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Risk Factors for Urosepsis in Older Adults: A Systematic Review

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Abstract

Objective: To identify factors that predispose older adults to urosepsis and urosepsis-related mortality. **Method:** A systematic search using PubMed and CINAHL databases. Articles that met inclusion criteria were assessed using the Strengthening the Reporting of OBservational studies in Epidemiology (STROBE) criteria and were scored on a 4-point Likert-type scale. **Results:** A total of 180 articles were identified, and six met inclusion criteria. The presence of an internal urinary catheter was associated with the development of urosepsis and septic shock. Although a number of factors were examined, functional dependency, number of comorbidities, and low serum albumin were associated with mortality across multiple studies included in this review. **Discussion:** Little scientific evidence is available on urosepsis, its associated risk factors, and those factors associated with urosepsis-related mortality in older adults. More research is warranted to better understand urosepsis in this vulnerable population in an effort to improve the quality of patient care.

Keywords

mortality, older adults, systematic review, urosepsis

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Urosepsis is defined as sepsis in which the urinary tract is the known or the strongly suspected source of infection. Approximately 25% of all adult sepsis cases are urosepsis, and urinary tract infection has been identified as the source in approximately 10% to 30% of all severe sepsis or septic shock cases (Wagenlehner, Weidner, & Naber, 2007). Mortality rates for patients with urosepsis range from 25% to 60% (Ackermann & Monroe, 1996; Meyers et al., 1989; Rosser, Bare, & Meredith, 1999). Complicated urinary tract infections (UTIs) are the most frequent cause of sepsis in older adults above 65 years of age (Kalra & Raizada, 2009). These complex infections occur in patients with anatomical or functional abnormalities, which impede urine flow, or in immunosuppressed individuals, and usually precede urosepsis.

The Centers for Disease Control and Prevention (CDC) National Center for Healthcare Statistics reported that the number of admissions for sepsis almost doubled between 2000 and 2008 (Hall, Williams, DeFrances, & Golosinskiy, 2011). This is evidence to suggest that sepsis increases on average by 9% annually (Martin, Mannino, Eaton, & Moss, 2003) as a result of an aging population, a rise in chronic disease, increased use of invasive procedures, immunosuppressant medications, chemotherapy, organ transplantation, and antibiotic resistance (CDC, 2014). Sepsis is now the 10th leading cause of overall death in the United States (Heron et al., 2009) claiming 220,000 lives annually (Joint Commission Center for Transforming Healthcare, 2014). An estimated 28% to 50% of patients who develop severe sepsis in the United States die, which is more than prostate cancer, breast cancer, and acquired immune deficiency syndrome (AIDS)-related deaths combined (Wood & Angus, 2004), and it is the leading cause of death in intensive care units in high-income countries (Russell, 2006). The Agency for Healthcare Research & Quality (AHRQ) has reported sepsis as the most expensive condition treated in U.S. hospitals, at a cost of more than US$20 billion in 2011 (Torio & Andrews, 2013).

More than 60% of the patients who develop severe sepsis are older adults above 65 years of age (Angus et al., 2001). Although older adults represent only 12% of the U.S. population, they account for 65% of all sepsis cases in hospitals (Martinet al., 2003). Older adults are 13 times more likely to develop sepsis and have a twofold higher risk of death from sepsis than other

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adults even when controlling for race, sex, comorbid conditions, and the severity of illness (Martin et al., 2003). Older adults are particularly predisposed to sepsis due to their many comorbidities, repeated and lengthy hospitalizations, reduced ability to fight infections, and their functional limitations related to aging (Nasa, Juneja, & Singh, 2012). A sudden deterioration in condition to severe sepsis or septic shock is common in older adults (Nasa et al., 2012). In this review, we attempt to determine which factors predispose older adults to urosepsis and urosepsis-related mortality.

Method

A systematic search of the PubMed and CINAHL databases included the following combinations of search terms: "bacteremic urinary tract infection," "nosocomial" and "urosepsis," "sepsis" and "elderly," "urosepsis" and "catheter," "urosepsis" and "diarrhea," "urosepsis" and "E-coli," "urosepsis" and "elderly," "urosepsis" and "Foley," "urosepsis" and "gastrointestinal," "urosepsis" and "geriatric," "sepsis" and "older adults," and "urosepsis" and "older adults." Two study investigators (BP and GG) screened the abstracts identified in this search for appropriate topical content and identified additional articles through a review of the reference lists from the articles found during the original search. Criteria for inclusion were as follows: (a) studies that focused on urosepsis in older adults, and (b) studies published within the last 10 years. Exclusion criteria included (a) studies not published in English, and (b) studies on sepsis that did not identify the urosepsis patients within the larger sepsis sample.

Our search of the scientific literature was conducted in November 2015 and resulted in 180 articles. After application of inclusion and exclusion criteria, six articles remained for analysis. The research team enlisted the assistance of the university's health science center librarian, but the articles she found did not meet inclusion and exclusion criteria even when the team expanded the search to include articles in print for 15 years or more.

All members of the study team screened the six remaining articles for content. Two investigators (BP and GG) independently evaluated the quality of the articles using the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) criteria as reported elsewhere (Vandenbroucke et al., 2007). The investigators independently applied a 4-point Likert-type scale to the criteria, with 1 = *poor*, 2 = *fair*, 3 = *good*, and 4 = *excellent*. If a particular criterion did not apply, it assigned a value of "not applicable." Investigators then met to compare scoring and adjusted discrepancies in scores based on mutual agreement of quality and content. Scores were totaled for each article to create a raw score and then divided it by the number of items used from the STROBE Scale to generate an adjusted score. Raw scores were adjusted to account for items that were not applicable to individual articles, so as not to negatively affect the scores based on these exclusions. The adjusted score is a more accurate representation of the quality of the articles.

Table 1. Raw and Adjusted STROBE Mean Scores for Studies on Urosepsis.

Authors	Raw *M* score	Adjusted *M* score
Bahagon, Raveh, Schlesinger, Rudensky, and Yinnon (2007)	49.5	2.48
Chin et al. (2010)	51.5	2.86
Kizilbash, Petersen, Chen, Naik, and Trautner (2013)	66.5	3.50
Shigemura et al. (2013)	50.5	2.66
Tal et al. (2005)	49.5	2.61
van Nieuwkoop et al. (2010)	56.5	3.14

Note. STROBE = STrengthening the Reporting of OBservational studies in Epidemiology.

Results

The six studies that met inclusion criteria were conducted in five different countries (Israel, Japan, the Republic of Korea, the Netherlands, and the United States) and across care settings, reflecting the global nature of this problem. All of the studies selected provided data on known risk factors for urinary tract infection (UTI) and sepsis that have been identified by the CDC (see Table 2; CDC, 2014, 2015). The raw STROBE scores of the articles ranged from 49.5 to 66.5 and the adjusted scores ranged from 2.48 to 3.5 with a mean of 2.88. A summary of raw and adjusted mean STROBE scores for each study can be found in Table 1.

Demographic Factors

The studies included in this review reported important information on a total of 1,586 patients, of which 801 were male and 785 were female (see Table 2). Four of the studies reported on the mean age of patients, which ranged from 67.2 to 83.6 years, and one study (van Nieuwkoop et al., 2010) reported that the median patient age was 66 years (range, 46-78 years). Three studies (Bahagon, Raveh, Schlesinger, Rudensky, & Yinnon, 2007; Tal et al., 2005; van Nieuwkoop et al., 2010) reported a significant association between older age and female gender and the development of bacteremic UTI; one study (Shigemura et al., 2013) did not find an association between age and bacteremic UTI. In a multicenter trial of medical units (n = 35) and emergency departments (n = 8), it was reported that patients older than 65 years of age admitted with febrile UTIs were nearly 2.5 times ($p < .001$) more likely to develop bacteremia than patients under the age of 65 (van Nieuwkoop et al., 2010). Similarly, patients admitted with a history of

Table 2. Characteristics of the Studies Included in Review (*n* = 1,586 Patients).

			Patients	Age	Comorbidity	Catheter	Antibiotic	Culture (+)	Death
Study	Country	Setting	*n*	*M*	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Bahagon, Raveh, Schlesinger, Rudensky, and Yinnon (2007)	Israel	ED	350	74	Yes; NR	76 (22%)	132 (38%)	GNO 174 (50%)	NR
Chin et al. (2010)	China	AC	86	73	10 (12%)	28 (33%)	4 (5%) 7 (8%)[a]	GNO 79 (92%) GPO 7 (8%)	10 (12%)
Kizilbash, Petersen, Chen, Naik, and Trautner (2013)	The United States	AC	308	72	Charlson score 4.1, mean	Indwelling 258 (84%) External 186 (57%)	277 (84%)	GNO 285 (93%) GPO 101 (33%) Yeast 58 (19%)	65 (21%)
Shigemura et al. (2013)	Japan	AC	70	68	51 (73%)	39 (55.5%)	NR	GNO 42 (60%) GPO 39 (58%)	NR
Tal et al. (2005)	Israel	SA; ED	191	83	191 (100%)	169 (88%)	NR	GNO 169 (88%) GPO 24 (12%)	63 (33%)
van Nieuwkoop et al. (2010)	Netherlands	PC; ED	581	66	301 (52%)	45 (8%)	167 (29%)	Blood (*n* = 131) GNO 118 (90%) GPO 4 (3%) Other 9 (7%) Urine (*n* = 559) GNO 370 (66%) GPO 22 (4%) Other 21 (3%)	NR

Note. ED = emergency department; NR = not reported; GNO = gram-negative organism; AC = acute care; GPO = gram-positive organism; SA = subacute; PC = primary care.
[a]Inappropriate use.

shaking chills were 2.3 times ($p = .025$) more likely to be diagnosed with bacteremic UTI (Bahagon et al., 2007). Two studies examined patient race and ethnicity, and reported no association between race or ethnicity and the development of urosepsis (Chin et al., 2010; Kizilbash, Petersen, Chen, Naik, & Trautner, 2013). Five of the six studies reported on patient comorbid diseases; however, only one study (van Nieuwkoop et al., 2010) reported an association between comorbid disease and urosepsis, where diabetes was significantly associated with a 80% increase in the odds of urospesis ($p = .035$).

The use of urinary catheters was reported in all of the six studies. Kizilbash et al. (2013) reported 444 episodes of catheter-associated bacteriuria in 308 patients admitted to medical and extended care wards of a large tertiary care center; patients with catheter-associated UTIs were nearly 3 times more likely to develop bacteremia than patients with catheter-associated asymptomatic bacteriuria (95% confidence interval [CI] = [1.24, 6.22]). Patients with external catheters were half as likely to develop bacteremias as patients with indwelling catheters (95% CI = [0.22, 0.99]). In a retrospective study of 70 patients diagnosed with urosepsis in the Urology Department of Kobe University Hospital between 2000 and 2010, Shigemura et al. (2013) found patients with an indwelling catheter prior to a UTI were 4 times more likely to develop urospetic shock ($p = .04$). Uroseptic patients with shock also exhibited significantly higher C-reactive protein (CRP) levels ($p < .001$), as compared with urosepsis patients without shock. Urinary tract occlusions and dosing of immunosuppressants were not reported to be associated with shock in urosepsis patients. In a retrospective chart review of all patients admitted to the emergency department of Shaare Zedek Medical Center, 350 patients were identified with UTI (Bahagon et al., 2007). It was reported that patients with an indwelling catheter were 3.3 times ($p = .014$) more likely to develop bacteremic UTI.

In a retrospective study of 191 patients diagnosed with urosepsis in a large community-based geriatric hospital, Tal et al. (2005) found bacteremic patients with chronic urinary catheters were less likely to develop urosepsis than patients with transient urinary catheters, and patients with no catheter were more likely to acquire infection than patients with a chronic catheter. The investigators did not find the source of admission (family vs. nursing home) to be a significant risk factor for gram-negative urosepsis.

Microbial Factors

All six studies reported *Escherichia coli* to be the most common organism isolated by culture (Bahagon et al., 2007; Chin et al., 2010; Kizilbash et al., 2013; Shigemura

et al., 2013; Tal et al., 2005; van Nieuwkoop et al., 2010). Chin et al. (2010) reported that *E. coli* was more commonly found in patients admitted with community-acquired urosepsis (93.8% of cases) when compared with hospital-acquired urosepsis (66.7%) cases. Chronic urinary catheter insertion was associated with gram-positive organisms, and not gram-negative bacteria. They also reported the proportion of *E. coli* among gram-negative organisms in women to be significantly higher than that of men (92.8% vs. 60% respectively). No differences were reported in antibiotic susceptibility between patients with gram-negative organisms (community vs. hospital-acquired). Non-*E. coli* gram-negative organisms proved less susceptible to cefotaxime, cefoperazone/sulbactam, and aztreonam. The use of urinary catheters did not appear to correlate with antibiotic resistance among gram-negative organisms. In terms of gram-positive organisms, all three *Staphylococcus aureus* organism isolates were methicillin-resistant, and two of the three *Enterococcus* isolates were ampicillin-resistant. Similarly, Tal et al. (2005) found non-*E. coli* gram-negative organisms less sensitive than *E. coli*. This was particularly true with respect to the antibiotics gentamycin and ceftriaxone ($p \leq .001$). Unlike the Chin findings, Tal et al. (2005) found that patients with chronic urinary catheters were significantly less sensitive to ciprofloxacin, gentamycin, ampicillin, and ceftriaxone ($p \leq .05$). Two of the six studies (Chin et al., 2010; van Nieuwkoop et al., 2010) identified *Klebsiella* as the second most common organism isolated, whereas two other studies reported *Staphylococcus aureus* to be the second most common organism isolated (Shigemura et al., 2013). Other organisms commonly isolated included *Enterobacter, Pseudomonas*, and *Proteus*. Bahagon et al. (2007) reported *E. coli* to be the causative pathogen in half of isolates cultured, but no bacterial strain was significantly associated with the development of bacteremia.

Shigemura et al. (2013) reported no significant association between gram-negative organisms, imipenum resistance, and shock in patients with urosepsis. Antimicrobial treatment for bacteriuria and the organisms cultured were not associated with development of bacteremia from any source within 30 days (Kizilbash et al., 2013). Similarly, van Nieuwkoop et al. (2010) reported that antibiotic treatment for an existing UTI was not associated with bacteremia. A summary of reported risk factors for urosepsis and urosepsis-related mortality can be found in Table 3.

Urosepsis-Related Mortality

Tal et al. (2005) reported that dementia was associated with a 5.7-fold ($p = .0003$) increase in the likelihood of death, and a hospital stay greater than 20 days was associated with a twofold ($p = .0397$) increase in the likelihood of death. Two studies (Chin et al., 2010; Tal et al., 2005) reported that an increase in the number of comorbid diseases was associated with higher mortality rates. Of these, one study reported a mortality rate of 7.6% with two comorbidities or less, and 25% with three or greater (Chin et al., 2010). The mortality rate reported by Tal et al. (2005) increased from 17.2% among patients with two to three comorbidities, to 35.4% among patients with four to five, and to 51.1% among patients with six or more comorbid diseases. For each additional reported comorbidity among uroseptic patients, there was a 29% ($p = .0203$) increase in the likelihood of death. One study (Kizilbash et al., 2013) reported on the Charlson comorbidity score, where it was found that each unit increase in the Charlson score was associated with a 10% (95% CI = [1.01, 1.21]) increase in the likelihood of death.

Patients with hospital-acquired infections (HAIs) died at a much higher rate when compared with those with community-acquired infections (29.2% vs. 4.8%; $p = .0005$; Chin et al., 2010). However, Tal et al. (2005) reported no significant difference in mortality between patients admitted from homes versus nursing homes, and those who developed nosocomial versus community-acquired infection. Kizilbash et al. (2013) found patients with pure growth of *Candida* in their urine culture were 3.6 times (95% CI = [1.57, 8.26]) more likely to die when compared with those with gram-negative organisms in the urine. Tal et al. (2005) found no significant differences in mortality between patients with gram-positive organism versus gram-negative infections, nor between those with specific types of gram-negative organisms. Chin et al. (2010) reported functional dependency to be significantly associated with an almost 11-fold (95% CI = [2.2, 54.6]) increase in mortality. Similarly, Tal et al. (2005) found patients with a diagnosis of dementia were more than 5.7 times ($p = .0003$) more likely to die than those without this condition. Other factors found to be associated with higher mortality included use of urinary catheters ($p = .001$) and recent exposure to antibiotics ($p = .021$); however, these factors did prove to be significant when included in a multivariate model (Chin et al., 2010). Kizilbash et al. (2013) did not find catheter-associated UTIs, catheter-associated asymptomatic bacteriuria, antibiotics given for bacteriuria, urinary catheter type (external vs. indwelling), nor catheter duration to be predictors of mortality. There was no relationship reported between malignancy or urinary tract disorders, and urosepsis-related mortality.

Laboratory values and mortality. Tal et al. (2005) reported that neutrophilia was associated with a 13% ($p = .0001$) increase in the likelihood of death, and that lactate dehydrogenase (LDH) was associated with a minimal, but significant, increase in the likelihood of death (odds ratio [OR] = 1.003; $p = .0351$). Chin et al. (2010) reported low serum albumin levels were associated with a 27% (95% CI = [2, 361.2]) increase in mortality. The

Table 3. Risk Factors Associated With Urosepsis and Urosepsis-Related Mortality in Multivariate Analyses.

Study	Risk factors
Urosepsis	
Bahagon, Raveh, Schlesinger, Rudensky, and Yinnon (2007)	Residence, indwelling catheter, shaking and chills, presence of bands, neutrophilia
Kizilbash, Petersen, Chen, Naik, and Trautner (2013)	Catheter-associated urinary tract infection, indwelling catheter
Shigemura et al. (2013)	Indwelling catheter
van Niewkoop et al. (2010)	Biomarker procalcitonin
Urosepsis-Related Mortality	
Chin et al. (2010)	Functional dependence, low serum albumin
Tal et al. (2005)	Dementia, number of diagnoses, hospital stay > 20 days, neutrophils, lactate dehydrogenase

lab results reported are common physiological markers associated with sepsis and, with the exception of albumin, are not modifiable risk factors.

Discussion

A number of factors identified in our systematic review may contribute to the development of urosepsis in older adults, but further investigation is needed, as a lack of consensus exists among the studies reviewed. There appeared to be disagreement in the literature on the effect of age, gender, race, number and types of comorbidities, organism class, antimicrobial treatment, and source of admission on risk of developing urosepsis.

One of the surprising findings from this review is the mixed results on catheter usage as a risk factor for urosepsis. In the Tal et al. (2005) study, patients without catheters were reported to have higher non-*E. coli* gram-negative infection rates when compared with those with chronic catheters, whereas patients transiently catheterized acquired more of these organisms than those with chronic catheters. The authors attributed the latter finding to more frequent manipulation of the catheter (Tal et al., 2005), but the reason for the first finding is unclear. One explanation for this finding could be misclassification bias. According to Schwartz, Frenette, Lee, Green, and Jayaraman (2015), a catheter-associated UTI (CAUTI) is defined as "a UTI that occurred in a patient with a catheter in place at the time of infection" (p. 349). It is possible, however, that study participants had their catheter removed prior to data collection or because of the intervention under study, and subsequently developed a UTI after removal (Schwartz et al., 2015). These infections would be classified as UTIs, and not a CAUTI, although the cause may have been the catheter (Schwartz et al., 2015). As a result, the CAUTI rate in catheterized patients may represent a biased underestimate, and inflate the uncatheterized patient rates of infection. Another possible explanation is patients with chronic catheters received better pericare in the Tal et al. (2005) study than those without. Patients with catheters may also be more likely to be treated for other infections with antibiotics that prophylactically protected them from UTI. A final explanation is that the uncatheterized group in this sample may have contained more immunosuppressed individuals.

Another interesting finding from this review was that patients with gram-positive infections (Chin et al., 2010) were significantly more likely to die than patients with gram-negative infections (57.1% vs. 7.6%). This is surprising, as gram-negative bacteremia is associated more with septic shock and mortality than gram-positive bacteremia (Abe et al., 2010). In a study published in *Critical Care* (Abe et al., 2010), the investigators reported that patients with gram-negative bacteremia exhibited a greater inflammatory response as evidenced by higher CRP and interleukin-6 (IL-6) serum levels than patients with gram-positive bacteremia, and were more likely to develop septic shock. The gram-negative bacteremic group demonstrated a higher mortality rate of 40% versus 28% in the gram-positive group.

The Chin et al. (2010) study only included seven patients with gram-positive organisms, and 79 with gram-negative organisms, so it would be difficult to draw any strong conclusions from this result given the small sample of patients with gram-positive organisms. The gram-positive organisms, however, demonstrated significant antibiotic resistance in Chin et al.'s (2010) study (5/7 gram-positive organisms), which might explain the unusual findings. Organism resistance is known to be a risk factor for mortality in patients diagnosed with bacteremia (Cosgrove, 2006).

Also noteworthy is that of the 10 patients who died in the Chin et al. (2010) study, seven were ordered inappropriate initial antibiotic therapy. Of the 21 patients ordered inappropriate initial antibiotic therapy, 33% (7/21) of them died, compared with just 4.6% (3/65) of those who received appropriate initial therapy. This reflects the importance of ordering timely, appropriate antibiotic therapy. Failure to properly intervene early in the septic process is a known risk factor for mortality. Kumar et al. (2006) reported on average a 7.6% decrease in survival for every hour delay in the delivery of appropriate antibiotic therapy in septic patients.

Factors identified from this review as possible predictors of mortality included urinary incontinence,

presence of urinary catheter, functional dependency, number of comorbidities, source of infection, class of organisms, recent antibiotic therapy, appropriateness of initial empiric antibiotic therapy, and low serum albumin level. Of these factors, functional dependency, the number of comorbidities, and a low albumin were consistently associated with mortality across studies. Hypoalbunemia may be related to inflammatory changes in the sepsis process, or reflect individuals with poor baseline nutrition levels. Further investigation to determine the relevance of this finding is warranted.

This systematic review had several limitations. First, there were a limited number of articles that examined urosepsis and mortality in older adults. Because data were retrospective, it was impossible to determine cause and effect between demographic and clinical risk factors for urosepsis and urosepsis-related mortality. The global nature of the studies included in this review may limit the generalizability of the results. Furthermore, sepsis management may differ from country to country, and the factors associated with infection and mortality could differ between locations.

We found that the literature on urosepsis is dated, despite the fact that sepsis recognition and management guidelines have changed dramatically in the last decade. Early goal-directed therapy protocols in many U.S. hospitals have improved sepsis outcomes (Rivers et al., 2001). The more recent PROCESS (ProCESS Investigators et al., 2014), ARISE (Peake et al., 2014), and PROMISE (Mouncey et al., 2015) trials found results that will no doubt lead to changes in the current management of urosepsis. In addition, approval of the Centers for Medicare and Medicaid Services new sepsis bundle measures in 2015 will lead to sweeping changes in management, as hospitals face the prospect of reimbursement loss for the most expensive condition they treat.

This systematic review elucidates the lack of quality evidence regarding risk factors for urosepsis, and urosepsis-related mortality in older adults. Research is necessary to advance the scientific understanding of urosepsis and how urosepsis outcomes have changed since the advent of early goal-directed therapy and how new changes in policy and practice will affect outcomes in older adults.

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