Vancomycin use in a rural hospital: a 3-year retrospective study

Megan Bollinger, MD, CFPC
Northern Ontario School of Medicine, Sioux Lookout, Ont.

Marsha Hamilton, RN
Sioux Lookout Meno Ya Win Health Centre, Sioux Lookout, Ont.

Kurt Schroeder, BSc(Pharm)
Interlake Regional Health Authority, Selkirk, Man.

Sonia Link, BSc(Pharm)
Sioux Lookout Meno Ya Win Health Centre, Sioux Lookout, Ont.

Jasmyn Nguyen
Dominic Chu
Royal College of Surgeons in Ireland, Dublin, Ireland

Wilma Hopman, MA
Kingston General Hospital, and Department of Community Health and Epidemiology, Queen's University, Kingston, Ont.

Raphael Saginur, MD, FRCPC
Division of Infectious Diseases, Ottawa Hospital Research Institute, and Faculty of Medicine, University of Ottawa, Ottawa, Ont.

Len Kelly, MD, MClin Sci, FCFP, FRRM
Anishinaabe Bimaadiziwin Research Program, Sioux Lookout, Ont.

Correspondence to: Megan Bollinger; mbollinger@nosm.ca

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Introduction: Urban centres often perform audits of vancomycin use as they face outbreaks of resistant organisms. We undertook this study to understand the indications and duration of intravenous vancomycin in a rural setting.
Methods: We conducted a retrospective chart audit for all patients who received intravenous vancomycin over a 3-year period at a rural hospital in northwestern Ontario.
Results: Vancomycin was used intravenously in 180 patients during the study period. It was used for short courses (median 3 d), and serum levels were below target 72% of the time.
Conclusion: High rates of invasive methicillin-resistant *Staphylococcus aureus* bacteremia and limited antibiotic choices in the field likely contributed to short courses of this antibiotic. Further study on clinical severity and antibiotic choice is needed. Additionally, weight-based dosing may result in target serum levels being achieved more frequently.

Introduction : Les centres urbains effectuent souvent des vérifications de l'utilisation de la vancomycine en raison du risque d'éclosions d'infections causées par des agents pathogènes résistants. Nous avons entrepris cette étude pour comprendre les indications et la durée de l'antibiothérapie par vancomycine intraveineuse en région rurale.
Méthodes : Nous avons procédé à une analyse rétrospective des dossiers de tous les patients qui ont reçu de la vancomycine intraveineuse sur une période de 3 ans dans un hôpital rural du Nord-Ouest de l'Ontario.
Résultats : La vancomycine a été administrée par voie intraveineuse chez 180 patients durant la période de l'étude. Elle a été utilisée pendant de courtes périodes (durée médiane 3 jours) et les taux sériques étaient inférieurs aux taux ciblés 72 % du temps.
Conclusion : Les taux élevés de bactériémie invasive à *Staphylococcus aureus* méthicillinorésistant et le choix limité d'antibiotiques sur le terrain ont probablement contribué à la brièveté des antibiothérapies avec cet agent. Des études plus approfondies sur la gravité des cas cliniques et le choix des antibiotiques s'imposent. De plus, l'établissement de la dose en fonction du poids corporel pourrait favoriser l'atteinte plus fréquente des taux sériques cibles.

INTRODUCTION

Antibiotic stewardship is an increasing prerogative in all clinical settings. The discussion often focuses on tertiary care centres. However, rural hospitals face their own inherent issues concerning available antibiotics, diagnostic resources, and patient and geographical factors. In clinical practice, the initial choice of antibiotic is usually empiric. Also, in settings without an on-site laboratory facility, there may be delays in receiving microbiological results, thereby requiring clinicians to use local bacterial prevalence to guide therapy.

In northwestern Ontario, there has been a dramatic increase in community-associated methicillin resistant *Staphylococcus aureus* (CA-MRSA) infections.[1] These infections, which are most often in skin or soft tissue, are almost universally susceptible to sulfamethoxazole–trimethoprim, clindamycin or doxycycline, but

more invasive infections of suspected MRSA are often treated with vancomycin.[2] We have documented a rise in life-threatening invasive CA-MRSA bacteremia, with cases occurring monthly in our region.[3] A 6-week course of vancomycin is the treatment of choice for these invasive infections, which can have a death rate as high as 23%.[4–6] Vancomycin is an effective antibiotic in certain life- and limb-threatening infections. However, its widespread use is implicated in an increasing incidence of vancomycin-resistant enterococcus,[7] and it has inherent toxicities.

The Meno Ya Win Health Centre in Sioux Lookout serves a primarily First Nations population of 28 000 people in northwestern Ontario. The population lives in 31 remote communities that are distributed across 385 000 km^2 (an area half the size of Ontario) and linked by fixed-wing air transportation and seasonal winter roads.[8] Communities typically receive their medical services from in-community nurses, with monthly physician visits. Poor housing, overcrowding, food and water insecurity, and a pandemic of intravenous drug use are contributing factors to high rates of illness due to infectious diseases.[3] Patients are often triaged "at a distance" by telephone communication between a community nurse and a Sioux Lookout physician. Antibiotic therapy can be started in the community by physician order and blood samples drawn but then shipped to the hospital for processing. Without road access, community nurses "medevac" patients in the case of serious illness. Ornge, which manages the air ambulance service, stocks only vancomycin and ceftriaxone as antibiotics. The Sioux Lookout Meno Ya Win Health Centre has an on-site microbiology laboratory, but until recently was not capable of on-site testing of vancomycin trough levels.

We undertook a 3-year retrospective clinical audit of our use of vancomycin to assess what clinical diagnoses were being treated with the antibiotic, to evaluate our dosing and monitoring, and to examine what eventual culture results were obtained to tailor the antibiotic regimen.

METHODS

Chart audit

A retrospective chart audit was conducted for all patients who received intravenous vancomycin at the Sioux Lookout Meno Ya Win Health Centre between June 1, 2010, and June 1, 2013. Audit information included patient demographics, clinical diagnosis, and specific information regarding vancomycin dose and course. Concurrent antibiotics; monitoring parameters, including vancomycin trough level (before the fourth dose) and serum creatinine; culture results; sensitivities; and patient disposition were also included. Initial serum trough levels were the only ones recorded in our audit, because the research focus was on antibiotic initiation. Target vancomycin levels were deemed to be 15–20 mg/L. There are 3 common dosing methods for vancomycin for adult patients with normal renal function: 1) 1 g intravenously every 12 hours; 2) 15 mg/kg intravenously every 12 hours; 3) loading dose of 25–30 mg/kg, followed in 12 hours by one of the above doses every 12 hours. We typically used the first method.

Data analysis

Data were collected in a Microsoft Excel spreadsheet and imported into IBM SPSS (version 21.0 for Windows) for statistical analysis. The data were analyzed descriptively, including means and standard deviations (SDs) for continuous data, and frequencies and percentages for categorical data. Analysis was done for the entire sample in subsets, as appropriate.

The research review committee of the Sioux Lookout Meno Ya Win Health Centre and the Lakehead University's Research Ethics Board gave ethics approval.

RESULTS

Between June 2010 and June 2013, intravenous vancomycin was ordered for 180 inpatients, all of whom were included in this chart audit. Half of the patients were male (50.8%). Patient age ranged from 8 days to 93 years, with a mean of 45.4 (SD 19.8) years. The frequency of β-lactam allergies was 15.0% (27 patients), with only one being a documented anaphylactic reaction.

Most of the infections treated with vancomycin were skin and soft tissue infections (34.4%), followed by bone and joint infections (Table 1).

Prior and concomitant antibiotic use

Antibiotics had been used in the preceding 24 hours in 43.2% of patients. The most commonly used antibiotics were ceftriaxone (19.2%) and clindamycin (11.4%). Another antibiotic was used concomitantly with vancomycin in 77.6% of cases, most commonly ceftriaxone (33.3% of total cases).

Dosing and length of treatment

In the initial dosing of the 104 adults with normal renal function, the vancomycin dose was empiric in 77.6% of cases, with 1 g given intravenously every 12 hours. Weight was recorded or estimated 43.3% of the time (78/180 patients). Weight-based dosing in adults occurred in 27 patients but was not statistically associated with achieving the target range of vancomycin levels (3 patients had levels within the target range, 8 had levels below the target range and 3 had levels above the target range) because many of these patients did not have vancomycin levels listed in their charts (13/27). Serum creatinine values were recorded in most charts (89.4%, 161/180), and 13.7% (22/161) had a degree of renal failure (estimated glomerular filtration rate < 90 mL/min).

The duration of treatment with vancomycin ranged from 1 to 90 (mean 6.59, SD 10.16) days. Data were skewed because 1 patient received treatment for 90 days; the median length of treatment was 3 (interquartile range 2–7) days. For skin and soft tissue infections, half of the patients took vancomycin for 3 days or less (Fig. 1). Patients transferred to other facilities were not counted.

Drug monitoring

Serum vancomycin trough levels were reported for 60.0% (108/180) of patients receiving intravenous vancomycin. The levels of 13.3% (24/180) of patients could not be accessed because they had already discontinued the medication before the timing of the fourth dose. Of the patients with trough levels, only 12.0% (13/108) of those levels fell within the ideal target range, whereas 72.2% (78/108) were suboptimal. There was no record of trough levels in the chart in 30.8% (48/156) of patients who received at least 4 doses (Table 2).

Culture results

Of patients given vancomycin, 65.6% had blood cultures done. Blood cultures were performed for all cases of endocarditis and most cases of respiratory and central nervous system infection. Blood cultures were not done for 53.2% of cases of skin and soft tissue infection (Table 3).

In the 35 patients with positive results on blood culture, methicillin-resistant *S. aureus* (MRSA) was grown with a frequency of 31.4% (11/35), methicillin-susceptible *S. aureus* was found in 14.3% of cases (5/35), and group A *Streptococcus* in 20.0% of cases (7/35) (Tables 3 and 4).

More than half (58.3%) of the patients had a nonblood culture. These cultures were positive 62% of the time, showing a greater frequency of a positive culture result from a source other than blood (30%) (Table 5).

Culture results were stratified by syndrome into the following categories: skin and soft tissue, bone and joint, diabetic foot, respiratory, endocarditis, central nervous system and other infections.

Table 1: Suspected infection as indication for vancomycin, *n* = 180

Infection site	No. (%) of patients
Skin and soft tissue*	62 (34.4)
Bone and joint†	30 (16.7)
Respiratory	41 (22.8)
Diabetic foot	18 (10.0)
Central nervous system‡	6 (3.3)
Endocarditis	6 (3.3)
Other§	17 (9.4)

*Included cellulitis, abscess and necrotizing fasciitis.
†Included osteomyelitis and septic arthritis.
‡Included meningitis and suspected brain abscess.
§Included gastrointestinal and genitourinary infections, febrile neutropenia, dialysis line infections, bacteremia without a known source, septic otitis media, pancreatitis and some postoperative treatment.

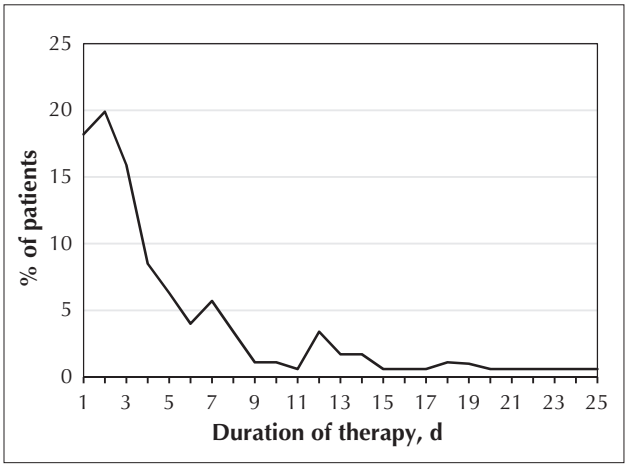

Fig. 1. Duration of therapy in 180 inpatients given intravenous vancomycin.

Table 2: Measured trough levels, *n* = 108*

Initial trough level, mg/L	No. (%) of patients
< 5	16 (14.8)
5–10	44 (40.7)
10.1–15	18 (16.7)
15.1–20 (target range)	13 (12.0)
> 20	17 (15.7)

*Levels were not measured in 72 patients.

There was considerable variability in the frequency of cultures performed, including 31.7% of respiratory cultures, likely reflecting the limited utility of sputum cultures in a non–intensive care setting. In suspected infections of the central nervous system, cerebrospinal fluid was sent for culture in 83.3% of cases; 1 patient with known lung cancer and bone metastases was transferred with headache for advanced imaging before lumbar puncture in a tertiary care centre. A substantial number of swabs were done for diabetic foot infections, all of which showed positive results for a wide variety of potential pathogens. This may demonstrate colonization rather than true infection due to these organisms.

We had no reported cases of resistance to vancomycin for gram-positive organisms from any source in these 180 patients.

Table 3: Results of blood cultures, by site of infection

Infection site	% (no.) of patients: Blood culture performed	% (no.) of patients: Positive result	Most frequent culture isolates
Bone and joint	60.0 (18/30)	44.4 (8/18)	MSSA (2/8)
Skin and soft tissue	46.8 (29/62)	24.1 (7/29)	MRSA, group A *Streptococcus* (3/7 each)
Respiratory	82.9 (34/41)	26.5 (9/34)	MRSA (4/9)
Diabetic foot	66.7 (12/18)	25.0 (3/12)	MRSA, viridans streptococci, group B *Streptococcus* (1/3 each)
Endocarditis	100.0 (6/6)	33.3 (2/6)	MSSA, *Streptococcus salivarius* (1/2 each)
Central nervous system	83.3 (5/6)	33.3 (2/6)	MSSA, group A *Streptococcus* (1/2 each)
Other	76.5 (13/17)	30.8 (4/13)	—
Total	65.6 (117/180)	29.7 (35/118)	—

MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*.

Table 4: Bacterial isolates from positive blood cultures, *n* = 35

Bacteria isolated	% (no.) of patients
MRSA	31.4 (11)
MSSA	14.3 (5)
Group A *Streptococcus*	20.0 (7)
Streptococcus viridans	8.6 (3)
Streptococcus pneumoniae	8.6 (3)
Group B *Streptococcus*	2.9 (1)
Gram-negative bacteria	5.7 (2)
Bacillus species (likely contaminant)	2.9 (1)
Coagulase-negative *Staphylococcus*	8.6 (3)

MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*.

Table 5: Results of nonblood cultures, by site of infection

Infection site	% (no.) of patients: Culture performed	% (no.) of patients: Positive result	Most frequent culture isolate(s)
Bone and joint	76.7 (23/30)	65.2 (15/23, 3 mixed)	MRSA (7/18)
Skin and soft tissue	61.3 (38/62)	60.5 (23/38, 9 mixed)	MRSA (14/32), group A *Streptococcus* (11/32)
Respiratory	31.7 (13/41)	27.3 (3/11 sputum), 0.0 (0/2 pleural fluid)	1/3 each MRSA, MSSA and *Haemophilus influenzae*
Diabetic foot	83.3 (15/18)	100.0 (15/15, 6 mixed)	Gram-negative (7/21), MRSA (6/21)
Endocarditis	0.0 (0/6)	NA	—
Central nervous system	83.3 (5/6)	60.0 (3/5)	1/3 each MSSA, group A *Streptococcus*, *Bacillus*
Other	64.7 (11/17)	36.4 (4/11)	Gram-negative (2/4)
Total	58.3 (105/180)	63.0 (66/107)	—

MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*; NA = not applicable.

Disposition

Most patients (73.2%) were eventually discharged home, and 20.8% were transferred to a facility with an intensive care unit. Three patients died of their infection: a neonate with invasive group A streptococcal meningitis, a 19-year-old with pneumonia without positive cultures and a 73-year-old with osteomyelitis who later had respiratory failure secondary to aspiration pneumonia. Three patients with bone and joint infections required amputations of the infected site.

After culture results were returned, vancomycin was discontinued in 28.4% of cases. Of 101 patients with a positive result on blood or tissue culture, excluding those who died or were transferred, 38.2% of patients were stepped down to another antibiotic and 61.8% continued taking vancomycin. Severity of infection was not assessed in our study, so it is unknown whether daptomycin or a more commonly used antibiotic such as sulfamethoxazole–trimethoprim, tetracycline or clindamycin would have been acceptable alternatives. The high incidence of MRSA in tissue cultures (42.4% [28/66]) demonstrates the need for one of the above therapies, including vancomycin, where antibiotics were clinically warranted.

Toxicity

Nephrotoxicity (a serum creatinine increase of > 50%) occurred in 3.9% of patients (7/180). Of those 7 patients, 3 had trough levels above the therapeutic range (> 20 mg/L), 2 had levels below the range and for 2 patients the trough levels were unknown. The initial mean dose for patients who had nephrotoxicity was 1021.43 (SD 107.46) mg. One patient had a possible case of red man syndrome (a vancomycin-related dermatologic reaction requiring a slowing of the infusion rate). There were no reports of ototoxicity found in this audit. There was 1 case of possible vancomycin-induced neutropenia; the patient's medication was then changed to cefazolin for coverage of postoperative endocarditis following pacemaker insertion.

DISCUSSION

Four main findings arise from this clinical audit of vancomycin use: below-target dosing, short duration of use, inadequate monitoring of serum trough levels and blood cultures done for 65.6% of cases with vancomycin use.

Dosing

Serum levels were subtherapeutic 72% of the time in our audit.

Initial doses should be based on actual body weight, even for obese patients, to achieve target therapeutic concentrations. Weight was recorded or estimated in only 43.3% of patients. This is not a standard procedure in our hospital, and it provides an additional barrier to ordering a weight-based dose. The traditional dose of 1 g every 12 hours is likely inadequate for an adult patient with normal renal function and serious MRSA infections. This has been reinforced by several large American studies.[9–11]

Even use of a larger loading dose (25–30 mg/kg) appears to be safe and potentially leads to faster achievement of therapeutic levels, according to a guideline by the Infectious Diseases Society of America (IDSA).[10] There are no data to support that this improves clinical outcomes, but this might be considered for seriously ill patients (Grade B recommendation: moderate evidence to support use).[10] Vancomycin is primarily excreted unchanged in the urine; therefore, initial adjustments of dose (or time) intervals must be made for renal insufficiency.[12–14] For patients with serious MRSA infections, vancomycin serum trough concentrations of 15–20 mg/L are recommended, and this is the target range in our facility. If the strain has a higher resistance, measured as a minimum inhibitory concentration of 2 or greater, then higher doses are needed, which increases the risk of toxicity. This may prompt the use of an alternate antibiotic such as linezolid or daptomycin.[9]

Duration of use

Ideally, antibiotic selection should be tailored based on culture results. Exposing infectious organisms to multiple inappropriate antimicrobial agents may increase the potential development of resistance. In this audit, those with severe skin and soft tissue infections were commonly given vancomycin for several days, and then switched to another agent. This was sometimes done before serum vancomycin trough levels were assessed. This practice may be a function of the availability of vancomycin in northern nursing stations and medical transportation services, or of physician preference. Initial patient triaging is often done at a distance, and patient transportation can take hours or days depending on weather, perceived acuity and transportation availability. Our clinical setting also has high rates of CA-MRSA, including cases of life-threatening invasive bacteremia,[1,3] and

this finding will have to be balanced with use of very short courses of vancomycin identified in this audit.

In cases of sepsis or severe skin and soft tissue infection, a short course of vancomycin, pending culture results, might be the best practice in our setting. The audit did not rate clinical severity due to the retrospective nature of the study, and it would be prudent to be aware of this usage pattern. More research will be needed to understand whether vancomycin is the best initial choice and why it is often stopped after a short course. It is not clear whether the initial choice of antibiotic reflects available drugs at the nursing station and the transportation service, and the distant "over-the-phone" assessment, which is a fact of life in our region. Vancomycin requires several half-lives to reach therapeutic levels when dosed in the manner most commonly seen in this audit; such practice may lead to the development of resistance without establishing effective serum levels and duration of treatment.

Monitoring

Monitoring of vancomycin has a dual purpose in guiding maintenance dosing to achieve therapeutic serum concentrations and assessing the risk of nephrotoxicity. According to the IDSA guideline, trough levels of greater than 10 mg/L are needed to prevent resistance, whereas a level of 15–20 mg/L is targeted for treatment of pathogens with complicated infections, including endocarditis, osteomyelitis, meningitis and hospital-acquired pneumonia.[10] Samples should be drawn to assess trough concentrations before the fourth dose, when steady state levels are likely achieved. Frequency of trough-level testing depends on the patient's status and clinical course; more frequent monitoring is recommended for patients with fluctuating renal function. For prolonged courses, vancomycin levels should be checked weekly in hemodynamically stable patients.[10,12] Available evidence does not support the monitoring of peak serum vancomycin concentrations.[10] Monitoring of vancomycin to prevent ototoxicity is not supported by the literature because this toxicity is often due to concomitant use of other ototoxic medications (particularly aminoglycosides) and does not correlate with serum concentrations of vancomycin.[10] Our audit found trough levels missing in 40% of the charts. Trough measurement is particularly important in our population, because we do see high rates of renal failure,[15] even though we saw very little nephrotoxicity in this audit. The missing trough levels are partly explained by the antibiotic often being stopped early, but we will need to be more focused on appropriate trough levels particularly if we move to increased dosing. Interestingly, an IDSA guideline from 2011[16] allowed that serum levels may not be needed in stable patients who are given the 1 g every 12 hours. Because we had a majority of patients with initial trough levels below the target range and our patient population already has a high rate of renal failure, attention to monitoring serum levels needs to continue in our facility.

Cultures

We have high rates of skin and soft tissue infections with CA-MRSA in our region[1] as well as increasing rates of life-threatening invasive disease. Of the positive blood cultures, 31.4% (11/35) were MRSA (Table 4), as were 40.9% (27/66) of the positive tissue cultures (Table 5). Because bacteremia from CA-MRSA is often secondary to soft tissue or bone infections, serological surveillance with blood cultures is prudent and should likely be commonplace if vancomycin is initiated in our population. Our audit noted a 65.6% rate of clinicians ordering blood cultures concomitant with vancomycin institution. As the gravity of the diagnosis increased, blood culture results were more likely to be recorded in the charts (i.e., 100% of endocarditis cases and 82% of both respiratory and central nervous system infections). Gathering appropriate deep swabs, rather than superficial swabs, after debriding wounds also should become routine practice.

Comparison with other studies

Data are lacking for comparison with other vancomycin audits conducted in rural hospitals. Urban-based audits have focused on clinical indications to use vancomycin. A nearby centre demonstrated 60% "inappropriate vancomycin use" most often associated with empiric use for treatment of sepsis.[17] Our setting differs from a tertiary care centre's use of vancomycin audits, where outbreaks of both vancomycin-resistant enterococcus and health care–associated methicillin-resistant *S. aureus* are major concerns.

Limitations

Our communities and hospital are now experiencing a shifting pattern of MRSA infections with very high rates of CA-MRSA, for which alternative antibiotics are available.[2] The exception is the

recently rising incidence of invasive CA-MRSA bacteremias for which a prolonged (2–6 wk) course of intravenous vancomycin is one of the recommended choices of treatments. Our data set was collected before the increased incidence of CA-MRSA bacteremias. We suspect that longer courses of vancomycin will become increasingly common in future audits.

The audit occurred during the introduction of electronic medical laboratory reporting. Although paper charts were considered to be complete, the transition may have left some data off the paper charts. To the best of our ability, we checked electronic charts as well. Additionally, serum vancomycin laboratory samples at the time of the audit needed to be shipped to another centre, which potentially affected the timing and integrity of the results.

Because the regional air ambulance service stocks only vancomycin and ceftriaxone, these antibiotics might be favoured as initial antibiotic choices for patients with sepsis being transported from remote communities. This may also be a factor in the audit findings of early cessation of this antibiotic, once patients were triaged and reassessed on admission to hospital. Pharmaceutical limitations in northern nursing stations and air ambulance presently also preclude the choice of newer (and less cost-effective) agents such as linezolid or daptomycin (also effective against MRSA) as agents of first choice where they may be needed.[18]

CONCLUSION

Most courses of vancomycin were brief, and more work is required to assess the appropriateness of vancomycin use and duration of therapy in rural and remote settings. In a region with increasing rates of invasive CA-MRSA bacteremia, we will need to be familiar with vancomycin's indication, dosing, monitoring and toxicity. Our antibiotic use and infectious disease surveillance can also inform the appropriateness of antibiotic supplies in remote communities and regional air ambulance services for northwestern Ontario. Our results show areas in which further education can be done in our hospital to improve dosing strategies and monitoring, and to encourage reflection on antibiotic choices. Empiric dosing may deliver subtherapeutic serum levels in our population, and weight-based dosing may be more appropriate.

Competing interests: None declared.

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