

BMJ Open Outcomes in hospitalised patients with sepsis, severe sepsis or septic shock and reported penicillin allergy: a retrospective cohort study

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ABSTRACT

Objective To determine outcomes in hospitalised patients with sepsis and reported penicillin allergy (PcnA).

Design Observational retrospective cohort study using data from electronic health records.

Setting A large single health system with 11 hospitals of small, medium and large sizes including a 630-bed tertiary care teaching hospital.

Participants Patients (n=5238) ≥18 years of age, hospitalised with sepsis, severe sepsis or septic shock between 1 January 2016 and 31 December 2018, received antibacterial agents, and had documented PcnA status. Patients <18 years of age at admission were excluded.

Outcome measures Primary outcomes evaluated were inpatient mortality and 30-day mortality posthospital discharge. Secondary outcomes were hospital length of stay, 30-day readmissions, duration of antibiotic use, rate of *Clostridium difficile* infection and total cost of care.

Results There was no difference in outcomes including inpatient or 30-day mortality, hospital length of stay, in-hospital antibiotic duration, *C. difficile* infection, total cost of care and 30-day readmission rate between patients labelled with a PcnA vs patients who did not report PcnA (non-PcnA).

Conclusion In this retrospective single health system study, there was no difference in key outcomes including inpatient or 30-day mortality in patients admitted with sepsis and reported PcnA compared with patients who reported no PcnA.

INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by dysregulated host responses to infection,^{1 2} with high patient morbidity and mortality.³ In the USA, in 2013, cost of care was US\$20 000–US\$40 000/hospitalised patient and US\$23.7 billion dollars annually.^{4 5} Survivors suffer from long-term physical and cognitive disabilities leading to additional health implications.⁶

In bacterial sepsis, early and appropriate antibiotic administration improves outcomes.^{7–10} Reported antimicrobial

Strengths and limitations of this study

- Large retrospective electronic medical record-based data from single health system is analysed in this study.
- Authors targeted reported penicillin allergy and its effect on health outcomes in sepsis which is an important area of further research.
- The measurement of outcomes may have been less accurate and consistent than would have been attained with a prospective study design.
- Patients who have not reported penicillin allergy may still be allergic to penicillin.
- The cohorts used in the study may not have been representative of an entire population of patients but instead those seen within our healthcare system.

allergies are considered in antimicrobial regimen selection.¹¹ Nationally, ~20% of hospitalised patient's records describe a penicillin allergy (PcnA), but <10% with a reported PcnA have a true clinically relevant allergy when objectively evaluated with rigorous skin testing.^{12 13} PcnA may become part of a patient's history or medical record even if the documented reaction was due to other medications or was non-immune mediated. Patients with reported childhood PcnA are reluctant to receive penicillins although they are low risk for true allergy. Those PcnA patients with negative skin testing usually tolerate penicillins well without adverse outcomes.¹⁴

Overall cross reactivity is low between penicillins, cephalosporins and carbapenems for PcnA patients.^{15 16} Antibiotic specific risks depend on the side chain structure.¹⁷ Beta-lactam antibiotics are among the leading causes of drug induced anaphylaxis leading clinicians instead to administer alternative antibiotics that displace first line therapies

and increase adverse events in PcnA patients. A PcnA label is associated with increased antibiotic resistance due to increased use of broad-spectrum and non-beta lactam antibiotics.¹⁸

PcnA patients are more likely to receive carbapenems, fluoroquinolones, clindamycin and vancomycin.^{10 18} In a large study hospitalised PcnA patients had increased rates of methicillin-resistant *Staphylococcus aureus* (MRSA) (2.6% vs 2.2%) and vancomycin-resistant Enterococci (0.6% vs 0.5%) than those without PcnA.¹⁹ PcnA patients can experience a 50 min delay in antibiotic initiation,²⁰ and more surgical site infections likely because of suboptimal coverage from second-line antibiotics.²¹ Other reported adverse outcomes include increased rates of *Clostridium difficile* infection and longer hospital stays.¹⁹ Outcomes are relatively unknown for patients admitted with severe infections and reported PcnA. Potential explanations are that hospitalised sepsis patients frequently receive different antibiotic classes. Penicillins alone are uncommonly used even without reported allergy in patients presenting with sepsis.

Recently, robust antimicrobial stewardship programmes (ASPs) have been implemented to address appropriate and timely antibiotic choices. The Centers for Disease Control and Prevention recommend that all hospitals have ASPs to minimise adverse events and reduce antibiotic resistance.²² Some ASPs also incorporate PcnA skin testing proven to be safe and effective even for critically ill patients.²³ Our research question was, 'What are the health outcomes of inpatients with sepsis, severe sepsis, and shock who were labelled as having PcnA compared with inpatients who were not labelled as having PcnA?' Subsequently, the objective of this study was to compare antibiotic use patterns and outcomes between patients with reported PcnA and non-PcnA hospitalised with sepsis, severe sepsis, and septic shock in a health system with active ASPs.

METHODS

Study population and data collection

Hospitalised eligible patients ≥ 18 years were identified from electronic medical records (EMRs) at an 11-hospital system in Minnesota and Western Wisconsin. Patient's data were collected from 1 July 2016 to 30 June 2018 from our organisation's electronic data warehouse. The study's sample size was obtained after the initial data extract was verified to include all eligible participants. Selection bias was minimal because we included all eligible patients in the cohorts with and without a PcnA label. There was no direct involvement of patients or the public in design and conduct of the study, choice of outcome measures, recruitment or dissemination of the results because of the retrospective study design. The research question was developed based on self-reported PcnA status by hospitalised patients at admission. This information was entered into their medical records and informed provider's medical decision making even though published

evidence indicates that the majority of these patients do not have true clinically relevant allergy when objectively tested through rigorous skin testing.^{11 12 24}

Study design

Patients were selected by electronic health record query of diagnosis codes containing sepsis, severe sepsis or septic shock during specific hospital encounter. Patients with labelled PcnA were compared against those who did not have PcnA label (Non-PcnA). Our rationale was that choices of second line antibiotics in reported PcnA can cause adverse outcomes. Those who did not receive antibiotics were excluded because sepsis can be caused by non-bacterial infections and a reported PcnA may not change the choice of antimicrobial agent. In our health system larger referral hospitals frequently get patient transferred from other hospitals and emergency department outside our health system and data on antibiotic administered before transfer (in emergency department) was not available in some patients. Patient with missing complete antibiotics data were excluded (figure 1). Age, gender, race, body mass index, insurance coverage, risk of mortality, severity of illness and LACE score (to evaluate risk of readmission) were the covariates. Primary outcomes evaluated were inpatient mortality and 30-day mortality posthospital discharge. Secondary outcomes were hospital length of stay (LOS), 30-day readmissions, duration of antibiotic use, rate of *C. difficile* infection and total cost of care.

Statistical analysis

Patients were categorised as reported PcnA and non-PcnA. Subgroup analysis was performed on PcnA patients who received cephalosporin alone, cephalosporin with another class of antibiotics, or antibiotics other than a cephalosporin. In the PcnA subgroup, patients who received penicillins were excluded. Inpatient and 30-day post discharge mortality, hospital LOS, total cost of care, antibiotic duration, *C. difficile* infection in hospital and 30-day readmission were evaluated. Means, SD, medians and Q1–Q3, frequencies and proportions, were used to describe the PcnA and non-PcnA groups' patient characteristics and outcomes, as appropriate. Comparisons between the PcnA and non-PcnA groups were conducted using two-sample independent t-tests, Mann-Whitney U tests, χ^2 tests and Fisher's exact tests. The descriptive analysis of the three PcnA subgroups were conducted likewise to the main analysis. One-way analysis of variance, χ^2 and Kruskal-Wallis tests were conducted, as appropriate, to compare patient characteristics and outcomes across the three PcnA subgroups. Pairwise comparisons were conducted using a Bonferroni correction.

Adjusted analysis was conducted with the primary and secondary outcomes for both the main and the subgroup analysis to address potential bias in estimated effects of a PcnA label. To reduce multicollinearity, risk of mortality and severity of illness variables were both recoded into two categories: 'minor and moderate' and 'major and

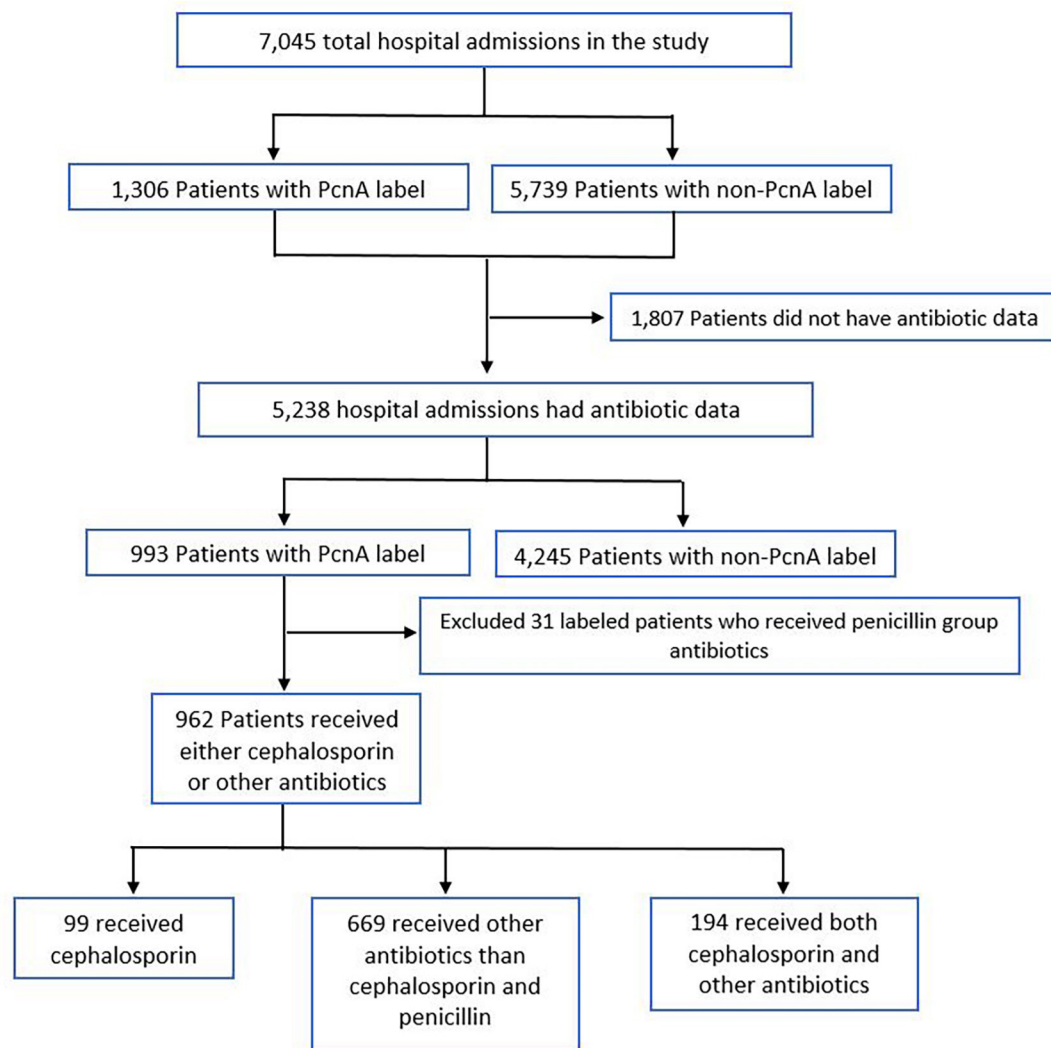


Figure 1 Study population identification. PcnA, penicillin allergy.

extreme'. Logistic regression was used to test for differences in inpatient mortality, *C. difficile* in hospital and 30-day readmission between the PcnA and non-PcnA groups. Unadjusted and adjusted ORs and their respective 95% CIs were calculated. Potential confounding variables for each model were selected based on clinical importance and a $p < 0.2$ in the unadjusted tests. These variables were further controlled using a backward elimination method. The Firth logistic regression method was used to analyse the inpatient outcomes mortality and *C. difficile* due to the small number of events. Differences between the PcnA and non-PcnA groups in hospital LOS, total cost of care and duration of antibiotics were tested using negative binomial regression and the same model selection process as stated for the logistic regression models.

Regression analysis was also used to test for differences among the three antibiotics subgroups. Inpatient mortality and 30-day readmission were all analysed using Firth logistic regression in unadjusted models. Unadjusted ORs and their respective 95% CI were calculated. Differences among the subgroups in rates of 30-day

readmission were also tested in an adjusted Firth logistic regression model. Differences among the three antibiotics subgroups in hospital LOS, total cost of care and duration of antibiotics were tested using negative binomial regression. Confounders for all adjusted regression models were selected in the same manner as described in the main analysis. Wald tests were used to test for the significance of the three (1) category antibiotics variable as a whole in each model. Two-tailed p values were computed for all tests, with significance at $p < 0.05$. All statistical analyses were conducted using R software V.3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria.)

Patient and public involvement

There was no direct patient involvement. Data were used from electronic database.

RESULTS

We identified 7045 hospitalised patients with a documented diagnosis of sepsis, severe sepsis, or septic shock.

Table 1 Characteristics of hospitalised patients with a PCNA label versus no PCNA label

	No PcnA label	PcnA label	P value
n	4245	993	
BMI, mean (SD)	30.2 (8.9)	31.3 (10.5)	0.002*
White race, n (%)	3709 (88.5)	931 (94.3)	<0.0001*
Male, n (%)	2308 (54.4)	404 (40.7)	<0.0001*
Current or former tobacco use, n (%)	2361 (59.1)	591 (62.9)	0.0327*
Private insurance status, n (%)	1120 (26.4)	265 (26.7)	0.846
Risk of mortality, n (%)			0.632
Minor	471 (11.2)	98 (9.9)	
Moderate	786 (18.6)	195 (19.8)	
Major	1556 (36.9)	358 (36.3)	
Extreme	1406 (33.3)	336 (34)	
Severity of illness, n (%)			0.231
Minor	133 (3.2)	22 (2.2)	
Moderate	960 (22.8)	224 (22.7)	
Major	1997 (47.3)	459 (46.5)	
Extreme	1129 (26.8)	282 (28.6)	
Cancer, n (%)	1063 (25.6)	213 (21.7)	0.0106*
COPD, n (%)	628 (15.1)	188 (19.1)	0.002*
Diabetes mellitus, n (%)	1332 (32.1)	367 (37.4)	0.0016*
CAD, n (%)	932 (22.5)	213 (21.7)	0.606
Stroke, n (%)	603 (14.5)	172 (17.5)	0.019*

*Statistically significant results, $p < 0.05$.

BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; PcnA, penicillin allergy.

Of those, 1807 patients were missing antibiotic data or did not receive antibiotics during the hospitalisation and were excluded. Of the remaining 5238 patients, 993 (18.9%) had a reported PcnA label in their EMR and 4245 (81.1%) did not (figure 1). A higher proportion of patients with reported PcnA were female (59.3%) and white (94.3%) compared with non-PcnA patients (table 1). Significantly more PcnA compared with non-PcnA patients reported allergic reactions (4.7% vs 0%, $p < 0.0001$).

Antibiotic use in both groups has been described in figure 2. Cephalosporin use was similar in both groups. In PcnA patients, 29.8% received cephalosporin antibiotics compared with 31.3% for non-PcnA patients ($p = 0.358$). Use of other classes of antibiotics (non-PcnA, non-cephalosporin) was more common in PcnA patients (89.1% vs 82.7%, $p < 0.001$).

Use of multiple antibiotics during hospitalisation was more common in non-PcnA patients, with 29.6% of patients receiving more than one class of antibiotics compared with 21.9% of patients in the PcnA group

Antibiotic class	No PcnA	%	PcnA	%
Penicillin	742	17.50%	31	3.10%
Cephalosporin	1329	31.30%	296	29.80%
Aminoglycoside	12	0.3%	6	0.6%
Antimycobacterial	38	0.9%	3	0.3%
Carbapenem	1	0.0%	0	0.0%
Colistins	9	0.2%	4	0.4%
Fluoroquinolone	1154	27.2%	336	33.8%
Fosfomycin	16	0.4%	2	0.2%
Glycopeptide (e.g. Vancomycin)	1513	35.6%	350	35.2%
Licosamide (e.g. Clindamycin)	373	8.8%	121	12.2%
Macrolid	15	0.4%	7	0.7%
Macrolide	611	14.4%	140	14.1%
Nitroimidazoles	597	14.1%	159	16.0%
Oxazolidinones (e.g. Linezolid)	37	0.9%	14	1.4%
Sulfonilamides	11	0.3%	6	0.6%
Tetracyclines	244	5.7%	66	6.6%

Figure 2 Antibiotic groups used in non-PcnA and PCNA patients. PcnA, penicillin allergy.

($p < 0.0001$, table 2). Antibiotics associated with a higher risk of *C. difficile* infection were more commonly used in the PcnA group (33.8% received fluoroquinolones compared with 27.2% in the non-PcnA group, $p < 0.0001$). A licosamide (clindamycin) was used in 12.2% of PcnA patients vs 8.8% of non-PcnA patients ($p = 0.001$). Glycopeptide (vancomycin) use was similar in both groups (35.2% for PcnA vs 35.6% for non-PcnA, $p = 0.814$).

Differences were noted in antibiotic use by type and decision to treat with an antibiotic regimen including penicillins for PcnA versus non-PcnA patients ($p < 0.05$). Primary and secondary outcomes between PcnA and non-PcnA patients were not different including 30-day mortality, hospital LOS, antibiotic duration, peripherally inserted central catheter use, hospital-acquired *C. difficile* infections and total cost of care (table 2). Regression analysis was performed to adjust for patient characteristics to examine outcomes including mortality, hospital LOS, 30-day readmissions, occurrence of *C. difficile* in the hospital, total cost of care and days on antibiotics. Significant differences were not seen among the groups. Therefore, the number needed to treat/harm was not calculated.

After subgroup analysis, out of 993 patients with a reported PcnA, 31 received penicillins and were excluded. The remaining 962 patients were divided into three groups for analysis: those who received cephalosporins only, those who received other classes of antibiotics only, and those who received cephalosporins and other classes of antibiotics simultaneously (figure 1). In a global comparison across the three antibiotic subgroups (table 3), we found differences for age ($p = 0.0452$), severity of illness ($p = 0.0089$) and occurrence of heart failure ($p = 0.041$).

Further testing was performed to detect differences among the three antibiotics subgroups. Significant differences in age ($p = 0.039$) and incidence of heart failure ($p = 0.047$) were found between the groups who received other antibiotics and those who received both

Table 2 Unadjusted outcomes and antibiotics use for hospitalised patients

	No PcnA label	PcnA label	P value
n	4245	993	
Inpatient mortality, n (%)	156 (3.7)	38 (3.8)	0.820
30-day mortality, n (%)	332 (7.8)	76 (7.7)	0.859
LOS in days, median (Q1–Q3)	4.06 (2.81–6.36)	4.02 (2.79–6.28)	0.422
Total drug cost in thousands of dollars, median (Q1–Q3)	3.22 (2.06–5.57)	3.30 (2.05–5.60)	0.619
Total cost of care in thousands of dollars, median (Q1–Q3)	10.20 (6.32–18.21)	10.39 (6.26–17.89)	0.265
Days on antibiotics, median (Q1–Q3)	3 (2–5)	3 (2–5)	0.675
Ventilator, n (%)	299 (7.0)	66 (6.6)	0.658
<i>Clostridium difficile</i> in hospital, n (%)	109 (2.6)	34 (3.4)	0.136
Allergic reaction, n (%)	0 (0)	47 (4.7)	<0.0001*
Cause of allergic reaction (of those with a reaction), n (%):			N/A
Drug	0 (0)	10 (21.3)	
Unknown	0 (0)	37 (78.7)	
PICC line, n (%)	448 (10.6)	120 (12.1)	0.163
ICU admission, n (%)	1168 (27.5)	263 (26.5)	0.512
Readmission, 30 days, n (%)	929 (21.9)	225 (22.7)	0.596
Total use, antibiotic groups, n (%)			
Pcn	742 (17.5)	31 (3.1)	<0.0001*
Cephalosporin	1329 (31.3)	296 (29.8)	0.358
Other	3510 (82.7)	885 (89.1)	<0.0001*
Antibiotic use patterns, n (%)			
Pcn only	215 (5.1)	7 (0.7)	<0.0001*
Cephalosporin only	484 (11.4)	99 (10)	0.1967
Other only	2287 (53.9)	669 (67.4)	<0.0001*
Cephalosporin and other	732 (17.2)	194 (19.5)	0.088
Cephalosporin and Pcn	36 (0.8)	2 (0.2)	0.0307*
Pcn and other	414 (9.8)	21 (2.1)	<0.0001*
Pcn, cephalosporin and other	77 (1.8)	1 (0.1)	<0.0001*

*Statistically significant results $p < 0.05$.

ICU, intensive care unit; LOS, length of stay; NA, not available; Pcn, penicillin; PcnA, penicillin allergy; PICC, peripherally inserted central catheter.

cephalosporins and other antibiotics in pairwise comparisons with Bonferroni corrections.

In the subgroup analysis, unadjusted outcomes were assessed by antibiotic type (table 4). In a global comparison across the three groups, significant differences were found in median LOS in days ($p < 0.0001$), median total drug cost in thousands of dollars ($p = 0.00393$), median total cost of care in thousands of dollars ($p = 0.000172$), median days of antibiotics use ($p < 0.0001$) and occurrence of *C. difficile* in hospital ($p = 0.0138$). For the readmission logistic regression model, the type of antibiotic administered achieved significance using the Wald test ($p = 0.028$, data not shown).

Using an adjusted logistic regression model, no significant differences were found in 30-day mortality across the three antibiotic groups. Using the patient group who received other antibiotics as the reference category, those

patients who received both cephalosporins and other antibiotics had higher odds of 30-day readmission (OR=1.54, 95% CI 1.04 to 2.27). Patients who received cephalosporins and other antibiotics had a longer hospital LOS (incidence rate ratio, IRR=1.25, 95% CI 1.13 to 1.38), higher total cost of care (IRR=1.28, 95% CI 1.12 to 1.46), and more days on antibiotics (IRR=1.59, 95% CI 1.42 to 1.78), (table 5).

DISCUSSION

We did not find major differences in outcomes between patients with a reported PcnA compared with non-PcnA patients who have documented diagnosis of sepsis, severe sepsis or septic shock. Our study is a retrospective data analysis of electronic health record based queries. We included patients with clinician documented sepsis who

**Table 3** Characteristics of patients with a PcnA label according to type of antibiotic administered

	Cephalosporin	Other	Cephalosporin and other	P value
n	99	669	194	
BMI, mean (SD)	31.8 (9.5)	30.7 (9.1)	32.5 (11.3)	0.0631
Pulse (min), mean (SD)	67 (12)	66 (16)	66 (13)	0.917
Age, mean (SD)	65.7 (17.7)	64.8 (17.7)	68.3 (15.5)	0.0452*
White race, n (%)	95 (96.9)	621 (93.4)	185 (95.9)	0.208
Male, % (n)	45 (45.5)	264 (39.5)	81 (41.8)	0.489
Current or former tobacco use, n (%)	58 (59.2)	386 (61.3)	127 (69.8)	0.083
Private insurance, n (%)	32 (32.3)	184 (27.5)	44 (22.7)	0.188
Risk of mortality, n (%)				0.052
Minor	15 (15.2)	63 (9.5)	18 (9.3)	
Moderate	26 (26.3)	137 (20.6)	30 (15.5)	
Major	27 (27.3)	245 (36.9)	70 (36.3)	
Extreme	31 (31.3)	219 (33)	75 (38.9)	
Severity of illness, n (%)				0.0089*
Minor	5 (5.1)	14 (2.1)	3 (1.6)	
Moderate	32 (32.3)	151 (22.7)	39 (20.2)	
Major	42 (42.4)	307 (46.2)	91 (47.2)	
Extreme	20 (20.2)	192 (28.9)	60 (31.1)	
Cancer, n (%)	14 (14.1)	154 (23.3)	40 (20.7)	0.109
Heart failure, n (%)	19 (19.2)	120 (18.2)	52 (26.4)	0.041*
COPD, n (%)	15 (15.2)	127 (19.2)	38 (19.7)	0.596
CKD, n (%)	21 (21.2)	137 (20.8)	33 (17.1)	0.512
Diabetes mellitus, n (%)	32 (32.3)	240 (36.4)	83 (43)	0.137
Hypertension, n (%)	44 (44.4)	343 (52)	109 (56.5)	0.149
CAD, n (%)	19 (19.2)	145 (22)	45 (23.3)	0.723
Stroke, n (%)	16 (16.2)	121 (18.3)	32 (16.6)	0.777
Liver disease, n (%)	6 (6.1)	48 (7.3)	13 (6.7)	0.893
Surgery 4 weeks prior to antibiotic use, n (%)	4 (4.0)	57 (8.5)	12 (6.2)	0.207

*Statistically significant results, $p < 0.05$.

BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; PcnA, penicillin allergy.

received antibiotics during the hospital visit. Our hypothesis was as far as treating clinician was treating patient for suspected bacterial infection with antibiotics, documented PcnA will affect antibiotic choices and potentially outcomes. Our findings agreed with previously reports for PcnA patients including more use of fluoroquinolones and clindamycin which could have led to more adverse outcomes. However, our non-PcnA group had a larger percentage of patients who received multiple antibiotic classes. Possibly in the PcnA group, fewer classes of antibiotics were administered due to concern for allergic reactions.

Cephalosporins and vancomycin use was similar in both groups. Vancomycin is frequently substituted in patients with reported PcnA in preoperative prophylaxis.²⁴ In previous studies, patients with methicillin-susceptible *S. aureus* infection and treated with cefazolin or an

anti-staphylococcal PcnA had lower mortality compared with patients treated with vancomycin.²⁵ In studies where reported PcnA had adverse outcomes, overuse of vancomycin was implicated as a possible cause. Another explanation for our findings is that the causative pathogen is initially unidentified for many hospitalised sepsis patients, and vancomycin is commonly used to treat a potential MRSA infection especially as initial broad spectrum coverage.

ASPs are expanding in hospitals due to risks associated with inappropriate antibiotic use and Joint Commission standard requirements.²⁶ These programmes improve outcomes in patients presenting with severe infections.²⁷ At each hospital within our health system, ASPs and PcnA management varied and no ASP had a formal mechanism in place to review PcnA allergies and delabel or challenge PcnA allergies before initiation of antibiotics for sepsis.

Table 4 Unadjusted outcomes of patients with a PCNA label by antibiotic administered

	Cephalosporin	Other	Cephalosporin and other	P value
n				
Inpatient mortality, n (%)	1 (1.0)	30 (4.5)	5 (2.6)	0.181
30-day mortality, n (%)	2 (2.0)	58 (8.7)	14 (7.2)	0.0656
LOS in days, median, (Q1–Q3)	3.9 (2.9–6.2)	3.9 (2.7–6.0)	4.8 (3.3–8.0)	<0.0001*
Total drug cost in thousands of dollars, median (Q1–Q3)	2.77 (1.92–4.80)	3.20 (1.98–5.48)	3.62 (4.21–6.86)	0.00393*
Total cost of care in thousands of dollars, median (Q1–Q3)	8.75 (6.13–16.39)	9.93 (5.83–16.69)	12.32 (8.16–21.55)	0.000172*
Days of antibiotics use, median (Q1–Q3)	2 (1–3)	3 (2–5)	5 (4–8)	<0.0001*
Ventilator, n (%)	5 (5.1)	46 (6.9)	13 (6.7)	0.7931
<i>Clostridium difficile</i> in hospital, n (%)	0 (0)	30 (4.5)	3 (1.5)	0.0138*
Allergic reaction, n (%)	4 (4.0)	29 (4.3)	12 (6.2)	0.5557
Cause of allergic reaction (of those with a reaction), n (%)				0.2724
Drug	2 (50.0)	5 (17.2)	3 (25.0)	
Unknown	2 (50.0)	24 (82.8)	9 (75.0)	
PICC line, n (%)	6 (6.1)	81 (12.1)	30 (15.5)	0.0662
ICU admission, n (%)	25 (25.3)	177 (26.5)	51 (26.3)	0.9682
Readmission, 30 days, n (%)	27 (27.3)	137 (20.5)	50 (25.8)	0.132

*Statistically significant results, $p < 0.05$.

ICU, intensive care unit; LOS, length of stay; PcnA, penicillin allergy; PICC, peripherally inserted central catheter.

PcnA allergies/intolerances that could be safely challenged are often discovered within 48 hours of antibiotic initiation and the reviewing ASP pharmacist or physician, dependent on site, decides whether to change antibiotics for individual patients. Sepsis order sets are reviewed and updated by antimicrobial stewardship staff and infectious disease providers on an annual basis when institutional antibiograms are refreshed. Antibiotics in this order set include source specific sepsis recommendations as well as alternatives in PcnA allergic patients. ASPs likely have a role in our outcomes by influencing providers' choice of antibiotics, especially considering the finding of similar cephalosporin use in both groups.

In the PcnA subgroup analysis, patients who received both cephalosporins and other classes of antibiotics were sicker with a higher severity of illness. This finding reflects common practice where sicker patients get more classes of antibiotics for broader antimicrobial coverage in the early part of hospitalisation. In the patient group receiving only cephalosporins, no patients had hospital-acquired *C. difficile* infection compared with 30 patients (4.5%) with this infection who received other antibiotics, but the outcome was not statistically significant. After adjusting for variables including severity of illness, patients who received combined cephalosporin and other antibiotics had an increased hospital LOS, more days on antibiotics and a greater total cost of care. There was no difference in 30-day mortality or 30-day readmissions. Possibly, multiple antibiotic use may play a more

significant role than reported PcnA and choice of antibiotics in adverse outcomes among sepsis patients where early use of broad-spectrum antibiotics is common despite reported PcnA. Robust ASPs can also help in optimising antibiotic choices and reducing adverse outcomes.

Limitations

Our retrospective study relied on EMRs for data accuracy and was at a single healthcare system which may limit generalisability of the findings. We also get large number of patients transferred from hospitals and emergency department outside our health system and some electronic health record is not integrated which lead to exclusion of patients where antibiotic data before transfer to our health system was missing. We did not evaluate time to first antibiotic use. Some studies have suggested adverse outcomes in patients presenting with infection and reported PcnA could be due to a delay in antibiotic administration. Our intention was also to look at real-world situations among all hospitalised patients with diagnosis of sepsis so most of our patients were not very ill and overall mortality was low so this study may not be applicable to sicker patients in intensive care units and could have contributed in detecting mortality outcomes among two groups. We also did not look at reported causes of sepsis due to concern about limited documentation in EMR and reduce in sample size. We also did not categorise patients based on severity of reported PcnA and we did not have data available if patients ever had penicillin

**Table 5** Regression analysis of outcomes of hospitalised patients with a reported PCNA by type of antibiotic administered

Regression models	Unadjusted OR	95% CI	P value
30-day readmission			
Cephalosporin only	1.49	0.90 to 2.38	0.106
Cephalosporin and other	1.38	0.94 to 2.00	0.091
30-day mortality			
Cephalosporin only	0.27	0.04 to 0.80	0.045*
Cephalosporin and other	0.78	0.39 to 1.40	0.429
	Adjusted OR	95% CI	P value
30-day readmission			
Cephalosporin only	1.65	0.99 to 2.68	0.049
Cephalosporin and other	1.54	1.04 to 2.27	0.03*
30-day mortality			
Cephalosporin only	0.35	0.05 to 1.08	0.113
Cephalosporin and other	0.70	0.34 to 1.29	0.267
	Incidence rate ratio	95% CI	P value
Hospital LOS			
Cephalosporin only	1.11	0.97 to 1.27	0.135
Cephalosporin and other	1.25	1.13 to 1.38	<0.001*
Total cost of care			
Cephalosporin only	1.13	0.95 to 1.35	0.187
Cephalosporin and other	1.28	1.12 to 1.46	<0.001*
Days on antibiotics			
Cephalosporin only	0.87	0.74 to 1.03	0.115
Cephalosporin and other	1.59	1.42 to 1.78	<0.001*

Other antibiotics group is the reference category.

*Statistically significant results, $p < 0.05$.

LOS, length of stay; PcnA, penicillin allergy.

skin testing. We only looked at antibiotics administered during the hospitalisation and did not review discharge prescriptions which also could be a limiting factor.

CONCLUSION

Despite limitation our study suggests that hospitalised patients with reported PcnA who had documented sepsis, severe sepsis or septic shock and received antibiotics did not have worse outcomes compared with Non-PcnA. Use of multiple classes of antibiotics was common in both groups. Antibiotics with higher risk of *C. difficile* were used more commonly with reported PcnA. More research is needed to evaluate the impact of reported PcnA in patients hospitalised with infections.

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