Guided Medication Dosing for Inpatients With Renal Insufficiency

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Renal insufficiency is relatively common among hospitalized patients, and is associated with an increase in hospitalization-related morbidity and mortality.1–4 Persons with acute and chronic renal insufficiency are hospitalized with increased frequency compared with those nonaffected, due to renal disease per se, and to the effects of renal insufficiency on other medical conditions, including congestive heart failure and chronic liver disease.5–6 Practitioners caring for these patients are faced with the challenges of managing the complex interplay between renal insufficiency and other organ system disease, and of altering diagnostic studies (eg, angiography) and therapeutics to avoid further renal injury. With regard to renal insufficiency and pharmacotherapeutics, the majority of clinicians’ attention has been directed at avoiding nephrotoxic drugs in patients at risk for worsening renal failure; comparatively little attention has been paid to the disposition of drugs, nephrotoxic and non-nephrotoxic, in patients with renal insufficiency. In prescribing drugs for patients with renal insufficiency, most practitioners rely on their clinical experience or the advice of consultant physicians or pharmacists to guide dosing regimens. Since few clinicians are expert in this area, and medication orders can rarely be delayed until consultation is obtained, the capacity to provide information on drug disposition in real

Context Usual drug-prescribing practices may not consider the effects of renal insufficiency on the disposition of certain drugs. Decision aids may help optimize prescribing behavior and reduce medical error.

Objective To determine if a system application for adjusting drug dose and frequency in patients with renal insufficiency, when merged with a computerized order entry system, improves drug prescribing and patient outcomes.

Design, Setting, and Patients Four consecutive 2-month intervals consisting of control (usual computerized order entry) alternating with intervention (computerized order entry plus decision support system), conducted in September 1997–April 1998 with outcomes assessed among a consecutive sample of 17828 adults admitted to an urban tertiary care teaching hospital.

Intervention Real-time computerized decision support system for prescribing drugs in patients with renal insufficiency. During intervention periods, the adjusted dose list, default dose amount, and default frequency were displayed to the order-entry user and a notation was provided that adjustments had been made based on renal insufficiency. During control periods, these recommended adjustments were not revealed to the order-entry user, and the unadjusted parameters were displayed.

Main Outcome Measures Rates of appropriate prescription by dose and frequency, length of stay, hospital and pharmacy costs, and changes in renal function, compared among patients with renal insufficiency who were hospitalized during the intervention vs control periods.

Results A total of 7490 patients were found to have some degree of renal insufficiency. In this group, 97151 orders were written on renally cleared or nephrotoxic medications, of which 14440 (15%) had at least 1 dosing parameter modified by the computer based on renal function. The fraction of prescriptions deemed appropriate during the intervention vs control periods by dose was 67% vs 54% (P<.001) and by frequency was 59% vs 35% (P<.001). Mean (SD) length of stay was 4.3 (4.5) days vs 4.5 (4.8) days in the intervention vs control periods, respectively (P=.009). There were no significant differences in estimated hospital and pharmacy costs or in the proportion of patients who experienced a decline in renal function during hospitalization.

Conclusions Guided medication dosing for inpatients with renal insufficiency appears to result in improved dose and frequency choices. This intervention demonstrates a way in which computer-based decision support systems can improve care.

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See also Patient Page.
time might be of great value to the practicing clinician and the patient.

The problem of error in medicine has been found to be important and costly. Adverse drug events (ADEs) are common and often associated with errors. Even basic computerization of physician ordering with relatively little decision support was associated with a 55% decrease in serious medication errors, and an 84% decrease in near misses or potential ADEs in 1 study by our group. However, only a 17% decrease was seen in preventable ADEs. The study suggested that computerized advice regarding the dosing of drugs in the setting of renal insufficiency might be among the most potent additional preventive strategies.

Thus, we hypothesized that the incorporation of guided dosing algorithms for inpatients with renal insufficiency into an existing computer order entry system would result in a larger proportion of appropriate dose and frequency orders, and would be associated with shorter lengths of stay (LOS), lower costs, and a lower frequency of worsening renal function.

**METHODS**

**Study Setting**

The study was carried out at Brigham and Women’s Hospital, a 720-bed urban tertiary care academic medical center in Boston, Mass. The Brigham Integrated Computing System (BICS) provides administrative and clinical computing services at BWH. All inpatient orders are entered into BICS, including orders for medications, laboratory and radiology studies, and for nursing interventions. The BICS order entry application provides the physician with a range of possible dose amounts for that medication (dose list) along with 1 dose that is highlighted as the default or recommended dose amount (FIGURE 1A). The clinician is also offered a highlighted frequency as the recommended dosing interval (Figure 1B). The clinician can also hit an additional key to see the data used for calculation of creatinine clearance. Nearly all laboratory, radiology, and pathology results, admission vital signs (including weight), and demographic information can be accessed.

The BICS system had for some years contained an on-line, noninteractive version that could be accessed separately from the order entry system. In an attempt to enhance the impact of this application within the BICS, its internal logic was integrated with the computerized laboratory results reporting system, and was incorporated into the order entry system. Based on information already in the reporting system, the new application first determined whether a patient had renal insufficiency, defined as an estimated creatinine clearance of less than 80 mL/min (1.34 mL/s), by the Cockroft-Gault equation. Next, based on the real-time calculation of the estimated creatinine clearance and the drug being prescribed, the application would modify the above-described dose list, default dose amount, and default frequency (dosing interval) in the BICS (FIGURE 2).

**Knowledge Base**

After reviewing the relevant literature, an expert panel including a nephrologist, a pharmacist, and a general internist con-
vended to review all medications in the hospital’s drug formulary and selected those medications that were renally cleared and/or nephrotoxic. New dosing suggestions were generated in a subset of approximately 500 medications (approximately 2500 in total). To smooth dose recommendations, renal insufficiency was divided into 3 categories: mild (estimated creatinine clearance, 50-80 mL/min [0.84-1.34 mL/s]), moderate (estimated creatinine clearance, 16-49 mL/min [0.27-0.82 mL/s]), and advanced (estimated creatinine clearance, ≤15 mL/min [≤0.25 mL/s]). The expert panel then determined optimal adjustments in dose list, default dose amount, and default frequency for each of the medications in the application in each of the renal insufficiency categories. The nonfixed variables in the estimated creatinine clearance calculation (ie, weight, serum creatinine) were the weight entered by the nurse or physician into the BICS database on admission, and any medication was ordered, the application was active, and any medication was ordered, the application was active, and the patient was entered by the laboratory and updated regularly during the hospital stay.

**Patient Population**

All persons admitted to the medical, surgical (including subspecialty surgical services), neurology, and obstetrics and gynecology services between September 1997 and April 1998, whose admission and discharge were within the boundaries of 4 consecutive 2-month periods were included in the study. Admission periods did not overlap.

**Intervention and Evaluation**

When renal insufficiency was detected and any medication was ordered, the application potentially modified 1 or more of the dose list, default dose amount, and default frequency. To test the effect of this application, an intervention trial was designed. The study periods consisted of 4 alternating 8-week blocks of intervention and control subperiods. Throughout the intervention and control periods, the application was active, determining whether the dose list, default dose amount, and default frequency needed adjustments. During the intervention periods, the adjusted dose list, default dose amount, and default frequency were displayed to the order-entry user and a notation was provided that adjustments had been made based on renal insufficiency. During the control periods, these recommended adjustments were not revealed to the order-entry user, and the unadjusted parameters were instead displayed.

A log was kept of all instances in which an application medication was ordered and the application adjusted the dose list, default dose amount, and/or default frequency. A log was also kept of the order finally made by the ordering physician. A selection was considered appropriate if the dose amount or frequency interval did not exceed the parameters set forth by the expert panel.

If use of a particular medication was considered potentially harmful, the application would provide feedback to the ordering physician, accompanied by a recommendation for a suitable substitute when appropriate. For instance, if meperidine hydrochloride were prescribed for a patient with an estimated creatinine clearance of less than 15 mL/min (<0.25 mL/s), a warning regarding its potential for promoting seizures would be issued, with a suggestion that an alternative narcotic analgesic be prescribed. The clinician could then either accept or override such a recommendation.

**Patient Outcomes**

Patient outcomes were determined during discrete admissions. Length of stay was recorded in days. Hospital and pharmacy costs were estimated from billed charges and institution-specific charge-to-cost ratios.

**Statistical Analysis**

Continuous data were presented as mean (SD) or median (interquartile range), and compared with the t test or Wilcoxon rank-sum test, as appropriate. Categorical data were presented as proportions and compared using the χ² test. Multivariable linear regression analysis was used to compare LOS and costs (both log-transformed) in the intervention and control periods. Age, sex, and diagnosis related group (DRG) weight were used as covariates in these analyses. In addition, we evaluated (using multiplicative interaction terms) whether the effect of the application intervention differed by age, sex, or DRG weight. To determine whether the exclusion of patients whose admission extended across study periods exerted any meaningful effects on the analyses of...
LOS, costs, and renal function, we repeated the analyses without these exclusions. Each patient was assigned to the group (intervention or control) based on the day of admission. All reported $P$ values were based on 2-tailed tests of statistical significance. Analyses were conducted using SAS statistical software (SAS Institute Inc, Cary, NC).

**RESULTS**

**Patients**

There were 19982 admissions that either began or ended during the 8-month study period; we focused on the 17828 that were wholly contained within a study subperiod. There were 7887 (39.5%) admissions wholly contained in the 2 intervention periods and 9941 (49.7%) admissions wholly contained in the 2 control periods (corresponding to 58912 and 70821 patient-days, respectively). There were 2154 (10.8%) admissions that straddled a study-period boundary and were excluded. In-hospital mortality rates were 1.8% and 1.9% (intervention vs control, $P=.61$). Mean (SD) age (52.5 [18.4] years vs 52.5 [18.3] years; $P=.95$) and sex (61.4% vs 61.8% female; $P=.78$) were not significantly different across periods. The mean DRG weight was higher during the control periods (2.3 vs 2.1 in intervention periods; $P=.004$). The majority of patients (11 896 [60.1%]) had estimated creatinine clearance values greater than 80 mL/min (>1.34 mL/s). One in 4 patients (4927 [24.9%]) had mild renal insufficiency. Fifteen percent had moderate (2563 [12.9%]) or advanced (414 [2.1%]) renal insufficiency. The mean estimated creatinine clearance at admission was higher during the intervention periods (90.9 vs 84.7 mL/min [1.52 vs 1.41 mL/s] in control periods; $P<.001$).

**Drug Orders**

There were a total of 2 278 723 orders during the study period, 773 113 of which were medication orders and 108 337 of which were orders for nephrotoxic and/or renally cleared medications. We excluded 11 386 orders because of missing dose amount (3 794 [33.3%]) or frequency interval (3 102 [44.8%]), or because of an uninterpretable estimated creatinine clearance value (3 696 [32.5%]), usually indicating an aberrant weight measurement, and for a variety of other less common reasons (2 588 [22.7%]). These exclusions left 97 151 orders for analysis (orders could be excluded for >1 reason).

Of the 97 151 analyzable orders, the application generated a suggestion for the clinician in 14 440 (15%). Table 1 shows a detailed array of these suggestions. Table 2 shows the proportion of orders deemed appropriate, stratified by whether the application’s suggestion was dose-related, frequency-related, or both. In the intervention vs control periods, the frequency of appropriate orders was 51% vs 30% for all relevant orders, 67% vs 54% for orders involving dose changes, and 59% vs 35% for orders involving frequency changes, respectively ($P<.001$ for all comparisons).

**LOS, Costs, and Renal Function**

Table 3 shows unadjusted LOS and costs (hospital and pharmacy) during the intervention and control periods. The rightward half of the table shows the effect of including the 2154 hospitalizations that overlapped. Hospitalizations were categorized as intervention or control based on conditions on the day of admission.

The adjusted mean LOS (adjusted for age, sex, and DRG weight) remained significantly shorter during the intervention period, both when overlapping hospitalizations were included ($P=.002$) and when they were excluded ($P<.001$). The effect of the application on LOS was attenuated at higher DRG weights ($P<.001$). In contrast, there were no significant differences in adjusted mean total or pharmacy costs between intervention and control periods.

A 10-mL/min (0.17-mL/s) decrement in estimated creatinine clearance from admission to discharge was considered to be of clinical significance. The percentage of patients whose estimated creatinine clearance declined by more than 10 mL/min (0.17 mL/s) was 11.8% and 11.5% (intervention vs control, $P=.43$). The mean (SD) changes in estimated creatinine clearance were 1.9 (0.2) mL/min (0.03 [0.003] mL/s) and 2.3 (0.2) mL/min (0.04 [0.003] mL/s) during the corresponding periods ($P=.18$).

**COMMENT**

We were successful in designing and implementing a computer order entry-based application that provided real-time drug prescription decision support to physicians. Compared with control periods during which information was readily available on-line but not incorporated into the order-entry process, the application intervention led to a statistically significant and clinically meaningful increase in the proportion of prescriptions considered appropriate for inpatients with renal insufficiency.

The large improvements in appropriateness of dosing and frequency were probably realized in part because the application is largely transparent to the clinician. Its key characteristics are that it remembers a huge amount of data essentially impossible for clinicians to...

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**Table 1. Catalog of Application Suggestions**

<table>
<thead>
<tr>
<th>Type of Intervention</th>
<th>Total No. of Orders</th>
<th>Control Period (Alteration Not Revealed)</th>
<th>Intervention Period (Alteration Revealed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All types</td>
<td>97 151</td>
<td>58 160</td>
<td>38 399</td>
</tr>
<tr>
<td>Total</td>
<td>14 440</td>
<td>8 950</td>
<td>5 490</td>
</tr>
<tr>
<td>Dosing alteration only</td>
<td>3 490</td>
<td>2 136</td>
<td>1 354</td>
</tr>
<tr>
<td>Frequency alteration only</td>
<td>4 787</td>
<td>2 986</td>
<td>1 801</td>
</tr>
<tr>
<td>Dosing and frequency alteration</td>
<td>6 163</td>
<td>3 828</td>
<td>2 335</td>
</tr>
<tr>
<td>Warnings</td>
<td>253</td>
<td>0</td>
<td>253</td>
</tr>
<tr>
<td>Substitute medication</td>
<td>27</td>
<td>0</td>
<td>27</td>
</tr>
</tbody>
</table>

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master (and keep updated), and it makes it easy to do the right thing. Nonetheless, despite the overall improved appropriateness of dosing, 49% of orders for the application’s drugs were still inappropriate in the intervention group. Some physicians may have been reluctant to reduce drug dosages, particularly among more critically ill patients. Others may have simply disregarded the advice in favor of their own established practice patterns. Future studies with this application and similar applications should investigate the reason(s) for accepting or rejecting on-line advice regarding medication ordering, and it might be worthwhile to consider stronger suggestions in specific situations.

A number of other studies have evaluated the impact of decision support on dosing of medications for patients with renal insufficiency. For example, Rind et al10 developed an application that alerted physicians caring for inpatients when there was an increase in the patient’s serum creatinine concentration. An alert was triggered by a 0.5 mg/dL (44.2 µmol/L) increase in serum creatinine if the patient was prescribed a potentially nephrotoxic medication (eg, aminoglycoside), and a 50% increase in serum creatinine, to at least 2.0 mg/dL (176.8 µmol/L), if prescribed a medication that was renally excreted (eg, digoxin). The alert was delivered by e-mail to physicians who had accessed computer-based information on the affected patient in the 3 days preceding and following the increase in serum creatinine. The intervention resulted in a significant decrease in the frequency of more severe renal dysfunction, although fewer than half of the recipients (44%) found the alerts helpful and 28% found them “annoying.” It is also noteworthy that Rind et al excluded patients on all services other than medicine, and all patients with preexisting moderate or severe renal insufficiency (serum creatinine >3.0 mg/dL [265.2 µmol/L]).

In another important study, one in a series evaluating the influence of computerized decision support, investigators at LDS Hospital in Salt Lake City, Utah, incorporated renal function assessment into an application that assisted physicians in prescribing antibiotics in an intensive care unit.11 These authors found that the use of their program decreased the frequency of inappropriate antimicrobial prescriptions (ie, orders for drugs to which patients had reported allergies, antibiotic susceptibility mismatches, and excessive drug dosages), and ADEs. Among patients who received recommended regimens, there was a significant decrease in LOS and drug and total hospital costs. More recently, Nightingale et al12 implemented a program in the renal unit of a British teaching hospital. Clinicians cancelled more than half of their orders when they were warned that the drug dosage they had requested was excessive. In the Nightingale et al study, there were no formal comparisons made between presystem and postsystem implementation periods with regard to appropriateness of orders, costs, complications, or hospital LOS.

The application used here differs from prior applications in that it is generalized to all hospitalized patients, provides suggestions for a wide range of drugs, and does so in real time. Feedback is most likely to be successful if it is delivered in real time, and in close temporal proximity to the decisions being made.9 As noted earlier, while we found that computerized physician order entry reduced the frequency of serious medication errors, it had a bigger impact on errors that did not actually injure patients.9 We believe—although this needs to be validated—that part of the reason for the larger impact on potential ADEs than actual ADEs was that the systems evaluated did not include sophisticated decision support, such as that pro-

Table 2. Rates of Appropriate and Inappropriate Orders in Intervention vs Control Periods*

<table>
<thead>
<tr>
<th></th>
<th>All Orders With Dose or Frequency Alteration</th>
<th>Dose Alteration</th>
<th>Frequency Alteration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td>P Value‡</td>
</tr>
<tr>
<td>Inappropriate†</td>
<td>2714 (49)</td>
<td>6298 (70)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Appropriate</td>
<td>2776 (51)</td>
<td>2652 (30)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5490</td>
<td>8950</td>
<td></td>
</tr>
</tbody>
</table>

*Values expressed as number (percentage).
†Defined as an excessive dose (higher than recommended) or frequency (more frequent than recommended).
‡χ² Test of proportions.

Table 3. Unadjusted Length of Stay and Costs in Intervention and Control Periods*

<table>
<thead>
<tr>
<th>Without Overlapping Admissions†</th>
<th></th>
<th></th>
<th>With Overlapping Admissions†</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td>P Value</td>
<td>Intervention</td>
<td>Control</td>
</tr>
<tr>
<td>Length of stay, mean (SD), d‡</td>
<td>4.3 (4.5)</td>
<td>4.5 (4.8)</td>
<td>.009</td>
<td>5.3 (7.1)</td>
<td>5.4 (7.4)</td>
</tr>
<tr>
<td>Total costs, $</td>
<td>4881 (2974-9383)</td>
<td>4968 (3035-9590)</td>
<td>.52</td>
<td>5211 (3093-10497)</td>
<td>5282 (3156-10570)</td>
</tr>
<tr>
<td>Pharmacy costs, $</td>
<td>168 (77-417)</td>
<td>166 (79-416)</td>
<td>.64</td>
<td>185 (82-497)</td>
<td>179 (83-479)</td>
</tr>
</tbody>
</table>

*Values presented as median (interquartile range) unless otherwise indicated.
†An overlapping admission is defined as an admission spanning across intervention and control periods. For the purpose of the comparison, the admission was assigned to the group (intervention vs control) active on the first admission day.
‡Median (interquartile range) for intervention and control is 3 (2-3), although Wilcoxon rank-sum tests are significant due to differences in distribution.
GUIDED MEDICATION DOSING

vided by the application described here. With widespread application of sophis-
ticated decision support, major reductions in ADE frequency as well as improvements in efficiency should be possible.

It is unclear why LOS was reduced by the new application’s activity. Typi-
cally, LOS is a downstream indicator of quality of care. Because of resource con-
straints, we were unable to evaluate the more subtle effects of the application. For example, avoidance of overdosing of se-
lected drugs in elderly patients may have led to fewer central nervous system or gastrointestinal tract adverse effects or other complications. Alternatively, LOS may have been reduced by other sever-
ity factors, which were not adjusted for by age, sex, and DRG weights.

The application had no effect on costs, but an effect may have been present but obscured since all patients were included in the cost analyses. In other words, restricting the analytic popula-
tion to individuals prescribed selected nephrotoxic or renally cleared medica-
tions might have allowed us to show a
tion to individuals prescribed selected
but an effect may have been present but
calculated. Fourth, the program did not send notices (pages or e-mails) to clinicians as soon as it had evidence of worsening renal function, as did that of Rind et al, but only alerted the clinician at the next occasion when the clinician was ordering a medication. Finally, since the in-
tervention was tested at a teaching hospital where house officers write the
majority of medication orders, the re-
sults may not be generalizable to other, non-teaching hospital settings.

In summary, a computer order entry-
based application to guide medication dose and frequency choices for inpatients with renal insufficiency was tested and resulted in a significant improvement in the ap-
propriateness of drug prescription. Pro-
vision of real-time advice in drug prescrip-
tion may prove to be among the most use-
ful applications of medical informatics technology. Such applications may pro-
vide clinicians “a better cockpit” and re-
sults in enhanced safety and increased ef-
ciciency at minimal cost, with little intru-
sion into practice.

Author Contributions: Study concept and design: Chertow, Kuperman, Komaroff, Bates. Acquisition of data: J. Lee, Kuperman, Burdick, Horsky, Seger, R. Lee, Mekala, Song. Analysis and interpretation of data: Chertow, J. Lee, Kuperman, Burdick, Horsky, Mekala, Komaroff, Bates. Drafting of the manuscript: Chertow, J. Lee, Kuperman, Bates. Critical revision of the manuscript for important in-
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perman, Burdick, Seger, R. Lee, Mekala, Song, Komaroff, Bates. Study supervision: Chertow, Kuperman, Komaroff, Bates. Financial Disclosures: Dr Bates is a consultant and serves on the advisory board for McKesson Med-
Management, a company that assists hospitals in pre-
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vvelops drug delivery systems, and the advisory board for Zynx, which develops evidence-based algo-
rithms. He is a consultant for Alaris, which makes in-
travenous drug delivery systems. Dr Bates also has received honoraria for speaking from the Eclipsys Corp, which has licensed the rights to the Brigham and Women’s Hospital Clinical Information System for possible commercial development. Dr Bates is also a coinventor on patent No. 6029138 held by Brigham and Women’s Hospital on the use of deci-
sion support software for medical management, li-
censed to the Medicalis Corp. He holds a minority eq-

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