Clinical Blood Isolates from Hemodialysis Patients: Distribution of Organisms and Antimicrobial Resistance, 2007–2014

Courtney K Lawrence, Chris Sathianathan, Mauro Verrelli, Philippe Lagacé-Wiens, Robert Ariano, Grace Badejo, Michelle L Boyce, J Christine Davis, and Sheryl A Zelenitsky

Can J Hosp Pharm. 2020;73(4):266-71

ABSTRACT

Background: Given the morbidity and mortality associated with bloodstream infections in hemodialysis patients, understanding the microbiology is essential to optimizing treatment in this high-risk population.

Objectives: To conduct a retrospective surveillance study of clinical blood isolates from adult hemodialysis patients, and to predict the microbiological coverage of empiric therapies for bloodstream infections in this population.

Methods: Clinical blood isolate data were collected from the 4 main outpatient hemodialysis units in Winnipeg, Manitoba, from 2007 to 2014. The distribution of organisms and antimicrobial susceptibilities were characterized. When appropriate, changes over time were tested using time series analysis. Study data were used to predict and compare the microbiological coverage of various empiric therapies for bloodstream infections in hemodialysis patients.

Results: The estimated annual number of patients receiving chronic hemodialysis increased steadily over the study period ($p < 0.001$), whereas the number of blood isolates increased initially, then decreased significantly, from 180 in 2011 to 93 in 2014 ($p = 0.04$). Gram-positive bacteria represented 72.6% (743/1024) of isolates, including *Staphylococcus aureus* (36.9%, 378/1024) and coagulase-negative staphylococci (23.1%, 237/1024). Only 26.1% (267/1024) of the isolates were gram-negative bacteria, the majority Enterobacteriaceae. The overall rate of methicillin resistance in *S. aureus* was 17.5%, and although annual rates were variable, there was a significant increase over time ($p = 0.04$). Antibiotic resistance in gram-negative bacteria was relatively low, except in *Escherichia coli*, where 13.5% and 16.2% of isolates were resistant to ceftriaxone and ciprofloxacin, respectively. Empiric therapy with vancomycin plus an agent for gram-negative coverage was predicted to cover 98.8% to 99.7% of blood isolates from hemodialysis patients, whereas cefazolin plus an agent for gram-negative coverage would cover only 67.5% to 68.4%.

Conclusions: In an era of increasing antimicrobial resistance, data such as these and ongoing surveillance are essential components of antimicrobial stewardship in the hemodialysis population.

Keywords: hemodialysis, microbiology, surveillance, resistance, antimicrobial stewardship

RÉSUMÉ

Contexte : Étant donné la morbidité et la mortalité associées aux infections du sang parmi les patients en hémodialyse, la compréhension de la microbiologie est essentielle à l'optimisation du traitement de cette population exposée à un risque élevé.

Objectifs : Mener une étude de surveillance rétrospective des isolats de sang cliniques des patients adultes en hémodialyse et prédire la couverture microbiologique des thérapies empiriques contre les infections du sang dans cette population.

Méthodes : Les données relatives aux isolats de sang cliniques ont été recueillies dans les quatre unités ambulatoires principales d'hémodialyse à Winnipeg (Manitoba), entre 2007 et 2014. La caractérisation a porté sur la distribution des organismes et les susceptibilités aux antimicrobiens. L'évolution dans le temps a été testée au besoin à l'aide d'une analyse chronologique. Les données de l'étude ont permis de prédire et de comparer la couverture microbiologique de diverses thérapies empiriques contre les infections du sang pour les patients en hémodialyse.

Résultats : On estime que le nombre annuel de patients recevant une hémodialyse chronique a augmenté régulièrement au cours de la période de l'étude ($p < 0{,}001$); le nombre d'isolats de sang a tout d'abord augmenté, puis il a grandement diminué : de 180 en 2011, il est passé à 93 en 2014 ($p = 0{,}04$). Les bactéries à Gram positif représentaient 72,6 % (743/1024) des isolats, y compris les *Staphylococcus aureus* (36,9 %, 378/1024) et les staphylocoques à coagulase négative (23,1 %, 237/1024). Seulement 26,1 % (267/1024) des isolats étaient des bactéries à Gram négatif, la majorité desquelles étant des Enterobacteriaceae. Le taux général de résistance à la méticilline de *S. aureus* était de 17,5 %, et bien que les taux annuels étaient variables, une augmentation importante a été observée avec le temps ($p = 0{,}04$). La résistance aux antibiotiques des bactéries à Gram négatif était relativement faible, sauf *Escherichia coli,* où respectivement 13,5 % et 16,2 % des isolats étaient résistants à la ceftriaxone et à la ciprofloxacine. On prévoyait que la thérapie empirique à la vancomycine associée à un agent pour la couverture à Gram positif couvrirait de 98,8 % à 99,7 % des isolats de sang des patients en hémodialyse, tandis que la céfazoline associée à un agent de la couverture à Gram négatif ne couvrirait que 67,5 % à 68,4 %.

Conclusions : À une époque qui se caractérise par une augmentation de la résistance aux antimicrobiens, des données comme celles-ci et celles portant sur la surveillance continue sont des composantes essentielles de la bonne gestion de l'utilisation des antimicrobiens pour les patients adultes en hémodialyse.

Mots-clés : hémodialyse, microbiologie, surveillance, résistance, gestion de l'utilisation des antimicrobiens

INTRODUCTION

Infectious diseases are associated with significant morbidity and are the second leading cause of death among patients receiving hemodialysis (HD).[1] Notable risk factors for infection include comorbidities (e.g., diabetes), immunosuppression associated with renal disease, and the requirement for vascular access.[2] Bloodstream infections in HD patients can also lead to serious complications such as septic thrombosis, osteomyelitis, and endocarditis.[3] In general, the treatment of bloodstream infections in this population is associated with high failure rates, poor clinical outcomes, and substantial health care costs.[4]

It is important to understand the microbiology of infections in high-risk populations where antimicrobial resistance rates and emerging trends can inform the selection of empiric therapy. Such surveillance is especially relevant in HD patients given their regular contact with health care settings, high rates of infection, and frequent use of antibiotics.[4,5] Bloodstream infections in HD patients are most often associated with gram-positive skin flora, followed by gram-negative bacteria and occasionally yeast.[2] The more common pathogens in this population are associated with resistance concerns such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* spp. (VRE), extended-spectrum β-lactamase-producing (ESBL) Enterobacteriaceae, and multidrug-resistant *Pseudomonas* spp. and *Acinetobacter* spp.[6,7] Clinical practice guidelines for the management of intravascular catheter–related infections in HD patients are broad, recommending "vancomycin and coverage for gram-negative bacilli, based on the local antibiogram (e.g., third-generation cephalosporin, carbapenem, or β-lactam/β-lactamase combination)" and cefazolin as an alternative to vancomycin in units with a low prevalence of MRSA.[8]

Despite the value of microbiological surveillance, studies in HD patients are limited,[2,4,9,10] and there are no current data for Canada. Our primary objective was to conduct a retrospective surveillance study of clinical blood isolates from the 4 main HD units serving adult patients in Winnipeg, Manitoba, from 2007 to 2014. The secondary objective was to use these data to predict the microbiological coverage of empiric therapies for bloodstream infections in the HD population.

METHODS

Surveillance data of clinical blood isolates from the 4 main outpatient HD units serving adult patients in Winnipeg, Manitoba, from January 2007 to December 2014 were extracted from the provincial microbiology information system (Delphic LIS, Auckland, New Zealand). Because the data were not linked to individual patients, research ethics approval was not required. During the study period, the 4 main HD units—the Sherbrook Centre Dialysis Unit and Central Dialysis Unit in the Health Sciences Centre, St Boniface Hospital Dialysis Unit, and Seven Oaks Hospital Dialysis Unit—served approximately 68% of patients receiving chronic HD in the Manitoba Renal Program.

Information on each clinical blood isolate was documented, specifically the date, location (HD unit), vascular site, organism identification, and antimicrobial susceptibilities. Importantly, these data excluded likely contaminants such as skin flora, unless culture results were positive in 2 sets of blood samples. Given the de-identified nature of surveillance data, additional steps were taken to exclude duplicate isolates (i.e., those with identical susceptibilities collected from different vascular sites at the same time in the same HD unit).[8]

The clinical blood isolates were characterized, and the distribution of organisms was detailed. Trends in the annual number of clinical isolates relative to the estimated number of HD patients were tested using a time series analysis with the Mann–Kendall trend test ($\alpha = 0.05$). Antimicrobial susceptibility rates were determined for the most common and clinically relevant pathogens (e.g., resistance concerns). Trends in antimicrobial resistance were also tested using time series analysis when the sample size exceeded 10 isolates of an organism in each year. All statistical analyses were conducted using SYSTAT 13 (Systat Software Inc., San Jose California).

The study data were used to predict the microbiological coverage of various empiric therapies for bloodstream infections in HD patients. The predictions were based on our distribution of clinical blood isolates for organisms with at least 15 isolates. Empiric regimens were selected based on the aforementioned clinical practice guidelines and included vancomycin or cefazolin plus ceftazidime, piperacillin-tazobactam, meropenem, ciprofloxacin, tobramycin, or gentamicin for gram-negative coverage.[8] The predicted coverage of each empiric regimen was calculated by weighting the likelihood of each organism and summing the percentage of isolates susceptible to each antibiotic.

RESULTS

A total of 1024 clinical blood isolates (from 953 blood cultures) met the inclusion criteria. Of these isolates, the largest percentage were gram-positive bacteria (72.6%, 743/1024), followed by gram-negative bacteria (26.1%, 267/1024) and yeast (1.4%, 14/1024). Most blood cultures (93.2%, 888/953) contained a single isolate. While the estimated annual number of patients receiving chronic HD increased steadily over the study period ($p < 0.001$), the annual number of clinical blood isolates increased initially, then decreased significantly, from 180 in 2011 to 93 in 2014 ($p = 0.04$) (Figure 1). This trend was largely explained by a reduction in gram-positive bacterial isolates. As detailed in Table 1, staphylococci accounted for

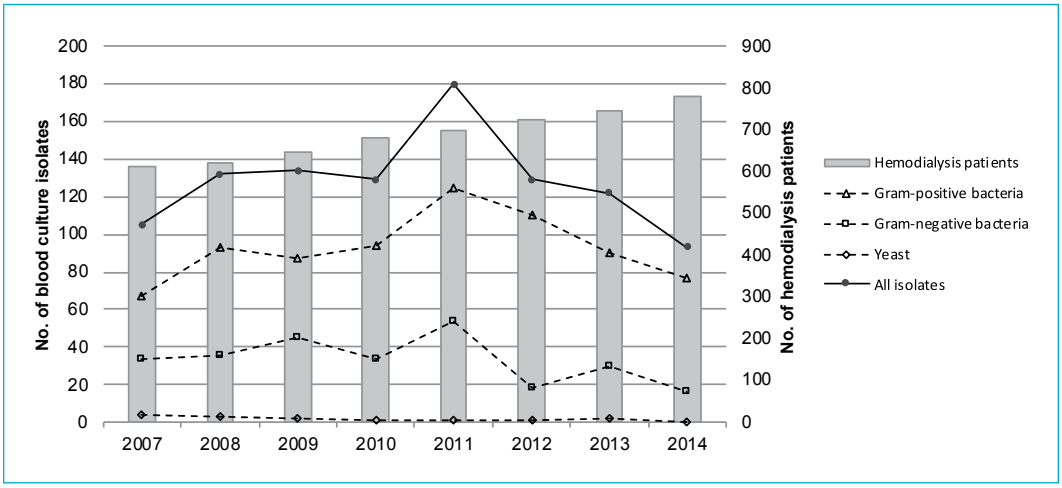

FIGURE 1. Annual number of clinical blood isolates and estimated annual number of patients receiving chronic hemodialysis, 2007 to 2014.

60.1% (615/1024) of clinical blood isolates, including *S. aureus* (36.9%, 378/1024) and coagulase-negative staphylococci (CoNS; 23.1%, 237/1024). The most common gram-negative bacteria were *Enterobacter* spp. (4.5%, 46/1024), *Klebsiella* spp. (4.2%, 43/1024), and *Escherichia coli* (3.6%, 37/1024).

Antimicrobial susceptibility data are shown in Table 2. The overall rate of oxacillin (methicillin) resistance in *S. aureus* (i.e., MRSA) was 17.5% (66/378), with a significant upward trend from 6.7% (2/30) in 2007 to 26.0% (13/50) in 2014 (p = 0.04) (Figure 2). The overall rate of oxacillin (methicillin) resistance in CoNS was 64.6% (153/237), but annual rates were variable with no notable trend over time (Figure 2). Only 2 VRE isolates (both *Enterococcus faecium*) were identified during the study. All gram-negative bacteria except *E. coli* had susceptibility rates above 90% for the third-generation cephalosporins, piperacillin-tazobactam, meropenem, ciprofloxacin, gentamicin, and tobramycin. For *E. coli*, ceftriaxone and ceftazidime resistance was identified in 13.5% (5/37) and 10.8% (4/37) of isolates, respectively, including 2 isolates that were ESBL producers. *Escherichia coli* also had the highest rate of ciprofloxacin resistance among the gram-negative bacteria (16.2%, 6/37).

The predicted microbiological coverage of empiric therapies was based on the current study's distribution of staphylococci, *Enterococcus faecalis*, *E. faecium*, *Streptococcus* spp., *Klebsiella* spp., *E. coli*, *Enterobacter* spp., *Serratia* spp., *Pseudomonas* spp., and *Acinetobacter* spp., which accounted for 88.1% (902/1024) of all isolates. The combinations of vancomycin with any of the agents for gram-negative coverage were predicted to cover 98.8% to 99.7% of the clinical blood isolates, whereas cefazolin plus an agent for gram-negative coverage would cover 67.5% to 68.4%. There were no differences based on the gram-negative coverage, whereby meropenem would cover less than 1% more isolates than ceftazidime, piperacillin-tazobactam, ciprofloxacin, tobramycin, or gentamicin.

TABLE 1. Distribution of Clinical Blood Isolates, 2007–2014

Organism	No. of Isolates* (n = 1024)	% of Isolates*
Gram-positive bacteria		
Staphylococcus spp.	615	60.1
S. aureus	(378)	(36.9)
S. epidermidis	(182)	(17.8)
Other CoNS†	(55)	(5.4)
Enterococcus spp.	59	5.8
E. faecalis	(45)	(4.4)
E. faecium	(12)	(1.2)
Streptococcus spp.	31	3.0
Other	38	3.7
Gram-negative bacteria		
Enterobacter spp.	46	4.5
E. cloacae	(35)	(3.4)
Klebsiella spp.	43	4.2
K. pneumoniae	(29)	(2.8)
Escherichia coli	37	3.6
Pseudomonas spp.	35	3.4
P. aeruginosa	(29)	(2.8)
Acinetobacter spp.	19	1.9
A. baumannii	(8)	(0.8)
Serratia spp.	19	1.9
Other	68	6.6
Yeast		
Candida spp.	14	1.4

*Isolate numbers and percentages for individual species are shown within parentheses.
†Coagulase-negative staphylococci other than *S. epidermidis*.

DISCUSSION

The current study provides important information about the microbiology of clinical blood isolates from HD patients over 8 years in Manitoba. There was a steady increase in the number of patients receiving chronic HD, whereas the number of isolates peaked in 2011 and then declined significantly. The reason for a spike in the number of isolates in 2011 is unclear. As expected, gram-positive bacteria accounted for most blood isolates (72.6%), followed by gram-negative bacteria (26.1%), and yeast (1.4%). In comparison, a CANWARD study of clinical blood isolates from hospitalized patients reported distributions of 51% and 46% for gram-positive and gram-negative bacteria, respectively.[11] Whereas *S. aureus* was the most common organism in HD patients (i.e., 36.9% in our study compared with 7.7% in CANWARD), *E. coli* was most prevalent in hospitalized patients (i.e., 22.6% in CANWARD compared with 3.6% in our study).[11]

Notably, our distribution of blood isolates was similar to reports of clinically confirmed bloodstream infections in HD patients from Australia (2008–2015),[4] the United States (2007–2011 and 2014),[2,9] and Denmark (1995–2010).[10] The percentages of *S. aureus* (36.9%) and CoNS (23.1%) in our

TABLE 2. Antimicrobial Susceptibilities of Clinical Blood Isolates, 2007–2014

Isolate	No. of isolates*	Susceptibility (%)										
		Oxacillin	Ampicillin	Vancomycin	Cefazolin	Ceftriaxone	Ceftazidime	Piperacillin-tazobactam	Meropenem	Ciprofloxacin	Gentamicin	Tobramycin
S. aureus	378	82.5	–	100	–	–	–	–	–	–	–	–
S. epidermidis	182	31.3	–	100	–	–	–	–	–	–	–	–
Other CoNS†	55	49.1	–	100	–	–	–	–	–	–	–	–
E. faecalis	45	–	91.1	100	–	–	–	–	–	–	–	–
E. faecium	12	–	16.7	83.3	–	–	–	–	–	–	–	–
Enterobacter spp.	46	–	–	–	–	–	–	97.8	100	100	100	100
Klebsiella spp.	43	–	–	–	88.4	100	100	100	100	100	100	100
E. coli	37	–	–	–	75.7	86.5	89.2	94.6	100	83.8	94.6	94.4
Pseudomonas spp.	35	–	–	–	–	–	94.3	94.3	97.1	94.3	97.1	100
Acinetobacter spp.	19	–	–	–	–	–	94.7	100	100	94.7	100	100

*Number of isolates, except for tobramycin (for which numbers of isolates were as follows: 42 for *Enterobacter* spp., 41 for *Klebsiella* spp., 36 for *E. coli*, and 34 for *Pseudomonas* spp.).
†Coagulase-negative staphylococci other than *S. epidermidis*.

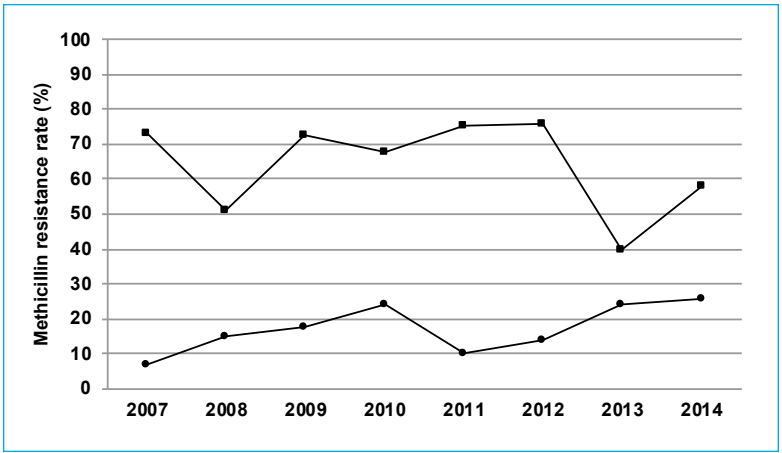

FIGURE 2. Rates of methicillin resistance in *Staphylococcus aureus* (n = 378, circles) and coagulase-negative staphylococci (n = 237, squares), 2007 to 2014.

study were also similar to their infection rates of 28% to 33% for *S. aureus* and 25% to 31% for CoNS.[2,4,9] Although our percentage of gram-negative bacteria was comparable to the aforementioned studies, *E. coli* was less common (3.6%) compared to the infection rates in Australia (8.1%)[4] and Denmark (12.6%).[10]

Our overall rate of methicillin resistance in *S. aureus* was 17.5%. This compared to 22.5% in clinical isolates (all specimen types) from hospitalized patients in Canada during the same time period.[12] Our increase in methicillin resistance from 6.7% in 2007 to 26.0% in 2014 is also consistent with a significant rise in community-acquired MRSA bloodstream infections observed in Canada between 2012 and 2017.[13] As expected, there was considerable geographic variability in MRSA resistance in clinically confirmed bloodstream infections in HD patients reported elsewhere, including none in Denmark (1995–2010),[10] 14% (2008–2015)[4] and 40% (2014)[2] in Australia, and 46% in the United States (2007–2011).[9] Our rate of vancomycin resistance in enterococci was only 3.4%, lower than the rates of 11.4% to 21.7% reported in those studies.[2,4,9] Our rate of ceftriaxone resistance in *E. coli* of 13.5% was comparable to theirs of 9% to 18%; our study was the only one to report ESBL status.[2,4,9] Despite global concerns about multidrug resistance in *Pseudomonas* spp. and *Acinetobacter* spp., there are limited susceptibility data in the HD population. Although our numbers were small, resistance rates for these organisms were relatively low compared with clinical blood isolates from hospitalized patients in Canada (the CANWARD study).[11]

Our predictions of microbiological coverage with empiric therapies showed that replacing vancomycin with cefazolin, in combination with an agent for gram-negative coverage, would reduce the overall coverage of clinical blood isolates in HD patients by more than 30%. Although our rate of methicillin resistance in *S. aureus* was only 17.5%, the high prevalence of methicillin resistance in CoNS (i.e., 64.6%) suggests that all staphylococcal pathogens should be considered to ensure appropriate empiric therapy. Conversely, there was no advantage to using the broader-spectrum agents such as piperacillin-tazobactam or meropenem to cover gram-negative pathogens. Our predictions also found that vancomycin plus ciprofloxacin would cover 98.8% of clinical blood isolates in HD patients, and may be an acceptable alternative for those with serious β-lactam allergy or aminoglycoside intolerance.

When interpreting the findings of the current study, it is important to consider the specific geographic context, particularly in terms of resistance rates. Even so, these data are informative and fill a notable gap in the study of infectious diseases in dialysis patients. Because our study was limited to the characterization of clinical blood isolates, not clinically confirmed infections, steps were taken to maintain clinical relevance by excluding duplicate cultures. Without access to patient identifiers, the possibility of repeat culture(s) of the same isolate on days following the index culture could not be ruled out. Therefore, the data were re-examined to identify the number of potential repeat isolates using a broad definition of the same organism, with identical susceptibilities, collected in the same HD unit within 7 days. According to this analysis, the number of possible repeats would not have exceeded 6% of all isolates. Our interpretation of some resistance patterns was limited by changes made to the cephalosporin and carbapenem susceptibility break points against Enterobacteriaceae and *Pseudomonas* spp. in 2012. Most importantly, continued surveillance in HD patients is needed to maintain the relevance of this initial work, particularly given the trends in methicillin resistance and the emergence of VRE and ESBL-producing organisms near the end of our study.

CONCLUSION

This study provides insight on the distribution of organisms and antimicrobial susceptibilities of clinical blood isolates from multiple HD units in Manitoba over 8 years. The large sample size allowed for a longitudinal analysis, which is rarely available for this patient population. In an era of increasing antimicrobial resistance, data such as these and ongoing surveillance are essential components of antimicrobial stewardship in the HD population.

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Courtney K Lawrence, BScPharm, is a PhD student with the College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba.

Chris Sathianathan, MD, FRCPC, is a Nephrologist with the Manitoba Renal Program at St Boniface Hospital, and is also an Assistant Professor with the Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba.

Mauro Verrelli, BSc, MD, MHA, FRCPC, is a Nephrologist with the Manitoba Renal Program at St Boniface Hospital, and is also an Associate Professor with the Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba.

Philippe Lagacé-Wiens, MD, FRCPC, DTM&H, is a Medical Microbiologist with Clinical Microbiology, Diagnostic Services, Shared Health at St Boniface Hospital, and is also an Assistant Professor with the Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba.

Robert Ariano, BScPharm, PharmD, is a Clinical Pharmacist at St Boniface Hospital and is also a Clinical Professor with the College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba.

Grace Badejo, HBSc Microbiology, BScPharm, is a Community Pharmacist and Associate at Shoppers Drug Mart, Winnipeg, Manitoba.

Michelle L Boyce, BSc, BScPharm, ACPR, is a Hospital Pharmacist at the Ottawa Hospital, Ottawa, Ontario. At the time of this study, she was a candidate for the ACPR designation, which has now been conferred.

J Christine Davis, BScPharm, PharmD, ACPR, is a Clinical Pharmacist with the Manitoba Renal Program at St Boniface Hospital, and is also a Clinical Assistant Professor with the College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba.

Sheryl A Zelenitsky, BScPharm, PharmD, is a Professor in the College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, and is also a Nil-Salaried Clinical Pharmacist with the St Boniface Hospital, Winnipeg, Manitoba.

Competing interests: Wolters Kluwer-Lexicomp has asked J Christine Davis to be a consultant (compensated) for drug dosing in kidney disease (outside the submitted work). No other competing interests declared.

Address correspondence to:
Dr Sheryl Zelenitsky
College of Pharmacy, Rady Faculty of Health Sciences
University of Manitoba
750 McDermot Avenue
Winnipeg MB R3E 0T5

e-mail: zelenits@umanitoba.ca

Funding: This work was supported by internal funding (S.A.Z.).