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Urinary tract infections in the frail elderly: Issues for diagnosis, treatment and prevention★

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Abstract. Urinary tract infections (UTIs) are among the most common infections in frail elderly adults, whether they are community dwelling, live in long term care facilities (LTCFs) or are hospitalized. UTIs cause substantial morbidity and mortality in frail elderly men and women. While many major risk factors in these individuals may not be modifiable, improved attention to incontinence management, judicious use of antimicrobials and urinary catheters, and, in women, appropriate use of topical estrogen may be useful in reducing UTIs. Future strategies may also include the appropriate use of new urinary catheter technology and emerging vaccines.

Introduction

Urinary tract infections (UTIs) are among the most common infections in frail elderly adults, whether they are community dwelling, live in long term care facilities (LTCFs) or are hospitalized. For most healthy adults, UTIs may be a nuisance requiring short term antimicrobial therapy; however, in frail elderly adults, UTIs can result in bacteremia, systemic antimicrobial therapy, hospitalization, decreased functional status and death. In addition, frail elderly adults have unique issues regarding location of medical care (e.g., LTCFs), goals of medical care (e.g., curative vs. palliative), and biological response to infection. Consequently, this paper will provide an overview in the frail elderly regarding the epidemiology and pathogenesis of UTIs and review selected issues regarding diagnostic approach, management and prevention interventions.

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Definitions

Defining frailty

Differing concepts and definitions for frailty have been proposed [1]. Most of these include concepts of multi-system impairment, instability, progressiveness, and increased vulnerability to adverse events. Fried and colleagues summarized these concepts from a geriatric perspective, stating that frailty is "… a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems and causing vulnerability to adverse outcomes" [2]. Further, Fried et al. conceptualized a phenotype for frailty to include at least three of the following; weight or muscle loss, muscular weakness, poor endurance, slow walking speed or low activity. In a community living cohort of more than 5000 older (≥65 years) adults, 7% were frail by Fried's phenotypic definition. Using older adults who were not frail as a comparison, frail older adults had higher 3 year mortality (18% vs. 3%, $P = 0.001$) and 7-year mortality (43% vs. 12%, $P = 0.001$). In elderly adults (≥85 years), 25% were frail [3].

In addition to the concepts of frailty presented above, clinicians should also consider disability

among older adults. Currently, 74% of adults age ≥85 years have a disability, 58% have severe disability, and 35% require assistance for activities of daily living [3]. While not all older adults who have functional disability would be considered frail, the presence of disability may be an intermediate marker for individuals progressing to frailty.

UTI and asymptomatic bacteriuria

Normally, the urinary bladder is sterile. In frail older adults, the bladder can become colonized with bacteria, typically from the gastrointestinal tract [4]. Determining whether bacteriuria represents colonization or true infection is both difficult and controversial. Consequently, three potential definitions have been proposed: (1) symptomatic UTI (e.g., clinical syndrome + evidence of inflammation + bacteriuria); (2) asymptomatic UTI (e.g., no clinical syndrome + evidence of inflammation + bacteriuria); (3) asymptomatic bacteriuria (e.g., no clinical syndrome + no inflammation + bacteriuria). The microbiological diagnosis of bacteriuria is defined as a bacterial species present with $\geq 10^5$ cfu/ml from an appropriately collected urine specimen. Pyuria is defined as the presence of ≥5 WBCs per high power field on microscopy. Typically, clinical symptoms for the UTI syndrome are dysuria, flank pain, suprapubic pain, fever, cloudy urine, or urine with foul odor. In frail elderly, atypical symptoms may present with UTI such as altered mental status, new incontinence, urinary retention or nausea or vomiting.

The majority of frail elderly LTCF residents with bacteriuria also have pyuria without clinical symptoms of UTI [5]. Furthermore, treatment of asymptomatic bacteriuria with antimicrobial agents has not been shown to result in improved patient outcomes [6]. Currently, guidelines recommend against treatment of asymptomatic bacteriuria or asymptomatic UTI. Whether to treat for UTI when frail elderly patients have pyuria, bacteriuria, and atypical symptoms (e.g., altered mental status, decreased intake, new incontinence) remains controversial [5].

Epidemiology of UTIs in the elderly

In frail elderly, UTIs account for 25% of all community-acquired bacterial infections and 25–30% of all bacterial infections in institutionalized older adults [4, 7]. The prevalence of asymptomatic bacteriuria in the elderly is approximately 50% in women and 30% in men. Asymptomatic bacteriuria often spontaneously resolves in older adults. Whether and over what time period asymptomatic bacteriuria progresses to symptomatic UTI is an active area of investigation and is not completely understood [4, 7]. Among hospitalized patients, UTIs are the most common nosocomial infection accounting for 35% of all nosocomial infections [8]. In older women, recurrence after an initial UTI occurs in 60% of women within 10 years with 10% of women having ≥10 UTIs [9]. Women with recurrent UTIs have a higher 10 year mortality than women without recurrent UTIs (37% vs. 28%, $P < 0.001$) [9]. In older adults with septicemia, over 40% have UTIs as the presumed source [10]. Age alone is not independently associated with increased mortality from bacteremic UTI although exposure to a urinary catheter is [11].

Pathogenesis and risk factors

Factors associated with increased risk for UTI can be divided into three broad groups: bacterial factors, host factors, predisposing factors. Bacterial factors include the presence of virulence factors (e.g., proteases, hemolysins), specific bacterial adherence factors (e.g., fimbriae, pili) or nonspecific adherence factors (e.g., hydrophobicity, negative electrostatic charges) [12, 13]. Host factors include low pH, micturition dysfunction, and a thinning mucopolysaccharide layer in the urinary epithelium. Mechanical obstruction to urine flow through urinary obstruction or urinary stasis increases risk for colonization and subsequent mucosal invasion and infection. Functional host factors may include urinary tract abnormalities such as dysfunction of the uretero-vesicular valves or ureteral peristalsis. In women, hormonally mediated changes in vaginal pH and subsequently in vaginal flora impact both increase the risk of urinary tract colonization and infection. Finally, the density of adhesion-type receptors in urinary epithelium may play a role in modulating infection risk by impacting the likelihood that bacteria will adhere to bladder epithelium [12]. For all frail elderly, presence of a chronic indwelling urinary

catheter dramatically increases risk for bacteriuria, pyuria and symptomatic UTI, both primary and recurrent [12, 13].

Risk factors for recurrent UTI vary. In pre-menopausal women, major risk factors include sexual intercourse, spermicidal exposure, history of maternal UTI, or UTI in childhood [14]. In post-menopausal women, incontinence, cystocele, post-void residual urine, and any history of UTI in the post-menopausal period are risk factors for recurrent UTI. In institutionalized older adults, urinary catheterization and incontinence are risk factors for recurrent UTI as well as antimicrobial exposure and decreased functional status [14].

An important aspect of risk for infections in older adults to consider is the response and functionality of the immune system. Previous research has demonstrated that aging-related immune system changes include decreased humoral and cellular immune reactivity [15, 16]. In addition, age-related decreases in the specificity of the immune response and decreased discrimination between "self" and "non-self" occur. These changes lead to decreased ability to respond appropriately to new antigen challenge and to maintain immunologic memory. However, changes in immunity due exclusively to the aging process are relatively minor in impact when compared to the impact of co-morbid diseases such as diabetes mellitus, cancer, chronic renal disease and autoimmune or chronic inflammatory disorders. In addition, secondary causes of immune dysfunction include macronutrient and micronutrient malnutrition, metabolic changes (e.g., hyperglycemia) and selected medications (e.g., immunosuppressant) [15, 16]. Finally, host response to UTI is probably governed, at least in part, by interleukin-6 (Il-6). Bacteremic and febrile patients with UTI tend to have higher levels of Il-6 which also tends to grossly correlate with severity of disease [17].

Most UTIs in both women and men are caused by enteric, gram negative bacilli [18]. The most common single organism is *Escherichia coli* although *Proteus mirabilis*, *Klebsiella pneumoniae*, *Citrobacte*r spp., *Serratia* spp., and *Enterobacter* spp. are also isolated from frail elderly with UTIs. *Enteroocci* and *Staphylococcus* spp. are the most common gram positive cocci causing UTIs. Recent studies have demonstrated that *E. coli* with specific virulence genes (e.g., uropathogenic specific protein, iron) may be more likely to cause both UTI and pyelonephritis [19]. Furthermore, the ability of genetically different *E. coli* strains to cause bacteremia varies in human sub-populations, suggesting that host characteristics partially determine the virulence of individual *E. coli* strains [20].

Clinical diagnosis

Appropriate clinical diagnosis of symptomatic UTI in frail elderly individuals may be difficult. In institutionalized elderly, only 4–8% of residents with fever and bacteriuria have clinical findings consistent with UTI [21]. In residents with an indwelling urinary catheter, about 25% of individuals with fever and bacteriuria had UTI [21]. In cognitively impaired frail elderly, eliciting symptoms or signs referable to the urinary tract (e.g., dysuria, frequency, flank pain) can be extraordinary difficult. Using more non-specific symptoms (e.g., changes in mental status, decreased oral intake) can be misleading. In cognitively impaired elderly, new urinary incontinence should be considered as a potentially useful symptom or sign to indicate UTI, although further studies are needed to better define its sensitivity and specificity for predicting UTI.

Urinalysis (UA) in healthy, young adults is very useful in detecting UTIs. However, the presence of pyuria, either by direct microscopy (e.g., ≥5 WBCs on high powered field) or dipstick (e.g., positive leukocyte esterace) is less helpful in frail elderly. For example, in 214 chronically incontinent asymptomatic nursing home residents, 45% had pyuria and 43% had bacteriuria. Of those who had pyuria, 59% had bacteriuria but 31% did not [22]. In a study of newly catheterized hospitalized patients of all ages (mean age = 60 years), the positive predictive value of pyuria was 32% [23]. Use of pyuria or bacteriuria as indicators of UTI in frail elderly patients without clinical symptoms is not recommended.

Treatment

Guidelines are available regarding empiric antimicrobial selection in treating UTIs [24–26]. These guidelines can be used to guide antimicrobial selection but clinicians should also take into con-

sideration local antimicrobial susceptibility profiles and patient characteristics. In general, for older women with cystitis or uncomplicated UTI receiving treatment in an ambulatory setting, 3–7 days of trimethoprim-sulfamethoxazole (TMP-SMX) or a fluroquinolone is recommended. For older men with cystitis or lower tract UTI treated in an ambulatory setting, TMP-SMX or fluroquinolones for 7 days are suggested along with evaluation for urinary tract abnormality, prostatic abnormality, or bladder obstruction/dysfunction. For older men with acute prostatitis, longer therapy (e.g., 14 days) is recommended. Chronic prostatitis should be treated for 4–6 weeks. For older adults with catheter related UTI, UTIs associated with azotemia or obstruction or for UTI in a transplant patient, broad spectrum intravenous antimicrobial therapy targeted to usual pathogens (e.g., *Enterobacteriacea*, enterococci, *Pseudomonas aeruginosa*) is recommended, at least until culture results are available.

Prior to the initiation of antimicrobial therapy for UTIs in frail elderly, clinicians should consider several important questions [18]: (1) Is there a clinical indication for therapy in this patient?; (2) Has a urine specimen for UA and culture been collected prior to start of antimicrobial therapy? (3) Can therapy be postponed until UA and culture results are available? (4) For patients with recurrent UTIs, have the previous UA and culture results been reviewed? Once antimicrobial therapy is started, clinicians should plan to review both laboratory data and patient status at 48–72 hours. If studies suggest that UTI was not present or if the patient is not responding to therapy, then clinicians should reevaluate both the diagnosis of UTI and the choice of therapy. Finally, in frail elderly adults with recurrent symptomatic UTIs should undergo urologic evaluation to evaluate for urinary tract abnormalities that may require additional surgical or nonsurgical interventions.

Especially in frail elderly, clinicians should consider barriers to optimal therapy such as: (1) Can the patient take oral therapy or fluids? Oral intake may be inadequate so as to limit the use of oral antimicrobial therapy or increase the risk of complications (e.g., dehydration, azotemia); (2) Is the patient cognitively impaired? Cognitive impairment may mean that a care-giver must administer medications and will need instructions regarding the dosing and duration of therapy.

While substantial variability exists regarding antimicrobial resistance in pathogens causing UTIs, recent trends suggest both increasing resistance to commonly used antimicrobials and increased rates of multi-drug resistance among UTI-related bacterial isolates [27]. Previous treatment for UTI may increase the risk of infection with an antimicrobial resistant organism, especially in institutionalized frail elderly [18]. Recently, national outbreaks of TMP-SMX-resistant *E. coli* UTIs in relatively healthy adults suggest that antimicrobial resistance occurs not only due to widespread use of TMP/SMX, but also through cross-transmission of antimicrobial resistant clones [28, 29]. Cross-transmission of antimicrobial-resistant organisms is an especially important mechanism for frail elderly individuals in institutions (e.g., LTCFs) or who are hospitalized. Recently, the US Centers for Disease Control and Prevention have developed a campaign to prevent antimicrobial resistance through four strategies: (1) preventing infection by reducing risk factors (e.g., urinary catheters); (2) effectively diagnosing infection; (3) wise use of antimicrobial agents; (4) preventing transmission. Specific educational materials for clinicians have been developed for use when treating hospitalized adults, dialysis patients, and surgical patients. Materials will be available for long-term care residents in late spring 2004. Additional information and materials are available from the campaign website: http://www.cdc.gov/drugresistance/healthcare.

Current and emerging prevention strategies

Hormonal

In post-menopausal women, atrophic vaginitis is both relatively common and a significant risk factor for UTI. Vaginal topical estrogen has been used successfully to treat atrophic vaginitis, reduce bacteriuria, and decrease risk for UTIs in post-menopausal women [30]. However, there are barriers to acceptance of this therapy, especially in institutionalized women, since the intervention requires periodic administration of topical vaginal estrogen. An indwelling estradiol vaginal ring has also been shown to reduce recurrent UTI in post-menopausal women but may difficult to place and lead to local complications in some frail elderly

women [31]. In incontinent elderly women in nursing homes, oral estrogen with progestin was effective in improving atrophic vaginitis but not in improving continence or reducing UTIs [32]. More recently, an estriol pessary was not as effective as a pessary with nitrofurantoin in reducing UTIs in women. There were no changes in vaginal pH or vaginal lactobacillus colonization suggesting that the estrogenic effect of the estriol pessary may have been suboptimal when compared to previous studies using alternate delivery mechanisms for estrogen [33]. For frail elderly women with recurrent UTIs, clinicians should evaluate closely for atrophic vaginitis or chronic bacteriuria and, if present, consider treatment with topical estrogen therapy or an indwelling estradiol vaginal ring.

Urinary continence management

An important risk factor for UTIs in frail elderly individuals is the presence of urinary incontinence. A detailed discussion of the evaluation and management of urinary incontinence is beyond the scope of this review. However, key performance indicators for appropriate evaluation and management of urinary incontinence have been proposed recently and include [34]: (1) initial evaluation and identification of incontinence followed by targeted history taking, physical examination and diagnostic testing; (2) discussion of incontinence treatment options; (3) consideration of behavioral therapy; (4) appropriate use of urodynamic testing; (5) surgical intervention for selected patients with stress incontinence; (6) appropriate selection of patients with overflow incontinence who may require urinary catheters for management of incontinence [34]. In institutionalized elderly, prompted voiding and provider-feedback programs have been successful in improving continence management [35, 36].

Cranberry juice

Cranberry juice has been proposed as a preventive intervention for individuals with recurrent UTIs. Historically, the mechanism was thought to be due to increased urine acidity. In 2001, a systematic review of five studies found no evidence that cranberry juice prevented UTIs, however these studies were limited by low numbers, high dropout and overall poor quality [37]. Since the systematic review, results of two recent randomized controlled trials using cranberry juice extracts suggest that recurrent UTI may be reduced by as much as 20% [38, 39]. The proposed mechanism for this effect is that substances in the juice actually inhibit adherence by bacteria to urinary epithelium. However, additional clinical and basic research is needed to confirm and extend these results.

Urinary catheter technology

Urinary catheters are used to manage patients who have incontinence or obstruction to urinary drainage and increase risk for UTI dramatically. Primary prevention strategies have focused on improved incontinence management and removal of catheters. Unfortunately, many attending physicians may not be aware patients have urinary catheters, even when these catheters are considered inappropriate [40]. Programs to improve infection control in hospitalized patients have had some success in reducing both catheter use and UTI rates [41–43]. However, some frail elderly adults will require long-term, if not lifelong, urinary catheters for continence management and drainage, whether they reside in hospitals, nursing homes, or at home. In these patients, novel catheter technologies, such as antimicrobial and silver impregnated catheters, may be beneficial [44]. Compared to standard urinary catheters, trials of both antimicrobial – (e.g., nitrofurazone, minocycline-rifampin) or silver – impregnated catheters have demonstrated substantial reductions (30–70%) in bacteriuria and UTIs [45]. A recent decision analysis suggests that despite a higher catheter cost, use of silver impregnated catheters would probably be cost saving at a population level in addition to preventing UTIs [46].

Immunization

Vaginal mucosal immunization has proposed as a mechanism by which to stimulate mucosal antibody production so as to impair bacterial adherence on urinary epithelium [47, 48]. A current vaccine in development utilizes a mixture of 10 uropathogenic bacterial organisms and has been shown to reduce recurrent UTI by 30–40% [47, 48]. Because the mucosal vaccine would require several applications and the effect is relatively short-lived, this strategy, like administration of vaginal topical estrogen, has barriers in terms of care-giver

workload and acceptability. However, continued investigation and vaccine development in this area could lead holds promise for a more acceptable vaccine strategy for frail elderly women.

Conclusion

UTIs cause substantial morbidity and mortality in frail elderly men and women. While many major risk factors in these individuals may not be modifiable, improved attention to incontinence management, judicious use of antimicrobials and urinary catheters, and, in women, appropriate use of topical estrogen may be useful in reducing UTIs. Future strategies may also include the appropriate use of new urinary catheter technology and emerging vaccines.

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