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Vancomycin for Surgical Prophylaxis?

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The increasing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) has resulted in a reevaluation of the role of vancomycin for surgical prophylaxis. Two systematic reviews of randomized control studies have concluded that cephalosporins are as effective as vancomycin for the prevention of surgical site infections (SSIs). However, most of these studies were conducted more than 10 years ago and cannot be generalized to the current rates of MRSA. Several time-series analyses have recently evaluated the effectiveness of vancomycin for surgical prophylaxis in institutions with a high prevalence of MRSA. Decision analysis models have also been used to estimate thresholds of MRSA prevalence for which vancomycin would minimize the incidence and cost of SSIs. Combination therapy and the emergence of resistant pathogens following vancomycin prophylaxis are reviewed. Vancomycin is not recommended for routine use in surgical prophylaxis but may be considered as a component of a MRSA prevention bundle for SSIs in selective circumstances.

The prevention of surgical site infections (SSIs) remains a major focus of attention due to the increased risks of morbidity and mortality, and large economic costs [1, 2]. In the United States, SSIs are considered the second most common healthcare-associated infection and occur as a serious complication of an estimated 300 000–500 000 surgical procedures each year [3, 4]. Methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococci have become the primary pathogens associated with SSIs in cardiothoracic, vascular, orthopedic, and neurosurgical operations. MRSA SSIs have been associated with increased mortality, length of hospital stay, and costs compared with SSIs due to other organisms, including methicillin-susceptible *S. aureus* (MSSA) [5–7]. Community-acquired MRSA (CA-MRSA) strains have noticeably increased in the United States during the past decade and are becoming prevalent among MRSA strains in hospitals [8–10]. In some hospitals, CA-MRSA strains are now responsible for a significant proportion of SSIs [10, 11]. These concerns are very much focused on prosthetic joint insertion and any procedure involving sternotomy or insertion of vascular grafts and other devices because of the unique consequences of deep infections in these settings.

The appropriate use of perioperative antibiotic prophylaxis is a key intervention for preventing SSIs in clean and clean-contaminated surgery. However, the evolving epidemiology and increasing prevalence of MRSA are challenging current guidelines for antibiotic prophylaxis and the role of vancomycin in the United States. The purpose of this review is to summarize the available data regarding pharmacological properties and efficacy of vancomycin for surgical prophylaxis.

SURGICAL PROPHYLAXIS GUIDELINES AND PHARMACOLOGICAL PROPERTIES OF VANCOMYCIN

Vancomycin has been available clinically for more than 50 years and has demonstrated a steady increase in use with the resurgence of MRSA infections since the 1980s [12]. As early as the 1990s, the use of vancomycin in some United States hospitals had been equally divided among 3 indications: empiric therapy, treatment of culture-proven infections, and surgical prophylaxis [13]. First- or second-generation cephalosporins (eg, cefazolin, cefuroxime) are generally considered the preferred agents in patients receiving perioperative antibiotic

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prophylaxis for most surgical procedures [14–18]. Vancomycin has been commonly recommended as an alternative agent for patients with a life-threatening β-lactam allergy. Depending on the specific guideline and/or type of surgical patient (eg, cardiac), vancomycin has also been recommended as either a primary or as an adjuvant agent (combined with cefazolin or an aminoglycoside) for patients who are presumed or known to have *S. aureus* colonization, in institutions where a "high" prevalence of MRSA exists, and when a surgical procedure involves a prosthetic joint insertion, sternotomy or vascular graft insertion [14–17]. The recommended dose of vancomycin in these guidelines is a fixed dose of 1000–1500 mg or a weight-adjusted dose of 10–15 mg/kg.

The pharmacological properties of vancomycin are limited when compared with cephalosporins. In terms of microbiological and pharmacodynamics features, vancomycin has slower bactericidal activity, a narrow antimicrobial spectrum that does not include gram-negative pathogens, uncertainty regarding increasing minimum inhibitory concentration (MIC) values of *S. aureus*, gives poor clinical outcomes when used against vancomycin-intermediately susceptible *S. aureus* strains, and potentially serious adverse events [19, 20]. The area under the concentration-time curve (AUC) divided by the MIC (AUC/MIC) has been recommended as the pharmacokinetic-pharmacodynamic parameter that is most predictive of bacteriological and clinical efficacy. A target AUC/MIC value of ≥400 has been recommended, and higher doses of vancomycin have been suggested when MIC values for *S. aureus* are ≥1 μg/mL [21]. Whether these recommendations are applicable in determining the vancomycin dosage for surgical prophylaxis has not been studied.

Plasma pharmacokinetics of vancomycin are altered in several patient populations, including patients with renal impairment, and those who are morbidly obese, critically ill, or undergoing cardiopulmonary artery bypass surgery (Figure 1) [22, 23]. Protein binding of vancomycin is approximately 55% in healthy subjects and decreases in patients with lower albumin concentrations. Although vancomycin penetrates into most body tissues and fluids, drug concentrations at surgical sites demonstrate wide interpatient variability and are influenced by disease states and/or the degree of inflammation present. Skhirtladze et al [24] recently demonstrated that interstitial tissue concentrations were significantly lower ($P = .002$) in diabetic patients (median, 3.7 mg/L; range, 0.4–15.5 mg/L) compared with nondiabetic patients (median, 11.9 mg/L; range, 2.2–38.4 mg/L) following cardiac surgery. Payne et al [25] confirmed that the tissue penetration of vancomycin into fat samples was quite variable (range, 0.32–7.35 mg/kg) and significantly lower (median, 1.8 mg/kg) than tissue penetration that occurred in plasma (median, 11.0 mg/L) and vessel wall (median, 5.07 mg/kg) samples in patients undergoing vascular surgery. In both studies, vancomycin was administered as a loading dose followed by a continuous intravenous infusion until steady-state conditions were achieved. These multidose studies may not reflect tissue penetration commonly associated with single-dose administration of vancomycin for surgical prophylaxis in the United States.

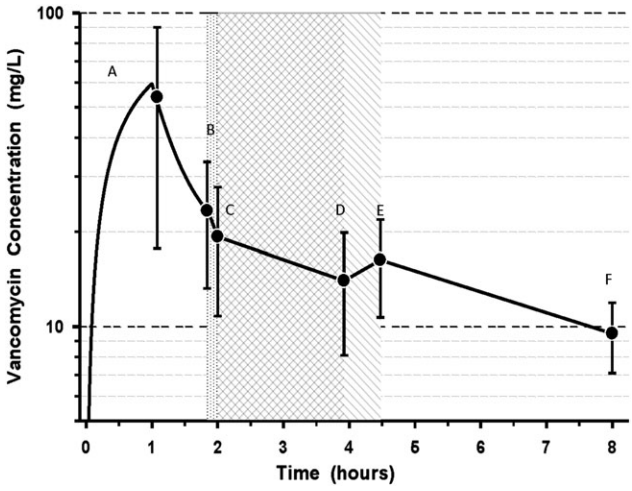

Figure 1. Serum vancomycin concentrations during cardiopulmonary bypass surgery. *A,* Administration of vancomycin (1-hour infusion). *B, C,* Hemodilution with cardioplegic solution. *C, D,* Clamping of the aorta and induction of hypothermia causes a decrease in the serum vancomycin concentration. *D, E,* Rewarming process causes an increase in the vancomycin concentration as the serum and tissue concentrations are reaching equilibrium. *E, F,* Elimination of vancomycin from the serum is resumed once the patient's condition is hemodynamically stable.

CLINICAL STUDIES INVESTIGATING VANCOMYCIN FOR SURGICAL PROPHYLAXIS

Two systematic reviews have been conducted to compare the rate of SSIs in patients receiving antibiotic prophylaxis with a glycopeptide (either vancomycin or teicoplanin) versus a β-lactam agent [26, 27]. Bolon et al [26] conducted a meta-analysis and reported outcomes in 5761 cardiothoracic patients from 7 randomized, controlled studies conducted between 1988 and 2002. β-lactam antibiotics and glycopeptides were demonstrated to be equally effective for the prevention of SSIs within 30 days of cardiac surgery (risk ratio [RR], 1.135; 95% confidence interval [CI], .906–1.422). Subset analyses suggested that β-lactam antibiotics were more effective than glycopeptides for the prevention of chest SSIs (RR, 1.468; 95% CI, 1.106–1.951) but glycopeptides were more effective than β-lactam antibiotics for the prevention of SSIs caused by methicillin-resistant gram-positive bacteria (RR, 0.543; 95% CI, .330–.895). Trends in favor of β-lactam agents included the prevention of deep-chest SSIs (RR, 1.327; 95% CI, .907–1.941) and SSIs caused by gram-positive

bacteria (RR, 1.363; 95% CI, .975–1.905). There was a trend toward glycopeptides being superior to β-lactam agents in the prevention of leg infections (RR, 0.765; 95% CI, .582–1.006).

Chambers et al [27] performed a systematic review of randomized, controlled studies that compared the clinical effectiveness of a glycopeptide versus a β-lactam agent for antibiotic prophylaxis in adult patients undergoing clean or clean-contaminated surgical procedures. A total of 14 studies were identified between 1990 and May 2008, including 5 studies used in the meta-analysis by Bolon et al [26]. Among the other 9 studies assessed, teicoplanin was the glycopeptide evaluated when patients were undergoing cardiac, vascular, or orthopedic surgery. The authors concluded that glycopeptides and β-lactam agents demonstrated similar effectiveness for the prevention of SSIs. Only 1 study demonstrated a statistically significant difference in infection rates between antibiotic prophylaxis with vancomycin (3.7%) and cefazolin or cefamandole (12.8%; RR, 0.29; 95% CI, .11–.81) [28]. In addition, there was insufficient evidence to determine what level of MRSA prevalence was required to justify the clinical and economical use of a glycopeptide instead of a β-lactam agent for surgical prophylaxis.

Both reviews provide insight to the randomized clinical studies comparing the use of glycopeptides versus β-lactam agents for surgical prophylaxis. However, most of these studies were performed more than a decade ago and do not account for the increasing prevalence and changing epidemiology of MRSA, including the emergence of CA-MRSA. In addition, these reviews were associated with several limitations, including heterogeneity among the evaluated studies (eg, differences in definitions and surveillance of SSIs), data pooling of 2 glycopeptide agents versus having an adequate number of vancomycin studies, and inapplicability of the data to specific patient types (eg, prosthetic valves or implants). Thus, it is important to review the recent literature and observational studies to determine what benefits, if any, occur when vancomycin is used for surgical prophylaxis.

Two randomized, prospective studies have evaluated antibiotic prophylaxis in hospitals with a ''high'' prevalence of MRSA [29, 30]. Tacconelli et al [29] randomized patients undergoing surgery for cerebrospinal shunt placement to receive either vancomycin or cefazolin. The prevalence of MRSA in 2001 for a 1700-bed university hospital was reported as 1 new case of MRSA infection per 100 hospital admissions. Shunt infections developed in 4% of patients (4 of 88) receiving vancomycin and 14% (12 of 88) receiving cefazolin (RR, 0.33; 95% CI, .11–.99; $P = .03$). The infecting pathogen was MRSA in 2 of 4 patients (50%) receiving vancomycin and 9 of 12 (75%) patients receiving cefazolin. Five of the infected patients receiving cefazolin died. Finkelstein et al randomized 855 patients undergoing cardiothoracic surgery to either vancomycin or cefazolin [30]. The prevalence of new cases of MRSA infection or colonization in the cardiac surgery ward was reported to be 3.0 and 2.6 per 100 admissions in 1995 and 1996, respectively. The overall rates of SSIs were similar in both groups (9.5% for vancomycin and 9.0% for cefazolin). A trend toward more methicillin-resistant gram-positive infections was observed in the cefazolin group (4.2% vs 2.0%; $P = .09$). In comparison, infections caused by methicillin-susceptible staphylococci were more frequently observed in patients receiving vancomycin (3.7% vs 1.3%; $P = .04$). Bloodstream infections were reported only in patients with chest wounds and occurred more frequently in patients with SSIs (20.9% for the vancomycin group; 23% for the cefazolin group) than in patients without SSIs (2.6% for the vancomycin group; 2.2% for the cefazolin group).

Three clinical studies have used pre- and postintervention periods to assess the effect of switching to vancomycin for surgical prophylaxis in patients undergoing cardiothoracic surgery [31–33]. Garey et al [31] demonstrated that a change from cefuroxime to vancomycin antibiotic prophylaxis decreased the average monthly SSI rate by 2.1 cases per 100 coronary artery bypass graft procedures when compared with patients undergoing cardiac valve replacement surgery. A lower incidence of infections caused by MRSA and coagulase-negative staphylococci was associated with the change in SSI rates during this 4-year study of 6465 patients. Spelman et al [32] similarly reported a significant ($P < .001$) decrease in SSI rates (10.5 to 4.9 infections per 100 surgical procedures) after switching the antibiotic prophylaxis regimen from cefazolin to vancomycin plus oral rifampin in 1114 coronary artery bypass graft procedures. The incidence of MRSA infections decreased from 65% during the 12-month preintervention period to 0% in the 12-month postintervention period.

A recent time-series analysis evaluated the use of vancomycin and a MRSA bundle program, an increasingly used targeted infection control strategy. Walsh et al [33] implemented a comprehensive MRSA bundle program in which vancomycin was added to the routine cefazolin prophylaxis regimen for patients who tested positive for nasal MRSA carriage. Other components of this program included (1) decolonization of all cardiothoracic staff who screened positive for nasal MRSA carriage, (2) application of nasal mupirocin ointment for 5 days in all patients starting 1 day before surgery, (3) application of topical mupirocin to exit sites after removal of chest and mediastinal tubes, and (4) rescreening of patients for MRSA colonization at the time of hospital discharge. This program resulted in a significant reduction in the SSI rate (2.1% to 0.8%; $P < .001$), as well as a 93% reduction in postoperative MRSA wound infections (from 32 infections per 2767 procedures during the 3-year preintervention period to 2 infections per 2496 procedures during the 3-year postintervention period). These 3 interrupted time-series analyses

provide evidence of the potential impact that a vancomycin antibiotic prophylaxis regimen may have in institutions with high prevalence of MRSA infections. In addition, a bundled approach to preventing MRSA SSIs may be more critical than just a single intervention.

Several investigators have evaluated the effects of combining vancomycin with other antibiotics for preventing MRSA SSIs [32–35]. As previously discussed, Spelman et al combined oral rifampin and vancomycin in their prophylaxis regimen, whereas Walsh et al added vancomycin to cefazolin in patients with preoperative MRSA colonization [32, 33]. Dhadwal et al [34] conducted a randomized, double-blind controlled study to compare the efficacy of a 48-hour, weight-based dosing of vancomycin plus gentamicin and rifampin versus a 24-hour cefuroxime regimen for antibiotic prophylaxis of sternal wound infections in a high-risk group of patients undergoing coronary artery bypass surgery. The infection rates significantly ($P = .004$) decreased from 23.6% (25 infections in 106 patients) in the cefuroxime comparator group to 8.4% (8 infections in 95 patients) in the combination vancomycin group. Patrick et al [35] conducted a randomized study to compare cefazolin versus combinations of cefazolin plus either vancomycin or daptomycin in 181 low-risk patients undergoing elective vascular surgery. Only 6 postoperative MRSA infections were reported in this study (2 in the cefazolin group, 4 in the vancomycin plus cefazolin group, 0 in the daptomycin plus cefazolin group), making the interpretation of the differences between antibiotic regimens very difficult.

The development of vancomycin resistance among gram-positive pathogens and the suspected weaker activity against MSSA have been major reasons why vancomycin has not been routinely recommended for surgical prophylaxis. Merrer et al [36] conducted a prospective cohort study to assess the emergence of vancomycin-resistant strains of enterococci (VRE) and *S. aureus* in 263 patients undergoing surgery for femoral neck fracture after receiving vancomycin versus cefazolin antibiotic prophylaxis. The prevalences of MRSA and VRE carriage at admission were 6.8% and 0.4%, respectively. At 7 days after surgery, the acquired rate of MRSA and VRE carriage was 2% (1 of 148 patients receiving cefazolin, 5 of 102 patients receiving vancomycin; $P = .04$) and 1% (3 patients receiving cefazolin; 0 patients receiving vancomycin), respectively. The development of SSIs occurred in 6 of 152 cefazolin-treated patients (4%; MSSA isolated in 3 infections) and 2 of 106 vancomycin-treated patients (2%; MSSA isolated in 1 infection).

IMPACT OF MRSA PREVALENCE ON SURGICAL ANTIBIOTIC PROPHYLAXIS

Vancomycin is recommended for surgical prophylaxis when an institution has a "high" prevalence of MRSA among *S. aureus* isolates. However, there is no consensus on what constitutes a "high" MRSA prevalence. Several recent studies have developed decision analysis models to determine the threshold of MRSA prevalence at which vancomycin would minimize the incidence and cost of SSIs [37–40]. For coronary artery bypass surgery, the authors of 2 studies have recommended a MRSA prevalence threshold of 3% among infections caused by *S. aureus* [37, 38]. Miller et al [37] suggested that lower rates of MRSA prevalence (eg, 3%–10%) were within the error of their model and that surgical prophylaxis with vancomycin would have a modest effect in reducing the incidence of SSIs. For vascular surgery, a MRSA prevalence of 50% was suggested before a β-lactam agent is replaced with vancomycin for surgical prophylaxis [39]. These authors also suggested that an aminoglycoside should be added to the prophylactic regimen once the prevalence of MRSA reaches 10%, which is in agreement with the recent guidelines from the British Society of Antimicrobial Chemotherapy.

Elliot et al [40] developed an economic model to explore the cost-effectiveness of vancomycin and/or a cephalosporin for surgical prophylaxis in patients undergoing hip arthroplasty. These authors recommended that a cephalosporin be considered for prophylaxis when the rate of MRSA SSIs is 0% or when the rate of MRSA infection is ≥0.20% and the rate of non-MRSA infections ≤0.1%. Vancomycin was recommended when the rate of MRSA SSIs is ≤0.15% and the rate of non-MRSA SSIs ≥0.1% or when the rate of MRSA infections is ≤0.20% and the rate of other infections ≥0.2%. Combination therapy (eg, vancomycin plus a cephalosporin) was recommended when the rate of MRSA SSIs is ≥0.25% and the rate of non-MRSA SSIs ≥0.2%.

Each of these decision analysis studies had their limitations and provided only indicative economic evidence about the threshold of MRSA prevalence. The lack of available evidence from randomized controlled studies with a high prevalence of MRSA infections was one of the most important factors that influenced modeling assumptions, the inclusion of variables, and decision-making conclusions [41]. Whether data from other types of study designs (eg, interrupted time series) could provide useful information to be incorporated into these models remains to be determined.

CONCLUSIONS

Vancomycin has been commonly recommended as either a primary or adjuvant agent for perioperative prophylaxis in patients who are presumed or known to have *Staphylococcus* colonization, in institutions where a "high" prevalence of MRSA exists, and when a surgical procedure involves a prosthetic joint insertion, sternotomy or vascular graft insertion [2,14–18]. Several systematic analyses concluded that no clear

benefit in clinical effectiveness or cost-effectiveness has been demonstrated for the routine prophylaxis use of vancomycin compared with cephalosporins. However, most of these studies were conducted before the increasing prevalence of MRSA and do not reflect current clinical situations. Although 2 randomized studies have been conducted in institutions with a high MRSA prevalence, the differences in SSI rates and outcomes were conflicting [29, 30].

Similarly, several studies have employed decision analysis models to calculate MRSA prevalence thresholds for which vancomycin would have clinical benefit and be more cost-effective than cephalosporins for surgical prophylaxis [37–40]. Although these studies provide compelling arguments for when vancomycin is more effective, they all suffer from one common limitation: the lack of randomized, controlled studies to provide baseline probabilities for the clinical effectiveness of each treatment at different rates of MRSA prevalence. Implementation of a MRSA prevention bundle may significantly reduce MRSA SSIs [42, 43]. However, it is likely that no single MRSA-specific intervention (eg, adding or switching to vancomycin) can optimally prevent SSIs. The time-series analyses provide convincing data on the clinical effectiveness of vancomycin in preventing SSIs when MRSA prevalence is high [31–33]. Although the study by Walsh et al provides strong evidence for the reduction of MRSA SSIs, vancomycin (in combination with cefazolin) was used only selectively in cardiothoracic patients who screened positive for MRSA colonization. Whether vancomycin is a critical component in "bundled approaches" for perioperative prophylaxis has yet to be decided for most types of surgery. Further research is desperately needed to determine which components of a MRSA prevention bundle are essential in successfully preventing MRSA SSIs [42].

Finally, the dose and administration times of vancomycin need to be properly selected. Although most published studies have used a fixed dose of 1000 mg ("one size fits all"), recent recommendations have suggested weight-adjusted doses of 15–20 mg/kg (based on actual body weight) [2, 44]. These recommendations have been extrapolated from treatment guidelines in the United States generated to overcome the large variability in tissue penetration [21–25], and preliminary evidence suggests that a 20 mg/kg dose of vancomycin was associated with a lower rate of sternal wounds in patients undergoing cardiothoracic surgery [44]. Vancomycin should be infused at a rate of 10–15 mg/minute (≥1 h/1000 mg) to minimize infusion-related adverse events (eg, red man syndrome, hypotension). The larger doses required in obese patients will require infusion times of 2–3 hours [2]. It is recommended that the infusion be started 60–120 minutes before the first incision and be continued into the operative period if necessary.

Note

Potential conflicts of interest. All authors: No reported conflicts.

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