

# Risk of Bloodstream Infection in Patients With Chronic Kidney Disease Not Treated With Dialysis

Matthew T. James, MD; Kevin B. Laupland, MD, MSc; Marcello Tonelli, MD, SM; Braden J. Manns, MD, MSc; Bruce F. Culleton, MD, MS; Brenda R. Hemmelgarn, PhD, MD; for the Alberta Kidney Disease Network

**Background:** Patients with end-stage renal disease requiring dialysis are at high risk for bloodstream infection and infection-related death. Whether patients with chronic kidney disease who are not receiving dialysis are also at increased risk of bloodstream infection is less clear.

**Methods:** We examined the association between chronic kidney disease not being treated with dialysis and bloodstream infection in a cohort of patients 66 years or older. All patients required at least 1 outpatient serum creatinine measurement enabling estimation of glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease Study equation. Cox proportional hazards models with censoring at the initiation of renal replacement therapy or death were used to determine associations between eGFR, bloodstream infection, and death within 30 days of community-onset bloodstream infection, adjusting for potential confounders.

**Results:** In 25 675 patients followed up for a median of 3.2 years, 797 developed at least 1 bloodstream infec-

tion, of which most (75%) were community-onset infections. Compared with patients with an eGFR of 60 mL/min/1.73 m<sup>2</sup> or higher, adjusted hazard ratios (95% confidence intervals) for bloodstream infection according to eGFR were, respectively, 1.24 (1.01-1.52), 1.59 (1.24-2.04), and 3.54 (2.69-4.69) in those with an eGFR of 45 to 59, 30 to 44, and less than 30 mL/min/1.73 m<sup>2</sup>. The associations were consistent for both community-onset and nosocomial infections. Compared with patients with an eGFR of 60 mL/min/1.73 m<sup>2</sup> or higher, the risk of death within 30 days of community-onset bloodstream infection was significantly greater in those with an eGFR less than 30 mL/min/1.73 m<sup>2</sup> (hazard ratio, 4.10; 95% confidence interval, 2.06-8.14).

**Conclusion:** Older adults with chronic kidney disease not being treated with dialysis are at increased risk of bloodstream infection and of death following community-onset bloodstream infection.

*Arch Intern Med.* 2008;168(21):2333-2339

**C**HRONIC KIDNEY DISEASE (CKD), defined by an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m<sup>2</sup> or evidence of structural kidney damage, affects at least 20% of adults 65 years or older and has been independently associated with hospitalization and death.<sup>1,2</sup> The excess risk of morbidity and mortality in patients with CKD is largely attributable to cardiovascular events<sup>3,4</sup>; however, recent cohort studies have suggested that CKD is also a risk factor for noncardiovascular morbidity and mortality<sup>5</sup> including that caused by infection.<sup>6,7</sup> Few studies have investigated associations between CKD and specific infectious conditions.

Bacteremia is the second leading cause of death in patients with end-stage renal

disease (ESRD) requiring dialysis.<sup>8,9</sup> The high rate of bloodstream infection in patients receiving hemodialysis is attributable in part to the requirement for vascular access.<sup>10,11</sup> While not as high as in patients receiving dialysis, reported rates of hospitalization because of septicemia in patients with CKD not being treated with dialysis seem to be 3- to 4-fold greater than in patients without CKD.<sup>12</sup> However, it is unclear whether this observation is attributable to the consequences of CKD or explained by the older age and greater burden of comorbidities in patients with CKD.

We sought to determine the association between CKD not treated with dialysis and bloodstream infection in a large community-based cohort of older adults. Cognizant that an increased rate of hospitalization for patients with CKD could

Author Affiliations are listed at the end of this article.

Group Information: A list of the Alberta Kidney Disease Network appears at <http://www.akdn.info/contact.html>.

explain increased rates of bloodstream infection from nosocomial infections alone, we also analyzed community-onset and nosocomial bloodstream infection as separate outcomes.<sup>13</sup> We hypothesized that patients with a lower eGFR would be more likely than patients with preserved renal function to develop bloodstream infection, independent of age or comorbidities.

## METHODS

### STUDY POPULATION

The cohort included all adults 66 years or older with at least 1 outpatient serum creatinine measurement between July 1, 2001, and December 31, 2001, as identified from the Calgary Laboratory Services database in Calgary, Alberta, Canada. Calgary Laboratory Services provides testing for the entire Calgary Health Region (catchment population, 1.1 million, with 80 567 subjects 66 years or older in 2001) using a single regional laboratory and standardized methods that are routinely recalibrated against reference standards. To avert classifying episodes of acute renal failure as CKD, laboratory measurements associated with a hospital admission were excluded. Patients were excluded if they were receiving renal replacement therapy (hemodialysis, peritoneal dialysis, or kidney transplantation) at study enrollment or if the baseline estimate of kidney function was clinically implausible (eGFR >150 mL/min/1.73 m<sup>2</sup>; n=80).

### MEASUREMENT OF KIDNEY FUNCTION

The GFR for each patient was estimated using the abbreviated Modification of Diet in Renal Disease Study equation (eGFR = 186 × plasma creatinine<sup>-1.154</sup> × age<sup>-0.203</sup> × 0.742 [if female]).<sup>14</sup> Black race was omitted from the equation because this variable was unavailable in the data source, although this is unlikely to bias results because less than 1% of the population of Calgary is black.<sup>15</sup> Serum creatinine measurements were analyzed in a single laboratory, eliminating the potential for interlaboratory measurement variation. We have previously reported indirect calibration of eGFR results for this laboratory using an isotope dilution mass spectrometry reference standard and the modified Modification of Diet in Renal Disease Study equation,<sup>16</sup> with valid estimates obtained.<sup>17</sup> Furthermore, we have observed minimal intralaboratory variation in eGFR over time in our setting, as previously described.<sup>18</sup> We used the first eGFR determined during the study entry period to define baseline kidney function.

### OUTCOMES

The primary outcome of interest was first bloodstream infection isolated in any clinical setting. All blood was cultured by Calgary Laboratory Services using an automated blood culture system (BacT/Alert; Organon Teknika Corp, Durham, North Carolina). Calgary Laboratory Services performs almost all (>95%) standard microbiology testing for hospitals, nursing homes, physician offices, and community collection sites in the Calgary Health Region.<sup>13</sup> A blood culture set consisted of an aerobic and an anaerobic bottle pair obtained from a single draw. Organisms were isolated and speciated using standard methods. A bloodstream infection was defined as the growth of a pathogenic organism (bacteria or yeast) from at least 1 set of blood cultures and was determined by linking each patient to the Calgary Laboratory Services microbiology database using their unique provincial health care numbers. Organisms frequently associated with skin contamination (coagulase-negative staphylo-

cocci, viridans group streptococci, and *Bacillus*, *Corynebacterium*, or *Propionibacterium* species) were excluded from the primary analysis because of the difficulty in establishing their clinical significance.<sup>13,19</sup> Further analyses were also performed by subdividing first bloodstream infection into community-onset or nosocomial bloodstream infection. Infections were defined as community-onset if submitted from community-based collection sites or identified within the first 2 days of admission to an acute care facility<sup>13</sup> and as nosocomial if identified after 2 days of admission to an acute care facility. The secondary outcome of interest was death within 30 days of community-onset bloodstream infection, with date of death determined by linkage to the Alberta Bureau of Vital Statistics, which maintains records of deaths of all residents of the province of Alberta. Patients were followed up to December 31, 2004, for all outcomes, with censoring at date of death or initiation of renal replacement therapy. Emigration from the Calgary Health Region was not identified; however, the 2002-2003 population estimates for emigration from Calgary of less than 2%<sup>20</sup> were not expected to bias results.

### COVARIATES

The cohort was linked to provincial administrative data to obtain a measure of comorbidity based on prescription drug use in the 6 months before the index serum creatinine concentration as determined by the Chronic Disease Score, which is a validated index weighted on patterns of drug use, with higher scores reflecting increased comorbidity.<sup>21</sup> Prescription drug use was also used to define the presence of diabetes mellitus, defined as at least 1 prescription for insulin or an oral hypoglycemic agent in the year before cohort entry. Hemoglobin and albumin measurements were obtained from the Calgary Laboratory Services database. Although unavailable for all patients, during the study, hemoglobin levels were determined in 17 979 patients (70% of the cohort), and serum albumin levels in 5 493 patients (21%). Linkage to the Southern Alberta Renal Program database was performed to determine whether patients were receiving care in a dedicated CKD clinic<sup>22</sup> and to exclude patients receiving renal replacement therapy at study enrollment. The Southern Alberta Renal Program provides ESRD care to all patients within the Calgary Health Region and maintains computerized records of all patients receiving dialysis, renal transplantation, or nondialysis CKD care.<sup>23</sup>

### STATISTICAL ANALYSES

Baseline characteristics according to eGFR were summarized as mean and standard deviation for normally distributed continuous variables, percent prevalence for dichotomous variables, and median with interquartile range for variables with a nonnormal distribution. Differences in baseline characteristics according to eGFR were compared using analysis of variance, the  $\chi^2$  test, and the Kruskal-Wallis test, as appropriate. Adjusted rate of first bloodstream infection and mortality were calculated using Poisson regression, adjusting for age, sex, diabetes mellitus, and comorbidity score (as quartiles of the Chronic Disease Score). To control for factors specific to the specialized care of patients with CKD that may influence the risk of bloodstream infection, we also adjusted for care in a dedicated CKD clinic.

The association between eGFR and risk of first bloodstream infection was determined using Cox proportional hazards models including adjustment for age, sex, diabetes mellitus, comorbidity score (as quartiles of the Chronic Disease Score), and care in a dedicated CKD clinic. The modifying effects of sex and diabetes were tested by including interaction terms and testing their statistical significance in the Cox proportional hazards models. Patients were censored at death or

**Table 1. Baseline Characteristics in 25 675 Study Patients According to eGFR<sup>a</sup>**

Characteristic	eGFR, mL/min/1.73 m <sup>2</sup>			
	≥60 (n=18 734)	45-59 (n=4136)	30-44 (n=1926)	<30 (n=879)
Age, mean (SD), y	74.4 (6.5)	77.5 (7.2)	79.3 (7.4)	78.6 (7.4)
Female, %	53.9	61.4	62.5	59.6
Diabetes mellitus, %	12.7	16.0	19.5	23.3
Comorbidity score, median (IQR)	2067 (1475-2936)	2588 (1889-3588)	2949 (2076-4064)	3554 (2293-4775)
eGFR, median (IQR), mL/min/1.73 m <sup>2</sup>	79 (70-91)	53 (50-57)	39 (35-42)	23 (18-27)
Hemoglobin concentration, mean (SD), g/dL <sup>b</sup>	14.0 (1.5)	13.5 (1.6)	12.8 (1.8)	11.9 (1.8)
Serum albumin concentration, mean (SD), g/dL <sup>c</sup>	3.7 (0.4)	3.6 (0.5)	3.6 (0.5)	3.5 (0.5)
Care in dedicated CKD clinic, %	0	0	0.7	9.8

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range.

SI conversion factor: To convert hemoglobin and serum albumin to grams per liter, multiply by 10.0

<sup>a</sup>All *P* values < .001. *P* value across categories calculated by  $\chi^2$  test for categorical variables, analysis of variance for measured variables, and Kruskal-Wallis test for comorbidity score.

<sup>b</sup>Available for 17 979 patients (70%).

<sup>c</sup>Available for 5493 patients (21%).

initiation of renal replacement therapy (hemodialysis, peritoneal dialysis, or renal transplantation). The association between level of kidney function and risk of death within 30 days of community-onset bloodstream infection was determined using Cox proportional hazards models including adjustment for age, sex, diabetes mellitus, comorbidity, and care in a CKD clinic, with censoring at death not related to bloodstream infection or at initiation of renal replacement therapy.

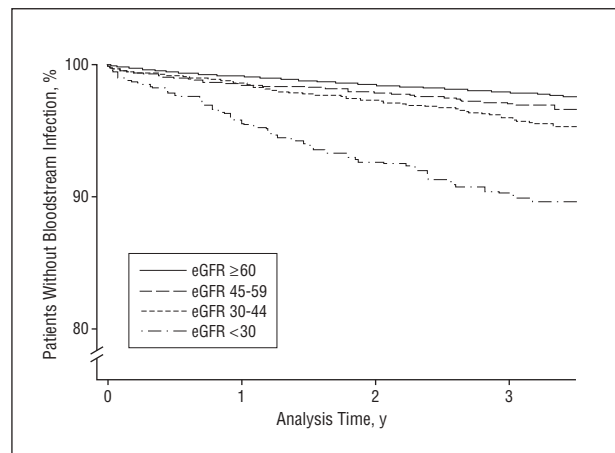
Additional analyses were performed including adjustment for hemoglobin and albumin concentrations in a subgroup of the cohort with these measurements and using Poisson regression models that included repeat infections (subsequent bloodstream infection with a different microbial species or a bloodstream infection with the same microbial species >6 months after the initial infection) in the same patient. The proportional hazards assumptions were tested and met using log-negative-log plots and scaled Schoenfeld residuals and by including time-dependent covariates (for eGFR, age, sex, diabetes, and comorbidity score) in the Cox models. All statistical analyses were conducted using commercially available software (STATA, version 10; STATA Corp, College Station, Texas). The conjoint health research ethics board of the University of Calgary approved the study.

## RESULTS

### CHARACTERISTICS OF THE COHORT

A total of 25 675 patients met criteria for enrollment in the cohort, of whom 6941 (27.0%) had CKD as defined by an eGFR less than 60 mL/min/1.73 m<sup>2</sup>. Patients with an eGFR less than 60 mL/min/1.73 m<sup>2</sup> were older, more likely to be female, had greater comorbidity, had lower hemoglobin and serum albumin concentrations, and were more likely to receive care in a CKD clinic (**Table 1**). One hundred eighteen patients with an eGFR less than 15 mL/min/1.73 m<sup>2</sup> who were not receiving dialysis at cohort enrollment were included in the “eGFR less than 30 mL/min/1.73 m<sup>2</sup>” category.

Median follow-up was 3.2 years (interquartile range, 3.1-3.4 years). During follow-up, 154 patients (0.6%) progressed to ESRD requiring renal replacement therapy, including 0.3% of patients with an eGFR of 45



**Figure.** Kaplan-Meier curves for first bloodstream infection according to estimated glomerular filtration rate (eGFR; mL/min/1.73 m<sup>2</sup>).

to 59 mL/min/1.73 m<sup>2</sup>, 1.2% with an eGFR of 30 to 59 mL/min/1.73 m<sup>2</sup>, and 12.6% with an eGFR of less than 30 mL/min/1.73 m<sup>2</sup> at study enrollment. A total of 2198 patients (8.6%) died during follow-up, including 6.6%, 12.3%, and 24.2% of patients with an enrollment eGFR of 60 mL/min/1.73 m<sup>2</sup> or higher, 30 to 59 mL/min/1.73 m<sup>2</sup>, and less than 30 mL/min/1.73 m<sup>2</sup>, respectively.

### RISK OF BLOODSTREAM INFECTION

Bloodstream infection was rare, with 873 episodes in 797 patients (3.1% of the cohort) during the follow-up period. The **Figure** shows the Kaplan-Meier curves for first bloodstream infection according to the eGFR. Rates of bloodstream infection were significantly greater (*P* < .05, log-rank test) at all eGFRs less than 60 mL/min/1.73 m<sup>2</sup>, in particular in patients with an eGFR less than 30 mL/min/1.73 m<sup>2</sup>, in whom rates of bloodstream infection were at least 4-fold higher compared with patients with an eGFR of 60 mL/min/1.73 m<sup>2</sup> or higher. In adjusted Cox proportional hazards models, there was a graded increase in the risk of bloodstream infection with lower eGFR (**Table 2**).

**Table 2. Risk of First Bloodstream Infection According to eGFR**

Outcome	eGFR, mL/min/1.73 m <sup>2</sup>	Time at Risk, Person-Years	No. of Patients With Infection	Incidence (95% CI) per 100 Person-Years <sup>a</sup>	HR (95% CI) <sup>a</sup>
Any bloodstream infection	≥60	57 304	475	0.55 (0.46-0.67)	1 [Reference]
	45-59	12 235	153	0.75 (0.52-1.08)	1.24 (1.01-1.52)
	30-44	5410	93	1.71 (1.05-2.77)	1.59 (1.24-2.04)
	<30	2051	76	4.24 (2.16-8.46)	3.54 (2.69-4.69)
Community-onset bloodstream infection	≥60	57 492	360	0.45 (0.37-0.56)	1 [Reference]
	45-59	12 301	113	0.54 (0.34-0.84)	1.17 (0.92-1.49)
	30-44	5436	71	0.73 (0.44-1.21)	1.60 (1.20-2.13)
	<30	2079	53	1.38 (0.81-2.37)	2.95 (2.11-4.14)
Nosocomial bloodstream infection	≥60	57 941	115	0.10 (0.07-0.16)	1 [Reference]
	45-59	12 442	40	0.15 (0.06-0.33)	1.43 (0.96-2.13)
	30-44	5527	22	0.16 (0.06-0.41)	1.54 (0.92-2.59)
	<30	2129	23	0.54 (0.22-1.29)	5.10 (3.18-8.20)

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

<sup>a</sup>Adjusted for age, sex, diabetes mellitus, comorbidity score, and care in a dedicated chronic kidney disease clinic.

**Table 3. Percentage of Patients With Bloodstream Infections Caused by Various Microbial Species According to eGFR**

Species	eGFR, mL/min/1.73 m <sup>2</sup>				P Value for Trend
	≥60	45-59	30-44	<30	
<i>Escherichia coli</i>	0.92	1.14	1.65	2.76	<.001
<i>Staphylococcus aureus</i>	0.40	0.58	0.99	3.42	<.001
<i>Streptococcus</i> species, not including <i>Streptococcus pneumoniae</i>	0.24	0.48	0.72	0.62	.01
<i>Klebsiella pneumoniae</i>	0.26	0.34	0.57	0.77	.004
<i>S pneumoniae</i>	0.16	0.24	0.21	0.22	.72
<i>Enterococcus</i> species	0.26	0.34	0.41	1.10	<.001
Anaerobes	0.26	0.29	0.21	1.43	<.001
<i>Pseudomonas aeruginosa</i>	0.11	0.24	0.21	0.55	.001
<i>Proteus mirabilis</i>	0.074	0.072	0.010	0	.70
<i>Candida</i> species	0.032	0.024	0.021	0.055	.001
Other gram-positive organisms	0.30	0.41	0.66	0.88	.002
Other gram-negative organisms	0.048	0.096	0.052	0.011	.57

Abbreviation: eGFR, estimated glomerular filtration rate.

Compared with patients with an eGFR of 60 mL/min/1.73 m<sup>2</sup> or higher, the risk of any bloodstream infection increased by 24% in patients with an eGFR of 45 to 59 mL/min/1.73 m<sup>2</sup> (hazard ratio [HR], 1.24; 95% confidence interval [CI], 1.01-1.52) and was more than 3-fold higher in patients with an eGFR less than 30 mL/min/1.73 m<sup>2</sup> (3.54; 2.69-4.69). Tests for interaction involving sex by eGFR and diabetes mellitus by eGFR were nonsignificant ( $P = .15$  and  $.71$ , respectively), demonstrating that the increased likelihood of infection in patients with lower levels of kidney function was not modified by these characteristics.

Of the 797 patients who developed a bloodstream infection, 597 (75%) had the onset of first bloodstream infection in a community setting. Compared with patients with an eGFR of 60 mL/min/1.73 m<sup>2</sup> or higher, adjusted HRs for community-onset bloodstream infection increased incrementally with lower eGFR (Table 2). The minority of patients with bloodstream infection (25%) developed the infection during a hospitalization. Although adjusted rates of nosocomial bloodstream infection were lower than those for community-onset blood-

stream infection, significant associations between eGFR and nosocomial bloodstream infection were also observed for patients with more severe CKD (eGFR < 30 mL/min/1.73 m<sup>2</sup>) (Table 2).

The microbial etiology of all bloodstream infections according to eGFR is given in **Table 3**. Infections with *Escherichia coli* and *Staphylococcus aureus* accounted for most bloodstream infections at all eGFRs. Rates of infection with a variety of gram-positive organisms, gram-negative organisms, and anaerobes all increased across lower levels of kidney function.

#### RISK OF DEATH WITHIN 30 DAYS OF COMMUNITY-ONSET BLOODSTREAM INFECTION

Of the 597 patients who developed a community-onset bloodstream infection, 80 (13.4%) died within 30 days of the onset of infection. Mortality after community-onset bloodstream infection was low, and compared with patients with an eGFR of 60 mL/min/1.73 m<sup>2</sup> or higher, patients with an eGFR of 45 to 59 mL/min/1.73 m<sup>2</sup> and 30

**Table 4. Risk of Death Within 30 Days of Community-Onset Bloodstream Infection According to eGFR**

eGFR, mL/min/1.73 m <sup>2</sup>	Time at Risk, Person-Years	No. of Deaths After Infection	Incidence (95% CI) per 100 Person-Years <sup>a</sup>	HR (95% CI) <sup>a</sup>
≥60	58 174	43	0.02 (0.01-0.05)	1 [Reference]
45-59	12 745	16	0.03 (0.01-0.13)	1.34 (0.74-2.40)
30-44	5580	10	0.04 (0.01-0.17)	1.61 (0.79-3.27)
<30	2419	11	0.08 (0.02-0.39)	4.10 (2.06-8.14)

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

<sup>a</sup>Adjusted for age, sex, diabetes mellitus, comorbidity score, and care in a dedicated chronic kidney disease clinic.

to 44 mL/min/1.73 m<sup>2</sup> demonstrated no significant differences in adjusted HR for death after bloodstream infection (**Table 4**). However, compared with patients with an eGFR of 60 mL/min/1.73 m<sup>2</sup> or higher, those with more severe CKD (eGFR <30 mL/min/1.73 m<sup>2</sup>) were at significantly higher risk of death (HR, 4.10; 95% CI, 2.06-8.14).

#### ADDITIONAL ANALYSES

To address the possibility that the association between eGFR and bloodstream infection could be explained by consequences of CKD including anemia or hypoalbuminemia, we performed additional analyses limited to 4251 members of the cohort with measurements of hemoglobin and albumin concentrations. After further adjustment for hemoglobin and albumin concentrations, there was no longer an association between bloodstream infection and eGFR at eGFR 30 to 59 mL/min/1.73 m<sup>2</sup> (HR, 1.00; 95% CI, 0.67-1.48). However, an independent association remained between the risk of bloodstream infection and eGFR less than 30 mL/min/1.73 m<sup>2</sup> (HR, 2.24; 95% CI, 1.38-3.63), which suggests that these factors do not completely explain the increased risk of bloodstream infection at lower eGFRs. Analyses using Poisson regression that included repeat bloodstream infections in the same patient produced similar conclusions as the primary analyses for time to first bloodstream infection.

#### COMMENT

Older adults with CKD were at increased risk of bloodstream infection, most of which were of community onset. The magnitude of this association increased across all eGFRs less than 60 mL/min/1.73 m<sup>2</sup>, even after adjustment for common risk factors, and was most apparent in patients with an eGFR less than 30 mL/min/1.73 m<sup>2</sup>. Although death following community-onset bloodstream infection was uncommon, the risk was increased more than 4-fold in patients with an eGFR less than 30 mL/min/1.73 m<sup>2</sup> compared with those with an eGFR of 60 mL/min/1.73 m<sup>2</sup> or higher.

Previous investigations have firmly established ESRD as a strong risk factor for septicemia<sup>8-11</sup>; however, few epidemiologic reports have addressed the risk of infections in patients with CKD not treated with dialysis. Recent data from the United States Renal Data Service in which CKD was identified from hospital billing codes suggest that higher rates of hospital admission because of septicemia are noted in patients with CKD compared with

those without CKD.<sup>12</sup> There are a number of limitations to this information, including insensitive definitions of CKD and septicemia based on administrative data<sup>24</sup> and the inability to determine severity of kidney disease or to control for confounders. Our study expands on the association between bloodstream infection and CKD not treated with dialysis suggested by the United States Renal Data Service data, using a more sensitive measure of CKD and an objective measure of infection. Furthermore, our results complement those of other studies that have identified associations between CKD and infection-related hospitalization and death.<sup>6,7</sup>

The etiology of the increased risk of bloodstream infection observed in patients with CKD is likely multifactorial. Renal dysfunction may be a marker of other conditions that increase susceptibility to infection, although common risk factors including age, sex, diabetes, and comorbidity did not entirely explain the increased risk of bloodstream infection in our study. While it is unlikely that unmeasured confounders such as malignant neoplasms or immunosuppressant use can completely explain the association between CKD and bloodstream infection because of their low prevalence in community-based populations with CKD,<sup>2,25</sup> we cannot exclude the possibility of residual confounding owing to the comorbidity measure used or from lack of data for variables such as medical procedures. However, the magnitude of effect at lower eGFR suggests that this association is unlikely to be completely eliminated even with further adjustment. Although we did perform analyses excluding nosocomial infections to minimize confounding from higher rates of hospitalization in the CKD population, we are unable to exclude infections that may have been a consequence of outpatient procedures requiring intravenous access or dialysis access creation. Nevertheless, the high rate of infection with gram-negative organisms is unlikely to be explained by inoculation during intravenous cannulation.

It is possible that urologic disease may explain some of the increased risk of bloodstream infection with CKD owing to infections from urinary tract sources. Alternatively, this association could be explained by several consequences of CKD that have been proposed to contribute to infection, including malnutrition, chronic inflammation, retention of uremic solutes, trace element deficiencies, and metabolic abnormalities.<sup>26</sup> Furthermore, abnormalities in neutrophil and lymphocyte function that occur in the setting of ESRD suggest that impairment of immune function may contribute to infection susceptibility in the setting of CKD.<sup>27,28</sup> We were unable to directly de-

termine which of these elements contributed to risk of bloodstream infection in this study, although additional adjustment for hemoglobin and albumin concentrations (proxies for nutritional status and inflammatory disorders that may be on the causal pathway to infection)<sup>8,11,29</sup> did not entirely explain the increased risk in patients with an eGFR less than 30 mL/min/1.73 m<sup>2</sup>. Further research is needed to clarify mechanisms of infection susceptibility in patients with CKD.

Although this study provides novel information on the relationship between CKD not treated with dialysis and infection, it has limitations. Our cohort was restricted to patients older than 65 years from a single Canadian Health Region and relied on laboratory data to define the study cohort, potentially limiting the generalizability of our findings to elderly white patients who sought medical care. Given that older adults are more likely to access the health care system and undergo laboratory testing, this is unlikely to substantially bias our results, which reflect current clinical care and target a population with the highest risk of both bloodstream infection and CKD.<sup>1,13</sup> It is also possible that misclassification of patients insofar as CKD stage may have occurred as a result of inaccuracies in eGFR measurement in elderly patients.<sup>30,31</sup> However, our direct assessment of kidney function is a distinct advantage in comparison with previous studies. Our findings may be vulnerable to ascertainment bias if patients with lower levels of kidney function were more likely to have blood cultures performed. Although no standardized protocols exist for blood-culturing practices in our health region, it is reassuring that previous studies have demonstrated that rates of ordering of common microbiology laboratory tests are not determined by the presence or absence of specialist care.<sup>32</sup>

These findings have implications for future CKD research and management. Bloodstream infection is a severe, though relatively rare, manifestation of bacterial disease from several potential sites of infection. Further research is needed to characterize sources of infection and the potential for additional morbidity from infections that are not manifested by bacteremia. Inasmuch as existing CKD cohort studies suggest that 42% of deaths may not be attributable to cardiovascular causes,<sup>3</sup> further study is necessary to determine the degree to which infection contributes to the increased risk of death in CKD populations. Interventions that prevent bacterial infections may provide an opportunity to improve morbidity and mortality associated with CKD.

In conclusion, the results of this study demonstrate that CKD is associated with an increased risk of bloodstream infection and death following community-onset bloodstream infection in older adults. The causes and implications of this association warrant further study. Our findings suggest that health care providers should consider the possibility of bacterial infections and should reduce modifiable risks for infections when caring for patients with CKD. Strategies with the objective of reducing the risk of bacterial infection in community-based CKD cohorts deserve further study.

Accepted for Publication: June 16, 2008.

Author Affiliations: Departments of Medicine (Drs James,

Laupland, Manns, Culleton, and Hemmelgarn) and Community Health Sciences (Drs James, Laupland, Manns, and Hemmelgarn), University of Calgary, and Division of Nephrology, Foothills Medical Centre (Dr Hemmelgarn), Calgary, Alberta, Canada; Department of Medicine, University of Alberta (Dr Tonelli), and Institute of Health Economics (Drs Tonelli and Manns), Edmonton, Alberta, Canada; and Baxter Healthcare, Deerfield, Illinois (Dr Culleton).

**Correspondence:** Brenda R. Hemmelgarn, PhD, MD, Department of Medicine, University of Calgary, Foothills Medical Center, 1403 29th St NW, Calgary, AB T2N 2T9, Canada (Brenda.Hemmelgarn@Calgaryhealthregion.ca).

**Author Contributions:** Drs James and Hemmelgarn had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* James, Laupland, and Hemmelgarn. *Acquisition of data:* James, Laupland, and Hemmelgarn. *Analysis and interpretation of data:* James, Laupland, Tonelli, Manns, Culleton, and Hemmelgarn. *Drafting of the manuscript:* James and Hemmelgarn. *Critical revision of the manuscript for important intellectual content:* Laupland, Tonelli, Manns, Culleton, and Hemmelgarn. *Statistical analysis:* James and Hemmelgarn. *Obtained funding:* Hemmelgarn. *Administrative, technical, and material support:* Laupland. *Study supervision:* Tonelli, Manns, Culleton, and Hemmelgarn.

**Financial Disclosure:** Dr Culleton became an employee of Baxter Healthcare, Deerfield, Illinois, after the protocol was approved and funded.

**Funding/Support:** This study was supported in part by the Kidney Foundation of Canada and the Alberta Kidney Disease Network; by a Shire Biochem–KRESCENT Joint Fellowship and an Alberta Heritage Foundation for Medical Research Award (Dr James); by Population Health Investigator Awards from the Alberta Heritage Foundation for Medical Research (Drs Tonelli and Hemmelgarn); and by New Investigator Awards from the Canadian Institutes for Health Research (Drs Tonelli, Manns, and Hemmelgarn).

**Role of the Sponsor:** Baxter Healthcare had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

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