Approaching and analyzing a large literature on vancomycin monitoring and pharmacokinetics

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THE CASE

At morning rounds in your hospital's intensive care unit, a resident from the team presents a 55-year-old woman (weight 129 lbs) with a past medical history of multiple sclerosis, cerebellopontine angle meningioma, hypothyroidism, and a neurogenic bladder requiring a Foley catheter. This patient was transferred from her nursing home 3 days ago with a fever and altered mental status. Results from the nursing home bacterial culture of the patient's urine revealed Gram negative rods. Bacterial culture of blood drawn from her peripheral intravenous (IV) line at the nursing home indicated Gram positive cocci. Blood cultures redrawn upon hospital admission are still pending and require confirmation.

According to the patient's chart, she began empiric treatment at the nursing home with vancomycin (1,000 milligrams [mg] intravenously every 12 hours) and piperacillin-tazobactam (3.375 g IV every 6 hours) for urosepsis 4 days ago. The patient's current serum creatinine is 0.56 micrograms per deciliter (mg/dL) (normal range: 0.6–1.1 mg/dL) [1], and her estimated creatinine clearance is 104 milliliters per minute (mL/min) (normal range: 88–128 mL/min) [2]. Her current body temperature is 97.2° Fahrenheit. Today is day 4 of this patient's vancomycin and piperacillin-tazobactam regimen and hospital day 3.

In reviewing the plan for the next twenty-four hours, the attending physician notes that the patient currently has a standing order for a laboratory test of the vancomycin trough level in her serum, with the blood sample to be taken just prior to the next dose of the drug. On day three of antibiotic therapy, the patient's serum vancomycin trough level was eleven mcg/mL, and, on day four, the trough was eighteen mcg/mL. The institution's target range for the serum trough level of vancomycin is five to twenty mcg/mL.

The attending physician initiates a discussion with the team—including a fellow, three residents, a pharmacist, a dietitian, the unit's nurses, and you, as the team's librarian—about monitoring of vancomycin. The clinician queries the team about the rationale for the standing order for vancomycin trough monitoring. The residents indicate that they often order this lab test when a patient is receiving vancomycin in an attempt to ensure therapeutic effectiveness and to prevent adverse effects of the drug but are not aware of any documentation behind the practice. The pharmacist comments that clinical practice can sometimes evolve before supporting evidence exists and that standards of practice at a hospital may not always be supported by evidence from the literature. In response to this discussion, the group asks you to identify any evidence supporting or disproving the practice of routine monitoring of trough levels in patients being treated with vancomycin in the adult critical care setting. Figures 1 and 2 provide elaboration from the team's attending physician and pharmacist on the significance of this question to clinical practice on the unit.

THE QUESTION

Is there evidence that monitoring serum vancomycin trough levels prevents drug toxicity and/or ensures therapeutic dosing of the drug?

UNDERSTANDING THE CONCEPTS

Before you begin your literature search, you first consider the nuances of this patient's case, described further in Table 1. She is a nursing home resident and has significant comorbidities including a benign brain tumor and multiple sclerosis with unknown disabilities. The etiology of her currently altered mental status is unknown, but nursing home staff reports it to be a change from her baseline condition. The presence of a Foley catheter is a risk factor for a urinary tract infection; however, this patient's diagnosis of urosepsis, referring to a serious systemic infection caused by bacteria originating in the urinary tract, is much more severe and demands aggressive therapy [12]. The data presented on rounds also indicate that the patient is not obese, an important consideration for both drug dosing and prognosis. Also, her serum creatinine and estimated creatinine clearance are normal, suggesting that the patient does not have renal impairment.

In addition to developing familiarity with this patient's specific circumstances, understanding a few basic pharmacokinetic concepts and the therapeutic agent being used in this case will aid you in searching, reading, and interpreting the literature. Peak and trough values are important concepts in understanding drug disposition, the way an individual therapeutic agent or drug distributes in and is managed by the human body. The peak level refers to the predicted highest concentration between doses, and the trough refers to the lowest predicted concentration just before the next dose. Serum levels of the antibiotic must be high enough during the dosing interval (i.e., the period in between doses of the agent) to kill the infecting organism and prevent further growth. After IV dosing, a drug may be distributed throughout the body, may only target certain organs, or may not be absorbed at certain sites. Knowing the pattern and timing of drug distribution is vital to identifying correct dosing intervals. In critical care, in which an infection typically needs to be treated aggressively to avert significant patient morbidity and mortality, clinicians attempt to

Figure 1
Attending physician commentary

Historically, drug levels have been monitored to avoid toxicity and, in some cases, to ensure that a therapeutic concentration has been achieved. Unfortunately, in many instances serum drug levels correlate poorly with efficacy and/or toxicity. Usually, peak drug concentrations are highly predictable based on patient weight and dose of the drug—in most cases alleviating the need for ''peak'' concentration monitoring. Despite scant evidence that monitoring of vancomycin is necessary to ensure efficacy, the practice remains common.

Drug toxicity is related to dose and frequency; concomitant medications; and patient co-morbidities, such as obesity or renal and hepatic dysfunction. Of these, renal insufficiency is the most common organ dysfunction altering drug levels in hospitalized patients. Because the kidney is largely responsible for clearing vancomycin from the human body and because vancomycin can also cause kidney dysfunction, monitoring its level, especially a ''trough level,'' has been a common practice. In this patient, body weight is not excessive and the creatinine level is normal (accompanied by a normal calculated glomerular filtration rate), suggesting that renal considerations do not warrant monitoring. In addition, because vancomycin is cleared in the urine, which is also the site of presumed infection, urine levels of the drug would be expected to be many times that found in plasma, again raising the question of the utility of plasma levels.

Given the scant evidence that blood vancomycin levels are helpful in predicting efficacy or helping to avoid toxicity, some experts now recommend that patients with reasonably intact renal function can forgo vancomycin testing. Dosing at Vanderbilt is guided by an internally developed nomogram based on patient weight and typical pharmacokinetic parameters of drug clearance. Empiric testing at this hospital suggests that such an approach provides plasma levels in traditionally recommended ranges without the discomfort, risk, and cost of blood level monitoring. However, this observation does not answer the question of the importance of achieving certain peak or trough levels.

Figure 2
Pharmacist comments

The concept of a desired therapeutic range for serum concentrations of drugs was first proposed about thirty-five years ago by Koch-Weser [3]. This article included tables of desired therapeutic ranges for serum drug concentrations, suggesting the usual values associated with adequate response and acceptable toxicity for a patient population.

The primary sources for establishing reported therapeutic ranges were often not published and therefore may not be found in the literature. In some cases, it appears that these ranges were established based on similarities with other similar drugs. For example, the desired therapeutic range for tobramycin appears to be arbitrarily set to duplicate the historical accepted ranges for gentamicin, a similar antibiotic [4]. In the case of vancomycin, the range appears to have been set to approximate serum concentrations measured during initial trials. The desired trough serum concentration for vancomycin appears to have been increased recently based on the assumption that resistance to vancomycin may require use of higher serum concentrations, as noted below.

A recent large retrospective review of patients with methicillin-resistant *Staphylococcus aureus* (MRSA) health care–associated pneumonia [5] suggested that aggressive dosing strategies for vancomycin (e.g., trough concentrations of more than fifteen micrograms per milliliter [mcg/mL]) may not offer any advantage over traditional dose targets (range, five to fifteen mcg/mL).

It is also worthwhile to note that one might expect this topic to evolve as investigators scrutinize the appropriateness of testing in this situation. As the data accrue, periodic review of this question will likely be necessary to ensure that the answer to the question does not change based on recent publications.

infuse the highest possible dose as rapidly as possible without causing side effects. Understanding the pharmacokinetics of an antibiotic helps to effectively treat the infection and prevent adverse effects.

Developing a better understanding of the history of this agent may also help guide your literature search and interpretation of the citations you find. Vancomycin was approved for use in the United States by the Food and Drug Administration (FDA) in 1958 for treating penicillin-resistant *Staphylococcus aureus* infection, was nicknamed ''Mississippi Mud'' due to its color from impurities, and was initially isolated from soil in Borneo and India [14]. Because vancomycin has been used since the 1950s, you find background information in a number of sources, with varying content and level of detail. For example, CRLOnline discusses the drug's mechanism of action and pharmacodynamics and provides a dosage recommendation [15]. This text also provides reference ranges for laboratory monitoring of patients being treated with vancomycin, recommending timing of blood draws to assess peak and trough levels; however, no reference to supporting evidence is provided.

The Micromedex DrugPoint summary for vancomycin [16] includes a ''Monitoring'' category, which cites target peak and trough levels along with a recommendation about measuring only troughs, but also lists exceptions:

> peak and trough level monitoring is still warranted in certain high-risk patients such as those receiving concomitant nephrotoxic agents, sites of infection with difficult penetration (CNS, endocarditis), patients with rapidly changing renal function, or patients with a poor therapeutic response. [7]

The Drug Point summary does not provide references but does include a link to a full drug monograph in DrugDex [17]. The ''Pharmacokinetics'' section of the monograph discusses measuring serum peak and trough and mentions a guide for therapeutic monitoring, noting that the recommendations are derived from ''observations'' of recommended doses and citing a 1999 study [18].

An UpToDate search of vancomycin retrieves ''Vancomycin dosing and serum concentration monitoring in adults,'' which includes the subsections ''Serum concentration monitoring'' and ''Utility of monitoring serum concentration'' [19]. The UpToDate review discourages routine monitoring and trough monitoring, recommending such practices if the patient has end stage renal disease and is likely to receive more than one dose of vancomycin, has other apparent instability or changes in renal function, is receiving another nephrotoxic agent, or is morbidly obese. The section describing indications for monitoring cites no supporting references, however.

At this point, you realize that there is likely to be a large body of literature discussing vancomycin dosing (over 600 references in the Micromedex bibliography alone) and the literature is likely to be controversial, due to the acknowledged lack of evidence to support monitoring.

CONSTRUCTING A LITERATURE SEARCH

Table 2 includes example search strategies for a number of resources that may provide useful information describing vancomycin monitoring practices.

Searching the earliest years after vancomycin approval is problematic due to the lack of abstracts (eliminating a key textword source) and subheadings. The majority of the 1950–1965 OLDMEDLINE citations [20] have been incorporated into PubMed, and a recent *NLM Technical Bulletin* news item notes that the Other Terms (subject terms from the original print indexes) have been mapped to Medical Subject Headings

Table 1
Key concepts for this case's medical concepts

Concept	Definition
Vancomycin	A large glycopeptide (a short chain of amino acids with sugar molecules attached) that binds irreversibly to the cell wall. Vancomycin is generally used to treat infections caused by Gram-positive bacteria, including methicillin-resistant *Staphylococococcus aureus* (MRSA) and *Clostridium difficile*, but resistance to vancomycin in these bacteria has been reported. Most Gram-negative bacteria are resistant, and vancomycin-resistant *Enterococci* (a Gram-positive organism) have also been reported in association with overuse of vancomycin [6].
Pharmacokinetics: peak and trough	The absorption, distribution to target organs, and elimination of drugs from the body. A peak level refers to the maximum concentration measured at a specific point after dosing. The trough refers to the drug concentration at the lowest point just before the next scheduled dose [7].
Creatinine clearance rate	Measure of effectiveness of the kidney to filter creatinine, a waste product, from the blood. This estimate is used to monitor patients for potential kidney dysfunction. Creatine clearance is expressed as milliliters per minute (mL/min) [2].
Clearance	Refers to the body's ability to eliminate a drug and is affected by the patient's disease process, age, weight, and/or other agents the patient is receiving [7].
Drug monitoring	Measurement of a specific drug in a body fluid (e.g., blood serum) at standard intervals, with the goal of adjusting drug dosage as necessary to maintain a constant level or concentration (steady state). Regular monitoring is usually employed when an agent's specific ''therapeutic range'' is narrow between effective therapy and toxicity [3, 8].
Cerebellopontine angle meningioma	Meningiomas are classified as benign tumors comprising cells lining the arachnoid villae (the apparatus responsible for absorption of cerebrospinal fluid). Typical presenting symptoms might include tinnitus, hearing loss, vertigo, ataxia, headache, or facial weakness; the primary treatment for these tumors is surgery. Incidence increases with age, and more women are affected compared to men [9]. Location of the meningioma in the cerebellopontine angle may lead to hearing loss and facial nerve findings on MRI [10].
Neurogenic bladder	A urinary dysfunction in which the bladder does not void properly, caused most commonly by a nervous system tumor, injury to nerves enervating the urinary tract, or inflammatory conditions such as multiple sclerosis [11].
Urosepsis	A severe infection in the genitourinary tract usually occurring as a urinary catheter–related or other health care–associated infection after invasive genital-urinary procedures [12].
Urine culture	To examine a patient's urine for the presence of bacteria, a urine specimen is placed on an agar plate and maintained at body temperature. Within 24 to 48 hours, any microorganisms present in the specimen form colonies. Further laboratory investigation identifies the bacteria and explores the organism's sensitivity to specific antibiotics to aid clinicians in determining an appropriate course of treatment [13].

(MeSH) for approximately 75% of the 1.7 million OLDMEDLINE records [21], which will likely increase the chances that a MeSH-based search strategy will still find relevant citations from this portion of the PubMed dataset. However, given that the older citations were indexed with different practices due to the nature of the print indexes (e.g., sometimes including fewer subject terms and/or subheadings), you will likely find it useful to supplement your more focused search strategies with broader strategies. For example, a classic article by Anderson et al. is currently indexed in PubMed with only the major subject term and substance ''Anti-Bacterial Agents'' [22], necessitating your use of a much broader search than a simple vancomycin-based strategy. Due to the volume of the literature, you may want to consider these older citations separately, using the broader search only in OLDMEDLINE to obtain a more manageable retrieval set and using the narrower search in the more recent literature.

In addition to the work by Anderson et al. noted above, other older items will likely also provide essential background information for understanding how the biomedical community's knowledge of vancomy-

Table 2
Search strategy examples

Database	Search string sample
PubMed	(vancomycin[mesh] OR vancomycin[tw] OR vancomycin resistance[mesh]) AND clinical trial[pt] AND English[la]
PubMed	(''vancomycin''[MeSH Terms] OR vancomycin[ti]) AND (clinical trial[pt] OR ''clinical trial''[All Fields] OR prospective*[tiab] OR retrospective*[tiab] OR guideline[tiab] OR guidelines[tiab] OR practice guideline[pt]) AND English[la]
PubMed	(Drug Monitoring[mh] AND Vancomycin[mh]) OR (Vancomycin/administration and dosage[mh] AND monitor*) AND English[la]
PubMed after 1988	''Vancomycin/pharmacokinetics''[MeSH]
PubMed: example strategy for examining the older literature	(''Vancomycin''[MeSH] OR vancomycin[tw]) AND English[lang] AND (''1950''[EDAT] : ''1970''[EDAT])
Web of Science	TS=(vancomycin SAME (monitor* or pharmacokinetic* or peak or trough) AND TI=vancomycin
Cochrane Database Wiley Interscience	''vancomycin AND (pharmacokinetics OR trough OR peak OR monitoring) in Title, Abstract or Keywords
All EBM Reviews Ovid	vancomycin.mp. and (drug monitoring or therapeutic monitoring).mp. or peak.mp. or trough.mp. or (nephrotoxicity or toxicity or ototoxicity).mp.)
UpToDate	Vancomycin

cin pharmacokinetics has evolved since the drug's discovery in the 1950s [23–25]. Though these initial studies may not prove useful for your overall summary of the literature (discussed further below), they provide excellent insight into the origins of the vancomycin pharmacokinetic levels examined in the more recent literature.

The Fairbrother and Williams 1956 article, for example, reports testing results of vancomycin sensitivity for 1,350 organisms, including 540 strains of *S. aureus*, with all proving sensitive [23]. This paper notes a key limitation of in-vitro studies, however, in terms of the generalizability of the results to a clinical setting, emphasizing ''in-vitro sensitivity tests do not provide an absolute criterion of clinical efficiency; they only indicate activity . . . under laboratory conditions which tend to be favorable to the antibiotic.'' You also find that the limitations of generalizing the results of in-vitro studies echo through much of the literature debating the utility of therapeutic drug monitoring in patients receiving vancomycin [24–27].

Another example of an early in-vitro study of vancomycin's effects is provided by a 1956 paper by Geraci et al. examining *Micrococcus pyogenes* in several populations, both human and animal, detailing measurement of vancomycin concentrations in body fluids after both IV and oral dosing and examining the sensitivities of multiple pathogens [28]. These investigators established that a serum vancomycin concentration of 2.5 mcg/mL completely inhibited 110 of 112 strains of *M. Pyogenes*. This finding became an important standard established for vancomycin sensitivity for many organisms, despite the lack of validation in subsequent clinical trials, providing some insight into the weaknesses of the evidence base supporting vancomycin dosing and monitoring practices.

A 1970 study by Washington et al. is key due to the authors' perspective on vancomycin dosing and monitoring. These authors noted there was no experimental evidence or even ''universal agreement'' defining in-vitro susceptibility or resistance of a microorganism to an antibiotic [29]. Washington went on to say that as a general rule if the antibiotic blood levels exceeded the in-vitro MIC level by two to four times, then ''the organism is usually considered to be sensitive.'' As with the work by Geraci et al., this study highlights the way in which experimental in-vitro results became the foundation for clinical practice in vancomycin monitoring and dosing, without the strength of validation through clinical trials.

In addition to understanding the growth of the vancomycin-related literature by examining these older citations, perusing the bibliographies of the relevant articles you identify during your searching process is another way to find additional items not retrieved by your search strategy. Though it can be considerably time consuming, this hand-searching step is essential if you wish to conduct a comprehensive search and produce a high-quality and thorough end product.

As you scan through your search retrieval sets, you realize that a number of studies examine the use of vancomycin without quantitative sensitivity or pharmacokinetic data. Such studies may be useful to support selecting vancomycin as a therapeutic agent but omit data that would support informed clinical decision making about how or when such patients should be monitored during vancomycin therapy. In your results, you also note a lack of clinical trials examining correlation between vancomycin monitoring and clinical outcomes, finding that most primary data on the topic focus on either laboratory testing results or retrospective considerations of vancomycin pharmacokinetics in critically ill populations.

Of the items you peruse in your search results, you focus most closely on the studies that include either in-vitro sensitivity data or research examining associations between therapeutic drug monitoring and clinical outcomes (e.g., duration of therapy, cumulative dose, resolution of infection, mortality) in adult patients receiving vancomycin. You also consider key opinion pieces and guideline statements to reflect areas of consensus and debate related to laboratory monitoring during vancomycin therapy. To address the question, you select a final group of articles including a set of practice guidelines that contain recommendations for vancomycin monitoring [30], a review that provides an excellent summary of the debate surrounding this issue [31], and several studies from more recent years that yield in-vitro and observational clinical data illustrating potential utility and limitations of vancomycin monitoring [32–39].

SUMMARIZING THE LITERATURE

One of your key challenges in summarizing this literature lies in illustrating for the clinical team the areas of consensus and debate related to this question. Figure 3 provides a sample overall summary of the literature, beginning with a synthesis of the perspective you developed in your detailed examination of the older literature from the time period closer to the Food and Drug Administration's approval of vancomycin for use in the United States, followed by brief summarization of:

- a set of 2005 practice guidelines from the American Thoracic Society and the Infectious Diseases Society of America, noting the rationale for the guidelines and the acknowledged paucity of evidence to inform decision making on the issue [30]
- a thorough review from 1994 that emphasized the lack of data supporting vancomycin testing practices and the potential economic impact of over-testing [31]
- individual studies highlighting various aspects of this debate [32–39]
- an overall conclusion regarding your understanding of the literature on the topic

CONCLUDING REMARKS

When you present the literature to your team, they are not surprised at your evaluation of the scant evidence to support connections between routine peak and trough monitoring and actual clinical outcomes or toxicity and realize that this is a huge and confusing lit-

Figure 3
Overall summary of the literature

Despite the fact that vancomycin has been available since the 1950s, there is a paucity of literature linking positive clinical outcomes from therapeutic drug monitoring of vancomycin drug levels. The practice of routine drug monitoring seems to be largely based on the rationale that targeting the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) [3] will provide a sufficient drug concentration over a time period to efficiently resolve an infection while reducing the potential for renal adverse effects and ototoxicity. Items included below provide insight into the limited in vitro and clinical data used to extrapolate therapeutic levels of vancomycin and their potential significance in terms of toxicity and treatment effectiveness, as well as examples of commentary noting the debate in the literature regarding the lack of evidence to inform drug-monitoring decisions in the care of patients receiving vancomycin.

In 2005, the American Thoracic Society and the Infectious Diseases Society of America published a guideline that recommends a vancomycin dose of fifteen milligrams per kilogram per twelve hours (mg/kg/twelve hrs) and a trough target concentration of fifteen to twenty mcg/mL in patients with normal kidney and liver function with health care–associated pneumonia, while acknowledging the lack of clinical data to support the recommendations [30]. Regarding the rationale for the recommendation despite the lack of evidence, the guideline notes that inadequate dosing and failure to achieve sustained serum concentrations may lead to increased resistance, progression of infection, and higher mortality.

Cantu et al. in 1994 reviewed the evidence for the effectiveness of vancomycin monitoring for peak and trough as well as toxicity, concluding that, despite the ''well-entrenched'' practice, there was no evidence to support cause and effect between serum level and either outcome or toxicity [31]. The investigators noted that their own institution, Johns Hopkins Hospital, performed about 6,500 assays in 1991 and estimated there were more than 5 million assays throughout the United States annually, engendering considerable cost. They recommended development of a nomogram for vancomycin dosing based on age, weight, and estimated renal function. This paper has been cited in the literature over 100 times since publication.

Several studies provide evidence further emphasizing the controversial nature of this topic and noting specific considerations in patients with current renal dysfunction or risk factors for the development of this adverse effect. Some authors also emphasize the potential utility of a nomogram to support dosing and monitoring in adult critically ill patients receiving vancomycin.

Iwamoto et al. conducted a retrospective examination of data from 184 patients with MRSA infection receiving intravenous (IV) vancomycin [32]. Investigators observed a significant decrease in creatinine clearance in the 111 patients who did not receive therapeutic drug monitoring (TDM) when compared with the 73 patients who received TDM during vancomycin therapy ($P < 0.05$). These results highlight the potential development of renal adverse effects in some patients receiving vancomycin without therapeutic drug monitoring.

Regarding the relationship between vancomycin serum levels and resolution of infection, a subgroup analysis in the Iwamoto et al. study examined patients with either MRSA bacteremia or pneumonia who received TDM (n = 53) to those not being monitored (n = 46). Differences in cumulative dose and duration of therapy were not significantly different between the two groups (see Table 2 of the Iwamoto article). The authors note that, despite the potential reduction in adverse renal effects noted in patients receiving TDM, monitoring was not associated with significant differences in either cumulative dose or duration of therapy, implying potential lack of TDM effect on drug dosing or resolution of infection.

In another important study, Karam et al. (1999) conducted a retrospective comparison among critical care and trauma patients in a 340-bed teaching hospital in Detroit [33]. This study compared (1) a retrospective group of 120 patients who were given IV vancomycin between January 1995 and October 1996 and monitored for peak and trough values with dosing adjustments to (2) a group of 120 patients prospectively dosed between November 1996 and May 1997 using a simple vancomycin nomogram based on the patient's weight and estimated creatinine clearance. Patients in the prospective group were excluded if their estimated creatinine clearance was < 30 mL/min and their weight < 50 kg. In the prospective group, a single trough measurement was made after day 5. If the value was 5–20 mcg/mL, no change in vancomycin dosing was made; if the trough value measured was < 5 mcg/mL, the dosing interval was decreased to the next interval; if the trough was > 2 mcg/mL, the dose was cut by 50%. The nomogram was validated by actual versus predicted trough concentrations. Seventy-two (94%) patients dosed by the nomogram had trough concentrations in the target range of 5–20 mcg/mL. Average duration of therapy was 9.9 ± 9.4 days in the nomogram group and 86.6 ± 7.2 days for the pharmacokinetic group. There were no statistically significant differences between the pharmacokinetic-monitored group versus the nomogram group with respect to organism eradication or persistence, cure, improvement, failure, or toxicity. Nephrotoxicity was not significantly different between the 2 groups (16/85 in the pharmacokinetic group vs. 15/86 dosed by nomogram). Authors acknowledged that their patient population was young and the nomogram was most reliable in patients with an estimated creatinine clearance above 60 mL/min.

An in-vitro vancomycin susceptibility study by Sakoulas et al. (2004) examined 30 different MRSA isolates from 30 patients with known clinical outcomes in a phase II and IV prospective randomized clinical trial (RCT) from 16 states and 24 hospitals to determine the relationship between bactericidal activity and outcome. Peak and trough values were not considered in this study [34]. Authors speculate that the wide vancomycin killing range, with varying levels of vancomycin required to successfully destroy the isolates during laboratory testing, might be an explanation for the mixed therapeutic effectiveness results observed in clinical outcome studies of vancomycin. Of note, this study was also selected by the Faculty of 1000 (a collective of subject experts in medicine and the life sciences who rate the merit of individual articles' contribution to the field) [35], raising the question of whether microbiology labs should begin to measure and report changes in MIC after initiation of vancomycin therapy. Other recent studies focus on continuous vancomycin dosing versus standard bolus and use of the lower trough concentration threshold value to prevent inadequate dosing rather than employing trough measurements to prevent toxicity [30, 36, 37].

Pharmacokinetics of vancomycin continue to be studied in various populations, comparing continuous versus bolus dosing and using models attempting to predict concentration with little success [37, 38]. Data from two recent studies report outcomes from target vancomycin trough levels or initial MIC measurements in MRSA infections in hospitalized patients [5, 39]. One study found no association between trough levels and mortality [5], while the other investigation found an increased risk of nephrotoxicity in patients with high trough levels [39].

Existing evidence does not seem to support routine serum therapeutic monitoring for vancomycin dosing to improve clinical outcome in patients with sufficient creatinine clearance; however, regular monitoring to allow for dose adjustment in patients with renal dysfunction and those receiving other nephrotoxic agents is currently recommended due to the potential side effects of excessive vancomycin dosing in this population subset. This topic is clearly the focus of debate and merits regular surveillance to gauge how the literature on this issue develops over time.

erature. They are particularly interested in the specific articles used to support your synthesis of the literature and your skill in distinguishing real evidence from anecdotal or opinion-based recommendations and practices.

At a local charge of $250 for each peak and trough measurement for a patient receiving vancomycin, the charges for this testing combination approached $1.2 million at your institution in one recent year. Debating routine measurement of vancomycin levels and its associated costs without evidence of many benefits, as revealed by your examination of the literature in conjunction with the clinical team's interpretation and expertise, leads to changes in your institution's computerized provider order entry system (CPOE). To support informed clinician decision making on vancomycin monitoring, the CPOE system now advises against measuring peak values. If an order for a trough level is requested, a new popup screen called the ''Vancomycin Trough Level Order Advisor'' appears. The clinician must select an exception criterion (e.g., renal dysfunction, obesity, > 7 days duration of therapy, suspected treatment failure due to low serum levels) to order the drug monitoring and complete a consult form for pharmacist advice before the order is accepted. Such standardization of practices is one strategy for facilitating the systematic incorporation of evidence into clinical practices.

Your comprehensive review of the evidence in the literature—read and critiqued by physicians, pharmacists, or others—has become a catalyst for practice change in your institution. In this case, the attending physician and pharmacist concur about the existing lack of evidence and move to systematize changes in

vancomycin test-ordering practices throughout the institution. Using your skills as part of the clinical team can assist the library in proving that your services have a direct return on investment and make you a highly valued team member.

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