12 Urinary Tract Infections

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Recent advances have led to a renewed interest in urinary tract infections in females. First, current research has reassessed the previously used definition of infection as a positive culture with ≥100,000 colonies per ml. Norden and Kass[1] originally defined a positive culture as $\geq 10^5$ colonies per ml because they found a 96% predictability of a third positive culture if the 2 previous cultures were positive. However, their studies primarily involved pregnant women who were asymptomatic at the time of culture and were not known to be at high risk for recurrent disease. Other authors[2,3] reported that symptomatic disease is often associated with colony counts of less than 10^5 colonies per ml. These studies have thus led to reconsideration of the best way to define infection microbiologically. The roles of new pathogens such as *Chlamydia trachomatis,* herpes simplex virus (HSV), and *Staphylococcus saprophyticus* have also been demonstrated in recent studies.

Second, new techniques are being developed that more precisely localize the site of infection.[4–6] It has been shown that approximately 50% of patients with apparent lower tract infection have renal involvement. Older studies looking at recurrence rates and modes of therapy did not distinguish upper from lower tract disease. Recent studies are now exploring differences between these two populations.

Third, the older dictum of therapy for 7–10 days for all urinary infections is being challenged. Studies are currently under way to evaluate 1-day or single-dose therapy for selected patients.[7] Conversely, extended follow-up and management are recommended for other subgroups. Finally, through careful analysis of these new data plus advances in immunology, we are arriving at a new understanding of the heterogeneous nature and pathogenesis of what used to be referred to as simply a urinary tract infection.

Incidence

Dysuria

Dysuria occurs commonly in pregnant and non-pregnant women. In 1969 Waters[8] surveyed 2,933 women aged 20–64 years, and 21.8% of these women had reported dysuria in the previous year. Contrary to other reports, in this study there was no significant age effect on the proportion of women with dysuria. Approximately half of the women consulted physicians when dysuria occurred. Interestingly, the proportion of women who sought medical attention was significantly higher in the younger age group. This factor may thus partially account for the usual assumption that dysuria is more common in younger women.

Asymptomatic Bacteriuria

The incidence of asymptomatic bacteriuria (ASB) in pregnancy varies between 4 and 7%[9] when defined as ≥100,000 colonies per ml. Factors associated with an increased incidence include non-white race, lower socioeconomic status, increasing parity, history of prior urinary tract infection (UTI), and older age. The

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prevalence of bacteriuria in women in general increases with age and sexual activity. Specific underlying diseases such as sickle cell trait or diabetes may double the incidence. Most asymptomatic bacteriuria will be detected at the first prenatal visit. If the first culture is negative, only about 1% of the population will subsequently develop a positive culture later in pregnancy. It is thus reasonable to conclude that ASB usually antedates a pregnancy since a similar incidence can be found in non-pregnant women.[9]

Pyelonephritis

Pyelonephritis is relatively rare in non-pregnant women, but during pregnancy acute pyelonephritis remains a common medical complication with an overall incidence of 1–2%. If the practitioner screens for and treats ASB, the incidence of symptomatic disease will decrease. If untreated, approximately 28% of pregnant women with ASB will develop acute pyelonephritis. If they are treated, this incidence can be reduced to 2–4%. Thus the diagnosis and treatment of ASB during pregnancy can prevent episodes of acute pyelonephritis.[10]

Etiologic Agents

The etiologic agents responsible for UTI in pregnancy differ little from those isolated from non-pregnant women (Table 12-1). *Escherichia coli* accounts for over 80% of the infections, with the remainder being caused by *Klebsiella, Proteus mirabilis, S. saprophyticus,* and enterococci. In women with multiple previous infections, associated stones, or urologic abnormalities, organisms such as *Proteus, Klebsiella, pseudomonas,* and *Staphylococcus aureus* become more frequent. The clinician must distinguish true UTI attributable to these bacterial uropathogens from other infections that produce dysuria. These include urethritis due to sexually transmitted agents such as *C. trachomatis, N. gonorrhoeae,* and HSV and vaginitis due to *Trichomonas* or yeast.[11]

Table 12-1. Usual Causes of Acute Urinary Tract Infection in Women.

Acute uncomplicated: 90% *Escherichia coli; Staphylococcus saprophyticus*
Recurrent infections: *E. coli* still most common, but increased drug resistance; *Proteus, Klebsiella,* enterobacter, enterococci also found
Associated with calculi: *Proteus, Klebsiella,* Enterococci, *Staphylococcus aureus*
Associated with manipulation-obstruction: *Proteus, Klebsiella, Serratia, Pseudomonas,* enterobacter, enterococci
Bacteremic infection: *S. aureus*

Pathogenesis

Physiologic Changes in the Urinary Tract of Pregnant Women

A number of well-documented alterations in the anatomic and functional characteristics of the urinary tract occur during pregnancy. These include (1) marked dilatation of the ureters (right greater than left) and renal pelvises; (2) decreased ureteral peristalsis; (3) increase in the volume of ureteral urine from 2–4 ml to greater than 50 ml; (4) decreased bladder tone associated with increased volume of urine in the bladder, increased bladder capacity, and decreased emptying of the bladder; and (5) marked hypertrophy of the longitudinal musculature of the ureter (Waldeyer's sheath). These changes begin in the sixth to seventh week of gestation and gradually progress until term. After delivery these physiologic alterations rapidly resolve and are gone in two thirds of patients by 1 month following delivery.

The major factor responsible for so-called physiologic hydroureter of pregnancy has been thought to be either obstruction of the ureter due to the enlarged pregnant uterus or hypertrophy of the muscular sheath in the lower third of the ureter. More recently studies suggest that hormonal influences, specifically increased production of progesterone and estrogen during pregnancy, may be an important factor in the causation of hydroureter of pregnancy. The cumulative effect of these physiologic and anatomic alterations produces increased susceptibility to ascending infection in patients who have bladder bacteriuria.

Host-Bacterial Interactions

The facts that (1) most pregnant women experience infection with the same organisms that

Table 12-2. Host Defense Mechanisms in Urinary Tract Infection.

Urethral length and angle
Urine flow (dilution, flushing)
Urine pH, and osmolarity
Urine concentration of urea and organic acids
Phagocytic cells in bladder wall
Local and/or systemic antibody
Bladder mucopolysaccharide

Table 12-3. Important Virulence Properties of *Escherichia coli*: Strains Causing Urinary Tract Infection.

Pili (type I and gal-gal)
O antigen
K antigen
Hemolysin
Serum resistance
Antimicrobial resistance

infect non-pregnant women and (2) most infections in pregnant women can be detected at the first prenatal visit (and thus may often have been acquired prior to pregnancy) both suggest that the pathogenesis of infection in pregnancy closely resembles that seen in non-pregnant women (Table 12-2). Infecting bacteria originate in fecal flora and establish introital colonization prior to urinary infection.[12] Introital and urethral colonization with *E. coli* may be long lived in women with recurrent UTI, in which *E. coli* replace the normal introital flora (mainly lactobacilli, staphylococci, and anaerobes). In some studies, women susceptible to repeated infections also appear to have uroepithelial cells that support bacterial adherence to a greater degree than do similar cells from women without recurrent UTI.[13] Sexual intercourse, often temporally related to the onset of UTI, facilitates infections by causing movement of bacteria from the colonized introitus and urethra into the bladder.[14]

E. coli strains that cause UTI belong to a small number of serogroups and for years have been thought to possess properties that enhance their virulence. Recent studies have demonstrated this to be most strikingly true for strains that cause acute pyelonephritis. These strains possess specific attachment organelles or pili that mediate their adhesion to renal epithelial cells (Table 12-3). Specifically, the so-called P pilus mediates attachment of *E. coli* bearing this ligand to a disaccharide receptor (α-gal-1, 4-β-gal) on renal epithelial cells. Over 90% of *E. coli* strains causing acute pyelonephritis have been found to bear P pili, while P pili are found on only 30–40% of cystitis strains and 10–15% of fecal strains from women without UTI.[15,16] Pyelonephritis-causing *E. coli* strains also produce hemolysins and resist the normal bactericidal action of serum. In animal models these properties appear to be important in the ability of these strains to cause pyelonephritis.[15]

Clinical Presentation

Symptoms do not accurately predict either the presence of urinary infection or its location. Gallagher and associates[3] observed 130 non-pregnant patients with symptomatic disease. Patients without infection were defined as those with sterile cultures or colony counts of less than 10,000 colonies per ml. The relationship of symptoms to microbiologic diagnosis is shown in Table 12-4. Recently Stamm et al.[2] studied acutely dysuric non-pregnant women and found similar results. Approximately 30% of symptomatic patients had sterile cultures. Furthermore, among symptomatic women with positive cultures, approximately half had colony counts greater than 10^5 colonies per ml while the remainder had colony counts between 10^2 and 10^5 colonies per ml. In studies using localization procedures such as the bladder washout or antibody-coated bacteria test, 30–40% of women with symptoms of lower tract infection actually have renal involvement.

As previously described, the incidence of ASB is similar in both pregnant and non-pregnant women, but pregnancy does appear to alter the pattern of symptomatic disease. Pregnant women seem to accept urinary frequency as a normal occurrence. In addition, they rarely have complaints of dysuria. Symptomatic cystitis was reported in only 1.3% of a pregnant population.[17] Thus, while dysuria is the most common presenting symptom in non-pregnant women with UTI, pregnant women

Table 12-4. Correlation of Symptoms with Bacteriuria.

	Bacteriuria Present ($>10^4$ cfu/ml)	Bacteriuria Absent ($\leq 10^4$ cfu/ml)
Symptoms considered diagnostic of urinary tract infection	79%	60%
Symptoms present:		
Fever	36	15
Dysuria	92	72
Hematuria	23	13
Frequency	91	94
Loin pain	34	32
Lower abdominal pain	64	64

Adapted from Gallagher et al.[3]
cfu-colony forming units.

often do not seek care until they develop full-blown pyelonephritis. The incidence of pyelonephritis in pregnancy ranges from 1% in patients screened and treated for ASB to 3–4% in patients if no screening tests are used. It is probable that this change in symptomatic presentation is related to the urinary tract alterations that occur during pregnancy.

Recurrent Disease

It is important to distinguish the difference between persistence of infection, relapse, and reinfection. Persistence of bacteriuria indicates the continued isolation of the original organism while the patient is still receiving therapy. This often occurs because the organism is resistant to the antibiotic or because the concentration of the drug in the urine or serum may be inadequate. Antibiotic failures also occur when the prescribed dosage is inaccurate or the patient fails to comply with drug therapy. Occasionally during treatment, superinfection with a new resistant organism will occur, requiring a change in therapy.

Differentiation between relapse and reinfection can be confusing. Table 12-5 lists characteristics of both. Relapse usually refers to recurrence of significant bacteriuria with the same species and serologic strain of organism that was originally documented. It usually appears within 2–3 weeks of completion of therapy and is often associated with upper tract involvement, congenital malformation, or renal stones. Reinfection refers to an infection that occurs, after cessation of therapy, with a different strain of microorganism or a different serologic type of the original infecting strain.

Turck and co-workers[18] in a series of nonpregnant patients found that recurrences in patients with renal bacteriuria was usually due to a relapse with the same species and strain of microorganism that was present before therapy. In contrast, in patients with bladder bacteriuria, most recurrent infections were characterized by reinfection with a new organism. Leveno et al.[19] studied bladder versus renal bacteriuria during pregnancy and also found that patients with upper tract infection were more likely to have relapses while patients with bladder involvement tended to have reinfections.

Present data show some 20–30% of infected

Table 12-5. Characteristics of Relapse and Reinfection.

	Relapse	Reinfection
Site	Kidney	Bladder
Strain	Same	Different
Onset	<7 days	>7 days, usually months
Treatment	2–6 weeks (?) Serum levels important	Short Urinary levels important
Antibody coating of bacteria	Positive	Negative
Prophylaxis	Not indicated	Successful

patients will eventually have some type of recurrence. Mabeck,[20] observed both treated and untreated non-pregnant women with uncomplicated UTI. At the end of 1 month, the recurrence rate was 40% in the placebo-treated group and 34% in the treated group. At 12 months it was found that the urine was sterile in 54% of the placebo group but in only 64% of the treated group. Similar results were found by Zinner and Kass[21] when they observed patients who had ASB during pregnancy: 10–14 years later, 29% of women treated for ASB during pregnancy had recurrent bacteriuria vs. 25% of the placebo treated group. A control group of women without ASB during pregnancy had only a 5% incidence of bacteriuria at 10–14 years. Harris and Gilstrap[22] studied recurrent pyelonephritis during pregnancy and found that without continuing surveillance and treatment, some 60% of patients would have a recurrence that required rehospitalization.

Whaley and co-workers[23] performed intravenous pyelography on 131 subjects who had ASB during pregnancy. At 2 or more months postpartum, 93 had persistent bacteriuria, while 38 had either spontaneous clearing or were treated with antibiotics. Of the patients with persistent bacteriuria 51% had some type of abnormality of the urinary tract. In addition, abnormal findings were also detected in 37% of those patients who no longer had bacteriuria on follow-up. This difference in abnormalities between the 2 groups was not statistically significant. Perhaps more predictability can be attained when the newer localization techniques are utilized to study recurrence rates in patients given different forms of therapy.

Complications and Sequellae of Urinary Tract Infection in Pregnancy

Effects of Bacteriuria of Pregnancy on the Pregnant Woman

Because of the physiologic alterations outlined previously, bacteriuria during pregnancy carries with it a substantial risk of development of acute pyelonephritis. In most reported studies assessing this risk, approximately 30% of pregnant women with untreated ASB have developed acute pyelonephritis.[9] Detection and treatment of ASB can reduce this risk to approximately 3%. Thus, untreated ASB in pregnancy confers an approximately 10-fold increased risk of developing acute pyelonephritis. Because most women who develop ASB of pregnancy can be detected by a screening culture at the initial prenatal visit, this single screening culture (when coupled with adequate treatment for ASB) can lead to prevention of 70–80% of acute pyelonephritis in pregnancy. An additional 1% of pregnant women who do not have bacteriuria at the initial visit develop it later, and 10–20% of these women develop acute pyelonephritis. Screening cultures of the urine later in pregnancy can detect the development of second- and third-trimester bacteriuria and will further reduce the occurrence of acute pyelonephritis in pregnancy.

It has become clear that women with ASB cannot be considered a homogeneous group. Localization of ASB by means of the bladder washout technique, direct ureteral catheterization, assessment of the maximum concentrating capacity of the kidney, or the more recent antibody-coated bacteria assay indicates that approximately 50% of women with ASB have renal infection despite absence of clinical evidence of pyelonephritis. The remaining women have infections localized to the lower urinary tract. Further, several studies have demonstrated that those patients with asymptomatic renal infection incur the greatest risk of developing acute pyelonephritis during pregnancy.[9] In addition, these women with ASB involving the kidney more often develop relapsing infection after initial attempts to eradicate the bacteriuria. Thus, a simple and rapid method of identifying women with renal involvement could identify a subset of women with ASB at highest risk of subsequent symptomatic infection.

Aside from the clearly increased risk of develoing pyelonephritis during pregnancy, it has not been possible to establish with certainty any other adverse maternal effects of ASB durng pregnancy. Some studies have demonstrated an increased occurrence of hypertension during pregnancy in women with bacteriuria. However, other studies have failed to find this association, and studies of whether eradication of bacteriuria reduces the occurrence of

hypertension in pregnancy have been conflicting. It seems probable that only women having bacteriuria involving the kidney would be likely to develop hypertension during pregnancy, and this factor has often not been considered in studies of hypertension in pregnancy. Further, socioeconomic status is a confounding variable known to influence the prevalence of both bacteriuria and hypertension during pregnancy.

Several studies have evaluated the likelihood of development of persistent bacteriuria or urinary infection following bacteriuria in pregnancy. These studies clearly indicate that women with bacteriuria in pregnancy have an increased probability of developing bacteriuria and symptomatic urinary infection after pregnancy, whether or not their original bacteriuric episode was treated. Zinner and Kass,[21] for example, found that the incidence of bacteriuria 10–14 years after pregnancy was 25% in women given a placebo for bacteruria of pregnancy, 29% in women whose initial infection during pregnancy was treated, and 5% in a group of matched non-bacteriuric pregnant women. The risk of subsequent UTI after pregnancy appears to be greatest in those women who have upper tract infection or relapsing infection after treatment during pregnancy. These findings are consistent with the hypothesis that infection during pregnancy is simply a part of the natural history of UTI in these women, that is, those women identified as being bacteriuric during pregnancy were probably at increased risk of developing bacteriuria before and also after pregnancy because of factors that are not specifically related to pregnancy itself. To date, however, it has not been possible to demonstrate an apparent increase in impaired renal function or eventual renal impairment that can be traced to bacteriuria or pyelonephritis during pregnancy. Long-term follow-up of patients experiencing bacteriuria during pregnancy indicates that many such women have radiologic changes such as congenital abnormalities, stones, ureteral dilatation, or findings consistent with chronic pyelonephritis. The total proportion of women with such abnormalities has ranged from 18–80%, and seems highest in those women who have had either symptomatic pyelonephritis or asymptomatic upper tract infection during pregnancy. Whether these radiologic changes represent the cause or effect of bacteriuria during pregnancy remains unclear.

Effects of Urinary Tract Infection During Pregnancy on the Fetus

It has been well documented that 20–50% of pregnant women who have symptomatic pyelonephritis during pregnancy may go into premature labor.[9] This complication can be effectively dealt with by treating the initiating infection and, if necessary, the premature contractions. Much more controversial, however, has been the relationship of ASB during pregnancy to prematurity, low birth weight, or small-for-birth-date infants. Elder et al.[10] originally reported an association between ASB and prematurity and found that eradication of bacteriuria during pregnancy reduced the rate of premature delivery. Since this original work, many conflicting reports have appeared in the literature assessing the possible effects of ASB on pregnancy outcome. Several studies have confirmed the original observation. However, other apparently well done case-control studies have not found an effect of ASB on prematurity, and in other case-control studies, treatment of ASB has not reduced the incidence of prematurity.[9] On balance, however, these studies suggest that there is indeed an association between bacteriuria of pregnancy and low-birth-weight offspring. Further, the mothers of most of the low-birth-weight infants appear to have evidence of chronic renal disease. The association of chronic renal disease and low-birth-weight infants is also found in mothers with coexistent renal disease and diabetes, hypertension, or collagen vascular disease. Many explanations doubtlessly underlie the inability of all studies to come to similar conclusions. These include the proportion of patients in each study who are experiencing silent renal infection, the definition of prematurity versus small-for-gestational-age infants, the fact that prematurity undoubtedly is a multifactorial syndrome, and the inclusion in some studies of non-bacteriuric patients (those with contaminated urine). Studies evaluating the effectiveness of treatment could also be confounded by the failure to take into account other genital infections (such as chlamydia and mycoplasma infections) that might influence pregnancy outcome. Even if it is associated with prema-

ture labor, ASB could account for only 5–10% of all premature births. The mechanism by which ASB might predispose to premature labor has been hypothesized to be either a direct effect of bacterial endotoxin upon the uterus (causing stimulation of muscular contractions) or, more likely, upon the placenta (resulting in decidual necrosis and hemorrhage and subsequent prostaglandin release).

Other effects of ASB upon the fetus have been hypothesized, including increase in abortion or stillbirth, increased occurrence of bacteriuria in infants born to infected mothers, and infected amniotic fluid syndrome. To date little evidence supports the association of these entities with bacteriuria of pregnancy.

Diagnostic Considerations

Urinalysis and Other Rapid Screening Tests

For years, microscopic urinalysis has been utilized to rapidly screen for UTI. Most often, an attempt is made to detect bacteriuria or pyuria on a spun or an unspun specimen of urine examined microscopically. In examination for bacteriuria, the unspun method yields fewer false positives and is as sensitive as the spun method. Although a gram stain of unspun urine correlates reasonably well with cultures of $\geq 10^5$ colonies per ml, it will not reliably detect lesser quantities of bacteria. Besides being used for detection of bacteriuria, urinalysis can also be used to detect pyuria, leukocyte casts, and red blood cell casts. Leukocytes in the urine can be enumerated either by using a hemocytometer chamber to count WBCs per mm^3 in unspun urine (abnormal = 10 WBC per mm^3) or by microscopically examining the urinary sediment after centrifugation (abnormal = 1 WBC per high power field).[24] The former method is much more accurate. Dipstick analysis may be used to detect the presence of proteinuria.

Another dipstick test, the nitrite test, first described by Griess in 1879, depends upon the ability of bacteria to reduce the nitrates that are normally present in urine to nitrites that are normally absent. This test was the first of many rapid methods developed to detect bacteriuria by non-cultural means. In our studies[25] and those of others, the nitrite test has been relatively specific, but often has demonstrated sensitivity of only 50–75% or less, compared with cultures growing $\geq 10^5$ colonies per ml. More recently, the nitrite stick has been combined with a dipstick method originally used for detection of leukocytes in urine through demonstration of leukocyte esterase activity. If one considers as positive any urine showing a positive nitrite or leukocyte esterase reaction, the sensitivity of the dipstick method improves to 85–95%, and some infections characterized by bacteriuria with less than 10^5 colonies per ml can even be detected. Another rapid urine screening device, the Bac-T-Screen, detects both pyuria and bacteriuria and has been demonstrated to have a sensitivity of 95%, compared wth colony counts of $\geq 10^5$ per ml. This test will also detect >90% of infections characterized by $\geq 10^2$ colonies per ml if they are accompanied by >25 WBC per mm^3. If further experience with these rapid screening devices proves as promising as initial reports, they may be very useful for rapid office screening.[26]

Culture

At present, the midstream urine culture remains the gold standard for diagnosing urinary tract infection. The results of the culture should be available within 24–48 hr, and at that time treatment can be discontinued, maintained, or revised. For screening of asymptomatic patients, culture also remains the gold standard. To reduce screening costs, office culture systems such as the dip-slide method may be utilized and positive results referred for further work-up and sensitivity studies. These office methods compare favorably with standard culture methods in terms of sensitivity and specificity.

Localization Procedures

Numerous studies have shown that symptomatology does not necessarily correlate with the site of the UTI. While most women with fever, costovertebral angle tenderness, and leukocytosis probably have renal involvement, many patients without these signs probably do also. Localization of UTI has been attempted by various direct and indirect techniques[27]

Table 12-6. Techniques for Localization of Urinary Tract Infections.

Direct
Ureteral catheterization
Renal biopsy
Bladder washout
Indirect
Serum antibodies
Urine concentration test
Urinary enzyme excretion
Antibody-coated bacteria in urine

(Table 12-6). Invasive techniques include ureteral catheterization, direct renal biopsy, and bladder washout. Because of the potential hazards of these procedures, most investigators have relied upon indirect methods of measurement such as serum antibodies, urine concentrating ability, urinary enzyme tests, the presence of antibody-coated bacteria in the urine, or the pattern of response to therapy.

Patients with pyelonephritis often have selective damage to tubular function that results in a temporary defect in the kidney's concentrating ability. Patients with upper tract disease will also commonly manifest a rising titer of serum antibodies to the infecting organism. Theoretically, serum antibodies should be present only in women with renal bacterial invasion and not in women with bacteriuria confined to the bladder. Rather than looking at antibodies in serum, Thomas[4] and Jones[5] and their co-workers have studied antibody coating of bacteria in urine. These workers used direct immunofluorescence and found that the presence of specific antibodies coating the pathogenic organisms in the urine closely correlated with the diagnosis of upper tract infection. However, subsequent studies have shown the technique to lack the specificity and sensitivity necessary for use as a diagnostic test in individual patients. For the individual patient, none of the currently available localization tests is accurate enough for routine clinical use. In population studies these tests indicate renal involvement in 25–50% of patients with ASB in pregnancy. A similar percentage of non-pregnant patients with lower urinary tract symptoms also have evidence of upper tract involvement by localization tests. The converse also holds in that some patients with upper tract symptoms have only bladder involvement.[6,27] In addition, these diagnositc techniques have been used only to study patients with infections characterized by greater than 10^5 colonies per ml. Their reliability probably decreases even further when infections with lower colony counts are considered.

Management

It is ironic that despite numerous articles about the effectiveness of various treatment methods and follow-up of women with UTI, there remain a paucity of data and confusion as to what actually constitutes a UTI. As mentioned earlier, Norden and Kass[1] defined a positive culture as $\geq 10^5$ colonies per ml and found a 96% predictability of a third positive culture if the 2 previous cultures were positive. They did not use symptomatic disease as an end point. All of the pregnant patients they studied were asymptomatic at the time these cultures were obtained and were not known to be at high risk for recurrent disease. They found that if these low-risk patients with ≥100,000 colonies per ml were left untreated, approximately 20–30% went on to develop symptomatic disease. Other authors[2,3] reported the occurrence of symptomatic infection with colony counts of less than 10^5 colonies per ml.

Given the above, it is obvious that women with UTI are not a homogeneous group that can be identified by simply obtaining cultures showing ≥100,000 colonies per ml. The management of these patients must therefore be individualized (Table 12-7).

Management of Non-Pregnant Women with Symptomatic Urinary Tract Infections

The management of women with dysuria recently has been reviewed in detail elsewhere.[11] Initially the clinician must distinguish among acute UTI, vaginitis, and urethritis with sexually transmitted agents such as *Chlamydia trachomatis, Neisseria gonorrhoeae,* and herpes simplex virus. Table 12-8 outlines the usual characteristics of these syndromes. In women with probable UTI, the initial urine for culture and sensitivity tests should usually be obtained prior to initiation of therapy. The most common mode of therapy has been antibiotic treat-

Table 12-7. Suggested Treatment Regimens in Selected Clinical Situations.

Clinical Situation	Expected Pathogen(s)	Antibiotic Therapy	Expected Outcome	Comments	Special Considerations in Pregnancy
Acute uncomplicated cystitits, no clinical evidence of pyelonephritis	*Escherichia coli* >90%	7 days sulfa, nitrofurantoin, naladixic acid; or single dose TMP-SMX* or amoxicillin	>95% cure, relapse rare; may have subsequent reinfection	Nearly any agent effective. For single dose rx: patient must have short duration of symptoms and return for follow-up	Avoid single dose rx in pregnancy; preferred drugs ampicillin-amoxicillin, nitrofurantoin or sulfa (except near term).
Acute pyelonephritis, no clinical evidence of stones or urologic disease, no evidence of sepsis	*E. coli* >90%	At least 10–14 day course of ampicillin, cephalosporin, TMP-SMX*	>75% cure; 10–20% relapse with same strain 5–10 days after therapy completed	With relapse, rule out calculi or urologic disease; then treat for 2–6 weeks with appropriate drug to eradicate focus	Hospitalize patient for parenteral antibiotics (ampicillin, cephalospins)
Acute pyelonephritis with suspected gram-negative sepsis	*E. coli, Klebsiella, Proteus*	10–14 day course of therapy; start with aminoglycoside until sensitivities known	65% cure; may relapse as described above	Hospitalization, prompt parenteral antibiotics, other measures to manage shock mandatory; relieve obstruction if present	None
Infection with calculi or urologic abnormality	*E. coli, Proteus, Klebsiella, Pseudomonas;* occasionally *Staphylococcus* or enterococcus	7–10 day course directed by culture results and sensitivities	Dependent upon relief of underlying condition	Therapy before culture results known depends on degree of illness; use aminoglycoside in sicker patients, ampicillin or cephalosporin in less sick patients	None
Nosocomial infection in catheterized patients, no clinical evidence of pyelonephritis or sepsis	*E. coli, Proteus, Klebsiella, Pseudomonas, Serratia,* enterococcus	Often none if catheter can be withdrawn; if catheter cannot be withdrawn, treat only immunosuppressed patients or those at high risk of sepsis (old age, severe underlying disease)	Easily eradicated if catheter withdrawn; treatment usually fails otherwise	Therapy based on culture results and sensitivities; if sepsis present, treat as outlined above; urinary antiseptics may reduce bacteriuria	None
Asymptomatic bacteriuria	*E. coli* >90%	Treat like acute uncomplicated cystitis	80% cure	Obtain 2 positive cultures before treating; treatment failure can be followed or treated for 2–6 weeks	Only 1 positive culture required; follow-up as outlined in table 12-9

* Trimethoprim-sulfamethoxazole

Table 12-8. Syndromes Causing Acute Dysuria in Women.

Site	Pathogens	Pyuria	cfu/ml	Clinical Features
Vaginitis	*Trichomonas vaginalis, Candida albicans,* Nonspecific Vaginitis	–	$<10^2$	External dysuria; vaginal discharge, burning, or odor; no frequency or urgency
Urethritis	*Chlamydia trachomatis, Neisseria gonorrhoeae,* Herpes virus	+	$<10^2$	Gradual onset, no hematuria, frequency or urgency, new sexual partner; associated cervicitis
Cystitis	*Escherchia coli, Staphylococcus saprophyticus*	+	$10^2 \geq 10^5$	Abrupt onset, hematuria, suprapubic pain, frequency, urgency
Early pyelonephritis	*E. coli, S. saprophyticus*	+	$10^2 \geq 10^5$	Same as above
No pathogen	None (?)	–	$<10^2$	Variable

cfu = colony forming units

ment for 7–10 days, but an alternative approach introduced recently is single-dose therapy. The relative advantages and disadvantages of this form of therapy have been reviewed elsewhere.[28] On balance, single-dose therapy is less expensive and associated with fewer side effects than the conventional 7–10 days of therapy, but cure rate may be somewhat lower. However, single-dose regimens have been widely recommended and used for management of acute uncomplicated cystitis in young non-pregnant women.

A wide variety of effective drugs exist for the treatment of urinary tract infections, including the sulfonamides, trimethoprim-sulfamethoxazole, trimethoprim alone, nitrofurantoin, and ampicillin or amoxicillin. In general, the cephalosporins and aminoglycosides should be reserved for treatment of infection with resistant organisms.

Other adjunctive therapies can reduce urinary stasis and prevent introduction of bacteria into the bladder. Thus, patients should be instructed to avoid holding urine in the bladder and to avoid lengthy intervals between voiding. They should be counseled to maintain an adequate fluid intake. It has also been shown that sexual intercourse is associated with the introduction of bacteria into the urethra and bladder. Some authors therefore recommend a single dose of either sulfa drug or nitrofurantoin after intercourse in high-risk patients to prevent infection.

Between 2 and 6 weeks after discontinuation of therapy, recultures should be obtained to detect relapse or reinfection. Patients with repeated episodes of either symptomatic or asymptomatic disease with the same strain (i.e., relapse) should be considered candidates for further urologic work-up including intravenous pyelography. Selective studies have shown that up to 50% of these patients may have abnormalities of the urinary tract.

Management of Pregnant Patients with Asymptomatic Bacteriuria

The increased risk of acute pyelonephritis during the later stages of pregnancy in women with symptomatic bacteriuria and the implications of this infection for both the mother and the fetus clearly justify screening all pregnant women for ASB (Table 12-9). All pregnant women should be screened at their initial prenatal visit and ideally at one subsequent visit during the third trimester. Although formal cost-benefit analyses have not been carried out or published, it seems likely that this approach would clearly reduce both maternal and fetal morbidity and mortality and is well worth the expense. A variety of screening techniques have become available, ranging from the simple Gram stain of unspun urine or automated devices for detection of bacteriuria to standard urine culture. Selection of the most appropriate method usually depends upon local availability and cost. Specimens should be collected by means of a standard clean-catch midstream technique. Catheterization for collection of a urine specimen is not usually necessary in this situation and represents an unnecessary hazard to the pregnant woman. Although supra-

Table 12-9. Management of Urinary Tract Infections during Pregnancy.

Symptomatic Patients
Obtain urine culture and urinalysis
Treat empirically
Check results in 48 hr, modify therapy accordingly
Follow-up: Culture every week until negative, then obtain cultures every 2 weeks; postpartum IVP if bacteriuria recurrent
Asymptomatic Patients
Obtain urine culture at first visit
Routine nitrite-leukocyte esterase dipstick testing or other screening test at each prenatal visit
Culture reported back as:
Positive ($\geq 10^5$ pathogenic colonies per ml)
Treat (consider short-term therapy)
Follow-up: Culture every week until negative, then obtain cultures every 2 weeks; postpartum IVP if bacteriuria recurrent
Negative (no growth or non-pathogens)
Routine care
Follow-up: Repeat urine culture in third trimester
Gram-Negative Bacilli $<10^5$ pathogenic colonies per ml (with or without non-pathogens)
Repeat urine culture and sensitivity as soon as possible
Consider treatment in high-risk patients

pubic bladder aspiration in pregnant women has been safely performed in many studies, the small attendant risk and additional time it requires are not justified for routine clinical purposes.

Some authors recommend treatment for ASB only after obtaining 2 positive cultures at $\geq 10^5$ colonies per ml. Since pregnant women are at greater risk for complications, we currently will treat after only 1 positive culture, thus accepting a 85–90% predictability. During pregnancy some women will have repeated cultures with $\geq 10^3$ gram-negative bacilli per ml, and they should probably be treated also. Ampicillin and amoxicillin can be used safely throughout pregnancy. In early pregnancy the sulfa drugs may be used for treatment. Most patients will respond to 10–14 days of treatment with the above regimens. Although single-dose regimens have been used in pregnancy, we favor treatment of at least 7 days because of the increased risk of upper tract infection in pregnant women. Sulfa should be avoided in the last months of pregnancy because it may cause kernicterus in the newborn. Sulfa combinations, including combination with trimethoprim, should be avoided throughout pregnancy because of the possibility of teratogenic effects. The nitrofuratoins have been used throughout pregnancy with safety, but adverse reactions are always a possibility and high-risk patients should be observed for glucose 6-phosphate dehydrogenase deficiency.

Treatment effectiveness is monitored by obtaining posttreatment cultures and cultures at subsequent prenatal visits. Patients with recurrent disease should be treated; they are also candidates for postpartum intravenous pyelography. These patients should be monitored carefully during labor and postpartum because of the increased risk of recurrence during these periods.

Management of Pregnant Patients with Pyelonephritis

We strongly recommend hospitalization of all pregnant patients with probable pyelonephritis. Patients with pyelonephritis often experience a high fever, and it is often forgotten that the temperature of the fetus is approximately 1 C higher than the maternal temperature. The possibility of significant teratogenic brain damage exists if the maternal febrile episodes are not treated appropriately with antipyretics and, if necessary, cooling blankets.

In 1932 during the preantibiotic era, Dodds[29] described 84 patients with pyelitis during the antenatal period. In 2 patients the urine cleared spontaneously prior to delivery. Overall there was a 40% prematurity rate. At 1 year follow-up, culture was still positive in 50% of women. When one is treating pyelonephritis

in pregnancy the goals are to prevent prematurity, reduce maternal morbidity, and prevent recurrence throughout the pregnancy. These goals may be accomplished by early treatment with appropriate antibiotics followed by close surveillance with cultures.

With few exceptions, patients with pyelonephritis during pregnancy should be treated initially with intravenous administration of antibiotics. Intravenous therapy should be continued at least until clinical improvement occurs and fever has decreased. We also recommend obtaining a negative culture. Hydration alone may in part account for a decrease in fever, since Dodds showed that approximately 80% of patients not treated with antibiotics became afebrile within 5 days.[29] Thus the fever curve alone should not be used as an end point for therapy. Oral therapy should be given to complete a total antibiotic course of at least 2 weeks. Invasive urologic manipulation and intravenous pyelography should be avoided unless patients are unresponsive to initial medical management. Ultrasound may be used to look for suspected calculi.

After discharge, patients should be seen within 1 week for repeat culturing and continued surveillance. We found that approximately 30% of our patients had reccurent positive cultures within the first 2 weeks after discharge. Cultures should be obtained at each visit. Treatment should be initiated if cultures show $\geq 10^3$ pathogens per ml. These high-risk patients should also be treated immediately if they are symptomatic.

Clinic follow up of patients with positive cultures includes weekly visits until cultures are negative. Once negative cultures are attained, a culture should be obtained every 2 weeks until delivery. Serveillance should continue until 6 weeks post partum. Postpartum observation with an intravenous pyelogram should be considered for those patients with recurrent bacteriuria.

There is confusion over the efficacy of suppressive therapy during pregnancy for those patients afflicted by pyelonephritis. We[30] prospectively evaluated the efficacy of suppressive therapy in 200 pregnant women with acute pyelonephritis during pregnancy. While our results dramatized the beneficial effects of close surveillance of these patients by means of cultures, they cast serious doubt upon the need for suppressive therapy. A present, we do not recommend suppressive therapy unless there is underlying chronic renal disease.

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