

## Accuracy of calculated creatinine among amputees: case presentation and literature review

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### Abstract

**Dosing vancomycin for patients who do not follow population pharmacokinetics can be challenging. Standard predictive clinical equations do not account for extreme patient characteristics. In particular, serum creatinine is significantly reduced while creatinine clearance is overestimated in patients with amputations. The “missing” body part must be accounted for when executing a dosing regimen for these challenging patients. In addition, health care profes-**

**sionals must judiciously review the patient holistically, practice evidence-based medicine, and consider the overestimation of renal function, when calculating doses for this and other agents. While current literature does not provide a clear consensus for this population, there are several factors to take into consideration when determining the optimal dose in patients presenting to the hospital requiring medications dosed by changes in renal function. We recently had one such case.**

**Key words:** Creatinine, amputee, amputation, creatinine clearance, vancomycin, glomerular filtration rate, GFR.

### Introduction

The accuracy of equations predicting creatinine clearance (CrCl) may be altered by several patient factors, such as malnutrition, obesity, old age, unstable renal function, amputations, spinal cord injury, and critically illness. (1) These special considerations also determine if some medications should be dosed based on actual body weight, ideal body weight, or adjusted body weight. (2) Examples of these medications include aminoglycosides, low-molecular-weight heparins (LMWH), acyclovir, and vancomycin. (2) For example, aminoglycoside

dosing interval strategies of conventional (multiple daily dosing) or extended interval dosing (once daily dosing), is chosen based on a patient's CrCl and other factors. (3) Extended interval dosing must not be used in patients with renal insufficiency. (3) In addition, actual body weight should be used unless the patient has obesity. (3) The latter may be defined as actual body weight greater than 20% of ideal body weight, or a body mass index (BMI) of 30 or greater. (3) Obese patients should be dosed only using adjusted body weight. (3,4) LMWH are dosed based on actual body weight, and the dose should be decreased when renal function is below 30 ml/min. (5) Acyclovir, on the other hand, is dosed based on actual body weight, unless the patient is obese, in which case ideal body weight should be used. Dosing concentration, as well as the interval, should also be modified according to CrCl.

In general, CrCl makes a significant difference in the dosing interval of renally excreted medications, therefore, it is imperative to measure this parameter as accurately as possible. Due to variability, drug concentrations may be monitored when considered appropriate and useful. Goals of monitoring include preventing toxicity, evaluating efficacy, and clinical management. (2)

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## Case presentation

A 56-year-old gentleman with a past medical history of coronary artery disease, hypertension, atrial fibrillation, congestive heart failure, transient ischemic attack, myocardial infarction, chronic pain, left leg amputation, and previous infection with methicillin resistant *Staphylococcus aureus* (MRSA) of the left hip, presented to emergency department with a three-day onset of productive cough, chest pain, generalized fatigue, weakness, fever, body aches, chills, nasal congestion, pain in his lower back and right lower extremity, and onset of shortness of breath. He also reported having multiple infected abscesses from orthopedic devices for his left hip disarticulation amputation. The patient was a smoker for over 20 years and drank 5-6 beers daily. In the emergency department (ED), a chest computed tomography (CT), revealed moderate size consolidation in the right lower lobe with surrounding ground glass opacities in the right lower and middle lobes, and a small right pleural effusion (**Figure 1**). Blood and sputum cultures were collected, ceftriaxone and azithromycin administered one time in the ED and a diagnosis of healthcare-associated pneumonia (HCAP) was made. Vancomycin 1500 mg every 12 hours was initiated empirically pending culture results and the Clinical Institute Withdrawal Assessment (CIWA) protocol was started. The patient's body weight was 90.7 kilograms, with a body mass index of 28.6 kg/m<sup>2</sup>. At the time vancomycin was initiated, the blood urea nitrogen (BUN) and serum creatinine (SCr) were 13 mg/dl and 0.87 mg/dl respectively. Using the Cockcroft-Gault equation, his estimated CrCl, based on regular ideal body weight, was calculated to be 97.9 ml/min. However, when taking into account the patient's estimated body weight loss due to his amputation, his estimated CrCl was 84 ml/min. After three vancomycin doses, a trough level was obtained about an hour prior to the next scheduled dose, which resulted in a level of 11 mcg/ml. Blood and sputum cultures and sensitivities revealed methicillin sensitive *Staphylococcus aureus* (MSSA) and antibiotics were de-escalated to cefazolin 2 grams every 8 hours. His right Groshong catheter of 4 months was removed with peripherally inserted central catheter (PICC) lines and catheter tip cultures and sent to lab. Later a CT of the abdomen showed fluid collection with gas at the left hip which was then drained and sent to the lab. PICC line cultures grew MSSA while catheter tip and body fluid cultures did not isolate any organisms. Infectious diseases and cardiology consult teams agreed to order a transthoracic echocardiogram (TEE), which dis-

played mild to moderate mitral regurgitation and mild tricuspid regurgitation on the color-flow Doppler, but no evidence of endocarditis. Patient also had new complaints of upper thoracic spine area and a magnetic resonance imaging (MRI) thoracic-spine was ordered to rule out osteo/diskitis due to tenderness. The scan revealed mild osseous edema within the T5 segment and disc bulge at T11-12, but no convincing evidence of discitis. The patient then began complaining of left wrist pain, however, x-ray of the wrist was unremarkable. After a few days, left wrist swelling improved. After 14 days, the patient was clinically stable with no other acute events. An order for a new Groshong catheter placement was completed and the patient was discharged home on cefazolin for 4 weeks of intravenous (IV) antibiotics.

## Discussion

Dosing in amputees can be challenging. In our case, two different creatinine clearance values were clinically significant enough to make a difference between every 8 versus 12-hour interval dosing.

Clinicians must consider the percentage of estimated body weight lost (% EBWL) in patients with amputations. These changes in therapy may have a major impact on achieving therapeutic versus non-therapeutic concentrations, and influencing the probability of toxicity.

For example, vancomycin remains one of the most common antibiotics used in the United States for the treatment of infections caused by MRSA. (6) This glycopeptide exhibits slow bactericidal properties by inhibiting cell wall synthesis. (7) The antibiotic binds to the d-alanyl-d-alanine portion of the bacterial cell wall and blocks peptidoglycan polymerization. (7) Some studies have shown vancomycin to display concentration-independent, time-dependent pharmacokinetic-pharmacodynamic (PK/PD) properties. (8) The area under the plasma concentration-time curve to minimum inhibitory concentration (AUC/MIC) ratio is recommended as the preferred parameter to measure vancomycin's efficacy and prevent toxicity. (6,8) Yet, despite the vast amount of research performed on this drug, controversies and conflicting evidence still remain. (6) These issues include serum concentration expected to reach toxicity, interpretation of laboratory parameters to measure efficacy, and the potential for nephrotoxicity and ototoxicity with different dosing concentrations. (9) Evidence-based research in dosing vancomycin in obese and amputee patients is limited, however, initially all populations are generally dosed using

actual body weight (ABW) while trough levels are used to adjust dosing regimens. (6,10-12) Trough concentrations are typically drawn one hour prior to achieving steady state in patients with normal renal function. (6,11)

The Cockcroft-Gault equation is commonly used to calculate CrCl to measure renal status. (3) The calculation is based on SCr and body weight, therefore, clearance may not accurately be reflected in patients with certain characteristics. For example, patients with lower muscle mass have reduced SCr levels, but consuming a meal-filled with protein would elevate the serum creatinine. (13) In addition, conditions such as obesity, increased muscle mass, geriatric populations, amputations, pregnancy, unstable renal function, and cystic fibrosis have extremes in their volume of distribution or metabolism, which is not accounted for in equations formulated for average healthy population kinetics. (13)

#### *The effect of amputation on pharmacokinetics*

Every year, approximately 185,000 individuals in the United States receive a limb amputation. (14,15) In addition, 2 million Americans are living with the loss of an extremity. (14,15) An estimated 54% is caused by diabetes, 45% due to trauma, and less than 2% from cancer of the bone and joint. (14,15) The pharmacokinetics of this population can be difficult, especially if limbs were amputated secondary to complications of diabetes along with poor renal function. (3,16)

Lower limb amputees have an even greater reduction in muscle mass. (16,17) This often results in an overestimation of CrCl. (2) When calculating ideal body weight (IBW) for an amputee, the missing body part must be accounted for by decreasing the IBW by a certain percentage. (3) A variety of manuscripts have yielded the body percentage weight that should be subtracted (**Figure 2**). (16,17) For example, if a patient has a below the knee amputation (BKA), multiply 6% times the IBW, then subtract that number from the IBW to get the new estimated ideal body weight. Alternatively, subtract 0.06 from 1, then multiply the difference by IBW. Standard equations are depicted in **Table 1**.

An above the knee amputation (AKA) would subtract 15% from the IBW, and a bilateral (B/L) AKA would subtract from IBW by 30%. If the patient's actual body weight is more than 125% of the newly calculated ideal body weight, one may then consider using adjusted body weight instead. (3) If actual body weight is used, clinicians will err on the side of caution when determining the initial

dose.

Some authors have described the percentage weight of each body part that should be subtracted from the ideal body weight in a patient with an amputation as follows: (3)

- Hand: 0.6%
- Forearm and hand: 2.2%
- Upper arm: 2.7%
- Total arm: 4.9%
- Foot: 1.4%
- Lower leg (knee and foot): 6%
- Thigh: 9.7%
- Total leg: 15.6%

Some authors consider the glomerular filtration rate (GFR), as a more accurate reflection of overall kidney function. (14,18) It factors in more variables into the equation such as age, gender, racial origin, and body size, and it declines with age. (14,19) However, estimated GFR (eGFR) is still limited due to the use of SCr as its main factor, and being based on population averages. (14,19) One retrospective study compared the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations in measuring eGFR, and concluded that the CKD-EPI equation overestimated eGFR in patients with a BMI of less than 20, while the MDRD formula overestimated GFR in critically ill patients overall. (20-23) This overestimation may be attributed to malnutrition, or decreased muscle mass in the critically ill population that was evaluated. The study % EBWL by using the Osterkamp method: (20,24)

- Partial hand: 0.35%
- Hand/wrist disarticulation: 0.7%
- Partial foot: 0.75%
- Foot: 1.5%
- Below elbow: 1.5%
- Above elbow: 3.65%
- Below-knee amputation: 3.7%
- Knee disarticulation: 4.4%
- Above-knee amputation: 10.95%
- Hip disarticulation: 16%

In the study results, an overestimation of renal function was correlated with loss of patient extremities. Moreover, patients with traumatic amputations may have lower SCr than what is reflected in laboratory parameters, providing a falsely elevated GFR. A reduced SCr can also be due to low protein intake, malnutrition, muscle atrophy, and immobility. (2) Another theory for this reduced SCr is that amputations can also lead to hyperfiltration, but this is yet to be proven. (20) The variation in serum creatinine may result in potential errors of

medication dosing based on renal function. (19) It is possible that an alternate kidney biomarker, such as cystatin C, may assess renal clearance more accurately in this patient population. (19) This low-molecular-weight protein is produced at a constant rate, and freely filtered through the glomerulus. (25) It is similar to creatinine in that plasma concentrations rise as GFR decreases, having an inverse relationship. However, cystatin C levels may be increased in the male gender, smoking, and increased height and weight. (13,25) In comparison to creatinine, not as many factors affect this biomarker. (19,25) It may be a more useful marker than creatinine, however, a limited number of assays are available and a standard measure has not yet been confirmed. (19,25)

### Conclusions

Medication dosing in amputees can be a challenge for clinicians. Documentation of missing extremities may not be adequately stated in patient charts or the information may be overlooked. Amputees have a reduced level of SCr, leading equations to overestimate true renal function. Utilizing laboratory tests, past medical history, and clinical judgement plays a significant role when dosing vancomycin and other agents in this selected population, as the pharmacokinetic/pharmacodynamic data is limited.

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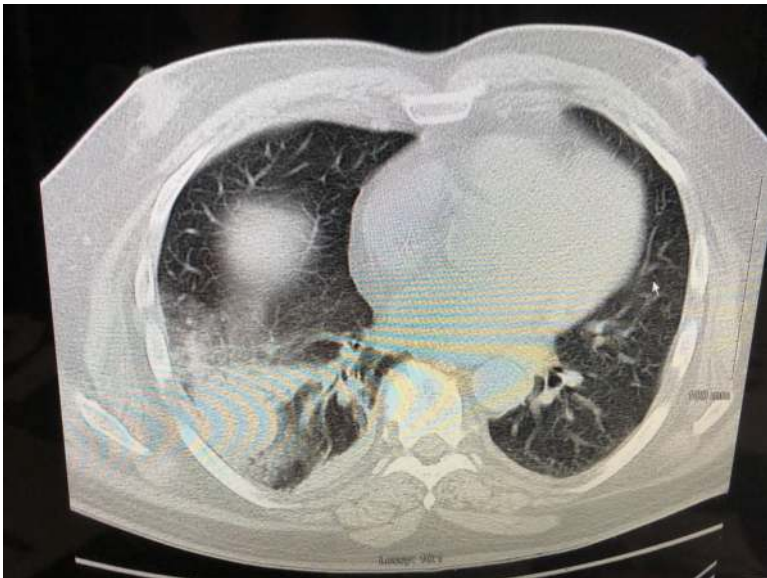
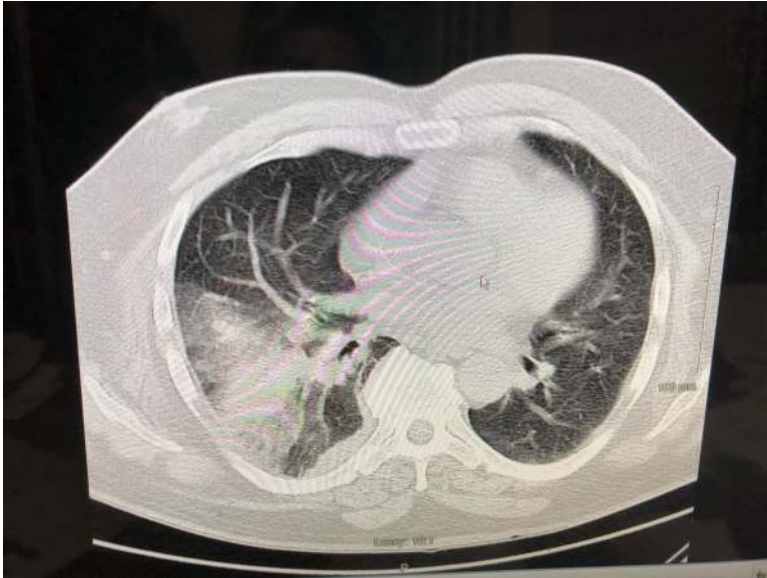
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**Table 1.** Standard equations in calculation of creatinine clearance

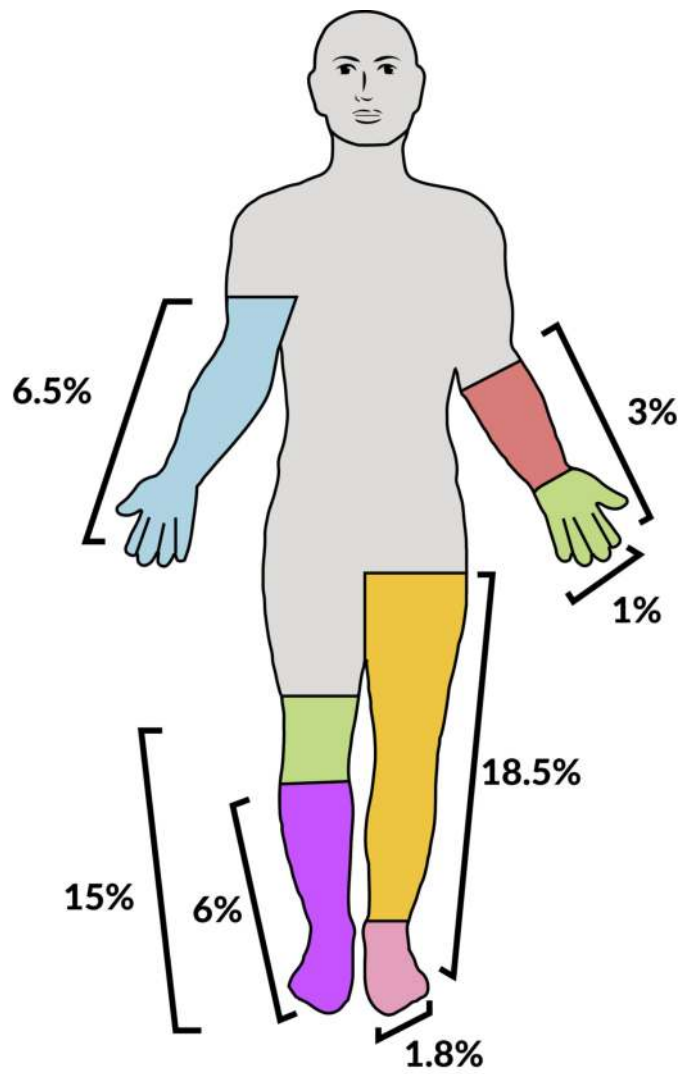
Equations (2,11,14)	
CrCl	$[(140 - \text{age of patient}) / (72 \times \text{SCr})] \times \text{weight in kg} (\times 0.85 \text{ if female})$
IBW	Males: $50 \text{ kg} + (2.3 \text{ kg})(\text{height in inches} - 60)$ Females: $45.5 \text{ kg} + (2.3 \text{ kg})(\text{height in inches} - 60)$
Amputation IBW	$(1 - \text{EBWL}) \times \text{IBW}$
AdjBW	$\text{IBW} + 0.4 (\text{ABW} - \text{IBW})$
Vancomycin dosing	15-20 mg/kg (based on actual body weight)

Legend: CrCl=creatinine clearance; IBW=ideal body weight; EBWL=estimated body weight lost; AdjBW=adjusted body weight; ABW=actual body weight.

**Figure 1.** CT scan showing consolidation in the right lower lobe



**Figure 2.** Figure depicts the percentage of adjustment needed to be done in calculation based on the body parts amputated



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