, See **Figure 1**), patients who received in-person AI evaluation had term deliveries with similar frequency (93% vs 91%,  $p=0.38$ , data not shown). After adjusting for potential confounders, compared to patients who were not evaluated, in-person AI evaluation was associated with no difference in term delivery (aOR 1.54 [95% CI 0.64, 3.71]). The frequency of C-section was similar by in-person AI evaluation status (26% vs 26%,  $p=0.90$ , data not shown); in the adjusted model, there was no difference in rate of C-section delivery (aOR 1.09 [95% CI 0.65, 1.84]) between pregnant patients who were evaluated in-person versus not.

## DISCUSSION

We used e-consults to identify and triage 389 obstetric patients with reported penicillin allergy in a large northeastern academic medical center; we evaluated 222 pregnant patients in-person in the third trimester with resultant delabeling of 94% of them without any severe reactions or discernable impact related to timing or mode of delivery. To our knowledge, this study is at least twice as large as any penicillin-allergic pregnant cohort that has undergone penicillin allergy evaluation in the literature to date.<sup>10,11</sup> Compared to the patients who were recommended for an in-person AI evaluation but did not complete the in-person AI evaluation, patients evaluated in-person had large and significant over 3-fold reduction in broad-spectrum beta-lactam-alternative antibiotic use, which included an approximately 17-fold lower odds of vancomycin use, over 6-fold lower odds of clindamycin use, and an over 2.5-fold lower odds of gentamicin use. These reductions accompanied an 18-fold increased odds of penicillin use, with first-line GBS prophylaxis with penicillin increasing 27-fold. Although both in-person evaluated and not evaluated patients had the same e-consult guidance encouraging cefazolin use if needed during delivery, in-person AI evaluation was still associated with an almost 2-fold increased odds of first-line cefazolin use for C-section prophylaxis.

We performed penicillin allergy assessment in pregnant women as a quality improvement initiative, with e-consults in the 1st trimester and in-person evaluations in the 3<sup>rd</sup> trimester, notably prior to GBS identification and with delivery mode (vaginal vs C-section) largely unknown. Given that GBS is a known penicillin indication, prior studies of penicillin allergy in pregnancy have tested patients only with known GBS.<sup>9,10</sup> In our study, we tested 60 patients (27%) who ultimately had GBS and, of these, most (93%) had first-line penicillin administered for GBS treatment. In our adjusted analysis, in-person AI evaluation was associated with a 27-fold increase in first-line penicillin use for GBS. Likewise, we evaluated 57 patients (26%) who ultimately had a C-section and more than 90% of these evaluated patients received cefazolin as C-section prophylaxis to reduce the risk of surgical site infection. Beyond these two primary indications, beta-lactam antibiotics are also considered first-line treatments for urinary tract infections, peripartum fevers, mastitis, and preterm premature rupture of the membranes, where

penicillin and macrolides are associated with a 3-fold reduced risk of endometritis.<sup>34</sup> While it is notable that a majority (more than 60%) of pregnant patients ultimately received antibiotics at some point in their pregnancy or the immediate post-partum period, we assessed many patients whose penicillin allergy testing results did not immediately inform antibiotic prescribing during their pregnancy or the post-partum period. However, safe removal of an unverified penicillin allergy was potentially still worthwhile given other potential benefits,<sup>4</sup> although to examine this would require a longer follow-up period.

Beta-lactam antibiotic prophylaxis has been associated with a reduced risk of surgical site infection after C-section, with an adjusted odds ratio of 0.43 [95% CI 0.22, 0.83]).<sup>35</sup> Because cefazolin is specifically recommended for C-sections, but has a low cross-reactivity with penicillins, our e-consults recommended that cefazolin could be used without an in-person AI evaluation in all patients with potentially IgE-mediated penicillin reactions more than 5 years ago. While it does appear as though this e-consult advice was followed in patients who did not receive an in-person AI evaluation (57% of such patients did receive cefazolin), cefazolin use for C-section was approximately 2-fold higher in the patients who received the e-consult and then an in-person evaluation for penicillin allergy (91% of such patients received cefazolin). One possible explanation for this finding could be that the vast majority of in-person evaluations resulted in penicillin allergy label removal, and therefore, no allergy alert would appear when cefazolin was ordered, whereas for those who received an e-consult only, this alert would need to be overridden upon ordering cefazolin. This is important clinical effectiveness information to consider as methods to increase perioperative cefazolin use in patients reporting a penicillin allergy are urgently needed. Our findings, as well as those reported elsewhere,<sup>36-39</sup> support that the most effective method to ensure cefazolin use in patients reporting a penicillin allergy is preoperative penicillin allergy testing, which has been consistently associated with the highest cefazolin use (more than 90% of tested patients).<sup>38,39</sup>

Public health organizations have stressed the importance of antibiotic stewardship as a critical component of fighting antibiotic resistance.<sup>40-44</sup> Recently, US professional societies recommended penicillin allergy assessment as part of antibiotic stewardship practices.<sup>44</sup> In this study, we identified that

penicillin allergy assessment in pregnant women was associated with significant reductions in use of alternative antibiotics including vancomycin, clindamycin, and gentamicin. These alternative antibiotics are often also associated with increased adverse effects, including renal toxicity and *Clostridioides difficile* colitis.<sup>45</sup> Additionally, the use of unnecessarily broad-spectrum antibiotics during labor and delivery may also have adverse consequences on the gut microbiome of infants, with potential downstream infant risks such as atopic disease.<sup>46</sup> Antibiotic stewardship in Obstetric patients should therefore include penicillin allergy assessments, as recommended by ACOG in their 2018 practice bulletin.<sup>23</sup>

We used e-consults to identify and triage pregnant patients with reported penicillin allergy and recommended that 93% present for an in-person AI evaluation with history-appropriate penicillin skin testing. There were just 12 patients with recent or severe reactions where we recommended beta-lactam avoidance and 14 patients with penicillin intolerances or where no further evaluation was recommended. While intolerance reactions were infrequently observed in our study, this may reflect a referral bias as it may have been that obstetricians were not sending e-consults for patients with clear penicillin intolerance histories but only those with potential penicillin allergies. While the use of the e-consult facilitated a high-volume triage process with clear communication between AI and Obstetrics, 39% of patients recommended for an in-person AI evaluation did not present for this evaluation, which suggests a multitude of opportunities for education and/or operational improvement. We believe that increased education of Obstetrics staff might improve patient interest in testing as often patients were asked if they were interested in penicillin allergy testing without appropriate context. Additionally, there were likely some obstetricians and/or patients who may have had unanswered questions or concerns about allergy testing in pregnancy (e.g., 21 patients canceled; 8 patients “no showed,” and 7 patients refused). Had we used synchronous telemedicine consults, rather than asynchronous EHR-based consults, it is possible that more patients would have been interested in testing and/or received an in-person AI evaluation. Since pregnant patients often prefer to limit their tests and medications while pregnant, alternative methods to capture this population and improve obstetric antibiotic use might consider methods to increase penicillin

allergy evaluation in young women of childbearing age before they conceive (e.g., preconception counseling).

Obstetric patients have typically been excluded from studies assessing penicillin allergy, likely due to safety-related concerns for the woman and the growing fetus. Our cohort of 220 tested pregnant patients shows similar allergy outcomes as reported previously in nonpregnant populations, including few patients who were skin test positive and/or reacted to the amoxicillin challenge.<sup>47,48</sup> In all, one patient had subjective symptoms with skin testing, one patient developed an immediate-onset rash during the 1-hour observation period, and two patients had delayed rashes. No treatments beyond antihistamines were needed. We also did not observe any association between having penicillin allergy testing and adverse outcomes such as premature delivery or C-section delivery. With limited prior data on penicillin allergy evaluation in pregnancy, including reports of 28 patients<sup>9</sup> and 56 patients,<sup>10</sup> we hope that this larger study will encourage allergists to expand their penicillin allergy testing to include pregnant women in the third trimester.

This retrospective analysis was limited to e-consults placed by MGH Obstetrics for penicillin allergy. It is possible that some patients were missed; for example, a pregnant patient from an outside (i.e., non-MGH) obstetrician might have been referred and would not have been part of this cohort. Our approach required an extra appointment for >90% of the patients in their 3<sup>rd</sup> trimester; since some patients delivered earlier, these patients could not receive an in-person AI evaluation. Although many patients received antibiotics, retrospective EHR review was inadequate to assess all antibiotic allergy/tolerance outside of the allergist's office. We considered antibiotic use as our outcome as opposed to surgical site infections, as such analysis would be underpowered due to their low frequency.<sup>49</sup> Our data are representative of one large, urban academic medical center and may not be generalizable.

We illustrate a novel program for penicillin allergy evaluation using e-consults with almost 400 patients screened, 220 pregnant women tested, and 209 patients effectively delabeled of their penicillin allergy. We determined the frequency of antibiotic use in this population if proactively assessed (60%). We identified large and significant changes to antibiotic selection associated with in-person AI evaluation

for penicillin skin testing: reduced vancomycin, reduced clindamycin, reduced gentamicin, and increased penicillin use. In-person AI evaluation was associated with a 27-fold increase in use of first-line penicillin as GBS prophylaxis. In collaboration with obstetricians, allergists should identify safe and feasible methods to evaluate pregnant patients with penicillin allergy histories to optimize antibiotic use in the peripartum period.

**Acknowledgements:**

Sincerest thanks to Benjamin Slawski, NP for performing many of the clinic visits for our patients as well as Susan A. Goldstein, MSIE and Jason H. Wasfy, MD, M.Phil for their ongoing support for the e-consult system.

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## TABLES/FIGURES

### Figure Legends

**Figure 1.** Flow chart of Allergy/Immunology (AI) e-consults and In-Person Consults for Obstetric Patients with Reported Penicillin Allergy

\* 1 patient with selective aminopenicillin allergy and 1 patient delabeled based on history

† 1 patient had a recent reaction and 1 patient had severe cutaneous adverse reaction; these reactions were not appropriately documented in the electronic health record.

‡ 1 patient with positive intradermal test to ampicillin, 1 patient with positive intradermal test to benzylpenicilloyl polylysine, and 1 patient with subjective symptoms (sensation of throat/tongue swelling) during skin testing

¶ 2 patients deferred challenge due to anxiety, 2 physicians deferred challenge due to recent or severe reactions not known from documentation in the electronic health record.

*Abbreviations:* AI, Allergy/Immunology; e-Consult, electronic consult

**Figure 2.** Antibiotic Utilization in Obstetric Patients with Reported Penicillin Allergy. This figure demonstrates antibiotic use and its associated timing (pregnancy, delivery, post partum) for each group of obstetric patients who received an e-consult. Beta-lactams, beta-lactam alternatives, and both are indicated by color according to the frequency of their use.

*Abbreviations:* AI, Allergy/Immunology; e-Consult, electronic consult

**Figure 3.** Antibiotic Utilization for Group B *Streptococcus* and C-Section Prophylaxis in Obstetric Patients with Reported Penicillin Allergy. This figure demonstrates patients who ultimately had GBS or C-sections with their associated antibiotic use.

\*Penicillin for Group B Strep and cefazolin for C-section surgical site infection prophylaxis

*Abbreviations:* AI, Allergy/Immunology; e-Consult, electronic consult; Group B Strep, Group B *Streptococcus*; C-section, Caesarian section.

617 **Table 1.** Clinical characteristics of obstetric patients by allergy/immunology in-person evaluation status.

| <b>Demographics</b>                        | All<br>(n=363) | In-Person AI<br>Evaluation<br>(n=222) | No In-Person AI<br>Evaluation<br>(n=141) |
|--------------------------------------------|----------------|---------------------------------------|------------------------------------------|
| Age ( $\mu$ + SD)                          | 33 $\pm$ 4     | 34 $\pm$ 4                            | 33 $\pm$ 5                               |
| Patients of advanced maternal age*         | 142 (39)       | 83 (37)                               | 59 (42)                                  |
| Race                                       |                |                                       |                                          |
| White                                      | 271 (75)       | 163 (73)                              | 108 (77)                                 |
| Black                                      | 14 (4)         | 8 (4)                                 | 6 (4)                                    |
| Hispanic                                   | 34 (9)         | 17 (8)                                | 17 (12)                                  |
| Asian                                      | 26 (7)         | 20 (9)                                | 6 (4)                                    |
| Other                                      | 18 (5)         | 14 (6)                                | 4 (3)                                    |
| Body mass index ( $\mu$ + SD) <sup>†</sup> | 31 $\pm$ 5     | 30 $\pm$ 5                            | 32 $\pm$ 6                               |
| <b>Obstetric History Details</b>           |                |                                       |                                          |
| Gravidity (Median+IQR)                     | 2 [1, 3]       | 2 [1, 2]                              | 2 [1, 3]                                 |
| 1                                          | 142 (39)       | 101 (46)                              | 41 (29)                                  |
| 2                                          | 117 (32)       | 70 (32)                               | 47 (33)                                  |
| 3                                          | 53 (15)        | 25 (11)                               | 28 (20)                                  |
| 4                                          | 30 (8)         | 18 (8)                                | 12 (9)                                   |
| 5 or more                                  | 21 (6)         | 8 (4)                                 | 13 (9)                                   |
| Parity (Median + IQR)                      | 1 [0, 2]       | 1 [0, 1]                              | 1 [0, 2]                                 |
| 0                                          | 139 (38)       | 97 (44)                               | 42 (30)                                  |
| 1                                          | 117 (32)       | 73 (33)                               | 44 (31)                                  |
| 2                                          | 56 (15)        | 25 (11)                               | 31 (22)                                  |
| 3                                          | 26 (7)         | 15 (7)                                | 11 (8)                                   |
| 4                                          | 12 (3)         | 8 (4)                                 | 4 (3)                                    |
| 5 or more                                  | 13 (4)         | 4 (2)                                 | 9 (6)                                    |
| <b>Allergy History</b>                     |                |                                       |                                          |
| Penicillin allergy                         |                |                                       |                                          |
| Reaction symptoms                          |                |                                       |                                          |
| Rash                                       | 169 (47)       | 98 (44)                               | 71 (50)                                  |
| Urticaria                                  | 143 (39)       | 99 (45)                               | 44 (31)                                  |
| Angioedema/swelling                        | 31 (9)         | 14 (6)                                | 17 (12)                                  |
| Gastrointestinal symptoms                  | 13 (4)         | 8 (4)                                 | 5 (4)                                    |
| History of positive skin test              | 8 (2)          | 8 (4)                                 | 0 (0)                                    |
| Itching/flushing                           | 13 (4)         | 7 (3)                                 | 6 (4)                                    |
| Shortness of breath                        | 9 (2)          | 4 (2)                                 | 5 (4)                                    |
| Joint pain                                 | 2 (1)          | 2 (1)                                 | 0 (0)                                    |
| Anaphylaxis                                | 6 (2)          | 0 (0)                                 | 6 (4)                                    |
| Other                                      | 12 (3)         | 10 (5)                                | 2 (1)                                    |
| Unknown                                    | 19 (5)         | 9 (4)                                 | 10 (7)                                   |
| Timing 5 or more years ago <sup>‡</sup>    | 306 (84)       | 208 (94)                              | 98 (70)                                  |
| Cephalosporin allergy                      | 23 (6)         | 13 (6)                                | 10 (7)                                   |
| Number of other antibiotic allergies       |                |                                       |                                          |
| 0                                          | 332 (91)       | 206 (93)                              | 126 (89)                                 |
| 1                                          | 26 (7)         | 12 (5)                                | 14 (10)                                  |
| 2 or more                                  | 5 (1)          | 4 (2)                                 | 1 (1)                                    |

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*Abbreviations:* AI, Allergy/Immunology;  $\mu$ , mean; SD, standard deviation; IQR, intra-quartile range.

\*Advanced maternal age is defined as age > 35 years old

<sup>†</sup> At the time of delivery

<sup>‡</sup>Timing was unknown in 44 (12%) of patients; 9 (4%) evaluated and 35 (25%) not evaluated

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**Table 2.** Unadjusted and adjusted antibiotic use outcomes for obstetric patients with a penicillin allergy history by allergy/immunology in-person evaluation status

|                                   | In-Person AI Evaluation<br>(n = 222) | No In-Person AI Evaluation<br>(n=141) | Unadjusted OR* (95% CI) | Adjusted OR* (95% CI) <sup>†</sup> |
|-----------------------------------|--------------------------------------|---------------------------------------|-------------------------|------------------------------------|
| <b>Beta-lactam alternatives</b>   | 33 (15)                              | 51 (36)                               | 0.31 (0.19, 0.51)       | 0.29 (0.17, 0.50)                  |
| Vancomycin                        | 2 (1)                                | 15 (11)                               | 0.08 (0.02, 0.34)       | 0.07 (0.01, 0.33)                  |
| Clindamycin                       | 13 (6)                               | 38 (27)                               | 0.17 (0.09, 0.33)       | 0.17 (0.08, 0.34)                  |
| Gentamicin                        | 17 (8)                               | 24 (17)                               | 0.40 (0.21, 0.78)       | 0.39 (0.19, 0.78)                  |
| <b>Narrow beta-lactams</b>        | 122 (55)                             | 47 (33)                               | 2.44 (1.57, 3.78)       | 2.42 (1.52, 3.84)                  |
| Penicillin use                    | 76 (34)                              | 4 (3)                                 | 17.8 (6.35, 50.0)       | 18.0 (6.30, 51.2)                  |
| Cefazolin                         | 60 (27)                              | 38 (27)                               | 1.00 (0.62, 1.62)       | 0.91 (0.55, 1.51)                  |
| Cephalexin                        | 3 (1)                                | 7 (5)                                 | 0.26 (0.07, 1.03)       | 0.41 (0.10, 1.75)                  |
| <b>First-line antibiotic use</b>  | 103 (46)                             | 22 (16)                               | 4.68 (2.77, 7.92)       | 5.36 (3.05, 9.41)                  |
| GBS prophylaxis (penicillin)      | 58 (26)                              | 2 (1)                                 | 24.6 (5.90, 102.5)      | 26.9 (6.32, 114)                   |
| C-section prophylaxis (cefazolin) | 52 (23)                              | 20 (14)                               | 1.85 (1.05, 3.26)       | 1.94 (1.06, 3.52)                  |

\*Odds ratios (OR) compare patients who received an in-person AI evaluation (n=222) compared to patients where in-person AI evaluation was recommended but not completed (n=141)

<sup>†</sup>Adjusted for age, race, body mass index, parity, and reaction to penicillin angioedema/shortness of breath/anaphylaxis.

Frequency of use of macrolides, sulfonamides, tetracyclines, linezolid, daptomycin, cephalosporins in the 2nd, 3rd, 4th and 5th generations, carbapenems, and aztreonam was ≤5% peripartum and not specifically assessed.

Abbreviations: AI, Allergy/Immunology; OR, odds ratio; CI, confidence interval

