





## Original Article

# Prevalence of reported penicillin allergy and associations with perioperative complications, length of stay, and cost in patients undergoing elective cancer surgery

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## Abstract

**Objective:** Up to 10% of patients report penicillin allergy (PA), although only 1% are truly affected by Ig-E-mediated allergies. PA has been associated with worse postoperative outcomes, but studies on the impact of reported PA in cancer patients are lacking, and especially in these multimorbid patients, a non-complicated course is of utmost importance.

**Methods:** Retrospective analysis of patients undergoing elective oncological surgery at a tertiary reference center. Data on surgical site infections (SSI), postoperative complications (measured by Clavien-Dindo classification and Comprehensive Complication Index (CCI)), hospitalization duration, and treatment costs were collected.

**Results:** Between 09/2019 and 03/2020, 152 patients were identified. 16/152 patients (11%) reported PA, while 136/152 (89%) did not. There were no differences in age, BMI, Charlson Comorbidity Index, and smoking status between groups ( $p > 0.4$ ). Perioperative beta-lactam antibiotics were used in 122 (89.7%) and 15 (93.8%) patients without and with reported PA, respectively. SSI and mean numbers of infections occurred non-significantly more often in patients with PA ( $p = 0.2$  and  $p = 0.47$ ). The median CCI was significantly higher in PA group (26 vs. 51;  $p = 0.035$ ). The median hospitalization duration and treatment costs were similar between non-PA and PA groups (4 vs 3 days,  $p = 0.8$ ; 16'818 vs 17'444 CHF,  $p = 0.4$ ).

**Conclusions:** In patients undergoing cancer surgery, reported PA is common. Failure to question the unproven PA may impair perioperative outcomes. For this reason, patient and provider education on which reactions constitute a true allergy would also assist in allergy de-labeling. In addition, skin testing and oral antibiotic challenges can be performed to identify the safe antibiotics and to de-label appropriate patients.

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## Introduction

Penicillin allergy is one of the most frequently self-reported allergies in today's health care with approximately 10% of patients reporting a penicillin allergy.<sup>1</sup> Nevertheless only 1% of the general population are truly affected by Ig-E-mediated allergies and most lose their sensitivity during follow-up.<sup>2</sup> Reported penicillin allergies have been shown to be associated with worse patient outcomes. They are associated with surgical site infections, increased prevalence of multidrug-resistant bacteria, increased adverse events, higher mortality, longer hospital stays, and higher

treatment costs by the use of alternative antibiotics.<sup>3–6</sup> Reporting a therefore most likely unjustified penicillin allergy is very common but seems to have negative consequences. Since cancer patients undergoing oncological surgery are usually older, have more comorbidities and other risk factors that can influence a worse perioperative course (e.g. smoking), it is particularly important to know the influence of penicillin allergy in these patients and thus possibly prevent it.

However, none of the numerous studies that investigated the impact of penicillin allergy on perioperative outcomes included cancer patients; hence, there is no evidence in the current literature about the effect in oncologic surgery.

Therefore, the aim of this analysis was to assess the prevalence of reported penicillin allergy and the association with surgical site infections, complications, hospitalization duration, and treatment costs in patients undergoing elective cancer surgery.

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**Table 1.** Baseline characteristics of all patients and stratified by reported penicillin allergy

Characteristics	Total cohort	Reported penicillin allergy	
	<i>n</i> = 152	No (Group 1), <i>n</i> = 136	Yes (Group 2), <i>n</i> = 16
<b>Age</b>	62 (53, 71)	62 (53, 71)	64 (53, 67)
<b>BMI</b>	26.1 (22.9, 29.0)	26.1 (23.1, 29.1)	24.4 (22.4, 27.5)
Missing	56	50	6
<b>Charlson comorbidity index</b>	5 (4, 6.5)	5 (4, 6)	4.5 (4, 7.5)
Missing	1	1	0
<b>Smoking status</b>			
Never smoked	78 (53%)	67 (52%)	11 (69%)
Former smoker	42 (29%)	38 (29%)	4 (25%)
Current smoker	26 (18%)	25 (19%)	1 (6.2%)
Missing	6	6	0
<b>Other reported antibiotic allergies</b>	5 (3.3%)	4 (2.9%)	1 (6.2%)
<b>Number of reported antibiotic allergies</b>			
1	19 (95%)	4 (100%)	15 (94%)
2	1 (5.0%)	0 (0%)	1 (6.2%)
<b>Perioperative antibiotic prophylaxis applied</b>			
Cefazolin	116 (76%)	102 (75%)	14 (88%)
Cefazolin and Metronidazole	17 (11%)	16 (12%)	1 (6.2%)
Co-Trimoxazole	0 (0%)	0 (0%)	0 (0%)
Clindamycin	2 (1.3%)	1 (0.7%)	1 (6.2%)
Amoxicillin	5 (3.3%)	5 (3.7%)	0 (0%)
Unknown	12 (7.9%)	12 (8.8%)	0 (0%)
<b>Perioperative beta-lactam antibiotics</b>	137 (90.1%)	122 (89.7%)	15 (93.8%)

Note. IQR: Interquartile range.

Median (IQR); *n* (%).

Wilcoxon rank sum test; Fisher's exact test.

## Methods

We retrospectively reviewed all patients who underwent elective oncological surgery at a tertiary reference center between September 2019 (after introduction of a new electronic health record software) and March 2020 (before the COVID wave). We included patients from different specialties including visceral, gynecological, urological, head and neck and thoracic cancers. Exclusion criteria were minor procedures such as surgery under local anesthesia or endoscopic intervention (*n* = 35), procedures without necessary perioperative antibiotic prophylaxis (*n* = 0), unavailability of data on the perioperative antibiotic regimen (*n* = 4), and postoperative follow-up of less than 30 days (*n* = 0). Patients were then divided into two groups, either in the group without reported penicillin allergy (group 1) or in the penicillin allergy group (group 2).

The primary objective of this study was to compare the incidence of surgical site infections, complication rate, and severity between the two groups. Surgical site infection was defined as skin or wound infection or abscess at the surgery site. Complications were recorded within the first 30 days after surgery, and the severity of complications was assessed using the Clavien-Dindo classification (CDC).<sup>7</sup> CDC grade I were not evaluated, arguing that most of them would not have been reliably entered into the patient's medical record by clinicians. To summarize

complications over time for each procedure, the Comprehensive Complication Index (CCI)<sup>8</sup> was used. The CCI summarizes complications for each patient in a numerical value between 0 and 100, representing the total burden of complications, whereby 0 represents no complication and 100 represents patient death. The secondary objective of the study was to compare length of hospital stay and total treatment costs between the two groups.

The following characteristics were extracted from the medical chart: patients' baseline characteristics, reported penicillin allergy, perioperative antibiotics applied, type of surgical procedure, peri- and postoperative infection, infection type, infection site, costs, and length of inpatient stay.

All patients received at least one single-shot intraoperative antibiotic therapy according to the in-house recommendation for perioperative antibiotic prophylaxis. In cases of reported penicillin allergy, the choice of alternative antibiotic therapy was made in adherence to our in-house infectious disease guidelines. These guidelines are formulated based on the broader guidelines pertinent to the region of the operation and consider the local antimicrobial resistance scenarios. The Department of Infectious Diseases is responsible for the regular updating of these guidelines. The postoperative follow-up was not standardized and was performed at the surgeon's discretion or according to the corresponding oncological guideline.

Fisher's exact test and Pearson's chi-squared test were used to assess associations between categorical variables, while Mann-Whitney U-test was used to assess differences in continuous variables between the two surgical techniques. All tests were two-sided, and a  $p$ -value  $< 0.05$  was considered as statistically significant. All statistical analyses were performed using R (Version 4.0.3, Vienna, Austria, 2020). All patients enrolled had previously signed a general consent, and the study was approved by the local ethics committee (BASEC ID 2020-02389).

## Results

A total of 191 patients were identified. After applying the inclusion and exclusion criteria, 152 patients remained for the final analysis. Of these, 16 (11%) patients reported a penicillin allergy while 136 (89%) did not. Patients median age was 62 (IQR 53, 71) years. Patient characteristics of the total cohort and of the two groups are summarized in Table 1.

Groups did not differ in BMI, Charlson Comorbidity Index, smoking status, other reported antibiotic allergies, number of reported allergies, perioperative antibiotic prophylaxis they received, and the perioperative use of beta-lactam antibiotics (all  $p > 0.2$ ). The types of surgery performed in both groups are listed in Table 2.

Table 3 lists the results of the total cohort and two groups after surgical procedures. Surgical site infections occurred more often in group 2 (3 patients, 19%) compared to group 1 (11 patients, 8.1%), but this showed to be non-statistically different ( $p = 0.2$ ). There were no significant differences in the incidence of postoperative urinary tract infection, and none of the patients experienced sepsis. Total complications were the same in both groups with 46 (34%) in group 1 and 6 (38%) in group 2 ( $p = 0.8$ ). There was also an increased mean number of complications in group 2 (1.75) compared to group 1 (0.89), but this was not statistically significantly different ( $p = 0.47$ ). Major complications, which included all with CDC of 3 or higher, were more common in group 2, but this was not found to be statistically significantly different ( $p = 0.2$ ). The CCI was found to be significantly higher in group 2 with 51 (IQR 41, 61), compared to group 1 with 26 (IQR 21, 45) ( $p = 0.035$ ).

There were no differences in hospitalization duration and total treatment costs. The median hospitalization duration was 4 (IQR 3, 6) days and 3 (IQR 3, 6) days in groups 1 and 2, respectively. The median treatment costs were CHF 16,818 (IQR 10,635, 22,534) and CHF 17,444 (16,004, 22,599) in groups 1 and 2, respectively.

## Discussion

In the present study, we found that patients with reported penicillin allergy who underwent oncologic surgery had a non-significantly higher risk for surgical site infections, complications per patient, and overall complications. A significantly higher CCI was found in patients with penicillin allergy compared to patients without reported penicillin allergy. We found no difference between groups in terms of length of hospital stay and higher treatment costs.

Our results extend the literature describing the association of reported penicillin allergy with postoperative complications. Most of them focused on the effect of penicillin allergy in patients undergoing orthopedic surgery.<sup>5,9-15</sup> Some others examined this in patients undergoing colorectal and abdominal surgery,<sup>9,16,17</sup> cardiac interventions,<sup>9</sup> oral surgery,<sup>18</sup> or gynecologic surgery.<sup>9</sup> However, to the best of our knowledge, there is no study that has

**Table 2.** Performed surgeries within the two groups

	No penicillin allergy (Group 1), $n = 136$	Reported penicillin allergy (Group 2), $n = 16$
<b>Surgery</b>		
Hysterectomy	10 (7.4%)	1 (6.2%)
Prostatectomy	10 (7.4%)	-
Adnexectomy	2 (1.5%)	-
Cystoprostatectomy	2 (1.5%)	-
Kidney/Ureter/Adrenal Resection	2 (1.5%)	-
Mastectomy	63 (46%)	11 (69%)
Gastrectomy	2 (1.5%)	2 (12%)
HNO MKG tumor resection	15 (11%)	1 (6.2%)
Rectum amputation	3 (2.2%)	-
Wedge resection liver	2 (1.5%)	-
Pancreas resection	4 (2.9%)	-
Lung resection	7 (5.1%)	-
Deep lymph node resection retro/pelvic	4 (2.9%)	1 (6.2%)
Colpectomy	1 (0.7%)	-
Colon resection	5 (3.7%)	-
Omentectomy	1 (0.7%)	-
Laryngopharyngectomy	1 (0.7%)	-
Neck dissection	2 (1.5%)	-

$n$  (%).

investigated the impact of a reported penicillin allergy in patients who have undergone cancer surgery.

Most of the studies that investigated the impact of reported penicillin allergy on postoperative outcomes defined the occurrence of surgical site infections as the primary end point and were able to demonstrate a higher incidence in patients with penicillin allergy.<sup>5,9,18</sup> In a 2017 study by Blumenthal and colleagues, the authors retrospectively examined the impact of reported penicillin allergy on the incidence of surgical site infections in 8,385 patients undergoing hip arthroplasty, knee arthroplasty, hysterectomy, colon surgery, and coronary artery bypass grafting and found reported penicillin allergy in 11% of patients. Moreover, in their descriptive statistics, they could show a higher but not significantly risk for infectious complications in patients with reported penicillin allergy compared those without penicillin allergy, with 3.5% versus 2.6%, respectively ( $p = 0.1$ ). In their multivariable marginal structural model, the effect of reporting penicillin allergy on the development of SSI was fully mediated by receipt of non-beta-lactam antibiotics. The same conclusion was reached by Wilhelm and colleagues, who identified the use of non-beta-lactam antibiotics as perioperative prophylaxis as the sole independent predictor of surgical site infection in their multivariable regression analysis.<sup>19</sup> The use of beta-lactam antibiotics in 94% of our patients with reported penicillin allergy may thus explain why we did not detect a significant difference in the incidence of infectious complications, as shown in other studies.

However, despite recommendations in most guidelines to use beta-lactam antibiotics as perioperative prophylaxis, the literature

**Table 3.** Postoperative outcome characteristics of all patients and stratified by reported penicillin allergy

Characteristics	Total cohort		Reported penicillin allergy		p-value
	n = 152		No (Group 1), n = 136	Yes (Group 2), n = 16	
<b>Overall complications occurred</b>	52 (34%)		46 (34%)	6 (38%)	0.8
<b>Number of complications per patient</b>					0.47
Median (IQR)	0.00 (0.00, 1.00)		0.00 (0.00, 1.00)	0.00 (0.00, 3.00)	
Mean (SD)	1.00 (1.85)		0.89 (1.67)	1.75 (2.96)	
<b>Highest Clavien-Dindo classification</b>					0.3
CDC grade II	16 (11%)		16 (12%)	0 (0%)	
CDC grade IIIa	25 (16%)		20 (15%)	5 (31%)	
CDC grade IIIb	8 (5.3%)		7 (5.1%)	1 (6.2%)	
CDC grade IVa	0 (0%)		0 (0%)	0 (0%)	
CDC grade IVb	3 (2.0%)		3 (2.2%)	0 (0%)	
CDC grade V	0 (0%)		0 (0%)	0 (0%)	
<b>Major complications (<math>\geq</math> Clavien-Dindo III)</b>	36 (24%)		30 (22%)	6 (38%)	0.2
<b>Comprehensive Complication Index</b>	26 (21, 49)		26 (21, 45)	51 (41, 61)	<b>0.035</b>
<b>Surgical site infection</b>	14 (9.2%)		11 (8.1%)	3 (19%)	0.2
Skin or wound infection	11 (7.2%)		8 (5.9%)	3 (19%)	
Abscess	3 (2.0%)		3 (2.2%)	0 (0%)	
<b>Urinary tract infection</b>	4 (2.6%)		4 (2.9%)	0 (0%)	>0.9
<b>Sepsis</b>	0 (0%)		0 (0%)	0 (0%)	
<b>Length of stay (days)</b>	4 (3, 6)		4 (3, 6)	3 (3, 6)	0.8
<b>Total treatment costs (CHF)</b>	17,059 (10,638, 22,579)		16,818 (10,635, 22,534)	17,444 (16,004, 22,599)	0.4
Missing	5		4	1	

Note. IQR: Interquartile range; SD: standard deviation; CDC: Clavien-Dindo classification. n (%); Median (IQR).

Pearson's chi-squared test; Fisher's exact test; Wilcoxon rank sum test.

suggests that non-beta-lactam antibiotics such as vancomycin, clindamycin, gentamycin, or fluoroquinolones are commonly used in patients with reported penicillin allergy.<sup>3,9</sup> This is due to the fear of possible cross-reactivity between penicillin and other beta-lactams. However, cephalosporins and other beta-lactams are known to be widely safe to use in patients with established penicillin allergy because the likelihood of immunologic cross-reactivity is very low.<sup>3,20</sup> Thus, a 2021 systematic review and meta-analysis demonstrated a dual antibiotic allergy to penicillin and cefazolin of 0.6% in patients with reported penicillin allergy and 3% in patients with verified penicillin allergy.<sup>21</sup> However, the literature recommends preoperative testing of reported penicillin allergy to ensure, if indicated, beta-lactam antibiotic prophylaxis to prevent even the small possibility of a cross-reaction and postoperative infection complications.<sup>22</sup> In case of rapid assessment of penicillin allergy in cancer patients requiring urgent surgery, the PEN-FAST score is an established rule that accurately identifies patients at low risk of allergy.<sup>23</sup> We believe that allergy de-labeling is particularly important in cancer patients, as they tend to be older and have more comorbidities, exposing them to an even higher risk of complications.

The CCI is known to be a more sensitive alternative to measure overall morbidity instead of counting the number of complications. It is calculated as the sum of all Clavien-Dindo complications weighted by their severity<sup>8</sup>. Moreover, this continuous

complication score has the advantage of reflecting the overall burden of the postoperative course that affects patients' health and quality of life<sup>24</sup>. In the present study, the influence of reported penicillin allergy on CCI was investigated for the first time, and we recorded a significantly higher CCI in these patients. Fifty percent of the complications recorded in the penicillin allergy group were surgical site infections and more complications were recorded per patient, which explains the higher CCI. Thus, it appears that if an infectious complication occurs, it has a severe downstream effect and add more postoperative complications. This could be explained by the need to manage infection complications with alternative antibiotics, which in turn may promote further adverse postoperative outcomes by additional complications.

Previous studies investigating the impact of reported penicillin allergy on hospitalization duration and treatment costs have reported conflicting results.<sup>5,6,16,25,26</sup> Our patient groups showed no difference in hospitalization duration and treatment costs, but this should be considered with caution as our cohort consists of patients with different surgical procedures, which in turn are associated with different hospitalization durations and costs and thus may be strong confounders for these end points.

The present study has several limitations. First, the retrospective study design did not include potential confounders for the occurrence of postoperative complications, such as simple or multiple comorbidities. Furthermore, we lack specific data on



wound classifications, which could influence surgical site infections and related outcomes. Moreover, it should be noted that patients with different cancer types at different disease stages were included, and that, in addition to the heterogeneity of the surgeries performed, may have an impact on complications, hospitalization duration, and treatment costs. Second, the small single-center cohort allowed only a purely descriptive analysis, so that we recorded an insufficient number of end points, and thus, no analyses with adjustment for possible confounders were possible.

In patients scheduled for elective cancer surgery, reported penicillin allergy is common. Failure to question the unproven antibiotic allergies may impair perioperative outcomes. For this reason, patient and provider education on which reactions constitute a true allergy would also assist in allergy de-labeling. In addition, skin testing and oral antibiotic challenges can be performed to identify the safe antibiotics and to de-label appropriate patients.

**Author contribution.** Nico Christian Grossmann: Conceptualization, Formal analysis, Investigation, Methodology, Visualization, Roles/Writing – original draft.

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Nobody: Funding acquisition, Project administration, Resources, Software.

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