Research Paper ■

Reducing Vancomycin Use Utilizing a Computer Guideline:

Results of a Randomized Controlled Trial

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Abstract **Background:** Vancomycin-resistant enterococci represent an increasingly important cause of nosocomial infections. Minimizing vancomycin use represents a key strategy in preventing the spread of these infections.

Objective: To determine whether a structured ordering intervention using computerized physician order entry that requires use of a guideline could reduce intravenous vancomycin use.

Design: Randomized controlled trial assessing frequency and duration of vancomycin therapy by physicians.

Participants and Setting: Three hundred ninety-six physicians and 1,798 patients in a tertiary-care teaching hospital.

Intervention: Computer screen displaying, at the time of physician order entry, an adaptation of the Centers for Disease Control and Prevention guidelines for appropriate vancomycin use.

Main Outcome Measures: The frequency of initiation and renewal of vancomycin therapy as well the duration of therapy prescribed on a per prescriber basis.

Results: Compared with the control group, intervention physicians wrote 32 percent fewer orders (11.3 versus 16.7 orders per physician; $P = 0.04$) and had 28 percent fewer patients for whom they either initiated or renewed an order for vancomycin (7.4 versus 10.3 orders per physician; $P = 0.02$). In addition, the duration of vancomycin therapy attributable to physicians in the intervention group was 36 percent lower than the duration of therapy prescribed by control physicians (26.5 versus 41.2 days; $P = 0.05$). Analysis of pharmacy data confirmed a decrease in the overall hospital use of intravenous vancomycin during the study period.

Conclusion: Implementation of a computerized guideline using physician order entry decreased vancomycin use. Computerized guidelines represent a promising tool for changing prescribing practices.

■ **J Am Med Inform Assoc.** 1998;5:554–562.

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This work was supported by grant R01-HS08927 from the Agency for Health Care Policy and Research.

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Received for publication: 4/8/98; accepted for publication: 7/9/98.

Since the first report of their isolation in 1988,[1,2] vancomycin-resistant enterococci (VRE) have become a major health threat in hospitals throughout North America and Europe.[3,4] The Centers for Disease Control and Prevention reported that VRE already constituted 7.9 percent of national enterococcal isolates in 1993.[5] The emergence of VRE clearly represents a problem in itself, as no established antimicrobial therapy currently exists.[6] Even more alarming, however, is the possibility that vancomycin resistance will

emerge among staphylococci, the most common of nosocomial pathogens. Demonstration of the transfer of plasmid-mediated resistance to staphylococci has already occurred in the laboratory setting,[7] and isolation of intermediately resistant clinical strains has recently been described.[8,9]

Expert recommendations cite more prudent use of vancomycin as the key strategy in containing the problem of VRE.[10] Clinicians and researchers have considered different means of limiting inappropriate and excess antibiotic use at least since the 1970s, because of cost considerations as well as concern over the emergence of resistant organisms.[11,12] Strategies have included specialized ordering forms,[13] individualized feedback,[14] performance feedback,[15] and continuing education.[16] In the case of vancomycin in particular, restriction and monitoring of drug ordering by members of the pharmacy and infectious diseases departments have been tried.[4,17] However, these approaches have yielded mixed results and, even when successful, require continued resources of time and money to maintain.

A promising alternative approach to changing physicians' prescribing behavior is offered by physician computer order entry, in which orders are written online and decision support can be provided at the time the orders are written.[18,19] With such an approach, the guidelines for use of a particular drug can be displayed when the drug is ordered, and these guidelines are immediately available to all providers. We undertook a randomized controlled trial using the provider order-entry system at our hospital to display guidelines for the appropriate use of intravenous vancomycin. Our goal was to determine whether this intervention would reduce vancomycin ordering.

Methods

Study Site

Brigham and Women's Hospital (BWH) is a 720-bed university-affiliated hospital with approximately 35,000 admissions per year. In 1995, there were 78 new cases of VRE at the hospital, 49 of which were obtained from specimens collected for clinical indications; the rest were detected through surveillance cultures in response to index cases (unpublished data from Infection Control at BWH).

Physicians at BWH write orders using a computerized provider order-entry application, which has been described previously.[20] Interns and residents enter the vast majority of all patient orders, as only housestaff, along with fellows and a small number of attendings in surgery and obstetrics and gynecology, can write orders that do not require cosignature. The order-entry system accepts orders for all aspects of patient care, including laboratory and radiologic tests as well as all medication orders. This same computer system allows all providers (not just those writing orders) access to clinical data on patients, including laboratory results, reports from diagnostic studies, discharge summaries, and notes from ambulatory visits in most of the clinics associated with the hospital.

Design

The study was a randomized controlled trial comparing the use of vancomycin by physicians randomly assigned to the intervention group with the use of vancomycin by a control group of providers who had no exposure to the intervention. It was possible that physicians in the control group could learn of the intervention from physicians in the study group, but as discussed later, any such cross-over exposure would be expected to bias the study toward the null hypothesis. The study was approved by the hospital's institutional review board.

Nonphysicians who were authorized to enter orders that required eventual signing off by physicians were also randomized. These nonphysicians consisted mostly of nurses entering verbal orders from physicians, but also some pharmacists likewise entering verbal orders and a few physician assistants. In total, this group contributed only 10 percent of all vancomycin orders, and the vast majority of members of this group contributed only a single order for vancomycin. Thus, we excluded these data because of their small contribution to the overall vancomycin orders and because these users were generally not in a position to make independent prescribing decisions.

All users of the clinical computer system at BWH have a sequentially assigned internal identification number that remains unknown to them. Randomization was performed using the even or odd character of this number, which has no connection with any provider characteristics such as department affiliation, seniority, or level of training. Other studies conducted at BWH use this same method of randomization, but assignment to the experimental group does not consistently involve either the even or odd identification numbers.

Intervention

The intervention consisted of showing computerized guidelines for vancomycin ordering at the time of initial vancomycin ordering and after 72 hours of ther-

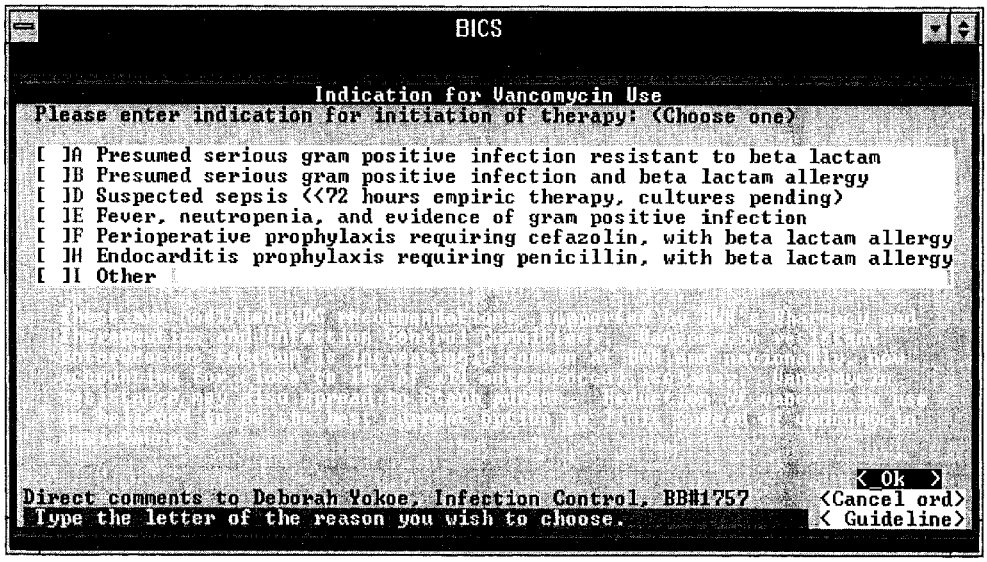

Figure 1 The intervention screen for initial vancomycin orders as it appeared to physicians in the intervention group during the study period.

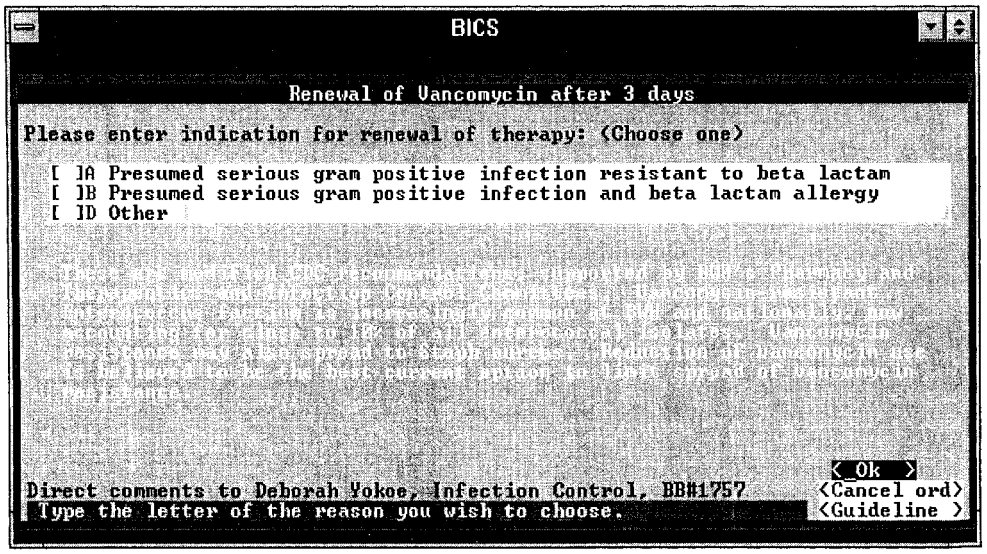

Figure 2 The computer screen for renewal of vancomycin orders as it appeared to physicians in the intervention group of the study.

apy. The initial screen presented (Figure 1) contained an adaptation of the indications for vancomycin use developed by the Centers for Disease Control[10] and approved by the BWH Pharmacy and Therapeutics Advisory Committee and Infection Control Committee. This screen appeared whenever a clinician in the intervention group initiated an order for intravenous vancomycin. Providers were required either to enter an indication or to abort the order. The "other" category required the user to enter free text describing their indication. Any response in the "other" category was accepted.

Previous work has shown that vancomycin is often prescribed for inappropriately long periods of time.[21] Thus, we also displayed a screen asking providers their indication for continuing vancomycin use after 72 hours of therapy. Physicians in the intervention group were presented with the guidelines screen shown in Figure 2, whereas the control physicians encountered only the usual computer prompt to renew or discontinue the order after 72 hours of therapy.

Outcomes

The primary outcomes of the study consisted of the number of vancomycin orders and duration of vancomycin therapy prescribed by providers in the intervention and control groups. The global utilization of vancomycin in the hospital constituted a secondary outcome for the study. Adjusting for monthly changes in the hospital census, we compared the number of

patients who received vancomycin and the amount of vancomycin dispensed before and after the intervention. One would expect any change in the vancomycin utilization suggested by this comparison to represent approximately half the true effect, since the pharmacy data make no distinction between the control and intervention groups. However, we hoped to provide some external corroboration that a real effect on vancomycin utilization had occurred, if the physician order entry data showed a positive impact of the intervention.

Data Sources

We recorded each vancomycin order in a computer log containing the service on which the patient received treatment, the department affiliation and study status of the ordering provider (intervention or control), as well as the indication selected for vancomycin use by providers exposed to the guidelines screens. To estimate the amount of vancomycin prescribed by each provider, we used the dates and times of the orders from this computer log and calculated the duration of vancomycin therapy attributable to each provider.

We obtained data from the pharmacy system on the monthly utilization of vancomycin in the hospital. These data contained the number of patients who received at least one dose of vancomycin as well as the amount (in units and grams) of vancomycin dispensed. We also obtained census information for the study and comparison periods in connection with the analysis of the pharmacy data.

Analysis

Results for the numbers of orders and ordering rates are reported as means with standard deviations as well as medians with 25- and 75-percent quartiles because of the non-normality of the results and the expectation that far outliers would have an important influence on the overall amount of vancomycin used. The primary univariate comparisons between the control and intervention groups were made using the Wilcoxon rank-sum statistic, since the data were not normally distributed. For the secondary outcomes of global vancomycin utilization before and after the intervention, we performed univariate comparisons as above but also used piecewise linear regression[22] to analyze the trend in monthly vancomycin utilization. With this technique, the effect of the intervention can be detected either by a change in the vertical intercept if the change is abrupt or by a change in the slope if providers learned gradually from the intervention.

Table 1 ■

Department Affiliations for Vancomycin Prescribers

Department	Control No. (%)	Intervention No. (%)	Total No. (%)
Medicine	97 (49)	98 (49)	195 (49)
Surgery	62 (31)	46 (23)	108 (27)
Orthopedics	14 (7)	19 (10)	33 (8)
Obstetrics/gynecology	13 (6)	21 (11)	34 (8)
Neurology	4 (2)	7 (4)	11 (3)
Emergency medicine	3 (2)	5 (2)	8 (2)
Anesthesia	5 (2)	2 (1)	7 (2)
Total	198	198	396

Table 2 ■

Numbers of Orders per Physician in the Intervention and Control Groups

Order Type	Control	Intervention	*P* Value (Wilcoxon)
Initiate (*n*)	1911	1345	—
Renew (*n*)	1392	888	—
Total orders (*n*)	3303	2233	—
Initiate orders per prescriber	9.6 ± 14.5 4.0 (1.0–12)*	6.8 ± 9.5 3.0 (1.0–9.0)+	0.03
Renewal orders per prescriber	7.0 ± 16.2 0.0 (0.0–5.0)*	4.5 ± 11.3 0.0 (0.0–3.0)*	0.16
Total orders per prescriber	16.7 ± 29.2 5.0 (1.0–15)*	11.3 ± 19.9 3.0 (1.0–11)*	0.04

* Numbers represent the mean with the standard deviation followed by the median with the 25–75% quartiles in parentheses.

Results

From June 20, 1996, through March 30, 1997, 396 physicians wrote 5,536 orders for vancomycin for 1,798 patients. The distribution of the physicians by department between the control and intervention groups was nearly balanced (Table 1). Since the use of vancomycin tends to cluster among patients on particular services and patients with lengthy hospitalizations, we checked the average length of stay for the patients of physicians in both groups as well as the services of the patients for whom they ordered vancomycin. There were no significant differences between the intervention and control group physicians with respect to the average length of stay of their patients or the services on which the patients received their care.

Comparison of the numbers of orders by type in the two groups (Table 2) showed that the number of initial orders per physician in the intervention group was 29 percent lower than the number of the control group (6.8 ± 9.5 compared with 9.6 ± 14.5 orders per physician; $P = 0.03$). Physicians in the intervention

Table 3 ■

Main Outcome Parameters for Prescribers of Vancomycin

Parameter	Control Group (n = 174)	Intervention Group (n = 171)	P Value (Wilcoxon)
Patients per physician	10.3 ± 15.1 4.0 (1.0–12)*	7.4 ± 11.4 3.0 (1.0–9.0)*	0.02
Vancomycin days per physician	41.2 ± 76.7 11 (3.3–44)*	26.5 ± 47.6 7.5 (2.8–32)*	0.05
Duration of therapy prescribed per course of therapy	2.0 ± 1.1 1.8 (1.4–2.4)*	1.8 ± 1.1 1.7 (1.2–2.2)*	0.05

*Numbers represent the mean with standard deviation followed by the median with the 25%–75% quartiles in parentheses.

group also wrote 36 percent fewer renewal orders compared with physicians in the control group (4.5 ± 11.3 compared with 7.0 ± 16.2 orders per physician; P = 0.16). We hypothesized that the renewal guidelines might have less impact on services on which long courses of vancomycin are common, specifically the hematology-oncology and bone marrow transplant services. However, analysis of the ordering data excluding patients from these services left the results for the renewal orders unchanged. Overall, though, the total number of orders for physicians in the intervention group was 32 percent lower than in the control group (11.3 ± 19.9 compared with 16.7 ± 29.2 orders per physician; P = 0.04).

The initiation and renewal of vancomycin therapy are not necessarily linked, as one physician might renew an order that another had initiated. Also, a physician might write multiple renewal orders on a single patient requiring a prolonged course of vancomycin. Thus, we also compared the total number of patients for whom each physician had written either an initiation or renewal order for vancomycin. As shown in Table 3, physicians in the intervention group prescribed vancomycin for 28 percent fewer patients than did control group physicians (7.4 ± 11.4 compared with 10.3 ± 15.1 patients; P = 0.02). When we compared the duration of vancomycin therapy ordered per physician (also shown in Table 3), we found that physicians in the intervention group prescribed vancomycin for 36 percent fewer days than physicians in the control group (26.5 ± 47.6 compared with 41.2 ± 76.7 days; P = 0.05). The number of days of vancomycin per course of treatment was also lower for the physicians in the intervention group, with a mean of 1.8 ± 1.1 days compared with 2.0 ± 1.1 for the control group (P = 0.05).

After the randomized trial began, the percentage of patients in the entire hospital who received vancomycin at least once during their hospitalization decreased by 15 percent compared with the months immediately prior to the study (P < 0.01; Table 4). The average amount of vancomycin in grams dispensed per month also decreased by 15 percent (P = 0.01; Table 4). However, the small decrease in the amount of vancomycin dispensed on a per patient basis was not statistically significant. To evaluate whether or not these reductions in the hospital-wide use of vancomycin could be attributed to the intervention, we used piecewise linear regression. The analysis of the percentage of hospitalized patients who received vancomycin at least once (Figure 3) shows that both the slope and vertical axis intercept changed significantly

Table 4 ■

Pharmacy Data on Hospital Use of Vancomycin during Study Period and Historical Control Period

	Prestudy Period*	Study Period*	P (Wilcoxon)
Hospital census†	20,879	21,069	—
No. (%) patients receiving vancomycin	2,715 (13.0)	2,341 (11.1)	0.0
Grams vancomycin dispensed	27,985	23,103	—
Grams vancomycin/census	1.3	1.1	0.01
Grams vancomycin/patients receiving vancomycin	10.3	9.9	0.4

*The prestudy period extended for the nine months from September 1, 1995, to May 31, 1996. In this table, the study was considered to include the nine months from July 1, 1996, to March 31, 1997. The month of June 1996 was excluded entirely as the intervention began during that month and there was no way to track the global pharmacy data for a fraction of a month.
†The term ''census'' refers to the number of patients admitted to the hospital in a given period, excluding obstetric admissions and newborns, since these patients have a very low association with vancomycin use.

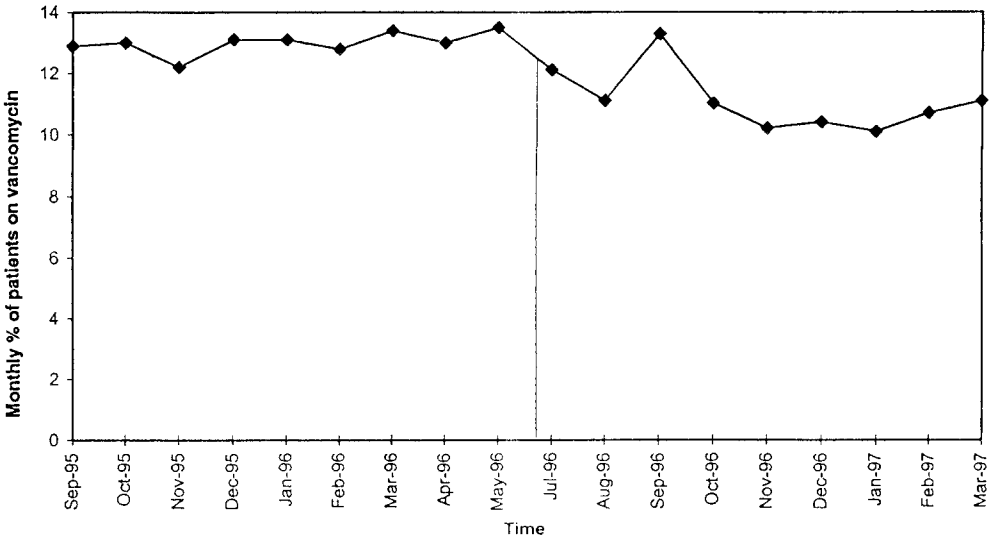

Figure 3 The variation in the monthly percentage of patients in the hospital on vancomycin. The values on the vertical axis were obtained by dividing the number of patients on vancomycin each month by the number of patients in the hospital that month and multiplying by 100 to yield percentages. The vertical line between the months of May and July on the horizontal axis marks the beginning of the study period. Piecewise linear regression revealed that both the slope and vertical intercept changed significantly ($P = 0.04$ and $P = 0.01$, respectively) after the intervention.

($P = 0.04$ and $P = 0.01$, respectively) after the intervention. In Figure 4, the amount of vancomycin dispensed per month corrected for hospital census shows a steady decrease (i.e., a negative slope), but this decrease was not significantly affected by the intervention. Last, while the analysis in Table 4 suggests a small but statistically significant decrease of 10 percent in the amount of vancomycin dispensed per patient, this small change was not statistically significant in the piecewise analysis.

We also evaluated the frequencies of the indications entered for initiation and renewal of vancomycin therapy (Tables 5 and 6). We do not have a measure of the accuracy of the indications entered, although in other domains accuracy has been high.[23] Also, physicians could enter any free text they chose under the "other" category, decreasing the chance that users would deliberately enter inaccurate indications. Only approximately 10 percent of orders were entered as "other." For the initiation orders, no single category accounted for a large proportion of these orders, but for the renewals, the vast majority of "other" indications related to fever in patients on the hematology-oncology or bone marrow transplantation services.

The annual hospital costs for vancomycin have been just under $300,000 per year for the past three years

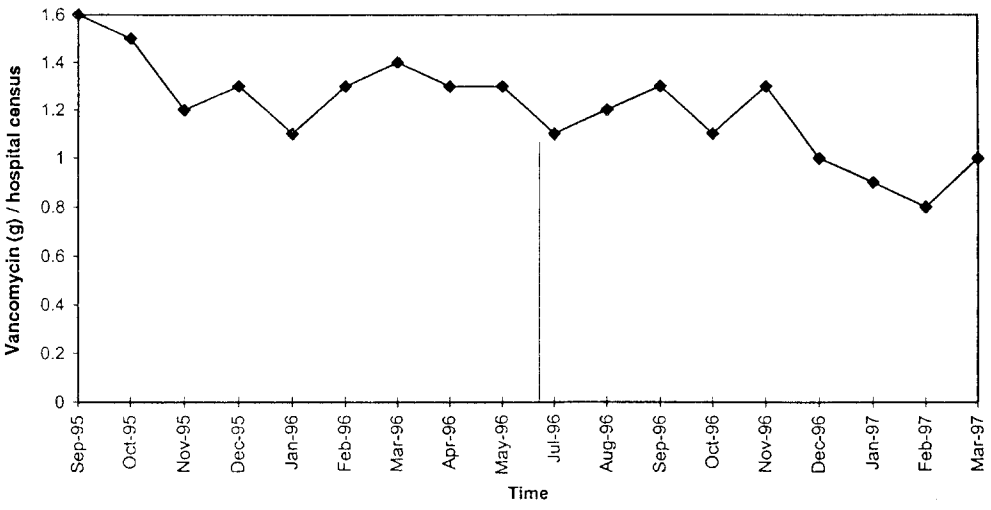

Figure 4 The amount of vancomycin dispensed per month. The values on the vertical axis were obtained by dividing the number of grams of vancomycin dispensed each month by the number of hospitalized patients that month. The horizontal axis shows the calendar months. Again, the vertical line between May and July corresponds to the beginning of the study period. While the amount of vancomycin dispensed each month can be seen to decrease steadily over time, this decrease was not significantly affected by the intervention.

Table 5 ■

Indications Entered for Initiating Vancomycin Orders

Indications	No. (%)
Presumed gram-positive infection resistant to beta lactam	642 (47.7)
Suspected sepsis (< 72 h empiric therapy, cultures pending)	134 (10.0)
Perioperative prophylaxis requiring cefazolin, with beta lactam allergy	142 (10.6)
Fever, neutropenia, and evidence of gram-positive infection	118 (8.8)
Presumed serious gram-positive infection and beta lactam allergy	106 (7.9)
Endocarditis prophylaxis requiring penicillin, with beta lactam allergy	14 (1.0)
Other	189 (14.0)
Total	1345 (100)

at our institution. Thus, this intervention has a projected savings of as much as $90,000 per year from decreased vancomycin utilization. However, in many instances, a different antibiotic may be chosen instead of vancomycin, so that these projected savings will be partially offset by increased purchases of first-generation cephalosporins and penicillinase-resistant penicillins. The daily cost of vancomycin at 2 g per day is approximately $12/day in our hospital, whereas the cost of a first-generation cephalosporin such as cefazolin at 3 g per day is approximately $9/day. Thus, if cefazolin were substituted for vancomycin in all cases in which providers chose not to order vancomycin, the cost savings of the intervention would consist of 25 percent of the $90,000 figure above, i.e., a savings of $22,500/yr.

Comment

In this study, a computerized ordering guideline resulted in a significant change in antibiotic ordering practice. Physicians exposed to the intervention ordered approximately 30 percent less vancomycin than physicians in the control group in terms of frequency of ordering, numbers of patients on vancomycin, and duration of vancomycin therapy prescribed per patient. The study took place against a background of a general 15 percent reduction in vancomycin use, as measured by grams of vancomycin dispensed per month adjusted for monthly census, in our hospital during the study period. However, because of the randomized controlled design of the study, the observed 30 percent decrease in frequency and duration of vancomycin therapy represents an effect beyond that attributable to this background historical trend. Also, piecewise linear regression analysis of the pharmacy data confirmed that our intervention had an effect on reducing vancomycin use independent of the secular trend of reduced vancomycin ordering during the study period. For this reason, the computerized guidelines for vancomycin ordering were generalized to all users of the order entry system and have been left in place since completion of the study.

Researchers at LDS Hospital in Utah have described an elegant decision support system for treatment of infections and have demonstrated that this system has substantially improved the quality of the prescribing practices of physicians and reduced antibiotic costs at that institution.[24,25] This decision support system presents data available from the computerized patient records relevant to antibiotic prescription and even presents a recommendation for antibiotic selection to the physician users. The type of system in place at LDS Hospital will undoubtedly find application at other hospitals in conjunction with the implementation of computer order entry systems. However, the complexity of the system will likely delay widespread availability for some time. In contrast, the approach used in the present study is much simpler and more readily generalizable to computer order entry systems in the short term.

Anglim et al. published a study evaluating the impact of a computerized ordering guideline for vancomycin[26] and reported a 50 percent decrease in vancomycin use, a larger reduction than we observed. However, there are several important methodologic differences between the two studies. The intervention these authors describe was implemented without a control group of providers for comparison, so the effect of the intervention itself cannot be separated from general changes in ordering practice that may have occurred. At our hospital there was a secular trend of decreasing vancomycin use before the study began. Thus, the 50 percent reduction in vancomycin orders observed by Anglim et al. could represent the combined effect of the computer intervention and general

Table 6 ■

Indications for Renewing Vancomycin Orders at 72 Hours

Reason	No. (%)
Presumed gram-positive infection resistant to beta lactam	682 (76.8)
Presumed serious gram-positive infection and beta lactam allergy	51 (5.7)
Other	155 (17.4)
Total	888 (100)

changes in ordering practice occurring during the study period, as a result of heightened awareness of the problem of VRE and other infection control strategies.

These authors also report a reduction in the prevalence of VRE isolates detected by their surveillance program after their intervention went into effect. We observed a similar marked decrease in the isolates of VRE at our institution (both clinical isolates and surveillance cultures) during our study. We did not report further on this outcome because the decrease seemed merely to reflect the fact that an outbreak of VRE had occurred shortly before the study began. Control of the outbreak by general infection control measures presumably resulted in the observed decrease in VRE before any microbiologic effect of reduced vancomycin use could reasonably have been expected to occur. Because the study by Anglim et al. was undertaken in response to an outbreak of VRE at their institution, the reduction in monthly incidence of VRE isolates they observed could reflect regression to the mean. Nonetheless, decreasing vancomycin use represents the key strategy in containing the spread of VRE, and Anglim's data as well the data presented here both suggest that computerized guidelines may provide a powerful tool for changing prescribing practice.

In general, physician practice has proved difficult to change. Systematic review of educational strategies for changing physician behavior reveals that traditional strategies such as continuing medical education conferences produce little long-term benefit in terms of physician performance or health care outcomes,[15] although they may alert physicians to the need for a specific change in practice. Multifaceted interventions and educational outreach interventions have been more successful, although such interventions require more resources to implement and often still have only moderately favorable results.[15] A recent study of a computerized decision support system for aiding clinicians in the outpatient management of diabetic patients showed a two-fold increase in compliance with established clinical practice guidelines for physicians exposed to the intervention.[27] However, this positive effect on the practice of the intervention group physicians corresponded to an absolute compliance with the practice guidelines of only 32 percent, underscoring the magnitude of the task often facing investigators hoping to modify physician behavior. In our study, a simple intervention, requiring a relatively small investment both to implement and to maintain, resulted in a significant impact in the behavior of interest, namely, parenteral vancomycin ordering.

The major limitations of our study are that we did not gather data on appropriateness or on adverse outcomes. The study from the University of Virginia by Anglim et al.,[26] discussed above, and an earlier study of vancomycin use at the University of Iowa[20] documented remarkably similar values of 61 percent and 63 percent, respectively, for the proportion of vancomycin orders deemed inappropriate by the investigators. We did not formally audit appropriateness in this study, but were recently participants in a Massachusetts Peer Review Organization (MassPRO) study, in which charts from 1995 were audited by MassPRO reviewers. The hospital's guideline-supported vancomycin use rate using the Centers for Disease Control guidelines was 42 percent (range among hospitals, 33%–53%), exactly the mean rate for the six hospitals sampled (unpublished data, D. Yokoe). These data suggest that the appropriateness of vancomycin use at our institution is similar to that in other hospitals.

Regarding this intervention and appropriateness, it is our impression that improvement occurred but that many of the orders remain inappropriate according to the Centers' guidelines. It is also possible that the intervention resulted in the decision not to use vancomycin in cases in which its use would have been appropriate. Because no therapeutic equivalent exists for vancomycin, it is possible that adverse outcomes could have resulted. However, the guidelines screens we used were, if anything, more liberal than the original CDC guidelines, and these guidelines have been developed by panels of experts specifically to improve antibiotic ordering practice without compromising patient outcomes. Other potential criticisms of our study might include contamination of the control group through awareness of the intervention as a result of communication among the physicians in both groups. Also, a Hawthorne effect might have produced reductions in vancomycin ordering in both groups independent of the intervention itself. However, in both these cases, the expected effect would be a bias toward the null, suggesting an underestimate by our study of the true effect of the intervention.

In conclusion, implementation of a computerized ordering guideline resulted in a reduction in vancomycin use at a tertiary-care hospital with a prevalence of VRE close to national averages. The intervention was readily incorporated into the existing computer order entry system at our institution and required negligible resources to maintain. The intervention also facilitates further improvements in vancomycin use by allowing us to target specific indications and providers. In general, the process of having a follow-up review of the orders entered using computer guidelines may pro-

vide an effective adjunct in the effort to control the use of drugs that should be prescribed sparingly, such as vancomycin and imipenem.

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