Urinary Tract Infection and Asymptomatic Bacteriuria Guidance

Urinary tract infection (UTI) is the most common indication for antimicrobial use in hospitals and a significant proportion of this use is inappropriate or unnecessary. The Antimicrobial Stewardship Program at the Nebraska Medical Center has developed guidelines to facilitate the evaluation and treatment of UTIs.

Ordering of Urine Culture: Urine cultures should only be obtained when a significant suspicion for a UTI exists based on patient symptoms. Urine culture data should always be interpreted taking into account the results of the urinalysis and patient symptoms. In the urinalysis the presence of leukocyte esterase suggests WBC will be present while nitrites suggest that gram-negative organisms are present. Neither of these findings is diagnostic of a UTI.

Indication for urine culture:

- When signs or symptoms suggest a urinary tract infection is present (see below)
- In patients who cannot provide history (intubated, demented) and have sepsis without another source to explain it

Urine culture **NOT** recommended:

- Change in urine color, odor, or turbidity – these are typically due to patient hydration and **not** indicators of infection
- Patient lacks symptoms of UTI
- Automatically in workup of fever or sepsis – patients who can provide a history should not have a urine culture obtained as part of fever evaluation unless symptoms suggest a UTI is present
- Pre-operatively except in urologic surgery where mucosal bleeding is anticipated
- When a urinary catheter is placed or changed
- At admission
- After treatment of UTI to document cure

Interpretation of Urine Culture: Bacteria are frequently noted on urinalysis and cultured from urine specimens. The presence of bacteria in the urine may indicate one of 3 conditions: 1) specimen contamination; 2) urinary tract infection (UTI); or 3) asymptomatic bacteriuria (ASBU). When evaluating the clinical significance of a urine culture these 3 conditions must each be considered and classification should be based upon history and exam findings coupled with urine findings. Specimen contamination should always be considered as this is common, particularly in female patients. High numbers of

squamous cells on the urinalysis (>20) suggests contamination and results of the culture should generally be ignored.

In patients with a positive urine culture, where no contamination exists, clinicians must determine if the patient is exhibiting symptoms of a UTI. Symptoms typical of a UTI are urinary frequency or urgency, dysuria, new onset hematuria, suprapubic pain, costovertebral tenderness or fever. Patients with a urinary catheter in place may have more vague symptoms such as new onset or worsening fever, chills, pelvic discomfort, acute hematuria and altered mental status with no other identifiable etiology.

It is important to recognize that pyuria is ***not*** an indication for treatment. Pyuria is the presence of an increased number of polymorphonuclear leukocytes in the urine (generally >10 WBC/hpf) and is evidence for genitourinary tract inflammation. Pyuria can be seen in patients with catheter use, sexually transmitted diseases, renal tuberculosis, interstitial nephritis, or ASBU. The absence of pyuria is a strong indicator that a UTI is **not** present and is useful in ruling out a UTI.

Asymptomatic Bacteriuria

Patients with positive urine cultures who lack symptoms of a UTI have the diagnosis of **asymptomatic bacteriuria**. ASBU is more common in some patient populations and the prevalence increases with advancing age (Table 1). It is also associated with sexual activity in young women. Patients with impaired urinary voiding or indwelling urinary devices have a much higher prevalence of ASBU.

Table 1: Prevalence of asymptomatic bacteriuria in selected populations

Population	Prevalence, %
Healthy, premenopausal women	1.0-5.0
Pregnant women	1.9-9.5
Postmenopausal women aged 50-70	2.8-8.6
Diabetic patients	
Women	9.0-27
Men	0.7-11
Elderly person in the community (≥70 yrs.)	
Women	10.8-16
Men	3.6-19
Elderly person in a long-term care facility	
Women	25-50
Men	15-40
Patients with spinal cord injuries	
Intermittent catheter use	23-89
Sphincterotomy and condom catheter in place	57
Patients undergoing hemodialysis	28
Patients with indwelling catheter use	
Short-term	9-23
Long-term	100

Screening for and treating ASBU patients should only occur if the bacteriuria has an associated adverse outcome (such as development of a symptomatic urinary tract infection, bacteremia, progression to chronic kidney disease, etc.) that can be prevented by antimicrobial therapy. There are only 2 clinical situations where these criteria are clearly met. Pregnant women should be screened and treated for ASBU, as they have a significantly increased risk of developing pyelonephritis as well as experiencing a premature delivery and delivering a low birth weight infant. Prior to transurethral resection of the prostate (TURP) or any other urologic procedure with a risk of mucosal bleeding, patients should be screened for bacteriuria, as it has been associated with a major increase in the risk for post-procedure bacteremia and sepsis. Treatment of ASBU in both these situations has been demonstrated to prevent these complications.

Unfortunately many patients with ASBU receive treatment which they do not benefit from and in fact are likely harmed by. The unnecessary treatment of ASBU can lead to antibiotic resistance, adverse drug effects, *C. difficile* infection, and contribute unnecessarily to the costs of medical care. Gandhi and colleagues described antibiotic use for 3 months on a single medicine ward with 54% (224/414) of patients treated with antimicrobials and UTI the most common diagnosis (N=49). Of those who were treated for a UTI, 32.6% had no symptoms suggestive of a UTI. In another study Cope, et al. analyzed 280 catheterized patients at a VA with 58.6% considered to have ASBU. Thirty-two percent of ASBU patients received treatment (inappropriately) with 3 patients developing a *C. difficile* infection. Linares, et al. found 26% of 117 patients with ASBU at his institution were treated inappropriately for an average of 6.6 days and the treatment resulted in 2 cases of *C. difficile* infection and one case of QT prolongation. They then introduced an electronic reminder which did not decrease the incidence of inappropriate treatment (still 26%) but decreased duration of therapy to 2.2 days and with no antibiotic adverse events noted.

Patients at TNMC are not excluded from this inappropriate treatment. An analysis of 68 patients with positive urine cultures on 2 medical wards at TNMC over 3 months in 2011 revealed that 22 (32.4%) were asymptomatic using a very liberal definition of symptoms. Antimicrobials were inappropriately prescribed to 36.4% (8/22) of those with ASBU. This resulted in two patients developing clinically significant diarrhea with one of them being diagnosed with a *C. difficile* infection.

The take home message is that treatment of ASBU is common and results in significant patient harm. Clinicians should be aware of this when making decisions about the treatment of possible UTI.

<u>Who to screen and treat for asymptomatic bacteriuria:</u>

- Pregnant women (at least once in early pregnancy)
- Patients prior to a urologic procedure for which mucosal bleeding is anticipated (i.e. TURP, etc.)
- Kidney transplant patients are a group where the data is unclear and no recommendation can be made

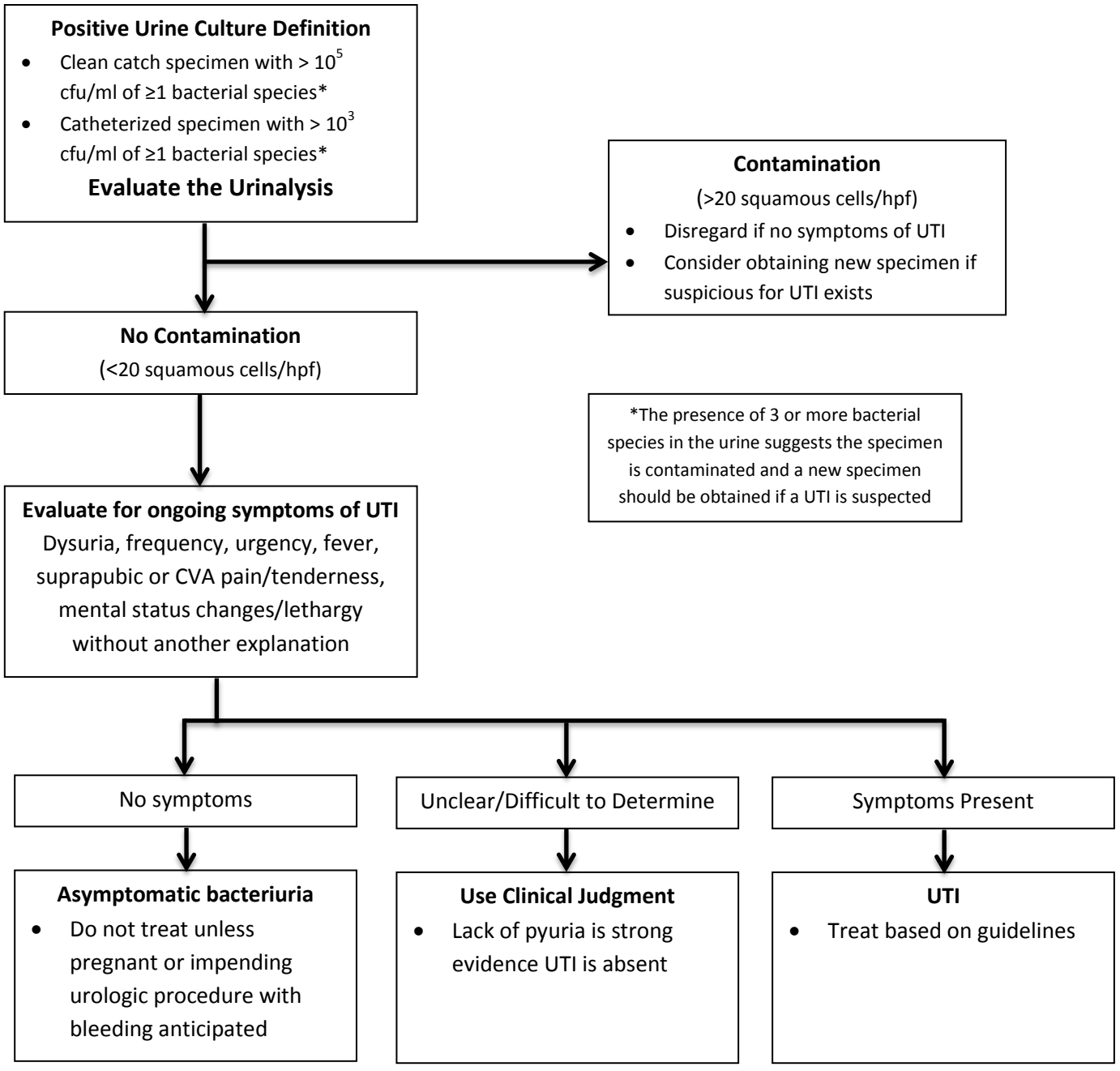
<u>Who not to screen or treat for asymptomatic bacteriuria:</u>

- Premenopausal, non-pregnant women
- Diabetic women

- Older persons living in the community
- Elderly institutionalized residents of long-term care facilities
- Spinal cord-injured patients
- Patients with an indwelling urethral catheter (do not treat asymptomatic funguria either)

Positive Urine Culture Algorithm

This algorithm is designed for common clinical situation where the treating clinician is required to interpret urine culture results 24-48 hours after they were obtained by another provider and the clinical situation that prompted the testing is not clear.



Treatment of Urinary Tract Infections in Adults

Complicated vs. Uncomplicated UTIs

If it is determined that a patient has a urinary tract infection based on symptoms, UA, and urine culture (see algorithm below), a decision must be made on how to treat the infection. Multiple factors play a role deciding on the most appropriate therapy choice and duration including: type of UTI (complicated or uncomplicated), if concern for pyelonephritis exists, patient allergies, location of patient (hospital, community, or long-term care facility), recent history of UTI or antibiotic exposure, previous urinary pathogens isolated, and cost of agent to be prescribed.

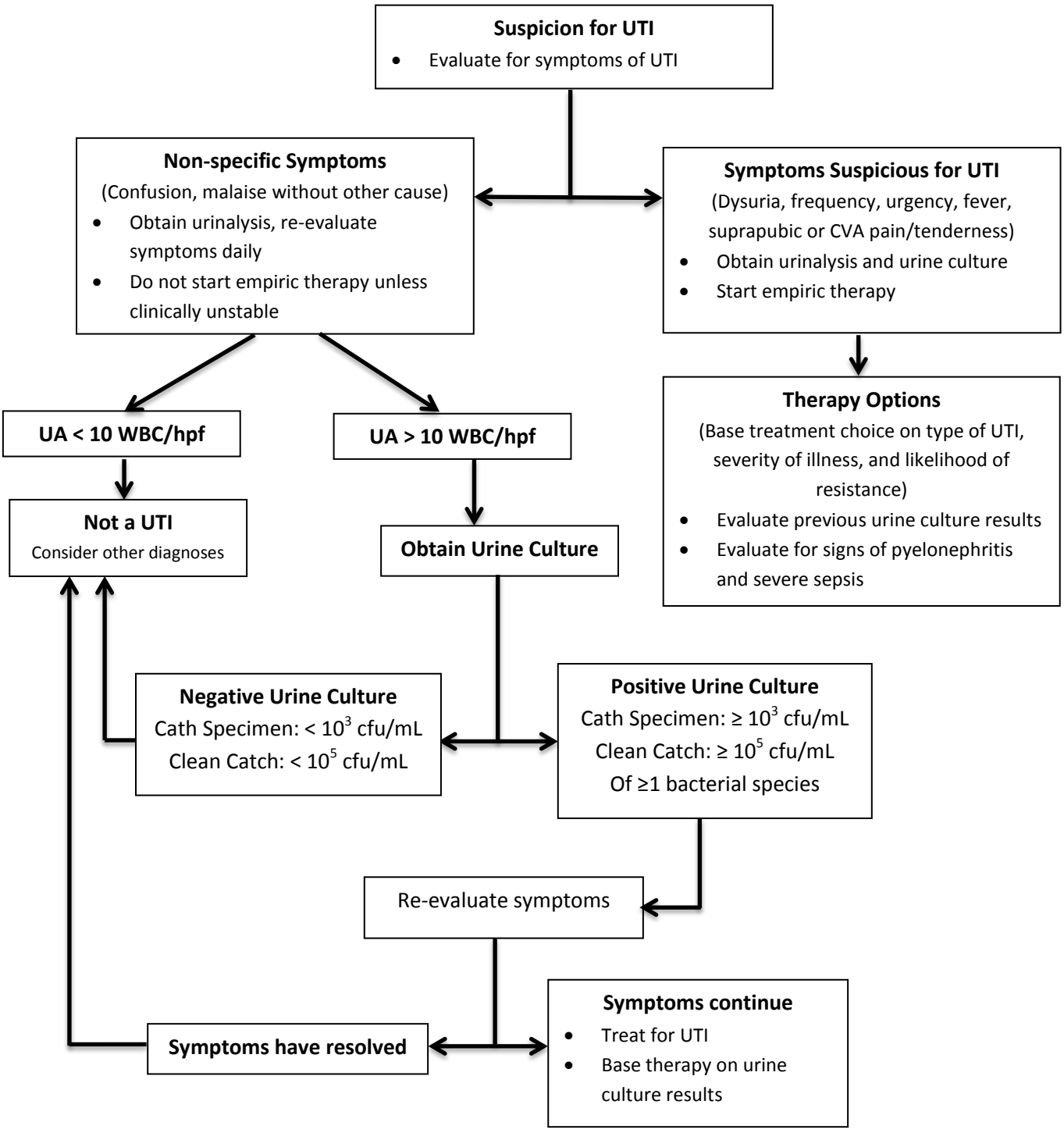
Patients with UTI can generally be seperated into 2 clinical groups: *complicated* and *uncomplicated*. A complicated UTI is a UTI in the setting of an underlying condition or factor which increases the risk of treatment failure. Some of these factors include:

- Male sex
- Diabetes
- Pregnancy
- Symptoms ≥ 7 days prior to seeking care
- Hospital acquired infection
- Renal failure
- Urinary tract obstruction
- Presence of an indwelling urethral catheter, stent, nephrostomy tube or urinary diversion
- Recent urinary tract instrumentation
- Functional or anatomic abnormality of the urinary tract
- History of urinary tract infection in childhood
- Renal transplantation
- Immunosuppression

Put another way episodes of acute cystitis occuring in healthy, premenopausal, nonpregnant women with no history suggestive of an urinary tract abnormalities are considered uncomplicated urinary tract infections and all other UTIs are classified as complicated.

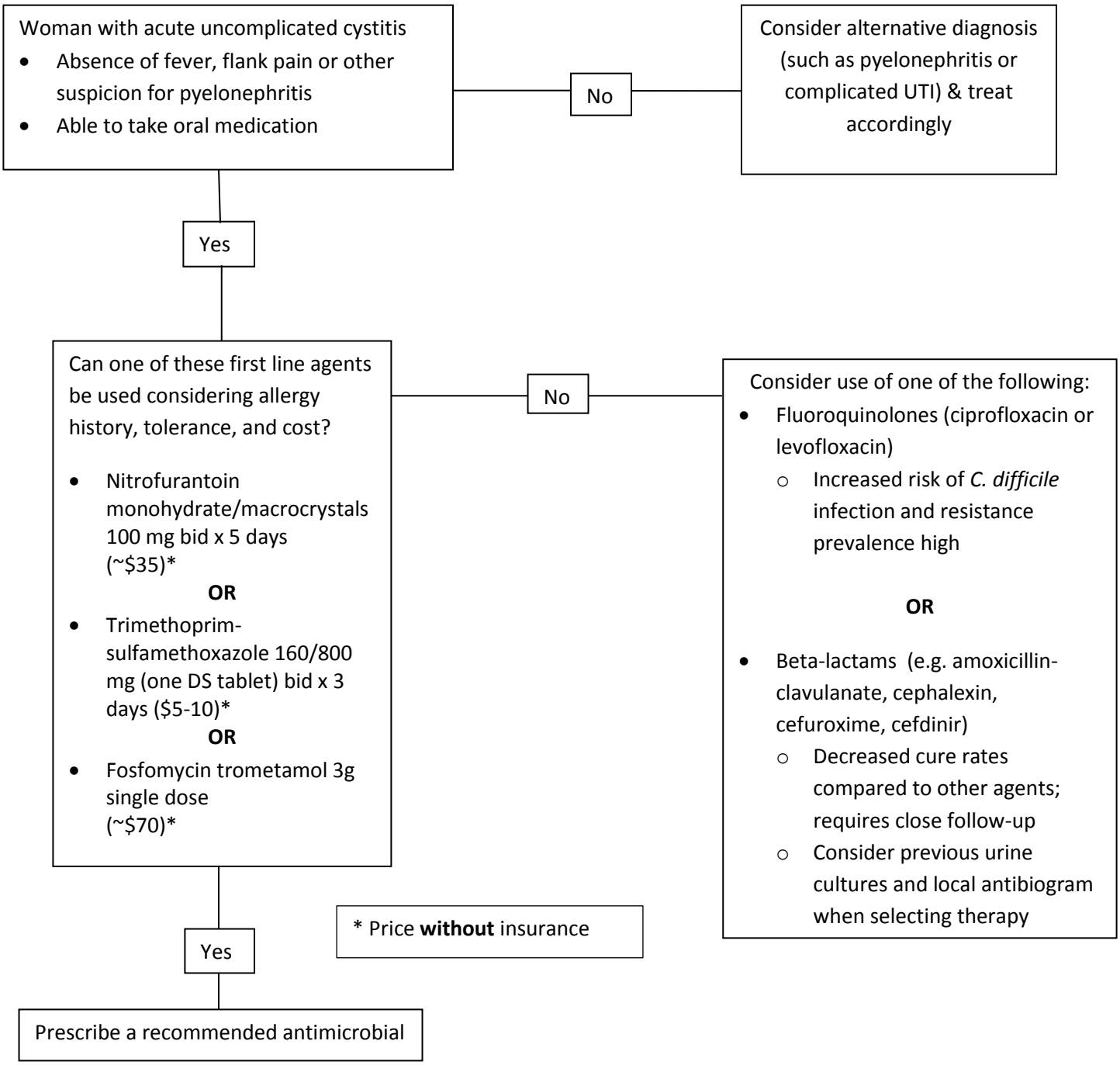
In patients with uncomplicated UTIs, *E. coli* is responsible for 75-95% of infections and empiric therapy should be directed at this pathogen. *E. coli* is still the most common pathogen in complicated UTIs, but other pathogens such as *Klebsiella*, *Proteus*, and *Enterobacter* are also noted. Inlcuded below are treatment guidelines for acute uncomplicated cystitis, complicated UTI, and pyelonephritis based upon local susceptibility and the Infectious Diseases Society of America guidelines.

UTI Treatment Algorithm



Treatment of Uncomplicated Cystitis in Women

Uncomplicated cystitis is defined by the presence of typical lower urinary tract symptoms (dysuria, frequency, urgency, hematuria) and lack of upper tract sypmtoms (see below) in an otherwise healthy pre-menopausal female.



Treatment of Complicated UTI

Complicated UTIs are defined above but generally are UTIs which occur in women who have abnormalities of the urinary tract or immune function which predispose them to treatment failure or UTIs which occur in men. Much less data is available to guide treatment recommendations in this patient group. The pathogens causing complicated UTIs are more diverse, more drug resistant, and specific guidelines for this syndrome are not available. The guidance below is primarily directed at outpatients and inpatients with complicated UTIs should have therapy based on previous culture results, severity of illness, and the local antibiogram.

Treatment duration has traditionally been 10-14 days, but recent data from the VA suggested 7 days of therapy for men with complicated UTIs was adequate. Based on these data treatment durations **of 7-10 days** are generally recommended, although shorter durations of fluoroquinolone therapy (5-7 days) have achieved excellent cure rates.

Complicated Cystitis:

1. Ciprofloxacin 500mg PO bid or levofloxacin 250mg PO qday
2. Trimethoprim-sulfamethoxazole 160/800 mg (one DS tablet) bid

Alternatives with less data or less activity:

1. Oral beta-lactams (oral 2nd and 3rd generation cephalosporins are more active based upon our antibiogram than agents such as cephalexin or amoxicillin/clavulanate)
2. Nitrofurantoin 100 mg PO BID (not recommended in patients with concern for pyelonephritis or those with poor renal function)

Treatment of Pyelonephritis

The presence of pyelonephritis is suggested by the presence of upper urinary tract symptoms such as fever, CVA tenderness, nausea, vomiting, and signs of severe sepsis. Patients with pyelonephritis should be evaluated for hospitalization and a decision made on the site of care based on severity of illness and host factors (ability to take oral agents, allergies, history of antimicrobial resistance, home support, etc.).

An important factor to consider when choosing therapy for pyelonephritis is the likelihood of bacterial resistance to common therapies. Numerous studies have been published evaluating risk factors for resistance in UTI pathogens and common risk factors associated with the isolation of multi-drug resistant (MDR) pathogens have generally included:

- Residence in a long-term care facility
- Recent receipt of broad spectrum antibiotics (including fluoroquinolones)
- History of recurrent UTIs
- History of having an MDR urinary pathogen
- Nosocomial UTI

These risk factors particularly identify patients at risk for resistance to fluoroquinolones and/or 3rd-generation cephalosporins (typically via production of an extended-spectrum beta-lactamase (ESBL)). It should be noted that baseline *E. coli* resistance to quinolones at TNMC is roughly 20% while resistance to 3rd-generation cephalosporins such as ceftriaxone is much less (around 5%).

Non-hospitalized/early pyelonephritis:

1. Oral ciprofloxacin 500 mg bid OR Levofloxacin 750mg daily
2. Oral trimethoprim-sulfamethoxazole (TMP-SMX) 160/800 mg [1 double-strength tab] twice daily

Due to high resistance rates in *E. coli* **all** patients should receive an initial one-time intravenous dose of ceftriaxone 1 gram or a consolidated 24 hour dose of an aminoglycoside (i.e. gentamicin 5 mg/kg)

Patients requiring hospitalization: Fluoroquinolones and TMP/SMX are not recommended for patients admitted with pyelonephritis due to high rates of resistance (~20%). When susceptibilities results return patients may be de-escalated to a FQ or TMP/SMX if they are susceptible.

No risk factors for multi-drug resistant organisms:

1. Ceftriaxone 1g IV q24h (2g if > 80kg)
2. **Severe beta-lactam allergy**: Aztreonam 2g IV q8h

Risk factors for multi-drug resistant organisms:

1. Piperacillin/tazobactam 4.5g IV q8h, infused over 4 hours **OR**
2. Ertapenem 1g IV q24h **OR**
3. Cefepime 1g q6h
4. **Severe beta-lactam allergy**: Aztreonam 2g IV q8h **PLUS** vancomycin per pharmacy consult

Patients with severe sepsis or septic shock consider the addition of:

1. Gentamicin 7 mg/kg IV q24h (extended-interval dosing)
2. Vancomycin per pharmacy consult

The addition of other antimicrobials (gentamicin, vancomycin) should be based upon severity of illness and likelihood of resistance.

Treatment Duration: Traditionally pyelonephritis has been treated for 10-14 days but studies have demonstrated that patients treated with fluoroquinolones for 5-7 days had similar cure rates to those treated for 14 days. When patients are started on beta-lactams and transitioned to fluoroquinolones a treatment course of 5-7 days of the FQ is likely adequate.

Table 1: Treatment Duration for Pyelonephritis and Complicated UTI

Agent	Duration of Therapy
Fluoroquinolones (ciprofloxacin, levofloxacin)	5-7 days
Beta-lactams	10-14 days
TMP/SMX	14 days

Catheter-Associated Urinary Tract Infections (CA-UTIs)

Diagnosis: In patients with indwelling urethral or suprapubic catheters or those who receive intermittent catheterization, UTIs typically presents without the usual lower urinary tract symptoms of dysuria, frequency, or urgency. Despite this, CA-UTI is defined by the presence of both symptoms and a positive urine culture:

- Symptoms and/or signs compatible with UTI may include: new onset or worsening of fever, rigors, altered mental status, malaise, or lethargy with no other identified cause; flank pain; costovertebral angle tenderness; new onset hematuria; or pelvic/suprapubic discomfort
    - Symptoms in patients with spinal cord injury may include increased spasticity, autonomic dysreflexia, or a sense of unease as well
- $\geq 10^3$ colony-forming units (cfu)/mL of ≥ 1 bacterial species in a single catheter urine specimen or in a midstream voided urine specimen from a patient whose urethral, suprapubic, or condom catheter has been removed within the previous 48 hours is considered a positive urine culture

Pyuria and bacteriuria are very common in the presence of a urinary catheter are not an indication for treatment in patients who lack symptoms of a UTI.

Evaluation and Treatment (see algorithm below):

- Always obtain a urine culture prior to initiation of antimicrobial therapy.
    - If the indwelling catheter has been in place for > 2 weeks at the onset of CA-UTI and is still indicated, replace the catheter and obtain urine culture from new catheter.
    - If urinary catheter no longer indicated, remove catheter and obtain culture from a voided midstream urine specimen.
- Patients who have a CA-UTI and have had their catheter longer than 14 days should have the catheter exchanged
- Choose therapy based on severity of illness and risk factors for resistant pathogens
- Treat with antimicrobials for 7-14 days depending on severity and clinical response
    - Prompt resolution of symptoms = 7 days
        - Levofloxacin x 5 days may be considered in patients who are not severely ill
    - Delayed response or severely ill = 10-14 days

Table 2: Treatment Options for CA-UTI

	First Line Therapy	Alternative Therapy
Mild/moderate illness – treat as per complicated cystitis guidance	Levofloxacin 250mg PO qday **OR** TMP/SMX 1 DS Tab BID	Oral 2nd and 3rd-gen cephalosporins Ceftriaxone 1g IV qday (if previous pathogen resistant to FQ or hospitalized >5 days) Aztreonam (beta-lactam allergy)
Severely ill – treat as per MDR-risk pyelonephritis guidance	Piperacillin/tazobactam 4.5g IV q8h over 4 hours **OR** Ertapenem 1g IV qday **OR** Cefepime 1g q6h	Aztreonam 2g IV q8h + vancomycin pharmacy to dose (beta-lactam allergy)

TNMC Urinary Antibiogram

Urine culture data from 6/2012-6/2013 was utilized to develop the following charts demonstrating The Nebraska Medical Center susceptibility rates of uropathogens. This data should serve as a guide for initial empiric antimicrobial therapy for pyelonephritis and complicated UTIs and also as guidance to evaluate the activity of specific agents when early identification data is available (i.e. lactose-fermenting Gram-negative rods or Enterococci). As per above, once susceptibility results are available, antimicrobials should be tailored appropriately.

Gram-Negative Organisms Isolated from the Urine

% Susceptible	*E. coli* (N=2014)	*Klebsiella pneumoniae* (N=405)	*Proteus mirabilis* (N=184)	*Pseudomonas aeruginosa* (N= 134)	Enteric (Lactose-Fermenting) Gram-neg rods	Non-lactose Fermenting Gram-neg rods (oxidase neg)
Amikacin	99.7	100	98.9	95.5	99.8	98.6
Ampicillin	58.5	4.4	84.8	XX	47.5	76.9
Ampicillin/sulbactam	61.5	84.9	92.9	XX	64.4	86.5
Cefepime	97.3	99.3	100	84.7	97.4	100
Cefuroxime (parenteral)	91.7	93.8	100	XX	89.3	91.3
Ceftriaxone	95.9	98.1	100	XX	94.3	98.4
Cephalothin	29.5	87.7	85.6	XX	37.3	71.2
Ciprofloxacin	79.6	97.5	69	68.9	82.6	67.8
Levofloxacin	79.9	98.5	73.9	66.4	83.4	72.6
Ertapenem	100	100	100	XX	99.8	100
Gentamicin	92.9	99	91.3	75.4	94.2	90.4
Imipenem	99.8	99.8	23.4	76.7	99.3	22.6
Meropenem	99.9	100	100	76.1	99.8	99.5
Nitrofurantoin	97.7	43.3	0	XX	86.2	0.5
Piperacillin/tazobactam	97.8	98	99.5	86.8	96.7	99.5
Tobramycin	92.9	99.7	91.3	96	94.3	89.9
TMP/SMX (Bactrim)	77.8	90.4	78.3	XX	80.2	77.4

XX=not generally susceptible

Gram-Positive Organisms Isolated from the Urine

% Susceptible	*Enterococcus faecalis* (N=292)	*Enterococcus faecium* (N=60)	*Enterococcus (species pending)*	*Staphylococcus aureus* (N=82)
Ampicillin	100	8.1	83.9	XX
Oxacillin	XX	XX	XX	54.9
TMP/SMX (Bactrim)	XX	XX	XX	100
Daptomycin	100	61.4	97.7	100
Levofloxacin	68.7	6.6	57.6	47.6
Linezolid	99.3	98.4	98.6	100
Nitrofurantoin	99	14.8	83.9	100
Vancomycin	98.3	21.3	84.5	100

XX=not generally susceptible

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Reviewed and Approved by Antimicrobial Stewardship Subcommittee of Pharmacy and Therapeutics Committee of the Nebraska Medical Center, July 2014

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