Philippine Clinical Practice Guidelines on the Diagnosis and Management of Urinary Tract Infections in Adults

2013 Update

(Part 1)

This guideline is intended for use by a broad range of health care professionals, including general practitioners, medical specialists, administrators, policy makers and nurses.

Suggested Citation

Task Force on UTI 2013, Philippine Practice Guidelines Group in Infectious Diseases. Urinary Tract Infections in Adults 2013 Update. PPGG-ID Philippine Society for Microbiology and Infectious Diseases Volume ___ No ___ Quezon City, Philippines. Copyright PSMID 2013
ISBN _____

Philippine Clinical Practice Guidelines on the Diagnosis and Management of Urinary Tract Infections in Adults 2013 Update Part 1

Uncomplicated Urinary Tract Infections
Urinary Tract Infections in Pregnancy

BLANK

Task Force Members

Organizations: PSMID, POGS, PSN, PUA, PAFP
Chair: Mediadora C. Saniel
Co-chair: Marissa M. Alejandria

Uncomplicated Urinary Tract Infection Cluster

Thea C. Patino (Head)
Evalyn A. Roxas (Head)
Karen Marie R. Gregorio
Annabelle M. Laranjo
Kathryn U. Roa
Rommel P. Sumilong
Anna Marie S. Velasco
Rosally P. Zamora

Urinary Tract Infection in Pregnancy and Asymptomatic Bacteriuria in Adults Cluster

Ricardo M. Manalastas Jr. (Head)
Louella P. Aquino
Shahreza L. Baquiran
Sybil Lizzane R. Bravo
Jennifer T. Co
Maria Meden P. Cortero
Lorina Q. Esteban
Analyn F. Fallarme
May Gabaldon
Jill R. Itable
Alfredo M. Lopez, Jr
Helen V. Madamba
Josefa Dawn V. Martin
Erwin R. De Mesa
Sharon Faith B. Pagunsan
Oliver S. Sanchez
Katha W. Ngo-Sanchez

Research Associates: Richelle G. Duque
Grace Kathleen T. Serrano

Table of Contents

List of Tables

List of Algorithms

INTRODUCTION

Urinary tract infections (UTI) were 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 updated the recommendations following an extensive review of more recent literature. This was the first time that the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system was used to develop guidelines in infectious diseases in the country. The outputs were 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 was 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 were 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.

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. Strength of Recommendation and Quality of Evidence[1,2]

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:

a. Balance of benefits versus harms and burdens
b. 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?
c. Resource implications: financial costs/implications, infrastructure, equipment, human resources/expertise, cost-effectiveness
d. Feasibility: Is the recommendation achievable in the setting where the greatest impact is expected?

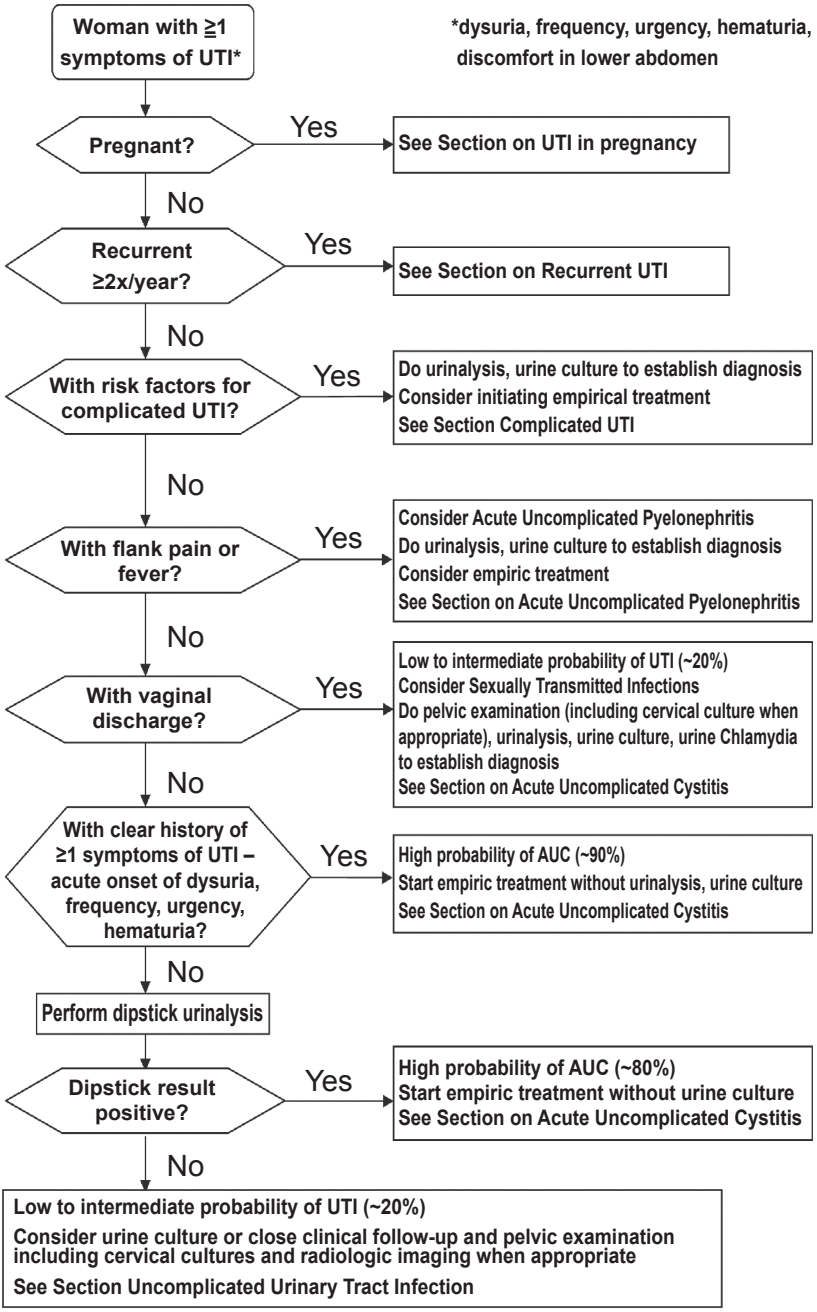
A series of face-to-face meetings of the task force with representatives from all four clusters was held to discuss each cluster's draft outputs. The task force members developed a consensus in grading the quality of the evidence and strength of the recommendations using the GRADE technique. Throughout 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.

References

1. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 336:924–6.
2. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al. Going from evidence to recommendations. BMJ 2008; 336:1049–51.

Algorithm 1. Evaluating a Woman with Symptoms of Acute Urinary Tract Infection



ACUTE UNCOMPLICATED URINARY TRACT INFECTIONS

Acute Uncomplicated Cystitis
Acute Uncomplicated Pyelonephritis

ACUTE UNCOMPLICATED URINARY TRACT INFECTIONS

ACUTE UNCOMPLICATED CYSTITIS IN WOMEN

Section Summary

Definition of acute uncomplicated cystitis (AUC)

- Clinically, AUC is suspected in premenopausal non-pregnant women presenting with acute onset of dysuria, frequency, urgency, and gross hematuria; and without vaginal discharge.
- Urinalysis is not necessary to confirm the diagnosis of AUC in women presenting with one or more of the above symptoms of UTI in the absence of vaginal discharge and complicating conditions enumerated in Table 2.
- Women presenting with urinary symptoms plus vaginal discharge should undergo further evaluation.
- Conditions that define complicated UTI (cUTI) must be absent as obtained on history-taking.

Strong recommendation, High quality of evidence

Approach to management

- Empiric antibiotic treatment is the most cost-effective approach in the management of AUC.
- Pre-treatment urine culture and sensitivity is NOT recommended.
- Standard urine microscopy and dipstick leukocyte esterase (LE) and nitrite tests are not prerequisites for treatment.

Strong recommendation, High quality of evidence

Antibiotic treatment

- Antibiotics recommended for use in AUC are presented in Table 4. Efficacy in terms of clinical cure, cost effectiveness, safety, and tolerability were considered in the choice of antibiotics. In addition, the propensity to cause collateral damage and local susceptibility rates were given greater weights in the choice of antibiotic recommendations.

- Ampicillin or amoxicillin should NOT be used for empirical treatment given the relatively poor efficacy and very high prevalence of antimicrobial resistance to these agents worldwide.

Strong recommendation, High quality of evidence

- Trimethoprim-sulfamethoxazole160/800 mg BID for three days should be used ONLY for culture-proven susceptible uropathogens due to high prevalence of local resistance and high failure rates.

Strong recommendation, High quality of evidence

- Nitrofurantoin monohydrate/macrocrystals (100 mg BID for five days) is recommended as the first line treatment for AUC due to its high efficacy, minimal resistance, minimal adverse effects, low

propensity for collateral damage, and reasonable cost. However, the nitrofurantoin monohydrate/macrocrystal formulation is not locally available. Thus, nitrofurantoin macrocrystal formulation 100 mg is recommended, but it should be given four times a day for five days.

Strong recommendation, High quality of evidence

- Fosfomycin (3 g in a single dose) is also a recommended antibiotic due to its high efficacy, convenience of a single dose, low propensity for collateral damage, good activity against multidrug-resistant uropathogens, and minimal adverse effects. However, there are no local resistance data to date.

  Strong recommendation, High quality of evidence

- Pivmecillinam (400 mg BID for three to seven days) can be used in areas where it is available, as it has reasonable treatment efficacy. However, it is not currently available in the country. Local resistance data is also absent.

  Strong recommendation, High quality of evidence

- Quinolones should NOT be used as a first line drug despite their efficacy due to the high propensity for collateral damage.

  Strong recommendation, High quality of evidence

- Beta-lactam agents, including amoxicillin-clavulanate, cefaclor, cefdinir, cefpodoxime proxetil, ceftibuten, and cefuroxime are appropriate choices for therapy when other recommended agents cannot be used.

  Strong recommendation, High quality of evidence

<u>Duration of treatment</u>

- Nitrofurantoin should be given for five days, while fosfomycin is given as a single dose.
- For the alternative agents:
  - A three day course for fluoroquinolone is recommended.
  - A seven-day regimen for beta-lactams (amoxicillin-clavulanate, cefaclor, cefdinir, cefixime, cefpodoxime proxetil, ceftibuten, and cefuroxime) is recommended.

<u>Duration of treatment for elderly women</u>

- In otherwise healthy elderly women with AUC, the recommended duration of treatment is the same as with the general population (See Table 3).

  Strong recommendation, High quality of evidence

<u>Course of action for patients who do not respond to treatment</u>

- Patients whose symptoms worsen or do not improve after completion of treatment should have a urine culture done;

and antibiotic should be empirically changed pending result of sensitivity testing.

- Patients whose symptoms fail to resolve after treatment should be managed as complicated UTI.

Strong recommendation, Low quality of evidence

Post-treatment laboratory tests

- Routine post-treatment urine culture and urinalysis in patients whose symptoms have completely resolved are NOT recommended as it does not provide any added clinical benefit.

Strong recommendation, Low quality of evidence

Recommendations and Summary of Evidence

1. **When is AUC suspected in women?**
   - **Clinically, AUC is suspected in premenopausal non-pregnant women presenting with acute onset of dysuria, frequency, urgency, and gross hematuria; and without vaginal discharge.**
   - **Urinalysis is not necessary to confirm the diagnosis of AUC in women presenting with one or more of the above symptoms of UTI in the absence of vaginal discharge and**
   - **Women presenting with urinary symptoms plus vaginal discharge should undergo further evaluation.**
   - **Conditions that define complicated UTI must be absent as obtained on history-taking.**

   Strong recommendation, High quality of evidence

Table 2. Conditions that define complicated UTI[1–7]

Presence of an indwelling urinary catheter or intermittent catheterization
Incomplete emptying of the bladder with >100 ml retained urine post-voiding
Impaired voiding due to neurogenic bladder, cystocoele
Obstructive uropathy due to bladder outlet obstruction, calculus, urethral or ureteric strictures, tumors
Vesicoureteral reflux & other urologic abnormalities including surgically created abnormalities
Chemical or radiation injuries of the uroepithelium
Peri- or post-operative UTI
Azotemia due to intrinsic renal disease
Renal transplantation
Diabetes mellitus
Immunosuppressive conditions – e.g. febrile neutropenia, HIV-AIDS
UTI caused by unusual pathogens (M. tuberculosis, Candida spp.)
UTI caused by antibiotic-resistant or multi-drug resistant organisms (MDROs)
UTI in males except in young males presenting exclusively with lower UTI symptoms
Urosepsis

Summary of Evidence

In a recent systematic review of 16 studies (N=3,711 patients) by Giesen et al., the diagnostic accuracy of symptoms and signs of uncomplicated UTI was compared to the gold standard, urine culture, across three different reference standards, 10^2, 10^3 and 10^5 CFU/mL. Six symptoms were significant in determining the probability of UTI. The presence of dysuria, frequency, urgency, hematuria, and nocturia increased the probability of UTI, with hematuria having the highest diagnostic utility (Positive likelihood ratio 1.72, sensitivity 0.25 (95% confidence interval {CI} 0.21, 0.29), specificity 0.85 (95% CI 0.81, 0.89)). The presence of vaginal discharge, on the other hand, decreases the probability of UTI.[8]

An earlier systematic review by Bent et al.[9] also assessed the usefulness of signs and symptoms in the diagnosis of UTI. In this review, the presence of dysuria, frequency, hematuria, back pain, and costovertebral tenderness increased the probability of UTI, while the absence of dysuria, absence of back pain, positive history of vaginal discharge, positive history of vaginal irritation, and the finding of vaginal discharge on physical examination decreased the probability of UTI.[9]

The findings of Giesen et al.[8] were similar to the findings of Bent et al.,[9] where no one symptom or sign was sufficient to make the diagnosis of UTI with certainty. A combination of signs and symptoms was needed to determine the diagnosis. The two studies differed in that Bent et al.[9] combined the different studies with different diagnostic thresholds ranging between ≥102 CFU/mL and ≥105 CFU/mL while Giesen et al.8 analyzed the studies based on three defined diagnostic thresholds: ≥102 CFU/mL, ≥103 CFU/mL and ≥105 CFU/mL.

Table 3. Accuracy of clinical signs and symptoms in the prediction of urinary tract infections*

Signs/Symptoms	Summary Positive Likelihood Ratios (95% CI)*	Summary Negative Likelihood Ratios (95% CI)*	Summary Positive Likelihood Ratios (95% CI)†	Summary Negative Likelihood Ratios (95% CI) †
Dysuria	1.5 (1.2, 2.0)	0.5 (0.3, 0.7)	1.3 (1.2, 1.4)	0.5 (0.4, 0.6)
Frequency	1.8 (1.1, 3.0)	0.6 (0.4, 1.0)	1.1 (1.0, 1.2)	0.6 (0.5, 0.7)
Hematuria	2.0 (1.3, 2.9)	0.9 (0.9, 1.0)	1.7 (1.3, 2.3)	0.9 (0.8, 0.9)
Urgency	-	-	1.2 (1.1, 1.3)	0.7 (0.6, 0.9)
Nocturia	-	-	1.3 (1.1, 1.6)	0.8 (0.6, 0.9)
Fever	1.6 (1.0, 2.6)	0.9 (0.9, 1.0)	1.3 (0.6, 2.6)	1.0 (0.9, 1.0)
Flank pain	1.1 (0.9, 1.4)	0.9 (0.8, 1.1)	0.8 (0.7, 1.1)	1.1 (1.0, 1.2)
Lower abdominal pain	1.1 (0.9, 1.4)	0.9 (0.8, 1.1)	1.0 (0.9, 1.2)	1.0 (0.9, 1.1)
Absence of vaginal discharge	3.1 (1.0, 9.3)	0.3 (0.1, 0.9)	-	-
Absence of vaginal irritation	2.7 (0.9, 8.5)	0.2 (0.1, 0.9)	-	-
Back pain	1.6 (1.2, 2.1)	0.8 (0.7, 0.9)	0.9 (0.7, 1.1)	1.1 (0.9, 1.3)
Vaginal discharge on physicalexam	1.1 (1.0, 1.2)	0.7 (0.5, 0.9)	0.6 (0.5, 0.8)	1.1 (1.0, 1.2)
Combination of symptoms				
1. dysuria and frequency present, vaginal discharge and irritation absent	22.6			
2. dysuria absent, vaginal discharge or irritation present	0.1-0.2			
3. dysuria or frequency present, vaginal discharge or irritation present	0.3-0.5			

**Adapted from Bent 2002*

†Adapted from Giesen 2010 (diagnostic value at a reference standard threshold of ≥ 10^2 CFU/ml)

2. What is the best approach in the management of a patient suspected to have AUC?

- **Empiric antibiotic treatment is the most cost-effective approach in the management of AUC.**
- **Pre-treatment urine culture and sensitivity is NOT recommended.**
- **Standard urine microscopy and dipstick leukocyte esterase (LE) and nitrite tests are not prerequisites for treatment.**

Strong recommendation, High quality of evidence

Summary of Evidence

In a randomized controlled trial (RCT), 309 women aged 18-70 years old presenting to primary care with suspected uncomplicated UTI were randomized into five management approaches: (a) empiric antibiotics given immediately; (b) empiric antibiotics started if symptoms persist after 48 hours; (c) antibiotics offered only if two or more of the following signs and symptoms are present: cloudy urine, smelly urine, nocturia, and dysuria; (d) antibiotics given if dipstick is positive for either nitrite or leucocytes and trace of blood; and (e) symptomatic treatment initially, then antibiotics targeted to the specific pathogen when culture results come out. The study concluded that all strategies resulted in similar symptom control, with no significant differences in severity of symptoms. However, symptoms lasted 37% longer in patients who had to wait at least 48 hours before starting antibiotics, and 73% longer in those who waited for the culture results compared to the immediate antibiotics group.[10]

Since the RCT on the five management approaches showed no significant difference in symptom control, a cost-effectiveness analysis was done, which yielded no difference in resource implications among the five management approaches.[11] It is recommended that a cost-effectiveness analysis on the management of AUC also be conducted in the Philippines.

3. **Which antibiotics are effective for acute uncomplicated cystitis?**
   - **Antibiotics recommended for use in AUC are presented in Table 4. Efficacy in terms of clinical cure, cost effectiveness, safety and tolerability were considered in the choice of antibiotics. In addition, the propensity to cause collateral damage and local susceptibility rates were given greater weights in the choice of antibiotic recommendations.**

Comment: *Collateral damage is the "ecological adverse effects" of antibiotic therapy. Such adverse effects include selection of drug-resistant organisms and colonization or infection with multi-drug resistant organisms.*[12,13]

Table 4. Antibiotics that can be used for acute uncomplicated cystitis

	Antibiotics	Recommended dose and duration	Leading Brand Unit Price (Php)	Total (Php)	Generic Brand Unit Price (Php)	Total (Php)
Primary	**Nitrofurantoin monohydrate/ macrocrystal (NOT sold locally)**	100 mg BID for 5 days per orem (PO)	N/A	**N/A**	N/A	**N/A**
	Nitrofurantoin macrocrystals	100 mg QID for 5 days PO	53.50/cap	**1,070.00**	N/A	**N/A**
	Fosfomycin trometamol	3 g single dose PO	477.00/ sachet	**477.00**	N/A	**N/A**
Alternative	**Pivmecillinam (NOT sold locally)**	400 mg BID for 3–7 days PO	N/A	**N/A**	N/A	**N/A**
	Ofloxacin	200mg BID for 3 days PO	53.50/tab	**321.00**	28.00/tab	**168.00**
	Ciprofloxacin	250mg BID for 3 days PO	32.50/tab	**195.00**	16.25/tab	**97.50**
	Ciprofloxacin extended release	500mg OD for 3 days PO	49.60/tab	**148.80**	N/A	**N/A**
	Levofloxacin	250mg OD for 3 days PO	189.50/ 500 mg tab	**284.25**	49.00/ 500 mg tab	**73.50**
	Norfloxacin	400mg BID for 3 days PO	77.50/tab	**465.00**	32.50/tab	**195.00**
	Amoxicillin-clavulanate	625mg BID for 7 days PO	48.90/tab	**684.60**	29.75/tab	**416.50**
	Cefuroxime	250mg BID for 7 days PO	66.50/tab	**931.00**	36.75/tab	**514.50**
	Cefaclor	500mg TID for 7 days PO	86.00/cap	**1,806.00**	49.75/cap	**1,044.75**
	Cefixime	200mg BID for 7 days PO	137.50/cap	**1,925.00**	108.00/tab	**1,512.00**
	Cefpodoxime proxetil	100mg BID for 7 days PO	54.25/tab	**759.50**	N/A	**N/A**
	Ceftibuten	200 mg BID for 7 days PO	136.00/tab	**1,904.00**	N/A	**N/A**
ONLY if with proven susceptibility	**Trimethoprim-sulfamethoxazole (TMP-SMX)**	160/800 mg BID for 3 days PO	33.75/tab	**202.50**	17.50/ Tab	**105.00**

**Prices listed were taken from the drug prices of Mercury Drug Store as of December 2013*

- **Ampicillin or amoxicillin should NOT be used for empirical treatment given the relatively poor efficacy and the very high prevalence of antimicrobial resistance to these agents worldwide.**
  Strong recommendation, High quality of evidence

Summary of Evidence

Since 2004, the Philippine Practice Guidelines Group in Infectious Diseases (PPG-ID) Task Force on UTI has not recommended the use of ampicillin and amoxicillin because of the consistently high resistance rates of *E. coli* to the said antibiotics[15] (see Table 5).

In the past, data on local resistance rates of *E. coli* was based only on laboratory surveillance such as the Department of Health's Antimicrobial Resistance Surveillance Program (ARSP). Recently, a prospective study on the prevalence of trimethoprim-sulfamethoxazole resistant *E.coli* among women with uncomplicated UTI was done in a tertiary hospital in Pasig City.[16] The much lower resistance rates in this study may be due to rigorous inclusion criteria of the study (only previously healthy, mostly premenopausal women with uncomplicated acute cystitis and pyelonephritis were included), and are more likely reflective of the prevalence of community-acquired *E. coli* resistance than what is reported in laboratory-based surveillance. Knowledge of the local antimicrobial susceptibility patterns of *E. coli* is important in empirical antibiotic selection for uncomplicated UTI.

Table 5. Percent Resistance of Urinary *E. coli* (outpatient urine specimens)

Antimicrobial Agent	ARSP 2010* N=247	ARSP2011** N=775	ARSP2012*** N=988	AUUTI study 2011+ N=181
TMP-SMX	72	65.8	63.9	41.4
Nitrofurantoin	7.6	11.8	9.8	5.1
Ciprofloxacin	57.4	49	50.6	Levo-5.6
Co-amoxiclav	36.2	27	24.5	11.6
Cefuroxime	59.8	38.9	31.2	5.1
Cefazolin	–	–	–	6.6
Ampicillin	85.4	81.5	–	64.1

*Note: *Antimicrobial Resistance Surveillance Program (ARSP), 2010 report [17]*
***Antimicrobial Resistance Surveillance Program(ARSP), 2011 report [18]*
**** Antimicrobial Resistance Surveillance Program(ARSP), 2012 report [19]*
+From a study on uncomplicated UTI in a tertiary hospital in Pasig City [16]

- Trimethoprim-sulfamethoxazole 800/160 mg BID for three days should be used ONLY for culture-proven susceptible uropathogens due to high prevalence of local resistance and high failure rates.
  Strong recommendation, High quality of evidence

Summary of Evidence

The role of TMP-SMX in the treatment of AUC has evolved in recent years because of the changing landscape in antimicrobial utilization and consequent development of resistance. In the 2010 update of the Infectious Diseases Society of America (IDSA) guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis, TMP-SMX is still considered an appropriate agent for AUC as long as the local resistance rates of uropathogens to TMP-SMX do not exceed 20%.[12] In a randomized controlled trial of women with acute cystitis,

clinical cure rates were significantly lower among TMP-SMX–treated women who had a TMP-SMX–non-susceptible isolate compared with those who had a susceptible isolate.[20] Hence, in vitro resistance should be considered in choosing an antimicrobial as it correlates with clinical and bacteriologic failures.

- **Nitrofurantoin monohydrate/macrocrystals (100 mg twice daily for five days) is recommended as the first line treatment for acute uncomplicated cystitis due to its high efficacy, minimal resistance, minimal adverse effects, low propensity for collateral damage, and reasonable cost. However, the nitrofurantoin monohydrate/macrocrystal formulation is not locally available. Thus, nitrofurantoin macrocrystal formulation 100 mg is recommended, but it should be given four times a day for five days.**
  Strong recommendation, High quality of evidence

Summary of Evidence

Nitrofurantoin, a urinary tract agent almost exclusively employed for treatment of AUC, has been used for more than five decades. However, its popularity was hampered by concerns about efficacy, tolerance, and the recommended seven-day dosing regimen. Recent trials and meta-analyses showed that nitrofurantoin has comparable efficacy with other antibiotics used for treating AUC. With increasing antibiotic resistance and development of collateral damage, nitrofurantoin has the advantage of lower resistance rates and less adverse effects than the traditional antibiotics used for uncomplicated cystitis.[20,21] Nitrofurantoin remained active against most uropathogens. A randomized controlled trial in 2002 showed that patients on nitrofurantoin macrocrystal 100 mg QID for three days had significantly better clinical and bacteriologic outcomes compared to placebo.[22] A recent randomized controlled trial showed that a five-day course of nitrofurantoin monohydrate/macrocrystal 100mg BID was as effective as a three-day course of TMP-SMX double-strength tablet BID in terms of clinical and microbiologic cure.[20] A systematic review of antimicrobial agents used to treat uncomplicated cystitis in women showed that short-term and long-term cure for nitrofurantoin was similar to that of TMP-SMX.[21] Compared to TMP-SMX, nitrofurantoin had similar adverse event rates; however, nitrofurantoin was less likely to cause rash compared with TMP-SMX. This same systematic review showed that the nitrofurantoin group had higher short-term symptomatic cure compared with the beta-lactams. Antimicrobial resistance rates of *E.coli* urine isolates causing AUC consistently showed high resistance rates against TMP-SMX while nitrofurantoin remained consistently active vs. *E. coli*. Demonstration of efficacy,

with reports of low drug resistance based on international and local susceptibility patterns, minimal adverse effects, low risk for collateral damage, and cost effectiveness make nitrofurantoin an excellent primary drug of choice for AUC.

- **Fosfomycin (3 g in a single dose) is also a recommended antibiotic for acute uncomplicated cystitis due to its high efficacy, convenience of a single dose, low propensity for collateral damage, good activity against multidrug-resistant uropathogens, and minimal adverse effects. However, there are no local resistance data to date.**
  Strong recommendation, High quality of evidence

Summary of Evidence

The convenient single-dose regimen, good in vitro activity against resistant gram-negative rods, and minimal propensity for collateral damage make fosfomycin a rational choice. Two RCTs supported the use of fosfomycin trometamol for treatment of UTI[23,24] as its clinical efficacy is comparable with other first-line agents against AUC. In addition, a systematic review demonstrated that it has activity against multidrug resistant pathogens.[25] A recent meta-analysis comparing fosfomycin with other antibiotics showed no difference in clinical success, microbiological success, and occurrence of adverse events.[26] In fact, fosfomycin was superior against trimethoprim, beta-lactams, and nitrofurantoin in terms of microbiologic success.[26] Aside from comparable efficacy, the convenience of a single dose makes fosfomycin a promising drug for the treatment of AUC. However, local susceptibility data is currently not available on this drug.

- **Pivmecillinam (400 mg BID for three to seven days) can be used in areas where it is available, as it has reasonable treatment efficacy. However, it is not currently available in the country. Local resistance data is also absent.**
  Strong recommendation, High quality of evidence

Summary of Evidence

Pivmecillinam, an extended spectrum penicillin and the oral form of mecillinam, has reasonable treatment efficacy for AUC because of its specificity for the urinary tract, and minimal propensity for collateral damage. A double blind RCT done in Sweden concluded that pivmecillinam was better than placebo in the treatment of AUC.[27] Another RCT showed that pivmecillinam at 400 mg BID for three days was as effective as norfloxacin 400 mg BID for three days in terms of early symptomatic cure.[28] In some European countries, its low

resistance rates have made pivmecillinam a popular first-line choice for AUC. However, it is not available in the Philippines.

- **Quinolones should NOT be used as a first line drug for acute uncomplicated cystitis despite its efficacy due to the high propensity for collateral damage**.
  Strong recommendation, High quality of evidence

Summary of Evidence

Fluoroquinolones are still accepted as highly efficacious agents for acute cystitis. However, the 2010 IDSA guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis update recognized the high risk for collateral damage associated with the use of fluoroquinolones.[12] The specific adverse effects of fluoroquinolones are infections with methicillin-resistant *S. aureus* and increasing fluoroquinolone resistance of gram-negative bacilli. Other considerations in the Philippine setting include endemic infections such as tuberculosis and typhoid fever. As such, fluoroquinolones should be considered as alternative agents only and their use should be limited to cases wherein other agents cannot be used.

- **Beta-lactam agents, including amoxicillin-clavulanate, cefaclor, cefdinir, cefpodoxime proxetil, ceftibuten, and cefuroxime are appropriate choices for therapy when other recommended agents cannot be used.**
  Strong recommendation, High quality of evidence

Summary of Evidence

Beta-lactams have generally been proven inferior in cure rates compared to other agents for treatment of acute uncomplicated cystitis. In the 2004 update of the PPGG-ID Guidelines on UTI, the efficacy rates of beta-lactam agents were lower than that of TMP-SMX and fluoroquinolones. The postulated mechanism for beta lactam inferiority in the treatment of UTI was related to its lower rate of eradication of vaginal uropathogens.[15]

Three RCTs directly compared a beta-lactam with traditional first-line agents. The first trial compared the efficacy and safety of cefpodoxime proxetil 100 mg twice daily for three days with TMP-SMX 160/800 mg twice daily for three days.[29] There were no significant differences in both clinical and bacteriological outcomes. The second study compared amoxicillin-clavulanate 500/125 mg twice daily for three days with ciprofloxacin 250 mg twice daily for three days in the treatment of uncomplicated cystitis. Clinical and

microbiological cure rates of amoxicillin-clavulanate were inferior to that of ciprofloxacin.[30] A third trial compared cefpodoxime proxetil 100 mg twice daily for three days with ciprofloxacin 250 mg twice daily for three days in the treatment of acute uncomplicated cystitis. Clinical cure rates of cefpodoxime did not reach the criteria for non-inferiority to ciprofloxacin.[31]

Beta lactams are also associated with collateral damage, specifically, emergence of gram-negative extended spectrum beta-lactamase (ESBL) resistance to these agents. As such, they are considered as alternative agents to be used when TMP-SMX, fluoroquinolones, or nitrofurantoin are contraindicated.

4. **What is the effective duration of treatment for acute uncomplicated cystitis?**
   - **Nitrofurantoin should be given for five days, while fosfomycin is given as a single dose.**
   - **For the alternative agents:**
     - **A three day course for fluoroquinolone is recommended.**
     - **A seven-day regimen for beta-lactams (amoxicillin-clavulanate, cefaclor, cefdinir, cefixime, cefpodoxime proxetil, ceftibuten, and cefuroxime) is recommended.**

   Strong recommendation, High quality of evidence

Summary of Evidence

One of the reasons why nitrofurantoin was less popular in the past is the recommended seven-day dosing regimen. Initial RCTs comparing nitrofurantoin with placebo used a seven-day regimen. However, a randomized controlled trial done in 2007 showed that a five-day treatment regimen with nitrofurantoin had similar clinical efficacy compared to a three-day regimen with TMP-SMX.[20] The Task Force, therefore, recommends five-day duration of nitrofurantoin for AUC.

A systematic review comparing fosfomycin with several antibiotics used single dose fosfomycin and showed either no significant difference between comparators and fosfomycin or some results favoring the use of fosfomycin.[26] We, therefore, recommend a single dose of 3g sachet of fosfomycin for AUC.

A high quality meta-analysis of 32 trials with 9,605 patients compared a three-day regimen with a multi-day (five days or longer) regimen for treatment of uncomplicated UTI in women. No significant difference was noted between a three-day regimen and a multi-day regimen in both short-term and long-term symptomatic failure rates for all antimicrobial agents studied. The agents included in the meta-

analysis were TMP-SMX, fluoroquinolones, nitrofurantoin, and beta-lactams. In terms of both short-term and long-term bacteriological failure, a statistically significant difference favoring a multi-day (5-10 days) regimen was noted. However, in terms of incidence of adverse events, a statistically significant difference favoring the three-day regimen was seen. As such, a three-day fluoroquinolone regimen was as effective as a 5-10 day regimen in achieving symptomatic cure. However, in cases where bacteriological eradication was indicated, the longer duration of treatment (5-10 days) was more effective.[32]

The 2010 update of the IDSA guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis also advocated a three-day regimen for fluoroquinolones not only due to its efficacy but also due to the significantly higher adverse event rate of fluoroquinolones. This was further compounded by the issues on collateral damage seen with the use of fluoroquinolones, making the three-day regimen more appropriate.[12]

For beta-lactams, there was no significant difference between the two treatment regimens in the incidence of both short-term and long-term bacteriologic failure.[32] Although a three-day regimen appeared to be as efficacious as a multi-day regimen even for beta-lactams, the efficacy rates of this antimicrobial class have been considered inferior to TMP-SMX, fluoroquinolones, and nitrofurantoin. This was due to the lower urine concentration of beta-lactams and its inferior ability in eradicating *E. coli* in vaginal and fecal reservoirs.[15] Thus, a seven-day regimen is still warranted for beta-lactams.

5. **In elderly women (>65 years) with acute uncomplicated cystitis, what is the effective duration of treatment?**
   - **In otherwise healthy elderly women with AUC, the recommended duration of treatment is the same as with the general population (See Table 4).**
     Strong recommendation, High quality of evidence

Summary of Evidence

An updated Cochrane systematic review that included 15 RCTs (N=1,644 patients) assessed the effectiveness of single dose, short-course, and long-course antimicrobial regimens in the treatment of symptomatic lower UTI in elderly women. The outcomes evaluated included persistent UTI, clinical failure, adverse reactions, and treatment acceptability. There was a statistically significant difference in the incidence of persistent UTI in the single dose treatment arm compared to both the short-course and long-course treatments. Comparing short course (3-6 days) with long-course (7-14 days)

treatment, there was no significant difference in the incidence of persistent UTI, clinical failure, and adverse reactions. The review suggested that the single dose therapy was less effective while the shorter duration of therapy was sufficient treatment for elderly women with uncomplicated, symptomatic lower UTI.[33]

6. **What should be done for women whose symptoms worsen, do not completely resolve, or do not improve after completion of treatment?**
   - **Patients whose symptoms worsen or do not improve after completion of treatment should have a urine culture done, and, the antibiotic should be empirically changed pending result of sensitivity testing.**
   - **Patients whose symptoms fail to resolve after treatment should be managed as complicated UTI.**

     Strong recommendation, Low quality of evidence

Summary of Evidence

The task force found no new evidence to support a change in the recommendations from the previous guideline.

Patients whose symptoms worsen or do not improve after therapy may harbor a resistant pathogen. This will require a urine culture and administration of a new antibiotic pending result of the sensitivity testing.[34]

7. **What is the clinical utility of a post-treatment urine culture?**
   - **Routine post-treatment urine culture and urinalysis in patients whose symptoms have completely resolved are NOT recommended as it does not provide any added clinical benefit.**

     Strong recommendation, Low quality of evidence

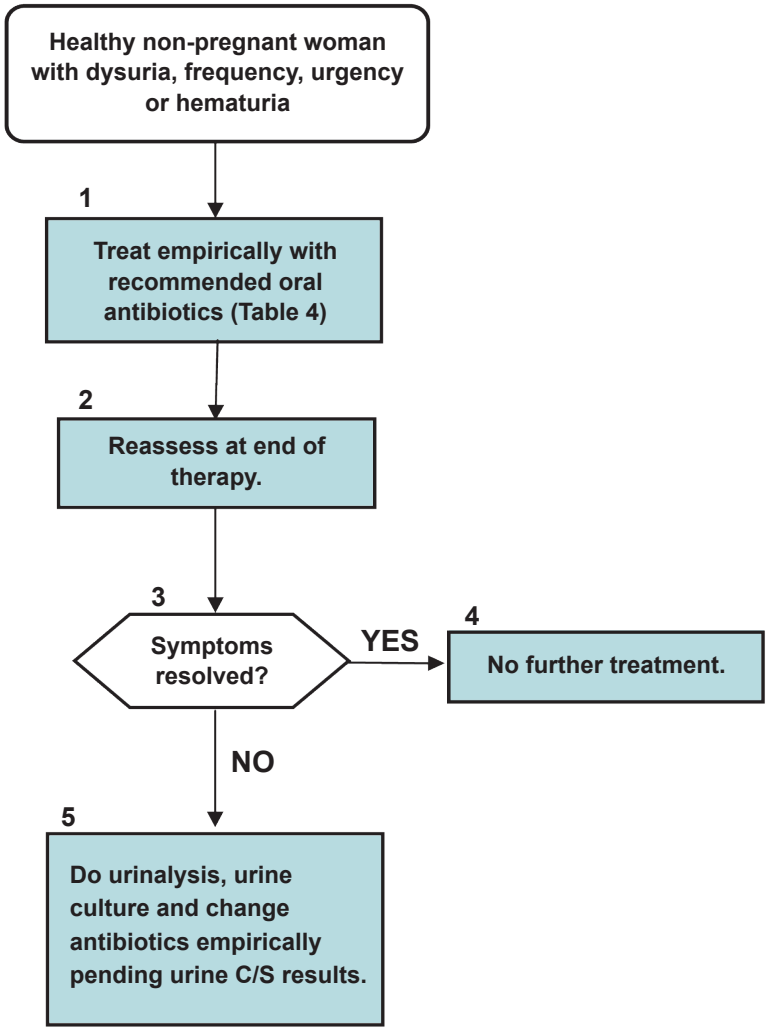
Summary of Evidence

The task force found no new evidence to support a change in the recommendations from the previous guideline.

Informal cost benefit analysis of data from retrospective observational studies showed that routine screening after treatment was costly per case detected and provided no added clinical benefit.[35,36] A retrospective study on 141 women treated for acute cystitis was done to determine whether obtaining a single follow-up urine culture reduced the incidence of subsequent episodes of UTI. Sixty-one women did not have a follow up culture while 80 had post treatment

urine cultures. The two groups were equal with regards to race, recording of negative intravenous pyelogram, UTI, pyelonephritis, asymptomatic bacteriuria, or recurrent UTI episodes. Symptomatic UTI developed within three months in 8.2% of the no follow-up culture group, and 15% of the follow-up culture group. Among the women in the follow-up culture group, only three out of 80 had a positive culture and only one of these three developed symptomatic UTI.[35]

Algorithm 2. Management of Acute Uncomplicated Cystitis



References

1. Nickel JC. Special considerations in the management of urinary tract infections. International Congress and Symposium Series: Management of Urinary Tract Infections 1990. p. 85–95.
2. Ronald AR, Harding GK. Complicated urinary tract infections. Infect Dis Clin North Am 1997; 11:583–92.
3. Williams DN. Urinary tract infection: Emerging insights into appropriate management. PostGrad Med 1996; 99:189– 201.
4. Stamm WE, Hooton TM. Management of urinary tract infection in adults. N Engl J Med 1993; 329:1328–34.
5. Rubin RH, Shapiro ED, Andriole VT, Davis RJ, Stamm WE. Evaluation of new anti-infective drugs for the treatment of urinary tract infection. Infectious Diseases Society of America and the Food and Drug Administration. Clin Infect Dis 1992; 15 Suppl 1:S216–27.
6. Kumazawa J, Matsumoto T. Complicated UTIs. Bergan T, ed. UTIs. Infectiology. Vol 1. Basel: Karger 1997. pp. 19–26.
7. Rubin RH. Infectious disease complications of renal transplantation. Kidney international 1993 Jul; 44(1):221–36.
8. Giesen LGM, Cousins G, Dimitrov BD, Van de Laar F a, Fahey T. Predicting acute uncomplicated urinary tract infection in women: a systematic review of the diagnostic accuracy of symptoms and signs. BMC Fam Pract. BioMed Central Ltd 2010 Jan; 11(1):78.
9. Bent S, Nallamothu BK, Simel DL, Fihn SD, Saint S. Does This Woman Have an Acute Uncomplicated Urinary Tract Infection? JAMA 2002; 287(20):2701–10.
10. Little P, Moore M V, Turner S, Rumsby K, Warner G, Lowes JA, et al. Effectiveness of five different approaches in management of urinary tract infection: randomised controlled trial. BMJ 2010; 340:c199.
11. Turner D, Little P, Raftery J, Turner S, Smith H, Rumsby K, et al. Cost effectiveness of management strategies for urinary tract infections: results from randomised controlled trial. BMJ 2010; 340:c 346.
12. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011 Mar; 52(5):e103–20.
13. Paterson DL. “Collateral Damage” from Cephalosporin or Quinolone Antibiotic Therapy. Clin Infect Dis 2004; 38(Suppl 4):S341–345.
14. Fourcroy JL, Berner B, Chiang Y, Cramer M, Rowe L, Shore N. Efficacy and Safety of a Novel Once-Daily Extended-Release Ciprofloxacin Tablet Formulation for Treatment of Uncomplicated Urinary Tract Infection in Women. Antimicrob Agents Chemother 2005; 49(10):4137–43.
15. Task Force on Urinary Tract Infections Philippine Practice Guideline Group Infectious Disease. The Philippine Clinical Practice Guidelines on the Diagnosis and Management of Urinary Tract Infections in Adults Update 2004. Quezon City, Philippines: PPGG-ID Philippine Society for Microbiology and Infectious Diseases 2004.
16. Gangcuangco LM, Alejandria M, Alfaraz L, Ata RM, Gamponia K, Henson KE, et al. Prevalence and risk factors for trimethoprim-sulfamethoxazole-resistant E. coli in uncomplicated urinary tract infections in a developing country. Poster session presented at: 51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). Chicago, Illinois, USA 2011.
17. Sia SB, Carlos CC. The Antimicrobial Resistance Surveillance Program Progress Report. 2010.
18. Research Instititue for Tropical Medicine. Antimicrobial Resistance Surveillance Program Progress Report Summary 2011, pp. 6–10.
19. Antimicrobial Resistance Surveillance Reference Laboratory. Antimicrobial Resistance Surveillance Program 2012 Annual Report 2012, pp. 33–7.

20. Gupta K, Hooton TM, Roberts PL, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. Arch Intern Med 2007 Nov; 167(20):2207–12.
21. Zalmanovici Trestioreanu A, Green H, Paul M, Yaphe J, Leibovici L. Antimicrobial agents for treating uncomplicated urinary tract infection in women. Cochrane Database Syst Rev 2010; (10):CD007182.
22. Christiaens TCM, Meyere M De, Verschraegen G, Peersman W, Heytens S, Maeseneer JM De. Randomised controlled trial of nitro- furantoin versus placebo in the treatment of uncomplicated urinary tract infection in adult women. Br J Gen Pract 2002; 52:729–34.
23. Minassian M a, Lewis D a, Chattopadhyay D, Bovill B, Duckworth GJ, Williams JD. A comparison between single-dose fosfomycin trometamol (Monuril) and a 5-day course of trimethoprim in the treatment of uncomplicated lower urinary tract infection in women. Int J Antimicrob Agents 1998 Apr; 10(1):39–47.
24. Stein GE. Comparison of single-dose fosfomycin and a 7-day course of nitrofurantoin in female patients with uncomplicated urinary tract infection. Clinical therapeutics 1999 Nov; 21(11):1864–72.
25. Falagas ME, Kastoris AC, Kapaskelis AM, Karageorgopoulos DE. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, Enterobacteriaceae infections: a systematic review. Lancet Infect Dis. Elsevier Ltd 2010 Jan; 10(1):43–50.
26. Falagas ME, Vouloumanou EK, Togias AG, Karadima M, Kapaskelis AM, Rafailidis PI, et al. Fosfomycin versus other antibiotics for the treatment of cystitis: a meta-analysis of randomized controlled trials. J Antimicrob Chemother 2010 Sep; 65(9):1862–77.
27. Ferry S a, Holm SE, Stenlund H, Lundholm R, Monsen TJ. Clinical and bacteriological outcome of different doses and duration of pivmecillinam compared with placebo therapy of uncomplicated lower urinary tract infection in women: the LUTIW project. Scand J Prim Health Care 2007 Mar; 25(1):49–57.
28. Nicolle LE, Madsen KS, Debeeck GO, Blochlinger E, Borrild N, Bru JP, et al. Three days of pivmecillinam or norfloxacin for treatment of acute uncomplicated urinary infection in women. Scand J Infect Dis 2002 Jan; 34(7):487–92.
29. Kavatha D, Giamarellou H, Alexiou Z, Vlachogiannis N, Pentea S, Gozadinos T, et al. Cefpodoxime-Proxetil versus Trimethoprim-Sulfamethoxazole for Short-Term Therapy of Uncomplicated Acute Cystitis in Women. Antimicrob Agents Chemother 2003; 47(3):897–900.
30. Hooton TM, Scholes D, Gupta K, Stapleton AE, Roberts PL, Stamm WE. Amoxicillin-clavulanate vs ciprofloxacin for the treatment of uncomplicated cystitis in women: a randomized trial. JAMA 2005 Feb; 293(8):949–55.
31. Hooton TM, Roberts PL, Stapleton AE. Cefpodoxime vs ciprofloxacin for short-course treatment of acute uncomplicated cystitis: a randomized trial. JAMA 2012 Feb; 307(6):583–9.
32. Milo G, Katchman E, Paul M, Christiaens T, Baerheim A, Leibovici L. Duration of antibacterial treatment for uncomplicated urinary tract infection in women. Cochrane Database Syst Rev 2005; (2):CD004682.
33. Lutters M, Vogt-Ferrier NB. Antibiotic duration for treating uncomplicated , symptomatic lower urinary tract infections in elderly women. Cochrane Database Syst Rev 2008; (3):CD001535.
34. Barry HC, Ebell MH, Hickner J. Evaluation of suspected urinary tract infection in ambulatory women: a cost utility analysis of office based strategies. J Fam Pract 1997; 44:49–60.
35. Winickoff RN, Wilner SI, Gall G, Laage T, Barnett GO. Urine culture after treatment of uncomplicated cystitis in women. South Med J 1981; 74(2):165–9.
36. Schultz HJ, McCaffrey LA, Keys TF, Nobrega FT. Acute cystitis: a prospective study of laboratory tests and duration of therapy. Mayo Clin Proc 1984; 59(6):391–7.

ACUTE UNCOMPLICATED PYELONEPHRITIS IN WOMEN

Section Summary

Definition of acute uncomplicated pyelonephritis (AUP)

- AUP is suspected in otherwise healthy women with no clinical or historical evidence of anatomic or functional urologic abnormalities, who present with the classic syndrome of fever (T ≥38°C), chills, flank pain, costovertebral angle tenderness, nausea and vomiting, with or without signs and symptoms of lower UTI.
- Laboratory findings include pyuria (≥5 WBC/HPF of centrifuged urine) on urinalysis and bacteriuria with counts of ≥10,000 CFU/mL on urine culture.

Strong recommendation, Moderate quality of evidence

Pre-treatment diagnostic tests

- Urinalysis and Gram stain are recommended. Urine culture and sensitivity test should also be performed routinely to facilitate cost-effective use of antimicrobial agents and because of the potential for serious sequelae if an inappropriate antimicrobial agent is used.
- Strong recommendation, Moderate quality of evidence
- Blood cultures are NOT routinely recommended except in patients with signs of sepsis.

Strong recommendation, High quality of evidence

Biomarkers

- Biomarkers (procalcitonin, mid-regional pro-atrial natriuretic peptide, C-reactive protein) are NOT recommended since they are not clinically useful in determining the need for admission or in predicting adverse outcomes such as recurrence and prolonged hospitalization.

Strong recommendation, Low quality of evidence

Indications for admission

- The following are the indications for admission:
  - Inability to maintain oral hydration or take medications
  - Concern about compliance
  - Presence of possible complicating conditions
  - Severe illness with high fever, severe pain, marked debility, and signs of sepsis

Strong recommendation, Moderate quality of evidence

Antibiotic treatment

- Several regimens found to be effective in AUP are listed in Table

6. Primary drugs of choice and alternative drugs are presented. Efficacy, cost effectiveness, safety, tolerability, local susceptibility, and propensity for collateral damage were considered for the choice of the antibiotic.

- The aminopenicillins (ampicillin or amoxicillin) and first generation cephalosporins are NOT recommended because of the high prevalence of resistance and increased recurrence rates in patients given these beta-lactams.
  Strong recommendation, Moderate quality of evidence

- Because of high resistance rates to TMP-SMX, this drug is NOT recommended for empiric treatment but can be used when the organism is found to be susceptible on urine culture and sensitivity.
  Strong recommendation, Moderate quality of evidence

- Quinolones are recommended as the first line treatment for acute uncomplicated pyelonephritis not requiring hospital admission.
  Strong recommendation, High quality of evidence

- In patients not requiring hospital admission, an initial single IV/IM dose of ceftriaxone or aminoglycoside may be considered followed by any of the oral antibiotics in Table 6.
  Strong recommendation, Moderate quality of evidence

- For patients with acute uncomplicated pyelonephritis requiring hospitalization, ceftriaxone,fluoroquinolones or aminoglycosides are recommended as empiric first-line treatment.
  Strong recommendation, Moderate quality of evidence

- Intravenous antibiotics can be shifted to any of the listed oral antibiotics once the patient is afebrile and can tolerate oral drugs. The choice of continued antibiotic therapy should be guided by the urine culture and sensitivity results once available.
  Strong recommendation, Moderate quality of evidence

- For suspected enterococcal infection, ampicillin may be combined with an aminoglycoside.
  Weak recommendation, Low quality of evidence

- Carbapenems and piperacillin-tazobactam should be reserved for acute pyelonephritis caused by multi-drug resistant organisms that are susceptible to either drug.

Duration of treatment

- The recommended duration of treatment is 14 days. Selected fluoroquinolonescan be given for 7-10 days.
  Strong recommendation, High quality of evidence

Role of radiologic imaging

- Routine urologic evaluation and routine use of imaging procedures are NOT recommended.
  Strong recommendation, Moderate quality of evidence

- Consider early radiologic evaluation if the patient has a history of urolithiasis, urine pH ≥ 7.0, or renal insufficiency.
  Strong recommendation, Moderate quality of evidence

- Consider radiologic evaluation if the patient remains febrile within 72 hours of treatment or if symptoms recur to rule out the presence of nephrolithiasis, urinary tract obstruction, renal or perinephric abscesses, or other complications of pyelonephritis.
  Weak recommendation, Low quality of evidence

- Obtain urologic consultation if workup shows abnormalities.
  Weak recommendation, Low quality of evidence

Follow-up laboratory tests

- In patients who are clinically responding to therapy (usually apparent in <72 hours after initiation of treatment), a follow-up urine culture is NOT necessary.
  Weak recommendation, Low quality of evidence

- Routine post-treatment cultures in patients who are clinically improved are also not recommended.
  Weak recommendation, Low quality of evidence

- In women whose symptoms do not improve during therapy and in those whose symptoms recur after treatment, a repeat urine culture and sensitivity test should be performed.
  Weak recommendation, Low quality of evidence

Recurrence of symptoms

- Recurrence of symptoms requires antibiotic treatment based on urine culture and sensitivity test results in addition to assessing for underlying genitourologic abnormality.
  Weak recommendation, Low quality of evidence

- The duration of re-treatment in the absence of a urologic abnormality is two weeks.
  Weak recommendation, Low quality of evidence

- For patients whose symptoms recur and whose culture shows the same organism as the initial infecting organism, a four- to six-week regimen is recommended.

  Weak recommendation, Low quality of evidence

Recommendations and Summary of Evidence

1. **When is AUP suspected?**
   - **AUP is suspected in otherwise healthy women with no clinical or historical evidence of anatomic or functional urologic abnormalities, who present with the classic syndrome of fever (T≥38°C), chills, flank pain, costovertebral angle tenderness, nausea and vomiting, with or without signs and symptoms of lower UTI.[1]**
   - **Laboratory findings include pyuria (≥5 WBC/HPF of centrifuged urine) on urinalysis and bacteriuria with counts of ≥10,000 CFU/mL on urine culture.[2]**

   Strong recommendation, Moderate quality of evidence

Summary of Evidence

Acute pyelonephritis usually occurs in otherwise healthy women; however, information regarding risk factors for pyelonephritis is limited. In a population-based case-control study of women with pyelonephritis, 18 to 49 years of age, the factors associated with pyelonephritis risk were: (1) frequency of sexual intercourse in the previous 30 days, odds ratio (OR) 5.6 (95% CI 2.8, 11.0) for >3 times per week, (2) recent UTI, OR 4.4 (95% CI 2.8, 7.1), (3) diabetes, OR 4.1 (95% CI 1.6, 10.9), (4) recent incontinence, OR 3.9 (95% CI 2.6, 5.9), (5) new sexual partner in the previous year, OR 2.2 (95% CI 1.4, 3.6), (6) recent spermicide use, OR 1.7 (95% CI 1.1, 2.8), and (7) UTI history in the participant's mother, OR 1.6 (95% CI 1.1, 2.5).[3]

2. **What are the recommended diagnostic tests for acute uncomplicated pyelonephritis?**
   - **Urinalysis and Gram stain are recommended. Urine culture and sensitivity test should also be performed routinely to facilitate cost-effective use of antimicrobial agents and because of the potential for serious sequelae if an inappropriate antimicrobial agent is used.**

     Strong recommendation, Moderate quality of evidence

   - **Blood cultures are NOT routinely recommended except in patients with signs of sepsis.**

     Strong recommendation, High quality of evidence

Note: Signs of sepsis, as described in the previous guideline, include the presence of any two of the following:

- Temperature >38 ^{o}C or <36^{o}C,
- Leukopenia (WBC < 4,000) or leukocytosis (WBC > 12,000),
- Tachycardia (HR> 90 beats/min),
- Tachpynea (RR> 20/min or $PaCO_2$< 32 mmHg),
- Hypotension (SBP < 90 mmHg or > 40 mmHg drop from baseline)[4]

Summary of Evidence

In a retrospective study in Korea, a prospective database of 735 women with pyelonephritis was analysed to construct and validate a model that aimed to predict bacteremia, and direct the proper use of blood cultures. The following were identified as independent risk factors for bacteremia: age>65 years (OR 5.18), vomiting (OR 2.40), heart rate >110 beats/min (OR 2.35), segmented neutrophils >90% (OR 3.17), and urine WBC ≥50/HPF (OR 4.27). Weights were assigned to each factor (total score of 15) and the model stratified patients into having low (0 to 3), intermediate (4 to 6), or high (7 to 15) risk for bacteremia. In conclusion,the said model was helpful in assessing the need for blood cultures and the need for hospital admission for intravenous antibiotic administration in patients with uncomplicated pyelonephritis.[5]

Blood cultures contribute to the management of acute pyelonephritis when the blood culture results are discordant with the results of the urine culture. A prospective observational multicenter cohort study determined the risk factors for bacteremia with a uropathogen that was not cultured or recognized in the urine. Of 583 evaluable patients, 432 (74%) were urine culture positive, and 136 (23%) were positive for bacteremia. Five percent of the blood cultures were discordant with the urine culture. The presence of a urinary catheter, OR 2.8 (95% CI 1.0, 7.5), malignancy, OR 2.7 (95% CI 1.1, 6.9), and active antimicrobial UTI treatment, OR 3.3 (95% CI 1.5,7.1) were statistically significant factors associated with discordant results. The mortality rates after a 90-day follow up were as follows: over-all rate 4.8%, patients with discordant results (17.2%) vs. patients with concordant results (4.2%) risk ratio (RR) 4.2 (95% CI 1.7, 10.1).[6] However, the presence of urinary catheter and active antimicrobial UTI treatment are characteristics of complicated UTI.

In a prospective study by Velasco et al.[7] where they analyzed the data of 583 women older than 18 years old, only 2.4% of the 583 women had discordant culture results. Modification of initial antibiotic therapy based on culture results was not needed. There was also

no difference in the clinical evolution of the infection in both the discordant and the nondiscordant groups. The study concluded that blood cultures may not be routinely needed.[7]

3. **Can biomarkers help determine which patients can be treated as outpatients, or which patients will have adverse outcomes?**
   - **Biomarkers (procalcitonin, mid-regional pro-atrial natriuretic peptide, C-reactive protein) are NOT recommended since they are not clinically useful in determining the need for admission or in predicting adverse outcomes such as recurrence and prolonged hospitalization.**
     Strong recommendation, Low quality of evidence

Summary of Evidence

A multicenter, prospective, observational study in 12 emergency departments in France evaluated 582 consecutive patients to assess the effectiveness of procalcitonin (PCT), mid-regional pro-atrial natriuretic peptide (ANP), and C-reactive protein (CRP) measurements in guiding emergency physicians on deciding if a patient with acute pyelonephritis should be admitted to the hospital. Performance characteristics were tested for various cut-offs of CRP, PCT, and ANP. The likelihood ratios were not clinically relevant whatever the biomarker or threshold. The study concluded that none of these three markers could reliably help physicians in their decision-making process.[8]

Another French study evaluated the discriminatory power and predictive accuracy of procalcitonin for adverse outcomes in patients with acute pyelonephritis. Nineteen percent of 58 patients analyzed had adverse medical outcomes which included: "(1) a perceived need for hospitalization: presence of severe sepsis defined by the presence of concomitant systemic inflammatory response and organ dysfunction, urgent urologic surgical procedures related to pyelonephritis, evidence of renal abscess, admission to intensive care; (2) subsequent hospitalization, and, (3) pyelonephritis-related death". Procalcitonin varied widely, and although the median level was higher in patients with adverse medical outcomes compared with those without adverse medical outcomes, the difference was not statistically significant (0.51 ng/mL vs. 0.08 ng/mL, p=0.07). There was no useful threshold that could accurately discriminate between the two groups.[9]

The utility of procalcitonin in predicting bacteremia was evaluated in a prospective observational multicenter cohort study of 581 adults

with febrile UTI. A single procalcitonin level >0.25 µg/L had the best diagnostic performance in predicting the presence of bacteremia,95% sensitivity (95% CI 89%, 98%), specificity 50% (95% CI 46%, 55%). The use of this biomarker decreased the number of blood cultures taken by 40% but still enabled identification of 94% to 99% of patients with bacteremia. This translated to cost-savings for the patients.[10] However, blood cultures are recommended to be taken prior to the initiation of antibiotics. Waiting for the results of procalcitonin levels to determine which patients would require blood cultures would result in inappropriate delay in treatment.

The use of C-reactive protein as a marker of prolonged hospitalization and AUP recurrence was analyzed in 202 consecutive patients in six different institutes in South Korea. Simple logistic regression analysis revealed that there was a significant correlation between the CRP level at discharge and recurrence of acute pyelonephritis ($p<0.001$). There was greater incidence of recurrence in patients with CRP >4mg/dL at discharge compared with patients with CRP <4 mg/dL ($p=0.045$). Patients with a maximal CRP of >15 mg/dL during admission, on the other hand, had longer hospitalization stays compared to patients with maximal CRP <15 mg/dL ($p<0.001$). The need for intravenous antibiotic therapy in these patients was greater ($p< 0.001$).[11] The clinical utility of knowing that patients with certain CRP levels have a higher recurrence rate or have prolonged hospitalization remains unclear.

Because of the limited availability, limited clinical utility, and the cost of these biomarkers, especially in resource limited settings, routine use of biomarkers in the management of AUP is not recommended.

4. **What are the indications for admission in patients with acute uncomplicated pyelonephritis?**
   - **The following are the indications for admission:**
     - **Inability to maintain oral hydration or take medications;**
     - **Concern about compliance;**
     - **Presence of possible complicating conditions;**
     - **Severe illness with high fever, severe pain, marked debility, and signs of sepsis**

   Strong recommendation, Moderate quality of evidence

Summary of Evidence

There are no new RCTs directly comparing inpatient vs. outpatient management. However, in the multicenter, double-blind, randomized non-inferiority study by Klausner et al. comparing a five-day course of levofloxacin 750 mg OD with a 10-day course of ciprofloxacin 500 mg

BID, most of the subjects were treated with oral antibiotics.[12]Patients with acute pyelonephritis, including ones with bacteremia, were treated in the community and demonstrated high microbiologic and clinical success rates with both levofloxacin and ciprofloxacin. This showed that patients with AUP can be safely treated as outpatients with antibiotics that have good oral bioavailability.

5. **What drugs can be used for empiric treatment of acute uncomplicated pyelonephritis?**
   - **Several regimens found to be effective in AUP are listed in Table 6. Primary drugs of choice and alternative drugs are presented. Efficacy, cost effectiveness, safety, tolerability, local susceptibility, and propensity for collateral damage were considered for the choice of the antibiotic.**

Table 6. Empiric treatment regimens for acute uncomplicated pyelonephritis

Antibiotic		Dose, Frequency and Duration
ORAL		
Primary	Ciprofloxacin	500 mg BID for 7-10 days
	Ciprofloxacin extended release	1000 mg OD for 7 days
	Levofloxacin	250 mg OD for 7-10 days
		750 mg OD for 5 days
	Ofloxacin	400 mg BID for 14 days
Alternative	Cefixime	400 mg OD for 14 days
	Ceftibuten	400 mg OD for 14 days
	Cefuroxime	500 mg BID for 14 days
	Co-amoxiclav (when GS shows gram-positive orgs)	625 mg TID for 14 days
PARENTERAL (given until patient is afebrile)		
Primary	Ceftriaxone	1-2 g q24 hours
	Ciprofloxacin	400 mg q12 hours
	Levofloxacin	250-750 mg q24 hours
	Ofloxacin	200-400 mg q 12 hours
	Amikacin	15 mg/kg BW q 24 hours
	Gentamicin +/- ampicillin	3-5 mg/kg BW q24 hours
Alternative	Ampicillin-sulbactam (when GS shows gram-positive orgs	1.5 g q6 hours
Reserved for MDROs	Ertapenem (if ESBL prevalence > 10%)	1 g q24 hours
	Piperacillin-tazobactam	2.25-4.5 g q6-8 hours

- **The aminopenicillins (ampicillin or amoxicillin) and first generation cephalosporins are NOT recommended because of the high prevalence of resistance and increased recurrence rates in patients given these beta-lactams.**
  Strong recommendation, Moderate quality of evidence

- **Because of high resistance rates to TMP-SMX, this drug is NOT recommended for empiric treatment but it can be used when the organism is found to be susceptible on urine culture and sensitivity.**
  Strong recommendation, Moderate quality of evidence

- **Quinolones are recommended as the first line treatment for acute uncomplicated pyelonephritis not requiring hospital admission.**
  Strong recommendation, High quality of evidence

- **In patients not requiring hospital admission, an initial single IV/IM dose of ceftriaxone or aminoglycoside may be considered followed by any of the oral antibiotics in Table 6.**
  Strong recommendation, Moderate quality of evidence

- **For patients with acute uncomplicated pyelonephritis requiring hospitalization, ceftriaxone, fluoroquinolones, or aminoglycosides are recommended as empiric first-line treatment.**
  Strong recommendation, Moderate quality of evidence

- **Intravenous antibiotics can be shifted to any of the listed oral antibiotics once the patient is afebrile and can tolerate oral drugs. The choice of continued antibiotic therapy should be guided by the urine culture and sensitivity results once available.**
  Strong recommendation, Moderate quality of evidence

- **For suspected enterococcal infection, ampicillin may be combined with an aminoglycoside.**
  Weak recommendation, Low quality of evidence

- **Carbapenems and piperacillin-tazobactam should be reserved for acute pyelonephritis caused by multi-drug resistant organisms that are susceptible to either drug.**
  Strong recommendation, Moderate quality of evidence

Summary of Evidence

There were no randomized clinical trials on treatment of AUP solely. All of the studies included males and complicated UTI.

Ciprofloxacin and extended-release Ciprofloxacin
One randomized, double-blind trial compared the efficacy of 1000 mg of extended-release ciprofloxacin (Cipro XR) once daily with ciprofloxacin 500 mg twice daily, each given for 7-14 days in patients with complicated UTI or acute pyelonephritis. The clinical and bacteriologic cure rates did not differ significantly. Therates of adverse events were similar.[13]

Levofloxacin vs. ciprofloxacin
A multicenter, double-blind, randomized, non-inferiority trial compared levofloxacin 750 mg PO/IV daily for five days with ciprofloxacin 400 mg IV and/or 500 mg PO BID for 10 days in patients with AUP and complicated UTI.[14] Subgroup analysis of the patients with AUP showed that microbiological eradication was achieved in 83% of the 94 levofloxacin-treated patients and 80% of 98 ciprofloxacin-treated patients in the modified intention-to-treat (MITT) population (N=192). In the microbiologically evaluable (ME) population (N=156), 92% of the 80 levofloxacin-treated subjects vs. 93% of the 76 ciprofloxacin-treated subjects achieved microbiologic eradication. Clinical success was achieved in 86% of levofloxacin treated subjects in the MITT population vs. 81% in the ciprofloxacin-treated subjects. In the ME population, clinical success was achieved in 92% of the levofloxacin treated vs. 90% ciprofloxacin-treated subjects.[12]

Ertapenem vs. ceftriaxone
A combined analysis of two randomized, double-blind, multicenter trials[15,16] comparing ertapenem 1 g once a day with ceftriaxone 1 g once a day followed by appropriate oral therapy after ≥3 days of parenteral therapyshowed that 98% of 121 ertapenem-treated and 99% of 102 ceftriaxone-treated microbiologically evaluable acute pyelonephritis patients achieved microbiological response at completion of parenteral therapy. At test of cure, 91% of 127ertapenem-treated patients vs. 93% of 106 ceftriaxone-treated patients had microbiologic response. Adverse events were also similar in both study groups.[17]

TMP-SMX resistance
E. coli is the most prevalent pathogen for uncomplicated UTI. Increasing TMP-SMX resistance makes this antibiotic a poor choice for AUP. In a recent surveillance study done in 11 university-affiliated emergency departments in the United States of America from 2001-2004, TMP-SMX resistance was found to be approximately 24%.[19]

Fluoroquinolone resistance
In the same study in university-affiliated emergency departments in the United States mentioned earlier, fluoroquinolone resistance

was<10%.[19] The IDSA guideline recommended an initial one-time intravenous dose of a long-acting parenteral antimicrobial, such as 1 g of ceftriaxone, or, a consolidated 24-h dose of an aminoglycoside, if the prevalence of fluoroquinolone resistance exceeds 10%.[20] This recommendation required an accurate knowledge of the prevalence of resistance in the studied population. The Antimicrobial Resistance Surveillance Program 2012 Data which consolidated the percent resistance of urinary *E. coli* from different regional hospitals in the Philippines reported ciprofloxacin resistance of 50.6%.[21] However, this may not be representative of the true prevalence of resistance in the community since the *E. coli* isolates were submitted from government hospitals and not limited to patients with uncomplicated UTI. A prospective cohort on acute uncomplicated UTI including acute pyelonephritis from a private tertiary hospital in Pasig City reported fluoroquinolone resistance prevalence of less than 10%.[22]

Given the lack of reliable epidemiologic data on the prevalence of fluoroquinolone resistance among uropathogens, knowledge of risk factors for fluoroquinolone resistance may aid in the selection of initial antibiotics for acute pyelonephritis. A nested case–control study within a cohort study of adults with febrile UTI seen in primary healthcare centers or emergency departments in the Netherlands found that recent hospitalization, urinary catheter, and fluoroquinolone use in the past six months were independent risk factors for fluoroquinolone resistance in community-onset febrile UTI caused by *E. coli*.[23]

Extended spectrum beta lactamase producing E. coli
In a retrospective cohort study in Korea, extended-spectrum beta-lactamase production in *E. coli* isolates was 0.8% in community-associated acute pyelonephritis vs. 15.9% in healthcare associated acute pyelonephritis ($p<0.001$).[24] In a prospective cohort of 239 patients with AUC and AUP from a tertiary hospital in Pasig City, *E. coli* was the most common uropathogen isolated comprising 76% of isolates with<2% rate of ESBL-production out of 181 *E. coli* isolates causing uncomplicated UTI.[22]

Multiple studies have sought to determine the prevalence rate of community-acquired UTIs caused by ESBL-producing organisms. A retrospective study in Switzerland found that among 123 patients with UTI due to ESBL-producing *E. coli*, 79 (64%) had community-acquired UTI and 44 (36%) had healthcare-associated UTI. Resistance rates for commonly used antibiotics in community-acquired isolates were as follows: amoxicillin-clavulanic acid, 69.6% resistance; ciprofloxacin, 84.8% resistance; norfloxacin, 83.9% resistance; trimethoprim-sulfamethoxazole, 75.9% resistance; nitrofurantoin,15% resistance;

and fosfomycin, 0% resistance.[25] It should be noted that these isolates have high resistance to commonly used antimicrobials except for nitrofurantoin and fosfomycin.

In a retrospective study of 58 patients with bacteremic UTIs, multiple logistic regression analysis showed that male gender, OR 9.2 (95% CI 1.7, 50.6), and healthcare facility residency, OR 15.5 (95% CI 2.4, 98.9) were independent risk factors for ESBL-producing infections.[26] Among 2,312 patients with UTI in Korea, 13% were infected with ESBL-producing bacteria, and the risk of such an infection was twice higher in inpatient UTI. The multivariate analysis showed that the following were clinically significant risk factors for ESBL-producing uropathogens: inpatient origin, OR 1.7 (95% CI 1.3, 2.2); previous hospitalization, OR 2.5 (95%CI 1.8, 3.5); female sex, OR 1.4 (95% CI 1.1, 2.0); foley catheterization, OR 2.4 (95% CI 1.6, 3.6), exposure to cefaclor, OR 1.7 (95% CI 1.1, 2.5); and exposure to cefminox, OR 1.5 (95% CI 1.1, 2.2).[27]

Another prospective study showed an ESBL positivity rate of 6.3% (17/269) in uncomplicated UTIs and 17.4% (34/195) in complicated UTIs (p>0.001). Multivariate analysis showed that the following were associated with ESBL positive *E. coli*: (1) having more than three urinary tract infection episodes in the preceding year, OR 3.8 (95% CI 1.8, 8.1), (2) use of a beta-lactam antibiotic in the preceding three months, OR 4.6 (95% CI 2.0, 0.7), and(3) prostatic disease, OR 9.6 (95% CI 2.1, 44.8).[28] On the other hand, another case control study done in Spainshowed that among different factors studied, only previous exposure to second-generation cephalosporins was strongly associated with ESBL-producing *E. coli* after multivariate analysis, OR 21.4 (95% CI 5.4, 85.2).[29] Patients presenting with acute pyelonephritis with risk factors for ESBL-producing organisms may benefit from early initiation of therapy effective for these organisms.

6. **What is the effective duration of treatment for AUP?**
   - **The recommended duration of treatment is 14 days. Selected fluoroquinolones can be given for 7-10 days.**
     Strong recommendation, High quality of evidence

Summary of Evidence

The standard recommended duration of treatment for AUP is 14 days. However, in an era of increasing antibiotic resistance, short courses of antibiotics are preferred.

The FUTIRST trial by van Nieuwkoop *et al*. is an on-going randomized, placebo-controlled double-blind multicenter non-inferiority trial on

400 patients in the Netherlands with community-acquired febrile UTI. It compared seven days of ciprofloxacin (or seven days of empirical β-lactam ± gentamicin IV with early switch to oral ciprofloxacin) followed by seven days of placebo (short treatment arm) vs. seven days of ciprofloxacin (or seven days of empirical β-lactam ± gentamicin IV with early switch to oral ciprofloxacin) followed by seven days of blinded ciprofloxacin, which represented the standard 14-day treatment arm.[30]

In the study by Peterson et al., levofloxacin 750 mg given for five days had similar efficacy rates to ciprofloxacin 400 IV/500 mg PO BID given for 10 days.[14]

A recent prospective, non-inferiority trial comparing the efficacy of ciprofloxacin for 7 days vs. 14 days in women with community-acquired AUP concluded that acute pyelonephritis in women, including older women, and those with more severe infection, can be treated successfully and safely with oral ciprofloxacin for seven days.[31]

Thus, in a stable patient diagnosed with AUP, without any contraindication, a seven-day duration of treatment with selected quinolones can be used.

7. **Who will require work up for urologic abnormalities?**
   - **Routine urologic evaluation and routine use of imaging procedures are NOT recommended.**
     Strong recommendation, Moderate quality of evidence
   - **Consider early radiologic evaluation if the patient has a history of urolithiasis, urine pH ≥ 7.0 or renal insufficiency.**
     Strong recommendation, Moderate quality of evidence
   - **Consider radiologic evaluation if the patient remains febrile within 72 hours of treatment or if symptoms recur to rule out the presence of nephrolithiasis, urinary tract obstruction, renal or perinephric abscesses, or other complications of pyelonephritis.**
     Weak recommendation, Low quality of evidence
   - **Obtain urologic consultation if workup shows abnormalities.**
     Weak recommendation, Low quality of evidence

Summary of Evidence

Recommendations regarding urologic evaluation have been based mostly on expert opinion and small single-center observational studies. A prospective observational study on adult patients with febrile UTI in eight emergency departments in the Netherlands sought to develop a "clinical rule" to help ascertain the need for radiologic imaging. In the multivariate analysis, the following predictors were significantly associated with the finding of a clinically relevant urologic disorder: history of urolithiasis, urine pH ≥7.0, and renal insufficiency (glomerular filtration rate based on modification of diet in renal disease formula (MDRD) ≤40 mL/min/1.73m^3). The prediction rule included these three variables with one point assigned for each. In the derivation cohort (n=336) with a cut-off point of ≥1 point, the negative predictive value (NPV) for any clinical relevant radiologic finding was 93%; positive predictive value (PPV) was 24%; sensitivity was 72%; and the specificity was 62%. In the validation cohort (n=131), the NPV was 89% and PPV was 20% for clinically relevant radiologic findings. They estimated a relative reduction of 40% in radiologic imaging if the prediction rule was used. The median duration of fever was two days in this study. Duration of fever ≥3 days was not associated with any clinically relevant radiologic finding, univariate OR 1.17 (95% CI 0.61, 2.23).[32]

8. **Is a follow-up urine culture recommended?**
   - **In patients who are clinically responding to therapy (usually apparent in <72 hours after initiation of treatment), a follow-up urine culture is NOT necessary.**
     Weak recommendation, Low quality of evidence

   - **Routine post-treatment cultures in patients who are clinically improved are also not recommended.**
     Weak recommendation, Low quality of evidence

   - **In women whose symptoms do not improve during therapy and in those whose symptoms recur after treatment, a repeat urine culture and sensitivity test should be performed.**
     Weak recommendation, Low quality of evidence

Summary of Evidence

The recommendations were based on expert opinion consensus. We did not find any studies demonstrating the clinical utility of follow-up urine cultures during treatment and post-treatment of patients who are responding to therapy. In patients not improving, it is necessary to repeat the urine culture and sensitivity to rule out antibiotic resistance.

9. **What is the recommended management for patients whose symptoms recur?**
   - **Recurrence of symptoms requires antibiotic treatment based on urine culture and sensitivity test results, in addition to assessing for underlying genitourologic abnormality.**
     Weak recommendation, Low quality of evidence

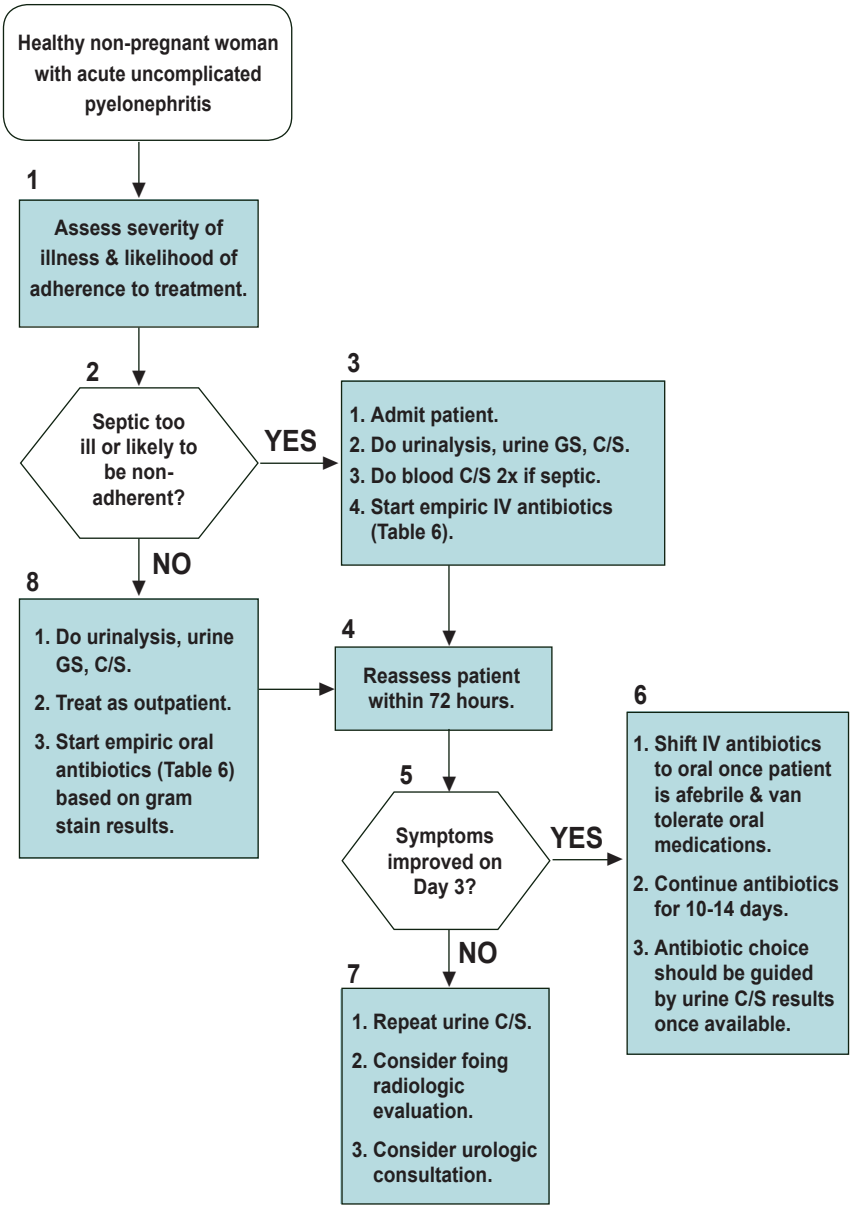
   - **The duration of re-treatment in the absence of a urologic abnormality is two weeks.**
     Weak recommendation, Low quality of evidence

   - **For patients whose symptoms recur and whose culture shows the same organism as the initial infecting organism, a four- to six-week regimen is recommended.**
     Weak recommendation, Low quality of evidence

Summary of Evidence

We did not find any randomized controlled trials that determined the optimum duration of treatment for women with recurrent pyelonephritis.

Algorithm 3. Treatment of acute uncomplicated pyelonephritis in non-pregnant women



References

1. Rubin RH, Beam Jr TR, Stamm WE. An approach to evaluating antibacterial agents in the treatment of urinary tract infection. Clin Infect Dis 1992; 14(Suppl 2):S246–51; discussion S253–4.
2. Roberts F. Quantitative urine culture in patients with urinary tract infection and bacteremia. Am J Clin Pathol 1986; 85:616–8.
3. Scholes D, Hooton TM, Roberts PL, Gupta K, Stapleton AE, Stamm WE. Risk Factors Associated with Acute Pyelonephritis in Healthy Women. Ann Intern Med 2005; 142:20–7.
4. Task Force on Urinary Tract Infections Philippine Practice Guideline Group Infectious Disease. The Philippine Clinical Practice Guidelines on the Diagnosisand Management of Urinary Tract Infections in Adults Update 2004. Quezon City, Philippines: PPGG-ID Philippine Society for Microbiology and Infectious Diseases 2004.
5. Kim KS, Kim K, Jo YH, Kim TY, Lee JH, Lee SJ, et al. A simple model to predict bacteremia in women with acute pyelonephritis. The Journal of infection [Internet]. Elsevier Ltd 2011 Aug [cited 2013 Oct 14]; 63(2):124–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21722666
6. Van Nieuwkoop C, Bonten TN, Wout JWV, Becker MJ, Groeneveld GH, Jansen CL, et al. Risk factors for bacteremia with uropathogen not cultured from urine in adults with febrile urinary tract infection. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America [Internet] 2010 Jun 1 [cited 2013 Oct 14];50(11):e69–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20420504
7. Velasco M, Martínez JA, Moreno-Martínez A, Horcajada JP, Ruiz J, Barranco M, et al. Blood cultures for women with uncomplicated acute pyelonephritis: are they necessary? Clinical infectious diseases : an official publication of the Infectious Diseases Society of America [Internet] 2003 Oct 15; 37(8):1127–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14523779
8. Claessens Y-E, Schmidt J, Batard E, Grabar S, Jegou D, Hausfater P, et al. Can C-reactive protein, procalcitonin and mid-regional pro-atrial natriuretic peptide measurements guide choice of in-patient or out-patient care in acute pyelonephritis? Biomarkers In Sepsis (BIS) multicentre study. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases [Internet] 2010 Jun; 16(6):753–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19747215
9. Lemiale V, Renaud B, Moutereau S, N'Gako A, Salloum M, Calmettes MJ, et al. A single procalcitonin level does not predict adverse outcomes of women with pyelonephritis. European urology [Internet] 2007 May [cited 2013 Oct 14]; 51(5):1394–401. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17207908
10. Van Nieuwkoop C, Bonten TN, van't Wout JW, Kuijper EJ, Groeneveld GH, Becker MJ, et al. Procalcitonin reflects bacteremia and bacterial load in urosepsis syndrome: a prospective observational study. Critical care (London, England) [Internet]. BioMed Central Ltd 2010 Jan [cited 2013 Oct 14];14(6):R206. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3220019&tool=pmcentrez&rendertype=abstract
11. Yang WJ, Cho IR, Seong DH, Song YS, Lee DH, Song KH, et al. Clinical implication of serum C-reactive protein in patients with uncomplicated acute pyelonephritis as marker of prolonged hospitalization and recurrence. Urology [Internet]. Elsevier Inc. Elsevier Inc 2009 Jan [cited 2013 Oct 14]; 73(1):19–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18930516
12. Klausner H a, Brown P, Peterson J, Kaul S, Khashab M, Fisher AC, et al. A trial of levofloxacin 750 mg once daily for 5 days versus ciprofloxacin 400 mg and/or 500 mg twice daily for 10 days in the treatment of acute pyelonephritis. Current medical research and opinion [Internet] 2007 Nov [cited 2013 Oct 14]; 23(11):2637–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17880755

13. Talan D a, Klimberg IW, Nicolle LE, Song J, Kowalsky SF, Church D a. Once daily, extended release ciprofloxacin for complicated urinary tract infections and acute uncomplicated pyelonephritis. The Journal of urology [Internet] 2004 Feb [cited 2013 Oct 14]; 171(2 Pt 1):734–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14713799
14. Peterson J, Kaul S, Khashab M, Fisher AC, Kahn JB. A double-blind, randomized comparison of levofloxacin 750 mg once-daily for five days with ciprofloxacin 400/500 mg twice-daily for 10 days for the treatment of complicated urinary tract infections and acute pyelonephritis. Urology [Internet] 2008 Jan [cited 2013 Oct 14]; 71(1):17–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18242357
15. Jimenez-cruz F, Jasovich A, Cajigas J, Jiang QI, Imbeault D, Woods GL, et al. A Prospective, Multicenter, Randomized, Double-Blind Study Comparing Ertapenem and Ceftriaxone followed Bby Appropriate Oral Therapy for Complicated Urinary Tract Infections in Adults. Urology 2002; 60(16-22).
16. Tomera KM, Burdmann EA, Reyna OGP, Jiang Q, Wimmer WM, Woods GL, et al. Ertapenem versus Ceftriaxone Followed by Appropriate Oral Therapy for Treatment of Complicated Urinary Tract Infections in Adults : Results of a Prospective , Randomized , Double-Blind Multicenter Study. Antimicrobial Agents and Chemotherapy 2002; 46(9):2895–900.
17. Wells WG, Woods GL, Jiang Q, Gesser RM. Treatment of complicated urinary tract infection in adults: combined analysis of two randomized, double-blind, multicentre trials comparing ertapenem and ceftriaxone followed by appropriate oral therapy. The Journal of antimicrobial chemotherapy [Internet] 2004 Jun [cited 2013 Sep 16]; 53 Suppl 2:ii67–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15150185
18. Naber KG, Llorens L, Kaniga K, Kotey P, Hedrich D, Redman R. Intravenous doripenem at 500 milligrams versus levofloxacin at 250 milligrams, with an option to switch to oral therapy, for treatment of complicated lower urinary tract infection and pyelonephritis. Antimicrobial agents and chemotherapy [Internet] 2009 Sep [cited 2013 Sep 22]; 53(9):3782–92. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2737884&tool=pmcentrez&rendertype=abstract
19. Talan D a, Krishnadasan A, Abrahamian FM, Stamm WE, Moran GJ. Prevalence and risk factor analysis of trimethoprim-sulfamethoxazole- and fluoroquinolone-resistant Escherichia coli infection among emergency department patients with pyelonephritis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America [Internet] 2008 Nov 1 [cited 2013 Oct 14]; 47(9):1150–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18808361
20. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011 Mar 1; 52(5):e103–20.
21. Antimicrobial Resistance Surveillance Reference Laboratory. Antimicrobial Resistance Surveillance Program 2012 Annual Report 2012, pp. 33–7.
22. Gangcuangco LM, Alejandria M, Alfaraz L, Ata RM, Gamponia K, Henson KE, et al. Prevalence and risk factors for trimethoprim-sulfamethoxazole-resistant E. coli in uncomplicated urinary tract infections in a developing country. Poster session presented at: 51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). Chicago, Illinois, USA 2011.
23. Van der Starre WE, Van Nieuwkoop C, Paltansing S, van't Wout JW, Groeneveld GH, Becker MJ, et al. Risk factors for fluoroquinolone-resistant Escherichia coli in adults with community-onset febrile urinary tract infection. The Journal of antimicrobial chemotherapy [Internet] 2011 Mar [cited 2013 Oct 10]; 66(3):650–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21123286
24. Ha YE, Kang C-I, Joo E-J, Park SY, Kang SJ, Wi YM, et al. Clinical implications of healthcare-associated infection in patients with community-onset acute pyelonephritis. Scandinavian journal of infectious diseases [Internet] 2011 Aug

[cited 2013 Oct 14]; 43(8):587–95. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21453206
25. Meier S, Weber R, Zbinden R, Ruef C, Hasse B. Extended-spectrum β-lactamase-producing Gram-negative pathogens in community-acquired urinary tract infections: an increasing challenge for antimicrobial therapy. Infection [Internet] 2011 Aug [cited 2013 Sep 21]; 39(4):333–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21706226
26. Yang Y-S, Ku C-H, Lin J-C, Shang S-T, Chiu C-H, Yeh K-M, et al. Impact of Extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella pneumoniae on the outcome of community-onset bacteremic urinary tract infections. Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi [Internet]. Taiwan Society of Microbiology 2010 Jun [cited 2013 Oct 14]; 43(3):194–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21291846
27. Lee DS, Lee CB, Lee S-J. Prevalence and risk factors for extended spectrum Beta-lactamase-producing uropathogens in patients with urinary tract infection. Korean journal of urology [Internet] 2010 Jul [cited 2013 Oct 14];51(7):492–7. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2907500&tool=pmcentrez&rendertype=abstract
28. Azap OK, Arslan H, Serefhanoğlu K, Colakoğlu S, Erdoğan H, Timurkaynak F, et al. Risk factors for extended-spectrum beta-lactamase positivity in uropathogenic Escherichia coli isolated from community-acquired urinary tract infections. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases [Internet] 2010 Feb; 16(2):147–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19689464
29. Calbo E, Romaní V, Xercavins M, Gómez L, Vidal CG, Quintana S, et al. Risk factors for community-onset urinary tract infections due to Escherichia coli harbouring extended-spectrum beta-lactamases. The Journal of antimicrobial chemotherapy [Internet] 2006 Apr [cited 2013 Oct 14]; 57(4):780–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16492721
30. Van Nieuwkoop C, van't Wout JW, Assendelft WJ, Elzevier HW, Leyten EM, Koster T, et al. Treatment duration of febrile urinary tract infection (FUTIRST trial): a randomized placebo-controlled multicenter trial comparing short (7 days) antibiotic treatment with conventional treatment (14 days) [Study Protocol]. BMC Infect Dis [Internet] 2009; 9:131. Available from: http://www.biomedcentral.com/1471-2334/9/131
31. Sandberg T, Skoog G, Hermansson AB, Kahlmeter G, Kuylenstierna N, Lannergård A, et al. Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised, open-label and double-blind, placebo-controlled, non-inferiority trial. The Lancet [Internet] 2012. Available from: http://dx.doi.org/10.1016/S0140-6736(12)60608-4
32. Van Nieuwkoop C, Hoppe BPC, Bonten TN, Van't Wout JW, Aarts NJM, Mertens BJ, et al. Predicting the need for radiologic imaging in adults with febrile urinary tract infection. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America [Internet] 2010 Dec 1 [cited 2013 Oct 14]; 51(11):1266–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21034195

URINARY TRACT INFECTIONS IN PREGNANCY

Asymptomatic Bacteriuria
Acute Cystitis
Acute Uncomplicated Pyelonephritis

URINARY TRACT INFECTIONS IN PREGNANCY

ASYMPTOMATIC BACTERIURIA IN PREGNANCY

Section Summary

Definition of asymptomatic bacteriuria (ASB)

- ASB in pregnancy is the presence of >100,000 CFU/mL of the same uropathogen in two consecutive midstream urine specimens or ≥100 CFU/mL of a single uropathogen in one catheterized urine specimen. Symptoms attributable to urinary infection should be absent.

  Strong recommendation, High quality of evidence

- In settings where obtaining two consecutive urine cultures is not feasible, or is difficult, one urine culture is an acceptable alternative for the diagnosis of ASB in pregnancy.

  Weak recommendation, Low quality of evidence

Indication for screening

- Screen ALL pregnant women for asymptomatic bacteriuriaonce, between the 9th to 17th week age of gestation (AOG), preferably on the 16th week AOG.

  Strong recommendation, High quality of evidence

Diagnostic test

- A standard urine culture of clean-catch midstream urine is the test of choice in screening for asymptomatic bacteriuria.

  Strong recommendation, High quality of evidence

- Urinalysis is not recommended as an initial screening test.

  Strong recommendation, high quality of evidence

- Urine dipsticks for leukocyte esterase and/or nitrite tests are not recommended for screening for asymptomatic bacteriuria .

  Strong recommendation, High quality of evidence

- In the absence of urine culture, urine gram stain of uncentrifuged urine (more than one organism per oil immersion field) is recommended for screening for asymptomatic bacteriuria in pregnancy.

  Strong recommendation, Moderate quality of evidence

- Dipslide culture technique may be used as an alternative to urine culture in settings where it is available.

  Strong recommendation, High quality of evidence

Antibiotic treatment

- Antibiotic treatment for asymptomatic bacteriuria is indicated to reduce the risk of acute cystitis and pyelonephritis in pregnancy as well as the risk of low birth weight neonates and preterm infants.

  Strong recommendation, High quality of evidence

- Treatment with antibiotics should be initiated upon diagnosis of ASB in pregnancy. Among the antibiotics that can be used are nitrofurantoin (not for near term), co-amoxiclav, cephalexin, cefuroxime, fosfomycin, and TMP-SMX (not on the first and third trimester) depending on the sensitivity results of the urine isolate.

  Strong recommendation, High quality of evidence

Duration of treatment

- Duration of treatment will depend on the antibiotics that will be used, but short-course (seven days) treatment is preferred over single-dose regimens.

  Strong recommendation, High quality of evidence

Follow-up laboratory tests

- A follow-up urine culture should be done one week after completing the course of treatment.

  Weak recommendation, Low quality of evidence

- Monitoring should be done every trimester until delivery.

  Weak recommendation, Low quality of evidence

Recommendations and Summary of evidence

1. **When is asymptomatic bacteriuria in pregnancy diagnosed?**
   - **ASB in pregnancy is the presence of >100,000 CFU/mL of the same uropathogen in two consecutive midstream urine specimens or ≥100 CFU/mL of a single uropathogen in one catheterized urine specimen. Symptoms attributable to urinary infection should be absent.**

     Strong recommendation, High quality of evidence

   - **In settings where obtaining two consecutive urine cultures is not feasible, or is difficult, one urine culture is an acceptable alternative for the diagnosis of ASB in pregnancy.**

     Weak recommendation, Low quality of evidence

Summary of Evidence

The task force found no new evidence that would merit a change in the recommendations from the previous guideline. In the 2004 update of the Philippine Clinical Practice Guidelines on the Diagnosis and Management of Urinary Tract Infections in Adults, bacteriuria was defined as bacterial counts of ≥100,000 CFU/mL in two consecutive urine specimens based on Rubin et al.[1] Nicolle et al. in 20052cited Kass in 1957 which noted that in >95% of cases in certain asymptomatic groups, a bacterial count of 100,000 CFU/mL in a midstream clean catch urine specimen can be confirmed by a concomitant count in a catheterized specimen. On the other hand, lower bacterial counts were not usually confirmed by the catheterized specimen.[2] A second urine culture for asymptomatic bacteriuria was done to discriminate between true bacteriuria and contamination. In the absence of symptoms, Kass in 1956 showed that the quantitative threshold of >100,000 CFU/mL from midstream urine or catheterized urine was useful to distinguish true bacteriuria from contamination.[3] Other investigators have validated this threshold.[4,5] Because these individuals were asymptomatic, two consecutive cultures yielding the same organism/s from midstream urine specimens were needed for the diagnosis. However, in a brief report evaluating the molecular identity of 32 *E. coli* isolates obtained in two consecutive urine cultures from 16 patients with asymptomatic bacteriuria, Geerlingset al. found different E. coli isolates in seven of them.[6] This implied that nearly half (44%) of the patients who had been previously classified as having asymptomatic bacteriuria were re-infected with a different strain. Thus, obtaining two consecutive urine cultures to accurately diagnose asymptomatic bacteriuria in pregnant women may not necessarily identify the etiologic agent.

2. **Do all pregnant women have to be screened for asymptomatic bacteriuria?**
   - **Screen ALL pregnant women for asymptomatic bacteriuria once, between the 9th to 17th week AOG, preferably on the 16th week AOG.**
     Strong recommendation, High quality of evidence

Summary of Evidence

The Task Force found no new evidence that would merit a change in the recommendations from the previous guideline.

Prevalence of asymptomatic bacteriuria

In a prevalence study conducted among Filipino pregnant women at a tertiary-care government hospital in Manila, the overall prevalence rate was 1.9% in women with two consecutive urine cultures. However, because only 54% of the women in this study had second cultures

done, a sensitivity analysis was done. Asymptomatic bacteriuria was defined as two urine cultures showing significant bacteriuria or one result showing significant bacteriuria in the absence of a follow-up culture. In this second scenario, the overall prevalence rate was 4.3%. The most common isolates from Filipino pregnant patients with definite asymptomatic bacteriuria were Escherichia coli (63%), *Klebsiella pneumonia* (12%), Enterococcus (12%), *Staphylococcus saprophyticus* (7%), *Staphylococcus aureus* (4%), and *Klebsiella ozanae* (2%).[7]

In the same study, the significant risk factors associated with asymptomatic bacteriuria in pregnant women among those who had two urine cultures were: age of gestation <12 weeks AOG, OR 3.2 (95% CI 2.55, 3.89), and hemoglobin levels <100mg/dL, OR 2.75 (95% CI 1.95, 3.54). If women with one urine culture only were included, the significant risk factors on logistic regression analysis were: age of gestation <12 weeks AOG, OR 2.35 (95% CI 2.15, 2.55), and history of UTI, OR 1.57 (95% CI 1.01, 2.44).[7] Foreign data showed that asymptomatic bacteriuria occurs in 3-10% of all pregnant women and if left untreated can affect both maternal and fetal outcome. The prevalence increases among high-risk pregnant women, such as diabetics (12.5%) and those with a previous history of UTI (18.5%).[8]

Benefits

The risk of acquiring bacteriuria increased with the duration of pregnancy, highest between the 9th and 17th weeks AOG. The 16th gestational week appeared to be the optimal time to obtain a single screening test for bacteriuria because treatment given at this time would provide the greatest number of bacteriuria-free gestational weeks.[9,10] The two most important complications of untreated asymptomatic bacteriuriawere acute cystitis and acute pyelonephritis. Fetal complications such as low birth weight (LBW) and preterm delivery have been associated with asymptomatic bacteriuria.

3. **What is the optimal screening test for asymptomatic bacteriuria in pregnancy?**
   - **A standard urine culture of clean-catch midstream urine is the test of choice in screening for asymptomatic bacteriuria.**
     Strong recommendation, High quality of evidence
   - **Urinalysis is not recommended as an initial screening test.**
     Strong recommendation, high quality of evidence
   - **Urine dipsticks for leukocyte esterase and/or nitrite tests are not recommended for screening for asymptomatic bacteriuria.**
     Strong recommendation, High quality of evidence

- **In the absence of urine culture, urine gram stain of uncentrifuged urine (more than one organism per oil immersion field) is recommended for screening for asymptomatic bacteriuria in pregnancy.**

Strong recommendation, Moderate quality of evidence

Summary of Evidence

Urine culture is still the test of choice for detecting asymptomatic bacteriuria in pregnant women. No other currently available screening tests have a high enough sensitivity and negative predictive value to replace the urine culture.

In a recent descriptive, cross-sectional study conducted in Bangladesh, Ullahet al. in 2012 investigated the validity of five screening tests in predicting asymptomaticbacteriuria in pregnancy: (a) bacterial counts per oil immersion field in the gram stain of urine, (b) leukocyte esterase dipstick test, (c) nitrite dipstick test,(d) combined Leukocyte esterase and nitrite dipstick test, and (e) microscopic leukocyte count per high power field (urinalysis) compared to the gold standard, urine culture. The study included 600 pregnant women and identified 24 cases of asymptomatic bacteriuria. The most common isolated organism was *Staphylococcus saprophyticus* (41.6%), followed by *E. coli*, *Pseudomonas spp.*, and *Klebsiella sp.*[11] Of the five screening tests, bacterial count per oil immersion field of urine gram stain had the highest sensitivity (92%) and specificity (97%), using a cut-off of ≥1 organism/OIF. The other tests showed lower sensitivity and specificity values. A positive leukocyte esterase dipstick test (+ve) was found to have a relatively high sensitivity of 87.5% but poor specificity of 39.2%indicative of a high false positive rate. Using a cut-off of +++ve increased the specificity to 79.5% but decreased the sensitivity to 33.3%. The nitrite dipstick test had a low sensitivity of 29.2% and a specificity of 99.7%. The low sensitivity of the nitrite dipstick test may be due to its inability to detect non-nitrate reducing organisms. In this study, the organism most commonly isolated was *S. saprophyticus* which is not nitrate-reducing. If the criterion was having either of the two dipstick tests as positive, combining the leukocyte esterase and the nitrite dipstick tests yielded 91.7% sensitivity and 39.2% specificity. However, if the criterion is having both dipstick tests as positive, then the sensitivity would only be 25%, and the specificity 99.7%. The lower ability of the combined positive test to identify asymptomatic bacteriuric pregnant women was attributed to the inability of nitrite dipstick tests to recognize non-nitrate reducing organisms. They, therefore, suggested that dipstick tests may not be suitable screening tests for populations where non-nitrate reducing organisms were common or where there was a high chance of contamination. For urinalysis on the other hand, leukocyte counts ≥8/HPF had a sensitivity of 58.3% and a specificity of 80.7%.

The authors concluded that in areas where manpower costs were low, such as Bangladesh, India, Pakistan, and Nepal, gram stain may be a promising, cost-effective screening test for asymptomatic bacteriuria.[11]

Another study done in Argentina also does not support the use of dipsticks (leukocyte esterase and nitrite) for screening of asymptomatic bacteriuria in pregnant women. In this study, they also compared chemical dipsticks with the urine culture as gold standard. They defined a positive dipstick result as having either a positive leukocyte esterase or a positive nitrate tests or having both tests as positive. They found the sensitivity of the dipstick test to be 53% (95% CI 48, 58) and the specificity 92% (95% CI 91, 93).[12]

Table 7. Computed Likelihood Ratios for the different screening tests compared with urine culture

Screening Test	Positive Likelihood Ratio	Negative Likelihood Ratio	Post-test Probability Given a Positive Test	Post-test Probability Given a Negative Test	Sensitivity (%)*	Specificity (%)*
Leukocyte esterase (LE)						
LE + ve	1.44	0.32	13.75	3.4	87.5	39.2
LE ++ ve	1.37	0.79	10	7.9	50.0	63.5
LE +++ ve	1.62	0.84	15.12	8.4	33.3	79.5
Nitrite (N)						
N	97.3	0.71	91.45	7.24	29.2	99.7
Combined LE (+ve) and N						
LE activity or/and nitrite present	1.51	0.21	14.24	2.26	91.7	39.2
LE activity and nitrite present	83.3	0.75	90.16	7.6	25.0	99.7
Leukocytes count						
≥ 6/HPF	1.78	0.58	16.37	5.99	62.5	64.9
≥ 8/HPF	3.02	0.52	24.93	5.41	58.3	80.7
≥10/HPF	2.46	0.77	21.29	7.8	33.3	86.5
Bacteria count by Gram staining						
At least 1/OIF	32.75	0.085	78.27	0 .92	91.7	97.2
At least 2/OIF	95.28	0.33	91.28	3.5	66.7	99.3
At least 3/OIF	47.57	0.67	83.95	6.86	33.3	99.3

*Sensitivity and specificity values were based on the study by Ullah 2012[11]

- **Dipslide culture technique may be used as an alternative to urine culture in settings where it is available.**
  Strong recommendation, High quality of evidence

Summary of Evidence

An ancillary study done in Argentina assessed the accuracy of dipslide test and chemical dipsticks (nitrites, leukocyte esterase, or both) in screening for asymptomatic bacteriuria in pregnancy. They compared these two modalities with the traditional urine culture as the gold standard. In this study, dipslide had a sensitivity of 98% (95% CI 96, 99) and a specificity of 99.6% (95% CI 99.3, 99.8). The positive likelihood ratio of dipslide was 225 (95% CI 113, 449), and the negative likelihood ratio was 0.02 (95% CI 0.01, 0.05). Given a pretest probability of 15.2%, a positive dipslide increased the probability of having bacteriuria to 98%, and a negative dipslide decreased said probability to less than 1%. The authors concluded that dipslide devices may be considered as an alternative to traditional urine cultures.[12]

4. **Is treatment indicated for asymptomatic bacteriuria in pregnancy?**
   - **Antibiotic treatment for asymptomatic bacteriuria is indicated to reduce the risk of acute cystitis and pyelonephritis in pregnancy as well as the risk of low birth weight neonates and preterm infants**.
     Strong recommendation, High quality of evidence

Summary of Evidence

An updated Cochrane systematic review of 14 studies comparing antibiotic treatment to placebo or no treatment showed that antibiotic treatment was effective in clearing bacteriuria in asymptomatic pregnant women,RR 0.25(95% CI 0.14, 0.48). Bacteriuria persisted in 66% of women who were not given antibiotic treatment. The direction of the effect seen in the different trials was consistent even if there was a significant statistical heterogeneity among the trials. This heterogeneity may be explained by differences in study design and in the definition of variables.[13]

Aside from clearing bacteriuria, antibiotic treatment was also associated with a reduction in the incidence of pyelonephritis, RR 0.23 (95% CI 0.13, 0.41). In the untreated group, the over-all incidence of pyelonephritis was 21% (ranging from 2.5% to 36%). The number needed to treat (NNT) to prevent one episode of pyelonephritis in pregnant women with asymptomatic bacteriuria was 7 (95% CI 6, 8). A 75% reduction in the incidence of pyelonephritis was expected from the treatment of asymptomatic bacteriuria.[13]

Antibiotic treatment was also associated with a reduction in the incidence of low birth weight babies, RR 0.66 (95% CI 0.49, 0.89). However, no difference was seen in terms of the incidence of preterm deliveries. Antibiotic treatment was not associated with reduction the incidence of preterm deliveries (defined as gestational age of less than 38 weeks), RR 0.37 (95% CI 0.10, 1.36) based on the three studies that reported this outcome. In one of these three studies, the study only enrolled women with group B streptococcal bacteriuria.[13]

This systematic review described above has a few limitations. There were concerns in terms of the quality of the studies included and some of the research methods were not completely stated. Most of the studies also date from the 1960's and 1970's (except for three), and some of the antibiotics used in these studies were no longer available. Also, tetracycline, a drug used in one of the studies, was contraindicated in pregnancy. However, the results seen in this review (clearing of bacteriuria, reduction of pyelonephritis, and reduction of incidence of low birth weight babies) were still applicable to other antibiotics that were active against urinary pathogens and were safe to use in pregnancy.[13]

5. **Which antibiotics are effective for asymptomatic bacteriuria in pregnancy?**
   - **Treatment with antibiotics should be initiated upon diagnosis of ASB in pregnancy. Among the antibiotics that can be used are nitrofurantoin (not for near term), co-amoxiclav, cephalexin, cefuroxime, fosfomycin, and trimethoprim-sulfamethoxazole (not on the first and third trimester) depending on the sensitivity results of the urine isolate.**
     Strong recommendation, High quality of evidence

Summary of Evidence

Comparing different single-drug regimens used for asymptomatic bacteriuria in pregnancy, a Cochrane Review by Guinto et al. in 2010concluded that no one specific regimen can be recommended over the otherseven though antibiotic treatment was effective in clearing bacteriuria. Increasing antibiotic resistance, however, complicated the choice of empiric regimens and was likely to become an increasing problem. Five studies were involved in the said review. Two of these studies compared cephalosporins (cefuroxime and cephalexin) with antibiotics in pregnancy category B which have less association with *E. coli* resistant strains (fosfomycin trometamol and pivampicillin/pivmecillinam). No significant difference in efficacy was noted between the cephalosporins and fosfomycin or pivampicillin/pivmecillinam. Another study compared two different beta-lactam

antibiotics, ampicillin and pivmecillinam. Both of these drugs were Category B drugs. Antibiotic resistance to ampicillin was increasing while pivmecillinam still had good activity against *E. coli*. There was no significant difference in the effect of either drug on persistent infection or recurrent infection. However, pivmecillinam was associated with a higher incidence of vomiting in pregnant women given the drug. Another study which was part of the said Cochrane Review compared nitrofurantoin given for one day vs. nitrofurantoin given for seven days. Nitrofurantoin was used because there was less reported antibacterial resistance related to its use compared with other antibiotics like penicillins or TMP-SMX. There was no significant difference in symptomatic infections, incidence of preterm deliveries, and tolerance of subjects. However, more treatment failures were seen in patients treated for only one day, suggesting that the longer treatment duration (seven days) for nitrofurantoin was preferable.[14]

6. **What is the duration of treatment for asymptomatic bacteriuria in pregnancy?**
   - **Duration of treatment will depend on the antibiotics that will be used, but, short-course (seven days) treatment is preferred over single-dose regimens.**
     Strong recommendation, High quality of evidence

Summary of Evidence

The authors of a Cochrane systematic review of 13 RCTs comparing a single dose regimen for asymptomatic bacteriuria in pregnancy with a short duration regimen (four to seven days) concluded that the four- to seven-day treatment regimen may be preferable over the one-day treatment regimen. In the most recent update of this systematic review published in 2010, three new trials were included. One study compared a single dose of fosfomycin trometamol with a five day course of cefuroxime axetyl (N =90). The outcomes measured were cure rates and side effects. The second study compared a single dose of fosfomycin with a seven-day course of amoxicillin-clavulanate (N= 131). They found no difference between the two groups in terms of cure, recurrences, and persistence. The third study included in this review compared two different dosing regimens of nitrofurantoin (N=778; dosing regimens: one day vs. seven day- regimen). It showed a significantly higher cure rate in women given the seven-day regimen. Much of the data for the meta-analysis came from this study. The authors concluded that longer duration of treatment may be more effective than single dose, however, longer regimens may present with concerns on compliance.[15]

Table 8. Antibiotics that can be used for asymptomatic bacteriuria in pregnancy

Antibiotics	Recommended dose and duration	FDA Risk Category
Cephalexin	500 mg BID for 7 days	B
Cefuroxime axetyl	500 mg BID for 7 days	B
Fosfomycintrometamol	3 g in a single dose	B
Amoxicillin-clavulanate	625mg BID for 7 days	B
Cefuroxime	500mg BID for 7 days	B
Nitrofurantoinmacrocrystal	100 mg QID for 7 days; 100 mg BID for monohydrate/ macrocrystal (not available locally) for 7 days	B (May cause hemolyticanemia, 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)
TMP-SMX	160/800 mg BID for seven days	C (avoid in 1st and 3rd trimester)

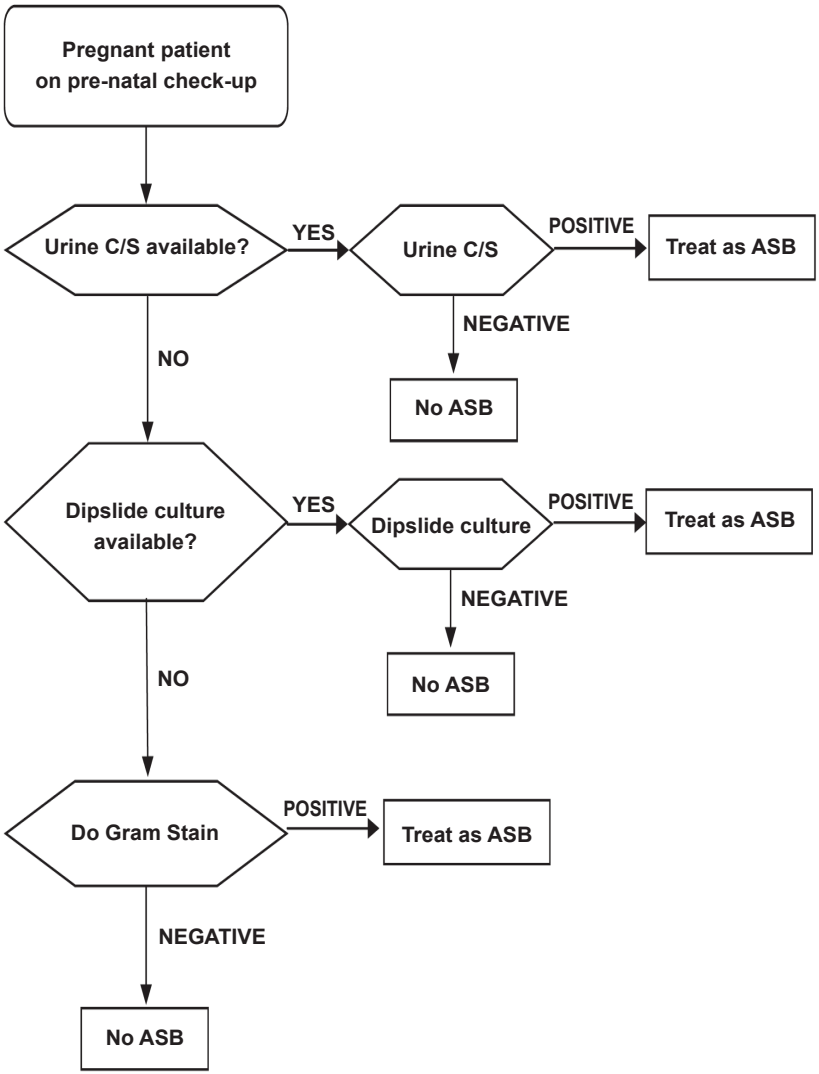
- **A follow up urine culture should be done one week after completing the course of treatment.**
  Weak recommendation, Low quality of evidence

Summary of Evidence

The Task Force found no new evidence that would merit a change in the recommendations from the previous guidelines.

- **Monitoring should be done every trimester until delivery.**
  Weak recommendation, Low quality of evidence

Algorithm 4. Alternative diagnostic evaluation for asymptomatic bacteriuria in settings where urine culture is not available



References

1. Rubin RH, Shapiro ED, Adrioce VT, Davis RJ, Stamm WE. General guidelines for the evaluation of new anti-infective drugs for the treatment of urinary tract infection. Clin Infect Dis 1992; (Suppl 1):S216–27.
2. Nicolle LE, Bradley S, Colgan R, Rice JC, Schaeffer A, Hooton TM. Infectious Diseases Society of America Guidelines for the Diagnosis and Treatment of Asymptomatic Bacteriuria in Adults. Clin Infect Dis 2005; 40:643–54.
3. Kass EH. Asymptomatic infections of the urinary tract. Trans Assoc Am Phys 1956; 69:56–64.
4. Bartlett RC, Galen RS. Predictive value of urine culture. Am J Clin Pathol 1983; 79:756–7.
5. Platt R. Quantitative definition of bacteriuria. Am J Med 1983; 75:44–52.
6. Geerlings SE, Brouwer EC, Gaastra W, Hoepelman AI. Is a second urine specimen necessary for the diagnosis of asymptomatic bacteriuria? A Brief Report. Clin Infect Dis 2000; 31:E3–4.
7. Sescon NI, Garingalao-Molina FG, Ycasiano V, Saniel M, Manalastas R. Prevalence of asymptomatic bacteriuria and associated risk factors in pregnant women. Phil J Microbiol Infect Dis 2003; 32:63–9.
8. Golan A, Wexler S, Amit A, Gordon D, David MP. Asymptomatic bacteriuria in normal and high-risk pregnancy. Eur j Obstet Gyne and Reprod Biol 1989; 33:101–8.
9. Stenqvist K, Dahlen-Nilsson I, Lichin-Janson G. Bacteremia in pregnancy. Am J Epidemiol 1989; 129:372.
10. Andreole VT, Patterson TF. Epidemiology, natural history and management of urinary tract infections in pregnancy. Med Clin North Am 1991; 75:359–73.
11. Ullah A, Barman A, Ahmed I, Salam A. Asymptomatic bacteriuria in pregnant mothers: a valid and cost-effective screening test in Bangladesh. Journal of obstetrics and gynaecology [Internet] 2012 Jan [cited 2013 Oct 12]; 32(1):37–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22185534
12. Mignini L, Carroli G, Abalos E, Widmer M. Accuracy of Diagnostic Tests to Detect Asymptomatic Bacteriuria During Pregnancy. Obstet Gynecol 2009; 113(2):346–52.
13. Smaill FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. Cochrane Database of Systematic Reviews 2007; (2): CD000490.
14. Guinto VT, De Guia B, Festin MR, Dowswell T. Different antibiotic regimens for treating asymptomatic bacteriuria in pregnancy. Cochrane Database of Systematic Reviews 2010; (9):CD007855.
15. Widmer M, Gülmezoglu AM, Mignini L, Roganti A. Duration of treatment for asymptomatic bacteriuria during pregnancy. Cochrane Database of Systematic Reviews 2011; (12): CD000491.

ACUTE CYSTITIS IN PREGNANCY

Section Summary

Definition

- In an otherwise healthy, pregnant woman, acute cystitis in pregnancy is characterized by urinary frequency, urgency, dysuria, and bacteriuria without fever and costovertebral angle tenderness. Gross hematuria may also be present.

Pre-treatment diagnostic tests

- In pregnant women suspected to have AUC, obtain a pre-treatment urine culture and sensitivity test of a midstream clean-catch urine specimen.
  Strong recommendation, Moderate quality of evidence

- In the absence of a urine culture, the laboratory diagnosis of acute cystitis can be determined by:
  a) The presence of significant pyuria defined as:
     - ≥ 8 pus cells/mm3 of uncentrifuged urine, OR
     - ≥ 5 pus cells/HPF of centrifuged urine

     AND
  b) A positive leukocyte esterase and nitrite test on dipstick.
  Strong recommendation, Moderate quality of evidence

Antibiotic treatment

- Treatment of acute cystitis in pregnancy should be instituted immediately to prevent the spread of the infection to the kidney.
  Strong recommendation, High quality of evidence

- Since *E. coli* remains to be the most common organism isolated, antibiotics to which this organism is most sensitive and which are safe to give during pregnancy should be used.
  Strong recommendation, High quality of evidence

- A seven-day treatment with an oral antimicrobial agent that is safe for use in pregnancy is recommended; except for fosfomycin which is given as a single dose.
  Strong recommendation, Low level of evidence

- In the absence of a urine culture and sensitivity, empiric therapy should be based on local susceptibility patterns of uropathogens.
  Strong recommendation, Low level of evidence

Antibiotic resistance based on culture and sensitivity

- If the patient is clinically responding to the present treatment, there is no need to revise the antibiotic if resistance to the empirically started antibiotic is reported on urine culture. Adjust antibiotic therapy based on urine culture results ONLY when

there is no improvement in the clinical signs and symptoms and laboratory results or when there is worsening of the patient's condition.

Strong recommendation, Low quality of evidence

Follow-up laboratory tests

- Post-treatment urine culture one to two weeks after completion of therapy should be obtained to confirm eradication of bacteriuria and resolution of infection in pregnant women.

  Strong recommendation, Low level of evidence

- Pregnant patients with pyelonephritis, recurrent UTIs, concurrent gestational DM, concurrent nephrolithiasis or urolithiasis, and pre-eclampsia should be monitored at monthly intervals until delivery to ensure that urine remains sterile during pregnancy.

  Strong recommendation, Low level of evidence

Recommendations and Summary of Evidence

1. **When do you suspect acute cystitis in pregnancy?**
   - **In an otherwise healthy, pregnant woman, acute cystitis in pregnancy is characterized by urinary frequency, urgency, dysuria, and bacteriuria without fever and costovertebral angle tenderness. Gross hematuria may also be present.**[1]

Summary of Evidence

The 2004 update of the PPGG-ID Task Force on UTI's definition of acute cystitis in pregnancy was based on clinical symptoms such as dysuria, frequent urination, and lower abdominal or suprapubic pain, without fever.[2]

2. **Is a pre-treatment diagnostic test required in acute cystitis in pregnancy?**
   - **In pregnant women suspected to have acute uncomplicated cystitis, obtain a pre-treatment urine culture and sensitivity test of a midstream clean catch urine specimen.**

     Strong recommendation, Moderate quality of evidence

   - **In the absence of a urine culture, the laboratory diagnosis of acute cystitis can be determined by:**
     a) The presence of significant pyuria defined as:
     - **≥ 8 pus cells/mm3 of uncentrifuged urine, OR**
     - **≥ 5 pus cells/HPF of centrifuged urine**

     AND

     b) A positive leukocyte esterase and nitrite test on dipstick.

     Strong recommendation, Moderate quality of evidence

Summary of Evidence

The physiologic changes during pregnancy like increased physiological vaginal discharge, increased laxity of pelvic tissues, and the discomfort due to an enlarging abdominal mass makes it important to confirm the diagnosis of UTI. The diagnosis should be confirmed so that unnecessary exposure of the fetus to antimicrobial agents may be avoided.[3] A cross-sectional study by McGready et al. in 2010 noted the utility of urine sediment microscopy in the initial evaluation of pregnant women with symptomatic UTI. In this study, they found that urine sediment microscopy with cut-off of epithelial cells < 5 and WBC ≥ 7, had a sensitivity of 97%, specificity of 82%, PPV of 55%, and NPV of 99%. It also had a post-test probability of 37.1% if microscopy was positive.[4]

3. **What is the treatment for acute cystitis in pregnancy?**
   - **Treatment of acute cystitis in pregnancy should be instituted immediately to prevent the spread of the infection to the kidney.**
     Strong recommendation, High quality of evidence

   - **Since *E. coli* remains to be the most common organism isolated, antibiotics to which this organism is most sensitive and which are safe to give during pregnancy should be used.**
     Strong recommendation, High quality of evidence

   - **A seven-day treatment with an oral antimicrobial agent that is safe for use in pregnancy is recommended; except for fosfomycin which is given as a single dose.**
     Strong recommendation, Low level of evidence

   - **In the absence of a urine culture and sensitivity, empiric therapy should be based on local susceptibility patterns of uropathogens.**
     Strong recommendation, Low level of evidence

Summary of Evidence

The incidence of acute cystitis during pregnancy was 1.3%.[1,5] Infection occurs during the second trimester and may not necessarily be preceded by asymptomatic bacteriuria during the previous weeks. In UTI in pregnancy, the welfare of both the mother and the fetus are at stake, making treatment failure or even incomplete response less acceptable.[6]

There was limited data assessing the superiority of one antibacterial regimen over another in terms of efficacy, patient compliance, and safety during pregnancy. A Cochrane review of RCTs on antibiotics for the treatment of symptomatic UTIs in pregnancy could not show that one treatment regimen was better than another. Rates of cure were high and there were very few complications.[7] A retrospective case-control study investigating the association between antibacterial use and birth defects found that cephalosporins, erythromycins, and penicillinswere relatively safe to use in pregnancy. On the other hand, major birth defects were noted to be associated with women who took sulfonamides and nitrofurantoins. Further studies on the safety profile of nitrofurantoin and sulfonamides were needed. The data on quinolones suggested an increased association with cardiac defects. Quinolones were not recommended to be used in pregnancyunless there are overriding reasons for their use.[8] Since this study was a retrospective case-control study, it was subject to certain biases including recall bias, selection bias, and the presence of confounding factors such as the underlying infection for which the antibiotic was used.[8,9] More studies are needed to further investigate these reported associations.

Empiric use of co-amoxiclav for preterm labor with rupture of membranes was associated with an increased risk of neonatal necrotizing enterocolitis. This may be explained by the disruptions in the microbial colonization of the neonatal gut by low-virulence microflora allowing subsequent colonization by more virulent micro-organisms following birth. Another explanation could be the ability of the immature gut to absorb exotoxins completely, leading to mucosal damage which could lead to NEC.[10]

Table 9. Antibiotics that can be used for acute cystitis in pregnancy

Antibiotics	Recommended Dose and Duration	Pregnancy Category	Birth Defects / Neonatal Complications	Comments/ Qualifiers
Cephalexin	500 mg QID for 7 days	B	None	Safe to use in any trimester
Cefadroxil	1 g BID for 7 days	B	None	Safe to use in any trimester
Cefuroxime	500mg BID for 7 days	B	None	Safe to use in any trimester
Cefaclor	500mg TID for 7 days	B	None	Safe to use in any trimester
Cefixime	200mg BID for 7 days	B	None	Safe to use in any trimester
Cefpodoxime	100mg BID for 7 days	B	None	Safe to use in any trimester
Nitrofurantoin	100 mg QID for 7 days for macrocrystals 100 mg BID for monohydrate/ macrocrystals (not available locally)	B	Hemolyticanemia, anophthalmia, hypoplastic left heart syndrome, ASD, cleft lip and palate[8]	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.
Fosfomycin trometamol	3 g single dose	B	None	Safe to use in any trimester
Pivmecillinam	400 mg BID for 7 days	B	None	Safe to use in any trimester
Amoxicillin-clavulanate	625mg BID for 7 days		Neonatal necrotizing enterocolitis[10]	Avoid in women at risk of preterm labor[10]
TMP-SMX	160/800 mg BID for 7 days	C	Anencephaly, hypoplastic left heart syndrome, choanal atresia, transverse limb defect, diaphragmatic hernia[8]	May be given on the second and third trimester of pregnancy. Use in the first trimester of pregnancy is appropriate when no other suitable alternative antibiotics are available. *Use only for culture- proven susceptible uropathogens due to high prevalence of local resistance.

4. In clinically improving patients whose urine culture result shows an organism resistant to the empirically started antibiotic, should the antibiotic be changed based on the susceptibility report?

- **If the patient is clinically responding to the present treatment, there is no need to revise the antibiotic if resistance to the empirically started antibiotic is reported on urine culture. Adjust antibiotic therapy based on urine culture results ONLY when there is no improvement in the clinical signs and symptoms and laboratory results or when there is worsening of the patient's condition.**

  Strong recommendation, Low quality of evidence

Summary of Evidence

There were no studies addressing this specific issue. Because of the higher likelihood of antimicrobial resistance or of a suboptimal treatment response in a pregnant woman compared with a non-pregnant woman, and the adverse consequences to the fetus if treatment fails or if treatment response is delayed or incomplete, the 2013 ACP PIER clinical guideline recommended that antibiotic therapy be modified based on the results of culture and sensitivity tests.[3] However, clinical and bacteriologic cures were often achieved even when the organisms were resistant in vitro to the selected agent; thus a change in antibiotic therapy was not mandatory, so long as the patient was responding clinically as observed by the physician.[11] The consensus of our expert panel is that there is no need to shift the antibiotics if the patient is clinically responding. However, clearance of bacteriuria should be documented at the end of antibiotic therapy (Please see recommendation regarding repeat cultures below). For patients who are not responding clinically, antibiotic treatment should definitely be modified based on culture and sensitivity results.

5. **What is the clinical utility of a post-treatment urine culture?**
   - **Post-treatment urine culture one to two weeks after completion of therapy should be obtained to confirm eradication of bacteriuria and resolution of infection in pregnant women.**
     Strong recommendation, Low level of evidence

   - **Pregnant patients with pyelonephritis, recurrent UTIs, concurrent gestational DM, concurrent nephrolithiasis or urolithiasis, and pre-eclampsia, should be monitored at monthly intervals until delivery to ensure that urine remains sterile during pregnancy.**
     Strong recommendation, Low level of evidence

Summary of Evidence

Pregnant women who have had a bacteriuric episode during the pregnancy may require closer monitoring because they have an increased risk for repeated episodes of bacteriuria during the course of the pregnancy.[3] Pregnant women may present with severe pyelonephritis. Pyelonephritis could also lead to other conditions such as premature labor, fetal distress syndrome, shock, disseminated intravascular coagulation, and death.[3] Thus, it is critical that bacteriuria be eradicated and documented through urine cultures.

There was no evidence regarding the frequency of monitoring for recurrence of ASB in pregnant women. A review by Wing et al.[12]

suggested clinic follow-up within two weeks after acute therapy of acute pyelonephritis during which a urine culture was obtained as a "test of cure". In studies on treatment of APN in pregnancy, follow-up cultures were done on the 5th-14th day post-treatment.[13-15]

There is no evidence to support optimal timing of repeat urine cultures during the rest of pregnancy. Acute pyelonephritis tends to occur in the latter stages of pregnancy, usually in the last trimester.[16]

Pregnant patients at high risk for developing acute cystitis or acute pyelonephritis are discussed in the section on asymptomatic bacteriuria in pregnancy.

References

1. Harris RE. Acute urinary tract infections and subsequent problems. Clin Obstet Gyne 1984; 27:874–90.
2. Task Force on Urinary Tract Infections Philippine Practice Guideline Group Infectious Disease. The Philippine Clinical Practice Guidelines on the Diagnosis and Management of Urinary Tract Infections In Adults Update 2004. Quezon City, Philippines: PPGG-ID Philippine Society for Microbiology and Infectious Diseases 2004.
3. Johnson JR, Stapleton A, Trautner BW, Drekonja D, Korenstein D, Lynn RB. Urinary Tract Infection [Internet]. ACP Smart Medicine 2013. Available from: http://smartmedicine.acponline.org/content.aspx?gbosId=114
4. McGready R, Wuthiekanun V, Ashley E, Tan S, Pimanpanarak M, Vilapai-nguen SJ, et al. Diagnostic and Treatment Difficulties of Pyelonephritis in Pregnancy in Resource-Limited Settings. Am J Trop Med Hyg 2010; 83(6):1322 – 1329.
5. Harris RE, Gilstrap III LG. Cystitis during pregnancy: a distant clinical entity. Cystitis during pregnancy: a distant clinical entity 1981; 57(57):578–80.
6. Johnson JR, Stapleton A, Trautner BW. Urinary Tract Infection. ACP Physicians Information and Education Resource [Internet] 2011; Available from: http://pier.acponline.org/physicians/diseases/d162/d162.html
7. Vazquez JC, Abalos F. Treatments for symptomatic urinary tract infections during pregnancy (Review). Cochrane Database of Systemic Reviews 2011; (I): CD002256.
8. Crider KS, Cleves MA, Reefhuis J, Berry RJ, Hobbs CA, Hu DJ. Antibacterial Medication Use During Pregnancy and Risk of Birth Defects: National Birth Defects Prevention Study. Arch Pediatr Adolesc Med 2009; 163(11):978–85.
9. Sulfonamides, Nitrofurantoin, and Risk of Birth Defects. Committee Opinion No. 494. American College of Obstetricians and Gynecologists. Obstet Gynecol 2011; 117:1484–5.
10. Kenyon S, Taylor D, Tarnow-Mordi W. Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE I randomised trial. The Lancet [Internet] 2001 Mar; 357(9261):979–88. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0140673600042331
11. Johnson J. Urinary tract infection. Pier clinical guidance from ACP [Internet] 2003; Available from: http://pier.acponline
12. Wing DA, Park AS, Debuque L, Millar LK. Limited clinical utility of blood and urine

cultures in the treatment of acute pyelonephritis during pregnancy. Am J Obstet Gynecol 2000; 182:1437–41.
13. Millar LK, Wing DA, Paul RH. Outpatient treatment of pyelonephritis in pregnancy: a randomized controlled trial. Obstet Gynecol 1995; 86:560–4.
14. Wing DA, Hendershott CM, Debuque L, Millar LK. A randomized trial of three antibiotic regimens for the treatment of pyelonephritis in pregnancy. Obstet Gynecol 1998; 92:249–53.
15. Wing DA, Hendershott CM, Debuque L, Millar LK. Outpatient treatment of acute pyelonephritis in pregnancy after 24 weeks. Obstet Gynecol 1999; 94:683–8.
16. Kunin C. Pyelonephritis. Pier clinical guidance from ACP [Internet] 2003; Available from: http://pier.acponline.

ACUTE UNCOMPLICATED PYELONEPHRITIS IN PREGNANCY

Section Summary

Definition

- The classic syndrome of AUP in healthy adult women is also applied to pregnant women. AUP is characterized by fever (T> 38°C), chills, flank pain, costovertebral angle tenderness, nausea and vomiting, with or without signs and symptoms of lower urinary tract infection. Laboratory findings include pyuria (≥ 5 WBC/HPF of centrifuged urine) on urinalysis and bacteriuria with counts of >10,000 CFU/mL on urine culture.

  Strong recommendation, Moderate quality of evidence

Diagnostic tests

- Urinalysis and Gram stain are recommended.

  Strong recommendation, Moderate quality of evidence

- Urine culture and sensitivity test should also be performed routinely to facilitate cost-effective use of antimicrobial agents and because of the potential for serious sequelae if an inappropriate antimicrobial agent is used.

  Strong recommendation, Moderate quality of evidence

- Blood cultures are NOT routinely recommended except in patients with signs of sepsis.

  Strong recommendation, High quality of evidence

- Routine renal ultrasound is of limited clinical benefit and should be reserved for women who fail to respond to initial treatment.

  Strong recommendation, Low quality of evidence

Indications for admission

The following are considered as indications for admission:

- Inability to maintain oral hydration or take medications
- Concern about compliance
- Presence of possible complicating (co-morbid) conditions
- Severe illness with high fever, severe pain, marked debility
- Signs of preterm labor
- Signs of sepsis

  Strong recommendation, Low quality of evidence

Antibiotic treatment

- In the absence of a urine culture and sensitivity, empiric therapy should be based on local susceptibility patterns of uropathogens. Since *E. coli* remains to be the most common organism isolated,

antibiotics to which this organism is most sensitive and which are safe to give during pregnancy should be used.

Strong recommendation, Moderate quality of evidence

Duration of treatment

- The recommended duration of treatment is 14 days.

  Strong recommendation, Low quality of evidence

Follow-up laboratory tests

- Post-treatment urine culture should be obtained after completion of antibiotic treatment to confirm resolution of the infection ("test of cure"). The patient should be followed up for symptoms of recurrent infection and monthly urine cultures should be performed until delivery.

  Weak recommendation, Low quality of evidence

Recurrence of Symptoms

- Recurrence of symptoms requires antibiotic treatment based on urine culture and sensitivity test results in addition to assessing for underlying genitourologic abnormalities.

  Weak recommendation, Low quality of evidence

- The duration of re-treatment in the absence of a urologic abnormality is two weeks.

  Weak recommendation, Low quality of evidence

- For patients whose symptoms recur and whose culture shows the same organism as the initial infecting organism, a four- to six-week regimen is recommended.

  Weak recommendation, Low quality of evidence

Prevention of recurrent UTI in pregnancy

- No pharmacologic intervention has been proven to be effective in the prevention of recurrent UTI in pregnancy.

- Non-pharmacologic intervention in the form of close surveillance (follow-up with urine cultures every two weeks until 36 weeks) has been proven to be non-inferior to nitrofurantoin in preventing recurrent symptomatic UTI in pregnancy.

  Strong recommendation, Moderate quality of evidence

- Cranberry juice is not recommended in the prevention of UTI as it does not reduce asymptomatic bacteriuria and recurrence of UTI in pregnant women.

  Strong recommendation, Moderate quality of evidence

Recommendations and Summary of Evidence

1. When is acute uncomplicated pyelonephritis in pregnancy suspected?
   - The classic syndrome of AUP in healthy adult women is also applied to pregnant women. AUP is characterized by fever (T> 38°C), chills, flank pain, costovertebral angle tenderness, nausea and vomiting, with or without signs and symptoms of lower urinary tract infection. Laboratory findings include pyuria (≥ 5 WBC/HPF of centrifuged urine) on urinalysis and bacteriuria with counts of > 10,000 CFU/mL on urine culture.[1-3]

   Strong recommendation, Moderate quality of evidence

Summary of Evidence

In a retrospective 12-year population-based study of singleton deliveries, the incidence of antenatal pyelonephritis was found to be 0.07%,[4] which was lower than the 1-2 % mentioned by McGreadyet al. as reported in antepartum universal screening described in earlier literature.[5] The most common symptom reported was costovertebral angle tenderness. Other symptoms include headache, rigors or chills, anorexia, nausea, dysuria, muscle pain, and vomiting. Independent risk factors associated with acute antepartum pyelonephritis were nulliparity, OR 2.0 (95% CI 1.4, 2.9; p<0.001), previous history of urinary tract infection, OR 10.3 (95 % CI 4.8, 22.1; p<0.001), and younger maternal age, OR 0.96 (95% CI 0.93, 0.99; p=0.009).[4] Based on cases reported in two two-year longitudinal studies by Hill et al. in 2005[6] and by McGready et al.[5] in 2010, the occurrence of pyelonephritis was noted to be highest in the second trimester (> 50% of cases occurred in the second trimester).[5,6]

2. **What are the recommended diagnostic tests for acute uncomplicated pyelonephritis in pregnancy?**
   - **Urinalysis and Gram stain are recommended.**

     Strong recommendation, Moderate quality of evidence

   - **Urine culture and sensitivity test should also be performed routinely to facilitate cost-effective use of antimicrobial agents and because of the potential for serious sequelae if an inappropriate antimicrobial agent is used.**

     Strong recommendation, Moderate quality of evidence

   - **Blood cultures are NOT routinely recommended except in patients with signs of sepsis.**

     Strong recommendation, High quality of evidence

- **Routine renal ultrasound is of limited clinical benefit and should be reserved for women who fail to respond to initial treatment.**
  Strong recommendation, Low quality of evidence

Summary of Evidence

Urinalysis
There was higher sensitivity and negative predictive values for urine sediment microscopy (urinalysis) over urine dipstick test with a negative post-test probability of 9.7% among pregnant women with acute pyelonephritis.[5] However, due to the study's limited sample size and the test's inter-observer variability, these results should still be viewed with caution.

There is no new data directly comparing different diagnostic tests for antenatal pyelonephritis.

Blood culture
The previous guidelines cited Winget al. wherein data was pooled from three randomized controlled trials that included 391 pregnant women with pyelonephritis.[7] Urine (98%) and blood culture (99%) results were correlated with clinical management decisions, outcome, length of hospital stay, and cost. In this study, only 6% of the participants required changes from initial antibiotic therapy. Most antibiotic changes were made because of a perceived lack of response to treatment rather than based on culture and sensitivity results. Only in four of the 25 cases was the initial antibiotic regimen changed solely because of bacteremia despite adequate response to the initial treatment with ceftriaxone. The reasons for initial antibiotic changes were: persistent fever (6/25), persistent costovertebral angle tenderness (4/25), leukocytosis with WBC count > 20,000 cells/mm^3 (3/25), recurrent pyelonephritis (2/25), signs of sepsis (1/25), persistent temperature elevation and bacteremia (1/25), and persistent temperature elevation and CVA tenderness (1/25). Blood culture results directly influenced management by prolonging the duration of hospitalization because women with bacteremia were hospitalized for a mean of 4.6 days, SD 2.6 days while those without bacteremia were confined for a mean of 2.6 days, SD 1.5 days ($p<0.001$) despite similar clinical outcomes.[7]

Renal ultrasound
A retrospective review of hospital records of 171 pregnant women diagnosed with pyelonephritis admitted over a seven-year period showed limited benefit of renal ultrasonography for pregnant women

with pyelonephritis. Of the 171 women whose records were reviewed, seventy-five (43.9%) underwent renal ultrasonography. Twenty-six of them (34.7%) had normal results. Mild renal pelvis dilatation (6 to 10 mm) was noted in 25 (33.3%) patients, moderate dilatation (11 to 15 mm) in 16 (21.3%) patients, and severe dilatation (≥16 mm) in 8 (10.7%) patients. Other noted abnormalities were duplicated collecting systems and renal calculi, each of which was found in two cases (2.7%). All the patients were treated with antibiotics. Ureteral stents were not necessary. Comparing women who underwent renal ultrasonography to those who did not, they found no difference in maternal characteristics or pregnancy outcomes. Because renal ultrasonography rarely affected management and did not significantly affect pregnancy outcomes, its use is of limited value in pregnant women with pyelonephritis.[8]

3. **What are the indications for admission in patients with acute uncomplicated pyelonephritis in pregnancy?**
   - **The following are considered as indications for admission:**
     - **Inability to maintain oral hydration or take medications;**
     - **Concern about compliance;**
     - **Presence of possible complicating (co-morbid) conditions;**
     - **Severe illness with high fever, severe pain, marked debility;**
     - **Signs of preterm labor;**
     - **Signs of sepsis.**

     Strong recommendation, Low quality of evidence

Summary of Evidence

In a Cochrane systematic review done in 2011[9], they did a meta-analysis of three RCTs (n=340 pregnant women) comparing outpatient vs. inpatient management for patients with antenatal acute pyelonephritis beyond 24 weeks gestation.It was shown that outpatient therapy was not inferior to inpatient with respect to clinical and bacteriologic cure 5 to 14 days after initiation of therapy with an RR of 1.07 (95% CI 1.00, 1.14).[9] Excluded in these trials were patients unable to maintain oral hydration or take medications; cases where there was concern about compliance; presence of possible complicating (co-morbid) conditions; severe illness with high fever, severe pain, marked debility, signs of preterm labor, and signs of sepsis - indications for admission stated in the previous recommendation.

Because most patients who have pyelonephritis are dehydrated, initial management should include IV hydration and urine output monitoring. For appropriate candidates for out-patient therapy, an

initial observation period of 24 hours is needed to confirm maternal and fetal well-being. During this time, antimicrobial therapy, hydration, and laboratory evaluation is initiated. Upon discharge, instructions should be given to return to the emergency room immediately if signs of sepsis, respiratory insufficiency, or preterm labor develop. Twenty-four hours after discharge, patient should be evaluated for appropriate clinical response.

4. **What drugs can be used for empiric treatment of acute uncomplicated pyelonephritis?**
   - **In the absence of a urine culture and sensitivity, empiric therapy should be based on local susceptibility patterns of uropathogens. Since *E. coli* remains to be the most common organism isolated, antibiotics to which this organism is most sensitive and which are safe to give during pregnancy should be used.**

   Strong recommendation, Moderate quality of evidence

Summary of Evidence

There were no randomized clinical trials on treatment of acute antenatal pyelonephritis alone. All of the studies included healthy non-pregnant females, males, and complicated UTI (See Summary of Evidence of AUC in Pregnancy).

There was limited data that assessed the superiority of one antibacterial regimen over another in terms of efficacy, patient compliance and safety during pregnancy. A Cochrane review of RCTs on antibiotics for the treatment of symptomatic UTIs in pregnancy was not able to show that one treatment regimen was better than another. Rates of cure were high and there were very few complications.[9] Cephalosporins, erythromycins, and penicillins were relatively safe to use in pregnancy. On the other hand, major birth defects were associated with women who took sulfonamides and nitrofurantoin. Further studies on the safety profile of nitrofurantoin and sulfonamides were needed. Quinolones may be associated with an increased risk of cardiac defects. At present, quinolones are not recommended for use in pregnant women unless there are overriding reasons for their use.[10]

The study of Crider et al. in 2009 on the relationship between antibiotics and birth defects were found to have several limitations. First, there is the possibility of recall bias because the respondents were interviewed from 6 weeks to 2 years after the pregnancy, and the antibiotic prescribed was not confirmed by medical records. Also, since this was a retrospective cross-sectional, observational study,

only associations could be made. There were also confounding factors such as the infection for which the antibiotic was prescribed, which could also account for the birth defects noted.[10,11] In a Committee Opinion of the American College of Obstetrics and Gynecology, they said that benefits and risks (including potential for teratogenesis or of maternal adverse reactions) of antibiotics prescribed should be considered and discussed with patients, especially for antibiotics prescribed in the first trimester. If there were no other suitable antibiotics available, sulfonamides or nitrofurantoin may still be considered as possible antibiotic choices during the first trimester. Said antibiotics may also still be used as first-line agents for the treatment and prevention of UTI in the second and third trimesters.[11]

Table 10. Empiric treatment regimens for acute uncomplicated pyelonephritis in pregnant women

Antibiotic		Dose, Frequency and Duration	Category
PARENTERAL (given until patient is afebrile)			
Primary	Ceftriaxone	1-2 g IV q 24 hours	B
	Cefotaxime	1 -2 g IV q 8 hours	B
	Ceftazidime	2 g IV q 8 hours	B
Alternative	Ampicillin-sulbactam (when GS shows gram-positive organisms)	1.5 g IV q6 hours	B
Reserved	Piperacillin-tazobactam	2.25 g IV to 4.5 g IV q 6-8 hours	B
ORAL (given when patient is 48 hours afebrile and based the parenteral medication given and/or sensitivity results) see comments and qualifiers under AUC in pregnancy			
	Cephalexin	500 mg QID to complete 14 days	B
	Cefadroxil	1 g BID to complete 14 days	B
	Cefuroxime axetyl	500mg BID to complete 14 days	B
	Cefaclor	500mg TID to complete 14 days	B
	Cefixime	200mg BID to complete 14 days	B
	Cefpodoximeproxetil	100 mg BID to complete 14 days	B
	Amoxicillin-clavulanate	625mg BID to complete 14 days	B

5. What is the effective duration of treatment for AUP?

- **The recommended duration of treatment is 14 days.**
  Strong recommendation, Low quality of evidence

Summary of Evidence

Intravenous antimicrobial therapy is usually continued until the patient is afebrile for 48 hours and symptoms have improved before switching to an oral regimen to complete a total of 14 days therapy.

If the patient fails to respond clinically within 72 hours, further evaluation should be done to investigate for the presence of antibiotic resistance, urolithiasis, perinephric abscess formation or urinary tract abnormalities. The antibacterial regimen should be modified based on urine culture/sensitivity results.

There was no literature found showing superiority of 14-day course of treatment over shorter duration. Fourteen-day course of treatment was based on expert consensus.

6. **What is the clinical utility of a post-treatment urine culture in acute pyelonephritis in pregnancy?**
   - **Post-treatment urine culture should be obtained after completion of antibiotic treatment to confirm resolution of the infection ("test of cure"). The patient should be followed up for symptoms of recurrent infection and monthly urine cultures should be performed until delivery.**
     Weak recommendation, Low quality of evidence

Summary of Evidence

Please refer to the section on post-treatment urine culture in *Acute Cystitis in Pregnancy*.

7. **What is the recommended management for patients whose symptoms recur?**
   - **Recurrence of symptoms requires antibiotic treatment based on urine culture and sensitivity test results, in addition to assessing for underlying genitourologic abnormalities.**
     Weak recommendation, Low quality of evidence

   - **The duration of re-treatment in the absence of a urologic abnormality is two weeks.**
     Weak recommendation, Low quality of evidence

   - **For patients whose symptoms recur and whose culture shows the same organism as the initial infecting organism, a four to six-week regimen is recommended.**
     Weak recommendation, Low quality of evidence

These recommendations were based on expert opinion. There was scarcity of evidence regarding duration of management of recurrent urinary tract infections in pregnancy.

8. **How can recurrent UTI in pregnancy be prevented?**
   - **No pharmacologic intervention has been proven to be effective in the prevention of recurrent UTI in pregnancy.**

   - **Non-pharmacologic intervention in the form of close surveillance (follow-up with urine cultures every two weeks until 36 weeks) has been proven to be non-inferior to nitrofurantoin in preventing recurrent symptomatic UTI in pregnancy.**

     Strong recommendation, Moderate quality of evidence

   - **Cranberry juice is not recommended in the prevention of UTI as it does not reduce asymptomatic bacteriuria and recurrence of UTI in pregnant women.**

     Strong recommendation, Moderate quality of evidence

Summary of Evidence

In a Cochrane review of a randomized controlled trial comparing daily nitrofurantoin plus close surveillance with close surveillance alone for recurrent UTI in pregnancy, there was no significant difference between the two groups in terms of reduction of recurrent UTI. However, they did see a significant reduction of ASB in patients given daily nitrofurantoin plus close surveillance (Note: this outcome was reported for patients who had >90% attendance during follow-up).[12]

The use of nitrofurantoin (50 mg orally three times /day) with close surveillance (follow-up every two weeks until 36 weeks) was shown to be a possible intervention for the reduction of ASB in pregnancy but not in the reduction of recurrent urinary tract infection.

Cranberry juice cocktail multiple daily dosing showed 57% reduction in ASB, incidence rate ratio 0.43 (95% CI 0.14, 1.39) and 41% reduction in all UTI, incidence rate ratio 0.59 (95% CI 0.22, 1.60); however, both were statistically not significant.[13] Furthermore, the most common cause of drop out in this study was gastrointestinal upset in the groups initially taking three doses of cranberry juice.

References

1. Harris RE. Acute urinary tract infections and subsequent problems. Clin Obstet Gyne 1984; 27:874–90.
2. Roberts F. Quantitative urine culture in patients with urinary tract infection and bacteremia. Am J Clin Pathol 1986; 85:616–8.
3. Rubin RH, Shapiro ED, Adrioce VT, Davis RJ, Stamm WE. General guidelines for the evaluation of new anti-infective drugs for the treatment of urinary tract infection. Clin Infect Dis 1992; (Suppl 1):S216–27.
4. Farkash E, Weintraub AY, Sergienko R, Wiznitzer A, Zlotnik A, Sheiner E. Acute antepartum pyelonephritis in pregnancy: a critical analysis of risk factors and outcomes [Abstract]. Eur J Obstet Gynecol Reprod Biol 2012; 162(1):24–7.
5. McGready R, Wuthiekanun V, Ashley E, Tan S, Pimanpanarak M, Vilapai-nguen SJ, et al. Diagnostic and Treatment Difficulties of Pyelonephritis in Pregnancy in Resource-Limited Settings. Am J Trop Med Hyg 2010; 83(6):1322 – 1329.
6. Hill JB, Sheffield JS, McIntire DD, Wendel Jr GD. Acute pyelonephritis in pregnancy. Obstet Gynecol 2005; 105(1):18–23.
7. Wing DA, Park AS, Debuque L, Millar LK. Limited clinical utility of blood and urine cultures in the treatment of acute pyelonephritis during pregnancy. Am J Obstet Gynecol 2000; 182:1437–41.
8. Seidman D, Soriano D, Dulitzki M, Heyman Z, Mashiach S, Barkai G. Role of renal ultrasonography in the management of pyelonephritis in pregnant women[Abstract]. J Perinatol 1998; 18(2):98–101.
9. Vazquez JC, Abalos E. Treatments for symptomatic urinary tract infections during pregnancy. Cochrane Database of Systematic Reviews 2011; (1):CD002256.
10. Crider KS, Cleves MA, Reefhuis J, Berry RJ, Hobbs CA, Hu DJ. Antibacterial Medication Use During Pregnancy and Risk of Birth Defects: National Birth Defects Prevention Study. Arch Pediatr Adolesc Med 2009; 163(11):978–85.
11. Sulfonamides, Nitrofurantoin, and Risk of Birth Defects. Committee Opinion No. 494. American College of Obstetricians and Gynecologists. Obstet Gynecol 2011; 117:1484–5.
12. Schneeberger C, Geerlings SE, Middleton P, Crowther CA. Interventions for preventing recurrent urinary tract infection during pregnancy (Review). Cochrane Database of Systematic Reviews 2012; (11):CD009279.
13. Wing D a, Rumney PJ, Preslicka CW, Chung JH. Daily cranberry juice for the prevention of asymptomatic bacteriuria in pregnancy: a randomized, controlled pilot study. The Journal of urology 2008 Oct; 180:1367–72.

• ACKNOWLEDGEMENT •

The UTI Task Force is grateful for the funding support given by the Philippine Society for Microbiology and Infectious Disease for the development and printing of this Clinical Practice Guidelines.

Philippine Society for Microbiology and Infectious Diseases
No. 116 9th Avenue, Cubao
Quezon City 1109 Philippines