Antibiotic prophylaxis and risk of *Clostridium difficile* infection after coronary artery bypass graft surgery

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Abstract

Objective—Antibiotic use, particularly type and duration, is a crucial modifiable risk factor for *Clostridium difficile*. Cardiac surgery is of particular interest because prophylactic antibiotics are recommended for 48 hours or less (vs 24 hours for noncardiac surgery), with increasing vancomycin use. We aimed to study associations between antibiotic prophylaxis (duration/vancomycin use) and *C difficile* among patients undergoing coronary artery bypass grafting.

Methods—We extracted data on coronary artery bypass grafting procedures from the national Premier Perspective claims database (2006–2013, n = 154,200, 233 hospitals). Multilevel multivariable logistic regressions measured associations between (1) duration (<2 days, "standard" vs 2 days, "extended") and (2) type of antibiotic used ("cephalosporin," "cephalosporin + vancomycin," "vancomycin") and *C difficile* as outcome.

Results—Overall *C difficile* prevalence was 0.21% (n = 329). Most patients (59.7%) received a cephalosporin only; in 33.1% vancomycin was added, whereas 7.2% received vancomycin only. Extended prophylaxis was used in 20.9%. In adjusted analyses, extended prophylaxis (vs standard) was associated with significantly increased *C difficile* risk (odds ratio, 1.43; confidence interval, 1.07–1.92), whereas no significant associations existed for vancomycin use as adjuvant or primary prophylactic compared with the use of cephalosporins (odds ratio, 1.21; confidence interval, 0.92–1.60, and odds ratio, 1.39; confidence interval, 0.94–2.05, respectively). Substantial inter-hospital

variation exists in the percentage of extended antibiotic prophylaxis (interquartile range, 2.5–35.7), use of adjuvant vancomycin (interquartile range, 4.2–61.1), and vancomycin alone (interquartile range, 2.3–10.4).

Conclusions—Although extended use of antibiotic prophylaxis was associated with increased *C difficile* risk after coronary artery bypass grafting, vancomycin use was not. The observed hospital variation in antibiotic prophylaxis practices suggests great potential for efforts aimed at standardizing practices that subsequently could reduce *C difficile* risk.

Graphical Abstract
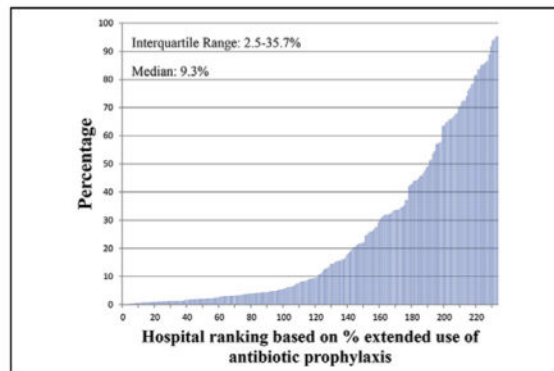
There is substantial hospital variation in antibiotic pro-phylaxis more than 48 hours in patients undergoing CABG.

Keywords

Clostridium difficile; coronary artery bypass graft; antibiotic prophylaxis; vancomycin

Clostridium difficile infections are an increasing problem in hospitalized patients, currently affecting more than 300,000 hospitalizations annually in the United States.[1] The development of *C difficile* compromises patient safety[2] and increases length of hospital stay and costs of hospitalization, with overall cost estimates of *C difficile* of up to $3.2 billion per year.[3–5] Antibiotic use is regarded as a crucial modifiable risk factor for *C difficile,* with studies demonstrating increased risks associated with the extended use of antibiotics, number of antibiotics used, and use of cephalosporins, clindamycin, and fluoroquinolones in particular.[6–8] Because prophylactic antibiotics are routinely administered to patients undergoing surgery, characteristics of this practice provide an important target to explore in efforts to reduce *C difficile*. Of particular interest are patients undergoing cardiac surgery because they differ from those undergoing general surgery regarding, for example, the use of cardiopulmonary bypass, hypothermia, the length of surgery, or indwelling chest catheters after surgery.[5,9] Therefore, several guidelines (eg, Society of Thoracic Surgeons) recommend 48 hours or less for antibiotic prophylaxis compared with 24 hours or less for noncardiac surgery.[10–13] A cephalosporin (usually cefazolin) is recommended as the antibiotic of choice; vancomycin is recommended as an adjuvant or the primary prophylactic antibiotic in a high-risk case for staphylococcal infection or β-lactam/penicillin allergy, respectively.[14] However, concerns have been raised on the effect of both the longer duration

of prophylaxis and the increasing use of vancomycin on the risk for resistant organisms and *C difficile*.[15,16] Moreover, *C difficile* has recently been found to be one of the main infections after cardiac surgery and is increasingly recognized as an important contributor to morbidity and mortality in this patient group.[5,17]

By using a nationwide claims-based database, we therefore sought to study the association between characteristics of antibiotic prophylaxis and *C difficile* in patients undergoing coronary artery bypass grafting (CABG) surgery with or without valve repair/replacement. The specific characteristics of interest were the extended use of prophylactic antibiotics (2 days after surgery) and the use of vancomycin as an adjuvant to cephalosporins or as the primary prophylactic antibiotic. We hypothesized both characteristics to be associated with an increased risk for *C difficile* in patients undergoing CABG.

MATERIALS AND METHODS

Data Source and Study Design

For this retrospective study, we used data from the Premier Perspective database[18] (Premier Inc, Charlotte, NC) containing surgical hospital discharges from January 2006 to December 2013. This database contains complete billing information on a patient's hospitalization. Apart from International Classification of Diseases-9th revision Clinical Modification (ICD-9 CM) codes and Current Procedural Terminology codes, this claims-based dataset provides standardized billing items. Up to 30 ICD-9 CM codes can be recorded for each hospitalization. Before data are incorporated in the Premier database, the vendor performs a rigorous data validation and quality assurance process. This process involves a 7-step integrity analysis, followed by approximately 150 sampling and statistical validity and integrity assurance crosschecks on all hospital-supplied data. For standardized codes, such as ICD-9 and Current Procedural Terminology codes, the codes are ascertained to be valid for the time period the patient record is reported. The dataset is increasingly used by a variety of study groups addressing clinical questions.[19,20] These data meet the requirements of de-identification as defined by the Health Insurance Portability and Accountability Act and were exempt from consent requirements of the Mount Sinai Medical Center Institutional Review Board (project HS#: 14-00,647).

Study Sample

The cohort contained CABG procedures (with or without valve repair/replacement) performed from 2006 to 2013 indicated by ICD-9 CM code 36.1 (including subcodes). Exclusion criteria were based on previous studies.[8,16] We excluded cases with unknown gender or discharge type (n = 602), systemic antibiotic use before surgery (n = 87,407), no billing for antibiotic use on the day of surgery (17,031), a switch in antibiotic class or gaps in antibiotic use of 1 or more days (to distinguish between treatment and prophylaxis, n = 55,958), and patients who died, developed *C difficile,* or were discharged within 2 days after surgery (n = 1466), the minimum plausible induction time for *C difficile* to be associated with the studied exposure.[21] Finally, we also excluded patients who were billed for prophylactic antibiotics other than cephalosporins or vancomycin (n = 4357). In particular, the exclusion of patients who died within 2 days was applied to keep our cohort strategy

similar to a comparable study[16] that studied the association between adjuvant vancomycin and *C difficile* risk in patients undergoing CABG. The main rationale is that these patients were not at risk of developing *C difficile* because 2 days is the minimum plausible induction time. To have a sufficient sample size per cluster, we also included only hospitals with more than 50 CABG procedures.[22]

Study Variables

The main exposures of interest were the extended use of prophylactic antibiotics and the use of vancomycin as an adjuvant to cephalosporins or the primary prophylactic antibiotic. Prophylactic antibiotic use was categorized into parenteral use of a cephalosporin only, a cephalosporin and vancomycin, or vancomycin only. Use was defined as billing for prophylaxis on the day of surgery or both the day of surgery and the day after (standard) versus billing for prophylaxis up to day 2 after surgery or later (extended).

Patient demographics included age, gender, and race (white, black, other). Healthcare-related variables included transfer from another hospital, type of insurance (commercial, Medicaid, Medicare, uninsured, other), hospital teaching status, and the mean annual number of CABG surgeries per hospital. Procedure-related variables included the day of procedure (as a measure of preoperative stay), the number of grafts involved (1- 4), concomitant valve repair/replacement, use of an internal thoracic artery graft, previous CABG surgery, emergency admission, and year of procedure. Variables related to comorbidity burden were Quan and colleagues'[23] update of the Deyo adaptation of the Charlson comorbidities and index, and the use of antacid medications (proton pump inhibitors and H2 receptor antagonists) because these medications have been associated with increased *C difficile* risk.[24]

The main outcome, *C difficile* 48 hours or more postoperatively, was defined as the presence of all of the following criteria[16]: (1) having an ICD-9 code 008.45, (2) billing for a stool study for *C difficile*, and (3) billing for *C difficile* therapy, that is, intravenous or oral metronidazole or oral vancomycin 2 days or more after surgery.

Statistical Analysis

The univariable association between extended antibiotic use and study variables was assessed using chi-square tests and *t* tests for categoric and continuous variables, respectively. To demonstrate potential inter-hospital variability, the percentage (y-axis) of (1) extended antibiotic use, (2) adjuvant vancomycin use, and (3) just vancomycin use by hospital (x-axis) was illustrated on separate graphs.

A multilevel multivariable logistic regression was then performed to measure the association among extended antibiotic use, vancomycin use, and *C difficile*. It included a random intercept term that varies at the level of each hospital and accounts for correlation of patients within hospitals. The model was adjusted using all variables found significant at the *P* less than .15 level from the univariable tests and had at least 10 cases within each category. Adjusted odds ratio (OR), 95% confidence interval (CI), and *P* value are reported and to be used together as a measure of overall significance. Hospital variation in *C difficile* was

measured using the intraclass correlation coefficient of the final model. Model discrimination was evaluated using the C-statistic.

Similar to others, we chose to use a conservative measure of *C difficile* defined by 3 criteria.[16] However, numerous studies often have relied only on ICD-9 coding because a high sensitivity (71%) and specificity (99%) for *C difficile* have been demonstrated.[25,26] Therefore, we assessed sensitivity to the definition of *C difficile* diagnosis by repeating the model with *C difficile* defined as just the presence of ICD-9 code 008.45, irrespective of a stool sample or antibiotic therapy indication.

RESULTS

The final study sample consisted of 154,200 CABG surgeries performed in 233 hospitals (Figure 1).

Characteristics

Overall, 92,013 (59.7%; range, 0–100) of patients received a cephalosporin only as prophylaxis; in 51,109 patients (33.1%; range, 0–100), vancomycin was added, and in 11,078 patients (7.2%; range, 0–82.6), vancomycin was used as the primary prophylactic. Extended prophylaxis was used in 32,291 (20.9%; range, 0–95.4) cases.

Table 1 provides a breakdown of the characteristics of antibiotic prophylaxis, patient demographics, healthcare-related variables, and procedure-related variables by standard versus extended antibiotic prophylaxis. Although statistically significant, there were no major differences between the standard group and the extended antibiotic prophylaxis group. Most notable (comparing standard vs extended antibiotic prophylaxis), mean age differed only slightly (65.4 vs 65.7 years), as did the mean Deyo–Charlson comorbidity index (0.96 vs 0.93) (both *P*<.01). Appendix E1 provides more insight into the distribution of *C difficile* by the study variables. Appendix E2 provides the separate Deyo–Charlson comorbidities by standard versus extended antibiotic prophylaxis.

Univariable and Multivariable *Clostridium difficile* Risk

Overall, *C difficile* was observed in 329 patients (0.21%) with great hospital-level variation (range, 0–2; interquartile range [IQR], 0.1–0.3). Those who received extended antibiotic prophylaxis (compared with standard prophylaxis) had a higher *C difficile* prevalence: 0.30% versus 0.19%, respectively (*P*<.01) (Table 2). When looking at type of antibiotic prophylaxis, higher *C difficile* risks were observed for adjuvant vancomycin (0.25%) and vancomycin only (0.33%) compared with the use of cephalosporins (0.18%) (*P*<.01).

After adjustment for relevant covariates (Table 3), the association with increased *C difficile* risk remained: extended prophylaxis (vs standard) (OR, 1.43; CI, 1.07–1.92). However, there was no significant association between *C difficile* and vancomycin use as adjuvant or alone (compared with the use of cephalosporins) (OR, 1.21; CI 0.92–1.60, and OR, 1.39; CI, 0.94–2.05, respectively).

The results were comparable when using a less-restrictive definition of *C difficile* (n = 398, overall prevalence 0.26%). The model's c-statistic was 0.76 for the main model and 0.75 for the sensitivity analysis. The intraclass correlation coefficient of the final model was 15.1% depicting the proportion of variation between hospitals that explains the outcome of *C difficile*.

To assess the potential effect of missing data on our multivariable results, we also studied the *C difficile* rates in 2 excluded groups: (1) those with unknown gender or discharge type (n = 602; no *C difficile* cases) and (2) those who were not billed for antibiotics on the day of surgery (n = 17,031; *C difficile* rate 0.56%). Because the latter is higher than the *C difficile* rate found in the study cohort (0.21%), the exclusion might have led to a bias of our effect estimates toward the null, meaning that our results could be an underestimation of the actual effect.

Hospital Variation in Antibiotic Prophylaxis Characteristics

Figures 2–4 show the extent of inter-hospital variation of the percentage of extended antibiotic prophylaxis use (IQR, 2.5–35.7), the percentage of adjuvant vancomycin (IQR, 4.2–61.1), and the percentage of vancomycin use as the primary prophylactic (IQR, 2.3–10.4), respectively. Appendix E3 provides a breakdown for these figures by hospital teaching status and hospital location (urban vs rural), showing no apparent differences between hospital types.

DISCUSSION

In this large population-based study using data from 154,200 patients who underwent CABG surgery in 233 hospitals, we found extended antibiotic prophylaxis to be associated with increased risks for *C difficile.* On the basis of *C difficile* definition, this increased risk ranged from 43% to 39%. Conversely, the use of vancomycin, as the primary prophylactic or added to a cephalosporin, was not associated with an increased *C difficile* risk. We further demonstrated substantial inter-hospital variation in antibiotic prophylaxis characteristics, which suggests great potential for efforts aimed at standardizing these practices, which subsequently could reduce *C difficile* risks.

Several recent studies have emphasized the importance of *C difficile* and its link to antibiotic prophylaxis in patients undergoing cardiac surgery.[2,17,27] Traditionally, the prevention of surgical site infections is considered the main objective of antibiotic prophylaxis. However, a recent study shifted the focus to other infections after cardiac surgery. By using prospective and detailed data from more than 5000 patients, Gelijns and colleagues[17] demonstrated the majority (79%) of infections after cardiac surgery to be pneumonia, bloodstream infections, or *C difficile*. Adding more priority to this topic are the current developments at the Centers for Medicare & Medicaid Services (CMS). As of October 2008, the CMS does not reimburse care related to several so-called hospital-acquired conditions, including some infections. Although *C difficile* infections have been considered, they have not yet been included in this list.[28] However, as regular reevaluations have been announced, *C difficile* infections might be included in the future, potentially resulting in a considerable financial burden for hospitals.

In this study, we focused on 2 characteristics that are perhaps the most important modifiable risk factors for *C difficile*[6–8]: the extended use of prophylactic antibiotics and the type of antibiotic used for prophylaxis, in our study the use of vancomycin alone or as an adjuvant. Currently, extended use has a different definition in cardiac surgery than in noncardiac surgery: more than 48 hours versus more than 24 hours postoperatively, respectively. Two recent meta-analyses have focused on the question of optimal duration in light of surgical site infections after cardiac surgery. However, the trials that were included in these meta-analyses mostly did not report on adverse events such as resistant bacteria or *C difficile*.[9,29] Moreover, analysis of recent data has shown a similar postoperative infection risk for less than 24 hours compared with less than 48 hours of antibiotic prophylaxis.[17] This underlines the need for additional studies, particularly those that assess effect on surgical site infections and adverse events.

Data on vancomycin as a risk factor for *C difficile* are sparse, as are data on a potential mechanism of action. Although oral vancomycin is excreted in the stool and can serve as treatment of *C difficile*, intravenous administration does not. Moreover, intravenous vancomycin has been linked to ecologic disturbances of the intestinal microflora predisposing *C difficile* overgrowth.[21,30,31] Only 1 previous study has assessed the role of vancomycin addition to cephalosporins in *C difficile* after cardiac surgery.[16] The *C difficile* prevalence in this respective cohort of patients undergoing CABG was 0.4% (n = 256). In line with our findings, the authors did not find an association between adjuvant vancomycin and *C difficile* risk. Moreover, they used a propensity score analysis to adjust for confounding, whereas we have used a multilevel multivariable logistic regression approach. The fact that both strategies demonstrate no association of vancomycin use (while using similar definitions) with increased *C difficile* risk adds to the robustness of this finding. Important future work could be aimed at (hospital-specific) factors affecting the choice of specific antibiotics as prophylaxis. Although guidelines specifically mention adjuvant vancomycin in case of high risk for staphylococcal infection, or vancomycin as primary prophylactic antibiotic in β-lactam/penicillin–allergic patients, additional data on the rationale for antibiotic choice seem imperative.[10–12,14] Moreover, guidelines, however complete, may not always be applicable to every situation. White and colleagues[27] have recently described their institutional transition from cephalosporin-based antimicrobial prophylaxis for cardiac surgery to flucloxacillin (or teicoplanin) and gentamicin after several apparent prophylaxis failures, continued institutional presence of methicillin-resistant staphylococcus aureus, and ongoing problems with *C difficile*. They found their practice change to have decreased *C difficile* without changing the incidence of wound infections or renal complications.[27]

Inter-hospital variation in antibiotic prophylaxis practices has been described for several procedures, including cardiac surgery.[17,32] The significant variation demonstrated in the current study suggests great potential for efforts such as Surgical Care Improvement Project (SCIP), a collaboration between the CMS and the Centers for Disease Control and Prevention to improve and standardize surgical care by a set of measures eventually reducing surgical complications, including surgical site infections.[33] A number of studies have assessed the impact of SCIP on outcomes, including surgical infections in mostly noncardiac surgery, however, with mixed results.[34,35] Although several SCIP measures have been retired

recently (January 2015), continuing evaluation of practice standardization and outcomes and implementation barriers of SCIP measures will be crucial in its success.

Study Limitations

The main limitation of our study is the lack of detailed clinical information in the billing dataset used; data are collected for the purpose of billing, not research. This limitation particularly pertains to the indications for the billed antibiotics for which we cannot distinguish between prophylaxis and treatment in case of extended use or if there were any particular reasons to use vancomycin; this might have resulted in indication bias. In addition, what is captured in billing databases does not necessarily reflect what is actually administered to the patient because there might be a mismatch between the two. We have tried to account for this by limiting our dataset to patients with antibiotic use starting on the day of surgery and excluding combinations of antibiotic use (except for vancomycin combined with cephalosporins). Moreover, we expect the effect of the mismatch to be minimal because our study objective focused on daily use without going into details on dosages. Another limitation, partly referring to the lack of clinical information, pertains to the definition of *C. difficile* from billing data for the inpatient period only. The latter seems particularly important because a substantial proportion (45%) of infections after cardiac surgery (including *C difficile*) occur after hospital discharge.[17] Although the effect of this limitation theoretically could go in both directions, we believe, on the basis of the described effects of antibiotic use on *C difficile*,[6–8] that it results in an underestimation of the effect of extended antibiotic prophylaxis on *C difficile*. Several other mechanisms also emphasize the conservative measure of our effect estimates. The excluded group of patients with no billing for antibiotics on the day of surgery (n = 17,031) (Figure 1) had a higher *C difficile* rate than our study cohort (0.56% vs 0.21%, respectively); the same was true for the group of patients using prophylactic antibiotics other than those used in the study (n = 4357; *C difficile* rate 2.6%). Moreover, we used a restrictive *C difficile* definition as previously described[16] and found the same results when using a more inclusive ICD-9 only definition, illustrating the robustness of our findings. Adding to this, but also illustrating the heterogeneity in populations, our *C difficile* prevalence estimates are comparable to some[27] but not other studies demonstrating higher prevalences.[5,17] Given the limitations pertaining to the use of billing data to answer clinical questions, we believe that our study provides some useful insights. Important next steps are additional retrospective studies looking into the effect of antibiotic prophylaxis on *C difficile* risk in other procedures and using other data sources. Furthermore, well-designed prospective studies would shed additional light on this important clinical question, which would also benefit from a (multicenter) clinical registry in which all variables of interest geared toward this question (eg, exact timing and duration of prophylaxis) are captured. A study geared toward prophylaxis patterns and the incidence of all postoperative infections would be needed to consider actual changes in antibiotic guidelines. The objective would be to weigh the risk of particularly *C difficile* and resistant organisms against infections (eg, mediastinitis) that might be positively affected by a longer duration of prophylaxis or the use of vancomycin. Theoretically, reducing postoperative mediastinitis with a longer duration of antibiotic prophylaxis at the expense of more *C difficile* may be completely justified.

CONCLUSIONS

With the use of billing data from 154,200 patients who underwent CABG, we found extended antibiotic prophylaxis to be associated with increased risks for *C difficile,* whereas the use of vancomycin was not. Substantial inter-hospital variation in antibiotic prophylaxis characteristics suggests great potential for efforts aimed at standardizing these practices, which could subsequently reduce *C difficile* risks. Current patient safety and financial stakes combined with possible future reimbursement penalties demand prioritization of this issue and effective strategies to decrease *C difficile*.

Acknowledgments

Abbreviations and Acronyms

CABG	coronary artery bypass grafting
CI	confidence interval
CMS	Centers for Medicare & Medicaid Services
ICD-9 [CM]	International Classification of Diseases-9th revision [Clinical Modification]
IQR	interquartile range
OR	odds ratio
SCIP	Surgical Care Improvement Project

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Central Message

Although extended use of antibiotic prophylaxis was associated with increased *C difficile* risk after CABG surgery, vancomycin use was not.

Perspective

In patients undergoing CABG, extended antibiotic prophylaxis was associated with increased *C difficile* risks with substantial inter-hospital variation in antibiotic prophylaxis characteristics. Current patient safety and financial stakes combined with possible future reimbursement penalties demand prioritization of this issue and effective strategies to decrease *C difficile*.
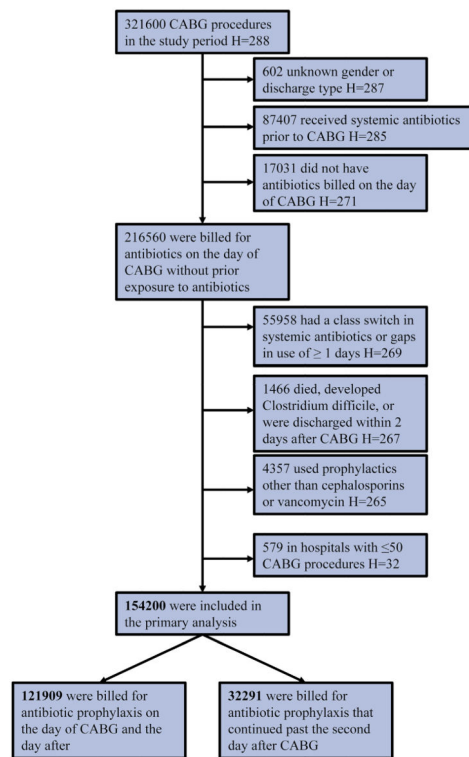
FIGURE 1.

Patient flow chart.* *Patients may belong to more than 1 exclusion criteria in each step. "H" stands for the number of hospitals; because exclusions are on the patient level, the number of hospitals mentioned in each step does not reflect the number of hospitals excluded. In any of the exclusion steps, no complete hospitals (ie, all CABG cases in those hospitals) are excluded. *CABG*, Coronary artery bypass grafting.
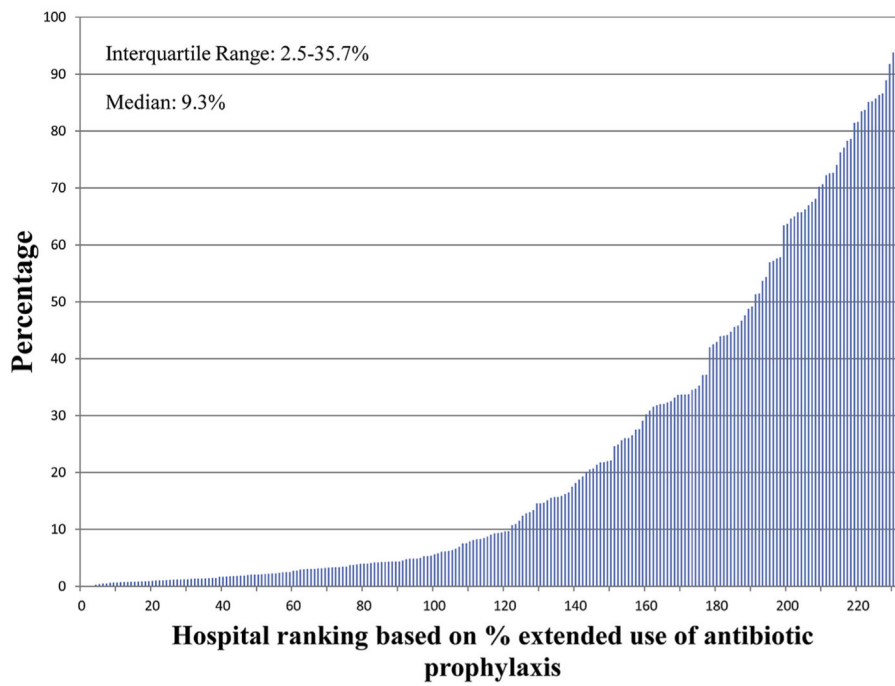
FIGURE 2.
Percentage of CABG surgeries in which there is extended antibiotic prophylaxis, by hospital.

FIGURE 3.
Percentage of CABG surgeries in which vancomycin is added to cephalosporins for antibiotic prophylaxis, by hospital.

FIGURE 4.

Percentage of CABG surgeries in which vancomycin is used as primary antibiotic prophylactic, by hospital.

APPENDIX E3.

Hospital variation in characteristics of antibiotic prophylaxis by hospital teaching status and location (urban vs rural).

TABLE 1

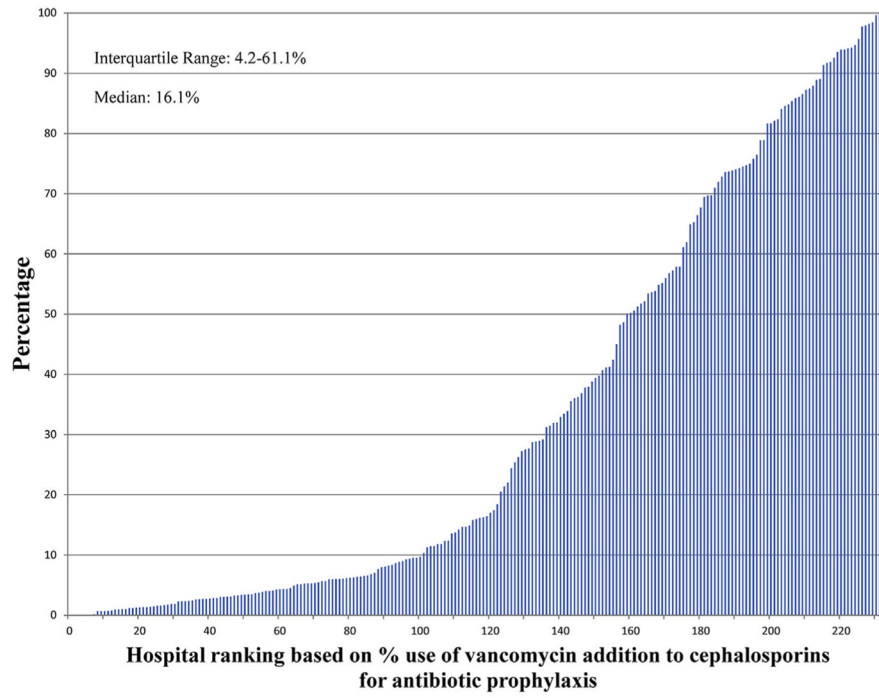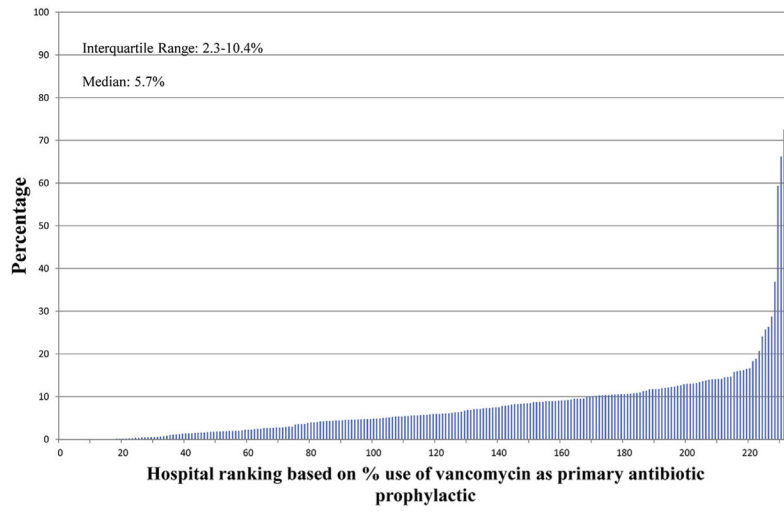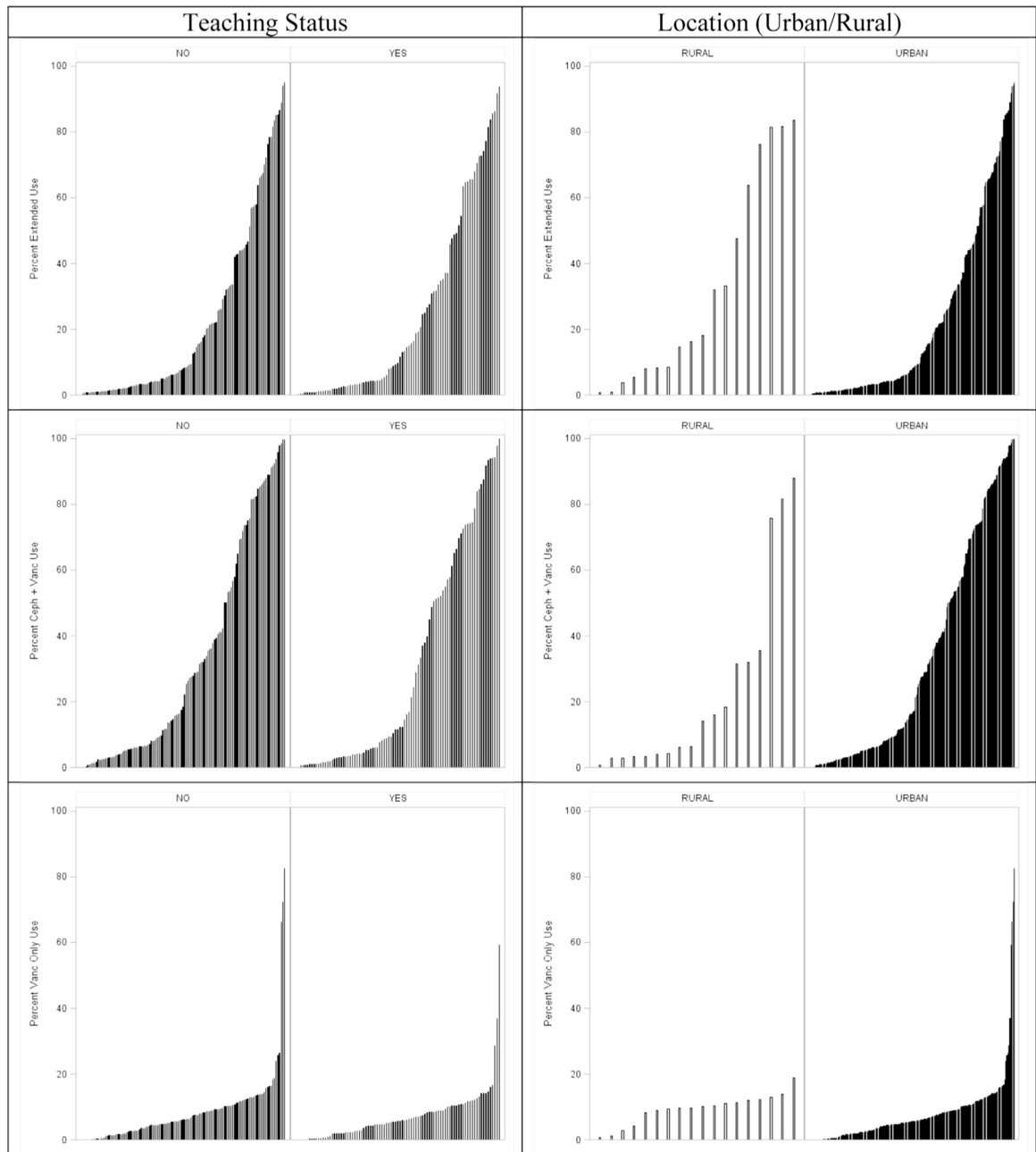Patient demographics, healthcare related, procedure related, and comorbidity variables by standard versus extended use of antibiotic prophylaxis

Characteristics	Antibiotic prophylaxis				P value[†]
	Standard		Extended		
	N[*]	%[*]	N[*]	%[*]	
Antibiotic prophylaxis group					<.01
Cephalosporin only	71,934	59.0	20,079	62.2	
Cephalosporin with Vancomycin	40,357	33.1	10,752	33.3	
Vancomycin only	9618	7.9	1460	4.5	
Patient demographics					
Age continuous [*]	65.4	10.6	65.7	10.8	<.01
Age category					<.01
<45 y	3449	2.8	924	2.9	
45–54 y	16,155	13.3	4112	12.7	
55–64 y	35,541	29.2	9232	28.6	
65–74 y	40,217	33.0	10,633	32.9	
>75 y	26,547	21.8	7390	22.9	
Gender					.25
Female	30,681	25.2	8027	24.9	
Male	91,228	74.8	24,264	75.1	
Race					<.01
White	92,037	75.5	22,330	69.2	
Black	7471	6.1	1782	5.5	
Other	22,401	18.4	8179	25.3	
Healthcare related					
Transfer from other hospital	16,878	13.8	4750	14.7	<.01
Insurance type					<.01
Commercial	42,685	35.0	10,959	33.9	
Medicaid	5831	4.8	1739	5.4	
Medicare	65,238	53.5	17,497	54.2	
Uninsured/other	8155	6.7	2096	6.5	

Characteristics	Antibiotic prophylaxis				P value†
	Standard		Extended		
	N*	%*	N*	%*	
Hospital teaching status					
Nonteaching	54,998	45.1	15,334	47.5	<.01
Teaching	66,911	54.9	16,957	52.5	
Mean annual no. of CABGs per hospital*	211	144	184	123	<.01
Procedure related					
Mean day of procedure	1.6	2.2	1.6	2.2	.97
1	23,435	19.22	6519	20.19	<.01
2	42,651	34.99	11,456	35.48	.10
3	33,978	27.87	8861	27.44	.12
4	14,958	12.27	3997	12.38	.60
Concomitant valve repair/replacement	16,892	13.86	4872	15.09	<.01
ITA graft	106,835	87.64	27,762	85.97	<.01
Previous CABG surgery	290	0.2	68	0.2	.36
Emergency admission	26,399	21.7	7448	23.1	<.01
Year of procedure					
2006	16,108	13.2	4284	13.3	<.01
2007	16,362	13.4	4022	12.5	
2008	14,308	11.7	3553	11.0	
2009	16,119	13.2	3171	9.8	
2010	16,244	13.3	3594	11.1	
2011	15,186	12.5	3996	12.4	
2011	14,677	12.0	4794	14.8	
2013	12,905	10.6	4877	15.1	
Comorbidity burden					
Mean Deyo–Charlson comorbidity index*	0.96	1.33	0.93	1.30	<.01
Use of antacid medications	116,377	95.5	31,095	96.3	<.01

CABG, Coronary artery bypass grafting; *ITA*, internal thoracic artery.

*
Continuous variable mean and standard deviation instead of N and %, respectively.

†Chi-square test for categoric variables, *t* test for continuous variables.

TABLE 2

Extended antibiotic prophylaxis and type of antibiotic by *Clostridium difficile* occurrence

| | *C difficile* | | | |
| | No | Yes | | |
Characteristics	**N**	**N**	**%**	***P* value[*]**
Duration of antibiotic prophylaxis				
Extended	32,193	98	0.30	<.01
Standard	121,678	231	0.19	
Type of antibiotic prophylaxis				
Cephalosporin only	91,848	165	0.18	<.01
Cephalosporin with Vancomycin	50,982	127	0.25	
Vancomycin only	11,041	37	0.33	

[*] Chi-square test.

TABLE 3

Adjusted [*] association between antibiotic prophylaxis measures and *Clostridium difficile*

	Definition of *Clostridium difficile*	
	Restrictive	**Less restrictive (sensitivity analysis)**
	OR[*] (95% CI)	**OR[*] (95% CI)**
Extended antibiotic prophylaxis		
No	Reference	Reference
Yes	1.43 (1.07–1.92)	1.39 (1.08–1.82)
Type of antibiotic prophylaxis		
Cephalosporin only	Reference	Reference
Cephalosporin with Vancomycin	1.21 (0.92–1.60)	1.16 (0.90–1.48)
Vancomycin only	1.39 (0.94–2.05)	1.37 (0.96–1.95)

CI, Confidence interval; *OR*, odds ratio.

[*] Adjusted for age, race, transfer from another hospital, insurance type, hospital teaching status, mean annual number of CABG surgeries per hospital, preoperative hospital stay, number of grafts, concomitant valve repair/replacement, internal thoracic artery graft, emergency admission, year of procedure, Deyo–Charlson comorbidities, use of antacid medications; all $P<.05$.

APPENDIX E1

Patient demographics, healthcare related, procedure related, and comorbidity variables by yes or no for *Clostridium difficile*

Characteristics	C difficile				P value[†]
	No		Yes		
	N*	%*	N*	%*	
Antibiotic prophylaxis					
Duration					
Extended	122,124	79.1	234	69.9	<.01
Standard	32,320	20.9	101	30.1	
Type of antibiotic					
Cephalosporin only	92,146	59.7	168	50.1	<.01
Cephalosporin with vancomycin	51,187	33.1	130	38.8	
Vancomycin only	11,111	7.2	37	11.0	
Patient demographics					
Age continuous*	65.4	10.7	70.2	10.8	<.01
Age category					
<45 y	4394	2.8	7	2.1	<.01
45–54 y	20,324	13.2	24	7.2	
55–64 y	44,879	29.1	60	17.9	
65–74 y	50,942	33.0	111	33.1	
>75 y	33,905	22.0	133	39.7	
Gender					
Female	38,736	25.1	125	37.3	<.01
Male	115,708	74.9	210	62.7	
Race					
White	114,474	74.1	251	74.9	.88
Black	9258	6.0	18	5.4	
Other	30,712	19.9	66	19.7	
Healthcare related					
Transfer from other hospital	21,615	14.0	70	20.9	<.01
Insurance type					

| Characteristics | C difficile | | | | P value† |
| | No | | Yes | | |
	N*	%*	N*	%*	
Commercial	53,784	34.8	59	17.6	<.01
Medicaid	7589	4.9	21	6.3	
Medicare	82,795	53.6	243	72.5	
Uninsured/other	10,276	6.7	12	3.6	
Hospital teaching status					
Nonteaching	70,640	45.7	160	47.8	.46
Teaching	83,804	54.3	175	52.2	
Mean annual no. of CABGs per hospital*	205	141	188	141	.26
Procedure related					
Mean day of procedure	1.6	2.2	1.9	2.4	<.01
No. of grafts					
1	30,002	19.4	73	21.8	.27
2	54,189	35.1	108	32.2	.28
3	42,914	27.8	88	26.3	.54
4	18,979	12.3	51	15.2	.10
Concomitant valve repair/replacement	21,738	14.1	94	28.1	<.01
ITA graft	134,815	87.3	272	81.2	<.01
Previous CABG surgery	358	0.2	0	0.0	.38
Emergency admission	33,938	22.0	82	24.5	.27
Year of procedure					
2006	20,406	13.2	49	14.6	.24
2007	20,376	13.2	50	14.9	
2008	17,839	11.6	39	11.6	
2009	19,262	12.5	51	15.2	
2010	19,864	12.9	30	9.0	
2011	19,261	12.5	33	9.9	
2011	19,562	12.7	42	12.5	
2013	17,874	11.6	41	12.2	
Comorbidity burden					

| Characteristics | C difficile | | | | |
| | No | | Yes | | |
	N*	%*	N*	%*	P value†
Mean Deyo–Charlson comorbidity index *	0.95	1.3	2.02	1.9	<.01
Use of antacid medications 147,661	95.6 324	96.7		.32	

CABG, Coronary artery bypass grafting; *ITA*, internal thoracic artery.

*
Continuous variable mean and standard deviation instead of N and %, respectively.

†
Chi-square test for categoric variables, *t* test for continuous variables.

APPENDIX E2

Deyo–Charlson comorbidities by standard versus extended use of antibiotic prophylaxis

	Antibiotic prophylaxis				
	Standard		Extended		
Comorbidities	N	%	N	%	P value[*]
Deyo–Charlson comorbidity grouping					
Myocardial infarction	46,017	37.6	12,416	38.3	.02
Congestive heart failure	23,970	19.6	6622	20.4	<.01
Peripheral vascular disease	18,933	15.5	4648	14.3	<.01
Cerebrovascular disease	11,696	9.6	3033	9.4	.27
Dementia	359	0.3	89	0.3	.57
Chronic pulmonary disease	30,157	24.6	7226	22.3	<.01
Rheumatologic disease	2331	1.9	619	1.9	.96
Peptic ulcer disease	1800	1.5	451	1.4	.28
Mild liver disease	1844	1.5	492	1.5	.89
Moderate/severe liver disease	202	0.2	55	0.2	.86
Diabetes	44,951	36.7	12,272	37.9	<.01
Diabetes with chronic complications	6857	5.6	1591	4.9	<.01
Hemiplegia or paraplegia	589	0.5	185	0.6	.04
Renal disease	15,156	12.4	3677	11.3	<.01
Any malignancy	2983	2.4	758	2.3	.30
Metastatic solid tumor	316	0.3	63	0.2	.04

[*]
Chi-square test.