

ARTICLE

# Presence and Accuracy of Drug Dosage Recommendations for Continuous Renal Replacement Therapy in Tertiary Drug Information References

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## ABSTRACT

**Background:** Clinicians commonly rely on tertiary drug information references to guide drug dosages for patients who are receiving continuous renal replacement therapy (CRRT). It is unknown whether the dosage recommendations in these frequently used references reflect the most current evidence.

**Objective:** To determine the presence and accuracy of drug dosage recommendations for patients undergoing CRRT in 4 drug information references.

**Methods:** Medications commonly prescribed during CRRT were identified from an institutional medication inventory database, and evidence-based dosage recommendations for this setting were developed from the primary and secondary literature. The American Hospital Formulary System—Drug Information (AHFS—DI), Micromedex 2.0 (specifically the DRUGDEX and Martindale databases), and the 5th edition of *Drug Prescribing in Renal Failure* (DPRF5) were assessed for the presence of drug dosage recommendations in the CRRT setting. The dosage recommendations in these tertiary references were compared with the recommendations derived from the primary and secondary literature to determine concordance.

**Results:** Evidence-based drug dosage recommendations were developed for 33 medications administered in patients undergoing CRRT. The AHFS—DI provided no dosage recommendations specific to CRRT, whereas the DPRF5 provided recommendations for 27 (82%) of the medications and the Micromedex 2.0 application for 20 (61%) (13 [39%] in the DRUGDEX database and 16 [48%] in the Martindale database, with 9 medications covered by both). The dosage recommendations were in concordance with evidence-based recommendations for 12 (92%) of the 13 medications in the DRUGDEX database, 26 (96%) of the 27 in the DPRF5, and all 16 (100%) of those in the Martindale database.

**Conclusions:** One prominent tertiary drug information resource provided no drug dosage recommendations for patients undergoing CRRT. However, 2 of the databases in an Internet-based medical information application and the latest edition of a renal specialty drug information resource provided recommendations for a majority of the medications investigated. Most dosage recommendations were similar to

## RÉSUMÉ

**Contexte :** Les cliniciens s'appuient couramment sur des sources tertiaires d'information pour guider les posologies médicamenteuses chez les patients sous traitement continu de remplacement de la fonction rénale (TCRFR). On ignore si les recommandations posologiques dans ces sources couramment utilisées reflètent les données probantes les plus actuelles.

**Objectif :** Déterminer la présence et l'exactitude des recommandations sur la posologie des médicaments utilisés chez les patients sous TCRFR dans quatre sources d'information sur les médicaments.

**Méthodes :** On a dressé la liste des médicaments couramment prescrits durant le TCRFR à partir d'une base de données des médicaments en inventaire dans un établissement, puis on a défini des recommandations posologiques fondées sur des données probantes issues de la littérature primaire et secondaire. L'American Hospital Formulary System—Drug Information (AHFS—DI), le Micromedex 2.0 (en particulier les bases de données DRUGDEX et Martindale) et la 5<sup>e</sup> édition de *Drug Prescribing in Renal Failure* (DPRF5) ont été évalués à la recherche de recommandations posologiques sur des médicaments utilisés en cours de TCRFR. Les recommandations posologiques dans ces sources tertiaires ont été comparées aux recommandations tirées de la littérature primaire et secondaire pour établir une concordance.

**Résultats :** Des recommandations posologiques fondées sur des données probantes ont été rédigées pour 33 médicaments administrés aux patients sous TCRFR. L'AHFS—DI n'a fourni aucune recommandation posologique spécifique au contexte du TCRFR, alors que la DPRF5 a fourni des recommandations posologiques pour 27 (82 %) des médicaments et le logiciel d'application Micromedex 2.0 pour 20 (61 %) des médicaments (13 [39 %] dans la base de données DRUGDEX et 16 [48 %] dans la base de données Martindale, dont 9 médicaments traités dans les deux sources). Les recommandations posologiques concordent avec celles fondées sur des données probantes pour 12 (92 %) des 13 médicaments de la base de données DRUGDEX, 26 (96 %) des 27 médicaments de la DPRF5 et tous les 16 médicaments (100 %) de la base de données Martindale.

**Conclusions :** Une importante source tertiaire d'information sur les médicaments n'a fourni aucune recommandation posologique sur des médicaments utilisés chez les patients sous TCRFR. En revanche, deux des bases de données comprises dans une application Web d'information

those derived from the primary and secondary literature. The most recent edition of the DPRF is the preferred source of information when prescribing dosage regimens for patients receiving CRRT.

**Key words:** renal failure, continuous renal replacement therapy, dosage adjustments, drug information

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## INTRODUCTION

Continuous renal replacement therapy (CRRT) is frequently used for critically ill patients with renal failure.<sup>1</sup> CRRT produces less hemodynamic instability, allows for more gradual fluid and solute shifts, and better facilitates convenient titration of fluid removal than intermittent renal replacement therapy.<sup>2</sup> The pharmacokinetics of many medications prescribed for critically ill patients are significantly altered during CRRT, which necessitates dosage adjustments to ensure that the goals of pharmacotherapy are met.<sup>3–6</sup> Clinicians often rely on tertiary drug information resources, such as the American Hospital Formulary System—Drug Information (AHFS–DI)<sup>7</sup> and Micromedex<sup>8</sup> to guide drug dosing in renal failure. Specialty drug information resources such as *Drug Prescribing in Renal Failure* (DPRF)<sup>9</sup> are also used in the setting of renal dysfunction to help select drug dosing regimens. However, a previous systematic assessment of drug dosage recommendations for various degrees of renal function revealed that tertiary drug information references may not be suitable for clinical use because of wide variation in the recommendations.<sup>10</sup> The authors of a recent editorial revealed that less than 20% of currently used drugs have been studied in the setting of CRRT.<sup>11</sup> Furthermore, it is unknown whether drug dosage recommendations for the CRRT setting are provided in tertiary drug information resources and if so, whether the recommendations are concordant with recommendations derived from the primary and secondary literature. This study was undertaken to determine the presence and accuracy of drug dosage recommendations in the setting of CRRT in 4 commonly used drug information references.

## METHODS

### Selection of Drugs and Synthesis of Evidence-Based Dosage Recommendations

A convenience sample of the medications most commonly used in the 27-bed intensive care unit (ICU) of an academic tertiary care hospital was identified a priori from the institu-

médicale et la dernière édition d'une source d'information sur les médicaments utilisés en néphrologie ont fourni des recommandations pour la majorité des médicaments examinés. La plupart des recommandations posologiques étaient similaires à celles tirées des sources d'information primaires et secondaires. La plus récente édition du DPRF est la source préférée pour l'établissement des schémas posologiques chez les patients qui reçoivent un TCRFR.

**Mots clés :** insuffisance rénale, traitement continu de remplacement de la fonction rénale, ajustements posologiques, information sur les médicaments

tion's drug inventory database and an ICU quality assurance database. This list of medications was used for literature searches in the PubMed (1950–2011), Embase (1980–2011), and International Pharmaceutical Abstracts (1965–2011) databases. The literature searches targeted in vivo studies examining dosage or pharmacokinetic information for the drugs of interest for all venovenous modes of CRRT in adults. Medical Subject Headings (MeSH terms) used for the searches included “hemodiafiltration” and “hemofiltration”. The generic names of the specified medications were searched with either MeSH terms or text words. When applicable, MeSH subheadings were used, including “administration and dosage” and “pharmacokinetics”. Finally, text word searches were performed for “continuous renal replacement therapy”, “continuous venovenous hemodiafiltration”, “continuous venovenous hemodialysis”, and “continuous venovenous hemofiltration”. Terms referring to electrolytes, insulin, micronutrients, opioid analgesics, sedatives, vasopressors, and inotropes were excluded because dosing of these agents is frequently and readily adjusted on the basis of clinical or laboratory monitoring for efficacy and toxicity. Studies of drug removal (in patients undergoing CRRT) in the setting of toxicity were also excluded, because a drug's toxicokinetics may significantly differ from its usual pharmacokinetic properties.<sup>12</sup>

Evidence-based drug dosage recommendations in CRRT were generated by one critical care clinical pharmacy specialist (S.K.G.), who extracted recommendations from each of the included pharmacokinetic studies and created a range of recommended dosages to reflect the variation in recommendations across the studies. Dosage variability for any particular drug was due primarily to small sample sizes in the studies or, more importantly, differences in patient populations, CRRT equipment, CRRT modes, and other techniques used. Two recently published comprehensive evidence-based reviews that provided antibacterial and antifungal dosing recommendations for patients undergoing CRRT<sup>6,13</sup> were also included, to ensure that our recommendations were consistent. The final dosage recommendations were considered the reference standard for comparison purposes in this study.

## Selection of Tertiary Drug Information References

The following tertiary drug information references were frequently used by clinicians at the academic tertiary care ICU and were selected for evaluation: the AHFS–DI (electronic access June 2011 via MedicinesComplete subscription service, Pharmaceutical Press, London, UK),<sup>7</sup> Micromedex 2.0 (electronic access June 2011),<sup>8</sup> and the 5th edition of the DPRF (DPRF5).<sup>9</sup> Two drug information databases contained within the Micromedex 2.0 application were evaluated: DRUGDEX<sup>14</sup> and *Martindale: The Complete Drug Reference*.<sup>15</sup> *The Canadian Compendium of Pharmaceuticals and Specialties*<sup>16</sup> was not evaluated because it was not routinely used by clinicians in the study ICU, and a previous evaluation suggested that drug dosing recommendations in CRRT were largely absent from this reference.<sup>17</sup>

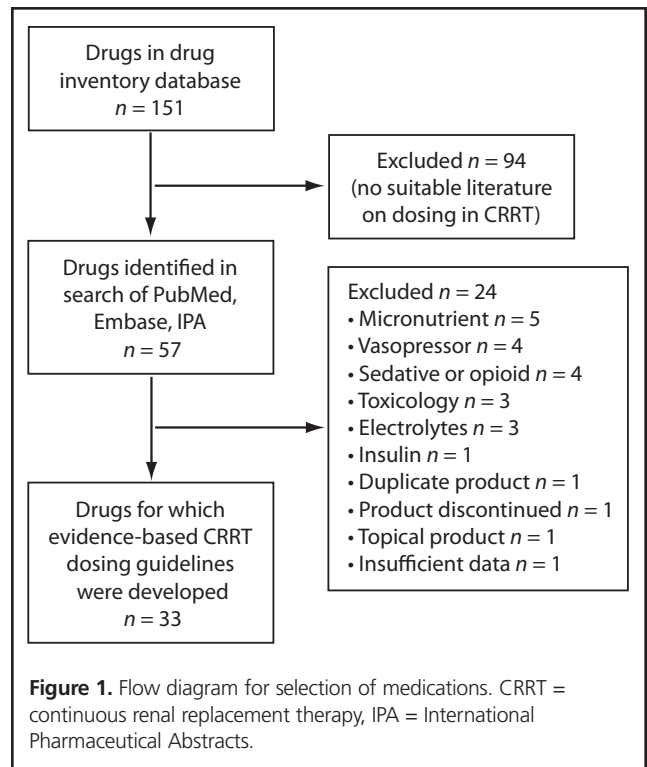
## Data Synthesis

The 4 drug information resources were evaluated for the presence and accuracy of drug dosage information for all modes of CRRT by one investigator (S.K.G.), who was not blinded to the tertiary reference being evaluated. Recommendations provided in the tertiary references were compared against the reference standard evidence-based recommendations developed from the literature and were considered concordant if the total daily dose fell within the range of the evidence-based reference standard. Only maintenance dosage regimens were evaluated for concordance. Summary descriptive statistics are reported where appropriate.

## RESULTS

The systematic process for selecting medications yielded a total of 33 medications used in critically ill patients undergoing CRRT (Figure 1). In addition to the previously stated exclusions, 3 other medications were excluded for the following reasons: duplicate product (piperacillin), product discontinued in Canada (ofloxacin), and database identification of a topically administered product (chloramphenicol). The literature search yielded 55 articles providing dosage recommendations for these 33 medications,<sup>6,13,18-70</sup> from which evidence-based drug dosage recommendations were generated. The presence of dosage recommendations in the 4 tertiary drug information references and their concordance with the evidence-based recommendations are summarized in Table 1. The following therapeutic classes of medications were included: anti-infectives, immunosuppressives, antithrombotics, anticonvulsants, and acid suppressants.

No dosage recommendations for any of the 33 drugs were provided in the AHFS-DI. Recommendations for 13 (39%) of the medications were provided in DRUGDEX, for 16 (48%)



**Figure 1.** Flow diagram for selection of medications. CRRT = continuous renal replacement therapy, IPA = International Pharmaceutical Abstracts.

in *Martindale*, and for 27 (82%) in DPRF5. The 2 Micromedex 2.0 databases together (DRUGDEX and/or *Martindale*) provided recommendations for 20 (61%) of the medications. The recommendations were concordant with the evidence-based reference standard recommendations for 12 (92%) of the 13 drugs covered in DRUGDEX, 26 (96%) of the 27 drugs covered in DPRF5, and all 16 (100%) of those covered in *Martindale*. Both cases of discordance involved recommendations for fluconazole: specifically, the dose recommended in DRUGDEX was higher than the reference standard, and the dose recommended in DPRF5 was lower than the reference standard.

## DISCUSSION

To the authors' knowledge, this is the first attempt to determine the presence and accuracy of drug dosage recommendations for patients receiving CRRT in high-quality tertiary drug information references. It may be a surprise to many practitioners that one of the most prominent North American tertiary drug information resources, the AHFS–DI, does not provide any drug dosage recommendations for patients undergoing CRRT. Several factors may explain the paucity of recommendations in this reference. The AHFS–DI is a compilation of comparative, unbiased, evidence-based drug information.<sup>7</sup> The information presented in its monographs is derived from pertinent references in the literature and expert therapeutic guidelines.<sup>7</sup> Notwithstanding the increasing body of literature concerning pharmacokinetic alterations during

**Table 1. Drug Dosing Recommendations for Continuous Renal Replacement Therapy (CRRT)\***

Drug	Reference Standard (Maintenance Dosage)	DRUGDEX <sup>14</sup>	Martindale <sup>15</sup>	DPRF5 <sup>9</sup>
Acyclovir	5–10 mg/kg IV q12–24h <sup>6,18</sup>	NR	5–10 mg/kg IV q12–24h	5–10 mg/kg IV q24h
Amikacin	5–7.5 mg/kg IV q24–48h <sup>6,19,20</sup>	4.5–10.5 mg/kg per day IV divided q12–18h	NR	7.5 mg/kg IV q24–72h
Amoxicillin	1000 mg PO q6h <sup>19,21</sup>	NR	NR	NR
Amphotericin, lipid complex	5 mg/kg IV q24h <sup>13,22</sup>	NR	NR	5 mg/kg IV q24h
Amphotericin, liposomal	3–5 mg/kg IV q24h <sup>13,22,23</sup>	NR	NR	NR
Basiliximab	20 mg IV q96h × 2 <sup>24</sup>	NR	NR	NR
Cefepime	1000 mg IV q8h or 2000 mg IV q12h <sup>6,25,26</sup>	NR	1000 mg IV q8h or 1000–2000 mg IV q12h	1000–2000 mg IV q12h
Cefotaxime	1000–2000 mg IV q6–12h <sup>6,27</sup>	1000–2000 mg IV q12h	1000–2000 mg IV q6–12h	1000 mg q12h
Ceftazidime	1000 mg IV q8–12h or 2000 mg IV q12h <sup>6,28,29</sup>	1000–2000 mg IV q24–48h	1000–2000 mg IV q8–12h	1000–2000 mg q12h or 3000 mg/day CIVI
Ceftriaxone	1000–2000 mg IV q12–24h <sup>6,30,31</sup>	1000–2000 mg IV q12–24h	NR	250–2000 mg IV q12–24h
Cefuroxime	750–1500 mg IV q12h <sup>27</sup>	NR	NR	1000 mg IV q12h
Ciprofloxacin	200–400 mg IV q12–24h <sup>6,32,33</sup>	NR	400 mg IV q12–24h	400 mg IV q24h
Colistimethate	2–3 mg/kg IV q12–48h <sup>6,34</sup>	2–3 mg/kg IV q12h	2–3 mg/kg IV q12–48h	NR
Cotrimoxazole	2.5–10 mg/kg (TMP) IV q12h <sup>6,19,35</sup>	NR	2.5–10 mg/kg IV q12h	2.5–10 mg/kg IV q12h
Cyclosporine	3–5 mg/kg per day IV <sup>36,37</sup>	NR	NR	100% usual dose
Enoxaparin	30 mg SC q12h <sup>†38</sup>	NR	NR	NR
Fluconazole	800 mg IV/PO q24h <sup>13,39–42</sup>	500–600 mg IV/PO q12h	200–800 mg IV/PO q24h	200–400 mg IV/PO q24h
Ganciclovir	1.25–2.5 mg/kg IV q24h <sup>6,43</sup>	NR	1.25–2.5 mg/kg IV q24h or 2.5 mg/kg IV q12h	1.25–2.5 mg/kg IV q24h
Gentamicin	1–2.5 mg/kg IV q24–48h <sup>6,44</sup>	0.3–1.75 mg/kg IV q12h‡	1–2.5 mg/kg IV q24–48h	1.7 mg/kg IV q12–48h
Imipenem–cilastatin	500 mg IV q6–8h <sup>6,45</sup>	500 mg IV q6–8h	500 mg IV q6–8h	500 mg IV q6h
Levofloxacin	250–750 mg IV/PO q24h <sup>6,32,46</sup>	NR	250–750 mg IV/PO q24h	500 mg IV/PO q48h
Linezolid	600 mg IV/PO q12h <sup>47,48</sup>	NR	NR	600 mg IV/PO q12h
Meropenem	500–1000 mg IV q8–12h <sup>6,49–56</sup>	1000 mg IV q12h	500 mg IV q6–12h or 1000 mg IV q8–12h	1000–2000 mg IV q12h
Metronidazole	500 mg IV q6–12h <sup>6,21</sup>	500 mg IV q6–12h	NR	250–500 mg IV q8–12h
Moxifloxacin	400 mg IV/PO q24h <sup>57,58</sup>	NR	NR	400 mg IV/PO q24h
Phenytoin	5–7 mg/kg per day IV divided q8–12h <sup>59</sup>	100% usual dose	NR	100% usual dose
Piperacillin–tazobactam	2.25–3.375 g IV q6–8h <sup>6,60,61</sup>	NR	NR	4.5 g IV q8h
Ranitidine	50 mg IV Q12h or 150 mg PO q24h <sup>62</sup>	NR	NR	150 mg PO q12–24h
Tacrolimus	0.03–0.04 mg/kg per day IV <sup>63</sup>	NR	NR	NR
Ticarcillin–clavulanate	2–3.1 g IV q6–8h <sup>6,64</sup>	NR	NR	3.1 g IV q8–12h
Tobramycin	1–2.5 mg/kg IV q24–48h <sup>6,19</sup>	0.3–1.75 mg/kg IV q12h‡	1–2.5 mg/kg IV q24–48h	1.7 mg/kg IV q24–48h
Vancomycin	7.5–15 mg/kg IV q12–48h <sup>6,37,65–69</sup>	500 mg IV q24–48h or 1000 mg IV q48h§	10–15 mg/kg IV q24–48h or 7.5–10 mg/kg IV q12h	1000 mg IV q24–96h§
Voriconazole	400 mg PO q12h × 2, then 200 mg PO q12h <sup>13,70</sup>	NR	No adjustment needed; use PO	100% usual dosage

CIVI = continuous IV infusion; DPRF5 = *Drug Prescribing in Renal Failure*, 5th edition; NR = no dosage reported; TMP = trimethoprim.

\*No CRRT drug dosage recommendations in American Hospital Formulary System—Drug Information.<sup>7</sup>

†For prophylaxis of venous thromboembolism.

‡30%–70% of usual dose recommended.

§Assume 70-kg body weight.

CRRT, the quality of existing data may not meet the editorial standards required for inclusion in the AHFS–DI monographs. For example, a recent systematic review of pharmacokinetic studies involving patients with sepsis who were receiving CRRT revealed that a significant proportion of studies failed to provide key information that readers would need to design an antimicrobial dosage regimen for their patients.<sup>71</sup> Also, the US Food and Drug Administration (FDA) does not require manufacturers to perform research addressing the role of renal function on drug dosage.<sup>72</sup> Although the FDA has produced a draft guidance document for industry covering study design, analysis, and impact on dosage and labelling for various degrees of renal dysfunction,<sup>73</sup> the final recommendations, once released, will be nonbinding. These factors, combined with the reality that CRRT is a relatively rare medical intervention, may explain the absence of recommendations in the AHFS–DI.

Both DRUGDEX and Martindale provided drug dosage recommendations for less than half of the medications considered in this study. These drug information databases fall under the umbrella of the Micromedex 2.0 application. Information provided in the Micromedex 2.0 databases results from comprehensive, ongoing review of recommendations published in the world's medical journals, performed by in-house editorial staff.<sup>8</sup> The editorial process consists of 5 steps: identification of literature and topics for discussion, creation of content, internal review of content, review by the Micromedex editorial board, and final clinical review and approval.<sup>74</sup> Perhaps the relative paucity of drug dosage recommendations for CRRT in the DRUGDEX and Martindale databases can be explained by the low volume of high-quality CRRT pharmacokinetic studies.<sup>11,71</sup> Given that the Micromedex query field searches both databases, it is reassuring that the application yielded recommendations for a total of about two-thirds of the medications examined. Furthermore, both of the component databases in Micromedex provided concordant recommendations for the majority of medications, which suggests that their recommendations are reliable for use in clinical practice. In fact, the Martindale resource often cited an evidence-based review that was used in creating our reference standard recommendations.<sup>6</sup>

The most recent edition of the DPRF, the DPRF5, provided drug dosage recommendations for most of the medications considered in this study. Three of the 6 medications without CRRT dosage recommendations (liposomal amphotericin, basiliximab, and colistimethate) did not appear in the DPRF5's index, and therefore no dosage recommendations for any degree of renal dysfunction were provided. Although dosing of amphotericin and basiliximab does not change in the setting of CRRT, we believe that this information should be stated in tertiary drug information resources, to eliminate guesswork. The fluconazole dosage recommendation in the

DPRF5 was lower than the reference standard recommendation and constituted the only discordant recommendation in this resource.

The 21st century has brought with it a movement toward electronic point-of-care drug information resources. The wide variety of smartphone-based drug information applications and Internet-based resources now available may lessen the relevance of the current analysis in today's health care environment. However, 2 of the databases evaluated were Internet-based, and a third was available both in print and via the Internet. We did not evaluate the Internet version of the DPRF, which includes revised prescribing suggestions intended to account for the possibility that printed compendiums of drug dosage recommendations are out of date by the time they are published.<sup>75</sup> Other comprehensive electronic tertiary resources that are frequently used, such as the Clinical Pharmacology database maintained by Elsevier, were not evaluated but may contain drug dosage recommendations for CRRT that reflect the most current evidence.

Several limitations to this study merit consideration. Drug dosage recommendations for CRRT should not be considered in terms of "one size fits all". Multiple factors influence the selection of a particular drug dosage during CRRT, such as the drug's physicochemical and pharmacokinetic properties, the mode of CRRT, the CRRT dose prescribed, circuit downtime, filter type and size, and the patient's residual renal function.<sup>76</sup> Irrespective of the effects of CRRT, a number of other patient-related factors during critical illness may alter the pharmacokinetic disposition of many drugs and the dosage required to achieve desired goals. For example, the early stages of multiple organ dysfunction syndrome are often associated with an increased volume of distribution for many antimicrobials,<sup>77</sup> which may necessitate the administration of higher-than-usual initial doses to achieve the desired pharmacokinetic–pharmacodynamic goals.<sup>77</sup> The heterogeneity surrounding CRRT techniques, equipment, and patient factors that could alter the pharmacokinetic parameters of many drugs, combined with relatively low number of patients who are exposed to this therapy, has undoubtedly contributed to the lack of drug dosage recommendations in tertiary resources. The evidence-based reference standard dosage recommendations generated for this study encompassed a wide variety of CRRT modes, equipment, and doses, and the discordant dosage recommendations observed in this study may be explained by this variety. Ideally, we would have preferred to evaluate the concordance of dosage recommendations stratified by each venovenous mode of CRRT, but the paucity of relevant published studies made this approach infeasible. When evaluating concordance, we did allow for wide variation in dosage recommendations because of the heterogeneity of the modes and dosage of CRRT used in each study. This allowance may have resulted in an overestima-

tion of concordance, and it should be emphasized that drug dosage recommendations in CRRT should be tailored to the CRRT prescription and patient-related variables. Importantly, the reference standard dosing recommendations developed for this analysis were derived from pharmacokinetic studies that did not evaluate the association between dosage during CRRT and clinically important outcomes. The unproven assumption was that the reference standard dosing recommendations would achieve desired clinical outcomes. Another factor that may limit the applicability of these results is the relatively small number of medications examined. It is conceivable that drug dosage recommendations for other medications administered to patients undergoing CRRT are included in the drug information resources assessed and that they are concordant with recommendations in the primary and secondary literature. The clinical relevance of the sample of medications assessed in this study may also be questioned according to the importance of renal function in the elimination of each medication and their respective therapeutic windows.<sup>71</sup> However, this does not appear to have been a major factor in the current study, because the kidney is a significant route of elimination for the majority of medications examined. Only one nonblinded investigator evaluated whether the dosage recommendations in the tertiary references were concordant with the reference standard dosage recommendations. Duplicate extraction and assessment by a second investigator could have reduced the risk of errors. Blinding of the data extraction and assessment processes would also have reduced the risk of bias. Finally, only 2 of the drug information databases contained within the Micromedex 2.0 application were evaluated. Other databases contained within this comprehensive application may have included dosing information for drugs administered to patients undergoing CRRT. However, if this information does exist, it may not be readily found by clinicians performing a quick search of the application.

## CONCLUSIONS

One prominent North American tertiary drug information resource did not provide drug dosage recommendations for 33 medications that may be prescribed for patients receiving CRRT. However, 2 drug information databases contained within a comprehensive medical information application and the latest edition of a tertiary drug information resource that specializes in drug dosage recommendations for various degrees of renal dysfunction provided recommendations for many of the medications. For the most part, the recommended dosage regimens provided by these drug information resources were consistent with recommendations derived from the primary and secondary literature. Given the frequency and accuracy of recommendations in the most recent edition of DPRF (DPRF5), we recommend that it be used as the preferred reference for selection of drug dosage regimens during CRRT.

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