Complicated urinary tract infection in adults

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BACKGROUND: Complicated urinary tract infection occurs in individuals with functional or structural abnormalities of the genitourinary tract.
OBJECTIVE: To review current knowledge relevant to complicated urinary tract infection, and to provide evidence-based recommendations for management.
METHODS: The literature was reviewed through a PubMed search, and additional articles were identified by journal reference review. A draft guideline was prepared and critically reviewed by members of the Association of Medical Microbiology and Infectious Disease Canada Guidelines Committee, with modifications incorporated following the review.
RESULTS: Many urological abnormalities may be associated with complicated urinary infection. There is a wide spectrum of potential infecting organisms, and isolated bacteria tend to be more resistant to antimicrobial therapy. Morbidity and infection outcomes in subjects with complicated urinary infection are principally determined by the underlying abnormality rather than the infection. Principles of management include uniform collection of a urine specimen for culture before antimicrobial therapy, characterization of the underlying genitourinary abnormality, and nontreatment of asymptomatic bacteriuria except before an invasive genitourinary procedure. The antimicrobial regimen is determined by clinical presentation, patient tolerance, renal function and known or anticipated infecting organisms. If the underlying abnormality contributing to the urinary infection cannot be corrected, then early post-treatment recurrence of infection is anticipated.
CONCLUSIONS: The management of complicated urinary infection is individualized depending on patient variables and the infecting organism. Further clinical investigations are necessary to assist in determining optimal antimicrobial regimens.

Key Words: *Antimicrobials; Complicated; Guidelines; Urinary infection*

Des infections urinaires récurrentes chez les adultes

HISTORIQUE : Des infections urinaires récurrentes s'observent chez des personnes ayant une anomalie fonctionnelle ou structurelle de l'appareil génito-urinaire.
OBJECTIF : Analyser les connaissances actuelles sur les infections urinaires récurrentes et fournir des recommandations probantes de prise en charge.
MÉTHODOLOGIE : Les publications ont été analysées au moyen d'une recherche dans PubMed, et d'autres articles ont été repérés par un examen des références des magazines scientifiques. Un projet de lignes directrices a été préparé et a fait l'objet d'une révision critique par les membres du comité des lignes directrices de l'Association pour la microbiologie médicale et l'infectiologie Canada. Les modifications découlant de la révision ont été incorporées au texte.
RÉSULTATS : De nombreuses anomalies urologiques peuvent s'associer à des infections urinaires récurrentes. Il existe un vaste spectre d'organismes infectieux potentiels, et les bactéries isolées ont tendance à résister davantage à la thérapie antimicrobienne. Les issues de la morbidité et de l'infection chez les sujets atteints d'infections urinaires récurrentes sont principalement déterminées par l'anomalie sous-jacente plutôt que par l'infection. Les principes de prise en charge incluent un prélèvement uniforme d'urine en vue d'une uroculture avant la thérapie antimicrobienne, la caractérisation de l'anomalie génito-urinaire sous-jacente et le non-traitement de la bactériurie asymptomatique, sauf en prévision d'une intervention génito-urinaire effractive. Le schéma antimicrobien est déterminé par la présentation clinique, la tolérance du patient, la fonction rénale et les organismes infectieux connus ou anticipés. Si l'anomalie sous-jacente qui contribue à l'infection urinaire ne peut être corrigée, une récurrence rapide de l'infection est à prévoir après le traitement.
CONCLUSIONS : La prise en charge des infections urinaires récurrentes est personnalisée selon les variables propres au patient et à l'organisme infectieux. D'autres explorations cliniques s'imposent pour contribuer à déterminer la thérapie antimicrobienne.

The present guideline addresses current knowledge regarding complicated urinary tract infection in adults, and reviews evidence relevant to management. Recommendations are developed based on published clinical trials, where available. The level of evidence is rated using Infectious Diseases Society of America criteria (Table 1) (1). The target audience for the present paper is all physicians who manage patients with complicated urinary infection. The management of pregnant women is not addressed.

DEFINITIONS

A complicated urinary tract infection is a urinary infection occurring in a patient with a structural or functional abnormality of the genitourinary tract. For the purposes of the present guideline, urinary infection in pregnant women is not considered to be complicated urinary infection, and is therefore not addressed. The quantitative criteria of at least 10^8 colony-forming units (cfu)/L (at least 10^5 cfu/mL) is generally appropriate for the microbiological identification of complicated

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TABLE 1
Strength of recommendations and quality of evidence

Category	Definition
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for or against use
Grade	
I	Evidence from at least one properly randomized, controlled trial
II	Evidence from at least one well-designed clinical trial without randomization from cohort or case-controlled analytical studies, or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities that is based on clinical experience, descriptive studies or reports of expert committees

Data from reference 1

urinary infection (2). For asymptomatic women, two consecutive urine specimens with the same organism(s) isolated is the recommended criteria. Recurrent urinary infection, either through relapse or reinfection, is common in patients who experience complicated urinary infection. A relapse is a recurrent infection with an organism similar to the pretherapy isolate, usually following persistence of the organism in the genitourinary tract. A reinfection is a recurrent infection with a new organism.

CHARACTERISTICS OF COMPLICATED URINARY TRACT INFECTION

Genitourinary abnormalities

A wide variety of genitourinary abnormalities may be associated with complicated urinary infection (Table 2) (3). The most common determinant of infection is interference with normal voiding, leading to impaired flushing of bacteria from the genitourinary tract. Mechanisms of infection include obstruction with incomplete urinary drainage, persistence of bacteria in biofilm on stones or indwelling devices (4), or increased introduction of organisms into the genitourinary tract through instrumentation. The risk of infection varies with different abnormalities. For instance, a chronic indwelling catheter is uniformly associated with bacteriuria (5), while infection complicating a single obstructing ureteric stone may be transient, especially with stone removal.

Patient population

Complicated urinary infection occurs in both women and men, and in any age group. Because uncomplicated urinary infection is rare in men, any male urinary infection is usually considered complicated (6). Recurrent urinary infection in postmenopausal women is associated with genetic and behavioural risk factors similar to those in younger women with acute uncomplicated urinary infection, including a greater likelihood of being a nonsecretor and history of prior urinary infection (7). However, postmenopausal women with recurrent urinary infection are also more likely to have increased residual urine volume, cystoceles and prior genitourinary surgery than are women without infection, and these associations are consistent with complicated infection. Thus, as a population, postmenopausal women with recurrent urinary infection encompass elements consistent with both uncomplicated and complicated urinary infection.

TABLE 2
Structural and functional abnormalities of the genitourinary tract associated with complicated urinary infection

Obstruction	Ureteric or urethral strictures
	Tumours of the urinary tract
	Urolithiasis
	Prostatic hypertrophy
	Diverticulae
	Pelvicalyceal obstruction
	Renal cysts
	Congenital abnormalities
Instrumentation	Indwelling urethral catheter
	Intermittent catheterization
	Ureteric stent
	Nephrostomy tube
	Urological procedures
Impaired voiding	Neurogenic bladder
	Cystocele
	Vesicoureteral reflux
	Ileal conduit
Metabolic abnormalities	Nephrocalcinosis
	Medullary sponge kidney
	Renal failure
Immunocompromised	Renal transplant

Clinical presentation

Asymptomatic urinary infection, or asymptomatic bacteriuria, is the most common clinical presentation of complicated urinary infection. In some populations, the prevalence of bacteriuria is very high, reaching 100% in patients with chronic indwelling catheters (5), 30% to 40% in patients with a neurogenic bladder managed by intermittent catheterization (8), and 50% in elderly nursing home residents (9). The clinical presentation of symptomatic infection in patients with complicated urinary infection varies across a wide spectrum, ranging from mild lower tract irritative symptoms, such as frequency and urgency, to severe systemic manifestations, such as bacteremia and sepsis. Complete urinary obstruction or trauma to the bacteriuric genitourinary tract, especially with hematuria, appear to be associated with more severe clinical presentations.

Infecting organisms

A wide variety of organisms are isolated from patients with complicated urinary infection (Table 3) (10-15). *Escherichia coli* is the most common organism isolated, but is isolated more frequently in women than in men (9,16,17). *E coli* strains isolated from symptomatic patients with complicated urinary infection have a lower prevalence of genetic or phenotypic virulence characteristics and are less likely to originate from a uropathogenic clone than strains isolated from patients with acute uncomplicated infection (18). This observation is consistent with the host abnormality being the principal determinant of infection, with organism factors less important. Many other Gram-negative organisms are isolated from complicated urinary infection (Table 3). Urease-producing organisms such as *Proteus mirabilis*, *Providencia stuartii* and *Morganella morganii* are common, especially in patients with indwelling urological devices. Chronic *Pseudomonas aeruginosa* infection is problematic for

TABLE 3
Organisms isolated from populations with complicated urinary tract infection (UTI)

	Population (reference)*					
Organism isolated	Chronic catheter, women (10)	Intermittent catheter (11)	Complicated UTI (12)	Hospitalized (13)	Short-term catheter (14)	Elderly institutionalized men (15)
Escherichia coli	39	35	60	35	10	15
Klebsiella pneumoniae	21	26	11	15	NS	8.2
Proteus mirabilis	55	16	5.3	7.5	6	42
Providencia species	58	10	0	–	NS	22
Pseudomonas aeruginosa	32	23	2.2	12	12	27
Other Gram-negative organisms†	39	36	19.5	24	4	9.4
Enterococcus species	NS	10	6.8	1.1	12	7.1
Group B streptococcus	NS	1.4	–	1.1	NS	2.4
Coagulase-negative staphylococcus	NS	1.4	1.5	1.1	24	2.4
Other Gram-positive organisms	39	5.8	2.3	0.6	4	3.5
Yeast	NS	NS	NS	NS	28	NS

**Expressed as a percentage of patients. Patients may have more than one organism isolated; †Includes* Citrobacter *species,* Enterobacter *species,* Morganella morganii*,* Serratia marcescens*, and nonfermenters other than* P aeruginosa*. NS Not stated*

some patients. Enterococci and coagulase-negative staphylococci are the most common Gram-positive organisms. These organisms are isolated more frequently from asymptomatic infection, and are associated with lower levels of pyuria (19,20). *Candida* species are also frequently isolated. Elderly patients and patients with chronic urological devices often have polymicrobial bacteriuria (9,10).

Organisms isolated from patients with complicated urinary infection tend to be more resistant to antimicrobials than strains isolated from uncomplicated urinary infection (21). Strains of common uropathogens with acquired resistance, such as *E coli*, and organisms with intrinsic resistance, such as *P aeruginosa* and yeast, are both isolated. Repeated antimicrobial courses in patients with recurrent infection and nosocomial acquisition through urological interventions contribute to the increased prevalence of resistance (22).

Complications of infection

Acute urinary infection may be associated with severe morbidity, such as septic shock or even death. Acute or chronic infection is occasionally associated with suppurative complications, such as paraurethral abscesses, renal or perirenal abscess, and metastatic infection including bone and joint infection or endocarditis. These complications, however, are relatively uncommon and are more likely to occur in patients with comorbidities such as diabetes, those with chronic urological devices, or those with urinary obstruction (23,24). Renal failure was previously a common cause of death in spinal cord injury patients with recurrent urosepsis. Current management strategies that maintain a low bladder pressure prevent reflux and progression to renal failure, despite a continued high incidence of urinary infection experienced by these patients (8). When renal failure occurs in patients with complicated urinary infection, deterioration in renal function is usually attributable to the underlying urological defect rather than infection.

PRINCIPLES OF MANAGEMENT

Clinical assessment

The clinical presentation may be straightforward for symptomatic patients. Acute lower tract irritative symptoms include frequency, urgency, dysuria, suprapubic discomfort, and new or increased incontinence. Acute pyelonephritis presents with costovertebral angle pain or tenderness, often with fever, and variable lower tract symptoms. Some patients with neurological illnesses may be more difficult to assess because of atypical presentations (8,25,26). Patients with spinal cord injuries may present with symptoms such as increased bladder and leg spasms (8) or autonomic dysreflexia (25), and patients with multiple sclerosis may experience increased fatigue and deterioration in neurological function (26). The individual patient often experiences consistent symptoms with each episode and will frequently attribute specific complaints to urinary infection. Cloudy or foul-smelling urine is often interpreted by patients and caregivers as urinary infection. While these findings may accompany bacteriuria, they are not diagnostic of symptomatic infection (27). The identification of symptomatic infection in patients with chronic symptoms or impaired communication, such as long-term care facility patients, is more problematic. Clinical deterioration without genitourinary-localizing symptoms is seldom due to urinary infection in residents without a chronic indwelling catheter (28). Fever without localizing findings is, however, a common presentation of urinary infection in patients with chronic indwelling catheters.

Urine culture

A urine specimen for culture obtained before the initiation of antimicrobial therapy confirms the diagnosis of urinary infection and identifies the infecting organism and susceptibilities. The wide variety of potential infecting organisms and increased likelihood of more resistant organisms makes the urine culture essential for optimal antimicrobial management. A quantitative count of at least 10^8 cfu/L in a voided specimen is consistent with infection in the noncatheterized patient (2). For a urine specimen obtained by in and out catheterization, any quantitative count of a potential uropathogen is considered consistent with infection. A quantitative count of at least 10^5 cfu/L is sufficient for a microbiological diagnosis in urine specimens obtained by intermittent catheterization (29), or in patients with short-term (30) or long-term (10) indwelling catheters.

TABLE 4
Prevalence of asymptomatic bacteriuria in populations at risk for symptomatic episodes of complicated urinary infection

Population (reference)	Prevalence of bacteriuria (%)
Elderly (9)	
Community	
Women	6–17
Men	1.5–15
Institutionalized	
Women	27–57
Men	19–37
Catheterized	
Intermittent (31)	38–58
Short-term indwelling (32)	9–23
Chronic indwelling (10)	100
Ureteral stents (33)	45–100

A positive urine culture confirms, but is not diagnostic of, symptomatic urinary infection. In populations with a high prevalence of asymptomatic bacteriuria (Table 4) (31-33), a positive urine culture has a low positive predictive value for symptomatic infection. For instance, in noncatheterized bacteriuric elderly institutionalized patients with fever and no localizing signs or symptoms, bacteriuria has only a 10% positive predictive value for a urinary source of fever (28). A negative urine culture, however, has a high negative predictive value, and is useful to exclude urinary infection.

Urinalysis

Symptomatic urinary infection is usually accompanied by pyuria identified by urinalysis or a positive leukocyte esterase dipstick test. However, pyuria is also present in most patients with asymptomatic bacteriuria (9,19,29). Noninfectious causes of urinary tract inflammation in patients at risk for complicated urinary infection are also characterized by pyuria. Thus, pyuria is consistent with, but not diagnostic of, urinary infection, and pyuria in the bacteriuric patient does not identify symptomatic infection. There is, however, a high negative predictive value for pyuria, and a urinalysis without pyuria may reliably exclude symptomatic urinary infection (34,35). White blood cell casts are found on urinalysis in some subjects with renal infection. They are, however, nonspecific, and present in interstitial nephritis and other tubulointerstitial disorders with inflammation, in addition to infection.

Characterization of underlying abnormality

Recurrent infection may be prevented if the genitourinary abnormality that promotes infection can be corrected. The abnormality may be apparent – for example, a spinal cord injury patient managed with intermittent catheterization or a patient with an ileal conduit or nephrostomy tube. Where complicated urinary infection is suspected but abnormalities have not been defined, a diagnostic investigation to characterize the potential underlying abnormality is indicated. The diagnostic approach will be determined by the patient history, clinical presentation and access to testing. Diagnostic imaging may include renal and pelvic ultrasound, intravenous pyelography, computed tomography or magnetic resonance imaging. Urological assessment such as cystoscopy, retrograde pyelography or urodynamic studies may also be indicated.

Patients presenting with severe clinical presentations such as sepsis, or those who fail to respond to initial therapy, may require urgent evaluation to exclude an obstructed urinary tract or abscess, which may require drainage. Men who present with a first urinary infection without prior genitourinary instrumentation frequently have an abnormality identified following investigations (6). For healthy young women with recurrent cystitis or acute pyelonephritis, however, investigations have a low diagnostic yield and are not routinely recommended (36). Postmenopausal women with a new onset or increased frequency of recurrent infection should be assessed to characterize abnormalities, such as bladder diverticula or cystoceles (7). Recurrent infection following a bladder suspension or other gynecological surgery may suggest bladder outlet obstruction, and urodynamic studies may be appropriate. Patients with a previously characterized abnormality and increased frequency or severity of symptomatic episodes may require repeat evaluation to exclude new or progressive abnormalities.

ANTIMICROBIAL THERAPY

Asymptomatic urinary infection

Prospective, randomized trials of treatment or no treatment of asymptomatic bacteriuria consistently conclude that antimicrobial therapy for asymptomatic bacteriuria is not beneficial in most populations (Table 5) (37-44). Clinical trials have documented no benefit for the treatment of asymptomatic bacteriuria in subjects with chronic indwelling catheters (42), elderly men or women residing in nursing homes (17,37-39), patients with spinal cord injury managed with intermittent catheterization (41) and women with diabetes (44). These studies also document harmful outcomes with antimicrobial therapy, including adverse drug effects and reinfection with more resistant organisms.

A prospective, randomized, placebo-controlled trial (43) addressed treatment of asymptomatic catheter-acquired bacteriuria persisting 48 h following catheter removal in women. Within 14 days, 36% of placebo recipients had spontaneous resolution of bacteriuria, but 26% of recipients with persistent bacteriuria developed symptoms. Women younger than 60 years of age or those infected with Gram-positive organisms were more likely to have spontaneous resolution. In the treatment arm, single-dose and 10-day trimethoprim-sulfamethoxazole (TMP/SMX) therapy were equivalent for cure. Older women were significantly less likely to be cured with any duration of treatment. Thus, young women with persistent catheter-acquired bacteriuria with a Gram-negative organism following catheter removal may benefit from treatment of bacteriuria. An alternate approach – to treat only if symptoms develop – has not been evaluated in clinical trials.

Periodically screening urine cultures, with treatment of asymptomatic bacteriuria if present, is recommended for renal transplant patients, especially in the initial post-transplant period (45). Prophylactic antimicrobial therapy given both perioperatively and on a continuing basis to prevent *Pneumocystis carinii* pneumonia and other infections is now routine practice for solid organ transplant recipients (46). Prophylaxis decreases the occurrence of symptomatic and asymptomatic urinary infection from 30% to 60% to less than

TABLE 5
Prospective, randomized trials of treatment (T) or nontreatment (NT) of asymptomatic bacteriuria in patients at risk of complicated urinary tract infection (UTI)

Population (reference)	Patients studied	Study duration	Outcomes
Elderly institutionalized men (15)	16 T, 20 NT	24 months	No differences in symptomatic infection or mortality
Elderly institutionalized women (37)	26 T, 24 NT	12 months	No differences in symptomatic UTI, mortality; with therapy, adverse drug effects increase, and resistance with reinfection increases
Elderly institutionalized women (38)	358	8.5 years	No difference in mortality
Elderly institutionalized women (39)	33 T, 38 NT	3 days	No improvement in chronic incontinence with antibiotic treatment
Elderly women, geriatric apartment (40)	63 T, 61 NT	6 months	No significant decrease in symptomatic UTI with treatment
Intermittent catheter (41)	27 NT	Mean 42 days	Similar rates of recurrent symptomatic UTI in treated and not treated
	19 T	Mean 44.4 days	
Chronic indwelling catheter (42)	17 T	Mean 32 weeks	Infection: 0.63/week for T and 0.61/week for NT;
	18 NT	Mean 26.5 weeks	Fever: 0.18 days/week for T and 0.22 days/week for NT; Strains resistant to cephalexin: 64% for T and 25% for NT
Women, postcatheter removal (43)	70 T, 42 NT	6 weeks	Therapy significantly decreases symptomatic infection within 14 days for women younger than 60 years of age
Diabetic women (44)	55 T, 50 NT	36 months	No difference in symptomatic UTI or complications of diabetes; increased adverse antimicrobial effects with therapy

5% of patients (47). Recent studies report no association between asymptomatic bacteriuria and renal graft loss (48,49). Bacteriuric patients with graft loss also experience recurrent symptomatic urinary infection, and graft loss appears to be attributable to urological abnormalities rather than infection (50). Thus, with current management following renal transplant, it is not clear what additional benefit is achieved by screening for or treating bacteriuria.

There is a high likelihood of postprocedure bacteremia and sepsis when bacteriuria is present at the time of trauma to the genitourinary mucosa. As many as 25% of bacteriuric men experience bacteremia following cystoscopy, and 80% following open prostatectomy (51). Ten per cent to 16% of patients with postprocedure bacteremia progress to sepsis (52). These complications are minimized by treatment of asymptomatic bacteriuria to achieve sterile urine at the time of the procedure (51-53). Conceptually, this is prophylaxis to prevent sepsis rather than treatment of asymptomatic bacteriuria. Antimicrobial therapy may be initiated immediately before the procedure. The range of urological procedures for which pretreatment is indicated remains controversial. Treatment is recommended for transurethral resection of the prostate, open prostatectomy, laser prostatectomy and cystoscopy in men (51). Catheter change in patients with chronic indwelling catheters is seldom associated with fever, and antimicrobial treatment before chronic urethral catheter replacement is not recommended (54,55). Perioperative antibiotics may not prevent bacteremia accompanying nephrostomy tube replacement (56). The role of antimicrobial therapy to prevent complications with this intervention requires further evaluation.

Symptomatic infection

Antimicrobial selection: The wide variety of potential infecting organisms and increased likelihood of resistance make uniform recommendations for empirical therapy problematic. Wherever possible, antimicrobial therapy should be delayed pending results of urine culture and organism susceptibility, so specific therapy can be directed at the known pathogen. Where empirical therapy is initiated, the antimicrobial choice should be reassessed once culture results become available, usually within 48 h to 72 h.

Many comparative clinical trials of treatment of complicated urinary infection have been reported. Evaluation of these studies is frequently compromised by variability in study subjects, small sample size, lack of blinding or placebo control, variable follow-up and exclusion of patients with resistant isolates. Published reports in English describing comparative studies of adequate sample size with at least short-term follow-up (five to nine days post-therapy) are summarized in Table 6 (57-84).

These studies generally report equivalent outcomes for the comparative arms. Because patients with resistant isolates are usually excluded from evaluation, the relevance of these studies to empirical antibiotic therapy is not clear. Most reports compare two fluoroquinolone antimicrobials or a fluoroquinolone with an antimicrobial of another class. Comparative trials of fluoroquinolones usually report equivalence, but sparfloxacin was found to be less effective than ciprofloxacin at short-term outcome in one study (70). Sparfloxacin is primarily metabolized rather than excreted in the urine, suggesting that fluoroquinolones that achieve high urinary levels are preferred for treatment. Norfloxacin, which has low tissue levels but high urinary levels, was as effective as other fluoroquinolones that achieve higher tissue levels (50,75-77). In two reported studies (73,80), treatment with a fluoroquinolone was superior to TMP/SMX. Comparative studies including older antimicrobials are limited, but some of these agents remain useful for the treatment of selected patients. Amoxicillin or ampicillin remains the therapy of choice for susceptible enterococci and group B streptococcal infection. Nitrofurantoin is effective for the treatment of lower tract infections, including vancomycin-resistant enterococci. This agent is, however, not effective for the treatment of upper tract infection, or for infection with *Klebsiella pneumoniae*, *P mirabilis* or *P aeruginosa*, and should be avoided in patients with renal failure.

TABLE 6
Comparative clinical trials of complicated urinary tract infection (UTI)

		Outcomes (% cured)				
		Short-term (5–9 days post)		Long-term (4–6 weeks post)		
Trial (reference)	Regimens (n)	Micro	Clin	Micro	Clin	Comments
Blinded, ITT (57)	Prulifloxacin 600 mg od, 10 d (98);	98.00	94.80	82.30	83.40	
	Ciprofloxacin 500 mg bid, 10 d (108)	93.50	93.30	79.10	82.10	
Blinded, ITT (58)	Ciprofloxacin 1 g od ER, 7 d – 14 d (379);	89.20	89.90	67.80	76.70	
	Ciprofloxacin 500 mg bid, 7 d – 14 d (407)	81.40	88.90	55.20	73.40	
Blinded, ITT (59)	Gatifloxacin 200 mg od, 5 d – 14 d (274);	77.00	69.00	70.00	71.00	Pyelonephritis, 30% of subjects
	Gatifloxacin 400 mg od, 5 d – 15 d (280);	78.00	70.00	71.00	70.00	
	Ciprofloxacin 500 mg bid, 5 d – 14 d (269)	73.00	65.00	69.00	74.00	
Open (60)	Ciprofloxacin 500 mg bid, 2 weeks (38);	89.00	92.00	75.00	83.00	Men only, presenting with fever and UTI
	Ciprofloxacin 500 mg bid, 4 weeks (4)	97.00	92.00	85.00	88.00	
Blinded (61)	Ertapenem 1 g od × 3 d oral;	85.60	85.60	NS	NS	Pyelonephritis, 52% of subjects
	Ceftriaxone 1 g od × 3 d oral	84.90	84.90	NS	NS	
Blinded, susceptible only (62)	Gatifloxacin 400 mg od, 7 d – 10 d (189);	92.00	92.00	75.00	84.00	
	Ciprofloxacin 500 mg bid, 7 d – 10 d (183)	83.00	93.00	63.00	74.00	
Blinded, susceptible only (63)	Ertapenem 1 g od, ≥3 days* (78);	92.00	NS	75.00	NS	*Oral ciprofloxacin
	Ceftriaxone 1 g od, ≥3 days* (90)	93.00	NS	78.00	NS	
Blinded, ITT (64)	Piperacillin/tazobactam 2 g/0.5 g q8h, 5d – 14d (161);	57.80	83.00	49.10	65.20	Pyelonephritis, 12% subjects
	Imipenem 500 mg q8h, 5 d – 14 d (166)	48.60	79.90	48.60	66.90	
Blinded placebo, ITT (65)	Ciprofloxacin 250 mg bid, 7 d (214);	90.10	97.20	77.10	87.70	Women only, post-menopausal
	Ofloxacin 200 mg bid, 7 d (88)	87.20	97.20	76.10	87.30	
ITT (66)	Ciprofloxacin 500 mg od, 7 d – 20 d (75);	84.00	97.30	77.80	82.00	Significantly increased rate
	Ciprofloxacin 250 mg bid, 7 d – 20 d (88)	90.90	95.50	77.50	80.00	of superinfection with 500 mg od
ITT (67)	Levofloxacin 250 mg od, 7 d – 10 d (171);	95.50	84.80	NS	NS	
	Lomefloxacin 400 mg od, 14 d (165)	92.10	82.40	NS	NS	
ITT (68)	Fleroxacin 400 mg od, 7 d – 14 d (103);	81.00	91.00	>70.00	NS	
	Ciprofloxacin 500 mg bid, 7 d – 14 d (108)	80.00	92.00	>70.00	NS	
Susceptible only (69)	Lomefloxacin 400 od, 15 d (149);	87.00	85.00	NS	NS	Acute pyelonephritis, 27% of subjects.
	Ciprofloxacin 500 mg bid, 15 d (129)	81.00	76.00	NS	NS	
Blind, ITT (70)	Sparfloxacin 200→100 mg od, 10 d – 14 d (252);	72.60	88.60	62.90	85.80	Short-term: End of treatment;
	Ciprofloxacin 500 mg bid, 10 d – 14 d (264)	81.40	85.40	67.40	84.80	Long-term: ≥21 days post-therapy
ITT, susceptible only (71)	Meropenem 500 mg q8h (116);	73.00	90.00	53.00	59.00	Short-term: End of treatment;
	Imipenem/cilastatin 500 mg q6h (82)	58.00	90.00	39.00	49.00	Long-term: ≥21 days post-therapy. P=0.002
Susceptible only (72)	Enoxacin 400 mg q12h, 10 d – 14 d (100);	96.50	92.10	86.10	98.00	
	TMP/SMX 160/800 mg q12h, 10 d – 14 d (95)	94.70	100	75.60	100	
Blinded ITT (73)	Lomefloxacin 400 mg od 10 d – 14 d (68);	91.00	96.00	73.00	90.00	
	TMP/SMX 160/800 mg bid, 10 d – 14 d (65)	57.00	91.00	47.00	77.00	
Susceptible only (74)	Fleroxacin 400 mg od IV, 4 d – 21 d (320);	94.00	86.00	NS	NS	
	Ceftazidime 0.5 g – 2 g tid or 1 g – 2 g bid, 4 d – 21 d (154)	95.00	89.00	NS	NS	
Blinded susceptible only (75)	Fleroxacin 400 mg od × 10 d (163);	94.00	90.80	80.00	NS	
	Norfloxacin 400 mg bid × 10 d (163)	92.00	87.70	73.00	NS	
Blind placebo control susceptible only (76)	Fleroxacin 400 mg od × 10 d (94);	98.00	96.00	NS	NS	29% of patients had uncomplicated UTI
	Norfloxacin 400 mg bid × 10 d (96)	89.00	84.00	NS	NS	
Blinded placebo susceptible only (77)	Fleroxacin 200 mg od × 10 d (71);	96.00	86.00	NS	NS	
	Fleroxacin 400 mg od × 10 d (61);	92.00	95.00	NS	NS	
	Norfloxacin 400 mg bid × 10 d (58)	90.00	86.00	NS	NS	
Susceptible only (78)	Cefpirome 1 g IV q12h ≥5 d (594);	89.4*	86.30	79	NS	*Two to 15 days after antibiotic
	Ceftazidime 1 g IV q12h ≥5 d (303)	87.00	82.10	76	NS	

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TABLE 6 – CONTINUED
Comparative clinical trials of complicated urinary tract infection (UTI)

		Outcomes (% cured)				
		Short-term (5–9 days post)		Long-term (4–6 weeks post)		
Trial (reference)	Regimens (n)	Micro	Clin	Micro	Clin	Comments
ITT, susceptible only (79)	Ciprofloxacin 500 mg oral q12h, 7 d – 10 d (37);	63*	81.00	21	69	51% had indwelling catheter
	Aminoglycoside 1 mg/kg – 1.7 mg/kg q8h, 7 d – 10 d (28)	15*	82.00	23	58	No significant difference in time to retreatment; resistance emergence in 62%, 70% of failures. P<0.001
Susceptible only (80)	Ciprofloxacin 200 mg q12h IV ≥2 d → 500 mg po bid, 14 d (38);	100†	100	92	NS	*More ceftazidime patients had renal failure at enrollment (P=0.018);
	Ceftazidime 500 mg IV q8h ≥4 d* (39)	87.00	92.00	88	NS	†Short term is end of therapy (P=0.003)
Blinded (81)	Enoxacin 400 mg bid, 14 d (89);	93.00*	100			*P=0.03
	TMP/SMX 160/800 mg bid, 14 d (88)	83.00*	98.00			
Blinded (82)	Ceftazidime 500 mg q12h, 7 d – 12 d (27);	74.00*	NS	42	NS	*P=0.079
	Moxalactam 500 mg q12h (2 g q12h) 7 d – 12 d (27)	52.00*	NS	50	NS	
Susceptible only (83)	Netilmicin 2 mg/kg q12h, ≥5 d (116);	94.00*	NS	NS	NS	*P=0.037
	Cefoperazone 1 g to 2 g q12h, ≥5 d (116)	56.00*	NS	NS	NS	
Blinded (84)	Cefoperazone 1 g bid, 5 d (116);	68.20*	59.50*	NS	NS	*P<0.05
	Carbenicillin 2 g bid, 5 d (116)	50.00	30.20	NS	NS	

bid Twice a day; Clin Clinical; d Days; ER Extended release; ITT Intent to treat; IV Intravenous; Micro Microbiological; NS Not stated; od Once daily; po By mouth; q6h Every six hours; q8h Every eight hours; q12h Every 12 hours; TMP/SMX Trimethoprim-sulfamethoxazole

Patients with symptomatic infection can usually be treated with oral therapy (85). Patients who are hemodynamically unstable, unable to tolerate oral medication, or in whom gastrointestinal absorption is impaired, require parenteral therapy. Clinical trials of parenteral therapy for complicated urinary infection have reported efficacy for a wide variety of agents, but there are limited comparative studies. Aminoglycosides (79,83,86), fluoroquinolones (74,79,85,87), piperacillin/tazobactam (64,88,89), ceftazidime (74,78,80,82) and carbapenems (61,64,71,82) have all been reported to achieve high rates of clinical and microbiological cure.

Duration of therapy: The optimal duration of antimicrobial therapy for the treatment of acute symptomatic episodes has not been systematically studied. Because of the wide variation in underlying abnormalities and clinical presentations, a uniform recommendation for treatment duration is likely not appropriate. Most clinical trials have evaluated seven to 14 days of therapy, but as short as five days and as long as 20 days have been reported (Table 6). A prospective randomized clinical trial (90) of three or 14 days of ciprofloxacin therapy in spinal cord injury patients reported fewer symptomatic relapses post-therapy with the 14-day treatment. In another prospective randomized trial, men presenting with febrile urinary tract infection had similar outcomes with either two or four weeks of ciprofloxacin therapy (60). A seven-day regimen is currently suggested for patients presenting with symptoms consistent with lower tract infection, and a longer course of 10 to 14 days is recommended for patients with more severe presentations manifested by fever, bacteremia or hypotension.

Anticipated outcome: The natural history of untreated symptomatic complicated urinary infection has not been reported. Successful antimicrobial therapy will usually ameliorate symptoms promptly, with substantial clinical improvement in 48 h to 72 h. Patients who fail to respond in this time frame should be reassessed to exclude urinary obstruction or abscess (which may require drainage), to exclude resistance of the infecting organism to the antimicrobial agent, or to consider an alternate diagnosis other than urinary infection. When the genitourinary abnormality predisposing to infection persists, a high frequency of recurrent infection is anticipated, usually at least 50% by six weeks post-therapy (3,12,91). Recurrent infection may be either symptomatic or asymptomatic. Post-therapy recurrence usually depends on whether the underlying abnormality is still present. Resistance of the pretherapy-infecting organism to the antimicrobial used for treatment is also associated with failure or relapse (62).

Long-term therapy

Suppressive antimicrobial therapy may be considered for selected patients with frequent, recurrent, symptomatic infection in whom the underlying genitourinary abnormality cannot be corrected. This may include patients with ureteric stents, renal transplant patients and some individuals with renal failure. Patients with struvite stones that cannot be removed may also benefit from continuous antimicrobial therapy to prevent further stone enlargement and preserve renal function (92). The decision to institute suppressive therapy is made on an individual basis. Systematic studies of optimal antimicrobial regimens for suppressive therapy, including dose and duration, have not been reported. Long-term norfloxacin therapy for suppression of chronic and recurrent infections in patients with severe urological conditions has been evaluated in two studies (93,94). In a placebo-controlled study (93), norfloxacin therapy continued for 24 weeks had significantly fewer symptomatic recurrences when compared with only 12 weeks therapy. A second trial (94) reported similar microbiological

and clinical outcomes with a regimen of norfloxacin 400 mg twice a day for one month followed by an additional two months of either 400 mg once daily or continuing full dose. Thus, at least for norfloxacin, prolonged suppressive therapy is beneficial for selected complex patients with recurrent infection, and therapy remains effective if continued at a reduced dose after an initial period of full-dose therapy.

Unique populations

Urological devices: Urological devices that remain in situ, such as indwelling urethral catheters, ureteric stents and nephrostomy tubes, rapidly become coated with a biofilm (4). This biofilm contains a high concentration of microorganisms, particularly urease-producing organisms such as *P mirabilis*, M *morganii* or *Providencia* species. Organisms growing in the biofilm are relatively protected from both antimicrobials and host defenses. The biofilm, which is a reservoir for organisms, causes relapsing infection post-treatment, and infecting organisms become increasingly resistant to antimicrobials with repeated courses of antimicrobial therapy (79). Replacement of a chronic indwelling catheter before initiating antimicrobial therapy for symptomatic urinary infection results in a more rapid defervescence of fever and decreased incidence of short-term symptomatic relapse (21). This suggests there is a clinical benefit associated with the removal of biofilm-laden devices before initiating therapy for symptomatic patients.

Resistant bacteria: Patients with frequent recurrent infection may experience reinfection with progressively resistant organisms, with concomitant decrease in therapeutic options for subsequent infections (95). *P aeruginosa* is particularly problematic in some patients (96,97). Mucoid strains highly resistant to multiple antimicrobials, reminiscent of lung isolates from cystic fibrosis patients, may be isolated. Antimicrobial therapy for the treatment of highly resistant organisms must be directed by organism susceptibility. Parenteral therapy is necessary when infecting organisms are no longer susceptible to available oral agents (96-98).

Fungal urinary infection: Fungal urinary infection is usually identified in patients who are diabetic, have indwelling urethral catheters or other urological devices, and have received broad-spectrum antimicrobial therapy (99). *Candida albicans* is the most common isolate. *Candida glabrata* is the second most frequent species (99), and may be increasing with the widespread use of azoles, to which this species is less susceptible (100). A prospective, randomized, placebo-controlled clinical trial (101) reported no clinical benefits with the treatment of asymptomatic funguria. Most episodes of funguria in patients with an indwelling catheter will resolve spontaneously following catheter removal.

Both azoles and amphotericin B are effective for the treatment of symptomatic fungal urinary infection (102-104). Amphotericin B bladder washout is as effective as short-course systemic amphotericin B for the treatment of bladder infection but requires an indwelling urethral catheter and restricts mobility; as such, it is now seldom used (102). Fluconazole is as effective as amphotericin B bladder irrigation for the treatment of funguria (103,104). Fluconazole is excreted in the urine and is the preferred azole, although comparative trials of this agent with itraconazole, ketoconazole or voriconazole are not reported. Non-albicans *Candida* species may have increased resistance to azoles, and systemic amphotericin B may be necessary to treat infection with some of these species. Echinocandin antifungals are not excreted in the urine, and the role of these antifungals in the treatment of urinary infection is not yet known.

Patients with renal failure: The optimal treatment of urinary infection in patients with renal failure is not well studied. Patients with renal failure have decreased renal blood flow, with impaired urinary antimicrobial excretion and lower urine antimicrobial levels. Bacteria may be more difficult to eradicate from the urinary tract, presumably because of the decreased urine antibiotic levels. Recurrent infection is common following therapy, but the majority of patients, including those with end-stage renal disease, can be effectively treated. Case reports and case series report that ampicillin (104), TMP/SMX (105) and cephalosporins (106,107) are all effective. Fluoroquinolones are widely used and appear effective, but they have not been systematically evaluated. Aminoglycosides are reported to be less effective for the treatment of patients with renal failure (108). Nitrofurantoin is contraindicated in patients with renal failure because of the accumulation of metabolites which may cause peripheral neuropathy (109). Whether longer durations of antimicrobial therapy provide a clinical benefit for the initial treatment of urinary infection in patients with renal failure has yet to be studied.

PREVENTION

The major strategy to prevent complicated urinary infection involves characterizing and correcting the underlying genitourinary abnormality that promotes infection. When correction is not possible, patients with persistent abnormalities remain at risk for recurrent infection. Clinical trials of prophylactic antimicrobial therapy suggest this approach is ultimately unsuccessful due to reinfection with resistant organisms. Prospective, randomized trials of prophylactic antimicrobial therapy have been reported for patients with short-term indwelling catheters (110-112) and spinal cord injury patients (113,114). While a decrease in the frequency of symptomatic infection may initially occur, emergence of resistant organisms ultimately limits efficacy (111,113). Currently, there are no adult populations at risk for recurrent complicated urinary infection in whom long-term prophylaxis to prevent urinary infection is routinely recommended.

A prospective, randomized, placebo-controlled crossover trial of cranberry tablets three times daily to prevent infection in spinal cord injury patients reported no impact of cranberry products on bacteriuria or pyuria (115). However, a randomized, controlled trial of an educational program designed to reduce urinary infection in spinal cord injured patients demonstrated significantly lower bacterial counts and a trend to fewer symptomatic episodes in subjects randomized to the educational intervention (116). The elements of the educational program included written material, a self-administered test of bladder management, review of catheter technique by an experienced nurse, discussion with a physician about accessing care for urinary infection, and follow-up by telephone. The observed improvement continued for at least six months.

Investigations of different antibacterial catheter materials and coatings to prevent infection in patients with indwelling urological devices, including urethral catheters, have not shown consistent benefit (16,117). Antibacterial substances added to the catheter drainage bag do not prevent symptomatic infection (118-120), and daily periurethral care with either soap and water or antiseptics does not decrease infection

acquisition in patients with indwelling catheters (121-123). Future developments in catheter biomaterials to inhibit biofilm formation may limit biofilm-associated infections, but benefits from this approach have not yet been realized for clinical practice (124).

RECOMMENDATIONS

Diagnosis

The diagnosis of symptomatic urinary tract infection in patients without indwelling urological devices should be considered only when localizing genitourinary signs or symptoms are present (AII).

1. For patients with indwelling urological devices, systemic symptoms, such as fever in the absence of localizing genitourinary signs and symptoms, may be consistent with symptomatic urinary tract infection (AII).
2. A urine specimen should be obtained for culture and susceptibility testing before institution of antimicrobial therapy for every episode of complicated urinary tract infection (AI).
   - A single urine specimen with a quantitative count of at least 10^8 cfu/L (at least 10^5 cfu/mL) is consistent with urinary infection in symptomatic subjects (AII).
   - A quantitative count of at least 10^8 cfu/L (at least 10^5 cfu/mL) on two consecutive specimens is the appropriate diagnostic criteria to identify asymptomatic bacteriuria in women (BII).
   - Any quantitative count of organisms is consistent with bacteriuria for individuals with urine specimens obtained by bladder catheterization (AII).

Treatment

1. Screening for and treatment of asymptomatic bacteriuria is not recommended (AI).
2. Pyuria in a urine specimen, in the absence of symptoms, is not an indication for antimicrobial therapy (AII).
3. If clinically feasible, the initiation of antimicrobial therapy should be delayed until the results of the urine culture are available (AIII).
4. Empirical antimicrobial therapy should be initiated when the clinical presentation is of sufficient severity (AII).
   - Selection of an antimicrobial for empirical therapy should be individualized, considering patient tolerance, clinical presentation, recent prior antimicrobial exposure, prior urine culture results, and known or suspected institutional susceptibilities (AII).
   - Empirical antimicrobial regimens should be reassessed and modified, if appropriate, when urine culture results are available and the initial clinical response is evaluated (AIII).
5. Oral antimicrobial therapy is appropriate for the treatment of most episodes of symptomatic urinary infection (AI).
6. Parenteral therapy is indicated if patients are unable to tolerate oral therapy, have impaired gastrointestinal absorption, have hemodynamic instability, or if the infecting organism is known or suspected to be resistant to oral agents (AI).
7. The duration of therapy should be seven days for individuals with lower tract symptoms, and 10 to 14 days for individuals presenting with upper tract symptoms or sepsis syndrome (BIII).
   - Patients with chronic urological devices should receive as short a duration of therapy as possible to limit antimicrobial pressure leading to resistance emergence (AIII).
8. A urine culture to document bacteriological cure after treatment is not recommended if the patient is asymptomatic (BII).

Investigations

1. Patients presenting with symptomatic urinary infection who may have complicated urinary infection, including male patients of any age, older women, and any woman with recurrent symptomatic episodes presenting with systemic manifestations, should have genitourinary investigations to characterize the structural and functional status of the genitourinary tract (AII).
2. Patients who fail to respond to therapy or who present with severe manifestations, including sepsis syndrome, should have urgent evaluation with imaging to exclude obstruction, abscess or other abnormalities requiring immediate intervention (AII).

Prevention

1. Wherever possible, underlying genitourinary abnormalities should be corrected (AII).
2. Prophylactic antimicrobial therapy to prevent recurrent urinary tract infection is not recommended for patients with complicated urinary tract infection (AI).
3. Suppressive antimicrobial therapy is indicated to prevent frequent, recurrent symptomatic infection or deterioration in renal function for selected patients with persistent genitourinary abnormalities (AII).
4. Indwelling urethral catheters for bladder drainage should be used only when clear clinical indications exist, and should be removed as soon as clinically feasible (AII).
   - Patients requiring indwelling catheters should have catheters inserted using sterile aseptic technique, be maintained with a closed drainage system, and have catheter care managed to limit potential trauma to the urethra and bladder (AI).
5. For young women with catheter-acquired urinary tract infection, the treatment of bacteriuria persisting 48 h after catheter removal may be considered (BI).
6. The need for continuing catheterization in subjects with chronic indwelling catheters should be re-evaluated on an ongoing basis (AIII).

- Catheters should be replaced before initiating antimicrobial therapy for the treatment of a symptomatic episode (AI).
- Care of the catheter should minimize trauma (AIII).
- Prophylactic antimicrobial therapy is not recommended with catheter replacement (AII).
- Routine replacement of chronic indwelling catheters is not recommended (AIII).

7. For long-term care facility residents with bladder emptying maintained by intermittent catheterization, a clean procedure is appropriate for catheterization (AI).

8. Information is insufficient to make recommendations for or against routine antimicrobial therapy for stent or nephrostomy tube replacement (CII).

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