

Preoperative Antibiotic Prophylaxis in the Penicillin-Allergic Patient

Daniel A. Osei, MD, Martin I. Boyer, MD

BECAUSE OF THEIR efficacy against these gram-positive cocci, cephalosporin antibiotics are commonly used as first-line prophylaxis against surgical site infection (SSI). Although this antibiotic class is largely effective, some thought must be given to situations in which cephalosporins cannot be used. Furthermore, picking an alternative to cephalosporins becomes relevant clinically because of a substantial cost difference between 2 commonly available choices. This review attempts to highlight the issues involved in the decision-making process between 2 commonly used antistaphylococcal agents: intravenous clindamycin and intravenous vancomycin.

Cephalosporins belong to the class of antibiotics known as beta-lactams, so called because they contain a beta lactam ring at the core of the molecular structure. These bacteriocidal agents inhibit bacterial cell wall synthesis. Because of similar molecular structures, the hapten side chains that cause a hypersensitivity reaction in a penicillin-allergic patient may also cause a similar reaction to cephalosporins. Cephalexin, the most commonly used oral antibiotic in orthopedic surgery, has a side chain identical to ampicillin.¹

The exact rate of cross-reactivity between cephalosporins and penicillins is unknown. Early reports may have overestimated the rate of cross-reactivity, because the original cephalosporins likely contained trace amounts of penicillin. Lin² reported on 15,987 patients with known penicillin allergy treated with cephalosporins and found an 8.1% reaction rate, compared with 1.9% of patients who did not have a history of penicillin allergy.

Patients with an allergy to penicillins or cephalosporins can develop dermatologic reactions, fevers, serum-sickness reactions, or anaphylaxis. Rates for such reactions range from 0.001% to 2.8%.^{3,4} Anaphylaxis is the most serious of reactions, and reports of anaphylaxis-related fatality are noted in the literature.⁵ In patients who have documented anaphylaxis with administration of cephalosporin antibiotics, and in patients who are at high risk for methicillin-resistant *Staphylococcus aureus* (MRSA) either because of known colonization or previous history of MRSA infection, or due to residence in an area with a recent MRSA outbreak, prophylactic cephalosporin use is contraindicated. Although approximately 10% of individuals report a history of penicillin allergy,⁶ many patients who report an allergic reaction become less allergic over time or may never have had a true allergy. This trend is also found among children: although an 8% to 14% penicillin allergy rate is often quoted, modern studies have suggested an incidence rate between 0.3% and 3%.^{7,8} Because it is difficult to determine absolute risk, some surgeons will administer an alternative antibiotic when patients report a history of allergy. Alternatively, a cephalosporin test dose may be given in the operating room if the patient does not have a history of severe immunoglobulin E-mediated allergic reaction and does not report a history of anaphylaxis.⁹

In cases where cephalosporin antibiotics are contraindicated, the Centers for Disease Control and Prevention guidelines recommend vancomycin or clindamycin as second-line choices for SSI prophylaxis.¹⁰ Although both antibiotics are used frequently in orthopedic surgery, data are lacking that guide use of one or the other antibiotic.

Clindamycin is a lincosamide antibiotic. It is a bacteriostatic agent that acts by binding the 50s ribosomal subunit of bacteria, limiting bacterial protein synthesis and cell wall production. It also limits the ability of the bacterium to adhere to host cells.¹¹ Clindamycin demonstrates excellent activity against many species of staphylococci (including *Staphylococcus aureus*) and streptococci. It achieves high levels both in phagocytic cells and in bone, making it effective at preventing and

From the Department of Orthopaedic Surgery, Washington University School of Medicine, Saint Louis, MO.

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Corresponding author: Daniel A. Osei, MD, Department of Orthopedic Surgery, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8233, Saint Louis, MO 63110; e-mail: oseid@wustl.edu.

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treating hand- or orthopedic-related infections. Many studies have demonstrated the efficacy of clindamycin in treating community-acquired MRSA (CA-MRSA), which makes it an attractive prophylaxis option for patients for whom the risk of MRSA is high and preoperative antibiotics are indicated.^{12,13} The most common adverse events associated with clindamycin are gastrointestinal upset and allergy; diarrhea has been reported in up to 20% of patients.¹⁴ Clindamycin administration has also been associated with development of *Clostridium difficile* pseudomembranous enterocolitis, which can be fatal.¹⁵ Although clindamycin reactions are relatively common, allergies are rare, occurring in less than 1% of patients.¹⁶ At our institution, the hospital acquisition cost for a standard 600-mg dose of clindamycin is 3.5 times higher than cefazolin (roughly \$1 per standard 1-g dose of cefazolin).

Vancomycin is a glycopeptide antibiotic that acts similarly to the beta-lactams, inhibiting cell wall synthesis in gram-positive bacteria.¹¹ Whereas many antibiotics have been shown to be effective at treating CA-MRSA, vancomycin has consistently shown the lowest rates of resistance. Le and Lieberman¹⁷ reported a susceptibility rate approaching 100% to vancomycin across all studies of CA-MRSA in children. Although vancomycin is highly effective against MRSA, it is inferior to methicillin and other beta-lactams in treating

methicillin-sensitive *S aureus*. Vancomycin toxicity has been reported: notably ototoxicity, thrombocytopenia, and superinfection. The risk is potentiated when vancomycin administration is combined with an aminoglycoside. Ensuring that the serum peak dose stays within the recommended therapeutic levels (15–20 mg/L) can minimize the risk of toxicity.¹⁸ When used for preoperative SSI prophylaxis, the single dose given rarely leads to serum levels high enough to cause toxicity. The most common adverse effect is a nonspecific, nonallergic mast cell degranulation commonly referred to as “red man syndrome,” because of an inappropriately high infusion rate that causes flushing or an erythematous rash that commonly affects the face, neck, and torso. This is prevented by slow infusion and pretreatment with antihistamines.¹⁹ Like clindamycin, true immunoglobulin E-mediated allergic reaction to vancomycin is rare, occurring in less than 1% of patients.²⁰ Vancomycin is expensive and has a hospital acquisition cost 7.6 times higher than cefazolin.

The choice of antibiotic for prophylaxis against SSI must take into account the antibiotic’s ability to reduce the risk of infection, the risk of adverse effects or allergic reaction, and cost. For hand surgery, preoperative antibiotics must provide coverage against the pathogens commonly found in skin flora, notably *S aureus*, MRSA, and coagulase-negative staphylococci. Vancomycin acts to inhibit bacterial cell wall synthesis

TABLE 1. Comparison of Common Preoperative Antibiotics

Drug	Cefazolin	Vancomycin	Clindamycin
Prophylactic dosing ²² (adults)	1 g if < 86 kg 2 g if > 86 kg	1 g	600 mg
Pediatric dosing ^{17,22}	20–30 mg/kg	15 mg/kg	10–20 mg/kg
Dosing in renal impairment ²¹	Creatinine clearance (mL/min) 10–35: 500–1,000 mg every 12 h < 10: 500–1,000 mg every 24 h End stage: 2 g after each dialysis	Requires infectious disease consultation for pharmacokinetic assessment	No change
Timing of administration ²²	Up to 60 min before surgery	Up to 120 min before surgery	Up to 60 min before surgery
Time to intraoperative redosing ²²	2–5 h	6–12 h	3–6 h
Efficacy against MSSA	++++	+++	++++
Efficacy against MRSA	–	++++	++
Soft tissue/bone penetration	++++	+++	++++
Adverse effects	Gastrointestinal upset Allergy (cross-reactivity with penicillins) Anaphylaxis (< 0.001%)	Red man syndrome (> 10%) Ototoxicity (< 1%) Drug fever (< 1%) Allergy (< 1%)	Skin rash (10%) Diarrhea (10%) <i>C difficile</i> colitis (1% to 5%) Anaphylaxis (< 0.1%)
Cost ratio	1	7.6	3.5

MSSA, methicillin-sensitive *S aureus*.

and is bacteriocidal. Clindamycin inhibits bacterial protein synthesis and is bacteriostatic. Both show excellent activity against skin flora and have the advantage over cephalosporins of activity against MRSA. Vancomycin has a low allergy rate but is associated with red man syndrome and ototoxicity. Clindamycin also has low allergy rates but is associated with a 1% to 5% risk of *C difficile* colitis. Both vancomycin and clindamycin are much more expensive than cefazolin, with vancomycin costing more than twice as much as clindamycin (Table 1).

Taking all factors into consideration, to date, vancomycin is the community standard for prophylaxis against SSI in patients who cannot receive penicillins or cephalosporins. It is preferred over clindamycin because a much higher percentage of *S aureus* isolates are resistant to clindamycin (3% to 17%) with vancomycin (< 1%).¹¹ Resistance rates are highly variable; in regions with low clindamycin resistance, the lower cost favors its use. Clindamycin resistance increases when hospital-acquired *S aureus* is considered. At our institution in the year 2010, of the 1,862 tested strains of *S aureus*, 51% were resistant to clindamycin, whereas only 2% were vancomycin resistant.

The following points bear repeat mention: (1) Patients with documented anaphylaxis to cephalosporin antibiotics, as well as patients who are at high risk for MRSA (with a known colonization or previous history of MRSA infection, or living in a region with a recent MRSA outbreak) represent absolute contraindications to cephalosporin use. (2) If cephalosporins are contraindicated, Centers for Disease Control and Prevention guidelines recommend either vancomycin or clindamycin for SSI prophylaxis. (3) Clindamycin administration has been associated with development of *C difficile* pseudomembranous enterocolitis, which can be fatal. (4) Too-rapid vancomycin administration can cause a nonspecific, nonallergic mast cell degranulation called red man syndrome. This is prevented by slow infusion and pretreatment with antihistamines.

REFERENCES

1. Batchelor FR, Dewdney JM, Weston RD, Wheeler AW. The immunogenicity of cephalosporin derivatives and their cross-reaction with penicillin. *Immunology* 1966;10:21–33.
2. Lin RY. A perspective on penicillin allergy. *Arch Intern Med* 1992; 152:930–937.
3. Norrby SR. Side effects of cephalosporins. *Drugs* 1987;34(Suppl 2):105–20.
4. Arndt KA, Jick H. Rates of cutaneous reactions to drugs: a report from the Boston Collaborative Drug Surveillance Program. *JAMA* 1976;235:918–923.
5. Hoffman DR, Hudson P, Carlyle SJ, Massello W III. Three cases of fatal anaphylaxis to antibiotics in patients with prior histories of allergy to the drug. *Ann Allergy* 1989;62:91–3.
6. Solensky R, Earl HS, Gruchalla RS. Clinical approach to penicillin-allergic patients: a survey. *Ann Allergy Asthma Immunol* 2000;84: 329–333.
7. Graff-Lonnevig V, Hedlin G, Lindfors A. Penicillin allergy: a rare paediatric condition? *Arch Dis Child* 1998;63:1342–1346.
8. Surtees SJ, Stockton MG, Gietzen TW. Allergy to penicillin: fable or fact? *BMJ* 1991;302:1051–1052.
9. Kelkar PS, Li JT. Cephalosporin allergy. *N Engl J Med* 2001;345: 804–809.
10. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. *Am J Infect Control* 1999;27:97–132.
11. Brunton L, Lazo J, Parker K. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 11th ed. New York: McGraw-Hill, 2005.
12. Fergie JE, Purcell K. Community-associated methicillin resistant *Staphylococcus aureus* infections in south Texas children. *Pediatr Infect Dis J* 2001;20:860–863.
13. Buckingham SC, McDougal LK, Cathey LD, Comeaux K, Craig AS, Fridkin SK, et al. Emergence of community-associated methicillin-resistant *Staphylococcus aureus* at a Memphis, Tennessee children's hospital. *Pediatr Infect Dis J* 2004;23:619–624.
14. Gurwith MJ, Rabin HR, Love K. Diarrhea associated with clindamycin and ampicillin therapy: preliminary results of a cooperative study. *J Infect Dis* 1977;135(Suppl):S104.
15. Tedesco FJ, Barton RW, Alpers DH. Clindamycin-associated colitis. A prospective study. *Ann Intern Med* 1974;81:429–433.
16. Mazur N, Greenberger PA, Regaldo J. Clindamycin hypersensitivity appears to be rare. *Ann Allergy Asthma Immunol* 1999;82: 443–445.
17. Le J, Lieberman JM. Management of community-associated methicillin-resistant *Staphylococcus aureus* infections in children. *Pharmacotherapy* 2006;26:1758–1770.
18. Lodise TP, Patel N, Lomaestro BM, Rodvold KA, Drusano GL. Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. *Clin Infect Dis* 2009;49:507–514.
19. Symons NL, Hobbes AF, Leaver HK. Anaphylactoid reactions to vancomycin during anaesthesia: two clinical reports. *Can Anaesth Soc J* 1985;32:178–181.
20. Anne S, Middleton E Jr, Reisman RE. Vancomycin anaphylaxis and successful desensitization. *Ann Allergy* 1994;73:402–404.
21. Aronoff GR, Berns JS, Brier ME, Golper TA, Morrison G, Singer I, et al. Drug prescribing in renal failure, dosing guidelines for adults. 4th ed. Philadelphia: American College of Physicians, 1999:39–62.
22. Bratzler DW, Houch PM. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. *Clin Infect Dis* 2004;38:1706–1715.