ORIGINAL ARTICLE

Activity of Commonly Used Antimicrobial Prophylaxis Regimens against Pathogens Causing Coronary Artery Bypass Graft and Arthroplasty Surgical Site Infections in the United States, 2006–2009

Sandra I. Berríos-Torres, MD;[1] Sarah H. Yi, PhD;[1] Dale W. Bratzler, DO, MPH;[2] Allen Ma, PhD;[3] Yi Mu, PhD;[1] Liping Zhu, MD, MPH;[1] John A. Jernigan, MD, MS[1]

(See the commentary by Anderson and Sexton, on pages 240–242.)

BACKGROUND. Coronary artery bypass graft (CABG) and primary arthroplasty surgical site infection (SSI) rates are declining slower than other healthcare-associated infection rates. We examined antimicrobial prophylaxis (AMP) regimens used for these operations and compared their spectrum of activity against reported SSI pathogens.

METHODS. Pathogen distributions of CABG and hip/knee arthroplasty complex SSIs (deep and organ/space) reported to the National Healthcare Safety Network (NHSN) from 2006 through 2009 and AMP regimens (same procedures and time period) reported to the Surgical Care Improvement Project (SCIP) were analyzed. Regimens were categorized as standard (cefazolin or cefuroxime), β-lactam allergy (vancomycin or clindamycin with or without an aminoglycoside), and extended spectrum (vancomycin and/or an aminoglycoside with cefazolin or cefuroxime). AMP activity of each regimen was predicted on the basis of pathogen susceptibility reports and published spectra of antimicrobial activity.

RESULTS. There were 6,263 CABG and arthroplasty complex SSIs reported (680,489 procedures; 880 NHSN hospitals). Among 6,574 pathogens reported, methicillin-sensitive *Staphylococcus aureus* (23%), methicillin-resistant *S. aureus* (18%), coagulase-negative staphylococci (17%), and *Enterococcus* species (7%) were most common. AMP regimens for 2,435,703 CABG and arthroplasty procedures from 3,330 SCIP hospitals were analyzed. The proportion of pathogens predictably susceptible to standard (used in 75% of procedures), β-lactam (12%), and extended-spectrum (8%) regimens was 41%–45%, 47%–96%, and 81%–96%, respectively.

CONCLUSION. Standard AMP, used in three-quarters of CABG and primary arthroplasty procedures, has inadequate activity against more than half of SSI pathogens reported. Alternative strategies may be needed to prevent SSIs caused by pathogens resistant to standard AMP regimens.

Infect Control Hosp Epidemiol 2014;35(3):231-239

More than 400,000 coronary artery bypass graft (CABG) and almost 1 million primary hip and knee arthroplasty procedures are performed annually in the United States.[1,2] Complex (deep incisional and organ/space) surgical site infections (SSIs) complicate approximately 0.5%–4.0% of CABGs, 0.2%–1.1% of primary hip arthroplasties, and 1.6% of primary knee arthroplasties, resulting in increased morbidity, mortality, length of stay, and cost of hospitalization.[3-11] Prevention of SSIs following these and other surgical procedures has become a national public health priority.[12]

Antimicrobial prophylaxis (AMP) is recognized as a core SSI prevention strategy. Several professional groups have published guidelines for selecting appropriate AMP.[13-16] Data from the Centers for Medicare & Medicaid Services' (CMS's) national Surgical Care Improvement Project (SCIP) suggest that compliance with recommended AMP is high, yet national SSI rates have not decreased as rapidly as those of other healthcare-associated infections also targeted in national quality improvement efforts.[17,18] Efforts to enhance the effectiveness of SSI prevention strategies, including an assessment of the current AMP guideline recommendations, are needed.

AMP selection should be based on the regimens' expected spectrum of activity against those pathogens commonly known to cause SSIs associated with the given procedure. Changes in the type and frequency of pathogens may have important implications, especially if resistance to standard

Affiliations: 1. Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia; 2. College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; 3. Oklahoma Foundation for Medical Quality, Oklahoma City, Oklahoma.

Received September 23, 2013; accepted November 24, 2013; electronically published January 29, 2014.

 0899-823X/2014/3503-0004$15.00. DOI: 10.1086/675289

AMP becomes prevalent. Recent observations suggest that a growing proportion of SSIs following cardiac and arthroplasty procedures are caused by organisms that may be resistant to first- and second-generation cephalosporins (standard AMPs recommended in current guidelines).[13-16,19]

To inform future AMP recommendations and SSI prevention strategies, we used national data to compare the predicted activity of current AMP against the pathogens responsible for complex SSIs following CABG and primary hip and knee arthroplasty procedures.

METHODS

The study period was January 1, 2006, through December 31, 2009.

SSI Surveillance Population

We used data from National Healthcare Safety Network (NHSN) facilities using standardized protocols to report CABG and primary hip and knee arthroplasty SSIs during the study period.[20] NHSN is a secure, Internet-based surveillance system managed by the Centers for Disease Control and Prevention's Division of Healthcare Quality Promotion (DHQP).

AMP Regimen Surveillance Population

Hospital personnel abstracted AMP data from medical records and submitted quarterly reports to the national Quality Improvement Organization Clinical Data Warehouse, which stores facility-level reported SCIP performance measure data for quality improvement and public reporting. The data warehouse includes identifiable patient-level information from all hospitals that submit performance measure data under the Hospital Inpatient Quality Reporting Program. Data submitted are subject to random validation audits by an independent CMS contractor. AMP regimens recorded included all antimicrobials administered from the time of patient arrival through the first 48 hours after anesthesia end time for hip and knee arthroplasties and 72 hours for CABGs.

Procedures

Inpatient, elective, and emergency CABG and primary hip and knee arthroplasty procedures in patients 18 years or older were included. CABG procedures included those with sternal and harvest site incisions (NHSN procedure code CBGB; *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] procedure codes 36.10–36.14, 36.19) and those with sternal incisions only (NHSN procedure code CBGC; ICD-9-CM procedure codes 36.15–36.17, 36.2).[20] Arthroplasty procedures included primary hip (NHSN procedure codes HPRO: primary [total and partial]; ICD-9-CM procedure codes 00.85–00.87, 81.51, 81.52) and knee (NHSN procedure code KPRO; ICD-9-CM procedure code 81.54) codes. SCIP excluded codes 36.2 (heart revascularization by arterial implant) and 00.85–00.87 (hip resurfacing procedures).[21] On the basis of previously described NHSN and SCIP criteria, 70,812 (9.4%) NHSN and 252,218 (9.4%) SCIP records were excluded from analysis.[21,22]

SSIs, Pathogen Distribution, and Susceptibility

SSIs reported to NHSN were classified as superficial, deep, and organ/space. We combined deep and organ/space into "complex." Facilities could report up to 3 isolates per SSI. Susceptibility testing was reported as intermediate, susceptible, resistant, or not tested. *Staphylococcus aureus* isolate resistance was defined as resistance to oxacillin (methicillin).

AMP Regimens and Predicted Activity against Pathogens Reported to NHSN

We compared the pathogens reported to NHSN against the predicted spectrum of activity of recommended AMP regimens. Because confidentiality is protected by federal law for the 2 databases, they were not linked for this analysis. Twelve recommended AMP regimens were identified and assigned to 3 broad categories according to established guidelines.[13-16,23] Use of cefazolin or cefuroxime was categorized as standard, use of vancomycin or clindamycin with or without an aminoglycoside as β-lactam allergy, and use of cefazolin or cefuroxime with vancomycin and/or an aminoglycoside as extended spectrum.

The predicted susceptibility of each reported isolate to each antimicrobial agent in the 12 recommended AMP regimens was calculated. Predicted susceptibility was based on the results of actual susceptibility tests reported to NHSN when available for a particular isolate. When actual susceptibility testing results were not available for a particular isolate, the likelihood of susceptibility was determined using 2 alternative approaches: (1) imputation based on the average value of actual susceptibility testing results of other isolates in the data set or (2) assignment of an expected value. In the first alternative approach ("imputed susceptibility"), actual susceptibility testing results from other patient isolates of the same genus and species were used if adequate data were available. We defined a pathogen as having adequate data when at least 10 isolates of the pathogen were reported to NHSN and susceptibility test results were reported for at least 20% of these isolates for the relevant antimicrobial agent. When imputed susceptibility could not be used, we assigned an expected value for each pathogen-drug combination on the basis of information contained in the package insert and in a standard textbook for each antimicrobial.[24] Actual, imputed, and expected susceptibility values were used for 55%, 12%, and 34% of isolate-regimen pairs, respectively.

Human Subjects Consideration

The human subjects research liaison of the National Center for Emerging and Zoonotic Infectious Diseases reviewed and

TABLE 1. Facility, Procedure, and Patient Characteristics by Procedure Type, 2006–2009

Characteristic	NHSN			SCIP		
	CABG (n = 205,935)	Arthroplasty (n = 474,554)	Total (n = 680,489)	CABG (n = 428,541)	Arthroplasty (n = 2,007,162)	Total (n = 2,435,703)
Facility characteristics						
Facility type						
Nonprofit	289 (85)	686 (84)	742 (84)	808 (67)	2,241 (63)	2,246 (63)
For profit	37 (11)	86 (11)	92 (10)	245 (20)	699 (20)	717 (20)
Government	11 (3)	33 (4)	35 (4)	157 (13)	612 (17)	615 (17)
Military[a]	1 (0)	3 (0)	3 (0)	...	...	...
Veterans Affairs[a]	3 (1)	2 (0)	4 (0)	...	...	...
Physician owned[a]	0 (0)	4 (0)	4 (0)	...	...	...
Total facilities	341 (100)	814 (100)	880 (100)	1,210 (100)	3,552 (100)	3,578 (100)
Medical school affiliation	217 (64)	332 (41)	375 (43)	670 (55)	1,035 (29)	1,038 (29)
No. of beds						
≤200	78 (23)	475 (58)	488 (55)	202 (17)	2,046 (58)	2,071 (58)
201–500	175 (51)	267 (33)	298 (34)	670 (55)	1,135 (32)	1,136 (32)
501–1,000	86 (25)	71 (9)	92 (10)	302 (25)	334 (9)	334 (9)
>1,000	2 (1)	1 (0)	2 (0)	36 (3)	37 (1)	37 (1)
Mean ± SD	383 ± 219	217 ± 194	232 ± 205	414 ± 264	229 ± 224	229 ± 223
Geographic region						
Midwest	43 (13)	59 (7)	69 (8)	324 (27)	962 (27)	971 (27)
Northeast	143 (42)	455 (56)	473 (54)	156 (13)	572 (16)	573 (16)
South	87 (26)	133 (17)	166 (19)	461 (38)	1,287 (36)	1,295 (36)
West	68 (20)	167 (21)	173 (20)	261 (22)	700 (20)	705 (20)
US Virgin Islands and Puerto Rico[b]	...	...	...	8 (1)	31 (1)	34 (1)
Procedure characteristics						
Procedure duration, minutes						
Mean	253	96	144	241	101	124
Median	241	90	110	228	91	100
Patient characteristics						
Male gender	147,305 (72)	188,254 (40)	335,559 (49)	315,927 (74)	760,451 (38)	1,076,378 (44)
Age, mean ± SD, years	66 ± 11	66 ± 12	66 ± 12	65 ± 11	68 ± 12	67 ± 12

NOTE. Data are no. (%), unless otherwise indicated. National Healthcare Safety Network (NHSN) missing data are as follows: facility type—arthroplasty (1); ASA score—CABG (12); elective—CABG (3); gender—arthroplasty (1); wound classification—CABG (6), arthroplasty (1); ASA—CABG (15); gender (SCIP)—CABG (386), arthroplasty (764). CABG, coronary artery bypass graft; SD, standard deviation; SCIP, Surgical Care Improvement Project.

[a] SCIP does not report on these variables.

[b] NHSN does not collect US Virgin Islands and Puerto Rico surgical site infection data.

approved the routine reporting of healthcare-associated infection data to NHSN, determining that such reporting constitutes surveillance and not research. Likewise, the human subjects research liaison for DHQP determined that examination of reported pathogens in these data and the use of deidentified AMP data reported to SCIP does not constitute human subjects research and is not subject to further institutional review.

Statistical Analysis

Unadjusted pooled mean SSI incidence rates were calculated as the number of SSIs per 100 procedures. All isolates reported were included in the pathogen distribution calculations. Procedure-specific selection of AMP regimen was calculated as the total number of procedures per AMP regimen. Spectrum of activity against pathogens was calculated for each of the 12 regimens and reported as a range for each of the 3 broad categories (ie, standard, β-lactam allergy, and extended-spectrum regimens). For example, 45% of arthroplasty pathogens were predicted to be covered by cefazolin and 48% by cefuroxime; therefore, standard AMP regimens were predicted to cover 45%–48% of these pathogens. Because meaningful differences were not observed for pathogen distribution, AMP regimen selection, and expected spectrum of activity when stratified by arthroplasty type (ie, hip and knee) or year, results were pooled among arthroplasties and years. SAS (ver. 9.3; SAS Institute) was used for data management and analysis.

TABLE 2. Complex Surgical Site Infection Pathogen Distribution, National Healthcare Safety Network Surveillance System, 2006–2009

	Pathogenic isolates					
	CABG		Arthroplasty		Total	
Pathogen	No. (%)	Rank	No. (%)	Rank	No. (%)	Rank
Staphylococcus aureus[a]						
Methicillin-sensitive *S. aureus*	616 (19)	1	904 (28)	1	1,520 (23)	1
Methicillin-resistant *S. aureus*	550 (17)	3	634 (19)	2	1,184 (18)	2
Coagulase-negative staphylococci	573 (17)	2	512 (16)	3	1,085 (17)	3
Enterococcus species	193 (6)	6	240 (7)	4	433 (7)	4
Pseudomonas aeruginosa	223 (7)	4	116 (4)	7	339 (5)	5
Escherichia coli	197 (6)	5	117 (4)	6	314 (5)	6
Streptococcus species	66 (2)	11	212 (7)	5	278 (4)	7
Enterobacter species	142 (4)	8	88 (3)	8	230 (3)	8
Proteus species	131 (4)	10	75 (2)	9	206 (3)	9
Klebsiella pneumoniae, Klebsiella oxytoca	144 (4)	7	53 (2)	10	197 (3)	10
Serratia species	137 (4)	9	47 (1)	11	184 (3)	11
Candida albicans	52 (2)	12	6 (0)	13	58 (1)	12
Acinetobacter baumannii	29 (1)	13	23 (1)	12	52 (1)	13
Other *Candida* species or NOS	14 (0)	14	5 (0)	14	19 (0)	14
Other[b]	226 (7)	15	197 (6)	15	423 (6)	15
Total	3,316 (100)		3,258 (100)		6,574 (100)	

NOTE. CABG, coronary artery bypass graft; NOS, not otherwise specified.

[a] *S. aureus* oxacillin testing: intermediate (2 CABG), not tested (20 CABG, 29 arthroplasty), and missing (1 CABG).

[b] Includes amoeba (1), fungi (5), mycobacteria (5), gram negatives (188), gram positives (218), yeast (5), and anaerobe-NOS (1).

RESULTS

CABGs

Demographics. Most CABGs were elective (91%), had clean wounds (98%), and had an American Society of Anesthesiologists (ASA) score of 3 or more (99%). Other hospital, procedure, and patient characteristics are summarized in Table 1.

SSIs and pathogen distribution. During the study period, 341 hospitals reported 3,003 CABG complex SSIs (unadjusted rate per 100 procedures, 1.46) among 205,935 CABG procedures to NHSN. Pathogen information was available for 88% (n = 2,640); 69% (n = 2,081) were monomicrobial, 19% (n = 559) were multimicrobial, and 12% (n = 363) had no pathogen isolated. The 3,316 CABG pathogens included 1,186 (36%) *S. aureus* (methicillin-sensitive *S. aureus* [MSSA], 616 [19%]; methicillin-resistant *S. aureus* [MRSA], 550 [17%]), 573 (17%) coagulase-negative staphylococci, 223 (7%) *Pseudomonas aeruginosa*, and 197 (6%) *Escherichia coli* as the most commonly reported (Table 2). Gram-negative pathogens accounted for 34% of the CABG isolates.

AMP regimens and predicted spectrum of activity. AMP regimens for 428,541 CABG procedures were compared against the SSI pathogens reported. Standard regimens were used in 67% (n = 285,217) and had predicted activity against 36%–42% of the pathogens reported, depending on whether cefazolin or cefuroxime was used; β-lactam allergy regimens were used in 10% (n = 44,972), with predicted activity against 41%–93% of the pathogens; and extended-spectrum regimens were used in 14% (n = 59,264), with predicted activity against 75%–95% of the pathogens. Ten percent of the regimens reported did not correspond to any of the recommended regimens (Tables 3, 4).

Arthroplasties

Demographics. Most arthroplasties were elective (98%), had clean wounds (98%), and had an ASA score of 3 or more (59%). Other hospital, procedure, and patient characteristics are summarized in Table 1.

SSIs and pathogen distribution. During the study period, 814 hospitals reported 3,260 complex SSIs in 474,554 primary arthroplasties (unadjusted rate per 100 procedures, 0.69). Pathogen information was available for 85% (n = 2,776); 73% (n = 2,374) were monomicrobial, 12% (n = 402) were multimicrobial, and 15% (n = 484) had no pathogen isolated. The 3,258 arthroplasty pathogens (n = 1,633, 50% hips) included 1,566 (48%) *S. aureus* (MSSA, 904 [28%]; MRSA, 634 [19%]), 512 (16%) coagulase-negative staphylococci, 240 (7%) *Enterococcus* species, and 212 (7%) *Streptococcus* species as the most commonly reported (Table 2). Gram-negative pathogens accounted for 18% of the primary arthroplasty isolates (22% of hips vs 15% of knees).

AMP regimens and expected spectrum of activity. AMP regimens for 2,007,162 primary arthroplasty procedures were

https://doi.org/10.1086/675289 Published online by Cambridge University Press

TABLE 3. Antimicrobial Prophylaxis Regimen Selection, Surgical Care Improvement Project, 2006–2009

Antimicrobial prophylaxis regimen	CABG	Arthroplasty	Total
Standard	285,217 (67)	1,537,136 (77)	1,822,353 (75)
Cefazolin	223,766 (52)	1,517,359 (76)	1,741,125 (71)
Cefuroxime	61,451 (14)	19,777 (1)	81,228 (3)
β-lactam allergy	44,972 (10)	241,707 (12)	286,679 (12)
Vancomycin	38,263 (9)	148,359 (7)	186,622 (8)
Clindamycin	2,338 (1)	81,069 (4)	83,407 (3)
Vancomycin + aminoglycoside	4,313 (1)	8,826 (0)	13,139 (1)
Clindamycin + aminoglycoside	58 (0)	3,453 (0)	3,511 (0)
Extended spectrum	59,264 (14)	137,407 (7)	196,671 (8)
Cefazolin or cefuroxime + vancomycin	54,184 (13)	73,637 (4)	127,821 (5)
Cefazolin + aminoglycoside + vancomycin	893 (0)	2,682 (0)	3,575 (0)
Cefuroxime + aminoglycoside + vancomycin	205 (0)	10 (0)	215 (0)
Other	43,070 (10)	151,990 (8)	195,060 (8)
Total	428,541 (100)	2,007,162 (100)	2,435,703 (100)

NOTE. Data are no. (%). CABG, coronary artery bypass graft.

compared against the pathogens reported. Standard regimens were used in 77% (n = 1,537,136), with predicted activity against 42%–46% of the pathogens reported depending on whether cefazolin or cefuroxime was used; β-lactam allergy regimens were used in 12% (n = 241,707), with expected activity against 71%–97% of the pathogens; and extended-spectrum regimens were used in 7% (n = 137,407), with expected activity against 83%–97% of the pathogens. Eight percent of the regimens reported did not correspond to any of the recommended regimens (Tables 3, 4).

DISCUSSION

Among facilities reporting CABG and arthroplasty event data to NHSN during the years 2006–2009, standard AMP regimens recommended in current guidelines and used in the majority of these procedures nationally likely had inadequate activity against more than half of the complex SSI pathogens reported. These findings may be explained by disproportionate impact of widely used standard regimens on susceptible pathogens, leaving a residual subset of "breakthrough" SSIs caused by resistant pathogens, or by emergence of resistant pathogens to replace or add to a proportion of susceptible pathogens. Regardless, the problem of SSI caused by AMP-resistant pathogens in this population is one of considerable magnitude.[25,26] Prevention strategies that more effectively address the current and future burden of SSI caused by these pathogens are needed.

One potential strategy is to modify current AMP guidelines so the regimens recommended for routine use, either in all or a subset of high-risk patients, have spectra of antimicrobial activity that better match the pathogens reported to cause SSIs. In response to the prevalence of β-lactam-resistant gram-positive pathogens among SSI, some published guidelines recommend routine use of extended-spectrum regimens (eg, standard cephalosporin regimens with vancomycin and/or an aminoglycoside) in facilities where the "prevalence of MRSA is high," but the recommendations are ambiguous and do not provide specific metrics to guide the decision.[13-16] Our results suggest that the prevalence of MRSA among complex SSIs following CABG and primary arthroplasty procedures is 18% (Table 2). If one considers coagulase-negative staphylococci and enterococci, the prevalence of cephalosporin-resistant gram-positive pathogens among complex SSIs may be as high as 42%. When resistant gram-negative and other pathogens are considered, the overall prevalence of pathogens resistant to standard AMP regimens increases to 55%–59% (Table 4). This level of resistance raises the question of whether a national threshold has been reached, exhorting surgeons to routinely use AMP regimens with a spectrum of antimicrobial activity broader than currently recommended standard regimens in all or in specifically defined high-risk patients. Along these lines, the Society of Thoracic Surgeons has recommended mupirocin as a routine topical prophylactic measure and vancomycin as an adjuvant agent to cephalosporins in patients at high risk for MRSA infection.[14] A recently published decision analysis model suggests that, given current levels of MRSA prevalence, routine use of glycopeptides in patients undergoing CABG would be more effective and cost-saving compared with standard regimens.[27] However, several cautionary factors stand as barriers to recommending widespread use of broader-spectrum regimens.[28]

The need to minimize SSI risk and cost must be weighed against the potential unintended consequences of expanding the spectrum of AMP regimens, most notably an increase in selective antimicrobial pressure that could contribute to the expansion of antimicrobial resistance. The relative increase in overall antimicrobial use that would result from routine use of broader-spectrum regimens for these procedures has not been quantified, and the risk of unnecessary exposure could be minimized if their use were limited to high-risk

TABLE 4. Predicted Susceptibility of Surgical Site Infection Isolates to Antimicrobial Prophylaxis Regimens, National Healthcare Safety Network Surveillance System, 2006–2009

	Susceptible isolates		
Antimicrobial prophylaxis regimen	CABG (n = 3,318)	Arthroplasty (n = 3,259)	Total (n = 6,577)
Standard	1,414 (43)	1,585 (49)	2,999 (46)
Cefazolin	1,202 (36)	1,465 (45)	2,667 (41)
Cefuroxime	1,408 (42)	1,577 (48)	2,985 (45)
β-lactam allergy	3,164 (95)	3,198 (98)	6,362 (97)
Vancomycin	2,029 (61)	2,551 (78)	4,580 (70)
Clindamycin	1,362 (41)	1,707 (52)	3,069 (47)
Vancomycin + aminoglycoside	3,126 (94)	3,159 (97)	6,286 (96)
Clindamycin + aminoglycoside	3,092 (93)	3,132 (96)	6,224 (95)
Extended spectrum	3,164 (95)	3,178 (98)	6,342 (96)
Cefazolin + vancomycin	2,499 (75)	2,807 (86)	5,306 (81)
Cefuroxime + vancomycin	2,709 (82)	2,923 (90)	5,631 (86)
Cefazolin + aminoglycoside	3,078 (93)	3,101 (95)	6,178 (94)
Cefuroxime + aminoglycoside	3,087 (93)	3,111 (95)	6,198 (94)
Cefazolin + aminoglycoside + vancomycin	3,154 (95)	3,167 (97)	6,322 (96)
Cefuroxime + aminoglycoside + vancomycin	3,163 (95)	3,178 (98)	6,342 (96)

NOTE. Data are no. (% predicted susceptibility). CABG, coronary artery bypass graft.

patients. However, data to guide and validate the effectiveness of targeted antimicrobial strategies are lacking.

Another concern is the lack of definitive evidence that SSI rates will be effectively reduced by modifying currently recommended systemic regimens.[28-30] A meta-analysis of 7 randomized trials comparing SSI rates among cardiac surgery patients who received glycopeptide or β-lactam regimens found no statistically significant difference in the overall occurrence of SSIs at 30 days, although in a subanalysis glycopeptides were superior in preventing methicillin-resistant gram-positive SSIs.[31] For cardiac surgery, the findings did not support substituting standard prophylaxis with β-lactam agents in favor of glycopeptides. Results are difficult to interpret, however, as the meta-analysis included studies performed before 2000; the results may no longer be valid given changes in practices regarding AMP timing and an increase in the prevalence of MRSA among cardiac SSIs.[17,32,33] In addition, the studies examined glycopeptides as a replacement for, rather than as an adjunct to, β-lactam regimens. Our observation that a substantial proportion of SSIs are caused by either gram-negative pathogens or methicillin-susceptible staphylococci argues against the rationale for substituting glycopeptides as a replacement for β-lactam regimens given their lack of gram-negative coverage, their relatively inferior bactericidal activity against methicillin-susceptible staphylococci, and potential disadvantage in fatty tissue and sternal bone penetration.[31,34-36] Additional questions about the effectiveness of broadening the spectrum of AMP are raised by epidemiologic evidence suggesting that resistant pathogens may in some instances gain access to the surgical site postoperatively, when the effect of AMP might be minimal.[37]

Other infection control strategies may be effective in addressing the problem of standard AMP-resistant SSIs, as either an alternative or an adjunct to use of broader-spectrum AMP regimens. In this study, MSSA (28%) was the most common pathogen in CABG and primary arthroplasty complex SSIs, followed by MRSA (18%). Preoperative screening for *S. aureus* carriage is commonly being used to guide the use of perioperative decolonization strategies or to modify systemic AMP regimens.[38] If this strategy effectively reduces the incidence of *S. aureus* SSIs, it could serve as an adjunct to standard AMP, help avoid unnecessary use of broader-spectrum regimens, and bridge the gap in standard regimen coverage. However, this strategy would not fully address SSIs caused by other pathogens resistant to standard AMP regimens. Supplementary infection control practices, such as the routine use of alcohol-based surgical skin preparations and emerging medical technologies like *S. aureus* vaccines, may help address the issue, but either their impact is unknown or they are currently unavailable.[39,40]

The strength of our study lies in that it incorporates data from 2 large national data sets. However, our study was limited by the inability to link AMP regimen use with patient- or facility-specific SSI pathogen distribution data. Without patient-level data linkage, we could not determine whether individual patients with an infection received an AMP regimen that was active against their specific pathogen (ie, confirming whether the infection represented an AMP breakthrough). Given the high prevalence of adherence to standard AMP recommendations and the lack of reason to suspect that patients with infections caused by resistant pathogens were more likely to have received a nonstandard regimen, it seems likely that a large proportion of such patients received a regimen inactive against their SSI pathogen. Our inability to link facility-level data resulted in the inclusion of AMP regimens from facilities not reporting to NHSN. It seems unlikely that

TABLE 5. Research Questions to Inform Optimization of Cardiac and Arthroplasty Antimicrobial Prophylaxis Recommendations

1. Would modifying currently recommended antimicrobial regimens effectively reduce SSI rates?
2. How much of a relative increase in overall antimicrobial use would result from implementing the routine use of broader-spectrum regimens?
3. Can the risk/benefit ratio of using broader-spectrum regimens be optimized through the use of algorithms that identify subsets of patients at highest risk of developing SSIs caused by pathogens resistant to standard antimicrobial regimens?
4. What is the role of postoperative exposure to resistant bacteria in SSI pathogenesis, and what implications does it have for SSI prevention?
5. Do in vitro susceptibility results predict in vivo SSI prevention across AMP regimens, and do they translate into improved clinical outcomes?

NOTE. SSI, surgical site infection.

antimicrobial use patterns vary systematically among facilities on the basis of their NHSN participation status. However, it is important to note that the group of facilities reporting to NHSN is not necessarily nationally representative, particularly during the study period (2006–2009). In addition, while 45% of pathogen susceptibilities used in this analysis were imputed or assigned an expected value, our findings did not change substantially when the analysis was restricted to isolates that included actual susceptibility test results (Table A1). Finally, we had no information on the use of topical regimens, such as nasal mupirocin or alcohol-based surgical scrubs.

In summary, our observations suggest the currently recommended and most commonly used AMP regimens for CABG and primary arthroplasty procedures have limitations in their predicted spectrum of antimicrobial activity against the most commonly reported complex SSI–related pathogens. The lack of clear evidence-based guidance places clinicians in a conundrum when facing the competing goals of preventing SSI caused by AMP-resistant pathogens and minimizing unnecessary use of extended-spectrum agents. Our study does not provide sufficient information to determine precisely how or whether AMP recommendations should be modified or refined, but it does suggest a critical need to clarify the ambiguity around the use of broader-spectrum regimens. Examples of specific research questions that would advance the field if answered are listed in Table 5.

Until stronger evidence is available to inform future guidelines, clinicians may benefit from evaluating not only the prevalence of resistant pathogens among SSIs but also the SSI rate or standardized infection ratio at the facility-, unit-, and/or surgeon-specific level to help guide the choice of AMP. Routine use of standard AMP may be reasonable if standardized infection ratios (SIRs)[18] for CABG and arthroplasty procedures using these regimens are favorable in comparison to other facilities in the United States. If the SIR is high despite optimized SSI prevention efforts and if AMP-resistant SSI pathogens are commonly isolated, then consideration of routine use of an expanded AMP regimen may be warranted.

ACKNOWLEDGMENTS

Financial support. This work was supported in part by the Centers for Medicare & Medicaid Services (4-1411-OK-0312 to D.W.B. and A.M.).

Potential conflicts of interest. D.W.B. reports that funds were paid to his institution by the Oklahoma Foundation for Medical Quality and by Telligen (consultant), Premier (healthcare quality lecture at a national meeting), and VHA, Inc. (video presentation on the Partnership for Patients). His institution received a venous thromboembolism surveillance grant (1U50DD000899-01) from the Centers for Disease Control and Prevention. All other authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

Address correspondence to Sandra I. Berríos-Torres, MD, 1600 Clifton Road NE, MS A-31, Atlanta, GA 30333 (zbn6@cdc.gov).

Presented in part: 49th Annual Meeting of the Infectious Diseases Society of America; Boston, Massachusetts; October 23, 2011.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. The contents of this publication do not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US government. The authors assume full responsibility for the accuracy and completeness of the ideas presented.

APPENDIX

TABLE A1. Summary of Combined Coronary Artery Bypass Graft (CABG) and Arthroplasty Complex Surgical Site Infection Isolates with Actual, Imputed, and Expected Susceptibilities to Standard Antimicrobial Prophylaxis Regimen (AMPR) for the Most Frequent Pathogen Groups, National Healthcare Safety Network, 2006–2009

Pathogen group[a]	AMPR	Isolates reported, no.	No. of isolates			Susceptibility of isolates		
			Actual[b]	Imputed[c]	Expected	Actual	Imputed	Expected
Staphylococcus aureus	Standard[d]	2,757	2,692 (98)	65 (2)	0 (0)	1,519 (56)	37 (56)	...
Coagulase-negative staphylococci	Standard	1,087	161 (15)	246 (23)	680 (63)	44 (27)	54 (22)	0 (0)
Enterococcus species	Standard	433	4 (1)	0 (0)	429 (99)	2 (50)	...	0 (0)
Pseudomonas aeruginosa	Standard	339	1 (0)	0 (0)	338 (100)	1 (100)	...	0 (0)
Escherichia coli	Standard	314	22 (7)	0 (0)	292 (93)	22 (100)	...	292 (100)
Streptococcus species	Standard	278	9 (3)	0 (0)	269 (97)	9 (100)	...	269 (100)
Enterobacter species	Standard	230	0 (0)	0 (0)	230 (100)	...	...	230 (100)
Proteus species	Standard	206	44 (21)	1 (0)	161 (78)	41 (93)	1 (88)	161 (100)
Klebsiella pneumoniae, *Klebsiella oxytoca*	Standard	197	13 (7)	0 (0)	184 (93)	13 (100)	...	184 (100)
Serratia species	Standard	184	16 (9)	0 (0)	168 (91)	0 (0)	...	0 (0)
Acinetobacter baumannii	Standard	52	0 (0)	0 (0)	52 (100)	...	...	0 (0)

NOTE. Data are no. (%).

[a] Pathogen groups are limited to the 11 most frequent bacterial pathogens (n = 6,077 isolates) for CABG + arthroplasty in the pathogen distribution shown in Table 2.

[b] Most of the actual results were based on oxacillin susceptibility testing.

[c] Values were imputed only for pathogen groups with at least 10 reported isolates and susceptibility testing for ≥20% isolates for a given AMPR for each procedure group.

[d] Standard AMPR is a summary variable representing susceptibility to a single-drug, standard AMPR (cefazolin or cefuroxime). In the case of differing susceptibilities, the AMPR with the highest susceptibility value between cefazolin and cefuroxime was used; if isolates were not tested for susceptibility to cefazolin or cefuroxime, oxacillin or methicillin susceptibility results were used if available.

REFERENCES

1. De Frances CJ, Lucas CA, Buie VC, Golosinskiy A. *2006 National Hospital Discharge Survey*. June 30 ed. Hyattsville, MD: National Center for Health Statistics, 2008.
2. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project net (H·CUPnet) website. 2011 *Nationwide Inpatient Sample (NIS)*. Published 2013. http://hcupnet.ahrq.gov/. Accessed June 27, 2013.
3. Abboud CS, Wey SB, Baltar VT. Risk factors for mediastinitis after cardiac surgery. *Ann Thorac Surg* 2004;77(2):676–683.
4. Sharma M, Fakih MG, Berriel-Cass D, Meisner S, Saravolatz L, Khatib R. Harvest surgical site infection following coronary artery bypass grafting: risk factors, microbiology, and outcomes. *Am J Infect Control* 2009;37(8):653–657.
5. Urquhart DM, Hanna FS, Brennan SL, et al. Incidence and risk factors for deep surgical site infection after primary total hip arthroplasty: a systematic review. *J Arthroplasty* 2010;25(8):1216–1222.
6. Kurtz SM, Ong KL, Lau E, Bozic KJ, Berry D, Parvizi J. Prosthetic joint infection risk after TKA in the medicare population. *Clin Orthop Relat Res* 2010;468(1):52–56.
7. Risnes I, Abdelnoor M, Almdahl SM, Svennevig JL. Mediastinitis after coronary artery bypass grafting risk factors and long-term survival. *Ann Thorac Surg* 2010;89(5):1502–1509.
8. Hollenbeak CS, Murphy DM, Koenig S, Woodward RS, Dunagan WC, Fraser VJ. The clinical and economic impact of deep chest surgical site infections following coronary artery bypass graft surgery. *Chest* 2000;118(2):397–402.
9. McGarry SA, Engemann JJ, Schmader K, Sexton DJ, Kaye KS. Surgical-site infection due to *Staphylococcus aureus* among elderly patients: mortality, duration of hospitalization, and cost. *Infect Control Hosp Epidemiol* 2004;25(6):461–467.
10. Kurtz SM, Lau E, Watson H, Schmier JK, Parvizi J. Economic burden of periprosthetic joint infection in the United States. *J Arthroplasty* 2012;27(suppl 8):61.e1–65.e1.
11. Hellmann M, Mehta SD, Bishai DM, Mears SC, Zenilman JM. The estimated magnitude and direct hospital costs of prosthetic joint infections in the United States, 1997 to 2004. *J Arthroplasty* 2010;25(5):766–771.
12. US Department of Health and Human Services. *HHS Action Plan to Prevent Healthcare Associated Infections: Appendix G*. http://www.hhs.gov/ash/initiatives/hai/actionplan/. Accessed March 5, 2012.
13. Medical Letter. Antimicrobial prophylaxis for surgery. *Treat Guidel Med Lett*. 2009;7(82):47–52.
14. Engelman R, Shahian D, Shemin R, et al. The Society of Thoracic Surgeons practice guideline series: antibiotic prophylaxis in cardiac surgery, part II: antibiotic choice. *Ann Thorac Surg* 2007;83(4):1569–1576.
15. American Academy of Orthopaedic Surgeons. *Information Statement: Recommendations for the Use of Intravenous Antibiotic Prophylaxis in Primary Total Joint Arthroplasty*. Published 2004. http://www6.aaos.org/news/PDFopen/PDFopen.cfm?page_url

=http://www.aaos.org/about/papers/advistmt/1027.asp. Accessed February 8, 2012.
16. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm* 2013;70(3):195–283.
17. Bratzler DW, Hunt DR. The surgical infection prevention and surgical care improvement projects: national initiatives to improve outcomes for patients having surgery. *Clin Infect Dis* 2006; 43(3):322–330.
18. Malpiedi PJ, Peterson KD, Soe MM, et al. *2011 National and State Healthcare-Associated Infection Standardized Infection Ratio Report.* Published 2013. http://www.cdc.gov/hai/pdfs/SIR/SIR-Report_02_07_2013.pdf. Accessed June 13, 2013.
19. Anderson DJ, Arduino JM, Reed SD, et al. Variation in the type and frequency of postoperative invasive *Staphylococcus aureus* infections according to type of surgical procedure. *Infect Control Hosp Epidemiol* 2010;31(7):701–709.
20. Centers for Disease Control and Prevention. *National Healthcare Safety Network: Surgical Site Infection (SSI) Event.* http://www.cdc.gov/nhsn/PDFs/pscManual/9pscSSIcurrent.pdf. Accessed February 8, 2012.
21. QualityNet. *Specifications Manual for National Hospital Inpatient Quality Measures.* Version 1.04a–3.0c. http://www.qualitynet.org/dcs/ContentServer?c=Page&pagename=QnetPublic%2FPage%2FQnetTier4&cid=1228695698425. Accessed June 15, 2012.
22. Mu Y, Edwards JR, Horan TC, Berrios-Torres SI, Fridkin SK. Improving risk-adjusted measures of surgical site infection for the national healthcare safety network. *Infect Control Hosp Epidemiol* 2011;32(10):970–986.
23. Bratzler DW, Houck PM; Surgical Infection Prevention Guidelines Writers Group. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. *Clin Infect Dis* 2004;38(12):1706–1715.
24. Mandell GL, Bennet JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practices of Infectious Diseases.* 6th ed. Philadelphia: Elsevier Churchill Livingstone, 2005.
25. Anderson DJ, Kaye KS, Chen LF, et al. Clinical and financial outcomes due to methicillin resistant *Staphylococcus aureus* surgical site infection: a multi-center matched outcomes study. *PLoS ONE* 2009;4(12):e8305.
26. Kurtz SM, Ong KL, Schmier J, et al. Future clinical and economic impact of revision total hip and knee arthroplasty. *J Bone Joint Surg Am* 2007;89(suppl 3):144–151.
27. Miller LG, McKinnell JA, Vollmer ME, Spellberg B. Impact of methicillin-resistant *Staphylococcus aureus* prevalence among *S. aureus* isolates on surgical site infection risk after coronary artery bypass surgery. *Infect Control Hosp Epidemiol* 2011;32(4):342–350.
28. Chambers D, Worthy G, Myers L, et al. Glycopeptide vs. non-glycopeptide antibiotics for prophylaxis of surgical site infections: a systematic review. *Surg Infect (Larchmt)* 2010;11(5):455–462.
29. Sewick A, Makani A, Wu C, O'Donnell J, Baldwin KD, Lee GC. Does dual antibiotic prophylaxis better prevent surgical site infections in total joint arthroplasty? *Clin Orthop Relat Res* 2012; 470(10):2702–2707.
30. Crawford T, Rodvold KA, Solomkin JS. Vancomycin for surgical prophylaxis? *Clin Infect Dis* 2012;54(10):1474–1479.
31. Bolon MK, Morlote M, Weber SG, Koplan B, Carmeli Y, Wright SB. Glycopeptides are no more effective than β-lactam agents for prevention of surgical site infection after cardiac surgery: a meta-analysis. *Clin Infect Dis* 2004;38(10):1357–1363.
32. Bratzler DW, Houck PM, Richards C, et al. Use of antimicrobial prophylaxis for major surgery—baseline results from the National Surgical Infection Prevention Project. *Arch Surg* 2005; 140(2):174–182.
33. Rubin ZA, Edwards JR, Horan TC, Jernigan JA. Staphylococcal surgical site infection following coronary artery bypass and joint replacement surgery: National Nosocomial Infections Surveillance System, 1994–2003. In: *Program and Abstracts of the Society for Healthcare Epidemiology of America's 15th Annual Scientific Meeting.* Arlington, VA: Society for Healthcare Epidemiology of America, 2005. Abstract 42.
34. Finkelstein R, Rabino G, Mashiah T, et al. Vancomycin versus cefazolin prophylaxis for cardiac surgery in the setting of a high prevalence of methicillin-resistant staphylococcal infections. *J Thorac Cardiovasc Surg* 2002;123(2):326–332.
35. Kitzes-Cohen R, Farin D, Piva G, et al. Pharmacokinetics of vancomycin administered as prophylaxis before cardiac surgery. *Ther Drug Monit* 2000;22(6):661–667.
36. Martin C, Alaya M, Mallet MN, et al. Penetration of vancomycin into mediastinal and cardiac tissues in humans. *Antimicrob Agents Chemother* 1994;38(2):396–399.
37. Manian FA, Meyer PL, Setzer J, Senkel D. Surgical site infections associated with methicillin-resistant *Staphylococcus aureus*: do postoperative factors play a role? *Clin Infect Dis* 2003;36(7):863–868.
38. Diekema D, Johannsson B, Herwaldt L, et al. Current practice in *Staphylococcus aureus* screening and decolonization. *Infect Control Hosp Epidemiol* 2011;32(10):1042–1044.
39. Darouiche RO, Wall MJ Jr, Itani KM, et al. Chlorhexidine-alcohol versus povidone-iodine for surgical-site antisepsis. *N Engl J Med* 2010;362(1):18–26.
40. Lucero CA, Hageman J, Zell ER, et al. Evaluating the potential public health impact of a *Staphylococcus aureus* vaccine through use of population-based surveillance for invasive methicillin-resistant *S. aureus* disease in the United States. *Vaccine* 2009; 27(37):5061–5068.