Beta Lactam Allergies

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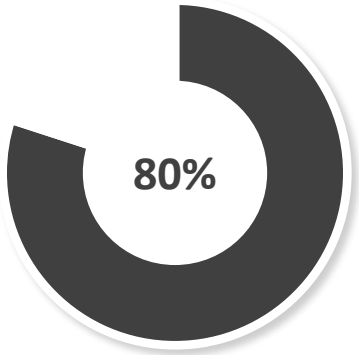
American Academy of Allergy Asthma & Immunology

Centers for Disease Control and Prevention
National Center for Emerging and Zoonotic Infectious Diseases

Penicillin Allergy Statistics

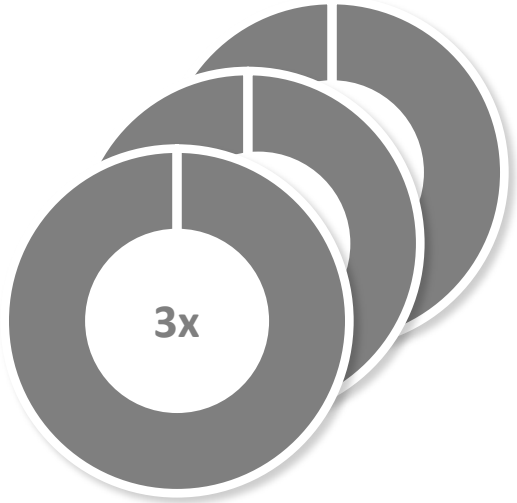
False Reporting

9 out of 10 reporting penicillin allergy are not truly allergic when tested



“Grow out of it”

80% of patients with IgE-mediated penicillin allergy lose their sensitivity after 10 years.



Adverse Events

Patients labeled penicillin-allergic have a threefold increased risk of adverse events (ADE)

Penicillin Allergies: Post-operative Infections

- 8,385 patients at Mass General Hospital
- Undergoing hip and knee arthroplasty, hysterectomy, colon surgery and CABG
- 11% Penicillin Allergy Rate
- 2.7% Surgical Site Infection (SSI) Rate

Patients with reported penicillin allergy had a 50% increased odds of SSI, attributable to the receipt of second-line perioperative antibiotics

Clinical Infectious Diseases
MAJOR ARTICLE

The Impact of a Reported Penicillin Allergy on Surgical Site Infection Risk

Kimberly G. Blumenthal,[1,2,3,4] Erin E. Ryan,[5,6] Yu Li,[1,2] Hang Lee,[4,7] James L. Kuhlen,[8] and Erica S. Shenoy[2,4,5,6]

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(See the Editorial Commentary by Dellinger et al on pages 337–8.)

Background. A reported penicillin allergy may compromise receipt of recommended antibiotic prophylaxis intended to prevent surgical site infections (SSIs). Most patients with a reported penicillin allergy are not allergic. We determined the impact of a reported penicillin allergy on the development of SSIs.

Methods. In this retrospective cohort study of Massachusetts General Hospital hip arthroplasty, knee arthroplasty, hysterectomy, colon surgery, and coronary artery bypass grafting patients from 2010 to 2014, we compared patients with and without a reported penicillin allergy. The primary outcome was an SSI, as defined by the Centers for Disease Control and Prevention's National Healthcare Safety Network. The secondary outcome was perioperative antibiotic use.

Results. Of 8385 patients who underwent 9004 procedures, 922 (11%) reported a penicillin allergy, and 241 (2.7%) had an SSI. In multivariable logistic regression, patients reporting a penicillin allergy had increased odds (adjusted odds ratio, 1.51; 95% confidence interval, 1.02–2.22) of SSI. Penicillin allergy reporters were administered less cefazolin (12% vs 92%; $P < .001$) and more clindamycin (49% vs 3%; $P < .001$), vancomycin (35% vs 3%; $P < .001$), and gentamicin (24% vs 3%; $P < .001$) compared with those without a reported penicillin allergy. The increased SSI risk was entirely mediated by the patients' receipt of an alternative perioperative antibiotic; between 112 and 124 patients with reported penicillin allergy would need allergy evaluation to prevent 1 SSI.

Conclusions. Patients with a reported penicillin allergy had a 50% increased odds of SSI, attributable to the receipt of second-line perioperative antibiotics. Clarification of penicillin allergies as part of routine preoperative care may decrease SSI risk.

Keywords. prophylaxis; antibiotic; healthcare-associated infections; surgical site infections; allergy.

Surgical site infections (SSIs) account for 40% of all healthcare-associated infections among hospitalized patients [1]. Surgical site infections result in substantial morbidity and mortality [2] and an estimated attributable cost exceeding $25 000 (2017 US dollars) per case [1, 3, 4]. Surgical site infections additionally influence perceptions of hospital quality; the Centers for Medicare and Medicaid Services Inpatient Prospective Payment System publicly reports SSIs through the Centers for Disease Control and Prevention's National Healthcare Safety Network (NHSN), with data made available to patients on Hospital Compare [1, 5]. For these reasons, reducing SSIs is a national healthcare priority [6–9].

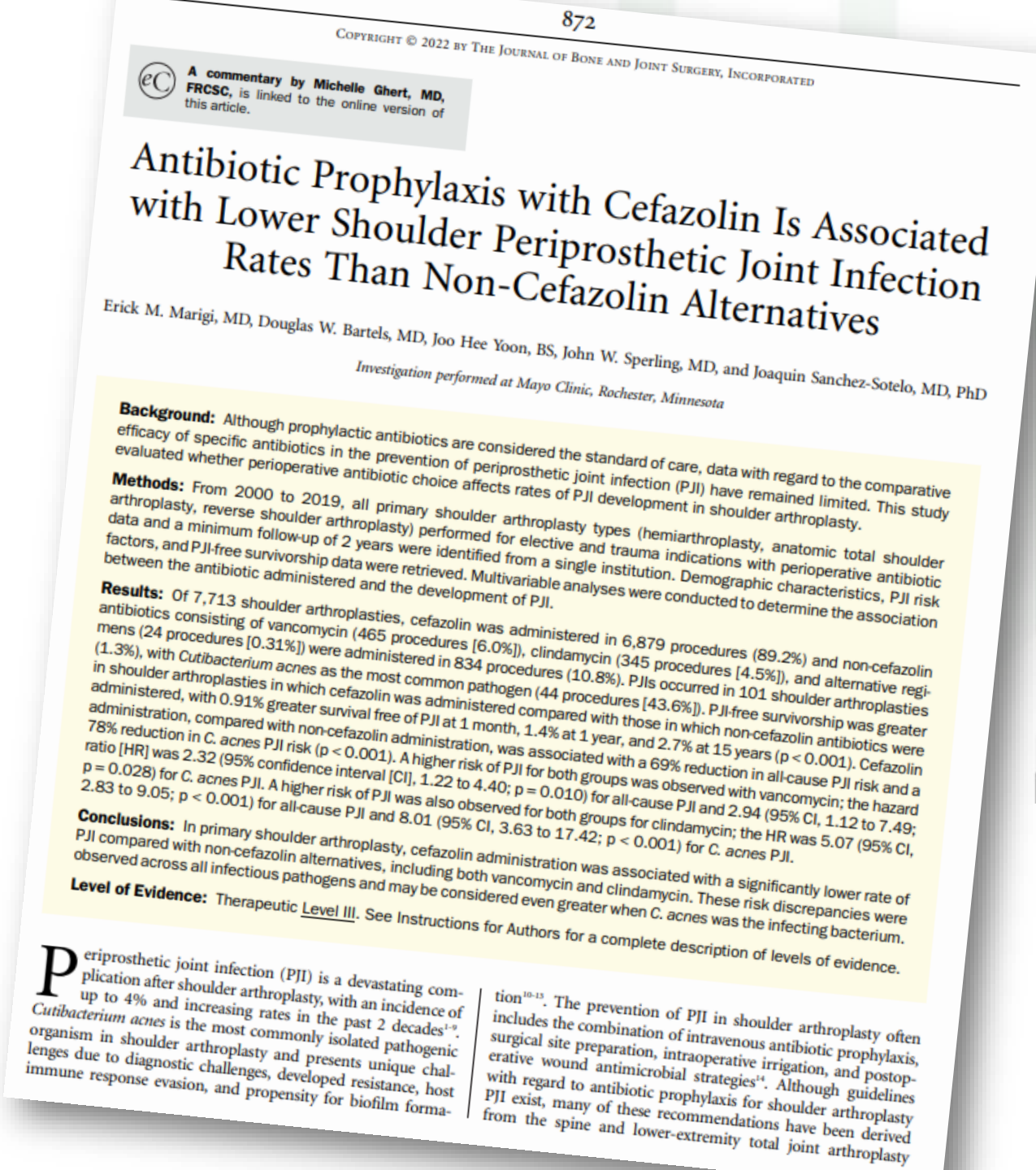
Appropriate use of perioperative antibiotics can decrease the incidence of SSIs [10–12]. For most surgical procedures, a beta-lactam antibiotic is the preferred perioperative antibiotic [13]. Cefazolin, a first-generation cephalosporin antibiotic, is often the recommended beta-lactam antibiotic because of its activity against methicillin-susceptible *Staphylococcus aureus* [MSSA] and *Streptococcus* species), bactericidal activity, and favorable pharmacokinetics whereby the drug rapidly reaches optimal antibacterial concentrations in tissues [13–15]. For the 10% of patients who report a prior penicillin allergy [16, 17], non–beta-lactam antibiotics (eg, clindamycin, vancomycin) may be administered [18–21]. This is despite evidence demonstrating that 90%–99% of patients with a reported penicillin allergy are not truly allergic (ie, there is no immediate hypersensitivity) and <3% of patients with an allergy to penicillin will also react to cefazolin [22–25].

A reported penicillin allergy has been associated with increased healthcare-associated infections, including 23% increased odds of *Clostridium difficile*, 14% increased odds of methicillin-resistant *Staphylococcus aureus* [MRSA] colonization or infection, and 30% increased odds of vancomycin-resistant *Enterococcus* (VRE) colonization or infection [26]. Few

Penicillin Allergies: Post-operative Infections

- 7,713 patients at Mayo Clinic
- Undergoing primary shoulder arthroplasty
- Cefazolin administered in 89.2% of cases
- 1.31% Prosthetic Joint Infection (PJI) Rate

Cefazolin administration is associated with a significantly lower rate of PJI compared with non-cefazolin alternatives.



A commentary by Michelle Ghert, MD, FRCSC, is linked to the online version of this article.

Antibiotic Prophylaxis with Cefazolin Is Associated with Lower Shoulder Periprosthetic Joint Infection Rates Than Non-Cefazolin Alternatives

Erick M. Marigi, MD, Douglas W. Bartels, MD, Joo Hee Yoon, BS, John W. Sperling, MD, and Joaquin Sanchez-Sotelo, MD, PhD

Investigation performed at Mayo Clinic, Rochester, Minnesota

Background: Although prophylactic antibiotics are considered the standard of care, data with regard to the comparative efficacy of specific antibiotics in the prevention of periprosthetic joint infection (PJI) have remained limited. This study evaluated whether perioperative antibiotic choice affects rates of PJI development in shoulder arthroplasty.

Methods: From 2000 to 2019, all primary shoulder arthroplasty types (hemiarthroplasty, anatomic total shoulder arthroplasty, reverse shoulder arthroplasty) performed for elective and trauma indications with perioperative antibiotic data and a minimum follow-up of 2 years were identified from a single institution. Demographic characteristics, PJI risk factors, and PJI-free survivorship data were retrieved. Multivariable analyses were conducted to determine the association between the antibiotic administered and the development of PJI.

Results: Of 7,713 shoulder arthroplasties, cefazolin was administered in 6,879 procedures (89.2%) and non-cefazolin antibiotics consisting of vancomycin (465 procedures [6.0%]), clindamycin (345 procedures [4.5%]), and alternative regimens (24 procedures [0.31%]) were administered in 834 procedures (10.8%). PJIs occurred in 101 shoulder arthroplasties (1.3%), with *Cutibacterium acnes* as the most common pathogen (44 procedures [43.6%]). PJI-free survivorship was greater in shoulder arthroplasties in which cefazolin was administered compared with those in which non-cefazolin antibiotics were administered, with 0.91% greater survival free of PJI at 1 month, 1.4% at 1 year, and 2.7% at 15 years ($p < 0.001$). Cefazolin administration, compared with non-cefazolin administration, was associated with a 69% reduction in all-cause PJI risk and a 78% reduction in *C. acnes* PJI risk ($p < 0.001$). A higher risk of PJI for both groups was observed with vancomycin; the hazard ratio [HR] was 2.32 (95% confidence interval [CI], 1.22 to 4.40; $p = 0.010$) for all-cause PJI and 2.94 (95% CI, 1.12 to 7.49; $p = 0.028$) for *C. acnes* PJI. A higher risk of PJI was also observed for both groups for clindamycin; the HR was 5.07 (95% CI, 2.83 to 9.05; $p < 0.001$) for all-cause PJI and 8.01 (95% CI, 3.63 to 17.42; $p < 0.001$) for *C. acnes* PJI.

Conclusions: In primary shoulder arthroplasty, cefazolin administration was associated with a significantly lower rate of PJI compared with non-cefazolin alternatives, including both vancomycin and clindamycin. These risk discrepancies were observed across all infectious pathogens and may be considered even greater when *C. acnes* was the infecting bacterium.

Level of Evidence: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

Periprosthetic joint infection (PJI) is a devastating complication after shoulder arthroplasty, with an incidence of up to 4% and increasing rates in the past 2 decades[1-9]. *Cutibacterium acnes* is the most commonly isolated pathogenic organism in shoulder arthroplasty and presents unique challenges due to diagnostic challenges, developed resistance, host immune response evasion, and propensity for biofilm formation[10-13]. The prevention of PJI in shoulder arthroplasty often includes the combination of intravenous antibiotic prophylaxis, surgical site preparation, intraoperative irrigation, and postoperative wound antimicrobial strategies[14]. Although guidelines with regard to antibiotic prophylaxis for shoulder arthroplasty PJI exist, many of these recommendations have been derived from the spine and lower-extremity total joint arthroplasty

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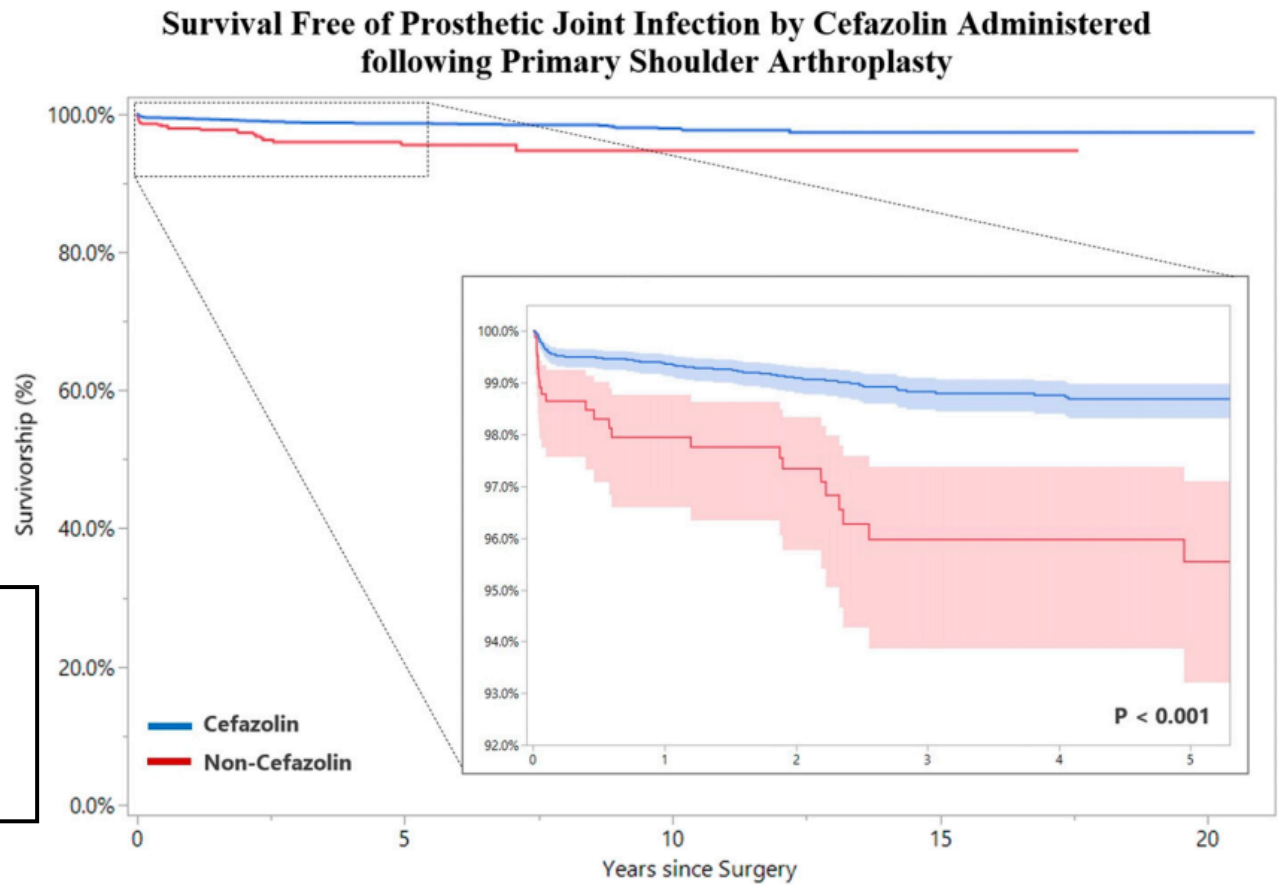
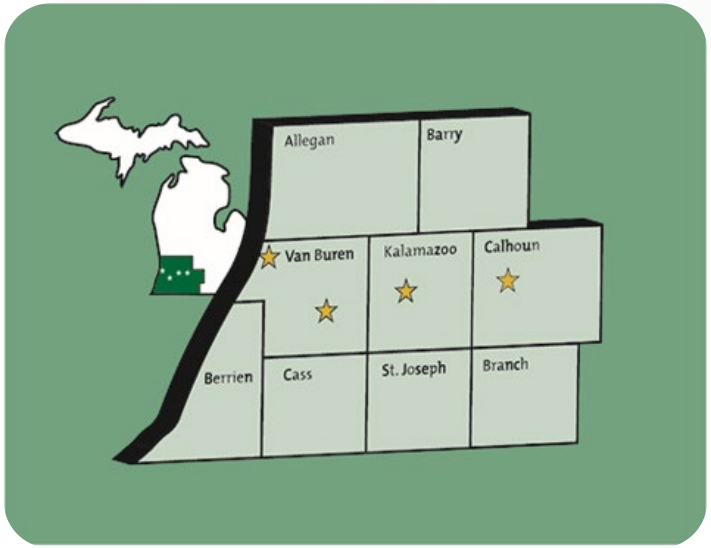


Bronson Healthcare Group

4 Hospital System in Southwest Michigan

Bronson Methodist Hospital (BMH)

- 434 Licensed Beds
- 21 Operating Rooms



BHG Penicillin Allergies: 4 Year Summary

4,302

7.9% Percent of Total Patients

Inpatients with Penicillin Allergy

26% Anaphylaxis, Shortness of Breath, Angioedema

63% Rash, Hives, Extremity Swelling, Itching, Palpitations, Hypotension

2% Nausea, Vomiting, Diarrhea

*9% listed as 'unknown' or blank

7,492

8.1% Percent of all Encounters

Encounters with Penicillin Allergy

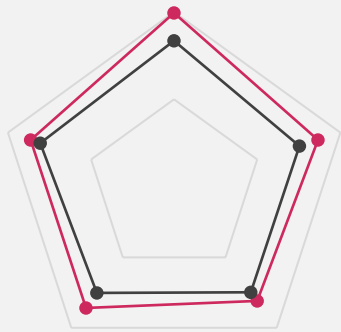
Readmission Rates

8.9%

Allergy

7.7%

No Allergy



n= 58,801 patients

7,856

13% Percent of all Surgeries

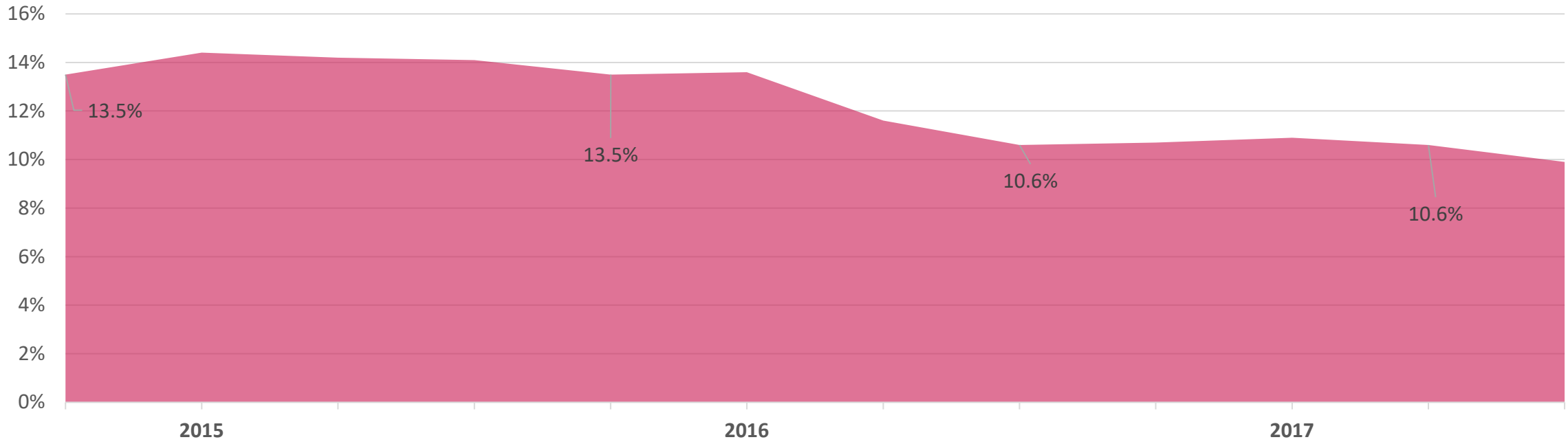
Surgery with Penicillin Allergy

499

- 62 (12.4%) Reported PEN allergy
  - 47 received 2nd line therapy

Post – Operative Infections

BHG Clindamycin Pre-Op– Historical Data (2015-17)



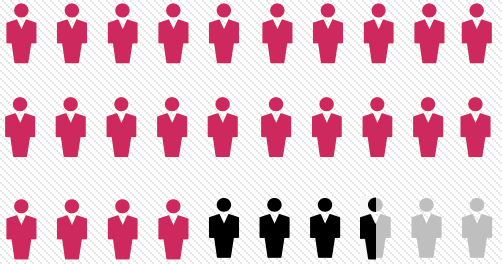
Use of clindamycin associated with higher rates of SSI when compared to cefazolin for pre-surgical prophylaxis

Blumenthal et al CID 2018

12.2%

Received Clindamycin Pre-Op therapy as alternative

3 year average



Cefazolin (80%)

Clindamycin (12%)

Other (8%)

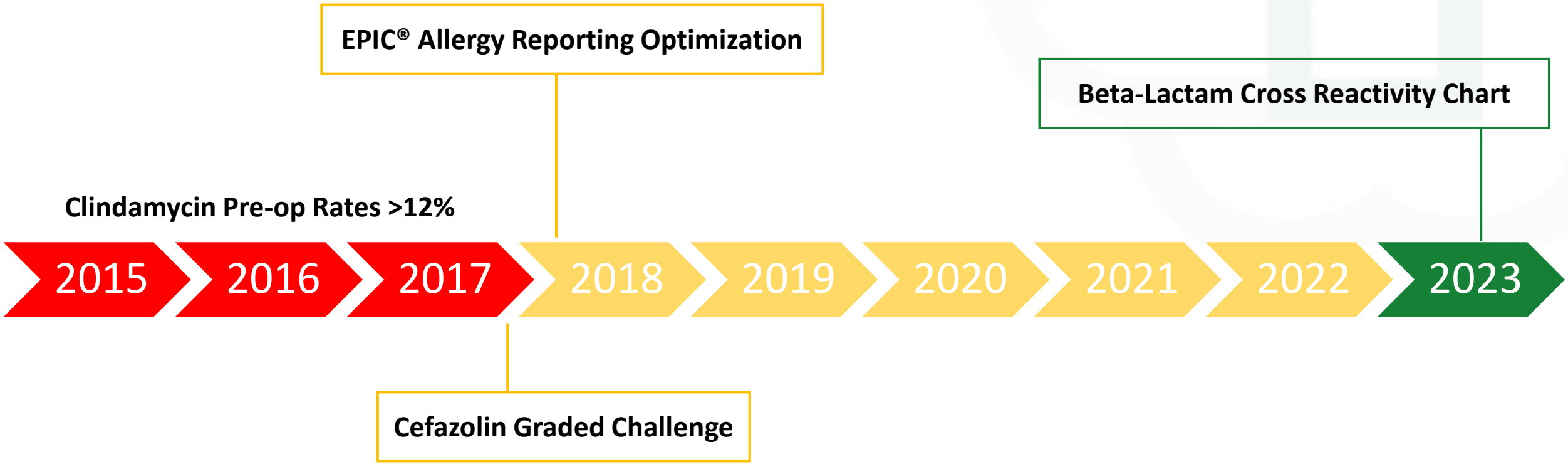
BMH Interventional Strategies

Improved EPIC® Allergy Reporting Selections

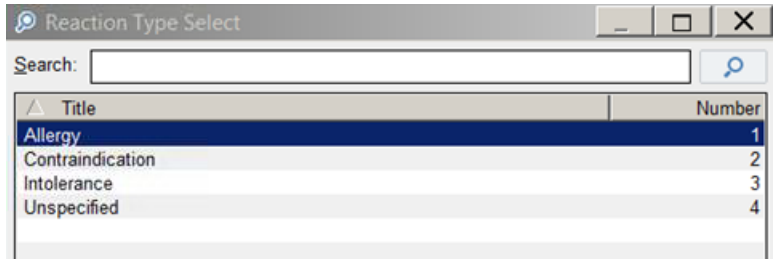
Cefazolin Graded Challenge

Beta- Lactam Side Chain Chart

BHG Interventional Strategy Timeline



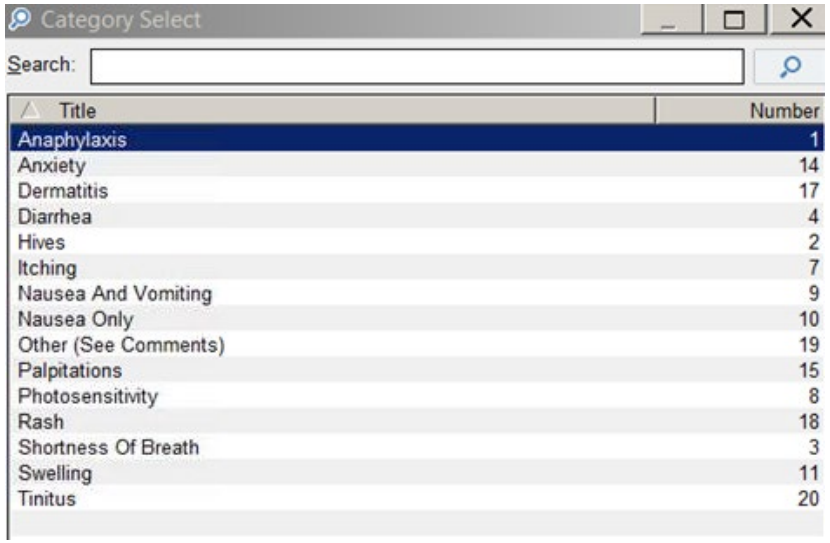
EPIC® Allergy Documentation Enhancements



Title	Number
Allergy	1
Intolerance	3
Other (specify in comments)	5

Remove:
Contraindication
Unspecified

Add:
Other- Specify in comments



Title	Number
Anaphylaxis	1
Diarrhea	4
Hives (raised area, itchy)	2
Hypotension	21
Itching	7
Myalgia	22
Nausea and/or Vomiting	9
Not listed (specify in comments)	19
Palpitations	15
Photosensitivity	8
Rash (flat, red, speckled area)	18
Shortness of Breath (difficulty breathing)	3
Swelling (angioedema)	24
Swelling (extremities)	11
Tinnitus	20
Unknown (specify in comments)	23

Remove:
Anxiety
Other (See Comments)

Add:
Hypotension
Unknown (specify in comments)
Myalgia

Replace:
Dermatitis, Hives, Rash:
- Hives- (raised area, itchy)
- Rash- (flat area, red area, speckled)

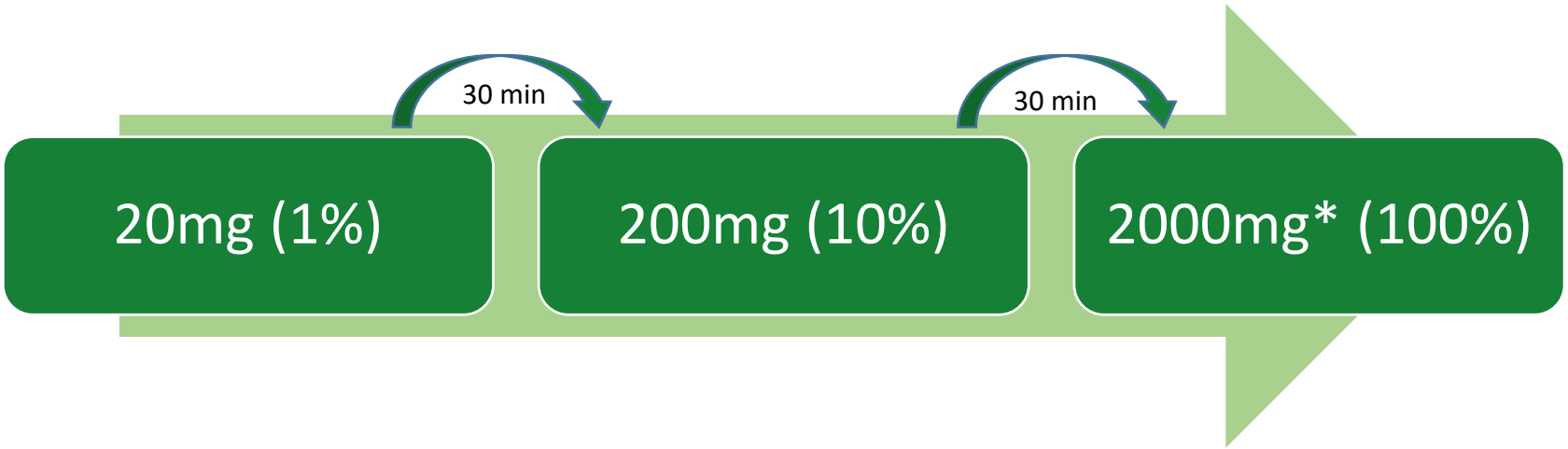
Shortness of Breath:
- Shortness of breath – difficulty breathing

Swelling:
- Swelling - extremities
- Swelling – angioedema

Other (see comments):
- Not Listed (specify in comments)

Nausea only
Nausea and Vomiting
- Nausea and/or Vomiting

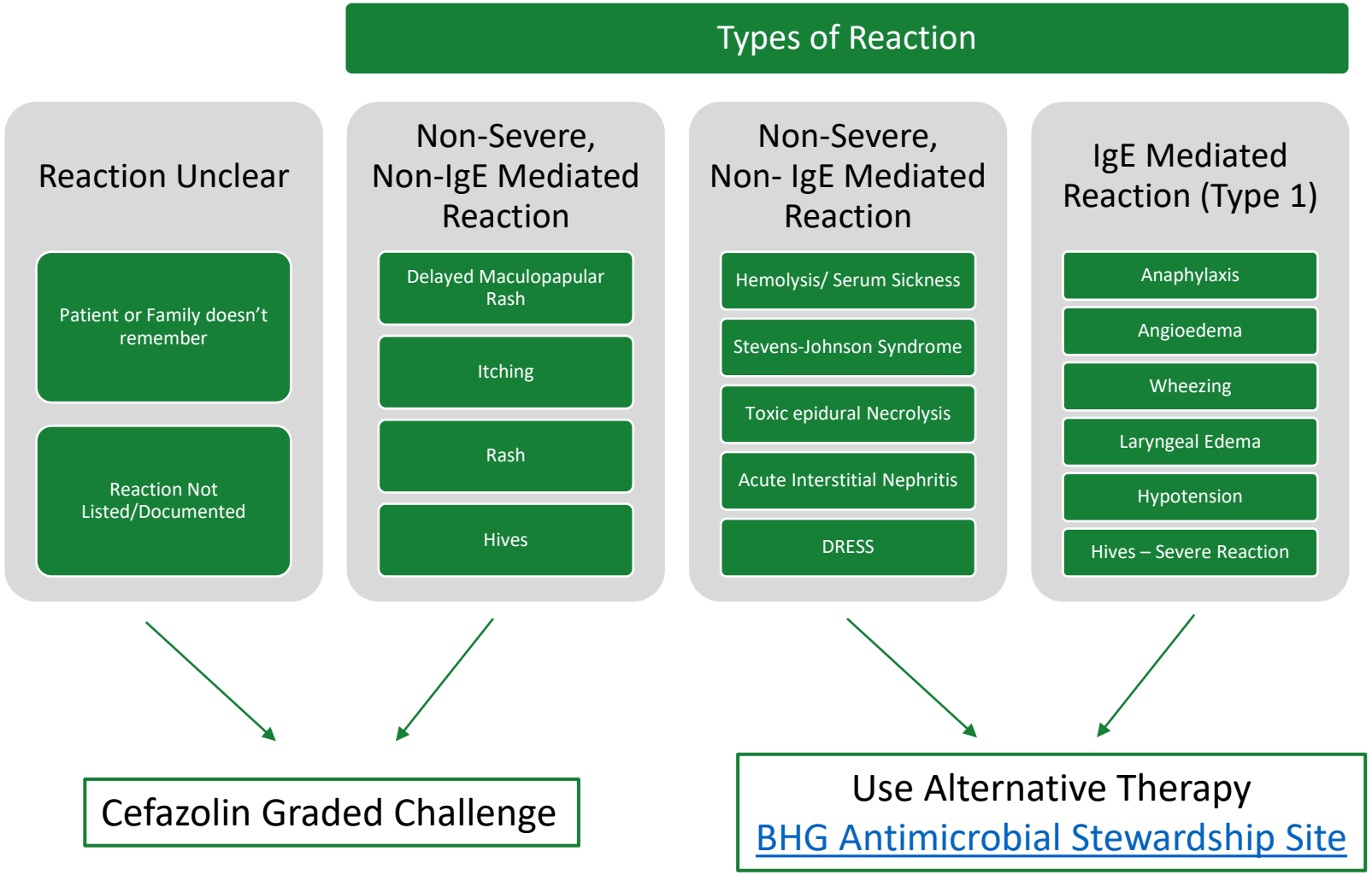
Cefazolin Graded Challenge



- Patient screened during pre-surgical office visit
- Cefazolin graded challenge orders placed and patient scheduled for OR
- First and second dose given by RN in pre-op
- Final dose administered by anesthesia provider (15-60 min before incision)

*3 gm for patient ≥120 kg

Cefazolin Graded Challenge

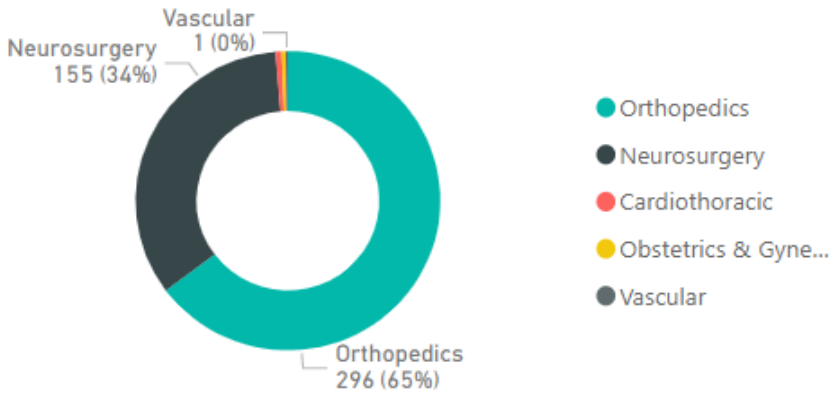


All

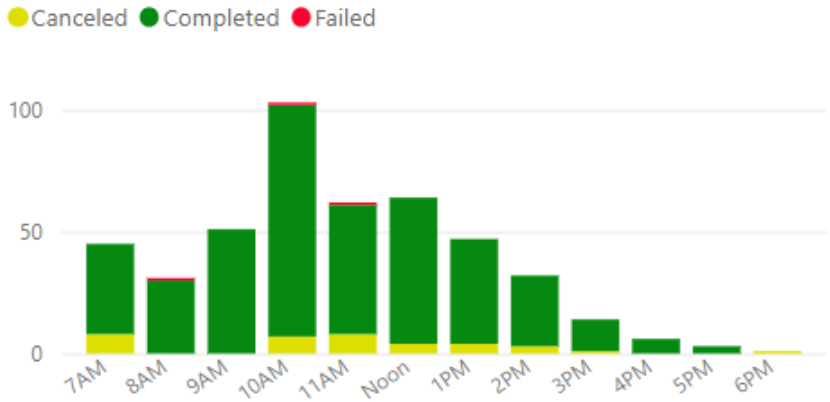
BHG – Cefazolin Graded Challenge

Patients	Completed	Canceled	Failed	Age	Weight	Abx Time to Incision (avg)
464	425	36	3	67	87 kg	39.5 min

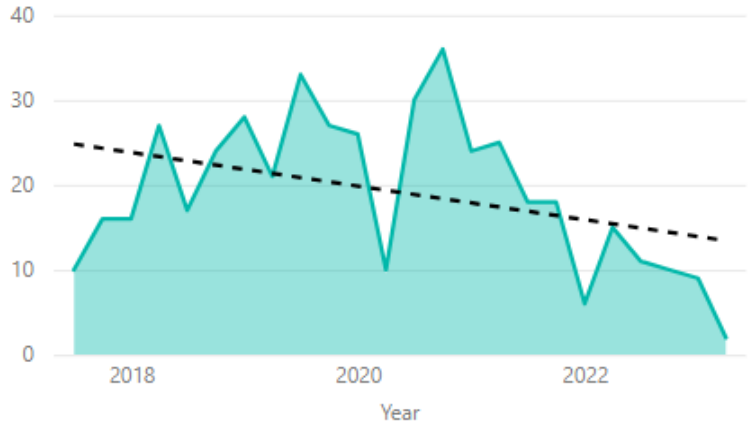
Ancef Graded Challenge Cases by Surgery Group



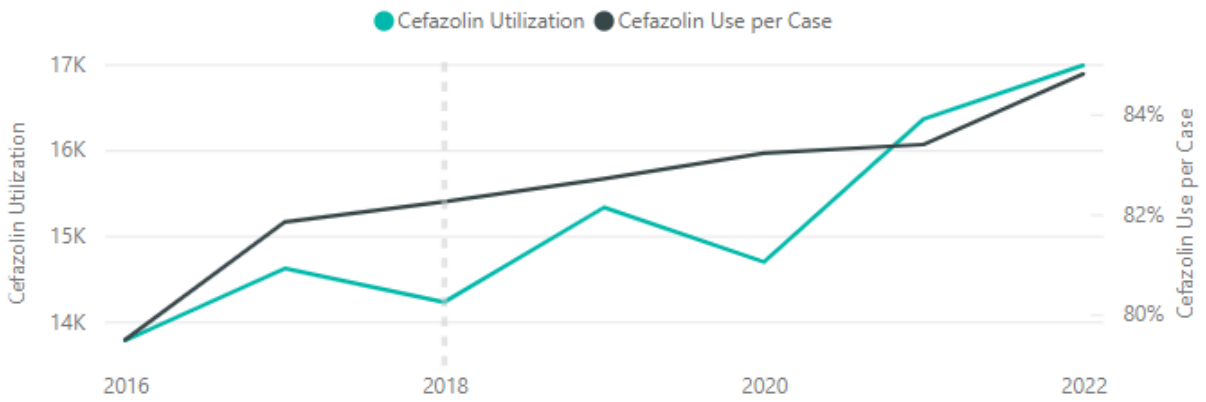
Ancef Graded Challenge Cases by Time of Incision



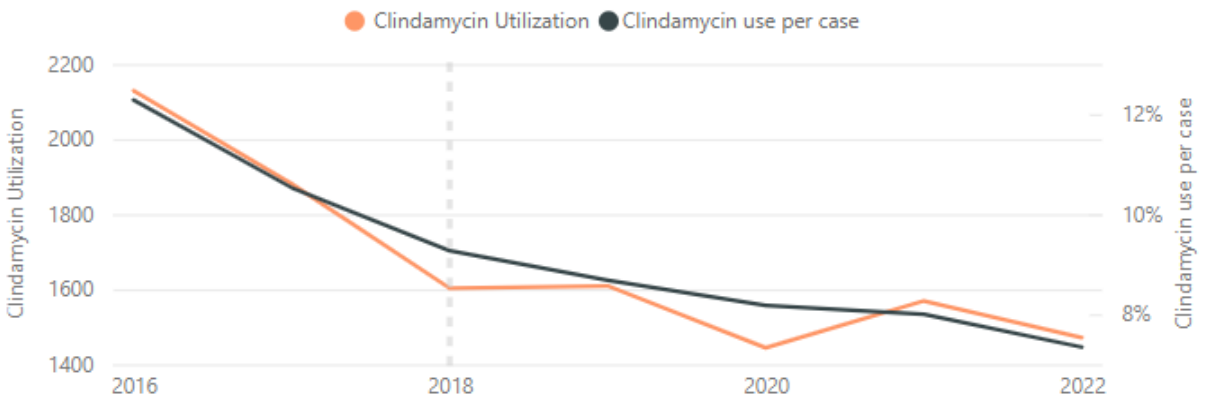
Ancef Graded Challenge Cases Cases Performed Trend



Cefazolin Cases



Clindamycin Cases



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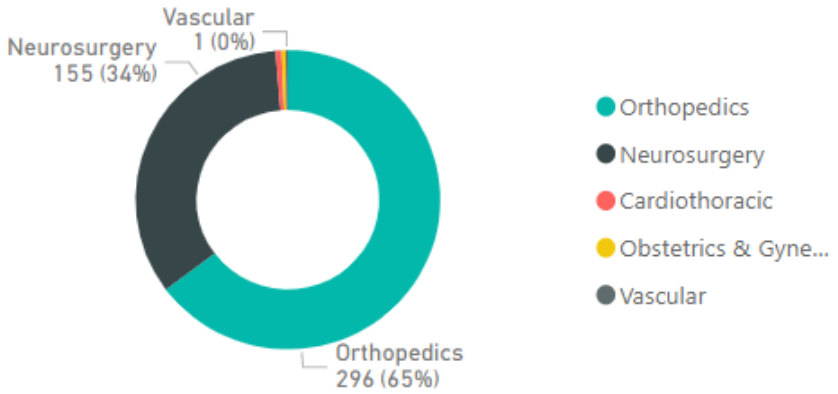

Ancef Graded Challenge Cases by Time of Incision

Ancef Graded Challenge Cases Cases Performed Trend

Cefazolin Cases

Clindamycin Cases

All

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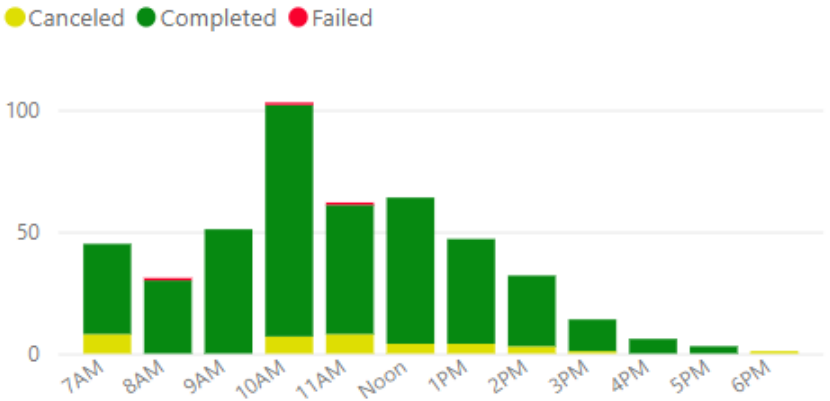
Ancef Graded Challenge Cases by Surgery Group

Ancef Graded Challenge Cases by Time of Incision



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Cefazolin Cases

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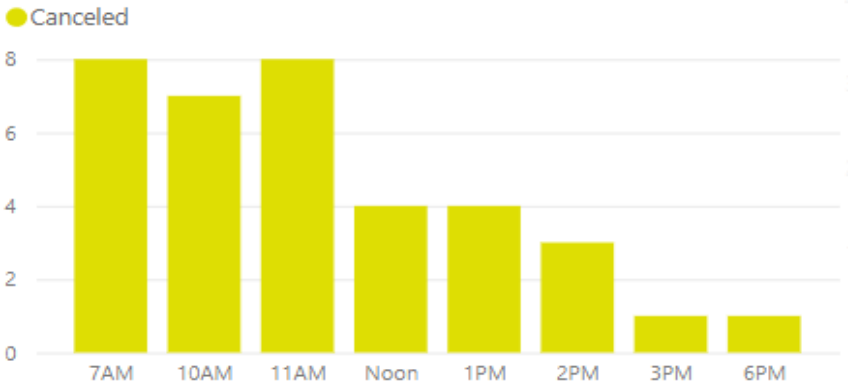

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Cefazolin Cases

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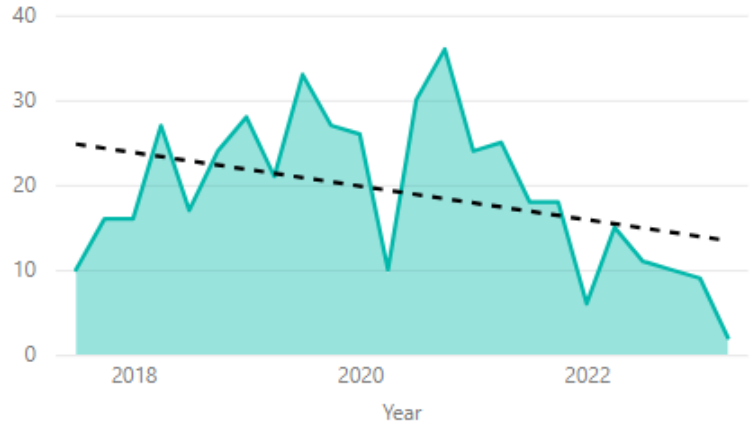

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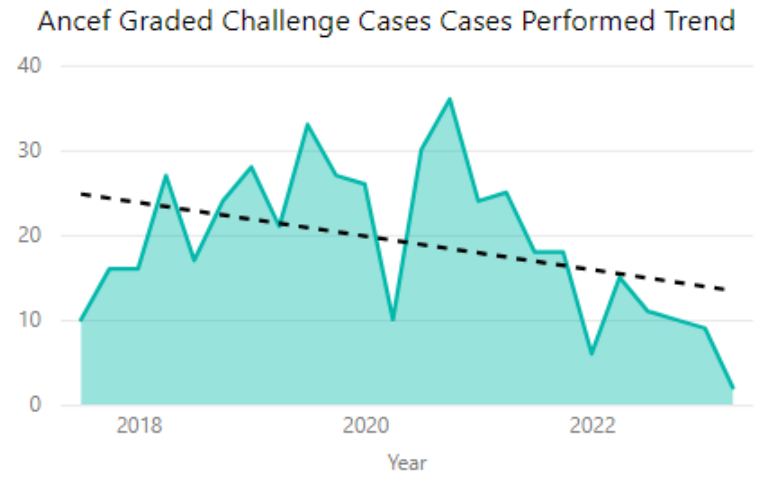
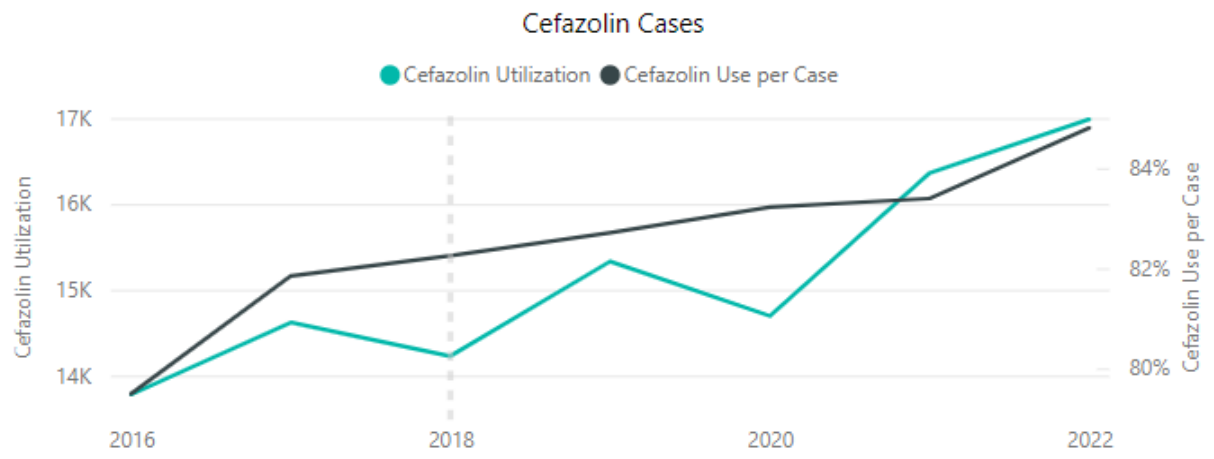
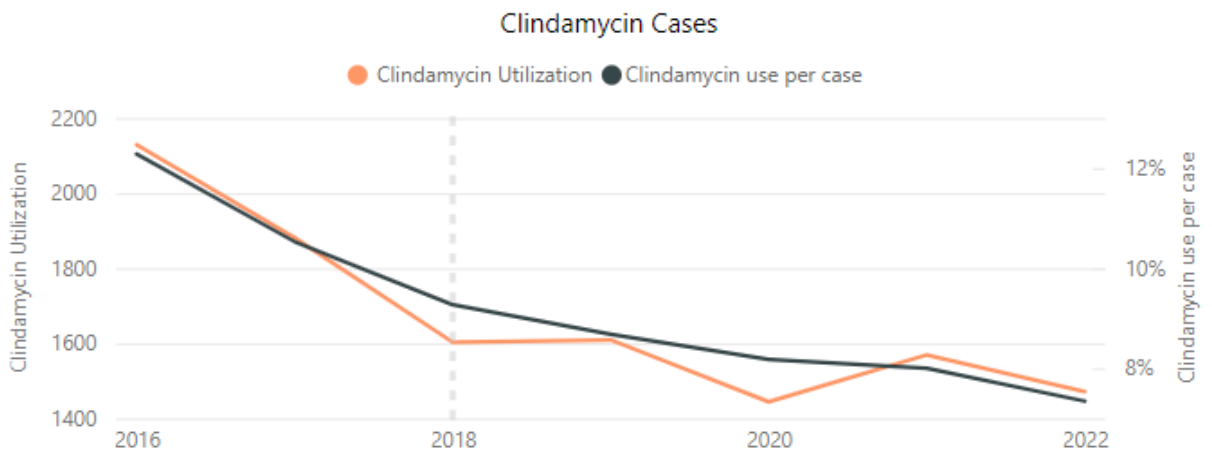
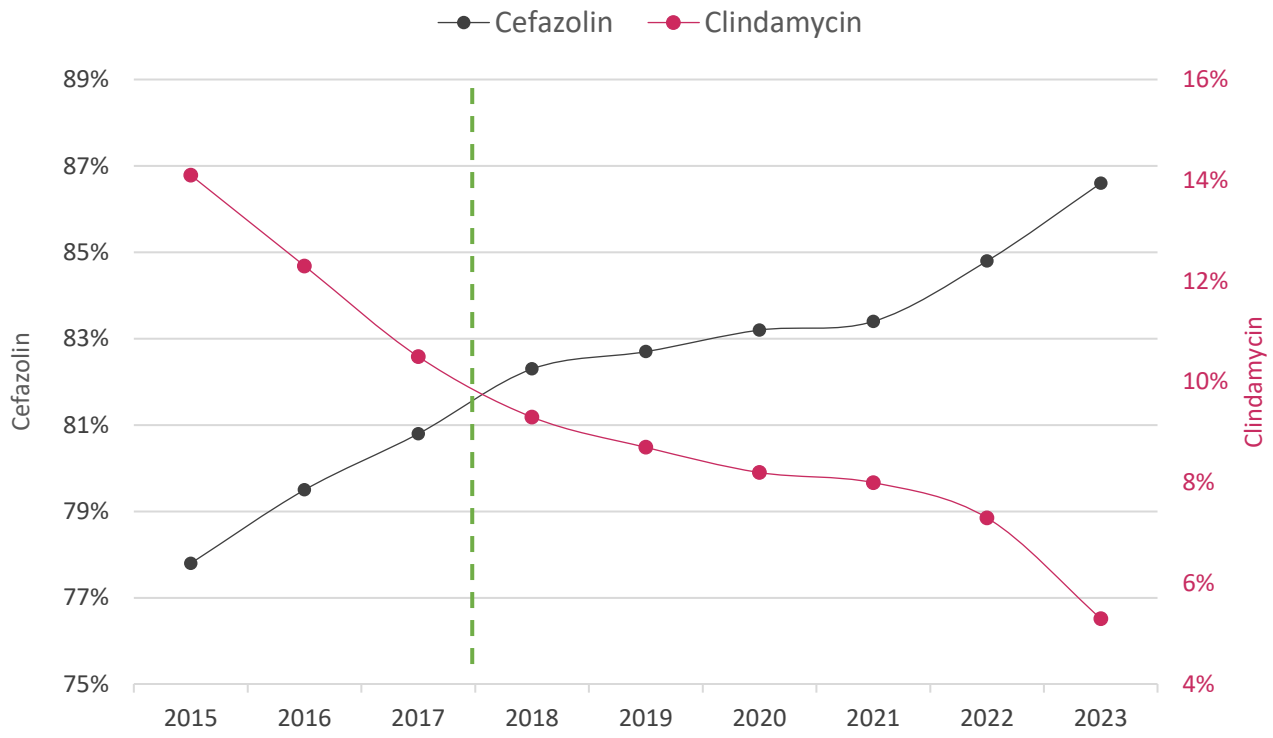






BHG Pre-Operative Antimicrobial Prophylaxis

Pre-Operative Antibiotic Use – By Year



Comprehensive data for inpatient surgeries at BMH from 2015-23 where pre-operative antimicrobial prophylaxis was indicated

Reduction in Clindamycin Pre-op Prophylaxis **62%**

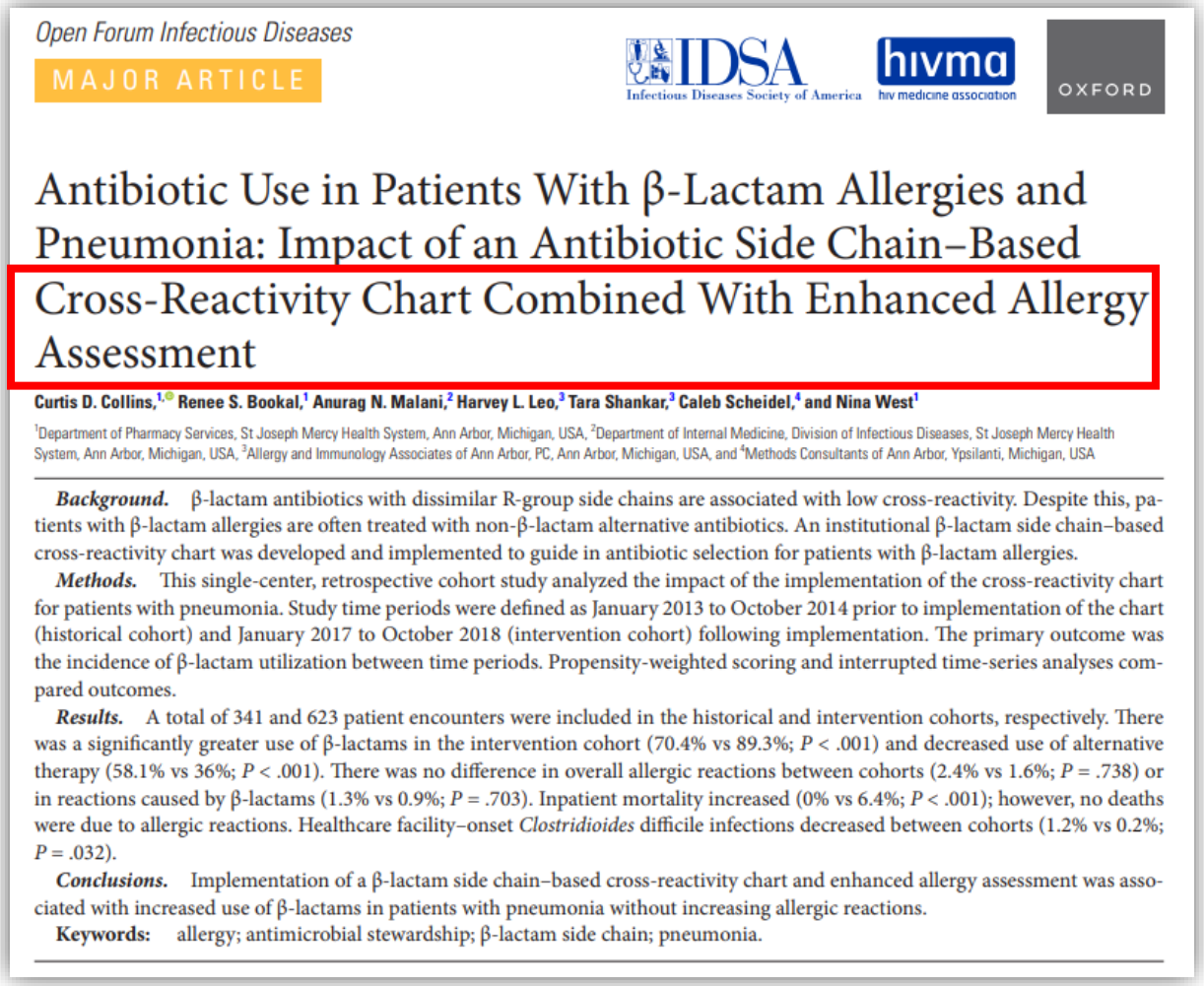
Increase in Cefazolin Pre-op Prophylaxis **12%**

Reduction in patients reporting PEN allergy **14%**

Reduction in non-allergies reported as PEN* **39%**

*Diarrhea, Nausea, Vomiting, Unknown

Future Direction



Open Forum Infectious Diseases

MAJOR ARTICLE

Antibiotic Use in Patients With β-Lactam Allergies and Pneumonia: Impact of an Antibiotic Side Chain–Based Cross-Reactivity Chart Combined With Enhanced Allergy Assessment

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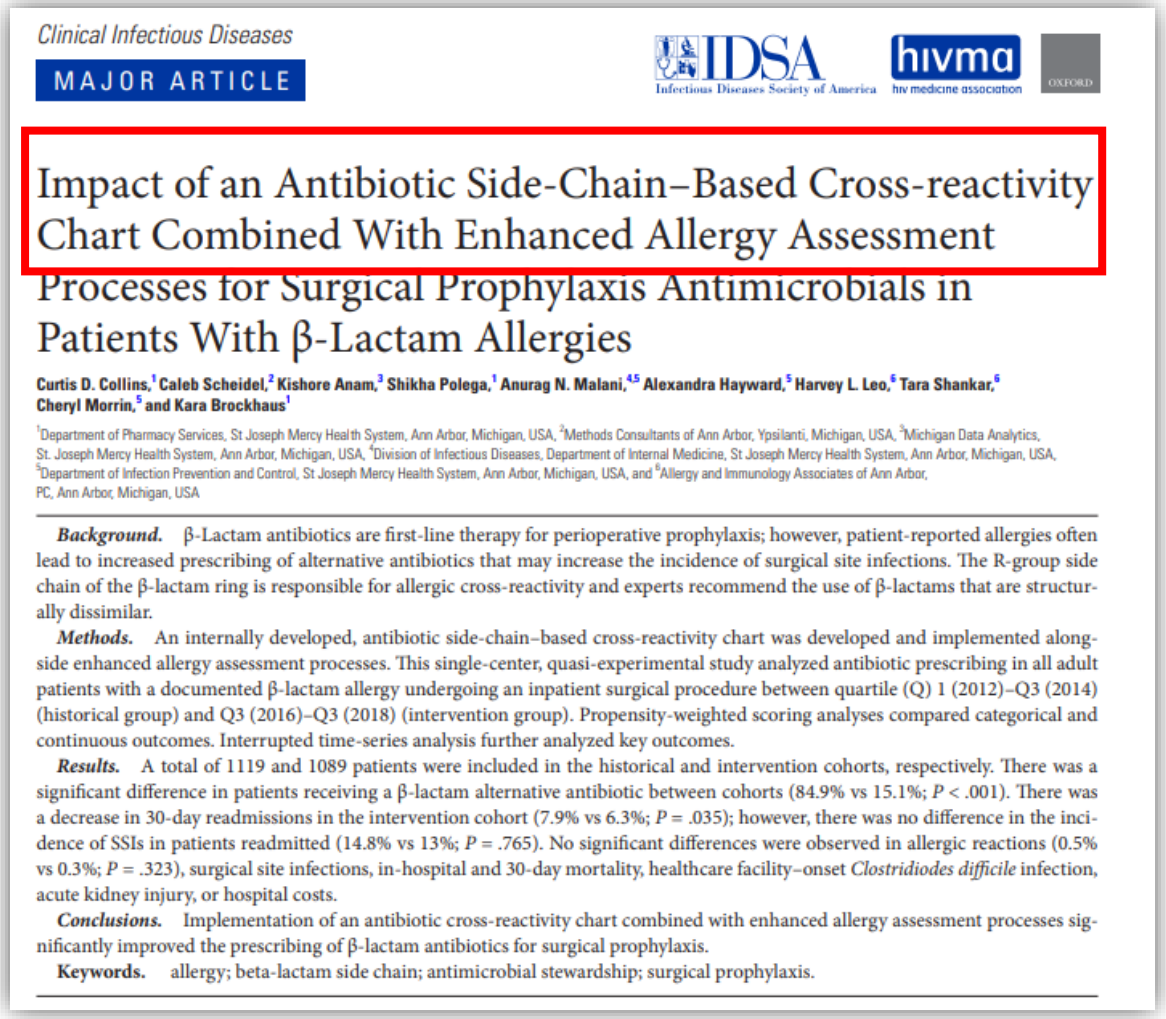
Background. β-lactam antibiotics with dissimilar R-group side chains are associated with low cross-reactivity. Despite this, patients with β-lactam allergies are often treated with non-β-lactam alternative antibiotics. An institutional β-lactam side chain–based cross-reactivity chart was developed and implemented to guide in antibiotic selection for patients with β-lactam allergies.

Methods. This single-center, retrospective cohort study analyzed the impact of the implementation of the cross-reactivity chart for patients with pneumonia. Study time periods were defined as January 2013 to October 2014 prior to implementation of the chart (historical cohort) and January 2017 to October 2018 (intervention cohort) following implementation. The primary outcome was the incidence of β-lactam utilization between time periods. Propensity-weighted scoring and interrupted time-series analyses compared outcomes.

Results. A total of 341 and 623 patient encounters were included in the historical and intervention cohorts, respectively. There was a significantly greater use of β-lactams in the intervention cohort (70.4% vs 89.3%; $P < .001$) and decreased use of alternative therapy (58.1% vs 36%; $P < .001$). There was no difference in overall allergic reactions between cohorts (2.4% vs 1.6%; $P = .738$) or in reactions caused by β-lactams (1.3% vs 0.9%; $P = .703$). Inpatient mortality increased (0% vs 6.4%; $P < .001$); however, no deaths were due to allergic reactions. Healthcare facility–onset *Clostridioides* difficile infections decreased between cohorts (1.2% vs 0.2%; $P = .032$).

Conclusions. Implementation of a β-lactam side chain–based cross-reactivity chart and enhanced allergy assessment was associated with increased use of β-lactams in patients with pneumonia without increasing allergic reactions.

Keywords: allergy; antimicrobial stewardship; β-lactam side chain; pneumonia.



Clinical Infectious Diseases

MAJOR ARTICLE

Impact of an Antibiotic Side-Chain–Based Cross-reactivity Chart Combined With Enhanced Allergy Assessment Processes for Surgical Prophylaxis Antimicrobials in Patients With β-Lactam Allergies

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Background. β-Lactam antibiotics are first-line therapy for perioperative prophylaxis; however, patient-reported allergies often lead to increased prescribing of alternative antibiotics that may increase the incidence of surgical site infections. The R-group side chain of the β-lactam ring is responsible for allergic cross-reactivity and experts recommend the use of β-lactams that are structurally dissimilar.

Methods. An internally developed, antibiotic side-chain–based cross-reactivity chart was developed and implemented alongside enhanced allergy assessment processes. This single-center, quasi-experimental study analyzed antibiotic prescribing in all adult patients with a documented β-lactam allergy undergoing an inpatient surgical procedure between quartile (Q) 1 (2012)–Q3 (2014) (historical group) and Q3 (2016)–Q3 (2018) (intervention group). Propensity-weighted scoring analyses compared categorical and continuous outcomes. Interrupted time-series analysis further analyzed key outcomes.

Results. A total of 1119 and 1089 patients were included in the historical and intervention cohorts, respectively. There was a significant difference in patients receiving a β-lactam alternative antibiotic between cohorts (84.9% vs 15.1%; $P < .001$). There was a decrease in 30-day readmissions in the intervention cohort (7.9% vs 6.3%; $P = .035$); however, there was no difference in the incidence of SSIs in patients readmitted (14.8% vs 13%; $P = .765$). No significant differences were observed in allergic reactions (0.5% vs 0.3%; $P = .323$), surgical site infections, in-hospital and 30-day mortality, healthcare facility–onset *Clostridiodes difficile* infection, acute kidney injury, or hospital costs.

Conclusions. Implementation of an antibiotic cross-reactivity chart combined with enhanced allergy assessment processes significantly improved the prescribing of β-lactam antibiotics for surgical prophylaxis.

Keywords. allergy; beta-lactam side chain; antimicrobial stewardship; surgical prophylaxis.

Future Direction

Supplement Figure 1. Beta-lactam Cross-Reactivity Chart

Antibiotic Ordered \ Antibiotic Allergy	"Penicillin"	"Cephalosporin"	Amoxicillin/Amox/clav	Ampicillin/Amp/sulb	Aztreonam	Cefaclor	Cefazolin	Cefepime	Cefotaxime	Cefoxitin	Cefdinir	Ceftaroline	Ceftriaxone	Cefuroxime	Cephalexin	Ceftazidime/avibactam	Ceftolozane/tazobactam	Nafcillin	Penicillin G	Piperacillin/tazobactam
Amoxicillin/Amox/clav [16-21]	N	CPa,b		Nb	Yb	Na,b	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Nb	Yb	Yb	CPb	Nb	CPb
Ampicillin/Amp/sulb [16-21]	N	Cpa,b	Nb		Yb	Na,b	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Nb	Yb	Yb	CPb	Nb	CPb
Aztreonam [17, 19, 21]	Yb	Yb	Yb	Yb		Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Nb	CPb	Yb	Yb	Yb
Cefaclor [16-21]	N	N	Na,b	Na,b	Yb		Yb	Ya,b	Yb	Yb	Yb	Yb	UAa	UAa	Na,b	Yb	Yb	Yb	UAb	CPb
Cefazolin [16-21]	Ya,b	N	Yb	Yb	Yb	Yb		Yb	Yb	Ya,b	Yb	Yb	Ya,b	Ya,b	Yb	Yb	Yb	Yb	Yb	Yb
Cefepime [16-19, 21]	Ya,b	N	Yb	Yb	Yb	Ya,b	Yb		Nb	Yb	UAb	UAb	Na,b	Na,b	Yb	CPb	CPb	Yb	Yb	Yb
Cefotaxime [16-21]	Ya,b	N	Yb	Yb	Yb	Yb	Yb	Nb		UAb	UAb	UAb	Na,b	Na,b	Ya,b	Na,b	CPb	Yb	Yb	Yb
Cefoxitin [16-21]	UAb	N	Yb	Yb	Yb	Yb	Ya,b	Yb	UAb		Yb	Yb	UAb	Nb	Ya,b	Yb	Yb	Yb	Nb	Yb
Cefdinir [16-19, 21]	Yb	N	Yb	Yb	Yb	Yb	Yb	UAb	UAb	Yb		UAb	UAb	Yb	Yb	UAb	UAb	Yb	Yb	Yb
Ceftaroline [17-19, 21]	Yb	N	Yb	Yb	Yb	Yb	Yb	UAb	UAb	Yb	UAb		UAb	UAb	Yb	UAb	UAb	Yb	Yb	Yb
Ceftriaxone [16-21]	Ya,b	N	Yb	Yb	Yb	UAa	Ya,b	Na,b	Na,b	UAb	UAb	UAb		Na,b	UAa,b	Na,b	UAb	Yb	Yb	Yb
Cefuroxime [16-21]	Ya,b	N	Yb	Yb	Yb	UAa	Ya,b	Na,b	Na,b	Nb	Yb	UAb	Na,b		Ya,b	UAa,b	UAb	Yb	Yb	Yb
Cephalexin [16-21]	Na,b	N	Nb	Nb	Yb	Na,b	Yb	Yb	Ya,b	Ya,b	Yb	Yb	UAa,b	Ya,b		UAa	Yb	CPa	Nb	CPb
Ceftazidime/avibactam [16-21]	Ya,b	N	Yb	Yb	Nb	Yb	Yb	CPb	Na,b	Yb	UAb	UAb	Na,b	UAa,b	UAa		Nb	Yb	Yb	Yb
Ceftolozane/tazobactam [17, 19, 21]	Yb	N	Yb	Yb	CPb	Yb	Yb	CPb	CPb	Yb	UAb	UAb	UAb	UAb	Yb	Nb		Yb	Yb	Nc
Ertapenem [18]	Ya,b	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb
Meropenem [18]	Ya,b	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb
Nafcillin [17, 19]	CPb	Yb	CPb	CPb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	CPa	Yb	Yb		CPb	CPb
Penicillin G [16-21]	N	CPb	Nb	Nb	Yb	UAb	Yb	Yb	Yb	Nb	Yb	Yb	Yb	Yb	Nb	Yb	Yb	CPb		CPb
Piperacillin/tazobactam [17-19]	N	UA	CPb	CPb	Yb	CPb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	CPb	Yb	Nc	CPb	CPb	

a Comparison data in beta-lactam allergic patients; b Side chain extrapolation of beta-lactam antibiotic; c Extrapolation of beta-lactamase inhibitor

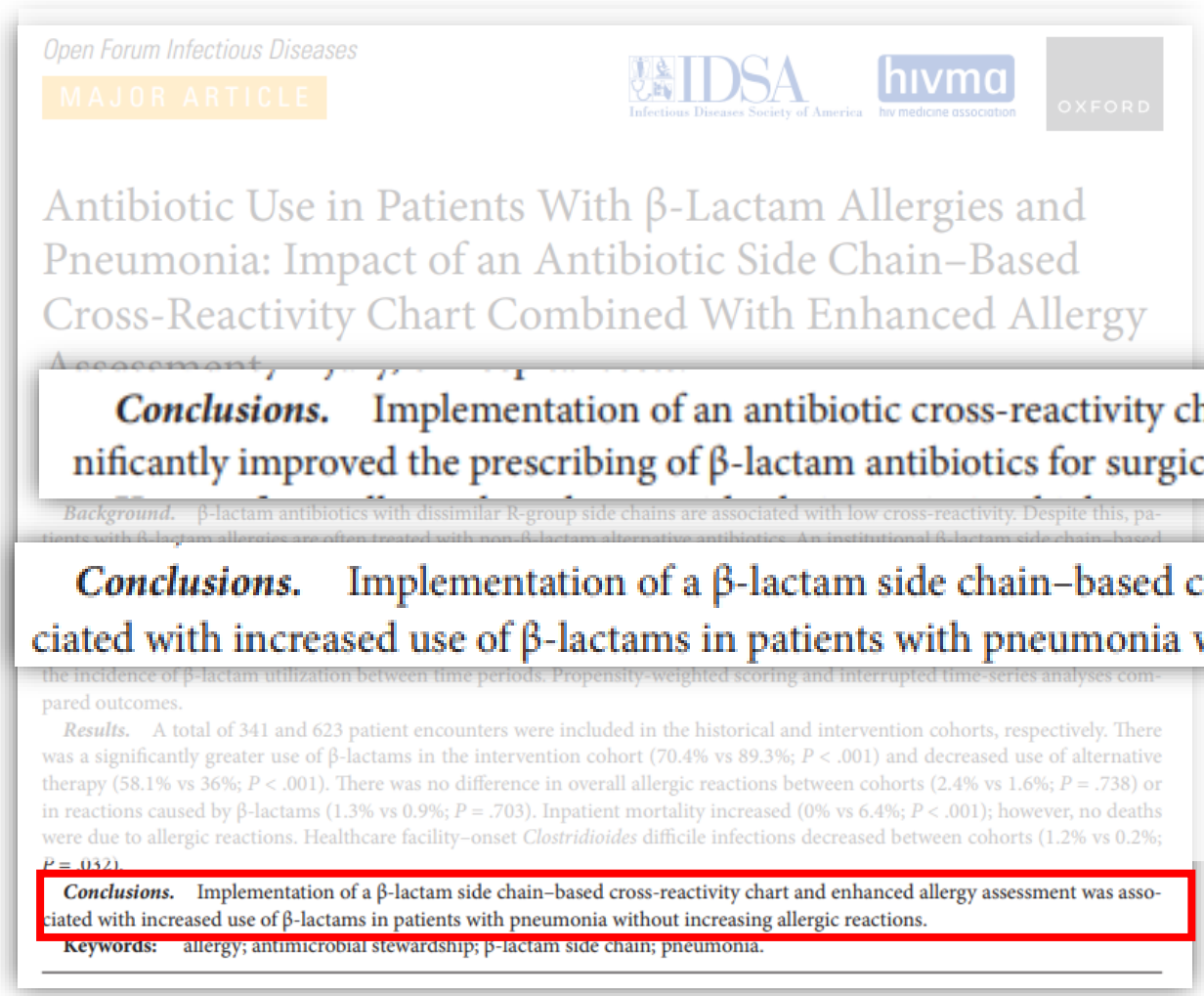
Y The order may be ordered/verified as long as any reaction other than type I-IV hypersensitivity reactions (HSRs). This includes general or non-specific allergy listings. For type I HSRs, a beta-lactam with a different side chain CAN be safely administered; however, prescribers should be notified to communicate this information and confirm the order. Avoid use in type II-IV HSRs.

UA "OK Unless Anaphylaxis" Agent may have limited or conflicting data or share a similar (not identical) side chain. Order/verify as long as the reaction is NOT listed as a type I-IV HSR.

N Should not be ordered/verified due to a higher likelihood of cross-reactivity. If ordered, the prescriber should be notified, and a different agent considered.

CP "Call Prescriber" The agent may have limited or conflicting data or share a similar (not identical) side chain. Risk/benefit should be evaluated.

Future Direction



Open Forum Infectious Diseases

MAJOR ARTICLE

Antibiotic Use in Patients With β-Lactam Allergies and Pneumonia: Impact of an Antibiotic Side Chain–Based Cross-Reactivity Chart Combined With Enhanced Allergy

Conclusions. Implementation of a β-lactam side chain–based cross-reactivity chart and enhanced allergy assessment was associated with increased use of β-lactams in patients with pneumonia without increasing allergic reactions.

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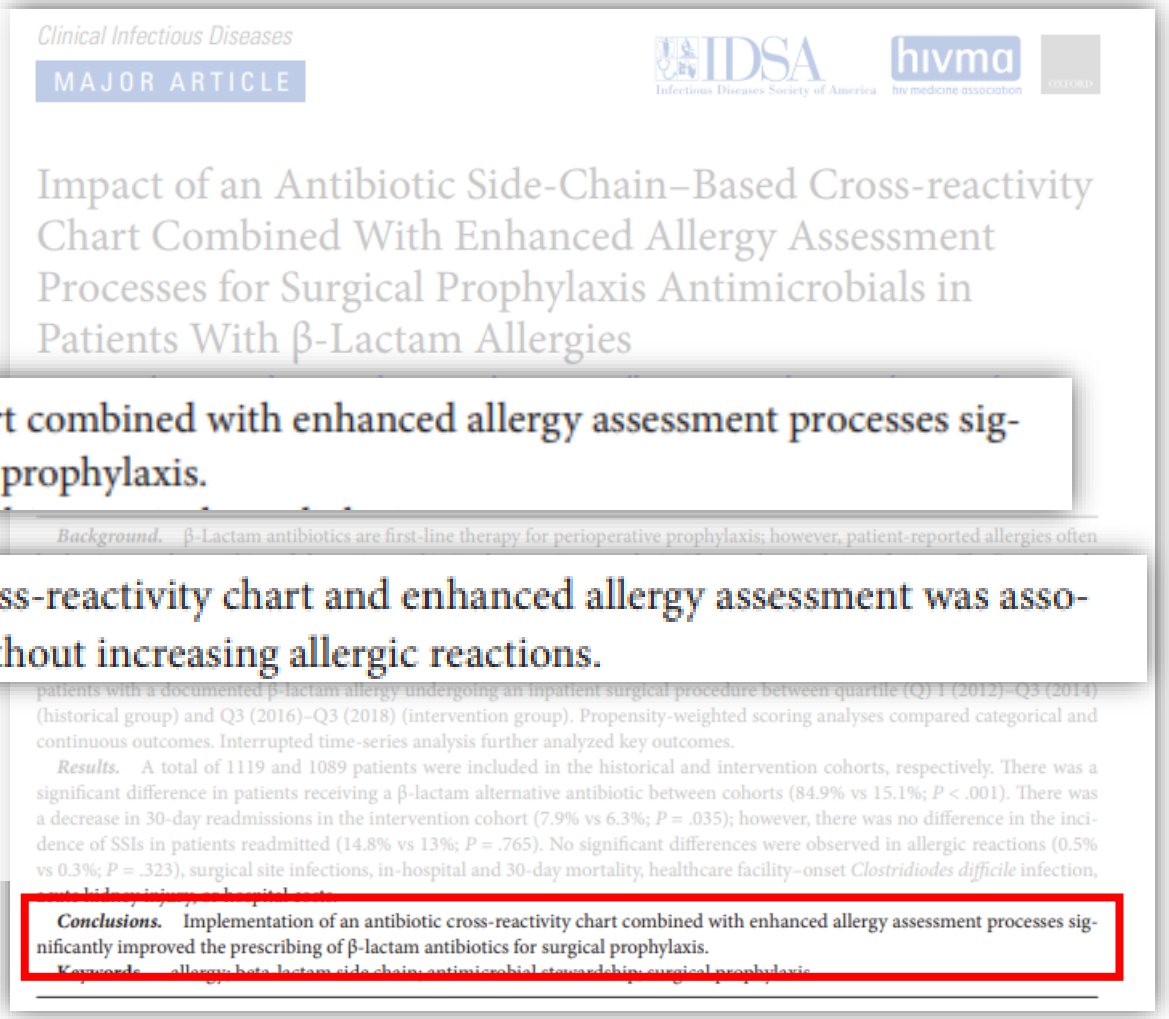

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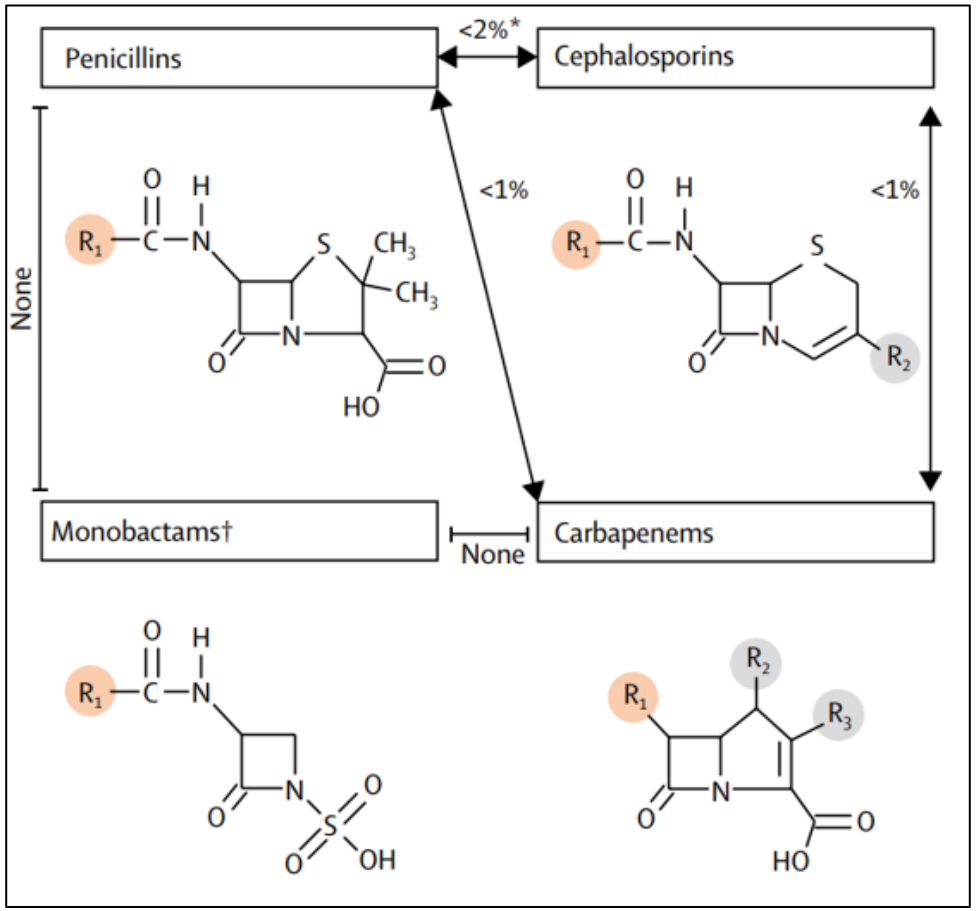
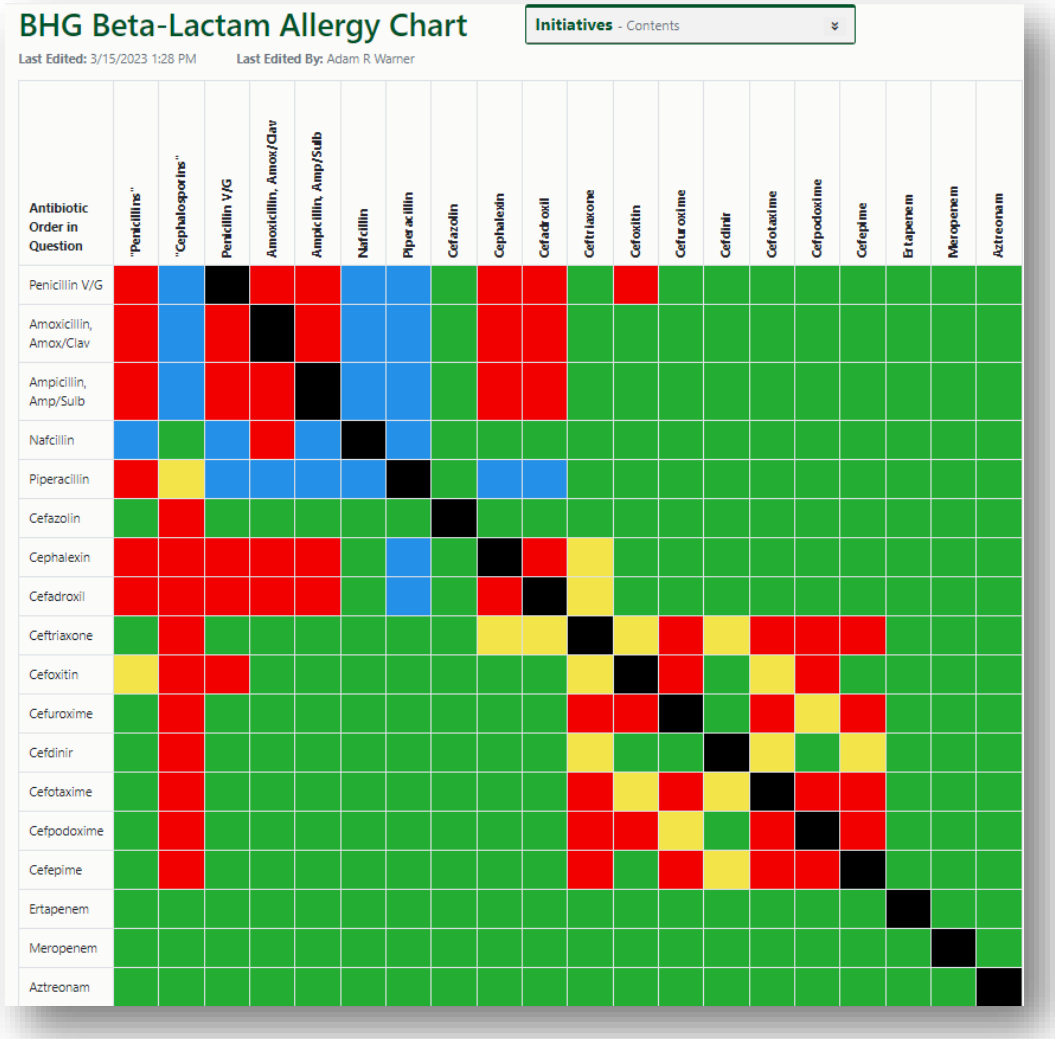
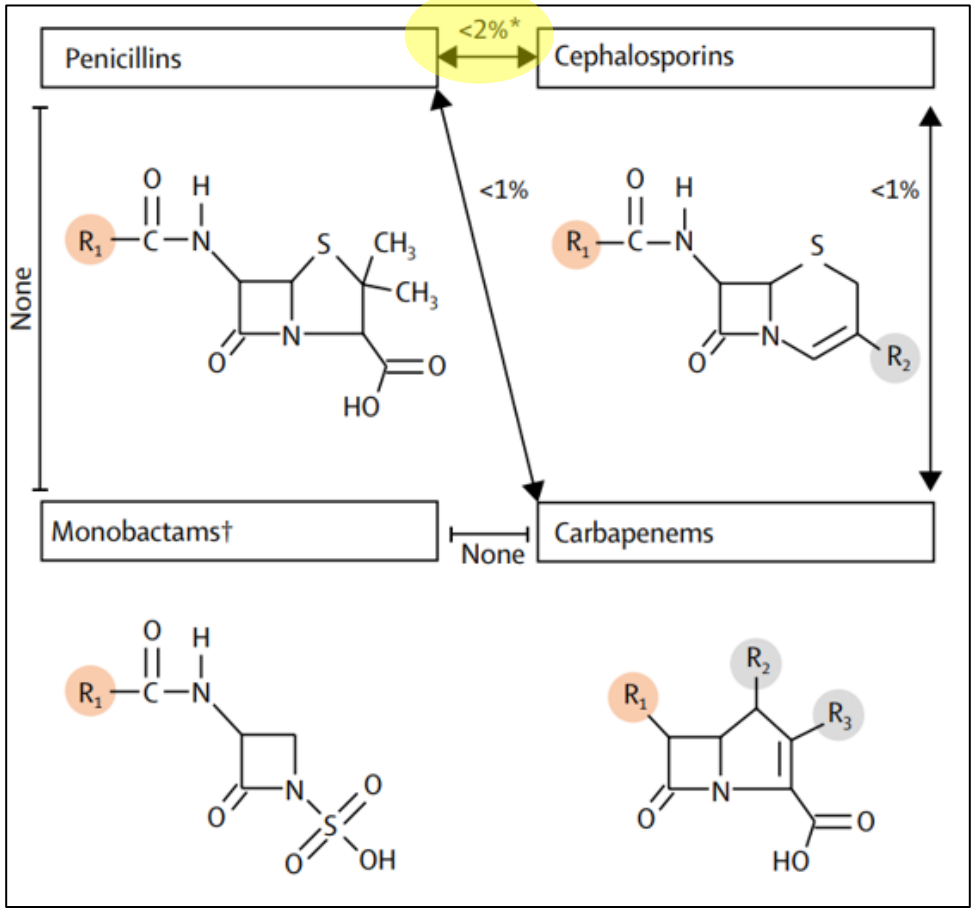
Future Direction at Bronson



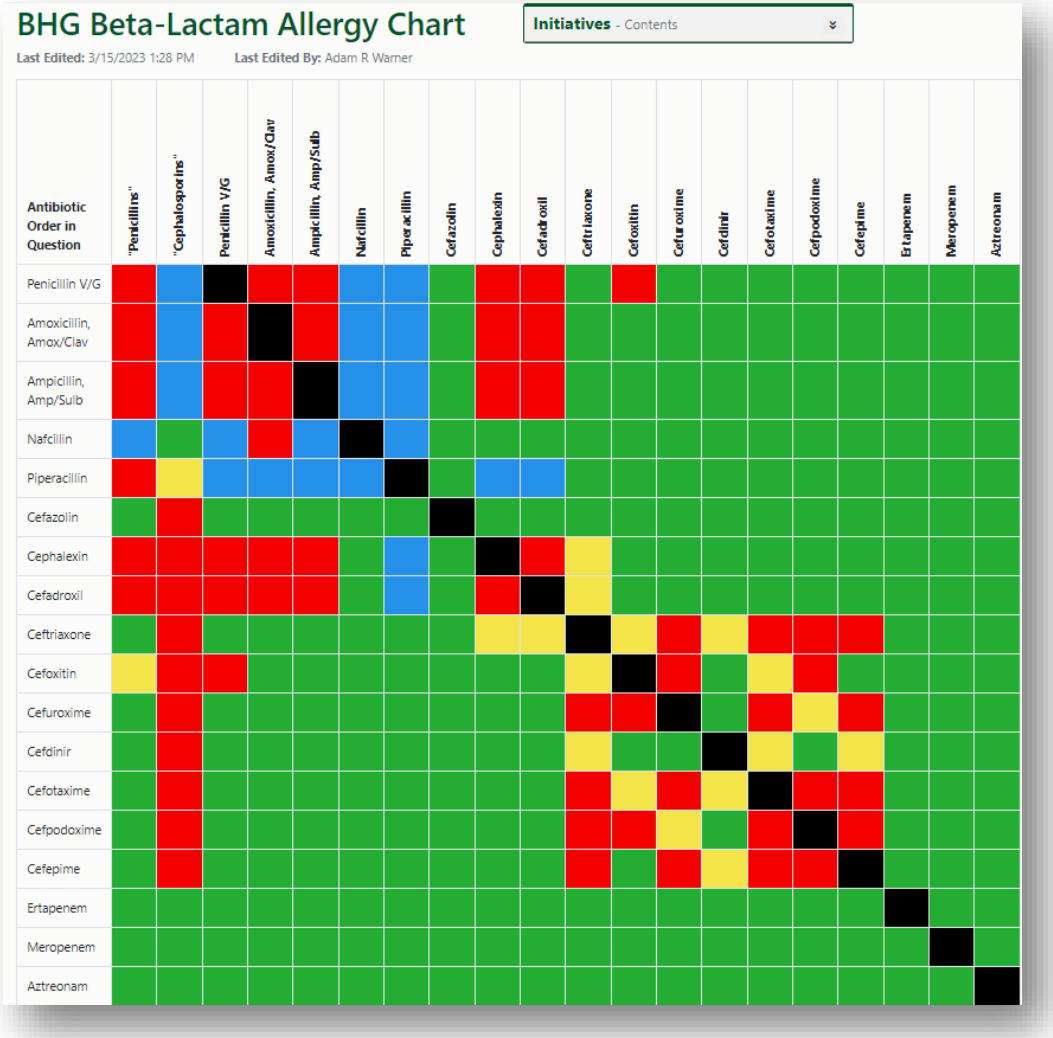


Future Direction at Bronson

Not “about 10%”



Which penicillin or cephalosporin matters



Future Direction

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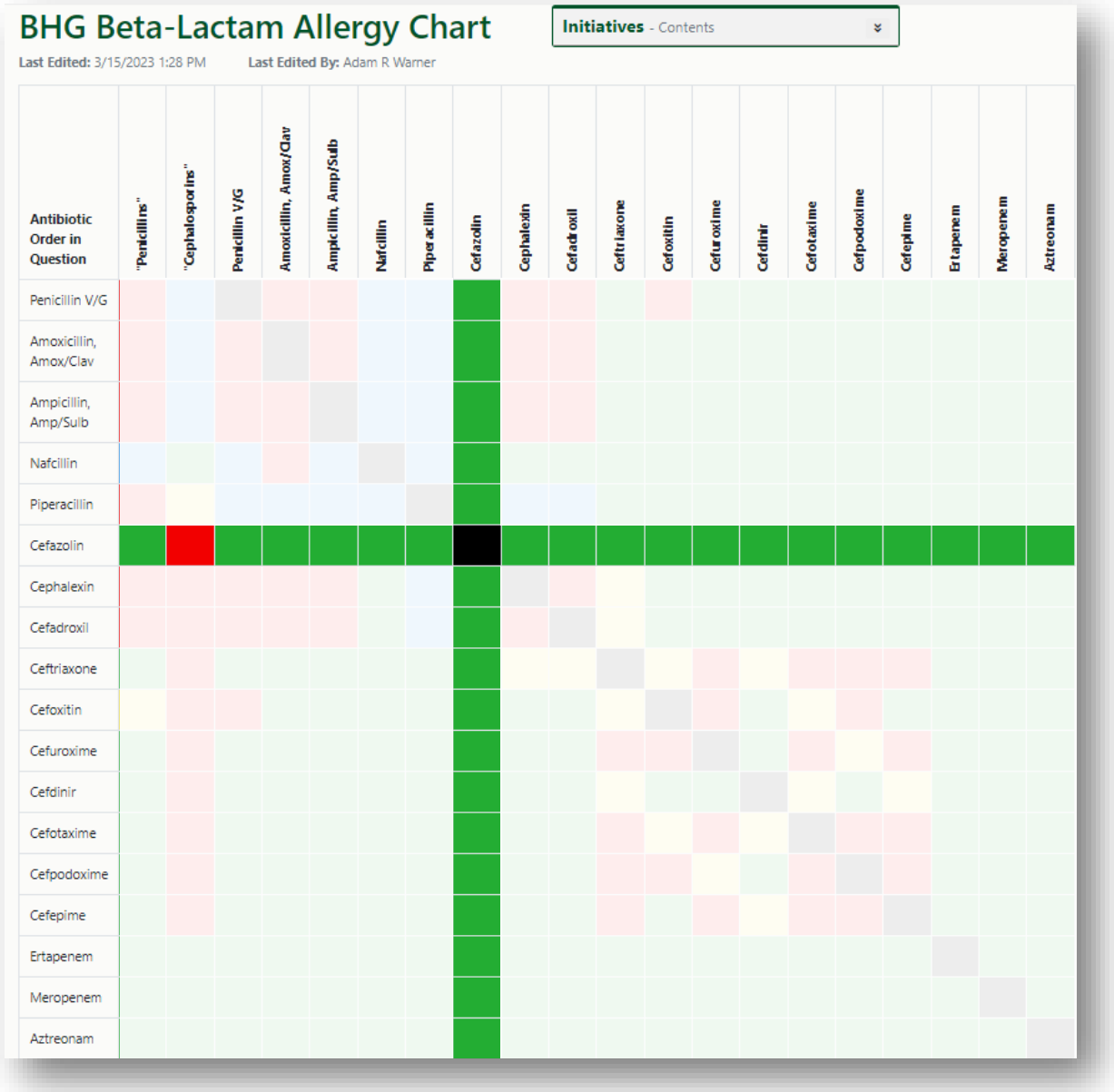

Questions?