Urinary Tract Infections in Older Adults: Current Issues and New Therapeutic Options

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Urinary tract infections (UTIs) are the most common infectious problem among older adults both in the community and institutional settings. With the expected increase in this population, UTI-related costs—both human and financial—will rise in a parallel fashion. The diagnosis of symptomatic UTI among older adults is complicated by the high prevalence of asymptomatic bacteriuria, which does not require any treatment, and the difficulty in interpreting the signs and symptoms of UTI in a population in which significant comorbidities can undermine the communication between the patient and the medical team. Another important issue is the constant increase in antimicrobial resistance, especially in long-term care facilities, where antimicrobial use is greater than in the community. Newer agents are now available for the treatment of UTI among older adults, targeting both the usual and the multiresistant uropathogens. Rational use of antimicrobials in the treatment of UTI in the older adult is important to both provide appropriate care and control the spread of resistant organisms in this population.

Key words: *urinary tract infection, older adults, UTI management, antimicrobials*

Introduction

Symptomatic urinary tract infection (UTI) is considered the most important bacterial infection in the general population. The financial implications for the health care system are staggering: more than US$2 billion annually for the total cost of both community- and hospital-acquired infections in the U.S. alone.[1] Among the populations at special risk for UTI are older adults. For older adults living in a community setting, it is the second most common infection diagnosed.[1] In long-term care (LTC) facilities, UTIs are consistently reported as the leading site of infection. The prevalence of bacteriuria in patients without an indwelling catheter is between 25% and 50% for women and 15% and 40% for men, and the rate of symptomatic infection with fever for both males and females is between 0.046 and 0.126 per 1,000 patients-days in an LTC facility.[2,3]

The purpose of this article is to review the particular characteristics of UTI among older adults, including the diagnostic challenges presented to the clinician in this particular setting. Other important topics include the microbiology of UTI in this population and some recent additions to the antimicrobial armamentarium available for its treatment.

The Older Adult Population

There is a great diversity among the older population (>65 years). A large proportion live independently in community settings (95%), others in LTC facilities (5%).[4] The epidemiology, risk factors, diagnosis, and management of UTI are affected by the different characteristics of these two populations. In the community setting, the rate of UTI accounts for 24% of all diagnosed infections, followed by respiratory tract infections.[5] The risk of infection has been mostly associated with incontinence in older women (33–50% are affected)[6] as well as the presence of cystoceles, previous surgery, increased residual urine volume, and bladder diverticuli.[7] For men, chronic urinary retention associated with prostatic hypertrophy, bacterial prostatitis, and incontinence are the principal risk factors for UTI.[3,4] Despite the fact that most of the older adults live in a community setting, the majority of studies have focused primarily on residents of LTC facilities. It is the most common infection reported in LTC facilities,[2,3,7,8] accounting for 25–30% of all bacterial infections.[8] In this particular setting, the use of chronic indwelling catheters (for 5–10% of the institutionalized population),[2,3] the presence of significant comorbidities, incontinence of both urine and bowel, and the risk of transmission of uropathogens from resident to resident[3,7,9] have been associated with both asymptomatic and symptomatic infections. Thus, the more impaired or frail the individual, the higher the risk for a symptomatic or asymptomatic UTI. It is of note that, as in the general population, women >65 years old experience symptomatic UTI more frequently than do men.[7,10]

Asymptomatic Bacteriuria

The urinary tract is usually sterile. Asymptomatic bacteriuria or asymptomatic UTI is a microbiological diagnosis defined as "the isolation of a specified quantitative count of bacteria in an appropriately collected urine specimen obtained from a person without symptoms or signs referable to urinary infection."[11] The specimen should be optimally collected to prevent bacterial contamination. When possible, voided midstream urine is the preferred specimen in adults; however, it necessitates a good micturition control and adequate volume in the bladder.[12] This can be problematic for many older adults. A clean-catch can be obtained from men or women, but it can be difficult in the context of LTC. Other acceptable collection techniques include a freshly applied condom catheter for men and in-and-out catheterization, although a risk of inducing a UTI exists with the latter method.[3] Catheter specimens should be aspirated directly from the catheter using a sterile needle and placed in a sterile container.[12] Unacceptable specimens include bedpan urine and bags because of the increased risk of contamination.[3,12] Transport to the laboratory should be timely.

According to the Infectious Diseases Society of America 2005 guidelines,[11] the quantitative definition of asymptomatic bacteriuria is as follows: for women, isolation of the same bacterial species with a quantitative count of $\geq 10^5$ CFU/mL in two consecutive voided urine specimens; for men, isolation of one bacterial species with a quantitative count of $\geq 10^5$ CFU/mL in one voided urine specimen; or isolation of one bacterial species isolated with a quantitative count of $\geq 10^2$ CFU/mL in a single catheterized urine specimen for men or women.

Asymptomatic bacteriuria is common among older adults and practically universal among those with indwelling catheters.[7] The prevalence in healthy older women living in the community is around 20%, and in men >75 years old is 6–15%. In LTC facilities, the percentages are even higher: 25–50% in women and 15–40% in men.[11] The rise in prevalence parallels the increase in comorbidities, especially neurological, associated with micturition problems.[3,7]

The recommendations by the Infectious Diseases Society of America[11] and the Society for Healthcare Epidemiology of America[3] are clear concerning asymptomatic bacteriuria in the older population, whether residing in the community or in LTC facilities: routine screening and treatment are not recommended. There have been several studies[13–16] showing no benefits associated with the treatment of asymptomatic infections as measured in the rate of subsequent symptomatic infections, improvement of chronic urinary symptoms, or survival. Moreover, some harm can be caused, mostly associated with side effects of antimicrobials and increased resistance in uropathogens.[3,4,11]

It is to be noted that pyuria is common among persons with asymptomatic bacteriuria. This seems to reflect the fact that asymptomatic bacteriuria is more than mere colonization: there is an immune response associated with the presence of a significant amount of bacteria in the urinary tract.[3] Among older adults in LTC facilities, 90% of those with bacteriuria, 30% of those without bacteriuria, and 50–100% of those with an indwelling catheter have pyuria.[3,4,17–19] In this context, the presence of pyuria is not an indication for treatment.[11]

Symptomatic Urinary Tract Infection

The fact that both asymptomatic bacteriuria and pyuria are so prevalent among older adults is problematic for the clinician. Although the absence of bacteriuria may exclude a UTI in an older patient, the presence of a positive culture does not confirm it. Classic symptoms and signs for UTI include dysuria, incontinence, increased frequency, urgency, hematuria, and suprapubic pain; when pyelonephritis is present, flank tenderness and fever are usually encountered.[20] In older adults, though, one should look for other signs also, such as delirium or falls (this is different than the nonspecific symptoms of weakness and fatigue discussed below). Nicolle, in two excellent reviews on UTI among older adults,[7,21] points out that a diagnosis of UTI should be based on a very thorough clinical evaluation, the exclusion of other possible diagnoses, and the presence of new signs and symptoms localized to the genitourinary tract. A new onset of urinary tract symptoms can indicate the presence of a UTI, although attention should be given to differentiating these symptoms from chronic symptoms.

A good clinical evaluation is frequently impaired by the difficulty in obtaining a reliable history from patients who are often unable to communicate their symptoms adequately. However, nonspecific symptoms such as general weakness, fatigue, and malaise cannot be relied upon to make the difference between asymptomatic and symptomatic infections, especially if the patient is afebrile.[3,7,22] The presence of fever, while directing the clinician in the direction of an infectious process, cannot identify with certainty the origin of its focus: a study by Orr *et al.*[23] shows that a urine culture, even in the presence of fever, has a low predictive value[3,4]—serological criteria actually showed that only 10% of significant fever episodes among older adults in LTC facilities can be attributed to UTI. Since UTI is a common source of bacteremia in residents of LTC facilities, especially if an indwelling catheter is present,[24] a blood culture can be done. A positive culture with a known uropathogen or the same species found in the urine culture helps in substantiating the diagnosis. A prudent approach, the exclusion of other possible focuses of infection, and the follow-up of the patient's symptoms is probably the most appropriate course to follow before a treatment for UTI is started, recognizing that, in some instances, no other focus will be found or that the severity of the illness will warrant empirical antibiotic therapy.

The Microbiology of Urinary Tract Infection among Older Adults

The most common organisms causing bacteriuria (in the general population and in older adults) are in the family *Enterobacteriaceae* (Table 1).

Table 1: Common Uropathogens in Older Adults

Gram-Negative Organisms	Gram-Positive Organisms
Escherichia coli	*Enterococcus* spp.
Proteus mirabilis	*Streptococcus* spp.
Klebsiella pneumoniae	*Staphylococcus* spp.
Pseudomonas aeruginosa	
Enterobacter cloacae	
Providencia spp.	
Morganella morganii	
Serratia spp.	
Citrobacter spp.	

Sources: Adapted from Smith et al., 2000,[2] and Blondeau and Tillotson, 2005.[30]

E. coli has been well studied for its bacterial virulence factors; especially important is the enhanced ability of these bacteria to adhere to the uroepithelial cells (whether by pili, fimbriae or different types of adhesins). Other pathogens such as *P. mirabilis* and *K. pneumoniae* have shown similar virulence characteristics.[20] Although the majority of UTIs are caused by a single organism, polymicrobial infections occur in about 10–25% of cases among older adults.[3,4,25]

Host factors—including a decrease in cellular and humoral immunities, comorbidities such as diabetes, chronic urinary tract problems leading to stasis, micturition dysfunction, and low urinary pH[8]—probably all contribute to the increased prevalence of bacteriuria, especially in residents of LTC facilities. The presence of an indwelling catheter or other urinary device that can become colonized is also an important source of infection. The catheters can become coated with biofilm, rendering the antimicrobial agents present in the urine ineffective because of their poor capacity to kill the bacteria protected by this thick extracellular matrix.[20,25] Infection transmission from patient to patient can also occur through the hands of caregivers.[25]

The emergence of resistant uropathogens to antimicrobials used as a first line of treatment has become an important problem. Many strains of *E. coli* are currently resistant to ampicillin because of beta-lactamase production. The resistance to co-trimoxazole (trimethoprim/sulfamethoxazole) has also increased; the SENTRY Antimicrobial Surveillance Program[26] data from the year 2000 indicate that the rate of resistance to co-trimoxazole in North America is 23%. This is harmonious with the Canadian resistance data for 2001 and 2002, which show resistance in 15% of the isolates of *E. coli* (Bayer Pharmaceuticals, data on file). It seems that this increase of resistance is strongly associated with the extensive use of co-trimoxazole.[27] Despite their increased use in the past decade, fluoroquinolones have retained their activity against *E. coli* and the other gram-negative uropathogens implicated in UTI. The TRUST surveillance study indicates that the susceptibility of *E. coli* to ciprofloxacin has remained high, at 94.5%, higher in fact than ampicillin (56.8%) and co-trimoxazole (76.2%).[28] The problem of resistance is unfortunately even more acute for older adults, especially those in LTC facilities. It is due in part to the presence of pathogens, such as *P. aeruginosa*, that are more resistant to antimicrobials per se and to the extensive use of antimicrobials in this particular setting. Also, patients with poorer functional status are more likely to harbour resistant flora.[25] Those patients are also the most likely to have a decreased immune response and urinary devices in place, thus increasing their chance of being exposed to antimicrobial treatment.

The prevalence of resistance in LTC facilities, as reported in 2000 by Wright *et al.*,[29] was much higher than in the general population. They reported a 68% resistance to co-trimoxazole and 41% resistance to fluoroquinolones, and 61% of their isolates were multidrug resistant.

In a review by Smith *et al.*[2] on microbiology in LTC facilities, 43% of *Staphylococcus aureus* organisms were methicillin-resistant *Staphylococcus aureus* (MRSA), and 2% of enterococci were vancomycin-resistant enterococci (VRE). Since the gap between the reported rate of resistance in the general population and in LTC residents can be wide, clinicians should be aware of the resistance rate for common uropathogens in their own facilities.

Management of Symptomatic Urinary Tract Infection among Older Adults

In the presence of clinical symptoms and signs suggestive of a UTI, it is recommended to obtain a pretherapy culture in order to tailor management to the current pathogens present in the urine and their pattern of antimicrobial susceptibility. The clinician should take into account the possible side effects of the antimicrobial chosen, drug interactions, any previous antimicrobials used in the particular patient, and the susceptibility pattern encountered in the patient's community or LTC facility. In the context of increasing resistance to trimethoprim/sulfamethoxazole, fluoroquinolones have been recommended as first-line therapy for UTI among older adults, especially in the community setting.[4,18] Ciprofloxacin and levofloxacin can be used; both compounds have a very good safety profile[18,30] (Table 2).

If it is not possible to wait for results of a pretherapy culture because the patient is severely ill, a previous culture

result can be used to aid in the choice of therapy; however, this should be reviewed in light of the new urine culture result when it becomes available. In this context, an agent with a broader spectrum of activity might be necessary.[3,7,25,27] This point is underlined by the review of Smith *et al.*, showing that among patients who had been prescribed an antibiotic within the past month, 35% of isolates retrieved in cultures were sensitive and 65% were resistant to the antibiotic of recent use.[2]

Raz *et al.*[31] also reported a better outcome, defined as shorter time to defervescence and lower rate of reinfection, when patients with a chronic indwelling catheter had it changed when diagnosed with a symptomatic UTI. The duration of treatment recommended for women with a lower UTI is usually 7 days; it is extended to 14 days when signs of upper urinary tract involvement, such as flank tenderness or fever, are present. Men are usually treated for a longer period of time, 10–14 days.[18] Relapses, both asymptomatic and symptomatic, are common following treatment; 50% of men and women have a positive urine culture within 6 weeks after treatment. In this context, urine culture should not be done as a test of cure. It is to be noted that a symptomatic relapse in a man within 6 weeks of treatment demands a longer retreatment of 6–12 weeks because of assumed prostatic involvement.[3,18]

Table 2: Incidence (%) of Common Adverse Events

Event	Ciprofloxacin*	Levofloxacin	Linezolid	Ertapenem
Diarrhea	2	1.2	—	10.3
Headache	1	0.1	—	5.6
Nausea	3	1.2	—	8.5
Dizziness	1	0.3	—	2.1
Vaginitis	1	0.8	—	1.4
Discontinuation	3.5	3.7	—	4.7

*Cipro XL.
Sources: Ball et al., 1999[35]; Breen et al., 1999[36]; Blondeau, 2000.[37]

New Antimicrobials for Older Adults

Among the new available antimicrobials, some can be used for UTI treatment (Table 3). It is to be noted that these drugs have also been approved for other indications (the clinician can refer to the product monograph or other reviews on the subject).

Fluoroquinolones

Fluoroquinolones are broad-spectrum agents available both in oral and parenteral preparations. Ciprofloxacin has been widely used for almost two decades now, both in community and hospital settings. It has been shown to be remarkably safe and has been used extensively in UTI treatment. A new extended-release formulation, Cipro XR (XL in Canada), has been approved for therapy in community-acquired acute cystitis and uncomplicated pyelonephritis. It is available in 500 mg and 1,000 mg daily

Table 3: Approved Indications* for Various Antimicrobial Agents

Compound	Administration	Clinical Indications	Bacteriological Indications	Source
Ciprofloxacin†	Oral	UTI (complicated, uncomplicated), uncomplicated pyelonephritis	Ec, Kp, Pm, Ef, Pa, Ssap	www.pharma.bayer.com
Linezolid	Oral, IV	VAP, VREF‡, NP, SSTI (complicated, uncomplicated), CAP	MSSA, MRSA, MDRSP, Spy, Sag	www.pfizer.com
Ertapenem	Intravenous, intramuscular	IAI (complicated), SSTI (complicated), CAP, UTI (complicated), API	HiBLN, Mc, PSSP, Bacteroides spp.§, Ec, Kp, Cc, El, Spy, Pb, Pepto, MSSA	

API = acute pelvic infection; CAP = community-acquired pneumonia; Cc = *Clostridium clostridioforme*; Ec = *Escherichia coli*; Ef = *Enterococcus faecium*; El = *Eubacterium lentum*; HiBLN = *Haemophilus influenzae* beta-lactamase negative; IAI = intra-abdominal infection; Kp = *Klebsiella pneumoniae*; Mc = *Moraxella catarrhalis*; MDRSP = multidrug-resistant *Streptococcus pneumoniae*; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*; NP = nosocomial pneumonia; Pa = *Pseudomonas aeruginosa*; Pb = *Prevotella bivia*; Pepto = *Peptostreptococcus* spp.; Pm = *Proteus mirabilis*; PSSP = penicillin-susceptible *Streptococcus pneumoniae*; Sa = *Staphylococcus aureus*; Sag = *Streptococcus agalactiae*; Spy = *Streptococcus pyogenes*; Ssap = *Staphylococcus saprophyticus*; SSTI = skin and skin structure infection; VAP = ventilator-associated pneumonia; VREF = vancomycin-resistant *Enterococcus faecium*.
*In North America.
†Cipro XL.
‡Serious or life-threatening infection associated with VREF.
§Bacteroides spp. = *B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, and B. uniformis.*

Table 4: Comparative In Vitro Activity of Various Antimicrobial Compounds against Select Microorganisms

	MIC_{90} (mg/L)			
Microorganism	Ciprofloxacin	Levofloxacin	Linezolid	Ertapenem
Streptococcus pneumoniae	1–2	1–2	1–2	0.015–2
Staphylococcus aureus				
MSSA	0.5–2	0.25–2	1–4	0.25
MRSA	0.5–128	0.06–16	1–4	16
Enterococcus spp.	2–128	0.5–50	1–4	>16
Chlamydia pneumoniae	1–2	0.25–0.5		
Klebsiella pneumoniae	0.031–1	0.125–1		≤0.03
Klebsiella spp.	0.063	0.125		≤0.03
Enterobacter spp.	0.016–0.031	0.031		0.5–4
Citrobacter spp.	0.125	1		≤0.03–0.25
Proteus spp.	0.125	0.125		
Legionella spp.	0.12	0.015–0.03	4–8	
Pseudomonas aeruginosa	0.39–4	4–32		16
Salmonella spp.	0.03	0.03		≤0.008
Shigella spp.	0.06			≤0.008
Aeromonas spp.	≤0.008			0.25
Streptococcus pyogenes	0.5–3.13	0.5–2	1–4	0.008–0.25
Haemophilus influenzae	0.016	0.016	8	0.06
Moraxella catarrhalis	0.031	0.063	4–8	0.016
Mycoplasma hominis				
Mycoplasma pneumoniae	0.78–8	0.5–1		
Streptococcus agalactiae	2	0.5	2	0.06
Neisseria spp.	0.004	0.008		0.12†
Clostridium spp.	0.5–32	0.39*	8	0.12–8
Peptostreptococcus spp.	0.5–8	2–3.13	1	0.06–0.5
Propionibacterium acnes				
Bacteroides spp.	8–16	1–16	4	0.03–4
Fusobacterium spp.	2	4	0.5	0.12–0.5

MIC_{90} = minimal inhibitory concentration required to inhibit the growth of 90% of organisms; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*.

* *Clostridium perfringens*.

† *Neisseria gonorrhoeae*.

dosages. As with the regular ciprofloxacin, 35% of the total oral dose is excreted in the urine.[32] The urinary drug concentration far exceeds the minimal inhibitory concentration required to inhibit the growth of 90% of strains (MIC_{90}) (Table 4) for common uropathogens over a 24-hour dosage administration interval.[33] This formulation has been evaluated in a multicentre, double-blind, randomized trial comparing it to immediate-release ciprofloxacin for complicated UTIs (e.g., presence of indwelling catheter, urinary retention, and neurogenic bladder). Both treatments were bacteriologically effective against various pathogens including *E. coli*. The extended-release formulation was slightly more effective in patients with a complicated UTI than the immediate-release ciprofloxacin (89.2% versus 81.4% eradication rate).[34] The safety and tolerability of this new formulation were similar in trials to those of the regular formulation of ciprofloxacin.

Ertapenem

Ertapenem is a carbapenem, part of the larger beta-lactam group, and it has been approved for use in complicated UTI (Table 3). Like the other carbapenems, it has a broad-spectrum of activity encompassing gram-positive and gram-negative bacteria and aerobic and anaerobic pathogens, with the exception of *P. aeruginosa* (Table 4). It is available in both intramuscular and intravenous formulations with a 1 g daily dosage. Since ertapenem is mainly excreted in the urine, dosage adjustments are required in patients with renal insufficiency. Clinical and microbiological trials have shown success in 83.6–93.6% of ertapenem-treated patients, compared with 80.4–91.5% of those treated with other comparative agents.[30]

Linezolid

Since VRE and MRSA are a growing problem both in community- and hospital-based settings, linezolid, a new antimicrobial, is a valuable addition to the therapeutic armamentarium for these multiresistant bacteria. Linezolid has been approved for treatment of VRE infections (Table 3). Part of a new class of antimicrobials named oxazolidinones, linezolid is active against gram-positive bacteria including *Staphylococcus* spp., *Enterococcus* spp., *Streptococcus* spp., VRE, and MRSA (Table 4). Gram-negative bacteria are not part of its spectrum of activity. It is available in oral and parenteral formulations and has an excellent oral bioavailability (close to 100%). Clinical responses in the context of studies on skin and soft tissue infection, community-acquired pneumonia, and VRE infections ranged from 70 to 90%. The main side effects of this drug have been hematological changes including neutropenia and occasional neuropathies, usually when the course is continued for more than 14 days. Careful monitoring is thus required when the treatment is to be given for more than 14–21 days[30] (Table 2).

Conclusion

The current demography of Western countries shows that the population of older adults will increase steadily in the near future. The budget and human resources devoted to the proper care of this important population will increase in a parallel fashion. Since UTI is a major infectious problem in older adults, it is important that clinicians understand the particular challenges associated with its diagnosis and treatment in order to provide the best care possible. As we have seen, the clinical diagnosis of symptomatic UTI can be difficult in a population with a high prevalence of asymptomatic bacteriuria, for which treatment is not warranted and can even be harmful. Communication difficulties in patients with functional impairment can also make the diagnosis difficult, hindering the clinician's ability to determine the presence of new signs or symptoms. Another major issue is the continuing emergence of resistant bacterial strains; it is a pressing issue in the institutionalized population, where increased antimicrobial use contributes to the selection of resistant clones. It is then ever more important for the clinician to use antimicrobials judiciously among older adults. New compounds are available to treat UTI in the older adult; the clinician is invited to complete this short summary by looking at the product monographs and choosing the appropriate antibiotic in the context of possible side effects, drug interactions, site of infection, and microbiology results including drug susceptibility. Rational use of antimicrobials in the treatment of UTI in the older adult is called for in order to both provide appropriate care and control the spread of resistant organisms in this population.

Key Points

- Antimicrobial resistance is compromising drug therapy.
- E. coli remains the predominant uropathogen.
- Newer antimicrobial agents have been introduced to the market.
- The ciprofloxacin once daily formulation is clinically equivalent to twice daily dosing.
- Urinary tract infection in older adults may be more common due to underlying medical condition and management or therapeutic intervention.

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