World Journal of Urology (2020) 38:2709–2720
https://doi.org/10.1007/s00345-020-03159-2

TOPIC PAPER

Treatment of urinary tract infections in the old and fragile

Guohua Zeng[1] · Wei Zhu[1] · Wayne Lam[2] · Ayberk Bayramgil[3]

Received: 27 October 2019 / Accepted: 4 March 2020 / Published online: 27 March 2020

Abstract

Introduction Urinary tract infection (UTI) is highly prevalent in the frail elderly population. This review aimed to outline the diagnostic, treatment, and prevention of UTI in the frail aging population.

Methods Pubmed and Web of Science search to identify publications until March 2019 relating to the management of UTI in the elderly population was performed. A narrative review of the available literature was performed.

Results 64 publications were considered as relevant and included in this review. The diagnosis of symptomatic UTI in the old and fragile could be challenging. Routine screening and antimicrobial therapy for asymptomatic bacteriuria should not be recommended for frail elderly patients. Cautious choice of antibiotics should be guided by uropathogen identified by culture and sensitivity. Understanding local antibiotic resistance rates plays a fundamental part in selecting appropriate antimicrobial treatment. Impact of associated adverse effect, in particular those with effects on cognitive function, should be considered when deciding choice of antibiotics for symptomatic UTI in the elderlies. Optimal management of comorbidities such as diabetes mellitus, adequate treatment of urinary incontinence, and judicious use of urinary catheter is essential to reduce the development of UTI.

Conclusion UTI is a significant but common problem in elderly population. Physicians who care for frail elderly patients must be aware of the challenges in the management of asymptomatic UTI, and identifying symptomatic UTI in this population, and their appropriate management strategies. There is strong need in studies to evaluate nonantimicrobial therapies in the prevention of UTI for the frail elderly population.

Keywords Urinary infection · Elderly · Frail · Asymptomatic bacteriuria · Review

Introduction

Urinary tract infections (UTIs) are extremely common, affecting 150 million people each year worldwide [1]. Frail elderly patients, often associated with a range of disabilities as incontinence, immobility, and cognitive impairment, are at particularly high risk for the development of UTIs [2]. This is likely due to the altered physiology in this population that increases their susceptibility to both infection and urinary bacterial overgrowth. UTIs are the leading causes of bacteremia, need of systemic antimicrobial therapy, hospitalization, decreased functional status, urosepsis, or even death in frail elderly patients [3].

Correct diagnosis of UTI is challenging in the elderly population. They often lack typical signs and symptoms, but rather present with very wide variation of non-specific presenting symptoms including malaise, eating disorders, tiredness, or generalized weakness [4]. Furthermore, the specimen collection is sometimes difficult for frail elderly. As such, misdiagnosis of UTI in this population is not uncommon. Literature reported that UTI was erroneously diagnosed in 40% of the elderly in hospital [5], with frequent over-diagnosis and subsequent overtreatment. Antibiotic therapy may be prescribed for symptoms that represent bladder dysfunction or localized vaginal symptoms rather than true UTIs, and thus will not confer the intended benefit.

Guohua Zeng and Wei Zhu equally contributed to this work and should be considered as co-first authors.

✉ Guohua Zeng
gzgyzgh@vip.sina.com

[1] Department of Urology and Guangdong Key Laboratory of Urology, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510230, Guangdong, China

[2] Division of Urology, Department of Surgery, Queen Mary Hospital, Hong Kong SAR, China

[3] Department of Internal Medicine, Istanbul Medipol University, Istanbul, Turkey

There are many challenges to diagnosing and treating UTI specifically in the frail elderly population because of a lack of evidence-based guidelines. The purpose of this review is to identify age-related changes which increase the risk of UTI, challenges in correctly making the diagnosis in the aging patients, and to outline the treatment and prevention of UTI in the frail elderly population.

Methods

We performed a narrative review through the PubMed and Web of Science databases for relevant articles in English published until March 2019. The search was performed using the following keywords: "urinary tract infection", "elderly", "frail", and "asymptomatic bacteriuria." Original research articles, reviews, abstracts, and opinion articles were included and reviewed by all the authors.

Various concepts for frailty have been suggested, but no formal consensus has yet been achieved. In this review, people over 65 years of age who meets at least three of following clinical features (low grip strength, weight loss, low levels of activity, low energy, and slowed walking speed) were defined as "frail elderly" according to the standardized definition proposed by Fried et al. [3]

The literature searches identified 701 publications, which were screened for inclusion. Finally, 64 publications were considered as relevant and included in this review.

Prevalence

The prevalence of UTI increases with age in both sexes, and increases from 12 to 29 per 100 person years at risk in community-dwelling elderly populations to 44–58 per 100 residents per year at risk in long-term care facilities [4, 6–8]. UTI is second only to respiratory infections in elderly populations older than aged 65 years [9].

Asymptomatic bacteriuria

Asymptomatic bacteriuria is defined as the presence of bacteria in urine on microscopy or quantitative culture, without symptoms suggestive of UTI [10]. The prevalence of asymptomatic bacteriuria rises with age in both male and female, and is very common in the elderly population. However, its significance remains unclear. In man, asymptomatic bacteriuria is present in nearly 10% of men over the age of 80 in the community [11], and between 15 to 40% of male residents of long-term care facilities [6]. For women, the prevalence of asymptomatic bacteria rises from 3.5% in the general population to 16% to 18% in women over 70 years of age. Some epidemiological studies even reported that asymptomatic bacteriuria affects up to 50% of older women [12, 13]. This is likely attributed to the development of vulvovaginal atrophy caused by the altered relationship between estrogen, production of glycogen, and *Lactobacilli* colonization in the elderly women. The colonization by *Lactobacilli* decreases vaginal pH through the production of lactic acid via glucose metabolism, subsequently decreases the defense ability against harboring bacteria. Other factors such as pelvic organ prolapse and urinary incontinence in the elderly female population also play important roles in increasing their risk in developing bacteriuria.

The high incidence of asymptomatic bacteriuria is a remarkable aspect of institutionalized elderly people: from 25 to 50% of women and 15% to 40% of men [4]. The incidence is especially higher in the severely disabled elderlies. It is also important to note that the use of long-term urinary catheters, not an uncommon practice amongst the elderly population, predisposing them to develop asymptomatic bacteriuria. The incidence of asymptomatic bacteriuria in individuals increases by 3–10% per day, eventually reaching 100% in patients with chronic indwelling catheters [14]. One way to decrease the prevalence of asymptomatic bacteriuria in patients requiring a long-term catheter is to consider the use of condom-based catheter [15, 16]. It is also interesting to note that up to 90% of the aging population also have asymptomatic pyuria, which is significantly higher than the younger population.

Fundamentally, clinicians should be able to firmly counsel patients that asymptomatic bacteriuria is generally a benign condition in older populations, and should not require antimicrobial treatment. Importantly, it has been established that the presence of asymptomatic bacteriuria is not linked to long-term adverse effects, such as cardiovascular diseases, renal failure, genitourinary diseases, or reduced survival time [10].

UTI

UTI is generally defined as an infection that affects part of the urinary tract [17]. Definition of symptomatic UTI varies significantly across previous epidemiological studies. Therefore, defining the true incidence of UTI in the elderly population has been challenging. UTI is a very common problem in the elderly population. The prevalence of UTI is higher in older females when compared with the male counterpart, and the magnitude of this gender difference is significantly wider when compared with the younger population. Among community-dwelling older adults, the prevalence of UTI ranges from 0.07 in postmenopausal women per person per year [18] to 0.01 per person per year in adults over 85 [19]. In men, the estimated annual incidence of UTI ranges from 0.05 in men between 65 and 74 years of age, and rise to 0.08 in men over the age of 85 [20]. UTI is a leading cause for American nursing home residents requiring acute

hospital admission, but UTI itself is seldom a direct cause of mortality in this group of patients [7]. However, increased mortality was reported in elderly patients with long-term indwelling catheters [21], although it is important to note that this cohort of patients in general are associated with multiple comorbidities with significant functional impairment. The reported excess in mortality in patients with long-term indwelling catheter is, therefore, expected.

Risk factors

Risk factors for developing UTI in older people are different from the younger population. Age-associated cognitive impairment, immunologic abnormality, and increasing number of comorbidities made older people more susceptible to UTI. Table 1 summarized the common risk factors for UTI in the elderly population.

Urinary incontinence

Urinary incontinence is common and appears to be an important risk factor for UTI in the frail elderly population. The results from a population-based cases study of women aged 55–75 years showed that urinary incontinence was related to the rise of UTI. A previous study demonstrated that urinary incontinence with a frequency of greater than once monthly was independently associated with UTI risk factor (OR 1.36; 95% CI 1.03–1.78). The amount of urine lost, however, was not a significant risk factor of UTI in the same study [22]. Caljouw et al. [6] carried out a population-based prospective follow-up study of 86-year-old people and found self-reported urinary incontinence was one of the strongest predictors for UTI development in this cohort of studied population. It has been postulated that as urine leaks out of the lower urinary tract, the process creates an environment which acts as a medium for bacteria to develop and ascend into the urinary tract.

Table 1 Common risk factors for UTI in the old and fragile

Common risk factors for UTI in the old and fragile
General
Urinary incontinence
Cognitive impairment
Immunologic abnormality
Chronic indwelling catheter
Diabetes Mellitus
Urologic obstruction
Neurogenic bladder
Recent urologic instrumentation
Older men
Prostatic disease
Older women
Cystocele
Atrophic vaginitis

Cognitive impairment

Elderly patients with Alzheimer's disease or dementia have reduced cognitive and functional capacities which progress over time. As symptoms worsen, this group of patients may have significant difficulty in communicating symptoms and presentation. The diagnosis of UTI may be challenging and often delayed. Maintaining good general hygiene in elderly patients with cognitive impairment could be difficult, and access for extra care is desperately needed but often limited. In patients with advanced dementia, the ability in the voluntary control of both bladder and bowel urges declines. This, together with reduced physical mobility, may also contribute to the increased risk of UTI development in this population. Several studies demonstrated that impaired cognitive status predict the development of UTI amongst the elderlies [6, 23].

Immunologic abnormality

The immune system is an important host-defense system essential to protect against diseases for maintenance of life. However, the immune system function declines with age, with decreased humoral and cellular immune reactivity [24]. This leads to immune senescence and the acquired immune deficiency in the frail elderlies, compromising their immune response and increases the risk of developing UTI. There are many reasons why the immune system effectiveness declines with age, all of which are essential for clinicians to appreciate to reduce risk of UTI in this cohort of patients. These risk factors can generally be divided into host factors and social factors. Host factors include associated comorbidities (e.g., diabetes, renal failure), medication use (e.g., immunosuppressant), micturition dysfunction, metabolic changes, and immune senescence. Social factors may include poor nutrition, residing in a long-term care facility and poor understanding of prevention [25]. When UTI is developed in this population, the immune response is, therefore, less potent or effective, and as such morbidity and mortality in this population is comparatively higher.

Prostatic disease

Benign prostate hyperplasia (BPH) is a common risk factor leading to UTI in older men. BPH causes urinary outflow obstruction and urinary stasis, which promotes colonization of bacteria into the bladder. High post-void residual and urinary stasis result from chronic obstruction have been

described to be important risk factors for the development of asymptomatic bacteriuria and UTI in older man [26].

Diabetes mellitus

Bacteriuria and UTI occur more commonly in older adults with diabetes than in people without this disease. Severe UTI complications are usually seen in diabetic patients, like perinephric abscess, bacteremia, and renal papillary necrosis. Duration of having diabetes, poorly controlled diabetes with high HbA1c, glucosuria, and pyuria in this population has also been identified as risk factors for harboring asymptomatic bacteriuria [27].

There are multiple potential mechanisms to explain how diabetes contribute to the increased risk of UTI. Higher glucose concentrations in urine can allow the growth of pathogenic bacteria. High levels of renal parenchymal glucose create a favorable environment for microorganism growth and propagation. Associated impairment in the immune system in patients with diabetes also contributes to the pathogenesis of UTI. In addition, patients with diabetes are often associated with autonomic neuropathy. This results in bladder and voiding dysfunctions, decreasing its physical bacterial clearance ability, thereby facilitating bacterial growth [28].

Chronic indwelling catheter

Among institutionalized elderly, urinary catheterization appears to be the most important risk factor associated with UTI. Urinary catheterization is also a risk factor associated with fungal infections, especially for older people with previous antibiotic use or diabetes. It is well known that any indwelling device in the urinary tract is prone to the rapid development and coating by biofilm within a short timeframe, which predisposes these patients to develop UTI. A biofilm is an assemblage of microbial organisms with a surface and enclosed in an extracellular matrix consisting polysaccharide materials primarily. The biofilm incorporates urine components, such as Tamm–Horsfall protein or magnesium or calcium ions. The biofilm facilitates microbial adhesion to catheter surfaces in ways that hamper for removal with gentle washing. This provides a stable and protective environment for microorganisms, which acts as a shield to evade attacks by antimicrobial agents. Biofilm formation can also cause catheter encrustation and catheter obstruction [29].

Microorganisms may also reach the catheter via an intraluminal route, which occurs mainly when organisms access the catheter's internal lumen by failing a closed drainage system or contaminating the drainage bag. Such organisms usually come from exogenous sources and are often arise from cross-transmission of organisms through medical staff [29].

Diagnosis

Asymptomatic bacteriuria

Asymptomatic bacteriuria is defined as the presence of significant quantity of bacteria in uncontaminated urine collected without signs or symptoms of UTI (Table 2). It should be kept in mind that the presence of bacteriuria does not always represent an active disease that requires treatment [30]. One would argue if urine should be collected for culture and sensitivity if elderly patients were clearly asymptomatic, as positive results would not necessarily alter the management in these patients anyways. In women, the microbiological diagnosis of bacteriuria is defined as two consecutive voided urine samples with the same bacterial species present with $\geq 10^5$ cfu/mL. In men, the bacteriuria is diagnosed as a single, clean-catch-voided urine sample with one bacterial species present with $\geq 10^5$ cfu/mL.

Many frail elderly patients have difficulties to cooperate for urine samples collection, because of incontinence or reduced cognitive function especially during sepsis. For these patients, a specimen obtained by in-and-out catheter should be considered. For samples obtained by means of urethral catheterization, counts of 10^2 cfu/mL or more are diagnostic of bacteriuria [10]. For patients who have a chronic indwelling urinary catheter, it should ideally be removed, and culture should then be acquired from a freshly inserted catheter [31]. It is difficult for frail elderly men to provide a midstream-voided urine specimen for diagnostic testing. For these men, the use of a clean condom external collection device could be considered to collect urine for microscopy and sensitivity analysis. For patients using external catheter devices, the quantitative count of $\geq 10^5$ cfu/mL is appropriate [32]. It is important to note that urine culture by bladder needle aspiration has been recommended as the gold standard method for diagnosing bacteriuria, but realistically this has seldom been used in elderly population.

UTI

The diagnosis of UTI for the elderly follows a similar criterion to the diagnosis of UTI for the young populations, which required bacteriuria associated with genitourinary symptoms (Table 2). In the elderly population, accepted clinical conditions include fever, frequency, dysuria, bladder pain, flank pain, gross hematuria, and deteriorating urgency or urinary incontinence [33]. Changes in behavior or mental status have frequently been included in the criteria but both lack specificity. For older people who are

Table 2 Diagnosis of asymptomatic bacteriuria and UTI in elderly population

Bacteriuria	Women
	Two consecutive voided urine samples with the same bacterial species present with $\geq 10^5$ cfu/mL
	Men
	A single, clean catch-voided urine sample with one bacterial species present with $\geq 10^5$ cfu/mL
	Urine sample obtained by means of urethral catheterization
	Sample obtained by means of urethral catheterization with one bacterial species $\geq 10^2$ cfu/mL
	Patients using external catheter devices
	A urine sample with one bacterial species present with $\geq 10^5$ cfu/mL
Asymptomatic bacteriuria	The presence of significant quantity of bacteria in uncontaminated urine collected without signs or symptoms of UTI
UTI	Bacteriuria associated with genitourinary symptoms
	Accepted clinical criteria include
	Fever (defined as temperature > 37.9 °C or 1.5 °C increase above baseline temperature)
	Dysuria
	Frequency
	Suprapubic pain
	Gross hematuria
	Costovertebral angle tenderness
	Change in behavior or mental status
	New or worsening urgency or urinary incontinence

cognitively intact and who are able to report symptoms well, UTI diagnosis is not difficult. However, among frail elderlies who are often cognitively impaired or have hearing or speech difficulties, distinguishing asymptomatic bacteriuria from UTI is often challenging. A survey of older people in primary care showed that UTI was the second most common infection that physicians initially overlooked. The main reason for difficulties in making the diagnosis at an earlier stage was due to challenges encountered with history taking in this population of patients [34]. A cohort study in nursing home residents reported that the most common symptoms of UTI were altered mental status (39%), behavioral changes (19%), hematuria or pyuria (15.5%), and fever or chills (12.8%) [35]. For older adults with a long-term indwelling catheter, fever without urinary tract localizing symptoms is the most common feature of UTI [36]. The lack of clear history obtainable from the frail and cognitively impaired elderly patients means that collateral history from patients' relatives or carers is essential. Careful and systematic clinical and physical assessments should be conducted to derive if UTI should be a differential diagnosis or not [5].

The presence of dysuria is a strong predictor of bacteriuria with pyuria in nursing home residents, and new dysuria has been demonstrated to be the most valuable clinical finding in correctly identifying UTI in older adults [35, 37]. On the other hand, although behavioral changes, altered mental status, general malaise, and non-mechanical falls in the elderly population are generally accepted as part of the clinical symptoms suggesting UTI by many clinicians, these signs lack specificities and do not necessarily correlate with bacteriuria or pyuria as demonstrated in previous studies [35]. Interestingly, change in characters of the urine (color or odor) also do not reliably correlate with the presence of UTI. These symptoms are, therefore, not useful criterion as guidance to initiate treatment, and have been suggested to be associated with overtreatment and antibiotic overprescribing [38, 39]. Rather than an underlying pathology, these urine changes may simply suggest need for increased fluid intaking, which indicates a reduced thirst response in the elderly or maybe because of drugs (e.g., multivitamins) or diet (e.g., asparagus). As a result, in most cognitively impaired patients with a change in mental status and/or urine color or odor, hydration should be considered first and only to conduct further investigations and treatments if not responsive to such intervention.

Pyuria is highly sensitive but less specific for UTI, especially among patients with a urinary catheter in whom pyuria is prevalent. Diagnosing UTI based on pyuria alone would result in extensive antibiotic overprescribing, especially for patients with pyuria accompanying asymptomatic bacteriuria. However, the absence of pyuria is useful for excluding UTI. The utility of pyuria for UTI diagnosis in clinical practice is similar to that of D-dimer for pulmonary embolism diagnosis. A negative outcome is of great value for patients with all but the highest pretest risks of disease, while a positive outcome is necessary but not sufficient to determine the diagnosis. A urine sample should be tested for pyuria

in patients in long-term care facilities. If pyuria is negative, UTI is eliminated and urine culture or treatment should not be pursued [40].

To overcome the diagnostic challenges in this population, criteria for antibiotic treatment for bacteriuria in long-term care facilities were established. It was recommended that antibiotics should be administrated for patients with no urinary catheter with acute dysuria alone or fever and one of the following symptoms: urinary urgency or frequency, suprapubic pain or tenderness, hematuria, or urinary dysfunction. For patients with a chronic indwelling catheter, the necessary criteria for administrating antibiotics include fever, new costovertebral angle pain or tenderness, shaking chills, or new onset of delirium [33]. The implementation of these criteria was proven to be safe and reduce antimicrobial use for UTI [41].

Management

Asymptomatic bacteriuria

It is widely known that routine testing and antimicrobial therapy for asymptomatic bacteriuria are not recommended for frail elderly persons [10]. Although antimicrobial therapy could eliminate bacteriuria, it increases expense, the risk of adverse effects, and superinfection by drug-resistant microorganisms [42]. Guidelines state that one-third of the people treated with antibiotics will come to harm [43]. Antimicrobial therapy does not alleviate chronic urianry symptoms, and does not prevent recolonization or minimize the risk of developing UTI. Bacteriuria is almost common in elderly people with long-term indwelling catheters. However, treating asymptomatic bacteriuria has no benefit on symptomatic episodes and the incidence of fever [44]. Antimicrobial treatment for asymptomatic bacteriuria in the elderly is only recommended for the following situations: (1) prior to transurethral resection of the prostate and (2) prior to urologic operations in which mucosal bleeding is expected [10].

UTI

Choosing the correct antibiotic and duration of antibiotic therapy are two important issues we should consider when treating UTI in the elderlies. The choice of antibiotic should fundamentally be personalized and tailored according to each individual elderly patient. The selection should be considered by bacterial pathogens, antibiotic resistance rates, side effects, and patient comorbidities.

Specifically, in frail elderly patients who have been institutionalized, or in those who have had received frequent courses of antibiotics, the range of potential pathogens causing UTI could be very broad, and antibiotic resistance could subsequently be very high. As a result, unnecessary antibiotic courses should be avoided and narrow-spectrum agents should be recommended whenever possible and safe. This practice would also aid to reduce the risk of developing *Clostridium difficile*-related infections, which causes significant morbidity and mortality in elderly populations [45].

Commonly, antibiotic with high levels of urinary excretion is recommended in the treatment of UTI (Table 3). For uncomplicated bacterial cystitis, depending on local guideline recommendations, frequently used first-line antimicrobial therapies include nitrofurantoin, and trimethoprim/sulfamethoxazole (TMP/SMX), usually administered for a period of 3–7 days depending on severity. Nitrofurantoin is not effective for pyelonephritis and bacterial prostatitis due to its limited tissue penetration ability. Common uropathogens such as *K. pneumoniae, P. mirabilis*, and *P. aeruginosa* are also resistant to this agent. However, nitrofurantoin is effective against various not uncommon multi-resistant uropathogens such as extended spectrum β-lactamase-producing *E coli* and vancomycin-resistant *enterococci* [46]. A retrospective study showed that male elderly with UTI treated with nitrofurantoin had an overall 77% clinical cure rate, which is comparable to other agents [47]. Historically, nitrofurantoin is relatively contraindicated in patients with renal insufficiency that is more common in older patients

Table 3 Treatment modalities of UTI in older persons

Term	References	Treatment modalities
Uncomplicated bacterial cystitis	[43–47, 51]	Nitrofurantoin or TMP/SMX administered for a period of 3–7 days
Pyelonephritis or complicated UTI	[54–58]	Fluoroquinolones, second- or third-generation cephalosporins, or gentamicin administered for a period of 7–14 days
Recurrent UTI in elderly women	[59]	Long-term prophylactic antibiotics: 6 months of TMP/SMX (40 mg/200 mg daily), trimethoprim (100 mg daily), nitrofurantoin (100 mg daily), or 1 year of nitrofurantoin (50 mg daily)
Recurrent UTI in elderly men	[52]	Medical or surgical treatment to reduce residual urine volume
UTI in patients with chronic indwelling catheters	[60–64]	Systemic antibiotic therapy is recommended for catheterized patients with associated symptoms suggestive of UTI-related bacteremia or pyelonephritis The optimal duration of antimicrobial therapy has not been evaluated (commonly varies between 5 and 21 days according to patients' condition)

UTI urinary tract infection, *TMP/SMX* trimethoprim/sulfamethoxazole

[48]. However, recent evidence suggests that nitrofurantoin can be safely administrated to patients with creatinine clearance ≥ 40 mL/min/1.73m^2 [49, 50]. It should be noted that nitrofurantoin is potentially associated with pulmonary and liver toxicities. This does not mean that all patients with past medical histories of pulmonary or hepatological diseases should avoid this drug completely, as it is a versatile antimicrobial therapy for UTI. However, in patients with respiratory or significant gastrointestinal symptoms, careful assessment for their suitability and monitoring should be carried out.

The optimum duration of a given antibiotic for elderly patients with uncomplicated lower UTI is still debated. A Cochrane review published in 2008 reviewed evidence for the appropriate duration of antibiotic treatment for uncomplicated UTI in elderly females. The review enrolled 15 randomized controlled studies including 1644 elderly females. The study found that, comparing to the long-course antibiotic treatment of 7–14 days, short course (3–6 days) was appropriate to treat uncomplicated UTI in elderly females [51]. Subsequent to this review, a well-designed, double-blind, randomized controlled trial further confirmed that a 3-day course of antibiotic treatment was not inferior to a 7-day course for the treatment of uncomplicated symptomatic UTI in elderly women. Importantly and perhaps unsurprisingly, this study also demonstrated that shorter antimicrobial courses were better tolerated amongst elderly patients. The 7-day course caused more frequent adverse events including somnolence, cephalalgia, anorexia, sicchasia, and emesis [43]. Similarly, regarding treatment of UTI in the male population, no clinical study thus far has demonstrated superiority of long-course antibiotics of 7–14 days versus shorter courses, but adverse effects associated with unnecessary antibiotic therapy have been well documented.

Frail elderly patients with pyelonephritis or complicated UTI carry a higher risk of systemic complications. These patients often require hospital admissions and parenteral therapies. Initial empirical therapy of acute pyelonephritis is usually with fluoroquinolones, second- or third-generation cephalosporins, or gentamicin [43, 52, 53]. This is then subsequently tailored according to results of microscopy and sensitivity results, especially if uropathogens identified are resistant to the initiated empirical treatment, regardless of clinical response.

Fluoroquinolones, the most frequent antibiotics administered in outpatient care [54], has often been viewed as an effective empirical antimicrobial treatment of choice. However, with it being a popular choice of antibiotics being used globally over the years, attention must be paid to potential development of drug resistance, particularly in patients aged 65 years and older [54]. Some studies even suggested that fluoroquinolones should only be used if sensitivity testing results are available [55]. In addition, the specific adverse-effect profile of fluoroquinolones must be considered when the elderly population is managed with these drugs. The consensus from the FAD advisory panel in 2015 suggested that fluoroquinolones should be avoided for treatment of uncomplicated urinary tract infection due to its disabling and potentially permanent side effects of the tendons, muscles, joints, nerves, and central nervous system [56]. Fluoroquinolones can cause central nervous system side effects that are a particular concern in the elderly population. Elderly patients, especially those with suspected central nervous system disorders, are prone to develop neurotoxic complications. For these patients, fluoroquinolones should be used with caution, and close supervision is necessary to monitor for such symptoms including confusion, weakness, loss of appetite and tremor or depression [57].

Alternatively, gentamicin is commonly used in patients with pyelonephritis or complicated UTI, as it is very effective against most Gram-negative organisms. However, with its variable bioavailability amongst patients and its potential associated toxicities, cautious drug-level monitoring is required. Careful attention should be paid to appropriate dosing in the frail elderly, who not uncommonly have unrecognized renal impairment, and gentamicin dose adjustment should be cautiously carried out accordingly [58]. The duration of gentamicin course of UTI is usually between 7 and 14 days. However, if the patient's condition worsens despite being offered correct choice of antibiotics according to sensitivity results, further investigations such as renal ultrasound should be carried out to rule out potential structural abnormalities, such as abscess formation or upper urinary tract obstruction.

Recurrent UTI

Recurrent UTI refers to two or more infections in 6 months or 3 or more infections in 1 year. Most recurrences are thought to represent re-infections rather than relapses (including recurrences caused by the same uropathogenic strain), although occasionally a persistent focus can produce relapsing infections.

Among elderly women with recurrent symptomatic UTI, the use of long-term prophylactic antibiotics for 6–12 months has been shown to be effective at reducing UTI episodes [59]. Commonly used prophylactic antibiotic regimens include 6 months of TMP/SMX (40 mg/200 mg daily), trimethoprim (100 mg daily), nitrofurantoin (100 mg daily), or 1 year of nitrofurantoin (50 mg daily). All regimes have been demonstrated to be effective in reducing episodes of recurrent UTI in older women patients, but with minimal adverse effects [37].

In elderly man with recurrent UTI, it is important to consider uroflowmetry, radiological, and endoscopic investigation to exclude any potentially serious underlying causes such as

malignancy before treatment is commenced. However, bladder outflow obstruction by BPH is by far the commonest contributing risk factor. Medical or surgical treatment should be offered for these patients with an aim to reduce residual urine volume and to subsequent decrease the risk of re-infections [52]. However, the use of long-term prophylactic therapy in the management of chronic recurrent prostatitis remains controversial, and further studies are required to clarify which specific cohort of patients would benefit from suppressive antimicrobial therapy.

UTI in patients with chronic indwelling catheters

Many frail elderly patients require long-term urethral catherization, with an estimated 5–10% of residents of long-term care facilities relying on chronic indwelling catheters for bladder drainage. Specific attentions should be paid in managing UTI in this group of patients. In patients with indwelling catheter in situ for over 1 week in duration, the urethral catheter should ideally be changed prior to collection of the urine specimen for culture. Such practice has been shown to reduce the incidence of contamination by catheter biofilm. This has also shown to provide rapid defervescence and decreased symptomatic relapse post-therapy in patients with long-term urethral catheter [60]. Systemic antibiotic therapy should be recommended for catheterized patients with associated symptoms suggestive of UTI-related bacteremia or pyelonephritis. However, the optimal duration of antimicrobial therapy has not been evaluated, although commonly varies between 5 and 21 days according to the bacterial species, patient co-morbidities, and patient response following initiation of treatment. Long-term antibiotic suppressive treatment in patients with long-term urethral catheter is not recommended as catheterized urine cannot be permanently sterilized [61].

Elderly population with catheter care is more susceptible to fungal UTI. For patients with fungal UTI, the catheter should be removed, if possible. The following urine culture should be performed several days late to see if the fungaluria has eradicated. If the fungaluria has eradicated, no more workup is required. For patients with chronic indwelling catheters and asymptomatic fungaluria, administering antifungal agents is not recommended because it will not help to eradicate fungaluria and will not improve the long-term clinical outcomes. If patients have symptomatic fungaluria, appropriated antifungal agents should be given to treat each specific fungal UTI [2].

Prevention

Chronic indwelling catheters

The best way to prevent patients with urinary catheters from developing UTI is to avoid using urinary catheters to begin with. If a urinary catheter has been inserted, duration should be kept as short as possible [62]. When encountering patients with chronic indwelling catheters, clinicians should always question reasons behind why a long-term urinary catheter was inserted in the first place [55], and re-evaluate regularly to reconsider if this is still required and if a trial without catheter can safely be carried out. The use of patient urinary catheter reminders following initial insertion of urinary catheter may be helpful to avoid patients from having urinary catheters beyond the planned necessary time, and to remind health-care providers to review if urinary catheters could be removed, especially for hospitalized patients [63].

Appropriate catheter care to prevent unnecessary catheter-associated mechanical genito-urethral injury, and early identification of catheter obstruction help to reduce risk of UTI and potential subsequent systemic infections. The use of an external condom catheter in men or intermittent self-catheterization for incontinence management may also help to lower the risk of infection. Silver alloy-coated catheters have not been shown to decrease the frequency of catheter-associated UTI [64]. It has been reported that antimicrobial-coated catheters could slightly decrease the risk of catheter-associated UTI, but are associated with more frequent catheter removal, more uncomfortable caused by catheter, and higher cost [65]. Chronic indwelling catheters should not be changed very frequently. Additional exchanges on top of routine replacements are required only if obstructed, or symptomatic UTI following initiation of antimicrobial treatment [66]. Systemic antibiotic prophylaxis for patients with long-term urinary catheters does not reduce rates of bacteriuria, catheter-associated UTI, or death [66], and should not be recommended.

Cranberry juice

Cranberry juice or capsule administration has been recommended to prevent UTI with the benefits of few side effects and ease of administration. The mechanism has traditionally been thought to be caused by elevated acidity in urine. The present hypothesis is that cranberries function mainly by preventing the adhesion of type 1 and P-fimbriae strains to the urothelium. Without adherence, the bacteria cannot infect the mucosal surface [67]. Several clinical trials have investigated the effect of cranberry juice on UTI prevention in the elderly. Avorn et al. [68] performed a randomized controlled study to evaluate the effect of intake of cranberry juice on UTI prevention in elderly women. They found that the rates of bacteriuria and pyuria presence concurrent with UTI symptoms in the cranberry group were comparable to the placebo group. McMurdo et al. [69] carried out a double-blind, placebo-controlled trial to assess whether cranberry juice was able to reduce UTI episodes in older patients in hospital. Results also showed that the rate of symptomatic

UTI was no significant difference between the placebo and the cranberry group. Therefore, the evidence of using cranberry juice for the prevention of UTI in the elderly is still controversial.

Hormonal

The role of estrogen therapy in the prevention of UTI in older women remains uncertain. Loss of estrogen in postmenopausal women leads to decreased glycogen, epithelial thinning, and vaginal alkalization [70]. Estrogen supplement in postmenopausal women has been demonstrated to decrease intravaginal pH and promote *lactobacilli* colonization, which replaces more pathogenic colonizing bacteria including *Escherichia coli* and enterococcus species. Current evidence suggests that vaginal administration of estrogens reduced the UTI risk compared to placebo in postmenopausal women with a history of recurrent UTI. However, the effect of vaginal administration of estrogens was far less effective than prophylactic nitrofurantoin. Side effects of intravaginal estrogen are frequent but not severe. Vaginal irritation is the most common adverse effect and might occur in up to 20% of elderly women [71]. Oral estrogens, however, did not show to reduce UTI risk compared to placebo in elderly females with a history of recurrent UTI in another study [72].

Fluid intaking

Many elderly suffered from incontinence may limit fluid intake that is a major problem that is somewhat neglected. Fluid restriction is not recommended as it could increase the risk of UTI. Increasing oral fluid intake to dilute contaminating bacteria has been frequently recommended by clinicians to prevent recurrent UTI. However, this recommendation is only based on an expert committee opinion [73]. There is a lack of well-designed randomized controlled trials or high-level evidence to support this.

D-mannose

D-mannose, a simple sugar found in many fruits, is a new supplement that is being studied for its potential ability to prevent UTI with few side effects. D-Mannose help prevent *E. coli* adhesion to the bladder via binding of the mannose receptors, which may help reduce the risk of recurrence UTI. In a randomized placebo-controlled study, prophylactic use of D-mannose significantly reduced the risk of recurrent UTI, and was shown to be as effective as nifrofurantoin [74]. In addition, the effect of D-mannose on blood glucose level is minimal. Thus, it is safe for use by patients with diabetes [75].

Vaccine

Vaccine is a promising alternative to antibiotics for preventing recurrent UTI in frail elderly patients. There are several vaccines, such as Uro-Vaxom®, Urovac®, Uromune®, and ExPEC4V, that are currently undergoing randomized control trials. Uro-Vaxom® is an oral tablet consisted of bacterial lysates from *E. Coli*. Many clinical studies have proved that Uro-Vaxom® is well tolerated and can effectively reduce UTI recurrence rates [76]. Urovac® consists of ten heat-killed uropathogenic species including six strains of *E. coli* and one *Enterococcus faecalis, Proteus vulgaris*, *Morganella morganii*, and *Klebsiella pneumoniae*. Clinical studies also confirmed that Urovac® could reduce the risk of UTI recurrence [77]. Uromune® is a polyvalent bacterial preparation of whole heat-inactivated bacteria including *E. coli*, *Klebsiella pneumoniae, Enterococcus faecalis,* and *Proteus vulgaris*. The results from a multicentric prospective study revealed that Uromune® could effectively reduce the UTI recurrence rate and improve the quality of life in frail institutionalized older adults [78]. The advantages of this sublingual vaccine include easy administration, rare and local side effects, and being practical for its use in frail institutionalized older adults [79]. While preliminary studies on UTI vaccines show potential, further large cohorts prospective randomized controlled studies with long-term follow-up are still necessary to evaluate the long-term effect of vaccine [80].

Conclusion

UTI is an important and very common issue encountered by many clinicians involved in the care of the elderly population. Several specific risk factors predispose this group of patients to be more susceptible to develop UTI. Asymptomatic bacteriuria is particularly frequent in this population, and appropriate management principles must be appreciated. Diagnosis of symptomatic UTI that requires treatment can be very challenging in the frail and elderly patients, in particular those with cognitive impairment or communication difficulties. Meticulous selection of antimicrobial therapy should be offered for patients with symptomatic UTI according to uropathogen susceptibility profiles, local bacterial resistance trends, possible antibiotics adverse effects and their possible interactions with other medications, and their co-morbidities. Management of UTI in elderly patients with long-term catheter remains challenging. There is evidence that prophylactic antibiotics are able to reduce risk of recurrent UTI in correctly selected elderly patients. Other UTI prevention strategies commonly used still lack high-level evidence support.

Author contributions GZ: Project development and manuscript editing. WZ: Data collecting and manuscript writing. WL: manuscript writing and editing. AB: Reviewed the manuscript.

Funding This work was financed by grants from the National Natural Science Foundation of China (No. 81870483 and No. 81800625), and Natural Science Foundation of Guangdong Province (2018A030310296).

Complaince with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals The study does not involve any human participants and animals.

Informed consent Informed consent is not applicable in the study.

References

1. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ (2015) Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol 13:269–284
2. Kim SJ, Ryu JH, Kim YB, Yang SO (2019) Management of Candida urinary tract infection in the elderly. Urogenit Tract Infect 14:33
3. Fried LP, Tangen CM, Walston J et al (2001) Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 56:M146–156
4. Nicolle LE (2009) Urinary tract infections in the elderly. Clin Geriatr Med 25:423–436
5. McMurdo ME, Gillespie ND (2000) Urinary tract infection in old age: over-diagnosed and over-treated. Age Ageing 29:297–298
6. Caljouw MA, den Elzen WP, Cools HJ, Gussekloo J (2011) Predictive factors of urinary tract infections among the oldest old in the general population. A population-based prospective follow-up study. BMC Med 9:57
7. Nicolle LE, Strausbaugh LJ, Garibaldi RA (1996) Infections and antibiotic resistance in nursing homes. Clin Microbiol Rev 9:1–17
8. Stevenson KB (1999) Regional data set of infection rates for long-term care facilities: description of a valuable benchmarking tool. Am J Infect Control 27:20–26
9. Curns AT, Holman RC, Sejvar JJ, Owings MF, Schonberger LB (2005) Infectious disease hospitalizations among older adults in the United States from 1990 through 2002. Arch Intern Med 165:2514–2520
10. Nicolle LE, Bradley S, Colgan R, Rice JC, Schaeffer A, Hooton TM (2005) Infectious diseases society of America Guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis 40:643–654
11. Rodhe N, Löfgren S, Matussek A, André M, Englund L, Kühn I, Mölstad S (2008) Asymptomatic bacteriuria in the elderly: high prevalence and high turnover of strains. Scand J Infect Dis 40:804–810
12. Monane M, Gurwitz JH, Lipsitz LA, Glynn RJ, Choodnovskiy I, Avorn J (1995) Epidemiologic and diagnostic aspects of bacteriuria: a longitudinal study in older women. J Am Geriatr Soc 43:618–622
13. Kaye D, Boscia JA, Abrutyn E, Levison ME (1989) Asymptomatic bacteriuria in the elderly. Trans Am Clin Climatol Assoc 100:155–162
14. Gould CV, Umscheid CA, Agarwal RK, Kuntz G, Pegues DA (2009) Guideline for prevention of catheter-associated urinary tract infections, p 61
15. Saint S, Kaufman SR, Rogers MAM, Baker PD, Ossenkop K, Lipsky BA (2006) Condom versus indwelling urinary catheters: a randomized trial. J Am Geriatr Soc 54:1055–1061
16. Saint S, Lipsky BA, Baker PD, McDonald LL, Ossenkop K (1999) Urinary catheters: what type do men and their nurses prefer? J Am Geriatr Soc 47:1453–1457
17. Rowe TA, Juthani-Mehta M (2013) Urinary tract infection in older adults. Aging Health 9:519–528
18. Jackson SL, Boyko EJ, Scholes D, Abraham L, Gupta K, Fihn SD (2004) Predictors of urinary tract infection after menopause: a prospective study. Am J Med 117:903–911
19. Eriksson I, Gustafson Y, Fagerström L, Olofsson B (2010) Prevalence and factors associated with urinary tract infections (UTIs) in very old women. Arch Gerontol Geriatr 50:132–135
20. Griebling TL (2005) Urologic diseases in America Project: trends in resource use for urinary tract infections in men. J Urol 173:1288–1294
21. Kunin CM, Douthitt S, Dancing J, Anderson J, Moeschberger M (1992) The association between the use of urinary catheters and morbidity and mortality among elderly patients in nursing homes. Am J Epidemiol 135:291–301
22. Hu KK, Boyko EJ, Scholes D, Normand E, Chen C-L, Grafton J, Fihn SD (2004) Risk factors for urinary tract infections in postmenopausal women. Arch Intern Med 164:989
23. High KP, Bradley S, Loeb M, Palmer R, Quagliarello V, Yoshikawa T (2005) A new paradigm for clinical investigation of infectious syndromes in older adults: assessment of functional status as a risk factor and outcome measure. Clin Infect Dis Off Publ Infect Dis Soc Am 40:114–122
24. Richards CL (2004) Urinary tract infections in the frail elderly: issues for diagnosis, treatment and prevention. Int Urol Nephrol 36(3):457–463. https://doi.org/10.1007/s11255-004-4870-6
25. (2019) Pharmacy MAEZ Pharm D, MS, CGP Senior Care Consultant Pharmacist and President of MZ Associates, Inc, Norwich, New York. Recipient of the Excellence in Geriatric Pharmacy Practice Award from the Commission for Certification in Geriatric Predisposition to Infection in the Elderly. https://www.uspharmacist.com/article/predisposition-to-infection-in-the-elderly, https://www.mzassociatesinc.com. Accessed 24 May 2019
26. Rodhe N (2006) Asymptomatic bacteriuria in a population of elderly residents living in a community setting: prevalence, characteristics and associated factors. Fam Pract 23:303–307
27. Turan H, Serefhanoglu K, Torun AN, Kulaksizoglu S, Kulaksizoglu M, Pamuk B, Arslan H (2008) Frequency, risk factors, and responsible pathogenic microorganisms of asymptomatic bacteriuria in patients with Type 2 diabetes mellitus. Jpn J Infect Disease 61(3):236
28. Nitzan O, Elias M, Chazan B, Saliba W (2015) Urinary tract infections in patients with type 2 diabetes mellitus: review of prevalence, diagnosis, and management. Diabetes Metab Syndr Obes 8:129–136. https://doi.org/10.2147/DMSO.S51792
29. Saint S, Chenoweth CE (2003) Biofilms and catheter-associated urinary tract infections. Infect Dis Clin North Am 17:411–432
30. Nicolle LE (2003) Asymptomatic bacteriuria: when to screen and when to treat. Infect Dis Clin North Am 17:367–394
31. Hooton TM, Bradley SF, Cardenas DD et al (2010) Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. Clin Infect Dis 50:625–663
32. Nicolle LE, Long-Term-Care-Committee SHEA (2001) Urinary tract infections in long-term-care facilities. Infect Control Hosp Epidemiol 22:167–175

33. Loeb M, Bentley DW, Bradley S et al (2001) Development of minimum criteria for the initiation of antibiotics in residents of long-term-care facilities: results of a consensus conference. Infect Control Hosp Epidemiol 22:120–124
34. Singh H, Giardina TD, Meyer AND, Forjuoh SN, Reis MD, Thomas EJ (2013) Types and origins of diagnostic errors in primary care settings. JAMA Intern Med 173:418–425
35. Juthani-Mehta M, Quagliarello V, Perrelli E, Towle V, Van Ness PH, Tinetti M (2009) Clinical features to identify urinary tract infection in nursing home residents: a cohort study. J Am Geriatr Soc 57:963–970
36. Nicolle LE (2005) Catheter-related urinary tract infection. Drugs Aging 22:627–639
37. Mody L, Juthani-Mehta M (2014) urinary tract infections in older women: a clinical review. JAMA 311:844
38. Sloane PD, Kistler CE, Reed D, Weber DJ, Ward K, Zimmerman S (2017) Urine culture testing in community nursing homes: gateway to antibiotic overprescribing. Infect Control Hosp Epidemiol 38:524–531
39. Foley A, French L (2011) Urine clarity inaccurate to rule out urinary tract infection in women. J Am Board Fam Med JABFM 24:474–475
40. High KP, Bradley SF, Gravenstein S, Mehr DR, Quagliarello VJ, Richards C, Yoshikawa TT (2009) Clinical practice guideline for the evaluation of fever and infection in older adult residents of long-term care facilities: 2008 update by the Infectious Diseases Society of America. Clin Infect Dis Off Publ Infect Dis Soc Am 48:149–171
41. Loeb M, Brazil K, Lohfeld L, McGeer A, Simor A, Stevenson K, Zoutman D, Smith S, Liu X, Walter SD (2005) Effect of a multifaceted intervention on number of antimicrobial prescriptions for suspected urinary tract infections in residents of nursing homes: cluster randomised controlled trial. BMJ 331:669
42. Boscia JA, Kobasa WD, Knight RA, Abrutyn E, Levison ME, Kaye D (1987) Therapy vs no therapy for bacteriuria in elderly ambulatory nonhospitalized women. JAMA 257:1067–1071
43. Beveridge LA, Beveridge LA, Davey PG, Phillips G (2011) Optimal management of urinary tract infections in older people. Clin Interv Aging:173
44. Gray RP, Malone-Lee J (1995) Review: urinary tract infection in elderly people—time to review management? Age Ageing 24:341–345
45. Cove-Smith A, Almond MK (2007) Management of urinary tract infections in the elderly. Trends Urol Gynaecol Sex Health 12:31–34
46. Meier S, Weber R, Zbinden R, Ruef C, Hasse B (2011) Extended-spectrum β-lactamase-producing Gram-negative pathogens in community-acquired urinary tract infections: an increasing challenge for antimicrobial therapy. Infection 39:333–340
47. Ingalsbe ML, Wojciechowski AL, Smith KA, Mergenhagen KA (2015) Effectiveness and safety of nitrofurantoin in outpatient male veterans. Ther Adv Urol 7:186–193
48. Pearle MS, Calhoun EA, Curhan GC, Urologic Diseases of America Project (2005) Urologic diseases in America project: urolithiasis. J Urol 173:848–857
49. Oplinger M, Andrews CO (2013) Nitrofurantoin contraindication in patients with a creatinine clearance below 60 mL/min: looking for the evidence. Ann Pharmacother 47:106–111
50. Ahmed H, Farewell D, Francis NA, Paranjothy S, Butler CC (2018) Risk of adverse outcomes following urinary tract infection in older people with renal impairment: retrospective cohort study using linked health record data. PLOS Med 15:e1002652
51. Lutters M, Vogt-Ferrier NB (2008) Antibiotic duration for treating uncomplicated, symptomatic lower urinary tract infections in elderly women. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD001535.pub2
52. Schaeffer AJ, Nicolle LE (2016) Urinary tract infections in older men. N Engl J Med 374:562–571
53. Cortes-Penfield NW, Trautner BW, Jump RLP (2017) Urinary tract infection and asymptomatic bacteriuria in older adults. Infect Dis Clin North Am 31:673–688
54. Kallen AJ, Welch HG, Sirovich BE (2006) Current antibiotic therapy for isolated urinary tract infections in women. Arch Intern Med 166:635–639
55. Das R, Perrelli E, Towle V, Van Ness PH, Juthani-Mehta M (2009) Antimicrobial susceptibility of bacteria isolated from urine samples obtained from nursing home residents. Infect Control Hosp Epidemiol Off J Soc Hosp Epidemiol Am 30:1116–1119
56. Commissioner O of the (2019) FDA updates warnings for fluoroquinolone antibiotics. In: FDA. https://www.fda.gov/news-events/press-announcements/fda-updates-warnings-fluoroquinolone-antibiotics. Accessed 3 Jan 2020
57. Stahlmann R, Lode H (2010) Safety considerations of fluoroquinolones in the elderly: an update. Drugs Aging 27:193–209
58. Takahashi P, Trang N, Chutka D, Evans J (2004) Antibiotic prescribing and outcomes following treatment of symptomatic urinary tract infections in older women. J Am Med Dir Assoc 5:S11–15
59. Albert X, Huertas I, Pereiró II, Sanfélix J, Gosalbes V, Perrota C (2004) Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. Cochrane Database Syst Rev CD001209
60. Raz R, Schiller D, Nicolle LE (2000) Chronic indwelling catheter replacement before antimicrobial therapy for symptomatic urinary tract infection. J Urol 164:1254–1258
61. Tenke P, Kovacs B, Bjerklund Johansen TE, Matsumoto T, Tambyah PA, Naber KG (2008) European and Asian guidelines on management and prevention of catheter-associated urinary tract infections. Int J Antimicrob Agents 31:68–78
62. Nicolle LE (2001) The chronic indwelling catheter and urinary infection in long-term-care facility residents. Infect Control Hosp Epidemiol 22:316–321
63. Lo E, Nicolle LE, Coffin SE, Gould C, Maragakis LL, Meddings J, Pegues DA, Pettis AM, Saint S, Yokoe DS (2014) Strategies to prevent catheter-associated urinary tract infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol 35:464–479
64. Pickard R, Lam T, Maclennan G et al (2012) Types of urethral catheter for reducing symptomatic urinary tract infections in hospitalised adults requiring short-term catheterisation: multicentre randomised controlled trial and economic evaluation of antimicrobial- and antiseptic-impregnated urethral catheters (the CATHETER trial). Health Technol Assess Winch Engl 16:1–197
65. Lam TBL, Omar MI, Fisher E, Gillies K, MacLennan S (2014) Types of indwelling urethral catheters for short-term catheterisation in hospitalised adults. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD004013.pub4
66. Cooper FPM, Alexander CE, Sinha S, Omar MI (2016) Policies for replacing long-term indwelling urinary catheters in adults. Cochrane Database Syst Rev 7:CD01115
67. Hisano M, Bruschini H, Nicodemo AC, Srougi M (2012) Cranberries and lower urinary tract infection prevention. Clinics 67:661–667
68. Avorn J, Monane M, Gurwitz JH, Glynn RJ, Choodnovskiy I, Lipsitz LA (1994) Reduction of bacteriuria and pyuria after ingestion of cranberry juice. JAMA 271:751–754
69. McMurdo MET, Bissett LY, Price RJG, Phillips G, Crombie IK (2005) Does ingestion of cranberry juice reduce symptomatic urinary tract infections in older people in hospital? A double-blind, placebo-controlled trial. Age Ageing 34:256–261
70. Gupta K, Stamm WE (1999) Pathogenesis and management of recurrent urinary tract infections in women. World J Urol 17:415–420

71. Beerepoot MJ, Geerlings SE, van Haarst EP, van Charante NM, ter Riet G (2013) Nonantibiotic prophylaxis for recurrent urinary tract infections: a systematic review and meta-analysis of randomized controlled trials. J Urol 190:1981–1989
72. Perrotta C, Aznar M, Mejia R, Albert X, Ng CW (2008) Oestrogens for preventing recurrent urinary tract infection in postmenopausal women. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD005131.pub2
73. Lotan Y, Daudon M, Bruyère F, Talaska G, Strippoli G, Johnson RJ, Tack I (2013) Impact of fluid intake in the prevention of urinary system diseases: a brief review. Curr Opin Nephrol Hypertens 22:S1–S10
74. Kranjčec B, Papeš D, Altarac S (2014) D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. World J Urol 32:79–84
75. Shi Y-B, Yin D (2017) A good sugar, D-mannose, suppresses autoimmune diabetes. Cell Biosci. https://doi.org/10.1186/s13578-017-0175-1
76. Wade D, Cooper J, Derry F, Taylor J (2019) Uro-Vaxom® versus placebo for the prevention of recurrent symptomatic urinary tract infections in participants with chronic neurogenic bladder dysfunction: a randomised controlled feasibility study. Trials 20:223
77. Wawrysiuk S, Naber K, Rechberger T, Miotla P (2019) Prevention and treatment of uncomplicated lower urinary tract infections in the era of increasing antimicrobial resistance—non-antibiotic approaches: a systemic review. Arch Gynecol Obstet 300:821–828
78. ICS (2018) The impact of the use of vaccine against recurrent urinary tract infections in frail elderly patients. https://www.urotoday.com/conference-highlights/2018-ics/106622-ics-2018-the-impact-of-the-use-of-vaccine-against-recurrent-urinary-tract-infections-in-frail-elderly-patients.html. Accessed 4 Jan 2020
79. Ramírez Sevilla C, Gómez Lanza E, Manzanera JL, Martín JAR, Sanz MÁB (2019) Active immunoprophyilaxis with uromune® decreases the recurrence of urinary tract infections at three and six months after treatment without relevant secondary effects. BMC Infect Dis 19:901
80. Aziminia N, Hadjipavlou M, Philippou Y, Pandian SS, Malde S, Hammadeh MY (2019) Vaccines for the prevention of recurrent urinary tract infections: a systematic review. BJU Int 123:753–768