THE PHILIPPINE CLINICAL PRACTICE GUIDELINES ON THE DIAGNOSIS AND MANAGEMENT OF URINARY TRACT INFECTIONS IN ADULTS

UPDATE 2004

Philippine Practice Guidelines Group
Task Force on Urinary Tract Infections

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

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BACKGROUND

Urinary tract infection (UTI) continues to be among the top five reasons for consultations in health facilities nationwide. With the progressive development of new diagnostic and treatment modalities, patients are exposed to wide variations in clinical care and to potentially inappropriate and expensive health care practices. Using clinical practice guidelines (CPGs) can potentially minimize practice variations and irrational management decisions by providing systematically formulated management recommendations derived from a critical review of existing literature.

The Philippine Society for Microbiology and Infectious Disease (PSMID) has been active in CPG development for a number of years. Through the initiative of the PSMID, a consortium of collaborators was organized as the Philippine Practice Guidelines Group in Infectious Diseases (PPGG-ID) in 1997. The PPGG-ID was composed of 16 professional societies and its initial project was the development of evidence-based clinical practice guidelines on common infections in the Philippines.

The Task Force on UTI was the first to publish evidence-based recommendation on the diagnosis and management of UTI in 1998. The Philippine Clinical Practice Guidelines on the Diagnosis and Management of Urinary Tract Infection has been widely used and disseminated among health care providers, educators and administrators. The Philippine Health Insurance Corporation has also adopted the guideline in implementing reimbursement schemes. Furthermore, specific strategies for dissemination, particularly interactive case-oriented sessions with audit and feedback discussions, were demonstrated to be effective in disseminating guidelines with improved adherence as the outcome measure in a quasi-experimental study conducted among private practitioners in four institutions in the country [Saniel 2004].

Since the publication of the 1998 Clinical Practice Guidelines on the Diagnosis and Management of Urinary Tract Infections, new developments in the field of urinary tract infections have occurred in the last 5 years providing us with current evidence in the diagnosis, treatment and prevention of urinary tract infections in adults. Recognizing these new developments, the UTI Task Force was reconvened in December 2002 to update the 1998 recommendations. Members consisted of infectious disease specialists, nephrologists, urologists, obstetrician-gynecologists, clinical epidemiologists and general practitioners.

In updating the guideline, the model of Shekelle [2001] was followed wherein new evidence was assessed not only in terms of validity but also in the context of patient values, available health resources and improvements in current performance.

Dissemination and implementation of the updated guidelines are equally important tasks. Thus, the Task Force will also develop educational materials to facilitate dissemination, implementation and evaluation of this updated CPG. We are confident that this project, being the first CPG to be updated in the country, can serve as a model for updating and implementing other clinical guidelines.

Finally, this update aims to provide health care providers with evidence-based recommendations on the rational diagnosis and management of UTI in adults. These guidelines, however, cannot encompass all scenarios and under no circumstances should it replace sound clinical judgment of the physician.

Saniel MC, Acuin CS, Arciaga RS et al. Improving private practitioners' adherence to clinical practice guidelines: a quasi-experimental study in the Philippines. 2004; in process for publication

Shekelle P, Eccles MP, Grimshaw JM, Woolf SH. When should guidelines be updated? BMJ 2001; 323: 155-7

METHODS

Phase I: Preparation of Evidence-Based Draft (EBD)
The UTI Task Force (TF) collectively decided to update all existing syndromes in the 1998 CPG and added 2 items – Section XII on non-pharmacologic interventions and urinary candidiasis in Section IV on complicated UTI. Designated TF members formulated the clinical questions for each of the syndromes. The Task Force discussed and approved the questions in a consensus meeting. The Technical Working Group (TWG) then searched the MEDLINE database up to March 2004 and the Cochrane Library up to Issue 2, 2004. The HERDIN database was searched and experts in the field were contacted for published and unpublished local literature. The assigned TF and TWG member reviewed the search yield independently and relevant literature was retrieved, including literature missed in the 1998 CPG. Reference lists of retrieved articles were also reviewed. New evidences were appraised independently for validity. Existing recommendations were modified and new recommendations formulated accordingly based on critical review of new data. The evidence was summarized to include updates on prevalence, accuracy of diagnostic tests, benefits, harms and cost-effectiveness of interventions. The EBD was circulated to all TF members who discussed and reviewed the updated recommendations following an iterative process. The Task Force and TWG graded the recommendations using the scale modified from the Infectious Diseases Society of America *(See Appendix 1).*

Phase II: Preparation of the Intermediate Draft
The EBD was circulated to all panelists for review two weeks before the en banc meeting that was held on April 23, 2004. The panelists consisted of experts in the field of family medicine, internal medicine, nephrology, urology, obstetrics and infectious diseases designated as representatives of their respective societies. Using the nominal group technique, each panelist commented on the recommendations during the en banc meeting. The panelists considered not only the quality and comprehensiveness of the evidence but values placed on the evidence, applicability and availability of health resources and experts' opinion. A consensus was reached when $\geq$75% of the panelists agreed on a recommendation through independent and secret balloting. All issues modifying the recommendations e.g. availability of resources were added in the respective sections to come up with an intermediate draft.

Phase III: Preparation of the Penultimate Draft
Recommendations not resolved by consensus were circulated to the panelists by fax or e-mail using the modified Delphi Technique. The recommendations were again discussed and voted upon. Unresolved recommendations reached consensus after the first round and were incorporated in the penultimate draft.

Phase IV: Preparation of the Final Report
The penultimate draft was circulated to non-panelists stakeholders that included representatives from various hospitals and universities, professional societies, pharmaceutical companies, health maintenance organizations, educational influentials, policy makers and administrators one week before the scheduled public forum. The stakeholders gave their oral or written comments and feedback during the public forum held on July 1, 2004. These comments were considered in preparing the final draft of the guidelines for publication.

Phase V: Preparations for Dissemination and Implementation
The Task Force will develop educational and training materials adapted to specific target groups (e.g. specialists, general practitioners, paramedical personnel, and patients). Other expected outputs are implementation checklist and performance indicators for monitoring and evaluation (e.g. change in prescribing habits and utilization of cost-effective interventions).

I. ACUTE UNCOMPLICATED CYSTITIS IN WOMEN

1. When is acute uncomplicated cystitis (AUC) suspected in women?

Clinically, acute uncomplicated cystitis is suspected in non-pregnant women, 18-64 years old, presenting with dysuria, frequency, or gross hematuria, with or without back pain (Grade B). Risk factors for complicated urinary tract infection must be absent *(Table 1).*

Women who present with the above symptoms plus vaginal irritation or vaginal discharge must undergo further diagnostic tests to confirm the presence of acute uncomplicated cystitis or other concomitant conditions (Grade B).

Table 1. Risk factors for complicated UTI
Hospital acquired infection
Indwelling urinary catheter
Recent urinary tract infection
Recent urinary tract instrumentation (in the past 2 weeks)
Functional or anatomic abnormality of the urinary tract
Recent antimicrobial use (in the past 2 weeks)
Symptoms for > 7 days at presentation
Diabetes mellitus
Immunosuppression

Summary of evidence

Accuracy of symptoms: *In a systematic review of 9 studies [Bent 2002], four symptoms significantly increased the probability of UTI: dysuria, frequency, hematuria and back pain. Four symptoms and one sign significantly decreased its probability: absence of dysuria, absence of back pain, history of vaginal discharge, history of vaginal irritation and vaginal discharge on examination. In this review, the summary prevalence of UTI in five high quality prospective studies that included patients presenting with one or more symptoms of acute UTI with urine culture as the gold standard was 48% (95% CI 41% to 55%). Thus, with one or more symptoms of UTI, the probability of infection is about 50%. Specific combinations (dysuria and frequency present, vaginal discharge and vaginal irritation absent) raised the probability to >90% effectively ruling in the diagnosis based on history alone. (See Table 2)*

The above probabilities are consistent with a recent cross-sectional study [Medina-Bombardo 2003] on 343 women consulting their family physicians for urinary tract symptoms and underwent a guided medical examination, reactive test strip and urine culture. The pre-test probability among patients was 48% (95% CI 43% to54%). The probability of UTI increased in the presence of the following symptoms: painful voiding 1.31 (95% CI 1.12-1.54), urgency 1.29 (95% CI 1.12-1.50), urinary frequency 1.16 (95% CI 1.06-1.28) and tenesmus 1.16 (95% CI 1.02 – 1.32). Presence of genital discomfort, dyspareunia, vaginal discharge, positive lumbar fist percussion and perineal discomfort lowered the probability of UTI.

Table 2. 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)
Dysuria	**1.5 (1.2-2.0)**	**0.5 (0.3-0.7)**
Frequency	**1.8 (1.1-3.0)**	0.6 (0.4-1.0)
Hematuria	**2.0 (1.3-2.9)**	0.9 (0.9-1.0)
Fever	1.6 (1.0-2.6)	0.9 (0.9-1.0)
Flank pain	1.1 (0.9-1.4)	0.9 (0.8-1.1)
Lower abdominal pain	1.1 (0.9-1.4)	0.9 (0.8-1.1)
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)**
Vaginal discharge on physical exam	1.1 (1.0-1.2)	**0.7 (0.5-0.9)**

Combination of symptoms	
1. dysuria & frequency present, vaginal discharge & 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. See Glossarysection for definition of likelihood ratios (LR).*

Comments: *The nine studies reviewed by Bent [2002] could have included women with acute uncomplicated pyelonephritis. This explains why costovertebral angle tenderness was reported as a sign that strongly predicted UTI. For purposes of diagnosing acute cystitis however, the task force decided to exclude costovertebral angle tenderness. Studies included in the review that reported the accuracy of vaginal discharge on physical examination were methodologically poor.*

2. In women suspected of having uncomplicated cystitis, what is the clinical utility of diagnostic tests performed before treatment?

Pre-treatment urine culture and sensitivity is not recommended (Grade E).

Standard urine microscopy and dipstick leukocyte esterase (LE) and nitrite tests are not prerequisites for treatment (Grade D).

In women who present with additional symptoms such as vaginal discharge or vaginal irritation, either a standard urine microscopy or dipstick for LE and nitrites can be done to confirm the diagnosis (Grade B).

Summary of evidence

Accuracy of the test: *The dipstick test for leukocyte esterase and/or nitrites can be read as both positive, both negative, and either one positive. A systematic review [Hurlbut 1991] of 51 cohorts on the diagnostic accuracy of the dipstick test showed that either one being positive offered the most accurate index for the diagnosis of UTI with a positive likelihood ratio (LR) of 4.2 and negative LR of 0.3.*

A prospective study [Sultana 2001] of 400 women consulting at the emergency room for symptoms of UTI showed that performing dipstick urinalysis significantly improved the accuracy of clinical assessment in diagnosing UTI in symptomatic patients compared to clinical assessment alone. Sensitivity and specificity rates of either leukocyte or nitrite being positive were 82% and 84% respectively.

In another prospective study [Leman 2002] comparing standard urinalysis, dipstick urinalysis and urine microscopy for organisms or leukocytes; urinalysis had higher sensitivity and specificity rates. The 3 tests were performed on 60 women consulting at the emergency room with urine culture as gold standard. Screening for UTI in the emergency department is improved by adding leukocyte esterase and nitrite test. A positive urinalysis test for leukocytes and nitrites or urinalysis positive at levels of $\geq$ 500 leukocytes or $\geq$ 5 g/l protein should confirm a clinical diagnosis of UTI. If all urine testing is negative, alternative diagnosis should be considered.

Cost-effectiveness: *A decision-analysis model [Carlson 1985] that examined the cost-effectiveness of pre-treatment urine culture vs. urine culture obtained in patients whose symptoms persisted after 2 days of a multiple dose regimen of trimethoprim-sulfamethoxazole (TMP-SMX) showed that a pre-treatment urine culture did not significantly reduce symptom-days (3.24 to 2.97) but it increased the cost. A cost- utility analysis [Barry 1997] showed that empiric 7-day antibiotic therapy without urinalysis and urine culture is the most cost-effective option. If the pre-test probability of having UTI was < 30%, therapy guided by the result of a urinalysis is preferred. The pretest probability of having acute cystitis in a woman presenting with one or more symptoms of UTI is 50% as discussed previously [Bent 2002]. Thus, it is cost-effective to start treatment without fulfilling the diagnostic criterion of a positive urine culture.*

Table 3. Summary of performance characteristics of urinalysis and dipstick for LE/nitrites

Author (year)	Tests	Sensitivity (95% CI)	Specificity (95%CI)	Positive LR (95% CI)	Negative LR (95% CI)
Hurlbut 1991	dipstick for LE/nitrites			4.2	0.3
Sultana 2001	dipstick for LE/nitrites	82% (72 - 89)	84% (80 to 88)	1.27 (1.17-1.38)	0.22 (0.09-0.53)
Leman 2002	urinalysis for pyuria	95.8% (84 - 99)	50% (32-72)	2.02 (1.24 – 3.20)	0.09 (0.02-0.38)
	dipstick for LE/nitrites	87.5% (75- 95)	41.6% (20-61)	1.44 (0.98-2.12)	0.3 (0.11 – 0.84)
	microscopy for organisms or leukocytes	100%	38.9%		
ACP PIER 2003	urinalysis for pyuria	91%	50%		
	dipstick for LE/nitrites	88-92%	66-67%		

Comments: *Although urinalysis performs better as a screening test (see Table 3), delayed release of results in our setting limits its applicability because it can lead to fewer women receiving treatment. Thus, if dipstick test for LE and nitrite is available, this can be used to confirm the diagnosis in women with a low probability of cystitis. In a prospective study [Mc Isaac 2002] of 231 women who had standardized clinical assessment, dipstick testing and urine culture; combining classic symptoms with pyuria decreased unnecessary antibiotic use to 26.2% but fewer women received immediate treatment (66.4% vs 91.8%). Combining history with nitrites test also decreased unnecessary antibiotic use to 27.5% but more women (81.3%) received immediate antibiotic treatment.*

3. Which antibiotics are effective for acute uncomplicated cystitis?

Any of the antibiotics listed in Table 4 can be used for acute uncomplicated cystitis depending on local susceptibility patterns and host factors. The recommended antibiotics may change depending on the local patterns of susceptibility *(See Table 5).* Costs, pharmacologic properties and adverse effects are other factors to consider in the choice of antibiotics.

Ampicillin and amoxicillin should not be used (Grade E).

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

Antibiotics		Dose and Frequency	Duration	Unit Cost (PhP)	Total Cost (PhP)
TMP-SMX	(Grade A)	800/160 mg BID	3 days	27.50	165.00
Ciprofloxacin	(Grade A)	250 mg BID	3 days	56.00	336.00
Ofloxacin	(Grade A)	200 mg BID	3 days	50.00	300.00
Norfloxacin	(Grade A)	400 mg BID	3 days	27.75	166.50
Levofloxacin	(Grade A)	250 mg OD	3 days	112.50	337.50
Gatifloxacin	(Grade A)	400 mg	Single dose	199.75	199.75
Nitrofurantoin	(Grade A)	100 mg QID	7 days	22.25	623.00
Cefixime (Grade B)		400 mg OD	3 days	116.75	700.50
Cefuroxime (Grade B)		125-250 mg BID	3-7 days	80.50	1,127.00
Co-amoxiclav (Grade B)		625 mg BID	7 days	89.25	1,249.50

NOTE: Cost is based on Mercury drug prices as of 2004. When multiple brands are available, the cost of the most frequently used brand was obtained.

Summary of evidence

Benefits: *With susceptible organisms, the above antibiotic regimens have comparable efficacy rates ranging from 89% to 97% for cotrimoxazole and fluoroquinolones and 77% to 89% for nitrofurantoin and cephalosporins. (Please see related summary of evidence under Question 4 p.10)*

Resistance rates: *Because of consistently high rates of resistance of E.coli to ampicillin and amoxicillin locally (40% to 80%) [Carlos 2004, Dytan 1999, Raco 1998], these antibiotics should continue to be avoided.*

Foreign data report increasing resistance rates to TMP-SMX. In a 1999 study of 202 laboratories in the US, overall resistance rates for TMP-SMX among E coli isolates was 16.8% (range 7.4%-33.3%) and 1.7% for ciprofloxacin [Karlowsky 2001]. In an interim report from 505 centers in 16 European countries, resistance to TMP-SMX among E. coli isolates was 14.6% and 2.9% for ciprofloxacin [Kahlmeter 2000].

Available local data show higher resistance rates to TMP-SMX ranging from 64% to 68% [Carlos 2002, Magalit 2003, The Medical City 2001]. In the 2003 antibiotic resistance surveillance report of DOH, resistance rates of E.coli to TMP-SMX remained high at 70% for both in-patient (N=1,745) and outpatient urine isolates (N=645). In the same report, resistance rates for ciprofloxacin were 44% for outpatient isolates and 32% for in-patient isolates [Carlos 2004]. However, these are all hospital based surveillance data, which are more likely to overestimate the prevalence of community resistance rates because of 2 potential biases. One is culture selection bias wherein outpatients whose UTIs are serious, recurrent or do not respond to therapy or require hospitalization are more likely to have cultures perfomed. The other is sample selection bias wherein surveillance drawn from hospital laboratories is more likely to reflect inpatients, sicker patients and patients with complicated UTI [Hooton 2004]. The only available local data to date that would best approximate community resistance rates is a prospective study of pregnant women who were screened for asymptomatic bacteriuria at the out-patient department of the Philippine General Hospital. In this study 31% of 51 E. coli isolates were resistant to TMP-SMX [Sescon 2003].

On the other hand, resistance rates of E.coli to nitrofurantoin remained relatively low at 26% for outpatient isolates and 12% for inpatient isolates as of 2003. Among the beta-lactam agents, E.coli resistance rate to co-amoxiclav was 29%, 50% for cephalothin and 18% for cefuroxime [Carlos 2004]. (See Table 5)

Table 5. Antimicrobial resistance rates of *E. coli* outpatient urine isolates by disc diffusion*

Year	1999-2000**	2000	2001	2002	2003
Ampicillin	53% (Amoxicillin)	79%	79%	79%	80%
Co-amoxiclav	29%	27%	32%	25%	29%
Cefuroxime	2%	11%	12%	13%	18%
Cephalothin	18% (Cephalexin)	51%	-	52%	50%
Nitrofurantoin	0%	14%	12%	40%	26%
Ciprofloxacin	-	30%	-	45%	44%
Cotrimoxazole	31%	85%	65%	70%	70%

**Source: Carlos C. The 2000 - 2003 DOH Antimicrobial Resistance Surveillance Data*
*** 51 E coli isolates from outpatient pregnant women with asymptomatic bacteriuria [Sescon 2003]*

Predictors of resistance: *Local epidemiological studies on the factors associated with resistance are also lacking. Foreign observational studies have consistently demonstrated the association of previous antibiotic use with the emergence of resistant strains. A recent cross-sectional study [Donnan 2004] on 28 general practice areas in Scotland which analyzed prescribing data at the individual level found that the association with trimethoprim resistance was strongest for people recently exposed to trimethoprim up to six months (OR 9.19, 95% CI 6.35 to 13.3). No association between trimethoprim resistance and exposure to trimethoprim beyond 6 months was found (OR 1.00, 95% CI 0.82 to 1.23). A retrospective analysis of women 18-65 years with symptomatic UTI due to E. coli showed that those with recent antibiotic use other than TMP-SMX were twice as likely to be infected with TMP-resistant strains (OR 2.37; 95% CI 1.14-4.95); while women who had taken TMP-SMX had a 17-fold increased risk of resistance (OR 16.74, 95% CI 2.9-96.95) [Brown 2002]. A case-control study by Wright et al [2000] of patients evaluated at the emergency room for symptoms of cystitis, likewise, showed that use of TMP-SMX was the strongest predictor of resistance with a fivefold increased risk of TMP-SMX resistance among patients who were currently using TMP-SMX or had used it in the past 3 months. A history of recurrent UTI, however, was not independently associated with resistance [Brown 2002, Wright 2000].*

Clinical implications: *In-vitro and clinical data suggest that TMP-SMX resistance occurs at a high level and does lead to therapeutic failures. Investigators have shown that majority of TMP-SMX resistant E.coli have minimum inhibitory concentrations to TMP and TMP-SMX that are higher than the achievable steady state concentration of the drug in the urine. Secondary analyses from small treatment trials show that this resistance results in clinical failure in approximately 50% of patients treated with TMP-SMX for acute cystitis [Gupta 2003]. A large prospective study by Raz et al [2002] confirmed that clinical cure on the first follow-up visit was significantly higher among those with TMP-SMX susceptible uropathogens compared to those with TMP-SMX resistant pathogens (88% vs. 54% respectively, p<001). Bacteriologic eradication and long-term cure rates were also significantly higher among those with TMP-SMX susceptible vs. those with resistant pathogens. Brown et al [2002] also showed that clinical failure rates are significantly higher in women with TMP-SMX resistant organisms compared to those with susceptible organisms (45.5 % vs 4.2%; RR 10.7, 95% CI 3.4 to 34.60).*

Comments: *Because accurate and generalizable local data on susceptibility patterns are not available, TMP-SMX can still be used upon the discretion of the physician especially on patients with no history of previous antibiotic use. In areas however where resistance rates are known, a cost-analysis showed that when resistance rates to TMP-SMX exceed 22%, use of a fluroquinolone becomes more cost effective [Le 2001]. A cost-minimization model from a health maintenance organization perspective suggested that in areas where local TMP-SMX E.coli resistance exceeds 10% and resistance to ciprofloxacin remains low (0.5% to 6%), ciprofloxacin XR is an appropriate alternative to standard empiric therapy [Perfetto 2004].*

4. What is the effective duration of treatment for acute uncomplicated cystitis?

Three-day therapy is the recommended duration of treatment (Grade A) except for nitrofurantoin, which must be given for 7 days (Grade A).

Summary of evidence

TMP-SMX short-term vs longer duration therapy
Benefits: *A meta-analysis [Warren 1999] of 7 RCTs (N=946) showed that single dose TMP-SMX was significantly less effective in eradicating initial bacteriuria than longer durations of therapy (87% vs. 94%; RR 0.92, 95% CI 0.88, 0.96). However, eradication rates of 3-day regimens compared to ≥ 7-day therapy did not differ significantly in a metaanalysis of 2 RCTs (N=350, 93% vs. 94%; RR 0.98, 95% CI 0.93, 1.04). Recurrence rates, likewise, did not differ significantly both for the single dose regimen vs longer durations of therapy (17% vs 13%; RR 1.32, 95% CI 0.93, 1.88) and the 3-day vs ≥ 7-day regimens (19% vs 12%; RR 1.61, 95% CI 0.97, 2.66).*
Harms: *Women on 3-day regimens reported significantly lower incidence of adverse reactions compared to those on ≥ 7-day regimens (18% vs. 30%; RR 0.59, 95% CI 0.44, 0.80). Similarly, adverse effects were also significantly less among those on single dose regimen compared to those on longer durations of therapy (11% vs 28%; RR 0.38, 95% CI 0.28, 0.52) [Warren 1999].*

Short-term nitrofurantoin vs short-term TMP-SMX
Benefits: *In a randomized controlled trial, 3-day therapy with nitrofurantoin 100 mg QID was less effective than TMP-SMX 160/800 mg BID even against nitrofurantoin-sensitive bacteria in eradicating bacteriuria (84% versus 98%; RR 6.3 95% CI 0.80 to 50) and cure rates were significantly lower (61% vs 82%; RR 2.17, 95% CI 0.99, 4.76) [Hooton 1995].*
Harms: *No significant difference in adverse events was seen in patients receiving TMP-SMX and nitrofurantoin (35% vs 43%; RR 0.81 95% CI 0.48-1.38) [Hooton 1995]. Most commonly reported symptoms were nausea and headache.*

Short-term fluoroquinolone vs short-term TMP-SMX
Metaanalysis of three RCTs [Warren 1999] comparing 3-day ofloxacin (n=253) with 3-day TMP-SMX (n=191) showed no significant difference in eradication rates (95% vs. 96% RR 0.99, 95% CI 0.95, 1.04), recurrence rates (RR 0.86; 95% CI 0.45, 1.64) and adverse effects (RR 0.94; 95% CI 0.69, 1.29).

Short-term fluoroquinolone vs longer duration TMP-SMX

Benefits: *In a RCT [Iravani 1999] of 521 women with AUC there was no difference in bacteriologic eradication rates 4-10 days post therapy between 3-day ciprofloxacin100 mg BID and 7-day nitrofurantoin100 mg BID (88% vs 86%; RR 0.88, 95%CI 0.50 to 1.53) and between ciprofloxacin and 7-day TMP-SMX 160/800 mg BID (88% vs 93%). Continued eradication rates however at 4-6 weeks post therapy was significantly higher for ciprofloxacin than TMP-SMX (91% vs 79%; RR 0.50, 95%CI 0.26 to 0.95).*

Harms: *The overall adverse event rates did not differ significantly as follows: 20% ciprofloxacin, 26% TMP-SMX, 25% nitrofurantoin (RR 0.78, 95% CI 0.62 to 0.99 for ciprofloxacin vs. TMP-SMX; RR 0.90, 95%CI 0.70 to 1.14 for ciprofloxacin vs nitrofurantoin). Most common adverse events were nausea and headache [Iravani 1999].*

Short-term fluoroquinolones vs other short-term fluoroquinolones

Benefits: *Clinical and bacteriologic cure rates did not differ significantly between 3-day regimens of levofloxacin 250 mg OD and ofloxacin 200 mg BID in a RCT of 594 women with AUC [Richard 1998]. For levofloxacin, clinical and bacteriologic cure rates were 98% and 96.2% respectively; while for ofloxacin 97% and 92.7% respectively with RR for clinical cure of 1.01(95% CI 0.98 to 1.05) and RR for bacteriologic cure of 1.01(95% CI 0.97 to 1.08).*

A double-blind RCT [Richard 2002] of 1344 patients showed bacteriologic cure rates for single dose gatifloxacin, 3-day gatifloxacin and 3-day ciprofloxacin did not differ significantly at 90%, 95% and 89% respectively (RR 1.34, 95% CI-0.65 to 2.78 for gatifloxacin single dose vs ciprofloxacin 3 days). Clinical response rates were also not significantly different; 93% for single dose gatifloxacin, 95% for 3-day gatifloxacin and 93% for 3-day ciprofloxacin (RR 0.99, 95% CI 0.49 to 2.03). Sustained cure rates (29-42 days post treatment) were not significantly different (90%, 88% and 92% for single dose gatifloxacin, 3-day gatifloxacin and 3-day ciprofloxacin respectively).

A double blind, double dummy RCT [Henry 2002] of 891 patients with AUC compared the efficacy of extended release ciprofloxacin (Cipro XR) 500 mg OD for 3 days and ciprofloxacin 250 mg BID (cipro BID) for 3 days. Efficacy analysis of 422 patients showed that bacteriologic eradication (94.5% vs 93.7%, RR 0.88, 95% CI 0.41 to 1.89) and clinical cure rates (95.5% vs 92.7%, RR 1.4, 95% CI 0.92 to 2.24) for Cipro XR and cipro BID did not differ significantly. Likewise, bacteriologic (85.8% vs 81.3%; RR 0.76, 95% CI 0.48 to1.21) and clinical cure rates (83.1% vs 85.8%; RR 1.19, 95% CI 0.86 to 1.64) at 25-50 days post treatment did not differ significantly.

Harms: *Drug-related adverse events did not differ significantly between levofloxacin and ofloxacin in the RCT by Richard [1998]. Most common adverse events were headache and insomnia.*

Gatifloxacin OD had comparable treatment related adverse events to 3-day ciprofloxacin and 3-day gatifloxacin. Adverse events commonly reported were nausea, headache and diarrhea. [Richard 2002]

In the CiproXR study [Henry 2002], two patients in each group experienced 1 or more adverse events that led to discontinuation (RR 1.16, 95% CI 0.93 to 1.45). In the ciproXR group, 1 patient experienced abdominal pain, nausea and vomiting and 1 had pruritus and maculopapular rash. In the ciproBID group, 1 discontinued treatment due to nausea and 1 progressed to pyelonephritis.

Short-term cephalosporins vs short-term fluoroquinolones

In a RCT [Naber 1993] of 3-day cefuroxime 125 mg BID vs 3-day ofloxacin 200 mg BID in 163 women with AUC, bacteriologic eradication 7 days post-therapy did not differ significantly between cefuroxime (80%) and ofloxacin (89%) with RR 1.8 (95% CI 0.77, 4.22). Likewise, clinical cure rates did not differ (84.8% and 95.2% respectively; RR 3.12, 95% CI 0.90, 10.85).

No significant difference in clinical and bacteriologic cure rates was seen at 7 days between 3-day cefixime 400 mg OD and 3-day ofloxacin 200 mg BID (clinical cure: 89% vs 92%; RR 1.6, 95% CI 0.63 to 4.1 and bacteriologic cure: 83% vs 86%; RR 1.4, 95% CI 0.65 to 2.97) in a double-blind RCT of 106 women [Raz 1994]. Sustained clinical and bacteriologic cure rates likewise did not differ between cefixime and

ofloxacin (clinical cure: 81% vs 84%; RR 1.3, 95% CI 0.66 to 2.76) and (bacteriologic cure: 77% vs 80%; RR 1.28, 95% CI 0.67 to 2.45). Only one patient reported nausea and headache with ofloxacin.

Long-term cephalosporins vs other cephalosporins/beta-lactams
Pooled efficacy analysis of 2 clinical trials [Cox 1987] that compared cefuroxime 125 mg BID (48 patients) with cefaclor 250 mg TID (15 patients) and cephalexin 250 mg QID (24 patients) for 10 days showed that clinical cure rates for AUC did not differ significantly among cefuroxime (79%), cephalexin (79%) and cefaclor (73%). Bacteriuria recurred 4-6 weeks post treatment in 21% of patients treated with cefuroxime or cefaclor and in 30% of patients treated with cephalexin. The only adverse events reported were gastrointestinal disturbances and mouth ulcers in 2 patients.

In a RCT of 71 patients [Cooper 1992] comparing cephradine 500 mg BID and cefuroxime 125 mg BID for 7 days, clinical cure rates were 55% for cephradine and 79% for cefuroxime. Reinfection rates 1 week after treatment were 29% for cephradine and 18% for cefuroxime. Most common adverse events reported were vaginal irritation and diarrhea in 14% of patients on cephradine and 6% on cefuroxime.

Pooled efficacy analysis of 2 clinical trials [Williams 1987] comparing cefuroxime 250 mg BID for 5 days (140 patients) with augmentin 375 mg TID (89 patients) and cefaclor (38 patients) 250 mg TID reported clinical cure rates of 77% for cefuroxime, 84% for augmentin and 79% for cefaclor. Bacteriologic cure was documented in 72% of patients treated with cefuroxime, in 70% given augmentin and in 96% given cefaclor. Drug-related adverse events were primarily gastrointestinal in nature, e.g. diarrhea, in 10% of patients given cefuroxime, 11% on augmentin and 5% on cefaclor.

Comments: *For patients wherein TMP-SMX, fluoroquinolones or nitrofurantoin are contraindicated, beta-lactams such as co-amoxiclav and cephalosporins (cephradine, cefuroxime, cefixime, cefpodoxime proxetil, cefetamet) may be given as alternative agents for 7 days. In general, efficacy rates of beta-lactam agents are significantly lower compared to TMP-SMX and fluoroquinolones based on limited studies [Warren 1999]. Factors possibly contributing to the decreased effectiveness of beta-lactam agents are the much shorter period of time that beta-lactams are present in higher concentrations in urine, its inferior ability to effectively eradicate carriage of E. coli in vaginal and fecal reservoirs [Hooton 2003, Johnson 2003]. Its usefulness is also limited by the increased frequency of vulvovaginal candidiasis associated with its use and its cost [Nicolle 2002].*

5. In elderly women (>65 years) with acute uncomplicated cystitis what is the effective duration of treatment?

In otherwise healthy elderly women presenting with signs and symptoms of acute cystitis, a three-day course of any of the antibiotics listed in table 4 is also recommended (Grade A).

Summary of evidence
Benefits: *A recent double-blind RCT [Vogel 2004] on 183 women at least 65 years old with no comorbidities confirmed that 3-day therapy with ciprofloxacin 250 mg BID was not inferior to ciprofloxacin 250 mg BID for 7 days. Bacterial eradication was 98% for 3 days and 93% for 7 days (RR 0.32; 95% CI 0.07, 1.54). Similarly, there were no significant differences in relapse (RR 0.78; 95% CI 0.40, 1.52) and reinfection rates (RR 1.12; 95% CI 0.55, 2.28) 6 weeks post treatment for the 3-day and 7-day regimens. This RCT resolves the inconclusive result of the Cochrane systematic review of earlier RCTs with poor methodological quality [Lutters 2003]. The review showed that rate of persistent bacteriuria at short term follow up (2 weeks post treatment) was better in the short or longer treatment group than the single dose group (RR 1.84, 95% CI 1.18 to 2.86). The comparison of short (3-6 days) and longer treatments (7-14 days) did not show any significant difference but the summary estimates were imprecise because of the limited number of studies and small sample size.*
Harms: *In the RCT by Vogel [2004], adverse events were significantly higher for the 7-day group than the 3-day group. These include drowsiness, loss of appetite and nausea or vomiting.*

Comments: *Exercise caution when prescribing fluoroquinolones to elderly patients. In a non-systematic review by Sprandel [2003], fluoroquinolone-related disturbances in blood glucose control seemed to be more common among elderly patients. Gatifloxacin is associated with a higher frequency of disturbances to blood glucose. Blockade of adenosine triphosphate–sensitive potassium channels in pancreatic β-cells may result in a dose- or concentration-related increase or decrease in insulin release, which in part supports the observation that patients aged ≥65 years have an increased risk of severe hyperglycemia, secondarily due to age-related decreases in renal function and higher serum gatifloxacin concentrations.*

Drug-associated cardiac dysrhythmias and the prolongation of electrographic QTc intervals remain issues of concern in the clinical use of fluoroquinolones. Animal and in vitro models have demonstrated that fluoroquinolones are inhibitors of the human ether-a-go-go –related gene (HERG) potassium channel that can be associated with cardiac arrhythmias. Ciprofloxacin and levofloxacin are weak HERG potassium channel–inhibitors. The following rank order of potency has been suggested: sparfloxacin > grepafloxacin, moxifloxacin, gatifloxacin > levofloxacin, ciprofloxacin.

6. What should be done for women whose symptoms worsen, do not completely resolve or do not improve after completion of a 3-day therapy?

Patients whose symptoms worsen or do not improve after 3 days should have a urine culture and the antibiotic should be empirically changed, pending result of sensitivity testing (Grade C).

Patients whose symptoms fail to resolve after the 7- day treatment should be managed as a complicated urinary tract infection (Grade C). ***(See Section VI)***

Summary of evidence: *Patients whose symptoms worsen or do not improve after a 3-day therapy may harbor a resistant pathogen. This will require a urine culture and the administration of a new antibiotic pending result of the sensitivity testing [Barry 1997].*

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 (Grade D).

Summary of evidence: *Informal cost benefit analysis of data from retrospective observational studies showed that routine screening after treatment is costly per case detected and provides no added clinical benefit [Johnson 2003]. A retrospective study [Winickoff 1981] 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. 61 women did not have a follow up culture (NFU) while 80 had post treatment urine cultures (FU). The 2 groups were equal with regards to race, recording of negative IVP, UTI, pyelonephritis, asymptomatic bacteriuria or recurrent UTI episodes. Symptomatic UTI developed within 3 months in 8.2% of the NFU and 15% of the FU group. Among the women in the FU group, only 3 out of 80 had a positive culture, and only 1 of these 3 developed symptomatic UTI.*

II. ACUTE UNCOMPLICATED PYELONEPHRITIS IN WOMEN

1. When is acute uncomplicated pyelonephritis suspected?

In otherwise healthy women with no clinical or historical evidence of anatomic or functional urologic abnormalities, the classic syndrome of acute uncomplicated pyelonephritis (AUPN) 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 [Rubin 1992]. Laboratory findings include pyuria (≥ 5 wbc/hpf of centrifuged urine) on

urinalysis and bacteriuria with counts of ≥ 10,000 cfu of a uropathogen/ml on urine culture [Roberts 1986, Rubin 1992].

2. What are the recommended diagnostic tests for acute uncomplicated pyelonephritis?

Urinalysis and Gram stain are recommended (Grade B).

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

Summary of evidence
Benefits: *No studies have directly addressed the diagnostic utility of urine culture and sensitivity and urine gram stain in AUPN. However, these tests are recommended because treatment options are simplified if a likely pathogen is established. Differentiating between gram-positive and gram-negative pathogens can guide optimal empiric antibiotic selection and minimize the consequences of inappropriate choice in terms of cost, resistance and adverse drug reactions. A randomized clinical trial [Talan 2000] comparing ciprofloxacin with TMP-SMX provides indirect evidence that treatment outcomes are better when the antibiotic regimen is active against the patient's organism. Bacteriologic and clinical failure rates are significantly higher if the patient is receiving antibiotics to which the organism is resistant. Mean cost per cure was also higher by 25% for TMP-SMX treated patients because they required more interventions and a change in antibiotic regimen.*

Blood cultures are not routinely recommended (Grade D).

Blood cultures done twice are recommended for patients who present with signs of sepsis defined as presence of any two of the following: temperature >38 ^{0}C or < 36^{0}C, leukopenia (WBC< 4,000) or leukocytosis (WBC > 12,000), tachycardia (HR>90 beats/min), tachypnea (RR> 20/min or PaCO2 <32mmHg), or hypotension (SBP< 90mmHg or >40mmHg drop from baseline) (Grade C).

Summary of evidence
Benefits: *A prospective study [Velasco 2003] of 583 women with clinical symptoms of AUPN that assessed the utility of blood cultures showed that discordant cases (different organisms isolated in blood and urine) were found in only 2.4%. Clinical and microbiologic outcomes did not differ between these cases and the rest of the patients studied. No changes of antibiotic treatment were needed based on blood culture results. An earlier retrospective chart review [McMurray 1997] of 301 patients with AUPN showed similar results. Only 18% had positive blood cultures with only one patient having a discordant result that did not require a change in antibiotic regimen.*

3. Treatment
3.1 Can patients with acute uncomplicated pyelonephritis be treated as outpatients?

Non-pregnant patients with no signs and symptoms of sepsis, who are are likely to adhere to treatment and return for follow-up, may be treated as outpatients (Grade B).

An initial parenteral dose of ceftriaxone may be given followed by an oral antibiotic (Grade B). Other parenteral antibiotics with similar efficacy as ceftriaxone may also be considered (Grade C).

The following are considered as 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 (Grade B).

Summary of evidence
Benefits: *We found no RCTs directly comparing inpatient versus outpatient management. The feasibility however of outpatient therapy requires demonstration that oral antibiotic is as effective as parenteral. We found 2 RCTs comparing oral versus IV antibiotics.*

A multicenter randomized double blind trial [Mombelli 1999] compared oral ciprofloxacin 500 mg BID versus IV ciprofloxacin 200 mg q 12 hrs in 141 patients with acute pyelonephritis, community acquired UTI and hospital acquired UTI. Patients with severe sepsis, unable to take oral medication or had renal obstruction or renal foci of suppuration, were excluded from the study. Subgroup analysis of those with severe pyelonephritis (N=66) showed that mean duration of fever was similar for both oral and IV ciprofloxacin (2.2 days, 95% CI 1.7 to 2.6 vs 2.6 days, 95% CI 2 to 3.2; p=0.18). Microbiologic failure at 3-5 days of treatment was also not statistically different, 3% oral ciprofloxacin vs. 2% IV ciprofloxacin (RR 1.92, 95%CI 0.18 to 20.7).

In another randomized open trial [Sanchez 2002], single dose IV ceftriaxone followed by cefixime 400 mg OD (N=54) was compared with standard treatment of IV ceftriaxone 1 gram daily maintained until culture results are out followed by an oral antibiotic (N=51). Both groups remained hospitalized until they became afebrile and urine culture was out but during hospitalization no other treatment was given that could not have been accomplished at home. Clinical cure (91% vs 92%; RR 0.85 95%CI 0.24-2.98) and microbiologic eradication after 3 days of treatment (100% for both groups) did not differ significantly.

Retrospective observational studies [Israel 1991, Pinson 1994, Safrin 1998] have also shown that outpatient management of acute uncomplicated pyelonephritis in immunocompetent non-pregnant women is effective.

Harms: *In the ciprofloxacin study [Mombelli 1999], treatment was generally well tolerated and adverse events occurred in 2 patients only – 1 on oral therapy developed mental confusion and therapy had to be discontinued and 1 on parenteral therapy developed pruritus but was able to finish therapy. In the cefixime study [Sanchez 2002], no adverse effects were reported.*

Comments: *The main limitations of these 2 studies are the small sample sizes and the short- term follow-up of the patients.*

3.2 What drugs can be used for empiric treatment of acute uncomplicated pyelonephritis?

Several effective regimens (fluoroquinolones, aminoglycosides, 3rd & 2nd generation cephalosporins, extended spectrum penicillins) are recommended (Grade A). ***(See Table 6)***

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 (Grade E).

Because of high resistance rates to TMP-SMX ***(See Table 5),*** **this drug is not recommended for empiric treatment (Grade E) but can be used when the organism is susceptible on urine culture and sensitivity.**

Combining ampicillin with an aminoglycoside offers no added benefit, except when enterococcal infection is suspected (Grade C).

IV antibiotics can be shifted to any of the listed oral antibiotics *(Table 6)* once the patient is afebrile and can tolerate oral drugs (Grade B). The choice of continued antibiotic therapy should be guided by the urine culture and sensitivity results once available (Grade B).

Table 6. Empiric treatment regimens for uncomplicated acute pyelonephritis

Antibiotic and Dose	Frequency and Duration
ORAL	
Ofloxacin 400 mg	BID; 14 days
Ciprofloxacin 500mg	BID; 7-10days
Gatifloxacin 400 mg	OD; 7-10 days
Levofloxacin 250 mg	OD; 7-10 days
Cefixime 400 mg	OD; 14 days
Cefuroxime 500 mg	BID; 14 days
Amoxicillin-clavulanate 625 mg (when gram stain shows gram positive organisms)	TID; 14 days
PARENTERAL (given until patient is afebrile)	
Ceftriaxone 1-2gm	Q 24
Ciprofloxacin 200-400mg	Q 12
Levofloxacin 250-500 mg	Q 24
Gatifloxacin 400 mg	Q 24
Gentamicin 3-5 mg/kg BW (+/-ampicillin)	Q 24
Ampi-sulbactam 1.5 gm (if with gram positive organisms on gram stain)	Q6
Piperacillin- tazobactam 2.25 – 4.5 gm	Q6-8

Summary of evidence

There is relative paucity of well-controlled trials comparing the efficacy of various antibiotic regimens in acute uncomplicated pyelonephritis. The recommended regimens in Table 6 have comparable efficacy, provided the organism is susceptible. The recommendations have taken into consideration the limitations of local reports on sensitivity patterns and are not meant to exclude other effective regimens. For instance, aminoglycosides other than gentamicin may be used such as amikacin. The choice of empiric antimicrobial should largely be based on the epidemiological information available to the physicians in their locality.

The IDSA clinical practice guideline committee found 9 studies on pyelonephritis, 5 of which were RCTs. A systematic review [Warren 1999] of the four RCTs also confirmed the suboptimal outcomes of treatment with ampicillin or ampicillin-like compounds because of high resistance rates and, increased recurrence rates even with susceptible organisms compared with TMP-SMX.

Subsequent studies on newer fluoroquinolones not included in the IDSA review using ciprofloxacin as comparator have shown similar clinical cure and bacteriologic eradication rates as described below.

Fluoroquinolones

Benefits: *One RCT [Cox 2002] on 372 adults with complicated and uncomplicated pyelonephritis compared gatifloxacin 400 mg OD or ciprofloxacin 500 mg BID both for 7-10 days. For those with AUPN, bacteriologic cure rates 5-9 days post therapy did not differ significantly (92% for gatifloxacin versus 85% for ciprofloxacin). Clinical cure rates, likewise, were not significantly different at 4-11 days post therapy (100% for gatifloxacin and 95% for ciprofloxacin) and at 25-50 days post therapy (88% for gatifloxacin and 95% for ciprofloxacin).*

Richard et al [1998a] subanalyzed the pyelonephritis patients enrolled in 2 multicenter RCTs to compare the efficacy and safety of levofloxacin 250 mg OD for 10 days with ciprofloxacin 500 mg BID for 10 days [Richard 1998b, Study 1] and levofloxacin 250 mg OD for 7-10 days vs lomefloxacin 400 mg OD for 14 days [Klimberg 1998, Study 2]. In this combined report, 186 microbiologically evaluable patients were subanalyzed (89 levofloxacin, 58 ciprofloxacin, 39 lomefloxacin). Cure rates 5-9 days post-therapy were

similar for the levofloxacin-treated groups (90% in study 1 and 95% in study 2). For both studies, combined clinical cure rates were 92% for levofloxacin, 88% for ciprofloxacin and 80% for lomefloxacin (RR 0.65 95%CI 0.24,1.76 for levofloxacin vs ciprofloxacin). Combined bacteriologic eradication rates were similar at 94% for levofloxacin and 94% for ciprofloxacin or lomefloxacin (RR 0.91 95% CI 0.29, 2.87).

A recent randomized double-blind trial [Talan 2004] compared the efficacy of 1,000 mg extended release ciprofloxacin (CIP-XR) once daily vs ciprofloxacin 500 mg twice daily (CIP-BID), each for 7 to 14 days in 92 patients with AUPN. Clinical cure rates were similar (97.5 % for CIP-XR vs 96.2% for CIP-BID) and bacteriologic cure rates did not differ significantly (87.5% vs 98%; RR 6.63, 95% CI 0.81 to 54.51) 5-11 days afer therapy. Likewise, no difference in bacteriologic cure 28-42 days after therapy (75.8% vs 81.4%; RR 1.3, 95% CI 0.55 to 3.11) and continued clinical cure was seen (83.5% vs 95.5%; RR 3.5, 95% CI 0.75 to 16.3).

***Harms:** In the study by Cox [2002], adverse events reported included dizziness, diarrhea and vomiting in 11 % of patients in the gatifloxacin group and 6% in the ciprofloxacin group (RR for discontinuing the drug because of an adverse event is 1.16, 95% CI 0.51 to 2.62).*

In the study of Richard [1998a], adverse effects occurred in 2% of patients on levofloxacin, 8% in those taking ciprofloxacin and 5% for lomefloxacin (RR 0.32, 95%CI 0.08 to 1.25 for levofloxacin versus ciprofloxacin). Gastrointestinal symptoms were common with both ciprofloxacin and levofloxacin whereas rash was the most common adverse effect with lomefloxacin.

Adverse event rates in the trial by Talan [2004] were similar for CIP-XR and CIP-BID at 32%. Thirteen percent of CIP-XR and 13.5% of CIP-BID treated patients reported drug-related events. Most common drug-related events were nausea, diarrhea, vomiting, headache, dizziness and vaginal moniliasis.

***Comments:** The results of the gatifloxacin [Cox 2002] and levofloxacin [Richard 1998a] studies should be interpreted with caution because the efficacy rates were derived from subgroup analyses of AUPN patients. In addition, the efficacy rates of levofloxacin from 2 studies that differed in methodology were combined. Study 1 was a double-blind study conducted in 31 centers in USA and Canada while study 2 was an open-label study conducted in 29 centers in USA.*

Beta-lactams
***Benefits:** Subgroup analysis of AUPN in a RCT [Naber 2002] comparing piperacillin tazobactam and imipenem for complicated UTI showed that clinical cure rates did not differ significantly (81.3% for piperacillin and 73.3% for imipenem, p=0.92).*

An open, randomized trial comparing cefuroxime 250 mg BID and ofloxacin 200 mg BID for 10 to 12 days in 135 adult outpatients with AUPN showed no significant difference in clinical cure rates (92% for cefuroxime and 94% for ofloxacin) [Naber 1998].

No clinical trials were found on the effectiveness of first generation cephalosporins for acute uncomplicated pyelonephritis.

***Comments:** Because of the increasing resistance to TMP-SMX despite the lack of generalizable local data on resistance rates of E.coli, TMP-SMX is no longer recommended as a first line drug in the empiric treatment of AUPN because it is a potentially serious infection with serious sequelae.*

3.3 What is the effective duration of treatment for acute uncomplicated pyelonephritis?

The recommended duration of treatment is 14 days. Selected fluoroquinolones *(see Table 6)* can be given for 7-10 days (Grade A).

Summary of evidence
Benefits: *The IDSA guidelines recommend 2 weeks of therapy for AUPN based on a review of 4 RCTs [Warren 1999].*

In a RCT [Talan 2000] of 255 women comparing oral ciprofloxacin 500 mg BID vs TMP-SMX 160/800 mg BID in an outpatient setting, clinical and bacteriologic cure rates 4-11 days post therapy were significantly higher with 7-day ciprofloxacin compared to 14-day TMP-SMX. Clinical cure rate for ciprofloxacin was 96% versus 83% for TMP-SMX (RR 1.16; 95% CI 1.06 to 1.28). Bacteriologic cure rates were 99% for ciprofloxacin and 89% for TMP-SMX (RR 1.11, 95% CI 1.04 to 1.19). Sustained clinical cure rate 22-48 days post therapy was higher at 82% for ciprofloxacin vs 72% for TMP-SMX (RR 1.14, 95% CI 1.01 to 1.28). Sustained bacteriologic cure rates were 84% for ciprofloxacin and 74% for TMP-SMX (RR 1.14, 95% CI 1.01 to 1.28). Adverse drug events were less with ciprofloxacin (24%) compared to 33% for TMP-SMX (RR 0.73, 95% CI 0.53 to1.0).

4. Who will require work up for urologic abnormalities?

Routine urologic evaluation and routine use of imaging procedures are not recommended (Grade D).

Consider radiologic evaluation if the patient remains febrile within 72 hours of treatment or if with recurrence of symptoms to rule out the presence of nephrolithiasis, urinary tract obstruction, renal or perinephric abscesses or other complications of pyelonephritis (Grade C). Obtain urologic consultation if workup shows these abnormalities (Grade C).

Summary of evidence
Benefits: *In a prospective study wherein renal ultrasonography was used to evaluate the kidneys during the course of AUPN in 25 women admitted consecutively for treatment, the frequency of detecting underlying anatomic abnormalities and focal infectious complications (transient and not requiring intervention) was low at 4% (95% CI 0-12%) and 8% (95% CI 0-19%), respectively. Given the costs of radiologic work-up and the low diagnostic yield, women presenting with a first episode of AUPN do not require further investigation. Limiting radiologic evaluation to those patients who do not respond to appropriate antibiotic therapy 72 hours after initiation of treatment increases the number of patients with clinically significant urographic findings [Kanel 1988].*

5. 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 (Grade C).

Routine post-treatment cultures in patients who are clinically improved are also not recommended (Grade C).

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 (Grade C).

Summary of evidence: *The above recommendations are 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.*

6. What is the recommended management for patients whose symptoms recur?

Recurrence of symptoms requires antibiotic treatment based on rine culture and sensitivity test results, in addition to assessing for underlying genitourologic abnormality (Grade C).

The duration of re-treatment in the absence of a urologic abnormality is 2 weeks (Grade C).

For patients whose symptoms recur and whose culture shows the same organism as the initial infecting organism, a 4-6 week regimen is recommended (Grade C).

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

III. ASYMPTOMATIC BACTERIURIA IN ADULTS

1. When is asymptomatic bacteriuria diagnosed?

Asymptomatic bacteriuria (ASB) is defined as the presence of $\geq$ 100,000 cfu/ml of one or more uropathogens in two consecutive midstream urine specimens or in one catheterized urine specimen in the absence of symptoms attributable to urinary tract infection.

Summary of evidence
In the absence of symptoms, Kass [1956] showed that the quantitative threshold of $\geq$ 100,000 cfu/ml from midstream urine or catheterized urine was useful to differentiate infection from contamination. Other investigators have validated this threshold [Bartlett and Galen 1983, Platt 1983]. Because these patients are symptomless, two consecutive cultures yielding the same organism/s from midstream urine specimens are needed for the diagnosis.

2. Who are the patients that should be screened and treated for ASB?

Screening and treatment is recommended in the following: (1) patients who will undergo genitourinary manipulation or instrumentation (Grade B); (2) post-renal transplant patients up to the first 6 months (Grade B); (3) patients with diabetes mellitus with poor glycemic control, autonomic neuropathy or azotemia (Grade C); and all pregnant women (Grade A).

Any of the antibiotics for acute uncomplicated cystitis listed in Table 4 can be used for treatment of ASB (Grade C). A 7- to 14-day course is recommended (Grade C). ***For specific recommendations on pregnant women, please refer to Section IV.***

Summary of evidence
Genitourinary procedures
Benefits: *Genitourinary surgery with trauma and bleeding of the mucosa allows organisms in the urinary tract to invade the systemic circulation. In patients with bacteriuria undergoing a traumatic urologic procedure, 25-80% will have bacteremia if no treatment is given [Olson 2000]. Antimicrobial treatment of ASB before genitourinary manipulation or instrumentation can prevent bacteremia and sepsis [Olson 2000, Grabe 2001, Zhanel 1990]. A meta-analysis of 32 studies on antibiotic prophylaxis for transurethral resection of the prostate (TURP) found an average rate of bacteriuria and urinary tract infection of 26% in 4260 patients and sepsis in 4.4% [Berry 2002].*

Controversy exists on which urologic interventions require preoperative treatment of asymptomatic bacteriuria [Grabe 2001, Grabe 2004]. Where a high probability of bleeding into the genitourinary tract is anticipated, preoperative antimicrobial treatment is recommended. It is suggested that patients with

ASB should be treated before urodynamic studies, stent insertion, TURP and removal of ureteral stones [Grabe 2001].

Renal transplant patients

Prevalence and benefits: *In a prospective observational study [Mendoza 1997] of infections in renal allograft recipients at the National Kidney and Transplant Institute (NKTI), the prevalence of infections was highest at 54% during the first 3 months following transplantation. The infection rate declined to 23% at 4-6 months and 13% at 7-9 months post-transplantation. During the 10-12th month post-transplant, the prevalence was only 10%. Bacterial infections accounted for 76% of total infections in the first 3 months with pneumonia and urinary tract infection as the most frequent bacterial infections. There was no clear relation between occurrence of bacterial infection and the type of immunosuppressive regimens. No correlation between rejection and bacterial infections was found.*

Earlier studies have also shown that during the first 3 months post-transplant, UTIs occur at a high rate of 29-95% and are usually asymptomatic. Untreated UTIs among these transplant patients are frequently associated with overt pyelonephritis, bacteremia and allograft dysfunction [Korzeniowski 1991]. In a study of 50 post-renal transplant patients not given TMP-SMX or antiviral prophylaxis after transplantation, 47% of all infectious episodes (67% bacterial) occurred during the first 2 months. UTIs were the most common (n=144 episodes), especially asymptomatic bacteriuria (n=106 episodes). The frequency of infections was higher compared to studies using bacterial and viral prophylaxis [Martinez-Marcos 1994].

The presence or absence of asymptomatic bacteriuria in post renal transplant patients has not been associated with graft survival in a study by Griffin et al [1979]. In patients who survived for more than one year after transplantation, 42% had developed UTI. None of the infections led to serious complications or death. In another study [Cuvelier1985] evaluating occurrence of UTIs beyond 3 months post-transplantation, the incidence of UTI decreased progressively from 25% to 0%, with 50% of patients remaining free of infection during a follow-up period averaging 7 years. Late UTI did not affect graft or patient survival, or graft function at 5 years.

Currently, early post renal transplant therapy includes routine perioperative antibiotics, restriction of duration of urethral catheterization, and use of long-term prophylactic antibiotics to prevent all post-transplant infections. These interventions have decreased the occurrence of asymptomatic and symptomatic UTIs in the post-transplant period [Hoy 1985]. Because of the high prevalence of asymptomatic bacteriuria in the early post-renal transplant period, it may be appropriate for the clinician to screen for ASB for up to 6 months. Continued screening in a clinically stable renal transplant patient beyond 6 months does not seem to be beneficial given the low frequency of ASB and the lack of impact on graft survival [Nicolle 2003].

Diabetic patients

Prevalence: *There are no population-based surveys of ASB among Filipino diabetics. The prevalence of ASB among women undergoing treatment for diabetes is 7% to 13% generally threefold higher than nondiabetic women. The prevalence of ASB is not increased compared to nondiabetic men, ranging from 0.7 – 11.1%. Most studies have shown that the type or duration of diabetes, or the adequacy of diabetic control do not influence the prevalence of ASB [Zhanel 1991]. However, a survey among diabetic aboriginal women in Canada found that duration of the diabetes and presence of long-term complications including retinopathy, nephropathy and neuropathy were associated with ASB [Zhanel 1995]. This increased prevalence of ASB in diabetic women may be largely attributable to autonomic neuropathy leading to impaired bladder voiding [Patterson 1997]. A case-control study of 228 women with diabetes and 146 women without diabetes showed that impaired metabolic control of diabetes, as revealed by higher glycated hemoglobin levels, significantly increased the risk for developing ASB ($p < 0.05$) [Bonadio 2004].*

Benefits: *In a randomized controlled trial of 3- monthly screening and treatment compared with no treatment for ASB in 105 diabetic women by Harding et al [2002], more symptomatic UTIs occurred in the subset of diabetic patients with glycosuria and neuropathy [Kudva 2003].*

Comments: *Glycosuria predisposes diabetics to UTI because glucose can serve as a growth factor for bacteria, while neuropathy can be associated with abnormal GU motility. Clinicians should discuss antibiotic treatment with diabetic women who have ASB and glycosuria (poor glycemic control), autonomic neuropathy, or serum creatinine > 200 μmol/dl. Based on guidelines from the Philippine Diabetes Association, complications and risk assessment should be done at least once a year. This includes a urinalysis to screen not only for pyruia and hematuria but also for the presence of proteinuria.*

3. Who should not be screened and treated for ASB?

Routine screening and treatment for asymptomatic bacteriuria is not recommended for healthy adults (Grade D). Likewise, periodic screening and treatment for asymptomatic bacteriuria is not recommended in the following: (1) patients with diabetes mellitus with adequate glycemic control, no autonomic neuropathy or azotemia (Grade E); (2) elderly patients (Grade E); (3) patients with indwelling catheters (Grade E); (4) immunocompromised patients (Grade C); (5) other solid organ transplant patients (Grade C); (6) HIV patients (Grade C); (7) spinal cord injury patients (Grade D) and (8) patients with urological abnormalities (Grade C).

Summary of evidence

Diabetic patients

Prevalence: *Pleae see related summary of evidence under Question 2 p.20*

Benefits: *In a randomized controlled trial of 3- monthly screening and therapy or no therapy for ASB in 105 diabetic women [Harding 2002], no added benefit for screening and treatment of ASB in DM women was demonstrated. On intention-to-treat analysis after a mean follow-up of 27 months, the proportion of patients having ≥ 1 episode of symptomatic UTI did not differ between those who had antimicrobial therapy and those on placebo (41% vs. 40%). There was also no difference in terms of the time to a first symptomatic UTI episode. Llikewise, no significant difference in the occurrence of pyelonephritis, cystitis, or all episodes of UTI and hospitalizations due to UTI or to other causes was observed. Long-term prospective studies of the natural history of diabetic women also showed that accelerated progression to hypertension, renal failure or other long-term complications was similar for those with and without ASB [Geerlings 2001, Semetkowska-Jurkicwicz 1995].*

Harms: *In the RCT by Harding [2002] there was greater antimicrobial exposure and higher frequency of adverse drug effects among those treated for ASB. Women in the treatment group also had significantly more episodes of ASB following therapy.*

Elderly population

Prevalence: *There are no population-based studies on asymptomatic bacteriuria among elderly Filipinos. Various surveys of community populations in developed countries show that the prevalence of ASB increases with age irrespective of sexual activity. In women 50 to 60 years of age, the prevalence is 6-7% and 8-10% at 70-80 years [Kunin 1968]. In non-institutionalized elderly men, the prevalence is 12% [Mims 1990]. It is highest among institutionalized elderly women (25-57%) and men (15-37%). The prevalence in young to middle-aged adults is less than 5% in women and 1.5% in men [Nicolle 1997].*

Benefits: *Current evidence does not show significant benefit in the treatment of ASB in the elderly population. A cohort study of ambulatory elderly women showed that asymptomatic bacteriuria was not independently associated with mortality [Abrutyn 1994]. Controlled clinical trials on treatment versus no treatment of ambulatory elderly women found that treatment of ASB did not significantly reduce mortality and symptomatic episodes of UTI [Abutryn 1996, Boscia 1987]. RCTs comparing treatment versus no treatment on elderly institutionalized men and women showed no benefits with treatment [Abutryn 1994, Nicolle 1983, Nicolle 1987, Ouslander 1995]. An association with ASB and increased 5-year mortality was reported in elderly women in a Finnish study, however, subsequent reports with 5 and 9 years follow-up have not reported an association of ASB and survival for either men or women [Nicolle 2003, Sourander 1972].*

Harms: *Two RCTs among institutionalized elderly women showed increase rates of adverse reactions from antimicrobial therapy, with one showing an increased frequency of reinfection with resistant organisms [Nicolle 1987, Ouslander 1995].*

Patients with long-term indwelling catheters
Prevalence: *Urethral catheters remaining in-situ for over 30 days are considered chronic indwelling catheters. Bacteriuria is universal in patients with long-term indwelling catheters [Nicolle 2003]. Urine specimens obtained through the catheters samples the biofilm as well as bladder urine. The number of species and quantitative count of bacteria isolated in urine collected through a catheter in place for several days is greater than a simultaneous specimen collected through a freshly placed catheter [Tenney 1988, Raz 2000].*

Benefits and harms: *A RCT of treatment with cephalexin versus no treatment of ASB in long-term catheterized patients showed no benefit, and increased rates of antibiotic-resistant bacteria in the treated group [Warren 1982]. A noncomparative study of sequential antibiotic therapy in an elderly populatin also showed that treatment of ASB does not eliminate bacteriuria and usually results in replacement with organisms resistant to the antibiotic given [Alling 1975].*

Patients with short-term indwelling catheters
Prevalence: *The incidence of significant bacteriuria among catheterized patients with initially absent or low-count bacteriuria ranged from 18% - 62% within 2 days from catheterization [Stark and Maki 1984].*

Benefits: *In a randomized controlled trial [Harding 1991] of treatment with TMP-SMX versus no treatment of persistent catheter-acquired bacteriuria 48 hours following catheter removal, 26% of women in the placebo group developed symptoms within 14 days, while 36% had spontaneous resolution. In the non-treated group, bacteriuria resolved spontaneously in 74% of women <65 years of age and 4% of women over 65 years. Bacteriologic cure at 4 weeks was 89% in the treated group of women < 65 years and 62% of women over 65 years.*

Spinal cord-injured patients
Patients with spinal cord injury have a high prevalence of bacteriuria ranging from 20% to 98% [Nicolle 2003]. Prospective cohort studies however do not report progression to renal failure with bacteriuria if low bladder pressure is maintained either by intermittent catheterization, condom drainage or sphincterotomy as necessary [Sotolongo 1990]. A small placebo-controlled trial reported no decrease in symptomatic infection with treatment of bacteriuria [Mohler 1987].

Patients with genitourinary abnormalities
Among patients with genitourinary abnormalities, the incidence of asymptomatic bacteriuria depends on the primary renal disease: chronic glomerulonephritis, 12%; diabetic nephropathy, 13%; polycystic kidney disease, 41%; and chronic glomerulonephritis, 67% [Zhanel 1990].

Other immunocompromised patients
There is no evidence to recommend screening and treatment of ASB in solid organ transplant patients. Screening for ASB is not recommended in the CDC [2000] guidelines for infection prevention in bone marrow transplant recipients because of limited data. Even with the use of prophylactic antibiotics, infection-related fatality rates are not reduced [Murphy 1997].

The prevalence of bacteriuria in 222 female prostitutes in Kenya was 23%. The proportions of those who were HIV positive and HIV negative were similar and bacteriuria did not vary with the CD4+ count [Ojoo 1996]. The prevalence of ASB in HIV-infected men with CD4 count < 200/ml was 30% during 6-monthly screening over 2 years. In HIV infected men with CD4 counts of 200 – 500, the prevalence was 11%, which is similar to the prevalence in non-HIV infected men with CD4 counts > 500 [Hoepelman 1992]. There are no reports of negative clinical outcomes due to ASB in HIV patients.

Comments: *The criteria used in deciding whether to screen or not for any disease condition depends on the burden of the disease condition, performance characteristics of the screening test, the effectiveness of*

interventions for treatment or prevention of transmission once infection has been detected and the cost-effectiveness of the screening test and the treatment or preventive intervention [Fletcher1996].

4. What is the optimal screening test for ASB?

Screening by urine culture is recommended (Grade A).

In the absence of facilities for urine culture, significant pyuria (>10 wbc/hpf) or a positive gram stain of unspun urine (≥2 microorganisms/oif) in 2 consecutive midstream urine samples can be used to screen for ASB (Grade C). Urine culture and sensitivity testing are not necessary when urinalysis is negative for pyuria or urine gram stain is negative for organisms (Grade B).

Summary of evidence
Pyuria has a good predictive value in patient populations where the prevalence of ASB is at least 10%. With pyuria of > 10 wbc/hpf, the likelihood ratio for a significant urine culture result among ambulatory elderly men was 417; for 2 – 10 wbc/hpf LR was 2; for 0 – 1 wbc/hpf LR was 0.03 [Norman 1996].

IV. URINARY TRACT INFECTION IN PREGNANCY

A. ASYMPTOMATIC BACTERIURIA IN PREGNANCY

1. When is asymptomatic bacteriuria in pregnancy diagnosed?

Asymptomatic bacteriuria in pregnancy is the presence of ≥ 100,000 cfu/ml of one or more uropathogens in two consecutive midstream urine specimens or one catheterized urine specimen, in the absence of symptoms attributable to a urinary tract infection.

In settings where obtaining 2 consecutive urine cultures are not feasible or difficult, 1 urine culture is an acceptable alternative for the diagnosis of ASB in pregnancy (Grade C).

Summary of evidence
A second urine culture for ASB is done to discriminate between true bacteriuria and contamination. In the absence of symptoms, Kass [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. Other investigators have validated this threshold [Bartlett and Gale 1983, Platt 1983]. Because these individuals are symptomless, 2 consecutive cultures yielding the same organism/s from midstream urine specimens are needed for the diagnosis.

However, in a brief report evaluating the molecular identity of 32 E. coli isolates obtained in 2 consecutive urine cultures from 16 patients with ASB, Geerlings et al [2000] found different E. coli isolates in 7 of them. This implies that nearly half (44%) of the patients who had been previously classified as having ASB were reinfected with a different strain. Thus, obtaining 2 consecutive urine cultures to accurately diagnose ASB in pregnant women may not necessarily identify the etiologic agent.

2. Do all pregnant women have to be screened for ASB?

All pregnant women must be screened for ASB on their first prenatal visit between the 9th to 17th weeks, preferably on the 16th week age of gestation (Grade A).

Summary of evidence
Prevalence of ASB: *In a prevalence study [Sescon 2003] conducted among Filipino pregnant women at a tertiary-care government hospital in Manila, the overall prevalence rate was 1.9% in women with 2 consecutive urine cultures. However, because only 54% of the women in this study had second cultures*

done, a sensitivity analysis was done, with ASB defined as two urine cultures showing significant bacteriuria OR, in the absence of a follow-up culture, one result showing significant bacteriuria. In this second scenario the overall prevalence rate was 4.3%.

The most common isolates from Filipino pregnant patients with definite ASB were Escherichia coli 63%, Klebsiella pneumoniae 12%, Enterococcus 12%, Staphyloccus saprophyticus 7%, Staphylococcus aureus 4%, and Klebsiella ozanae 2% [Sescon 2003].

In the same study [Sescon 2003], the significant risk factors associated with ASB in pregnant women among those who had 2 urine cultures were: age of gestation < 12 weeks AOG (OR 3.2, 95% CI 2.55 to 3.89) and hemoglobin levels < 100mg/dl (OR 2.75, 95% CI 1.95 to 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 to 2.55) and history of UTI (OR 1.57, 95% CI 1.01 to 2.44).
Foreign data [Golan 1989] show 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%).

Benefits: *The risk of acquiring bacteriuria increases with the duration of pregnancy, highest between the 9th and 17th weeks of gestation. The 16th gestational week appears 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 [Stenqvist 1989, Andreole 1991].*

The two most important complications of untreated ASB are acute cystitis and acute pyelonephritis. Fetal complications such as low birth weight (LBW) and preterm delivery have been associated with asymptomatic bacteriuria.

In cohort studies, non-bacteriuric patients had only two-thirds the risk of LBW and half the risk of preterm delivery compared to untreated ASB. A meta-analysis of cohort and randomized treatment trials indicated a strong association between untreated ASB and low birth weight/preterm delivery and that antibiotic treatment is effective in reducing the occurrence of LBW [Romero 1989].

Preeclampsia has also been reported to increase susceptibility to infection. Kincaid-Smith and Bulba [1965] reported that hypertension in pregnancy was more frequent in women with bacteriuria than in those without bacteriuria. The result of a controlled prospective study comparing the frequency of bacteriuria in women who developed pre-eclampsia with that in women with uncomplicated disease was consistent with those previously reported [Hill 1986]. The prevalence of ASB in pre-eclampsia is 19%.

3. What is the optimal screening test for ASB in pregnancy?

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

In areas where urine culture is not available, the following can be used for screening: an initial gram stain of centrifuged urine (cut-off: same morphology of bacteria seen in >6 of 12 hpfs in centrifuged urine sample). If positive, this must be followed by a urinalysis to determine pyuria. A cut-off level of >5 wbc/hpf suggests ASB (Grade C). To minimize multiple visits to the lab and/or clinic, both tests can be requested simultaneously, but with the urinalysis being performed after a positive gram stain result. ***(Please see Algorithm section)***

Urine dipsticks for leukocyte esterase and/or nitrite tests are not recommended for screening for ASB in pregnancy (Grade E). Urinalysis alone is not recommended for screening (Grade E).

Summary of evidence

Rapid diagnostic tests: *There is no good evidence to support the use of rapid diagnostic tests in screening for ASB or as prescreening for patients who may need urine cultures. In a systematic review [Garingalao-Molina 2000] of 5 studies using urine dipsticks or urinalysis for bacteriuria and in 2 criterion standard studies [McNair 2000, Millar 2000] not included in the review, all yielded low sensitivity rates and variable specificity, positive and negative predictive values. (See Table 7)*

Table 7. Performance characteristics of reagent strips (%)

No	Study	Sensitivity	Specificity
1	Archbald 1984 (N=324)		
	Nitrites	37	100
	Microstix	33	98
2	Bachmann 1993 (N=1,047)		
	Leukocyte esterase (LE)	16.7	97.2
	Nitrites	45.8	99.7
	LE or Nitrites	50.0	96.9
	LE and Nitrites	12.5	100
3	McNeeley 1987 (N=694)		
	LE or Nitrites	69.6	83.4
4	Robertson 1986 (N=750)		
	LE	77.4	96.1
	Nitrites	43.4	98.9
	LE or Nitrites	92.0	95.0
	LE and Nitrites	32.2	94.2
5	Tincello 1998 (N=893)		
	Nitrites	18.8	99.5
	Test combined	33.3	91.1
	Millar 2000 (N=383)		
	Uriscreen	70	45
	Nitrites	45	97
	Leukocyte esterase (LE)	69	69
	Dipstick (LE+Nitrites)	81	97
	Microscopic using hemocytometer chamber		
	Pyuria (>5wbc/ml of centrifuged urine)	67	80
	Bacteria (1 or >)	93	43
	Pyuria+Bacteriuria	93	42
	McNair 2000 (N=528)		
	Urinalysis	80.6 (63.4- 91.2)	71.5 (67.3-75.4)
	Reagent strips	47.2 (30.8-64.3)	80.3 (76.4-83.7)

1-5 From a systematic review of studies by Garingalao-Molina 2000

Urine gram stain

There is evidence to support the use of urine gram stain as an alternative in screening for ASB or as prescreening for patients who may need urine cultures in view of its acceptable sensitivity. (See Table 8)

Table 8. Performance characteristics of urine gram stain (%)

Study	Sensitivity (95% CI)	Specificity (95% CI)
1. McNair 2000 (N=528)		
Gram Stain of Centrifuged Urine (same morphology of bacteria seen in >6 of 12 hpfs)	100 (88-100)	7.7 (5.6-10.5)
2. Bachmann 1993 (N= 1,047)		
Gram Stain		
Definite positive: 2 or > organisms/OIF	83.3	94.9
Borderline (1 organism/OIF) or Definite Positive	91.7	89.2

Urine microscopy for pyuria

There is some evidence to support the use of urine microscopy for pyuria in deciding which patients have ASB. In this overview of urine microscopy for pyuria, 2 studies uniformly yielded low sensitivity rates, acceptable specificity, and variable positive and negative predictive values. (See Table 9)

Table 9. Performance characteristics of urine microscopy for pyuria

Study	Sensitivity (%)	Specificity (%)
Archbald 1984 (N=324)		
Pyuria: 5 or more wbc/hpf	20	89
Bachmann 1993 (N=1,047)		
Pyuria: >10 wbc/hpf	25	99
Adjusted cut-off: >50 wbc/hpf	8.3	99.7

Benefits/Harms: *We found no data regarding the cost-effectiveness of doing a dipstick or urinalysis as an initial screening test for ASB in pregnancy in the absence of urine culture. A decision analysis by Rouse et al [1995] compared 2 screening strategies to detect asymptomatic bacteriuria during pregnancy using leukocyte esterase and urine culture. The cost of screening and treatment of asymptomatic bacteriuria per 1000 pregnancies was US$1,968 with dipstick and US$19,264 with culture. The cost of treating pyelonephritis with no screening was US$57,562, versus US$40,257 with dipstick and US$27,832 with culture. Therefore, both the dipstick and the culture strategy were cost-beneficial (based on a pyelonephritis cost of US$2,485) when compared with no screening. However, because it costs US$3,492 to prevent each additional case of pyelonephritis with culture that was not prevented by dipstick, the culture strategy was not cost-beneficial compared with the dipstick strategy. When compared with a policy of no screening, screening for and treatment of asymptomatic bacteriuria to prevent pyelonephritis in pregnancy is cost-beneficial whether based on the leukocyte esterase-nitrite dipstick or on urine culture.*

Comments: *An appropriate screening test must have an acceptable sensitivity and specificity to detect ASB in pregnancy. The approach of doing an initial gram-stain followed by urinalysis is recommended because there is no single rapid test that has adequate sensitivity and specificity rates. In the absence of urine cultures, the initial test for screening high-risk patients should be a gram stain because of its high sensitivity rate and its ability to screen out the true negatives with a reasonable degree of certainty. This must be followed by a urinalysis to determine pyuria because of its high specificity rates to confirm ASB in the absence of cultures. Doing the tests with an initial urinalysis followed by a gram stain will not effectively pick up ASB patients because of the low sensitivity of urinalysis. Urine culture, however, remains as the gold standard and optimal diagnostic test for ASB detection.*

Recognizing the low sensitivity of urinalysis and dipstick and the potential consequence of missing pregnant patients with ASB, the UTI-CPG task force modified the Philippine Guidelines on Periodic Health Examination (PHEX) recommendation of doing dipstick or urinalysis in the absence of urine c/s facilities followed by confirmation of positive results with urine c/s [Festin et al 2004]. This was discussed and approved in the public forum.

4. What is the effective treatment for ASB in pregnancy?

Antibiotic treatment for asymptomatic bacteriuria is indicated to reduce the risk of acute cystitis and pyelonephritis in pregnancy as well as to reduce the risk of LBW neonates and preterm infants (Grade A).

It is recommended that antibiotic treatment be initiated upon the diagnosis of ASB in pregnancy. Among the drugs that can be used are nitrofurantoin (not for those near-term), co-amoxiclav, cephalexin, and cotrimoxazole (not in the 1st and 3rd trimesters) depending on the sensitivity results of the urine isolate (Grade B). A 7-day course is recommended (Grade B).

A follow-up culture should be done one week after completing the course of treatment (Grade C).

Table 10. FDA Pregnancy risk and Hale's lactation risk categories for commonly prescribed antimicrobials in urinary tract infection

Category B, L1, L2	Category C, L3	Category D, L3
Nitrofurantoin Amoxicillin- clavulanate Cephalosporins	TMP-SMX (Avoid in 1st and 3rd trimester)	Aminoglycosides
Lactation Risk Category		
L1 – safest, controlled study = fails to demonstrate risk L2 – safer, limited number of women studied without risk L3 – moderately safe, no controlled study or controlled study shows minimal, non-life-threatening risk L4 – hazardous, positive evidence of risk, may be used if maternal life-threatening situation L5 – contraindicated, significant, and documented risk		
FDA Pregnancy Risk Categories		
Category A – well-controlled human study = no fetal risk in first trimester. No evidence of risk in 2nd , 3rd trimesters. Risk to fetus appears remote. Category B – animal studies do not demonstrate fetal risk, but no controlled study in humans OR animal studies show adverse effect but not demonstrated in human study. Category C – no controlled study in humans available. Animal studies reveal adverse fetal effects Category D – Positive evidence of human fetal risk. Use in pregnant woman occasionally acceptable despite risk. Category E – animal or human studies demonstrate fetal abnormality. Evidence of fetal risk based on human study. No indication in pregnancy.		

Adapted from: Fitzgerald MA. Urinary Tract Infection: Providing the Best Care. Available at http://www.medscape.com/viewprogram/1920, Accessed Feb 3, 2004.

Summary of evidence

Benefits: *A Cochrane systematic review [Smaill 2004] showed that antibiotic treatment of ASB in pregnancy was effective in clearing ASB (4 studies, OR 0.07, 95% CI 0.05 to 0.10); reducing the incidence of pyelonephritis (13 studies, OR 0.24, 95% CI 0.19 to 0.32) and the incidence of preterm delivery or low birth weight babies (10 studies, OR 0.60, 95% CI 0.45 to 0.80) compared to placebo or no treatment. The number of women needed to treat to prevent one episode of pyelonephritis is seven. Studies included in this review were conducted in the 1960s and '70s and antibiotics used were mainly sulfonamides and nitrofurantoin.*

Comments: *Despite the methodological weaknesses of the studies included in this metaanalysis, the results are consistent in reducing the incidence of pyelonephritis with treatment of ASB. The overall incidence of pyelonephritis in the untreated group was 19% (range: 0 to 29%). The presence of ASB further identifies a population at risk of developing acute pyelonephritis for which treatment is indicated [Smaill 2004].*

Because of poor methodology, a definitive conclusion concerning the reduction of preterm delivery cannot be drawn. On the other hand, the apparent reduction in preterm delivery is consistent with current theories about the role of infection as a cause of preterm birth [Smaill 2004].

Duration of treatment: *A Cochrane systematic review [Villar 2004] of eight RCTs comparing single dose with four to seven day treatment regimens for ASB in pregnancy found no differences in failure rates (RR 1.13, 95% CI 0.82 to 1.54) and recurrent asymptomatic bacteriuria (RR 1.08, 95% CI 0.70 to 1.66). However, the studies were significantly heterogeneous and were generally of poor quality. No differences were detected for preterm births and pyelonephritis although the sample sizes of the trials were small. There was a lower prevalence of adverse effects in short-course treatment compared to long-term treatment (RR 0.53, 95% CI 0.31 to 0.91). Antibiotics studied were amoxicillin, ampicillin, TMP-SMX, trimethoprim and sulphonamides.*

Comments: *Resistance rates of E. coli to amoxicillin and ampicillin remain high. Resistance rates to TMP-SMX are also high as reported in the 2000-2003 Antimicrobial Resistance Surveillance Program of the Department of Health. Because of the consitently high resistance rates, local antibiotic resistance data should be checked to guide antibiotic choice. (See section on acute uncomplicated cystitis). In the prospective study done by Sescon et al [2003] from 1999-2000 on ASB in pregnant women consulting at the PGH outpatient department, resistance rate of E.coli to TMP-SMX was 31%, 53% to amoxicillin, 29% to coamoxiclav, 18% to cephalexin, 2% to cefuroxime and no resistance to nitrofurantoin. E.coli comprised 50% of the isolates (51 out of 102 isolates).*

B. ACUTE CYSTITIS IN PREGNANCY

1. When do you suspect acute cystitis in pregnancy?

Acute cystitis is characterized by urinary frequency, urgency, dysuria and bacteriuria without fever and costovertebral angle tenderness. Gross hematuria may also be present [Harris 1984].

Summary of evidence
The diagnosis of acute cystitis even in pregnancy is still clinical and based on symptoms such as dysuria, frequent urination, and lower abdominal or suprapubic pain, without fever. (See Section I also on acute uncomplicated cystitis)

2. Is a pretreatment diagnostic test required in acute cystitis in pregnancy?

In pregnant women suspected to have acute uncomplicated cystitis, obtain a urine culture and sensitivity test of a midstream clean catch urine specimen (Grade B).

In the absence of a urine culture, the laboratory diagnosis of acute cystitis can be determined by the presence of significant pyuria defined as a) $\geq$ 8 pus cells/mm^3 of uncentrifuged urine OR b) $\geq$ 5 pus cells/hpf of centrifuged urine, and c) a positive leukocyte esterase and nitrite test (Grade C).

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 because unnecessary exposure of the fetus to antimicrobial therapy should be avoided when possible [Johnson 2003]. Urine culture results can confirm the diagnosis of bacterial UTI and define the susceptibility of the infecting organism especially when therapeutic options are limited by pregnancy. We did not find any trials assessing directly the clinical utility of rapid urine tests in diagnosing acute cystitis in pregnant women.

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 (Grade A).

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 (Grade A). TMP-SMX and fluoroquinolones are relatively contraindicated during pregnancy because of their potential teratogenicity and the third trimester risk of kernicterus with TMP-SMX. A 7- day course is recommended (Grade C).
In the absence of a urine culture and sensitivity, empiric therapy should be based on local susceptibility patterns of uropathogens (Grade C).

Summary of evidence
The incidence of acute cystitis during pregnancy is 1.3% [Harris 1981, 1984]. Infection occurs during the second trimester and may not necessarily be preceded by asymptomatic bacteriuria during the previous weeks. Failure of therapy or a delayed or incomplete response to therapy is less acceptable during pregnancy because the fetus is also at stake [Johnson 2003].

There is limited data that assessed the superiority of one antibacterial regimen over the other in terms of efficacy, patient compliance and safety during pregnancy. A Cochrane review [Vasquez 2004] of RCTs on antibiotics for the treatment of symptomatic UTIs in pregnancy did not show that one treatment regimen is better than another. Cure rates for all evaluated antibiotics were high.

4. In cases where the result of a urine culture shows an organism resistant to the empirically started antibiotic in a clinically improving patient, should the antibiotic be changed based on the susceptibility report?

Adjust antibiotic therapy based on urine culture results (Grade C).

Alternatively, repeat the urine culture. If sterile, continue with the same antibiotic. If bacteriuria persists, switch regimen based on culture result (Grade C).

Summary of evidence
There are no studies addressing this specific issue. The ACP PIER clinical guideline [2003] recommends that antibiotic therapy be adjusted based on culture results because of the higher likelihood of antimicrobial resistance or a suboptimal treatment response during pregnancy than in a nonpregnant woman; plus failure of therapy or a delayed or incomplete response is less acceptable during pregnancy because of adverse consequences to the fetus. However, clinical and bacteriologic cures are often achieved even when the organisms are resistant in vitro to the selected agent; thus a change in antibiotic therapy is not mandatory, so long as the patient is responding clinically as observed by the physician [Johnson 2003].

5. What is the clinical utility of a post-treatment urine culture?

Post-treatment urine culture should be obtained to confirm eradication of bacteriuria and resolution of infection in pregnant women (Grade C).

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 (Grade C).

Summary of evidence
Pregnant women who already had bacteriuria during pregnancy are at an increased risk for recurrent bacteriuria later in pregnancy, and may need closer monitoring than do women who were abacteriuric during initial screen [Johnson 2003]. Pyelonephritis is typically more severe in pregnant women and can progress to premature labor, fetal distress syndrome, shock, disseminated intravascular coagulation, and death [Kunin 2003]. Thus, it is critical that bacteriuria is eradicated and documented through urine cultures.

There is no evidence regarding the frequency of monitoring for recurrence of ASB in pregnant women. In a review by Wing [2000], the author suggests clinic follow-up within 2 weeks after acute therapy of acute pyelonephritis during which a urine culture is obtained as a "test of cure". Studies on treatment of APN in pregnancy do follow-up cultures on the 5th-14th day post-treatment [Millar 1995, Wing 1998, Wing 1999].

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 [Kunin 2003].

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

C. ACUTE PYELONEPHRITIS IN PREGNANCY

1. When is acute pyelonephritis in pregnancy suspected?

Acute pyelonephritis is characterized by shaking chills, fever (T>38 C), flank pain, nausea and vomiting, with or without signs and symptoms of lower urinary tract infections and physical finding of costovertebral angle tenderness. Urinalysis shows pyuria of $\geq$ 5 wbc/hpf of centrifuged urine and bacteriuria of $\geq$ 10,000 cfu of a uropathogen/ml of urine [Harris, 1984, Roberts 1986, Rubin 1992].

2. What is the appropriate diagnostic test to establish an etiologic diagnosis?

Gram stain of uncentrifuged urine is recommended to differentiate gram positive from gram-negative bacteriuria, the result of which can guide the choice of empiric antibiotic therapy (Grade B).

Urine culture and sensitivity test should also be performed routinely to guide the choice of antimicrobial agents because of the potential for serious sequelae if inappropriate antimicrobial regimen is used (Grade B).

Summary of evidence: *(See section II on acute uncomplicated pyelonephritis)*

Blood cultures are not routinely recommended for all pregnant patients with acute pyelonephritis (Grade D).

Summary of evidence

Pooled data from three randomized controlled trials that included 391 pregnant women with pyelonephritis correlated urine (98%) and blood culture (99%) results with clinical management decisions, outcome, length of hospital stay and cost [Wing 2000]. 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 4 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), 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.

Susceptibility results of the uropathogens to the antibiotics did not predict clinical cure. Among 22 women whose initial urine culture results showed resistance to cefazolin, only 1 required a change in antibiotic because of persistent CVA tenderness. The rest had adequate clinical response to the initial antibiotic.

Comments: *The above study suggests limited utility of both urine and blood culture studies in AUPN in pregnancy. Another study [MacMillan 1991] found that >90% of uropathogens causing AUPN in 156 pregnant women were sensitive to the initial antibiotic given and that changes in antibiotic therapy were primarily dictated by clinical response. They suggested 2 possible strategies that are practical and*

economical without compromising patient safety. The first strategy involves obtaining only one pretreatment urine culture and no blood cultures unless the patient has risk factors like bacterial endocarditis or undiagnosed heart murmurs. The second strategy intended for low risk patients involves the use of urine and blood cultures only if a clinical response is not apparent in 48 hours. Both strategies involve an increase in diagnostic uncertainty especially in the 2nd strategy since most cultures become sterile within the first 24 hours.

3. What antimicrobials are recommended for acute pyelonephritis in pregnant women?

All pregnant patients with acute pyelonephritis should be hospitalized and immediate antimicrobial therapy instituted (Grade B). Treatment duration is 10-14 days (Grade B).

Any of the antibiotics for acute uncomplicated pyelonephritis can be used *(see Table 6)* except for fluoroquinolones and aminoglycosides, which are relatively contraindicated in pregnancy (Grade B). In the absence of urine culture and sensitivity tests, empiric choice of antibiotic should be based on local susceptibility patterns of uropathogens (Grade C).

For pregnant patients with no signs and symptoms of sepsis and are able to take medications by mouth, consider outpatient therapy (Grade B).

Summary of evidence
Acute pyelonephritis is the most frequent complication of the urinary tract during pregnancy and the most common medical reason for hospitalization. The incidence increases as gestation progresses and has been observed in 1 – 2.5% of patients [Cunningham 1975, Gilstrap 1981]. This illness can potentially lead to maternal sepsis, shock, death and fetal wastage [Harris 1984].

A Cochrane systematic review [Vasquez 2004] of 8 RCTs (n=905 pregnant women) on which agent is effective for the treatment of symptomatic UTIs in pregnancy did not show that one treatment regimen is better than another. There were no significant differences among the different antibiotic regimens regarding cure rates, recurrent infection, incidence of preterm delivery, admission to neonatal intensive care unit, need for change of antibiotic, and incidence of prolonged pyrexia. Cure rates for all evaluated treatments were high and complications were rare. Antibiotics studied include nitrofurantoin, ceftriaxone, cefuroxime, cephazolin, cephalexin, cephradine, ampicillin and gentamicin. The small differences between treatment regimens, even in the comparison between outpatient and inpatient treatment where most outcomes seem to favor outpatient treatment, are likely due to chance because of the insufficient number of patients included in the studies and not to the type of intervention or treatment.

***Comments:** For antibiotics that are not contraindicated in pregnancy, data from non-pregnant women may be used for decision-making in the absence of data from pregnant women. However, pharmacodynamics of some drugs may differ in pregnancy from non-pregnant women; thus, data should be analyzed carefully.*

It must be noted that outpatient therapy for acute pyelonephritis as described in the trials included in the Cochrane review involved initial intravenous or intramuscular administration of an antibiotic, a 24 - 48 hour in-hospital observation and tocodynamic monitoring, and judicious control of fever. In general, patients with acute pyelonephritis are hospitalized and given intravenous antibiotic therapy until the patient is afebrile, after which oral antibiotic therapy can be given to complete 10-14 days.

4. What is the clinical utility of a post-treatment urine culture in AUPN in pregnancy?

Post-treatment urine culture should be obtained to confirm resolution of the infection. Patient should be monitored at intervals until delivery to confirm continued urine sterility during pregnancy. (Grade C)

***Summary of evidence:** (See section B)*

V. RECURRENT URINARY TRACT INFECTION IN WOMEN

A. When is recurrent UTI diagnosed?

Recurrent UTI is diagnosed when a non-pregnant woman with no known urinary tract abnormalities has episodes of acute uncomplicated cystitis documented by urine culture occurring more than twice a year [Kraft 1977, Stamm 1980].

B. When is prophylaxis for recurrent UTI indicated?

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

Summary of Evidence

Benefits: *There are no reports of long-term sequelae from recurrent UTI. Therefore, the decision to give prophylaxis rests more on weighing the benefit of alleviating the discomfort of UTI and avoiding the inconveniences associated with recurrent episodes versus the potential harm of drug prophylaxis and emergence of resistant strains. The decision should be individualized to the particular patient.*

Harms: *The reported incidence of adverse drug effects with prophylaxis ranges from 1.3% to 20% [Brumfitt 1995, Brumfitt 1991, Melekos 1997, Nicolle 1989, Samm 1980, Stapleton 1990]. Studies that monitored the vaginal and fecal flora during prophylaxis showed that the incidence of emergence of resistant strains is very low [Pfau 1994, Stamey 1977].*

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

C. How effective are prophylactic regimens in preventing recurrent UTI?

1. Antibiotic prophylaxis

If a decision is made to give antibiotic prophylaxis, either of the following is recommended: (1) continuous prophylaxis, defined as the daily intake of a low dose of antibiotic for 6-12 months (Grade A), or (2) post-coital prophylaxis, defined as the intake of a single dose of antibiotic immediately after sexual intercourse (Grade A).

Any of the antibiotics in Table 11 given either continuously for 6-12 months or as post-coital prophylaxis can reduce the clinical and microbiologic recurrence of UTI episodes (Grade A).

Summary of evidence

Continuous antibiotic prophylaxis vs placebo

A recent Cochrane systematic review [Albert 2004] of 10 RCTs (N=430 premenopausal and postmenopausal women) showed that continuous antibiotic prophylaxis for 6-12 months reduced the rate of UTI during prophylaxis compared to placebo. During active prophylaxis the rate range of microbiological recurrence/person-year was 0 to 0.9 episodes in the antibiotic group vs 0.8 to 3.6 with placebo. The RR of having one microbiological recurrence was 0.21 (95% CI 0.13, 0.34) favoring antibiotic prophylaxis with NNT=1.85. The RR for clinical recurrence was 0.15 (95% CI 0.08, 0.28). After prophylaxis, no difference in microbiological recurrence was seen in 2 studies (RR 0.82; 95% CI 0.44, 1.53). There were more adverse events in the antibiotic group (RR 1.78; 95% CI 1.06, 3.00). Adverse effects included vaginal and

oral candidiasis and gastrointestinal symptoms. Antibiotics studied in the RCTs included in this review were nitrofurantoin, norfloxacin, trimethoprim, TMP-SMX and cefalexin.

Continuous antibiotic prophylaxis vs another antibiotic regimen
Six RCTs (N=458 premenopausal and postmenopausal women) comparing different antibiotic regimens vs each other were included in the Cochrane review [Albert 2004]. Results were not pooled because of significant heterogeneity. Individual results of the studies [Brumfitt 1991, Brumfitt 1995, Nunez 1990, Seppanen 1988, Stamm 1980] showed no significant differences in infection rates over 6-12 months with one antibiotic over another. The only trial [Brumfitt 1985] that showed a difference compared nitrofurantoin 100 mg at bedtime with trimethoprim with a RR for microbiologic recurrence of 3.58(95% CI 1.33, 9.66) and a RR for clinical recurrence of 1.72 (95% CI 1.06, 2.79) favoring nitrofurantoin.

In the 6-month period after discontinuation of the 6-month prophylaxis, 48% of patients in the treatment groups developed at least one episode of UTI, a rate similar to that of the placebo group [Stamm 1980]. One other trial with a 6-month prophylaxis had similar results [Stamey 1977]. In one trial of 12-month prophylaxis, the authors report that 69% maintained improvement after discontinuation of prophylaxis but no details were provided [Brumfitt 1991].

Post-coital prophylaxis vs placebo
Post-coital administration of TMP/SMX (40 mg/200 mg as a single dose) given for 6 months was compared with placebo in a randomized controlled trial of 28 women regardless of whether their UTI episodes were temporally related to sexual intercourse or not. The proportion of patients who developed UTI was 75% in the placebo group and 12% in the post-coital prophylaxis group [Stapleton 1990].

Continuous antibiotic prophylaxis vs post-coital prophylaxis
One RCT [Melekos 1997] comparing post-coital versus continuous daily ciprofloxacin found no significant difference in rates of positive urine culture after 1 year (RR 0.9; 95% CI 0.55, 1.45); but the rate of discontinuance due to adverse drug reaction was higher in the continuous prophylaxis group (5.35%) compared to the postcoital prophylaxis group (1.3%). Continued suppression of gram-negative introital flora in 36% of women within one year of stopping continuous or postcoital ciprofloxacin prophylaxis was reported but there was no clinical correlation with actual episodes of urinary tract infection.

Table 11. Antibiotics proven effective in reducing the number of recurrences of UTI

Antibiotics	Recommended dose for continued prophylaxis	Recommended dose for post-coital prophylaxis
Nitrofurantoin	100 mg at bedtime	---
Trimethoprim	100 mg at bedtime	---
TMP/SMX	40mg/200mg at bedtime	40mg/200mg
Ciprofloxacin	125 mg at bedtime	125mg
Norfloxacin	200 mg at bedtime	200mg
Ofloxacin	----------	100mg
Pefloxacin	400 mg weekly	
Cefalexin	125 mg at bedtime	---
Cefaclor	250 mg at bedtime	---

References: Brumfitt 1991, Brumfitt 1995, Guibert 1995, Melekos 1997, Nicolle 1989, Stamm 1980

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

2. Hormonal treatments in post-menopausal women

Application of intravaginal estriol cream once each night for two weeks followed by twice-weekly applications for 8 months is recommended for the prevention of recurrent UTI in post-menopausal women (Grade A).

Summary of evidence
Benefits: *A randomized, double blind, placebo-controlled trial in 93 post-menopausal women showed that an estriol cream applied intravaginally significantly reduced the rate of symptomatic UTI episodes (0.5 episodes per patient-year vs 5.9 in the control group [Raz 1993].*

Low dose oral estrogen is not recommended for the prevention of recurrent UTI. (Grade D)

Summary of evidence
Benefits: *Estrogen therapy is associated with a return of the premenopausal lactobacillus-dominated vaginal flora, acid vaginal pH and reduced vaginal colonization with UTI, which probably account for the decreased risk of UTI. One RCT [Cardozo 1998] on 72 postmenopausal females >60 years old with 2 documented UTIs in the last 18 months, compared low dose oral estrogen 3mg/day versus placebo taken for 6 months and followed up for another 6 months. The proportion of women who developed at least one infection after 6 months did not differ significantly between estrogen and placebo (57% vs 51%; RR 1.11,95% CI 0.65 to1.82). Ouslander [2001] likewise did not find significant benefits with oral estrogen/progestin therapy in female nursing home residents.*

Harms: *There were 13 dropouts among patients taking estrogen due to hospital admission, bleeding, and cerebrovascular accident, poor compliance, adverse experiences, and depression. Nine dropouts in the placebo group were due to femur fracture, poor compliance, septicemia, cerebrovascular accidents, left arm paresis, and general decline in health.*

Comments: *The apparent difference in efficacy of topical versus systemic hormone replacement therapy may be due to differences in the populations studied rather than differences in drug regimens e.g. the RCT on topical estriol therapy had a younger patient population. Only 50 women completed the trial on oral estrogen [Cardozo 1998], which reduced the power of the study to detect a difference from 80% to 49%.*

3. Vaccines

There is insufficient evidence to recommend immuno-active E. coli fractions (Uro-Vaxom) for the prevention of recurrent UTI. (Grade C)

Summary of evidence
Benefits: *We found one meta-analysis [Bauer 2002] (5 RCTs, 601 females with recurrent UTI). All studies were conducted in European countries particularly Germany and Switzerland. The women received 1 capsule daily for the first 3 months. Reduction in the recurrences of urinary tract infection and bacteriuria defined as $>10^4$ or $>10^5$ bacteria/ml of urine were measured at the end of the 6-month observation period. Results from the five RCTs showed that Uro-Vaxom was better than placebo in reducing frequency of UTIs and of dysuria, bacteriuria and pyuria (summary estimate for the 5 trials was 0.68, 95% CI 0.64-0.72).*

Comments: *Uro-Vaxom is a bacterial extract consisting of immunostimulating components derived from 18 uropathogenic E. coli strains that have been shown to increase oxygen-free radicals and increase IgA in interstitial secretions. All results of the five studies are homogeneous and show benefit with Uro-Vaxom. However, the RCTs excluded from the analysis non-compliant patients and dropouts due to drug inefficacy and adverse drug reactions, which could have overestimated the treatment benefit. Selection and publication bias could not be ruled out because the authors did not provide details on their search strategies. The adequacy of randomization and allocation concealment was not mentioned in the review and RCTs, thus it is possible that treatment effects could have been overestimated due to selection bias. Well-designed RCTs including cost-effectiveness assessments are needed for this promising alternative.*

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

Any of the antibiotics for acute uncomplicated cystitis *(see Table 4)* may be used in the treatment of individual episodes of UTI in women with recurrent UTI (Grade B).

Consider intermittent self-administered therapy in highly educated and well-informed patients, wherein the patients are able to recognize the characteristic signs and symptoms of UTI and instructed to take 2 double-strength tablets of TMP/SMX single dose as soon as symptoms first appear (Grade A).

Breakthrough infections during prophylaxis should initially be treated with any of the antibiotics recommended for uncomplicated cystitis other than the antibiotic being given for prophylaxis. A urine culture should be requested and the treatment modified accordingly (Grade B).

Summary of evidence

Benefits: *Clinical trials on the treatment of individual episodes in recurrent UTI are limited. Amoxicillin-clavulanate, cephradine, ciprofloxacin and lomefloxacin have all been found to be effective [Buffet 1990, Cox 1992]. There are no published trials on 3-dav therapy for individual episodes of recurrent UTI in women. However, given the evidence that the microbial flora encountered in patients with recurrent UTI are similar to those in women with uncomplicated UTI where 3-day therapy is considered acceptable, it is very likely that 3-day or 7-day therapy with any of the antibiotics recommended for simple uncomplicated UTI will also be effective in this setting.*

In a trial where 38 patients with recurrent UTI were randomized to receive either continuous prophylaxis with TMP/SMX or intermittent self-administered therapy with TMP/SMX, 92% of symptomatic episodes in the self-therapy group were confirmed microbiologically and 86% of the infections responded to the single-dose treatment [Wong 1985]. Among those that did not respond or relapsed, none evolved into pyelonephritis and all were cured by a second longer course of therapy. A more recent study showed similar results and the women were highly accurate in identifying the presence of significant bacteriuria based on their voiding symptoms [Gupta 2001].

Self-administered antibiotic therapy reduces the time between onset of symptoms and initiation of treatment; avoids the inconvenience and cost of a clinic visit compared with the standard physician-directed treatment. This also minimizes exposure to antimicrobial agents compared to continuous or post-coital prophylaxis [Johnson 2003].

Harms: *Five and 3 patients developed side effects in the prophylaxis and self-therapy groups, respectively [Wong 1985]. The reported incidence of infections with organisms resistant to antibiotic being used for prophylaxis ranges from 12% for TMP/SMX [Stapleton 1990], 50% for norfloxacin [Brumfitt 1991], 54% for cefaclor [Brumfitt 1995], and 58% for nitrofurantoin [Brumfitt 1995].*

Costs: *Annual direct costs per person in the prophylaxis group were $256 versus $239 in the self-therapy group. The authors cautioned, however, that their population was a select group of women, many of whom had attended a special clinic on UTI and were sufficiently motivated to enroll in a long-term clinical study [Wong 1985].*

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

1. Indication for screening for urologic abnormalities

Routine screening for urologic abnormalities is not recommended for women with recurrent UTI (Grade E).

Certain risk factors associated with a higher incidence of urologic abnormalities have been identified. Screening is recommended for patients with: 1) gross hematuria during a UTI episode; 2) obstructive symptoms; 3) clinical impression of persistent infection; 4) infection with urea-splitting bacteria; 5) history of pyelonephritis; 6) history of or symptoms

suggestive of urolithiasis; 7), history of childhood UTI; and 8) elevated serum creatinine (Grade C).

Summary of evidence

The reported prevalence of urologic abnormalities in women with recurrent UTI significant enough to warrant a change in management ranges from 0% [Engel 1980, Fair 1979, Fowler 1981] to 6% [Fairchild 1982]. A systematic review [Mushlin 1989] estimated the overall prevalence at 0.8%. A study of 148 women, which included only those with at least one of the factors listed above, reported a prevalence of urologic abnormalities of 21% [Nickel 1991]. Because UTI during childhood is associated with reflux nephropathy, inclusion of this factor was also recommended although there is no data regarding its predictive value [Mushlin 1989].

2. Choice of screening procedure

Combined renal ultrasound and a plain abdominal radiograph are recommended (Grade B). Patients with anatomical abnormalities should be referred to a nephrologist and/or urologist for further evaluation (Grade C).

Summary of evidence

Most studies report urologic abnormalities identified from intravenous pyelography (IVP). However, IVP can cause mild generalized reactions (hypersensitivity reactions, nausea, vomiting and syncope) in 5 to 10% of patients [Mushlin1989]. In one study [Aslaksen 1990] where 120 women underwent both IVP and renal ultrasound (RUS), there was good agreement between the two modalities for diagnosis of hydronephrosis (kappa 0.91) but less agreement in the diagnosis of major pyelonephritis changes (kappa 0.79), ureteric calculi and renal calculi >5 mm (kappa 0. 78) and expansile lesions (kappa 0.38). In a study of 94 women with a history of UTI referred by their physician for IVP or RUS, the RUS and plain abdominal radiograph findings were compared with IVP and the only disagreement was in one patient where RUS detected a 1.5cm intrarenal mass not seen on IVP [McNicholas 1991]. In another study comparing combined ultrasound and plain abdominal radiograph with IVP performed on 89 women and 69 men with a history of UTI, the two modalities concurred in 152 of the 158 patients. RUS and plain film did not detect duplex kidney, small bladder diverticula, papillary necrosis and mild bilateral hydroureter of unexplained etiology [Spencer 1990].

VI. COMPLICATED URINARY TRACT INFECTION

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

Complicated UTI is significant bacteriuria, which occurs in the setting of functional or anatomic abnormalities of the urinary tract or kidneys (*See Table 12).* The cut-off for significant bacteriuria in complicated UTI has been set at 100,000 cfu/ml [Rubin 1992)]. However in certain clinical situations, low-level bacteriuria or counts < 100,000 cfu/ml may be significant as in catheterized patients [Stark 1984].

Table 12. Conditions that define complicated UTI

Presence of an indwelling urinary catheter or intermittent catheterization
Incomplete emptying of the bladder with >100 ml retained urine post-voiding
Obstructive uropathy due to bladder outlet obstruction, calculus and other causes
Vesicoureteral reflux & other urologic abnormalities including surgically created abnormalities
Azotemia due to intrinsic renal disease
Renal transplantation
Diabetes mellitus
Immunosuppressive conditions – e.g. febrile neutropenia; HIV/AIDS
UTI caused by unusual pathogens or drug-resistant pathogens
UTI in males except in young males presenting with exclusively with lower UTI symptoms

References: Nickel 1990, Rubin 1992, Ronald 1997, Stamm 1993, Williams 1996

Summary of evidence

Structural and anatomic abnormalities of the urinary tract interfere with the normal storage and flow of urine, which makes infection more likely, with a tendency to be more chronic unless abnormalities are corrected. Patients with hormonal, metabolic and immunologic deficiencies are more prone to infection by various pathways. Usually all these patients have pathogens that are more difficult to eradicate [Nickel 1988]. To date there is little evidence clarifying the epidemiology of complicated UTI. Population-based studies are lacking to describe the burden of illness of complicated UTI [Ronald 1997].

Some groups are better studied like catheter-associated UTI. In a prospective cohort study done in a public training institution in the Philippines from April to November 1998, the incidence of catheter-related UTI was 51.4% (n=214), 91% of which were acquired within 7 days of catheterization [Billote-Domingo 1999]. An earlier study in the same institution reported a 24.7% incidence (n=178) over a 3-month period [Alavaren 1993]. Range of duration of catheterization, however, was shorter at 2 to 12 days compared to 2 to 44 days in the more recent study. Another local study conducted in a tertiary private hospital reported a one-month prevalence of 13.6% (n=212) with a mean duration of catheterization of 12 days [Gler 2002]. Surveillance reports of the US National Nosocomial Infections Surveillance System between 1992 and 1997 revealed that 95% of nosocomial UTIs in medical ICUs occurred in catheterized patients (n=4701) [Richards 1999]. In two other studies, catheter-associated UTI presented with significant excess in morbidity [Givens 1980], higher cost and a threefold underlying mortality [Platt 1983].

Diabetes mellitus has been identified as an independent risk factor for the occurrence of nosocomial UTI [Platt 1986]. Morbidity that occurs with diabetics who develop UTI explains why these patients are included in the complicated UTI category [Patterson 1997].

Infections in renal transplant patients comprise a population, which has received much interest in research. It is now known that UTI is the most common infection that occurs post-transplant with the incidence ranging from 30-95% [Belitsky 1982, Ramsey 1979, Renoult 1994, Rubin 1993, Stuby 1989, Walter 1975]. Through the years, there is a trend towards a gradual decline in the incidence of infection due to the refinements in the post-operative care of transplant patients [Rubin 1993]. UTI in this group is associated with severe morbidity due to sepsis. The highest rates of UTI occur during the first seven days following transplant and consists mainly of catheter-associated UTI. In the Philippines, the National Kidney and Transplant Institute (NKTI) has the largest experience in kidney transplantation with 1,019 kidney transplants performed in 1,008 patients over a ten-year period from 1983-1994. A one-year prospective study in this institution by Mendoza et al [1997] followed the course of 513 patients post-transplant. UTI and pneumonia were the most frequently encountered bacterial infections in these patients.

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

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

A urine sample for gram stain, culture and sensitivity testing must always be obtained before the initiation of any treatment (Grade B).

Summary of evidence

Because of the wide range of organisms, which can cause complicated UTI and the possibility of antibiotic resistance, urine culture and sensitivity should be ordered before any treatment is started [Farland 1993, Neu 1992, Powers 1991,Williams 1996]. A urine gram stain will provide a clue to the organisms. Table 14 lists the spectrum of organisms seen in specific groups of patients with complicated UTI.

A local study [Dytan 1999] done in a tertiary private hospital in Metro-Manila reported that in 76 patients with complicated UTI, the most common organism was Escherichia coli (53.9%) followed by Klebsiella pneumoniae (14%) and Enterobacter spp. (3.9%). E. coli isolates (n=41) showed increased resistance against amoxicillin (55.6%), cotrimoxazole (57.5%), and nalidixic acid (54.6%). K. pneumoniae and Enterobacter spp. isolates showed similar resistance patterns as the E. coli isolates.

A recent local study [Ninalga 2003] conducted in 3 government hospitals in Metro-Manila also showed that E coli (45%) was the most common organism isolated followed by Klebsiella (21%), Pseudomonas aeruginosa (7%) and Proteus mirabilis (5%) in 85 patients with complicated UTI. Forty-nine percent of the patients had structural abnormalities, 25% were diabetics and 24% had indwelling urine catheters.

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

Patients with complicated UTI with marked debility and signs of sepsis, with uncertainty in diagnosis, with concern about adherence to treatment or who are unable to maintain oral hydration or take oral medications, require hospitalization (Grade C). Patients who do not fall under the above categories may be treated on an outpatient basis (Grade C).

Summary of evidence
There are no clinical trials that stratified patient outcomes by degree of illness and site of treatment.

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

For mild to moderate illness, oral fluoroquinolones are recommended (Grade A). For severely ill patients, broad-spectrum parenteral antibiotics should be used, choice of which would depend on the expected pathogens, results of the urine gram stain and current susceptibility patterns of microorganisms in the area (Grade C). ***See Tables 13 & 14.***

Summary of evidence
Because of the variety of conditions under complicated UTI and the limited clinical trials in these populations, generalizations on specific antibiotic regimens remain difficult. Drugs of choice for empiric therapy of complicated UTI have not been well established. There have been many published comparative drug trials in complicated UTI. Not until recently though, many were poorly designed or the definition of bacteriologic cure is not eradication of the initial pathogen.

Benefits**:** *A multicenter, prospective, double-blind, double-dummy randomized study [Raz 2000] compared the ciprofloxacin 250 mg BID to ofloxacin 200 mg BID given for 7 days in the treatment of 427 women with complicated lower UTI. No significant differences in efficacy rates among patients who received ciprofloxacin and ofloxacin were observed: 77.1% and 76.1% had sterile cultures 5-9 days after therapy respectively. Clinical cure 5-9 days post therapy was achieved in 97.2% of both groups and a month later in 87.7% and 87.3%, respectively. Adverse events were mild and similar in both groups.*

Another randomized, open-label multicenter study [Klimberg 1998] showed that once-daily levofloxacin for 7-10 days is as effective as and has a superior tolerability profile than lomefloxacin once daily for 14 days in the treatment of complicated UTIs. The intention-to-treat group consisted of 461 patients enrolled at 29 sites (232 levofloxacin, 229 lomefloxacin). Bacteriologic eradication rates were 95.3% (163 of 171) and 92.1% (152 of 165) for levofloxacin and lomefloxacin respectively. At the 5 to 9-day post-therapy visit, symptoms were completely resolved in 84.8% and 82.4% of levofloxacin-treated and lomefloxacin-treated patients respectively. Ten (2.6%) levofloxacin- and 18 (5.2%) lomefloxacin-treated patients reported drug-related adverse events. Eight (3.4%) patients discontinued levofloxacin and 14 (6.1%) patients stopped lomefloxacin because of adverse reactions.

An open noncomparative clinical trial [Alejandria 2003] on sequential therapy with IV levofloxacin for 3 days followed by oral levofloxacin to complete 14 days for complicated UTI in 3 tertiary government

hospitals in the Philippines showed 89% cure rate at day 14 on efficacy analysis and 72% on intention-to-treat analysis.

Table 13. Pathogens in Complicated UTI

Type of Complicated UTI	Pathogens	Reference
Catheter-associated UTI		
Short-term (<1 week)	*Escherichia coli* *Pseudomonas aeruginosa*	Warren 1997
Long-term (>1 week)	*Escherichia coli, Klebsiella sp.* *Enterobacter sp., Proteus mirabilis* Usually polymicrobial *E coli, Pseudomonas aeruginosa,* *Proteus mirabilis, Providencia stuartii,* *Morganella morgagnii, Citrobacter,* *Enterococcus, Candida species*	Saint 2003 Ouslander 1987
Catheter-associated UTI in Filipino patients	*E. coli, Klebsiella, Pseudomonas aeruginosa, Acinetobacter, Candida sp*	Billote-Domingo 1999 Alavaren 1993
Anatomic abnormalities	*Escherichia coli* *Klebsiella pneumoniae (37%)* *Pseudomonas aeruginosa* *Proteus mirabilis*	Childs 1993
UTI in diabetics	*Escherichia coli, Klebsiella pneumoniae* *Proteus mirabilis, Enterobacter* *Enterococcus* *Pseudomonas aeruginosa* *Candida*	Patterson and Andriole 1997
Renal transplant recipients	*Escherichia coli (29-61%)* *Proteus mirabilis* and *Klebsiella pneumoniae (30%)* *Gram-positive cocci (20%)* *Enterobacter* *Enterococci* *Serratia* *Acinetobacter* *Citrobacter* *Pseudomonas aeruginosa*	Schmaldienst and Horl 1997 Mendoza 1997
Neutropenic patients	Gram negative bacilli *Pseudomonas aeruginosa* *Staphylococcus aureus* *Candida*	Korzeniowski 1991
UTI in HIVpatients	*Escherichia coli, Enterobacter* *Klebsiella pneumoniae, Pseudomonas* *Enterococci, Staphylococcus aureus* *Cytomegalovirus, Adenovirus* *Toxoplasma, Pneumocystis carinii* *Blastomyces dermatidis* *Mycobacterium tuberculosis*	Sharifi and Lee 1997
Complicated UTI in Filipino patients (NKTI, PGH, Makati Medical Center, Cardinal Santos Medical Center, Davao Medical Center)	*Escherichia coli* *Klebsiella pneumoniae* *Pseudomonas aeruginosa* *Proteus mirabilis, Enterobacter*	Ninalga 2003 Magalit 2003 Dytan 1999 Raco 1998

Table 14. Antibiotics that may be used as empiric therapy for complicated UTI

Oral Regimen
Ciprofloxacin 250 -500 mg BID x 14 days
Norfloxacin 400 mg BID x 14 days
Ofloxacin 200 mg BID x 14 days
Levofloxacin 250-500 mg OD x 10-14 days
Parenteral Regimen
Ampicillin 1 gm q 6hrs + gentamicin 3 mg/kg/day q 24h
Ampicillin-sulbactam 1.5 gm to 3 gm q 6h
Ceftazidime 1-2 gm q 8h
Ceftriaxone 1-2 gm q 24h
Imipenem-cilastin 250-500 mg q 6-8 h
Piperacillin-Tazobactam 2.25 gm q 6
Ciprofloxacin 200-400 mg q 12hrs
Ofloxacin 200-400 mg q 12h IV
Levofloxacin 500 mg q 24h IV

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

Antibiotics are modified according to the results of the urine culture and sensitivity test. Patients started with parenteral regimen may be switched to oral therapy upon clinical improvement. The optimal duration of treatment is not completely established. At least 7-14 days of therapy is recommended (Grade B).

Summary of evidence

A randomized, double-blind, placebo-controlled trial [Dow 2004] compared 3-day (30 patients) and 14-day (30 patients) regimens of ciprofloxacin 250 mg BID for the treatment of acute UTI in patients with spinal cord injury. Most common infecting organisms were Klebsiella, Enterococcus and E coli. On intention-to-treat analysis, the 3-day regimen was associated with a higher rate of microbiological relapse at 6 weeks after initiation of therapy (37% vs 7%; RR 2.09, 95% CI 1.38 to 3.18). Short-term and long-term clinical cure did not differ significantly between the 3-day and 14-day regimens (short term: 63% vs 53%; RR 1.23, 95% CI 0.72 to 2.11; long- term: 37% vs 40%; RR 0.93, 95% CI 0.55 to 1.58). Likewise, microbiological cure (30% vs 47%; RR 0.69, 95% CI 0.39 to 1.23) and treatment failure (13% vs 37%; RR 0.46, 95% CI 0.19 to 1.11) did not differ significantly between the 2 regimens.

There are no data providing evidence on the advantage of 7, 10 or 14 days of antibiotic treatment in terms of likelihood of cure versus the incidence of adverse effects of prolonged antibiotic use.

Comments: *The higher rate of microbiological relapse in the 3-day regimen and the high rate of treatment failure among patients in the 14-day regimen were associated with the presence of ciprofloxacin-resistant organisms particularly enterococci. It is possible that the overall results for both treatment arms would have been different if an antimicrobial with better gram positive activity was studied. It should be noted also that patients with pyelonephritis, struvite stones, hydronephrosis or long-term indwelling catheters were excluded from the trial. Thus, these patients had mild illness; however, some of these patients may have had occult infections of the upper urinary tract to explain the higher relapse rates with the 3-day regimen. A second explanation for relapse is impaired vesical clearance of bacteriuria because of localized trauma, frequent instrumentation or incomplete bladder emptying [Dow 2004, Gupta 2004].*

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

Urine culture should be repeated one to two weeks after completion of medications (Grade C). If significant bacteriuria persists post-treatment, consider referral to specialties involved with the underlying problem that predisposes to complicated UTI (Grade C).

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

Further work-up to identify and correct the anatomical, functional or metabolic abnormality is indicated. Referral to the appropriate specialists, such as infectious diseases, nephrology or urology should be made as necessary (Grade C).

Summary of evidence
In most cases of complicated UTI, further intervention is necessary to eradicate the infection in addition to the administration of antibiotics. For instance, in the management of UTI with struvite stones, definitive treatment like extracorporeal shock wave lithotripsy and/or percutaneous nephrolithotomy or lithotripsy may be required in most patients. Bacteria live within the stone and persist contributing to stone growth. Patients who fail to undergo stone removal usually have progressive renal deterioration [Rose 1997]. Further work-up to identify anatomic abnormalities may include the following: plain abdominal and kidney-ureter-bladder radiographs, renal ultrasound, intravenous pyelogram, CT scans and MRI. Work-up for immunodeficient state may be done when considered.

SPECIFIC ISSUES OF CONCERN IN COMPLICATED UTI

A. CATHETER-ASSOCIATED UTI

1. Should all catheterized patients with bacteriuria be treated?

Catheterized patients with significant bacteriuria of $\geq$ 100 cfu/ml of urine, who develop signs and symptoms of UTI or fever or other signs of bacteremia should be treated with antibiotics. (Grade B)

Summary of evidence
The presentation of catheter-associated UTI varies from asymptomatic bacteriuria to overwhelming urinary tract-related bacteremia and possible death. Clinical manifestations may include local symptoms as lower abdominal discomfort or flank pain, or systemic symptoms, such as nausea, vomiting, and fever. Bacteremia is an important complication of catheter-associated UTI, with the urinary tract as the source in 11% to 40% of nosocomial bacteremic episodes. Patients with bacteremia may present with confusion, chills, fever, and hypotension [Saint 2003]. Blood and urine cultures before treatment will guide the clinician in the choice of antibiotics for definitive therapy. If catheter-related bacteremia is suspected or confirmed, antibiotics should be administered intravenously. For those with symptomatic catheter-associated UTI without clinical or microbiologic evidence of secondary bloodstream infection, an oral agent is effective. Although there are no clinical studies to guide the length of therapy for catheter-associated UTI, antimicrobial treatment usually varies from 7 to 21 days depending on the organism, co morbid conditions, and patient response [Saint 2003]. Patients with an indwelling catheter for at least one week before onset of infection should have the catheter replaced if the catheter is still necessary.

The following subsets of catheterized patients who have bacteriuria but are asymptomatic may benefit from antibiotic treatment: a) those whose bacterial agents cause high incidence of bacteremia in their institution; b) post-solid organ transplant patients; c) neutropenic patients; d) pregnant patients; e) those who will undergo urologic procedures; and f) those who may be part of an infection control plan to manage cluster infections in a unit (Grade C).

Summary of evidence
Some organisms in urinary catheter biofilms, such as Proteus sp, P. aeruginosa, Klebsiella pneumoniae, and Providencia sp, have the ability to hydrolyze urea in the urine to free ammonia. The resulting increase in local pH allows precipitation of minerals, such as hydroxyapatite or struvite. Mineral deposition within the catheter biofilm causes encrustations, which can build to block catheter flow and may act as a nidus for the formation of renal calculi [Rubenstein 2003].

The consequences are substantial because the bacteria persist inside these struvite stones even when the urine shows no growth. It should be eradicated by 3-5 days of antimicrobial therapy [Walsh 2002]. Therefore, all urea-splitting organisms must be eradicated. For staghorn calculi, the stone must be completely removed, or infection and stone formation will recur. Patients must remain on appropriate antimicrobial therapy until all fragments pass or are removed [Rubenstein 2003].

Catheterized patients with no risk factors and who do not belong to any of the above-mentioned subsets and are otherwise asymptomatic need not be treated with antibiotics (Grade E).

Summary of evidence
Asymptomatic bacteriuria need not be treated as long as the catheter remains in place because: (1) the risk of complications is low; (2) treatment does not prevent bacteriuria from recurring; and (3) treatment may lead to the presence of antimicrobial-resistant bacteria that are more challenging to treat [Saint 2003].

UTI in asymptomatic catheterized patients occupy a gray zone in recommendations regarding therapy. In a prospective trial of Warren [1982] comparing cephalexin vs control in afebrile, long-term (>1 week) catheterized patients with susceptible bacteriuria, results trended towards no difference in prevalence of bacteriuria, incidence of bacteriuric episodes, duration of bacteriuric episodes, number of bacterial strains per week, febrile days or catheter obstruction between cephalexin vs control. Instead, a difference was noted in the development of cephalexin-resistant bacteria. However, many patients in the control group received non-protocol antibiotics.

2. In addition to antibiotic therapy, what other interventions should be done in symptomatic patients with chronic indwelling catheter?

Whenever possible, the indwelling catheter should be removed to help eradicate the bacteriuria. (Grade A)

Summary of evidence
Benefits: *In a randomized controlled study, removal of the catheter resulted in the spontaneous resolution of bacteriuria within 14 days [Harding 1991]. This was seen more frequently in women who were 65 years old and younger. The most important and consistently demonstrated risk factor for developing bacteriuria is the duration of indwelling catheterization [Saint 2003]. Catheter-associated UTI occurs at a rate of 5-10% per day of catheterization and at 30 days, almost 100% of catheterized patients will demonstrate bacteriuria [Warren 1997].*

Long-term indwelling catheters should be replaced with new catheters before initiating antimicrobial therapy for symptomatic UTI. (Grade A)

Summary of evidence
Benefits: *An open clinical trial [Raz 2000] where symptomatic patients (n=54) with a chronic indwelling catheter and a clinical diagnosis of UTI were randomized to indwelling catheter replacement before initiating antimicrobial therapy or no replacement showed beneficial results with catheter replacement. Initial antimicrobial therapy consisted of 400 mg ciprofloxacin or 300 mg ofloxacin IV q 12 h then shifted to oral 500 mg ciprofloxacin or 200 mg ofloxacin twice daily once patients were afebrile for 24 hours. Polymicrobial bacteriuria significantly decreased 3 days after therapy was initiated, and 7 and 28 days*

after it was discontinued in 24 versus 8 (p=0.002), 18 versus 9 (p=0.01) and 13 versus 5 (p=0.02) patients, respectively. Catheter replacement was also associated with a shorter time to afebrile status, improved clinical status 72 hours after the initiation of therapy in 25 versus 11 patients (p<0.001) and a lower rate of symptomatic clinical relapse 28 days after therapy in 3 versus 11 patients (p=0.015).

Comments: *Observations should not be generalized to patients on short-term catheterization since bacterial biofilm formation is not likely to be as important. Some studies report that urine specimens for culture obtained via a chronic indwelling catheter yield a greater number of organisms isolated than specimens obtained from a newly inserted catheter in the same patient [Tenney 1988]. In the study by Raz [2000], the number of cases of polymicrobial bacteriuria decreased significantly after the catheter was changed. In the group with no catheter change, there was no difference in the incidence of polymicrobial bacteriuria in the 2 pre-therapy urine specimens.*

B. UTI IN DIABETIC PATIENTS

1. How should UTI in diabetic patients be managed?

Diabetic patients require pre-treatment urine gram stain and culture and a post-treatment urine culture. At least 7-14 days of oral antibiotics is recommended with an antibacterial agent that achieves high concentrations both in the urine and urinary tract tissues e.g. fluoroquinolones, cotrimoxazole (Grade C).

Diabetic patients who present with signs of sepsis should be hospitalized. Urine culture before starting therapy is indicated, as well as blood cultures if the patient is severely ill. Failure to respond to appropriate therapy within 48 to 72 hours warrants a plain abdominal radiograph of the KUB, a renal ultrasound, or a CT-scan (Grade C).

Summary of evidence
When UTIs occur in diabetics they are often more serious and protracted. Due to their immunocompromised state, they are at an increased risk for ascending renal infection, pyelonephritis, papillary necrosis, renal carbuncle, renal corticomedullary and perinephric abscess, and emphysematous pyelonephritis. Factors that may predispose diabetics to complicated infections include autonomic neuropathy leading to poor bladder emptying and urinary stasis, microangiopathy, leukocyte dysfunction, and frequent urinary tract instrumentation. In addition, diabetic nephrosclerosis and renal disease make delivery of antimicrobials less efficacious [Rubenstein 2003].

Benefits: *Strong evidence is lacking but experts agree that because of the concern for upper tract involvement, longer duration of antibiotic therapy is advocated in diabetic patients even with just lower UTI [Patterson 1997, Stamm 1983]. It is for this same reason and the predilection for upper tract complications and recurrent tract disease that UTIs and its treatment be documented by urine cultures.*

Failure to respond to therapy within 48 to 72 hours requires serious consideration for any of the severe complications of upper urinary tract infection peculiar to diabetes. This includes any of emphysematous pyelonephritis, emphysematous cystitis, renal papillary necrosis, acute focal or multifocal bacterial nephritis, renal cortical abscess, renal corticomedullary abscess, and xanthogranulomatous pyelonephritis. Emphysematous pyelonephritis, although rare, carries a poor prognosis if not detected early and treated with medical management alone. Mortality is up to 60% without surgical intervention [Evanoff 1987]. A plain abdominal film of the kidney, ureter and bladder can detect up to 85% of cases. A screening ultrasound should be considered early to rule out obstructive uropathy and detect parenchymal lesions. If there is a high degree of clinical suspicion despite a negative ultrasound, CT scanning should be pursued [Meiland 2002].

A multicenter, prospective, double-blind, double-dummy randomized study including 85 (20%) women with DM, has shown that a 7-day regimen with ciprofloxacin or with ofloxacin resulted in a cure rate of 90.1%

and 87.2% respectively, 5-9 days post-treatment. In the group of women with DM, the success rates were comparable (87.1% and 85.3%)[Raz 2000].
Local susceptibility patterns of the organism should guide choice of antibiotic therapy. Fluoroquinolones are a reasonable empiric choice. For seriously ill patients, including patients infected with Pseudomonas spp., such agents as imipenem, ticarcillin-clavulanate, and piperacillin-tazobactam may be considered [Stapleton 2002]. Patients suspected of having staphylococcus infection should be started on oxacillin, nafcillin, or vancomycin [Rubenstein 2003]. No randomized trials are available comparing the optimal duration and choice of antibiotics.

Gestational diabetes mellitus is not associated with increased risk of UTI or with maternal and perinatal morbidity because of infection. Microbiologic evidence of UTI was studied in 447 pregnant women with (n=149) and without (n=298) gestational diabetes mellitus after mid-pregnancy. No significant difference in asymptomatic bacteriuria, symptomatic infection and recurrent bacteriuria later in pregnancy were seen among those with and without gestational DM. E. coli was the commonest pathogen [Rizk 2001].

C. UTI IN RENAL TRANSPLANT PATIENTS

1. How should UTI in post-kidney transplant patients be managed?

UTI, which develops on the first three months post-transplant, including UTIs with signs of pyelonephritis or sepsis should be treated with parenteral broad-spectrum antibiotics until the urine cultures become negative. Therapy can be switched to oral agents according to the culture and sensitivity results to complete 4-6 weeks (Grade C).

Renal transplant patients who develop UTI after the first three months post-transplant with no evidence of sepsis may be treated as outpatients with oral antibiotics for 14 days (Grade C).

Summary of evidence
The timing of the UTI is the most important factor that determines morbidity from the infection. Early in-hospital UTI has been reported to lead to bacteremia in 12% of cases and graft infection in 90% of post-transplant UTI. Renal transplant patients are at highest risk of UTI immediately after transplant, particularly during the first 3 months. The risk falls progressively and reaches the same rate as the general population after 12 months. UTIs in the first three months post transplant are frequently associated with overt pyelonephritis [Rubin 1979], bacteremia, allograft dysfunction and a high rate of relapse when treated with the conventional two-week course of antibiotics. On the other hand, UTIs, which develop after the first three months, usually have a benign course and responds well with the routine antibiotic duration of 14 days. These UTIs are rarely associated with bacteremia, rarely requires hospitalization and have an excellent prognosis [Rubin 1981].

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

For renal transplant patients, prophylaxis with TMP/SMX (160/800 mg) twice daily during the hospitalization period immediately post-transplant, then once daily upon discharge is recommended (Grade A). The dose of TMP/SMX should be adjusted to the renal function. Prophylaxis should be given for at least 6 months (Grade C).

Summary of evidence
A randomized, double-blind, placebo-controlled study was done with 66 renal transplant patients per group using TMP/SMX initially 160/800 mg per day vs placebo [Fox 1990]. At the 7th month of the study the TMP/SMX dose was increased to twice daily based on serum levels that were consistently low. With an average of 8.5 months on the study drug (minimum of 3 weeks), there was an overall reduction in the incidence of bacterial infection during the entire post-transplant period including outpatient follow-up. In

particular, a significant reduction was observed in the frequency of UTI (24 UTIs in the TMP/SMX group vs 54 in the placebo group; p<0.005) and bloodstream infections (one in the TMP/SMX group vs 9 in the placebo group; p<0.005). Prophylaxis did not prevent UTI associated with urethral catheter during the early post-transplant period. Of the infections that occurred on prophylaxis, (75% were due to resistant organisms in the TMP/SMX group vs 24% in the placebo group (p<0.01). TMP/SMX was well tolerated. The dose was decreased to once daily after hospital discharge. At the time of discharge, surveillance cultures did not show significant differences in colonization by Gram-negative bacilli resistant to TMP/SMX between patients on prophylaxis vs placebo. However there was increase in colonization with methicillin-resistant Staphylococcus aureus with those on prophylaxis.

D. UTI IN PATIENTS WITH HIV/AIDS

1. What is the management of UTI in patients with HIV/AIDS?

In addition to the general management of complicated UTI, patients with HIV-AIDS and UTI should be evaluated to include other non-bacterial pathogens if clinically suspected and should be referred to an appropriate specialist (Grade C).

Summary of evidence
UTI in patients with HIV/AIDS are included in the category of complicated UTI because of the complexity of pathogens that are encountered (see Table 14). The data on this subset of patients is growing but still limited. The incidence of UTI in this group ranges from 8-50% [Sharifi and Lee 1997].

E. URINARY CANDIDIASIS

1. When is candiduria suspected or diagnosed?

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

Summary of evidence
There is no consensus on the definition of significant candiduria. Colony counts of $>10^4$ cfu/ml are associated with infection in patients without indwelling urinary catheters [Kozinn 1978] although clinically significant renal candidiasis has been reported with colony counts of 10^3/ml of urine [Schoenbeck 1972]. Absence of pyuria and low colony counts tend to rule out Candida infection [Lundstrom 2001], however results must be interpreted in the clinical context [Kozinn 1978, Schoenbeck 1972]. A small prospective study conducted in a tertiary hospital in Manila showed that colony counts were not predictive of significant infection or upper tract involvement. Bloodstream infection and severe sepsis can occur even with low colony counts, while very high counts may not necessarily indicate severe disease [Cantillep 1995].

2. When does candiduria require treatment?

Treatment of asymptomatic and minimally symptomatic candiduria is not recommended because it does not provide clear clinical benefits such as long-term ($\geq$2 weeks) eradication (Grade D).

Candiduria should be treated with appropriate antifungal agents in symptomatic patients, critically ill patients in ICUs, patients with neutropenia, post-renal transplant patients and those who will undergo urologic procedures (Grade C).

Summary of evidence

In a randomized, multicenter, placebo-controlled study, Sobel [2000] asymptomatic candiduria resolved with catheter removal in 41% of hospitalized, catheterized patients. After a new catheter was inserted, untreated candiduria resolved in 20% of chronically catheterized patients. In the same study, high short-term rates of eradication of Candida species from the urine occurred in patients who received fluconazole therapy, but the rates of candiduria 2 weeks after discontinuation of therapy were similar in the fluconazole and placebo groups and relapse was frequent. Long- term eradication rates were not associated with clear clinical benefits in the asymptomatic or minimally symptomatic population of predominantly elderly, debilitated patients in this study. A similar rate of resolution of untreated candiduria was found in observational studies. Asymptomatic candiduria rarely led to invasive disease or candidemia unless upper urinary tract obstruction was present [Ang 1993, Kauffman 2000, Storfer 1994].

Treatment of asymptomatic candiduria is suggested for neutropenic patients, critically ill patients and post-renal transplant patients, as it may be a clue to disseminated candidiasis or hematogenous dissemiation in these patients [Rex 2000]. Treatment should also be considered as a prophylactic measure for patients who are about to undergo invasive urologic procedures to avoid the risk of developing invasive candidiasis and candidemia [Lundstrom 2001, Sobel 1999].

Persistent candiduria in immunocompromised or noncatheterized patients warrants ultrasound or CT scan of the kidney to exclude clinically silent hematogenous renal candidiasis or upper tract obstruction and stasis [Rex 2000, Sobel 1999].

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

The first line of treatment is fluconazole 400 mg loading dose then 200 mg/day for 7-14 days (Grade A). The route of administration depends on the patient status and oral tolerability.

In certain clinical situations where drug resistance to fluconazole is suspected such as in patients with *Candida glabrata* or in patients suspected to have candidemia from an upper urinary tract obstruction or from other focus, bladder irrigation with amphotericin B at a dose of 0.3-1.0mg/kg per day for 1-7 days is recommended (Grade B).

Amphotericin is equally effective in lower urinary tract candidiasis, however because of the cost and difficulty in administration, its use must be limited to patients with indications for amphotericin use as above (Grade D).

Table 16. Summary of Treatment for Urinary Candidiasis

Condition	First-line treatment	Second-line treatment
Asymptomatic candiduria	Modify risk factors (rarely requires treatment)	Fluconazole 200 mg PO daily for 7-14 days for those with indications for treatment
Candida cystitis	Fluconazole 400 mg loading dose then 200 mg per day given orally for 7-14 days	Amphotericin B bladder irrigation (50 mg/L) for 5 days or IV amphotericin B 0.3 mg/kg given in a single dose.
Ascending pyelonephritis	Surgical drainage plus prolonged therapy with fluconazole 6 mg/kg/day OR IV amphotericin B 0.6mg/kg/day for 2-6 weeks to complete a total dose of 1-2 g	---
Renal candidiasis (hematogenous)	Prolonged therapy (2-6 weeks) with fluconazole 6 mg/kg /day OR amphotericin B $\geq$ 0.6 mg/kg /day for 4-6 weeks	---

Summary of evidence
Benefits: *Treatment of appropriately selected patients may reduce the risk of ascending and/or hematogenously disseminated disease. Treatment of persistently febrile patients who have candiduria but who lack evidence of infection at other sites may treat occult disseminated candidiasis. Inappropriate therapy may lead to emergence of resistant organisms [Pappas 2004].*

Asymptomatic candiduria
A randomized, double-blind, placebo-controlled, intention-to-treat multicenter trial [Sobel 2000] found that fluconazole loading dose of 400 mg followed by 200 mg OD for 14 days in hospitalized patients with candiduria, showed significant resolution of candiduria by day 14 (n=316, 50% vs 29%, $p < 0.001$), with higher short-term eradication rates among patients completing therapy (n=235, $p < 0.0001$). Completion rates of therapy in both groups however was < 80%. Adverse effects reported were elevated hepatic enzyme levels and increase in serum creatinine levels in both groups. Mortality rates (<9%) were similar in both groups.

Candida cystitis
Single-dose IV amphotericin B (0.3 mg/kg) has also been shown to be highly efficacious in the treatment of lower urinary tract candidiasis, with therapeutic concentrations being observed for considerable periods after administration [Fischer 1987].

A randomized controlled trial [Jacobs 1996] compared the efficacy and safety of oral fluconazole with amphotericin B bladder irrigation for treatment of funguria (≥ 10,000 cfu/mL of urine) in 109 hospitalized elderly patients. Indwelling catheters were present in 69% of patients. Two days after completion of treatment, funguria was eradicated in 96% of the patients treated with amphotericin B and 73% of those treated with fluconazole ($p<0.05$). At 1 month after study enrollment, the all cause mortality rate was greater among patients treated with amphotericin B bladder irrigation than those who received oral fluconazole (41% vs 22%, respectively; $p<0.05$). The proportion of patients without funguria at 1 month after study enrollment was similar in both groups (84% amphotericin B vs 80% fluconazole).

A local observational study [Cantillep 1995] reported higher cure rates with fluconazole in patients with Candida albicans (8 of 9 patients compared to 7 of 10 on ketoconazole and 5 of 8 on itraconazole). The same study showed higher relapse rates with ketoconazole (30%) and itraconazole (38%) compared to fluconazole (11%). No failures were seen with 10-14 day courses of Amphotericin B in 6 patients.

Ascending pyelonephritis
Ascending pyelonephritis due to candidal infection are often seen in hospitalized patients with diabetes and renal insufficiency, patients with variable papillary necrosis, and with obstructive uropathy. Systemic antifungal therapy (amphotericin B >0.6 mg/kg/d OR fluconazole 6 mg/kg/d), together with adequate drainage of the upper urinary tract is essential. The most important aspect of therapy is to relieve obstruction and to identify local complications through imaging [Lundstrom 2001].

Renal candidiasis
In renal candidiasis where there is hematogenous renal involvement, high-dose systemic amphotericin B (≥ 0.6 mg/kg per day) or parenteral fluconazole (6 mg/kg per day) is recommended in accordance with guidelines from the Mycoses Study Group [Rex 2000]. Duration of treatment is 4-6 weeks.

Comments: *Poor urinary concentrations of ketoconazole and itraconazole preclude their use in patients with candiduria [Graybill 1983]. In contrast, fluconazole is water-soluble, well absorbed orally and is excreted unchanged in the urine (>80%), and is associated with greater clinical efficacy [Sobel 1999]. Although the antifungal flucytosine may be useful in fluconazole-resistant Candida infections, it is not available in the Philippines.*

4. In adult non-neutropenic patients with asymptomatic candiduria wherein antifungal therapy is not recommended, what other maneuvers can be done to manage the candiduria?

For these patients, modification of risk factors that led to the development of candiduria is the first line approach. These include: control of diabetes and discontinuation of antibiotics if possible (Grade C). The removal of indwelling catheters and other urinary tract instruments such as stents is an important first step for the management of candiduria, and by itself generally results in spontaneous resolution of the candiduria (Grade B). If complete removal of these instruments is not possible, at least replacement of the device with new ones is beneficial (Grade A).

Summary of evidence

The most common risk factors associated with developing candiduria include urinary tract instrumentation, recent receipt of antibiotics, advanced age, diabetes mellitus and presence of an indwelling foley catheter. In a case-control study, Harris [1999] analyzed the risk factors associated with catheter-associated candiduria due to Candida glabrata (40 cases) and Candida albicans (289 cases). On multivariate analysis factors strongly associated with both candiduria were female gender ($p<0.05$) and being in the intensive care unit ($p<0.01$). Fluconazole use (adjusted OR 4.37; $p<0.01$) and quinolone use (adjusted OR 3.16; $p<0.01$) were specifically associated with C. glabrata candiduria but not with C. albicans candiduria [Harris 1999].

A previous underlying illness of diabetes mellitus [Goeke 1980], previous antibiotic use [Fischer 1982], advanced age [Kauffman 2000], use of immunosuppressive agents, use of IV catheters, interruption of the flow of urine, radiation therapy and genitourinary tuberculosis [Fischer 1991] have all been found to be significantly associated with the development of candiduria. The use of broad-spectrum antibiotics correlates significantly with candiduria. The strongest correlation is with the use of meropenem ($r=0.79$, $p<0.001$) and ceftazidime ($r=0.66$, $p=0.001$) [Weinberger 2003].

In a prospective multicenter surveillance study of funguria in hospitalized patients [Kauffman 2000], Candida albicans was found in 52% of 861 patients with funguria followed by Candida glabrata in 16% of patients. Another surveillance study between 1992 and 1997 of nosocomial infections in medical intensive care units [Richards 1999], revealed that C. albicans was more commonly reported in catheter-associated UTIs than in non-catheter-associated infections (982 of 4701 [21%] vs 33 of 255 [13%], $p=0.009$). Urinary infections from all fungal pathogens occurred more frequently in patients with urinary catheters than in those without urinary catheters (1858 of 4701 [40%] vs 57 of 255 [22%], $p<0.001$).

A randomized, multicenter, placebo-controlled trial [Sobel 2000] found that asymptomatic candiduria resolved with catheter removal in approximately 41% of hospitalized, catheterized patients. Untreated candiduria resolved in 20% of patients after changing the catheter.

Cantillep et al [1995], in an observational study of 55 patients in a tertiary hospital in Manila, reported that clinical improvement was significantly more common in patients whose catheters were removed whether or not treatment was given ($p<0.05$). The same study reported that a fatal infection was significantly more common in patients whose catheters were retained versus those whose catheters were removed ($p<0.05$). In a retrospective study [Sorongon 1994] conducted in 4 tertiary hospitals in Metro Manila from 1992-93, the prevalence rate of candiduria was 6.4% with C. albicans accounting for 73% of the cases. Use of broad-spectrum antibiotics, use of indwelling catheter and diabetes mellitus were the risk factors associated with candiduria.

VII. URINARY TRACT INFECTION IN MEN

A. UNCOMPLICATED CYSTITIS IN YOUNG MEN

1. What is the definition of uncomplicated cystitis in young men?

Urinary tract infection in men is generally considered complicated. However, the first episode of symptomatic lower urinary tract infection occurring in a young (15-40 years old)

otherwise healthy sexually active men with no clinical or historical evidence of a structural or functional urologic abnormality is considered as uncomplicated UTI.

Summary of evidence
This definition was adapted from Kim and Shaeffer [1994] and is used as the working definition in most textbooks and clinical studies. In a study by Krieger [1993], the mean incidence of uncomplicated lower UTI in healthy university men aged 15 to 40 years old with acute dysuria was 5 infections/10,000 men per year. In this population, factors implicated for UTI in men such as anatomical abnormalities, urinary tract instrumentation, bacterial prostatitis and lack of circumcision were seldom identified. A similar incidence of acute uncomplicated UTI in men was also recognized by Lipsky [1989], and further stated that a urologic evaluation is often unrewarding in these patients.

2. How is uncomplicated cystitis in males diagnosed?

Significant pyuria in men is defined as $\geq$ 10 wbc/mm^3 or $\geq$ 5 wbc/hpf in a clean catch midstream urine specimen. This shows good correlation with bladder bacteriuria and the growth of $\geq$ 1,000 colonies of one predominant species / ml of urine and best differentiates sterile from infected bladder urine (Grade C).

Summary of evidence
The presence of $\geq$ 10 wbc/mm^3 on urinalysis had a PPV of 77% and a NPV of 69%, sensitivity of 71% and specificity of 76% in the prediction of bladder bacteriuria. Growth of 1,000 cfu/ml had a sensitivity of 97% and a specificity of 97% [Lipsky 1987]. Norman et al [1986], likewise, estimated a good correlation of up to 88% between pyuria of > 10/mm^3 and significant bacteriuria.

3. What is the recommended diagnostic work-up for uncomplicated cystitis in men?

The recommended diagnostic work-up includes a urinalysis and urine culture. A pre-treatment urine culture should be performed routinely in all men with UTI (Grade C).

Routine urologic evaluation and use of imaging procedures are not recommended (Grade C).

Summary of evidence
In a review of UTI in young men, Stamm and Hooton [1993] recommended a urinalysis to screen for pyuria and a pre-treatment urine culture for patients with significant pyuria. Independent studies by Krieger [1993] and Lipsky [1987] both of which documented uncomplicated UTI in men showed that patients who do not have clinical or historical evidence of a functional or anatomic abnormality; neurologic disorders, genitourinary tract instrumentation and prostatitis respond well to a single course of antimicrobial therapy. Comprehensive urologic evaluation is probably not necessary in adult men with no obvious complicating factors who have a single episode of cystitis that responds promptly to antimicrobial treatment [Hooton 2003].

4. What is the recommended treatment?

Seven-day antibiotic regimens are recommended (Grade C). TMP-SMX or fluoroquinolones may be used depending on prevailing susceptibility patterns in the community or institution (Grade C). *See related section on acute uncomplicated cystitis in women for antibiotic choices.*

Summary of evidence
The etiologic agents causing UTI in men are similar to those in women, and tend to have the same susceptibility patterns. There are no studies supporting a short-course treatment. Seven-day regimens are

recommended because of the possibility of prostatic infection and high rates of early relapse. Pyelonephritis should be treated with a minimum of 10 to 14 days [Hooton 2003].

Fluoroquinolones provide the best antimicrobial spectrum and prostatic penetration for treating UTIs in men. Nitrofurantoin and beta-lactams should not be used for UTI in men because these agents do not achieve reliable tissue concentrations and are less effective for occult prostatitis. If enterococcus is suspected from the Gram stain, amoxicillin should be included in the regimen until the causative organism is identified [Hooton 2003].

Most infections are caused by single bacterial species, usually gram-negative bacilli. E. coli causes almost half of all infections. Less commonly isolated are Proteus, Providencia, Klebsiella, Enterobacter, Pseudomonas and Citrobacter [Lipsky 1989]. In a study of 38 previously healthy university men who presented with symptomatic UTIs over a year period, E.coli caused 93% of the episodes [Krieger 1993]. Gram-positive cocci e.g. Enterococcus, S. aureus or S. epidermidis cause about one-fifth of UTIs in men [Lipsky 1989].

B. PROSTATITIS SYNDROMES

1. What is the definition of prostatitis?

In recognition of the limitations of the traditional classification of prostatitis syndromes by Drach et al [1978], the National Institutes of Health (NIH) International Prostatitis Collaborative Network convened a consensus conference in 1998 to reevaluate and refine the classification of prostatitis syndromes. This consensus classification includes 4 categories and 2 subcategories as presented in Table 16.

Table 16. The NIH consensus classification of prostatitis syndromes [Krieger 1999]

Category	Characteristic clinical features
I Acute bacterial prostatitis	Acute infection of the prostate gland characterized by fever, chills, low back pain and perineal pain. Irritative voiding symptoms (dysuria, frequency, urgency, nocturia) are characteristic. Rectal examination reveals a markedly tender, swollen prostate.
II Chronic bacterial prostatitis	Recurrent infection of the prostate caused by persistence of the same organism despite treatment. Symptoms are irritative voiding & pain of varying degrees. Rectal examination reveals no characteristic finding.
III Chronic prostatitis / chronic pelvic pain syndrome (CP/CPPS)	No demonstrable infection; primarily pain complaints, plus voiding complaints and sexual dysfunction affecting men of all ages. Usually cause is unknown.
IIIA Inflammatory subtype	Symptomatic patients without bacteriuria but with inflammation (white cells) in semen, expressed prostatic secretions (EPS) or post-prostatic massage urine
IIIB Non-inflammatory subtype	No white cells in semen, EPS or post-prostatic massage urine
IV Asymptomatic inflammatory prostatitis	No subjective symptoms, inflammation detected either by prostate biopsy or the presence of white cells in expressed prostatic secretions or semen during evaluation of other genitourinary complaints

This classification has become the reference standard for research on these conditions.

The following recommendations on diagnosis and treatment of prostatitis were adapted from the 2002 Guidelines for the Management of Prostatitis developed by the Association for Genitourinary Medicine, Medical Society for the Study of Venereal Disease of the United Kingdom.

2. What diagnostic tests should be requested for a patient suspected to have prostatitis?

a. Acute bacterial prostatitis

Mid-stream urine sample for dipstick testing, culture for bacteria, and antibiotic sensitivity are recommended (Grade C).

Prostatic massage should not be performed on patients with acute bacterial prostatitis since this would be extremely painful, could precipitate bacteremia, and is likely to be of little benefit as pathogens are usually isolated from urine.

b. Chronic bacterial prostatitis

The lower urinary tract localization procedure, which has been the standard, is recommended in the investigation of chronic bacterial prostatitis (Grade C).

Summary of evidence

Strictly, symptoms should have been present for at least 6 months. In chronic bacterial prostatitis, direct microscopic examination of the expressed prostatic secretions (EPS) identifies significant prostatic inflammation at > 10 wbc/hpf. The presence of lipid-laden macrophages is more prostate specific and strengthens the diagnosis [Pewitt 1997]. Several other authors have also recommended this cut off of > 10 WBC in the EPS [Anderson 1979, Drach 1978, Meares 1980, Schaeffer 1981]. This pre- and post-massage test of prostatic fluid has been calculated to have 91% sensitivity [Nickel 1997]. The finding of fat-laden macrophages further localizes the site of inflammation to the prostate since these could not be seen from urethral exudates [Meares 1980].

Diagnosis can be further confirmed by doing the triple voided urine test. In this examination, prostatitis can only be diagnosed if the specimen is free of WBC. The diagnosis of prostatic infection is confirmed when the quantitative bacterial colony counts of EPS and the next 5 to 10 ml of urine (VB3) significantly exceed those of the urethral (VB1) and bladder (VB2) specimens. The colony count of the EPS and VB3 should exceed the VB1 by at least 1 logarithm.

Table 17. Lower urinary tract localization study [Krieger 2003]

Specimen	Procedure
Voided bladder 1 (VB1)	Initial 5–10 mL of urinary stream
Voided bladder 2 (VB2)	Midstream specimen
Expressed prostatic secretions (EPS)	Secretions expressed from prostate by digital massage after midstream specimen
Voided bladder 3 (VB3)	First 5–10 mL of urinary stream immediately after prostate massage
Unequivocal diagnosis of chronic bacterial prostatitis requires a 10-fold higher concentration of a uropathogen in the VB3 of EPS specimen when compared to the VB1 specimen. The organism is identical to organisms causing repeated episodes of bacteriuria.	

Recurrent UTI caused by the same pathogen are the hallmark of chronic bacterial prostatitis. Between episodes of symptomatic UTI, many patients have few symptoms despite persistent infection of the prostatic parenchyma. During such periods, when the patient does not have bacteriuria, lower urinary tract

localization studies can be used to prove that the prostate is the focus of recurrent infections. A 10-fold increase in the concentration of the uropathogen from VB1 to VB3, or failing this to the EPS, is considered a positive result provided this is the same pathogen responsible for episodes of bladder bacteriuria. It is often necessary to repeat the localization for patients who have negative studies or for patients who do not meet the one-log increase criterion [Krieger 2003].

***Comments**: Although the use of the lower urinary tract localization procedure has been the standard in the investigation of chronic prostatitis, the method is not very widely used because it is time consuming and does not necessarily alter management.*

c. Chronic prostatitis / Chronic pelvic pain syndrome

There is no gold-standard diagnostic test for chronic pelvic pain syndrome, and the methodologic quality of available studies of diagnostic tests is low.

Summary of evidence
A systematic review by Collins [2000] found no studies that evaluated the validity and diagnostic accuracy of the four-glass test, which is considered as the textbook standard test for categorizing chronic prostatitis as infectious, inflammatory or noninflammatory. Furthermore, surveys of physicians have indicated that it is not widely used.

For a presumptive diagnosis of prostatitis (all types), whether acute or chronic, seminal fluid analysis is recommended (Grade C).

Summary of evidence
In a study that had three specimens for VB3, EPS and SF testing taken from each of 140 patients attending the University of Washington Medical Center Prostatitis Clinic, inflammation was documented in 26%. Among the 140 subjects, 52% had inflammation in $\geq$ one sample. Inflammation was detected in EPS from 28% of the patients. These men represented 53% of the 73 subjects with inflammation in any of the three samples. The sensitivity of the EPS examination was similar to the sensitivity of the SFA, which demonstrated inflammation in 29% of the 140 subjects (not significant). These results were also comparable with the sensitivity of the VB3 evaluation, which demonstrated inflammation in 23% of 140 subjects (not statistically different from either the EPS or the SFA). Combining the VB3 and EPS evaluations resulted in diagnosis of 54 (74%) of the 73 cases with inflammation compared with 39 (52%) diagnosed by the EPS evaluation alone ($p<0.001$). The VB3 and SFA combination also resulted in diagnosis of 54 (74%) of the 73 cases with inflammation. In contrast, inflammation was documented in 69 (95%) of the 73 subjects by examining both EPS and SFA ($p<0.005$ compared with either the VB3-EPS combination or the VB3-SFA combination). Examining only the EPS resulted in diagnosis of half of the patients. An optimal diagnostic strategy required evaluation of the VB3 and SFA in addition to the traditional EPS examination [Krieger 2003].

3. What is the recommended treatment?

a. Acute bacterial prostatitis

As acute prostatitis is a serious and severe illness, empirical therapy should be started immediately (Grade C). Adequate hydration should be maintained, rest encouraged, and analgesics such as NSAIDs used (Grade C).

Empiric treatment with TMP/SMX or an oral fluoroquinolone may be started until culture and sensitivity results are known. The course of treatment should extend to at least 30 days to prevent the development of chronic prostatitis (Grade C). If there is no response within the first week, change the antimicrobial and do culture of EPS (Grade C).
Summary of evidence

In separate review articles Leigh [1993], Weidner [1992] and Meares [1980] showed that in acute and chronic bacterial prostatitis, E. coli still predominate, although other causative agents include Enterobacter, Klebsiella, Pseudomonas spp. and Serratia.

Seriously ill patients require hospitalization and parenteral antimicrobial therapy, such as an aminoglycoside-penicillin derivative combination or fluoroquinolones (Grade C). When complications of urinary retention or the development of a prostatic abscess occurs, referral to a urologist is recommended (Grade C).

Summary of evidence
Pewitt and Schaeffer [1997], Roberts [1997] and Meares [1980] in separate review articles have recommended the use of an aminoglycoside-penicillin derivative combination or a fluoroquinolone for initial parenteral therapy for acutely ill patients until an appropriate antibiotic, based on culture and sensitivity studies is substituted.

b. Chronic bacterial prostatitis

Treatment should be guided by antimicrobial susceptibility patterns.

For chronic bacterial prostatitis, first of line treatment is a quinolone such as:

- **Ciprofloxacin 500 mg BID for 28 days (Grade C) OR**
- **Ofloxacin 200 mg BID for 28 days (Grade C) OR**
- **Norfloxacin 400 mg BID for 28 days (Grade C)**

For those allergic to quinolones, the following are recommended:

- **Doxycycline 100 mg BID for 28 days (Grade C)**
- **Minocycline 100 mg BID for 28 days (Grade C) OR**
- **Trimethoprim 200 mg BID daily for 28 days (Grade C) OR**
- **TMP-SMX 160/800 mg BID for 28 days (Grade C)**

Summary of evidence
In a one-year follow-up study, 500 mg ciprofloxacin BID for two weeks was beneficial in 5 of 12 patients in the treatment of chronic bacterial prostatitis, particularly in cases of E. coli prostatitis. Ciprofloxacin treatment failed in 3 and therapy was discontinued in 1 because of side effects [Weidner 1987]. In another study [Weidner 1991], 10 out of 16 patients with refractory chronic bacterial prostatitis caused by E. coli were considered cured based on bacteriological results and clinical symptoms after being treated with 500 mg ciprofloxacin BID for 4 weeks. In 2 men, a second ciprofloxacin regimen showed success; therapy failed in 2; and in the other 2, therapy had to be discontinued due to side effects.

Fifteen consecutive men who had chronic bacterial prostatitis refractory to TMP/SMX and/or carbenicillin were treated with 400 mg norfloxacin BID for 28 days. All pathogens were susceptible to norfloxacin. Of the 14 patients followed for at least 6 months, 9 were cured of the initial infection. In 3 patients UTI recurred with new pathogens at 6, 560, and 820 days after negative prostatic fluid cultures post-therapy. Bacterial prostatitis with the original pathogen recurred in 5 patients within 2 months of completing therapy. The bacteria could not be eradicated however with 30 to 90 days of additional norfloxacin therapy despite remaining susceptible. Cure was achieved in 9 of 12 E. coli prostatitis and 3 of 5 patients with prostatic calculi. No patient experienced significant adverse effects [Shaeffer 1990].

Britton and Carson [1998] have noted 33-50% cure rates with TMP/SMX while the same study together with Roberts [1997] and Pewitt [1997] have reported 60-90% cure rates with fluoroquinolones.

Another study [Paulson 1978] showed that minocycline-hydrochloride 100 mg BID for 28 days, seemed equally effective as TMP/SMX 2 tablets BID for 90 days in the treatment of culture-proven bacterial prostatitis and in controlling symptomatic recurrence during the 12 months after cessation of therapy. 14

of 15 TMP/SMX-treated patients had negative cultures while on therapy and were symptom-free while 10 of 14 minocycline-treated patients had cultures cleared and had symptom relief while on therapy. 4 of 14 and 3 of 10 patients had recurrence, respectively. Four minocycline-treated patients were unable to tolerate the drug.

Some studies have looked at longer treatment periods of 90 days or more but there is no evidence that this is superior to 28 days.

***Comments:** In practice most experts would use doxycycline 100 mg twice daily for 28 days because of more toxicity with minocycline. Sensitivity testing to minocycline should be done, as many uropathogens are tetracycline resistant.*

Men with recalcitrant chronic bacterial prostatitis can be treated with radical transurethral resection of the prostate or total prostatectomy. For symptomatic relief, Sitz baths, anti-inflammatory agents, prostatic massage and other supportive measures can be given (Grade C). Long-term, low-dose suppressive therapy may be required for patients who do not respond to full dose treatment. TMP-SMX 80/400 mg once daily is recommended for 4 to 6 weeks (Grade C).

Summary of evidence
Prostatic calculi have been suggested as a source for recurrent infection. They are extremely common radiographically [Peeling 1984]. Transurethral prostatectomy was carried out on patients with severe, persistent symptoms: 16 patients with pathogenic bacterial prostatitis, 12 with Staphylococcus albus prostatitis, 15 with other urological disorders and 6 with negative findings. Comparison of the 4 sub-groups showed that three-quarters of each group improved but more patients in the pathogenic bacterial prostatitis group were asymptomatic [Smart 1976].

Several review articles [Meares 1980,Pewitt 1997,Roberts 1997] have advocated radical transurethral resection of the prostate with projected 30-100% cure rates in selected patients. Combination of prostatic massage with antibiotics [Hennenfent and Feliciano 1998] for treatment of refractory cases also showed favorable results. Low-dose, chronic suppressive therapy does not cure the infection but usually prevents bacteriuria and controls symptoms. Discontinuation of therapy however, results in recurrence of bacteriuria and symptoms [Meares 1980].

***Comments:** It is difficult to make evidence based recommendations about treatment because most studies have small patient numbers, are non-comparative, define chronic bacterial prostatitis in different ways, have no placebo group, use different doses of the drug studied for different lengths of time, use different treatment outcomes and have different periods of follow-up. These recommendations are based on the studies available plus expert opinion.*

Many antimicrobials penetrate the prostate gland poorly. In chronic bacterial prostatitis, the gland is either subacutely inflamed or non-inflamed.

c. Chronic prostatitis / Chronic pelvic pain syndrome (CP/CPPS)

Antibiotics or alpha-adrenergic blockers are not recommended for refractory or long-standing CP/CPPS (Grade D).

Summary of evidence
A recent multicenter randomized double-blind trial comparing 6 weeks of therapy with ciprofloxacin, tamsulosin, both drugs or placebo found that neither ciprofloxacin nor tamsulosin substantially reduced symptoms in 196 men with long-standing CP/CPPS with at least moderate symptoms [Anderson 2004].

An earlier Cochrane systematic review of 15 treatment trials [McNaughton Collins 2003] showed that there is little evidence to support the routine use of antibiotics or alpha-blocking drugs to help relieve chronic abacterial prostatitis. The trials were methodologically weak and involved small sample sizes.

Heat treatment may be useful to relieve chronic pelvic pain syndrome (Grade C).

Summary of evidence
The Cochrane systematic review [McNaughton Collins 2003] found five studies that evaluated different types of heat treatment (either transrectal microwave hyperthermia or transurethral microwave thermotherapy); three of the studies used sham treatments. These small studies demonstrated some benefit of clinical significance that merits further evaluation in well-designed larger studies.

A randomized double-blind sham controlled study using new prostatitis specific assessment questionnaires showed that transurethral microwave thermotherapy (TUMT) appears to be an effective, safe and durable treatment for patients with nonbacterial prostatitis unresponsive to traditional therapy [Nickel 1996]. Patients were assessed using a symptom severity index and symptom frequency questionnaire. The TUMT group (n=10) benefited from therapy compared to the sham group (n=10). Of the sham group, 50% had a favorable response after subsequent TUMT. Four patients complained of transient adverse reactions, including hematuria, impotence, premature ejaculation, urinary tract infection, urinary retention and urinary incontinence. All adverse reactions were transient and resolved within 3 weeks after treatment.

Comment: *Microwave thermotherapy is generally not being done locally for patients with prostatitis but is usually being given to patients with BPH.*

Allopurinol for nonbacterial prostatitis is not recommended at this time (Grade C).

Summary of evidence
A Cochrane systematic review [McNaughton Collins 2003] recommended that further studies are needed to determine the role of allopurinol in the treatment of nonbacterial prostatitis. One small trial of allopurinol for nonbacterial prostatitis showed patient-reported symptom improvement, investigator-graded prostate pain improvement, and concomitant changes in biochemical parameters. However, the measures used and the analyses presented were not sufficiently standardized and validated to conclude that changes in urine and prostatic secretion composition resulted in relief of symptoms. Although there were statistically significant findings in some of the measured outcomes, the clinical relevance is unclear. Further trials of allopurinol treatment using standardized and validated outcome measures and analyses are necessary to determine whether allopurinol is effective.

VIII. PREVENTION OF CATHETER-ASSOCIATED URINARY TRACT INFECTION

A. How effective are the different catheter care and management policies in preventing catheter-associated UTI?

1. Personnel

1.1 Only persons trained on correct aseptic techniques of catheter insertion and care should handle urinary catheters (Grade B).

Summary of evidence:
Benefits: *Within 48 hours of catheterization, women catheterized by licensed practical nurses and registered nurses had more than thrice (34%) and twice (21%) the rate of acquired bacteriuria, respectively, than patients catheterized by trained physicians (10%)[Garibaldi 1974].*

Costs: *Use of aseptic technique and sterile equipment by trained personnel was shown to be a cost-effective application of the CDC guideline for the prevention of catheter-associated UTI [Epstein 1985,Wong 1983].*

1.2 Hand washing should be done immediately before and after catheter insertion or care (Grade B).

Summary of evidence:
Benefits: *Hand hygiene is regarded as the most effective measure to prevent cross-transmission of potentially harmful organisms. Direct evidence of its effect on nosocomial infection is scarce, but data showing at least a temporal relationship are available. Carriage of exogenous organisms on the hands of hospital personnel causing cross-infections in patients has been implicated in reports of case clusters [Kaslow 1976, Maki 1973] and epidemics [Schaberg 1976] of nosocomial urinary tract infections. The role of cross-infection was demonstrated in a prospective study of case clustering in 15.5% of non-epidemic nosocomial bacteriuria of which 90% of clustered cases and 71 % of non-clustered cases were associated with indwelling urinary catheters [Schaberg 1980]. Hand washing before and after catheter care have been emphasized to minimize the risk of personnel hand contamination and to prevent cross infection [Garner 1985, Steere1975, Wong 1983]. Renewed emphasis of this measure together with spatial separation of infected catheterized patients, controlled the outbreak of catheter-associated urinary tract infections [Kaslow 1976, Maki 1973].*

2. Catheter insertion procedure-related interventions

2.1 Limit catheter use to carefully selected patients. Avoid unnecessary catheter use (Grade B). Routine catheterization during labor or immediately post-partum for collection of urine sample is not recommended (Grade C).

Summary of evidence*: Studies evaluating whether patients who were catheterized had indications for the use of such devices have found that initial catheterization was inappropriate 21% to 50% of the time [Gardam 1998, Jain 1995, Munasinghe 2001]. More importantly, continued catheter use was deemed inappropriate for almost half of the days that patients were catheterized in one study [Jain 1995] and for over one third of the days that patients were catheterized in another prospective evaluation [Hartstein 1981].*

Appropriate indications for indwelling urinary catheter use in hospitalized patients are the following: (1) when accurate and frequent measurements of urine output in critically ill patients are needed, (2) to aid in urologic surgery or other surgery of contiguous structures, (3) to relieve anatomic or functional urinary tract obstruction drainage e.g. patients with neurogenic bladder dysfunction, urinary retention or other congenital or acquired urologic abnormalities, (4) when urinary incontinence is present without obstruction in a patient with an open sacral or perineal wound and (5) just before, during or just after prolonged surgical procedures with general or spinal anesthesia [Gardam 1998, Kunin 1966, Munasinghe 2001, Saint 2003 ,Warren 1997, Wong 1983].

Two prospective studies have demonstrated that the presence of pathogenic bacteria in the periurethral area and an indwelling urethral catheter are two major risk factors that predispose to catheter-associated UTI [Daifuku 1984, Garibaldi 1980]. In both studies, majority (67-85%) of patients with positive meatal cultures who acquired catheter-associated UTIs had the same species of bacteria recovered from the meatal culture. 110 of the 612 patients (18%) with positive meatal culture acquired bacteriuria significantly ($p<0.0001$) than patients with negative cultures (28 of 601 or 5%)[Garibaldi 1980]. In female patients, approximately 70% of episodes of catheter-associated bacteriuria occur when bacteria ascend into the bladder urine by way of the catheter [Garibaldi 1980]. Antecedent rectal colonization with the same infecting organism preceded 78% of infections in women (14 of 18) and 29% (5 of 17) of infections in men [Daifuku 1984]. In addition, the indwelling catheter, by itself is an important site for bacterial attachment and persistence in catheterized patients [Stamm 1991]. Thus, true prevention begins by avoiding unnecessary catheter use.

Comments: *In one of the study sites of a recent collaborative quality improvement project, the use of written chart reminders in a provincial hospital in the Philippines reduced inappropriate catheter use from*

32% to 15% over a period of 6 months in a time series analysis. [Abstract presented at the 2004 Asian Pacific Society for Infection Control Conference and the 2004 International Conference on Improving the Use of Medicines].

2.2 Catheters should be inserted using aseptic technique and sterile equipment (Grade A). Handwashing and cleaning of the periurethral area with water before insertion of a sterile catheter with gloved hands may be acceptable alternatives (Grade B).

Summary of evidence

Benefits: *As previously mentioned, use of sterile equipment and correct aseptic technique by trained personnel proved to be cost-effective measures in preventing catheter-associated UTI [Epstein 1985], as prescribed by the 1983 CDC guideline. Specifically, these include the use of sterile gloves, sterile catheter, antiseptic solution for perineal cleansing, and water-soluble lubricating jelly for catheter insertion [Desatels 1962, Kass 1957,Kunin 1979, Wong 1983].*

One small RCT [Carapeti 1994] on 156 patients who underwent pre-operative catheterization compared sterile catheterization (scrubbing for 4 minutes, gowning up, wearing sterile gloves & using strict aseptic technique) versus clean, non-sterile technique, which involved washing the hands once using soap and water only. The trial found no significant difference in the development of UTI between the two groups (9.4% with sterile technique vs. 11% in the hand wash non-sterile group). A bigger RCT of 436 obstetric patients whose periurethral area was cleaned with water vs chlorhexidine 0.1% before insertion of the urine catheter also found no significant difference in the rates of UTI (water group 8.2% vs antiseptic group 9.2%; OR 1.13, 95% CI 0.58 to 2.21) [Webster 2001].

One small RCT of 177 females undergoing abdominal hysterectomy that examined whether UTI could be reduced by reversing the sequence of vaginal cleansing and urethral catheterization found no significant reduction in the incidence of UTI among those catheterized before vaginal cleansing (15%) versus those catheterized after vaginal cleansing (25%)[Chan 2000].

Comments: *The follow up period was short for both RCTS: 3 days post-op [Carapeti 1994] and 24 hours post-insertion of the catheter [Webster 2001]. In resource-constrained settings, simple handwashing with soap and water and cleaning of the periurethral area with water before insertion of a sterile catheter with gloved hands may be acceptable alternatives.*

2.3 Maintain a sterile, closed catheter system at all times (Grade B). Open drainage is unacceptable (Grade D).

Summary of evidence

Benefits: *A greater frequency of catheter-associated bacteriuria 48 hours after errors in catheter care by hospital personnel was observed than when there were no lapses in sterile technique or care of the closed drainage system [Garibaldi1974]. In this study, bacteriuria occurred in 13.3% when the catheter-tubing junction had been disconnected at least once and in 9.5% with closed catheter-tubing junction; 17.9% of cases acquired bacteriuria when improper technique was observed against 11.8% when improper technique was not observed. However, the differences were not statistically different. In another study, disconnection of the catheter junction was associated with high rate of infection that was twice the number of days than when there was no disconnection [Warren 1978]. More importantly, adherence to the sterile continuously closed system of urinary drainage reduced the rate of infection to 16-23% [Garibaldi 1974, Kunin 1966] from an inevitable 100% 4 days after insertion when open drainage was used [Kass 1959]. However, infection becomes almost 100% by 30 days with closed drainage [Burke 1986, Garibaldi 1974]. Thus, the principal benefit of closed drainage is to delay, if not prevent, the onset of infection.*

2.4 Urine specimens should he obtained aseptically without opening the catheter-collection junction (Grade B).

Summary of evidence
Benefits: *Urine for examination should be aspirated at the distal end of the catheter with sterile needle and syringe after disinfecting the area [Wong 1983]. It has been emphasized that the junction of the catheter and drainage tube should not be disconnected for this purpose [Garibaldi 1974, Huth 1992, Platt 1983, Warren 1978]. As previously discussed, disconnection of the catheter junctions, whether to collect urine specimens or to irrigate the bladder, was associated with high rates of infection [Garibaldi 1974, Warren 1978].*

2.5 Maintain unobstructed and adequate urine flow at all times (Grade B).

Summary of evidence
Benefits: *High bacterial colony counts can develop in the collection bag and ascend against the flow of urine to infect the urinary bladder within two days [Garibaldi 1974, Kunin 1966, Thorton 1970]. To achieve free flow of urine: (1) the collection bag should be lower than the level of the bladder at all times, (2) the catheter and collecting tube should be kept from kinking, (3) the catheter should not be clamped except when a culture specimen is collected or when the patient must be separated from the drainage bag, and (4) the bag should be emptied regularly [Reese 1997, Wong 1983].*

2.6 Remove the urinary catheter as soon as possible (Grade A). Consider instituting automatic stop orders or chart reminders to decrease prolonged unnecessary catheterization (Grade B).

Summary of evidence
Benefits: *One of the most important risk factors for the development of catheter-associated bacteriuria is the duration of catheterization [Garibaldi 1974, Harstein 1981]. The daily incidence of developing bacteriuria approximates 3% to as high as 16% per day [Burke 1986, Garibaldi 1974, Haley 1981, Kunin 1966]. Maki has demonstrated that the risk is highest at > 6 days (OR 5.1 to 6.8). Two prospective studies [Harstein 1981, Jain 1995] have demonstrated that a substantial proportion of catheter days were unnecessary and prompt removal would have theoretically prevented 40% of all infections. Thus, if the catheter can be removed before bacteriuria develops, postponement of bacteriuria becomes prevention [Warren 1997].*

A well-conducted prospective study by Domingo and colleagues [1999] at the medical wards and intensive care unit of the Philippine General Hospital likewise showed that duration of catheterization was significantly associated with acquisition of infection (OR 1.22, 95% CI 1.09-1.37) on multivariate analysis. The study also showed that peak incidence of catheter associated UTI occurred on the 5^{th}-7^{th} day of catheterization. The average number of days from catheter insertion to the development of UTI was 6.4 days (range 2-44 days). Since duration of catheterization is a modifiable risk factor, emphasis should be made on interventions to reduce the prolonged and inappropriate use of urine catheters to decrease the incidence of catheter-associated UTI.

Small studies on quality improvement interventions aimed to decrease duration of catheterization have shown small significant changes. For instance, a recent small before-and-after crossover study in a US medical center found that computerized urinary catheter reminder system decreased catheterization duration by nearly 3 days (p=0.1) [Cornia 2003]. Locally, a quality improvement project using written chart reminders decreased the duration of catheterization by 1.4 days. [Domingo 2003]. Although UTI rates were not measured, quality improvement interventions e.g. automatic stop orders or chart reminders are promising and may prove beneficial if sustained in the long term.

2.7 Do not change catheters and drainage bags at arbitrary fixed intervals (Grade D).

Summary of evidence
Benefits: *Experts agree that a catheter should not be changed on a routine schedule [Stamm 1993, Wong 1983]. Indications for catheter and drainage bag change include: (1) malfunction or leakage, (2) catheter obstruction, (3) contamination (e.g. disconnection between catheter and drainage tube), (4) bacteriuria*

that require antibiotics, (5) concretions in catheter lumen that may proceed to its obstruction, and (6) candiduria [Stamm 1995].

One small RCT of 153 patients with indwelling catheters for at least 3 days, which compared a 3- day drainage bag change versus no change found no significant difference in the rate of symptomatic UTI (13.9% in the 3 day change and 10.8% in the control group; p=0.7)[Keerasuntonpong 2003]. This study however does not confirm the hypothesis that frequent changes of the urinary drainage bag leads to breaks in a closed system, which increases the risk of developing UTI. At present, there is no evidence that retaining the urinary bag for patients with short-term indwelling catheters increases the risk of UTI.

3. Methods to avoid endogenous infection

3.1 Daily meatal care is not recommended (Grade E).

Summary of evidence
Benefits: *Five randomized controlled trials of either once or twice daily, meatal cleansing, whether using soap and water or polyantibiotic cream, did not find any significant reduction in catheter-associated UTI [Britt 1976, Burke 1981, Classen 1991, Huth 1992].*

4. Methods to avoid exogenous infection

4.1 Irrigation of the bladder with antimicrobial agents is not recommended (Grade D).

Summary of evidence
Benefits: *Randomized controlled trials have shown that bladder irrigation using antimicrobial agents did not prevent most catheter-associated bacteriuria [Bastable 1977, Davies 1987, Gillespie 1983, Warren 1978], even if given continuously [Bastable 1977, Maki 1972, Warren 1978].*

4.2 Instillation of disinfectants into the bag and the use of antireflux valves and vents are not recommended (Grade D).

Summary of evidence
Benefits: *Instillation of disinfectants in the drainage bag [Sweet 1984, Thomson 1984, Willie 1993] or the use of antireflux vents and valves [Garibaldi 1974, Keys 1979] did not reduce the incidence of bacteriuria in randomized controlled trials.*

4.3 Segregate infected from uninfected catheterized patients (Grade C).

Summary of evidence
Benefits: *Risks of cross-contamination can be minimized if a patient with catheter-associated UTI is not placed in the same room as another patient with an indwelling catheter [Maki 1972, Wong 1983]. Spatial separation of infected catheterized patients, in conjunction with emphasis on hand washing, controlled the outbreak of catheter-associated UTIs [Kaslow 1976, Maki 1973].*

5. Bacteriologic monitoring and prophylactic systemic antibiotics

5.1 Bacteriologic monitoring of catheterized patients is not recommended (Grade D).

Summary of evidence
Benefits: *Garibaldi [1982] studied the value of daily bacteriologic monitoring in catheterized patients and found that symptomatic catheter-associated UTIs in hospitalized patients tended to occur on the first day of bacteriuria. Thus, in most patients, there is no asymptomatic bacteriuria to treat to prevent symptomatic U'TI. Furthermore, it would require 250 urine cultures to prevent one symptomatic UTI.*

5.2 Use of systemic antibiotic prophylaxis in catheterized patients is not recommended (Grade D).

Summary of evidence
Benefits: *Most of the randomized clinical trials of antibiotic prophylaxis had positive outcomes; however, these studies were confined to certain groups of patients, such as males undergoing prostatectomy or other surgical operations. In addition, long-term follow-up showed that antibiotics were effective for the first few days (up to a week) but then resistant organisms appeared in the urine. Because of side effects, additional costs, and emergence of resistant bacteria, antibiotics to postpone bacteriuria or treat asymptomatic bacteriuria is discouraged [Kunin 1987, Mountokalakis 1985, Schaberg 1986, Slade 1985, Warren 1997].*

One small RCT of 70 patients with long-term urinary catheters demonstrated that the use of prophylactic antibiotic during routine replacement of the catheter did not prevent or delay the development of bacteriuria [Firestein 2001].

5.3 Patients at high-risk for complications of catheter-associated bacteriuria, such as renal transplant and granulocytopenic patients may benefit from antibiotic prophylaxis (Grade B).

Summary of evidence
Benefits: *One randomized, double blind study using TMP/SMX at a daily dose of 160/800 mg demonstrated the cost-benefit of TMP/SMX as prophylaxis against infections, including catheter-associated UTIs, in renal transplant patients [Fox 1990].*

B. How effective are the different types of indwelling urethral catheters in reducing the risk of catheter-associated UTI?

1. Antiseptic-impregnated catheters vs standard catheters

1.1 Consider using silver alloy catheters, if available, to reduce the risk of catheter-associated UTI (Grade B).

Summary of evidence
Benefits: *We found three systematic reviews. The most recent Cochrane systematic review (search date 2003, 17 parallel group trials involving 4237 hospitalized adults and one large cluster randomized crossover trial involving 27, 878 adults) looked into the effectiveness of the different types of indwelling urethral catheters in reducing the risk of UTI in adults who undergo short term urinary catheterization [Brosnahan 2004]. Three comparisons were addressed in this review one of which looked into antiseptic impregnated catheters versus standard catheters (n=11 trials, 3396 hospitalized adults). The antiseptic catheters were either impregnated with silver oxide or silver alloy.*

Silver oxide catheters were not associated with a statistically significant reduction in bacteriuria in short-term catheterized hospitalized adults (RR 0.89, 95% CI 0.68 to 1.15). Silver alloy catheters on the other hand significantly reduced the incidence of asymptomatic bacteriuria (RR 0.36, 95% CI 0.24 to 0.52) in hospitalized adults catheterized for less than one week. At greater than one week catheterization, the risk of asymptomatic bacteriuria was still reduced (RR 0.67, 95% CI 0.50 to 0.90). The risk of symptomatic UTI was also reduced with the use of silver alloy catheters (RR 0.60, 95% CI 0.50 to 0.73).

The earlier systematic reviews [Niel-Weise 2002, Saint 1998] found similar results that silver alloy catheters were more effective than standard catheters in reducing the risk of bacteriuria. Trials assessed in these two reviews were also included in the above review.

Another RCT (170 patients) compared a catheter with an active antibacterial device that slowly releases silver ions onto the inner surface of the system versus an ordinary catheter without the device. Frequency of UTI was the outcome (urine cultures at the time of catheterization, 6 days and 10 days after). It showed

no significant benefit for the antibacterial system in reducing UTI compared to control over 10 days (treatment: 19% vs control: 24%, hazard ratio 0.68, 95% CI 0.33, 1.28) [Reiche 2000].

The large cluster-randomized crossover trial [Karchmer 2000], which was excluded in the pooled analysis of the Cochrane review, compared silver alloy hydrogel-coated catheters versus silicone-coated catheters among hospitalized patients with wards as the unit of randomization. The outcome measured was incidence of nosocomial catheter associated UTI on a 12 month follow up. It showed no significant difference in the incidence of UTI per 100 patients (154/13,945 or 1.1% treatment group and 189/13,933 or 1.36% control group, RR 0.81, 95% CI 0.65-1.01). However, the relative risk of infection per 1000 patient days decreased to 0.79 (95% CI 0.63, 0.99) for study wards randomized to silver-coated catheters compared to those randomized to uncoated catheters. The relative risk of infection per 100 silver-coated catheters used on study wards compared with uncoated catheters was also significantly reduced at 0.68 (95% CI 0.54, 0.86).

Costs: *Economic analysis of the above trial [Karchmer 2003] showed that estimated hospital cost savings with the use of silver catheters ranged from $ 14,456 to $ 573,293. Two other economic evaluation studies modeled in hospitalized medical and surgical patients in England [Plowman 2001] and the USA [Saint 2000] demonstrated potential cost savings with the reduction of the incidence of UTI using silver alloy catheters.*

Harms: *The trials included in the reviews gave no information on adverse effects.*

Comments: *The trials included in the review were generally of poor methodological quality, which could have overestimated the magnitude of the benefits. Other limitations of the review include variation in the use of antibiotics and in the methods of urine specimen collection across the studies. The trials also used bacteriuria as a surrogate endpoint for symptomatic UTI.*

The cost of a silver alloy catheter is approximately $13 while a standard catheter costs $7. Use of the more expensive silver-coated catheter appeared to offer cost savings by preventing excess hospital costs from nosocomial UTI associated with catheter use. These catheters however are not generally available in the country. Silver oxide catheters are no longer manufactured.

Silver has broad-spectrum bactericidal properties against gram positive and gram-negative organisms. Coating urinary catheters with silver prevents adherence to and growth on the surface of the catheters by E.coli and Pseudomonas aeruginosa in vitro.

2. Antimicrobial-impregnated catheters vs standard catheters

2.1 The use of antimicrobial-impregnated catheters in reducing the risk of catheter-associated UTI is not recommended (Grade D).

Summary of evidence

Benefits: *The Cochrane systematic review by Brosnahan [2004] found one small RCT (124 patients undergoing radical prostatectomy), which compared minocycline and rifampin impregnated silicone catheters versus plain silicone catheters. This trial found that catheters impregnated with antibiotics reduced the incidence of gram-positive catheter associated bacteriuria at day 7 (15.2% vs. 39.7%) and at day 14 (58.5% vs. 83.5%; p< 0.001). Similar rates were found for gram-negative bacteriuria (46.4% vs. 47.1%) and candiduria (3.6% vs. 2.9%; p=1.0). Overall, the trial found a lower rate of asymptomatic bacteriuria in the antibiotic group at less than one week of catheterization (RR 0.36, 95% CI 0.18 to 0.73); but at greater than one week the result was not significant (RR 0.94, 95% CI 0.86 to 1.03) [Daouiche 1999]. There was also no significant difference in the rates of symptomatic UTI between the two groups (1/56 or 1.8% in the treatment group and 6/68 or 8.8% in the control group; RR 0.20, 95% CI 0.03, 1.63).*

Harms: *Adverse effects such as antimicrobial resistance were not investigated.*

Comments: *The main outcome measured was bacteriuria on urine cultures and zones of inhibition against E faecalis and E coli, and not the development of symptomatic UTI. The trial was not powered to detect symptomatic UTI. The follow up period of 14 days was relatively short and may not necessarily apply to patients who require long-term bladder drainage. Minocycline and rifampin are generally less active against gram-negative bacteria than gram-positive bacteria [Darouiche 1999]. Antimicrobial impregnated catheters are also not available locally.*

3. Other types of indwelling urethral catheters

3.1 Hydrophilic-coated catheters, if available, may be used for patients who require intermittent self-catheterization to reduce the degree of urethral trauma (Grade C).

Summary of evidence

Benefits: *One small RCT [Vapnek 2003] compared Lofric hydrophilic-coated catheters with standard polyvinyl chloride catheters among 61 patients with neurogenic bladder who can perform intermittent self-catheterization. There was no significant difference between the two groups in reducing the mean incidence of UTI after 12 months of study (mean of hydrophilic coated catheter group= 0.13 $\pm$ 0.18, mean of control = 0.14 $\pm$ 0.21, mean difference 0.01 $\pm$ 0.03, $p > 0.3$). However, the decrease in UTI rate from baseline was significantly higher in the hydrophilic-coated catheter group (0.44 to 0.14 or -0.3, p= 0.012) than in the control group (0.20 to 0.14 or -0.06, P=0.24) indicating that patients with higher rate of UTI may benefit more from hydrophilic-coated catheters. It also showed a significant decrease in the incidence of microhematuria (treatment: 0.31 $\pm$ 0.46 control: 0.65 $\pm$ 0.69, p= 0.027), which indicates that the hydrophilic-coated catheter decreased the degree of urethral trauma.*

Harms: *Three patients per group reported adverse events that may have been treatment related. In the LoFric catheter group 1 patient reported gross hematuria, one had epididymitis and one had infected penile prosthesis requiring hospitalization and surgical removal. In the polyvinyl group one patient reported gross hematuria, one reported epididymitis and one reported a bladder stone that was surgically removed. [Vapnek 2003]*

Comments: *The addition of a hydrophilic coating to standard polyvinyl chloride catheters decreases the coefficient of friction up to 90%. Decrease in friction should translate into decreased trauma, thereby decreasing the stricture rate, improving patient satisfaction and possibly decreasing the rate of urinary tract infection. However, this type of catheter is not available locally.*

3.2 Siliconised catheters may be used, if available, to decrease urethral side effects in men requiring short-term catheterization (Grade B).

Summary of evidence

Benefits: *We found one Cochrane systematic review [Brosnahan 2004], which included six trials of 653 hospitalized adults that compared different types of standard catheters. Three small trials investigated the urethral side effects of standard catheters in men. The outcome measurements differed in all three trials. The review found that silicone catheters reduced the risk of burning sensation in the urethra (one trial; RR 0.28, 95% CI 0.13 to 0.60 and decreased the cases of urethritis (one trial; RR 0.09, 95% CI 0.01 to 0.68) compared to non-silicone or latex catheters respectively. Another trial showed that full silicone lessened urethral inflammatory reactions compared to hydrogel coated latex or siliconised latex catheters.*

Three other small trials looked at the likelihood of infections between types of standard catheters. None of the trials provided sufficient evidence to suggest whether any of the standard catheters was better compared to another standard catheter in reducing the risk of bacteriuria in hospitalized adults catheterized short term. Catheters compared were silicone, latex, hydrogel, hydron-coated latex, and hydrogel coated latex and PVC balloon.

Comments: *Silicone catheters may be less likely to cause urethral side effects in men; however, this result should be interpreted with caution as the outcomes were measured only in single small trials and the*

outcome definitions and the types of specific catheters compared varied. Costs and availability are other issues to consider.

IX. NON-PHARMACOLOGIC INTERVENTIONS FOR UTI

How effective are non-pharmacologic interventions in preventing or treating urinary tract infections?

1. Cranberry juice and cranberry products are not recommended for the prevention of urinary tract infections in populations at risk (Grade D).

Summary of evidence

Benefits: *We found one systematic review of 4 crossover trials and 1 parallel trial with 304 patients, which compared cranberry juice with placebo [Jepson 2003]. Significant clinical and statistical heterogeneity of the trials precluded pooling of the results of the included trials in the review. The two small crossover trials on children with neuropathic bladder and the two trials on elderly men and women found no significant difference in the number of symptomatic UTIs observed in either the cranberry or placebo groups. The other small crossover trial [Walker 1997] on 19 women with recurrent lower UTI found significantly lower episodes of UTI in the cranberry group than in the placebo group but the dropout rate was high at 47%. Overall, the review found insufficient evidence to recommend cranberry juice for the prevention of UTIs in populations at risk.*

Two recent RCTs [Kontiakari 2001, Stothers 2002], which were not included in the systematic review, found significant reduction of UTI at 6 months with cranberry juice and tablets for prophylaxis against UTI.

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

The second trial is a double blind placebo-controlled RCT [Stothers 2002], which compared 1 year of treatment with pure unsweetened cranberry juice concentrates vs cranberry tablets among 150 sexually active women aged 21-72 years. Tablets were taken twice daily; juice 250 ml three times daily. Outcome measures were: (1) 50% reduction in symptomatic UTIs per year (symptoms + $\geq$ 100,000 single organism/ml) and (2) a >50% decrease in annual antibiotic consumption. The abstract reported that cranberry juice and tablets significantly decreased the number of patients experiencing at least one symptomatic UTI/year (20% and 18% respectively) compared with placebo (35%, $p<0.05$).

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

Harms: *Dropout rates in four of the five trials included in the systematic review were high (20-55%). Common reasons for withdrawal were the taste, caloric load and high cost of cranberry. The more recent RCT on women reported occasional complaints on the bitter taste of cranberry juice [Kontiokari 2001]. One study warned that ingesting large amounts of cranberries over a long duration might increase the risk*

of some types of urinary stones in high-risk patients because of the increased urinary excretion of oxalate and slight urinary acidification [Terris 2002].

***Comments**: The overall quality of the five trials included in the systematic review was poor, with small sample sizes. No intention-to-treat analysis was done in all the trials and dropout rates were high (20-55%), which could have overestimated the effectiveness of cranberry juice and its products. Thus, the results of the trials must be interpreted with caution.*

The recent RCT on women [Kontiokari 2001] is an open trial with unclear allocation concealment and it did not consistently demonstrate significant reduction in UTI at 12 months and on intention-to-treat analysis. Furthermore, the investigators prematurely stopped recruitment of patients because the cranberry juice supplier stopped producing the juice during the course of the study.

Although the RCT by Stothers provides evidence that cranberry tablet is a cost-effective option in the prevention of UTI, it is the consensus of the task force that cranberry juice or any of its products cannot be recommended at this time. High withdrawal rates in the earlier trials suggest that acceptability and long-term adherence may be difficult to achieve for long periods. Furthermore, there is no consistent evidence as to the effective amount, concentration and duration of intake of cranberry juice. The trials used a wide variety of cranberry products with varied dosing regimens and are not readily available in the Philippines.

Cranberries contain condensed tannins called proanthocyanidins, which prevent fimbriated E. coli from adhering to uroepithelial cells in the urinary tract. The antiadhesive property of cranberry probably helps prevent UTI by directly preventing E.coli from adhering to uroepithelial cells and by selecting for less adherent bacterial strains in the stool [Raz 2004]. However, clinical trials have not consistently demonstrated this benefit.

2. Cranberry juice and cranberry products are not recommended for the treatment of urinary tract infection (Grade D).

Summary of evidence

A Cochrane systematic review (search date 2001), found no properly randomized controlled trials assessing the effectiveness of cranberry juice for the treatment of UTI [Jepson 2003]. The review excluded two crossover trials because they did not measure relevant clinical outcomes [DuGan 1966, Nahata 1982]. To date, there is no good quality evidence to suggest that cranberry juice or its products is effective for the treatment of UTI in any specific population at risk for UTI [Jepson 2003].

3. Lactobacilli both in oral form and vaginal suppositories are not recommended in the prevention of UTI (Grade C).

Summary of evidence

***Benefits:** We found no systematic review. In an open RCT, a drink containing lactobacillus strain L rhamnosus GG was ineffective in reducing the rate of recurrence of first UTI compared to cranberry-lingonberry juice [Kontiokari 2001].*

A recent study [Cadieux 2002] comparing L rhamnosus GR-1 plus L fermentum RC-14 with a commercially available product containing L rhamnosus GG showed that the suppository containing L rhamnosus GR-1 plus L fermentum RC-14 was significantly better than L rhamnosus GG in colonizing the vagina of 29 healthy premenopausal women after menstruation. Vaginal cultures were obtained up to 21 days following instillation of the lactobacilli and DNA-based technique was used to distinguish the probiotic strains from indigenous flora. A small observational study on 10 women showed that L rhamnosus GR-1 plus L fermentum RC-14 suspended in sterilized skim milk can be given orally [Reid 2001].

***Comments:** It is important to understand the characteristics of the particular strain being promoted as a probiotic to prevent UTIs. L rhamnosus GR-1 is reported to contain key beneficial characteristics for candidate probiotic strains, namely highly effective adherence to vaginal epithelial cells, inhibitory to*

adherence of uropathogens, and growth inhibitory for pathogens of the urogenital tract. The other component, L fermentum RC-14 produces H2O2 and a biosurfactant and is highly adherent. Currently there are no adequately studied probiotic products for preventing UTIs. Multiple problems exist for the development of such a product such as identifying specific strains that colonize and inhibit uropathogen colonization of the vagina and survive storage and administration especially if taken orally, which require passage through the gut. [Miller 2002]

4. There is insufficient evidence to recommend coconut juice in the prevention or treatment of urinary tract infection (Grade C).

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

5. There is insufficient evidence to recommend oral water hydration in the prevention or treatment of UTI (Grade C).

Summary of evidence
We did not find any studies that looked into the effectiveness of water hydration in decreasing the episodes of UTI.

6. There is insufficient evidence to recommend drinking more water and voiding soon after intercourse to prevent urinary tract infection (Grade C).

Summary of evidence
Benefits: *We did not find any systematic review or randomized controlled trials. A case control study comparing 229 women 18-30 years old with recurrent UTI with 253 age-matched women found no significant difference in voiding habits (infrequent, post-coital, pre-coital, delayed voiding) or fluid intake (≤5 glasses of water a day). There was also no difference in "wiping" (front to back) techniques [Scholes 2000]. An earlier prospective study on risk factors for UTI in young women likewise showed that voiding and drinking habits do not make a difference in the development of UTIs [Hooten 1996].*

GLOSSARY OF TERMS

Terms used to assess accuracy or clinical utility of a diagnostic test/sign/symptom

Likelihood ratio (LR) – ratio of the probability of a test result/symptom (e.g. positive or negative) in patients with the disease to the probability in people who do not have the disease. It summarizes how many times more (or less) likely that patients with the disease are to have the test result/symptom compared to those without the disease. It expresses the likelihood that a given test result would be expected in a patient with the disease of interest as opposed to one without. A likelihood ratio > 1 indicates that the test result is associated with the presence of the disease, while a likelihood ratio < 1 indicates that the test result is associated with the absence of the disease. The further likelihood ratios are from 1 the stronger the evidence for the presence or absence of the disease. In general, likelihood ratios above 10 and below 0.1 are considered to provide strong evidence to rule in or rule out diagnoses respectively in most circumstances. When the diagnostic test reports results as being either positive or negative, the two likelihood ratios are called the positive likelihood ratio and the negative likelihood ratio. For tests with only two outcomes, the likelihood ratios can be computed directly from the sensitivities and specificities.

Negative predictive value (NPV) – proportion of patients with negative tests who do not have the disease/condition

Positive predictive value (PPV) – proportion of patients with positive tests who do have the disease/condition

Pre-test probability – the probability of the target condition being present before the results of a diagnostic test are available

Sensitivity – proportion of patients with the disease/condition correctly identified by the diagnostic test

Specificity – proportion of patients without the disease/condition correctly identified by the diagnostic test

Terms used to assess effectiveness of treatment and preventive interventions

Absolute risk reduction (ARR) – difference in the absolute risk (percentage or proportion of patients with the outcome) in the exposed (experimental event rate) vs the unexposed (control event rate)

Allocation concealment – randomization is concealed if the person making the decision about enrolling a patient is unaware of whether the next patient enrolled will be entered in the treatment or control group; accomplished through use of sealed, opaque envelopes, third party or central randomization

Intention-to-treat-analysis (ITT) – analyzing patient outcomes based on which group into which they were originally randomized regardless of whether they actually received the planned intervention

Number needed to treat (NNT) – the number of patients who need to be treated over a specific period to prevent one bad outcome

Number needed to harm (NNH) – the number of patients who would need to be treated over a specific period of time before one adverse effect of the treatment will occur

Odds ratio (OR) – ratio of the odds of having the event or target disorder in the exposed group to the odds of the same event or target disorder in a group that is not exposed

Relative risk (RR) – ratio of the risk of an event or outcome among the exposed population (with treatment or risk factor) to the risk among the unexposed (control or no risk factor)

Relative risk reduction (RRR) – an estimate of the proportion of baseline risk that is removed by the treatment, it is calculated by dividing the absolute risk reduction by the absolute risk in the control group

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IX. NONPHARMACOLOGIC INTERVENTIONS

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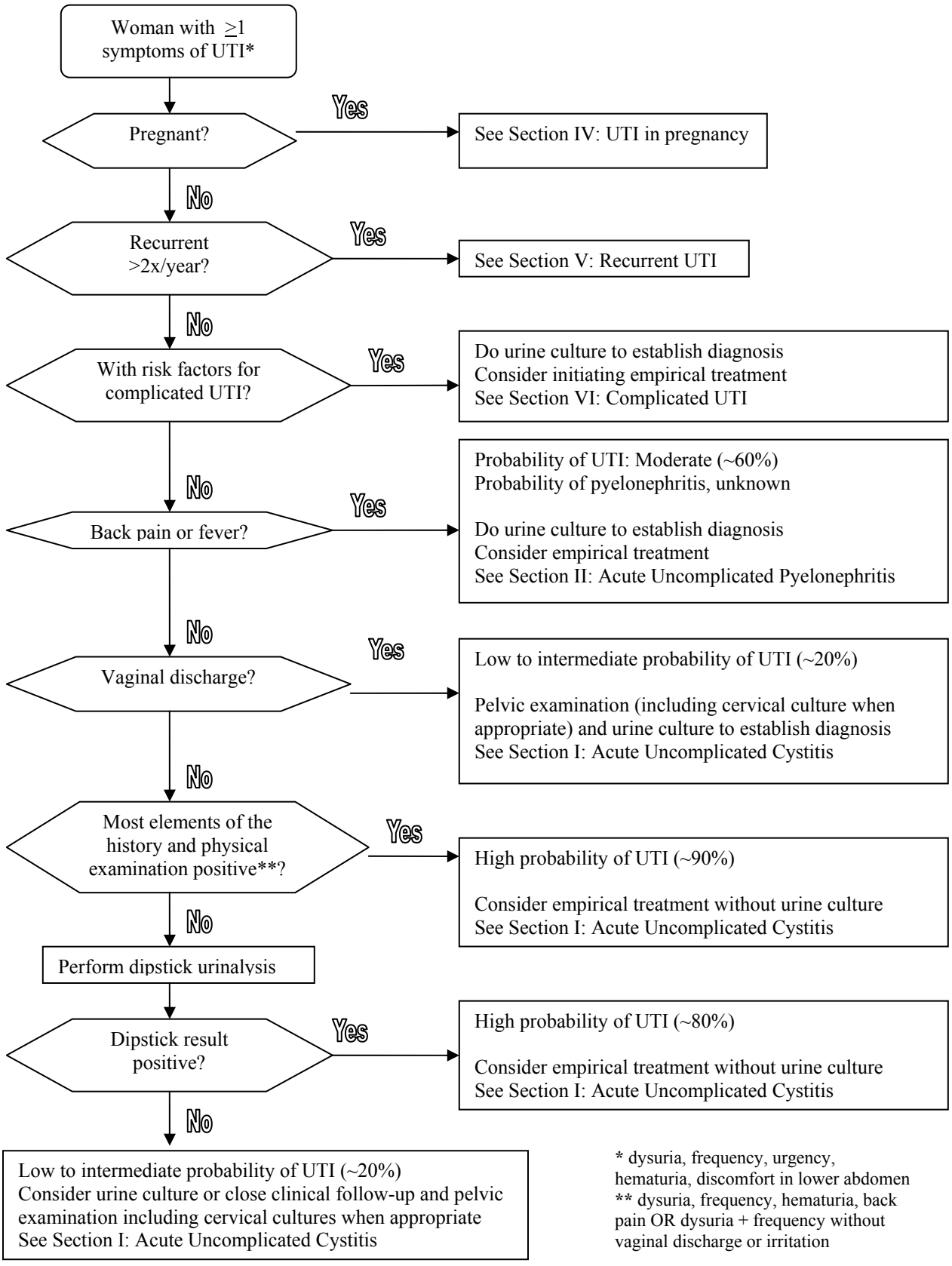
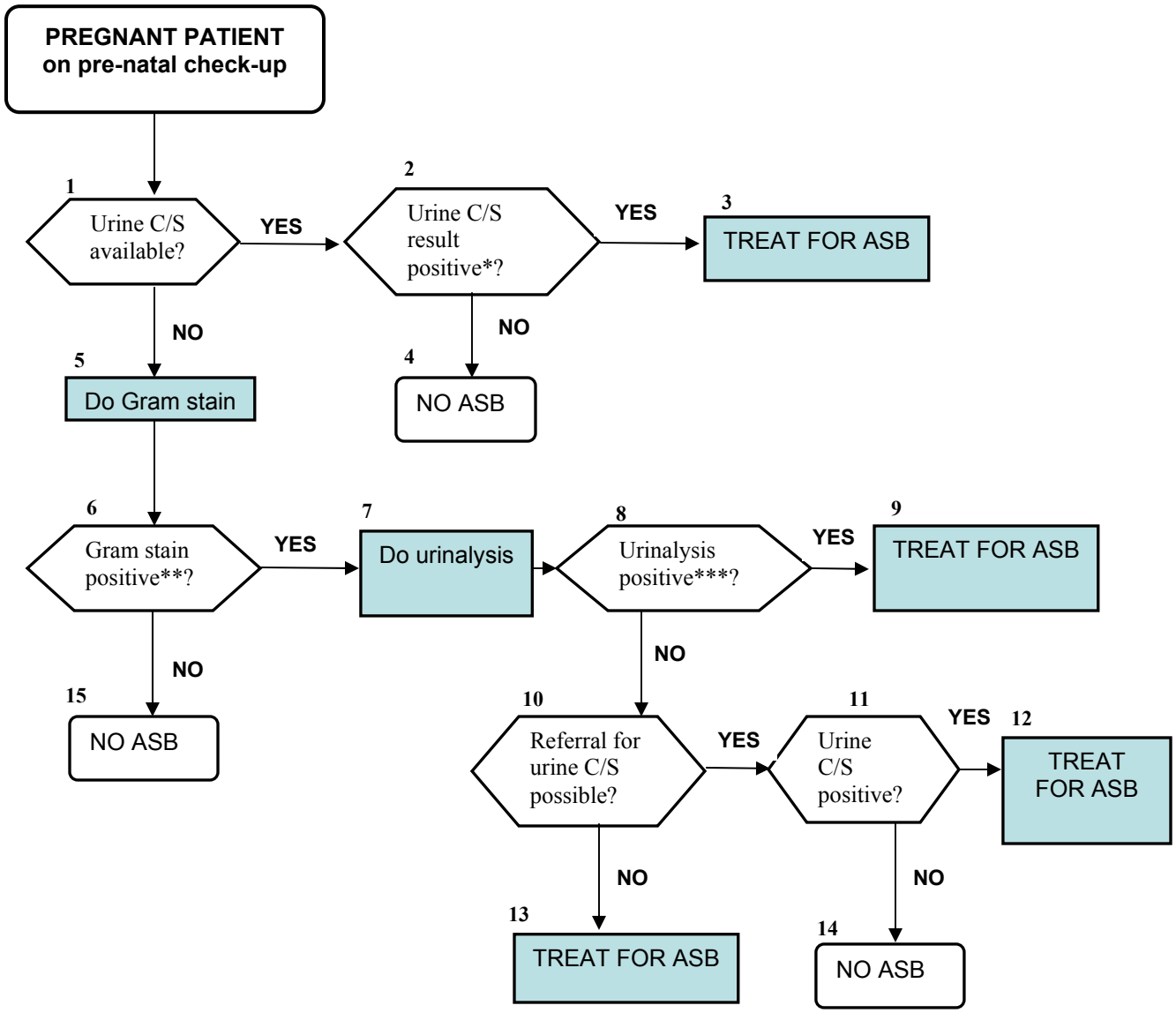
Algorithm 1. Evaluating a woman with symptoms of acute urinary tract infection



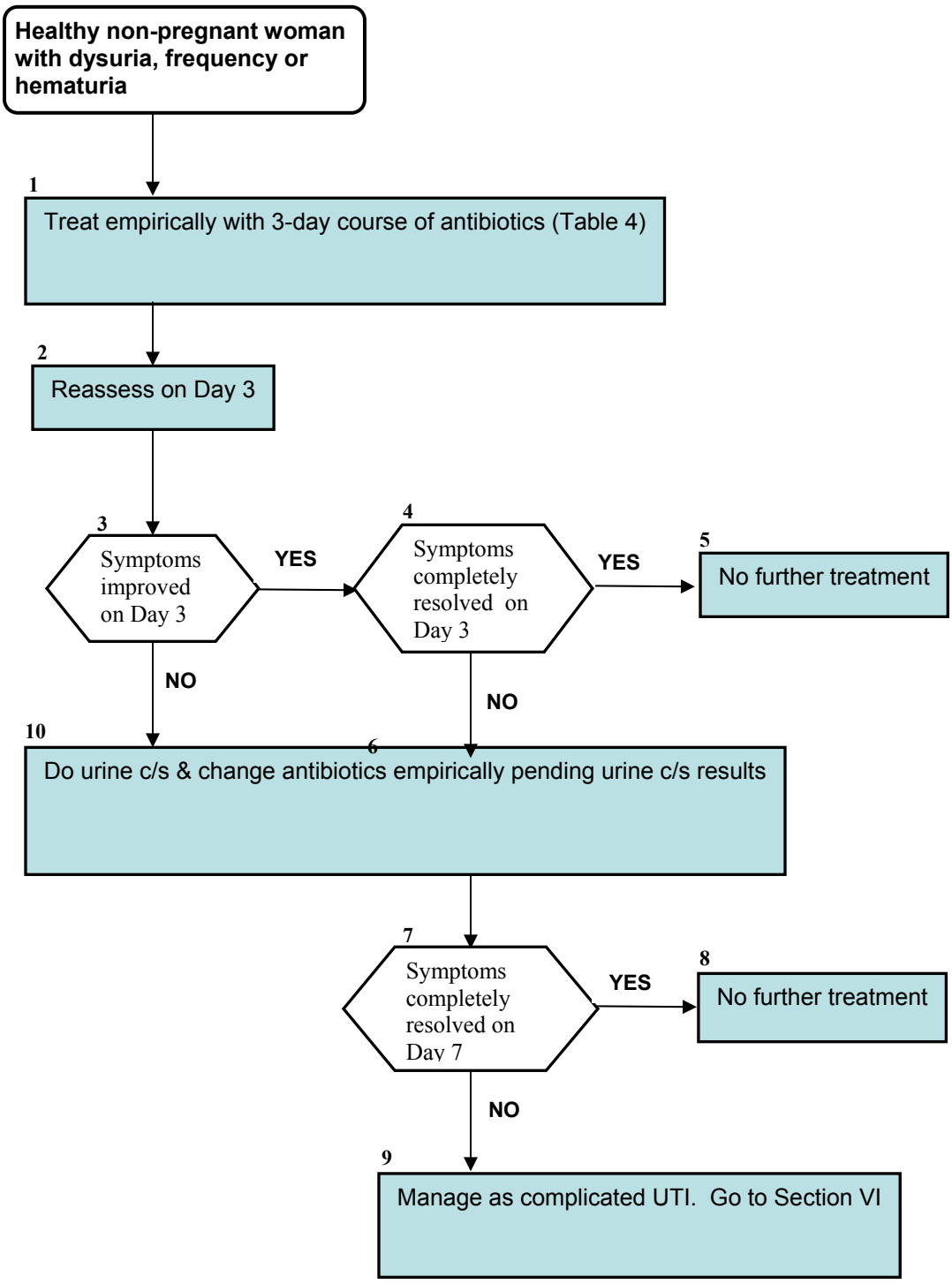
* dysuria, frequency, urgency, hematuria, discomfort in lower abdomen
** dysuria, frequency, hematuria, back pain OR dysuria + frequency without vaginal discharge or irritation

Algorithm 2. Alternative diagnostic evaluation for ASB in settings where urine culture is not available

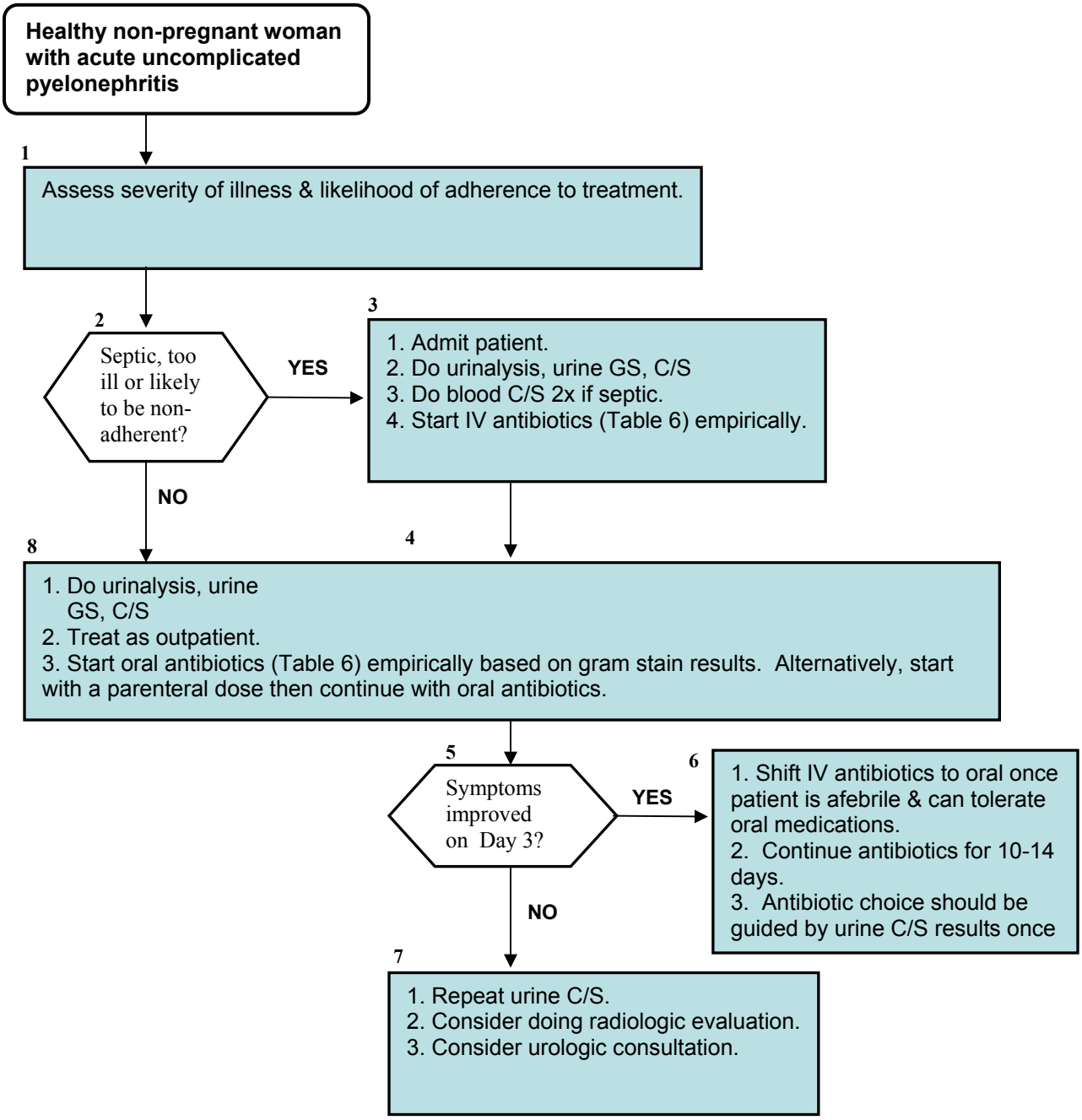


*Positive urine c/s: ≥ 100,000 cfu/ml of a uropathogen
**Positive Gram stain: > 6 of 12 hpf with bacteria of same morphology in centrifuged urine
***Positive urinalysis: ≥ 5wbc/hpf of centrifuged urine

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



Algorithm 4. Treatment of acute uncomplicated pyelonephritis in non-pregnant women



Appendix 1

Grading System for Recommendations

Categories reflecting the strength of recommendation

GRADE	DEFINITION
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for or against use
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use

Quality filters in assessing the evidence from literature

1. Studies on effectiveness of treatment and accuracy of diagnostic tests

Level of quality of evidence

I	Evidence from at least one properly randomized controlled trial
II	Evidence from at least one well-designed trial without randomization, from cohort or case-control analytic studies (preferably from more than one center), from multiple time-series studies or from dramatic results in uncontrolled experiments
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

2. Studies on prognosis or causation

Criteria for assessing quality of evidence

1. An inception cohort was chosen.
2. Reproducible and inclusion and exclusion criteria were used
3. Follow-up was complete for at least 80% of subjects.
4. Statistical adjustment was carried out for confounders or extraneous factors.
5. Reproducible descriptions of outcome measures were used.

Level of Quality of Evidence

I. All of the criteria were satisfied.
II. An inception cohort was selected but only 3 of 4 remaining criteria were satisfied.
III. An inception cohort was selected but only 2 of 4 remaining criteria were satisfied.
IV. An inception cohort was selected but only 1 of 4 remaining criteria was satisfied.
V. None of the 5 criteria was met.

3. Systematic reviews/ meta-analysis

Criteria for assessing quality of evidence

1. Comprehensive search of evidence
2. Focused criteria for selection of articles
3. Independent assessment of the validity of the articles cited
4. conclusions supported by data and analysis presented

Level of quality of evidence

I. All 4 criteria must be met.
II. 3 of 4 criteria are met
III. 2 of 4 criteria are met
IV. 1 or 4 criteria is met
V. None of the 4 criteria was met.

Appendix 2

Key points about urine collection

1. Clean-voided urine is recommended for adult females.
2. No special preparation is needed to collect specimens from pre-pubertal females.
3. No special preparation is needed for males, but the foreskin should be retracted.
4. Urethral catheterization may be needed in adults who are suspected to have infection and cannot provide a clean-voided specimen. In such case, inform the laboratory that the specimen is catheterized urine.

5. First void morning specimen yield the highest bacterial counts. In practice, the best time to collect is when the patient is able to provide an adequate sample.

6. Urine specimen should be delivered to the laboratory immediately and should be cultured within one hour after voiding or be refrigerated.

Appendix 3

Conditions that may be associated with sterile pyuria

Contamination during collection

Vaginal secretions
Foreskin secretions

Non-infectious causes of pyuria

Vesicoureteral reflux	Hypercalcemic nephropathy	Allergic interstitial pyuria
Analgesic nephropathy	Lithium toxicity	Sickle cell disease
Uric acid nephropathy	Hyperoxalosis	Sarcoidosis
Polycystic kidney	Heavy metal toxicity	Idiopathic interstitial cystitis
Acute tubular necrosis	Carcinoma of the bladder	Glomerulonephritis
Transplant rejection	Renal calculi	

Infectious diseases

Tuberculosis
Chlamydial and gonococcal urethritis
Leptospirosis
Viral cystitis

Infections adjacent to the urinary tract

Appendicitis
Diverticulosis

Appendix 4

Costs of diagnostic tests for UTI as of July 2004

Laboratory examination	Private rate (in PhP)	Government rate (in PhP)
Urinalysis (microscopic)	160 to 225	20 to 110
Urine gram stain	260 to 784	25 to 110
Urine culture/sensitivity	910 to 1100	120 to 510
Urinalysis (dipstick)*	18 to 25	-

Figures were from 4 government and 4 private hospitals in Metro Manila, except for urinalysis dipstick
**Rate taken from private laboratories in Metro Manila using 7- or 10-parameter rapid dipstick*

Appendix 5

Costs of antimicrobials used for UTI as of July 2004

Oral Antibiotics	Unit Cost (PhP)
TMP-SMX 160/800mg	27.50
Ciprofloxacin 250 mg	56.00
Ofloxacin 200 mg	24- 50.00
400 mg	73.00
Norfloxacin 400 mg	27.75
Levofloxacin 250 mg	109- 112.50
500 mg	172 –177.50
Gatifloxacin 400 mg	199.75
Nitrofurantoin 100 mg	22.25
Co-amoxiclav 625 mg	89.25
Cefalexin 250 mg	11-17.00
500 mg	17-29.50
Cefuroxime 250 mg	80.50
500 mg	142.00
Cefixime 200 mg	116.75
Fluconazole 50 mg	150.00
	469.75
150 mg	550.00
200 mg	

Parenteral Antibiotics	Unit Cost (PhP)
Cefazolin 500 mg/vial	234.75
1 gm/vial	390.75
Ceftriaxone 250 mg	355.50
500 mg	611.00
1 g	1,777.75
Ceftazidime 500 mg	607.00
1 g	1,100.00
Cefipime 1g	1,668.00
2 g	2,694.00
Ofloxacin 200 mg	1,389.50
Ciprofloxacin 200 mg	1,638.00
Levofloxacin 500 mg	1,300.50
Gatifloxacin 400 mg	1,375.50
Amikacin 250 mg	648.00
500 mg	1,184.25
Gentamicin 80 mg	184.75
Netilmicin 150 mg/1.5 ml	908.75
Ampicillin-Sulbactam 750 mg/vial	612.00
Imipenem 500 mg	1,281.25
Meropenem 500 mg	1,537.25

1 gm	2,568.00
Piperacillin-Tazobactam 2.25 g	1,298.00
	2,250.00
4.5 g	
Fluconazole	3,000.00
Amphotericin B	7,720.00

Source: Mercury drug store

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