Philippine Clinical Practice Guidelines on the Diagnosis and Management of Urinary Tract Infections in Adults 2015 Update: Part 2

Asymptomatic Bacteriuria in Adults, Recurrent Urinary Tract Infection, and Complicated Urinary Tract Infection

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INTRODUCTION

Urinary tract infections (UTI) are among the leading indications for seeking healthcare and using antimicrobials in the community and hospital settings. The Philippine Clinical Practice Guidelines on the Diagnosis and Management of Urinary Tract Infections in Adults were first published in 1998 and revised in 2004 to provide primary care physicians and specialists with evidence-based recommendations on the care of patients with UTI. The current guidelines further update the recommendations following an extensive review of more recent literature. For the first time the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system was used to develop guidelines in infectious diseases in the country. The outputs are consensus recommendations of a panel of clinicians convened by the Philippine Society for Microbiology and Infectious Diseases (PSMID) in collaboration with the Philippine Obstetric and Gynecological Society (POGS), Philippine Society of Nephrology (PSN), Philippine Academy of Family Physicians (PAFP), and Philippine Urological Association (PUA).

The focus of the guidelines is on diagnosis, treatment, and prevention of UTI in adults and consists of two parts:

Part One – Acute Uncomplicated UTI and UTI in Pregnancy
Part Two – Asymptomatic Bacteriuria, Recurrent UTI
and Complicated UTI

In formulating optimal approaches to the care of both outpatients and inpatients with UTI, the panel considered several issues related to changing prevalence and resistance patterns of uropathogens, availability and practicability of diagnostic tests, and cost-effectiveness and ecological adverse effects (collateral damage) of treatment.

The guidelines are not intended to supersede a healthcare provider's sound clinical judgment. Variations in clinical presentation, presence of comorbidities, or availability of resources may require adaptation of the recommendations to specific settings.

METHODOLOGY

The PSMID, in collaboration with POGS, PSN, PAFP, and PUA, convened a task force of clinicians representing different expertise including infectious diseases, nephrology, family medicine, obstetrics and gynecology, urology, and internal medicine. The members of this task force were divided into four clusters, each headed by a senior specialist, and served as the technical working group for formulating the guidelines. The areas covered were: Cluster A – uncomplicated UTI (acute cystitis and pyelonephritis), Cluster B – UTI in pregnancy and asymptomatic bacteriuria, Cluster C – complicated UTI, and Cluster D – recurrent UTI.

Each cluster conducted a review and analysis of the relevant English literature published since 2004 and, for some topics, even earlier studies. The quality of the evidence was evaluated using the GRADE system as indicated in Table 1. The cluster then drafted guideline recommendations and graded them as STRONG or WEAK depending on the quality of the evidence, balance of potential benefits and harm, and translation into practice in specific settings and patient groups. Thus, high-quality evidence did not necessarily constitute strong recommendations; conversely, strong recommendations could arise from low-quality evidence if the benefits outweigh the undesirable consequences.

Table 1. GRADE system

Category	Definition
Strength of Recommendation	
Strong	Desirable effects (benefits) clearly outweigh the undesirable effects (risks)
Conditional	Desirable effects probably outweigh the undesirable effects but the recommendation is applicable only to a specific group, population, or setting; or the benefits may not warrant the cost or resource requirements in all settings
Weak	Desirable and undesirable effects closely balanced;or uncertain, new evidence may change the balance of risk to benefit
No recommendation	Further research is required before any recommendation can be made
Quality of Evidence	
High	Consistent evidence from well-performed RCTs or strong evidence from unbiased observational studies; further research is very unlikely to change confidence in the estimate of the effect
Moderate	Evidence from RCTs with important limitations or moderately strong evidence from unbiased observational studies; further research is likely to have an important impact on confidence in the estimate of the effect
Low	Evidence for ≥ one critical outcome from observational studies, from RCTs with serious flaws or from indirect evidence; further research is very likely to have an important impact in the estimate of effect and is likely to change the estimate
Very Low	Evidence for ≥ one critical outcome from unsystematic clinical observations or very indirect evidence; any evidence of effect is very uncertain

In addition to quality of evidence, the following domains were considered in grading the strength of the recommendations:

1. Balance of benefits versus harms and burdens
2. Values and preferences: Is the recommendation likely to be widely accepted or Is there significant variability or uncertainty in values and preferences that the recommendation is unlikely to be accepted?
3. Resource implications: financial costs/implications, infrastructure, equipment, human resources/expertise, cost-effectiveness
4. Feasibility: Is the recommendation achievable in the setting where the greatest impact is expected?

A series of face-to-face meetings of the task force with representatives from all four clusters was held to discuss each cluster's draft outputs. The task force members

developed a consensus in grading the quality of the evidence and strength of the recommendations using the GRADE technique. Throughout the development process, expert advice on methodological issues was provided by a task force member proficient in the GRADE system. GRADE tables summarizing the quality of the evidence retrieved were generated for each guideline question.

Segments of the guidelines were presented in various fora including annual conventions of specialty societies such as POGS, PSN, and PSMID to elicit feedback. The guidelines were finalized after a few more meetings and e-mail correspondence among the task force members and cluster heads. At regular intervals, the task force leaders will determine the need for revisions to the guidelines. Implementation strategies will also be periodically reviewed.

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ASYMPTOMATIC BACTERIURIA IN ADULTS

Summary of recommendations

1. **When is asymptomatic bacteriuria diagnosed?**
   - **1.1. All diagnosis of asymptomatic bacteriuria (ASB) should be based on results of urine culture specimens that are collected aseptically and with no evidence of contamination.**
   - **1.2. For asymptomatic women, bacteriuria is defined as two consecutive voided urine specimens with isolation of the same bacterial strain in quantitative counts ≥ 100,000 cfu/mL.**
     Strong recommendation, High quality of evidence
   - **1.3. In men, a single, clean-catch voided urine specimen with one bacterial species isolated in a quantitative count ≥ 100,000 cfu/mL identifies bacteriuria.**
     Strong recommendation, High quality of evidence
   - **1.4. In both men and women, a single catheterized urine specimen with one bacterial species isolated in a quantitative count ≥ 100 cfu/mL identifies bacteriuria.**
     Strong recommendation, High quality of evidence
2. **What are the indications for screening and treatment of asymptomatic bacteriuria?**
   - **2.1. Screening and treatment is recommended in the following to prevent bacteremia and sepsis:**
     - **Patients who will undergo genitourinary manipulation or instrumentation**
       Recommendations vary per selected procedure
     - **All pregnant women**
       Strong Recommendation, High quality of evidence
   - **2.2. The choice of antibiotic depends on culture results. A seven-day regimen is recommended.**
     Strong Recommendation, Low quality of evidence
   - **2.3. For specific antibiotic recommendations for ASB in pregnancy, see Table 2.**

Table 2. Antibiotics that can be used for ASB in pregnancy

Antibiotics	Recommended dose and duration	FDA Risk Category
Cephalexin	500 mg BID for 7 days	B
Cefuroxime axetil	500 mg BID for 7 days	B
Fosfomycin trometamol	3 g single dose	B
Amoxicillin-clavulanate	625mg BID for 7 days	B
Nitrofurantoin* macrocrystal	100 mg QID for 7 days; 100 mg BID for 7 days for monohydrate macrocrystal formulation (not available locally)	B
Trimethoprim-sulfamethoxazole	160/800 mg BID for 7 days	C (avoid in 1st and 3rd trimester)

** May cause hemolytic anemia, anophthalmia, hypoplastic left heart syndrome, ASD, cleft lip and palate. May be given on the second trimester of pregnancy until 32 weeks AOG. Use in the first trimester of pregnancy is appropriate when no other suitable alternative antibiotics are available.*

3. Who should NOT be screened and treated for asymptomatic bacteriuria?

3.1. Routine screening and treatment for asymptomatic bacteriuria is not recommended for healthy adults.
Strong recommendation, Low quality of evidence

3.2. Likewise, periodic screening and treatment for asymptomatic bacteriuria is not recommended in the following:

- **Patients with diabetes mellitus**
  Strong recommendation, Moderate quality of evidence
- **Elderly patients**
  Strong recommendation, High quality of evidence
- **Patients with indwelling catheters**
  Weak Recommendation, Moderate quality of evidence
- **Solid organ transplant patients**
  Weak recommendation, Low quality of evidence
- **People living with human immunodeficiency virus (HIV)**
  Weak recommendation, Low quality of evidence
- **Spinal cord injury patients**
  Weak Recommendation, Very low quality of evidence
- **Patients with urologic abnormalities**
  Weak recommendation, Very Low quality of evidence

4. What is the optimal screening test for asymptomatic bacteriuria?

4.1. Screening by urine culture is recommended.
Strong Recommendation, High quality of evidence

4.2. In the absence of facilities for urine culture, significant pyuria (>10 wbc/hpf) or a positive gram stain of unspun urine (>2 microorganisms/oif) in two consecutive midstream urine samples can be used to screen for asymptomatic bacteriuria.
Strong Recommendation, Low quality of evidence

4.3. Urine culture and sensitivity testing are not necessary when urinalysis is negative for pyuria or urine gram stain is negative for organisms.
Strong Recommendation, Moderate quality of evidence

4.4. Pyuria accompanying asymptomatic bacteriuria is not an indication for antimicrobial treatment among patients for whom screening and treatment is not recommended.
Strong Recommendation, *Low quality of evidence*

DISCUSSION

1. When is asymptomatic bacteriuria diagnosed?

1.1. All diagnosis of asymptomatic bacteriuria (ASB) should be based on results of urine culture specimens that are collected aseptically and with no evidence of contamination.

1.2. For asymptomatic women, bacteriuria is defined as two consecutive voided urine specimens with isolation of the same bacterial strain in quantitative counts ≥ 100,000 cfu/mL.

Strong recommendation, High quality of evidence

Summary of Evidence

The definition of asymptomatic bacteriuria as bacterial counts more than or equal to 10^5 cfu/mL, in two consecutive urine specimens was based on studies done in the 1940s to 1950s, where such bacterial counts in clean, voided specimens were confirmed by a catheterized sample in more than 95% of cases.[1] According to Hooton et al, 2000, transient bacteriuria is common in healthy young women, and occurs in around 5% to 6% but rarely persists.[2] As such, if more than one specimen is used to identify bacteriuria, the prevalence will be lower.[1]

1.3. In men, a single, clean-catch voided urine specimen with one bacterial species isolated in a quantitative count ≥ 100,000 cfu/mL identifies bacteriuria.

Strong recommendation, High quality of evidence

Summary of Evidence

In asymptomatic, ambulatory men, *Enterobacteriaceae* counts of greater than or equal to 10^5 cfu/ml in a single, voided, urine specimen was reproducible in repeat cultures done within one week from initial culture in 98% of cases.[1,3]

1.4. In both men and women, a single catheterized urine specimen with one bacterial species isolated in a quantitative count ≥ 100 cfu/mL identifies bacteriuria.

Strong recommendation, High quality of evidence

Summary of Evidence

For both men and women whose specimens are drawn via urethral catheterization, bacteriuria is consistent with quantitative counts of greater than or equal to 100 cfu/mL.[1,4]

2. What are the indications for screening and treatment of asymptomatic bacteriuria?

2.1. Screening and treatment is recommended in the following to prevent bacteremia and sepsis:

- **Patients who will undergo genitourinary manipulation or instrumentation**

Recommendations vary per selected procedure

- **All pregnant women**
  Strong Recommendation, High quality of evidence

2.2. The choice of antibiotic depends on culture results. A seven-day regimen is recommended.
Strong Recommendation, Low quality of evidence

2.3. For specific antibiotic recommendations for ASB in pregnancy, see Table 2.

Table 2. Antibiotics that can be used for ASB in pregnancy

Antibiotics	Recommended dose and duration	FDA Risk Category
Cephalexin	500 mg BID for 7 days	B
Cefuroxime axetil	500 mg BID for 7 days	B
Fosfomycin trometamol	3 g single dose	B
Amoxicillin-clavulanate	625mg BID for 7 days	B
Nitrofurantoin* macrocrystal	100 mg QID for 7 days; 100 mg BID for 7 days for monohydrate macrocrystal formulation (not available locally)	B
Trimethoprim-sulfamethoxazole	160/800 mg BID for 7 days	C (avoid in 1st and 3rd trimester)

** May cause hemolytic anemia, anophthalmia, hypoplastic left heart syndrome, ASD, cleft lip and palate. May be given on the second trimester of pregnancy until 32 weeks AOG. Use in the first trimester of pregnancy is appropriate when no other suitable alternative antibiotics are available.*

Summary of Evidence

Genitourinary procedures

Genitourinary surgery with trauma and bleeding of the mucosa allows organisms in the urinary tract to invade the systemic circulation. Antimicrobial treatment of asymptomatic bacteriuria before genitourinary manipulation or instrumentation can prevent bacteremia and sepsis.[5-7] In patients with bacteriuria undergoing a traumatic urologic procedure, 25% to 80% will have bacteremia if no treatment is given.[5]

For patients who will undergo elective urologic procedures with asymptomatic bacteriuria on screening, they should be treated accordingly based on the culture result. For emergency cases, antibiotic prophylaxis is recommended with cultures ideally obtained prior to antibiotic administration.

For a detailed discussion on antibiotic prophylaxis prior to selected urologic procedures, refer to section on Complicated UTI.

Pregnant women

See the section on UTI in Pregnancy for discussion.

3. Who should NOT be screened and treated for asymptomatic bacteriuria?

3.1. Routine screening and treatment for asymptomatic bacteriuria is not recommended for healthy adults.

Strong recommendation, Low quality of evidence

3.2. Likewise, periodic screening and treatment for asymptomatic bacteriuria is not recommended in the following:

- **Patients with diabetes mellitus**
  Strong recommendation, Moderate quality of evidence
- **Elderly patients**
  Strong recommendation, High quality of evidence
- **Patients with indwelling catheters**
  Weak Recommendation, Moderate quality of evidence
- **Solid organ transplant patients**
  Weak recommendation, Low quality of evidence
- **People living with human immunodeficiency virus (HIV)**
  Weak recommendation, Low quality of evidence
- **Spinal cord injury patients**
  Weak Recommendation, Very low quality of evidence
- **Patients with urologic abnormalities**
  Weak recommendation, Very Low quality of evidence

Summary of Evidence

Healthy adults

Cai et al (2012) studied 673 young (age 18 to 40 years), asymptomatic, sexually active women with at least one symptomatic urinary tract infection (UTI) treated within the past 12 months prior to the current bacteriuric episode, with a urine culture showing at least 10^5 cfu/mL of uropathogens.[8] Screening and antibiotic treatment of asymptomatic bacteriuria in this population failed to show any benefit.

Diabetes Mellitus patients

There are no population-based surveys of ASB among Filipino diabetics. The prevalence of asymptomatic bacteriuria among women undergoing treatment for diabetes is 7% to 13%, generally threefold higher than in non-diabetic women. The prevalence of asymptomatic bacteriuria is not increased compared to non-diabetic men (ranging from 0.7 to 11.1%). Most studies have shown that the type or duration of diabetes, or the adequacy of diabetic control do not influence the prevalence of asymptomatic bacteriuria.[9] However, a survey among diabetic aboriginal women in Canada found that the duration of the diabetes and presence of long-term complications including retinopathy, nephropathy and neuropathy were associated with asymptomatic bacteriuria.[10] This increased prevalence of asymptomatic bacteriuria in diabetic women may be largely attributable to autonomic neuropathy leading to impaired bladder voiding.[11] A case-control study of 228 women with diabetes and 146 women without diabetes showed that impaired metabolic control of diabetes, as revealed by higher glycated hemoglobin levels, significantly increased the risk for developing asymptomatic bacteriuria ($p<0.05$).[12]

In the randomized controlled trial (RCT) by Harding et al (2002), there was greater antimicrobial exposure and higher frequency of adverse drug effects among those treated for asymptomatic bacteriuria.[13] Women in the treatment group also had significantly more episodes of asymptomatic bacteriuria following therapy.

No added benefit for screening and treatment of asymptomatic bacteriuria in diabetic women was demonstrated. On intention-to-treat analysis after a mean follow-up of 27 months, the proportion of patients having more than one episode of symptomatic UTI did not differ between those who had antimicrobial therapy and those on placebo (41% vs. 40%). There was also no difference in terms of the time to a first symptomatic UTI episode. Likewise, no significant difference in the occurrence of pyelonephritis, cystitis, or all episodes of UTI and hospitalizations due to UTI or to other causes was observed. They noted that glycosuria and neuropathy might be associated with symptomatic infection but not asymptomatic bacteriuria.[13]

Long-term prospective studies of the natural history of diabetic women also showed that accelerated progression to hypertension, renal failure or other long-term complications was similar for those with and without asymptomatic bacteriuria.[14,15]

Elderly patients

There are no population-based studies on ASB among elderly Filipinos. Various surveys of community populations in developed countries show that the prevalence of asymptomatic bacteriuria increases with age irrespective of sexual activity. In women 50 to 60 years of age, the prevalence is 6% to 7%; and 8-10% at age 70 to 80 years.[16] In non-institutionalized elderly men, the prevalence is 12%.[17] It is highest among institutionalized elderly women (25% to 57%) and men (15% to 37%). The prevalence in young to middle-aged adults is less than 5% in women and 1.5% in men.[18]

A cross-sectional study by Rodhe et al in 2006 showed that bacteriuria was common among the non-institutionalized elderly aged 80 and over, especially among the women, but still not as common as among the elderly in institutional settings.[19]

Lin et al (2006) did a prevalence study on ASB in 64 institutionalized elderly Chinese.[20] Overall prevalence of asymptomatic bacteriuria in this study was 57.8%. *Escherichia coli* was the most commonly isolated organism. No association was found between ASB and factors such as age, sex, functional status, indwelling catheter, previous history of UTI, or nutritional status of residents.

No recent study showed significant benefit in the treatment of ASB in the elderly population. A cohort study of ambulatory elderly women showed that ASB was not independently associated with mortality.[21] Controlled clinical trials on treatment versus no treatment of ambulatory elderly women found that treatment of ASB did not significantly reduce mortality and symptomatic episodes of UTI.[21,22] RCTs comparing treatment versus no treatment on elderly institutionalized men and women showed no benefits with treatment.[18,21,23,24] An association with asymptomatic bacteriuria and increased 5-year mortality was reported in elderly women in a Finnish study; however, subsequent reports with 5- and 9-year follow-up have not reported an association of asymptomatic bacteriuria and survival for either men or women.[23,25]

Two RCTs among institutionalized elderly women showed increased rates of adverse reactions from antimicrobial therapy, with one showing an increased frequency of re-infection with resistant organisms.[18,24]

Patients with indwelling catheters

See the section on SPECIFIC ISSUES OF CONCERN IN COMPLICATED UTI: CATHETER-ASSOCIATED UTI.

Spinal cord injury patients

No new evidence was found that would support a change in the recommendations from the previous guideline.

Patients with spinal cord injury have a high prevalence of bacteriuria ranging from 20% to 98%.[22] Prospective cohort studies however do not report progression to renal failure with bacteriuria if low bladder pressure is maintained either by intermittent catheterization, condom drainage or sphincterotomy, as necessary.[26] A small placebo-controlled trial reported no decrease in symptomatic infection with treatment of bacteriuria.[27]

Solid organ transplant patients

Studies on screening and treatment of asymptomatic bacteriuria among post-renal transplant patients are limited.

In a retrospective analysis of 189 renal transplant patients who were systematically screened for ASB, various outcomes were compared between those who developed asymptomatic bacteriuria and those who did not.[28] Ninety-six patients developed asymptomatic bacteriuria, and all of them were treated accordingly. Having more than one episode of bacteriuria was associated with pyelonephritis. Having more than five episodes of bacteriuria was associated with organ rejection. However, despite treatment, the incidence of pyelonephritis was higher in patients screened and treated for asymptomatic bacteriuria compared to those who did not develop bacteriuria (7.6 vs 1.07 episodes per 100 patient-years). There was also no difference in renal function prognosis measured in terms of creatinine, creatinine clearance and proteinuria in both groups when the number of asymptomatic bacteriuria episodes was taken into account. The authors concluded that screening and treatment of those with asymptomatic bacteriuria may be the reason for the similarity in terms of renal function prognosis to those who did not develop asymptomatic bacteriuria. It is important to note, however, that the authors were not able to compare outcomes between patients that developed bacteriuria who received treatment and those who did not receive treatment. Thus, the influence of screening and treatment of asymptomatic bacteriuria among post-renal transplant patients was not directly demonstrated in this study.

Similar findings were also seen in a review on 86 patients who received renal allografts, wherein one-fifth of the patients developed urinary infections by 6 months after transplantation.[29] There were no significant differences in the transplant function and in the patient and graft survival between the infected group and that of the sterile group.

Two retrospective studies evaluated the outcome of treating vs not treating asymptomatic bacteriuria in post-kidney transplant patients. Amari et al did a retrospective analysis on the outcome of 334 asymptomatic bacteriuria that occurred in 77 renal transplant recipients later than 1 month post-transplantation.[30] They observed no differences when comparing progression toward symptomatic UTI between all treated and untreated episodes (0/101 versus 4/233; p=0.32). Spontaneous clearance of the initial pathogen in all untreated episodes was as frequent as microbiological cure

of treated episodes (138/233 versus 55/101; p=0.47). In a retrospective cohort study by Green et al, no benefit was observed from the antibiotic treatment of asymptomatic bacteriuria in the short- and long-term follow-up.[31]

Several good quality studies have shown the advantage of antibiotic prophylaxis in the prevention of bacteriuria and bacteremia in renal transplant recipients. Antibiotic prophylaxis during the post-transplant period undermines the potential benefit of systematic screening for asymptomatic bacteriuria in this subset of patients. For a detailed discussion on antibiotic prophylaxis after renal transplantation, refer to the UTI in Renal Transplant Patients section under Complicated UTI.

For solid organ transplant patients other than renal transplant recipients, there is no evidence to recommend screening and treatment of asymptomatic bacteriuria. According to the American Society of Transplantation, there is no consensus whether asymptomatic bacteriuria should be treated in the transplant patient.[32] Even with the use of prophylactic antibiotics, infection-related fatality rates are not reduced.

People living with HIV

The prevalence of bacteriuria in 222 female prostitutes in Kenya was 23%. The proportions of those who were HIV-positive and HIV-negative were similar, and bacteriuria did not vary with the CD4+ count.[33] In a cross-sectional study comparing men with acquired immune deficiency syndrome (group A), men without HIV (group B) and men with asymptomatic HIV infection (group C), bacteriuria was significantly more frequent in group A (20 cases, 13.3%) than in groups B (3 cases, 1%-8%; p=0.00007) and C (3 cases, 3.2%; p=0.009). Ten cases of bacteriuria in group A (6.6%) were symptomatic while no case of symptomatic UTI was seen in groups B (p=0.0004) and C (p=0.008).[34] Morbidity was associated with symptomatic UTI but negative clinical outcomes due to asymptomatic bacteriuria in HIV patients were not reported.

Urologic abnormalities

Among patients with genitourinary abnormalities, the incidence of ASB depends on the primary renal disease.[7] Asymptomatic bacteriuria is not present more frequently in autosomal dominant polycystic kidney disease patients with normal kidney function and no diabetes, than in healthy people.[35] In a comparative study of prevalence of ASB in a Thai population, there was a higher overall prevalence of ASB in those with glomerulonephropathies when compared to the controls.[36] There were no reports showing increased risk of symptomatic infection or further complications as a consequence of ASB among patients with urologic abnormalities.

Comments: The criteria used in deciding whether to screen or not for any disease condition depends on the burden of the disease condition, performance characteristics of the screening test, the effectiveness of interventions for treatment or prevention of transmission once infection has been detected, and the cost effectiveness of the screening test and the treatment or preventive intervention.

4. What is the optimal screening test for asymptomatic bacteriuria?

4.1. Screening by urine culture is recommended.
Strong Recommendation, High quality of evidence

Summary of Evidence

Urine culture remains the gold standard for diagnosing asymptomatic bacteriuria, particularly in pregnant women, as no other tests have a high enough sensitivity and negative predictive value to replace urine cultures for screening.[37]

4.2. In the absence of facilities for urine culture, significant pyuria (>10 wbc/hpf) or a positive gram stain of unspun urine (>2 microorganisms/oif) in two consecutive midstream urine samples can be used to screen for asymptomatic bacteriuria.
Strong Recommendation, Low quality of evidence

4.3. Urine culture and sensitivity testing are not necessary when urinalysis is negative for pyuria or urine gram stain is negative for organisms.
Strong Recommendation, Moderate quality of evidence

Summary of evidence

Pyuria has a good predictive value in patient populations where the prevalence of asymptomatic bacteriuria is at least 10%. With pyuria of greater than 10 wbc/hpf, the likelihood ratio for a significant urine culture result among ambulatory elderly men was 417; for 2 to 10 wbc/hpf, the likelihood ratio was 2; for 0 to 1 wbc/hpf, the likelihood ratio was 0.03.[38]

4.4. Pyuria accompanying asymptomatic bacteriuria is not an indication for antimicrobial treatment among patients for whom screening and treatment is not recommended.
Strong Recommendation, *Low quality of evidence*

Summary of Evidence

In the absence of symptoms or signs referable to UTI, bacteriuria, although microbiologically significant, is not clinically significant. Pyuria is evidence of inflammation in the genitourinary tract and is common in persons with asymptomatic bacteriuria such as in young women.[2] diabetic women, elderly institutionalized patients, hemodialysis patients, bacteriuric patients with short-term catheters, and in individuals with long-term indwelling catheters in place – all of whom screening and treatment for asymptomatic bacteriuria is not recommended. Pyuria also accompanies other inflammatory conditions of the genitourinary tract in patients with negative urine culture results. The dilemma of the positive culture with pyuria in an asymptomatic patient can be avoided if urinalysis and urine cultures are not done on asymptomatic patients for whom screening and treatment is not recommended.[2,13,18,23]

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RECURRENT URINARY TRACT INFECTION IN WOMEN

Summary of recommendations

1. **How is recurrent urinary tract infection (rUTI) diagnosed?**
   - 1.1. **Recurrent UTI is diagnosed when a healthy non-pregnant woman with no known urinary tract abnormalities has 3 or more episodes of acute uncomplicated cystitis documented by urine culture during a 12-month period OR 2 or more episodes in a 6- month period.[1-3]**
   - 1.2. **Recurrent UTI may either be a relapse or a reinfection. Relapse occurs when the initial organism persists within the urinary tract and re-emerges despite adequate treatment usually occurring 1-2 weeks after stopping treatment. Reinfection, on the other hand, occurs when recurrent UTI is caused by a different bacterial isolate, or by the previously isolated bacteria after a negative intervening culture or an adequate period (≥ 2 weeks) between infections.[4,5]**
2. **Among those with recurrent UTI, who would benefit from further diagnostic evaluation?**
   - 2.1. **Routine screening for urologic abnormalities is not recommended for the general patient population.**
     Strong recommendation, low quality of evidence
   - 2.2. **Screening for urologic abnormalities is recommended in the following situations:**
     - **No response to appropriate antimicrobial therapy or rapid relapse after such therapy**
     - **Gross hematuria during a UTI episode or persistent microscopic hematuria**
     - **Obstructive symptoms**
     - **Clinical impression of persistent infection**
     - **Infection with urea-splitting bacteria (*Proteus*, *Morganella*, *Providencia*)**
     - **History of pyelonephritis**
     - **History of or symptoms suggestive of urolithiasis**
     - **History of childhood UTI**
     - **Elevated serum creatinine**
   - 2.3. **Patients with the above factors may benefit from further diagnostic evaluation as these risk factors have been identified to be associated with a higher incidence of urologic abnormalities.**
   - 2.4. **All women with recurrent UTI should undergo a complete history and physical examination to evaluate urogenital anatomy and estrogenization of vaginal tissues and to detect prolapse. Post-void residual urine should be measured.**
3. **What diagnostic work-ups are indicated in women with recurrent UTI?**
   - 3.1. **Radiologic or imaging studies and cystoscopy are not routinely indicated in patients with recurrent UTI.**
     Weak recommendation, low quality of evidence
   - 3.2. **Renal ultrasound or CT scan/stonogram may be done to screen for urologic abnormalities**
     Strong recommendation, low quality of evidence

3.3. Patients with anatomical abnormalities should be referred to a specialist (nephrologist or urologist) for further evaluation.
Strong recommendation, low quality of evidence

4. When is prophylaxis for recurrent UTI indicated?

4.1. Prophylaxis is recommended in women whose frequency of recurrence is not acceptable to the patient in terms of level of discomfort or interference with activities of daily living. Prophylaxis may be withheld according to patient preference if the frequency of recurrence is tolerable to the patient.
Strong recommendation, low quality of eviden

4.2. The following factors should guide the physician in determining the patient's risk-benefit profile and in deciding which prophylactic strategies will be used:
- **Frequency and pattern of recurrences**
- **Patient's lifestyle, compliance and willingness to commit to a specific regimen**
- **Plans for a pregnancy**
- **Antimicrobial resistance and susceptibility pattern of the organisms causing the patient's previous UTIs**
- **Risk of adverse events and drug allergies**

4.3. Prophylaxis should only be initiated after counseling and behavior modification have been attempted in order to minimize antibiotic exposure and possible adverse effects.
Strong recommendation, low quality of evidence

4.4. Antibiotic prophylaxis should be limited to women with recurrent UTI in whom non-antimicrobial strategies have not been effective and who prefer prophylactic antimicrobial therapy.
Strong recommendation, moderate quality of evidence

5. How effective are non-antimicrobial strategies in preventing recurrent UTI?

5.1. Behavioral changes

5.1.1. Behavioral changes can be useful antimicrobial-sparing measures in the prevention of recurrent UTI.
Weak recommendation, low quality of evidence

5.1.2. These behavioral measures include the following:
- **post-defecation and anal cleansing antero-posteriorly always in women to avoid contaminating the periurethral area with fecal flora**
- **post-coital douche or post coital urination**
- **liberal fluid intake especially after intercourse**
- **avoidance of tight-fitting underwear**
- **use of alternative form of contraception for women using spermicide-containing contraceptives**

5.2. Biologic mediators

5.2.1. Cranberry products

Cranberry juice and cranberry products are not recommended for the prevention of urinary tract infections in populations at risk because there is no consistent evidence as to

the effective amount, concentration and duration of intake of cranberry products. The inconclusive evidence on the effect of cranberry products in the prevention of UTI maybe due to different PACS (proanthocyanidins) used. The recommended dose for UTI prevention is daily consumption of 300 mL of cranberry juice cocktail or 500 mg capsules containing 36 mg PACs) taken twice a day as the anti-adhesion activity decreases over time. Among patients wherein long-term antibiotic prophylaxis for recurrent UTI is deemed necessary, the use of cranberry 500 mg capsules containing 36 mg PAC taken twice a day can be an option to avoid emergence of resistance of fecal and urine isolates of *E. coli* to trimethoprim, amoxicillin and ciprofloxacin.

Conditional recommendation, moderate quality of evidence

5.3. Hormonal treatments in post-menopausal women

5.3.1. Application of intravaginal estriol cream once each night for two weeks followed by twice-weekly applications for at least 8 months OR use of an estradiol releasing silicone vaginal ring for 3 months is recommended for the prevention of recurrent UTI in post-menopausal women

Strong recommendation, moderate quality of evidence

5.3.2. Data is insufficient to recommend vaginal estrogens over antibiotics for the prevention of recurrent UTI.

Weak recommendation, low quality of evidence

5.3.3. Low-dose oral estrogen is not recommended for the prevention of recurrent UTI.

Strong recommendation, high quality of evidence

5.4. Immunoprophylaxis for recurrent UTI

5.4.1. Immunoprophylaxis, using immune-active *E. coli* fractions, is recommended for the prevention of recurrent UTI. The dosing regimen is once daily per orem for 3 months.

Strong recommendation, moderate quality of evidence

5.4.2. A longer/extended dosing regimen (once daily for 3 months, rest for 3 months, 10 days per month for 3 months, and rest for 3 months) may be associated with a better control of recurrence in the longer term.

Weak recommendation, moderate quality of evidence

6. How effective are antibiotic prophylactic regimens in preventing recurrent UTI?

6.1. Prophylaxis is recommended in women whose frequency of recurrence is not acceptable to the patient in terms of level of discomfort or interference with activities of daily living. Prophylaxis may be withheld if the frequency of recurrence is tolerable to the patient.

6.2. If a decision is made to give antibiotic prophylaxis, either of the following is recommended:

- **Continuous prophylaxis, defined as the daily intake of a low-dose of antibiotic for 6-12 months**

Strong recommendation, moderate quality of evidence

OR

- **Post-coital prophylaxis, defined as the intake of a single dose of antibiotic immediately after sexual intercourse**
  Strong recommendation, moderate quality of evidence
  OR
- **Intermittent prophylaxis, defined as self-treatment with a single antibiotic dose based on patient's perceived need.**
  Weak recommendation, low quality of evidence

6.3. Any of the antibiotics in Table 4 given either continuously for 6 to 12 months or as post-coital prophylaxis can reduce the clinical and microbiologic recurrence of UTI episodes
Strong recommendation, moderate quality of evidence

Table 4. Antibiotics proven effective in reducing the number of recurrences of UTI[3,8,10,26,28,29,31,32,70,71]

Antibiotics	Recommended doses		
	Continuous prophylaxis	Post-coital prophylaxis	Intermittent prophylaxis
Nitrofurantoin	50-100 mg at bedtime	50-100 mg	50 mg
Trimethoprim	100 mg at bedtime	100 mg	
Cotrimoxazole	40 mg/200 mg at bedtime	40 mg/200 mg	40 mg/200 mg
CotrimoxazolE	40 mg/200 mg 3x/week	80 mg/400 mg	
Ciprofloxacin	125 mg at bedtime	125 mg	125 mg
Norfloxacin	200 mg at bedtime	200 mg	200 mg
Ofloxacin		100 mg	
Pefloxacin	400 mg weekly		
Cefalexin	125-250 mg at bedtime	125-250 mg	
Cefaclor	250 mg at bedtime		250 mg
Fosfomycin	3 g every 10 days		
Amoxicillin			500 mg
Cefuroxime			250 mg

7. How should individual episodes of UTI be treated in women with recurrent UTI?

7.1. Any of the antibiotics for acute uncomplicated cystitis (Table 5) may be used in the treatment of individual episodes of UTI in women with recurrent UTI.
Strong recommendation, moderate quality of evidence

Table 5. Antibiotics for acute uncomplicated cystitis

Antibiotics		*Recommended dose and duration*
Primary	Nitrofurantoin monohydrate macrocrystals (not sold locally)	100 mg BID for 5 days PO
	Nitrofurantoin macrocrystals	100 mg QID for 5 days PO
	Fosfomycin trometamol	3 g single dose PO
Alternative	Pivmecillinam (not sold locally)	400 mg BID for 3–7 days PO
	Ofloxacin	200 mg BID for 3 days PO
	Ciprofloxacin	250 mg BID for 3 days PO
	Ciprofloxacin extended release	500 mg OD for 3 days PO
	Levofloxacin	250 mg OD for 3 days PO
	Norfloxacin	400 mg BID for 3 days PO
	Amoxicillin-clavulanate	625 mg BID for 7 days PO
	Cefuroxime axetil	250 mg BID for 7 days PO
	Cefaclor	500 mg TID for 7 days PO
	Cefixime	200 mg BID for 7 days PO
	Cefpodoxime proxetil	100 mg BID for 7 days PO
	Ceftibuten	200 mg BID for 7 days PO
ONLY if with proven susceptibility	Trimethoprim-sulfamethoxazole (TMP-SMX)	160/800 mg BID for 3 days PO

7.2. Consider intermittent self-administered therapy in highly educated, well-informed, motivated patients, wherein the patients are able to recognize the characteristic signs and symptoms of UTI, are compliant with medical instructions and have a good relationship with a medical provider.
Strong recommendation, moderate quality of evidence

7.3. Breakthrough infections during prophylaxis should be treated empirically with any of the antibiotics recommended for uncomplicated cystitis other than the antibiotic being given for prophylaxis. Request for a urine culture and modify the treatment accordingly.

8. How effective are non-pharmacologic interventions treating urinary tract infections?

8.1. Cranberry juice and cranberry products are not recommended for the treatment of urinary tract infection.
Strong recommendation, low quality of evidence

8.2. There is evidence to recommend acupuncture for prevention of recurrent UTI among women when antibiotic prophylaxis is contraindicated.

8.3. There is no available evidence to recommend coconut juice in the prevention or treatment of UTI.

8.4. There is insufficient evidence to recommend oral water hydration (2 to 2.5 liters/day) in the prevention or treatment of UTI.
Weak recommendation, low quality of evidence

8.5. There is insufficient evidence to recommend drinking more water and voiding before and after intercourse to prevent UTI.
Strong recommendation, low quality of evidence

DISCUSSION

1. How is recurrent urinary tract infection (rUTI) diagnosed?

1.1. Recurrent UTI is diagnosed when a healthy non-pregnant woman with no known urinary tract abnormalities has 3 or more episodes of acute uncomplicated cystitis documented by urine culture during a 12-month period OR 2 or more episodes in a 6- month period.[1-3]

1.2. Recurrent UTI may either be a relapse or a reinfection. Relapse occurs when the initial organism persists within the urinary tract and re-emerges despite adequate treatment usually occurring 1-2 weeks after stopping treatment. Reinfection, on the other hand, occurs when recurrent UTI is caused by a different bacterial isolate, or by the previously isolated bacteria after a negative intervening culture or an adequate period (≥ 2 weeks) between infections.[4,5]

Summary of evidence

In a study of college women with cystitis, 25% experienced at least one culture-confirmed recurrence within the six months following the initial infection and 2.7% had a second recurrence during this same time period.[6] A 44% recurrence rate of UTI was reported within one year among Finnish women aged 17–82 who had *E. coli* cystitis.[7,8]

Recurrent UTI may either be a relapse or a reinfection. Reinfection is more common than relapse and often occurs within the first 3 months after the primary infection. When E. coli causes the initial infection, there is a higher risk of reinfection within the first 6 months than when the infection is caused by another pathogen.[9,10]

2. Among those with recurrent UTI, who would benefit from further diagnostic evaluation?

2.1. Routine screening for urologic abnormalities is not recommended for the general patient population.
Strong recommendation, low quality of evidence

2.2. Screening for urologic abnormalities is recommended in the following situations:

- **No response to appropriate antimicrobial therapy or rapid relapse after such therapy**
- **Gross hematuria during a UTI episode or persistent microscopic hematuria**
- **Obstructive symptoms**
- **Clinical impression of persistent infection**
- **Infection with urea-splitting bacteria (*Proteus*, *Morganella*, *Providencia*)**
- **History of pyelonephritis**
- **History of or symptoms suggestive of urolithiasis**
- **History of childhood UTI**
- **Elevated serum creatinine**

2.3. Patients with the above factors may benefit from further diagnostic evaluation as these risk factors have been identified to be associated with a higher incidence of urologic abnormalities.

2.4. All women with recurrent UTI should undergo a complete history and physical examination to evaluate urogenital anatomy and estrogenization of vaginal tissues and to detect prolapse. Post-void residual urine should be measured.

Summary of evidence

The reported prevalence of urologic abnormalities in women with recurrent UTI significant enough to warrant a change in management ranges from 0% to 6%.[11-14] A systematic review estimated the overall prevalence at 0.8%.[15] A study of 148 women, which included only those with at least one of the factors listed above, reported a prevalence of urologic abnormalities of 21%.[16] Because UTI during childhood is associated with reflux nephropathy, inclusion of this factor was also recommended although there is no data regarding its predictive value.[15]

A Canadian prospective study of 186 women with recurrent UTI who underwent cystoscopy and ultrasonography or excretory urography identified factors that would indicate urologic evaluation.[16] These include hematuria (gross hematuria and persistent microscopic hematuria between infections), pyelonephritis and a presentation that is not typical for simple uncomplicated UTIs (obstructive symptoms, infection with urea-splitting bacteria, clinical impression of persistent infection or urinary calculi). Diabetes itself did not warrant urologic evaluation.

Risk factors

In a large case-control study of women with and without a history of recurrent UTIs, multivariate analysis showed that the frequency of sexual intercourse was the strongest risk factor for recurrent UTI.[17] In premenopausal women, in addition to increased frequency of intercourse, use of a spermicide and new sexual partners are behavioral risk factors for recurrent UTI. Non-behavioral risk factors include UTI before age 15 and a maternal history of UTI.[8,10]

In postmenopausal women, estrogen loss, a non-secretor status of histocompatibility blood-group antigens and the presence of incontinence, significant pelvic floor prolapse and an increased post-void residual urine volume increase the risk for recurrent UTI.[18] The lack of estrogen causes marked changes in the vaginal microflora including loss of lactobacilli and increased colonization by *E. coli.* In a case-control study of 149 healthy postmenopausal women with a history of recurrent UTI and 53 controls without a history of UTI, mechanical and/or physiologic factors that affect bladder emptying were found to be strongly associated with recurrent UTIs. Multivariate analysis showed that urinary incontinence (odds ratio 5.79), a history of UTI before menopause (OR 4.85) and non-secretor status (OR 2.9) were the factors most strongly associated with recurrent UTI.

Positive predictive factors for recurrent UTIs in women are symptoms after intercourse, a prior history of pyelonephritis, absence of nocturia, and prompt resolution of symptoms (48 hours) after initiation of treatment. The main negative predictors are the presence of nocturia and persistence of symptoms between episodes of treated infection.[1,10]

3. What diagnostic work-ups are indicated in women with recurrent UTI?

3.1. Radiologic or imaging studies and cystoscopy are not routinely indicated in patients with recurrent UTI.
Weak recommendation, low quality of evidence

3.2. Renal ultrasound or CT scan/stonogram may be done to screen for urologic abnormalities
Strong recommendation, low quality of evidence

3.3. Patients with anatomical abnormalities should be referred to a specialist (nephrologist or urologist) for further evaluation.
Strong recommendation, low quality of evidence

Summary of evidence

In a prospective blinded observational study of 60 patients presenting for recurrent UTI, the diagnostic yield of intravenous urography was only 8.3% (i.e, 91.7% of the tests were negative), with an odds ratio for positive results at 0.22 (95% CI, 0.08-0.62).[20]

A prospective study of 100 young women for the evaluation of recurrent UTI was done in urologic departments in The Netherlands.[21] These women underwent a standardized workup consisting of a voiding diary, urinalysis and culture, abdominal x-ray with ultrasound or intravenous urography and cystoscopy. The radiologic studies revealed only one relevant abnormality.

However, in a database review which included 118 women with recurrent UTI who underwent cystoscopy, nine (8%) patients had significant findings.[22] Patients who were older than 50 years were associated with a higher risk of having a positive finding.

Most studies report urologic abnormalities identified from intravenous pyelography (IVP). However, IVP can cause mild generalized reactions (hypersensitivity reactions, nausea, vomiting and syncope) in 5 to 10% of patients. In one study where 120 women underwent both IVP and renal ultrasound (RUS), there was good agreement between the two modalities for diagnosis of hydronephrosis (kappa = 0.91) but less agreement in the diagnosis of major pyelonephritis changes (kappa = 0. 79), ureteric calculi and renal calculi >5 mm (kappa =0. 78) and expansile lesions (kappa = 0.38).[23] In a study of 94 women with a history of UTI referred by their physician for IVP or RUS, the RUS and plain abdominal radiograph findings were compared with IVP and the only disagreement was in one patient where RUS detected a 1.5 cm intrarenal mass not seen on IVP.[24] In another study comparing combined ultrasound and plain abdominal radiograph with IVP performed on 89 women and 69 men with a history of UTI, the two modalities concurred in 152 of the 158 patients. RUS and plain film did not detect duplex kidney, small bladder diverticula, papillary necrosis and mild bilateral hydroureter of unexplained etiology.[25]

4. When is prophylaxis for recurrent UTI indicated?

4.1. Prophylaxis is recommended in women whose frequency of recurrence is not acceptable to the patient in terms of level of discomfort or interference with activities of daily living. Prophylaxis may be withheld

according to patient preference if the frequency of recurrence is tolerable to the patient.
Strong recommendation, low quality of evidence

4.2. The following factors should guide the physician in determining the patient's risk-benefit profile and in deciding which prophylactic strategies will be used:
- **Frequency and pattern of recurrences**
- **Patient's lifestyle, compliance and willingness to commit to a specific regimen**
- **Plans for a pregnancy**
- **Antimicrobial resistance and susceptibility pattern of the organisms causing the patient's previous UTIs**
- **Risk of adverse events and drug allergies**

4.3. Prophylaxis should only be initiated after counseling and behavior modification have been attempted in order to minimize antibiotic exposure and possible adverse effects.
Strong recommendation, low quality of evidence

4.4. Antibiotic prophylaxis should be limited to women with recurrent UTI in whom non-antimicrobial strategies have not been effective and who prefer prophylactic antimicrobial therapy.
Strong recommendation, moderate quality of evidence

Summary of Evidence

Burden

The estimated burden of recurrent UTI is 1 in 4 women will have a recurrence within a year. Each episode of UTI is associated with 6 days of symptoms, 2 days of restricted activity, one day absence from work or class and a half day in bed.

Benefits

Although long-term sequelae such as renal failure, genitourinary cancer or increased mortality have not been reported from recurrent UTI, a woman with frequent recurrent urinary infection may experience substantial social and professional disruption attributable to symptomatic episodes.[4] Women who experience acute uncomplicated urinary infection are also at risk for acute non-obstructive pyelonephritis.[17] Therefore, the decision to give prophylaxis rests more on weighing the benefit of alleviating the discomfort of UTI and avoiding the inconveniences associated with recurrent episodes versus the potential harm of antibiotic prophylaxis and emergence of resistant strains. The goal of long-term management of recurrent UTI should be to improve the quality of life while minimizing antimicrobial exposure.[3] Patients should be counseled about the pros and cons of various prophylactic strategies and the decision to give prophylaxis should be individualized for each patient.

Antibiotic prophylaxis has been shown to reduce the risk of recurrence by approximately 95%.[26,27] Its use should be limited to women with recurrent UTI in whom non-antimicrobial strategies have not been effective and who prefer prophylactic antimicrobial therapy.

Risk factors

In a large case-control study of women with and without a history of recurrent UTIs, multivariate analysis showed that the frequency of sexual intercourse was the strongest risk factor for recurrent UTI.[17] In premenopausal women, in addition to increased frequency of intercourse, use of a spermicide and new sexual partners are behavioral risk factors for recurrent UTI. Non-behavioral risk factors include UTI before age 15 and a maternal history of UTI.[8,10]

In postmenopausal women, estrogen loss, a non-secretor status of histocompatibility blood-group antigens and the presence of incontinence, significant pelvic floor prolapse and an increased post-void residual urine volume increase the risk for recurrent UTI.[18] The lack of estrogen causes marked changes in the vaginal microflora including loss of lactobacilli and increased colonization by *E. coli.* In a case-control study of 149 healthy postmenopausal women with a history of recurrent UTI and 53 controls without a history of UTI, mechanical and/or physiologic factors that affect bladder emptying were found to be strongly associated with recurrent UTIs. Multivariate analysis showed that urinary incontinence (odds ratio 5.79), a history of UTI before menopause (OR 4.85) and non-secretor status (OR 2.9) were the factors most strongly associated with recurrent UTI.[17]

Harms

The reported incidence of adverse drug effects with antibiotic prophylaxis ranges from 1.3% to 20%.[28-33] In the Cochrane review by Albert 2004, all trials reported severe side effects necessitating withdrawal of antibiotic therapy, with a pooled RR of 1.58 (95% CI 0.47– 5.28), favoring the placebo group.[34] The most common described severe side effects were skin rash and nausea. The RR of having one side effect not requiring antibiotic withdrawal was 1.78 (95% CI 1.06 – 3.00) again favoring the placebo group. Most of the antibiotics used for antibiotic prophylaxis of recurrent UTI are also associated with a risk for acquiring *Clostridium difficile*-associated diarrhea (CDAD). This risk should be discussed with patients and patients with a history of recurrent CDAD should be offered non-antimicrobial preventive approaches.[8]

A surveillance study of antimicrobial resistance in women with cystitis from Europe and Brazil showed high rates of resistance to *E. coli* isolates, 29% for trimethoprim-sulfamethoxazole (cotrimoxazole) and 8% for fluoroquinolones.[35] In another study evaluating 2,478 *E. coli* isolates, the most common pattern of multi-resistance for *E. coli* isolates was for ampicillin/sulfamethoxazole (8.7% of strains), followed by ampicllin/sulfamethoxazole/trimethoprim/cotrimoxazole resistance (6.4% of all strains.). It was also noted that, with the exception of fosfomycin, resistance to any antibiotic agent is associated with an increased resistance to other antibiotic agents tested.[36]

Costs

Another relevant issue is cost-effectiveness of prophylaxis versus treating individual episodes of recurrent UTI. A cost-effectiveness study done in the United States in 1981 concluded that continuous prophylaxis with cotrimoxazole was more cost-effective than treating individual episodes.[37] However, these results cannot be directly applied in our setting because of differences in costs of physician charges, medications and extent of laboratory work-up.

5. How effective are non-antimicrobial strategies in preventing recurrent UTI?

5.1. Behavioral changes

5.1.1. Behavioral changes can be useful antimicrobial-sparing measures in the prevention of recurrent UTI.

Weak recommendation, low quality of evidence

5.1.2. These behavioral measures include the following:

- **post-defecation and anal cleansing antero-posteriorly always in women to avoid contaminating the periurethral area with fecal flora**
- **post-coital douche or post coital urination**
- **liberal fluid intake especially after intercourse**
- **avoidance of tight-fitting underwear**
- **use of alternative form of contraception for women using spermicide-containing contraceptives**

Summary of Evidence

There are no randomized trials regarding lifestyle modifications in preventing recurrent UTI. However, based on reviews and recommendations by various authors, they may be an important cornerstone of prevention since they carry a low risk of adverse effects.[3,10,38]

5.2. Biologic mediators

5.2.1. Cranberry products

Cranberry juice and cranberry products are not recommended for the prevention of urinary tract infections in populations at risk because there is no consistent evidence as to the effective amount, concentration and duration of intake of cranberry products. The inconclusive evidence on the effect of cranberry products in the prevention of UTI maybe due to different PACS (proanthocyanidins) used. The recommended dose for UTI prevention is daily consumption of 300 mL of cranberry juice cocktail or 500 mg capsules containing 36 mg PACs) taken twice a day as the anti-adhesion activity decreases over time.

Among patients wherein long-term antibiotic prophylaxis for recurrent UTI is deemed necessary, the use of cranberry 500 mg capsules containing 36 mg PAC taken twice a day can be an option to avoid emergence of resistance of fecal and urine isolates of *E. coli* to trimethoprim, amoxicillin and ciprofloxacin.

Conditional recommendation, moderate quality of evidence

Summary of evidence

Benefits

Cranberries contain condensed tannins called proanthocyanidins, which prevent fimbriated *E. coli* from adhering to uroepithelial cells in the urinary tract. The antiadhesive property of cranberry probably helps prevent UTI by directly preventing E.coli from adhering to uroepithelial cells and by selecting for less adherent bacterial strains in the stool.[39]

A recent Cochrane review of 6 cross-over studies, 11 parallel group studies with two arms; 5 with three arms, and 2 studies with a factorial design with a total of 4,473 participants assessed the effectiveness of cranberry products in preventing UTIs in susceptible populations.[40] It included studies comparing cranberry products to placebo, no treatment, water, methenamine hippurate, antibiotics, and *Lactobacillus*. RCTs cited in the 2004 UTI guideline development were included in this recent review.[41-43]

Cranberry versus placebo

The meta-analyses of 13 studies (2380 participants) showed that cranberry products did not significantly reduce the occurrence of symptomatic UTI compared to placebo, water or no treatment (RR 0.86, 95% CI 0.71 to 1.04). Subgroup analysis also failed to show significant reduction in UTI among women with recurrent UTIs (RR 0.74, 95% CI 0.42 to 1.31); older people (RR 0.75, 95% CI 0.39 to 1.44); pregnant women (RR 1.04, 95% CI 0.97 to 1.17); children with recurrent UTI (RR 0.48, 95% CI 0.19 to 1.22); cancer patients (RR 1.15 95% CI 0.75 to 1.77); and people with neuropathic bladder or spinal injury (RR 0.95, 95% CI: 0.75 to 1.20).

Cranberry versus antibiotics

Meta-analysis of two RCTs comparing the effectiveness of cranberry capsules with antibiotics in women showed that cranberry capsules did not significantly reduce the risk of repeat UTI (RR 1.31, 95% CI 0.85 to 2.02) compared to low-dose cotrimoxazole.[44,45] The NAPRUTI RCT among 221 premenopausal women showed that the proportion with at least 1 symptomatic UTI during the 1-year study period was slightly greater in the cranberry than in the cotrimoxazole group (78.2% versus 71.1%).[45] However, there were more fecal and urine resistant *E. coli* isolates in the cotrimoxazole (86.3 %) than in the cranberry arm (23.7%). Similar pattern of resistance was seen on trimethoprim, ciprofloxacin, and amoxicillin as early as 1 month of prophylactic treatment with cotrimoxazole.

Cranberry versus Lactobacillus

The RCT by Kontiokari (2001) compared cranberry-lingonberry juice 50 ml daily for 6 months, lactobacillus drink 5 days a week for one year, and placebo for the first recurrence of symptomatic UTI among 150 women who had *E.coli* infections.[42] Thirteen women dropped out from the study: four (8%) each in the cranberry and lactobacillus group and five (10%) in the control group usually because of change in residence. The RCT showed that regular drinking of cranberry juice significantly reduced the recurrence of UTI compared with the control group at 6 months (ARR 20%, 95% CI 3% to 36%; NNT 5, 95% CI 3 to 34). At 12 months, there was no significant reduction in the recurrence of UTI in the cranberry group compared to the control group (ARR 14%, 95% CI –4%, 32%). On intention-to-treat analysis, the significant reduction in UTI was not maintained (ARR 12%, 95% CI -4%, 28%).

Harms

Dropout rates in several studies were high (20-55%). Common reasons for withdrawal were the taste, caloric load, and high cost of cranberry.[40,42] One study warned that ingesting large amounts of cranberries over a long duration may increase the risk of some types of urinary stones in high-risk patients because of the increased urinary excretion of oxalate and slight urinary acidification.[46] Gastrointestinal effects such as hearburn, vomiting, diarrhea, and gastroenteritis were the common adverse effects reported in several studies included in the recent Cochrane review.[40]

Costs

The mean annual cost of prophylaxis was Can$ 624 for cranberry tablets and Can$ 1,400 for cranberry juice.[43] Cost savings were highest when patients experienced >2 UTIs per year and had >2 days of missed work. Total antibiotic consumption was less annually in both treatment groups compared with placebo. Cost effectiveness ratios demonstrated cranberry tablets were twice as cost-effective as organic juice for prevention. In this single trial that evaluated the issue of cost, Stothers (2002) concluded that cranberry tablets are more cost-effective than organic cranberry juice for the prevention of UTI.

Comments

While the RCT by Stothers provides some evidence that cranberry tablet or capsule is a cost-effective option in the prevention of UTI, it is the consensus of the task force that cranberry juice or any of its products cannot be recommended at this time because there is no consistent evidence as to the effective amount, concentration and duration of intake of cranberry products. The recommended amount for UTI prevention is daily consumption of 300 mL of cranberry juice cocktail or capsules containing 36 mg PACs (proanthocyanidins) taken twice a day as the anti-adhesion activity decreases over time.[46] Furthermore, high withdrawal rates in most of the trials (20%-55%) suggest that long-term adherence may be difficult to achieve for long periods.

Table 3. Available cranberry products in the Philippines

Product	Components	PAC component	Price per bottle
Cranbiotics (Futurebiotics)	Cranberry extract Lactobacillus sporogenes	120 mg (standardized for 30% PACs)	P615/60 caps
CranRx (Natures way)	Cranberry extract	500 mg (3X more Standardized PACs)	P400/30 caps
Cranberry concentrate (NOW foods)	Cranberry conc Vit C Sugar	5,600 mg (700 mg - 8:1 extract) whole cranberries	P410/90 caps
Cranberry GNC	Cranberry Fruit Powder	500 mg	P1,160
Fontana cranberry juice	Cranberry Vit C	NS	P84/ 1L

5.2.2. Probiotic lactobacilli

Lactobacilli both in oral form and vaginal suppositories are not recommended in the prevention of UTI.

Strong recommendation, high quality of evidence

Summary of evidence

Benefits

A recent RCT on 252 postmenopausal women with recurrent UTIs comparing low-dose once daily cotrimoxazole and twice daily oral capsules of *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 showed that after 12 months of prophylaxis, the mean number of clinical recurrence (2.9, 95% CI, 2.3 to 3.6) did not differ significantly between the antibiotic group (3.3 95% CI, 2.7 to 4.0) and the lactobacilli group (p=0.42).[48] The mean number of microbiologic recurrence and asymptomatic bacteriuria was 1.2 (95% CI, 0.9-1.6) in the cotrimoxazole group and 1.8 (95% CI, 1.4-2.3) in the lactobacilli group (p=0.02). The resistance to cotrimoxazole, trimethoprim, and amoxicillin increased from approximately 20% to 40% and approximately 80% to 95% in *E. coli* from the feces and urine of asymptomatic women and among *E. coli* causing a UTI among women after 1 month of cotrimoxazole prophylaxis.

One hundred young women with a history of recurrent UTI treated with antibiotics were randomized to receive an intra-vaginal capsule of *Lactobacillus crispatus* (Lactin-V) or placebo daily for 5 days then once weekly for 10 weeks. The study showed that recurrent UTI occurred in 15% of women receiving Lactin-V compared with 27% of women receiving placebo (RR 0.5 95% CI, 0.2–1.2).[49]

Other clinical trials of lactobacilli to prevent recurrent UTI were small and have not shown a benefit for lactobacilli over other preventive treatments or placebo based on a review done by Barrons, et al in 2008.[50]

Comments

It is important to understand the characteristics of the particular strain being promoted as a probiotic to prevent UTIs. *L. rhamnosus* GR-1 is reported to contain key beneficial characteristics for candidate probiotic strains, namely highly effective adherence to vaginal epithelial cells, inhibitory to adherence of uropathogens, and growth inhibitory for pathogens of the urogenital tract. The other component, L fermentum RC-14 produces H2O2 and a biosurfactant and is highly adherent. Currently there are no adequately studied probiotic products for preventing UTIs. Multiple problems exist for the development of such a product (identifying specific strains that colonize and inhibit uropathogen colonization of the vagina and survive storage and administration) especially if taken orally, which require passage through the gut.[51]

5.3. Hormonal treatments in post-menopausal women

Application of intravaginal estriol cream once each night for two weeks followed by twice-weekly applications for at least 8 months OR use of an estradiol releasing silicone vaginal ring for 3 months is recommended for the prevention of recurrent UTI in post-menopausal women

Strong recommendation, moderate quality of evidence

Summary of Evidence

Vaginal estrogen versus placebo

Benefits

A Cochrane systematic review investigated the efficacy and safety of estrogens for preventing recurrent UTI in post-menopausal women.[52] Two studies used vaginal estrogens; however, the authors did not pool these studies due to significant heterogeneity attributed to the varying type of application method used.[53,54] Raz 1993 compared topically applied intravaginal oestriol cream to placebo cream while Eriksen 1999 compared releasing silicone vaginal ring (containing 2 mg oestriol) with a no treatment control group.

In the study by Raz 1993, the use of intravaginal oestriol cream significantly reduced the rate of symptomatic UTI episodes (0.5 episodes per patient year in the oestriol group versus 5.9 in the control group, $p<0.001$).[53] In addition, the estrogen group had a cumulative likelihood of remaining disease free compared to the placebo group (0.95 versus 0.30, $p<0.001$) and had less antibiotic days than the placebo group (6.9 +/- 1.1 days versus 32.0 +/- 7.8 days, $p<0.001$) In the Eriksen 1999 study, use of a vaginal ring significantly reduced the rate of UTI by 36%.[54] Eriksen also reported that after 9 months, 45% of participants were free of UTI in the estrogen group versus 20% in the control group ($p<0.008$).

Harms

Adverse events reported by patients receiving vaginal estrogens and placebo included vaginal bleeding and non-physiologic discharge, and vaginal irritation, burning, or itching.[53,54] Based on the systematic review mentioned, there was no significant difference in adverse events between the groups treated with vaginal estrogens or placebo cream (RR 4.72, 95% CI 0.67 - 33.53; $I^2 = 67.5\%$).

5.3.1. Data is insufficient to recommend vaginal estrogens over antibiotics for the prevention of recurrent UTI.
Weak recommendation, low quality of evidence

Summary of evidence

Vaginal estrogen versus Antibiotics

Benefits

In the same Cochrane review by Perrotta 2008, two small studies compared vaginal estrogens and antibiotics, but the studies used different modes of estriol administration and different antibiotic comparators.[52] The Raz 2003 study used a vaginal pessary against oral nitrofurantoin while the Xu 2001 study used a vaginal cream against oral ofloxacin.[55,56] These two studies had conflicting results. In the Raz 2003 study involving 171 patients, the antibiotic group reported significantly less UTIs than the estrogen group after 3 months (RR 1.30, 95% CI 1.01 – 1.68).[55] On the other hand, the Xu 2001 study involving 45 patients reported significantly less UTIs in the estrogen group compared to the antibiotic group (RR 0.09, 95% CI 0.02 – 0.36).[56]

However, there was no significant difference in the number of women with recurrent UTI two months after stopping treatment (RR 0.56, 95% CI 0.09 – 3.5

Harms

In the study by Xu 2001, burning and itching were reported in the estrogen group. No side effects were reported for the antibiotic group.[56] In the study by Raz 2003 the adverse events were more frequent in the vaginal estrogen group necessitating dropouts (27/86 from the estrogen group and 23/85 from the nitrofurantoin group).[55] These included itching, burning, vaginal discharge and metrorrhagia in the estrogen group and fever, gastrointestinal upsets and urticaria in the nitrofurantoin group. When pooled, the RR for adverse events was 12.86 (95% CI 1.75 – 94.29)

5.3.2. Low-dose oral estrogen is not recommended for the prevention of recurrent UTI.

Strong recommendation, high quality of evidence

Summary of evidence

Benefits

Estrogen therapy is associated with a return of the premenopausal lactobacillus-dominated vaginal flora, acid vaginal pH and reduced vaginal colonization with organisms, all of which account for the decreased risk of UTI. A systematic review by Perrotta 2008 included four studies involving 2798 women and compared oral estrogens with placebo.[52,57-60] There was no significant difference in the number of women with UTI at the end of the treatment period (RR 1.08, 95% CI 0.88 to 1.33; I^2 = 0%).

Harms

In the same systematic review by Perrotta 2008, there were only two studies that reported adverse events.[52] Cardozo 1998 reported breast tenderness and mild vaginal bleeding, and Ouslander 2001 reported vaginal spotting and mild breast discomfort.[58,60] There were significantly less adverse events in the placebo group (2 studies, 104 women: RR 5.11, 95% CI 1.39 to 18.76; I^2 = 0%).

Adhesion blockers

UTIs caused by *E. coli* are initiated by adhesion of the bacteria to mannosylated receptors in the uroepithelium by means of FimH adhesin located on type 1 pili; theoretically, mannosides could block adhesion. D-mannose, available in health-food stores, may block adhesion; however, it has not been evaluated in clinical trials.[3]

5.4. Immunoprophylaxis for recurrent UTI

5.4.1. Immunoprophylaxis, using immune-active *E. coli* fractions, is recommended for the prevention of recurrent UTI. The dosing regimen is once daily per orem for 3 months.

Strong recommendation, moderate quality of evidence

Summary of evidence

Immunotherapy/immunoprophylaxis involves the administration of lyophilized bacterial lysates from 18 *E. coli* strains most frequently responsible for UTI, which then acts as an immunostimulant. Exposure to the immunostimulant enhances the patient's innate and adaptive immune system of the urinary tract mucosa causing it to promptly react to pathogenic *E. coli.*

The bacterial extract activates T-helper cells and stimulates the proliferation and activity of T and B lymphocytes, which migrate to the mucosal-associated lymphoid tissue of the urinary tract. These cells secrete increased levels of immunoglobulin A (sIgA) specific to the E. coli fragments. Administration of the vaccine also causes increased levels of bladder IFN-y and IL6 levels and upregulation of the PMN killing activity.

Three meta-analyses of 5 studies consistently demonstrated the effectiveness of immunoprophylaxis compared to placebo in preventing symptomatic bacteriuria, decreasing the episodes of dysuria, asymptomatic bacteriuria and the use of antibiotics.[61-63]

Pooled analysis of 6 RCTs showed that immunoprophylaxis significantly reduced the risk of recurrent UTI by 40% (RR = 0.60, 95% CI 0.53, 0.68).[64-69]

Limited information on adverse events from the RCTs showed good tolerability profile for immunoprophylaxis. Few adverse events were reported including pruritus, diarrhea, and headache with flushing. Adverse event rates ranged from 2.3 to 5.4%.

The six RCTs were of fair methodological quality. Most were properly randomized trials with adequate allocation methods. Most had sufficient blinding. Nearly all trials had significant patient drop out but these were in equal proportion across treatment groups. The results across the 6 trials were consistent. High value was given to reduction of recurrence**.**

No cost-effectiveness studies have been published to compare immunoprophylaxis versus treatment of individual UTI episodes.

5.4.2. A longer/extended dosing regimen (once daily for 3 months, rest for 3 months, 10 days per month for 3 months, and rest for 3 months) may be associated with a better control of recurrence in the longer term.

Weak recommendation, moderate quality of evidence

Summary of evidence

One RCT using an extended dosing regimen showed greater reduction in recurrent infection at the 6 month period compared to other RCTs using the once-daily dosing for 3 months. Adverse events associated with the extended regimen were minor.[68] The single RCT using the extended dosing regimen was a double blinded trial with proper randomization and adequate allocation concealment. However, the value of greater reduction of the risk, compared to the cost and inconvenience of extended/intensified treatment regimen needs to be considered. There is a need to assess the justification of higher cost of treatment with the risk and expected cost of a recurrent UTI.

6. How effective are antibiotic prophylactic regimens in preventing recurrent UTI?

6.1. Prophylaxis is recommended in women whose frequency of recurrence

is not acceptable to the patient in terms of level of discomfort or interference with activities of daily living. Prophylaxis may be withheld if the frequency of recurrence is tolerable to the patient.

6.2. If a decision is made to give antibiotic prophylaxis, either of the following is recommended:

- **Continuous prophylaxis, defined as the daily intake of a low-dose of antibiotic for 6-12 months**
  Strong recommendation, moderate quality of evidence
  OR
- **Post-coital prophylaxis, defined as the intake of a single dose of antibiotic immediately after sexual intercourse**
  Strong recommendation, moderate quality of evidence
  OR
- **Intermittent prophylaxis, defined as self-treatment with a single antibiotic dose based on patient's perceived need.**
  Weak recommendation, low quality of evidence

6.3. Any of the antibiotics in Table 4 given either continuously for 6 to 12 months or as post-coital prophylaxis can reduce the clinical and microbiologic recurrence of UTI episodes
Strong recommendation, moderate quality of evidence

Table 4. Antibiotics proven effective in reducing the number of recurrences of UTI[3,8,10,26,28,29,31,32,70,71]

Antibiotics	Recommended doses		
	Continuous prophylaxis	Post-coital prophylaxis	Intermittent prophylaxis
Nitrofurantoin	50-100 mg at bedtime	50-100 mg	50 mg
Trimethoprim	100 mg at bedtime	100 mg	
Cotrimoxazole	40 mg/200 mg at bedtime	40 mg/200 mg	40 mg/200 mg
CotrimoxazolE	40 mg/200 mg 3x/week	80 mg/400 mg	
Ciprofloxacin	125 mg at bedtime	125 mg	125 mg
Norfloxacin	200 mg at bedtime	200 mg	200 mg
Ofloxacin		100 mg	
Pefloxacin	400 mg weekly		
Cefalexin	125-250 mg at bedtime	125-250 mg	
Cefaclor	250 mg at bedtime		250 mg
Fosfomycin	3 g every 10 days		
Amoxicillin			500 mg
Cefuroxime			250 mg

Summary of evidence

Continuous antibiotic prophylaxis versus placebo

An updated Cochrane systematic review of 10 RCTs (N=430 premenopausal

and postmenopausal women) showed that continuous antibiotic prophylaxis for 6-12 months reduced the number of clinical and microbiological recurrences of UTI compared to placebo.[2] During active prophylaxis the rate of microbiological recurrence/person-year was 0 to 0.9 episodes in the antibiotic group versus 0.8 to 3.6 episodes in the placebo group. The RR of having one microbiological recurrence was 0.21 (95% CI 0.13 - 0.34) favoring antibiotic prophylaxis with NNT=1.85. The RR for clinical recurrence was 0.15 (95% CI 0.08 - 0.28). After prophylaxis, no difference in microbiological recurrence was seen in 2 studies (RR 0.82; 95% CI 0.44 - 1.53). There were more adverse events in the antibiotic group (RR 1.78; 95% CI 1.06 - 3.00). Adverse effects included vaginal and oral candidiasis, skin rash and nausea. Antibiotics included in this review were cotrimoxazole, nitrofurantoin, cephalexin and ciprofloxacin.

Continuous antibiotic prophylaxis versus another antibiotic regimen

Six RCTs (N=458 premenopausal and postmenopausal women) comparing different antibiotic regimens versus each other were included in the Cochrane review.[2] Results were not pooled because of significant heterogeneity. Individual results of the studies showed no significant differences in infection rates over 6-12 months with one antibiotic over another.[28,29,32,72-74] Antibiotics compared were nitrofurantoin, norfloxacin, cefaclor, trimethoprim, cotrimoxazole, and ciprofloxacin. The only trial that showed a difference compared nitrofurantoin 100 mg once daily with trimethoprim 100 mg once daily with a RR for microbiologic recurrence of 3.58 (95% CI 1.33-9.66) and a RR for clinical recurrence of 1.72 (95% CI 1.06, 2.79) favoring nitrofurantoin.

In the 6-month period after discontinuation of the 6-month prophylaxis, 48% of patients in the treatment groups developed at least one episode of UTI, a rate similar to that of the placebo group.[32] One other trial with a 6-month prophylaxis had similar results.[75] In one trial of 12-month prophylaxis, the authors report that 69% maintained improvement after discontinuation of prophylaxis but no details were provided.[29]

Continuous antibiotic prophylaxis versus non-antibiotics

The Cochrane review of Albert 2004 evaluated 2 studies that compared antibiotics (nitrofurantoin, trimethoprim) with methenamine hippurate and 1 study that compared trimethoprim with povidone iodine.[34] Only one study favored antibiotic prophylaxis in reducing recurrence of UTI. The Brumfitt 1981 study involving 99 patients (43 with nitrofurantoin, 56 with methenamine hippurate) showed that nitrofurantoin 50 mg every 12 hours prevented recurrence of UTI compared to methenamine hippurate with an RR of 0.7 (95% CI 0.10 – 0.75) favoring nitrofurantoin.[76]

Post-coital prophylaxis versus placebo

Post-coital administration of cotrimoxazole (40 mg/200 mg as a single dose) given for 6 months was compared with placebo in a randomized controlled trial of 28 women regardless of whether their UTI episodes were temporally related to sexual intercourse or not. The proportion of patients who developed UTI was 75% in the placebo group and 12% in the post-coital prophylaxis group.[33]

Continuous antibiotic prophylaxis versus post-coital prophylaxis

One RCT comparing post-coital versus continuous daily ciprofloxacin found no significant difference in rates of positive urine culture after 1 year (RR 0.9; 95% CI 0.55, 1.45); but the rate of discontinuance due to adverse drug reaction was higher in

the continuous prophylaxis group (5.35%) compared to the postcoital prophylaxis group (1.3%).[30] Continued suppression of gram-negative introital flora in 36% of women within one year of stopping continuous or postcoital ciprofloxacin prophylaxis was reported but there was no clinical correlation with actual episodes of urinary tract infection.

Continuous antibiotic prophylaxis versus intermittent prophylaxis

A recent RCT compared the effectiveness and safety of patient-initiated single dose (intermittent) against continuous low-dose antibiotic prophylaxis for post-menopausal women.[71] In the intermittent antibiotic group, a single-dose antibiotic was taken by patients every time they were exposed to conditions predisposing to UTI based on the patients' previous experience – such as, sexual intercourse, travelling, working or walking for a long time, emiction holdback, diarrhea or constipation. For each antibiotic, only one specific dose was used for all patients. They used any one of the following antibiotics based on previous antimicrobial susceptibility testing: furantoin 50 mg, sulphamethazine-trimethoprim 200/40 mg, norfloxacin 200 mg, ciprofloxacin 125 mg, amoxicillin 500 mg, cefaclor 250 mg or cefuroxime 250 mg.

Recurrent UTI episodes in both groups were significantly reduced (5.1 to 1.9 episodes/patient per year in the Intermittent Group ($p<0.001$) and from 4.7 to 1.4 episodes/patient year ($p<0.001$], in the Continuous Group).[71] The difference between the two groups was not statistically significant; however, the proportion of patients experiencing 0 or 1 episode of UTI per year in the continuous group was significantly higher than in the intermittent group (59.4% versus 35.5%; $p<0.05$).

On the other hand, the incidence of any adverse event in the continuous group was significantly higher than that in the intermittent group (92.5% versus 63.6%, $p<0.05$).[71] The continuous group had significantly higher gastrointestinal events compared with the continuous group (30.0% versus 9.1%, $p<0.05$), with a relative risk of 4.0 (95% CI 1.02 - 15.73; $p=0.045$, Fisher's exact test. In this study, the frequency of antibiotic used for the Intermittent group was 40.7 +/- 16.2 times/patient year, or approximately once a week, providing evidence that perhaps weekly prophylaxis may be as effective as daily prophylaxis. This study however is limited by its small sample size as <40 patients/group were included in the final analysis due to drop-outs (eight for the intermittent group and two for the continuous group).

Comments

Low-dose prophylaxis with antimicrobial agents that are concentrated in the urine can achieve inhibitory drug levels in the urine and prevent introduced bacteria from multiplying and colonizing the vagina. Sub-inhibitory drug levels may also decrease the expression of bacterial virulence factors and reduce fecal and vaginal reservoirs of *E. coli*.

It is important to determine if a patient will be able to comply with the recommended prophylactic regimen. In a retrospective cohort, compliance was the most important determinant of success of prophylaxis (OR 0.074; $p<0.0001$). Among the 51/181 subjects with failure of prophylaxis, 26/51 developed resistance to the administered agent.[77] In one study of long-term prophylaxis with cefaclor or nitrofurantoin, patients reported lack of compliance shortly before the onset of an episode of bacteriuria with cultures reporting susceptible strains.[28]

Comparative effectiveness of prevention strategies

A well-organized decision analysis using a Markov Chain Monte Carlo model compared the cost-effectiveness of 5 strategies in reducing recurrent UTI in women. The strategies evaluated were: nitrofurantoin prophylaxis, topical estrogen prophylaxis, daily cranberry prophylaxis, monthly acupuncture sessions and self-directed treatment with ciprofloxacin at the earliest symptom. The decision analysis showed that daily prophylactic use of nitrofurantoin resulted in the lowest number of UTIs per year (0.4) and the highest payer cost, but with the most quality-adjusted life days gained (QALDs) per year. Acupuncture resulted in the second-highest QALDs gained and decreased UTIs to 0.7 but this may be due to publication bias due to limited studies on acupuncture. Symptomatic self-treatment was the cheapest to both payers and patients due to decreased utilization of the health care system but no significant QALD was gained because the number of UTIs per year was not reduced. While daily antibiotic use is the most studied and effective prevention strategy, the impact of prolonged antibiotic use on antimicrobial resistance and antibiotic-related adverse events needs to be considered compared to non-antimicrobial strategies. Hence, clinicians may consider a combination of antimicrobial and non-antimicrobial prevention strategies depending on the patients' beliefs, preferences and values.[91, 92]

7. How should individual episodes of UTI be treated in women with recurrent UTI?

7.1. Any of the antibiotics for acute uncomplicated cystitis (Table 5) may be used in the treatment of individual episodes of UTI in women with recurrent UTI.
Strong recommendation, moderate quality of evidence

7.2. Consider intermittent self-administered therapy in highly educated, well-informed, motivated patients, wherein the patients are able to recognize the characteristic signs and symptoms of UTI, are compliant with medical instructions and have a good relationship with a medical provider.
Strong recommendation, moderate quality of evidence

Breakthrough infections during prophylaxis should be treated empirically with any of the antibiotics recommended for uncomplicated cystitis other than the antibiotic being given for prophylaxis. Request for a urine culture and modify the treatment accordingly.

Table 5. Antibiotics for acute uncomplicated cystitis

Antibiotics		*Recommended dose and duration*
Primary	Nitrofurantoin monohydrate macrocrystals (not sold locally)	100 mg BID for 5 days PO
	Nitrofurantoin macrocrystals	100 mg QID for 5 days PO
	Fosfomycin trometamol	3 g single dose PO
Alternative	Pivmecillinam (not sold locally)	400 mg BID for 3–7 days PO
	Ofloxacin	200 mg BID for 3 days PO
	Ciprofloxacin	250 mg BID for 3 days PO
	Ciprofloxacin extended release	500 mg OD for 3 days PO
	Levofloxacin	250 mg OD for 3 days PO
	Norfloxacin	400 mg BID for 3 days PO
	Amoxicillin-clavulanate	625 mg BID for 7 days PO
	Cefuroxime axetil	250 mg BID for 7 days PO
	Cefaclor	500 mg TID for 7 days PO
	Cefixime	200 mg BID for 7 days PO
	Cefpodoxime proxetil	100 mg BID for 7 days PO
	Ceftibuten	200 mg BID for 7 days PO
ONLY if with proven susceptibility	Trimethoprim-sulfamethoxazole (TMP-SMX)	160/800 mg BID for 3 days PO

***Summary* of evidence**

Benefits

Clinical trials on the treatment of individual episodes in recurrent UTI are limited. Amoxicillin-clavulanate, cephradine, ciprofloxacin and lomefloxacin have all been found to be effective.[78,79] There are no published trials on 3-dav therapy for individual episodes of recurrent UTI in women. However, given the evidence that the microbial flora encountered in patients with recurrent UTI are similar to those in women with uncomplicated UTI where 3-day therapy is considered acceptable, it is very likely that 3-day or 7-day therapy with any of the antibiotics recommended for simple uncomplicated UTI will also be effective in this setting.

In a trial where 38 patients with recurrent UTI were randomized to receive either continuous prophylaxis with cotrimoxazole or intermittent self-administered therapy with cotrimoxazole, 92% of symptomatic episodes in the self-therapy group were confirmed microbiologically and 86% of the infections responded to the single dose treatment.[80] The infection rate for those on prophylaxis was 0.2 episodes per patient year compared to 2.2 episodes per patient year for patients on intermittent self-therapy ($p<0.001$). Among those that did not respond or relapsed, none evolved into pyelonephritis and all were cured by a second longer course of therapy. In the self-treatment group, UTI was correctly diagnosed in 35/38 patients and self-treatment was effective in 30/35 infections. In a later study by Schaeffer and Stuppy 1999, among 34 women with a cumulative of 84 symptomatic UTI episodes, 78/84 (92%) responded clinically to self-treatment.[81] A study by Gupta 2001 showed similar results, the women

were highly accurate in identifying the presence of significant bacteriuria based on their voiding symptoms and no serious events were noted.[8,82]

Self-administered antibiotic therapy reduces the time between onset of symptoms and initiation of treatment; avoids the inconvenience and cost of a clinic visit compared with the standard physician-directed treatment. This also minimizes exposure to antimicrobial agents compared to continuous or postcoital prophylaxis.[83] However, use of this strategy should be limited to women with clearly documented recurrent infections and who are motivated, compliant with medical instructions and have a good relationship with a medical provider.[8]

Harms

Five and 3 patients developed side effects in the prophylaxis and self-therapy groups, respectively.[80] The reported incidence of infections with organisms resistant to antibiotic being used for prophylaxis ranged from 12% for cotrimoxazole, 50% for norfloxacin, 54% for cefaclor, and 58% for nitrofurantoin.[28,29]

Costs

Annual direct costs per person in the prophylaxis group were $256 versus $239 in the self-therapy group. The authors cautioned, however, that their population was a select group of women, many of whom had attended a special clinic on UTI and were sufficiently motivated to enroll in a long-term clinical study.[80]

8. How effective are non-pharmacologic interventions treating urinary tract infections?

8.1. Cranberry juice and cranberry products are not recommended for the treatment of urinary tract infection.
Strong recommendation, low quality of evidence

Summary of evidence

A recent Cochrane systematic review found no properly randomized controlled trials assessing the effectiveness of cranberry juice for the treatment of UTI.[84] The review excluded two crossover trials because they did not measure relevant clinical outcomes.[85,86] To date, there is no good-quality evidence to suggest that cranberry juice or its products is effective for the treatment of UTI in any specific population at risk for UTI.[84]

8.2. There is evidence to recommend acupuncture for prevention of recurrent UTI among women when antibiotic prophylaxis is contraindicated.

Two small RCTs evaluated the role of acupuncture compared with sham acupuncture or no treatment in the prophylaxis of recurrent UTIs. During a 6-month period, both studies demonstrated that acupuncture could play a significant role in preventing recurrent UTIs.[87,88] However, both studies had different acupoints. The main acupoints were Ren-3, Ub-23, and Ub-28 on the lower abdomen or back, and K-3, Sp-6, Sp-9, Liv-2 or Liv-3 on the lower extremities and on the lower abdomen or back (CV-3 or CV-4 and BL-23 or BL-28) or on the lower extremities (KI-3, SP-6, SP-9, ST-36, or LR-3.[87] Acupuncture was done 20 minutes twice weekly for 4 weeks.

One RCT involving 67 women with history of recurrent UTI randomized to either acupuncture treatment, sham acupuncture treatment, or no treatment showed that 85% of the acupuncture group were free of lower UTI during the 6-month observation period, compared with 58% of the sham group (P=0.05) and 36% of the control group (p=0.01).[87]

Another RCT of 94 women with 2 or more episodes of distal urinary symptoms for the past 12 months showed that 73% of women in the acupuncture group were free of UTIs during the 6-month observation period, compared with 52% of women in the control group (p=0.08).[88]

8.3. There is no available evidence to recommend coconut juice in the prevention or treatment of UTI.

Summary of evidence

We did not find any controlled or uncontrolled studies on coconut juice and its role in the prevention or treatment of UTI.

8.4. There is insufficient evidence to recommend oral water hydration (2 to 2.5 liters/day) in the prevention or treatment of UTI.

Weak recommendation, low quality of evidence

Summary of evidence

A study on 28 pre-menopausal women who had at least two idiopathic UTIs in the previous 6 months underwent assessment of urinary osmolality using a handheld probe to determine any association of urine osmolality with bacteriuria.[89] Results showed that lower osmolality over the 4-month period was measured, and that there was significantly fewer UTIs that developed during the study period (McNemar's chi^2=0.046).

8.5. There is insufficient evidence to recommend drinking more water and voiding before and after intercourse to prevent UTI.

Strong recommendation, low quality of evidence

Summary of evidence

Benefits

We did not find any systematic review or randomized controlled trials. However, a case control study comparing 229 women 18-30 years old with recurrent UTI with 253 age-matched women found no significant difference in voiding habits (infrequent, post-coital, pre-coital, delayed voiding) or fluid intake (≤5 glasses of water a day). There was also no difference in "wiping" (front to back) techniques.[17] An earlier prospective study on risk factors for UTI in young women likewise showed that voiding and drinking habits do not make a difference in the occurrence of UTIs.[90]

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COMPLICATED URINARY TRACT INFECTIONS: GENERAL CONSIDERATIONS

Summary of Recommendations

1. When is complicated urinary tract infection suspected or diagnosed?

Complicated UTI (cUTI) is significant bacteriuria plus clinical symptoms, which occurs in the setting of (1) functional or anatomic abnormalities of the urinary tract or kidneys, or (2) the presence of an underlying disease that interferes with host defense mechanisms, or (3) any condition that increases the risk of acquiring [persistent] infection and/or treatment failure (See Table 5). **The cut-off for significant bacteriuria in complicated UTI has been set at 100,000 CFU/mL. However, in certain clinical situations, such as in catheterized patients, low-level bacteriuria or counts < 100,000 CFU/mL maybe significant.**

2. In patients with suspected complicated UTI, what diagnostic tests should be done to assist the physician in managing the infection effectively?

2.1 A urine sample for gram stain, and culture and sensitivity testing must always be obtained before the initiation of any treatment.
Strong recommendation, Moderate quality of evidence

2.2 Additional ancillary diagnostic tests will depend on the nature of the complicated UTI (see sections below). **Imaging of the urinary tract is warranted whenever anatomic or structural abnormalities are suspected as contributing to a UTI. Such cases would include (a) pyelonephritis that is not responding to usual treatment, (b) severe pyelonephritis in certain high risk groups (e.g. DM), and (c) recurrent UTI in a man.**
Strong recommendation, Low quality of evidence

2.3 CT-scan is generally preferred over KUB ultrasound as it can better identify and localize the presence of urinary tract abnormalities or multiple lesions such as abscesses; however, the imaging modality to be used may depend on local availability.
Strong recommendation, Low quality of evidence

3. Do patients with complicated UTI need to be hospitalized?

3.1 The following patients with complicated UTI require hospitalization:

- **Patients with marked debility and signs of sepsis,**
- **Patients in whom there is uncertainty in diagnosis,**
- **Patients in whom there is concern about adherence to treatment, or,**
- **Patients who are unable to maintain oral hydration or take oral medications**

Strong recommendation, Low quality of evidence

3.2 Patients with *mild to moderate illness* (symptoms of fever and lower or upper UTI without urosepsis, circulatory failure and/or organ

dysfunction or failure), and who do not fall under the above categories may be treated on an outpatient basis.
Strong recommendation, Low quality of evidence

4. What antibiotics are recommended for empiric therapy of complicated UTI?

4.1 For mild to moderate illness, oral fluoroquinolones or amoxicillin/clavulanic acid may be used if there are no risk factors for infection with antibiotic resistant organisms (such as ESBL producing-organisms or *P. aeruginosa,* refer to Table 3) and if the resistance rates to these antibiotics are < 20%. Due to the varying antibiotic sensitivity patterns of the most common uropathogens, it is recommended that local antibiotic sensitivity patterns be considered in the choice of empiric antibiotics for this set of patients.
Strong recommendation, Moderate quality of evidence

4.2 For severely ill patients, broad-spectrum parenteral antibiotics (see Table 3) should be used, choice of which would depend on the following:

- **The expected pathogens,**
- **Results of the urine gram stain,**
- **The current susceptibility patterns of microorganisms in the area, and,**
- **Risk factors for the acquisition of drug-resistant organism (Table 9)**

Strong recommendation, Moderate quality of evidence

4.3 Fluoroquinolones are not recommended as empiric antibiotics for severely-ill patients due to the high rates of resistance locally.
Strong recommendation, low quality of evidence

4.4 Any underlying abnormalities or risk factors should be managed accordingly.
Strong recommendation, low quality of evidence

5. How long should antibiotics be given in complicated UTI?

5.1 In general, at least 7-14 days of therapy is recommended. Treatment duration may be extended depending on the clinical situation.
Strong recommendation, Moderate quality of evidence

5.2 Antibiotics are modified according to the results of the urine culture and sensitivity tests. Patients started with parenteral regimen may be switched to oral therapy upon clinical improvement.
Strong recommendation, Moderate quality of evidence

5.3 When an oral regimen is not available or if continuation of an intravenously-administered antibiotic is necessary, outpatient parenteral antibiotic therapy (OPAT) can be an option.

Strong recommendation, Moderate quality of evidence

5.4 Criteria for OPAT include:

- **An indication for parenteral antibiotic therapy (i.e. presence of an infection that warrants antibiotic use) in the absence of an oral or alternate routes of delivery**
- **No other clinical indication for hospitalization**
- **Consent of the patient and/or caregiver to participate (including an understanding of the benefits, risks, and economic considerations involved)**
- **Outpatient environment safe and adequate to support care (including logistic concerns, rapid and reliable communications between the OPAT team)**

  Strong recommendation, Moderate quality of evidence

6. After the completion of antibiotics, what tests or procedures are recommended to reduce the risk of recurrence of complicated UTI?

6.1 Urine culture should be repeated one to two weeks after completion of antibiotics.
Strong recommendation, Low quality of evidence

6.2 If significant bacteriuria persists post-treatment, consider referral to specialists (infectious diseases, nephrology, urology, etc.) to identify and correct any underlying problem (anatomical, functional, or metabolic) that predisposes the patient to complicated UTI.
Strong recommendation, Low quality of evidence

DISCUSSION

1. When is complicated urinary tract infection suspected or diagnosed?

Complicated UTI (cUTI) is significant bacteriuria plus clinical symptoms, which occurs in the setting of (1) functional or anatomic abnormalities of the urinary tract or kidneys, or (2) the presence of an underlying disease that interferes with host defense mechanisms, or (3) any condition that increases the risk of acquiring [persistent] infection and/or treatment failure (See Table 1). **The cut-off for significant bacteriuria in complicated UTI has been set at 100,000 CFU/mL. However, in certain clinical situations, such as in catheterized patients, low-level bacteriuria or counts < 100,000 CFU/mL maybe significant.**

Summary of evidence

Complicated UTIs (cUTIs) are a heterogeneous group of syndromes with varying underlying pathogenic mechanisms that would warrant diagnostic and/or therapeutic approaches that go beyond and are unique from those recommended for uncomplicated UTIs. The heterogeneity, poor characterization, or lack of stratification of complicating factors of the population included in various complicated UTI clinical studies make it difficult to give uniform recommendations in its diagnosis and management.[1] At best, complicated UTI (cUTI) can be defined as significant bacteriuria, which occurs in the setting of (1) functional or anatomic abnormalities of the urinary tract or kidneys, (2) in the presence of an underlying disease that interferes with host defense mechanisms, or (3) in the presence of any condition that increases the risk of acquiring or persistence of infection and/or treatment failure (see Table 6). The cut-off for significant bacteriuria in complicated UTI has been set at 100,000 cfu/ml.[2] However, in certain clinical situations, such as in catheterized patients, low-level bacteriuria or counts <100,000 cfu/ml may be significant.[3]

Complicated UTI can present as severe obstructive acute pyelonephritis which may progress to urosepsis or as catheter-associated post-operative UTI, which might resolve spontaneously with catheter removal. It may present with the usual symptoms of dysuria, urgency, frequency, flank pain, costovertebral angle tenderness, suprapubic pain, and fever, or with no symptoms at all.[4] It is important to note that the presence of these symptoms, especially lower urinary tract symptoms, does not equate with the presence of an infection. Other urological disorders such as benign prostatic hyperplasia (BPH) or surgical manipulations of the urogenital tract such as transurethral resection of the prostate (TURP) can also present with lower urinary tract symptoms.[4] Patients with hormonal, metabolic, and immunologic deficiencies are more prone to infection by various pathways. Usually, all these patients have pathogens that are more difficult to eradicate.[5] To date, there is little evidence clarifying the epidemiology of complicated UTI. Population-based studies that clearly describe the burden of illness of complicated UTI are lacking.[6]

Structural and functional abnormalities that impede urine outflow and cause urinary stasis

Structural and anatomic abnormalities of the urinary tract that interfere with the normal storage and flow of urine are among the most consistent elements associated with a complicated UTI.[7] This group of cUTIs include intrinsic and extrinsic

disorders of the kidney and renal infundibulum/pelvis (congenital abnormalities, calculi, neoplasms, aberrant vessels, strictures, inflammatory bowel disease, retroperitoneal hematoma/fibrosis), intrinsic or extrinsic abnormalities of the ureter (including calculi, tumours, vesico-ureteral reflux, radiation inflammatory sequelae, retroperitoneal fibrosis), pathology of the bladder and/or bladder neck (benign prostatic hyperplasia, prostate or bladder cancer, bladder neck contraction, vesical calculi), neurogenic bladder dysfunction, as well as disease of the urethra (e.g. polyps, structure, valves. These conditions increase the likelihood of infection, with a tendency to be more chronic, unless abnormalities are corrected. In the subset of cUTI patients with urinary stones, for example, the more problematic *Pseudomonas* spp. and other urease-producting bacteria, such as *Proteus* spp., seem to be more commonly involved.[8]

Table 6. Conditions that define complicated UTI

Presence of structural abnormalities causing urinary stasis and obstruction of the genitourinary tract
Obstructive uropathy due to carcinoma, bladder outlet obstruction, calculus, or cystocoele
Urethral or ureteric strictures, tumors, calculi and other urologic anatomic abnormalities
Polycystic kidney disease
Functional abnormalities that affect normal urine outflow
Incomplete emptying of the bladder with >100 ml retained urine post-voiding
Vesico-ureteral reflux
Neurogenic bladder, spina bifida, multiple sclerosis
Conditions that interfere with host defense mechanisms
Azotemia due to intrinsic renal disease
Renal transplantation
Diabetes mellitus
Immunosuppressive conditions – e.g. febrile neutropenia, myeloproliferative disorders, chemotherapy
Iatrogenic conditions
Presence of an indwelling urinary catheter or intermittent catheterization, stents
Peri- or post-operative UTI
Surgically created abnormalities
Pathogen-related complicating factors
UTI caused by unusual pathogens (M. tuberculosis, Candida spp.)
UTI caused by antibiotic-resistant or multi-drug resistant organisms (MDROs)
Others
UTI in males except in young males presenting exclusively with lower UTI symptoms
Chemical or radiation injuries of the uroepithelium
Urosepsis or severe pyelonephritis

Conditions that interfere with host defense mechanisms

While immunosuppression is a common risk factor for this group of complicated UTI patients, there are many other mechanisms that contribute to their susceptibility to severe infection and complications. In uremia, there is a physiologic loss of several urinary defence mechanisms such as the loss of the antibacterial properties of normal urine, due to urea or low pH and high osmolality.[4]

Neutropenic patients (PMNs < 100/mm^3) require special attention because they may not manifest with the usual symptoms of UTI like dysuria, frequency, and urgency. Pyuria may also be absent. In an early series by Sickles (1975) and cited by Korzeniowski (1991), the incidence of UTI was associated with the severity of neutropenia, increasing from 13% with PMNs > 1000/mm^3 to 56% with PMNs < 100/mm^3.[9]

Diabetes mellitus has been identified as an independent risk factor for the occurrence of nosocomial UTI.[10] Morbidity that occurs with diabetics who develop UTI explains why these patients are included in the complicated UTI category.[11] A separate section is also dedicated for cUTI among diabetics.

Catheter-associated urinary tract infection (CA-UTI)

Some groups of complicated UTI, such as those with catheter-associated UTI, are better studied. CA-UTI is one of the most common healthcare-associated infections worldwide.[12-14] This is the result of the widespread use of indwelling urinary foley catheters, which in most cases have been described to be unnecessary.[13] As much as five million patients are estimated to use these indwelling urinary catheters every year.[15]

CA-UTI can account for as much as 40% of all nosocomial infection.[15] The recent report of the International Nosocomial Infection Control Consortium (INICC) (2012) which was based on a prospective surveillance study of a cohort of 3,877 patients hospitalized in 10 Pediatric Intensive Care Units during 27,345 bed days in 10 cities of six developing countries (Colombia, El Salvador, India, Mexico, Philippines, and Turkey), noted a CA-UTI rate of 5.9 per 1000 urinary catheter- days.[16]

The incidence of CA-UTI in the Philippines has been studied in some institutions. In a prospective cohort study done at a 1500-bed tertiary government hospital in Manila in 1998, the incidence of catheter-related UTI was 51.4% (110 out of 214 catheterized patients), 91% of which were acquired within seven days of catheterization.[17] An earlier study in the same institution reported a 24.7% incidence (44 out of 178 catheterized patients) over a three month period.[18] Range of duration of catheterization, however, was shorter at 2 to 12 days compared to 2 to 44 days in the more recent study. Another local study conducted in a tertiary private hospital reported a relatively lower one-month prevalence of 13.6% (29 out of 212 catheterized patients) with a mean duration of catheterization of 12 days.[19] Interestingly, a recent local quality improvement study done at a tertiary government hospital in Manila noted zero incidence of CA-UTI during a two-month observation period among catheterized patients admitted to the general medical wards.[20]

A separate section has been dedicated for the recommendations on the diagnosis and management of CA-UTI. Additionally, the 2009 IDSA guidelines on CA-UTI entitled, “Diagnosis, Prevention and Treatment of Catheter-associated Urinary Tract Infection in Adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America” has included an excellent discussion on the

epidemiology and pathogenesis of CA-UTI and the reader is encouraged to use this material as reference.[13]

Renal transplant

Infections in the population of renal transplant patients have received much interest in the field of research. It is now known that UTI is the most common infection that occurs post-transplant, with the incidence ranging from 30-95%.[21-26] Through the years, there is a trend towards a gradual decline in the incidence of infection due to the refinements in the post-operative care of transplant patients.[24]

UTI in post-transplant patients is associated with severe morbidity due to sepsis. The highest rates of UTI occur during the first seven days following transplant and consists mainly of CA-UTI. In the Philippines, the National Kidney and Transplant Institute (NKTI) has the largest experience in kidney transplantation with 1,019 kidney transplants performed in 1,008 patients over a ten-year period from 1983-1994. A one-year prospective study in this institution by in 1997 followed the course of 513 patients post-transplant and noted that UTI and pneumonia were the most frequently encountered bacterial infections in these patients.[27] Refer to the section on cUTI among post-renal transplant patients for more details.

HIV/AIDS

UTI in patients with HIV/AIDS was previously included in the category of complicated UTI because of the higher risk for bacteriuria related to the degree of immunosuppression, especially among patients with AIDS (CD4 count <200 cells/mL.[28-32] However, most of these bacteriurias are asymptomatic and transient; whether or not these bacteriurias predispose to the occurrence of a subsequent UTI in this set of patients needs further investigation.[28,29,33] In a prospective cohort of 871 HIV-seropositive and 439 HIV-seronegative women, it was found out that within the 4280 person-years of follow-up, HIV infection was not associated with the development of UTI.[34] More studies are needed to characterize the effect of HIV on the risk of acquiring UTI [35]. It is also interesting to note at this point that in at least two studies, concomitant intake of TMP-SMX for *Pneumocystis* pneumonia (PCP) prophylaxis did not significantly influence the rate of bacteriuria. One reason for this is that the most common urinary pathogens already have high rates of resistance to TMP-SMX.[29,32]

While those with advanced HIV infection and UTI are at higher risk for unusual or atypical pathogens (e.g. cytomegalovirus, adenovirus, *Toxoplasma*, *Pneumocystis jiroveci*, *Blastomyces dermatidis*, *Mycobacterium tuberculosis*), the most common causes of UTI in these patients are not different from those that cause UTIs in HIV-seronegative individuals.[28,30,36] The management of UTI in patients with HIV is similar to the management of UTI in seronegative patients. For this reason, the committee has decided to remove HIV/AIDS in the list of conditions under complicated UTI. Patients with HIV/AIDS who do not respond to usual treatment should be evaluated for atypical or unusual pathogens listed previously, and should be referred to an appropriate specialist.

2. In patients with suspected complicated UTI, what diagnostic tests should be done to assist the physician in managing the infection effectively?

2.1 A urine sample for gram stain, and culture and sensitivity testing must always be obtained before the initiation of any treatment.
Strong recommendation, Moderate quality of evidence

2.2 Additional ancillary diagnostic tests will depend on the nature of the complicated UTI (see sections below). **Imaging of the urinary tract is warranted whenever anatomic or structural abnormalities are suspected as contributing to a UTI. Such cases would include (a) pyelonephritis that is not responding to usual treatment, (b) severe pyelonephritis in certain high risk groups (e.g. DM), and (c) recurrent UTI in a man.**
Strong recommendation, Low quality of evidence

2.3 CT-scan is generally preferred over KUB ultrasound as it can better identify and localize the presence of urinary tract abnormalities or multiple lesions such as abscesses; however, the imaging modality to be used may depend on local availability.
Strong recommendation, Low quality of evidence

Summary of evidence

In cases where it is possible, antimicrobial therapy should be delayed until the results of culture and sensitivity studies are released so that therapy would be targeted towards the identified pathogen. In cases where empiric treatment is started, re-assessment of the choice of antibiotic should be done as soon as culture results become available (usually within 48-72 hours).[37]

The importance of obtaining pre-treatment urine cultures in patients with complicated UTIs cannot be overemphasized for several reasons.[1,38-41] First, there is a wide range of organisms that can cause complicated UTI. Table 7 lists the most commonly reported pathogens in complicated UTI by several foreign and local studies. While *E. coli* remains to be the most commonly reported pathogen in cUTIs, the significance of more problematic organisms such as *Pseudomonas* spp., other urease-producing bacteria such as *Proteus* spp., staphylococci and enterococci have been recognized.[42]

The second reason why obtaining pre-treatment cultures is very important is because culture and sensitivity results will confirm that the infecting organism is susceptible to the empiric antibiotic started given the increasing rates of antibiotic resistance.[1] Finally, pre-treatment culture and sensitivity results will allow shifting of the initial empiric antibiotic to one with a narrower spectrum of coverage which may be cheaper and minimize selection of more resistant pathogens. Culture-guided antibiotic treatment is especially important among patients in whom prolonged antibiotic therapy is warranted or recurrent infections are more likely (e.g. complicated UTI patients for whom the complicating factor(s) is/are not readily reversible).

3. Do patients with complicated UTI need to be hospitalized?

3.1 The following patients with complicated UTI require hospitalization:

- **Patients with marked debility and signs of sepsis,**
- **Patients in whom there is uncertainty in diagnosis,**
- **Patients in whom there is concern about adherence to treatment, or,**

- **Patients who are unable to maintain oral hydration or take oral medications**

Strong recommendation, Low quality of evidence

Table 7. Pathogens in Complicated UTI

Type of Complicated UTI	Pathogens	Reference
Complicated UTI in Filipino patients (NKTI, PGH, MMC, CSMC, DMC)	*Escherichia coli, Klebsiella pneumonia, Enterobacter cloacae, Pseudomonas aeruginosa, Proteus mirabilis*	[43-47]
Catheter-associated UTI Short-term (<1 week) Long-term (>1 week)	 *Escherichia coli* *Pseudomonas aeruginosa* *Escherichia coli, Klebsiella sp., Enterobacter sp., Proteus mirabilis* Usually polymicrobial *E. coli, Pseudomonas aeruginosa, Proteus mirabilis, Providencia stuartii, Morganella morgagnii, Citrobacter, Enterococcus, Candida species*	 [48] [49, 50]
Catheter-associated UTI in Filipino Patients	*Escherichia coli, Klebsiella, Pseudomonas aeruginosa, Acinetobacter, Candida sp.*	[17, 18]
Anatomic abnormalities	*Escherichia coli, Klebsiella pneumoniae (37%), Pseudomonas aeruginosa, Proteus mirabilis*	[51]
UTI in diabetics	*Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterobacter, Enterococcus, Pseudomonas aeruginosa, Candida, Staphylococcus aureus*	[11, 52, 53]
Diabetics with indwelling bladder catheter	*Escherichia coli, Enterococcus, Pseudomonas aeruginosa*	[52]
Renal transplant recipients	*Escherichia coli (29-61%), Proteus mirabilis* and *Klebsiella pneumoniae (30%), Gram-positive cocci (20%), Enterobacter, Enterococci, Serratia, Acinetobacter, Citrobacter, Pseudomonas aeruginosa, Candida*	[27, 54-58]
Neutropenic patients	Gram negative bacilli, *Pseudomonas aeruginosa, Staphylococcus aureus, Candida*	[9]

3.2 Patients with *mild to moderate illness* (symptoms of fever and lower or upper UTI without urosepsis, circulatory failure and/or organ dysfunction or failure), and who do not fall under the above categories may be treated on an outpatient basis.
Strong recommendation, Low quality of evidence

Summary of evidence

The decision on the site-of-care and subsequent choice of empiric antibiotics is in part dependent on the clinical status of the patient. No disease severity classification system has been formulated and evaluated for complicated UTIs. Not surprisingly, there are no clinical trials that stratified patient outcomes by degree of illness and site of treatment. Clinical decision-making rests upon the status of the patient and the presence of risk factors for severe and/or persistent infection. Mild to moderate illness can range from an asymptomatic patient with complicating factors (as listed in Table 1) to the presence of fever and upper/lower UTI symptoms. Severe illness, on the other hand, can be characterized by urosepsis, circulatory failure, organ dysfunction and/or failure.[4]

4. What antibiotics are recommended for empiric therapy of complicated UTI?

4.1 For mild to moderate illness, oral fluoroquinolones or amoxicillin/clavulanic acid may be used if there are no risk factors for infection with antibiotic resistant organisms (such as ESBL producing-organisms or *P. aeruginosa,* refer to Table 3) and if the resistance rates to these antibiotics are < 20%. Due to the varying antibiotic sensitivity patterns of the most common uropathogens, it is recommended that local antibiotic sensitivity patterns be considered in the choice of empiric antibiotics for this set of patients.
Strong recommendation, Moderate quality of evidence

4.2 For severely ill patients, broad-spectrum parenteral antibiotics (see Table 3) should be used, choice of which would depend on the following:
a) The expected pathogens,
b) Results of the urine gram stain,
c) The current susceptibility patterns of microorganisms in the area, and,
d) Risk factors for drug-resistant organism (Table 9)
Strong recommendation, Moderate quality of evidence

4.3 Fluoroquinolones are not recommended as empiric antibiotics for severely-ill patients due to the high rates of resistance locally.
Strong recommendation, low quality of evidence

4.4 Any underlying abnormalities or risk factors should be managed accordingly.
Strong recommendation, low quality of evidence

Summary of evidence

The proper selection of empirical treatment for cUTI requires 3 things: (1) knowledge of the possible infectious agents based on the complicating factors present, (2) knowledge on the local antibiotic resistance patterns, and (3) an assessment of the severity of the underlying urological abnormality. The wide variety of pathogens that are implicated in complicated UTI tend to be more resistant to the common antibiotics used in clinical practice as described by several recent reviews of earlier studies.[1,37,59,60] This is attributed to the increased probability of complicated UTI patients for repeated antimicrobial exposure or healthcare-associated acquisition of these pathogens (e.g. frequent hospital visits for underlying medical condition, urological interventions).[37] The variety of conditions under complicated UTI and the limitations of the clinical trials in these populations are also very important factors that contribute to the difficulty in coming up with generalizations on specific antibiotic regimens.[61] Drugs of choice for empiric therapy of complicated UTI have not been well established. The earlier published comparative drug trials on complicated UTI were poorly designed or the definition of bacteriologic cure was not eradication of the initial pathogen.

One prospective, randomized, single-blind multicenter study involving 133 patients suspected of having cUTI showed that lomefloxacin (a fluoroquinolone) is superior over trimethoprim-sulfamethoxazole (TMP-SMX or cotrimoxazole) in terms of bacteriologic cure and clinical cure of symptomatic complicated UTI.[62] This study and the increasing rates of resistance to TMP-SMX in three local antibiotic susceptibility reports favour against the use of TMP-SMX in cUTI.[61] Similar with uncomplicated UTIs, the very high resistance rates to ampicillin and amoxicillin limit the use of these antibiotics to cases with culture-proven, susceptible isolates of enterococci or Group B streptococci.[61-63]

In 2005, Nicolle and the Association of Medical Microbiology and Infectious Diseases Canada Guidelines Committee reviewed at least 28 previously published comparative clinical trials on complicated UTI. The committee has validated the previously identified limitations of clinical trials on complicated UTI in terms of heterogeneity in study subjects, size of treatment effect, lack of blinding or allocation concealment, and variability of follow-up duration. Moreover, concerns on the usefulness in the choice of empiric antibiotics have been raised for those studies that excluded infections with drug-resistant organisms.[37] These available studies have shown that the different classes of fluoroquinolones are equally effective for the treatment of complicated UTI (except for sparfloxacin and moxifloxacin). For example, a multicenter, prospective, double-blind, double-dummy randomized study compared ciprofloxacin 250 mg BID to ofloxacin 200 mg BID given for seven days in the treatment of 427 women with complicated lower UTI.[64] No significant differences in efficacy rates among patients who received ciprofloxacin and ofloxacin were observed: 77.1% and 76.1% had sterile cultures five to nine days after therapy respectively. Clinical cure five to nine days post-therapy was achieved in 97.2% of both groups and a month later in 87.7% and 87.3%, respectively. Adverse events were mild and similar in both groups. Once daily administration of 1000mg of extended release ciprofloxacin has also been found to be at least as safe and effective as the 500 mg BID regimen in two clinical trials.[65,66] Levofloxacin 750 mg once daily for 5 days has been shown to be as effective as ciprofloxacin 400 mg (intravenous) or 500 mg (oral) twice daily for 10 days in the treatment of adults with cUTI and acute pyelonephritis, including patients with concurrent bacteremia.[67] On the other hand, sparfloxacin (not available locally) and the

newer moxifloxacin achieve relatively lower concentrations in urine and are not indicated for the treatment of UTI.[68,69]

Based on the studies enumerated above, the 2004 guideline recommended the use of oral fluoroquinolones for the treatment of mild to moderate complicated UTIs. However, there have been increasing reports of fluoroquinolone resistance among uropathogens in the past few years attributed to the spread of ESBL-producing bacteria.[61] It has been observed that when an isolate becomes ESBL-producing, particularly *E. coli*, fluoroquinolone resistance follows. Surveillance reports on the antimicrobial susceptibility of Gram-negative pathogens in the Asia-Pacific region have shown that among ESBL-producing *E. coli*, most antibiotic agents showed decreased in vitro activity compared with the ESBL-negative counterparts (Chen et al., 2011). In the study done at a private tertiary hospital in Pasig City, resistance to the fluoroquinolones was 100% for ESBL-producing *E.coli*.[44] In addition, fluoroquinolones have been shown to have detrimental effects ecologically. They have a tendency to select for resistant strains of *P. aeruginosa*, *P. mirabilis*, *Providencia* spp., and *Serratia* spp., and to induce cross-resistance to structurally unrelated antimicrobials.[70]

Considering the issue of increasing resistance together with the collateral damage that fluoroquinolones may cause (e.g. in tuberculosis, ESBL-production, selection of resistant strains stated above), it is therefore advised to use fluoroquinolones with caution and only after careful assessment of the patient's risk factors for acquiring drug-resistant organisms such as prior antibiotic use (third generation cephalosporins, fluoroquinolones) in the past three to six months, recent hospitalization or urological instrumentation (indwelling bladder catheter included) have been considered.

The Philippine Antimicrobial Resistance Surveillance Program (ARSP) performs laboratory surveillance to monitor antibiotic resistance from selected isolates from various sentinel sites in the country. The latest 2013 ARSP Data Summary Report showed that *E. coli* from inpatient urine specimens was least resistant to oral nitrofurantoin (%R 6%, n=1,622) followed by amoxicillin/clavulanic acid (co-amoxiclav) (%R 23%, n=1,974) (see Table 3).[71] Among the parenteral agents, ertapenem (%R 2%, n=1,059) had the lowest resistance rates followed by piperacillin-tazobactam and amikacin with resistance rates both at 6%. From 2012 to 2013, only ceftriaxone had a significant increase in resistance rate from 31% to 36% (p=0.006); the resistance rates of the other antibiotics did not differ significantly. These figures were pooled from data submitted by 22 sites throughout the entire Philippines; however, variability still exists from one institution to another. The ARSP 2013 Data Summary report thus recommends that treatment recommendation be based on local prevailing antibiotic sensitivity patterns. In a study done in a tertiary private hospital done in Metro Manila involving adult patients admitted for cUTI, similar trends in antibiotic resistance patterns were observed.[44] Resistance rates to the intravenous ertapenem and amikacin, and to the oral nitrofurantoin remain low. Note the high resistance rates to ciprofloxacin and levofloxacin. Given these data, the carbapenems and amikacin are good options for empiric treatment for patients in whom intravenous antibiotics are indicated. Oral antibiotic options would include nitrofurantoin and co-amoxiclav (Table 8). Note, however, that nitrofurantoin have only been approved for use in uncomplicated cystitis. The development of resistance and the lack of clinical studies favour against the use of this drug for severe or complicated UTIs.[61]

Table 8. Percent Resistance of Urinary *E. coli* (inpatient urine specimens)

Antimicrobial Agent	ARSP 2013*	ARSP 2015**	cUTI study 2013+
	%R	%R	ESBL-producing (n, %R)
Amikacin	6%	4.2%	0
Ampicillin	85%	83.9%	48 (100%)
Ceftazidime	-	-	44 (91.7%)
Ceftriaxone	36%	40.4%	47 (97.9%)++
Cefuroxime axetil	40%	38.1%	48 (100%)
Ciprofloxacin	46%	43.4%	-
Co-amoxiclav	23%	27.1%	38 (79.2)
Ertapenem	2%	5.7%	0
Gentamicin	-	-	24 (50.0%)
Imipenem	-	-	0
Levofloxacin	-	-	43 (93.8)
Meropenem	-	-	0
Nitrofurantoin	6%	6.5%	12 (34.3%)
Piperacillin-tazobactam	6%	10.7	16 (45.7%)
Tigecycline	-	-	5 (15.2%)
TMP-SMX	69%	67.9%	40 (83.3%)

%R (resistance rate) = percentage of isolates resistant
***Antimicrobial Resistance Surveillance Program (ARSP), 2013 report*
***Antimicrobial Resistance Surveillance Program(ARSP)*, 2015 report
+From a study on complicated UTI in a tertiary private hospital in Metro Manila
++Intravenous ceftriaxone

Another important consideration in choosing the appropriate empiric antibiotic regimen for complicated UTIs is the presence of risk factor(s) in acquiring antibiotic-resistant organisms (see Table 9). The global phenomenon of rising antimicrobial resistance among *Enterobacteriaceae* has likewise been observed in the region and in the Philippines. This problem includes ESBL (extended spectrum beta-lactamase) or KPC (*K. pneumoniae* carbapenemase) production, fluoroquinolone and TMP-SMX resistance and even multidrug-resistance [61]. ESBL-rate in the Asia-Pacific region is reported at 28.2%.[72] Several studies have already identified risk factors associated with the development of cUTI with antibiotic-resistant organisms and are summarized in Table 9. The role of staphylococci or enterococci have been found to be insignificant unless there are risk factors such as the presence of stones or foreign bodies.[4]

Locally, a cohort study done at a tertiary hospital in Manila in 2007 reported an ESBL rate of 13% out of 300 consecutive *Enterobacteriaceae* isolates from adult patients.[94] Another cohort study done in a private tertiary hospital (n=161 patients, 33.5% of hospital-acquired UTI) in Metro Manila from September 2011 to August 2012 looked into the prevalence of ESBL-producing organisms among patients with complicated UTI. They reported ESBL-rates of 29%. Multivariate analysis of risk factors done identified structural or anatomic abnormality and recurrent urinary tract surgery or instrumentation (OR 2.81, CI 1.26 to 6.29, p=0.012 and OR 18.16, CI 2.08 to 158.35. p=0.009) as significant risk factors for development of complicated UTI with an ESBL-producing organism. Further analysis of the *E. coli* subgroup in this study (n=96)

showed that structural or anatomic abnormality and fluoroquinolone intake in the preceding three months (OR 6.41, CI 1.95 to 21.03, p=0.002 and OR 5.43, CI 1.26 to 23.33. p=0.023) are significant risk factors for development of complicated UTI with an ESBL-producing organism.[44] In a similar study conducted in a government tertiary hospital, on the other hand, reported a higher ESBL rate of 37% (n=177) with mechanical ventilation (OR R 2.48, 95% CI 1.21-5.13, p=0.014) as the only significant factor associated with the development of ESBL infection on multivariate analysis.[86]

Table 9. Risk factors for the acquisition of antibiotic-resistant organisms.

ESBL-producing organisms	**Reference**
Prolonged stay in a hospital or healthcare facility	[73, 74]
Recent use of antibiotics* (fluoroquinolones, cephalosporins, B-lactams)	[75-83]
Recent hospitalization (past 3 months)	[78, 84]
Recent travel to ESBL-highly endemic areas (Asia, The Middle East or Africa) in the past 6 weeks	[77, 81]
Presence of Diabetes mellitus and/or other co-morbidities (e.g. neutropenia)	[73, 74, 77, 80]
Urinary catheterization, surgery or instrumentation and use of other invasive devices	[44, 73, 79, 80, 83]
Recent episode of UTI, recurrent UTI	[73, 74, 82, 85]
Structural or anatomical abnormality of the genitourinary tract, including prostatic disease	[44, 82]
Mechanical ventilation	[86, 87]
Pseudomonas (including multi-drug resistant Pseudomonas)	
Use of antibiotics in the past 2 months* (ciprofloxacin, BLICs)	[88-91]
Recent episode of UTI	[91, 92]
Previous urinary tract surgery, catheterization	[91-93]
Underlying urinary tract pathology (e.g. pathological VCUG results)	[89, 92, 93]
Recent stay in another healthcare unit/facility	[90]

*Includes antibiotic use for prophylaxis.

For severely ill patients and for those in whom antibiotic resistance, such as ESBL-production, is a concern, intravenous broad spectrum antibiotics listed in Table 10 are the next options.[44,59,61,95] Most uropathogens, including the ESBL-producing organisms, are sensitive to amikacin.[44,71] Anti-pseudomonal carbapenems are recommended for suspected *Pseudomonas aeruginosa* or *Acinetobacter sp* infections. Otherwise, the Group 1 carbapenem, ertapenem, may be used.[59] At least two studies of sound methodologic quality have demonstrated the effectiveness of ertapenem as an empiric antibiotic for complicated UTI.[96,97] Wells et al. (2004) compared the efficacy and safety of parenteral ertapenem for the treatment of complicated UTI in adults with ceftriaxone in two prospective, double-blind, randomized studies with similar design.[97] Ertapenem and ceftriaxone were administered at a dose of 1 g once daily. In both studies, patients could be switched to an oral agent after ≥3 days of parenteral study therapy. The duration of treatment was 10 to 14 days. At the primary efficacy end point

five to nine days after treatment, 229 (89.4%) patients in the ertapenem group and 204 (91.1%) patients in the ceftriaxone group had a favorable microbiological response (95% CI, –7.4 to 4.0), which indicates comparable outcomes in both treatment groups. In this combined analysis, ertapenem was found to be an effective therapy for the treatment of complicated UTIs in adults with moderate-to-severe disease. The more recent report by Park et al. (2012) was a prospective, multicenter, double-blinded, randomized study involving 271 patients with acute pyelonephritis or complicated UTI.[96] The efficacy and safety of ertapenem 1 g once daily were compared with ceftriaxone 2 g once daily, for the treatment of adults with acute pyelonephritis and complicated UTI. Results showed that ertapenem was equally effective and safe as ceftriaxone in achieving bacteriologic response at five to nine days after treatment with similar frequency and severity of reported adverse events.

Finally, together with initiation of antibiotics, any underlying abnormality or complicating factor should be addressed. Adequate glucose control should be achieved for diabetic patients. The need for an indwelling should be reassessed and any indwelling device should be removed soon as it is deemed to be not indicated anymore. Urologic abnormalities should be corrected whenever possible. Proper infection control practices should be exercised to minimize and prevent further infections.

5. How long should antibiotics be given in complicated UTI?

5.1 In general, at least 7-14 days of therapy is recommended. Treatment duration may be extended depending on the clinical situation.
Strong recommendation, Moderate quality of evidence

5.2 Antibiotics are modified according to the results of the urine culture and sensitivity tests. Patients started with parenteral regimen may be switched to oral therapy upon clinical improvement.
Strong recommendation, Moderate quality of evidence

Table 10. Antibiotics that may be used as empiric therapy for complicated UTI

Oral Regimen
• Ciprofloxacin 500 -750 mg BID or 1000 mg extended release tablet OD x 7-14d*
• Norfloxacin 400 mg BID x 7-14d*
• Ofloxacin 200 mg BID x 10-14d*
• Levofloxacin 500-750 mg OD x 7-14d*
• Amoxicillin/clavulanate 500 mg/125mg TID or 875 mg/125 mg BID x 7-14d
Parenteral Regimen
• Amikacin 15mg/kg q24h+
• Doripenem 500 mg q8h
• Ertapenem 1 gm. q24h
• Gentamicin 3-5 mg/kg/day q24h+
• Imipenem-cilastin 250-500 mg q6-8h
• Meropenem 1g q8h
• Piperacillin-Tazobactam 2.25-4.5 gms q6-8h

***Determine if patient has risk factors for drug-resistance prior to use.*
+Monitor kidney function especially for patients with impaired renal function at baseline

5.3 When an oral regimen is not available or if continuation of an intravenously-administered antibiotic is necessary, outpatient parenteral antibiotic therapy (OPAT) can be an option.
Strong recommendation, Moderate quality of evidence

5.4 Criteria for OPAT include:

- **An indication for parenteral antibiotic therapy (i.e. presence of an infection that warrants antibiotic use) in the absence of an oral or alternate routes of delivery**
- **No other clinical indication for hospitalization**
- **Consent of the patient and/or caregiver to participate (including an understanding of the benefits, risks, and economic considerations involved)**
- **Outpatient environment safe and adequate to support care (including logistic concerns, rapid and reliable communications between the OPAT team)**

Strong recommendation, Moderate quality of evidence

Summary of evidence

A randomized, double-blind, placebo-controlled trial (Dow et al., 2004) compared 3-day (n=30) and 14-day (n=30) regimens of ciprofloxacin 250 mg BID for the treatment of acute UTI in patients with spinal cord injury. The most common infecting organisms were *Klebsiella*, *Enterococcus*, and *E. coli*. On intention-to-treat analysis, the three-day regimen was associated with a higher rate of microbiological relapse at six weeks after initiation of therapy (37% vs. 7%; RR 2.09, 95% CI 1.38 to 3.18). Short-term (19-23 days after enrolment) and long-term (45-51 days) clinical cure did not differ significantly between the 3-day and 14-day regimens (short term: 63% vs.53%; RR 1.23, 95% CI 0.72 to 2.11; long- term: 37% vs. 40%; RR 0.93, 95% CI 0.55 to 1.58). Likewise, microbiological cure (30% vs. 47%; RR 0.69, 95% CI 0.39 to 1.23) and treatment failure (13% vs. 37%; RR0.46, 95% CI 0.19 to 1.11) did not differ significantly between the two regimens. There were more ciprofloxacin-resistant organisms isolated in the 14-day treatment regimen. The advantage of this 14-day regimen would have been more profound had there been similar number of ciprofloxacin-resistant isolates (e.g. Enterococci) in both arms. Reasons proposed for the higher rate of microbiological relapse in the three-day regimen include: (1) patients may have had occult infections of the upper urinary tract (which would warrant longer treatment duration), and (2) impaired vesical clearance of bacteriuria because of localized trauma, frequent instrumentation or incomplete bladder emptying.[98,99]

An open non-comparative clinical trial on sequential therapy with IV levofloxacin for three days followed by oral levofloxacin to complete 14 days for complicated UTI in three tertiary government hospitals in the Philippines showed 89% cure rate at day 14 on efficacy analysis and 72% on intention-to-treat analysis.[100]

No data is available providing evidence on the advantage of 7-, 10- or 14-day antibiotic treatment regimen in terms of likelihood of cure or the incidence of adverse effects with prolonged antibiotic use.

Outpatient parenteral antibiotic therapy (OPAT)

Outpatient parenteral antibiotic therapy (OPAT) has been practiced in developed countries such as the U.S. since the 1970s.[101] However, this concept has not gained as much popularity in the Philippines. OPAT is generally used to refer to the provision of parenteral antimicrobial therapy in at least 2 doses on different days without intervening hospitalization according to the 2004 IDSA Guidelines on Outpatient Parenteral Antibiotic Therapy.[102] There are no studies that looked solely into the outcomes of OPAT when used in cUTI but numerous studies have included cUTI as one of the indications for OPAT. These studies, although most are retrospective, that support the effectiveness and safety of this strategy.[102-104] In a recent survey conducted among adult infectious disease physicians in North America, 81% of the respondents indicated that they have treated at least 1 patient with OPAT per month on the average. Complications were rare and included intravenous line occlusion or clotting, nephrotoxicity and rash. This study found out that there remains a wide variation in the practice of OPAT.[105]

While there are variations in this strategy, OPAT requires at least 3 things: (1) an indication for treatment (i.e. presence of an infection that warrants antibiotic usage), (2) hospitalization is not needed to control the infection, and (3) alternate routes of drug delivery are not feasible or appropriate.[102] The primary goal of OPAT is to allow patients to complete treatment safely and effectively on an outpatient basis and avoid the inconveniences, complications, and expense of hospitali-zation. It is important that patient safety is not compromised for comfort or financial reasons in the conduct of OPAT. There are four models of OPAT based on where or who delivers the antibiotic: (1) administration in an infusion center, (2) delivery via visiting home services (e.g. physician, nurse), (3) self-administration or administration by a caregiver, and (4) delivery in a nursing home or long term care facility. It is important that the individual setting be assessed first and ensure that OPAT, through any of the four models described, is feasible. Table 11 summarizes the criteria for patient eligibility prior to OPAT and the corresponding issues that need to be addressed first.

Once a decision to push through with OPAT is made, it is important that the key elements be addressed to ensure that the patient receives comprehensive and quality care without compromising safety. Table 12 summarizes these key elements based on recommendation by IDSA in 2004.[102] Transition of care is very important prior to patients discharge. An OPAT plan should be documented in the discharge summary. Clear follow-up instructions and requests for necessary laboratory tests should be issued. For patients who will self-administer the antibiotics, vascular access education and sterile technique should have been ensured.[106]

6. After the completion of antibiotics, what tests or procedures are recommended to reduce the risk of recurrence of complicated UTI?

6.1 Urine culture should be repeated one to two weeks after completion of antibiotics.
Strong recommendation, Low quality of evidence

6.2 If significant bacteriuria persists post-treatment, consider referral to specialists (infectious diseases, nephrology, urology, etc.) to identify

and correct any underlying problem (anatomical, functional, or metabolic) that predisposes the patient to complicated UTI.
Strong recommendation, Low quality of evidence

Table 11. Criteria for Outpatient Parenteral Antibiotic Therapy (OPAT)

Criteria	Issues to be addresses
1. Is parenteral antimicrobial therapy indicated?	• Is there an infection that warrants parenteral antimicrobial therapy administration? • Is there an oral form or any other alternatives routes?
2. No other clinical indication for hospitalization	• Are there no clinical contraindications to discharge the patient from hospital?
3. Consent of the patient and/or caregiver to participate	• Does the patient and/or caregiver understand the benefits, risks, and economic considerations involved? • Does informed consent need to be documented? • Is the patient willing to comply with a follow-up plan?
4. Is the home or outpatient environment capable, safe and adequate to support care? Is OPAT feasible and doable?	• Are the patient and/or caregiver willing to participate and able to safely, effectively, and reliably deliver parenteral antimicrobial therapy? • Do the patient's medical care needs exceed resources available at the proposed site of care? • Are the logistics for OPAT available? • Are mechanisms for rapid and reliable communications about problems and for monitoring of therapy in place between members of the OPAT team?

References: Tice et al (2004) [102] and Muldoon et al (2014) [106]

Summary of evidence

Infection is likely to recur if the underlying abnormalities that predisposed the patient to complicated UTI are not corrected. Thus, it is necessary to check urine cultures one to two weeks after completion of antibiotics to document bacteriologic cure (Stamm & Hooton, 1993). There are, however, no convincing data indicating that clinical benefit is gained by knowing that asymptomatic bacteriuria is present after treatment for asymptomatic UTI and that it is beneficial to perform routine post-treatment urine cultures for asymptomatic patients. On the other hand, persistence or recurrence of symptoms after treatment of a symptomatic UTI episode warrants evaluation and retreatment.

In most cases of complicated UTI, further intervention is necessary to eradicate the infection in addition to the administration of antibiotics. For instance, in the management of UTI with struvite stones, definitive treatment like extracorporeal shock wave lithotripsy and/or percutaneous nephrolithotomy or lithotripsy may be required in most patients. Bacteria live within the stone and persist contributing to stone growth. Patients who fail to undergo stone removal usually have progressive renal deterioration.[107] Further work-up to identify anatomic abnormalities may include the following: plain abdominal and kidney-ureter-bladder radiographs, renal ultrasound, intravenous pyelogram, CT scans, and MRI. Work-up for immunodeficient state may be done when considered.

Table 12. **Key elements required for an outpatient parenteral antimicrobial therapy (OPAT) program.**

1. Health care team A. An infectious diseases specialist or physician knowledgeable about infectious diseases and the use of antimicrobials in OPAT B. Primary care or referring physicians available to participate in care C. Nurse expert in intravenous therapy, access devices, and OPAT D. Pharmacist knowledgeable about OPAT E. Case manager and billing staff knowledgeable about therapeutic issues and third party reimbursements F. Access to other health care professionals, including a physical therapist, a dietitian, an occupational therapist, and a social worker
2. Communications A. Physician, nurse, and pharmacist available 24 h per day B. System in place for rapid communication between patient and team members C. Patient education information for common problems, side effects, precautions, and contact lists
3. Outline of guidelines for follow-up of patients with laboratory testing and intervention as needed
4. Written policies and procedures A. Outline of responsibilities of team members B. Patient intake information C. Patient selection criteria D. Patient education materials
5. Outcomes monitoring A. Patient response B. Complications of disease, treatment, or program C. Patient satisfaction

Adapted from Muldoon, E.G., et al., *Are We Ready for an Outpatient Parenteral Antimicrobial Therapy Bundle? A Critical Appraisal of the Evidence.* Clinical Infectious Diseases, 2013. 57(3): p. 419-424.

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SPECIFIC ISSUES OF CONCERN IN COMPLICATED URINARY TRACT INFECTION

UTI IN DIABETIC PATIENTS

Summary of Recommendations

1. How should UTI in diabetic patients be managed?

1.1 Diabetic patients require pre-treatment urine gram stain and culture and a post-treatment urine culture. At least 7-14 days of oral or parenteral antibiotics listed in Table 8 (Complicated UTI: General Considerations) may be used.
Strong recommendation, Low quality of evidence

1.2 Diabetic patients who present with signs of sepsis should be hospitalized. Blood culture, in addition to urine culture, is indicated for severely ill patients before starting therapy. Failure to respond to empiric therapy within 48 to 72 hours warrants a plain abdominal radiograph of the KUB, a renal ultrasound, or a CT-scan.
Strong recommendation, Low quality of evidence

2. Should diabetic patients be screened and treated for asymptomatic bacteriuria?

Screening and treatment for asymptomatic bacteriuria among diabetic patients are not recommended because they do not reduce the occurrence of subsequent infectious complications.
Strong recommendation, High quality of evidence

DISCUSSION

1. How should UTI in diabetic patients be managed?

1.1 Diabetic patients require pre-treatment urine gram stain and culture and a post-treatment urine culture. At least 7-14 days of oral or parenteral antibiotics listed in Table 8 (Complicated UTI: General Considerations) may be used.
Strong recommendation, Low quality of evidence

1.2 Diabetic patients who present with signs of sepsis should be hospitalized. Blood culture, in addition to urine culture, is indicated for severely ill patients before starting therapy. Failure to respond to empiric therapy within 48 to 72 hours warrants a plain abdominal radiograph of the KUB, a renal ultrasound, or a CT-scan.
Strong recommendation, Low quality of evidence

Summary of evidence

When UTIs occur in diabetics, they are often more serious and protracted. Due to the immunocompromised state, they are at an increased risk for developing ascending renal infection, pyelonephritis, papillary necrosis, renal carbuncle, renal corticomedullary and perinephric abscesses, and emphysematous pyelonephritis.[1] Emphysematous pyelonephritis is a severe, necrotizing interstitial nephritis caused by gas-forming organisms probably acquired via a hematogenous route. Factors that may predispose diabetics to complicated infections include autonomic neuropathy leading to poor bladder emptying and urinary stasis, microangiopathy, leukocyte dysfunction, and frequent urinary tract instrumentation.[2] In addition, diabetic nephrosclerosis and renal disease make delivery of antimicrobials less efficacious.[3] In more recent studies, there was an increased risk of acute pyelonephritis caused by *Enterobacteriaceae* from the lower urogenital tract in patients with diabetes mellitus.[1] Infection with *Klebsiella* is common (25% compared with 12% in non-diabetics).[1,4]

Strong evidence is lacking but experts agree that because of the concern for subsequent upper tract involvement, longer duration of antibiotic therapy is advocated in diabetic patients even with just lower UTI.[5,6] In addition, the increased risk for recurrent tract disease among diabetics justify the need for pre- and post-treatment urine cultures. Failure to respond to therapy within 48 to 72 hours requires serious consideration for any of the severe complications of upper urinary tract infection peculiar to diabetes. This includes any of the ff: emphysematous pyelonephritis, emphysematous cystitis, renal papillary necrosis, acute focal or multifocal bacterial nephritis, renal cortical abscess, renal corticomedullary abscess, and xanthogranulomatous pyelonephritis. Emphysematous pyelonephritis, although rare, carries a poor prognosis if not detected early and treated with medical management alone. Mortality is up to 60% without surgical intervention.[7] A plain abdominal film of the kidney, ureter, and bladder can detect up to 85% of cases. A screening ultrasound should be considered early to rule out obstructive uropathy and detect parenchymal lesions. If there is a high degree of clinical suspicion despite a negative ultrasound, CT scanning should be pursued.[8]

A multicenter, prospective, double-blind, double-dummy randomized study of 427 women including 85 (20%) with DM, has shown that a seven-day regimen with ciprofloxacin or with ofloxacin resulted in a cure rate of 90.1%and 87.2% respectively,

five to nine days post-treatment. In the group of women with DM, the success rates were comparable (87.1% and 85.3%).[9] However, one should consider the increasing rates of resistance to fluoroquinolones as previously discussed. Risk factors for drug-resistance should be considered when contemplating the use of fluoroquinolones as the empiric antibiotic option.

Local susceptibility patterns of the organism should guide choice of antibiotic therapy. Oral or parenteral fluoroquinolones (for mild to moderate infections with no risk for drug-resistance) or ertapenem are reasonable empiric choices. For seriously ill patients, including patients infected with *Pseudomonas spp*., such agents as imipenem, ticarcillin-clavulanate, and piperacillin-tazobactam may be considered.[10] Patients suspected of having staphylococcus infection should be started on vancomycin if there are risk factors for developing such infections, such as presence of invasive devices, residence or exposure to a health-care facility, living in crowded places and men having sex with men. Shift to oxacillin or nafcillin once isolates are found to be susceptible to such antibiotics.

No randomized trials are available comparing the optimal duration and choice of antibiotics among diabetics.

Gestational diabetes mellitus is not associated with increased risk of UTI or with maternal and perinatal morbidity because of infection. Microbiologic evidence of UTI was studied in 447 pregnant women with (n=149) and without (n=298) gestational diabetes mellitus after mid-pregnancy. No significant difference in asymptomatic bacteriuria, symptomatic infection and recurrent bacteriuria later in pregnancy were seen among those with and without gestational DM. *E. coli* was the most common pathogen.[11]

2. Should diabetic patients be screened and treated for asymptomatic bacteriuria?

Screening and treatment for asymptomatic bacteriuria among diabetic patients are not recommended because they do not reduce the occurrence of subsequent infectious complications.

Strong recommendation, High quality of evidence

Summary of Evidence (also refer to Chapter on Asymptomatic bacteriuria)

Asymptomatic bacteriuria is common among diabetic women (8-14%).[12] On the other hand, the incidence of bacteriuria does not appear to be increased among diabetic men.[13] A case-control study of 228 women with diabetes and 146 women without diabetes showed that impaired metabolic control of diabetes, as revealed by higher glycated hemoglobin levels, significantly increased the risk for developing ASB ($p < 0.05$).[14]

One meta-analysis that evaluated whether asymptomatic bacteriuria is more common in patients with diabetes than among control subjects was recently conducted. The review included 22 studies and reported that indeed, asymptomatic bacteriuria occurs more frequently among diabetic patients and in all subsets of diabetic patients such as females (OR 2.6, 95% CI 1.6-4.1), males (OR 3.7, 95% CI 1.3-10.2), and in children and adolescents (OR 5.4, 95% CI 2.7-11).[15] Moreover, the study concluded that diabetic patients with asymptomatic bacteriuria had more albuminuria and symptomatic UTIs. This increased prevalence of ASB in diabetics may be largely attributable to autonomic neuropathy leading to impaired bladder voiding.[16]

Considering the potential risk to developing subsequent (more complicated) symptomatic UTIs among diabetics, a randomized, placebo-controlled, double-blinded trial that enrolled 105 diabetic women assigned to receive placebo or an antimicrobial agent was conducted.[17] Study results showed that the time to a first symptomatic episode (p=0.67 by the log-rank test), the rates of any symptomatic UTI (RR 1.19; 95% CI 0.28 to 1.81), pyelonephritis (RR 2.13; 95% CI 0.81 to 5.62), and hospitalization for UTI (RR 1.93; 95% CI 0.47 to 7.89) were similar in the placebo group and the antimicrobial-therapy group. The study concluded that screening and treatment for asymptomatic bacteriuria in diabetic women did not reduce complications. The Infectious Diseases Society of America (IDSA) likewise recommended against the screening or treatment of asymptomatic bacteriuria in this population in its 2005 Guidelines for the Diagnosis and Treatment of Asymptomatic bacteriuria.[1,17]

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SPECIFIC ISSUES OF CONCERN IN COMPLICATED URINARY TRACT INFECTION

CATHETER-ASSOCIATED URINARY TRACT INFECTION (UTI)

Summary of recommendations

1. **When is catheter-associated urinary tract infection (CA-UTI) suspected or diagnosed?**
   - **1.1 UTI in patients with an indwelling urethral or suprapubic catheter or in those undergoing intermittent catheterization is termed as CA-UTI. CA-UTI is diagnosed when:**
     - **Fever and/or other signs or symptoms compatible with UTI are present with no other identified source of infection;**
     - **At least 10^3 colony forming units (cfu)/mL of at least 1 bacterial species are present in a single catheter urine specimen or in a midstream voided urine specimen;**
     - **In a patient with an indwelling urethral, suprapubic or condom catheter, or which has been removed within the previous 48 hours.**

     Strong recommendation, Low quality of evidence
   - **1.2 There is no sufficient evidence to define the quantitative cut-off for CA-UTI among men with condom catheters.**

     Weak recommendation, Low quality of evidence

2. **Should patients with indwelling urethral, indwelling suprapubic, or intermittent catheterization be screened and treated for asymptomatic bacteriuria?**
   - **2.1 Screening and treatment of catheter-associated asymptomatic bacteriuria (CA-ASB) are not routinely recommended.**
     Strong recommendation, Moderate quality of evidence
   - **2.2 Screening and treatment of CA-ASB are recommended only for pregnant patients and those who will undergo urologic procedures.**
     Strong recommendation, Moderate quality of evidence
   - **2.3 Data is insufficient to make any recommendations regarding screening and treatment of CA-ASB among post-solid organ transplant and neutropenic patients.**

3. **In patients with suspected CA-UTI, what diagnostic tests should be done to assist the physician in managing the infection effectively?**

   3.1 Similar with the general recommendations in complicated UTI (cUTI), it is necessary to obtain urine gram stain and cultures BEFORE starting empiric antibiotic coverage for CA-UTI.
   Strong recommendation, Moderate quality of evidence

   3.2 In catheterized patients, pyuria alone is NOT diagnostic of CA-UTI and should not be interpreted as an absolute indication for initiating empiric antibiotics.

Strong recommendation, Moderate quality of evidence

3.3 The presence or absence of odorous or cloudy urine alone in catheterized patients is also not an indication for antibiotic treatment.
Strong recommendation, Low quality of evidence

4. How should urine for culture and sensitivity studies be collected from patients with suspected CA-UTI?

4.1 For patients in whom catheterization is still indicated, the urine specimen should be obtained from the freshly placed catheter prior to the initiation of antimicrobial therapy. Urine sample should be aspirated from the catheter port, or if not present, by puncturing at the distal end of the catheter with a sterile needle and syringe after disinfecting the area WITHOUT disconnecting the junction of the catheter and drainage tube.
Strong recommendation, Low quality of evidence

4.2 For individuals whose catheters can be or have been recently removed and requires no further catheterization, a mid-stream, clean catch urine should be obtained. Urine samples for culture should not be obtained from collection bags.
Strong recommendation, Low quality of evidence

4.3 Urine specimens for culture should be processed as soon as possible, preferably within one hour of obtaining the specimen. If this is not possible, the urine specimen should be refrigerated. Refrigerated specimens should be processed within 24 hours.
Strong recommendation, Low quality of evidence

5. What are the antibiotics that can be used for the treatment of CA-UTI?

5.1 Since CA-UTI is often a healthcare-associated infection, the choice of empiric antibiotics to be used will be institution-specific depending on the local susceptibility patterns and the severity of patient's illness. Refer to Table 14.
Strong recommendation, Low quality of evidence

5.2 Seven days of antimicrobial treatment is recommended for patients who have prompt resolution of symptoms and 10 to 14 days of antimicrobial treatment for patients whose response is delayed.
Strong recommendation, Low quality of evidence

6. What is the approach to the presence of the indwelling urinary catheter once the diagnosis of CA-UTI is made?

6.1 Whenever possible, the indwelling catheter should be removed to help eradicate the bacteriuria.
Strong recommendation, High quality of evidence

6.2 For patients in whom indwelling bladder catheterization is necessary, long-term indwelling catheters should be replaced with new catheters before initiating antimicrobial therapy for symptomatic UTI.
Strong recommendation, High quality of evidence

7. What strategies are effective in reducing the risk of CA-UTI?

Strategies for reducing the risk of CA-UTI

Strategy	**Strength of Recommendation**	***Level of Evidence***
Use indwelling catheters only when necessary	Strong	*Low*
Use aseptic technique including appropriate hand hygiene and sterile gloves	Strong	*Low to Moderate*
Allow only trained health personnel to insert Foley catheters	Weak	*Low*
Properly secure catheters after insertion to prevent movement and urethral traction	Weak	*Low*
Maintain a closed sterile drainage system.	Strong	*Moderate*
Maintain good hygiene at the catheter-urethral interface.	Strong	*Moderate*
Maintain unobstructed urine flow	Strong	*Moderate*
Remove catheters when no longer needed.	Strong	*High*
Do not change indwelling catheters or drainage bags at fixed intervals.	Weak	*Low*

It is recommended that appropriate strategies for the prevention of CA-UTI (listed in the Table above) be included and implemented in an institution-specific, multimodal, quality improvement bundle. Periodic assessment of compliance with these bundles, once instituted, is likewise recommended.
Strong recommendation, Moderate quality of evidence

8. Is condom catheter a reasonable alternative to indwelling catheterization in the prevention of CA-UTI?

Condom catheterization is an alternative to indwelling catheter for male patients in whom a urinary catheter is necessary provided post-void residual urine is minimal and the patient has no cognitive impairment.
Strong recommendation, High quality of evidence

9. Is intermittent catheterization a reasonable alternative to indwelling catheterization to prevent CA-UTI?

Intermittent catheterization can also be considered an alternative to short term *(strong recommendation, moderate quality of evidence)* **or long-term** *(weak recommendation, moderate quality of evidence)* **indwelling urinary catheterization with trained and dedicated healthcare staff. Intermittent catheterization, however, requires more manpower hours as well as the full cooperation of patients for frequent repeated catheterization.**

10. **Is suprapubic catheterization an alternative to urethral catheterization?**
    Suprapubic catheterization may be an alternative to urethral catheterization when there are excellent support mechanisms from the surgical and caregiver staff.
    Weak recommendation, Low quality of evidence
11. **What should NOT be done for patients with urinary catheters?**
    The following should NOT be done in an effort to reduce CA-UTI because their use has not been shown to prevent the development of subsequent bacteriuria or symptomatic UTI:

Strategy	**Strength of Recommendation**	***Level of Evidence***
Use of antibiotic–coated catheters	Strong	*High*
Routine use of systemic prophylactic antibiotics at the time of insertion, during and upon removal of indwelling urinary catheters	Strong	*Moderate*
Catheter or bladder irrigation with antimicrobial agents	Strong	*High*
Routine addition of antibiotics or antiseptics to drainage bags and antireflux vents and valves	Strong	*High*
Daily meatal care	Strong	*High*
Changing of catheters and drainage bags at arbitrarily fixed intervals	Weak	*Low*

12. **How can unnecessary long-term catheterization be avoided?**
    Consider using alternative strategies for timely removal and prevention of unnecessary long-term catheterization such as instituting automatic stop orders, nurse-based or electronic physician reminder systems or chart reminders.
    Weak recommendation, Moderate quality of evidence

DISCUSSION

1. **When is catheter-associated urinary tract infection (CA-UTI) suspected or diagnosed?**

1.1 UTI in patients with an indwelling urethral or suprapubic catheter or in those undergoing intermittent catheterization is termed as CA-UTI. CA-UTI is diagnosed when:

- **Fever and/or other signs or symptoms compatible with UTI are present with no other identified source of infection;**
- **At least 10^3 colony forming units (cfu)/mL of at least 1 bacterial species are present in a single catheter urine specimen or in a midstream voided urine specimen;**
- **In a patient with an indwelling urethral, suprapubic or condom catheter, or which has been removed within the previous 48 hours.**

Strong recommendation, Low quality of evidence

1.2 There is no sufficient evidence to define the quantitative cut-off for CA-UTI among men with condom catheters.

Weak recommendation, Low quality of evidence

Summary of Evidence

Since the last Philippine Clinical Practice Guidelines on UTI Update 2004, the diagnostic criteria for CA-UTI has evolved and improved. The quantitative count of at least 10^3 cfu/mL is a compromise between a sensitive level of detecting true bladder bacteriuria in a catheterized patient and the capability of most microbiology laboratories in quantifying growth on culture media.[1]

The presence of symptoms and signs suggestive of UTI among catheterized individuals is an essential component of the diagnosis. In patients with long-term indwelling catheters due to spinal injury, the following are also considered symptoms of possible CA-UTI: increased spasticity, autonomic dysreflexia, or sense of unease. Among those whose catheters have been recently removed, dysuria, urgent or frequent urination, or suprapubic pain or tenderness are signs and symptoms of a possible CA-UTI.

Bacteremia is an important complication of CA-UTI. Bacteremia with the urinary tract as the source occurs in 11% to 40% of nosocomial bacteremic episodes. Patients with bacteremia may present with confusion, chills, fever, and hypotension.[2] On the other hand, the diagnosis of CA-UTI should not be based on symptomatology alone. Not all lower urinary tract symptoms in catheterized patients should be attributed to CA-UTI. Cohort studies of catheterized patients have shown that the usual symptoms referable to the urinary tract such as fever, dysuria, frequent urination and urgency may not be as reliable in diagnosing an infection when a catheter is in place.[3-5] Patients with neurogenic bladder or elderly patients may not be able to show any local symptoms.[1] The entire clinical context should always be considered together with assessment of risk factors and microbiologic investigation.

Certain risk factors for CA-UTI have been identified by local and foreign studies which may help the clinician in the difficult dilemma of deciding whether or not to treat as CA-UTI. Table 13 below summarizes these risk factors.

2. **Should patients with indwelling urethral, indwelling suprapubic, or intermittent catheterization be screened and treated for asymptomatic bacteriuria?**
    - **2.1 Screening and treatment of catheter-associated asymptomatic bacteriuria (CA-ASB) are not routinely recommended.**
      Strong recommendation, Moderate quality of evidence
    - **2.2 Screening and treatment of CA-ASB are recommended only for pregnant patients and those who will undergo urologic procedures.**
      Strong recommendation, Moderate quality of evidence
    - **2.3 Data is insufficient to make any recommendations regarding screening and treatment of CA-ASB among post-solid organ transplant and neutropenic patients.**

Table 13. Risk factors for catheter-associated urinary tract infection, based on prospective studies and use of multivariable statistical modelling.[6]

Factor	*Relative Risk*
Prolonged catheterization >6 days	*5.1 - 6.8*
Female gender	*2.5 - 3.7*
Catheter insertion done outside the operating room	*2.9 - 5.3*
Urology Service	*2.0 - 4.0*
Other active site of infection	*2.2 - 2.4*
Diabetes	*2.3 – 2.4*
Malnutrition	*2.4*
Azotemia (creatinine > 2.0 mg/dL)	*2.1 – 2.6*
Ureteral stent	*2.5*
Monitoring of urine output	*2.0*
Drainage tube below bladder but above collection bag	*1.9*
Antibiotic usage	*0.1 – 0.4*

Summary of Evidence

The presence of bacteria is not infrequently seen in catheterized patients without any complaints, signs, and symptoms suggestive of UTI. This situation is regarded as CA-ASB, which is defined as the presence of significant bacteriuria in a patient WITHOUT signs or symptoms referable to the urinary tract.[1] Significant bacteriuria in patients with indwelling urethral, indwelling suprapubic or intermittent catheterization is the presence of at least 10^3 cfu/ml of at least 1 bacterial species in a single catheter urine specimen. For male patients on condom catheter, the presence of at least 10^5 cfu/ml of at least 1 bacterial species in a single catheter urine specimen from a freshly applied condom catheter is considered significant.

Both foreign and local studies have confirmed the inevitability of the occurrence of significant bacteriuria by the 30th day that the indwelling catheter remains in place.[7,8] The incidence of significant bacteriuria among catheterized patients with initially absent or low-count bacteriuria ranged from 18% to 62% within 2 days from catheterization.[9] It has also been described that the bacteriuria in otherwise healthy or asymptomatic catheterized patients will often resolve spontaneously with the removal

of the catheter.[10] It is difficult to fully assess the natural history of CA-ASB because patients with short-term indwelling catheters in acute care facilities often receive antimicrobial therapy for indications other than UTI. However, available evidence seems to point to the conclusion that CA-ASB does not present with an increased risk of progression to UTI.[5] A randomized control trial (RCT) of treatment with cephalexin versus no treatment of asymptomatic bacteriuria in long-term catheterized patients showed no benefit, and increased rates of antibiotic-resistant bacteria in the treated group.[11]

In another RCT of treatment with trimethoprim-sulfamethoxazole (cotrimoxazole) versus no treatment of persistent catheter-acquired bacteriuria 48 hours following catheter removal, 26% of women in the placebo group developed symptoms within 14 days, while 36% had spontaneous resolution.[12] Furthermore, in the non-treated group, bacteriuria resolved spontaneously in 74% of women younger than 65 years of age, and 4% of women over 65 years. Bacteriologic cure at 4 weeks was 89% in the treated group of women younger than 65 years and 62% of women over 65 years.

Finally, a non-comparative study of sequential antibiotic therapy in an elderly population also showed that treatment of asymptomatic bacteriuria does not eliminate bacteriuria and usually results in replacement with organisms resistant to the antibiotic given.[13] Therefore, CA-ASB need not be treated, and the catheter need not be removed because: (1) the risk of complications is low; (2) treatment does not prevent bacteriuria from recurring; and (3) treatment may lead to the emergence of antimicrobial-resistant bacteria (and *Clostridium difficile*) that are more challenging to treat.

Special populations which may benefit from antibiotic treatment and thus deserve screening and treatment of CA-ASB include pregnant women and those who will undergo urologic procedures. This recommendation is similar to their non-catheterized counterparts and based on a randomized controlled treatment trial in non-catheterized pregnant women that showed that eradication of ASB reduces the risk for pyelonephritis and adverse consequences in pregnancy (see also Chapter on Asymptomatic Bacteriuria in Pregnancy).[14] The conclusion was extrapolated to the catheterized pregnant women as no study had been done in this population. Similarly, patients who will undergo invasive genitourinary procedures associated with mucosal bleeding where high rates of post-procedure bacteremia and sepsis have been previously documented belong to the special population where screening for bacteriuria is recommended even if asymptomatic. Again no direct studies have been done on this subset of patients.

Because data is insufficient to make any recommendations, screening for CA-ASB in certain groups of immunocompromised patients (e.g. post-solid organ transplant patients on immunosuppressive therapy and neutropenic patients) will depend on the clinical situation. The decision will lie on the physician who should weigh the benefits of screening and consequences of non-treatment against the negative effects, which include suprainfections, unnecessary costs, collateral damage to microbial ecology and subsequent antibiotic resistance leading to impaired effectiveness of current and future antimicrobial agents.

3. In patients with suspected CA-UTI, what diagnostic tests should be done to assist the physician in managing the infection effectively?

3.1 Similar with the general recommendations in complicated UTI (cUTI), it is necessary to obtain urine gram stain and cultures BEFORE starting empiric antibiotic coverage for CA-UTI.
Strong recommendation, Moderate quality of evidence

3.2 In catheterized patients, pyuria alone is NOT diagnostic of CA-UTI and should not be interpreted as an absolute indication for initiating empiric antibiotics.
Strong recommendation, Moderate quality of evidence

3.3 The presence or absence of odorous or cloudy urine alone in catheterized patients is also not an indication for antibiotic treatment.
Strong recommendation, Low quality of evidence

Summary of evidence

Invariably, pyuria will develop for most catheterized patients due to the inflammation and irritation of the genitourinary mucosa with the foreign body in place. A prospective, cross-sectional study involving 761 newly catheterized patients reported that pyuria only had a sensitivity of 37% for predicting CA-UTI.[5] In addition, another study that performed sequential quantitative urine cultures and urinalyses on 177 urine specimens from 14 patients on long-term catheter use showed that there was pyuria even during asymptomatic periods.[15] During symptomatic infections, neither urinalyses nor urine cultures displayed changes (e.g. increased number of pus cells, increased colony counts) that may correlate with such events. Another prospective, cross-sectional study among patients with neurogenic bladder requiring chronic catheterization examined the relationship of pyuria with bacteriuria. The study concluded that levels of pyuria did not distinguish patients with bacteriuria from those without.[16]

Hence, pyuria alone is not diagnostic of CA-UTI and should not be interpreted as an absolute indication for initiating empiric antibiotics. The absence of pyuria in a symptomatic catheterized patient, on the other hand, makes the diagnosis of CA-UTI unlikely.[1] A properly collected urine specimen should be sent for urine cultures for the diagnosis of CA-UTI (Refer to Complicated UTI General Guidelines for summary of evidence).

4. How should urine for culture and sensitivity studies be collected from patients with suspected CA-UTI?

4.1 For patients in whom catheterization is still indicated, the urine specimen should be obtained from the freshly placed catheter prior to the initiation of antimicrobial therapy. Urine sample should be aspirated from the catheter port, or if not present, by puncturing at the distal end of the catheter with a sterile needle and syringe after disinfecting the area WITHOUT disconnecting the junction of the catheter and drainage tube.
Strong recommendation, Low quality of evidence

4.2 For individuals whose catheters can be or have been recently removed and requires no further catheterization, a mid-stream,

clean catch urine should be obtained. Urine samples for culture should not be obtained from collection bags.
Strong recommendation, Low quality of evidence

4.3 Urine specimens for culture should be processed as soon as possible, preferably within one hour of obtaining the specimen. If this is not possible, the urine specimen should be refrigerated. Refrigerated specimens should be processed within 24 hours.
Strong recommendation, Low quality of evidence

Summary of Evidence

Organisms yielded from urine cultures should accurately reflect the actual pathogen causing the infection. This will then be translated to accurate antimicrobial sensitivity testing and appropriate antibiotic choice for the patient. One study compared the qualitative and quantitative microbiology of paired urine samples from old urine catheters and newly inserted ones. Despite having a high sensitivity, urine microbiology of old catheters had poor specificity.[17] The number of species and quantitative count of bacteria isolated in urine collected through a catheter in place for several days is greater than a simultaneous specimen collected through a freshly placed catheter.[18,19] Thus, urine samples from newly-inserted catheters are the preferred specimens for pre-treatment cultures among patients with CA-UTI.

For patients whose catheters have been recently placed, urine sample should be aspirated from the catheter port, or if not present, by puncturing at the distal end of the catheter with sterile needle and syringe after thorough disinfection.[1] A closed system should always be maintained ensuring that the catheter and drainage tube are not disconnected from one another. For CA-UTI developing in a patient in whom the catheter has been in place for at least 2 weeks (and catheterization is still indicated), it is recommended that the catheter be replaced and the urine specimen taken after the new catheter has been inserted For individuals whose catheters can be or have been recently removed and requires no further catheterization, a mid-stream, clean catch urine should be obtained. Urine samples for culture should not be obtained from collection bags.

5. What are the antibiotics that can be used for the treatment of CA-UTI?

5.1 Since CA-UTI is often a healthcare-associated infection, the choice of empiric antibiotics to be used will be institution-specific depending on the local susceptibility patterns and the severity of patient's illness. Refer to Table 14.
Strong recommendation, Low quality of evidence

Seven days of antimicrobial treatment is recommended for patients who have prompt resolution of symptoms and 10 to 14 days of antimicrobial treatment for patients whose response is delayed.
Strong recommendation, Low quality of evidence

Summary of Evidence

The rationale for recommending the listed drugs of CA-UTI are extensions from that of cUTI in general. The choice of empiric antibiotic depends on the severity of illness, the risk factors for drug-resistance and the local antimicrobial susceptibility

patterns, given that most CA-UTIs are healthcare associated.[20] Kindly refer to the summary of evidence in the General Guidelines in the Management of cUTI.

For CA-UTI, it is very important to assess the risk factors of patients for the development of infections secondary to important nosocomial pathogens such as *Pseudomonas* or drug-resistant microorganisms. In a case-control study of 58 patients with infection from extended-spectrum beta-lactamase (ESBL)-producing organisms (bloodstream, urinary tract, vascular catheter) and 116 control patients, multivariate analysis showed that recent antibiotic treatment in another country with a high prevalence of ESBL (OR 27.01; 95% CI 2.38, 1733.28; p=0.042), antibiotic therapy within the past year (OR 2.88; 95% CI 1.13, 8.49; p=0.025) and mechanical ventilation (OR 10.6; 95% CI 1.06, 579.10; p=0.042) are all associated with ESBL-producing isolates.[21] A similar study, which included patients with *Klebsiella pneumoniae* bloodstream infections (n=147), reported that exposure to antibiotic therapy (OR 11.81; 95% CI 2.72, 51.08), prolonged hospitalization (OR 1.10; 95% CI 1.04, 1.16) and advanced age (OR 1.14; 95% CI 1.08, 1.21) were the significant factors for the isolation of ESBL-producing *Klebsiella.*[22] A local cohort study of UTI patients reported that structural or anatomic abnormality (OR 2.81, CI 1.26 to 6.29, p=0.012) and recent urinary tract surgery or instrumentation (OR 18.16, CI 2.08 to 158.35. p=0.009) and as significant risk factors for development of complicated UTI with an ESBL-producing organism on multivariate analysis.[23] The OR for fluoroquinolone intake in the preceding three months was 2.56 (95% CI 0.96, 6.87) but did not reach statistical significance.

Risk factors for *Pseudomonas* infection include male patient, being transferred from another intensive care unit (ICU); antibiotic already started at admission; prolonged ICU stay or more than 10 days of hospital stay; ICU incidence of *Pseudmonas*-infected patients; ICU with a high patient turnover; neurogenic bladder; history of prostatic surgery; urinary tract procedures; a foreign body in the urinary tract; and chronic corticosteroids use.[24,25]

In several published reviews, the recommended duration of treatment ranges from 7 to 14 days.[26,27] In the 2009 Infectious Disease Society of America (IDSA) Guidelines on the Diagnosis, Prevention and Treatment of Catheter-associated Urinary Tract Infection in Adults, the optimal treatment duration for CA-UTI appear to be between 3 and 14 days.[1] They have considered two studies involving catheterized patients with neurogenic bladder and spinal cord injury. These studies compared a 3-day course versus a longer course (10 days and 14 days) of antibiotics (either ciprofloxacin or cotrimoxazole). One study showed that rates of cure, persistence, and relapse were similar.[28] On the other hand, the more recent study reported that microbiological and symptomatic relapse were significantly greater among the patients who received the 3-day course.[29] These conflicting results and the fact that some of these studies included only patients with mild illness (not the entire spectrum of CA-UTI patients who tend to have more severe disease) and patients in whom the infecting isolates recovered were sensitive to the empiric antibiotic (data is unavailable regarding the effect of a three-day course of empiric antibiotic therapy when the pathogens isolated are resistant to the empiric antibiotic started) are the reasons for the recommended longer course of antibiotic treatment for CA-UTI.

Table 14. Antibiotics Options for the Treatment of CA-UTI

Antibiotic	Recommended Dose and Duration	Comments
Amikacin *(First line)*	15 mg/kg q24h	Be cautious in giving aminoglycosides in patients with renal insufficiency
Ertapenem	1g IV q24h[1]	For patients with no risk for *Pseudomonas* or *Enterococcus*
Anti-Pseudomonal carbapenems		For patients with risk for *Pseudomonas* infection For ESBL-producing Enterobacteriaceae
Doripenem[2] Imipenem-cilastin[3] Meropenem[4]	500 mg q8h 500 mg q6h 1 g q8h	
Vancomycin	1g IV q 12	For suspected staphylococcal infections[5]
Colistin (Colistimethate sodium)		For multidrug-resistant Enterobacteriaceae, *Klebsiella pneumonia* carbapenemase-producing (KPC) bacteria, Multi-drug resistant (MDR) *Pseudomonas* sp. or MDR *Acinetobacter* sp.
Colomycin[6]	31,250–62,500 IU/kg per day, divided in 2-4 equal doses (240-480 mg/kg/day)	
Coly-Mycin	Double the dose of colomycin (400-800 mg/kg/day)	
Tigecycline	100 mg IV loading dose then 50 mg IV q12	For vancomycin-resistant Enterococci For ESBL-producing Enterobacteriaceae (except *Pseudomonas* spp.
Ampicillin	1-2 g IV q6-8h	For susceptible enterococcal infections
Cefepime	1-2 g IV q8-12h	For *Pseudomonas* or *Acinetobacter* spp. infections
Ceftazidime	1-2 g IV q8h+	
Piperacillin-Tazobactam	4.5 g IV q24	
Levofloxacin	750 mg q24h	For mild infections with no history of previous third generation cephalosporin or fluoroquinolone use
Fluconazole		For fungal infections (see Section on Urinary Candidiasis and Candida Urinary Tract Infections for dosing regimens)
Amphotericin B ± 5-flucytosine		

[1]Ertapenem – Normal renal function and creatinine clearance (CrCl) >50-90: 1g IV q24h; CrCl <30: 500mg IV q24h
[2]Doripenem- CrCl >50-90: 500mg IV q8h; CrCl 30-50: 250mg q8h; CrCl 10-30: 250mg q12h; CrCl <10 no data
[3]Imipenem- CrCl >50-90: 250-500mg q6-8h; CrCl 10-50: 250mg q8-12h; CrCl 125-250mg q12h
[4]Meropenem- CrCl >50-90: 1g IV q8h; CrCl 10-50: 1g IV q12h; CrCl <10: 500mg IV q24h
[5]Risk factors for staphylococcal infection include: presence of an invasive medical device, surgical procedures like joint replacement, and contact with devices found in a hospital setting, immunocompromised state (HIV, cancer, or chemotherapy), enteral feeding, prolonged or recent hospitalization, prior levofloxacin or macrolide use[19].
[6]Colomycin- Creatinine 1.3–1.5mg/dL: 2 million IU q12h; creatinine 1.6–2.5 mg/dL: 2 million IU q24h; creatinine ≥2.6 mg/dL: 2 million IU q36h

6. **What is the approach to the presence of the indwelling urinary catheter once the diagnosis of CA-UTI is made?**

    a. **Whenever possible, the indwelling catheter should be removed to help eradicate the bacteriuria.**
    Strong recommendation, High quality of evidence

    b. **For patients in whom indwelling bladder catheterization is necessary, long-term indwelling catheters should be replaced with new catheters before initiating antimicrobial therapy for symptomatic UTI.**
    Strong recommendation, High quality of evidence

Summary of Evidence

In a RCT, removal of the catheter resulted in the spontaneous resolution of bacteriuria within 14 days.[30] This was seen more frequently in women who were 65 years old and younger. In a Cochrane review that looked into short-term catheter policies after urogenital surgeries in adult patients, the relative risk of catheter-associated bacteriuria when the catheter was removed earlier (1 day vs. 3 days) was 0.50 (95% CI 0.29, 0.87) demonstrating benefit of early catheter removal.[31]

An open clinical trial where symptomatic patients (n=54) with a chronic indwelling catheter and a clinical diagnosis of UTI were randomized to either indwelling catheter replacement before initiating antimicrobial therapy or no replacement showed results favoring catheter replacement.[32] For both groups, initial antimicrobial therapy consisted of 400 mg ciprofloxacin or 300 mg ofloxacin IV every 12 hours then shifted to oral 500 mg ciprofloxacin or 200 mg ofloxacin twice daily once patients were afebrile for 24 hours. Polymicrobial bacteriuria significantly decreased 3 days after therapy was initiated, and 7 and 28 days after it was discontinued, in 24 versus 8 (p=0.002), 18 versus 9 (p=0.01) and 13 versus 5 (p=0.02) patients, respectively. Catheter replacement was also associated with a shorter time to afebrile status, improved clinical status 72 hours after the initiation of therapy in 25 versus 11 patients (p<0.001) and a lower rate of symptomatic clinical relapse 28 days after therapy in 3 versus 11 patients (p=0.015).

Comment: *Observations should not be generalized to patients on short-term catheterization since bacterial biofilm formation is not likely to be as important. Some studies report that urine specimens for culture obtained via a chronic indwelling catheter yield a greater number of organisms isolated than specimens obtained from a newly inserted catheter in the same patient.*[33]

7. **What strategies are effective in reducing the risk of CA-UTI?**

    It is recommended that appropriate strategies for the prevention of CA-UTI (listed in Table 15) be included and implemented in an institution-specific, multimodal, quality improvement bundle. Periodic assessment of compliance with these bundles, once instituted, is likewise recommended.
    Strong recommendation, Moderate quality of evidence

Table 15. Strategies for reducing the risk of CA-UTI

Strategy	Strength of Recommendation	*Level of Evidence*
Use indwelling catheters only when necessary	Strong	*Low*
Use aseptic technique including appropriate hand hygiene and sterile gloves	Strong	*Low to Moderate*
Allow only trained health personnel to insert Foley catheters	Weak	*Low*
Properly secure catheters after insertion to prevent movement and urethral traction	Weak	*Low*
Maintain a closed sterile drainage system.	Strong	*Moderate*
Maintain good hygiene at the catheter-urethral interface.	Strong	*Moderate*
Maintain unobstructed urine flow	Strong	*Moderate*
Remove catheters when no longer needed.	Strong	*High*
Do not change indwelling catheters or drainage bags at fixed intervals.	Weak	*Low*

Summary of Evidence

It is unfortunate that many studies have reported inappropriate use of urinary catheters in as much as 21% to 50% of cases.[1,34,35] More importantly, continued catheter use was deemed inappropriate for almost half of the days that patients were catheterized in one study and for over one-third of the days that patients were catheterized in another prospective evaluation.[36,37] Limiting unnecessary catheterization will ultimately cause reduction in the occurrence of CA-ASB and CA-UTI.

Appropriate indications for indwelling urinary catheter use in hospitalized patients are the following: (1) when accurate and frequent measurements of urine output in critically ill patients are needed; (2) to aid in urologic surgery or other surgery of contiguous structures; (3) to relieve anatomic or functional urinary tract obstruction (e.g., patients with neurogenic bladder dysfunction, urinary retention or other congenital or acquired urologic abnormalities); (4) when urinary incontinence is present without obstruction in a patient with an open sacral or perineal wound; and (5) just before, during or just after prolonged surgical procedures with general or spinal anesthesia.[38-43] Routine catheterization of patients who will undergo caesarian section was unnecessary based on a systematic review of 3 trials (2 RCTS 1 non-RCT) with a total of 1,084 participants. Non-catheterized patients had lower incidence of UTI (RR 0.08 95% CI 0.01 to 0.64 for the 2 RCTs), lower rate of discomfort at first voiding and less time until first voiding.[44]

Hand hygiene is regarded as the most effective measure to prevent cross-transmission of potentially harmful organisms. Direct evidence of its effect on nosocomial infection is scarce, but data showing at least a temporal relationship are available. Carriage of exogenous organisms on the hands of hospital personnel causing cross-infections in patients has been implicated in reports of case clusters and epidemics of nosocomial UTI.[45-47] The role of cross-infection was demonstrated in a prospective study of case clustering in 15.5% of non-epidemic nosocomial bacteriuria of which 90% of clustered cases and 71 % of non-clustered cases were associated with

indwelling urinary catheters.[48] Hand washing before and after catheter care have been emphasized to minimize the risk of personnel hand contamination and to prevent cross infection.[43,49,50] Constant reminder and emphasis on hand hygiene, together with spatial separation of infected catheterized patients have been documented to control outbreaks of catheter-associated urinary tract infections.[45,46]

A greater frequency of catheter-associated bacteriuria 48 hours after errors in catheter care by hospital personnel was observed than when there were no lapses in sterile technique or care of the closed drainage system.[51] In this study, bacteriuria occurred in 13.3% when the catheter-tubing junction had been disconnected at least once, and in 9.5% with closed catheter-tubing junction; 17.9% of cases acquired bacteriuria when improper technique was observed against 11.8% when done properly. However, the differences were not statistically significant. In another study, disconnection of the catheter junction was associated with a higher rate of infection than when there was no disconnection.[52] More importantly, adherence to the sterile continuously closed system of urinary drainage reduced the rate of infection to 16% to 23% from an ineviTable 120% at 4 days after insertion when open drainage was used.[39,51,53] However, infection becomes almost 100% by 30 days with closed drainage.[51,54] Thus, the principal benefit of closed drainage is to delay, if not prevent, the onset of infection.

Use of aseptic technique and sterile equipment by trained personnel was shown to be a cost-effective application of the CDC guideline for the prevention of catheter-associated UTI.[43,55] Specifically, these include the use of sterile gloves, sterile catheters, antiseptic solution for perineal cleansing, and water-soluble lubricating jelly for catheter insertion.[43,55,57] One study noted that within 48 hours of catheterization, women catheterized by licensed practical nurses and registered nurses had more than thrice (34%) and twice (21%) the rate of acquired bacteriuria, respectively, than patients catheterized by trained physicians (10%).[51] One small RCT on 156 patients who underwent pre-operative catheterization compared sterile catheterization (scrubbing for four minutes, gowning up, wearing sterile gloves and using strict aseptic technique) versus clean, non-sterile technique, which involved washing the hands once using soap and water only. The trial found no significant difference in the development of UTI between the two groups (9.4% with sterile technique vs. 11% in the hand wash non-sterile group).[58] A larger RCT of 436 obstetric patients whose periurethral area was cleaned with water vs. chlorhexidine 0.1% before insertion of the urine catheter also found no significant difference in the rates of UTI (water group 8.2% vs. antiseptic group 9.2%; OR 1.13; 95% CI 0.58, 2.21).[59]

Interestingly, one small RCT of 177 females undergoing abdominal hysterectomy that examined whether UTI could be reduced by reversing the sequence of vaginal cleansing and urethral catheterization found no significant reduction in the incidence of UTI among those catheterized before vaginal cleansing (15%) versus those catheterized after vaginal cleansing (25%).[60]

Comment: *The follow-up period was short for both RCTS: 3 days post-operatively and 24 hours post-insertion of the catheter.[58,59] In resource-constrained settings, simple hand-washing with soap and water and cleaning of the periurethral area with water before insertion of a sterile catheter with gloved hands may be acceptable alternatives.*

High bacterial colony counts can develop in the collection bag and ascend against the flow of urine to infect the urinary bladder within 2 days.[39,51,61] To achieve free flow of urine: (1) the collection bag should be lower than the level of the bladder at all times; (2) the catheter and collecting tube should be kept from kinking; (3) the catheter should not be clamped except when a culture specimen is collected or when the patient must be separated from the drainage bag; and (4) the bag should be emptied regularly.[43,62]

The most important and consistently demonstrated risk factor for developing bacteriuria is the duration of indwelling catheterization.[2,37,51] CA-UTI occurs at a rate of 3% to 16% per day of catheterization, and at 30 days, almost 100% of catheterized patients will demonstrate bacteriuria.[39,42,51,57] Maki and Tambyah demonstrated that the risk is highest at beyond 6 days (OR 5.1 to 6.8).[6] Two prospective studies have demonstrated that a substantial proportion of catheter days were unnecessary, and prompt removal would have theoretically prevented 40% of all infections.[36,37] Thus, if the catheter can be removed before bacteriuria develops, postponement of bacteriuria becomes prevention.[42] A well-conducted prospective study by Domingo and colleagues (1999) at the medical wards and ICU of the Philippine General Hospital likewise showed that duration of catheterization was significantly associated with acquisition of infection (OR 1.22; 95% CI 1.09, 1.37) on multivariate analysis.[7] The study also showed that peak incidence of CA- UTI occurred on the 5th to 7th day of catheterization. The average number of days from catheter insertion to the development of UTI was 6.4 days (range 2-44 days). Since duration of catheterization is a modifiable risk factor, emphasis should be made on interventions to reduce the prolonged and inappropriate use of urine catheters to decrease the incidence of CA-UTI.

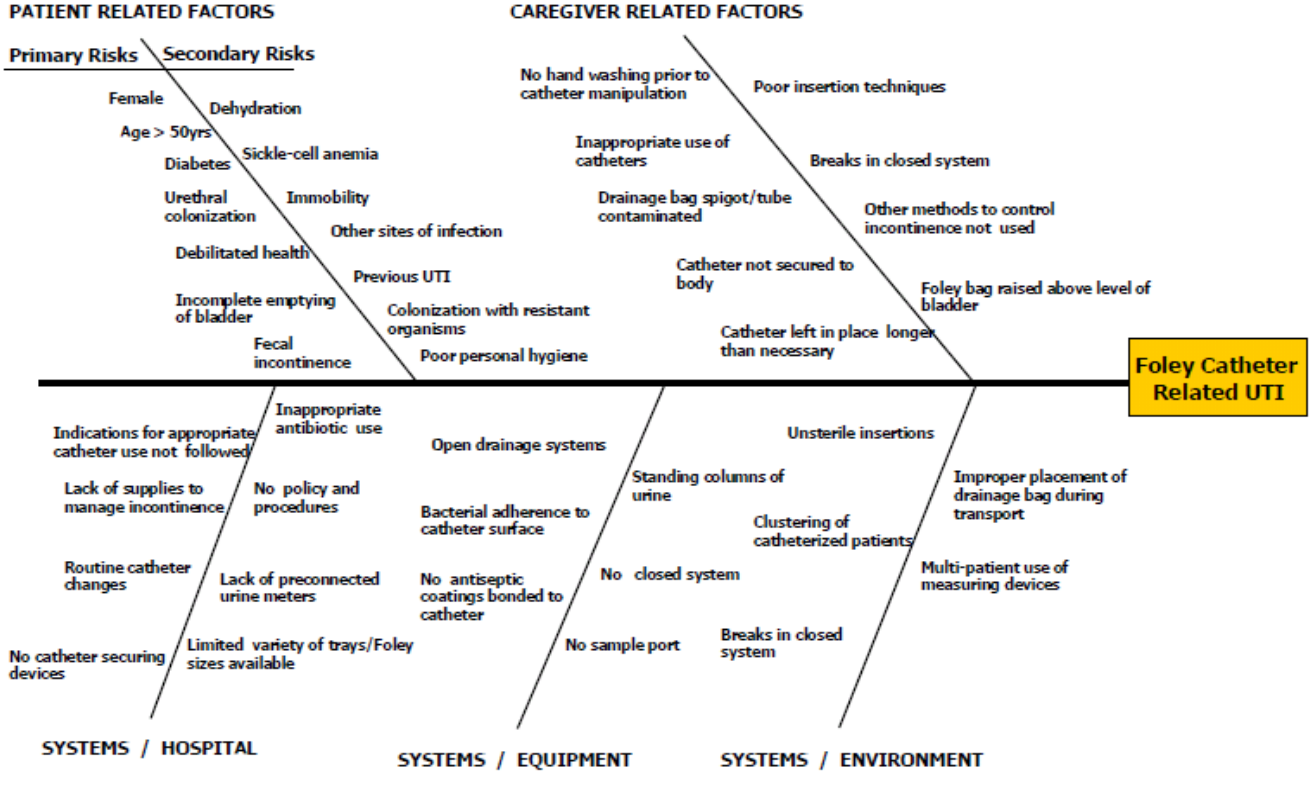
When requesting for urine culture, urine specimens should be obtained aseptically without opening the catheter-collection. It has been emphasized that the junction of the catheter and drainage tube should not be disconnected for this purpose.[51,52,63,64] As previously discussed, disconnection of the catheter junctions, whether to collect urine specimens or to irrigate the bladder, was associated with high rates of infection.[51,52]

More recently published literature have looked into the usefulness of comprehensive programs using a combination of proven individual strategies to reduce the overall risk of CA-UTI of individual patients and overall CA-UTI rates on an institutional level.[1,5,10,15-19,34,65] An example of a fish diagram that demonstrates the complexity of factors that lead to the development of CA-UTI is shown in Figure 1. This type of analysis can be used as a basis for a multimodal or institutional approach to the prevention of CA-UTI. The roles of infection control committees, therapeutics or infectious disease specialists as well as surveillance teams are emphasized to provide specific guidance applicable to their particular clinics, wards and ICUs, hospitals, nursing homes and other similar healthcare facilities where there is use of urinary catheters. This paradigm shift is best exemplified by the approaches of the Society of Healthcare Epidemiology of America and the Association for Professionals in Infection Control and Epidemiology (APIC) with their document *Guide to the Elimination of Catheter-Associated Urinary Tract Infections (CA-UTIs): Developing and Applying Facility-based Interventions in acute and Long-term Care Settings an APIC Guide 2008* (APIC 2008).[34,35]

The healthcare bundle approach which has gained popularity is endorsed by various groups including the Institute of Healthcare Improvements. This group of

FOLEY RELATED URINARY TRACT INFECTIONS

Cause and Effect Diagram



interventions has been shown to reduce the occurrence of CA-UTI and is well accepted by health professionals. An example of an institutional bladder bundle would include:[19]

- Aseptic insertion and proper maintenance of catheter.
- Use of bladder ultrasound to fully assess the need for and limit unnecessary indwelling catheterization.
- Use condom or intermittent catheterization in appropriate patients.
- Early removal of the catheter using reminders or stop orders.

8. Is condom catheter a reasonable alternative to indwelling catheterization in the prevention of CA-UTI?

Condom catheterization is an alternative to indwelling catheter for male patients in whom a urinary catheter is necessary provided post-void residual urine is minimal and the patient has no cognitive impairment.
Strong recommendation, High quality of evidence

Summary of Evidence

In males, the use of external condom catheters has been seen to significantly reduce the risk for CA-UTI in most studies. A randomized trial involving 75 men at the US Veterans Affairs Hospital showed that indwelling urethral catheter was associated with a 5-time increased risk for CA-UTI compared to appropriately sized condom catheters (HR 4.84; 95% CI 1.46, 16.02; p=0.01).[66]

9. Is intermittent catheterization a reasonable alternative to indwelling catheterization to prevent CA-UTI?

Intermittent catheterization can also be considered an alternative to short term *(strong recommendation, moderate quality of evidence)* **or long-term** *(weak recommendation, moderate quality of evidence)* **indwelling urinary catheterization with trained and dedicated healthcare staff. Intermittent catheterization, however, requires more manpower hours as well as the full cooperation of patients for frequent repeated catheterization.**

Summary of Evidence

Comparison of intermittent catheterization and indwelling catheterization shows lower CA-UTI, pyelonephritis, epididymitis, periurethral abscesses, urethral stricture, vesicourethral reflux, hydronephrosis, calculi and autonomic dysreflexia among those who undergo intermittent catheterization.[3] In a 38-month prospective study by Esclarin de Ruz et al with 128 cases of acute spinal cord injuries, the incidence rates per 100 person days for CA-UTI were 2.72 cases for men with indwelling urethral catheters, 0.41 cases for men with clean intermittent catheterization, 0.36 cases for men with condom catheters, and 0.34 cases for women with suprapubic catheterization.[67] The benefit of intermittent catheterization over short-term indwelling catheterization is better studied than long-term catheterization.

A Cochrane review (that found two trials) showed that catheter-associated bacteriuria occurred significantly more in patients with indwelling urethral catheterization (RR 2.90; 95% CI 1.44, 5.84).[68] Intermittent catheterization however

requires more manpower hours as well as the full cooperation of patients for frequent repeated catheterization; thus, it is still not a popular choice despite the evidence.

10. Is suprapubic catheterization an alternative to urethral catheterization?
Suprapubic catheterization may be an alternative to urethral catheterization when there are excellent support mechanisms from the surgical and caregiver staff.
Weak recommendation, Low quality of evidence

Summary of Evidence

In a Cochrane review of 14 randomized and quasi-randomized trials which compared indwelling urethral versus suprapubic catheterization, patients with urethral catheters showed more cases of catheter-associated bacteriuria (RR 2.60; 95%CI 2.12, 3.18); more re-catheterization (RR 4.12; 95% CI 2.94, 7.56) and greater discomfort (RR 2.98; 95% CI 2.31, 3.85).[68] Despite the better results with suprapubic catheters, experience is limited because of the invasive nature of the insertion requiring this to be done in the operating room by a skilled surgeon with risks for bleeding and visceral injury, as well as the need for specially trained caregivers to give continuing maintenance care.

11. What should NOT be done for patients with urinary catheters?

The following should NOT be done in an effort to reduce CA-UTI because their use has not been shown to prevent the development of subsequent bacteriuria or symptomatic UTI:

Table 16. Interventions NOT proven to reduce CA-UTI

Strategy	**Strength of Recommendation**	***Level of Evidence***
Use of antibiotic–coated catheters	Strong	High
Routine use of systemic prophylactic antibiotics at the time of insertion, during and upon removal of indwelling urinary catheters	Strong	Moderate
Catheter or bladder irrigation with antimicrobial agents	Strong	High
Routine addition of antibiotics or antiseptics to drainage bags and antireflux vents and valves	Strong	High
Daily meatal care	Strong	High
Changing of catheters and drainage bags at arbitrarily fixed intervals	Weak	Low

Summary of Evidence

Antibiotic-coated catheters

Despite the large amount of studies done with various catheter products, results are variable. In a Cochrane review of 23 randomized and quasi randomized trials, the following were shown: (1) silver oxide catheters were not associated with reduction in catheter-associated bacteriuria; and (2) silver alloy catheters showed lower

incidence of CA-ASB if catheterized for less than 1 week (RR 0.54; 95% CI 0.43, 0.67) and if for more than 1 week (RR 0.64; 95%CI 0.51, 0.80).[69] On the other hand, a larger study involving 3,036 patients comparing various catheters including silicone-based silver hydrogel coated catheters versus silicone-based hydrogel coated catheters showed no difference in protection against catheter-associated bacteriuria.[70]

When antibiotic-coated catheters were tested, a Cochrane review showed reduced rates of catheter-associated bacteriuria in minocycline and rifampin-coated catheters compared to standard catheters if used for less than 1 week (RR 0.36; 95%CI 0.18, 0.73) but not at more than 1 week.[71] Nitrofurazone-coated catheters were also associated with lower rates of catheter-associated bacteriuria at less than 1 week catheterization (RR 0.52; 95% CI 0.34, 0.78) but the benefit when used more than 1 week is less conclusive.

A recent parallel, three-group, multicenter, randomized controlled superiority trial enrolled 6,394 adult participants requiring short-term catheterization randomly allocated to receive a silver alloy-coated catheter, a nitrofural-impregnated catheter, or a standard polytetrafluoroethylene-coated catheter (control group).[72] Results showed that symptomatic UTI (primary outcome) occurred in 12.6%, 12.5% and 10.6% in the control group, silver alloy group and the nitrofural catheter group respectively, with the difference considered to be clinically insignificant. While the nitrofural catheter group appear to have lower rates of symptomatic infection, it was noted that the rate of catheter-related discomfort was higher in this group than with the control and silver alloy group. The study concluded that routine use of antimicrobial-impregnated catheters was not supported.

Systemic prophylactic antibiotics

One small RCT of 70 patients with long-term urinary catheters demonstrated that the use of prophylactic antibiotic during routine replacement of the catheter did not prevent or delay the development of bacteriuria.[73] A meta-analysis aimed to determine whether antibiotic prophylaxis at the time of removal of a urinary catheter reduces the risk of subsequent symptomatic UTIs was done recently.[74] It included six RCTs and one non-randomized controlled study with variable methodological quality ranging from low to moderate. They were heterogeneous in the type and duration of antibiotic prophylactic regimen used. The meta-analysis reported over-all benefit with the use of antibiotic prophylaxis in reducing the risk for CA-UTI (RR 0.45; 95% CI 0.28, 0.72) with a number-needed-to-treat of 17 (12 to 30). However, it is important to note that these studies were mostly confined to surgical patients such as males undergoing prostatectomy or other surgical operations. In addition, the study defined UTI as detection of measurable bacteriuria plus the presence of at least one sign or symptom. This definition may have overestimated the prevalence of UTI in the early post-operative period since most post-surgery patients complain of lower urinary tract complaints and develop bacteriuria without necessarily having UTI.[75] More randomized trials using similar treatment regimens are needed to support the use of antibiotic prophylaxis after catheter removal. Because of this reason and the increased risk for the development of adverse drug reactions, additional costs, and the possibility of emergence of resistant bacteria, routine antibiotic use to postpone bacteriuria or treat asymptomatic bacteriuria among catheterized patients is discouraged.[13,42,76,77]

Bladder irrigation

RCTs have shown that bladder irrigation using antimicrobial agents did not prevent most catheter-associated bacteriuria even if given continuously.[78-82] One cross-over study that included 32 women on long-term catheterization showed that 10 weeks of daily bladder irrigation with normal saline was similar to 10 weeks of no irrigation in terms of catheter-associated bacteriuria, catheter obstruction and febrile episodes.[83]

Addition of disinfectants or antiseptics to drainage bags

Instillation of disinfectants in the drainage bags or the use of antireflux vents and valves did not reduce the incidence of bacteriuria in RCTs.[50,84-87]

Daily meatal care

It seems logical that daily meatal care at the urethra-catheter interface would decrease bacterial colonization and thereby prevent subsequent UTI. However, large randomized trials have consistently shown no benefit with enhanced meatal care using povidone-iodine, silver sulfadiazine and polyantibiotic ointment or cream.[53,62,88]

On the contrary, one study that compared three groups: Group 1 – twice daily application of povidone-iodine at the urethra-catheter junction; Group 2 – once daily application of a non-antiseptic solution of green soap and water; and Group 3 – routine care (debris removal at usual baths), reported higher rates of catheter-associated bacteriuria in both treatment groups compared with routine care.[88] The proposed reasons for the lack of demonstrable advantage of this strategy include the lack of effect on the ascending route of infection within the catheter lumen; short-lived antiseptic effect of the topical agents; increased catheter manipulation during cleaning; and the development of protective biofilms on the surface.[3]

Catheter change at arbitrarily fixed intervals

Biofilms produced on the surface of catheters over time protect pathogens from antibiotic agents and from the patient's own immune response.[41] The practice of changing indwelling catheters on a routine schedule is based on the idea of decreasing microbial burden and biofilm formation as well as minimizing the likelihood of blockage and stasis. Due to lack of sufficient scientific evidence to support this strategy, experts agree that a catheter should not be changed routinely on a periodic interval.[3,43,89] Indications for catheter and drainage bag change include: (1) malfunction or leakage; (2) catheter obstruction; (3) contamination (e.g., disconnection between catheter and drainage tube); (4) bacteriuria that require antibiotics; (5) concretions in catheter lumen that may proceed to its obstruction; and (6) candiduria.[89]

12. How can unnecessary long-term catheterization be avoided?
Consider using alternative strategies for timely removal and prevention of unnecessary long-term catheterization such as instituting automatic stop orders, nurse-based or electronic physician reminder systems or chart reminders.
Weak recommendation, Moderate quality of evidence

Summary of Evidence

Small studies on quality improvement interventions aimed to decrease duration of catheterization have shown small significant changes. For instance, a recent

small before-and-after crossover study in a US medical center found that computerized urinary catheter reminder system decreased catheterization duration by nearly 3 days (p=0.1).[90] In a pre-post intervention study, healthcare worker education and the provision of an "indication sheet" for the use of urinary catheters prove to be effective in reducing the total number of catheters placed (2,029 in 2001; to 2,188 in 2002; 300 in 2004; and 512 in 2005).[91] A systematic review published in 2013, in fact, reported a 53% decrease in the rate of CA-UTI when these reminder strategies are put in place.[92]

Locally, a quality improvement project using written chart reminders decreased the duration of catheterization by 1.4 days (Domingo 2003). Although UTI rates were not measured, quality improvement interventions (e.g., automatic stop orders or chart reminders) are promising and may prove beneficial if sustained in the long term.

Comment: *In one of the study sites of a collaborative quality improvement project, the use of written chart reminders in a provincial hospital in the Philippines reduced inappropriate catheter use from 32% to 15% over a period of 6 months in a time-series analysis. [Abstract presented at the 2004 Asia Pacific Society for Infection Control Conference and the 2004 International Conference on Improving the Use of Medicines].*

The 2012 European Urology Association Guidelines on Urological Infections and the 2009 IDSA Guidelines on the Diagnosis, Prevention and Treatment of CA-UTI in Adults have both enumerated strategies such as automatic stop orders, electronic-based or nurse-based reminders (when possible) that may aid in minimizing catheter days.[3,93]

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SPECIFIC ISSUES OF CONCERN IN COMPLICATED URINARY TRACT INFECTION

RENAL ABSCESS

Summary of recommendations

1. When should renal abscess be suspected in patients presenting with upper urinary tract infection (UTI)?

Renal abscess should be strongly considered in diabetic patients presenting with hypotension and renal impairment. It can also be considered for patients suspected to have upper UTI who remain febrile and hypotensive 72 hours after initial intravenous (IV) antibiotic administration.
Strong recommendation, low quality of evidence

2. What are the diagnostic tests to be done in patients suspected of having renal abscess?

2.1 **Imaging should be done to confirm a diagnosis of renal abscess. A CT scan is preferred over ultrasound because of the former's higher sensitivity.**
Strong recommendation, low quality of evidence

2.2 **Urine and blood cultures should be requested for patients suspected of having renal abscess. An abscess aspirate, if drainage has been performed, should be sent for culture studies.**
Strong recommendation, low quality of evidence

3. In patients diagnosed with renal abscess, when is surgical intervention warranted?

3.1 For lesions less than 5 cm in diameter, antibiotics can be given alone and should be continued for 4-10 weeks until the abscess has completely regressed as evidenced by CT scan. Drainage need not be done.
Weak recommendation, low quality of evidence

3.2 Percutaneous drainage should be considered for renal and perirenal abscesses with sizes >5 cm. Open drainage should be considered for those with multiloculated abscesses and for those patients in whom percutaneous drainage is unsuccessful. Antibiotics should be given for a minimum of four weeks after drainage.
Strong recommendation, low quality of evidence

3.3 For patients treated with antibiotics alone, CT scan imaging should be repeated after four to six weeks.
Strong recommendation, low quality of evidence

4. What empiric antibiotics should be started on those suspected to have renal abscess?

4.1 The antibiotics chosen should have activity against gram-negative organisms, particularly *Escherichia coli*, *Klebsiella* sp., and *Proteus mirabilis*. Empiric antibiotics should be guided by local antimicrobial susceptibility patterns.

Always assess for patients' risk factors for drug resistance/ESBL-production and *Pseudomonas* infection when choosing empiric antibiotics. Antibiotics listed in the general guidelines in the management of complicated UTI may be used. Similarly, when other drug-resistant pathogens are considered, the antibiotics listed in the Table of antibiotic options for CA-UTI (Table 14) may be used.
Strong recommendation, low quality of evidence

4.2 **Vancomycin can be added for coverage of *Staphylococcus aureus* if there is another source of infection where *S. aureus* is suspected.**
Strong recommendation, low quality of evidence

DISCUSSION

1. When should renal abscess be suspected in patients presenting with upper urinary tract infection (UTI)?

1.1 Renal abscess should be strongly considered in diabetic patients presenting with hypotension and renal impairment. It can also be considered for patients suspected to have upper UTI who remain febrile and hypotensive 72 hours after initial intravenous (IV) antibiotic administration.

Strong recommendation, low quality of evidence

Summary of Evidence

Occasionally, abscesses can form in the kidneys, and diabetes is an important risk factor. It can have a high mortality rate if poorly treated.[1-5] The common signs and symptoms of renal abscess, as identified by five retrospective studies, are fever (75–93% of patients), costovertebral angle tenderness (75%), lumbar pain (36–64.5%), nausea and vomiting (30%), dysuria (8.9–12%), and anorexia (6–37%).[4-8] These signs and symptoms are similar to the presentation of other complicated UTI syndromes. However, several conditions would make one suspect renal abscess; such conditions include the presence of diabetes mellitus (DM), hypotension, renal impairment and the absence of response to initial antibiotic treatment.

Several studies have identified DM as the most common predisposing factor for the development of renal and perinephric abscesses.[2,4,5,8,9] The proposed reason for this predisposition is the defective chemotaxis, phagocytosis and bactericidal activity of phagocytes in patients with diabetes.[10-12] One study performed an analysis of the risk factors associated with the development of renal abscess.[7] The study included patients with suspected upper UTI, as evidenced by clinical symptoms of pyuria and flank pain, and who underwent computerized tomography (CT) scan imaging to look for evidence of acute pyelonephritis or renal abscess. Of the 130 study participants, 23 (17.7%) were diagnosed with renal abscess. On multivariate analysis, DM (OR 5.8 p=0.016), hypotension (OR 4.7 p=0.044), acute renal impairment (OR 13.4 p= 0.001) and leukocytosis of more than 20,000/L (OR 22.6 p=0.00) were associated with renal abscess.[7] In a 10-year cohort match control study to investigate the incidence of renal abscess in Taiwan, a total of 500,522 diabetics and 500,365 non-diabetic controls were included. There were 2,044 cases of renal abscess documented within the diabetic group, and these were compared to 448 cases in the control group. Significant factors associated with renal abscess were DM (HR 3.81 95% CI 3.44–4.23 p=0.00001) and female gender (HR 2.78 95% CI 2.51–3.088 p<0.0001). In this study, however, DM was not associated with increased in-hospital mortality rate compared to controls.[1]

Very few patients with acute UTI will be febrile for more than four days after antibiotic initiation.[13] A retrospective chart review of 70 patients hospitalized for febrile pyelonephritis reported that only 13% had fever that persisted for up to 72 hours.[14] Another retrospective study involving a chart review of 88 patients was done to identify clinical characteristics that can lead to early diagnosis of renal abscess. It concluded that in order to make an early diagnosis of renal abscess, emphasis should be placed on a protracted UTI course especially if an appropriate antibiotic regimen has already been started.[13] In addition, in one study that stratified patients into three groups based on disease severity [group 1: simple acute pyelonephritis (n=82), 7.3%; group 2: severe

acute pyelonephritis (n=25), 48%; and group 3: abscess (n=23), 43.5% p<0.001] occurrence of hypotension was associated with renal abscess formation and more severe disease.[7] On multivariate analysis, DM (OR 5.8 p=0.016) and hypotension (OR 4.7 p=0.044), together with acute renal impairment (OR 13.4 p=0.001), were statistically significant factors for the development of renal abscess.[7] Failure to respond to treatment after 72 hours of initial IV antibiotic administration, or clinical failure as evidenced by persistent hypotension, should make one suspect renal abscess formation.

2. What are the diagnostic tests to be done in patients suspected of having renal abscess?

2.1 Imaging should be done to confirm a diagnosis of renal abscess. A CT scan is preferred over ultrasound because of the former's higher sensitivity.
Strong recommendation, low quality of evidence

Summary of Evidence

CT scan is the imaging modality of choice in the evaluation of upper UTIs. CT scan is better than ultrasonography in detecting focal parenchymal abnormalities, defining the extent of disease and detecting perinephric fluid collections and abscesses.[15,16] Ultrasound, on the other hand, has the advantage of being more accessible and being less expensive; it can be done at the bedside and there is less patient exposure to contrast medium or radiation.[17] However, it is less sensitive in detecting renal abscesses with sizes <3 cm[18] and can miss the diagnosis in as much as 42.3% of cases.[2]

A retrospective study of 12 patients diagnosed with renal or perinephric abscess and nephritis compared the abilities of CT scan and sonography done within 48 hours to detect such lesions.[18] Results showed that for renal abscess, ultrasonography was able to detect two out of three cases seen on CT scan. For perinephric abscess, ultrasonography missed one of the three cases identified by CT scan. In cases of focal or multifocal bacterial nephritis, five cases were identified by CT scan while only two were seen on ultrasonography. Abscesses that were missed by ultrasound either have sizes <2 cm (multiple microabscesses) or were gas forming. In another retrospective study of 66 patients with retroperitoneal abscesses, wherein 72.7% involved the kidney, ultrasonography was diagnostic in 33 of 39 patients (84.6%) while CT scan was diagnostic in 38 of 40 patients (95%).[19]

2.2 Urine and blood cultures should be requested for patients suspected of having renal abscess. An abscess aspirate, if drainage has been performed, should be sent for culture studies.
Strong recommendation, low quality of evidence

Summary of Evidence

Culture positivity rates reported by several studies were 41–43% for urine, 31–40% for blood and 59% for pus/aspirate specimens.[2,4,7,8] Urine and blood cultures were not highly sensitive and were positive in less than half of cases.[4] However, several studies have reported that either blood or urine cultures parallel the bacteriology of the abscess; thus, their results can be used as a guide in the selection of antimicrobial

therapy. One study involving 88 patients with renal or perinephric abscess, with an 88.6% isolation rate of the etiologic organisms (from any specimen such as blood, urine or abscess aspirate), reported that 37% had identical pathogens in two or three of the cultures. Urine and abscess culture isolates were the same in 15% of cases, blood and abscess in 12.8% and blood and urine in only 1.3%.[13] Another retrospective study of 66 patients with retroperitoneal abscess reported higher rates of agreement—41.6% of urine culture results and 63.1% of blood culture results coincided with the abscess aspirate culture.[19]

An abscess aspirate, if drainage has been performed, should be sent for routine aerobic culture studies. An anaerobic culture can be requested if there is access to a microbiology laboratory that can perform such. Special media are required when performing anaerobic cultures (e.g., cooked meat broth), and the timing of inoculation is very important. Hence, there should be proper coordination ahead of time between the laboratory and the one who will acquire the samples (via aspiration or surgical drainage) to ensure adequacy, appropriateness and reliability of specimens.

3. **In patients diagnosed with renal abscess, when is surgical intervention warranted?**

3.1 **For lesions less than 5 cm in diameter, antibiotics can be given alone and should be continued for 4-10 weeks until the abscess has completely regressed as evidenced by CT scan. Drainage need not be done.**
Weak recommendation, low quality of evidence

3.2 Percutaneous drainage should be considered for renal and perirenal abscesses with sizes >5 cm. Open drainage should be considered for those with multiloculated abscesses and for those patients in whom percutaneous drainage is unsuccessful. Antibiotics should be given for a minimum of four weeks after drainage.
Strong recommendation, low quality of evidence

3.3 For patients treated with antibiotics alone, CT scan imaging should be repeated after four to six weeks.
Strong recommendation, low quality of evidence

Summary of Evidence

In at least six retrospective studies involving patients diagnosed with renal abscess, clinical regression was seen within 16 days to 16 weeks of antibiotics alone for abscesses <5 cm in size.[2,4,9,20-22] For abscesses >5 cm in size by CT scan, five studies have reported favorable outcomes with percutaneous drainage.[2,4,5,20,22] One retrospective study involving 32 patients with renal and perirenal abscesses (average abscess volume of 10–650 ml, size not specified) reported a cure rate of 67% with percutaneous drainage alone. Minimal complications were reported.[6] For abscess sizes between 3–5 cm, recommendations on the decision to treat with antibiotics alone or to perform drainage are varied.[2,4,9,20-22] The decision will ultimately rely on individual patient scenarios, taking into consideration the severity of infection, location, the presence of comorbidities and surgical risk assessment, among others.

In a study of 23 patients with abscess (size >3 cm), those treated with percutaneous drainage seem to have comparable outcomes to those treated directly

with surgical drainage.[23] Adjunctive therapy may be warranted only for certain situations such as the presence of loculation, the presence of a superinfected tumor or when kidney function is compromised.[6] Hence, regular clinical assessment is important in the course of treatment to guide in the proper timing and selection of appropriate surgical interventions.

4. What empiric antibiotics should be started on those suspected to have renal abscess?

4.1 The antibiotics chosen should have activity against gram-negative organisms, particularly *Escherichia coli*, *Klebsiella* sp., and *Proteus mirabilis*. Empiric antibiotics should be guided by local antimicrobial susceptibility patterns.

Always assess for patients' risk factors for drug resistance/ESBL-production and *Pseudomonas* infection when choosing empiric antibiotics. Antibiotics listed in the general guidelines in the management of complicated UTI may be used. Similarly, when other drug-resistant pathogens are considered, the antibiotics listed in Table 14 (Antibiotic options for CA-UTI) may be used.
Strong recommendation, low quality of evidence

4.2 **Vancomycin can be added for coverage of *Staphylococcus aureus* if there is another source of infection where *S. aureus* is suspected.**
Strong recommendation, low quality of evidence

Summary of Evidence

In recent years, gram-negative organisms including *E. coli*, *Klebsiella* sp., and *P. mirabilis* have been the predominant pathogens isolated from specimens (blood, urine and abscess aspirate) from patients with renal abscess.[2,5,6,13,24]

S. aureus infection of other location may result in bacteremia and metastasis to the renal parenchyma, resulting in abscess formation. Renal abscess patients with *S. aureus* as the pathogen usually have a history of ongoing skin infection.[25,26]

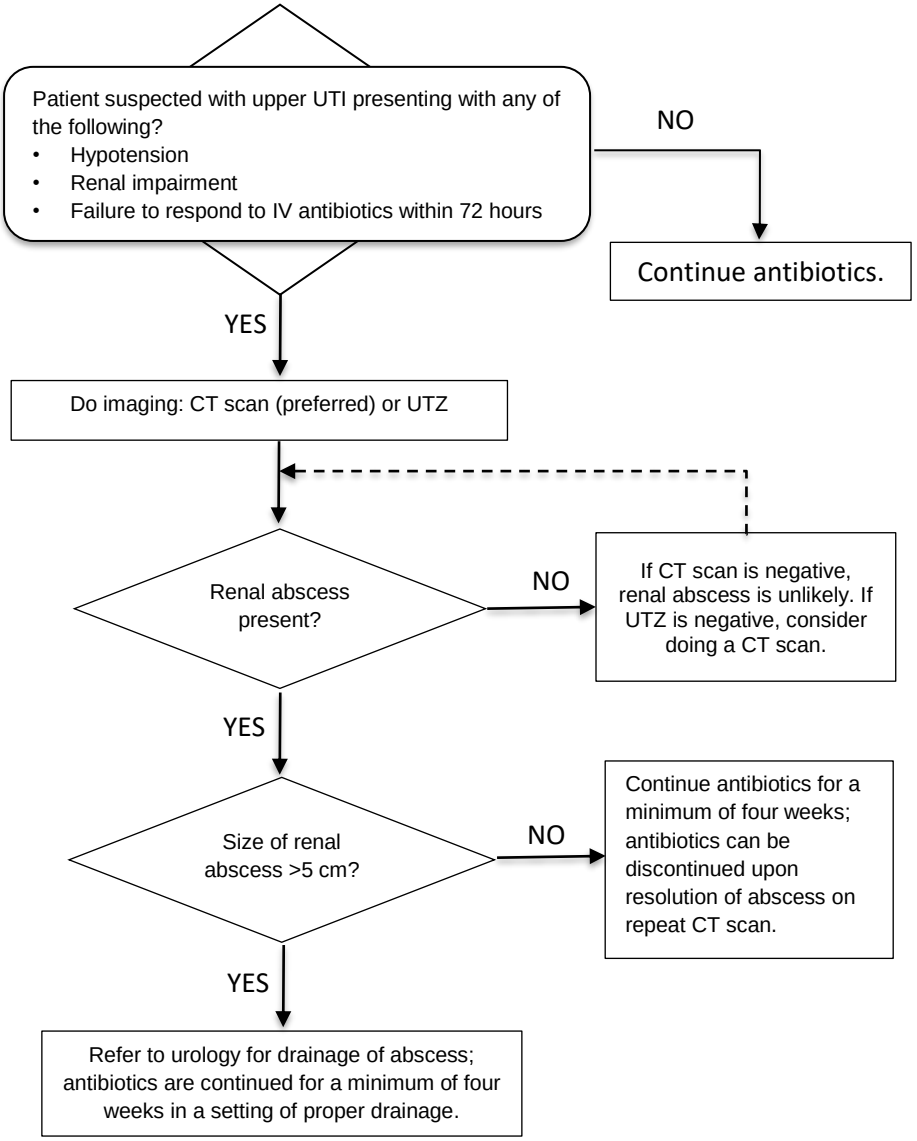

Figure 2. Management algorithm for the treatment of suspected renal anscess

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SPECIFIC ISSUES OF CONCERN IN COMPLICATED URINARY TRACT INFECTION

URINARY TRACT INFECTION IN RENAL TRANSPLANT PATIENTS

Summary of Recommendations

1. **How should urinary tract infection (UTI) in post–kidney transplant patients be managed?**

   1.1 **Post-transplant UTI can be managed by initial administration of empiric broad-spectrum antibiotics. Patients suspected of having drug-resistant gram-positive infections (e.g., *Enterococci*, methicillin-resistant *Staphylococcus aureus*) should be started on antibiotics that are active against such organisms. Specific therapy can be initiated once culture results are available and should be continued until the pathogen is eradicated.**
   Strong recommendation, low quality of evidence

   1.2 **Patients with early UTI (i.e., occurring within the first six months after transplantation) or UTI presenting with signs and symptoms of pyelonephritis or sepsis should be admitted and started on intravenous (IV) antibiotics. Treatment should be given for 14 days. When the results of urine culture are available, the IV antibiotics can be shifted to their oral equivalent (if available and clinically feasible) to complete the treatment duration.**
   Strong recommendation, low quality of evidence

   1.3 **Late cystitis (i.e., occurring after six months post-transplant) can be treated for seven days, while late pyelonephritis requires 14 days of antimicrobial therapy.**
   Strong recommendation, low quality of evidence

   1.4 **Patients with recurrent and relapsing UTI should be worked up for any functional or anatomic abnormalities and treated with a longer course of antibiotic.**
   Strong recommendation, low quality of evidence

2. **What is the effective antibiotic prophylaxis for post–kidney transplant patients to reduce the risk for UTI?**

   Oral TMP-SMX (160 mg/800 mg) taken twice daily immediately post-transplant, then once daily as soon as the catheter is removed or the patient is discharged, continued until 6 months post-transplantation, reduces the risk of bacteriuria and bacteremia in post–renal transplant recipients.
   Strong recommendation, moderate quality of evidence

DISCUSSION

1. How should urinary tract infection (UTI) in post–kidney transplant patients be managed?

1.1 **Post-transplant UTI can be managed by initial administration of empiric broad-spectrum antibiotics. Patients suspected of having drug-resistant gram-positive infections (e.g., *Enterococci*, methicillin-resistant *Staphylococcus aureus*) should be started on antibiotics that are active against such organisms. Specific therapy can be initiated once culture results are available and should be continued until the pathogen is eradicated.**
Strong recommendation, low quality of evidence

1.2 **Patients with early UTI (i.e., occurring within the first six months after transplantation) or UTI presenting with signs and symptoms of pyelonephritis or sepsis should be admitted and started on intravenous (IV) antibiotics. Treatment should be given for 14 days. When the results of urine culture are available, the IV antibiotics can be shifted to their oral equivalent (if available and clinically feasible) to complete the treatment duration.**
Strong recommendation, low quality of evidence

1.3 **Late cystitis (i.e., occurring after six months post-transplant) can be treated for seven days, while late pyelonephritis requires 14 days of antimicrobial therapy.**
Strong recommendation, low quality of evidence

1.4 **Patients with recurrent and relapsing UTI should be worked up for any functional or anatomic abnormalities and treated with a longer course of antibiotic.**
Strong recommendation, low quality of evidence

Table 17. Recommended empiric antibiotics for early post–kidney transplant UTI

Gram-Negative Organism	Gram-Positive Organism
meropenem	vancomycin
ertapenem	linezolid
imipenem	nitrofurantoin*
doripenem	tetracycline*
amikacin	
nitrofurantoin*	

* Reserved for asymptomatic bacteriuria or cystitis only

Summary of Evidence

The various syndromes of UTI may occur in the setting of kidney transplantation. Cystitis presents with lower urinary tract symptoms such as frequency, urgency, dysuria, and hematuria or suprapubic pain. Pyelonephritis, on the other hand, presents with upper urinary tract symptoms such as rigors and pyrexia, hematuria, loin

pain in native kidney and pain over the graft. It is important to take note, however, that because the innervation of the transplanted kidney is already severed, pain over the graft may not be present, or it may be difficult to localize. Recurrent UTI is defined as three or more UTI episodes in a 12-month period, including asymptomatic episodes. These infections are believed to be caused by different strains of infecting organisms. Relapsing UTI, on the other hand, results from the inability to eradicate the original infection. Pyuria is defined as the presence of at least 10 wbc/hpf of unspun midstream urine.[1]

UTI in the setting of kidney transplantation is complicated by several factors such as

- urologic instrumentation[1] and altered anatomy post-transplantation (e.g., ureteral anastomosis complications, etc.);[2]
- immunosuppression, which may mask the classical signs and symptoms of infection;[1] and
- significant drug interactions (e.g., trimethoprim-sulfamethoxazole [TMP-SMX] and aminoglycosides may interact with tacrolimus or cyclosporine).[3]

As of 2011, the most common organisms isolated from renal transplant patients at the National Kidney and Transplant Institute (NKTI) were *Escherichia coli* (46%), *Klebsiella* (20.6%) and coagulase-negative *Staphylococcus* (10.3%). The rate of extended-spectrum beta-lactamase (ESBL)–producing *E. coli* was around 12.4% (9% confirmed, 3.4% probable) while ESBL-producing *Klebsiella* was 30% (25% confirmed, 5% probable).

Timing of the UTI is the most important factor that determines morbidity from the infection. Early UTI is defined as UTI occurring within the first six months post-transplantation, while late UTI is defined as UTI occurring more than six months after kidney transplantation.[4,5] UTI is often associated with acute pyelonephritis and rapidly develops to bacteremia during the early post-transplant period. In the study by Chuang, post-transplant UTI was significantly associated with increased mortality (OR 3.5 95% CI 1.68-7.23).[6] Acute pyelonephritis has been shown to be an independent risk factor for decline in renal function; patients with this disorder get a 3.4-fold increase in their risk, compared to those who did not develop UTI or those who developed cystitis only. However, acute pyelonephritis was not associated with increased risk for graft loss;[7-9] neither does it affect patient survival.[10]

Patients with early UTI post-transplant presenting with acute pyelonephritis should be admitted and started on empiric IV antibiotics that cover for both gram-positive and gram-negative organisms. Urine culture and sensitivity should be performed before initiating empiric antibiotics; however, these should not delay antibiotics administration. Infection with an ESBL-producing organism should be considered in patients presenting with urosepsis.

There are currently no randomized trials on the duration of antibiotics for the treatment for UTI in transplant patients. Previously, it was recommended that pyelonephritis during the early post-transplant period be treated with antibiotics for six weeks, based on its treatment success in 13 out of a series of 14 patients.[2] More recent international guidelines recommend giving antibiotics for at least two weeks, based on low-quality evidence and as an extension of results from studies among non-transplant patients.[3,11,12]

Recurrent and relapsing UTI should be worked up for any functional or anatomic abnormality; the most common causes include ureteral reflux, stricture at the ureterovesical junction and neurogenic bladder.[3,11,12] There are currently no trials on the duration of antimicrobial therapy for relapsing or recurrent UTI, but it is recommended that antimicrobial therapy be given for a longer period of time.

Late UTI was previously considered to be of less clinical significance; however, a recent study from the United States Renal Data System showed that late UTI was an independent risk factor for increased mortality (adjusted hazard ratio [AHR] 2.93 95% CI 2.22–3.85 p<0.001) and graft loss (AHR 1.85 95% CI 1.29–2.64) even after consideration of cardiac and other complications.[13] This highlights the importance of clinically addressing UTI, whether early or late, in the course of kidney transplantation. In addition, an increased number of UTIs over time may also be associated with chronic rejection and renal scarring.[14,15]

2. What is the effective antibiotic prophylaxis for post–kidney transplant patients to reduce the risk for UTI?

Oral TMP-SMX (160 mg/800 mg) taken twice daily immediately post-transplant, then once daily as soon as the catheter is removed or the patient is discharged, continued until six months post-transplantation, reduces the risk of bacteriuria and bacteremia in post–renal transplant recipients.

Strong recommendation, moderate quality of evidence

Summary of Evidence

A meta-analysis by Green et al. in 2011, which included six randomized controlled trials (n=545) comparing antibiotic prophylaxis with other interventions beginning postoperatively and continued for at least one month during the first six months post-transplantation, showed that antibiotic prophylaxis decreased the risk of developing bacteriuria (RR 0.41 95% CI 0.31–0.56; three trials) and bacteremia (RR 0.13 95% CI 0.02–0.7); however, it did not affect graft function or patient mortality.[16]

Two studies included in the meta-analysis by Green et al. compared the effects of high-dose and low-dose TMP-SMX. One study was a prospective randomized double-blind study involving 132 patients, and it confirmed that TMP-SMX 320 mg/1600 mg every day during hospitalization was highly effective in preventing UTI, but a dose of 160 mg/800 mg was effective only if the foley catheter was removed. Prophylaxis did not prevent catheter-associated UTI in the early post-transplant period, but it decreased the probability of UTI threefold (p<0.001) after catheter removal.[17] The other study was double-blinded, but the allocation generation and concealment processes were less clearly described. High-dose TMP-SMX seems to be consistently more favorable than low dose, with bacteriuria occurring less frequently in the former than in the latter (25% vs. 50%, respectively).[18]

A recent retrospective cross-sectional study looked into the benefit of adding one month of daily 250 mg ciprofloxacin (taken twice a day) after a six-month course of TMP-SMX (taken daily for the first month then three times weekly for the next 5 months). At one year follow-up, the ciprofloxacin group showed fewer UTI occurrences (23.6% vs. 10.8%, p=0.01) and a shorter mean time to the first UTI (96.6±79.5 vs. 168±89.7

days, p=0.01).[19] This study, however, is limited by several issues, including the following:

- There are recall, selection and other biases inherent to the nature of the study design.
- The (low) dose of TMP-SMX used in the study has been found to be inferior compared to the standard recommended dose (160 mg/800 mg twice daily) based on previous randomized trials of sound methodologic quality.
- While the resistance patterns of the uropathogens isolated from those who developed UTI within the one-year post-transplant period were similar between the two treatment groups, there is no similar information for those that occur beyond the follow-up period (after one year).

The effectiveness of this regimen needs to be confirmed in a randomized controlled trial. As monotherapies, one randomized study compared the use of ciprofloxacin 250 mg daily vs. TMP-SMX 80 mg/400 mg, both taken for six months, as prophylaxis for post-transplant UTI.[20] Ciprofloxacin has been shown to be more effective than TMP-SMX in the prevention of UTI (RR 0.89), and with fewer adverse events.[20] However, the use of ciprofloxacin as prophylaxis is not recommended for several reasons: First, because ciprofloxacin has no activity against *Pneumocystis* sp., prophylactic monotherapy with ciprofloxacin resulted in a higher incidence of *Pneumocystis* pneumonia (14% vs. 0%).[20] Second, fluoroquinolone use has been associated with collateral damage such as the development of drug resistance (ESBL-production). Third, in a country where tuberculosis is highly endemic, it is prudent to reserve ciprofloxacin as a second-line drug for multidrug-resistant tuberculosis.

The optimal duration of antimicrobial prophylaxis for post-transplant UTI has not been well studied. Different trials have reported antimicrobial prophylaxis durations ranging from four[21,22] to six[20,23] to eight-and-a-half months.[17] The American Society of Transplantation (AST) recommends that antimicrobial prophylaxis be given for three to six months,[12] while the Kidney Disease Improving Global Outcomes (KDIGO) and the European Association of Urology (EAU) recommend prophylaxis for at least six months.[3,11] Currently, there are concerns on the increasing resistance to TMP-SMX. At the NKTI, the incidences of TMP-SMX–resistant *E. coli* were as follows: 78% in 2009, 79% in 2010, and 85% in 2011. The incidences of ciprofloxacin-resistant *E. coli* were as follows: 67.7% in 2009, 71.4% in 2010, and 70.8% in 2011. Despite its high resistance rates, antibiotic prophylaxis with TMP-SMX is still recommended.

Newer interventions, such as perioperative intravesical application of antibiotic solution after renal transplantation, have been looked into in one study. The intervention seems to be beneficial (RR 0.51 95% CI 0.34–0.76), but the allocation generation, concealment and blinding of the study were not clearly reported. More studies are needed before a recommendation regarding this intervention can be made.[24]

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SPECIFIC ISSUES OF CONCERN IN COMPLICATED URINARY TRACT INFECTION

Perioperative Antibiotic Prophylaxis for Patients Who Will Undergo Urologic Procedures

Summary of Recommendations

1. **Should patients who will undergo urologic procedures receive perioperative prophylactic antibiotics?**

   Selected patients should receive perioperative prophylactic antibiotics to prevent the occurrence of healthcare-associated infections arising from diagnostic and therapeutic urologic procedures. These patients include the following:

Patient Group	Strength of Recommendation	Quality of Evidence
Men who will undergo transrectal or transperineal prostate biopsy	Strong	High
Men who will undergo transurethral resection of the prostate (TURP)	Strong	High
Patients who will undergo clean, contaminated, open or laparoscopic urological surgeries such as pelvioureteric junction repair, nephron-sparing tumor resection, total prostatectomy, bladder surgery, partial cystectomy, urine diversion, orthotopic bladder replacement or ileal conduit	Strong	Low
Patients who will undergo complicated endourological surgery and shockwave lithotripsy, nephrostomy tube insertion, ureteroscopy of proximal or impacted stone, or percutaneous stone extraction	Strong	Low

   For other procedures, the decision to give perioperative prophylactic antibiotics will depend on the presence of risk factors for infectious complications, such as old age, deficient nutritional status, impaired immune response, diabetes mellitus, smoking, extreme weight, coexisting infection at a remote site, lack of control of risk factors, long preoperative hospital stay or recent hospitalization, history of recurrent urogenital infections, surgery involving bowel segment, colonization of microorganisms, long-term drainage, urinary obstruction or urinary stone.
   Strong recommendation, low quality of evidence

2. **What is the approach to giving perioperative antibiotic prophylaxis in a patient who will undergo a urologic procedure?**

   2.1 For patients who will undergo *emergency* urologic procedures, a single dose of intravenous (IV) amikacin or ertapenem one hour prior to the procedure is recommended.

Strong recommendation, low quality of evidence

2.2 Urine for Gram stain/culture and sensitivity (GS/CS) and blood sample for serum creatinine should ideally be obtained prior to the procedure and before the administration of amikacin.
Strong recommendation, low quality of evidence

2.3 For *elective* cases, do urine GS/CS prior to the procedure. If culture is positive, then treat as asymptomatic bacteriuria (ASB; see chapter on ASB) and start antibiotic therapy based on sensitivity results. If culture is negative, start prophylactic antibiotics if the patient will undergo TURP or transrectal or transperineal biopsy of the prostate, or if there are risk factors for infectious complications after the urologic procedure.
Strong recommendation, low quality of evidence

2.4 The duration of perioperative prophylaxis should be kept to a minimum. The decision on whether to continue or shift antibiotics and the duration after the procedure will depend on the best clinical judgment of the physician.
Strong recommendation, low quality of evidence

3. What antibiotics can be used for perioperative prophylaxis for patients who will undergo urologic procedures?

3.1 Amikacin 15 mg/kg or ceftriaxone 2 g IV single dose, one hour before the procedure, are the recommended antibiotics for perioperative prophylaxis prior to a urologic procedure.

In settings where resistance rates to cephalosporins and quinolones are high, aztreonam 1 gram IV may be given one hour before the procedure.
Strong recommendation, low quality of evidence

3.2 For patients who will undergo transrectal or transperineal prostate biopsy, ciprofloxacin 500 mg administered orally (PO) 12 hours prior to biopsy and repeated 12 hours after the first dose or ciprofloxacin 400 mg IV via one-hour infusion two hours prior to the procedure are acceptable options, provided resistance is not a concern.
Strong recommendation, low quality of evidence

3.3 Metronidazole 500 mg IV single dose one hour prior to the procedure is added for patients who will undergo urologic procedures with manipulation of the bowel segments.
Strong recommendation, low quality of evidence

DISCUSSION

1. **Should patients who will undergo urologic procedures receive perioperative prophylactic antibiotics?**

   Selected patients should receive perioperative prophylactic antibiotics to prevent the occurrence of healthcare-associated infections arising from diagnostic and therapeutic urologic procedures. These patients include the following:

Patient Group	Strength of Recommendation	Quality of Evidence
Men who will undergo transrectal or transperineal prostate biopsy	Strong	High
Men who will undergo transurethral resection of the prostate (TURP)	Strong	High
Patients who will undergo clean, contaminated, open or laparoscopic urological surgeries such as pelvioureteric junction repair, nephron-sparing tumor resection, total prostatectomy, bladder surgery, partial cystectomy, urine diversion, orthotopic bladder replacement or ileal conduit	Strong	Low
Patients who will undergo complicated endourological surgery and shockwave lithotripsy, nephrostomy tube insertion, ureteroscopy of proximal or impacted stone, or percutaneous stone extraction	Strong	Low

For other procedures, the decision to give perioperative prophylactic antibiotics will depend on the presence of risk factors for infectious complications, such as old age, deficient nutritional status, impaired immune response, diabetes mellitus, smoking, extreme weight, coexisting infection at a remote site, lack of control of risk factors, long preoperative hospital stay or recent hospitalization, history of recurrent urogenital infections, surgery involving bowel segment, colonization of microorganisms, long-term drainage, urinary obstruction or urinary stone.
Strong recommendation, low quality of evidence

Summary of Evidence

The goal of perioperative antibiotic prophylaxis is to prevent healthcare-associated infections arising from diagnostic and therapeutic procedures. Perioperative antibiotic prophylaxis has been controversial especially with the lack of good studies to support its use.[1,2] Among the various urologic procedures, the use of perioperative antibiotic prophylaxis is well documented only in transurethral resection of prostate and prostate biopsy.

Three systematic reviews have consistently reported the benefit of prophylaxis—the short course (<72 hours) regimen, in particular—in decreasing the incidence of postoperative bacteriuria (from 26% to 9%) and other related complications (e.g., fever, sepsis).[3-5] On the other hand, at least six randomized trials included in a systematic review have shown the benefit of prophylaxis in decreasing the incidence of

post-transrectal or transperineal core biopsy bacteriuria, although there has been no conclusive evidence on its effect on the development of subsequent symptomatic urinary tract infections (UTI).[5] Table 18 summarizes the evidence in the use of prophylaxis after various urological procedures. In coming up with the recommendations on the use of prophylaxis for each of these procedures, it is very important to consider three factors, keeping in mind that not all procedures are alike: (1) the level of invasiveness of the procedure, (2) the risk for infectious complication of the procedure (incidence of post-treatment bacteriuria or symptomatic UTI) and (3) the overall clinical status of the patient.[1]

Most of the trials have failed to consider the presence of risk factors that might render patients more prone to developing postoperative complications. The presence of these factors is a reason to administer antibiotic prophylaxis or prolong its duration in an otherwise low-risk urological procedure due to the vulnerability of this set of patients.

2. **What is the approach to giving perioperative antibiotic prophylaxis in a patient who will undergo a urologic procedure?**

    2.1 For patients who will undergo *emergency* urologic procedures, a single dose of intravenous (IV) amikacin or ertapenem one hour prior to the procedure is recommended.
    Strong recommendation, low quality of evidence

    2.2 Urine for Gram stain/culture and sensitivity (GS/CS) and blood sample for serum creatinine should ideally be obtained prior to the procedure and before the administration of antibiotic.
    Strong recommendation, low quality of evidence

    2.3 For *elective* cases, do urine GS/CS prior to the procedure. If culture is positive, then treat as asymptomatic bacteriuria (ASB; see chapter on ASB) and start antibiotic therapy based on sensitivity results. If culture is negative, start prophylactic antibiotics if the patient will undergo TURP or transrectal or transperineal biopsy of the prostate, or if there are risk factors for infectious complications after the urologic procedure (Table 19).
    Strong recommendation, low quality of evidence

    2.4 The duration of perioperative prophylaxis should be kept to a minimum. The decision on whether to continue or shift antibiotics and the duration after the procedure will depend on the best clinical judgment of the physician.
    Strong recommendation, low quality of evidence

Table 18. Summary of evidence on the use of prophylaxis in urologic procedures

Procedure	Recommendation	Evidence
Cystoscopy	Low quality evidence for the use of prophylaxis	• A systematic review of four randomized controlled trials (RCT) had conflicting results—two showed a decrease in the incidence of bacteriuria and symptomatic UTI with antibiotic prophylaxis, while the other two showed no decrease[5] • There is low incidence of bacteriuria and symptomatic UTI after cystoscopy[6,7]
Urodynamic investigation	Low quality evidence for the use of prophylaxis	• Five studies with poor methodologic quality[5] • There is low incidence of bacteriuria and symptomatic UTI after urodynamic studies[1]
Transurethral resection of bladder tumor (TURB)	Moderate quality evidence against the use of prophylaxis	• Two RCTs, which compared antibiotic prophylaxis with either placebo or no treatment, reported no significant difference in the rates of post-TURB bacteriuria between treatment groups[8,9] • No incidence of post-TURB symptomatic UTI in either group[9]
Extracorporeal shockwave lithotripsy (ESWL)	Moderate quality evidence against the use of prophylaxis	• Only one of 4 RCTs showed significant benefit with antibiotic prophylaxis.[10] Antibiotics used were ciprofloxacin, ofloxacin, ceftriaxone, and amoxicillin/clavulanic acid[5] • Post-ESWL symptomatic UTI rates were similarly low between treatment groups[5] • A meta-analysis of nine RCTs showed no benefit with the use of prophylaxis in terms of fever (RR 0.36, 95% CI 0.07 to 2.36), urine culture positivity (RR 0.77, 95% CI 0.54 to 1.11), and incidence of UTI (RR 0.54, 95% CI 0.29 to 1.01)[11]
Endoscopic removal of stones (via ureterorenoscopy)	Moderate quality evidence for the use of prophylaxis	• For therapeutic ureterorenoscopy such as endoscopic removal of stones, two RCTs[12,13] reported reductions in bacteriuria postoperatively with prophylaxis, but results reached significance only in one RCT (12.5% to 1.8%, n=113)[12] • No studies on diagnostic ureterorenoscopy alone
Percutaneous nephrolithotomy	Low quality evidence for the use of prophylaxis	• Small observational studies reported a reduction in postoperative fever and symptomatic UTI • One RCT included in the review by Bootsma et al reported a reduction in bacteriuria with antibiotic prophylaxis (bacteriuria: 12% in the placebo group, 5% in the prophylaxis group) but this was not statistically significant[13]
Clean, contaminated or open/laparoscopic urologic interventions such	Low quality evidence for the use of prophylaxis	• No direct studies available • Clean-contaminated procedures (opening of the urinary tract) may warrant prophylaxis[1]

as pelvioureteric junction repair, nephron-sparing tumor resection, total prostatectomy, bladder surgery, partial cystectomy, urine diversion, orthotopic bladder replacement, ileal conduit		• Based on general surgery studies, clean wounds do not warrant prophylaxis, while contaminated and dirty urological surgeries should receive therapeutic antibiotics and not prophylactic antibiotics[1,5]

Table 19. Generally accepted risk factors for infectious complication

General risk factors	Special risk factors associated with an increased bacterial load
Older age	Long preoperative hospital stay or recent hospitalization, complicated
Deficient nutritional status	History of recurrent urogenital infections
Impaired immune response	Surgery involving bowel segment
Diabetes mellitus	Colonization with microorganisms
Smoking	Long-term drainage
Extreme weight	Urinary obstruction
Coexisting infection at a remote site	Urinary stone
Lack of control of risk factors	

Adapted from Grabe et al.

Summary of Evidence

The goal of antibiotic prophylaxis is to prevent procedure-related infections. However, this should not be done at the expense of promoting bacterial resistance, increasing the risk for *Clostridium difficile*–associated diarrhea or incurring unnecessary cost for the patient.[14] A careful assessment of the patient and the individual clinical context is necessary to come up with the optimal prophylactic regimen. Timing of administration is very important in allowing the antibiotic to reach effective concentrations at the time of highest risk during the procedure.[1] The antibiotic prophylaxis should be given within one hour of the surgical incision (except fluoroquinolones and vancomycin, which may require 120 minutes)[1,14]

In emergency situations where a patient has to undergo immediate urologic procedures, a single dose of IV amikacin or ertapenem one hour prior to the procedure is recommended. Urine for GS/CS and blood sample for serum creatinine (for dose adjustment) should ideally be obtained prior to the procedure and before the administration of antibiotic. If this is not possible, a sample should be obtained during the procedure. Tailor the antibiotics once the culture results are available.

For elective cases, a urine sample should be sent for GS/CS prior to the procedure. If the pre-procedure culture is positive, then treat the patient as ASB if the patient will undergo urological procedures (see chapter on ASB) and start antibiotic treatment based on sensitivity results. It is recommended that urine culture be repeated 48–72 hours after the initial antibiotic dose. If the urine has been rendered sterile, one may proceed with the contemplated procedure. However, if the culture remains positive, one may proceed with the procedure but shift the antibiotic regimen to one that the isolate is susceptible to.

If the pre-procedure culture is negative, start prophylactic antibiotics for selected patients whose situations were discussed in the preceding section (i.e., undergoing TURP or transrectal or transperineal biopsy of the prostate, or with risk factors for infectious complications after the urologic procedure).

The decision to continue or shift antibiotics and the duration after the procedure will depend on the best clinical judgment of the physician. Perioperative prophylaxis should be kept to a minimum; it can be given as a single dose in most cases, or at least discontinued within 24 hours after the procedure.[14] Previously published guidelines suggest that antimicrobial prophylaxis is unnecessary after wound closure or upon termination of an endoscopic procedure, but these are based on low-quality evidence, i.e., expert opinion or extension of recommendations from general surgery studies.[14-16] A longer duration of antibiotic prophylaxis is frequently considered when there are significant risk factors for infectious complications; the presence of prosthetic material; in the presence of infection, for which a therapeutic regimen rather than prophylaxis is needed; and when an indwelling tube is manipulated.[1,14]

3. What antibiotics can be used for perioperative prophylaxis for patients who will undergo urologic procedures?

3.1 Amikacin 15 mg/kg or ceftriaxone 2 g IV single dose, one hour before the procedure, are the recommended antibiotics for perioperative prophylaxis prior to a urologic procedure.

In settings where resistance to cephalosporins and quinolone is high, aztreonam one gram IV may be given one hour before the procedure.

Strong recommendation, low quality of evidence

3.2 For patients who will undergo transrectal or transperineal prostate biopsy, ciprofloxacin 500 mg administered orally (PO) 12 hours prior to biopsy and repeated 12 hours after the first dose or ciprofloxacin 400 mg IV via one-hour infusion two hours prior to the procedure are acceptable options, provided resistance is not a concern.

Strong recommendation, low quality of evidence

3.3 Metronidazole 500 mg IV single dose one hour prior to the procedure is added for patients who will undergo urologic procedures with manipulation of the bowel segments.

Strong recommendation, low quality of evidence

Summary of Evidence

There are general guidelines in choosing the most appropriate prophylactic antibiotic for urological procedures, taking into account both the surgical site and the properties of the antimicrobial agent. The agent to be used should be effective against the most common pathogens that cause disease in the operative site. The most common pathogens that cause postoperative infections include the Enterobacteriaceae, Enterococci and Staphylococci.[1] A local prospective surveillance study conducted at the Philippine General Hospital reported that among 116 patients with prolonged indwelling urinary catheters, the most common isolates were *E. coli* (30%), *Enterobacter* spp. (22%) and *Pseudomonas aeruginosa* (9.7%).[17] There were overall high resistance rates to ampicillin (92.14%), ciprofloxacin (80.7%) and

cotrimoxazole (80%). Resistance rate to meropenem was low at 6.43%. These resistance patterns are consistent with the Philippine Antimicrobial Resistance Surveillance Program (ARSP) 2015 Data Summary Report. According to the ARSP, urinary *E. coli* isolated from inpatients had the lowest resistance rates to the non-anti-Pseudomonal carbapenem ertapenem (5.7%, n=1241) and amikacin (4.2%, n=2105). Resistance rates to cotrimoxazole (68%) and ampicillin (84%) remain very high. Resistance rates to ceftriaxone (40%, n=1973) and ciprofloxacin (43%, n=2096) continue to increase.[18] The resistance rates of *Klebsiella pneumoniae* are similar with *E. coli*.[18] Another prospective cohort study of patients diagnosed with complicated UTI (with catheter-associated UTI as the most common underlying condition, 80%) in two training hospitals in Metro Manila reports similar trends.[19] Sensitivity to meropenem, ertapenem and amikacin remained high at 87%, 76% and 82%, respectively.

Certain drug characteristics should be considered when choosing a prophylactic antibiotic. The drug should be able to reach therapeutic concentrations at the operative site and have adequately long half-life to maintain sufficient serum and tissue concentrations for the entire length of the procedure, thus minimizing the need for another dose. Cephalosporins (such as ceftriaxone), fluoroquinolones (such as ciprofloxacin) and aminoglycosides (amikacin) achieve good concentrations in the urinary tract, are generally efficacious, have long half-lives, and are relatively inexpensive.[1,20] Lastly, the antibiotic should be safe, cost-effective and cause no collateral damage to the patient and the environmental flora.[14]

Amikacin (15 mg/kg) or ceftriaxone (2 g IV single dose) one hour before the procedure is the recommended antibiotics for perioperative prophylaxis, considering these two drugs' good concentrations at the urogenital tract, adequate coverage for the most common uropathogens and long half-lives. Caution should always be taken when giving aminoglycosides to patients with renal insufficiency. Baseline and subsequent serum creatinine determinations may be prudent for monitoring kidney function.

For patients who will undergo transrectal or transperineal prostate biopsy, ciprofloxacin 500 mg PO 12 hours prior to biopsy and repeated 12 hours after the first dose or ciprofloxacin 400 mg IV one-hour infusion two hours prior to the procedure are acceptable options because fluoroquinolones achieve high levels of concentration in the prostate,[21] and with their good oral bioavailability, they can be conveniently given *per orem* on an outpatient basis.

Metronidazole 500 mg IV single dose one hour prior to the procedure is added for patients who will undergo urologic procedures with manipulation of the bowel segments because anaerobes are possible pathogens that may cause subsequent infections. Although they have the least resistance rates, carbapenems (e.g., meropenem, ertapenem) are reserved for high-risk patients with clear evidence of infection, to avoid selection pressure and the emergence of resistance against these broad-spectrum agents.

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SPECIFIC ISSUES OF CONCERN IN COMPLICATED URINARY TRACT INFECTION

URINARY CANDIDIASIS
Summary of Recommendations

1. What is candiduria, and what is its clinical significance?

Candiduria is defined as the presence of *Candida* species regardless of colony count in properly collected urine specimens taken on two separate occasions at least two days apart. The presence of candiduria may represent a whole spectrum of pathologic states, from invasive renal parenchymal disease, fungal balls in obstructed ureters and lower urinary tract infection (UTI), to benign conditions such as colonization.
Weak recommendation, low quality of evidence

2. What is the significance of yeast cells or hyphae on urine microscopy? What is the role of pyuria in the diagnosis of urinary candidiasis?

The presence of yeast cells or hyphae on microscopy, especially when there is pyuria, may be a clue that a fungal infection is present. However, these findings should be correlated clinically.
Weak recommendation, low quality of evidence

3. If antimicrobial therapy is deemed necessary for a patient with candiduria, what antifungal agents are effective for treatment?

3.1 The first line of treatment is fluconazole 400 mg loading dose, and then 200 mg/day for 7–14 days. The route of administration depends on patient status and oral tolerability.
Strong recommendation, low quality of evidence

3.2 In certain clinical situations such as prior azole use, refractory infection or suspicion of drug resistance to fluconazole (e.g., patients with suspected *C. glabrata* infection), IV amphotericin B deoxycholate (AmBd) at a dose of 0.3–1.0 mg/kg per day can be given.
Weak recommendation, low quality of evidence

3.3 For patients who will undergo urologic procedures and in whom candiduria was found to be present, fluconazole 200–400 mg (3–6 mg/kg) daily or AmBd 0.3–0.6 mg/kg daily for several days before and after the procedure is recommended.
Strong recommendation, low quality of evidence

4. What is the value of bladder irrigation in the management of urinary candidiasis?

Bladder irrigation with amphotericin B can be used as an adjunct therapy to systemic antifungal agents in the treatment of refractory cystitis (e.g., infections from *Candida* with either acquired or inherent resistance to azoles). When used, a continuous irrigation of amphotericin B at a concentration of 50 mg per liter of sterile water for a period of five days is recommended.
Weak recommendation, low quality of evidence

DISCUSSION

1. What is candiduria, and what is its clinical significance?

Candiduria is defined as the presence of *Candida* species regardless of colony count in properly collected urine specimens taken on two separate occasions at least two days apart. The presence of candiduria may represent a whole spectrum of pathologic states, from invasive renal parenchymal disease, fungal balls in obstructed ureters and lower urinary tract infection (UTI), to benign conditions such as colonization.
Weak recommendation, low quality of evidence

Summary of Evidence

There is no consensus on the definition of significant candiduria. Colony counts of $>10^4$ cfu/ml of *Candida* species have been associated with infection in patients without indwelling urinary catheters.[1] In other studies, clinically significant renal candidiasis has been reported with lower colony counts of 10^3/ml of urine.[2,3] Indeed, colony counts were not predictive of significant infection or upper tract involvement as reported in a prospective case-control study conducted in a local tertiary hospital involving 55 patients with positive urine cultures for *Candida* spp. The study was not able to find a level of colony count that could be associated with the presence or absence of fever, candidemia, relapse of candiduria and death (using Fisher's exact test).[4] The level of colony count was also not predictive of disease severity. Candidemia and sepsis can occur even in low colony counts, and high colony counts will not necessarily mean a more severe disease.[4]

Significant candiduria should also be differentiated from contamination and colonization. Contamination may result from the improper collection of urine specimens, especially in catheterized patients or in women with *Candida* in the perineum. Colonization, on the other hand, may involve the presence of *Candida* spp. on drainage catheters or other foreign bodies in the urinary tract. Both contamination and colonization can lead to increased colony counts in urine cultures. A second sterile urine examination, taken either after changing the urinary catheter or via clean catch, would be needed to better identify whether the increased colony count is due to infection or simply due to colonization or contamination.[5]

Candida albicans remains the most common species isolated, followed by *C. tropicalis* and *C. glabrata*, with prevalences ranging from 36–70%, 5–53% and 7–9%, respectively.[3,6-8] In a prospective multicenter surveillance study of funguria in hospitalized patients, *C. albicans* was found in 52% of 861 patients with funguria, followed by *C. glabrata* in 16%.[9] In a retrospective study conducted in four tertiary hospitals in Metro Manila from 1992–1993, the prevalence rate of candiduria was 6.4%, with *C. albicans* accounting for 73% of the cases.[7]

2. What is the significance of yeast cells or hyphae on urine microscopy? What is the role of pyuria in the diagnosis of urinary candidiasis?

The presence of yeast cells or hyphae on microscopy, especially when there is pyuria, may be a clue that a fungal infection is present. However, these findings should be correlated clinically.

Weak recommendation, low quality of evidence

Summary of Evidence

A gram stain of centrifuged urine showing yeasts may suggest fungal infection. *C. albicans*, as well as other *Candida* species which are less common such as *C. parapsilosis* and *C. tropicalis* may be seen as budding yeasts, 4–10 µm in diameter and possibly with hyphal elements, under microscopy.[10]

The absence of hyphae on microscopy, however, does not rule out *Candida* infection. *C. glabrata*, which presents on microscopy as smaller budding yeasts (2–4 µm in diameter) *without* hyphal elements, can cause UTI.[10] Additionally, it was noted in an experimental murine model that some non-hyphae-forming *C. albicans* variants can also cause UTI.[11]

Most patients with urinary catheters have pyuria in the urine as a nonspecific findin caused by the mechanical sloughing of the bladder mucosa by the catheter.[12] In patients without a urinary catheter, pyuria and the presence of yeasts, as well as the absence of bacterial growth, may point towards a *Candida* infection.[10]

On the other hand, the absence of pyuria on urine microscopy and low colony counts on urine culture may help rule out a *Candida* infection.[12] It is always prudent, however, to interpret these results in the proper clinical context, given their low diagnostic sensitivities and the absence of correlation with disease severity.[4,12]

3. What are the clinical presentations of candiduria, and when is treatment required?

See Table 19.

Summary of Evidence

Candiduria may have various clinical manifestations. Some patients may present with no symptoms, while others may be desperately ill. Fisher et al[13] put forward a classification scheme that may be useful in identifying which patients would require treatment. Fisher et al suggested that patients with candiduria be classified into five groups: (1) patients with asymptomatic candiduria who were previously healthy; (2) patients with asymptomatic candiduria who have predisposing factors and are being treated as outpatients; (3) patients with asymptomatic candiduria with predisposing factors who are being treated as inpatients; (4) patients with symptomatic candiduria (this includes patients with cystitis, pyelonephritis, urinary tract fungus balls, etc.); and (5) clinically unstable patients with candiduria.

Asymptomatic candiduria in previously healthy patients

Because contamination is not unusual, especially among female patients, whose vaginal area is normally inhabited by many organisms, a repeat urine culture should be performed to verify the presence of candiduria.[8,13,14] Once candiduria is confirmed, possible predisposing factors (Table 20) should be investigated through careful history-taking, physical examination and screening laboratory tests. It is also important to check for the possibility of a fungal genital mucositis in the glans or vagina.[12] In a previously healthy patient in whom no explanation for candiduria is found, careful observation is generally all that is necessary.[8,13,14] In most individuals without predisposing factors, candiduria is expected to resolve spontaneously in a matter of weeks or months.[13]

Table 19. Clinical presentations of candiduria

Clinical Presentation of Candiduria	Patient Characteristic	Removal of Predisposing Factor	Strength of Recommendation, Level of Evidence
Asymptomatic candiduria (previously healthy patient)	No explanation for candiduria found after extensive clinical investigation	• Careful observation • If repeat exam still grows fungi, check for possible fungal genital mucositis (vagina or glans)	Strong recommendation, low quality of evidence
Asymptomatic and minimally symptomatic patients (outpatients)	Predisposing factors that lead to the development of candiduria are present*	• No antifungal treatment recommended • Modification of risk factors is the first-line approach (e.g., control of diabetes, discontinuation of antibiotics, or removal of indwelling catheters and other urinary tract instruments**)	Strong recommendation, moderate quality of evidence
Asymptomatic candiduria and minimally symptomatic patients (inpatients)	Predisposing factors for infectious complications are present*	• Consider the possibility of disseminated candidiasis • Modification of risk factors • Give antifungal treatment for patients who will undergo urologic procedures • If necessary, do imaging studies of the kidneys and the urinary system to rule out abscess, fungus ball or other urologic abnormalities	Weak recommendation, low quality of evidence
Symptomatic candiduria	*Candida* cystitis or pyelonephritis, fungus ball, those with solid evidence of infection of the kidney or collecting system	• Modification of risk factors • Start antifungal treatment • Surgical intervention, when necessary	Strong recommendation, low quality of evidence
Candiduria in clinically unstable patients	ICU patients, suspected disseminated disease, neutropenic patients, septic patients	• Modification of risk factors • Start antifungal treatment	Strong recommendation, low quality of evidence

*Predisposing factors include DM, renal transplantation, extremes of age, broad-spectrum antibiotic use, instrumentation of the urinary tract, congenital or other structural abnormalities of the genitourinary tract, urinary stasis and interruption of the flow of urine, chronic renal failure and hemodialysis, bladder distension, nephrolithiasis, female sex, concomitant bacteriuria or genitourinary tuberculosis, prolonged hospitalization, intensive care unit (ICU) admission, indwelling urinary tract devices, malignancy, neutropenia and other immunosuppressed conditions, immunosuppressive therapy, prior surgery (urological and non-urological)

** If complete removal of these instruments is not possible, replacement of the device with new ones is still beneficial.

Table 20. Predisposing factors for candiduria and *Candida* UTIs[3,7,9,13,15-18]

- Diabetes mellitus
- Renal transplantation
- Extreme age
- Broad-spectrum antibiotic use†
- Instrumentation of the urinary tract
- Chronic renal failure and hemodialysis
- Female sex
- Concomitant bacteriuria or genitourinary tuberculosis
- Prolonged hospitalization
- Congenital or other structural abnormalities of the genitourinary tract
- ICU admission
- Indwelling urinary tract devices
- Malignancy
- Neutropenia and other immunosuppressed conditions
- Immunosuppressive therapy
- Prior surgery (urological and non-urological)
- Bladder distention
- Urinary stasis and interruption of the flow of urine
- Nephrolithiasis

† *The strongest correlation is with the use of meropenem (r=0.79, p<0.001) and ceftazidime (r=0.66, p=0.001).[20]*

Asymptomatic candiduria in predisposed outpatients

Several studies have looked into the association of the most common risk factors for candiduria and *Candida* UTI with the development of infectious complications. In a case-control study, Harris[19] analyzed the risk factors associated with catheter-associated candiduria due to *C. glabrata* (40 cases) and *C. albicans* (289 cases). Multivariate analysis showed that female gender [RR 2.93 (1.23–6.99) p=0.12 for *C. glabrata*; RR 2.54(1.67–3.89) p<0.001 for *C. albicans*], diabetes [RR 3.50 (1.57–7.83) p<0.01 for *C. glabrata* only], ICU admission [RR 3.14 (1.39–7.08) p<0.01 for *C. glabrata*; RR 3.57 (2.32–5.48) p<0.001 for *C. albicans*] and previous antibiotic use [RR 10.64 (2.36–47.97) p<0.001 for *C. glabrata*; RR 3.87 (2.24–6.68) p<0.001 for *C. albicans*] were strongly associated with candiduria from both species. It is interesting to note that prior use of fluconazole [RR 4.37 (1.32–14.43) p<0.01] and quinolone [RR 3.16 (1.14–8.80) p<0.01] were specifically associated with candiduria due to *C. glabrata* but not *C. albicans*.[19]

A similar prospective single-center case-control study involving 145 subjects with candiduria was done in India. *C. albicans* was isolated in 23% of cases, while non-*albicans* species were isolated in 71%, with *C. tropicalis* and *C. glabrata* as the predominant species.[15] Previous use of antibiotics (cephalosporin the most common) was noted in 91–92% of patients with candiduria. Univariate logistic regression analysis revealed the following factors to be associated with candiduria: hospital stay >10 days, ICU stay >5 days prior to culture, concomitant or recent urinary bladder catheterization, infections and antimicrobial use in the past, most recent plasma glucose >180 mg/dl and serum albumin <3 g/L. After multivariate analysis, the following factors retained significance of association (p≤0.05): recent antimicrobial use and plasma glucose >180 mg/dl. Significant association with death in candiduria (p≤0.05) was seen in the following factors using univariate logistic regression analysis: the use of urinary

diversion devices, the use of more than two classes of antimicrobials, stay in the ICU, and renal failure.[15]

Admission to the ICU was studied more closely in a prospective study that identified possible predisposing factors to *Candida* UTI.[3] The study reported that the isolation rate of *Candida* spp. increased with the number of days a patient was admitted at the ICU. Similar to earlier studies, statistically significant (p=0.001) higher *Candida* isolation rates were observed among patients who have stayed in the ICU for over a week than among those who have just been admitted.[3,21]

The use of indwelling urinary catheters has been notoriously associated with the development of catheter-associated UTI, with as much as 67% of candiduria patients having indwelling foley catheters at the time of the event.[3,18] One surveillance study of nosocomial infections in medical ICUs further reported that *C. albicans* was more commonly isolated in catheter-associated nosocomial UTIs than in non-catheter-associated nosocomial infections (21% vs. 13%, p=0.009).[22] UTI from all fungal pathogens occurred more frequently in patients with catheters than in those without (40% vs. 22%, p<0.001).[22]

Treatment of asymptomatic and minimally symptomatic candiduria is not recommended because it does not provide clear clinical benefits such as long-term (i.e., more than two weeks) eradication of the fungi. A randomized multicenter placebo-controlled study compared fungal eradication rates among 316 consecutive asymptomatic/minimally symptomatic candiduria patients whose risk factors for candiduria have been resolved and who had been given either fluconazole or placebo for 14 days.[23]

Short-term rates of eradication of *Candida* species from the urine were higher in patients who had received fluconazole therapy than those who did not (RR 1.7 95% CI 1.27–2.26 p<0.001). However, sub-analysis for those patients who were able to complete the recommended duration in both treatment groups showed that rates of candiduria two weeks after discontinuation of therapy were similar in the fluconazole and placebo groups (RR1.04 95% CI 0.84–1.23 p=0.7), and relapse rates were similar as well (9% vs. 4%, p=0.6).[23]

Long- term eradication rates were not associated with clear clinical benefits in the asymptomatic or minimally symptomatic population of predominantly elderly, debilitated patients in this study. This trend is also seen in another study that compared short-course antifungal regimens (fluconazole, IV amphotericin B and bladder irrigation with amphotericin B) with just the removal of the predisposing factors.[24]

The rates of spontaneous clearance were significantly lower in the treatment groups at day 1 post-treatment (40% vs. 58.6% vs. 55.2 vs. 82% for no treatment, fluconazole, IV amphotericin B and bladder irrigation with amphotericin B, respectively) but the rates tended to decrease at day 7.[24]

In an observational study of 55 patients in a tertiary hospital in Manila, clinical improvement was notably more common in cases where the catheter was removed. Clinical improvement was significantly more common in patients whose catheters were removed whether or not treatment was given (p<0.05).[4] The same study reported that fatal infections were significantly more common in patients whose catheters were retained compared with those whose catheters were removed (p<0.05). Clearly, for patients with asymptomatic or minimally symptomatic candiduria in whom predisposing factors are present, modification of these risk factors is the first-line approach and by itself generally results in the spontaneous resolution of the candiduria. If complete

removal of these instruments is not possible, replacement of the device with a new one is still beneficial.

Asymptomatic candiduria in predisposed inpatients

Despite candidemia being reported in <5% of patients in most ICUs, the possibility of disseminated candidiasis should be considered in all hospitalized patients with candiduria, especially among critically ill patients.[13] Candiduria is seen in as many as 46%–80% of persons with candidemia and may be the first and the only manifestation of disseminated or invasive candidiasis.[3,21,25,26]

The modification of risk factors that predispose to *Candida* UTI is still the recommended first-line strategy for this subset of patients. Changing or removing the catheter is recommended. Discontinuing antibiotics that are no longer necessary and treating other predisposing conditions simultaneously should also be done. In one cross-sectional study involving chart review of 188 patients with candiduria, patients were divided into two groups: group 1, patients who received any antifungal treatment; and group 2, patients who never received any antifungal treatment.[6] It was surprising to note that patients who received antifungal treatment were significantly more likely to have positive follow-up cultures (average follow-up time of 18 months) compared to those who did not (group 1: 23%, n=273; group 2: 7%, n=150; p<0.01). One limitation of this study is that more cultures were likely to be obtained from treated patients, thereby increasing the likelihood of positive follow-up cultures.[6] Several randomized control studies, despite having low- to moderate-quality assessments due to imprecision, inadequate description of randomization and allocation procedures, and indirectness (i.e., the included patients were not divided into clinical presentation groups, e.g., asymptomatic in previously healthy, asymptomatic among inpatients, and outpatients with risk factors and symptomatic candiduria), generally showed results towards not initiating antifungal therapy.[18,24,27] Based on these, it is recommended that antifungal treatment of candiduria in a hospitalized inpatient should be reserved only for those who have solid evidence of infection of the kidney or collecting system or disseminated candidiasis.

If, after the removal of the predisposing factors, the candiduria still persists, investigation for a more deep-seated infection should be done. Imaging studies of the kidneys and collecting system may reveal renal abscess, fungus ball, or other urologic abnormalities that may be responsible for the persistent funguria.[13,14]

Treatment should also be considered as a prophylactic measure for patients who are about to undergo invasive urologic procedures, to avoid the risk of developing invasive candidiasis and candidemia.[12,28]

Symptomatic candiduria

Symptomatic candiduria can present as any of the following syndromes:

1. **Cystitis**

   Candida cystitis may present with lower urinary signs and symptoms such as dysuria, hematuria, urgency and suprapubic tenderness.[5]

2. ***Candida* pyelonephritis**

   Candida pyelonephritis has a similar presentation to bacterial pyelonephritis. It may also be associated with candidemia, sepsis and septic shock.[5] The infection usually occurs via the hematogenous route but can also

occur through ascending infection in cases of obstruction, concomitant bacteriuria or immunosuppression.[13]

3. Fungus balls (bezoars and mycetomas) of the urinary tract

Reports of cases of fungus balls in the urinary tract are mostly from the pediatric population, especially in neonates.[29-37] This was also found in some reports of diabetic patients.[38,39] However, there has been a case report of two immunocompetent women with no known predisposing factors who presented with *Candida* mycetomas in the renal pelvis, causing urinary tract obstruction.[40]

On radiologic imaging, fungus balls may present as an intraluminal filling defect of the drainage system, which may lead to obstruction. It is important to note, however, that blood clots, radiolucent urinary calculi, air bubbles, inflammatory debris and transitional cell carcinoma can present similarly. On ultrasound, fungus balls commonly present as hyperechoic lesions of the collecting system, but in some instances, they can also be hypoechoic.[40]

Candiduria should be treated with appropriate antifungal agents in symptomatic patients.[8,12,14] Management of predisposing conditions should also be a part of the therapeutic regimen. Patients may require surgical interventions such as drainage or debridement in the case of abscesses; however, the decision to perform these interventions will depend on individual patient contexts and scenarios. In the case of *Candida* fungus ball, the location will determine the approach to therapy.[14] Systemic treatment with amphotericin B or fluconazole has been used. The use of systemic therapy is justifiable because fungus balls may have developed from systemic infection or from deep seated parenchymal infection. However, aside from systemic therapy, invasive procedures are also often necessary to remove the bulk of the mass and relieve obstruction.[8,13,14]

Candiduria in clinically unstable patients

Candiduria should be treated with appropriate antifungal agents in critically ill patients such as those admitted in the ICU, septic patients, those with neutropenia and those with suspected disseminated disease.[8,13,14] Decreasing the burden of infection for these patients at the earliest possible time may be lifesaving. At least two randomized controlled studies, although limited by their methodologic quality and indirectness, have demonstrated significantly higher short-term fungal clearance rates with antifungal administration as early as day 1 post-treatment.[23,24]

For critically ill patients, candiduria, whether symptomatic or not, should initially be regarded as a harbinger of disseminated candidiasis.[13] Since candiduria may be a manifestation of life-threatening disseminated infection in critically ill patients in some instances, it may require aggressive systemic antifungal treatment.[3,26,41] In a study involving 47 surgical ICU patients, the group treated with systemic fluconazole with APACHE Score II at the time of candiduria did not develop disseminated candidiasis.[25] If the candiduric patient's clinical condition is too unstable to permit an incremental approach to determine its cause, or if clinical evidence for disseminated candidiasis is compelling, systemic antifungal chemotherapy should be given immediately with fluconazole.

Persistent candiduria in immunocompromised or non-catheterized patients warrants ultrasound or CT scan of the kidney to exclude clinically silent hematogenous renal candidiasis or upper tract obstruction and stasis.[28,42]

4. If antimicrobial therapy is deemed necessary for a patient with candiduria, what antifungal agents are effective for treatment?

4.1 The first line of treatment is fluconazole 400 mg loading dose, and then 200 mg/day for 7–14 days. The route of administration depends on patient status and oral tolerability.
Strong recommendation, low quality of evidence

4.2 In certain clinical situations such as prior azole use, refractory infection or suspicion of drug resistance to fluconazole (e.g., patients with suspected *C. glabrata* infection), IV amphotericin B deoxycholate (AmBd) at a dose of 0.3–1.0 mg/kg per day can be given.
Weak recommendation, low quality of evidence

4.3 For patients who will undergo urologic procedures and in whom candiduria was found to be present, fluconazole 200–400 mg (3–6 mg/kg) daily or AmBd 0.3–0.6 mg/kg daily for several days before and after the procedure is recommended.
Strong recommendation, low quality of evidence

Summary of Evidence

Studies on the optimal drug for symptomatic candiduria are limited by their sample sizes, indirectness, study design and quality. One local observational study,[4] which included a limited number of patients with candiduria, reported that among the azoles, fluconazole showed the highest cure rate at 8 out of 9 patients, compared to 7 out of 10 on ketoconazole and 5 out of 8 on itraconazole. The same study showed higher relapse rates with ketoconazole (30%) and itraconazole (38%) compared to fluconazole (11%). No failures were seen with 10- to 14-day courses of amphotericin B in six patients. One randomized multicenter placebo-controlled study involving 316 consecutive asymptomatic/minimally symptomatic candiduria patients showed that short-term fungal-eradication rates were higher compared with placebo in patients who received fluconazole at a loading dose of 400 mg followed by 200 mg the next 13 days for a total of 14 days.[23]

Fluconazole is the drug of choice for *Candida* cystitis caused by most species of *Candida* (exceptions include infections caused by resistant species such as *C. glabrata* and *C. krusei*). The drug's *in vitro* activity and pharmacokinetics make it a good choice for *Candida* cystitis as it is highly water soluble and is primarily excreted in the urine. Fluconazole can be given at a dose of 200–400 mg orally daily for two weeks.[13,14] Other azoles are not as useful for cystitis because their active compound is minimally excreted in the urine: itraconazole <1%, voriconazole <5%, posaconazole <1%.[13] Although the antifungal flucytosine may be useful in fluconazole-resistant *Candida* infections, it is not available in the Philippines.

In certain clinical situations such as prior azole use, refractory infection or suspicion of drug resistance to fluconazole (e.g., patients with suspected *C. glabrata* infection), IV AmBd at a dose of 0.3–1.0 mg/kg per day can be given.[8]

Ascending pyelonephritis due to *Candida* infection is often seen in hospitalized patients with the following conditions: diabetes and renal insufficiency, variable papillary necrosis and obstructive uropathy.[43] Systemic antifungal therapy with fluconazole 200–400 mg (up to 6 mg/kg) daily for two weeks or AmBd 0.5–0.7 mg/kg daily for one to seven days, together with adequate drainage of the upper urinary tract, is essential.[14] Relief of obstruction and Investigation of possible local complications through imaging are of utmost importance.[43]

Patients who will undergo urologic procedures and in whom candiduria was found to be present should receive short-course prophylactic therapy with an antifungal agent.[12,28] Unfortunately, the optimal regimen for this indication is yet to be determined.[12] In a case series of four patients, a single-dose IV amphotericin B (0.3 mg/kg) has been shown to be efficacious in the treatment of lower urinary tract candidiasis, with therapeutic concentrations being observed for considerable periods after administration.[44] A study by Leu et al[24] showed a success rate of 72% in eradicating yeast from the urine with a single IV dose of amphotericin B. The Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Disease Society of America (IDSA) suggests fluconazole 200–400 mg (3–6 mg/kg) daily or AmBd 0.3–0.6 mg/kg daily for several days before and after the procedure, based on low-quality evidence.[14]

Most cases of fungus balls will require surgical debridement. Successful usage of IV fluconazole or AmBd has been reported in case series.[30,45] Based on low quality-evidence, the IDSA guidelines suggest fluconazole 200–400 mg (3–6 mg/kg) daily, or as an alternative, AmBd 0.5–0.7 mg/kg (with or without flucytosine), to be given until there is resolution of symptoms or until urine fungal cultures are negative. If there is access to the renal collecting system, such as the presence of a nephrostomy tube, AmBd irrigation at a concentration of 50 mg for every liter of sterile water can be given as adjunctive therapy.[14]

In renal candidiasis where there is hematogenous renal involvement, high-dose systemic amphotericin B (>0.6 mg/kg per day) or parenteral fluconazole (6 mg/kg per day) is recommended in accordance with guidelines for candidemia from the Mycoses Study Group[42] or the more recent IDSA guidelines.[14] Duration of treatment is 4–6 weeks.

Echinocandins are extensively metabolized, and very little drug can be recovered in the urine. However, in a retrospective review of data from the caspofungin database, this agent was found to be efficacious in three patients who had *Candida* pyelonephritis of ascending origin and in whom other antifungal therapies had failed.[46]

4. What is the value of bladder irrigation in the management of urinary candidiasis?

Bladder irrigation with amphotericin B can be used as an adjunct therapy to systemic antifungal agents in the treatment of refractory cystitis (e.g., infections from *Candida* with either acquired or inherent resistance to azoles). When used, a continuous irrigation of amphotericin B at a

concentration of 50 mg per liter of sterile water for a period of five days is recommended.
Weak recommendation, low quality of evidence

Summary of Evidence
The use of bladder irrigation with antifungal agents, most commonly amphotericin B, is not unusual in clinical practice, particularly in other countries. It has been used for the past several decades despite the absence of high-quality studies to support it.[47,48] Three randomized controlled trials comparing the rate of clearance of candiduria with fluconazole versus amphotericin B bladder irrigation have been analyzed in one meta-analysis.[24,48-50] All three studies were randomized, but the randomization processes and allocation generation and concealment processes were not clearly described. All point estimates of the OR (clearance of candiduria) for the three studies showed trends towards the use of amphotericin B bladder irrigation at day 1 post-treatment (pooled OR 0.57 95% CI 0.32–1.0). However, at day 5 post-treatment, both therapies already showed similar responses (pooled OR 1.51 95% CI 0.81–2.80).[50] In two of the three studies, the use of systemic fluconazole demonstrated prolonged beneficial effects that were not observed initially.[24,48] In fact, in the study by Jacobs et al, at one month after study enrollment, the all-cause mortality rate was greater among patients treated with amphotericin B bladder irrigation alone than among those who received oral fluconazole (41% vs. 22%, respectively; $p<0.05$).[48] The IDSA guidelines have, in fact, discouraged the use of this strategy due to a high relapse rate.[14] Thus, bladder irrigation with amphotericin B can be used only as an adjunct therapy to systemic antifungal agents in the treatment of refractory cystitis (e.g., infections from *Candida* with either acquired or inherent resistance to azoles). When used, a continuous irrigation of amphotericin B at a concentration of 50 mg per liter of sterile water for a period of five days is recommended over intermittent irrigation.[50]

Table 21. Summary of Treatment for Urinary Candidiasis

Patient Subset	First Line	Remarks
Candiduria with confirmed or suspected disseminated candidiasis/candidemia Clinically unstable patient with candiduria	• It is best to follow treatment guidelines for candidemia.‡ • Fluconazole 400–800mg (6 mg/kg) IV daily or amphotericin B (>0.6 mg/kg per day)§	
For patients undergoing urologic procedures	Fluconazole 200–400 mg (3–6 mg/kg) daily or AmBd 0.3–0.6 mg/kg daily for several days before and after the procedure	Several studies report equivalent results with the use of bladder irrigation with amphotericin B. However, its cost, difficulty in administration and high relapse rate limit its use.
Candida cystitis	Fluconazole 400 mg loading dose, and then 200 mg daily to complete two weeks *Alternative:* AmBd 0.3–0.6 mg/kg daily for one to seven days§	For non-*albicans* species, consider amphotericin§
Candida pyelonephritis	Fluconazole 200–400 mg daily for two weeks *Alternative:* AmBd 0.5–0.7 mg/kg daily for 1-7 days§	Consider surgical interventions, especially to relieve obstruction if there is any; identify local complications through imaging.
Urinary fungus ball	Surgical removal, plus: *First line:* Fluconazole 200–400 mg (3–6 mg/kg) daily to be given until there is resolution of symptoms or until urine fungal cultures are negative *Alternative:* AmBd 0.5–0.7 mg/kg	If there is access to the renal collecting system, such as the presence of a nephrostomy tube, AmBd irrigation at a concentration of 50 mg per liter of sterile water can be given as adjunctive therapy.

‡ Treatment for candidemia or disseminated candidiasis is beyond the scope of this guideline. The reader is referred to other relevant documents such as the Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Disease Society of America, available for download at the IDSA website, www.idsociety.org.

§ For patients with prior azole use, refractory infection or when there is suspicion of drug resistance to fluconazole (e.g., patients with suspected *C. glabrata* infection)

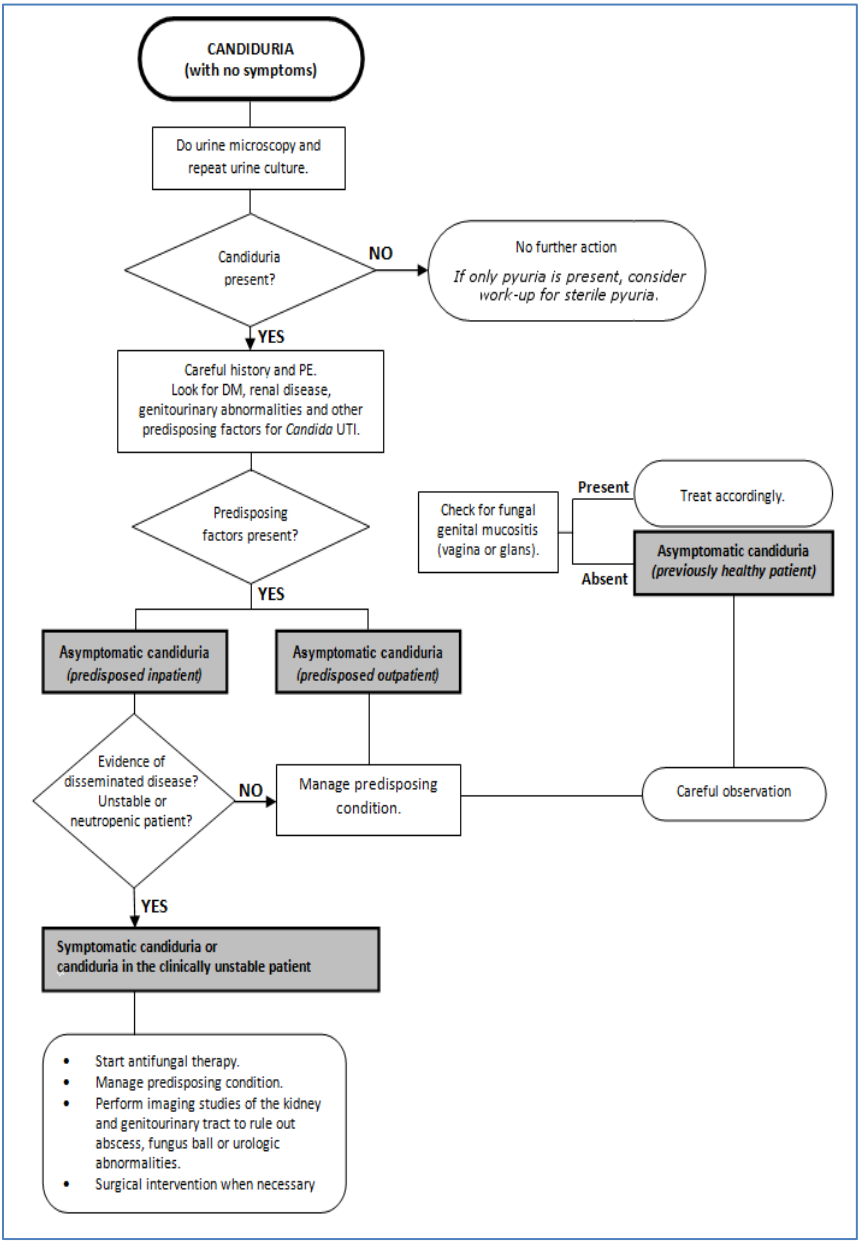

Figure 3. Algorithm for the management of candiduria

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