Review

Urinary tract infections in the elderly: a review of disease characteristics and current treatment options

Leocadio Rodríguez-Mañas MD, PhD
Servicio de Geriatría, Hospital Universitario de Getafe, Madrid, Spain

Abstract

Urinary tract infections (UTIs) are common in the elderly, and cover a range of conditions from asymptomatic bacteriuria to urosepsis. Risk factors for developing symptomatic UTIs include immunosenescence, exposure to nosocomial pathogens, multiple comorbidities, and a history of UTIs. European guidelines on urological infections recommend antimicrobial treatment only for symptomatic UTIs. Non-antimicrobial options to treat and prevent UTIs include among others cranberry products, OM-89 Escherichia coli bacterial lysate vaccine, and estrogen therapy in postmenopausal women, although evidence for their efficacy is weak. Another non-antimicrobial option to control and prevent UTIs is a medical device (Utipro Plus®) containing xyloglucan, gelatin, propolis, and extracts of Hibiscus sabdariffa. The device acts in the intestine as a mechanical barrier to protect against invasion by uropathogenic E. coli strains. A randomized controlled trial of Utipro Plus® in patients with uncomplicated UTIs provided good-quality evidence of its efficacy compared with placebo. In an observational study of Utipro Plus® in patients with recurrent UTIs, more than 80% women reported a return to their pre-UTI clinical status and about 30% transitioned from symptomatic UTIs to asymptomatic bacteriuria. New treatment strategies that offer a safe and effective non-antimicrobial means of managing UTIs could have an important role in the elderly.

Keywords: elderly patients, medical device, non-antimicrobial treatment, urinary tract infections.

Introduction

Urinary tract infections (UTIs) are common in the elderly, and cover a range of conditions from asymptomatic bacteriuria through to UTI-associated sepsis requiring hospitalization.1,2 Urinary growth of bacteria in the absence of urinary tract symptoms (i.e. asymptomatic bacteriuria) is most common and represents a commensal colonization.3 Asymptomatic bacteriuria has a prevalence of 1–5% in healthy premenopausal women, 4–19% in otherwise healthy elderly women and men, and 15–50% in institutionalized elderly individuals.4 Asymptomatic bacteriuria may protect against superinfecting symptomatic UTI, antimicrobial treatment is generally not indicated and may even be harmful.3,5 A diagnosis of symptomatic UTI in older adults generally requires the presence of localized genitourinary symptoms, pyuria, and a urine culture with an identified urinary pathogen.1,6 Antimicrobial therapy is indicated for symptomatic UTI.3 The classification system proposed by the European Association of Urology (EAU)3 and the EAU Section of Infections in Urology7 differentiates between low-risk uncomplicated UTIs and high-risk complicated UTIs based on the presence or absence of certain risk factors (Figure 1). EAU definitions for complicated, uncomplicated, recurrent, and catheter-associated UTIs are summarized in Table 1.3 Individuals at higher risk of a complicated UTI include postmenopausal women, patients with dysfunctional and/or reconstructed lower urinary tracts, patients with urinary tract catheters, all men, and elderly institutionalized patients,3 which describes a substantial proportion of the elderly population.

This narrative review considers the characteristics of UTIs – prevalence and incidence, disease burden, risk factors, and clinical presentation – in the elderly, and examines current treatment options to manage UTIs in the community. Relevant articles for inclusion were identified through literature searches using the PubMed database.
Prevalence and incidence

UTIs are significantly more common in adult women than men, possibly because of their shorter urethra, which permits easier passage of bacteria from the intestine.\textsuperscript{8,9} UTI is the second-most common infection in elderly women living in the community, and the most common cause of infection in hospitalized elderly women or those in long-term care.\textsuperscript{10} A prospective cohort study of postmenopausal community-dwelling women (aged 55–75 years) reported

Table 1. European Association of Urology urological infection guidelines classification of urinary tract infections.

| Term                          | Definition                                                                 |
|-------------------------------|---------------------------------------------------------------------------|
| Uncomplicated UTIs            | Acute, sporadic, or recurrent lower (uncomplicated cystitis) and/or upper (uncomplicated pyelonephritis) UTIs, limited to non-pregnant, premenopausal women with no known relevant anatomical and functional abnormalities within the urinary tract or comorbidities. |
| Complicated UTIs              | All UTIs which are not defined as uncomplicated: in a narrower sense, UTIs with an increased chance of a complicated course; that is, all men, pregnant women, patients with relevant anatomical or functional abnormalities of the urinary tract, indwelling urinary catheters, renal diseases, and/or with other concomitant immunocompromising diseases for example, diabetes. |
| Recurrent UTIs                | Recurrence of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last 6 months. |
| Catheter-associated UTIs      | UTIs occurring in a person whose urinary tract is currently catheterized or has had a catheter in place within the past 48 hours. |
| Urosepsis                     | Life-threatening organ dysfunction caused by a dysregulated host response to infection originating from the urinary tract and/or male genital organs. |

UTI, urinary tract infections. Reproduced from Bonkat et al. with permission.\textsuperscript{3}
an overall incidence of UTI at 7 cases per 100 person-years. By comparison, a study from the United States conducted between 1988 and 1994 in men aged 65–74 years estimated the incidence at 5 cases per 100 person-years. A Dutch study of UTIs in subjects older than 85 years reported a 1.7-fold higher risk in women (incidence 12.8 per 100 person-years) than men (incidence 7.8 per 100 person-years). Irrespective of gender, the incidence of clinically diagnosed UTI increases with age. A large observational study of UTIs in older adults (aged ≥65 years) conducted from 2004 to 2014, in the United Kingdom (UK), showed that, in women, the incidence increased from 9–11 cases per 100 person-years in subjects aged 65–74 years, to 11.4–14.3 cases and 14.7–19.8 cases per 100 person-years in subjects aged 75–84 and >85 years, respectively. Corresponding values in men were 2.8–3.0, 5.9–6.1, and 8.1–10.5 cases per 100 person-years.

**Social and economic burden**

Recurrent UTIs carry a substantial social and economic burden, and have a detrimental effect on patients’ quality of life (QoL). The economic cost of UTIs to healthcare systems is considerable. In the United States, the cost of UTIs is estimated to be at least US$2–3 billion per annum. An economic study of 20 hospitals in eight European countries with a high prevalence of multidrug resistant Gram-negative bacteria estimated that the mean cost per case of complicated UTIs was €5700, ranging from €4028 to €7740 per case. Higher patient costs were associated with admission, infection source and severity, comorbidity, and the presence of multidrug resistant bacteria. 

**Risk factors for symptomatic UTI and asymptomatic bacteriuria**

Risk factors for symptomatic UTI in the elderly differ from those in the younger population. Factors that increase the likelihood of developing UTIs include age-related changes in immune function (immunosenescence), exposure to nosocomial pathogens, and a higher number of comorbidities, although the strongest and most consistent risk factor for UTIs, namely a history of UTIs, is common to all age groups. Individuals with previous symptomatic UTIs have a 4–7-fold greater risk for future UTIs compared to those with no prior history. Relative to elderly subjects living in the community, institutionalized adults generally have more comorbidities and functional impairments, and a higher incidence of cognitive deficits, which predispose them to higher rates of asymptomatic bacteriuria and UTIs. The presence of a urinary catheter in institutionalized elderly individuals is a significant risk factor for UTIs. In institutionalized elderly women without a urinary catheter, the presence of bowel and/or bladder incontinence, functional disability, and dementia were significantly associated with persistent asymptomatic bacteriuria. In non-catheterized institutionalized elderly men, the only significant risk factor for persistent asymptomatic bacteriuria was cancer.

**Clinical presentation**

Localized genitourinary symptoms such as dysuria, urinary frequency, and urgency are classic symptoms of UTIs. However, many patients with complicated UTIs including elderly and catheterized patients do not present these symptoms. UTIs in elderly patients may instead manifest as confusion or delirium, increased lethargy, decreased fever response, new-onset incontinence, and anorexia. Distinguishing symptomatic UTI from asymptomatic bacteriuria in elderly patients can be difficult, but it is essential to ensure appropriate use of antimicrobials. Antibiotic stewardship is especially critical in older populations to reduce their risk of acquiring difficult-to-treat multidrug-resistant organisms and to avoid the common sequelae of antibiotic therapy on the vaginal and gastrointestinal tracts.

**Therapeutic options**

**Antimicrobial treatment for symptomatic UTIs**

Antimicrobial treatment is appropriate for symptomatic UTIs but not for asymptomatic bacteriuria. A meta-analysis of six randomized controlled trials (RCTs) involving 328 elderly patients with asymptomatic bacteriuria showed no significant benefit for antimicrobial treatment over placebo in the resolution of bacteriuria (risk ratio [RR]: 1.33; 95% confidence interval [CI]: 0.63–2.79). The 2018 EAU guidelines on urological infections recommend fosfomycin, piperacillin, or nitrofurantoin as first-line treatment for uncomplicated cystitis in adult women. Combination antimicrobial therapy with amoxicillin plus an aminoglycoside, or a second-generation cephalosporin plus an aminoglycoside, is recommended for treatment of complicated UTIs. For complicated UTI with systemic symptoms, empirical intravenous treatment with a third-generation cephalosporin is recommended. Although EAU guidelines state that fluoroquinolones may be considered for use in certain circumstances, the European Medical Agency (EMA) has suspended or restricted their use due to disabling and potentially permanent side effects involving muscles, tendons or joints, and the nervous system. The EMA advises special caution if using quinolones or fluoroquinolones in the elderly due to their higher risk of tendon injury. Elderly patients with UTIs are at high risk for developing urosepsis, especially those who are frail, depend on assistance for daily living, suffer from dementia, or are bedridden. Guidelines recommend immediate and empirical antimicrobial therapy with broad antimicrobial coverage against all likely
causative pathogens. Antimicrobial treatment can be adapted once culture results become available.\(^3\)

The 2018 EAU guidelines state that antimicrobials may be given as continuous low-dose prophylaxis for 3–6 months to prevent recurrent UTIs; regimens include nitrofurantoin, fosfomycin, cephalexin, or cefadroxil.\(^3\) A large retrospective cohort study from the UK reported on antibiotic prophylaxis for recurrent UTIs in 19,696 adults (79% women) aged ≥ 65 years.\(^{14}\) Prescription records were used to confirm ≥3 months’ prophylaxis with trimethoprim, cephalexin, or nitrofurantoin. Antibiotic prophylaxis was associated with reduced risk of clinical recurrence of UTIs (men: hazard ratio [HR]: 0.49, 95% CI: 0.45–0.54; women: HR: 0.57, 95% CI: 0.55–0.59) and acute antibiotic prescribing (men: HR: 0.54, 95% CI: 0.51–0.57; women: HR: 0.61, 95% CI: 0.59–0.62), but the authors called for further research to better understand the implications of prophylaxis on treatment-related adverse events, development of resistance, and QoL in this population.

Overuse and misuse of antimicrobials have contributed to the continued development of resistance, which is a serious public health threat.\(^{27–29}\) The classic example is methicillin-resistant *Staphylococcus aureus*, which is responsible for numerous difficult-to-treat infections in humans.\(^{30}\) *Escherichia coli* accounts for the majority of all UTIs, followed by *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa*.\(^6\) Persistent intestinal colonization of drug-resistant *E. coli*, *K. pneumoniae*, and *P. mirabilis* isolates has been implicated in the pathophysiology of UTIs, particularly in patients who experience recurrent UTIs.\(^{31}\) A meta-analysis of antimicrobials prescribed for bacterial UTIs in primary care (five studies, 14,348 participants) showed that development of antimicrobial resistance was greatest within the first month post-treatment, and that the effect could be maintained for up to 1 year. Odds ratios for resistance were 4.40 (95% CI: 3.78–5.12) within 1 month and 1.33 (95% CI: 1.2–1.5) within 12 months of antimicrobial treatment.\(^3\) A Norwegian study that compared antimicrobial resistance patterns of bacteria causing UTIs in the elderly living in the community with those living in nursing homes found no significant difference in resistance rates between the two groups. The most common urinary bacterial isolate was *E. coli*, detected in nearly two-thirds of patients (64% in each group).\(^{31}\)

The increasing antimicrobial resistance of uropathogens is challenging the paradigm of empirical antibiotic therapy for symptomatic UTIs, underscoring the need for alternative treatment strategies.

Non-antimicrobial and prophylactic treatment

Cranberry products

Cranberry products have been used widely for many years to treat and prevent UTIs, although the mechanism of action is unclear and disputed. A putative mechanism of action is preventing the adherence of P-fimbriated *E. coli* to uroepithelial cells on the bladder wall by proanthocyanidins contained in cranberries.\(^{25,34}\)

Meta-analyses of 24 studies involving 4473 participants did not support use of cranberry products for UTIs. Compared with placebo, water, or no treatment, cranberry products did not significantly reduce the overall occurrence of symptomatic UTIs (RR: 0.86; 95% CI: 0.71–1.04), or the occurrence of symptomatic UTIs in subgroups including women with recurrent UTIs (RR: 0.74; 95% CI: 0.42–1.31) and older people (RR: 0.75; 95% CI: 0.39–1.44).\(^{34}\)

A RCT of cranberry capsules administered to elderly women (n=185) with bacteriuria plus pyuria in residential care showed no significant difference compared with placebo in the presence of bacteriuria plus pyuria over 1 year (29.1 versus 29.0%). Similarly, there was no significant difference between cranberry capsules and placebo over 1 year in secondary measures, including symptomatic UTIs, mortality rate, hospitalizations, total antimicrobial utilization, and antimicrobials administered for suspected UTIs.\(^{35}\)

Collectively, the results from meta-analyses\(^{34}\) and a subsequent placebo-controlled RCT\(^{35}\) do not support the use of cranberry products for prevention of UTI.\(^{36}\)

**OM-89 *E. coli* bacterial lysate vaccine**

An oral non-antimicrobial prophylactic treatment for recurrent UTIs, based on lyophilized *E. coli* bacterial lysate (OM-89 vaccine), was developed more than 30 years ago. A systematic review and meta-analysis have described early studies of OM-89 (1985–2005) as being of low quality, with variable definitions of bacteriuria and UTI and with efficacy assessment limited to 6 months.\(^{37}\) A more recent 6-month observational study of OM-89, orally administered to 543 adults with recurrent lower UTIs for 3 months followed by a 3-month treatment-free period, reported a significant (p<0.0001) 59.3% decrease from baseline to 6 months in the mean number of UTIs. OM-89 also significantly improved QoL measures from baseline.\(^{35}\) In a small prospective observational study of adult women with uncomplicated, recurrent UTIs (n=21), OM-89 administered for 3 months significantly reduced the number of infections and improved QoL.\(^{17}\) RCTs are required before any definitive conclusions can be drawn about the efficacy of OM-89 in UTI.

**Estrogen therapy**

A decrease in estrogen is associated with several conditions that may promote recurrent UTIs in postmenopausal women: urinary incontinence, vesical prolapse, cystocele, and post-vaginal residual. As such, estrogen therapy has been used in postmenopausal women to prevent recurrent UTIs. However, a meta-analysis of 4 studies involving 2798 women found that oral estrogens failed to prevent UTIs compared to placebo (RR: 1.08; 95% CI: 0.88–1.33).\(^{38}\) Two small studies reported
that vaginal estrogen reduced UTIs compared with placebo, with calculated RRs of 0.25 (95% CI: 0.13–0.50) and 0.64 (95% CI: 0.47–0.86), respectively. As with OM-89, additional well-controlled studies of estrogen in UTI are required before any conclusions can be drawn.

(Xyloglucan-based medical devices)

Xyloglucan is a hemicellulose extracted from tamarind seeds that is used to restore the physiological function of mucosal epithelial cells. By forming a bio-protective film, xyloglucan prevents contact of mucosal cells with pathogens and their products, allergens, and pro-inflammatory compounds.41

A formulation containing xyloglucan 100 mg, gelatin 50 mg, propolis 100 mg, and extracts of Hibiscus sabdariffa 100 mg (Utipro Plus®; Noventre, Barcelona, Spain) is a class III medical device approved in the European Union for control and prevention of UTIs. In in vitro studies, the device was shown to create a protective physical barrier on human intestinal epithelial cells, which protected against E. coli intracellular invasion.42 In another in vitro study in intestinal and uroepithelial cell models, the device prevented contact of uropathogenic E. coli strains on cell walls, without altering E. coli cell integrity, and in the absence of demonstrable antibacterial activity.43 In experimental rat models of acute infectious gastroenteritis and UTI, preventive treatment with oral xyloglucan–gelose prior to induction of infection with Salmonella enterica and Enterococcus hirae significantly reduced associated intestinal morphological changes, tight junctions permeability, and neutrophil infiltration. Treatment with oral xyloglucan–gelose also decreased bacterial growth in the urinary tract, suggesting that it protects against ascending infection of uropathogens from fecal flora to urinary tract and against infection by the hematogenous route.44

The efficacy and safety of the xyloglucan–gelose medical device has been demonstrated in clinical trials. In a multicenter, double-blind, phase IV study, patients with uncomplicated UTIs were randomized to receive xyloglucan + gelose (n=20) or placebo (n=20) in combination with an antimicrobial agent for 5 days, as monotherapy for 5 days and, from Day 30 of the study, for 15 days per month for 2 months.45 Uroculture positivity (defined as a bacterial count ≥10^7 CFU/mL) decreased from 100% of patients at baseline to 0% at Day 11 with xyloglucan + gelose, with recurrence in 3 patients (15%) by Day 76; and from 100% patients at baseline to 45% at Day 11 with placebo, with recurrence in 14 patients (70%) by Day 76. Compared with placebo, xyloglucan + gelose significantly reduced the frequency of urinary incontinence and urgency of micturition (both p<0.05), with symptom resolution in all patients by Day 90. All adverse events reported during the study were unrelated to treatment. The efficacy of xyloglucan + gelatin to manage recurrent UTIs was evaluated in a prospective observational study in which 61 women received one capsule daily for 15 days each month for 6 months.46 At 1, 3, and 6 months from the start of treatment, the numbers of women reporting improvement in QoL and return to pre-UTI clinical status were 41, 47, and 51, respectively. At 6 months, 29.5% of women had transitioned from symptomatic UTI to asymptomatic bacteriuria. No adverse events were reported during the study period.

Increasing microbial resistance is a compelling reason to seek alternative treatment and prevention strategies for UTIs.6 Utipro Plus shows early promise in addressing this treatment gap. Complementing the protective barrier effect of xyloglucan on mucous membranes, hibiscus and propolis appear to have bacterial anti-adhesive effects at the urinary level.47,48 The ability of Utipro Plus to transition patients from symptomatic UTI to asymptomatic bacteriuria, which may protect against symptomatic recurrence, is an interesting finding and indicative of its lack of effect on normal microbiota.

(Other non-antibiotic approaches)

A systematic review evaluated a range of non-antibiotic approaches to manage uncomplicated UTIs including cranberry products, Canephron N (a phytodrug), probiotics (Lactobacillus spp.), non-steroidal anti-inflammatory drugs (ibuprofen, diclofenac), D-mannose, estrogens, vitamins (C and D), and immunotherapy.49 The review captured RCTs and observational studies published from 1999 to 2019, which involved generally healthy adult non-pregnant women with no risk factors for recurrent UTIs. The overall conclusion was that the evidence was insufficiently conclusive to recommend non-antibiotic options in place of antibiotic usage, although incorporating some of these measures in the management strategy of UTIs may contribute to avoidance of antimicrobial resistance. Evidence for the role of these non-antibiotic approaches in the elderly population is currently lacking.

Conclusions

Despite the high prevalence of UTIs in the elderly, treatment options are limited. Although the medical community may agree in principle about the need for rational antibiotic usage, the absence of effective alternatives to treat UTIs can be a genuine barrier to change. Utipro Plus is a promising non-antimicrobial option for control and prevention of UTIs. A RCT of Utipro Plus conducted in patients with uncomplicated UTIs provided good-quality evidence of its efficacy compared with placebo. In an observational study in patients with recurrent UTIs, 83.6% of women reported a return to their pre-UTI clinical status and about 30% transitioned to asymptomatic bacteriuria within 6 months. Elderly patients are not only more prone to UTIs but are also more likely to have comorbidities and require multiple medications. The option to use a device that acts in a physical manner (barrier effect) without pharmacological properties, and with potential to reduce antimicrobial use, has obvious appeal in this patient population. Although additional studies are required to fully ascertain the role of Utipro Plus in elderly patients with UTI in the community or under institutional care, early evidence suggests benefit.
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Correspondence: Leocadio Rodriguez-Mañas, Servicio de Geriatría, Hospital Universitario de Getafe, Carr. Madrid - Toledo, 28905 Getafe, Madrid, Spain. leocadio.rodriguez@salud.madrid.org

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