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Original Investigation

# Dosing Errors in Prescribed Antibiotics for Older Persons With CKD: A Retrospective Time Series Analysis

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**Background:** Prescribing excessive doses of oral antibiotics is common in chronic kidney disease (CKD) and in this population is implicated in more than one-third of preventable adverse drug events. To improve the care of patients with CKD, many ambulatory laboratories now report estimated glomerular filtration rate (eGFR). We sought to describe the rate of ambulatory antibiotic dosing errors in CKD and examine the impact of eGFR reporting on these errors.

**Study Design:** Population-based retrospective time series analysis.

**Setting & Participants:** Southwestern Ontario, Canada, from January 2003 to April 2010. Participants were ambulatory patients 66 years or older with CKD stages 4 or 5 (eGFR $< 30$ mL/min/1.73 m$^2$) who were not receiving dialysis.

**Predictor:** Introduction of eGFR reporting in ambulatory laboratories (January 2006).

**Outcome:** Antibiotic dosing errors.

**Measurements:** Using linked health care databases, we assessed the monthly rate of excess dosing of orally prescribed antibiotics that require dose adjustment in CKD. We compared this rate before and after implementation of eGFR reporting.

**Results:** 1,464 prescriptions were filled for study antibiotics throughout the study period. Prior to eGFR reporting, the average rate of antibiotic prescriptions dosed in excess of guidelines was 64 per 100 antibiotic prescriptions. The introduction of eGFR reporting had no impact on this rate (68 per 100 antibiotic prescriptions; $P = 0.9$). Nitrofurantoin, which is contraindicated in patients with CKD, was prescribed 169 times throughout the study period.

**Limitations:** Although we attribute the dosing errors to poor awareness of dosing guidelines, we did not assess physician knowledge to confirm this. Dosing errors lead to adverse drug events; however, the latter could not be assessed reliably in our data sources.

**Conclusions:** Ambulatory antibiotic dosing errors are exceedingly common in CKD care. Strategies other than eGFR reporting are needed to prevent this medical error.

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***INDEX WORDS:*** Orally prescribed antibiotics; antibiotic dosing errors; renal disease; chronic kidney disease (CKD); estimated glomerular filtration rate (eGFR) reporting; nitrofurantoin; adverse drug event; quality of care; medical error; drug dosing adjustment; drug safety.

**Editorial, p. 382**

Adverse drug events have been cited as 1 of 7 leading causes of death in the United States and Canada and are associated with significant costs to the health care system.[1-3] Antibiotics are the second most common cause of adverse drug events in the ambulatory setting among seniors.[4] Patients with chronic kidney disease (CKD) are at increased risk for adverse drug events for many reasons, including reduced ability to excrete water-soluble drugs.[5-7] Many adverse drug events in CKD could be prevented with improved recognition of CKD and adherence to drug dosing guidelines.[5] Unfortunately, an estimated 19%-69% of prescriptions are dosed excessively in this vulnerable segment of the population.[8-11]

To improve the recognition and management of CKD, many health care systems have begun reporting estimated glomerular filtration rate (eGFR) along with serum creatinine results. In some jurisdictions, eGFR reporting has increased nephrology consultations and the use of guideline-appropriate kidney-protective medication, but it is unclear whether this intervention has improved drug dosing.[12-14] Although several studies have evaluated compliance with CKD dosing guidelines in inpatient settings, knowledge about adherence in ambulatory care is limited.[10,15-17]

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We conducted this study to assess the frequency of excess dosing of orally prescribed antibiotics in older patients with CKD stages 4 or 5 (eGFR < 30 mL/min/1.73 $m^2$) who were not receiving dialysis. We also investigated whether the introduction of eGFR reporting was associated with a reduction in dosing errors.

## METHODS

### Study Overview and Setting

We conducted a population-based retrospective time series analysis of antibiotic prescriptions in Southwestern Ontario. We analyzed large health care databases in accordance with a prespecified protocol. All Ontarians have access to health care services, including physician visits, hospital care, and home care, and Ontario seniors additionally benefit from prescription drug coverage. The study was approved by the Institutional Review Board at Sunnybrook Health Sciences Centre, Toronto, Canada. The reporting of this study followed guidelines[18] for observational studies.

### Study Antibiotics

We selected oral forms of cefixime, cefprozil, cephalexin, ciprofloxacin, clarithromycin, nitrofurantoin, sulfamethoxazole-trimethoprim, and tetracycline as our study antibiotics. These antibiotics are prescribed frequently in Ontario and have maximum recommended daily doses in patients with CKD stages 4 and 5, regardless of the indication for antibiotic use (Table 1).

### Intervention

In January 2006, ambulatory laboratories in Ontario began reporting eGFR with every serum creatinine test as calculated by the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation.[19] Test results were paired with a prompt to aid the physician in the interpretation of the eGFR value (prompt described elsewhere[12]). Prompts were the same regardless of the patient's age, sex, or race. In the laboratory report, physicians were not provided with other guidelines on the appropriate treatment or management of patients with CKD.

**Table 1.** Maximum Daily Dose Cutoffs Used to Define Dosing Errors for Study Antibiotics

| Medication | eGFR[a] | Dose (mg) | Interval | Max Daily Dose (mg) |
|---|---|---|---|---|
| Cefixime | 20-40 | 300 | Daily | 300 |
| Cefprozil | <50 | 250 | Every 12 h | 500 |
| Cephalexin | 10-50 | 500 | Every 8 h | 1,500 |
| Ciprofloxacin | 10-50 | 500 | Daily | 500 |
| Clarithromycin | <30 | 500 | Daily | 500 |
| Nitrofurantoin | <60 | Contraindicated | | |
| Sulfamethoxazole-trimethoprim[b] | <30 | S, 800; T, 160 | Daily | S, 800; T, 160 |
| Tetracycline | 10-50 | 500 | Every 12 h | 1,000 |

*Note:* Appropriate and inappropriate doses were determined using the 2010 Canadian *Compendium of Pharmaceuticals and Specialties* guidelines. Daily doses that are greater than the maximum doses above were classified as inappropriate.

Abbreviations: eGFR, estimated glomerular filtration rate; Max, maximum; S, sulfamethoxazole; T, trimethoprim.

[a]eGFR (in mL/min/1.73 $m^2$) has been considered interchangeable with creatinine clearance (in mL/min).

[b]Formulations of sulfamethoxazole-trimethoprim include both chemicals in one pill or suspension.

### Data Sources

We used 5 linked Ontario health care databases to define patient characteristics, including kidney function and antibiotic use and dose. The Ontario Drug Benefits database accurately identifies ambulatory prescription medications dispensed to Ontario residents 65 years and older with an error rate of <1%.[20] The Registered Persons Database provides vital statistics. To assess baseline comorbid conditions and exclusion criteria, we used the Canadian Institute for Health Information Discharge Abstract Database, which contains detailed diagnostic and procedural information from all hospital admissions in Ontario, and the Ontario Health Insurance Plan database, which contains claims information for inpatient and outpatient services rendered to Ontario residents. Gamma-Dynacare is the largest provider of ambulatory laboratory services in Southwestern Ontario. Its database contains serum creatinine values that during the study period were standardized for use in the MDRD Study equation.[21]

### Identification of Patients and Outcomes

We divided our study period into monthly intervals beginning January 2003 and ending April 2010. We chose monthly intervals because most antibiotics are prescribed for short (3- to 14-day) durations. To ensure that only patients who had fully transitioned on to the Ontario Drug Benefits program were captured, all patients were required to have at least 1 year of drug coverage prior to the start of an interval in order to be included.

In each interval, we selected patients whose most recent eGFR in the 1 year prior was <30 mL/min/1.73 $m^2$. To eliminate patients with chronic infections and those who may have started an antibiotic course in the hospital, we excluded patients who had recent hospitalizations (in the 30 days prior to interval start) or who received an antibiotic prescription in the 4 months prior to interval start. We also excluded patients with end-stage renal disease (hemodialysis, peritoneal dialysis, or kidney transplantation) in the 5 years prior to interval start due to differences in drug dosing recommendations for these patients.

The best equation to estimate kidney function for the purposes of drug adjustment is controversial.[22] The US National Kidney Disease Education Program indicates that both the MDRD Study and Cockroft-Gault equations are appropriate for this purpose.[23-25] In this study, we estimated GFR using the MDRD Study equation, which when <30 mL/min/1.73 $m^2$ would also identify a patient with a Cockcroft-Gault result <30 mL/min (at this level of kidney function, agreement between both equations is good, although the MDRD Study equation generally yields a higher estimate of GFR).

For each interval, we determined the number of individuals prescribed a study antibiotic and the prescribed daily dose of that antibiotic. A prescription was classified as a dosing error if it exceeded the maximum daily dose recommended for patients with CKD in the Canadian *Compendium of Pharmaceuticals and Specialties,* a compilation of Health Canada–approved product monographs (Table 1).[26] The Canadian *Compendium of Pharmaceuticals and Specialties* is the pharmaceutical reference manual most frequently used by primary care physicians in Canada.[27] These maximum doses then were cross-referenced with the UpToDate and Epocrates websites to ensure consistency across commonly used dosing guidelines. Our primary outcome was the rate of total dosing errors per 100 prescriptions. The average rate of dosing errors per 1,000 patients with CKD per month also was determined.

### Analysis

We examined the association between eGFR reporting and dosing errors using retrospective time series analysis with autoregressive integrated moving average modeling. There were

36 preintervention periods (January 2003 to December 2005) and 52 postintervention periods (January 2006 to April 2010). We fit the models with 3-month lag intervals and a step function. We determined model appropriateness by examining the autocorrelation function at different lag periods using the Ljung-Box $\chi^2$ statistic.[28] All $P$ values were 2 sided, and we interpreted $P < 0.05$ as statistically significant. We performed analyses using R statistical software, version 2.11.1 (R Foundation for Statistical Computing) and SAS, version 9.2 (SAS Institute Inc).

### Additional Analysis

We determined the rate of excessive dosing of antibiotics that do not require renal dose adjustment and considered whether the introduction of eGFR reporting increased the use of these antibiotics. To do so, we selected oral forms of clindamycin, cloxacillin, and moxifloxacin as nonrenally cleared antibiotics. The outcomes of interest were the rate of excessive dosing per 100 prescriptions and the rate of use of these antibiotics per 1,000 patients with CKD.

Furthermore, we conducted a post hoc analysis of the impact of a variety of patient and physician characteristics on dosing errors. We examined the relationship between dosing errors and patient age, sex, residence, eGFR, income, and comorbid conditions. For physicians, we compared age, years since graduation, location of medical education, and specialty in physicians who prescribed one or more error and those who did not prescribe dosing errors. One-way analysis of variance and Kruskal-Wallis tests were used to compare continuous variables, and $\chi^2$ tests were used for categorical variables. All analyses were conducted using SAS, version 9.2.

## RESULTS

### Study Participants

The number of patients who met our inclusion criteria per month increased gradually with time, from 525 in early 2003 to 683 in early 2010, with an average of 667 patients per month. Characteristics of these patients were similar throughout the study period (Table 2).

### Antibiotics Dosed in Excess of Guidelines

Of the total 1,464 prescriptions filled for study antibiotics throughout the study period, 970 (66.3%) were for doses in excess of recommended guidelines (Table 3). On average, 25 prescriptions per 1,000 patients with CKD were filled per month, and 17 prescriptions per 1,000 patients with CKD per month were overdosed. Cephalexin was the most frequently prescribed antibiotic, with more than 425 prescriptions filled during the study period. It was dosed excessively at a rate of 61 per 100 prescriptions.

**Table 2.** Characteristics of Patients Before and After eGFR Reporting Among Select Months

| Characteristic | Before eGFR Reporting | | After eGFR Reporting | |
|---|---|---|---|---|
| | January 2003 (n = 525) | January 2005 (n = 604) | January 2007 (n = 691) | January 2009 (n = 623) |
| eGFR | | | | |
| 15-29 mL/min/1.73 m$^2$ | 467 (89) | 573 (95) | 656 (95) | 590 (95) |
| <15 mL/min/1.73 m$^2$ | 58 (11) | 31 (5) | 35 (5) | 33 (5) |
| Mean ± SD | 23.3 ± 5 | 23.9 ± 5 | 24.2 ± 5 | 24.2 ± 5 |
| Female sex | 321 (61) | 384 (64) | 469 (68) | 414 (66) |
| Age | | | | |
| 66-70 y | 52 (10) | 52 (9) | 70 (10) | 46 (7) |
| 71-75 y | 93 (18) | 101 (17) | 98 (14) | 100 (16) |
| 76-80 y | 134 (26) | 166 (27) | 165 (24) | 134 (22) |
| 81-85 y | 119 (23) | 147 (24) | 156 (23) | 160 (26) |
| ≥86 y | 127 (24) | 138 (23) | 202 (29) | 183 (29) |
| Mean ± SD | 80 ± 5 | 80 ± 5 | 81 ± 5 | 81 ± 5 |
| Rural residence[a] | 86 (16) | 99 (16) | 133 (19) | 101 (16) |
| Low income[b] | 116 (22) | 161 (27) | 154 (22) | 139 (22) |
| Diabetic | 144 (27) | 182 (30) | 238 (34) | 215 (35) |
| Hypertensive | 142 (27) | 203 (34) | 256 (37) | 282 (45) |
| Charlson Comorbidity Index score | | | | |
| 0 | 141 (27) | 145 (24) | 192 (28) | 194 (31) |
| 1 | 54 (10) | 77 (13) | 82 (12) | 61 (10) |
| 2 | 73 (14) | 77 (13) | 98 (14) | 101 (16) |
| ≥3 | 177 (34) | 178 (29) | 174 (25) | 140 (22) |
| No hospitalizations | 80 (15) | 127 (21) | 145 (21) | 127 (20) |

*Note:* Unless otherwise indicated, values are given as number (percentage).

Abbreviations: eGFR, estimated glomerular filtration rate; SD, standard deviation.

[a]Rural defined as population less than 10,000.

[b]Income categorized into quintiles, using average neighborhood income on the index date. Low income is defined as the lowest income quintile. There was no change in the other income quintiles over the study period.

**Table 3.** Total Prescriptions and Dosing Errors for Study Antibiotics

| Medication | Total Prescriptions | Dosing Errors |
|---|---|---|
| Ciprofloxacin | 271 | 147 (54) |
| Cefixime | 11 | 9 (82) |
| Cefprozil | 114 | 70 (61) |
| Cephalexin | 425 | 258 (61) |
| Clarithromycin | 251 | 130 (52) |
| Nitrofurantoin | 169 | 169 (100) |
| Sulfamethoxazole-trimethoprim | 214 | 185 (86) |
| Tetracycline | 9 | 2 (22) |
| Total | 1,464 | 970 (66) |

*Note:* Values are given as number or number (percentage).

Nitrofurantoin was prescribed 169 times, despite being contraindicated in patients with CKD.

### Impact of eGFR Reporting

Prior to eGFR reporting, the average rate for dosing errors in the study antibiotics was 64 per 100 antibiotic prescriptions; after implementation of eGFR reporting, the rate was 68 per 100 antibiotic prescriptions. The initiation of eGFR reporting was not associated with a decline in the rate of antibiotic dosing errors ($P = 0.9$; Fig 1).

### Additional Analysis

For nonrenally cleared antibiotics, there was an average of 5.6 prescriptions per month per 1,000 patients with CKD. The initiation of eGFR reporting was not associated with a significant change in the rate of antibiotic use. The average rate of dosing errors of nonrenally cleared antibiotics was 2 per 100 prescriptions.

A total of 1,166 unique patients were prescribed the study antibiotics during the study period. Characteristics of patients who were prescribed the correct dose of antibiotics were similar to those prescribed erroneous doses. However, patients who were younger, had diabetes, and lived in rural areas were at increased risk of dosing error (Table 4).

Of the 1,464 prescriptions filled throughout the study period, 1,265 could be linked to prescribing physicians. From these, 564 physicians who prescribed study antibiotics throughout the study period were identified. It appears that Canadian medical graduates and family physicians may be at increased risk of dosing errors, whereas internal medicine and subspecialists are at decreased risk (Table 5). Unfortunately, data for specialty and location of graduation were missing for many physicians.

## DISCUSSION

In older adults with CKD stages 4 and 5, excessive doses of antibiotics are common and occur in 2 of every 3 prescriptions. Nitrofurantoin frequently is prescribed to these patients despite being contraindicated due to reduced efficacy and increased risk of peripheral neuropathy.[29,30] Although eGFR reporting previously has been associated with increased recognition of CKD,[14] eGFR reporting was not associated with a reduction in the rate of dosing errors. It also did not lead to preferential use of nonrenally cleared antibiotics.

Similar findings have been shown by Quartarolo et al[31] in an inpatient setting in an academic center. In their evaluation, they found no significant difference in antibiotic dosing before and after reporting of eGFR on paper medical charts. The authors concluded that although eGFR reporting improved recognition of CKD among physicians, it did not lead to a change in physician prescribing behavior. Based on our results and those of Quartarolo et al,[31] we believe that poor knowledge of renal dosing

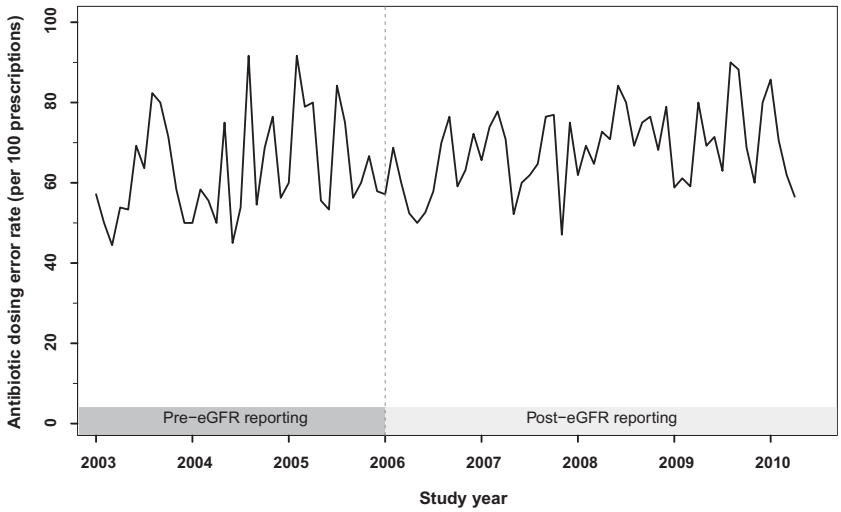


**Figure 1.** Ambulatory antibiotic dosing errors in non–dialysis-dependent patients with stages 4-5 chronic kidney disease. Abbreviation: eGFR, estimated glomerular filtration rate.

**Table 4.** Patient Outcome Characteristics for Entire Study Period

| Characteristic | No Errors (n = 347) | Any Error (1+) (n = 819) | P |
|---|---|---|---|
| eGFR | | | 0.2 |
| 15-29 mL/min/1.73 m$^2$ | 318 (92) | 768 (94) | |
| <15 mL/min/1.73 m$^2$ | 29 (8) | 51 (6) | |
| Mean ± SD | 24 ± 5 | 24 ± 5 | 0.6 |
| Female sex | 238 (69) | 544 (66) | 0.5 |
| Age | | | 0.04 |
| 66-70 y | 24 (7) | 83 (10) | 0.08 |
| 71-75 y | 48 (14) | 146 (18) | 0.09 |
| 76-80 y | 71 (21) | 177 (22) | 0.7 |
| 81-85 y | 82 (24) | 189 (23) | 0.8 |
| ≥86 y | 122 (35) | 224 (27) | 0.01 |
| Mean ± SD | 82 ± 8 | 80 ± 7 | <0.001 |
| Rural residence[a] | 44 (13) | 169 (21) | 0.001 |
| Low income[b] | 7 (2) | ≤5 (1) | 0.09 |
| Diabetic | 102 (29) | 301 (37) | 0.02 |
| Hypertensive | 138 (40) | 326 (40) | 0.9 |
| Charlson Comorbidity Index score | | | 0.4 |
| 0 | 80 (23) | 193 (24) | 0.9 |
| 1 | 50 (14) | 109 (13) | 0.6 |
| 2 | 49 (14) | 141 (17) | 0.2 |
| ≥3 | 126 (36) | 261 (32) | 0.1 |
| No hospitalizations | 42 (12) | 115 (14) | 0.4 |

*Note:* Unless otherwise indicated, values are given as number (percentage). For patients with a dosing error, characteristics were determined from a randomly selected month in which the patient had an inappropriate prescription. For patients who did not have dosing errors, characteristics were determined from a randomly selected month in which the patient had a prescription.

Abbreviations: eGFR, estimated glomerular filtration rate; SD, standard deviation.

[a]Rural defined as population less than 10,000.

[b]Income categorized into quintiles, using average neighborhood income on the index date. Low income is defined as the lowest income quintile.

**Table 5.** Physician Characteristics for Entire Study Period

| Characteristic | No Errors (n = 117) | Any Error (1+) (n = 447) | P |
|---|---|---|---|
| Age | | | |
| Mean ± SD | 52 ± 11 | 51 ± 11 | 0.6 |
| Median [IQR] | 50 [44-60] | 50 [43-59] | 0.7 |
| Years since graduation | | | |
| Mean ± SD | 26 ± 11 | 25 ± 11 | 0.5 |
| Median [IQR] | 24 [18-34] | 24 [17-32] | 0.4 |
| Location of medical education | | | 0.01 |
| Canada | 62 (53) | 292 (65) | 0.01 |
| International | 22 (19) | 72 (16) | 0.5 |
| Unknown | 33 (28) | 83 (19) | 0.02 |
| Specialty | | | <0.001 |
| IM or IM subspecialty | 11 (9) | 9 (2) | <0.001 |
| Family and ED | 57 (49) | 325 (73) | <0.001 |
| Other | 16 (14) | 30 (7) | 0.01 |
| Missing | 33 (28) | 83 (19) | 0.02 |

*Note:* Unless otherwise indicated, values are given as number (percentage). For physicians with a dosing error, characteristics were determined from a randomly selected month in which the physician had an inappropriate prescription. For physicians who did not have dosing errors, characteristics were determined from a randomly selected month in which the physician prescribed an antibiotic.

Abbreviations: ED, emergency department; IQR, interquartile range; IM, internal medicine; SD, standard deviation.

guidelines contributed to the failure of eGFR reporting to improve dosing. Poor knowledge of renal dosing rules and lack of medication information have been identified as major causes of prescribing errors.[32,33] Such errors appear to be more prevalent in ambulatory care than in hospitalized settings.[9] It also is possible that despite eGFR reporting, physicians remain unaware of their patients' kidney functions or do not have information regarding kidney function readily available when prescribing. Unfortunately, we were unable to assess physician awareness at the time of prescribing.

Our study has a number of strengths. To our knowledge, it is the first study to evaluate the impact of reporting eGFR on medication dosing in an ambulatory setting. We studied all older patients in our region using records that describe routine practice. These patients are a particularly vulnerable segment of the population. We also assessed data over a period of greater than 7 years to ensure that data were consistent. This was important given the great degree of variability we saw in excessively dosed prescriptions from one month to the next. To ensure that the phenomenon of two-thirds excessive dosing was isolated to renally cleared antibiotics, we also assessed the rate of excessive dosing of nonrenally cleared antibiotics. We found that only 2% of nonrenally cleared antibiotics were excessively dosed. Finally, to evaluate the effect of eGFR reporting, we used time series, which is a stronger and more robust methodology than the more conventional prestudy/poststudy design.[34]

Our study has some limitations. Ideally, we would have liked to measure adverse drug events. However, because adverse drug events from antibiotic dosing errors could not be ascertained reliably in our data sources, we focused solely on the process of care outcome of dosing errors. Importantly, the drugs we have selected are associated with significant toxicity, particularly in high doses and in patients with decreased kidney function.[35-37] Also, although we attribute the dosing errors to poor physician awareness of dosing guidelines, we cannot say this with complete certainty because we did not assess physician knowledge to confirm this. Some physicians may

have deliberately chosen to ignore the dosing guidelines (for example, as a result of severe or recurrent infection). However, such cases were unlikely, particularly because we excluded patients who were recently treated with antibiotics and/or who had recent hospitalizations. Furthermore, some physicians, particularly those practicing in urgent care settings, may be unaware of a patient's reported eGFR when prescribing study antibiotics. Unfortunately, given the limitations of our data sources, we were unable to ascertain in what clinical setting the antibiotic was prescribed. We would hope that these physicians are prescribing cautiously or using nonrenally cleared antibiotics in their elderly patients at risk of CKD. Interestingly, we saw no impact of eGFR reporting on the use of nonrenally cleared antibiotics.

Our findings suggest that simply reporting eGFR to physicians will not improve antibiotic dosing in patients with CKD. The inclusion of prompts warning physicians about the need for antibiotic dose adjustments in patients with CKD may help improve future iterations of eGFR reporting. However, in a recent cluster randomized trial, including management recommendations in the eGFR prompt did not increase the use of kidney-protective medications.[38] An alternative approach of computerized clinical decision support shows promise in improving prescribing patterns.[39] As more primary care physicians adopt electronic medical records, the optimal use of such systems requires consideration.[40]

Antibiotic dosing errors have been identified as one of the most common medication errors in inpatients with CKD.[41] These errors are costly for patients and health care systems because they increase the risk of adverse drug events.[2,29,42] Adverse drug events are an important cause of hospitalization and complications, especially among elderly patients.[3,6] They have been shown to increase community hospital costs by up to $3,420 and length of stay by 3.15 days.[43] Preventing dosing errors can improve the quality of patient care and patient outcomes. Given the frequency of antibiotic dosing errors observed in this study, it is apparent that there is a large care gap in antibiotic dosing in patients with CKD. Reporting of eGFR has not improved this. Further investigation into the patient-, physician-, and system-level factors that mediate this care gap are warranted to identify areas for improvement and guide optimal systems development.

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