Clinical Infectious Diseases

MAJOR ARTICLE

Empirical Antibiotic Treatment Does Not Improve Outcomes in Catheter-Associated Urinary Tract Infection: Prospective Cohort Study

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Background. Catheter associated urinary tract infection (CAUTI) is the most common healthcare-associated acquired infection. We aimed to describe the short- and long-term survival of patients with CAUTI and the impact of the empirical antibiotic treatment on survival rates.

Methods. In this prospective observational study we included consecutive adult patients with a chronic indwelling catheter-associated UTI and sepsis hospitalized in medical departments. The primary outcomes were 30-days all-cause mortality and long-term survival at end of the follow-up. A multivariate analysis using logistic regression and Cox proportional hazard model was performed to identify independent risk factors for an adverse outcome. A propensity-score model for receiving appropriate empirical antibiotic therapy was constructed and used to match patients.

Results. Overall, 315 consecutive patients with CAUTI were enrolled. The cohort consisted of elderly to very old patients (mean age 79.2 ± 11.5). The crude 30-day all-cause mortality rate was 30.8% (97/315). The median survival time was 82 days (interquartile range [IQR] 22–638). Appropriate early empirical treatment had no statistically significant association with 30-day mortality, propensity score-matched odds ratio (OR) 1.39 (0.76–2.55). Similarly, in the propensity-matched cohort, appropriate empirical treatment was not statistically associated with long-term survival (hazard ratio [HR] = 0.99, 95% confidence interval [CI] 0.75–1.3).

Conclusions. In our setting, patients with CAUTI had poor short- and long-term prognosis regardless of appropriate empirical antibiotic treatment. Avoiding empirical antibiotics for CAUTI might be an important antibiotic stewardship intervention in hospitals.

Keywords. catheter-associated urinary tract infection; appropriate empirical treatment; mortality; long-term survival.

Catheter associated urinary tract infections (CAUTI) are a global problem accounting for 40% of all healthcare acquired infections [1, 2]. In the United States, there are more than one million CAUTIs annually [3]. In elderly patients, chronic indwelling catheter is one of the leading causes of infection [4]. Bacteremia is less common and occurs in 1–4% of patients with long-term catheterization [5, 6].

Urinary tract infections are responsible for a major share of all antibiotic consumption in the hospital [7, 8]. Furthermore, the presence of a urinary catheter frequently triggers antibiotic prescription for fever alone among patients who cannot complain or whose poor baseline status does not allow assessment of the sepsis severity. Care home residents with urinary catheters had 440 annual antibiotic prescriptions per 100 inhabitants versus 188/100 inhabitants without catheters in a large study in the United Kingdom [9]. Empirical antibiotics used in this scenario are frequently broad-spectrum due to the high prevalence of resistant bacteria among patients with indwelling catheters [10–12].

Numerous studies have found a significant association of early appropriate empirical treatment for sepsis and septic shock with patients' survival [13–15]. This study aimed to determine whether appropriate, early, empirical antibiotic treatment is associated with improved survival among patients with CAUTI. A lack of association should prompt a careful consideration of the empirical antibiotic policy in these patients.

METHODS

Participants and Study Design

Between August 2010 and February 2015 we conducted a single-center prospective observational cohort study in a 900-bed, primary and tertiary-care, university affiliated hospital (Rabin Medical Center, Beilinson Hospital, Israel). We included adult patients (age ≥ 18) with an indwelling catheter in place for 7 days or more and symptomatic CAUTI defined as leukocyturia ≥10 cells/ ml and at least 2 out of 4 systemic inflammatory response syndrome (SIRS) criteria: (1) temperature >38° C or <36° C; (2) heart rate >90 beats/minute; (3) respiratory rate >20 breaths /

Received 26 March 2017; editorial decision 17 July 2017; accepted 30 July 2017; published online August 2, 2017.

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Clinical Infectious Diseases® 2017;65(11):1799–805

DOI: 10.1093/cid/cix680

minute or partial pressure of CO2 <32 mm Hg; and (4) white blood cell count >12 000/μL, <4000 μL, or >10% immature (band) forms; and bacteriuria of 10^3 or greater colony forming units (CFUs)/mL of one organism or 10^4 or greater CFUs/mL of 2 organisms or bacteremia caused by a typical uropathogens (Enterobacteriaceae or Enterococcus spp.), without an alternative apparent source of infection. Patients were identified by systematic daily screening of patient's charts in all medical departments.

Patients were excluded if they underwent invasive urological procedure within 30 days before recruitment or had urinary devices other than catheter, including stents, external drains, and so forth. Patients were included only once in the study, for the first episode fulfilling inclusion criteria. The study was approved by the Rabin Medical Center institutional review board, and need for consent was waived.

Definitions and Outcomes

Data were extracted from the patients' electronic medical records and from the hospital's computerized databases. For infections acquired out of hospital, the index point in time was defined as admission to the hospital. For hospitalized patients, the index point was defined as the time the urine culture defining the CAUTI was collected. Data were collected at 4 time points: at index, day 3, day 7, and day 30 after enrollment. At the end of the study, February 2015, long-term survival status was assessed through our hospital electronic records, which are updated by the Ministry of Interior database.

We collected demographic data, comorbidities including Charlson Score [16]; characteristics and clinical presentation of the current infection, SOFA score at sepsis onset [17], results of blood cultures, definition, and susceptibilities of the pathogen/s, (multidrug resistant Gram negative bacteria (MDR-GNB) was defined as extended spectrum beta-lactamase (ESBL) producing GNB and/or carbapenem-resistant Enterobacteriaceae (CRE) and/or MDR *Acinetobacter* spp.) and laboratory data.

We also collected data on the clinical management of the infection; appropriateness of the empirical antibiotic treatment (defined as drugs matching the in vitro susceptibility of the pathogen and given before culture results were available and within the first 48 hours of the index point); catheter replacement during the first 6 hours of the sepsis onset; definitive antimicrobial treatment and supportive treatment. The primary outcomes were 30-day all-cause mortality and long-term survival. The secondary outcomes were length of hospital stay; length of febrile illness; clinical failure (defined as death or presence of clinical signs or symptoms of infection at day 7) and rehospitalization within 30 days of the index point. Subgroup analysis of patients with Enterobacteriaceae bacteremia was predefined for 30-day mortality.

Statistical Methods

Crude mortality rates following CAUTI range from 12.7% to 33% [6, 18]. Assuming a 30% mortality rate in our cohort, in order to adjust for demographic data, clinical presentation and clinical management of CAUTI, we estimated that a sample size of 270 patients will be sufficient to identify 9 independent risk factors, using the rule of 10 events per one independent variable [19].

Statistical significance was set at $P < .05$ for 2-tailed comparisons. To identify variables associated with 30-day mortality univariate analysis was performed. Normality distribution was assessed through Kolmogorov-Smirnov normality test and visual inspection of quantile-quantile (QQ) plots. Categorical variables were tested using the χ^2 test or Fisher exact test, as appropriate. Continuous variables were examined using the student's *t* test if normally distributed and Mann-Whitney test if otherwise. Variables that were significantly associated with mortality on univariate analysis were entered into the logistic regression model after testing for multicollinearity. Multicollinearity was tested by a correlation matrix ($r \geq 0.5$ was considered a strong correlation) and the variance inflation factor (VIF) was tested to identify the severity of multicollinearity. If any of the VIF values exceeded 5, the variable was removed after clinical assessment based on prior knowledge of clinical correlations. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The Hosmer-Lemeshow statistic was used for goodness of fit.

A propensity-score model for receiving appropriate empiric therapy was constructed and used to match patients. Matching was performed using the nearest neighbor method, restricted by a caliper equal to 0.1 of the standard deviation of the score with a 1:1 ratio without replacement. Variables were chosen based on univariate analysis for appropriate empiric therapy, with the goal to derive the most balanced groups. The variables used where age, sex, nasogastric tube, bedridden status, heart failure, place of infection acquisition, home residence, prior antibiotic treatment. The area under the curve (C-statistic) of the model was fair, 0.66. Based on the method described by Hansen and Bowers [20], the difference between covariates was not significant ($P = .7$).

The association between individual variables and long-term survival was assessed using Kaplan-Meier analysis and tested for statistical significance using the log rank test. Age was categorized by quartiles and analyzed for the upper quartile (>85 years). A multivariate analysis using Cox proportional hazards model, with a similar variable selection process as previously described, was performed, and results are reported as hazard ratios (HR) with 95% CIs. The analysis was performed using IBM SPSS statistics 22.

RESULTS

During the study period we identified 315 consecutive patients with CAUTI sepsis. Baseline characteristics of patients are presented in Table 1. Patients were elderly to very old (mean age of 79.16 ± 11.5). Fifty-two percent (166/315) of the patients received antimicrobial treatment in the month prior to the

Table 1. Demographic and Clinical Characteristics of Patients and Risk Factors for 30-day Mortality

	Entire Cohort N = 315	Dead-30 day N = 97	Alive-30 day N = 218	*P*-value
Patient characteristics				
Female	134 (42.5%)	42 (43.3%)	92 (42.2%)	.856
Age	79.16 ± 1.51	81.77 ± 10.07	78.01 ± 11.96	.007
Previous 90 days hospitalization	198 (62.9%)	65 (67%)	133 (61%)	.309
Place of residence: -community	140 (44.4%)	36 (37.1%)	104 (47.7%)	.081
Place of residence: nursing home / long-term facility	175 (55.5%)	61 (34.8%)	117 (65.1%)	.768
Previous 30 day antibiotic treatment	166 (52.7%)	59 (60.8%)	107 (49.1%)	.054
Place of acquisition: home	75 (23.8%)	17 (17.5%)	58 (26.6%)	.081
Place of acquisition: nursing home/ long-term facility	127 (40.3%)	39 (40.2%)	88 (40.4)	.979
Place of acquisition: hospital	113 (35.9%)	41 (42.3%)	72 (33%)	.11
Functional capacity: dependent/bedridden	188 (59.7%)	65 (67%)	123 (56.4%)	.077
Previous UTI infection in the last year	180 (57.1%)	55 (56.7%)	125 (57.3%)	.916
Dementia	151 (47.9%)	52 (53.6%)	99 (45.4%)	.176
Permanent foreign bodies	78 (24.8%)	26 (26.8%)	52 (23.9%)	.575
Indwelling urinary catheter in place >30 days	200 (63.5%)	57 (58.8%)	143 (65.5%)	.245
Comorbidities				
Coronary artery disease	98 (31.1%)	31 (32%)	67 (30.7%)	.828
Heart failure	84 (26.7%)	38 (39.2%)	46 (21.1%)	.001
Solid tumor/ homological malignancies	58 (18.4%)	26 (26.8%)	32 (14.7%)	.010
Chronic renal failure	27 (8.6%)	10 (10.3%)	17 (7.8%)	.462
COPD	52 (16.5%)	18 (18.6%)	34 (15.6%)	.514
Charlson score	3 (1–4)	3 (2–4.5)	3 (1–4)	.019
Nasogastric tube	133 (42.2%)	50 (51.5%)	83 (38.1%)	.025
Central line	12 (3.8%)	9 (7.2%)	5 (2.3%)	.035
Tracheostomy / orotracheal tube	72 (22.9%)	26 (26.8%)	46 (21.1%)	.266
Sepsis presentation				
SOFA score	3 (1–6) N = 312	5 (3–7)	3 (1–5)	.000
Temperature at presentation	258 (81.9%)	76 (78.4%)	182 (83.5%)	.274
Saturation ≥92	237 (80.9%)	66/89 (74.2%)	171/204 (83.8%)	.053
Systolic blood pressure ≤90 mm Hg	53 (16.8%)	25 (25.8%)	28 (12.8%)	.005
Leucocytes (K/micl)	13.62 (10.36–17.68)	14 (11.3–19.1)	13.5(10.2–17.2)	.0354
MDR-GNB	174 (55.2%)	63 (64.9%)	111 (50.9%)	.021
Enterococcal infection	27 (8.6%)	9 (9.3%)	18 (8.3%)	.765
Bacteremia on sepsis onset (the first 48 hours)	77 (24.4%)	29 (29.9%)	49 (22.5%)	.159
Sepsis management				
Appropriate empirical treatment	155 (49.2%)	51 (52.6%)	104 (47.7)	.425
Appropriate empirical treatment: patients with bacteremia	45/77 (58.4%)	15/28 (53.6%)	30/49 (61.2%)	.512
Catheter replacement	98 (31.1%)	24 (24.7%)	74 (33.9%)	.103
Vasopressor support	32 (10.2%)	19 (19.6%)	13 (6%)	.000
Stress-dose corticosteroids	59 (18.7%)	24 (24.7%)	35 (16.1%)	.068
Mechanical ventilation	10 (3.2%)	6 (6.2%)	4 (1.8%)	.074

Continuous variables given as mean with SD if normally distributed or median with IQR for not normally distributed variables.

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range; MDR-GNB, multidrug resistant gram negative bacilli; SD, standard deviation; SOFA, sepsis related organ failure; UTI, urinary tract infection.

infection, and 56.7% (180/315) had urinary tract infections in the previous year. More than 60% (198/315) of the patients were hospitalized in the 3 months prior the infection, and 63.5% had an indwelling urinary catheter for over 30 days (200/315). Only 11% (35/315) of the cohort population was functionally independent. LTCF was the most common place of infection acquisition (40.3%, 127/315).

Patients presented with multiple comorbidities; 31% (98/315) had coronary heart disease, 27% (84/315) had chronic heart failure, and 18% (58/315) had current solid or hematological malignancy. The median Charlson comorbidity score was 3 (interquartile range (IQR) 1–4).

At index, the median SOFA score was 3 (IQR 1–6). Eighty-two percent of the patients (258/315) had fever at presentation, and 17% (53/315) were hypotensive. About one fourth of the study populations were bacteremic, and 55% (174/315) harbored MDR-GNB. Catheter was replaced in 98 patients (31.1%). In patients with community- onset infections (including patients from

Table 2. Risk Factors for 30-day Mortality, Univariate and Multivariate Logistic Regression Analysis, Hosmer-Lemeshow goodness of fit test $P = .257$, constant $\beta = -5.715$

Risk Factor	Univariate Analysis OR (95% CI)	Multivariate Logistic Regression Analysis OR (95% CI)
Appropriate empirical treatment	1.2 (0.75–1.96)	1.35 (0.78–2.32)
Age[a]	1.03 (1.01–1.06)	1.04 (1.01–1.07)
Malignancy	2.13 (1.18–3.82)	2.18 (1.13–4.2)
Heart failure	2.41 (1.43–4.06)	2.08 (1.16–3.73)
Nasogastric tube	1.73 (1.07–2.8)	1.43 (0.79–2.57)
SOFA score[b]	1.22 (1.17–1.34)	1.23 (1.1–1.36)
Central line	3.31 (1.02–10.7)	2 (0.53–7.54)
Functional capacity- Depended/ bedridden	1.57 (0.95–2.59)	1.44 (0.82–2.54)

Abbreviations: CI, confidence interval; OR, odds ratio; SOFA, sepsis related organ failure.

[a]Age: per 1-year increment.

[b]SOFA score: per 1 score-point.

LTCF), antibiotic therapy was initiated in the emergency room within 6 hours of presentation in 94% (200/212) of the patients.

30 Day All-Cause Mortality

The crude 30-day all-cause mortality rate was 30.8% (97/315). Risk factors associated with 30-day mortality by univariate analysis are presented in Table 1. On multivariate analysis, older age (OR 1.04 per 1-year increment, 95% CI: 1.01–1.07), congestive heart failure (OR 2.08; 95% CI: 1.16–3.73), active malignancy (OR 2.18; 95% CI: 1.13–4.2) and the SOFA score on presentation (OR 1.23 per an increment of 1 in the score, 95% CI: 1.1 to 1.36) were independent predictors of mortality (Table 2).

Forty-nine percent of the patients (155/315) received appropriate empirical antibiotic treatment. Appropriate empirical antibiotic treatment was not associated with 30-day mortality on univariate analysis (32.9%, 51/155 for appropriate vs. 28.8%, 46/160 for inappropriate, $P = .425$). After adjusting, the OR for mortality with appropriate empirical therapy remained statistically insignificant and greater than 1 (OR 1.35, 95% CI 0.78–2.32). Moreover, after propensity score matching (N = 238), the OR was similar (1.39, 95% CI 0.76–2.55). In the subgroup analysis of patients with Enterobacteriaceae bacteremia (N = 77), the univariate OR direction reversed, but remained statistically insignificant (OR for 30-day mortality with appropriate empirical antibiotics 0.73, 95% CI: 0.28–1.87).

Long-Term Survival

During the first 4 months of follow-up, there was a major decline in survival rate that leveled off in the following months (Figure 1). Although the overall median survival was 82 days (IQR 22–638), the median survival for patients >85 years was 48 days [(IQR 11–333), $P = .001$]. Patients who resided in LTCFs had shorter median survival compared to patients residing at home [52 days (IQR 17–172) vs. 202 days (IQR 27–1026), $P = .001$]. Survival rates were significantly lower for patients with hospital-acquired infections compared to community-onset infections. Comorbidities such as coronary artery disease, chronic heart failure, and malignancy were negatively associated with long-term survival (Figure 2). Other factors that were predictive of long-term survival are summarized in the Supplemental Table 3.

Cox regression analysis revealed that older age, previous antimicrobial treatment, place of residence, nasogastric tube,

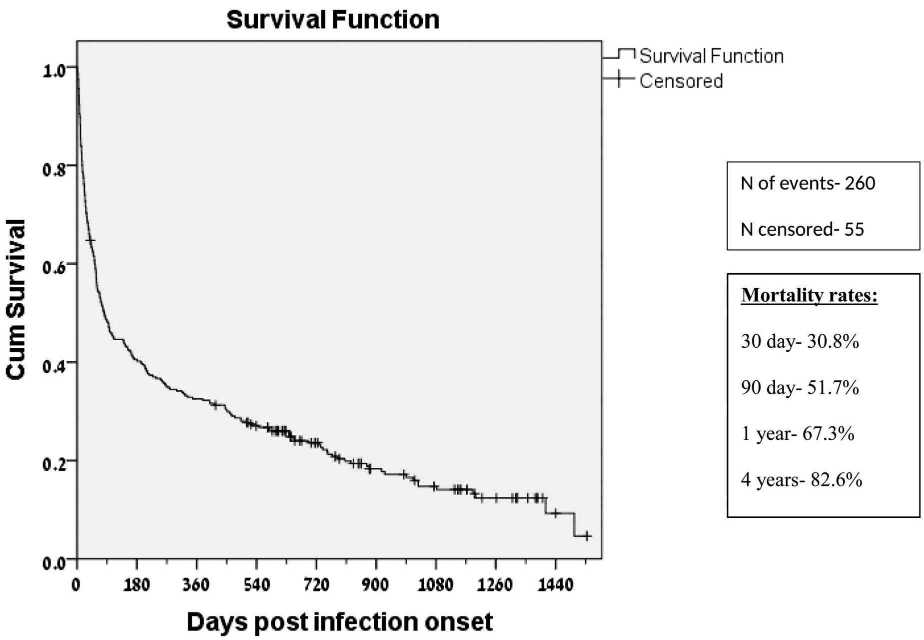

Figure 1. Overall survival in days in the whole study cohort.

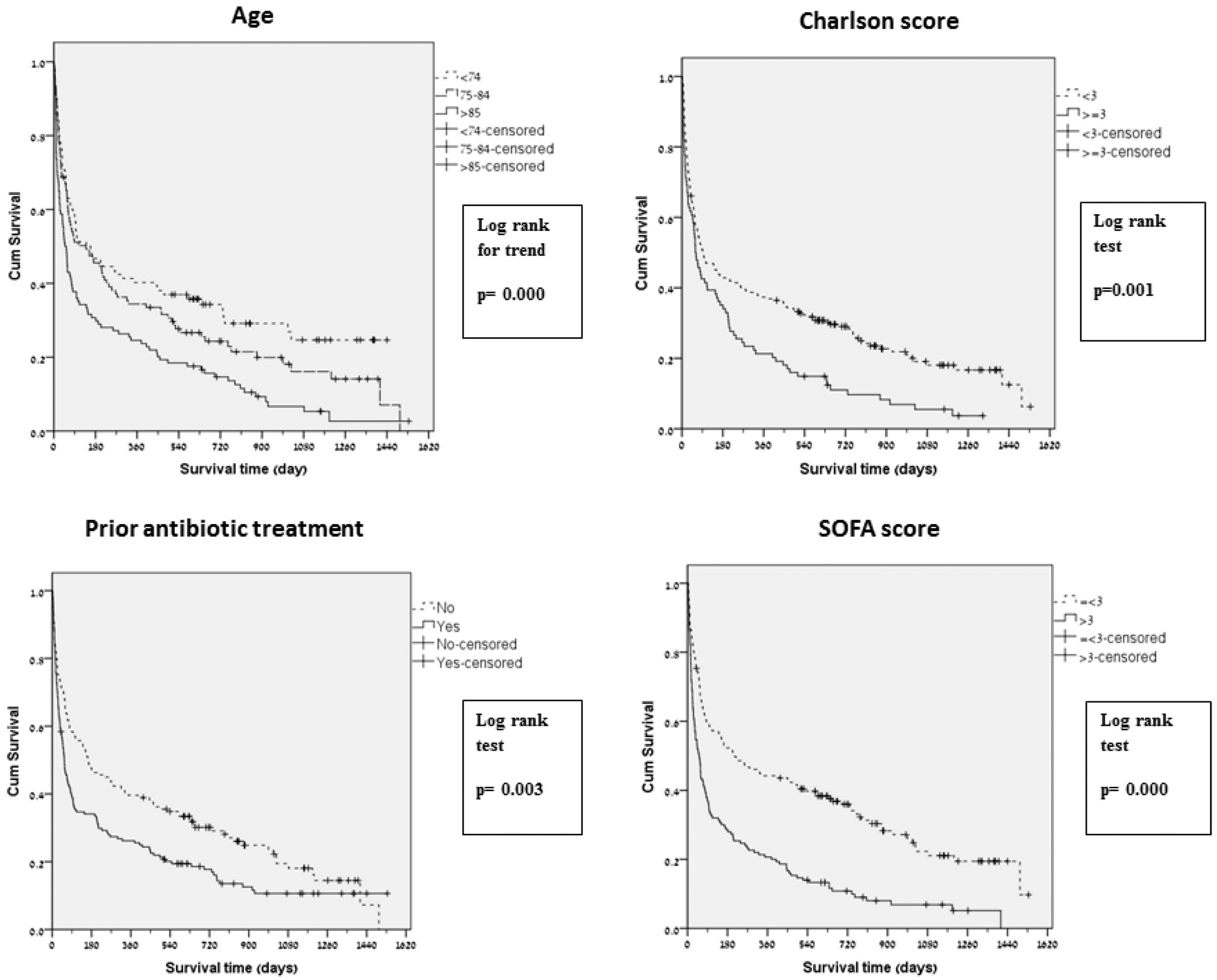

Figure 2. Kaplan-Meier survival curves of age, Sepsis-related Organ Failure Assessment (SOFA) score, Charlson score and prior antibiotic treatment.

increased SOFA score at presentation, and Charlson comorbidity index were independent predictors of long-term mortality (Table 3). Appropriate empirical treatment was not associated with long-term survival. On propensity score matching, the association between appropriate empirical treatment and survival remained statistically insignificant (HR = 0.99, 95% CI: 0.75–1.3).

Table 3. Independent Predictors of Long -Term Survival, Multivariate Cox Regression Analysis

Risk Factor	Hazard Ratio	95%CI
Age[a]	1.03	1.01–1.04
LTCF: place of residence	1.19	1.03–1.39
Charlson score[b]	1.11	1.04–1.18
SOFA score[c]	1.1	1.04–1.15
Nasogastric tube	1.4	1.05–1.85
Central line	1.79	0.98–3.26
Prior 30-day antibiotic treatment	1.33	1.03–1.72

Abbreviations: CI, confidence interval; LTCF, long-term care facility; SOFA, sepsis related organ failure.

[a]Age: per 1-year increment.

[b]Charlson score: per 1 score-point

[c]SOFA score: per 1 score-point.

Secondary Outcomes

The median length of hospital stay and length of febrile illness for patients discharged alive was 10 days (IQR 7–17) and 2 days (IQR 1–5), respectively. Eighteen percent of the patients were rehospitalized within 30 days from the index point. The clinical failure rate at day 7 was 64.7% (198/315). There was no significant association between appropriate empirical treatment and all secondary outcomes (Supplemental Table 1).

DISCUSSION

In this cohort of patients with CAUTI, the crude 30-day fatality rate was 30.8%, whereas half of the patients died within 82 days (IQR 22–638). At 1 year of follow-up, only 33% of patients survived. Appropriate antibiotic treatment had no significant effect on short- and long-term survival, or on the length of stay and length of febrile illness.

Our results are at odds with several previously published studies on different patient populations with severe bacterial infection. In a systematic review and meta-analysis of prospective studies inappropriate empirical antibiotic treatment was associated with a higher risk for a fatal outcome (OR 1.6, 95% CI: 1.37–1.86) [21]. This inconsistency may be explained in part by the fact that patients with indwelling catheters are mostly old and frail with numerous underlying diseases such as heart failure, ischemic heart disease, and diabetes. Another possible explanation for the lack of advantage of appropriate empirical treatment is the difficulty to distinguish between symptomatic urinary tract infection and febrile illness from a nonurinary source of infection among patients with long-term catheterization and bacteriuria. Almost all patients with chronic indwelling catheter are bacteriuric, and any febrile episode without a clear source might be regarded as CAUTI. This is commonly complicated by the patient's inability to report symptoms that are related to CAUTI due to chronic and acute mental changes and dementia. The association observed in the subgroup of Enterobacteriaceae bacteremia of our study (OR 0.73) is compatible with the benefit observed in other studies of patients with bacteremia, but the 95% CI (0.28–1.87) of this unpowered analysis leave very large doubt in a possible benefit. Furthermore, it is difficult to distinguish these patients empirically from other patients with CAUTI. Similar results to ours were published by Reisfeld et al. who examined the impact of appropriate empirical treatment on mortality among patients with cognitive decline and GNB bloodstream infections and found that appropriate empirical treatment was not associated with a significant mortality benefit in the sickest subgroup of patients with decubitus ulcers [22].

This study has several limitations. It is a single center study, but similar to other cohorts of patients with CAUTI in terms of demographics, inclusion criteria, and sepsis presentation [23, 24]. Treatment decisions were in the hands of the attending physician as for all studies assessing the impact of appropriate empirical antibiotic treatment. However, this is also the strength of these cohorts representing real-world patients with CAUTI. Multivariate analysis and propensity score matching were performed in an attempt to minimize selection bias. Another caveat is the composition of the cohort: many patients with impaired cognitive function, low functional status, and multiple comorbidities, and the fact that we practice in an environment with a high rate of resistant pathogens.

The knowledge that appropriate empirical treatment is not associated with improved survival among patients CAUTIs allows deferral of antibiotic treatment until better understanding of the fever cause. This might be an important aid to antibiotic stewardship in hospitals and LTCFs. We propose that patients with indwelling catheters presenting with sepsis be fully evaluated clinically and microbiologically. Those suspected of CAUTI with no other source of infection can be observed without antibiotic treatment. Sepsis trend and culture results will dictate directed antibiotic treatment. Our study suggests that such a strategy will not harm patients. When clinical assessment mandates rapid initiation of empirical therapy, a single, modest coverage, urinary-concentrating agent (such as aminoglycosides or a quinolone) might be beneficial (overcoming conventional resistance) and should be stopped as soon as deemed unnecessary. Evidence on short duration of antibiotic treatment for CAUTI, including bacteremic CAUTI is necessary.

In conclusion, elderly patients with CAUTI have poor short- and long-term prognosis. We found no benefit of early appropriate empirical treatment on patients' survival rates or other outcomes. Caregivers might consider supportive treatment until the cause of sepsis is elucidated and susceptibility patterns of the causative pathogen are known. Future studies should try and define subgroups of patients that benefit from early, empirical antibiotic treatment versus those who do not.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. The contribution of the ESCMID Study Group Elderly Infections (ESGIE, www.escmid.org/esgie) to this study is acknowledged.

Financial support. This work was supported by the Rabin Medical Centre Research Authority—The "young physician" funding and in part by the Israeli Ministry of Science, Technology and Space [grant 3-12075].

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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