



The association of penicillin allergy with outcomes after open ventral hernia repair

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Received: 23 April 2019 / Accepted: 30 September 2019
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Abstract

Background Up to 11% of patients report a penicillin allergy (PA), with 1–2% demonstrating a true IgE mediated allergy upon testing. PA patients often receive non-beta-lactam antibiotic surgical prophylaxis (non-BLP). This study evaluates the relationship of PA to outcomes after open ventral hernia repair (OVHR).

Methods A prospective institutional database was queried for patients undergoing OVHR. Demographics, operative characteristics, and outcomes were evaluated by the reported PA and the administration of beta-lactam prophylaxis (BLP).

Results Allergy histories were reviewed in 1178 patients. PA was reported in 21.6% of patients, with 55.5% reporting rash or hives, 15.0% airway compromise or anaphylaxis, and 29.5% no specific reaction. BLP was administered to 76.3% of patients, including 22.1% of PA patients and 89.9% of patients without PA. PA patients were more often female (64.6% PA patients vs. 56% non-PA, $p = 0.01$), with higher rates of chronic steroids, MRSA, anxiety, asthma, COPD, chronic pain, and sleep apnea ($p < 0.03$ all values). PA patients had higher rates of contaminated cases, including mesh infection and fistula. Of the 683 clean cases, 82.1% received BLP. Of the 117 clean contaminated cases (CDC wound class 2), 82.9% received BLP, which was associated with reduced long-term readmission for hernia complications (21.5 vs. 55%, $p = 0.002$, OR 0.27, CI 0.09–0.83). In the 120 CDC wound class 3 and 4 patients, 65.8% received BLP. In multivariate analysis, BLP was associated with lower rates of reoperation (OR 0.31, CI 0.12–0.76) and recurrence (OR 0.32, CI 0.11–0.86). BLP was given to 22.1% of the PA patients with no adverse reactions noted.

Conclusion PA patients had more comorbidities and complex ventral hernias. When controlling for contamination and MRSA history, BLP is associated with improved outcomes particularly in contaminated cases. PA may be a risk factor for patient complexity, and further studies are warranted to determine if allergy testing can be warranted in known or anticipated contaminated cases.

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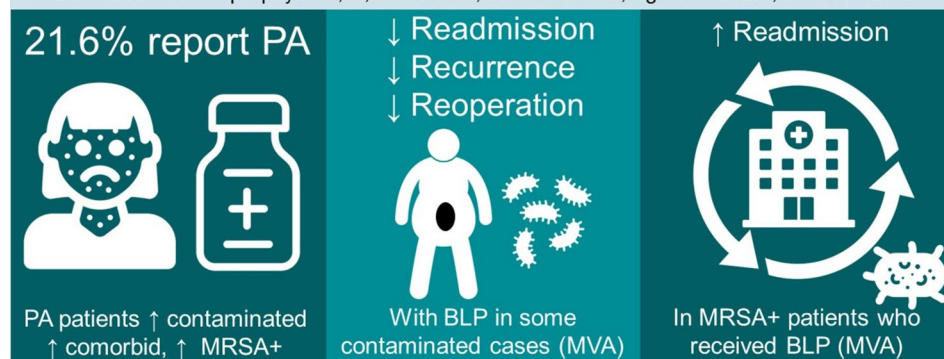
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Graphic abstract

The Association of Penicillin Allergy (PA) with Outcomes After Open Ventral Hernia Repair

BLP: Beta-lactam prophylaxis, 1,178 OVHR, 57.8% female, Age 58.5±12.4, BMI 33.4±7.8



Keywords Hernia · Ventral hernia · Penicillin allergy · Allergy

Hernia repair accounts for over 300,000 surgical cases in the United States of America annually, and complications after hernia repair are both costly and injurious to patients [1, 2]. Multiple factors have been demonstrated to impact the outcomes after repair, including BMI, diabetes, tobacco use, and wound class, which have all been shown to increase wound complications, and subsequently increase the rate of failure of the repair [1, 3]. The 2013 “Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery,” which has been endorsed and referenced by the American College of Surgeons, recommends preoperative cefazolin for clean hernia procedures with mesh placement [4]. This choice of antibiotic is tailored to the known, or the anticipated skin or enteric flora. In patients with beta-lactam allergies, clindamycin or vancomycin is recommended for prophylaxis. The use of non-beta-lactam antibiotics, usually for reported penicillin allergy, has been investigated in multiple patient populations, and it confers higher cost, drug toxicity, and risk of postoperative complication after administration when compared to first line beta-lactam prophylaxis (usually cefazolin) [5–9].

The use of clindamycin or vancomycin instead of cefazolin for hospitalized patients with reported penicillin allergy (PA), and without the history of VRE, MRSA or *C. diff*, has been associated with higher rates of subsequent VRE, MRSA, and *C. diff* infections [8, 10]. In patients undergoing free tissue transfer, the use of clindamycin for prophylaxis in PA patients is associated with higher rates of surgical site infections (SSI) [9, 11]. In a large study reviewing patients undergoing orthopedic, colorectal, gynecologic, and cardiac surgery, a reported PA was not associated with

previous history of MRSA or VRE, but was associated with the administration of non-beta-lactam surgical prophylaxis, and with higher postoperative rates of SSI [12].

Up to 11% of the United States of America population endorse a penicillin allergy. On close investigation, only 1–10% of patients with a reported penicillin allergy have any reactivity to penicillin skin tests [13–17]. This leaves 1–2% of the population with a true IgE mediated penicillin allergy, also known as a type 1 allergic reaction, which occurs 30–60 min after administration and can include anaphylaxis, urticaria, bronchitis, or exfoliative dermatitis [4]. In this less than 1% of the population, cross-reactivity to cephalosporins is related to the drug side chain, not to the beta-lactam ring, and is thus dependent on the generation of cephalosporin [9, 18–20]. There is low cross-reactivity to first and second generation cephalosporins (0.5–2%), [19] and almost no cross-reactivity to third and fourth generation cephalosporins (–0.8 to 0.2%) [9, 13, 18, 19, 21]. Finally, sensitivity to penicillin can decline over time. An estimated 80% of patients with an historic IgE mediated penicillin allergy do not sustain sensitivity over 10 years [20, 22]. Multiple studies have demonstrated the safety of cephalosporin antibiotics in patients with reported penicillin allergies [17, 23, 24]. Given the low incidence of true penicillin allergy, the low likelihood of cephalosporin cross-reactivity, and the potentially significant side effects of alternative prophylactic antibiotics, careful documentation and work up of penicillin allergy has been advocated when considering surgical prophylaxis [20].

Given these findings, a study was undertaken to investigate the previously unstudied impact of patient-reported

PA on choice of antibiotic prophylaxis and outcomes after open ventral hernia repair (OVHR), including clean cases and complex contaminated abdominal wall reconstruction.

Materials and methods

A prospective, institutional, hernia-specific database was queried for patients undergoing OVHR from 2007 to 2018 with allergy-specific data available. Patients were assessed for reported allergy to penicillin or any beta-lactam antibiotic (PA) and for the type of allergy to beta-lactam antibiotic. Type of allergy to penicillin or beta-lactam included “rash or hives,” “anaphylaxis or airway” (including mouth swelling, difficulty breathing, and wheezing), and “other”, which included no response listed or non-IgE mediated responses such as nausea, diarrhea, or yeast infection [25]. Charts were reviewed for perioperative surgical prophylaxis, which included beta-lactam prophylaxis and/or other prophylaxis. When more than one antibiotic was administered for prophylaxis (for example, cefazolin and metronidazole), both were noted.

Primary outcomes of interest included wound complications. Secondary outcomes included reoperation, length of stay, total charges, hernia recurrence, and readmission. This study was approved by the Institutional Review Board of Carolinas Medical Center.

Statistical analysis

Data were analyzed using standard statistical methods utilizing the SAS[®] program version 9.4 (SAS, Cary, NC, USA). Descriptive statistics including means and standard deviations, medians and inter quartile range (IQR) for continuous variables without normal distribution, or counts and percentages, were used to describe the study subjects. For continuous variables, comparisons were made between groups using *t* tests and Wilcoxon–Mann–Whitney tests. For categorical variables, χ^2 and Fisher’s exact tests were used to make comparisons between groups. Comparisons were performed between patients with and without a reported beta-lactam allergy (PA) and between patients who received beta-lactam surgical prophylaxis (BLP) and those who did not. Due to the retrospective nature of this data set, we are unable to determine the reason patients with reported PA received beta-lactam prophylaxis. Based on multiple prior studies which have established an antibiotic choice (as opposed to penicillin allergy) as the variable of interest in the context of penicillin allergy, we decided to perform multivariate analysis comparing patients who did and did not receive beta-lactam prophylaxis [9, 11, 12, 26].

When examining patients receiving BLP (considered “first line”), patients with a history of MRSA were examined

separately due to restricted antibiotic choice, and patients were examined within the subsets of wound contamination. Subsets included patients with “clean” cases (CDC wound class 1), patients with clean contaminated cases (wound class 2), and patients with frank or gross contamination (wound class 3–4). Variables used in multivariate logistic regression were selected based on factors identified as statistically different between groups in univariate analysis ($p < 0.05$), and factors known to potentially influence operative outcomes based on prior hernia studies. Multivariate analysis was performed to control for potential confounding factors including use of beta-lactam prophylaxis, chronic steroid use, preoperative defect size, sex, diabetes, history of COPD, and history of asthma. The level of significance was set at $p < 0.05$ for all comparisons. In order to control for the nature and presence of contamination, multivariate analysis was stratified by the subset of wound contamination, as discussed above.

Results

A total of 1178 patients with available allergy information underwent OHR in the study period. Mean BMI was 34.2 ± 7.7 kg/m², mean age was 58.5 ± 12.4 years, 57.8% were female, 31.1% had a history of diabetes, 14.9% had a history of smoking, and 8.5% had a history of MRSA. A total of 66% of hernias had a history of recurrence, with mean defect area of 150.8 ± 136.7 cm², and 26% of cases were contaminated (Tables 1, 2).

Allergy to penicillin or beta-lactam (98.2% penicillin, 1.8% other beta-lactam) was endorsed in 21.6% of patients, of whom 55.5% reported rash or hives, and 15.0% reported airway compromise (swelling, wheezing, difficulty breathing) or anaphylaxis. A total of 29.5% of patients with reported PA (6.2% of all patients) had no reaction specified. When examining antibiotic prophylaxis, it was found that 76.3% of patients received a BLP, including 22.1% of patients with a reported PA (38 patients) and 89.9% of patients without PA. Beta-lactam antibiotics included cefazolin (68.7% of patients), ertapenem (3.8%), and other beta-lactams (3.8%, Table 2). Other beta-lactams included 2.6% piperacillin-tazobactam, 0.6% cefepime, 0.2% ceftriaxone, and 0.4% ampicillin-sulbactam. Patients with PA were more likely to receive vancomycin for perioperative prophylaxis (38.3 vs. 10.5%) or clindamycin (36.2 vs. 1.2%) than patients without PA (Table 2). There were no adverse or allergic reactions noted with respect to BLP or non-BLP antibiotics in PA and non-PA groups.

When comparing patients with and without history of PA, there was no difference in age, BMI, hernia size, history of smoking, or history of recurrence ($p > 0.05$ all values, Table 1). There was also no difference in the performance

Table 1 Patient characteristics by reported penicillin allergy*

	All	Penicillin allergy		<i>p</i> -value
	<i>n</i> = 1178	No (78.4%)	Yes (21.6%)	
BMI (kg/m ²) (mean, SD)	34.2 ± 7.7	34.2 ± 7.9	34.0 ± 7.4	0.93
Age (years) (mean, SD)	58.5 ± 12.4	58.1 ± 12.7	59.9 ± 11.2	0.12
Female (%)	57.8	56.0	64.6	0.01
Diabetes (%)	31.0	30.6	32.2	0.61
Steroids (%)	6.9	5.8	10.6	0.01
h/o smoking (%)	15.0	14.3	17.7	0.18
Asthma (%)	17.7	16.0	23.6	0.005
Sleep apnea (%)	14.8	13.5	19.3	0.02
COPD (%)	8.4	7.5	11.8	0.03
h/o MRSA (%)	8.5	6.3	11.0	0.01
Anxiety (%)	23.90	21.4	33.1	0.0001
Chronic pain (%)	30.5	28.4	38.2	0.00

*Univariate analysis comparing patients with and without penicillin analysis

of panniculectomy and raising of skin flaps. PA patients were more commonly female (64.6% PA patients vs. 56% non-PA, $p=0.01$), with history of chronic steroids, anxiety, asthma, COPD, chronic pain, and/or sleep apnea ($p<0.03$ all values) (Table 1). Patients with reported PA were more likely to have a history of MRSA (11.0 vs. 6.3%, $p=0.01$), and a contaminated operating field (31.9 vs. 24.7% non-PA, $p=0.02$), which included higher rates of preexisting mesh infection (13.0 vs. 7.8%, $p=0.01$) or fistula at time of surgery (7.1 vs. 3.9%, $p=0.03$) (Table 2).

After OVHR, patients with reported PA had higher rates of readmission, percutaneous drain placement for seroma,

and wound complications (27.6 vs. 20.1%, $p=0.01$; 22.4 vs. 15.8%, $p=0.01$; 38.9 vs. 31.3%, $p=0.02$; respectively) when compared to non-PA patients, at an average follow-up of 30.1 ± 35.6 months. There was no difference in mean length of stay (8.0 ± 6.0 vs. 9.3 ± 10.0 days, $p=0.10$), or total hospital charges ($\$71,598.2 \pm 62,924.5$ vs. $\$83,741.7 \pm 85,407.3$, $p=0.14$).

Patients with a history of MRSA accounted for 100 OVHR during the time period examined, in whom PA was reported in 27.8%. Vancomycin was administered in 58.8% of MRSA positive patients, 15.8% received ertapenem, 6.2% clindamycin, and 30.9% cefazolin, as perioperative prophylaxis. Wound contamination was present in 36.8% of patients with a history of MRSA, including 18.6% with planned gastrointestinal tract entry, 19.6% with active mesh infection at the time of surgery, and 9.3% with fistula present. In patients with a history of MRSA, administration of BLP was associated with equivalent rates of recurrence and wound complications (51.4 vs. 46.6%, $p=0.6$), a higher 30-day readmission rate which neared statistical significance (31.6 vs. 15.3%, $p=0.06$), as well as a higher long-term readmission rate for hernia-related complications (44.7% vs. 25.4%, $p=0.05$). This trend persisted on multivariate analysis, with administration of BLP to MRSA positive patients associated with increased 30-day readmission rates (OR 4.31, CI 1.25–14.84) and nearing statistical significance with increased long-term readmission rates (OR 2.73, CI 1.00–7.47) (Table 3).

Patients without a history of MRSA were split into subsets by wound contamination and examined by BLP (Table 4). Clean cases accounted for 73.8% of OHR ($n=683$), 82.1% of whom received BLP. Of patients receiving BLP, 4.5% of patients had reported PA, and 95.7% received cefazolin. Of the clean cases which did not receive BLP (17.9%), 90.2%

Table 2 Hernia and operative characteristics by reported penicillin allergy*

Hernia characteristics	All	Penicillin allergy		<i>p</i> -value
	<i>n</i> = 1178	No (78.4%)	Yes (21.6%)	
Recurrent hernia (%)	66.0	66.1	65.8	0.91
Defect size (cm ²)	150.8 ± 136.7	153.0 ± 139.1	143.3 ± 127.8	0.39
Component separation	48.50	48.2	49.6	0.68
Contaminated (%)	26.2	24.7	31.9	0.02
Mesh infection	8.9	7.8	13.0	0.01
Fistula	4.6	3.9	7.1	0.03
Surgical antibiotic prophylaxis				
Beta-lactam antibiotic (%)	76.3	89.9	22.1	<0.0001
Cefazolin (%)	68.7	82.4	16.3	<0.0001
Ertapenem (%)	3.8	3.5	5.0	0.31
Other beta-lactam (%)	3.8	4.0	0.8	0.02
Vancomycin (%)	16.1	10.5	38.3	<0.0001
Clindamycin (%)	8.7	1.2	36.2	<0.0001

*Univariate analysis comparing patients with and without penicillin analysis

Table 3 Multivariate analysis of MRSA + patients undergoing hernia repair*

	Readmission OR (CI), <i>p</i> -value	Reoperation OR (CI), <i>p</i> -value	Wound complication OR (CI), <i>p</i> -value	Recurrence OR (CI), <i>p</i> -value
BLP	2.73 (1.00–7.47), <i>p</i> =0.51	2.18 (0.80–5.93), <i>p</i> =0.13	1.66 (0.64–4.31), <i>p</i> =0.30	0.56 (0.14–2.25), <i>p</i> =0.41
Defect	1.00 (0.99–1.00), <i>p</i> =0.63	1.00 (1.00–1.01), <i>p</i> =0.03	1.00 (1.00–1.01), <i>p</i> =0.11	1.00 (0.99–1.01), <i>p</i> =0.69
Female	2.28 (0.76–6.83), <i>p</i> =0.14	1.39 (0.47–4.14), <i>p</i> =0.55	2.05 (0.75–5.63), <i>p</i> =0.16	1.46 (0.31–7.01), <i>p</i> =0.65
Diabetes	1.28 (0.46–3.53), <i>p</i> =0.64	0.56 (0.20–1.61), <i>p</i> =0.28	1.24 (0.48–3.19), <i>p</i> =0.65	1.08 (0.26–4.52), <i>p</i> =0.91
Asthma	0.91 (0.26–3.21), <i>p</i> =0.88	1.44 (0.43–4.84), <i>p</i> =0.56	0.71 (0.22–2.34), <i>p</i> =0.57	4.75 (1.07–21.13), <i>p</i> =0.04
COPD	4.06 (0.73–22.63), <i>p</i> =0.11	2.09 (0.37–11.66), <i>p</i> =0.40	3.61 (0.61–21.20), <i>p</i> =0.16	2.66 (0.40–17.69), <i>p</i> =0.31
Steroids	2.16 (0.85–3.05), <i>p</i> =0.51	1.22 (0.51–3.27), <i>p</i> =0.84	0.39 (0.22–1.86), <i>p</i> =0.37	4.01 (0.13–4.20), <i>p</i> =0.67

BLP beta-lactam prophylaxis

*Multivariate analysis controlling for BLP, female sex, diabetes, asthma, COPD, defect size, and steroid use in patients with a history of MRSA

Table 4 Outcomes by beta-lactam antibiotic prophylaxis (BLP, in patients with no history of MRSA)*

	All	Clean (<i>n</i> =683)			Wound class 2 (<i>n</i> =117)			Wound class 3–4 (<i>n</i> =120)		
		BLP (82.1%)	Non-BLP (17.9%)	<i>p</i> -value	BLP (82.9%)	Non-BLP (17.1%)	<i>p</i> -value	BLP (65.8%)	Non-BLP (34.2%)	<i>p</i> -value
Penicillin allergy (%)	21.6	4.5	90.2	<0.0001	8.3	90.0	<0.0001	12.6	58.5	<0.0001
Cefazolin (%)	68.7	95.7	0.0	<0.0001	70.1	0.0	<0.0001	77.2	0.0	<0.0001
Vancomycin (%)	16.1	1.3	45.1	<0.0001	3.1	40.0	<0.0001	10.1	63.4	<0.0001
Clindamycin (%)	8.7	0.36	49.2	<0.0001	1.0	35.0	<0.0001	0.0	32.5	<0.0001
Outcomes										
Percutaneous drain (%)	17.2	6.7	13.6	0.01	20.6	15.0	0.57	22.8	26.8	0.62
Wound Complication (%)	32.9	25.1	31.4	0.16	43.0	50.0	0.57	37.2	60.0	0.02
Readmission (%)	21.7	15.2	20.3	0.16	21.5	55.0	0.002	30.4	34.2	0.67
Reoperation (%)	20.3	5.1	4.2	0.16	27.8	35.0	0.52	22.8	46.3	0.008
Recurrence (%)	10.7	6.1	3.4	0.24	21.5	20.0	0.88	13.9	31.7	0.02

*Univariate analysis comparing outcomes by administration of beta-lactam prophylaxis

had reported PA, and the most common antibiotics were clindamycin (49.2%) and vancomycin (45.1%). Patients receiving non-BLP had higher rates of wound complications and readmission. This finding did not persist on multivariate analysis controlling for multiple confounding factors, and BLP was not found to be associated with outcomes in this cohort (Table 5).

A total of 117 patients with no history of MRSA underwent OHR with clean contaminated cases (Wound Class 2). Sources of contamination included planned concomitant GI procedures (colectomy, small bowel resection, ostomy takedown and/or creation), GU procedures, or hepatobiliary procedure. Of these clean contaminated cases, 82.9% had BLP with additional non-BLP when appropriate such as cefazolin and metronidazole (Table 4). Of patients receiving BLP, 70.1% received cefazolin as one of their perioperative antibiotics, and 8.3% reported PA and received BLP. There were no adverse reactions in PA patients. Of the 17.1% of patients who did not receive BLP, 40.0% received vancomycin and 35.0% received clindamycin. Patients who received

BLP had equivalent rates of 30-day readmission (15.0 vs. 12.4%, *p*=0.7), and lower rates of all-time readmission for hernia-related complications on univariate analysis (21.5 vs. 55.0%, *p*=0.002). When controlling for confounding factors with multivariate analysis, BLP was associated with lower rates of all-time readmission for hernia related complications (OR 0.27, CI 0.09–0.83) (Table 6).

Contaminated or grossly contaminated cases (Wound class 3 or 4) with no history of MRSA accounted for 120 OHR. Sources of contamination included one or more of the following conditions: existing enterocutaneous fistulas (29.9%) with or without mesh involvement (59.0%, 33.3% respectively), infected mesh (57.5%), gross intestinal spillage (23.1%), and/or existing skin or subcutaneous tissue infection (57.5%). BLP was administered in 65.8% of cases, of whom 12.6% had reported penicillin allergy, and 77.2% received cefazolin (Table 4). Of the 34.2% of patients who had no BLP administered, 58.5% had a reported penicillin allergy, 63.4% received vancomycin, and 32.5% received clindamycin. Patients who did not

receive BLP had significantly worse outcomes with higher rates of wound complications (60.0 vs. 37.2%, $p = 0.02$), administration of BLP was associated with lower rates of reoperation (46.3 vs. 22.8%, $p = 0.008$), and recurrence

(31.7 vs. 13.9%, $p = 0.02$). On multivariate analysis,

Table 5 Multivariate analysis of patients undergoing uncontaminated (clean) hernia repair*

	Readmission OR (CI), p -value	Reoperation OR (CI), p -value	Wound complication OR (CI), p -value	Recurrence OR (CI), p -value
BLP	0.96 (0.56–1.64), $p = 0.89$	1.00 (0.57–1.76), $p = 0.99$	0.82 (0.51–1.33), $p = 0.42$	2.42 (0.72–8.19), $p = 0.16$
Defect	1.02 (1.01–1.02), $p = 0.04$	1.00 (0.99–1.01), $p = 0.57$	1.02 (1.01–1.04), $p = 0.005$	1.00 (0.99–1.03), $p = 0.89$
Female	1.69 (1.08–2.66), $p = 0.02$	1.10 (0.70–1.74), $p = 0.68$	1.75 (1.16–2.62), $p = 0.007$	0.71 (0.35–1.47), $p = 0.36$
Diabetes	1.75 (1.12–2.72), $p = 0.01$	1.73 (1.08–2.76), $p = 0.02$	2.04 (1.36–3.06), $p = 0.0005$	0.91 (0.40–2.06), $p = 0.82$
Asthma	1.37 (0.81–2.33), $p = 0.24$	1.44 (0.83–2.51), $p = 0.19$	1.62 (1.01–2.62), $p = 0.05$	1.95 (0.81–4.67), $p = 0.14$
COPD	1.57 (0.78–3.17), $p = 0.21$	1.31 (0.62–2.79), $p = 0.48$	2.33 (1.21–4.46), $p = 0.01$	0.64 (0.14–2.94), $p = 0.57$
Steroids	0.84 (0.29–3.74), $p = 0.65$	1.16 (0.73–1.85), $p = 0.94$	1.58 (0.64–2.57), $p = 0.68$	2.14 (0.34–2.50), $p = 0.72$

BLP beta-lactam prophylaxis

*Multivariate analysis controlling for BLP, female sex, diabetes, asthma, COPD, defect size, and steroid use in patients without history of MRSA, undergoing clean (wound class 1) hernia repair

Table 6 Multivariate analysis of clean contaminated cases undergoing hernia repair*

	Readmission OR (CI), p -value	Reoperation OR (CI), p -value	Wound complication OR (CI), p -value	Recurrence OR (CI), p -value
BLP	0.28 (0.09–0.89), $p = 0.03$	0.76 (0.23–2.49), $p = 0.66$	1.15 (0.37–3.54), $p = 0.81$	1.06 (0.25–4.41), $p = 0.94$
Defect	1.00 (1.00–1.01), $p = 0.20$	1.01 (1.00–1.01), $p = 0.002$	1.00 (1.00–1.06), $p = 0.046$	1.00 (1.00–1.00), $p = 0.54$
Female	4.78 (1.43–15.95), $p = 0.01$	1.25 (0.47–3.35), $p = 0.65$	1.76 (0.70–4.41), $p = 0.23$	0.58 (0.21–1.63), $p = 0.30$
Diabetes	1.67 (0.60–4.68), $p = 0.33$	0.57 (0.20–1.61), $p = 0.29$	1.38 (0.56–3.41), $p = 0.48$	0.50 (0.16–1.61), $p = 0.25$
Asthma	0.62 (0.13–2.95), $p = 0.55$	0.62 (0.15–2.58), $p = 0.51$	1.12 (0.32–3.87), $p = 0.86$	1.17 (0.29–4.85), $p = 0.83$
COPD	4.29 (0.72–25.60), $p = 0.11$	1.36 (0.27–7.00), $p = 0.71$	5.96 (0.64–55.63), $p = 0.12$	0.59 (0.06–5.41), $p = 0.64$
Steroids	0.98 (0.72–1.34), $p = 0.75$	0.62 (0.21–2.58), $p = 0.83$	1.23 (0.89–1.96), $p = 0.24$	0.73 (0.41–1.58), $p = 0.72$

BLP beta-lactam prophylaxis

*Multivariate analysis controlling for BLP, female sex, diabetes, asthma, COPD, defect size, and steroid use in patients without a history of MRSA, with clean contaminated cases (wound class 2 operations)

Table 7 Multivariate analysis of contaminated cases undergoing hernia repair*

	Readmission OR (CI), p -value	Reoperation OR (CI), p -value	Wound complication OR (CI), p -value	Recurrence OR (CI), p -value
BLP	1.03 (0.42–2.52), $p = 0.95$	0.31 (0.12–0.78), $p = 0.01$	0.52 (0.22–1.23), $p = 0.13$	0.30 (0.11–0.84), 0.02
Defect	1.00 (1.00–1.00), $p = 0.41$	1.00 (1.00–1.00), $p = 0.30$	1.00 (0.99–1.00), $p = 0.48$	1.00 (0.99–1.00), $p = 0.56$
Female	1.14 (0.45–2.87), $p = 0.79$	0.87 (0.33–2.31), $p = 0.78$	2.54 (1.03–6.27), $p = 0.04$	1.36 (0.43–4.30), $p = 0.60$
Diabetes	0.85 (0.34–2.13), $p = 0.73$	1.90 (0.75–4.78), $p = 0.18$	1.07 (0.44–2.58), $p = 0.88$	0.72 (0.24–2.20), $p = 0.57$
Asthma	1.16 (0.34–3.99), $p = 0.81$	2.64 (0.77–9.09), $p = 0.12$	0.64 (0.20–2.09), $p = 0.46$	2.96 (0.80–11.03), $p = 0.11$
COPD	6.62 (1.06–41.38), $p = 0.04$	2.06 (0.35–12.02), $p = 0.42$	5.01 (0.79–32.0), $p = 0.09$	0.25 (0.02–2.83), $p = 0.26$
Steroids	1.01 (0.21–2.34), $p = 0.98$	0.95 (0.37–1.15), $p = 0.88$	0.62 (0.20–1.43), $p = 0.70$	2.01 (0.12–4.39), $p = 0.67$

BLP beta-lactam prophylaxis

*Multivariate analysis controlling for BLP, female sex, diabetes, asthma, COPD, defect size, and steroid use in patients without a history of MRSA, with contaminated and grossly contaminated cases (wound class 4 and 4 operations)

reoperation (OR 0.31, CI 0.12–0.76) and recurrence (OR 0.32, CI 0.11–0.86) (Table 7).

Discussion

The safety of cephalosporins, specifically cefazolin, in patients with non-IgE mediated penicillin allergy has been well established. However, poor documentation of the allergy persists, leading to the selection of non-beta-lactam antibiotic surgical prophylaxis. This retrospective review of over a thousand patients demonstrates that patients reporting penicillin allergy are more comorbid at baseline. Reported penicillin allergy is associated with high rates of non-beta-lactam surgical prophylaxis, specifically vancomycin and clindamycin. Administration of BLP was associated with improved outcomes, particularly in contaminated cases. In patients with reported PA, administration of BLP was not associated with any adverse reactions.

The association of reported penicillin allergy with patient comorbidity is not commonly noted in the literature. In this study, rates of reported penicillin allergy were higher than rates in the general population (21.6% vs. 11% general population) [12, 20]. Reported PA was more common in female patients and patients with history of MRSA, COPD, asthma, chronic steroid use, sleep apnea, and chronic pain. These comorbidities may be multifactorial, with medical and surgical history contributing to both the likelihood of PA and of adverse outcomes associated with non-beta-lactam treatments. More comorbid patients may have higher rates of hospitalizations and exposure to penicillins, and thus the higher rates of reported PA. A 2015 study of over 50 thousand patient hospitalizations noted that rates of penicillin allergy were higher in female patients, and higher in patients with a history of prior hospitalization [27]. Asthma and COPD are also associated with smoke exposure and other allergic and immunogenic disease, and thus may mark “atopic” patients as susceptible to other allergic reactions [28]. Prior studies have demonstrated a 55% increased risk of MRSA when PA patients received non-BLP, and this may account for the higher rate of MRSA in this PA population (all patients had a history of prior operations) [8]. This comorbidity of patients with reported PA may reflect underlying disease process, sensitivity to medications, history of prior hospitalizations, history of surgical intervention, and history of treatment with non-BLP for surgical and nonsurgical indications, with adverse outcomes of non-ideal antibiotic coverage, such as MRSA infection.

In a 2018 study of 8385 patients undergoing general surgery procedures (hip arthroplasty, knee arthroplasty, hysterectomy, colon surgery, and CABG), *Blumenthal* et al. noted that penicillin allergy was associated with the administration of alternate antibiotics, and with an elevated odds

ratio of the surgical site infection (OR 1.51, CI 1.02–2.22) [12]. *Blumenthal* et al. do not distinguish between reported penicillin allergy and administration of non-beta-lactam antibiotics, and instead only presume non-BLP when PA is reported. Therefore, adverse outcomes in patients with reported PA may reflect the increased complexity of penicillin allergic patients, and not the outcomes of surgical prophylaxis. The complexity of PA patients and the impact of non-BLP was most apparent in patients with contaminated operations. Patients with wound class 3–4 had the highest rates of reported PA, as well as the highest rates of non-BLP antibiotics. Non-BLP was associated with increased rates of wound complication, reoperation, and recurrence, the findings which persisted in multivariate analysis. The complexity of these patients, with preexisting fistulas, wound infections, and mesh infections, may be both the cause and result of reported PA, with history of hospitalization and prior antibiotic exposure leading to reported PA, and complications of previous non-BLP leading to complex hernias requiring high-risk repair.

Patients with reported PA who receive BLP for surgery have low to absent rates of reaction to BLP, and patients with unknown or remote PA have similar rates of allergy as the baseline population (1.7%) [17, 18, 23–25]. Administration of non-BLP is associated with adverse drug reactions (clindamycin 1.5%), and incorrect dosing [7, 17, 25]. In patients undergoing orthopedic, cardiac, and colonic surgical intervention, patients who receive vancomycin due to reported PA have higher rates of wound complication [17, 29]. Use of non-BLP in PA patients has been associated with increased risk of VRE, MRSA, and *C. difficile* in hospitalized patients [8]. Finally, targeted testing for true PA is associated with increased use of BLP and a decrease in cost of treatment [5]. One study estimated that in a general surgery population, 112–114 patients would need allergy evaluation to prevent 1 SSI [12]. The choice of perioperative antibiotic in this patient cohort varied significantly between patients with and without reported penicillin allergy. Most patients without PA received cefazolin, including 95% of clean cases. However, 22.1% of patients with reported PA received BLP, with no recorded adverse reactions. Vancomycin and clindamycin were the most common antibiotics used in PA patients. These patterns of use and lack of adverse medication events are consistent with patterns of antibiotic usage in other surgical populations, including orthopedic, pediatric, gynecologic, and colorectal [7, 12, 30].

The present study reveals several important factors in the understanding of patients with reported penicillin allergy, and the impact of PA on choice of prophylactic antibiotic for open ventral hernia repair. Rates of reported penicillin allergy in complex OVHR are higher than the general population and are associated with a more comorbid patient population than non-penicillin allergic patients. Reported

penicillin allergy significantly impacts the choice of surgical antibiotic prophylaxis, as patients with reported PA more commonly receive clindamycin or vancomycin than cefazolin. Patients who did not receive first line surgical prophylaxis had worse outcomes, particularly in contaminated cases. It is unclear whether the administration of non-beta-lactam prophylaxis is an independent driver of worse outcomes, or the increased complexity of penicillin allergic patients leads to increased complications. Given the significant complexity of this patient population undergoing ventral hernia repair, this study may not be sufficiently powered to detect nuanced difference in patients who did and did not receive BLP, despite over one thousand patients included in review. Regardless, the impetus is on the surgeon to optimize antibiotic coverage, particularly in patients at higher risk of postoperative complications.

Finally, administration of beta-lactam prophylaxis to patients with reported penicillin allergy can be safe, and should be considered particularly in complex, contaminated open hernia repair. A review and correction of allergy history is appropriate in all patients undergoing surgical intervention, with careful attention paid to whether a reported penicillin allergy is potentially IgE mediated, or more consistent with intolerance [20]. Current guidelines include cefazolin as a first line prophylaxis for patients undergoing clean open ventral hernia repair, with clindamycin or vancomycin for patients with a penicillin allergy [4, 31]. In patients with known or anticipated contamination of OVHR, additional prophylaxis is tailored to the source of the contamination, and often includes metronidazole or gentamicin. In contaminated cases with a reported penicillin allergy, allergy workup or testing can be strongly considered, as these patients are demonstrated to be at highest risk of complications at baseline, and this study demonstrates that administration of non-BLP is associated with further adverse outcomes. Finally, this study demonstrates that patients with a history of MRSA who receive only beta-lactam prophylaxis may sustain adverse outcomes. This is in the context of a higher rate of adverse outcomes in MRSA positive patients at baseline [32]. However, some studies have supported the administration of vancomycin with a beta-lactam antibiotic for MRSA positive patients as beta-lactam antibiotics may have a synergistic role with vancomycin in treating MRSA + infections [33]. In these instances, the ability to provide adjuvant beta-lactam prophylaxis may significantly improve outcomes in a comorbid population.

Compliance with ethical standards

Disclosures Paul D Colavita MD is a speaker for Allergan. B Todd Heniford MD is a speaker for Allergan, performs education and research with stryker, and is on an advisory committee for WL Gore. Vedra

A Augenstein MD is a speaker for Allergan, Intuitive, Acclivity, and WL Gore. Authors Kathryn A Schlosser MD, Sean R Maloney MD, JM Horton, and Tanushree Prasad MA have no conflicts of interest or financial ties to disclose.

References

1. Cox TC, Blair LJ, Huntington CR, Colavita PD, Prasad T, Lincourt AE, Heniford BT, Augenstein VA (2016) The cost of preventable comorbidities on wound complications in open ventral hernia repair. *J Surg Res* 206:214–222. <https://doi.org/10.1016/j.jss.2016.08.009>
2. Poulouse BK, Shelton J, Phillips S, Moore D, Nealon W, Penson D, Beck W, Holzman MD (2012) Epidemiology and cost of ventral hernia repair: making the case for hernia research. *Hernia* 16:179–183. <https://doi.org/10.1007/s10029-011-0879-9>
3. Huntington C, Gamble J, Blair L, Cox T, Prasad T, Lincourt A, Augenstein V, Heniford BT (2016) Quantification of the effect of diabetes mellitus on ventral hernia repair: results from two national registries. *Am Surg* 82:661–671
4. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, Fish DN, Napolitano LM, Sawyer RG, Slain D, Steinberg JP, Weinstein RA, American Society of Health-System Pharmacists (ASHP), Infectious Diseases Society of America (IDSA), Surgical Infection Society (SIS), Society for Healthcare Epidemiology of America (SHEA) (2013) Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Surg Infect (Larchmt)* 14:73–156. <https://doi.org/10.1089/sur.2013.9999>
5. Chen JR, Tarver SA, Alvarez KS, Wei W, Khan DA (2018) Improving aztreonam stewardship and cost through a penicillin allergy testing clinical guideline. *Open forum Infect Dis* 5:ofy106. <https://doi.org/10.1093/ofid/ofy106>
6. Mattingly TJ, Fulton A, Lumish RA, Williams AMC, Yoon S, Yuen M, Heil EL (2018) The cost of self-reported penicillin allergy: a systematic review. *J allergy Clin Immunol Pract* 6:1649–1654. <https://doi.org/10.1016/j.jaip.2017.12.033>
7. Beltran RJ, Kako H, Chovanec T, Ramesh A, Bissonnette B, Tobias JD (2015) Penicillin allergy and surgical prophylaxis: cephalosporin cross-reactivity risk in a pediatric tertiary care center. *J Pediatr Surg* 50:856–859. <https://doi.org/10.1016/j.jpedsurg.2014.10.048>
8. Blumenthal KG, Lu N, Zhang Y, Li Y, Walensky RP, Choi HK (2018) Risk of methicillin resistant *Staphylococcus aureus* and *Clostridium difficile* in patients with a documented penicillin allergy: population based matched cohort study. *BMJ* 361:k2400. <https://doi.org/10.1136/bmj.k2400>
9. Pool C, Kass J, Spivack J, Nahumi N, Khan M, Babus L, Teng MS, Genden EM, Miles BA (2016) Increased surgical site infection rates following clindamycin use in head and neck free tissue transfer. *Otolaryngol Neck Surg* 154:272–278. <https://doi.org/10.1177/0194599815617129>
10. Macy E, Contreras R (2015) Adverse reactions associated with oral and parenteral use of cephalosporins: a retrospective population-based analysis. *J Allergy Clin Immunol* 135:745–752. <https://doi.org/10.1016/j.jaci.2014.07.062>
11. Murphy J, Isaiah A, Dyalram D, Lubek JE (2017) Surgical site infections in patients receiving osteomyocutaneous free flaps to the head and neck. does choice of antibiotic prophylaxis matter? *J Oral Maxillofac Surg* 75:2223–2229. <https://doi.org/10.1016/j.joms.2017.02.006>
12. Blumenthal KG, Ryan EE, Li Y, Lee H, Kuhlen JL, Shenoy ES (2018) The impact of a reported penicillin allergy on surgical site

- infection risk. *Clin Infect Dis* 66:329–336. <https://doi.org/10.1093/cid/cix794>
13. Trubiano JA, Adkinson NF, Phillips EJ (2017) Penicillin allergy is not necessarily forever. *JAMA* 318:82–83. <https://doi.org/10.1001/jama.2017.6510>
 14. Raja AS, Lindsell CJ, Bernstein JA, Codispoti CD, Moellman JJ (2009) The use of penicillin skin testing to assess the prevalence of penicillin allergy in an emergency department setting. *Ann Emerg Med* 54:72–77. <https://doi.org/10.1016/j.annemergmed.2008.12.034>
 15. Park M, Markus P, Matesic D, Li JTCC (2006) Safety and effectiveness of a preoperative allergy clinic in decreasing vancomycin use in patients with a history of penicillin allergy. *Ann Allergy Asthma Immunol* 97:681–687. [https://doi.org/10.1016/S1081-1206\(10\)61100-3](https://doi.org/10.1016/S1081-1206(10)61100-3)
 16. McDanel DL, Azar AE, Dowden AM, Murray-Bainer S, Noiseux NO, Willenborg M, Clark CR, Callaghan JJ, Haleem A (2017) Screening for beta-lactam allergy in joint arthroplasty patients to improve surgical prophylaxis practice. *J Arthroplasty* 32:S101–S108. <https://doi.org/10.1016/j.arth.2017.01.012>
 17. Epstein RH, St Jacques P, Wanderer JP, Bombulie MR, Agarwalla N (2016) Prophylactic antibiotic management of surgical patients noted as “allergic” to penicillin at two academic hospitals. *A A Case Rep* 6:263–267. <https://doi.org/10.1213/XAA.0000000000000253>
 18. Campagna JD, Bond MC, Schabelman E, Hayes BD (2012) The use of cephalosporins in penicillin-allergic patients: a literature review. *J Emerg Med* 42:612–620. <https://doi.org/10.1016/j.jemermed.2011.05.035>
 19. Pichichero ME (2005) A review of evidence supporting the American Academy of pediatrics recommendation for prescribing cephalosporin antibiotics for penicillin-allergic patients. *Pediatrics* 115:1048–1057. <https://doi.org/10.1542/peds.2004-1276>
 20. Shenoy ES, Macy E, Rowe T, Blumenthal KG (2019) Evaluation and management of penicillin allergy. *JAMA* 321:188. <https://doi.org/10.1001/jama.2018.19283>
 21. Tsuchiya K, Shiho O, Kondo M (1979) Immunological cross-reactivities of sulfocephalosporins. *J Antibiot (Tokyo)* 32:488–495
 22. Solensky R, Earl HS, Gruchalla RS (2002) Lack of penicillin resensitization in patients with a history of penicillin allergy after receiving repeated penicillin courses. *Arch Intern Med* 162:822–826
 23. Haslam S, Yen D, Dvirnik N, Engen D (2012) Cefazolin use in patients who report a non-IgE mediated penicillin allergy: a retrospective look at adverse reactions in arthroplasty. *Iowa Orthop J* 32:100–103
 24. Goodman EJ, Morgan MJ, Johnson PA, Nichols BA, Denk N, Gold BB (2001) Cephalosporins can be given to penicillin-allergic patients who do not exhibit an anaphylactic response. *J Clin Anesth* 13:561–564
 25. Gadde J, Spence M, Wheeler B, Adkinson NF (1993) Clinical experience with penicillin skin testing in a large inner-city STD clinic. *JAMA* 270:2456–2463
 26. Tan TL, Springer BD, Ruder JA, Ruffolo MR, Chen AF (2016) Is vancomycin-only prophylaxis for patients with penicillin allergy associated with increased risk of infection after arthroplasty? *Clin Orthop Relat Res* 474:1601–1606. <https://doi.org/10.1007/s11999-015-4672-4>
 27. Macy E, Contreras R (2014) Health care use and serious infection prevalence associated with penicillin “allergy”; in hospitalized patients: a cohort study. *J Allergy Clin Immunol* 133:790–796. <https://doi.org/10.1016/j.jaci.2013.09.021>
 28. Kronzer VL, Crowson CS, Sparks JA, Vassallo R, Davis JM (2019) Investigating asthma, allergic disease, passive smoke exposure, and risk of rheumatoid arthritis. *Arthritis Rheumatol*. <https://doi.org/10.1002/art.40858>
 29. Kheir MM, Tan TL, Azboy I, Tan DD, Parvizi J (2017) Vancomycin prophylaxis for total joint arthroplasty: incorrectly dosed and has a higher rate of periprosthetic infection than cefazolin. *Clin Orthop Relat Res* 475:1767–1774. <https://doi.org/10.1007/s11999-017-5302-0>
 30. Hawn MT, Richman JS, Vick CC, Deierhoi RJ, Graham LA, Henderson WG, Itani KMF (2013) Timing of surgical antibiotic prophylaxis and the risk of surgical site infection. *JAMA Surg* 148:649. <https://doi.org/10.1001/jamasurg.2013.134>
 31. Berrios-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, Reinke CE, Morgan S, Solomkin JS, Mazuski JE, Dellinger EP, Itani KMF, Berbari EF, Segreti J, Parvizi J, Blanchard J, Allen G, Kluytmans JAJW, Donlan R, Schechter WP (2017) Centers for disease control and prevention guideline for the prevention of surgical Site infection, 2017. *JAMA Surg* 152:784. <https://doi.org/10.1001/jamasurg.2017.0904>
 32. Baucom RB, Ousley J, Oyefule OO, Stewart MK, Phillips SE, Browman KK, Sharp KW, Holzman MD, Poulouse BK (2016) Evaluation of long-term surgical site occurrences in ventral hernia repair: implications of preoperative site independent MRSA infection. *Hernia* 20:701–710. <https://doi.org/10.1007/s10029-016-1523-5>
 33. Sakoulas G, Geriak M, Nizet V (2019) Is a reported penicillin allergy sufficient grounds to forgo the multidimensional antimicrobial benefits of β -lactam antibiotics? *Clin Infect Dis* 68:157–164. <https://doi.org/10.1093/cid/ciy557>

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