

CRITICAL TIMES

A q-o-monthly Newsletter

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Vancomycin: Reaching Consensus about Dosing and Monitoring Based on the Data by Mylinh Ho, Pharm.D., BCPS

Vancomycin is a glycopeptide antibiotic that has been used for nearly half a century to treat serious gram-positive infections involving MRSA. However, whether or not to monitor vanco serum levels and adjust dosing based on levels, has been a hot topic of debate for many years. There has not been good evidence in the past to show that monitoring vanco levels have been able to prevent and predict drug toxicity or determine efficacy in treating infections.

Vancomycin toxicities, particularly nephrotoxicity, have been overblown in the past. However, we now know that this has been linked to the impurities in older vancomycin formulations; today's formulations are up to 90-95% pure. At standard doses, (eg. 1g IVPB Q12H) in patients with normal renal function (~80 ml/min), there is little potential for nephro- or ototoxicity, especially in the absence of concomitant nephrotoxic drugs. However, many of our VA ICU patients do not fit into this category.

A consensus review recently published by the American Society of Health-System Pharmacists, IDSA and Society of ID Pharmacists can help guide clinicians on how to dose and monitor vancomycin based on the data.

Optimal Vancomycin Concentrations

It is very fortunate that after so many years of use, vancomycin has been able to maintain its activity against MRSA, however, resistance of vancomycin intermediate susceptible *S. Aureus* (VISA) has emerged.

Vanco is bactericidal in a concentration-independent manner against *S. aureus* and based on pharmacokinetic studies, an AUC/MIC ratio of ≥ 400 has been advocated to achieve effectiveness. Since it is not realistic to obtain multiple vanco levels to calculate AUC/MIC, trough serum concentrations are the most accurate and practical surrogate marker for AUC. Targeting higher trough levels should increase overall antibiotic exposure and microbial eradication.

Trough Recommendations

- Always maintain troughs **>10mg/L** to decrease resistance (when the MIC is <1)
- For complicated infections (eg., bacteremia, endocarditis, osteomyelitis, meningitis, HCAP/VAP), maintain troughs **15-20mg/L** (when the MIC is ≤ 1)
- If vancomycin MIC is ≥ 2 (2 still falling within the “susceptible” cutoff), alternative therapies should be considered since an AUC/MIC of ≥ 400 likely cannot be achieved without potential toxicity

Dosing Recommendations

Though your pharmacist is always available to provide vancomycin dose recommendations, here are some basic guidelines.

- Consider loading 25-30 mg/kg based on actual body weight, to rapidly achieve target concentrations in critically ill patient

- 15-20 mg/kg based on actual body weight Q8-12 hours are required for most patients with normal renal function when MIC ≤ 1
- In patients with dynamic renal function, call Pharmacy for assistance, though they'll likely call you first!
- For vancomycin MIC >2 , consider calling Infectious Diseases service for recommendations/approval of alternative therapy

Monitoring Recommendations

The best way to prevent vancomycin nephrotoxicity is to minimize the duration of therapy and avoid giving vanco along with other nephrotoxic medications if possible (eg. aminoglycosides, amphotericin, some chemotherapeutic agents). It still remains somewhat controversial whether or not to obtain vancomycin troughs and if doing so can decrease nephrotoxicity, but listed below is what the guideline recommends. Monitor in patients:

- Receiving aggressive dosing (eg., targeting 15-20mg/L)
- With unstable (improving or deteriorating) renal function
- On prolonged courses of vanco (exceeding 3-5 days) once weekly in hemodynamically stable patients and more frequently in patients who are hemodynamically unstable

All levels should be obtained at steady state, right before the 5th dose, to be most meaningful. Monitoring for ototoxicity is not recommended in patients receiving vanco monotherapy; consider if patient is on other ototoxic meds (eg. aminoglycosides). Neutropenia is an uncommon toxicity

and is not related to serum concentrations.

Concluding Thoughts

In the world of Pharmacy, these published consensus guidelines are of much practical significance and much overdue. Most of us base our vancomycin recommendations on what we remember from our training, or what feels comfortable to us. Some clinicians check levels too often, some don't ever check in attempts to save on costs. With these recommendations agreed upon by multiple panels of experts, we hope it will streamline the process of dosing and monitoring, optimize clinical outcomes and decrease resistance!

The Smart Care Story

by Brad WeeTom, RT

Smart Care, a knowledge based ventilator liberation protocol was developed by Michel Dojat ,PhD and Laurent Brochard,MD in 1997. On July 25, 2005 it was granted approval by the USA FDA as an option for the EvitaXL then officially launched in the US on October 11, 2005. It was this kind of technology, which had an influence on the late Dr. Geller's decision to go with the EvitaXL over its other competitors. Here at the VA the Respiratory therapy department has been using the Smart Care option since August 6, 2008.

How does Smart Care work?

Smart Care assesses the patient's ventilatory support needs based on three monitored parameters: spontaneous respiratory rate (F_{spn} , tidal volume (V_T) and expired end-tidal

carbon dioxide ($Et\ CO_2$) in PSV (Pressure Support Ventilation) mode only. These parameters help define a "Zone of Respiratory Comfort" (ZoRC) for each patient, depending on their size, airway type, diagnosis, time of day, and activity level, which are data entered by the clinician into Smart Care. The ZoRC for a normal adult >55kg per Smart Care is:

- fspn between 15 and 30 bpm
- $V_t > 300$ ml
- $EtCO_2$ below 55mmHg

The goal of Smart Care is to adjust the Pressure Support up or down keep the patient stable in their ZoRC, thus leading to towards extubation. Once the ventilator maintain normal ventilation at the lowest level of pressure support, Smart Care recommends: *Consider Separation.*

Before initiating Smart Care all appropriate alarms must be set (V_T , Minute Volume, F_{spn} , and $Et\ CO_2$) with the ventilator in the PSV mode. Other settings are: apnea ventilation active, in-line $Et\ CO_2$, PEEP+5 and tube compensation on.

It's been my personal experience that Smart Care is and remains an invaluable tool for providing excellent care for our veterans by reducing ventilator assistance, VAP rate, sedation use, and most importantly length of stay. It does require close monitoring, which means a lot of bedside interaction because it's not just a set it and forget it mode.

The summary above prompted a few follow up questions to the author. . .

1) I am not aware of this being used in any patient I have cared for, is this really in use when I have a patient on pure PS or CPAP?

Yes, this has been used in over 100 of such patients.

2) Does the ventilator display the actual pressure support used at a given time (with Smart Care), such that we can stop by the bedside and assess changes in a patient's pulmonary compliance??

Yes; the display screen can be customized such that you can look at the peak pressure delivered. The event log displays changes made.

3) Many therapists will recommend MMV when we are in the midst of the weaning process; is there a choice we have to make between MMV and Smart Care or can both be in place at the same time?

No. Smart care can only be used on pure CPAP. In this case MMV should be used as an "evaluation mode." The perceived safety advantages of MMV can be achieved by proper use of alarms with smart care. In MMV, you do not get an apnea alarm, the backup settings just kick in.

4) How is EtCO₂ measured? We typically see a display on the regular patient monitor. is this value being fed into the vent, or is the vent making an independent measure? I ask because the values displayed on the monitors are sometimes physiologically impossible—meaning they are sometimes greater than simultaneously obtained arterial values.

The ventilators have their own CO₂ measurement devices, and are not affected by the calibration of the monitor.

Care of the Bariatric Surgery Patient

Dan Eisenberg, MD

Bariatric Surgery

Weight loss (bariatric) surgery is the only effective treatment for morbid obesity, achieving significant and durable weight loss. Excess weight loss (EWL) in the range of 40-60%, sustained beyond 5 years (>10 years in some studies) is expected. Bariatric surgery is also a very effective treatment of obesity-related co-morbid conditions.

Candidates for Surgery

Candidates for bariatric surgery have a body mass index (BMI) greater than 40 kg/m² (corresponding to greater than 100 lbs overweight) or a BMI >35 kg/m² associated with co-morbid conditions.

Obesity-related co-morbid conditions include type 2 diabetes (DM), hypertension (HTN), obstructive sleep apnea (OSA), hyperlipidemia (HL), and degenerative joint disease (DJD). More than 80% of the bariatric population at the Palo Alto VA has at least 2 co-morbid conditions.

Obesity, along with co-morbid conditions, presents a relatively high-risk patient to surgery. Preoperative preparation of the bariatric patient involves surgical, medical, and behavioral medicine assessments. All patients have a cardiac assessment of some kind, frequently a cardiac perfusion scan or other stress test. All patients have an esophagogastroduodenoscopy to assess the esophagus and stomach. In addition, patients selectively undergo a sleep study, pulmonary function test, colonoscopy.

Persons with untreated psychiatric disorder, on-going smoking, cancer diagnosis within the past 5 years, or medically unfit to undergo elective surgery are excluded from surgery.

Surgical Options

At the Palo Alto VA there are 3 operations that are available to the bariatric patient. All operations are preferentially performed laparoscopically, requiring general anesthesia, muscle relaxation, and CO₂-pneumoperitoneum. In order to gain access to the gastroesophageal junction in the severely obese, the patient is placed in steep reverse-Trendelenburg position during the operation.

1. Gastric bypass – The stomach is transected into two unequal parts. Most of the stomach, duodenum and proximal jejunum are bypassed, as two intestinal anastomoses are constructed.
2. Sleeve gastrectomy – Approximately 75% of the stomach volume is transected and removed, leaving a “sleeve”-like stomach based on the lesser curvature. There is no rearrangement of the gastrointestinal tract (no anastomoses)
3. Adjustable gastric band – A silicone-based inflatable band is placed around the proximal-most portion of the stomach. Stomach is not transected. There is no gastrointestinal tract rearrangement.

Postoperative complications

- Leak from the GI tract (anastomotic or staple-line leak) – presents early with tachycardia

- Bleeding – also presents with tachycardia
- Injury to internal organ
- MI
- PE/DVT – SCD's are placed on patients in the operating room and they are given Heparin 5000 U SC on call to OR for DVT prophylaxis. Heparin subcutaneously is continued throughout the admission. Inferior Vena Cava filters are placed selectively before surgery.
- Nausea/Vomiting – This is usually self-limited. All patients are prescribed anti-emetics in the postoperative period. Unlike in other general surgical patients, nasogastric tubes should be avoided if possible.
- Pneumonia – Posture, bed positioning and use of incentive spirometry is of paramount importance
- Wound infection – Much less common in laparoscopic cases (as compared to open surgery). All patients are given a single dose of intravenous antibiotics on-call to OR (typically Ancef 2 gm).

Postoperative Considerations

In the immediate postoperative period patients are strictly NPO (no sips, no ice, no medications. Because a potential leak is such a serious complication, PO status is changed by the surgeon only). Most patients are admitted to the ward postoperatively. Occasionally, bariatric patients require close respiratory or cardiac monitoring, or intravenous medications, necessitating admission to the intensive care unit. The intensity of care in the postoperative period frequently depends on the severity of the patient's co-morbid conditions, as well as potential intraoperative complications.

Close monitoring begins in the PACU. Re-intubation may be difficult in

patients with OSA or obese patients with a large neck circumference. Narcotics or sedating medications may decrease upper pharyngeal muscle tone, and in obese patients with OSA could lead to airway compromise. Narcotics and sedatives should be used judiciously.

Posture and positioning are very important. All patients are kept with head of bed elevated to 30-45°. Patients who use CPAP for sleep at home should be restarted postoperatively, despite potential concerns of increasing intra-gastric pressure in the immediate postoperative period.

Postoperative mobilization begins on the evening following surgery. For pulmonary toilet as well as for DVT prophylaxis, patients strongly encouraged to spend time out of bed early postoperatively; either by sitting in chair or ambulating. Special bariatric equipment is available, if necessary, to assist with mobilization (wide chairs, bariatric wheelchairs, walkers, commodes, special lifts).

Pain control is important to ensure adequate mobility. As described above, however, narcotics and sedatives should be used judiciously. Patient-controlled-analgesia (PCA) is typically used in the early postoperative period.

Fluid shifts may be dramatic after bariatric surgery, although less commonly with the use of laparoscopic surgery. Nonetheless, dramatic shifts can be seen in morbidly obese patients who spend the time of operation in steep reverse-Trendelenburg position, and are then abruptly returned to supine position. This may be especially true in patients with significant leg edema preoperatively. In addition, patients with OSA may have an element of right- or

left-sided heart failure, thus making postoperative fluid shifts even more difficult to manage. In general, patients after bariatric surgery are maintained on a maintenance IV of 125 ml/hr, and accepting a minimal urine output of 30 ml/hr (despite their total body weight). In an uncomplicated postoperative course, urine output begins to increase as the patient mobilizes more on the first postoperative day. At the same time, IV fluids are then minimized.

Bariatric surgery causes significant metabolic changes. In the setting of gastric bypass and sleeve gastrectomy, metabolic changes precede weight loss. The specific physiologic changes responsible for this phenomenon are not well understood.

After gastric bypass and sleeve gastrectomy, patients are often discharged from the hospital off all preoperative diabetic medications. Changes in secretion patterns of gastrointestinal hormones are frequently implicated. Levels of GLP-1, GIP, and Ghrelin have been shown to change significantly immediately postoperatively, compared to non-operative controls. These dramatic changes are not seen to the same extent after placement of an adjustable gastric band; supporting the theory that some combination of bypassing the proximal small intestine, early delivery of food to the distal small intestine, and/or exclusion of the gastric fundus are responsible for the insulinotropic effect of bariatric surgery.

For this reason, bariatric patients are not restarted on their hypoglycemic medications in the postoperative period, and long-acting hypoglycemics can be dangerous. With few exceptions, patients are kept on a regular insulin sliding scale throughout the

postoperative period, as insulin sensitivity can change dramatically.

When patients are cleared to take PO, they are started on 1 ounce of water per hour. All medications that are given orally must be liquid, chewable, or crushed. When diet is further advanced, postoperative patients are permitted to take 2 ounces (only) of Ensure, three times a day. If nausea occurs, this is held for an hour and tried again when nausea subsides. It is unusual for patients to feel hungry in the first few days after surgery.

More Discussion on the Management of Severe Sepsis: What are We Doing Here??

Geoff Lighthall

A discussion on the pathophysiology of septic shock and the overview of thoughts surrounding treatment were presented in the previous issue of this newsletter. Clinicians used to the tight pairing between clinical conditions and preferred treatments (i.e. infectious disease) might be frustrated that no such generalizations can be made for severe sepsis. Indeed, if we deliver a brown paper shopping bag with a few liters of fluid, broad spectrum antibiotics, norepinephrine and epinephrine, one could do a really good job treating nearly everyone with severe sepsis. The problem is, some patients may need the fluids and antibiotics and nothing else, while others may need one or both of the pressor agents, either with or without additional fluid. Nobody can tell you who will need what! The answer can only come from time spent at the patient's bedside, with careful consideration of fluid needs and fluid

responsiveness, and need for inotropes and vasopressors. Some of the considerations governing such needs were discussed in the last newsletter. While careful analysis of the patient's condition is essential, the patient will suffer if treatment is delayed. So with these challenges in mind, what has the VA Palo Alto done to facilitate these goals for patients with severe sepsis and septic shock?

Order sets. A standard order set was developed nearly four years ago with the following benefits in mind: (1) minimize the time spent on computers writing orders; (2), maximize time at the bedside where one can actually understand what is going on with the patient; (3), improve the efficiency and completeness of ordering; and (4) maintain a thinking approach to patient care. There are two order sets, the first is used in the acute stabilization phase where the activities of source identification, end-organ assessments, hemodynamic control, and following of metabolic parameters predominates. The second order set is used a few hours later, once more is known about the patient and his pertinent issues. The two-part system prevents lab studies from running out of control, and also allows one to use information gained about the patient at that point to be built into longer range plans, such as renal dosing of drugs, feeding plans, vent management, and use of other adjuncts such as infusions of insulin or activated protein C.

Currently, the order sets are accessible throughout the hospital when taking the following pathway: Intensive Care Orders Menu → Additional orders → Sepsis Primary Stabilization, Sepsis Secondary Stabilization. Once the ER

order menu is constructed, a variant of the primary stabilization order set will be available. We have so far found that when the order set is remembered and used, a full set of appropriate orders can be generated in 2-3 minutes, with more time to spend at the patient's side and actually delivering care.

ICU outreach to wards. Ideally, we like to have the sickest patients in the ICU, but sometimes we cannot control this. Illnesses can evolve, patients that looked good on the ward sometimes fail to respond to therapy or conform to the "ideal course," and misperceptions of illness and triage errors do occur. New problems can also pop up in the course of other illnesses already under treatment. Accordingly, a medical emergency team (*eTeam*) was created to offer additional diagnostic and therapeutic resources to patients in need. Components of the system include both subjective and objective criteria for identifying patients in need, as well as an interdisciplinary group (ICU fellow, triage attending, anesthesiologist, pharmacist, nurse & respiratory therapist) that can assist the primary team and ward staff in the evaluation and treatment of a patient. Unique capabilities of our team include the ability to institute real time invasive and non-invasive monitoring, point of care ABG, electrolyte, lactate and hemoglobin analysis, trans thoracic echocardiography and rapid administration of medications. All of the professions involved have been instrumental in maintaining the quality of this system and providing meaningful input into areas of improvement. Most recently, the pharmacists have helped

gain approval to carry Zosyn, Vancomycin, and Cipro in the eTeam pharmacy supply. With an eTeam call, we can start delivering antibiotics to a septic patient within five minutes of a call!

ICU outreach to the ED. Steve Scherr MD and Jenifer Ellman RN are working with the ICU to more rapidly identify and treat septic patients that come in from elsewhere. Thus, even if the ICU is full or cannot take a patient for a while, important clinical milestones will be met regardless of location. The aspects of care that we are currently working on are early notification of the ICU, source identification and early broad-spectrum antibiotics, and proper fluid resuscitation (see chart below). Many similar efforts focus on early central lines as part of the resuscitation bundle, but in many situations, this procedure delays early therapy more than facilitate it. We have therefore chosen to focus on improving cardiac output with fluids and getting in antibiotics as our initial goals. Many patients might not even need a central line if properly hydrated, but if they do, it's easier to get a line into a vein that actually has some blood in it!

Data analysis. Tracking cases of sepsis and comparing to other benchmarks and for internal quality maintenance is of course important, but easier said than done. We are currently working with Robert Chang in the DSS office to identify patients and outcomes using and ICD-9 codes for standard diagnoses. The fidelity of an initial data set is in the process of being cross-checked and verified using known cases of severe sepsis and septic shock.

The variability in human disease essentially guarantees that we will never be perfect in our identification and treatment of patients with severe sepsis. Rather than take this as a defense for imperfect performance, we should take this as challenge to make improvements where we can. One essential step in the right direction is a change in the “ICU culture” from being reactive (meaning waiting to be consulted), to becoming more proactive in defining what patients and at what time in their illness will benefit from critical care resources. For severe sepsis, the earlier the better.

Minutes		30	60	90	120	
Key Events	Arrival Triage		Place IVs Cultures Labs	Likely art line if hypotensive		
		Case ID Write orders			Central line. ICU staff will place. Keep CVP > 8	
Key Therapy				Antibiotics		
			Fluid Load 2L	Additional fluids		
Key People and management		Notify ER Attending within 5 min	Notify ICU* within 30 min if hypotensive or lactate >4	Possibly vasopressors		
				Continue to reassess needs for additional fluids, monitoring lines, and additional studies and therapies		

General Timeline for Management of Severe Sepsis and Septic Shock

New Faces in the ICU: Daphine Ly, MD

The following is a brief biosketch provided by Daphine Ly, MD, the most recent physician to join the ICU attending rotation.

I came from Vietnam and grew up in California, with undergraduate training in Math and Computer Sciences from San Jose State. I worked as a software engineer for seven years prior to going to medical school at Albert Einstein College of Medicine in Bronx, NY. (1994-1998). I started my General Surgery residency in 1998 at UMDNJ Robert Wood Johnson University Hospital, and during this time spent two years doing

research on the role of integrins in wound healing. I finished my residency in 2005. I spent 3 years in Michael Longaker’s laboratory at Stanford University doing more research in wound healing, specifically keloid and a synthetic EGF. I then spent one year in Surgical Critical Care at Stanford University Hospital. After that I joined the PAVA as a full time staff general surgeon and intensivist. I have an academic appointment as a clinician educator with the department of surgery at Stanford. My interest is using computer simulation and computer informatic in resident education as well as patient care. My general surgery practice includes thyroid/parathyroid surgery, breast and melanoma.