

## UTI in pregnancy: 6 questions to guide therapy

Crucial are treatment, test of cure, frequent screening until delivery, and antibiotic suppression, when indicated.

### THE CASE: SIGNS AND SYMPTOMS

A 29-year-old nullipara at 18 weeks' gestation complains of fevers and back pain. She had a diagnosis of urinary tract infection with sulfonamide-resistant *Escherichia coli* at 9 weeks of gestation, which was treated with nitrofurantoin, 100 mg by mouth twice a day for 7 days. A test of cure by urine culture was negative.

Now her temperature is 101°F and she has right costovertebral angle tenderness.

How should you proceed?

**A**natomy is destiny, in the case of susceptibility to urinary tract infection (UTI).

The female urethra is only 3 cm to 4 cm long, and its proximity to the vagina, anus, and rectum facilitates colonization of normal gastrointestinal flora in the bladder.<sup>1</sup>

Sexual activity also facilitates migration of normal gastrointestinal flora to the female urethra.<sup>2</sup>

Anatomical features of pregnancy exacerbate the female predisposition to urinary tract infection. In pregnancy, hormonal and mechanical changes that occur in the urinary tract lead to urinary stasis and ureterovesical reflux—setting the stage for urinary tract infection (FIGURE 1).

### Who should be screened?

All pregnant women should be screened for UTI early in pregnancy, according to the American College of Obstetricians and Gynecologists.<sup>3</sup>

I recommend a urine culture screening for all pregnant women at their first prenatal visit.

### Screen often if she has risk factors

I recommend frequent screening (at least every trimester) by urine culture, in pregnant women with any of these risk factors:

- diabetes mellitus, including gestational diabetes<sup>4</sup>;
- urologic abnormalities—specifically, neurogenic bladder;
- prepregnancy (for example, 2 to 3 infections per year) and antepartum history of UTI prior to initiation of prenatal care<sup>5</sup>;
- sickle cell hemoglobinopathy.<sup>5</sup>

### Which test is best?

The gold standard for detecting bacteria in urine is by culture.

### Which threshold to use?

The standard definition of a positive urine culture from a clean-catch, midstream, voided specimen is  $\geq 100,000$  colony forming units (CFU) per mL of a single

**Screen all pregnant women early; screen those with risk factors often.**

organism. However, in symptomatic patients, the test's sensitivity is increased by lowering the cut-off to 100 CFU/mL of a single organism.<sup>6</sup> In women with urinary symptoms, only 50% of patients had 100,000 CFU/mL by urine culture collected from clean-catch, midstream, voided specimens, though all of them had positive cultures from suprapubic taps.

The clean-catch, midstream, voided specimen is the specimen of choice for practical purposes, since it is noninvasive and easily obtained in the office setting.

For the record: The presence of any organism represents UTI in specimens obtained via suprapubic aspiration of the bladder; 100 CFU/mL of a single organism is positive for specimens obtained by urethral catheterization.

**I recommend** that, when obtaining urine cultures via clean-catch, midstream, voided specimens:

- for *asymptomatic* patients, use a threshold of  $\geq 100,000$  CFU/mL of a single organism.
- in *symptomatic* patients, use  $\geq 100$  CFU/mL of a single organism.

#### What about rapid tests?

Urinary sediment analysis and urine dipstick testing offer speed and low cost, but with lower accuracy than urine cultures, which require 24 to 48 hours for results and cost more.

**Urinary sediment analysis** can diagnose pyuria, defined as a clean-catch, midstream, voided specimen, which is spun and which has  $>10$  leukocytes per high-power field.

Pyuria can occur without infection due to:

- previous treatment with antibiotics,
- contamination of urine sample by sterilizing solution,
- contamination of urine sample with vaginal leukocytes,
- chronic interstitial nephritis (such as analgesic abuse),
- uroepithelial tumor, and
- nephrolithiasis.

Pyuria on urinalysis has low sensitivity (25%) but high specificity (99%).

Bacteria visualized on microscopic examination is more sensitive (75%) but less specific (60%).<sup>7</sup>

**Urinary dipstick testing**—fast, convenient, and low in cost—is considered positive if it identifies either leukocyte esterase or nitrite. Positive leukocyte esterase signifies pyuria. Positive nitrite indicates the presence of enteric organisms that convert urinary nitrate to nitrite.

With either finding, dipstick sensitivity is only 50%, although specificity is 97%.<sup>7</sup>

**I recommend:**

- If a *symptomatic* patient's rapid test is positive, obtain a urine culture, empirically treat for UTI, and then use urine culture results to decide whether to continue treatment.
- If an *asymptomatic* patient's rapid test is positive, obtain a urine culture and treat only if the culture is positive.

## What urinary tract disorders occur in pregnancy?

First, determine if the patient has urinary tract symptoms and, if so, whether the symptoms are typical of upper or lower urinary tract infections.

#### Lower urinary tract symptoms:

- dysuria
- frequency
- urgency
- suprapubic pain
- hematuria in the absence of fever and systemic symptoms

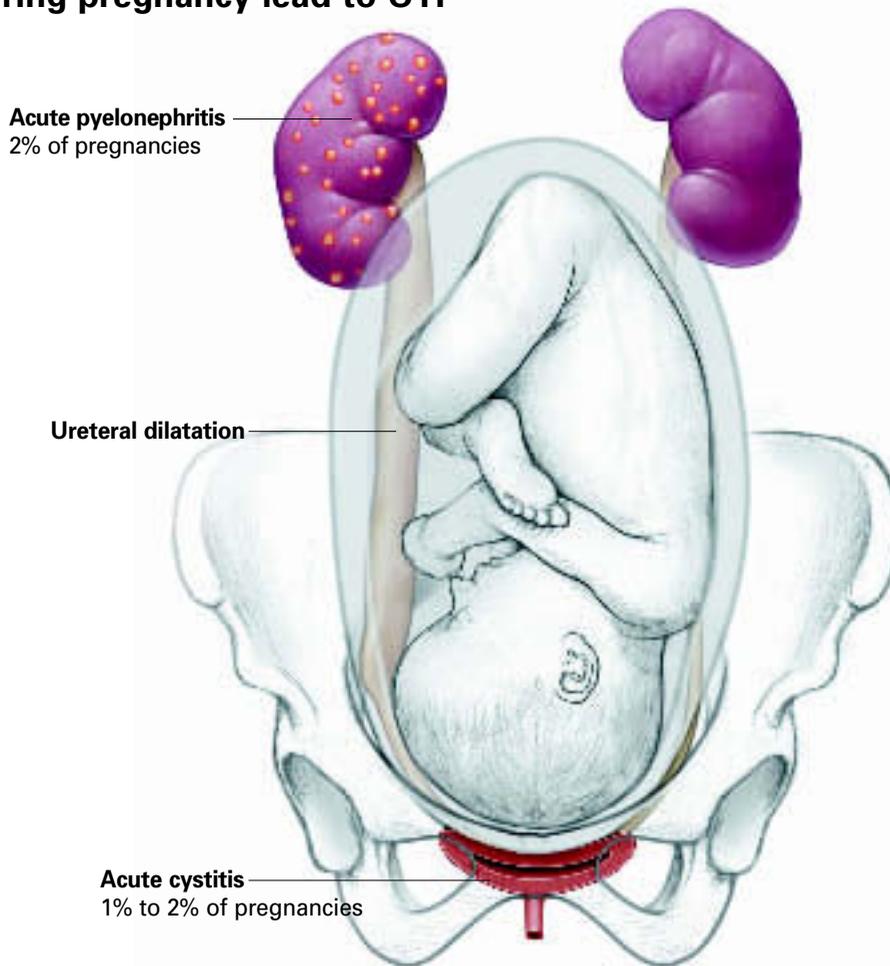
Frequency, of course, is difficult to ascertain in pregnancy, since most women experience this complication secondary to increased urinary output due to higher fluid intake, increased plasma volume expansion, and increases in renal blood flow and glomerular filtration rate.

#### Upper urinary tract symptoms:

- fever
- chills
- flank pain
- nausea and vomiting

**A threshold of 100 CFL/mL raises the sensitivity of a urine culture in symptomatic patients.**

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**FIGURE 1****How mechanical and hormonal changes during pregnancy lead to UTI****Mechanical changes**

lead to urinary stasis and ureterovesical reflux. Beginning in the sixth week of gestation and peaking at 22 to 24 weeks, approximately 90% of pregnant women develop **ureteral dilatation**, which remains until delivery. **Increased bladder volume** and **decreased bladder and ureteral tone** contribute to increased urinary stasis and ureterovesical reflux.<sup>30</sup>

**Hormonal changes**

lead to increased bacterial growth in the urine and possibly lowered resistance to bacteria. Up to 70% of pregnant women develop **glycosuria**, which encourages bacterial growth in the urine. **Increases in urinary progestins and estrogens** may lead to decreased ability of the lower urinary tract to resist invading bacteria.<sup>30</sup>

IMAGE: SCOTT BODELL

- The patient may or may not have the symptoms of lower urinary tract infection, as well.

**Positive culture and no symptoms**

This profile is typical of **asymptomatic bacteriuria**, a lower urinary tract infection that occurs in 2% to 7% of pregnancies.<sup>1</sup>

**Positive culture with symptoms**

This profile probably reflects either:

- **Acute cystitis**, a lower urinary tract infection affecting 1% to 2% of pregnancies,<sup>8</sup> or
- **Acute pyelonephritis**, an upper urinary tract infection affecting 2% of pregnancies.<sup>9</sup>

**What are the consequences of UTI in pregnancy?****Maternal complications**

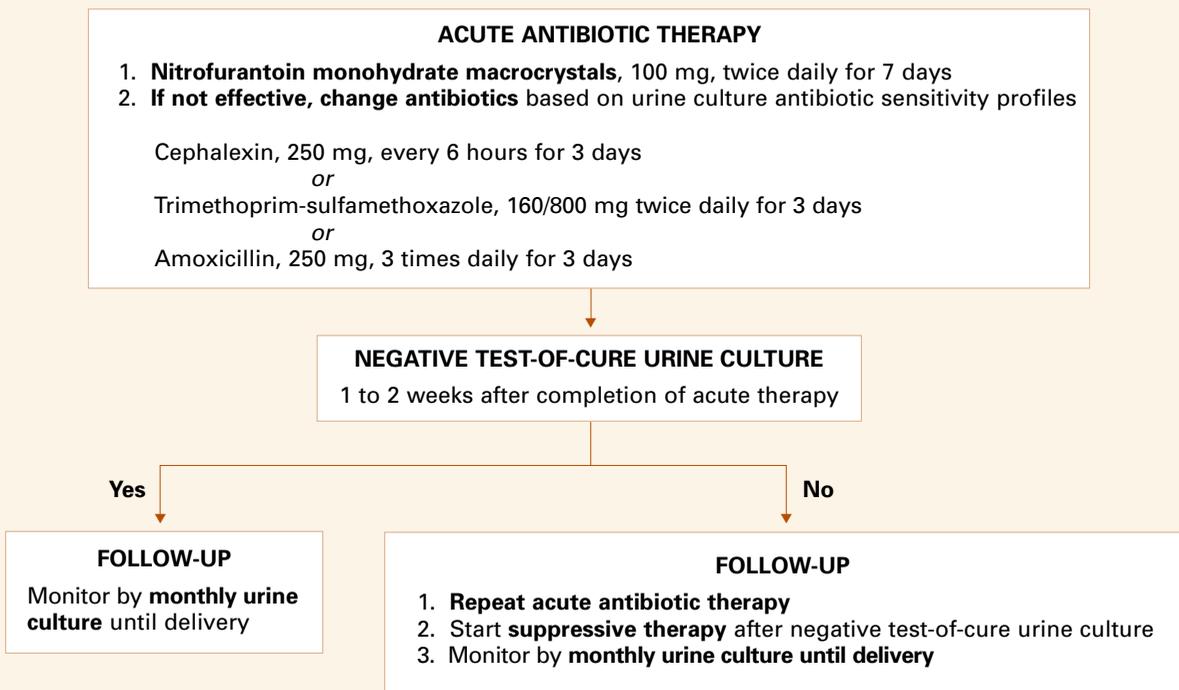
Asymptomatic bacteriuria does not plague the patient with bothersome effects, but if left untreated, asymptomatic bacteriuria will progress to symptomatic UTI: 25% will develop acute pyelonephritis, compared to 3% to 4% of treated patients<sup>10</sup>; 20% of women with severe pyelonephritis develop serious complications,<sup>11</sup> including:

- sepsis and septic shock,
- hemolysis and thrombocytopenia,<sup>12</sup>
- acute respiratory distress syndrome,<sup>13</sup>
- renal insufficiency.<sup>14</sup>

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**FIGURE 2**

**Management of asymptomatic bacteriuria or acute cystitis**



**When a rapid test is positive but the patient has no symptoms, treat only if urine culture is positive.**

**Adverse fetal outcomes**

Untreated asymptomatic bacteriuria is associated with preterm delivery and low birthweight.<sup>15-17</sup>

Acute pyelonephritis is linked to preterm birth.<sup>18,19</sup> Kaul et al,<sup>20</sup> in an experimental model of pyelonephritis in mice, confirmed that *E. coli* plays an important role in the pathogenesis of preterm delivery and low birthweight.

**What is the best treatment regimen?**

Data are insufficient to recommend any specific regimen.<sup>21,22</sup> The following strategies are based on evaluation of review articles.<sup>3,23</sup>

**Asymptomatic bacteriuria and acute cystitis**

**Nitrofurantoin monohydrate macrocrystals** is my first-line treatment. Nitrofurantoin has high concentrations in the urinary tract

but induces minimal resistance in gram-negative organisms.

**If nitrofurantoin is not effective**, I change antibiotics based on urine culture antibiotic sensitivity profiles (**FIGURE 2**).

Keep in mind the current resistance of *E. coli* to antibiotics: ampicillin, 28% to 39%; trimethoprim-sulfamethoxazole, 31%; and first-generation cephalosporins, 9% to 19%.<sup>24</sup>

**Single-dose treatment** for pregnant women with asymptomatic bacteriuria has been evaluated, given its lower cost and better compliance. However, evidence is insufficient to determine whether single-dose or longer-duration regimens are more effective.<sup>25</sup>

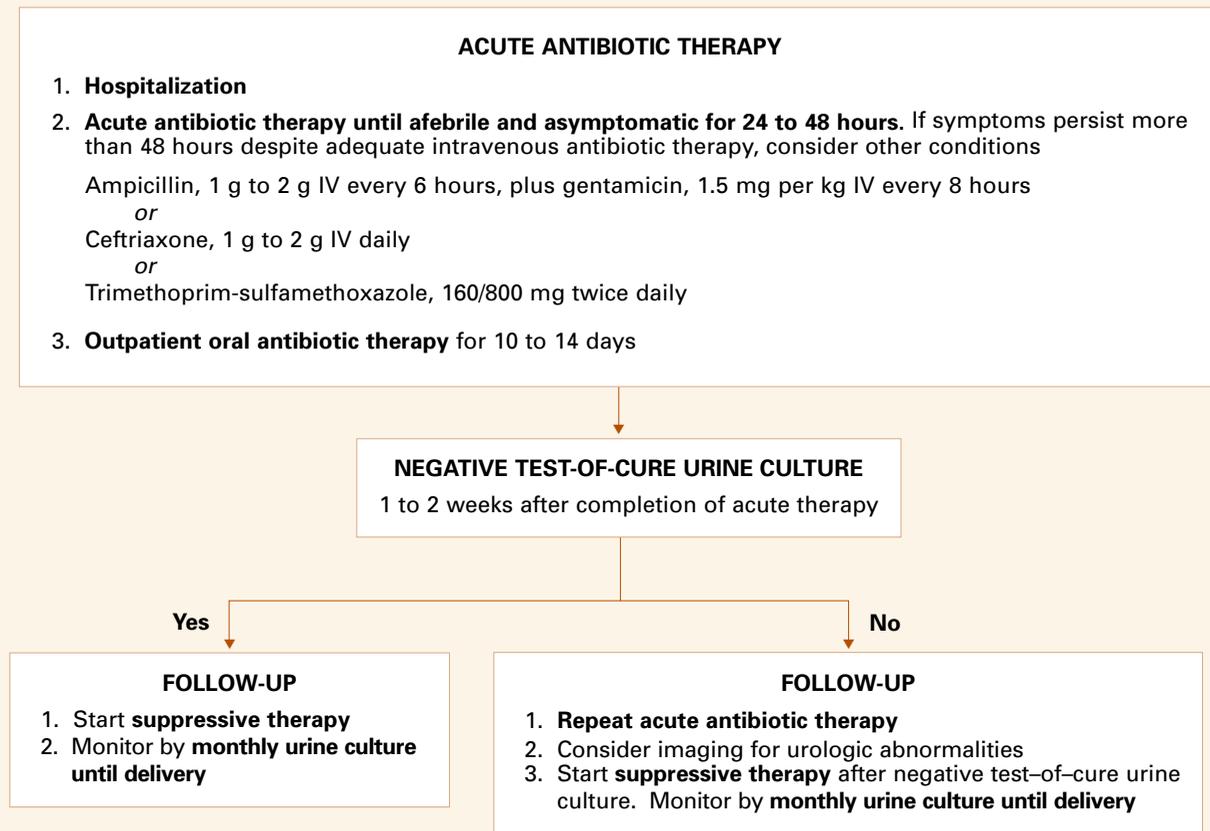
**I recommend longer-duration dosages** for now, until a large randomized controlled trial can derive conclusive data.

Remember that treatment success is not contingent upon duration of therapy—just be sure that the test-of-cure urine culture is negative 1 to 2 weeks after treatment is completed.

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**FIGURE 3**

### Management of acute pyelonephritis



#### Acute pyelonephritis

Management should include the following:

- hospitalization
- urine and blood cultures
- laboratory studies of complete blood cell count, electrolytes, creatinine, and liver function
- monitoring of vital signs and urine output
- intravenous (IV) crystalloid fluid to maintain urine output
- IV antibiotics (**FIGURE 3**)

If symptoms persist after 48 hours despite adequate IV antibiotic therapy, consider other causes such as resistant organisms, nephrolithiasis, perinephric abscesses, renal obstruction, or other infections.

Consider imaging by renal ultrasound

to assess the presence of nephrolithiasis, perinephric abscess, or obstruction.

**I recommend inpatient treatment** for pregnant women with acute pyelonephritis at this time, until further studies are available.

To evaluate outpatient treatment, Millar and colleagues randomized 120 women under 24 weeks' gestation either to inpatient IV cefazolin until 48 hours afebrile or to outpatient ceftriaxone intramuscularly. (Both treatment arms completed a course of oral cephalexin.) There were no differences in therapeutic response or birth outcomes, but 6 patients in the outpatient arm required hospitalization for IV therapy and 1 woman developed sepsis.<sup>26</sup>

The same researchers studied 92 patients of more than 24 weeks' gestation

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who received 2 doses of ceftriaxone intramuscularly, then were randomized to either continued inpatient therapy until 48 hours afebrile or discharge with reevaluation as an outpatient in 48 to 72 hours. Again, there were no differences in therapeutic response or birth outcomes; however, almost two-thirds of patients were excluded from the study as they did not meet criteria for outpatient management, due to sepsis, preterm labor, or concurrent medical conditions.<sup>27</sup>

### Adequate antibiotic coverage is crucial

To ensure adequate antibiotic coverage when treating UTI, it is important to understand which organisms cause these infections in pregnancy.

*E. coli* causes 75% to 90% of UTIs in nonpregnant women.<sup>28</sup> *Staphylococcus saprophyticus* causes 10% to 15% of UTIs in nonpregnant women, but less in pregnant women.

Group B *Streptococcus* (GBS)—another gram-positive organism—has important implications for pregnant women: Intrapartum prophylaxis is important, to prevent neonatal GBS disease.<sup>29</sup>

*Klebsiella*, *Enterobacter*, *Proteus*, and *Enterococcus* species<sup>28</sup> infrequently cause UTI in pregnancy.

## ■ What about prophylaxis and follow-up cultures?

### Expect recurrence

One third of pregnant women diagnosed with UTI will have recurrence.<sup>1</sup> Recurrence is either relapse (same strain, within 2 weeks of completing initial treatment for the original infection) or reinfection (different strain or same strain after more than 2 weeks).

### 2 UTIs or pyelonephritis warrant suppressive therapy

I recommend suppressive therapy if a pregnant woman is diagnosed with 2 lower urinary tract infections or acute

**TABLE**

### Suppressive therapy to prevent UTI recurrence

Suppressive therapy is recommended for any pregnant woman with:

- 2 lower urinary tract infections or
- acute pyelonephritis.

Do not initiate suppressive therapy until a negative test-of-cure urine culture confirms eradication of the acute infection.

ANTIBIOTIC	DOSE (ORAL)
Nitrofurantoin monohydrate macrocrystals or Cephalexin	50 mg at bedtime  250 mg at bedtime

pyelonephritis (TABLE).

**Nitrofurantoin** is the preferred agent, as it has high concentrations in the urinary tract but induces minimal resistance in gram-negative organisms.

**Start only after eradication** of the acute infection, as evidenced by a negative test-of-cure urine culture at least 1 to 2 weeks after treatment is discontinued.<sup>23</sup>

**Monthly urine cultures until delivery** I recommend monthly follow-up urine cultures until delivery.

Periodic follow-up screening is often recommended, but opinions differ on which test to use or how often to screen.

### THE CASE: DIAGNOSIS, TREATMENT, FOLLOW-UP, AND OUTCOME

The patient with upper urinary tract symptoms had a white blood cell count of 15, a urine dipstick positive for leukocyte esterase and nitrites, and a urine sediment analysis indicating pyuria.

She was diagnosed with acute pyelonephritis and started on ampicillin and gentamicin intravenously. Her urine culture drawn upon admission grew >100,000 CFU/mL of sulfonamide-resistant *E. coli*.

Within 48 hours, she showed clinical improvement and was discharged home with a 10-day course of nitrofurantoin. One week after completing treatment, her test-of-cure urine culture was negative and she was started on nitrofurantoin 50 mg every night at bedtime.

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**Make sure the urine culture is negative after either single-dose or other antibiotic treatment.**

For the rest of pregnancy, she underwent monthly screening urine cultures, which remained negative. She had an uncomplicated delivery at 38 weeks of gestation. ■

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**Change antibiotics based on urine culture sensitivity profiles.**

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