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Antibiotics and Infections in the Hospital: what could possibly go wrong?

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Disclosures: none

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Objective: review common and/or serious side effects and problems related to use of antibiotics in the hospital

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THE COMPLICATIONS OF ANTIBIOTIC THERAPY*

LOUIS WEINSTEIN

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THE development of the antimicrobial drugs has brought into the realm of treatable disease the vast bulk of the bacterial infections which, as short a time as fifteen years ago, were responsible for considerable human illness and death. The remarkable therapeutic and prophylactic accomplishments of these agents have exceeded, in many instances, the expectations of even the most optimistic. In the light of the rapid control of many infectious processes by chemotherapy, it is easy to appreciate the enthusiasm which greets each new agent as it appears and to understand the haste to use it in any suspected infection. This phase of uncontrolled and uncritical hyperenthusiasm which is characteristic for every new antibiotic usually lasts until enough experience has accumulated to allow a proper evaluation. It requires a year or more, as a rule, before the "chemotherapeutic coin" reveals itself as having two faces. The side which deservedly attracts attention first and which is studied with greatest enthusiasm is bright and gleaming with the promise of the near-panacea; the other side is less attractive, considerably more somber in appearance and detracts, in varying degree, from the glitter of the coin as a whole.

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TABLE I.—COMPLICATIONS OF ANTIBIOTIC THERAPY

Reactions Due to Sensitization

Morbilliform, scarlatiniform, urticarial, vesicular, bullous
    and purpuric rashes
Contact dermatitis
Erythema multiforme
Exfoliative dermatitis
Fever
Glossitis
Stomatitis
Cheilosis
Asthmatic breathing
Arthus reaction
Angioneurotic edema
Serum sickness
Anaphylactoid reactions
Eosinophilia
?Polyarteritis nodosa
?Disseminated lupus erythematosus

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COMPLICATIONS OF ANTIBIOTIC THERAPY   5 0 7

TABLE II.—COMPLICATIONS OF ANTIBIOTIC THERAPY

Toxic and Irritative Reactions

Albuminuria	Hepatitis
Hematuria	Depression of bone marrow
Cylindruria	Peripheral neuritis
Renal decompensation	Paresthesia
Stomatitis	Cerebral damage
Glossitis	Venous thrombosis
Nausea, vomiting	Pain at site of injection
Diarrhea	

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TABLE III.—COMPLICATIONS OF ANTIBIOTIC THERAPY

Reactions Resulting from Biologic Alterations in the Host and Infecting Agent

Negative nitrogen balance
Increased riboflavin excretion
Disturbance in electrolytes
Suppression of urobilinogen formation
Superinfection—bacterial and mycotic
Emergence of drug-resistant bacteria
Depression of immune response

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- 23 y old gentleman, with poorly controlled type 1 DM , not on any medications except insulin and Lisinopril (which he took on the day of admission)
- Presented to the emergency room with acute onset of fever, chills, redness and swelling of the right leg with severe pain
- Chronic wound of his right foot, with acute onset of swelling of his foot and leg, and purulent drainage from the wound
- Exam: HR 125 BP 96/54/ looking ill/ foul-smelling purulent drainage from a right heel wound, erythema and edema up to knee

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- Labs: WBC 21'000, Creat 0.8, Lactate 2.8
- The patient receives IV fluid per sepsis protocol, Vancomycin, Piperacillin-tazobactam, he is also started on an insulin drip
- Due to persistent hypotension, he also requires norepinephrine infusion
- The following day, his creatinine is up to 1.8, with urine output of less than 300 mL.
- Vancomycin trough is 24

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Which of these factors did most likely NOT contribute to AKI:

1. Septic shock
2. ACEi
3. Vancomycin/ piperacillin-tazobactam combination
4. High vancomycin loading-dose
5. High vancomycin trough level

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The Nephrotoxicity of Vancomycin

EJ Filippone[1,2], WK Kraft[3] and JL Farber[4]

Vancomycin use is often associated with nephrotoxicity. It remains uncertain, however, to what extent vancomycin is directly responsible, as numerous potential risk factors for acute kidney injury frequently coexist. Herein, we critically examine available data in adult patients pertinent to this question. We review the pharmacokinetics/pharmacodynamics of vancomycin metabolism. Efficacy and safety data are discussed. The pathophysiology of vancomycin nephrotoxicity is considered. Risk factors for nephrotoxicity are enumerated, including the potential synergistic nephrotoxicity of vancomycin and piperacillin-tazobactam. Suggestions for clinical practice and future research are given.

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LOADING DOSE

Go to: ⌄

The Guidelines recommend consideration of a loading dose of 25–30 mg/kg actual body weight for serious infections. Rosini *et al.* retrospectively evaluated 1,330 patients receiving vancomycin in the Emergency Department (ED), of which 851 received high doses (>20 mg/kg). VANT occurred in 7.7% with no difference in the high-dose group (5.8%) vs. the low-dose group (11.1%, $P < 0.001$).66 Results were unchanged using a cutoff of >25 mg/kg. An RCT compared 49 patients receiving a 15 mg/kg initial dose to 50 patients receiving 30 mg/kg in the ED and found no difference in the secondary endpoint of VANT, which overall occurred in only 5% of patients.67 To date, there is no evidence that a loading dose is associated with increased nephrotoxicity.

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VANCOMYCIN TROUGH LEVELS

Many studies have assessed the relationship between trough levels as a measure of exposure and VANT. In general, there is a major issue with reverse causation, in that reduced kidney function from any cause will lead to an elevated trough level. In an effort to reduce this bias, some studies consider only the initial trough level. Even that, however, does not obviate kidney injury from another cause. Some studies consider mean trough levels, others maximal troughs.

A dose–response relationship has been shown repeatedly. Lod-

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Clinical Infectious Diseases

MAJOR ARTICLE

IDSA — Infectious Diseases Society of America

hivma — hiv medicine association

OXFORD

Risk of Acute Kidney Injury in Patients on Concomitant Vancomycin and Piperacillin–Tazobactam Compared to Those on Vancomycin and Cefepime

Bhagyashri Navalkele,[1,2] Jason M. Pogue,[2,7] Shigehiko Karino,[1,2] Bakht Nishan,[2] Madiha Salim,[2] Shantanu Solanki,[2] Amina Pervaiz,[2] Nader Tashtoush,[2] Hamadullah Shaikh,[2] Sunitha Koppula,[2] Jonathan Koons,[2] Tanveer Hussain,[2] William Perry,[2] Richard Evans,[3] Emily T. Martin,[3] Ryan P. Mynatt,[4] Kyle P. Murray,[5] Michael J. Rybak,[2,4,6] and Keith S. Kaye[1,2]

[1]Department of Medicine, Detroit Medical Center, and [2]Wayne State University School of Medicine, Detroit; [3]Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor; [4]Department of Pharmacy Services, Detroit Receiving Hospital, [5]Department of Pharmacy Services, Huron Valley Sinai Hospital, [6]Anti-Infective Research Laboratory, Department of Pharmacy Practice, Wayne State University Eugene Applebaum College of Pharmacy and Health Sciences, and [7]Department of Pharmacy Services, Sinai-Grace Hospital, Detroit, Michigan

Background. Recent evidence suggests that among patients receiving vancomycin, receipt of concomitant piperacillin–tazobactam increases the risk of nephrotoxicity. Well-controlled, adequately powered studies comparing rates of acute kidney injury (AKI) among patients receiving vancomycin + piperacillin–tazobactam (VPT) compared to similar patients receiving vancomycin + cefepime (VC) are lacking. In this study we compared the incidence of AKI among patients receiving combination therapy with VPT to a matched group receiving VC.

Methods. A retrospective, matched, cohort study was performed. Patients were eligible if they received combination therapy for ≥48 hours. Patients were excluded if their baseline serum creatinine was >1.2mg/dL or they were receiving renal replacement therapy. Patients receiving VC were matched to patients receiving VPT based on severity of illness, intensive care unit status, duration of combination therapy, vancomycin dose, and number of concomitant nephrotoxins. The primary outcome was the incidence of AKI. Multivariate modeling was performed using Cox proportional hazards.

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Results. A total of 558 patients were included. AKI rates were significantly higher in the VPT group than the VC group (81/279 [29%] vs 31/279 [11%]). In multivariate analysis, therapy with VPT was an independent predictor for AKI (hazard ratio = 4.27; 95% confidence interval, 2.73–6.68). Among patients who developed AKI, the median onset was more rapid in the VPT group compared to the VC group (3 vs 5 days P =< .0001).

Conclusion. The VPT combination was associated with both an increased AKI risk and a more rapid onset of AKI compared to the VC combination.

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REVIEW ARTICLE

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Systematic Review and Metaanalysis of Acute Kidney Injury Associated With Concomitant Vancomycin and Piperacillin/Tazobactam

Drayton A. Hammond,[1,2] Melanie N. Smith,[3] Chenghui Li,[1] Sarah M. Hayes,[4] Katherine Lusardi,[2] and P. Brandon Bookstaver[5]

[1]Department of Pharmacy Practice, University of Arkansas for Medical Sciences, College of Pharmacy, and [2]Department of Pharmacy, University of Arkansas for Medical Sciences Medical Center, Little Rock; [3]Department of Pharmacy, Medical University of South Carolina, Charleston; [4]Department of Pharmacy, University of Minnesota Medical Center, Minneapolis; and [5]Department of Clinical Pharmacy and Outcome Sciences, College of Pharmacy at the University of South Carolina, Columbia

Concomitant vancomycin and piperacillin/tazobactam (PT) may be associated with increased acute kidney injury (AKI) compared to vancomycin without PT. Medline, Cochrane, and Scopus were searched through October 2016 using "vancomycin," "piperacillin," "tazobactam," and "AKI," "acute renal failure," or "nephrotoxicity." A registered meta-analysis (PROSPERO: CRD42016041646) with relevant scenarios was performed. Fourteen observational studies totaling 3549 patients were analyzed. Concomitant vancomycin and PT was associated with AKI in unadjusted odds ratio (OR, 3.12; 95% confidence interval [CI], 2.04–4.78) and in adjusted OR (aOR, 3.11; 95% CI, 1.77–5.47) analyses. Similar findings were seen assessing studies in adults (aOR, 3.15; 95% CI, 1.72–5.76), children (OR, 4.55; 95% CI, 2.71–10.21), and when <50% of patients received care in an intensive care unit (aOR, 3.04; 95% CI, 1.49–6.22) but not ≥50% (aOR, 2.83; 95% CI, 0.74–10.85). Increased AKI with concomitant vancomycin and PT should be considered when determining beta-lactam therapy.

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Incidence of Acute Kidney Injury in Critically Ill Patients Receiving Vancomycin with Concomitant Piperacillin/Tazobactam, Cefepime, or Meropenem.

Blevins AM[1], Lashinsky JN[2], McCammon C[2], Kollef M[3], Micek S[2,4], Juang P[5,4].

⊕ Author information

Abstract

Critically ill patients are frequently treated with empiric antibiotic therapy including vancomycin and β-Lactams. Recent evidence suggests an increased risk of acute kidney injury (AKI) in patients who received the combination of vancomycin and piperacillin/tazobactam (VPT) compared with patients who received vancomycin alone or vancomycin in combination with cefepime (VC) or meropenem (VM), but most studies have been conducted predominately in the non-critically ill population. A retrospective cohort study including 2492 patients was conducted in the intensive care units of a large university hospital with the primary outcome being the development of any AKI. The rate of any AKI, as defined by the KDIGO guidelines, was 39.3% for VPT patients, 24.2% for VC, and 23.5% for VM patients (p<0.0001 for both comparisons). Similarly, the incidence of stage two and three AKI were also significantly higher for VPT patients compared to the other groups. The rate of stage two and three AKI, respectively, was 15% and 6.6% for VPT patients, 5.8% and 1.8% for VC patients, and 6.6% and 1.3% for VM patients (p<0.0001 for both comparison). In multivariate analysis, the use of vancomycin in combination with piperacillin/tazobactam was found to be an independent predictor of AKI (OR 2.161 95% CI = 1.620-2.883). In conclusion, critically ill patients receiving the combination of VPT had the highest incidence of AKI when compared to critically ill patients receiving either VC and VM.

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Which of these factors did most likely NOT contribute to AKI:

1. Septic shock
2. ACEi
3. Vancomycin/ piperacillin-tazobactam combination
4. High vancomycin loading-dose
5. High vancomycin trough level

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- 53-year-old gentleman is admitted to the hospital for infection of his right total knee arthroplasty.
- He undergoes washout and liner exchange, and surgical culture grow MRSA.
- The patient wants to go home, he refuses to go to a nursing home for IV antibiotic therapy.
- In the hospital, he's on vancomycin IV twice a day, which the patient cannot do as an outpatient.
- He is transitioned to IV daptomycin at a standard dose of 6 mg per kilogram IV once a day

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Regarding the use of daptomycin, which statement is correct:

1. Co-administration of daptomycin with a statin is absolutely contraindicated due to a 10 fold increased risk of myopathy.

2. Daptomycin is a better drug than vancomycin to treat MRSA pneumonia, due to its high concentration in surfactant.

3. Unlike vancomycin, emergence of resistance to daptomycin is not a concern when treating infections such as endocarditis or osteomyelitis.

4. Acute kidney injury is a major side effect of daptomycin.

5. Daptomycin is the leading cause of drug-induced eosinophilic pneumonia

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Rhabdomyolysis and acute renal failure associated with the co-administration of daptomycin and an HMG-CoA reductase inhibitor

Randy O. Odero, Kerry O. Cleveland* and Michael S. Gelfand

In conclusion, this is the first case reporting reversible rhabdomyolysis and renal failure after the co-administration of daptomycin and an HMG-CoA reductase inhibitor. According to the package insert for daptomycin, experience with co-administration with HMG-CoA reductase inhibitors is limited, and their use might need to be suspended during therapy with daptomycin.[7] Consistent with earlier experiences, this patient's renal dysfunction improved within 10 days after stopping daptomycin.[2,7]

Additional clues to impending adverse effects of daptomycin may be obtained by monitoring renal and hepatic function tests. The current recommendation is to monitor the serum CPK concentration at least weekly, and more frequently if clinical conditions warrant.[7]

Effect of Statin Coadministration on the Risk of Daptomycin-Associated Myopathy

Ryan K. Dare,[1] Chad Tewell,[2] Bryan Harris,[3] Patty W. Wright,[3] Sara L. Van Driest,[4,5] Eric Farber-Eger,[6] George E. Nelson,[3] and Thomas R. Talbot[3]

[1]Division of Infectious Diseases, Department of Medicine, University of Arkansas for Medical Sciences, Little Rock; [2]St Vincent Health, Indianapolis, Indiana; and [3]Division of Infectious Diseases, Department of Medicine, [4]Division of General Pediatrics, Department of Pediatrics, [5]Division of Clinical Pharmacology, Department of Medicine, and [6]Vanderbilt Institute for Clinical and Translational Research, Vanderbilt University Medical Center, Nashville, Tennessee

Background. Daptomycin-associated myopathy has been identified in 2%–14% of patients, and rhabdomyolysis is a known adverse effect. Although risk factors for daptomycin-associated myopathy are poorly defined, creatine phosphokinase (CPK) monitoring and temporary discontinuation of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or "statins," has been recommended.

Methods. We conducted a single-center, retrospective, matched case-control risk factor analysis in adult and pediatric patients from 2004 to 2015. Patients in whom myopathy (defined as CPK values above the upper limit of normal) developed during daptomycin treatment were matched 1:1 to no-myopathy controls with at least the same duration of therapy. Risk factors independently associated with myopathy were determined using multivariable conditional logistic regression. Secondary analysis was performed in patients with rhabdomyolysis, defined as CPK values $\geq$10 times the upper limit of normal.

Results. Of 3042 patients reviewed, 128 (4.2%) were identified as having daptomycin-associated myopathy, 25 (0.8%) of whom had rhabdomyolysis; 121 (95%) of the 128 were adults, and the mean duration of therapy before CPK elevation was 16.7 days (range, 1–58 days). In multivariate analysis, deep abscess treatment (odds ratio, 2.80; P = .03), antihistamine coadministration (3.50; P = .03), and statin coadministration (2.60; P = .03) were independent risk factors for myopathy. Obesity (odds ratio, 3.28; P = .03) and statin coadministration (4.67; P = .03) were found to be independent risk factors for rhabdomyolysis, and older age was associated with reduced risk (0.97; P = .05).

Conclusions. Statin coadministration with daptomycin was independently associated with myopathy and rhabdomyolysis. This is the first study to provide strong evidence supporting this association. During coadministration, we recommend twice-weekly CPK monitoring and consideration of withholding statins.

Musculoskeletal toxicities in patients receiving concomitant statin and daptomycin therapy.

Kido K[1,2], Oyen AA[1], Beckmann MA[1], Brouse SD[3].

⊕ Author information

Abstract

PURPOSE: This article evaluates the musculoskeletal safety of concomitant therapy with daptomycin and Hydroxymethylglutaryl-coenzyme A (HMG CoA) reductase inhibitors (statins).

SUMMARY: Often indicated for severe gram-positive infections, daptomycin is commonly administered with statins but there is limited guidance on the appropriate management of concomitant therapy with daptomycin and statins. A narrative review was conducted to review contemporary clinical evidence of the safety of concomitant therapy with daptomycin and statins. A total of 5 studies were identified comparing daptomycin monotherapy versus daptomycin and statin concomitant therapy for the primary outcome of creatine phosphokinase (CPK) elevations in a variety of patient populations with systemic, skin/soft tissue, and bone/joint infections. Of these studies, 4 also compared myalgia or myopathy as a secondary outcome. Case studies, the case-control study and 1 prospective registry comparing statin alone versus daptomycin and statin concomitant therapy were excluded. These studies showed that concomitant therapy with daptomycin and statin was not significantly associated with CPK elevation or higher event rate of myalgia or myopathy, compared to daptomycin monotherapy.

CONCLUSION: Published cohort studies do not demonstrate a statistically significant difference in the rate of CPK elevations or musculoskeletal toxicities between patients receiving daptomycin monotherapy and daptomycin plus a statin. Patients receiving statins who start daptomycin therapy should continue statin but with weekly monitoring of CPK levels. Continuation of statins is especially important in high-risk patients receiving statins for secondary prevention for atherosclerotic cardiovascular diseases. If myalgia develops, it is reasonable to evaluate the degree of CPK elevation and reassess the need for statin use during daptomycin treatment.

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Inhibition of Daptomycin by Pulmonary Surfactant: In Vitro Modeling and Clinical Impact

Jared A. Silverman, Lawrence I. Mortin, Andrew D. G. VanPraagh, Tongchuan Li, and Jeff Alder

Cubist Pharmaceuticals, Lexington, Massachusetts

The lipopeptide daptomycin has been approved for use in skin and skin-structure infections but has failed to meet statistical noninferiority criteria in a clinical trial for severe community-acquired pneumonia. Daptomycin exhibited an unusual pattern of activity in pulmonary animal models: efficacy in *Staphylococcus aureus* hematogenous pneumonia and inhalation anthrax but no activity against *Streptococcus pneumoniae* in simple bronchial-alveolar pneumonia. Daptomycin was shown to interact in vitro with pulmonary surfactant, resulting in inhibition of antibacterial activity. This effect was specific to daptomycin and consistent with its known mechanism of action. This represents the first example of organ-specific inhibition of an antibiotic.

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REVIEW

YJBM

Vancomycin Resistance in *Staphylococcus aureus*

Will A. McGuinness, Natalia Malachowa, and Frank R. DeLeo*

Laboratory of Bacteriology, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Hamilton, MT

The evolution of *Staphylococcus aureus* during the modern antibiotic era has been delineated by distinct strain emergence events, many of which include acquisition of antibiotic resistance. The relative high burden of methicillin-resistant *S. aureus* (MRSA†) in healthcare and community settings is a major concern worldwide. Vancomycin, a glycopeptide antibiotic that inhibits cell wall biosynthesis, remains a drug of choice for treatment of severe MRSA infections. *S. aureus* strains exhibiting increased resistance to vancomycin, known as vancomycin intermediate-resistant *S. aureus* (VISA) (MIC = 4-8 µg/mL), were discovered in the 1990s. The molecular basis of resistance in VISA is polygenic and involves stepwise mutations in genes encoding molecules predominantly involved in cell envelope biosynthesis. *S. aureus* isolates with complete resistance to vancomycin (MIC ≥ 16 µg/mL) are termed vancomycin-resistant *S. aureus* (VRSA)—they were first reported in the U.S. in 2002. Resistance in VRSA is conferred by the *vanA* gene and operon, which is present on a plasmid. Although treatment of VRSA infections is challenging, the total number of human VRSA infections to date is limited (14 in the U.S.). By comparison, the burden of VISA is relatively high and the molecular mechanisms of resistance are less well-defined. VISA are associated with persistent infections, vancomycin treatment failure, and poor clinical outcomes. Here, we review in brief progress made toward understanding the acquisition of antibiotic resistance in *S. aureus*, with an emphasis on the molecular mechanisms underlying vancomycin resistance.

Emergence of resistance to daptomycin in a cohort of patients with methicillin-resistant *Staphylococcus aureus* persistent bacteraemia treated with daptomycin

O. Gasch[1]*, M. Camoez[1], M. A. Domínguez[1], B. Padilla[2], V. Pintado[3], B. Almirante[4], C. Martín[5], F. López-Medrano[6], E. Ruiz de Gopegui[7], J. R. Blanco[8], G. García-Pardo[9], E. Calbo[10], M. Montero[11], A. Granados[12], A. Jover[13], C. Dueñas[14] and M. Pujol[1] on behalf of the REIPI/GEIH Study Groups†

Among 579 episodes of MRSA bacteraemia included in our study, daptomycin was used as initial therapy in 44/518 (8%) patients, while 124/518 (24%) patients received the antibiotic as definitive therapy: 77 (65%) at 6 mg/kg and 41 (35%) at higher doses (NB - in 6 patients we did not know the exact doses of daptomycin used). Concomitantly with daptomycin, 13 (10%) patients

Table 1. Significant increases in daptomycin MIC were observed in subsequent isolates of 7 of 18 (39%) episodes. Death within

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Daptomycin-induced acute renal and hepatic toxicity without rhabdomyolysis.

Abraham G[1], Finkelberg D, Spooner LM.

⊕ Author information

Abstract

OBJECTIVE: To report a case of a patient who experienced acute renal and hepatic toxicity following administration of daptomycin and review previously published case reports of renal and hepatic dysfunction with daptomycin.

CASE SUMMARY: A 35-year-old man receiving daptomycin 4 mg/kg (275 mg) intravenously once daily (started 5 wk prior to presentation for presumed osteomyelitis) presented to the emergency department with elevations in serum creatinine and hepatic transaminase levels. He did not experience creatine kinase (CK) elevation or rhabdomyolysis. Following discontinuation of daptomycin, his renal and hepatic function improved.

DISCUSSION: To our knowledge, this is the first case of daptomycin-induced hepatotoxicity with acute renal failure in the absence of rhabdomyolysis and CK abnormalities. Previously published case reports described patients with a variety of elevations in liver function tests, serum creatinine, and CK with daptomycin. In our patient, the acute renal and hepatic toxicity was probable according to the Naranjo probability scale.

CONCLUSIONS: Although daptomycin is a well-tolerated antibacterial agent, clinicians should consider periodic monitoring of liver function and renal function tests to identify potential adverse effects.

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Medicine OPEN

Systematic Review and Meta-Analysis

Drug-induced eosinophilic pneumonia

A review of 196 case reports

Carmi Bartal, MD, MHA[*], Iftach Sagy, MD, Leonid Barski, MD

32	Daptomycin	Antibiotics
17	Minocycline	
12	Nitrofurantoin	
3	Azithromycin	
3	Dapsone	
2	Sulfonamide	
2	Ceftaroline	
2	Ethambutol	
1	Ampicillin	
1	Imipenem	
1	Isoniazid	
1	Piperacillin-tazobactam	
1	Cefaclor	
1	Clarithromycin	
1	Roxithromycin	
1	Tosufloxacin	
1	Tetracycline	
2	Dapsone-pyrimethamine	Antimalarial
2	Fansidar	
1	Mefloquine	
1	Atovaquone/proguanil	
3	Methotrexate	Chemotherapy
2	Gemcitabine	
1	Tegafur uracil UFT	
1	Fludarabine	
1	Aminoglutethimide	
1	Cisplatin	
4	Amitriptyline/Maprotiline	Antipsychotic
3	Venlafaxine	
2	Risperidone	
2	Clozapine	
2	Trazodone	
1	Paroxetine	
1	Duloxetine	
1	Sertraline	
3	Levetiracetam	Antiepileptic
3	Valproic acid	
3	Idantoin/Phenytoin	
1	Carbamazepine	
1	Captopril	Antihypertensive
1	Ifenprodil	
32	Mesalamine	Antiinflammatory
13	Sulfasalazine	
2	Ibuprofen	
2	Piroxicam	
2	Diclofenac	
1	Balsalazide	
1	Benzbromarone	
1	Nimesulide	
1	Bucillamine	
1	Naproxen	
2	Ustekinumab	Immunotherapy
2	Interferon alpha	
1	Infliximab	
1	Abatacept	
1	FK-506	
4	Amiodarone	Cardiac
1	Mexiletine	
1	Diltiazem	
1	Simvastatin	Lipid-reducing
3	Acetaminophen	Others
2	Progesterone	
1	Diaminodiphenyl sulfone	
1	Dabigatran	
1	Camostat mesilate	
1	Ranitidine	
1	Sodium cromoglycate	
196		Total

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CASE REPORT

Eosinophilic pneumonia induced by daptomycin☆

Don Hayes Jr. [a,*], Michael I. Anstead [a], Robert J. Kuhn [a,b]

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[b] Department of Pharmacy Practice and Science, University of Kentucky College of Pharmacy, Lexington, KY 40536, USA

Summary   We present a case of drug-induced eosinophilic pneumonia resulting from intravenous daptomycin being used as therapy for recurrent methicillin-sensitive *Staphlococcus aureus* endocarditis. The patient developed hypoxic respiratory failure requiring intubation and mechanical ventilation. Daptomycin therapy was discontinued immediately, and the patient improved significantly after the administration of intravenous corticosteroids allowing for extubation 3 days later.

Antimicrobial Resistance
and Infection Control

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Daptomycin-induced eosinophilic pneumonia - a systematic review

Priyasha Uppal[1], Kerry L. LaPlante[1,2,3], Melissa M. Gaitanis[1,3], Matthew D. Jankowich[1,3] and Kristina E. Ward[2*]

Abstract

Purpose: Eosinophilic pneumonia comprises a group of lung diseases in which eosinophils appear in increased numbers in the lungs and sometimes in the bloodstream. Several case reports link daptomycin use to this phenomenon.

Summary: We performed a systematic literature review to identify cases of eosinophilic pneumonia associated with daptomycin use. Relevant studies were identified by searching Pubmed/Medline, EMBASE, Google Scholar, Cochrane Database of Systematic Reviews, and Clin-Alert from inception to May 2016, and manual searches of reference lists. All case reports that include information regarding patient age, indication, clinical and objective findings, treatment and outcome were evaluated. Abstracts from conference proceedings as well as case reports not in English were excluded. Descriptive statistics were used to analyze the data. Thirty-five patient-cases were included in the final analysis. Patients most likely to be identified with daptomycin-induced eosinophilic pneumonia were male (83%) and elderly (mean age 65.4 ± 15 years). The dose for daptomycin ranged from 4 to 10 mg/kg/day, but included a large number of patients with renal dysfunction. The average duration of daptomycin therapy upon onset of EP symptoms was 2.8 ± 1.6 weeks. Majority of patients presented with dyspnea (94%), fever (57%) and were also found to have peripheral eosinophilia (77%) and infiltrates/opacities of CT/CXR (86%). Symptom improvement was seen after daptomycin discontinuation (24 h to 1 week). The majority of patients were also prescribed treatment with corticosteroids (66%).

Conclusion: Clinicians should be aware of daptomycin-induced eosinophilic pneumonia and its symptoms along with its presentation and treatment.

Keywords: Daptomycin, Eosinophilia, Pneumonia

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Regarding the use of daptomycin, which statement is correct:

1. Co-administration of daptomycin with a statin is absolutely contraindicated due to a 10 fold increased risk of myopathy.

2. Daptomycin is a better drug than vancomycin to treat MRSA pneumonia, due to its high concentration in surfactant.

3. Unlike vancomycin, emergence of resistance to daptomycin is not a concern when treating infections such as endocarditis or osteomyelitis.

4. Acute kidney injury is a major side effect of daptomycin.

5. Daptomycin is the leading cause of drug-induced eosinophilic pneumonia

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- A 70-year-old gentleman, with a past medical history of diabetes, hypertension, on insulin and an ACE inhibitor, presents to the hospital with a complaint of fever and chills for 2 days, night sweats, fatigue, without any other symptoms.

- He has a temperature of 102.5, heart rate of 90, respiratory rate of 20, blood pressure of 111/78. Physical exam is remarkable for a 1/6 holosystolic murmur at the apex, and few crackles at the right lung base.

- White cell count is 15,000, with a left shift. Creatinine is 0.8, at baseline. Lactate is 1.4. Rapid influenza test is negative. The chest x-ray shows a possible infiltrate at the right base.

- He has a history of a rash when he got a shot of penicillin as a child. He is started empirically on levofloxacin and Tamiflu.

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- Within 24 hours, all 4 blood cultures turned positive for gram-positive cocci in clusters. Vancomycin is added to the regimen. Repeat blood cultures at 48 hours are negative. Eventually, the organism is identified as MSSA.

- However, the patient develops cardiogenic shock, with evidence of mitral valve rupture, and needs emergent surgery. An MRSA nasal swab is negative.

- Reviewing his chart in the EHR, you find that he was prescribed Keflex as an outpatient 2 years ago for a skin and soft tissue infection.

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- Taking into account this history of penicillin allergy, which of the following statements is correct?

1. Given his history of penicillin allergy, administration of any beta-lactam antibiotic is absolutely contraindicated unless he undergoes skin testing for penicillin allergy first.

2. Since the patient is tolerating vancomycin well, there is no benefit to switch the patient to a beta-lactam antibiotic for definitive therapy of his MSSA infection.

3. For surgical prophylaxis in patients with a history of penicillin allergy, use of an alternative agent such as vancomycin or clindamycin +/- gentamicin (as opposed to cefazolin) is not associated with an increased risk of surgical site infection.

4. In a patient with a true penicillin allergy (by skin testing), cross-reactivity risk with cepahlosporins and carbapenems is about 2-3% or less.

5. In patients with a history of penicillin allergy without any additional details, true allergy (by skin testing) is present in about 10 % of patient.

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- Unless specified, all the following illustrations or quotes are from the following article

Figure 1: Classification of on-target and off-target ADRs

Pink panel illustrates an example of an on-target ADR. Blue panel (left) illustrates non-immunologically-mediated off-target effects: direct cellular toxicity or disruption of normal physiology, interaction with non-immune receptors, and interaction with immune receptors (eg, non-IgE-mediated mast-cell activation via G-protein coupled receptors). Blue panel (right) shows immunologically mediated adaptive immune responses (antibody-mediated [eg, IgE] immediate reactions or T-cell-mediated delayed reactions). Predisposition to both on-target and off-target reactions is driven by genetic variation, but also ecological factors that can vary over the course of an individual's lifetime. ADR=adverse drug reaction. Bid=BH3 interacting-domain death. *C difficile*=*Clostridioides difficile*. ER=endoplasmic reticulum. FcεR1=high-affinity IgE receptor. HSR=hypersensitivity reaction. MRGPRX2=MAS-related G-protein coupled receptor member X2. PKC=protein kinase C. PLCβ=phospholipase C β. ROS=reactive oxygen species. TCR=T cell receptor. UPR=unfolded protein response. *Dose-dependent. Reproduced from Peter et al.[2]

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	Mechanism	Presentation	Chronology or onset	Antibiotic examples	Diagnosis	Genetic (HLA) association[4]	Treatment	Antibiotic recommendations
Non-IgE-mediated*								
Flushing, itching, urticaria, and angio-oedema; occasionally presents like anaphylaxis	Direct mast-cell stimulation or basophil activation; MRGPRX2 implicated for certain direct mast-cell degranulators[5]	Cutaneous symptoms (most common), then respiratory symptoms (eg, wheezing), then cardiovascular symptoms (eg, hypotension)	Minutes to <1 h (typically during infusion)	Vancomycin or fluoroquinolones	History and physical exam; serum tryptase within 30 min to 1·5 h after reaction usually normal; drug challenge typically negative with lower dose (dose-dependent reaction)	..	Antihistamines alone typically suffice; epinephrine for those meeting anaphylaxis criteria; adjunctive treatment with corticosteroids and inhaled beta agonists as needed	Slow infusion or premedication with antihistamines or corticosteroids; use fewer associated drugs with similar mast-cell effects (eg, opioids)
Antibody-mediated								
IgE-mediated (type I HSR)								
Urticaria, angio-oedema, bronchospasm, and anaphylaxis	Mast-cell and basophil degranulation via IgE-crosslinking bound to the high-affinity IgE receptor (FcεR1)[6]	Itching, palmar erythema, rhinitis, wheezing, urticaria, angio-oedema, or anaphylaxis	<1 h typical, but can be considered within 6 h of exposure	Penicillins or cephalosporins	History, physical exam, elevated serum tryptase (measured within 30 min to 1·5 h after reaction), skin testing, and drug challenge	..	Antihistamines; epinephrine for those meeting anaphylaxis criteria; adjunctive treatment with corticosteroids and inhaled beta agonists as needed	Desensitisation protocol for implicated drug(s); caution with use of drugs in the same class and and structurally related drugs which are potentially cross-reactive
IgG-mediated (type II HSR)								
Cytopenias	Antigen-antibody interactions; IgG and complement-mediated phagocytosis or cytotoxicity	Haemolytic anaemia, thrombocytopenia, or vasculitis	Often <72 h, but can be up to 15 days	Penicillins, cephalosporins, sulphonamides, dapsone, or rifampicin	History, physical exam, targeted laboratory evaluation, and biopsy as indicated	..	Corticosteroids, other immunosuppressants or immunomodulators	Avoidance of implicated drug(s); caution with use of same class and and structurally related drugs which are potentially cross-reactive
Serum sickness or serum sickness-like reaction (type III HSR)								
Serum sickness	High antibody titres and circulating immune-complexes; IgM or IgG and complement†	Fever, rash, or arthralgia; uncommon in adults	Days to weeks (typically 1–3 weeks)	Penicillin, amoxicillin, cefaclor, or trimethoprim-sulfamethoxazole	History, physical exam, and laboratory evaluation including differential blood count, sedimentation rate, C-reactive protein, total complement, C3, C4, urinalysis to assess for proteinuria, and skin	..	Antihistamines and corticosteroids (systemic for severe cases only)	Avoidance of implicated drug(s); caution with use of same class and and structurally related drugs which are potentially cross-reactive

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Cell-mediated

Primary single organ disease

Acute interstitial nephritis‡	CD4 or monocyte immune injury to the renal tubulointerstitium	Rash, acute kidney injury, white cell casts in urinary sediment, peripheral blood eosinophilia, or eosinophiluria	3 days to 4 weeks	Semi-synthetic anti-staphylococcal penicillins (eg, nafcillin and oxacillin) fluoroquinolones, or rifampicin	History, physical exam, laboratory, urinalysis, and renal biopsy (severe cases)	..	Antihistamines, topical or systemic corticosteroids, and mycophenolate mofetil or cyclophosphamide (for renal failure not responsive to systemic corticosteroids)	Avoidance of implicated drug(s) and drugs in the same class advisable; limited data to support or negate cross-reactivity within same family (eg, cephalosporins often tolerated with semi-synthetic penicillin acute interstitial nephritis)
Drug-induced liver injury	CD4 then CD8 T-cell activation and FasL; TNF alpha and perforin to hepatocyte cell death	Transaminitis (cholestatic or mixed picture); hepatitis is the main presentation, but some cases are accompanied by rash, fever, or eosinophilia	From 5 days to 12 weeks (typically more than 4 weeks)	Amoxicillin–clavulanate, flucloxacillin, rifampicin, co-trimoxazole, nevirapine, efavirenz, nitrofurantoin,‡ or minocycline‡	History, physical exam, laboratory,§ and liver biopsy (severe cases)	HLA-B*57:01 (flucloxacillin) HLA-A*02:01; HLA-DRB1*15:01; HLA-DQB1*06:02 (amoxicillin–clavulanate) HLA-DRB1*01:01 and 01:02 (nevirapine)	Corticosteroids (after toxic or viral etiology excluded); antihistamines and topical corticosteroids (if concurrent rash)	Avoidance of implicated drug(s), drugs in same class, and structurally related drugs which are potentially cross-reactive

Isolated cutaneous disease¶

Maculopapular rash	Eosinophilic inflammation (CD4 and Th2) via IL-4, IL-5, IL-13, or eotaxin (type IVb HSR)	Morbilliform rash, often with peripheral blood eosinophilia	Days to weeks (typically in second week of therapy)	Amoxicillin or sulphonamide antibiotics	History, physical exam, laboratory evaluation (eosinophilia, no organ involvement), and biopsy (severe cases only) with eosinophilic infiltrate in the dermis or variable non-specific picture	--	Antihistamines, topical corticosteroids, or systemic corticosteroids (severe cases only)	Repeat exposure to implicated drug(s) may not result in same reaction, especially after a period of unexposed time; cross-reactivity is less defined; data exists on a treat-through approach for patients requiring therapy who develop this hyper-sensitivity reaction with monitoring for signs of SCAR
Fixed drug eruption||	Activated intraepidermal CD8 T cells release IFN gamma and cytotoxic granules	Erythematous or oedematous plaques of a round shape with gray or dusky center at same sites (often lip, tongue, face, or genitalia) with each exposure; burning and pain at involved sites	Days to weeks (within minutes on re-challenge)	Sulphonamide antibiotics or vancomycin	History, physical exam, biopsy with basal cell degeneration, pigmentary incontinence, dermal melanophages, patch testing (topical provocation), and drug challenge (systemic provocation)	--	Antihistamines, topical corticosteroids, or systemic corticosteroids (severe cases only)	Avoidance of implicated drug(s) advisable
Contact dermatitis or eczema**	Monocytic inflammation (Th1 and IFN gamma)	Erythema and oedema with vesicles or bullae**	Days to weeks	Bacitracin or ampicillin**	History, physical exam, biopsy (mixed superficial perivascular inflammation), patch testing, and drug challenge	--	Treatment similar to that for atopic dermatitis (mild cleansers, emollients, topical corticosteroids, and antihistamines) or systemic corticosteroids (severe cases only)	Avoidance of implicated drug(s) advisable

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Systemic or multisystem disease[4,7,9]

| Reaction	Immune mechanism	Clinical examples	Timing of onset	Drug examples	Diagnostic approach	HLA association	Treatment	Recommendations
Drug reaction eosinophilia and systemic symptoms syndrome	CD4 (IL-4, IL-5, IL-13) and CD8 T cells implicated (release of TNF alpha and IFN gamma); primary dermal lymphocytic infiltrate	Fever, rash, peripheral blood eosinophilia, lymphadenopathy, or organ involvement (often liver or kidney)	2–6 weeks	Vancomycin, rifamycin, sulphonamide antibiotics, dapsone, or all β-lactam antibiotics	History, physical exam, laboratory (assessment of absolute eosinophil count and organ involvement), biopsy, clinical scoring RegiSCAR,†† causality assessment Naranjo,‡‡ and patch testing (may identify culprit)	HLA-B*13:01 (dapsone in southeast Asians); HLA-B*35:05 (nevirapine in southeast Asians); HLA-B*53:01 (raltegravir in African ancestry)	Immediate removal of drug; antihistamines or corticosteroids (severe cases only)	Avoidance of implicated drug(s), drugs in the same class, and structurally related drugs which are potentially cross-reactive
Abacavir hyper-sensitivity syndrome	CD8 T cells; non-covalent binding to floor of antigen blinding cleft with altered peptide repertoire of endogenous peptides bound to HLA-B*57:01	Fever, malaise, gastrointestinal or respiratory symptoms; rash is mild to moderate, present in 70% of patients, and occurs late	From days to 3 weeks (typically 1 week)	Abacavir (no other drugs to date cause identical syndrome)	History, physical exam, and patch test (to confirm culprit)	HLA-B*57:01 (screening is guideline-based therapy in developed world)	Immediate removal of drug	Avoidance of abacavir only
Stevens-Johnson syndrome and toxic epidermal necrolysis	CD8 cytotoxic T cells via perforin, granulysin, granzyme B, or FasL (keratinocyte death, type IVc HSR)	Rash with desquamation, mucosal lesions (mouth, eyes, genitals) with mucositis, or fever SJS: <10% BSA SJS–TEN overlap: 10–30% BSA TEN: >30% BSA	4 days to 4 weeks (for many antimicrobials shorter latency is typical)	Sulphonamide antimicrobials, nevirapine, antimycobacterials, macrolides, or quinolones	History (blistering rash with skin sloughing), physical exam (Nikolsky and Asboe-Hansen signs), skin biopsy with keratinocyte necrosis (from partial to full thickness) of the epidermis, and clinical scoring (SCORETEN,§§ ALDEN,¶¶ Naranjo‡‡)	HLA-C*04:01 (nevirapine in Africans)	Immediate removal of drug; aggressive supportive care in intensive care unit or burn unit setting; pulse corticosteroids, etanercept, or cyclosporine	Avoidance of implicated drug(s), drugs in the same class, and structurally related drugs which are potentially cross-reactive
Acute generalised exanthe-matous pustulosis	T cells via IL-8 and granulocyte-macrophage colony-stimulating factor (neutrophilic inflammation, type IVd HSR)	Acute pustular eruption characterised by widespread non-follicular sterile pustules with fever, facial oedema, or neutrophilia; 25% of patients have oral involvement	<48 h (typically within 24 h); longer latency for pristinamycin and hydroxychloroquine	Aminopenicillins, clindamycin, other β-lactams, fluoroquinolones, sulphonamides, pristinamycin, terbinafine, or hydroxychloroquine (anti-malarial)	History, physical exam, fever, laboratory evaluation showing neutrophilic leukocytosis with mild eosinophilia; skin biopsy (subcorneal pustules or intraepidermal pustules filled with neutrophils), and patch testing (to help	··	Immediate removal of drug, topical corticosteroids, or systemic corticosteroids (severe cases and widespread involvement)	Avoidance of implicated drug(s), drugs in the same class, and structurally related drugs which are potentially cross-reactive; drugs reintroduced may be guided by patch testing

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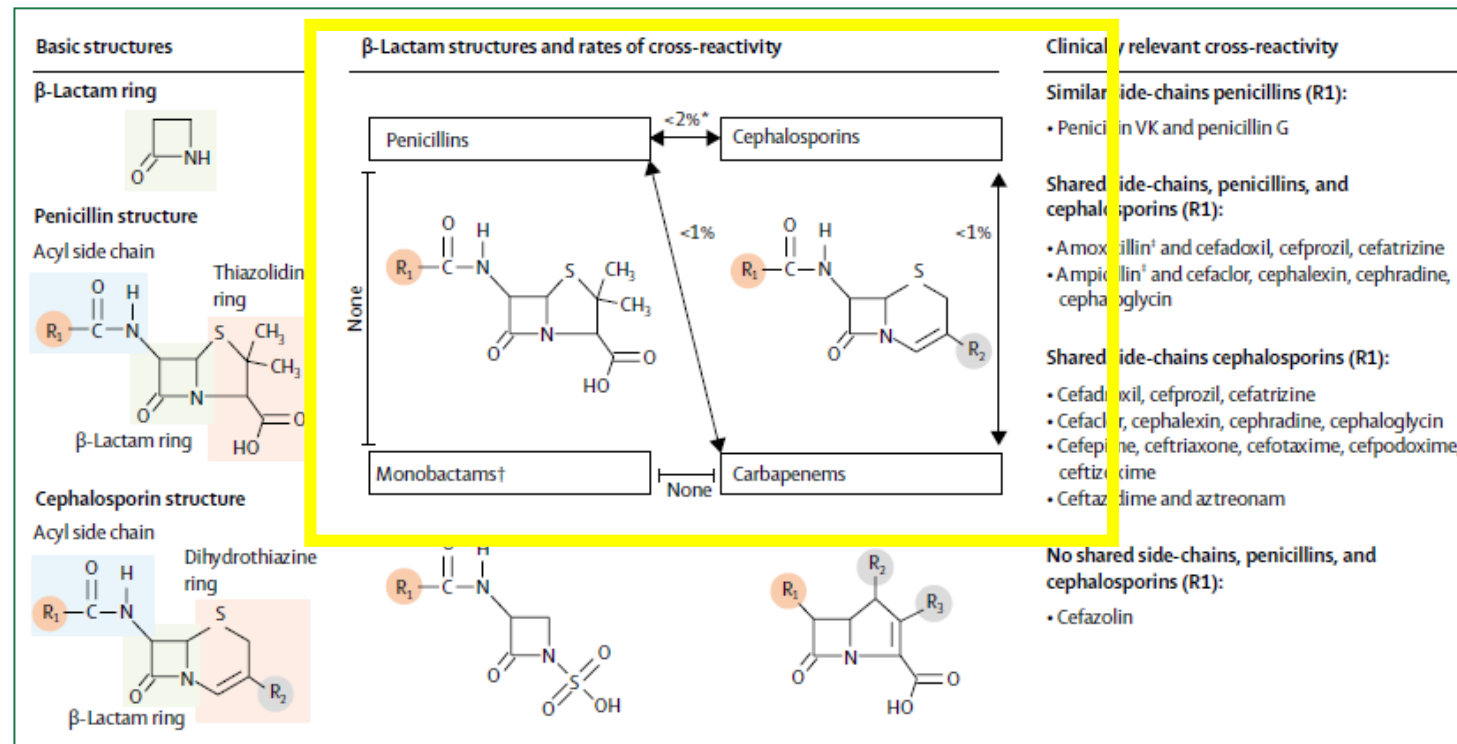
Figure 2: β-Lactam structure and cross-reactivity

β-Lactam antibiotics include penicillins, cephalosporins, carbapenems, and monobactams. Cross-reactivity is possible through the core β-lactam ring, adjacent thiazolidine (penicillin) or dihydrothiazine (cephalosporin) ring, and also from a side chain, R₁, or R₂ group (left panel). Cephalosporins have both an R₁ and R₂ group and penicillins only an R₁. Despite varied mechanisms, true cross-reactivity is largely based on R₁ side chains. Identical side chains in patients with IgE-mediated allergy pose the highest risk. However, cross-reactivity from side chains that are similar, but not identical, and from R₂ group similarity is possible and reported. The centre panel demonstrates the structure and rates of cross-reactivity between penicillins, cephalosporins, carbapenems, and monobactams. The right panel details the most clinically important cross-reactivity considerations. *Except for shared group aminopenicillins and cephalosporins. †Monobactams have no shared cross-reactivity with other β-lactams, with the exception for aztreonam and ceftazidime, which share an identical R1. ‡Amoxicillin and ampicillin are structurally similar aminopenicillins and should be considered clinically cross-reactive with each other and the respective cephalosporins with shared R₁ groups listed in the figure. Similar considerations exist for the aminocephalosporins.

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Cross-reactivity between β-lactam antibiotics has been described for IgE-mediated HSRs (figure 2).[84] Early cephalosporin formulations were likely to be contaminated with penicillin, leading to high estimates of β-lactam cross-reactivity (10%).[105] Although the cross-reactivity rate is currently calculated to be lower than these initial estimates (2%),[8] European allergy referral populations have documented high rates of β-lactam cross-reactivity in skin tests, predicted by shared side-chain structures.[106,107]

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Adverse reactions associated with oral and parenteral use of cephalosporins: A retrospective population-based analysis

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Background: Few studies have provided population-based, route-specific data on allergy to cephalosporin or incidence of serious adverse drug reactions (ADRs).

Objective: We investigated the incidence of new reports of cephalosporin-associated "allergy" and serious ADRs.

Methods: We identified all members of the Kaiser Permanente Southern California health plan given cephalosporins (from January 1, 2010, through December 31, 2012), all new reports of cephalosporin-associated allergy, and all serious ADRs.

Results: There were 622,456 health plan members exposed to 901,908 courses of oral cephalosporins and 326,867 members exposed to 487,630 courses of parenteral cephalosporins over the 3-year study period. New reports of allergy to cephalosporin

Abbreviations used	
ADR:	Adverse drug reaction
EHR:	Electronic health record
ICD-9:	*International Classification of Diseases, Ninth Revision*
RR:	Relative risk
SCAR:	Serious cutaneous adverse reaction
SJS:	Stevens-Johnson syndrome

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There were 65,915 individuals with a history of a penicillin allergy who received a total of 127,125 courses of cephalosporins. There were 3 cases of cephalosporin-associated anaphylaxis in this group. Physician-documented cephalosporin-associated anaphylaxis was about 2.9-fold more common in individuals with histories of penicillin allergy than in individuals with no history of drug allergy (3 of 127,125 courses; 95% CI, 0-1/19,880 vs 7 of 845,923 courses; 95% CI, 1/467,290-1/69,396). This difference was not statistically significant ($P = .1322$).

Benzylpenicillin			
Ampicillin			
Amoxicillin			β-Lactam ring
Piperacillin			Thiazolidine ring
			Penicillin
Cephalosporins			Dihydrothiazine ring, β-Lactam ring

		R₁	R₂
Aminocephalosporins	Cefaclor		Cl
	Cephalexin		CH₃
	Cefadroxil		CH₃
Other cephalosporins	Cefamandole		
	Ceftriaxone		
	Cefuroxime		
	Cefotaxime		
	Cefepime		
	Ceftazidime		

The 252 participants had experienced a total of 319 immediate reactions to penicillins (Table II).

One hundred and ninety-three patients (76.6%) had had an anaphylactic reaction, which was diagnosed according to the clinical criteria proposed by Sampson et al.[26] The remaining 59 patients had developed only cutaneous symptoms, mostly urticaria and angioedema.

All subjects had positive skin test results to at least 1 of the penicillin reagents tested (Table II): 140 subjects were positive to only semisynthetic penicillins (ampicillin, amoxicillin, and/or piperacillin), 100 to both classic penicillin reagents (PPL/BP-OL, MDM/MD, and benzylpenicillin) and semisynthetic penicillins, and 12 only to classic penicillin reagents.

Eighty-four subjects (33.3%; CI, 27.8% to 39.4%) displayed positive skin tests to at least 1 cephalosporin. Specifically, 68 were positive only to aminocephalosporins, 11 only to cephalosporins other than aminocephalosporins, and 5 to both aminocephalosporins and other cephalosporins. With regard to the 73 participants with positive skin tests to aminocephalosporins, 27 were positive only to cefadroxil; 22 to cephalexin, cefadroxil, and cefaclor; 8 to both cefaclor and cefadroxil; 5 to both cephalexin and cefadroxil; 5 only to cefaclor; 3 to both cephalexin and cefaclor; and 3 only to cephalexin. Table III summarizes the results of allergy tests in the 16 subjects who displayed positive responses to skin tests for cephalosporins other than aminocephalosporins, mostly to cefamandole and ceftriaxone.

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Unverified antibiotic allergy labels

Most patients labelled with a β-lactam allergy are not allergic (ie, they tolerate penicillin and related drugs).57 This mislabel occurs for a variety of reasons. First, the original reaction might not have been an allergy (there could be intolerance, a viral exanthem, or a drug-infection interaction). Even if the original reaction were immunological, it might not recur with re-challenge. IgE-mediated reactions to β-lactams can wane over time; approximately 80% of patients who are positive for a penicillin skin test and 60% of those positive for a cephalosporin skin test are no longer sensitive, as measured by skin testing after a period of 10 and 5 years, respectively.58,59 Mild delayed reactions that in many cases were T-cell-mediated do not reliably occur with re-challenge;60–62 such reactions, therefore, either did not represent adaptive immune responses or were immune responses that were lost in the absence of ongoing drug exposure. Among patients admitted to hospital with a documented penicillin allergy who were skin tested and challenged, 95% were not allergic and were de-labelled.63 Outpatients with documented penicillin allergies have also been largely (>98%) tolerant to penicillin.64,65 However, notable global variation in the frequency of confirmed IgEmediated penicillin allergy exists. Although some international variation might be tied to differential antibiotic prescribing patterns, other variations could be explained by differences in patient selection or demographic and genetic differences. For example, European studies confirm penicillin allergy in 18%–30% of evaluated patients, although confirmed allergy could include diagnostics in vitro.66,67

A systematic review and meta-analysis

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Edited by: Pascal Demoly

[Correction added on 11 May 2017 after first online publication: The author names were incorrect and have been corrected in this version.]

Abstract

Background: A documented penicillin allergy is associated with increased morbidity including length of hospital stay and an increased incidence of resistant infections attributed to use of broader-spectrum antibiotics. The aim of the systematic review was to identify whether inpatient penicillin allergy testing affected clinical outcomes during hospitalization.

Methods: We performed an electronic search of Ovid MEDLINE/PubMed, Embase, Web of Science, Scopus, and the Cochrane Library over the past 20 years. Inpatients having a documented penicillin allergy that underwent penicillin allergy testing were included.

Results: Twenty-four studies met eligibility criteria. Study sample size was between 24 and 252 patients in exclusively inpatient cohorts. Penicillin skin testing (PST) with or without oral amoxicillin challenge was the main intervention described (18 studies). The population-weighted mean for a negative PST was 95.1% [CI 93.8-96.1]. Inpatient penicillin allergy testing led to a change in antibiotic selection that was greater in the intensive care unit (77.97% [CI 72.0-83.1] vs 54.73% [CI 51.2-58.2], $P<.01$). An increased prescription of penicillin (range 9.9%-49%) and cephalosporin (range 10.7%-48%) antibiotics was reported. Vancomycin and fluoroquinolone use was decreased. Inpatient penicillin allergy testing was associated with decreased healthcare cost in four studies.

Conclusions: Inpatient penicillin allergy testing is safe and effective in ruling out penicillin allergy. The rate of negative tests is comparable to outpatient and perioperative data. Patients with a documented penicillin allergy who require penicillin should be tested during hospitalization given its benefit for individual patient outcomes and antibiotic stewardship.

KEYWORDS
antibiotic utilization, drug allergy, hospitalization, inpatient, penicillin testing

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

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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.

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The authors report that among the 922 patients who reported penicillin allergy, only 5 had evidence of the types of reactions that would preclude sensitivity testing or consideration of administering a cephalosporin (acute interstitial nephritis, blisters, Steven-Johnson syndrome/toxic epidermal necrolysis) and 25% had unknown reactions whereas 9% had symptoms such as headache, gastrointestinal (GI) upset, and so on. In our own experience at the University of Washington Medical Center, when we reviewed cefazolin administration for prophylaxis, we found the following. Of 14773 operations where prophylaxis was administered, 1723 (12%) patients reported a penicillin allergy. Two hundred eighty-two (16%) of the patients with documented penicillin allergy (including reported reactions of rash, hives, GI-related issues, and anaphylaxis) still received cefazolin, and none experienced any adverse reactions. Among the 10336 patients without any history of beta-lactam allergy, 9 (0.09%) experienced an allergic reaction [6]. As a consequence, our standard surgical prophylaxis order forms encourage the administration of cefazolin for patients listed as "allergic to penicillin" unless there is a history of anaphylaxis or Stephens-Johnson syndrome [6].

Comparative Effectiveness of Beta-Lactams Versus Vancomycin for Treatment of Methicillin-Susceptible *Staphylococcus aureus* Bloodstream Infections Among 122 Hospitals

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Background. Previous studies indicate that vancomycin is inferior to beta-lactams for treatment of methicillin-susceptible *Staphylococcus aureus* (MSSA) bloodstream infections. However, it is unclear if this association is true for empiric and definitive therapy. Here, we compared beta-lactams with vancomycin for empiric and definitive therapy of MSSA bloodstream infections among patients admitted to 122 hospitals.

Methods. This retrospective cohort study included all patients admitted to Veterans Affairs hospitals from 2003 to 2010 who had positive blood cultures for MSSA. Hazard ratios (HR) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression. Empiric therapy was defined as starting treatment 2 days before and up to 4 days after the first MSSA blood culture was collected. Definitive therapy was defined as starting treatment between 4 and 14 days after the first positive blood culture was collected.

Results. Patients who received empiric therapy with a beta-lactam had similar mortality compared with those who received vancomycin (HR, 1.03; 95% CI, .89–1.20) after adjusting for other factors. However, patients who received definitive therapy with a beta-lactam had 35% lower mortality compared with patients who received vancomycin (HR, 0.65; 95% CI, .52–.80) after controlling for other factors. The hazard of mortality decreased further for patients who received cefazolin or antistaphylococcal penicillins compared with vancomycin (HR, 0.57; 95% CI, .46–.71).

Conclusions. For patients with MSSA bloodstream infections, beta-lactams are superior to vancomycin for definitive therapy but not for empiric treatment. Patients should receive beta-lactams for definitive therapy, specifically antistaphylococcal penicillins or cefazolin.

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Outcome of Vancomycin Treatment in Patients with Methicillin-Susceptible *Staphylococcus aureus* Bacteremia[▽]

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Limited data on the clinical outcome of vancomycin treatment compared with that of beta-lactam treatment in patients with methicillin-susceptible *Staphylococcus aureus* bacteremia (MSSA-B) are available. We used different and complementary approaches: (i) a retrospective cohort study using a propensity score to adjust for confounding by treatment assignment and (ii) a matched case-control study. Of all patients with *S. aureus* bacteremia (SAB) in two university-affiliated hospitals over a 7-year period, 294 patients with MSSA-B were enrolled in the cohort study. The cases for the case-control study were defined as patients who received vancomycin treatment for MSSA-B; the controls, who were patients that received beta-lactam treatment for MSSA-B, were selected at a 1:2 (case:control) ratio according to the objective matching scoring system and the propensity score system. In the cohort study, SAB-related mortality in patients with vancomycin treatment (37%, 10/27) was significantly higher than that in those with beta-lactam treatment (18%, 47/267) ($P = 0.02$). In addition, multivariate analysis revealed that vancomycin treatment was associated with SAB-related mortality when independent predictors for SAB-related mortality and propensity score were considered (adjusted odds ratio of 3.3, 95% confidence interval of 1.2 to 9.5). In the case-control study using the objective matching scoring system and the propensity score system, SAB-related mortality in case patients was 37% (10/27) and in control patients 11% (6/54) ($P < 0.01$). Our data suggest that vancomycin is inferior to beta-lactam in the treatment of MSSA-B.

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- Taking into account this history of penicillin allergy, which of the following statements is correct?

1. Given his history of penicillin allergy, administration of any beta-lactam antibiotic is absolutely contraindicated unless he undergoes skin testing for penicillin allergy first.

2. Since the patient is tolerating vancomycin well, there is no benefit to switch the patient to a beta-lactam antibiotic for definitive therapy of his MSSA infection.

3. For surgical prophylaxis in patients with a history of penicillin allergy, use of an alternative agent such as vancomycin or clindamycin +/- gentamicin (as opposed to cefazolin) is not associated with an increased risk of surgical site infection.

4. In a patient with a true penicillin allergy (by skin testing), cross-reactivity risk with cepahlosporins and carbapenems is about 2-3% or less.

5. In patients with a history of penicillin allergy without any additional details, true allergy (by skin testing) is present in about 10 % of patient.

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Association of Adverse Events With Antibiotic Use in Hospitalized Patients

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IMPORTANCE Estimates of the incidence of overall antibiotic-associated adverse drug events (ADEs) in hospitalized patients are generally unavailable.

OBJECTIVE To describe the incidence of antibiotic-associated ADEs for adult inpatients receiving systemic antibiotic therapy.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort of adult inpatients admitted to general medicine wards at an academic medical center.

EXPOSURES At least 24 hours of any parenteral or oral antibiotic therapy.

MAIN OUTCOMES AND MEASURES Medical records of 1488 patients were examined for 30 days after antibiotic initiation for the development of the following antibiotic-associated ADEs: gastrointestinal, dermatologic, musculoskeletal, hematologic, hepatobiliary, renal, cardiac, and neurologic; and 90 days for the development of *Clostridium difficile* infection or incident multidrug-resistant organism infection, based on adjudication by 2 infectious diseases trained clinicians.

RESULTS In 1488 patients, the median age was 59 years (interquartile range, 49-69 years), and 758 (51%) participants were female. A total of 298 (20%) patients experienced at least 1 antibiotic-associated ADE. Furthermore, 56 (20%) non–clinically indicated antibiotic regimens were associated with an ADE, including 7 cases of *C difficile* infection. Every additional 10 days of antibiotic therapy conferred a 3% increased risk of an ADE. The most common ADEs were gastrointestinal, renal, and hematologic abnormalities, accounting for 78 (42%), 45 (24%), and 28 (15%) 30-day ADEs, respectively. Notable differences were identified between the incidence of ADEs associated with specific antibiotics.

CONCLUSIONS AND RELEVANCE Although antibiotics may play a critical role when used appropriately, our findings underscore the importance of judicious antibiotic prescribing to reduce the harm that can result from antibiotic-associated ADEs.

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30-Day ADEs

Of the 324 overall ADEs, 186 (57%) were 30-day ADEs. The median time to development of a 30-day ADE was 5 days (IQR, 3-8 days). The median times to 30-day ADEs for the various organ systems were as follows: cardiac, 11 days (IQR, 4-18 days); gastrointestinal, 5 days (IQR, 2-9 days); hematologic, 12 days (IQR, 6-24 days); hepatobiliary, 8 days (IQR, 4-12 days); renal, 5 days (IQR, 2-10 days); and neurologic, 3 days (IQR, 2-4 days). The most common ADEs were gastrointestinal, renal, and hematologic abnormalities, accounting for 78 (42%), 45 (24%), and 28 (15%) 30-day ADEs, respectively (Table 2). Table 3 and

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Clinically Significant ADEs

Antibiotic-associated ADEs were then categorized into clinically significant and non-clinically significant categories. Only 1 category was selected per patient, with the more severe category selected when multiple categories were met. A total of 314 (97%) of the 324 antibiotic-associated ADEs were considered clinically significant because of the following reasons: new hospitalization(s) (n = 10 [3%]), prolonged hospitalization (n = 77 [24%]), additional clinic or emergency department visits (n = 29 [9%]), and additional laboratory tests, electrocardiograms, or imaging (n = 198 [61%]). There were no deaths attributable to any antibiotic-associated ADE.

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Table 1. Criteria Used for Antibiotic-Associated Adverse Drug Events

Adverse Drug Event	Definition
Within 30 d of Antibiotic Initiation	
Non-*Clostridium difficile*-associated diarrhea	>3 Loose stools per day associated with antibiotic administration and documented as "diarrhea" in the medical record, in the absence of laxative use or preexisting enteritis. Patients with a positive *C difficile* PCR test result were excluded from this category
Nausea and vomiting	Nausea and vomiting associated with antibiotic administration, in the absence of an alternate explanation
Hematologic	Anemia (hemoglobin level <10 g/dL), leukopenia (white blood cell count <4500 cells/μL), or thrombocytopenia (platelet count <150 × 10^3/μL) with levels below patient's baseline and in the absence of bleeding or myelosuppressive therapies
Hepatobiliary	Cholestasis (total bilirubin level >3 mg/dL) or transaminitis (aspartate transaminase or alanine transaminase level >3 times patient's baseline) in the absence of existing hepatobiliary disease or recent biliary instrumentation
Renal	Increase in serum creatinine level >1.5 times patient's baseline in the absence of precipitating factors for acute kidney injury such as sepsis or the receipt of intravenous contrast or other nephrotoxic agents[24]
Neurologic	Altered mental status, peripheral neuropathy, or seizures in the absence of preexisting neurologic conditions, substance-related toxic effects, or infectious syndromes
Dermatologic	Rash, including hives, nonhives rashes, and red man syndrome, temporally associated with antibiotic administration with resolution on antibiotic discontinuation; excluding vancomycin-associated red man syndrome
Cardiac	QTc >440 ms in males or >460 ms in females in the absence of preexisting arrhythmias, based on ≥2 electrocardiograms
Anaphylaxis	Acute onset of respiratory compromise, hypotension, or end-organ dysfunction within minutes after initiation of antibiotic administration, in the absence of an alternative explanation
Myositis	Increase in creatine phosphokinase level >5 times patient's baseline, in the absence of existing myopathy or statin use
Within 90 d of Antibiotic Initiation	
C difficile infection	Clinical signs and symptoms consistent with *C difficile* infection in the setting of a positive *C difficile* PCR test result and the absence of laxative use
Infection with MDR organism[25]	Infection with any of the following organisms, in a patient without a history of colonization or infection with the same organism: methicillin-resistant *Staphylococcus aureus*; vancomycin-resistant enterococci; carbapenem-resistant Enterobacteriaceae; MDR *Acinetobacter*; MDR *Pseudomonas*; or a gram-negative organism with a greater than 2-fold increase in the minimum inhibitory concentration of an antibiotic compared with the initial infection

Abbreviations: MDR, multidrug-resistant; PCR, polymerase chain reaction.

SI conversion factors: To convert hemoglobin to grams per liter, multiply by 10.0; to convert white blood cell count to ×10^9 per liter, multiply by 0.001; to convert platelet count to ×10^9 per liter, multiply by 1.0; to convert bilirubin to micromoles per liter, multiply by 17.104.

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- QT prolongation
- Heartburn/esophagitis
- Nausea and vomiting
- Anemia/neutropenia
- Elevated transaminases
- AKI
- Encephalopathy

Table 2. Rates of 30-Day Antibiotic-Associated Adverse Drug Events in 1488 Hospitalized Patients Receiving Antibiotics per 10 000 Person-days (PD)[a]

Antibiotic Agent	No. of Patients Receiving Agent	Cardiac		Gastrointestinal[b]		Hematologic		Hepatobiliary		Renal		Neurologic		Other Events[c]	
		No.	Rate per 10 000 PD (95% CI)	No.	Rate per 10 000 PD (95% CI)	No.	Rate per 10 000 PD (95% CI)	No.	Rate per 10 000 PD (95% CI)	No.	Rate per 10 000 PD (95% CI)	No.	Rate per 10 000 PD (95% CI)	No.	Rate per 10 000 PD (95% CI)
β-Lactam[d]	1187	0	...	59	17.4 (13.5-22.4)	27	8.7 (5.3-11.3)	6	3.4 (3.1-7.9)	17	6.9 (3.1-12.9)	10	3.8 (1.5-5.3)	2	0.6 (0.1-2.2)
Ampicillin	63	0	...	2	11.6 (2.9-46.2)	1	5.6 (0.8-39.6)	0	...	1	5.6 (0.8-39.6)	0	...	0	...
Amoxicillin-clavulanate	102	0	...	3	12.6 (4.5-25.2)	0	...	0	...	0	...	0	...	0	...
Ampicillin-sulbactam	52	0	...	1	7.2 (1.0-51.2)	0	...	0	...	2	14.2 (13.9-49.6)	0	...	0	...
Oxacillin	33	0	...	4	37.1 (12.0-105.0)	1	10.8 (1.5-76.4)	2	21.6 (5.4-86.6)	0	...	0	...	0	...
Piperacillin-tazobactam	315	0	...	16	14.8 (13.1-23.0)	4	4.3 (1.6-11.4)	1	1.1 (0.2-7.9)	1	1.1 (0.2-7.9)	1	1.1 (0.2-7.9)	1	1.1 (0.2-7.9)
Cefazolin	79	0	...	0	...	1	4.4 (0.6-31.4)	0	...	2	8.2 (1.6-24.8)	0	...	0	...
Ceftriaxone	607	0	...	14	8.0 (4.7-13.5)	11	6.2 (3.4-11.3)	3	2.1 (1.4-12.3)	5	2.8 (1.2-6.8)	1	0.6 (0.1-3.9)	0	...
Cefpodoxime	89	0	...	2	7.7 (1.9-30.9)	0	...	0	...	0	...	0	...	0	...
Cefepime	414	0	...	10	8.5 (4.6-15.8)	6	5.0 (2.2-11.1)	0	...	6	5.0 (2.2-11.1)	7	6.7 (2.7-12.0)	1	0.8 (0.1-5.8)
Ertapenem	85	0	...	3	12.1 (3.9-37.6)	0	...	0	...	0	...	0	...	0	...
Meropenem	80	0	...	4	18.0 (6.8-48.0)	3	12.9 (4.2-40.1)	0	...	0	...	1	4.4 (0.8-29.4)	0	...
Non-β-lactams															
Aminoglycosides	32	0	...	0	...	0	...	0	...	2	21.2 (12.5-66.0)	0	...	0	...
Azithromycin	400	1	0.8 (0.1-5.9)	1	0.8 (0.1-5.9)	0	...	4	3.4 (1.3-9.0)	0	...	0	...	0	...
Clindamycin	193	0	...	3	5.4 (1.8-16.8)	0	...	0	...	0	...	0	...	0	...
Daptomycin	8	0	...	0	...	0	...	0	...	0	...	0	...	1	44.8 (6.3-318.3)
Doxycycline	57	0	...	2	12.4 (3.1-49.7)	0	...	0	...	0	...	0	...	0	...
Fluoroquinolones	394	1	0.9 (0.1-6.2)	5	4.4 (1.8-10.6)	1	0.9 (0.1-6.2)	3	2.6 (0.8-8.0)	1	0.9 (0.1-6.2)	1	0.9 (0.1-6.2)	1	0.9 (0.1-6.2)
Linezolid	23	0	...	0	...	0	...	0	...	0	...	1	15.8 (2.2-112.3)	0	...
Metronidazole	175	0	...	1	2.0 (0.3-14.2)	0	...	0	...	0	...	1	2.0 (0.3-14.2)	0	...
Trimethoprim-sulfamethoxazole	155	0	...	5	11.2 (4.7-26.9)	0	...	0	...	6	13.2 (5.9-29.3)	0	...	1	2.1 (0.3-15.1)
Intravenous vancomycin	544	0	...	2	1.3 (0.3-5.2)	0	...	0	...	19	12.1 (7.7-19.0)	0	...	2	1.3 (0.3-5.2)
Overall rates	1488[e]	2	0.4 (0.1-1.8)	78	18.2 (14.6-22.8)	28	6.4 (4.4-9.2)	13	2.9 (1.7-5.0)	45	10.6 (7.9-14.2)	13	2.9 (1.7-5.0)	7	1.6 (0.8-3.3)

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- Questions?