Adjuvant vancomycin for antibiotic prophylaxis and risk of *Clostridium difficile* infection after coronary artery bypass graft surgery

Brian T. Bateman, MD,[a,b] Jeremy A. Rassen, ScD,[a] Sebastian Schneeweiss, MD, ScD,[a] Katsiaryna Bykov, PharmD, MS,[a] Jessica Myers Franklin, PhD,[a] Joshua J. Gagne, PharmD, ScD,[a] Jennifer M. Polinski, ScD, MPH,[a] Jun Liu, MD, MPH,[a] Alexander Kulik, MD, MPH,[c] Michael A. Fischer, MD, MS,[a] and Niteesh K. Choudhry, MD, PhD[a]

Objective: The incidence of hospital-acquired *Clostridium difficile* infection (CDI) has increased rapidly over the past decade; patients undergoing major surgery, including coronary artery bypass grafting (CABG), are at particular risk. Intravenous vancomycin exposure has been identified as an independent risk factor for CDI, but this is controversial. It is not known whether vancomycin administered for surgical site infection prophylaxis increases the risk of CDI.

Methods: Using data from the Premier Perspective Comparative Database, we assembled a cohort of 69,807 patients undergoing CABG surgery between 2004 and 2010 who received either a cephalosporin alone (65.1%) or a cephalosporin plus vancomycin (34.9%) on the day of surgery. Patients were observed for CDI until discharge from the index hospitalization. In these groups, we evaluated the comparative rate of postoperative CDI with Cox models; confounding was addressed using propensity scores.

Results: In all, 77 (0.32%) of the 24,393 patients receiving a cephalosporin plus vancomycin and 179 (0.39%) of the 45,414 patients receiving a cephalosporin alone had postoperative CDI (unadjusted hazard ratio [HR], 0.73; 95% confidence interval [CI], 0.56-0.95). After adjusting for confounding variables with either propensity score matching or stratification, there was no meaningful association between adjuvant vancomycin exposure and postoperative CDI (HR, 0.85; 95% CI, 0.61-1.19; and HR, 0.85; 95% CI, 0.63-1.15, respectively). Results of multiple sensitivity analyses were similar to the main findings.

Conclusions: After adjustment for patient and surgical characteristics, a short course of prophylactic vancomycin was not associated with an increased risk of CDI among patients undergoing CABG surgery. (J Thorac Cardiovasc Surg 2013;146:472-8)

Clostridium difficile infection (CDI) occurs commonly among hospitalized patients and has more than doubled in frequency during the past decade.[1] Patients undergoing major surgery, including cardiac surgery, are at particular risk.[2,3] For these patients, CDI lengthens hospitalization,[2] increases the amount of time patients spend in the intensive care unit,[2] prolongs mechanical ventilation,[2] can cause the need for readmission,[4] and increases mortality.[3] Therefore, identifying risk factors for the development of CDI and developing strategies to decrease its occurrence in the postoperative period are urgently needed.

Antibiotic exposure is the single most important risk factor for the development of CDI.[5,6] Antibiotics alter the native colonic flora, which allows *C difficile* to proliferate.[7] Studies have demonstrated an association between short courses of perioperative antibiotic use and the risk of CDI.[8] Indeed, *C difficile* can proliferate after just a single dose of antibiotics for prophylaxis in surgery.[9] In contrast, the prophylactic administration of antibiotics has demonstrated benefit in the prevention of surgical site infection (SSI) after cardiac and other surgical procedures. On the basis of evidence from randomized controlled clinical trials, The Society of Thoracic Surgeons guidelines recommend prophylaxis with a beta-lactam antibiotic for this

From the Division of Pharmacoepidemiology and Pharmacoeconomics,[a] Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass; Department of Anesthesia, Critical Care, and Pain Medicine,[b] Massachusetts General Hospital, Boston, Mass; and Lynn Heart and Vascular Institute,[c] Boca Raton Regional Hospital, and Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, Fla.

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Address for reprints: Brian T. Bateman, MD, Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, MA 02115 (E-mail: BBateman@partners.org).

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Abbreviations and Acronyms
CABG = coronary artery bypass grafting
CDI = *Clostridium difficile* infection
CI = confidence interval
HR = hazard ratio
SSI = surgical site infection

purpose, including a cephalosporin among nonallergic patients, with the addition of vancomycin among those with known or presumed staphylococcal colonization, those from institutions with a high incidence of methicillin-resistant staphylococcal infections, those ''susceptible'' to colonization, or those receiving a prosthetic valve.[10]

There is concern that excessive use of vancomycin for SSI may lead to an increase in antibiotic resistance in *Staphylococcus* and *Enterococcus* organisms,[11,12] which has led to calls to curb its routine use for prophylaxis.[13] An addition potential concern is that vancomycin exposure may increase the risk for CDI. Exposure to intravenous vancomycin has recently been identified as an independent risk factor for the development of CDI in several studies of hospitalized patients,[14-16] but this remains controversial. Currently, there are limited data on whether adjuvant vancomycin used for SSI prophylaxis increases risk for CDI. We therefore sought to define the comparative risk of CDI associated with the adjunctive use of vancomycin as a prophylactic antibiotic versus use of a cephalosporin alone among patients undergoing coronary artery bypass grafting (CABG).

METHODS

Data Source

The study cohort was derived from the Premier Perspective Comparative Database. The database includes approximately one sixth of all hospitalizations in the United States. The database contains information about daily charges for all medications, procedures, and diagnostic tests conducted during each hospitalization, as well as patient demographic and hospital characteristics, discharge diagnoses, and discharge status (including death). Data are routinely audited, verified, and validated. Premier data have been extensively used to study medication use and health outcomes in the perioperative period.[17-19] The use of this data set for research was approved by the Institutional Review Board of the Brigham and Women's Hospital, Boston, Mass, and a Data Use Agreement was in place.

Cohort

We considered all patients who, during the course of a hospital stay, underwent a CABG (identified by procedure code 36.1, or any subcode thereof, from the *International Classification of Diseases, ninth revision*) between January 1, 2004, and December 31, 2010. Because the database does not record comorbidities or other information about patients at the time of their admission, we excluded patients who underwent CABG on the day of hospital admission, to allow time for accrual of information about patients' preoperative health status that might affect the choice of prophylactic antibiotic. We also excluded patients who were exposed to any systemic antibiotic from day 1 to the day before CABG to isolate the effect of the prophylactic antibiotics administered on the day of surgery. We further limited our analysis to those patients that received either a cephalosporin alone or a cephalosporin plus vancomycin, inasmuch as these are the most common prophylactic antibiotic regimens administered on the day of surgery in the United States and the ones that are in keeping with current guidelines for patients without a beta-lactam allergy.[10] Finally, we excluded those patients who died, were discharged, or had CDI develop in the first 2 postoperative days, inasmuch as 2 days is the minimum plausible induction time for CDI related to antibiotic exposure on the day of surgery.[14]

Classification of Drug Exposure and Study Outcome

Cephalosporin exposure was defined as charges on the day of surgery for 1 of the following intravenous medications: cefazolin, ceftriaxone, cefuroxime, cefadroxil, cefamandole, cefepime, cefonicid, cefoperazone, cefotaxime, cefotetan, ceftazidime, ceftizoxime, cephalothin, cephapirin, or cephradine. Vancomycin exposure was defined on the basis of charges on the day of surgery for intravenous vancomycin.

The main study outcome was CDI 48 hours or more postoperatively.[14] Our outcome was defined by the presence of all 3 of the following criteria: (1) a discharge diagnosis code of CDI (ICD 9 CM 008.45), (2) a charge code indicating that a stool study for *C difficile* toxin has been performed, and (3) a charge code indicating that appropriate CDI therapy (oral or intravenous metronidazole or oral vancomycin) had been initiated at least 2 hospital days after surgery. The time of the outcome event was defined by the third criterion, the date therapy was initiated.

Patient and Hospital-Level Covariates

We identified 5 groups of potential confounders: patient demographics, chronic comorbid conditions, markers of coexisting disease/disease severity, characteristics of the surgical procedure, and hospital characteristics. Demographics included age on admission, gender, marital status (classified as married, single, or other), race (classified as white, black, or other), and season and year of admission. The presence of chronic comorbid conditions was identified by discharge diagnoses including liver disease, malignancy, prior endocarditis, peripheral vascular disease, hemostatic disorder, carotid artery stenosis, prior stroke, and prior myocardial infarction.[20] The Romano modification[21] of the Charlson comorbidity index, a score indicating patients' severity of comorbid conditions, was also calculated for each patient.

Coexisting conditions and/or markers of disease severity were evaluated with drug use and procedures before the day of surgery and included diabetes mellitus, chronic obstructive pulmonary disease, end-stage renal disease, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, aldosterone agonists, beta-blockers, calcium channel blockers, loop diuretics, thiazide diuretics, aspirin, clopidogrel, dipyridamole, statins, fibrates, digoxin, antiarrhythmic medications (amiodarone, dronedarone, sotatol, procainamide, propafenone), proton pump inhibitor, H2 blocker, or sucralfate. We also assessed for preoperative charges for telemetry, echocardiogram, oxygen use, and intensive care use.

Surgical characteristics included type of admission (urgent/emergency vs elective), number of grafts, whether the patient received a thoracic artery graft, and whether the patient received an aortic, mitral, or tricuspid valve repair or replacement concurrently with their CABG.

Hospital characteristics were also assessed. Hospitals affiliated with medical schools accredited by the Association of American Medical Colleges Liaison Committee on Medical Education were classified as teaching hospitals and nonteaching hospitals otherwise. Geographic region of the hospital was classified as Midwest, Northeast, South, or West. Location was defined as urban or rural. The annualized volume of CABG patients treated by each hospital was estimated by dividing the total number of CABG patients for each hospital during the study time period by the number of years that each hospital performed 1 or more CABG operations. Hospitals were ranked in order of annualized volume and were then categorized into high-, medium- and low-volume hospital tertiles.[22]

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