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Impact of Methicillin-Resistant *Staphylococcus aureus* Prevalence among *S. aureus* Isolates on Surgical Site Infection Risk after Coronary Artery Bypass Surgery

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Abstract

OBJECTIVE—Cephalosporins are recommended for antibiotic prophylaxis to prevent cardiothoracic surgical site infections (SSIs) except in patients with β -lactam allergy or in settings with a “high” prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) among *S. aureus* isolates (hereafter, “MRSA prevalence”); however, “high” remains undefined. We sought to identify the MRSA prevalence at which glycopeptide prophylaxis would minimize SSIs relative to β -lactam prophylaxis.

METHODS—We developed a decision analysis model to estimate SSI likelihood when either glycopeptides or β -lactams were used for prophylaxis in cardiothoracic surgery. Event probabilities were derived from a systematic literature review. A similar cost-minimization model was also developed.

RESULTS—At 0% MRSA prevalence, SSI probability was 3.64% with glycopeptide prophylaxis and 3.49% with β -lactam prophylaxis. At MRSA prevalences of 10%, 20%, 30%, or 40%, SSI probabilities with glycopeptide prophylaxis did not change, but they were 3.98%, 4.48%, 4.97%, and 5.47% with β -lactam prophylaxis. The threshold of MRSA prevalence at which glycopeptide prophylaxis minimized SSI probability and cost was 3%. In sensitivity analyses, variations in most model estimates only modestly affected the threshold.

CONCLUSION—Glycopeptide prophylaxis minimizes the risk of SSIs and cost when MRSA prevalence exceeds 3%. At very low MRSA prevalence (between 3% and 10%), the SSI minimization provided by glycopeptide prophylaxis is small and may be within the error of the model. Given the current MRSA prevalence in most community and healthcare settings, clinicians should consider routine prophylaxis with vancomycin. Our findings may have important policy implications, as benefits in cardiothoracic surgery antibiotic prophylaxis must be weighed against the limitations of increased glycopeptide use.

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Surgical site infections (SSIs) are serious complications of operative procedures and are associated with significant morbidity and mortality. The annual cost of SSIs to the US healthcare system is more than \$1 billion.¹ Fortunately, perioperative antibiotic prophylaxis reduces the rate of SSI substantially.^{2,3}

For cardiothoracic surgery, US Centers for Disease Control and Prevention (CDC) guidelines recommend β -lactam antibiotics for perioperative prophylaxis unless the patient has a β -lactam allergy or the institution has a “high” prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) among *S. aureus* isolates (hereafter, “MRSA prevalence”).^{2,4} In those circumstances vancomycin, a glycopeptide antibiotic, is the recommended prophylactic agent. However, the guidelines acknowledge that there are no data defining what constitutes a “high” MRSA prevalence.

Despite their nearly universal activity against *S. aureus* strains, glycopeptide antibiotics are considered an alternative choice for prophylaxis for two important reasons. First, glycopeptide use may promote the emergence of vancomycin-nonsusceptible *S. aureus*.^{5,6} Second, vancomycin is inferior to β -lactams for the treatment of serious infections caused by methicillin-susceptible *S. aureus* (MSSA).⁷⁻⁹

Recently, there has been a global increase in MRSA prevalence, including a rise in community-associated infections among healthy persons without “traditional” risk factors for MRSA infection.¹⁰⁻¹⁴ There is now concern that β -lactam-based perioperative prophylaxis, which lacks activity against MRSA, may no longer be sufficient.^{15,16} On the basis of these considerations, we performed a decision analysis to determine the threshold of MRSA prevalence at which perioperative glycopeptide prophylaxis would minimize the incidence and cost of cardiothoracic SSIs, as compared to β -lactam prophylaxis.

METHODS

Our model focused on perioperative antibiotic prophylaxis for cardiothoracic surgery (rather than other surgical procedures) because (1) the risk of SSI with and without antibiotic prophylaxis is better defined for cardiothoracic surgery than for any other surgical procedure. Furthermore, (2) SSIs associated with these surgeries can be particularly severe, and (3) SSIs in this population are typically associated with skin flora and thus may have significance for other procedures that can be complicated by infection with a similar spectrum of pathogens (eg, orthopedic and vascular surgery).

To obtain data on SSI rates, we performed a systematic review of the literature, using the PubMed database from 1966 through April 22, 2010, and the search phrase “proph* AND surg* AND [antibio* OR antimicro* OR infect*] AND [van-comycin OR teicoplanin OR glycopeptide OR cef* OR ceph*].” Similar systematic searches were conducted using the Embase and Cochrane library databases. Identified articles were reviewed by 2 investigators (M.E.V. and L.G.M.) to select those that (1) involved cardiothoracic surgery, (2) were randomized, (3) had microbiological data, (4) were in English, and (5) provided a description of antibiotic delivery protocols. References from those articles were examined to identify additional investigations. Investigators from selected publications were contacted to obtain any additional data that were not published or were available in abstract form only.

Our systematic review of the PubMed database yielded a total of 2,472 articles. When articles published in languages other than English ($n = 535$) and those not involving human subjects ($n = 104$) were excluded, 1,833 articles remained to be reviewed. Of these, 9 investigations contained randomized, controlled data on perioperative antibiotic prophylaxis for cardiothoracic surgery: 5 trials compared β -lactam prophylaxis with glycopeptide prophylaxis,¹⁷⁻²¹ and 4 trials compared β -lactam prophylaxis with placebo

prophylaxis.^{3,22–24} Two investigations involved nonbypass cardiac surgery (both compared β -lactam prophylaxis with placebo prophylaxis),^{22,23} and data from these were not used for our analysis. Similar searches in Embase (5,384 articles) and Cochrane (1,091 articles) yielded no additional relevant articles.

Data from studies with similar design (eg, a β -lactam compared to a glycopeptide for SSI prophylaxis) were pooled and weighted by study size to determine the effect of prophylaxis. Because many studies did not describe the site of SSI, we defined SSI infections as any postoperative infection and combined data from both sternal and extremity sites (donor sites). From our selected articles, we also identified the proportion of SSIs infections that were caused by MRSA, MSSA, and non-*S. aureus* pathogens. These numbers were similarly pooled for studies with similar study designs and stratified by groups based on the antibiotic prophylaxis given (ie, β -lactam or glycopeptide).

Decision Tree Model

A decision tree (Figure 1) model was developed to simulate receipt of either glycopeptide prophylaxis (*upper tree arm*) or β -lactam prophylaxis (*lower tree arm*) by patients undergoing cardiothoracic surgery. The next branch point was likelihood that should an SSI occur, it would be caused by MRSA or MSSA. The final branch point was whether the patient got an SSI or not, stratified by MRSA, MSSA, or non-*S. aureus* pathogen. All probabilities in the model (*circular nodes*) were based on the systematic review of the literature described above. The decision tree was developed using TreeAge Data 4.0 software (TreeAge Software).

The base case model consisted of 2 idealized populations in which the *S. aureus* isolates encountered were always either MRSA or MSSA. The key variation in the model was thus the relative proportions of *S. aureus* isolates that were MRSA or MSSA, to simulate various real-world patient populations (MRSA prevalences of 0%, 5%, 10%, 20%, etc.).

Probabilities

Derivations of the 4 key probabilities for the tree (Figure 1) are summarized below.

Probability of SSI with glycopeptide prophylaxis when *S. aureus* isolate is MSSA—There were no randomized studies comparing glycopeptide prophylaxis with placebo prophylaxis. Because randomized studies have compared glycopeptide prophylaxis with β -lactam prophylaxis and β -lactam prophylaxis with placebo prophylaxis, we derived glycopeptide efficacy relative to placebo efficacy (Figure 1, *branch point F*) by multiplying previously derived efficacy proportions (ie, $[(\text{glycopeptide}/\beta\text{-lactam})^{\text{MSSA}} \times (\beta\text{-lactam}/\text{placebo})^{\text{MSSA}}] = (\text{glycopeptide}/\text{placebo})^{\text{MSSA}}$).

Probability of SSI with glycopeptide prophylaxis when *S. aureus* isolate is MRSA—The probability of having an SSI when glycopeptide prophylaxis was used and the patient was in contact with MRSA as the sole type of *S. aureus* (Figure 1, *branch point G*), was assumed to be the same as the probability of having an SSI if the patient encountered MSSA (Table 1, probability *F*), as it was assumed that glycopeptide prophylaxis worked equally well against MRSA and MSSA.

Probability of SSI with β -lactam prophylaxis when *S. aureus* isolate is MSSA—The probability of having an SSI when a patient received β -lactam antibiotic and was in contact with MSSA as a potential pathogen (Figure 1, *branch point I*) was the product of (1) the probability of SSI with placebo prophylaxis (Table 1, variable *B*) and (2) the ratio of the probability of SSI with β -lactam prophylaxis to that with placebo prophylaxis in presence of

MSSA (Table 1, variable *P*). Both of these probabilities were derived from systematic reviews of the literature.

Probability of SSI with β -lactam prophylaxis when *S. aureus* isolate is MRSA

—There are minimal data available that evaluate the efficacy of β -lactam antibiotics in preventing or treating infections caused by MRSA. Therefore, for our model the probability of developing an SSI when a patient received β -lactam prophylaxis and all *S. aureus* isolates were MRSA (Figure 1, *branch point H*) was estimated to be the sum of (1) the probability of SSI caused by non-*S. aureus* organisms (Table 1, variable *N*) and (2) the probability of SSI caused by *S. aureus* (Table 1, variable *L*). The latter term (ie, the probability of *S. aureus* infection with β -lactam prophylaxis in which all *S. aureus* isolates were MRSA) was the product of (1) the probability of SSI caused by *S. aureus* with glycopeptide prophylaxis when *S. aureus* isolates are MRSA (Table 1, variable *J*) and (2) the ratio of MRSA SSI rate with β -lactam prophylaxis to that with glycopeptide prophylaxis (Table 1, variable *Q*); this ratio was derived from a clinical trial that had a significant incidence of MRSA SSIs.¹⁹

Sensitivity Analyses

All probabilities in the model could be derived from 7 “primary probabilities,” which were derived from the systematic review of the literature (Table 1, variables *B*, *C*, and *M–R*). For each of these probabilities, we performed 2-way sensitivity analyses that compared the key probability in our model (the proportion of *S. aureus* that are MRSA; Table 1, variable *A*) with each of the primary probabilities. The ranges of the primary probabilities used were the lowest and highest estimates in the systematic review of the literature. For the variable with only a single reference in the literature, a wide range of probabilities was used (50%–300% of the value in the literature).

Cost-Minimization Model

Our cost-minimization model was the same as that described in Figure 1, except that the outcomes were costs rather than SSIs. The model took a program perspective for determining costs, in that we used payor reimbursement rates as an estimate for actual costs to the healthcare system.^{26,27} Specifically, we used the average Center for Medicare and Medicaid Services (CMS) reimbursement rates for 2010 Medicare Severity-Diagnosis Related Groups (MS-DRGs) 216–221 and 231–236 to estimate the cost of cardiothoracic surgical procedures without SSI. We used the mean of these MS-DRG reimbursements because cardiothoracic surgery procedures are heterogeneous and consist of various surgeries within these codes. The mean reimbursement for cardiovascular surgery based on these DRGs was \$31,286 (range \$18,870–\$53,259).²⁸

The cost of an SSI was estimated on the basis of 2010 MS-DRGs 856–858 (postoperative or posttraumatic infections). The mean reimbursement rate for these DRGs was \$14,487 (range \$7,062–\$25,723).²⁸ In addition, MRSA infections that complicate cardiothoracic surgery are associated with an increase in rates of overall mortality, mediastinitis-related death, and treatment failure, as compared with MSSA mediastinitis.²⁹ We therefore used a multiplier of 1.19 for additional costs of MRSA SSI, as the literature suggests that deep or organ/space MRSA infections cost 19% more than MSSA infections.³⁰

One-way sensitivity analysis was performed to determine the threshold of MRSA prevalence among *S. aureus* in which glycopeptide prophylaxis is cost minimizing compared to β -lactam prophylaxis. Two-way sensitivity analyses for the cost model included analyses identical to those described above for the surgical infection model. In addition, we performed 2-way sensitivity analyses for the 3 costs used in the model. The range for the 2-

way sensitivity analyses of cost was 50%–200% of the DRG cost. A range of 50%–200% of the increase in cost for MRSA infection was also used (Table 2).

RESULTS

In our model, the probability of developing an SSI when 0% of *S. aureus* isolates were MRSA was 3.64% with glycopeptide prophylaxis and 3.49% with β -lactam prophylaxis. Our key 1-way sensitivity analysis demonstrated that when the proportion of MRSA exceeds 3%, glycopeptide prophylaxis would minimize the rate of SSI, compared to β -lactam prophylaxis. (Figure 2). The difference in the probabilities of SSI infection between β -lactam and glycopeptide prophylaxis at relatively low MRSA prevalence (between 3% and 10% of isolates) was modest. When the proportion of MRSA increased to 10%, 20%, 30%, and 40% of isolates, mean rates of SSI with β -lactam prophylaxis were 3.98%, 4.48%, 4.97%, and 5.47%; however, mean rates of SSI with glycopeptide prophylaxis remained constant at 3.64%. (Table 3).

Two-way sensitivity analyses revealed that the 3% prevalence threshold did not differ by more than 2% (absolute value) when 5 of the 7 probabilities were varied (Figure 3). The 2 probabilities that affected the threshold by more than 2% were the ratio of the rate of MRSA SSI with β -lactam prophylaxis to that with placebo prophylaxis (Figure 3, variable *P*) and the ratio of rate of SSI with β -lactam prophylaxis to that with glycopeptide prophylaxis (Figure 3, variable *R*). When the ratio of the rate of MRSA SSI with β -lactam prophylaxis to that with placebo prophylaxis (variable *P*) was examined at the extreme ranges of the sensitivity analysis, the threshold for causing excess SSIs with β -lactam prophylaxis ranged from 0% to 8% MRSA prevalence. When the ratio of the rate of SSI with β -lactam prophylaxis to that with glycopeptide prophylaxis (variable *R*) was increased to 2.21, the threshold for causing excess SSIs climbed to approximately 20% MRSA prevalence (Figure 3). However, this ratio (valued at 1.043) is based on a large meta-analysis and is probably the most robust value in the model.³¹

Cost Analysis

At an MRSA prevalence of 0%, the mean estimated costs of cardiothoracic surgery were \$31,632 and \$31,813 with β -lactam and glycopeptide prophylaxis, respectively. At 10% MRSA prevalence, these costs were \$32,023 and \$31,823, respectively. At 40% MRSA prevalence, the mean estimated costs of cardiothoracic surgery using β -lactam and glycopeptide prophylaxis were \$33,196 and \$31,853, respectively. The threshold at which glycopeptide prophylaxis was cost minimizing was 3%. Two-way sensitivity analyses of the 7 primary probabilities in the model showed results similar to those of the SSI outcome model: cost variables had minimal impact on the threshold, with cost extremes changing the threshold by less than 2% (absolute value).

DISCUSSION

S. aureus is the major cause of SSI in patients undergoing cardiothoracic procedures. Unfortunately, the global spread of MRSA strains, which are uniformly resistant to β -lactam antibiotics, may decrease the efficacy of perioperative prophylactic β -lactam antibiotics. Indeed, recent data from the National Nosocomial Infections Surveillance System demonstrated that 13%–15% of deep SSIs are caused by MRSA.³² We sought to define the threshold of MRSA prevalence at which glycopeptide antibiotics would become more effective than β -lactams in preventing SSIs in cardiothoracic procedures. Our model demonstrated this MRSA prevalence threshold to be 3% of *S. aureus* strains, for both prevention of infection and cost minimization.

Two predominant forces drove the model: (1) glycopeptides are significantly more effective than β -lactams at preventing MRSA infections, and (2) the superiority of β -lactams for preventing MSSA infections is modest, as supported by a recent meta-analysis.³¹ While the superiority of β -lactams in the presence of high bacterial inocula (such as endocarditis) is generally observed,^{7–9} this superiority to glycopeptides may be less pronounced for prophylactic use, presumably because SSIs after clean procedures, such as cardiothoracic surgery, can result from low bacterial inocula.^{33,34} Furthermore, several investigations confirm that β -lactams are ineffective in the treatment of MRSA infections.^{35,36} The net result is that a relatively low MRSA prevalence quickly tips the balance in favor of glycopeptides as the agent more likely to minimize SSIs.

Several important aspects of our results should be emphasized. First, although the 3% threshold was consistent for both the SSI incidence and cost-minimization models, the superiority of glycopeptides for reducing the incidence of SSIs in the face of low MRSA prevalence was modest (Table 3). Specifically, at 5% MRSA prevalence, the number needed to treat³⁷ with glycopeptides (compared to that for β -lactams) to prevent 1 additional infection would be 1,000. At 10%, 20%, and 40% MRSA prevalence, the numbers needed to treat with glycopeptide prophylaxis to prevent 1 SSI are 286, 118, and 54, respectively.

S. aureus isolates that cause SSIs typically derive from strains colonizing the patient's anterior nares.³⁸ Sources of nasally colonizing *S. aureus* are diverse; they may be acquired in the community or in a healthcare institution.³⁹ A population-based investigation performed by the CDC demonstrated that 2.6% of *S. aureus* isolates colonizing the nares are MRSA.⁴⁰ However, the CDC study was done in the early stages of the community-associated MRSA "epidemic." More recent investigations have shown that up to 34% of *S. aureus* isolates colonizing the nares are MRSA.^{41–43} Furthermore, patients undergoing cardiothoracic surgery have often had contact with the healthcare system or have comorbidities that place them at greater risk of MRSA colonization.^{39,40} These data lead us to believe that MRSA prevalence in the United States far exceeds the 3% threshold that we determined in our model.

A decision analysis exploring cefazolin and vancomycin prophylaxis for cardiothoracic surgery was published by Zanetti et al.⁴⁴ They also found that cefazolin minimized cost when MRSA caused no more than 3% of *S. aureus* infections. However, their investigation was performed prior to the rapid rise of community-acquired MRSA infections. The authors considered an MRSA prevalence of 3% to be an extreme of the plausible range. Our model estimates the added risk and increased cost of SSIs across a much broader and more contemporary range of MRSA prevalence (0%–40%). Therefore, our model, unlike the model of Zanetti et al.,⁴⁴ addresses the current epidemiology of the MRSA epidemic and may inform critical policy debates. In addition, our model incorporates recent clinical trial data¹⁹ that were published after the Zanetti et al.⁴⁴ investigation. Nevertheless, the consistency in findings between our investigation and theirs may enhance the validity of our findings.

Our model is limited by the nature of the underlying data from which probabilities were derived. For example, as most published studies fail to differentiate between superficial, deep, and organ/space infections, this differentiation could not be made in our study. Despite this limitation, our model appears robust. Specifically, sensitivity analysis revealed that only 2 key probabilities affected the threshold value for MRSA prevalence: the relative efficacy of β -lactam prophylaxis and placebo prophylaxis (variable *P*) and the relative efficacy of glycopeptide prophylaxis and β -lactam prophylaxis (*R*). The former had only a modest impact, and the latter is the focus of a recent meta-analysis and probably the most accurate estimate of the model.³¹ In addition, our model did not distinguish SSIs caused by pathogens

other than *S. aureus* (eg, gram-negative pathogens) and did not specify SSI site. Nevertheless, in sensitivity analyses, varying rates of non-*S. aureus* infection had little impact on the 3% threshold. Finally, our estimates of costs are derived from reimbursement rates of the CMS Inpatient Prospective Payment System for MS-DRGs. These reimbursements are fixed, irrespective of actual costs incurred by the hospital and/or healthcare provider.⁴⁵ Therefore, with respect to costs to the overall healthcare system, including both providers and payors, our cost estimates based on reimbursement rates are likely to be conservative. In any case, sensitivity analysis with cost extremes changed the threshold for increased expenditures with β -lactam prophylaxis by less than 2%.

Our model was not designed to predict how newer infection control methods (such as chlorhexidine bathing protocols, mupirocin use, and *S. aureus* vaccines) and emerging medical technologies^{44–49} could influence the threshold at which vancomycin prophylaxis would decrease SSIs. Furthermore, our model was not designed to explore the impact of preoperative nasal swab screening for MRSA carriers. Until these potential advances are more fully investigated and better quantified, it would be premature to examine their impact in our analysis. In addition, our model does not quantify limitations of glycopeptide prophylaxis, such as the inability to give it as bolus⁵⁰ and the impact of increased use on promoting antibiotic resistance. Given the dearth of new antibiotics in development,^{51–53} the latter limitation is a crucial potential harm of increased glycopeptide use.

In summary, we found that when at least 3% of *S. aureus* isolates are MRSA, use of glycopeptide prophylaxis minimizes SSIs, compared to use of β -lactam prophylaxis, among patients undergoing cardiothoracic surgery. At extremely low MRSA prevalence (3%–10%), the SSI minimization provided by glycopeptide prophylaxis is small and may be within the error of the model. At MRSA prevalences found most commonly worldwide (15%–60%), our findings suggest that clinicians should consider glycopeptides as a more effective and cost-saving alternative to β -lactams for prophylaxis. Our findings may further assist policy makers in revising guidelines for surgical antibiotic prophylaxis. The need to minimize the frequency of SSIs in the face of rising β -lactam resistance must be weighed against the potential harm of increased glycopeptide use.

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REFERENCES

1. Martone WJ, Nichols RL. Recognition, prevention, surveillance, and management of surgical site infections: introduction to the problem and symposium overview. *Clin Infect Dis.* 2001; 33 suppl 2:S67–S68. [PubMed: 11486301]
2. Bratzler DW, Houck PM. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. *Clin Infect Dis.* 2004; 38:1706–1715. [PubMed: 15227616]
3. Fong IW, Baker CB, McKee DC. The value of prophylactic antibiotics in aortic-coronary bypass operations: a double-blind randomized trial. *J Thorac Cardiovasc Surg.* 1979; 78:908–913. [PubMed: 388085]

4. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Hospital Infection Control Practices Advisory Committee. Guideline for prevention of surgical site infection, 1999. *Infect Control Hosp Epidemiol.* 1999; 20:250–280. [PubMed: 10219875]
5. Hiramatsu K. Vancomycin-resistant *Staphylococcus aureus*: a new model of antibiotic resistance. *Lancet Infect Dis.* 2001; 1:147–155. [PubMed: 11871491]
6. Fridkin SK, Hageman J, McDougal LK, et al. Epidemiological and microbiological characterization of infections caused by *Staphylococcus aureus* with reduced susceptibility to vancomycin, United States, 1997–2001. *Clin Infect Dis.* 2003; 36:429–439. [PubMed: 12567300]
7. Small PM, Chambers HF. Vancomycin for *Staphylococcus aureus* endocarditis in intravenous drug users. *Antimicrob Agents Chemother.* 1990; 34:1227–1231. [PubMed: 2393284]
8. Geraci JE, Wilson WR. Vancomycin therapy for infective endocarditis. *Rev Infect Dis.* 1981; 3 suppl:S250–S258. [PubMed: 7342289]
9. Gentry CA, Rodvold KA, Novak RM, Hershow RC, Naderer OJ. Retrospective evaluation of therapies for *Staphylococcus aureus* endocarditis. *Pharmacotherapy.* 1997; 17:990–997. [PubMed: 9324187]
10. Deresinski S. Methicillin-resistant *Staphylococcus aureus*: an evolutionary, epidemiologic, and therapeutic odyssey. *Clin Infect Dis.* 2005; 40:562–573. [PubMed: 15712079]
11. Kaplan SL, Hulten KG, Gonzalez BE, et al. Three-year surveillance of community-acquired *Staphylococcus aureus* infections in children. *Clin Infect Dis.* 2005; 40:1785–1791. [PubMed: 15909267]
12. Frazee BW, Lynn J, Charlebois ED, Lambert L, Lowery D, Perdreau-Remington F. High prevalence of methicillin-resistant *Staphylococcus aureus* in emergency department skin and soft tissue infections. *Ann Emerg Med.* 2005; 45:311–320. [PubMed: 15726056]
13. Miller LG, Perdreau-Remington F, Bayer AS, et al. Clinical and epidemiologic characteristics cannot distinguish community-associated methicillin-resistant *Staphylococcus aureus* infection from methicillin-susceptible *S. aureus* infection: a prospective investigation. *Clin Infect Dis.* 2007; 44:471–482. [PubMed: 17243048]
14. King MD, Humphrey BJ, Wang YF, Kourbatova EV, Ray SM, Blumberg HM. Emergence of community-acquired methicillin-resistant *Staphylococcus aureus* USA 300 clone as the predominant cause of skin and soft-tissue infections. *Ann Intern Med.* 2006; 144:309–317. [PubMed: 16520471]
15. Fowler VG Jr, Miro JM, Hoen B, et al. *Staphylococcus aureus* endocarditis: a consequence of medical progress. *JAMA.* 2005; 293:3012–3021. [PubMed: 15972563]
16. Fridkin SK, Hageman JC, Morrison M, et al. Methicillin-resistant *Staphylococcus aureus* disease in three communities. *N Engl J Med.* 2005; 352:1436–1444. [PubMed: 15814879]
17. Saginur R, Croteau D, Bergeron MG, the ESPRIT Group. Comparative efficacy of teicoplanin and cefazolin for cardiac operation prophylaxis in 3027 patients. *J Thorac Cardiovasc Surg.* 2000; 120:1120–1130. [PubMed: 11088036]
18. Salminen U-S, Viljanen TUT, Valtonen VV, Ikonen TEH, Sahlman AE, Harjula ALJ. Ceftriaxone versus vancomycin prophylaxis in cardiovascular surgery. *J Antimicrob Chemother.* 1999; 44:287–290. [PubMed: 10473238]
19. 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; 123:326–332. [PubMed: 11828293]
20. Maki DG, Bohn MJ, Stolz SM, Kroncke GM, Acher CW, Myerowitz PD. Comparative study of cefazolin, cefamandole, and vancomycin for surgical prophylaxis in cardiac and vascular operations. A double-blind randomized trial. *J Thorac Cardiovasc Surg.* 1992; 104:1423–1434. [PubMed: 1434726]
21. Vuorisalo S, Pokela R, Syrjala H. Comparison of vancomycin and cefuroxime for infection prophylaxis in coronary artery bypass surgery. *Infect Control Hosp Epidemiol.* 1998; 19:234–239. [PubMed: 9605271]
22. Fekety FR Jr, Cluff LE, Sabiston DC Jr, Seidl LG, Smith JW, Thoburn R. A study of antibiotic prophylaxis in cardiac surgery. *J Thorac Cardiovasc Surg.* 1969; 57:757–763. [PubMed: 5770455]

23. Goodman JS, Schaffner W, Collins HA, Battersby EJ, Koenig MG. Infection after cardiovascular surgery—clinical study including examination of antimicrobial prophylaxis. *N Engl J Med.* 1968; 278:117–123. [PubMed: 4965378]
24. Austin TW, Coles JC, Burnett R, Goldbach M. Aortocoronary bypass procedures and sternotomy infections: a study of anti-staphylococcal prophylaxis. *Can J Surg.* 1980; 23:483–485. [PubMed: 6969109]
25. Penketh AR, Wansbrough-Jones MH, Wright E, Imrie F, Pepper JR, Parker DJ. Antibiotic prophylaxis for coronary artery bypass graft surgery. *Lancet.* 1985; 325:1500. [PubMed: 2861421]
26. Petitti, DB. Meta-analysis, decision analysis, and cost-effectiveness analysis: methods for quantitative synthesis in medicine. New York: Oxford University Press; 1994.
27. Stone PW, Chapman RH, Sandberg EA, Liljas B, Neumann PJ. Measuring costs in cost-utility analyses: variations in the literature. *Int J Technol Assess Health Care.* 2000; 16:111–124. [PubMed: 10815358]
28. Schmidt, K.; Ramsdell, S. 26th ed.. Salt Lake City, UT: Ingenix; 2009. 2010 DRG expert.
29. Mekontso-Dessap A, Kirsch M, Brun-Buisson C, Loisanche D. Poststernotomy mediastinitis due to *Staphylococcus aureus*: comparison of methicillin-resistant and methicillin-susceptible cases. *Clin Infect Dis.* 2001; 32:877–883. [PubMed: 11247711]
30. Engemann JJ, Carmeli Y, Cosgrove SE, et al. Adverse clinical and economic outcomes attributable to methicillin resistance among patients with *Staphylococcus aureus* surgical site infection. *Clin Infect Dis.* 2003; 36:592–598. [PubMed: 12594640]
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; 38:1357–1363. [PubMed: 15156470]
32. Rubin, ZA.; Benoit, SR.; Edwards, JR.; Horan, TC.; Jernigan, JA. Microbiology of deep surgical infections following coronary bypass, National Nosocomial Infections Surveillance System, 1994–2003. Paper presented at: 43rd annual meeting of the Infectious Diseases Society of America; October 6–9, 2005; San Francisco. (abstract 1152)
33. Kaiser AB, Kernodle DS, Parker RA. Low-inoculum model of surgical wound infection. *J Infect Dis.* 1992; 166:393–399. [PubMed: 1634811]
34. Talbot, TR.; Kaiser, AB. Surgical and trauma-related infections. In: Mandell, GL.; Bennet, JE.; Dolin, R., editors. Principles and practice of infectious diseases. 6th ed.. New York: Churchill Livingstone; 2005. p. 3536
35. Kernodle DS, Kaiser AB. Comparative prophylactic efficacy of cefazolin and vancomycin in a guinea pig model of *Staphylococcus aureus* wound infection. *J Infect Dis.* 1993; 168:152–157. [PubMed: 8515103]
36. Kernodle DS, Kaiser AB. Efficacy of prophylaxis with β -lactams and β -lactam- β -lactamase inhibitor combinations against wound infection by methicillin-resistant and borderline-susceptible *Staphylococcus aureus* in a guinea pig model. *Antimicrob Agents Chemother.* 1993; 37:702–707. [PubMed: 8494364]
37. Chatellier G, Zapletal E, Lemaitre D, Menard J, Degoulet P. The number needed to treat: a clinically useful nomogram in its proper context. *BMJ.* 1996; 312:426–429. [PubMed: 8601116]
38. von Eiff C, Becker K, Machka K, et al. Nasal carriage as a source of *Staphylococcus aureus* bacteremia. *N Engl J Med.* 2001; 344:11–16. [PubMed: 11136954]
39. Kluytmans J, van Belkum A, Verbrugh H. Nasal carriage of *Staphylococcus aureus*: epidemiology, underlying mechanisms, and associated risks. *Clin Microbiol Rev.* 1997; 10:505–520. [PubMed: 9227864]
40. Graham PL III, Lin SX, Larson EL. A U.S. population-based survey of *Staphylococcus aureus* colonization. *Ann Intern Med.* 2006; 144:318–325. [PubMed: 16520472]
41. Creech CB II, Kernodle DS, Alsentzer A, Wilson C, Edwards KM. Increasing rates of nasal carriage of methicillin-resistant *Staphylococcus aureus* in healthy children. *Pediatr Infect Dis J.* 2005; 24:617–621. [PubMed: 15999003]
42. Hisata K, Kuwahara-Arai K, Yamanoto M, et al. Dissemination of methicillin-resistant staphylococci among healthy Japanese children. *J Clin Microbiol.* 2005; 43:3364–3372. [PubMed: 16000461]

43. Davis KA, Stewart JJ, Crouch HK, Florez CE, Hospenthal DR. Methicillin-resistant *Staphylococcus aureus* (MRSA) nares colonization at hospital admission and its effect on subsequent MRSA infection. *Clin Infect Dis*. 2004; 39:776–782. [PubMed: 15472807]
44. Zanetti G, Goldie SJ, Platt R. Clinical consequences and cost of limiting use of vancomycin for perioperative prophylaxis: example of coronary artery bypass surgery. *Emerg Infect Dis*. 2001; 7:820–827. [PubMed: 11747694]
45. Emanuel EJ, Fuchs VR. Who really pays for health care? the myth of “shared responsibility.”. *JAMA*. 2008; 299:1057–1059. [PubMed: 18319416]
46. Darouiche RO, Wall MJ Jr, Itani KMF, et al. Chlorhexidine-alcohol versus povidone-iodine for surgical-site antisepsis. *N Engl J Med*. 2010; 362:18–26. [PubMed: 20054046]
47. Lin L, Ibrahim AS, Xu X, et al. Th1–Th17 cells mediate protective adaptive immunity against *Staphylococcus aureus* and *Candida albicans* infection in mice. *PLoS Pathogens*. 2009; 5:e1000703.
48. Stranger-Jones YK, Bae T, Schneewind O. Vaccine assembly from surface proteins of *Staphylococcus aureus*. *Proc Natl Acad Sci USA*. 2006; 103:16942–16947. [PubMed: 17075065]
49. Kuklin NA, Clark DJ, Secore S, et al. A novel *Staphylococcus aureus* vaccine: iron surface determinant B induces rapid antibody responses in rhesus macaques and specific increased survival in a murine *S. aureus* sepsis model. *Infect Immun*. 2006; 74:2215–2223. [PubMed: 16552052]
50. Kachroo S, Dao T, Zabaneh F, et al. Tolerance of vancomycin for surgical prophylaxis in patients undergoing cardiac surgery and incidence of vancomycin-resistant *Enterococcus* colonization. *Ann Pharmacother*. 2006; 40:381–385. [PubMed: 16478809]
51. Spellberg B, Powers JH, Brass EP, Miller LG, Edwards JE Jr. Trends in antimicrobial drug development: implications for the future. *Clin Infect Dis*. 2004; 38:1279–1286. [PubMed: 15127341]
52. Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: no ESCAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis*. 2009; 48:1–12. [PubMed: 19035777]
53. Mossialos, E.; Morel, CM.; Edwards, S.; Berenson, J.; Gemmill-Toyama, M.; Brogan, D. [Accessed June 24, 2010] Policies and incentives for promoting innovation in antibiotic research. http://www.euro.who.int/__data/assets/pdf_file/0011/120143/E94241.pdf

FIGURE 1.

Decision tree simulating prophylaxis type (glycopeptide or a β -lactam), type of *Staphylococcus aureus* encountered (methicillin-resistant [MRSA] vs methicillin-susceptible [MSSA]), and risk of surgical site infection (SSI) for a patient undergoing cardiovascular surgery. The node denoted by a square represents a choice decision (by the treating physician or based on a policy decision). All other nodes, denoted by circles, represent probabilities of an event occurring (see “Methods” for details). Letters inside nodes correspond to the variable name of a probability of an event, as defined in Table 1.

FIGURE 2.

Sensitivity analysis of rate of surgical site infection comparing antibiotic prophylaxis: probability of surgical site infection when the proportion of *Staphylococcus aureus* that is methicillin-resistant (MRSA; X-axis) increases from 0% to 50%. The proportion of infections does not vary when a glycopeptide is used (*circles*), but with β -lactam use (*diamonds*), the rate of surgical site infection increases as the MRSA prevalence increases. The threshold above which a glycopeptide minimizes surgical site infections, relative to β -lactams (where the lines cross), is when 3% of *S. aureus* strains are MRSA.

FIGURE 3.

Two-way sensitivity analyses of the proportion of *Staphylococcus aureus* that are methicillin-resistant (MRSA; X-axis) and the 7 “primary probabilities” in our model. These primary probabilities were those derived from the literature. The probabilities are described on the Y-axis and are followed by a letter that corresponds to their designation in Table 1. β -lactam prophylaxis minimizes surgical site infections (SSIs) in the diagonally crosshatched areas, and glycopeptide prophylaxis minimizes SSIs in the remaining areas. These graphs demonstrate that most probabilities had little impact on the 3% threshold at which glycopeptide prophylaxis is preferred. The ranges used for the sensitivity analysis are dictated by our predefined methods. The probability of SSI with glycopeptide prophylaxis

relative to that with β -lactam prophylaxis when *S. aureus* are methicillin-susceptible (MSSA; Table 1, variable *R*) may have some impact on the final threshold value; for this ratio, a value of 1.043 was used in the model. See text for details.

TABLE 1
Probabilities Used in the Decision Tree Model and the Ranges of These Probabilities Tested in Two-Way Sensitivity Analyses

Variable	Description	Derivation	Value	Range tested	Reference(s)
<i>A</i>	Proportion of <i>Staphylococcus aureus</i> isolates that are MRSA	...	0.1	0.0–0.5	
<i>B</i>	Probability of SSI with placebo prophylaxis	...	0.31	0.21–0.54	3, 23–25
<i>C</i>	Proportion of SSIs caused by <i>S. aureus</i> with placebo prophylaxis	...	0.79	0.7–1.0	3, 24
<i>D</i>	Probability of SSI caused by <i>S. aureus</i> with placebo prophylaxis	$B \times C$	0.24	NA	
<i>E</i>	Proportion of SSIs caused by non- <i>S. aureus</i> pathogen with placebo prophylaxis	$1 - C$	0.21	NA	
<i>F</i>	Probability of SSI with glycopeptide prophylaxis when <i>S. aureus</i> isolates are MRSA	<i>G</i>	0.0363	NA	
<i>G</i>	Probability of SSI with glycopeptide prophylaxis when <i>S. aureus</i> isolates are MSSA	$I \times R$	0.0363	NA	
<i>H</i>	Probability of SSI with β-lactam prophylaxis when <i>S. aureus</i> isolates are MRSA	$N + L$	0.088	NA	
<i>I</i>	Probability of SSI with β-lactam prophylaxis when <i>S. aureus</i> isolates are MSSA	$B \times P$	0.0349	NA	
<i>J</i>	Probability of SSI caused by <i>S. aureus</i> with glycopeptide prophylaxis when <i>S. aureus</i> isolates are MRSA	<i>K</i>	0.022	NA	
<i>K</i>	Probability of SSI caused by <i>S. aureus</i> with glycopeptide prophylaxis when <i>S. aureus</i> isolates are MSSA	$M \times R$	0.022	NA	
<i>L</i>	Probability of SSI caused by <i>S. aureus</i> with β-lactam prophylaxis when <i>S. aureus</i> isolates are MRSA	$Q \times J$	0.079	NA	
<i>M</i>	Probability of SSI caused by <i>S. aureus</i> with β-lactam prophylaxis when <i>S. aureus</i> isolates are MSSA	...	0.021	0.0–0.05	17–21
<i>N</i>	Probability of SSI caused by non- <i>S. aureus</i> pathogen with β-lactam prophylaxis	$(B \times E)(1 - O)$	0.009	NA	
<i>O</i>	Proportion of non- <i>S. aureus</i> SSIs prevented by β-lactam prophylaxis	...	0.87	0.0–0.9	3, 24
<i>P</i>	Ratio of rate of SSI with β-lactam prophylaxis to that with placebo prophylaxis when <i>S. aureus</i> isolates are MSSA	...	0.11	0.05–0.20	17–21
<i>Q</i>	Ratio of rate of MRSA SSI with β-lactam prophylaxis to that with glycopeptide prophylaxis when <i>S. aureus</i> isolates are MRSA	...	3.6	1.8–9.8	19
<i>R</i>	Ratio of probability of SSI with glycopeptide prophylaxis to that with β-lactam prophylaxis when <i>S. aureus</i> isolates are MSSA	...	1.043	0.22–2.21	17–21

NOTE. This table denotes each probability used in the decision tree (Figure 1). Note that many of probabilities are algebraic derivatives of other probabilities. Therefore, only probabilities that are based on the literature were used in the sensitivity analyses. MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; NA, not applicable; SSI, surgical site infection.

TABLE 2**Costs Used in Cost-Minimization Model**

Variable	DRG codes	Value	Range tested	Reference
Cost of cardiothoracic surgery	216–221, 231–236	\$31,286	\$18,870–\$53,259	28
Cost of surgical site infection	856–858	\$14,487	\$7,062–\$25,723	28
Ratio of cost of MRSA SSI to cost of MSSA SSI	NA	1.19	0.50–2.00	30

NOTE. DRG, diagnosis-related group; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; NA, not applicable; SSI, surgical site infection.

Sensitivity Analysis of Probability of Surgical Site Infection after Cardiothoracic Surgery Compared to Proportion of *Staphylococcus aureus* That Are MRSA or MSSA

TABLE 3

	Proportions of MRSA/MSSA among <i>S. aureus</i>									
	0/100	1/99	2/98	3/97	5/95	10/90	20/80	30/70	40/60	
SSI probability with glycopeptide prophylaxis, %	3.64	3.64	3.64	3.64	3.64	3.64	3.64	3.64	3.64	3.64
SSI probability with β -lactam prophylaxis, %	3.49	3.54	3.59	3.64	3.74	3.98	4.48	4.97	5.47	

NOTE. The data reflect the changing probability of SSI for patients undergoing cardiothoracic surgery with either glycopeptide or β -lactam prophylaxis. As the prevalence of MRSA among *S. aureus* increases, the SSI rate increases when β -lactam prophylaxis is used. The probability of SSI is constant when glycopeptide prophylaxis is used, regardless of MRSA prevalence. However, at relatively modest prevalences of MRSA, the absolute difference between β -lactam and glycopeptide prophylaxis is modest. MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; SSI, surgical site infection.