Urinary Tract Infections in Pregnancy

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Urinary tract infections (UTIs) represent the most common bacterial infection in pregnant and nonpregnant women [1,2]. Eight million women visit a physician annually for evaluation of UTIs [3] at a direct cost of $659 million [4] and aggregate cost of $1.6 billion [4,5]. Physiologic changes of pregnancy increase a woman’s susceptibility to UTI. Progesterone effects and mechanical compression by the gravid uterus impair emptying of the bladder and lead to increased bladder residual volume and vesicoureteral reflux. Relative stasis of urine in the ureters results in hydronephrosis. Furthermore, pregnancy-related changes in glomerular filtration rate increases the urinary glucose concentration and alkalinity, thereby facilitating bacterial growth [6]. In addition, alterations in maternal immunologic defense mechanisms occur in pregnancy [7]. The signs and symptoms of UTIs vary by the type of infection. UTI in pregnancy is classified by the site of bacterial proliferation as follows: asymptomatic bacteriuria (ASB; urine), cystitis (bladder), pyelonephritis (kidney).

Asymptomatic bacteriuria

ASB is defined as significant bacterial colonization of the lower urinary tract without symptoms. Traditional diagnostic criteria of significant bacteriuria include culture of $10^5$ colony forming units (CFUs)/mL of a single uropathogen on two consecutive clean catch urine specimens [6,7]. Recent evidence suggests that
lower colony counts ($\geq 10^2$–$10^3$ CFUs/mL) may demonstrate active infection and
eventually lead to pyelonephritis in pregnant women [8–10]. The incidence of
ASB during pregnancy is 2% to 14%—similar to that of nonpregnant women—
and translates into 80,000 to 400,000 cases in the United States each year [10,11].
Predisposing factors to ASB include low socioeconomic status, increasing age,
multiparity, sexual behavior, and a history of childhood UTIs (with or without
scarring). The prevalence of ASB also is increased markedly in certain pre-
existing medical conditions, such as diabetes mellitus, sickle cell disease, immu-
nocompromised states (eg, AIDS), urinary tract anatomic anomalies, and spinal
cord injuries. UTI before pregnancy is a predictor of the diagnosis of ASB at the
first prenatal visit [12].

Without treatment, ASB progresses to pyelonephritis in 20% to 40% of
pregnant women. In contrast, progression to pyelonephritis in nonpregnant
women is only 1% to 2%. Furthermore, the incidence of pyelonephritis in
pregnant women without ASB complicating early pregnancy is less than 1%.
With appropriate treatment in pregnancy, progression to pyelonephritis can be
decreased to 3% [13].

The causative organisms that are isolated in ASB, cystitis, and pyelonephritis
are similar in pregnant and nonpregnant women. Enterobacteriae, a group of
gram-negative rods, encompass most colonizing organisms, including Esche-
richia coli, the primary pathogen in 80% to 90% of initial UTIs and 70% to
80% of recurrent infections [6,12,14,15]. Other gram-negative pathogens in-
clude Klebsiella pneumoniae and Proteus mirabilis. Further pathogens include
Pseudomonas aeruginosa and gram-positive organisms, Streptococcus agalacti-
cae, and Staphylococcus saprophyticus. The most virulent strains of E coli
possess toxins and adhesins, pili, or fimbriae to allow adherence to urethrophe-
litum [12]. These protect the bacteria from urinary lavage and allow bacterial
multiplication and renal tissue invasion. Specific O-serotypes of E coli have been
epidemiologically related to the occurrence of acute pyelonephritis, recurrent
infection, parenchymal scarring, and renal failure [16]. Fimbriae P, found in
uropathogenic strains of E coli, aids in adherence to vaginal and renal epithelium
and causes upper UTI [17]. Recently, the class of DR adhesins also has been
associated with pyelonephritis in pregnancy, and a high rate of preterm delivery
in mice [18].

Screening for ASB in pregnancy is recommended by the U.S. Preventative
Services Task Force and the American College of Obstetricians and Gynecolo-
gists [19,20]. A urine culture should be obtained between 12 and 16 weeks of
pregnancy. Appropriate therapy for positive urine culture at this time leads to the
highest number of bacteria-free weeks in pregnancy. This recommendation is
based on a large epidemiologic study from Sweden [13]. Urine culture detects
approximately 80% of cases of ASB. The average cost of urine culture ranges
from $16 to $45. In a cost analysis, screening with urine culture is cost-effective
if the risk of ASB is greater than 2%, the risk of resultant pyelonephritis is greater
than 13%, or if the efficacy of treatment in preventing pyelonephritis is 38% [21].
In populations with a prevalence of ASB of at least 9%, urine culture was the
most cost-effective screening method [22]. Globally, disadvantages to urine culture lie in the delay to results (24–48 hours) and low yield with high cost in areas of low prevalence. Other screening modalities have been suggested as expedient, more cost-effective alternatives for detection of urinary tract infection but the usefulness is variable. Alternative modes of testing, such as urinary dipstick testing to screen for pyuria by the presence of nitrates and leukocyte esterase (ChemstripN test, Biodynamics, Indianapolis, Indiana), has a sensitivity that ranges from 50% to 92% and a negative predictive value of 99.2% [22]. Although rapid screening tests are less expensive and faster than urine culture, they are limited by their requirement of high bacterial concentrations (≥10^5 CFU/mL) for positive results [8]. In light of the current opinion to treat ASB at a much lower bacterial count in pregnancy, these tests would be inadequate as initial screening methods; urine culture remains the screening test of choice [6].

Treatment of asymptomatic bacteriuria in pregnancy

A variety of antibiotics has been used to treat ASB and seem to have similar efficacy [7] as seen in meta-analysis of various regimens in the Cochrane Database [23]. Treatment is empiric because causative bacteria are predictable. Increasing antimicrobial resistance among uropathogens poses a challenge to therapy. Although the susceptibility of these pathogens to antimicrobial therapy has changed, their prevalence has not. The pattern of resistance varies geographically. In the United States, resistance increases from east to west, with the highest prevalence of multi-drug-resistant phenotypes on the Pacific Coast [24]. This should be taken into account when determining appropriate therapy. Other factors to be considered in the selection of appropriate antimicrobial therapy include the spectrum of activity of the agent, potential side effects, duration of therapy, cost, and pharmacokinetics [25]. β-Lactam antibiotics, including ampicillin, are among the oldest antibiotics that are used to treat bacterial infection; however, the pharmacokinetic changes of pregnancy decrease plasma concentrations of β-lactams by up to 50% [7]. Although well-tolerated orally, increasing resistance levels of E. coli limits its use in the treatment of UTI. For example, E. coli resistance to ampicillin is greater than 60% in some centers [8]. Cephalosporins also are well-tolerated and safe in pregnancy; cephalixin is the most commonly used cephalosporin in pregnancy. Penicillins and cephalosporins are associated with allergic, and at times, anaphylactic reactions. Nitrofurantoin achieves therapeutic concentration only in urine. Therefore, it only is indicated for the treatment of uncomplicated UTIs [7]. With the low level of resistance to nitrofurantoin among uropathogens, it remains an ideal therapeutic agent and is safe for use in pregnancy. In an evaluation of national practice patterns from 1989 to 1998, nitrofurantoin was the most frequently used antimicrobial agent for UTIs among obstetrician-gynecologists [26]. The limitation of nitrofurantoin is its poor activity against Proteus spp. The main side effects are gastrointestinal, and have been mitigated by the current macrocrystalline formulations. Nitrofurantoin also may incite hemolytic anemia in patients who have glucose-
6-phosphate dehydrogenase deficiency. Trimethoprim-sulfamethoxazole, the primary agent used in the general population, is contraindicated in the first trimester of pregnancy because of its inhibitory effect on folate metabolism and resultant association with neural tube defects. Sulfonamides are not recommended in the third trimester because of the risk of kernicterus in the newborn and their effects on folate metabolism. Although fluoroquinolones attain high renal concentration and are used commonly in nonpregnant patients, the risk of arthropathy in the newborn contraindicates their use in pregnancy [7,10].

A longtime traditional preventative and therapeutic agent for UTI is cranberries, either in juice or tablet form. Cranberries contain proanthocyanidins which prevent the adherence of bacterial pathogens to uroepithelium, and thereby prevent UTIs. In a recent Cochrane Review, cranberries, in both forms, significantly reduced the incidence of UTIs in women over a 12-month period (relative risk 0.61; 95% CI: 0.40–0.91) when compared with placebo. Difficulty with compliance was noted in all evaluated trials [27]. No trials exist that describe the preventative effects of cranberry ingestion in pregnancy.

The current standard of practice is to treat pregnant patients who have ASB with at least 7 days of an oral antimicrobial agent [6,7,12,14]. If bacteriuria persists, a second 7- or 14-day course of the same or different antimicrobial agent is used. In nonpregnant women, short-course treatment (single-dose or 3 days) of uncomplicated lower UTI is as effective as a 7- to 14-day course. Committee guidelines of the Infectious Disease Society of America (IDSA), after a meta-analysis of the literature, support the effectiveness of 3-day oral antimicrobial treatment in nonpregnant women [28], which is the current standard of care [15]. Persistent bacteriuria and reinfection rates are similar with short-course treatment when compared with more conventional therapy; however, single-dose regimens seem to be associated with a higher rate of early recurrence by the original strain than the 7- to 14-day regimen [29]. Failure to eradicate uropathogens from the vaginal reservoir results in earlier recurrence. Three-day courses seem to be more effective than single-dose regimens in preventing early reinfection. Although firmly established in nonpregnant women, short-course therapy of ASB in pregnancy has not been evaluated adequately. Short-course regimens are preferable because of fewer side effects, decreased health care costs, and increased patient compliance [30]. Multiple studies suggest that short-course therapy is appropriate in pregnancy; a variety of 3-day and single-dose regimens has been proposed (Table 1). In general, no significant difference in recurrence rates has been seen between short-course and conventional therapies. Because of inadequate power in these studies, there is insufficient evidence to recommend this approach [31].

After ASB has been diagnosed in pregnancy—regardless of the chosen antimicrobial agent or the duration of therapy—repeat urine cultures should be obtained monthly throughout gestation because of the significant risk of recurrent bacteriuria [8,30]. Up to one third of pregnant women experience a recurrence [13,14,16].

Upon diagnosis of recurrence with the same uropathogen or reinfection with a new uropathogen, a second full course of antimicrobial therapy should be given.
Table 1
Suggested three-day regimens for the treatment of asymptomatic bacteriuria in pregnancy

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Regimen</th>
<th>Drug class</th>
</tr>
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<tbody>
<tr>
<td>Cephalexin</td>
<td>500 mg po qid</td>
<td>Class B</td>
</tr>
<tr>
<td>Nitrofurantoin macrocrystals</td>
<td>100 mg po qid</td>
<td>Class B</td>
</tr>
<tr>
<td>Nitrofurantoin monohydrate-macrocrystals</td>
<td>100 mg po bid</td>
<td>Class B</td>
</tr>
<tr>
<td>Amoxicillin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>500 mg po qid</td>
<td>Class B</td>
</tr>
<tr>
<td>Ampicillin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>500 mg po qid</td>
<td>Class B</td>
</tr>
</tbody>
</table>

Abbreviations: bid, twice a day; po, by mouth; qid, four times a day.
<sup>a</sup> Must check hospital susceptibilities before prescribing β-lactam monotherapy.

Treatment should be based on urine culture and sensitivities. With either situation, consideration should be given to implementing long-term nightly suppressive therapy with low-dose cephalexin (125–250 mg) or nitrofurantoin (50–100 mg) throughout the pregnancy and including the puerperium [32]. Suppression therapy also should be considered in women who have persistent bacteriuria, despite multiple courses of antimicrobial treatment, to prevent progression to symptomatic infection. Care must be used because prolonged use of antimicrobials, such as cephalosporins, may predispose women to chronic vaginal candidiasis [7]. Postpartum radiologic evaluation for urinary tract anomalies or urolithiasis should be considered in patients who have recurrent UTIs.

**Health consequences of asymptomatic bacteriuria in pregnancy**

The presence of ASB in pregnancy places patients at increased risk for the development of cystitis and pyelonephritis with their respective morbidities. A critical meta-analysis by Romero and colleagues [33] showed the relationship between ASB alone and preterm delivery and low birth weight infants. The risk of preterm delivery in women who had ASB during gestation was twofold greater than those who never were affected. With adequate treatment of ASB, the relative risk of low birth weight infants was 0.56 compared with an untreated group [33]. These findings were confirmed in a recent Cochrane review of available data which demonstrated the decreased incidence of pyelonephritis and low birth weight infants when ASB is treated [23]. Several theories have been suggested to explain the mechanism by which uncomplicated UTI triggers preterm labor and delivery. Bacterial endotoxin release is believed to provoke labor directly or through a prostaglandin-mediated cascade. Alternatively, it is believed that UTI predisposes women to amnionitis, and thus, preterm labor. Although previously suggested, ASB does not seem to be related to preeclampsia or anemia [34].

**Cystitis**

Acute bacterial cystitis presents with clinical signs and symptoms of urgency, frequency, dysuria, pyuria, and hematuria without evidence of systemic illness
Cystitis complicates 1% to 4% of all pregnancies [8]. Diagnosis, although mostly clinical, includes a positive urine culture with at least $10^5$ CFU/mL of a single uropathogen. Although routine surveillance during prenatal care is designed to minimize bacteriuria, this has had no effect on the incidence of cystitis. This suggests that most infections arise without antecedent bacteriuria [36]. On initial prenatal evaluation, most women who will have cystitis in pregnancy have negative screening cultures [37]. Unlike ASB, the diagnosis of cystitis in pregnancy does not increase the risk for developing pyelonephritis.

Risk factors for developing cystitis in pregnancy include those stated for ASB as well as a history of *Chlamydia trachomatis*, illicit drug use, and less than 12 years of education [38]. The spectrum of uropathogens that have been isolated in cystitis is similar to that seen in ASB. Therefore, the treatment modality of dosing and duration of therapy is the same. Follow-up surveillance, including monthly urine cultures for the duration of the pregnancy, is recommended. As with ASB, cystitis is associated with preterm labor and delivery [35].

Women may present with symptoms that are consistent with cystitis but with a negative urine culture. After confirming the lack of recent antibiotic use, the diagnosis of urethral syndrome should be considered. Urethral cultures for *Chlamydia* should be performed, followed by appropriate treatment [39].

**Pyelonephritis**

Acute pyelonephritis complicates 1% to 2% of all pregnancies and affects approximately 100,000 women in the United States annually [40]. Associated with marked fetal and maternal morbidity, it is the most severe form of UTI and the most common indication for antepartum hospitalization [2]. Risk factors for the development of pyelonephritis include those of ASB and cystitis as well as a history of pyelonephritis, urinary tract malformations, and calculi [13]. Patients who are at increased risk should be screened with monthly urine cultures. Because of the increasing mechanical compression of the enlarging uterus, pyelonephritis is most common during the second half of pregnancy; only 4% of cases present in the first trimester, 67% present in the second and third trimesters, and 27% present in the postpartum period [8]. Usually unilateral, pyelonephritis affects the right kidney more frequently secondary to dextrorotation of the uterus [6].

**Diagnosis of pyelonephritis in pregnancy**

Pyelonephritis presents with predominantly systemic signs and symptoms. These include fever; flank pain; costovertebral angle tenderness (CVAT); shaking chills; nausea; vomiting; and less commonly, symptoms of cystitis, such as dysuria and frequency. Most patients who have pyelonephritis also present with dehydration. The most common presenting symptoms are fever and flank pain [13]. Therapy largely is empiric and begun upon clinical diagnosis. Diagnosis is
confirmed with urine culture. Per the IDSA consensus, pyelonephritis is defined as the identification of at least $10^4$ CFU/mL of a single uropathogen in a midstream sample [28]. Microscopically, the diagnosis can be confirmed with the presence of 1 or 2 bacteria per high-power field on an unspun catheterized urine sample, or 20 bacteria per high-power field on a spun sample. These parameters correlate with more than $10^5$ CFU/mL of bacteria on urine culture. Additional diagnostic signs include the presence of pyuria or leukocyte casts [13].

Further laboratory investigation should include a complete blood cell count and serum chemistry evaluation. Hypokalemia, elevated serum creatinine, anemia, thrombocytopenia, and elevated lactate dehydrogenase due to endotoxin-mediated hemolysis may be encountered. Transient renal insufficiency with at least a 50% decrease in creatinine clearance is observed in more than 25% of patients [41]. Electrolyte abnormalities should be corrected. Most abnormalities should normalize spontaneously with treatment of the primary disease. Although self-limited, anemia often requires several weeks to resolve. Renal scarring has been described as a long-term sequela of acute pyelonephritis in pregnancy. The magnitude of renal scarring may be related to the inflammatory process. Interleukin-6, an endogenous pyrogen, correlates with the level of urinary tract inflammatory response [42], whereas interleukin-8, a chemoattractant for neutrophils, corresponds to the degree of pyuria and is related to renal scarring [43]. In a recent report, antimicrobial therapy significantly decreased these inflammatory markers within 6 hours. Normalization is almost achieved at 24 hours [44]. These findings emphasize the importance of rapid diagnosis and institution of therapy. Radiographic examination of women 10 to 20 years after diagnosis of pyelonephritis showed that those who were pregnant at the time of diagnosis were four times more likely to develop renal scarring [45]. However, functional renal impairment was not different between the pregnant and non-pregnant groups. One in 3000 women who have pyelonephritis in pregnancy develops renal failure, and pregnancy remains one of the most common conditions in which isolated pyelonephritis leads to renal failure [46]. Long-term follow-up of these patients is essential.

Although blood cultures are obtained frequently on initial evaluation, their usefulness in the assessment of pyelonephritis is limited. Bacterial pathogens that are isolated from blood cultures rarely differ from those that are found in the corresponding urine culture [47]. Furthermore, in a retrospective study of 156 cases of pyelonephritis in pregnancy, 90% of pathogens were sensitive to the initial empiric treatment; only 2% of blood cultures and 3% of urine cultures precipitated an adjustment in therapy [48]. Most changes in therapy were governed by clinical indications, such as persistent fever or CVAT. These findings were supported by a recent retrospective review of 391 cases of pyelonephritis in pregnancy; a change in management because of bacteremia alone occurred in only 1% of cases [49]. Although blood culture may help to guide antimicrobial therapy when faced with inadequate clinical response, limiting the use of cultures in the evaluation of pyelonephritis in pregnancy was estimated to result in an annual savings of $10 to $20 million [48]. Blood cultures have been and are
advocated in cases that are complicated by sepsis, temperature of at least 39°C, or respiratory distress syndrome.

Routine renal ultrasound evaluation is of limited clinical benefit and should be reserved for women who are unresponsive to initial treatment [50].

The uropathogens that are found in pyelonephritis are similar to those that cause ASB and cystitis. *E. coli* predominates, and is isolated in 70% to 80% of cases [49,51,52]. *Klebsiella pneumoniae* and *Proteus* spp appear less frequently, but play an important role in cases of recurrent pyelonephritis [53]. Gram-positive and anaerobic bacteria usually do not ascend to the upper urinary tract except in cases of instrumentation or obstruction.

*Treatment of pyelonephritis in pregnancy*

Because most patients who have pyelonephritis are dehydrated, initial management should include adequate intravenous hydration and close monitoring of urine output. Cooling blankets and antipyretics may be used to alleviate pyrexia [13]. The current standard of care includes hospitalization and parenteral antimicrobial therapy.

Initial antimicrobial treatment is empiric. Intravenous antimicrobial therapy, including regimens of ampicillin, plus gentamicin, cefazolin, and ceftriaxone, are equally efficacious (Table 2) [35,55]. First-line therapy often includes a first-generation cephalosporin. A commonly used regimen is cefazolin, 1–2 g intravenously every 6 to 8 hours. Cefazolin possesses the same spectrum of activity against the common causative organisms as do the broader-spectrum cephalosporins and penicillins and is less expensive. Although there have been reports of in vitro resistance to cephalosporins, clinical efficacy seems to be unchanged [16]. Ampicillin monotherapy has fallen into disfavor because of the high incidence of resistant bacteria, and therefore, usually is used in conjunction with gentamicin [53]. To avoid exacerbation of the renal insufficiency that commonly accompanies pyelonephritis, drug serum levels should be followed when using aminoglycosides, such as gentamicin. Other options include broad-spectrum penicillins, such as mezlocillin or piperacillin, and second- or third-generation cephalosporins [13].

Table 2
Suggested antimicrobial regimens for the treatment of pyelonephritis in pregnancy

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Regimen</th>
<th>Drug class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin (+) Gentamicin</td>
<td>2 grams IV q6 h</td>
<td>Class B</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2 mg/kg load, then 1.7mg/kg in 3 divided doses</td>
<td>Class C</td>
</tr>
<tr>
<td>Ampicillin-sublactam</td>
<td>3 grams IV q6 h</td>
<td>Class B</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1 gram IV/IM q24 h</td>
<td>Class B</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>0.75–1.5 grams IV q8 h</td>
<td>Class B</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>1–2 grams IV q6–8 h</td>
<td>Class B</td>
</tr>
<tr>
<td>Mezlocillin</td>
<td>3 grams IV q6 h</td>
<td>Class B</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>4 grams IV q8 h</td>
<td>Class B</td>
</tr>
</tbody>
</table>

Abbreviations: IM, intramuscularly; IV, intravenously; q, every.
With appropriate antimicrobial management, 75% of patients become asymptomatic and afebrile within 48 hours, whereas 95% will defervesce within 72 hours of treatment [13,16]. Failure to respond clinically after 72 hours of therapy most likely indicates a resistant pathogen, urinary tract anomaly, or urolithiasis. In case of poor response, management should include the addition or substitution of an aminoglycoside as well as radiographic evaluation to rule out other etiologies. Renal ultrasonography is used often but is of limited value because of its decreased sensitivity for detection of calculi during pregnancy [56]. Intravenous pyelography (IVP) may be used safely in pregnancy with one shot at 20 to 30 minutes to maximize detection and minimize radiation exposure to the fetus (Fig. 1) [56]. MRI also may garner information regarding urinary tract obstruction safely.

In an inpatient setting, parenteral antimicrobial therapy usually is continued until the patient is afebrile for 48 hours. The patient is switched to oral antimicrobial therapy for 2 weeks. A follow-up urine culture, or test of cure, is performed to ensure eradication of the bacteria [13].

Outpatient management for pyelonephritis in pregnancy has been proposed with the benefits of decreased health care costs and increased patient convenience [51,52,57–59]. Wing and colleagues described a series of randomized controlled trials that compared inpatient with outpatient management of pyelonephritis in pregnancy at less than 24 weeks and more than 24 weeks [51,52]. Patients who were randomized to outpatient management at less than 24 weeks received two

Fig. 1. Intravenous pyelogram (IVP) in pregnancy. IVP “one-shot” after 20 minutes demonstrates mild right hydronephrosis and hydroureter.
doses of ceftriaxone, 1 g intramuscularly, whereas inpatients received cefazolin, 1 g every 8 hours. Ninety-five percent of patients qualified for outpatient treatment and no significant differences in clinical or delivery outcomes was observed. In a separate investigation of women who were more than 24 weeks’ gestation, inpatient and outpatient enrollees received two doses of ceftriaxone, 1 g over 24 hours. Ninety percent of women were treated safely with ambulatory care; however at greater than 24 weeks’ gestation the number of patients who qualified for outpatient therapy was decreased by 50% because of evidence of complications that were due to pyelonephritis and necessitated inpatient management. Additionally, 51% of those women who were greater than 24 weeks who were randomized to outpatient therapy could not complete the study assignment or had to be readmitted for complications that were related to the primary infection. They concluded that in pregnancies beyond 24 weeks, outpatient management of pyelonephritis had limited usefulness. Although studies demonstrate the usefulness of ambulatory management of pyelonephritis in pregnancy, they also strongly advise that careful consideration must be made in selecting appropriate candidates to maximize efficacy and safety [13,16,51,52]. Selection criteria should include compliant patients with pregnancies at less than 24 weeks’ gestation at diagnosis, with no evidence of comorbid disease (eg, diabetes mellitus). In addition they should not exhibit signs or symptoms of sepsis, temperature greater than 38°C, recurrent upper urinary tract disease, inability to tolerate oral intake, or signs of preterm labor. For appropriate candidates, an initial observation period of 24 hours is needed to confirm maternal and fetal well-being. During this time, antimicrobial therapy, hydration, and laboratory evaluation is initiated. Upon discharge, adherence to close outpatient follow-up must be stressed. Instructions should be given to return to the emergency room immediately if signs of sepsis, respiratory insufficiency, or preterm labor develop. Twenty-four hours after discharge, patients should be evaluated for appropriate clinical response. As with inpatient therapy, a urine culture should be obtained after 2 weeks to confirm adequate treatment.

Because of the 20% recurrence rate of pyelonephritis before delivery [13], nightly suppression therapy after documented cure is advocated for all women who have a diagnosis of pyelonephritis in pregnancy. Continuous prophylaxis with low-dose nitrofurantoin, 100 mg daily, reduces recurrence by 95% [60]. In a retrospective review, a recurrence rate of 60% without suppression was reduced to 2.7% with daily suppressive treatment [61]. Suppression therapy should be continued until 4 to 6 weeks post partum. In addition, urine cultures to screen for recurrent bacteriuria should be obtained monthly for the remainder of the pregnancy.

**Complications of pyelonephritis in pregnancy**

Bacteremia occurs in 15% to 20% of cases of pyelonephritis; the most common pathogen is *E coli* [62]. Gram-negative bacteria possess endotoxin within their cell wall. Endotoxin-mediated damage includes that of capillary endothe-
lrium, diminished vascular resistance, and changes in cardiovascular output. When
the active component of endotoxin—lipid A—is released into the maternal
circulation, it precipitates a cascade response of proinflammatory cytokines,
histamine, and bradykinins that may lead to the more serious complications of
septic shock, disseminated intravascular coagulation, respiratory insufficiency,
and adult respiratory distress syndrome (ARDS).

Pyelonephritis is the most common cause of septic shock in pregnancy [62].
Patients who have septic shock require admission to intensive care, immediate
fluid resuscitation, and antimicrobial therapy. In cases of hypotension and
oliguria, the use of dopamine support may be necessary. Increased alveolar-
capillary membrane permeability—mediated by endotoxemia—results in pulmo-
nary edema and respiratory insufficiency. Although patients generally respond
well to oxygen therapy, worsening dyspnea, tachypnea, and hypoxemia may
signify progression to the highly morbid condition of ARDS [63]. ARDS, de-
fined as a disease of acute onset with bilateral infiltrates on chest radiograph and
hypoxemia without evidence of pulmonary hypertension [63], complicates 1% to
8% of cases of pyelonephritis in pregnancy [13]. Pulmonary injury manifests
within 48 hours of beginning antimicrobial therapy. Management includes
maternal stabilization and fetal monitoring. Baseline chest radiograph and arterial
blood gas should be obtained. Although adequate supplemental oxygen therapy
combined with diuresis often is sufficient, mechanical ventilation may be re-
quired. Delivery does not decrease maternal or fetal morbidity/mortality globally
and should be considered on a case-by-case basis [64]. In one retrospective
analysis, pulmonary injury in antepartum pyelonephritis was associated with
temperature of greater than 103\degree F in gestations of more than 20 weeks, and
tachycardia of more than 100 beats per minute [65]. ARDS also was diagnosed
more frequently in patients who had received \(\beta\)-sympathomimetic tocolytic
agents and excessive intravenous hydration. Tocolytics predispose women to
pulmonary edema through cardiovascular changes. Although all virulent bacteria
pose a threat for pulmonary injury, \textit{Klebsiella pneumoniae}, a common com-
munity and nosocomially acquired pulmonary pathogen, more frequently leads
to ARDS [65]. The incidence of preterm delivery in pyelonephritis is reported
from 6% to 50%, depending on gestational age at presentation and the use of
antimicrobial therapy [13]. Although uterine contractions often accompany pyelo-
nephritis, there often is little or no acute cervical change. A controversy exists in
the literature regarding the etiology of these contractions, fever versus endotoxin
release after antibiotic treatment, and their relationship to preterm delivery.
Antibiotic treatment alone of pyelonephritis significantly decreased the frequency
of contractions with no resultant association with pyrexia [54]; however, recent
murine models of gravid myometrium demonstrated a direct effect of endotoxin
release upon uterine contractility. The effect occurs through the release of
endogenous prostaglandins; an influx of calcium ions; and to a lesser extent,
inhibition of sodium pumps [66]. Yet similar murine models show that although
endotoxin-mediated inflammatory response increases the amplitude of uterine
contractions, it has no effect on their frequency [67]. Studies continue to examine
this topic. Because treatment of the primary disease often mitigates the uterine contractions that are seen with acute pyelonephritis, tocolysis use should be reserved for cases of documented cervical change [54].

Neonatal effects of urinary tract infections in pregnancy

There also has been a suggestion that UTI during pregnancy is associated with developmental delay and mental retardation in the neonate. Long-term infant follow-up per the National Collaborative Perinatal Project revealed that preschool intelligence quotient scores were 2.38 points lower in white male infants of mothers who had a UTI in pregnancy when compared with an unexposed cohort; however, no significant difference was noted among African American males or females [68,69]. Given the multifactorial nature of developmental delay and mental retardation, determining the cause is difficult, and no firm consensus has been reached on this apparent relationship. Recently, McDermott and colleagues [70] revisited this controversy. They found that the relative risk of infant cognitive delay with untreated UTI in pregnancy was 1.31 (95% CI, 1.12–1.54) when compared with unexposed infants. Furthermore, when comparing untreated women with treated women, the relative risk of infants who had mental retardation or developmental delay was 1.22 (95% CI, 1.02–1.46). These results support the association between UTI in pregnancy and cognitive delay and emphasize the importance of rapid diagnosis and treatment.

New directions

Ongoing research strives to improve prevention, detection of risk factors, and efficacy of treatment. In this era of increasing multidrug resistance, novel approaches that are directed at prevention of infection are underway. Methods to combat *E. coli* colonization, in particular, are under investigation; as a result, a myriad of vaccines directed against *E. coli* has emerged. Roberts and colleagues [17] described the efficacy of vaccination with purified *E. coli* PapDG protein. Pap G, an adhesion, is a crucial component of P fimbriae, which allows bacterial binding to vaginal and renal epithelium. Upon intraperitoneal administration of purified PapDG to cynomolgus monkeys, significant levels of specific antibody against PapDG were noted. On histologic comparison of renal tissue with a control group following inoculation of *E. coli* containing P fimbriae, vaccinated monkeys showed no evidence of pyelonephritis, whereas the control group had 22% to 33% positive histologic sections. Other vaccines that are under development include a parenteral formulation against *E. coli* type I fimbriae (MedImmune, Inc., Gaithersburg, Maryland) [71], which is commonly found in UTI isolates, and Urovac (Solco Basel Ltd., Basel, Switzerland) [72], a vaginally administered preparation which is directed against multiple uropathogens. These
vaccines hold promise for the future in mitigating and potentially eradicating the disease burden and societal costs of UTIs.

Summary

UTIs frequently complicate pregnancy with their concomitant morbidities. ASB, if left unrecognized and untreated, frequently progresses to pyelonephritis, and is associated with preterm delivery and low birth weight infants. A possible association exists between ASB and cognitive delay. Pyelonephritis is a serious medical condition in pregnancy and poses a significant medical risk to maternal, and, therefore, fetal well-being. Patients should be treated immediately and failure of response should be evaluated promptly. Close observation is necessary to detect complications, such as septic shock and respiratory insufficiency. When afebrile for 48 hours, patients may be discharged home with increased surveillance for the duration of the pregnancy. The risk of recurrence may be minimized with suppression therapy, or alternatively, monthly urine cultures.

References


