Burden of Community-Onset Escherichia coli Bacteremia in Seniors

Lisa A. Jackson, Patti Benson, Kathleen M. Neuzil, Marcus Grandjean, and Jennifer L. Marino

Background. Although Escherichia coli is a well-recognized cause of urinary tract infection in seniors, little is known about the burden of invasive E. coli infection in this population.

Methods. We conducted a population-based cohort study of 46,238 noninstitutionalized Group Health Cooperative members ≥65 years of age to ascertain incidences of community-onset E. coli bacteremia and, for comparison, pneumococcal bacteremia, and we then performed a case-control study to identify risk factors for community-onset E. coli bacteremia.

Results. The overall rate of community-onset E. coli bacteremia in the study cohort was 150 cases/100,000 person-years, which was ~3 times higher than the rate of pneumococcal bacteremia. In the case-control study, urinary catheterization and urinary incontinence were the only factors associated with an increased risk of E. coli bacteremia in men (62 cases), whereas cancer, renal failure, congestive heart failure, coronary artery disease, and urinary incontinence were associated with an increased risk of E. coli bacteremia in women (119 cases).

Conclusions. E. coli appears to be the leading cause of community-onset bacteremia in seniors, and, on the basis of these rates, we estimate that 53,476 cases occur in noninstitutionalized seniors each year in the United States. Community-onset E. coli bacteremia in seniors is, therefore, an infection of public health importance.
Retrospective Cohort Study

Study population. The study cohort was defined as Group Health Cooperative members \( \geq 65 \) years of age as of 1 March 1998 who had been enrolled in Group Health Cooperative for at least 1 year prior to that date and who were not residents of a nursing home. Study cohort members were followed from 1 March 1998 until the study end date of 28 February 2001, death, termination of Group Health Cooperative membership, or admission to a nursing home, whichever occurred first.

Identification of episodes of \( E. \) coli bacteremia. Cases of community-onset \( E. \) coli bacteremia were identified primarily from blood culture test results reported by the Group Health Cooperative central laboratory—which processes all blood culture specimens collected at Group Health Cooperative outpatient clinics, emergency departments, and hospitals—and results reported by the laboratory at an affiliated hospital. To identify episodes of \( E. \) coli bacteremia that occurred during hospitalizations at nonaffiliated facilities, the medical records of study cohort members who had a hospital discharge diagnosis of \( E. \) coli bacteremia (ICD9 codes 038.42 and 041.4) were also reviewed. An index date based on the date of the first positive blood culture was assigned for each episode. Nosocomial infections, defined as episodes in which the first \( E. \) coli isolate was obtained from a blood sample collected during a hospitalization and \( \geq 2 \) days after the date of admission or from a sample collected within 7 days after discharge from the hospital, were excluded.

Identification of episodes of pneumococcal bacteremia. Episodes of \( S. \) pneumoniae bacteremia in the study cohort had been identified, as part of a previous assessment, by laboratory test reports and by review of medical records pertaining to hospitalizations associated with a diagnosis of pneumonia (ICD9 codes 480.0 through 487.0) or pneumococcal or streptococcal bacteremia (ICD9 codes 038.0, 038.2, 041.0, 041.2, and 320.1) [12]. An index date based on the date of the first positive blood culture was assigned for each episode.

Analysis. Crude event rates were calculated by dividing the number of incident cases of either community-onset \( E. \) coli bacteremia or pneumococcal bacteremia by the cumulative person-years that elapsed during the study period. To allow the calculation of rates of community-onset \( E. \) coli bacteremia in persons with diabetes mellitus, diabetes status was defined by use of administrative data sources, as described elsewhere [12]. Incidence rate ratios were computed to compare rates between sex and diabetes groups.

Case-Control Study

Selection of case patients and control subjects. Case patients were defined as Group Health Cooperative members \( \geq 65 \) years of age who had an episode of community-onset \( E. \) coli bacteremia between 1 January 1998 and 31 December 2001. This group included the cohort study case patients, additional persons who had an episode of community-onset \( E. \) coli/bacteremia that occurred either before or after the cohort study period of 1 March 1998–28 February 2001, and persons who had an episode of community-onset \( E. \) coli bacteremia and were not included in the cohort study because they were \( <65 \) years of age on 1 March 1998.

Three frequency-matched control subjects were randomly selected for each case patient. Specifically, case patients were categorized jointly according to their age group (65–69, 70–74, 75–79, 80–84, 85–89, or \( \geq 90 \) years of age), sex, and index year of the \( E. \) coli bacteremia episode (1998, 1999, 2000, or 2001). For each group of case patients, we identified the population of Group Health Cooperative members of the same sex and in the same age group who were enrolled as of the last day of the case patients’ index year of the \( E. \) coli bacteremia episode and had at least 1 outpatient visit or hospitalization recorded during that index year. For each case patient, 3 control subjects were then randomly sampled from the corresponding population of eligible control subjects. Each control subject was assigned an index date, which was a randomly selected date during the case patient’s index year.

Data collection. Information on the characteristics of the bacteremic infections for case patients and on underlying conditions for case patients and control subjects was abstracted from the paper medical record. The presence of coronary artery disease, congestive heart failure, diabetes mellitus, emphysema or chronic obstructive pulmonary disease, asthma, leukemia/lymphoma, lung cancer, nonlung metastatic cancers, multiple myeloma, immunocompromising therapy (including chemotherapy), alcohol abuse, chronic renal failure, presence of an indwelling venous or arterial access device, urinary obstruction, urinary catheterization within 2 months preceding the index date, and urinary incontinence were defined from information recorded in the paper medical record within 1 year preceding the index date. Use of oral estrogen (including progesterone combinations) and intravaginal estrogen therapy within the 6 months preceding the index date was identified from the Group Health Cooperative computerized pharmacy database, which contains records of all prescriptions filled through Group Health Cooperative pharmacies.

Analysis. We hypothesized that predisposing factors for bacteremic infections from a urinary source may differ from those for bacteremic infections from other (primarily gastrointestinal) sources and that many of the bacteremic infections classified as being due to an unknown source during a review of medical records would have actually resulted from a urinary source. For these reasons, the primary risk factor analyses were restricted to cases of \( E. \) coli bacteremia classified as being due to a urinary source or to an unknown source. Alternate analyses that included only case patients with infections due to a known...
urinary source were not substantively different from the primary analyses. Preliminary analyses revealed differences between men and women in risk factors, so sex-stratified analyses are presented.

Multivariate analyses were conducted using unconditional logistic regression with backward stepwise selection. A variable was removed from the model if the probability of its likelihood-ratio statistic was $>0.10$, and it was reentered if the probability was $<0.05$, which was the entry value. Variables entered into the model-building process included diabetes mellitus, emphysema or chronic obstructive pulmonary disease, asthma, alcohol abuse, urinary tract obstruction, arterial or venous indwelling access device, and topical estrogen therapy (female model only), which were not selected for either final model, and the variables shown in table 3, which were selected for at least 1 final model. Age as a categorical variable of 5-year age groups (65–69 to $\geq 90$ years of age) was forced into both models.

### RESULTS

**Retrospective cohort study.** The 46,238 members of the study cohort contributed 122,365 person-years of observation during the 3-year study period, during which time 184 incident cases of community-onset *E. coli* bacteremia were identified. Of those, 165 cases were identified from examination of laboratory reports, and the remaining 19 cases were identified by review of medical records of 202 hospitalizations assigned a discharge diagnosis code of *E. coli* bacteremia. Of the 184 persons with

<table>
<thead>
<tr>
<th>Age at baseline, years</th>
<th>No. of cases</th>
<th>Incidence</th>
<th>In women:men incidence rate ratio (95% CI)</th>
<th>Incidence associated with diabetes mellitus</th>
<th>Incidence rate ratio associated with diabetes mellitus (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>In women</td>
<td>In men</td>
<td>In women with</td>
<td>In women without</td>
</tr>
<tr>
<td>65–69</td>
<td>33</td>
<td>97</td>
<td>125</td>
<td>64</td>
<td>1.96 (1.13–1.69)</td>
</tr>
<tr>
<td>70–74</td>
<td>36</td>
<td>107</td>
<td>109</td>
<td>105</td>
<td>1.03 (0.53–2.00)</td>
</tr>
<tr>
<td>75–79</td>
<td>42</td>
<td>147</td>
<td>157</td>
<td>134</td>
<td>1.17 (0.63–2.17)</td>
</tr>
<tr>
<td>80–84</td>
<td>30</td>
<td>177</td>
<td>210</td>
<td>124</td>
<td>1.69 (0.75–3.81)</td>
</tr>
<tr>
<td>$\geq 85$</td>
<td>43</td>
<td>452</td>
<td>448</td>
<td>462</td>
<td>0.97 (0.51–1.83)</td>
</tr>
<tr>
<td>Total</td>
<td>184</td>
<td>150</td>
<td>170</td>
<td>123</td>
<td>1.38 (1.02–1.87)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are cases per 100,000 person-years, unless otherwise indicated. CI, confidence interval.
community-onset *E. coli* bacteremia, 121 (66%) were women, and 43 (23%) were treated on an outpatient basis. The fatality rate within 14 days of the culture date was 7%.

The overall incidence of community-onset *E. coli* bacteremia in the study cohort was 150 cases/100,000 person-years. Incidence increased markedly by age, ranging from 97 cases/100,000 person-years in seniors 65–69 years of age to 452 cases/100,000 person-years in seniors ≥85 years of age. For comparison, 57 cases of *S. pneumoniae* bacteremia were identified in the study cohort during the same period, for an incidence of 46 cases/100,000 person-years. Rates of *E. coli* bacteremia were significantly higher than rates of pneumococcal bacteremia in each of the age groups presented in figure 1 (\( P < .02 \), for all comparisons).

Overall, women were at a 38% increased risk of infection, compared with men (table 1). In both women and men, rates of bacteremia tended to be higher in persons with diabetes mellitus than in those without it, although a statistically significant association between diabetes mellitus and higher risk of bacteremia was found only in women 65–69 years of age, women overall, and men 80–84 years of age.

**Case-control study.** A review of the paper medical record was completed for 211 eligible case patients and 769 control subjects. Of the case patients, 150 (71%) had an identified urinary source for *E. coli* bacteremia—defined as isolation of *E. coli* from urine (134/150) or a clinical diagnosis of urosepsis, pyelonephritis, or prostatitis—and 31 (15%) had *E. coli* bacteremia due to an unknown source. Of the remaining 30 case patients, 15 had biliary sepsis, 10 had pneumonia, and 1 each had appendicitis, ischemic colitis, necrotizing fasciitis, septic arthritis, or line sepsis. The case-control analysis was restricted to the 181 case patients who had *E. coli* bacteremia from a known urinary source or from an unknown source. Characteristics of those case patients, and of control subjects, are shown in table 2.
In men, urinary catheterization and urinary incontinence were the only factors independently associated with the risk of \textit{E. coli} bacteremia in the multivariate analysis (table 3). In male case patients, 39% were reported to have urinary incontinence or to have had urinary catheterization in the 2 months preceding the index date (table 2).

In contrast, urinary catheterization was uncommon in female case patients. In women, cancer, chronic renal failure, congestive heart failure, coronary artery disease without congestive heart failure, and urinary incontinence were independently associated with an increased risk of \textit{E. coli} bacteremia, and oral estrogen therapy was associated with a decreased risk of \textit{E. coli} bacteremia (table 3). Although diabetes mellitus was associated with an increased risk of \textit{E. coli} bacteremia from a urinary source in women in an age-adjusted model (odds ratio, 2.42 [95% confidence interval, 1.40–4.17]), this factor was not selected for the final multivariate model.

### DISCUSSION

In our study cohort of 46,238 Group Health Cooperative seniors, the incidence of community-onset \textit{E. coli} bacteremia was 150 cases/100,000 person-years, which is ∼3 times higher than the rate of pneumococcal bacteremia in this population. The rate of community-onset \textit{E. coli} bacteremia in seniors at Group Health Cooperative is also substantially higher than the rates of community-onset bacteremia due to \textit{Staphylococcus aureus}, Group A streptococci, and Group B streptococci in persons ≥65 years of age, as estimated from surveillance studies of other populations [13–15]. These comparisons suggest that \textit{E. coli} is the most common cause of community-onset bacteremia in seniors. Extrapolating our rate to the noninstitutionalized population of persons ≥65 years of age, we estimate that there are 53,476 cases of community-onset \textit{E. coli} bacteremia annually in seniors in the United States.

The majority of the cases of community-onset \textit{E. coli} bacteremia were due to an identified urinary source, which is consistent with findings of previous reports [11, 16]. As would be expected, we found that several factors previously associated with the risk of urinary tract infection in adults were also associated with the risk of community-onset \textit{E. coli} bacteremia in seniors. In men, urinary catheterization and urinary incontinence were strongly associated with an increased risk of \textit{E. coli} bacteremia, and urinary catheterization was a major risk factor for nosocomial urinary tract infection in men. Assessments of the use of urinary catheters in hospitals indicate that catheters are frequently used for inappropriate indications or are used longer than is necessary [17]. Less is known regarding the use of urinary catheters in an ambulatory setting, but it is possible that the pattern of use may be a potentially modifiable risk factor for \textit{E. coli} bacteremia in men ≥65 years of age in that setting.

In women, several conditions were independently associated with an increased risk of community-onset \textit{E. coli} bacteremia, including incontinence, congestive heart failure, and coronary artery disease without congestive heart failure. Incontinence has been identified as a risk factor for urinary tract infection in healthy postmenopausal women [18]. Community-based surveys indicate that at least 30% of women ≥65 years of age report the presence of incontinence but that only a minority of women with incontinence seek medical care for this condition [19–21]. Thus, our detected rate of incontinence of 9% in female control subjects is likely an underestimate of the true rate.
prevalence of this condition, which could be a more important contributing factor to the risk of community-onset \textit{E. coli} bacteremia than was estimated in our analyses.

In contrast, to our knowledge, congestive heart failure and coronary artery disease have not been reported as risk factors for urinary tract infection in women. One previous study—the Heart and Estrogen/Progestin Replacement Study, which was a randomized trial of the effects of hormone therapy on the secondary prevention of coronary events—included an evaluation of the relationship between congestive heart failure at baseline and the risk of urinary tract infection, but no association was identified [22]. In our study, heart disease may be a surrogate marker of poor health status. Alternatively, it is possible that an increased risk of infection could be due to specific biological factors, such as the disruption of urinary tract integrity—possibly as a result of diuretic use—or impaired hepatic clearance of circulating bacteria.

In our case-control study, oral estrogen therapy was associated with a significantly decreased risk of \textit{E. coli} bacteremia in women. Although 2 randomized trials have reported a reduction in the risk of recurrent urinary tract infection in postmenopausal women who use intravaginal estrogen preparations [23, 24], assessments of the use of oral estrogen therapy and the risk of urinary tract infection have yielded mixed results [18, 22, 25, 26]. It is possible that oral estrogen therapy modifies the risk of \textit{E. coli} bacteremia, but in our retrospective study we cannot exclude the possibility that preferential selection of estrogen therapy by relatively healthy women accounts for some or all of the observed association.

To our knowledge, these are the first population-based assessments of community-onset \textit{E. coli} bacteremia in seniors, and they provide initial estimates of disease rates and risk factors for infection. Limitations include the restriction of the study cohort to the Group Health Cooperative population, which may not be representative of all populations of seniors. However, because the rate of pneumococcal bacteremia of 44 cases/100,000 person-years in our study population is essentially identical to the reported rate of 45 cases/100,000 person-years in community-living seniors (according to a multistate population-based Centers for Disease Control and Prevention surveillance system [27]) findings from our population may be generalizable to other senior populations. Another limitation of our study was that information on underlying medical conditions and other exposures for case patients and control subjects was collected primarily by a review of the paper medical record. Such records are likely an incomplete source of information for potentially important risk factors, such as urinary incontinence and catheterization. Prospective studies that include more detailed assessments of the risk factors suggested by the present study would provide additional information.

\textit{E. coli} strains causing bacteremia and urinary tract infection appear to be genetically distinct from other gastrointestinal commensal \textit{E. coli} strains [28]. Russo and Johnson have proposed the designation “ExPEC,” for “extraintestinal pathogenic \textit{E. coli},” for these strains [29]. The invasion of the urinary tract or the bloodstream by ExPEC strains from the gastrointestinal tract is facilitated by a variety of genetically encoded virulence factors, including adhesions, toxins, and polysaccharide coatings. As has been noted, the specificity of ExPEC strains for extraintestinal \textit{E. coli} infection is important, because this implies that interventions specifically targeting ExPEC strains could be effective preventive measures [28].

Prevention of \textit{E. coli} bacteremia has not been a focus of vaccine development, but vaccines designed to prevent \textit{E. coli} urinary tract infection are being evaluated. One of these is a subunit vaccine that stimulates the production of antibodies against FimH, the adhesin on pili that mediates attachment of \textit{E. coli} type 1 to bladder cells [30]. If this vaccine is effective, it could theoretically prevent some proportion of invasive infections arising from a urinary source. It is also possible that alternate vaccine formulations could prevent bacteremic disease via other mechanisms of action [31–33]. Our estimates of the magnitude of the burden of disease due to community-onset \textit{E. coli} bacteremia in seniors suggest that an effective preventive intervention targeted toward high-risk groups could have a potentially meaningful public health and economic impact.

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References

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