



Maternal Health Task Force



# Urinary Tract Infections in Pregnancy

The Geneva Foundation for Medical Education and Research

## On successful completion of this module you should be able to answer the following questions:

- How are UTIs in pregnancy diagnosed and why is early diagnosis important?
- What is their burden and how are urinary tract infections in pregnancy classified and what is the significance?
- What are the effects of urinary tract infections on the mother and developing fetus/neonate?
- How should urinary tract infections be screened in pregnancy and how are they diagnosed?
- What is the current evidence regarding antibiotic choice in management of urinary tract infections in pregnancy?
- What are areas in which there is insufficient evidence, suggesting a need for further research?

## Definitions

According to the International Classification of Diseases (ICD-10), urinary tract infections are infections affecting structures participating in the secretion and elimination of urine: the kidneys, ureters, urinary bladder and urethra.

In pregnancy, these infections can lead to serious adverse maternal and neonatal outcomes.

Recurrent urinary tract infection is defined as more than one UTI before or during pregnancy. In non-pregnant women, recurrence is defined as three infections in the previous 12 months, or two episodes in the last six months.

Bacteriologic persistence is continued bacteriuria with the same organism 48 hours after initiation of treatment.

A “relapse” is a recurrent urinary tract infection where the organism that was previously treated persists in the urinary tract two weeks after completing treatment.

A “reinfection” is a ‘true’ recurrence. It is a urinary tract infection occurring after sterilization of the urine, with an organism **originating from outside of the urinary tract**, either a new bacterial strain or a strain previously isolated that has **persisted in the colonizing flora of the gut or vagina**, more than two weeks after treatment.

## Classification

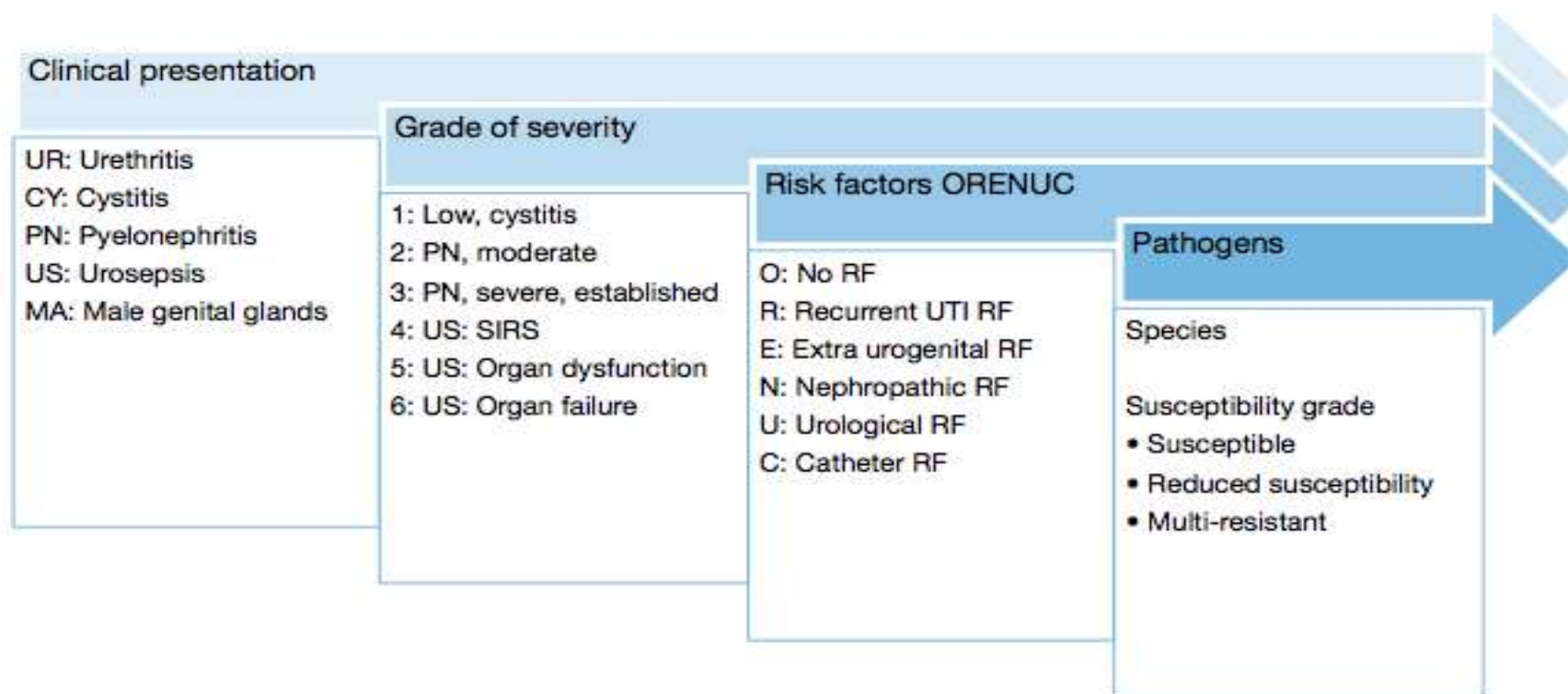
Classification of urinary tract infections is important for making informed clinical decisions, and for the purpose of research, quality measurement and teaching. It is based on:

- The clinical presentation and anatomical level of infection
- The grade or severity of infection
- Underlying risk factors and microbiological findings
- Causative pathogens and their susceptibility to treatment

Urinary tract infections are ascending in nature, with infecting organisms moving from the perineal region and vagina. **Anatomically**, therefore, the level of the urinary system reached by the infection can be the urethra (urethritis), bladder (cystitis), kidney (pyelonephritis) or in the blood stream (urosepsis).

The infection can also be grouped as an upper or lower urinary tract infection, where the kidneys are the threshold between these two levels. Symptoms suggestive of cystitis are regarded as lower urinary tract infections whereas symptoms suggestive of pyelonephritis characterize an upper urinary tract infection.

## Additive parameters of UTI classification and severity assessment



SIRS- Systemic inflammatory response syndrome

Note: this system classifies urinary tract infections in males and females and therefore male genital glands (MA) under clinical presentation is inapplicable in our context of discussion.

## Classification of urinary tract infections

**Severity** is graded on a scale of 1-6 as follows (and also includes an anatomical component):

- Grade 1: cystitis, low severity
- Grade 2: pyelonephritis with moderate symptoms
- Grade 3: established pyelonephritis with severe symptoms
- Grade 4: urosepsis with systemic inflammatory response syndrome(SIRS)
- Grade 5: urosepsis with organ dysfunction
- Grade 6: urosepsis with organ failure

**Risk factor** classification is also important in assessment of all patients with a UTI. Pregnancy is considered an extra-urogenital risk factor for urinary tract infections with severe outcomes.

Lastly, **pathogen susceptibility** in the classification of UTI informs treatment choice: (a) susceptible (b) reduced susceptibility (c) multi-resistant.

By cumulating the different parameters, a UTI in pregnancy can be classified as follows:

- CY-1R: *E. coli* (a): simple cystitis but recurrent with susceptibility to standard antibiotics.

## Epidemiology of urinary tract infections in pregnancy

UTIs are the most common bacterial infection during pregnancy. Studies have shown that the frequency of asymptomatic bacteriuria in pregnancy ranges between 2%-18.5%(Meads 2011). Cystitis, on the other hand, complicates about 1.3% of pregnancies (Schnarr 2008).

Pyelonephritis occurs in 2-4% of pregnancies with a 23% rate of recurrence immediately after birth. It occurs most commonly during the second half of pregnancy. It can however occur at any stage in pregnancy, and may develop after an earlier negative screening for bacteriuria (Schnarr 2008).

The greatest risk factor for pyelonephritis is asymptomatic bacteriuria. For example, in one study 24.8% of pregnant women whose asymptomatic bacteriuria was untreated developed pyelonephritis compared to 3.2% of those who were treated (Meads 2011). In another study 30% of pregnant women with bacteriuria developed pyelonephritis compared to 1.8% of those without (Meads 2011).

## Epidemiology of urinary tract infections in pregnancy

Pregnancy predisposes women to developing a UTI; however, a broader risk factor analysis is important in assessing any additional therapeutic measure that might be required, such as drainage in case of renal obstruction or abscess (Grabe 2014).

Certain co-morbidities have been associated with increased risk for UTI during pregnancy. The prevalence of UTI in pregnancy is related closely with socio-economic status. UTIs occur in up to 20% of pregnancies in disadvantaged groups (Vazquez 2003).

Other risk factors include: diabetes mellitus, recurrent UTI, and anatomical abnormalities of the urinary tract. Higher parity, sickle cell disease and age less than 15 years at first UTI have also been thought to be risk factors (Celen 2011, Kodner 2010).

Risk factors associated with recurrent urinary tract infection in general (outside pregnancy) include frequency of intercourse and certain sexual behaviors, secretory status of certain blood groups (Kinane 1982, Kodner 2010).

Çelen Ş, Oruç AS, Karayalçın R, Saygan S, Ünlü S, Polat B, Danişman N. Asymptomatic Bacteriuria and Antibacterial Susceptibility Patterns in an Obstetric Population. *ISRN Obstet Gynecol*. 2011;2011.

Grabe M, Bartoletti R, Bjerklund-Johansen TE, Çek HM, Pickard RS, Tenke P, Wagenlehner F, Wullt B. Guidelines on urological infections. *European Association of Urology*; 2014.

Kinane DF, Blackwell CC, Brettle RP, Weir DM, Winstanley FP, Elton RA. ABO blood group, secretor state, and susceptibility to recurrent urinary tract infection in women. *Br Med J (Clin Res Ed)*. 1982 Jul 3;285(6334):7-9.

Kodner CM, Thomas Gupton EK. Recurrent urinary tract infections in women: diagnosis and management. *Am Fam Physician*. 2010 Sep 15;82(6):638-43.



## Epidemiology of urinary tract infections in pregnancy

### Causative agents

*E. Coli* accounts for the majority of urinary tract infections, as high as 80%. Klebsiella, Enterobacter, and Proteus species, and enterococci infrequently cause uncomplicated cystitis and pyelonephritis. Candida species are an important cause of fungal UTIs especially in immunosuppressed patients and in those with in-dwelling catheters (Minardi 2011).

Group B Streptococcus and the genital mycoplasma *Ureaplasma urealyticum* are rare causes of UTI and are of significance particularly in pregnancy because of their association with chorioamnionitis (Tita 2010).

Minardi D, d' Anzeo G, Cantoro D, Conti A, Muzzonigro G. Urinary tract infections in women: etiology and treatment options. Int J Gen Med. 2011;4:333-43.

Tita ATN, Andrews WW. Diagnosis and management of clinical chorioamnionitis. Clin Perinatol. 2010 Jun;37(2):339-54.



## Percentage distribution of etiologic agents of urinary tract infections among outpatients and inpatients, by pathogen.

Pathogen	Outpatients		Inpatients	
	Percentage with pathogen	Reference(s)	Percentage with pathogen	Reference(s)
<i>Escherichia coli</i>	53–72	[5–9]	17.5–56.7	[5, 6, 8–14]
Coagulase-negative staphylococci	2–7.5	[5, 7]	2.1–12.5	[5, 8–14]
<i>Klebsiella</i> species	6–12	[5–7]	6.2–15.0	[5, 6, 8–14]
<i>Proteus</i> species	4–6	[5–7]	3.8–8.2	[5, 6, 8–13]
<i>Enterobacter</i> species	0.6–5.8	[5–7]	0.9–6.5	[5, 6, 8–14]
<i>Morganella morganii</i>	3.1–4.4	[6]	4.7–6.0	[6]
<i>Citrobacter</i> species	0.1	[5]	0.2–3	[5, 8, 9, 11–13]
<i>Enterococcus</i> species	1.7–12	[5–7]	6.5–15.8	[5, 6, 8–14]
<i>Staphylococcus aureus</i>	2	[5, 7]	1.6–3.5	[5, 8–12, 14]
<i>Staphylococcus saprophyticus</i>	0.2–2	[5, 7]	0.4	[5]
<i>Pseudomonas</i> species	0.1–4	[5–7]	1.3–11	[5, 6, 8–14]
<i>Candida</i> species	...	...	9.4–15.8	[8, 9, 14]
Other	3–8	[5–7]	1.8–26.3	[5, 6, 8, 10–14]

## Symptomatic vs Asymptomatic UTI

This distinction is based on presence of the classical symptoms of dysuria, frequency of urination, urgency, polyuria and suprapubic tenderness, haematuria or costovertebral angle tenderness.

In a symptomatic patient, the diagnosis is made based on typical symptoms of a lower or upper urinary tract infection backed by evidence of bacteriuria.

Asymptomatic bacteriuria is marked by an absence of symptoms, and a culture from a single midstream voided urine specimen yields the same bacterial strain in any trimester in quantitative counts of more than 100,000 colony-forming units/ml.

## Symptomatic urinary tract infections

### Cystitis

This is an infection of the urinary bladder in which a patient may present with dysuria, frequency and lower abdominal or supra-pubic pain, without fever. Pyuria may not be present (Schnarr 2008).

### Pyelonephritis

Pyelonephritis is an infection of the upper urinary tract in which a patient may present with fever, tachycardia, dysuria, abdominal pain, nausea and tenderness over the costo-vertebral angle on the side affected. It can be complicated by septic shock or renal abscess if not properly diagnosed and/or poorly treated (Meads 2011).

Pyelonephritis can also lead to medically-indicated preterm delivery, hospital stay, anaemia or respiratory dysfunction (Meads 2011).

Women who have suffered from pyelonephritis are also prone to another episode either in the same pregnancy or subsequent ones. The recurrence rate has been reported to be almost an eighth of women in the current pregnancy and a similar figure in subsequent pregnancies (Meads 2011).

## Other complications of UTI

Urinary tract infection in pregnancy has been associated with other adverse outcomes for the mother and baby.

In a large, population-based, retrospective study of 199,093 singleton pregnancies, patients with a UTI had significantly higher rates of intra-uterine growth restriction (IUGR), pre-eclampsia, caesarean deliveries and pre-term deliveries, even after controlling for age and parity.

However, no significant differences in 5-min Apgar scores less than 7 or perinatal mortality were noted between the groups.

## Urinary tract infection and preeclampsia

In another large, matched, nested case-control study based on data from the UK General Practice Research Database, 1533 women with UTI were individually matched against 14,236 women without UTI (Minassian 2013).

The odds ratio of preeclampsia increased with UTI and antibiotic administration (adjusted odds ratio 1.22; 1.03–1.45 and 1.28; 1.14–1.44 respectively). There was no such increase in odds ratio observed with respiratory tract infection, implying a role of UTI in preeclampsia (Minassian 2013).

An association between urinary tract infection and preeclampsia was also found in a secondary analysis of the WHO Global Survey on Maternal and Perinatal Health. This study sought to identify risk factors for preeclampsia and eclampsia in low- and middle-income countries (24 countries) in three regions (Bilano 2014).

The findings of the study, involving 276,388 women, showed that pyelonephritis or urinary tract infection increased the risk of preeclampsia (adjusted odds ratio: 1.13; 95%CI 1.03–1.24) (Bilano 2014).

A strength of these two studies is the large population pools from which the findings were drawn.

Bilano VL, Ota E, Ganchimeg T, Mori R, Souza JP. Risk Factors of Pre-Eclampsia/Eclampsia and Its Adverse Outcomes in Low- and Middle-Income Countries: A WHO Secondary Analysis. *PLoS ONE*. 2014 Mar 21;9(3):e91198.

Minassian C, Thomas SL, Williams DJ, Campbell O, Smeeth L. Acute Maternal Infection and Risk of Pre-Eclampsia: A Population-Based Case-Control Study. *PLoS ONE*. 2013 Sep 3;8(9):e73047.

## Urinary tract infection and preeclampsia

Though the exact mechanism through which urinary tract infections may lead to preeclampsia is not clearly understood, some authors hypothesize that urinary tract infections in childhood lead to renal scarring, and while this may be asymptomatic during childhood, consequences become symptomatic during pregnancy (Martinell 1990, Ozlü 2012).

The hypothesis is supported by histopathological findings of focal glomerulosclerosis in children who suffered from urinary tract infections, the same findings observed in women with preeclampsia (Ozlü 2012).

One study of 111 women from a tertiary referral center found a significantly greater incidence of bacteriuria in pregnant women who suffered from UTI in childhood (n=41) than in controls (n=65). Even though the incidence of bacteriuria doubled in those who had healed with scarring during the childhood infection, it failed to find a direct correlation with preeclampsia (Martinell 1990).

The authors postulate that this could be due to better clinical follow-up of the patients. Still, mean blood pressure was significantly higher in the women who had severe renal scarring from UTI in childhood than in controls (Martinell 1990).

Martinell J, Jodal U, Lidin-Janson G. Pregnancies in women with and without renal scarring after urinary infections in childhood. *BMJ*. 1990 Mar 31;300(6728):840-4.

Ozlü T, Alçelik A, Çalışkan B, Dönmez ME. Preeclampsia: is it because of the asymptomatic, unrecognized renal scars caused by urinary tract infections in childhood that become symptomatic with pregnancy? *Med Hypotheses*. 2012 Nov;79(5):653-5.



## Urinary tract infection and chorioamnionitis

A strong association between Group B Streptococcus (GBS) bacteriuria and chorioamnionitis exists. GBS is a less common uropathogen but disproportionately affects pregnant women and the elderly. It deserves careful consideration due to its association with early-onset neonatal disease (Allen 2012).

The risk of chorioamnionitis increases with untreated GBS bacteriuria during pregnancy, and more than 8 vaginal examinations during labour (Allen 2012).

It is thought that GBS B-hemolysin/cytolysin is indispensable in the pathogenesis of GBS bacteriuria and chorioamnionitis. It may achieve this by acting on the epithelial cells, hence causing pore formation in the placento-fetal barrier (Kulkarni 2013, Randis 2014).

The role of another less common pathogen, *Ureaplasma Urealyticum*, in causation of both urinary tract infection and chorioamnionitis is also well documented (Tita 2010).

Allen VM, Yudin MH, Bouchard C, Boucher M, Caddy S, Castillo E, Money DM, Murphy KE, Ogilvie G, Paquet C, van Schalkwyk J, Senikas V, Infectious Diseases Committee, Society of Obstetricians and Gynaecologists of Canada. Management of group B streptococcal bacteriuria in pregnancy. *J Obstet Gynaecol Can.* 2012 May;34(5):482-6.

Kulkarni R, Randis TM, Antala S, Wang A, Amaral FE, Ratner AJ.  $\beta$ -Hemolysin/cytolysin of Group B Streptococcus enhances host inflammation but is dispensable for establishment of urinary tract infection. *PLoS ONE.* 2013;8(3):e59091.

Randis TM, Gelber SE, Hooven TA, Abellar RG, Akabas LH, Lewis EL, Walker LB, Byland LM, Nizet V, Ratner AJ. Group B Streptococcus  $\beta$ -hemolysin/cytolysin breaches maternal-fetal barriers to cause preterm birth and intrauterine fetal demise in vivo. *J Infect Dis.* 2014 Jul 15;210(2):265-73.

Tita ATN, Andrews WW. Diagnosis and management of clinical chorioamnionitis. *Clin Perinatol.* 2010 Jun;37(2):339-54.



## Urinary tract infection and preterm delivery

The risk for preterm labour increases with GBS bacteriuria and additional antibiotics administered for other organisms causing UTI or other infections (Allen 2012).

It is postulated that some microorganisms may produce mediators of inflammation including arachidonic acid, phospholipase A2 and prostaglandins that cause cervical softening and an increase in myometrial free calcium content, leading to uterine contractions, a possible mechanism for preterm labour. B-hemolysin/cytolysin may be responsible for GBS-related preterm delivery (Randis 2012) .

Allen VM, Yudin MH, Bouchard C, Boucher M, Caddy S, Castillo E, Money DM, Murphy KE, Ogilvie G, Paquet C, van Schalkwyk J, Senikas V, Infectious Diseases Committee, Society of Obstetricians and Gynaecologists of Canada. Management of group B streptococcal bacteriuria in pregnancy. *J Obstet Gynaecol Can.* 2012 May;34(5):482-6.

Randis TM, Gelber SE, Hooven TA, Abellar RG, Akabas LH, Lewis EL, Walker LB, Byland LM, Nizet V, Ratner AJ. Group B Streptococcus  $\beta$ -hemolysin/cytolysin breaches maternal-fetal barriers to cause preterm birth and intrauterine fetal demise in vivo. *J Infect Dis.* 2014 Jul 15;210(2):265-73.

## Urinary tract infection and neonatal GBS disease

Heavy colonization of the genital tract with GBS at the time of delivery or rupture of membranes imposes the risk of vertical transmission, which may manifest as pneumonia and sepsis in the neonate (Allen 2012).

In subsequent pregnancies, it is recommended that any woman who has had a newborn affected by GBS receive treatment for any documented Group B Streptococcus in the course of pregnancy (regardless of level of colony-forming units per mL). Treatment should be initiated at the time of labour or rupture of membranes with appropriate intravenous antibiotics for the prevention of early-onset neonatal group B streptococcal disease (Allen 2012).

### Maternal Urinary Tract Infection and Neonatal UTI

There is evidence suggesting an association between maternal UTI during pregnancy and neonatal UTI. Two studies in Iran found a similar significant increase in the prevalence of UTI among neonates born to mothers who had a UTI during pregnancy compared to those whose mothers had no UTI in pregnancy (30% vs 6.8% respectively,  $p=0.001$ ) (Emamghorashi 2012; Khalesi 2014).

Allen VM, Yudin MH, Bouchard C, Boucher M, Caddy S, Castillo E, Money DM, Murphy KE, Ogilvie G, Paquet C, van Schalkwyk J, Senikas V, Infectious Diseases Committee, Society of Obstetricians and Gynaecologists of Canada. Management of group B streptococcal bacteriuria in pregnancy. *J Obstet Gynaecol Can.* 2012 May;34(5):482-6.

Emamghorashi F, Mahmoodi N, Tagarod Z, Heydari ST. Maternal urinary tract infection as a risk factor for neonatal urinary tract infection. *Iran J Kidney Dis.* 2012 May;6(3):178-80.

Khalesi N, Khosravi N, Jalali A, Amini L. Evaluation of maternal urinary tract infection as a potential risk factor for neonatal urinary tract infection. *J Family Reprod Health.* 2014 Jun;8(2):59-62.

## Screening: NICE, USPSTF and SIGN Recommendations.

As we have already seen, asymptomatic bacteriuria increases the risk of pyelonephritis in pregnant women, unlike in healthy non-gravid women. Therefore, routine screening for asymptomatic bacteriuria by midstream urine culture early in pregnancy during antenatal visits is recommended (Meads 2011).

The first booking (and therefore screening) should be around 10 weeks according to NICE guidelines while the U.S. Preventive Services Task Force recommends screening for asymptomatic bacteriuria at 12 to 16 weeks' gestation or at the first prenatal visit, if later (Meads 2011).

Standard quantitative urine culture should be performed routinely at the first antenatal visit. Women with bacteriuria, confirmed by a second urine culture, should be treated and have repeat urine cultures at each antenatal visit until delivery (SIGN 2012).

Women who do not have bacteriuria in the first trimester should not have repeat urine cultures. Dipstick testing should not be used to screen for bacterial UTI at the first or subsequent antenatal visits (SIGN 2012).

Healthcare Improvement Scotland, Scottish Intercollegiate Guidelines Network. Management of suspected bacterial urinary tract infection in adults: A National Clinical Guideline. Edinburgh: Scottish Intercollegiate Guidelines Network (SIGN); 2012.

Meads C. Screening for asymptomatic bacteriuria in pregnancy: External review against programme appraisal criteria for the UK National Screening Committee (UK NSC). UK National Screening Committee; 2011.

## Approach to patient management

It is important to note that symptomatic UTIs may mimic other common discomforts of pregnancy due to physiologic changes.

For example, nausea due to rising hCG levels and frequency of urination due to pressure on the urinary bladder and increased body fluid volume may be normal findings during pregnancy but could also signify a UTI. This means that signs and symptoms alone may be misleading.

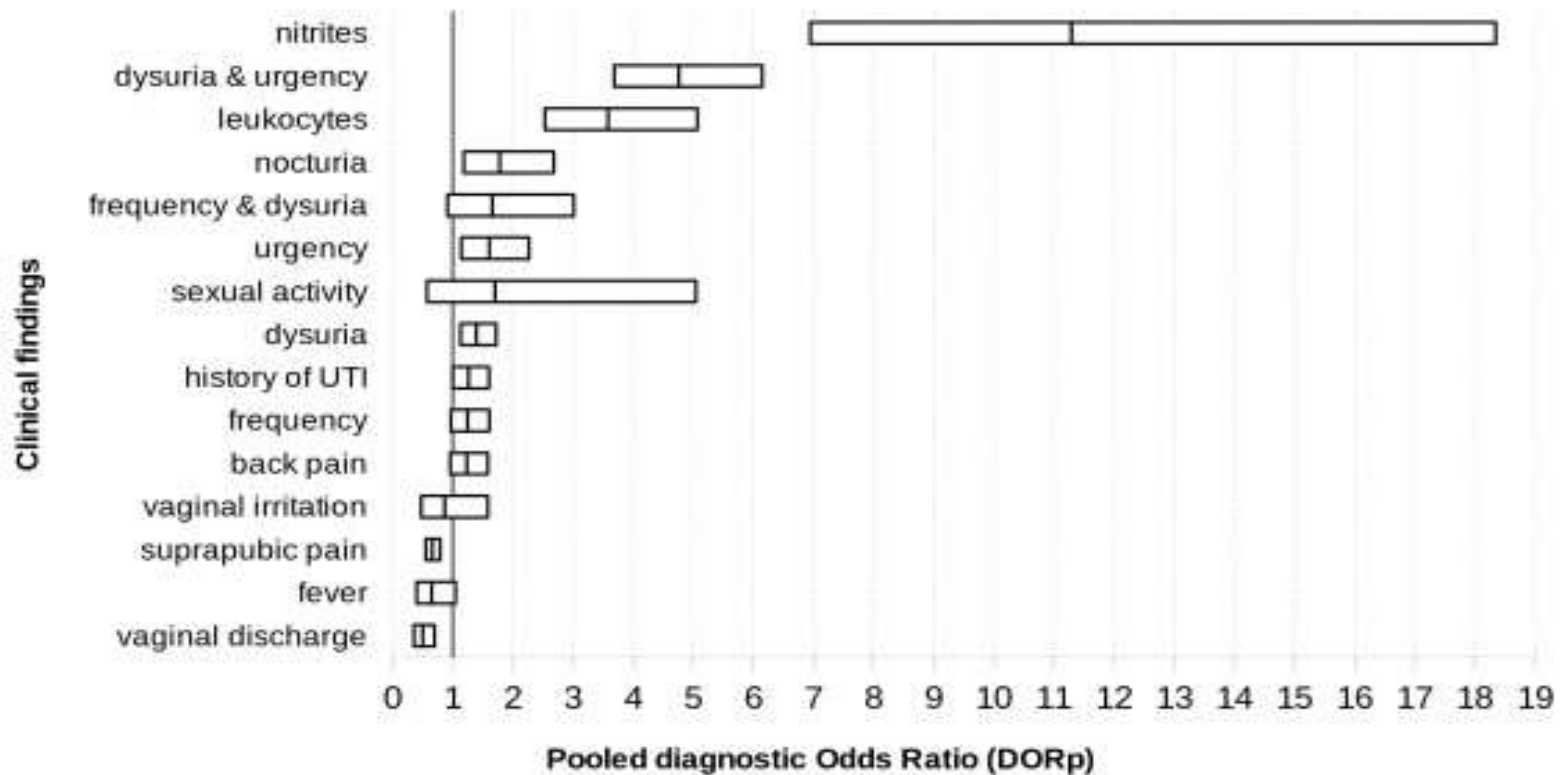
In a patient with cystitis, a history of fever, suprapubic tenderness, frequent micturation and hematuria may be present without evidence of systemic illness. Acute pyelonephritis may present with fever, nausea, anorexia and costovertebral tenderness which is more common on the right than left side.

Medina-Bombardo and colleagues conducted a systematic review and meta-analysis in 2011 to look at the odds of UTI associated with various signs and symptoms. Frequency combined with dysuria, sexual activity, urgency, and nocturia all signaled approximately double the odds of UTI.

Those with dysuria and urgency had a five-fold risk of UTI. However, the pooled odds ratio for UTI associated with presence of nitrites in the urine was 11, making it the most reliable sign of UTI in this pooled study. In the review however, costo-vertebral tenderness, useful in evaluating pyelonephritis or renal abscess, was not evaluated.

Even with no symptoms, because asymptomatic bacteriuria in pregnancy is an important risk factor for pyelonephritis, it should be ruled out.

## Comparative usefulness of clinical findings in the diagnosis of urinary tract infections



## Approach to patient management

In another systematic review and meta-analysis, the authors concluded that no single finding on history or examination was able to independently predict UTI.

Even urinalysis alone is generally insufficient to confirm UTI, as has been shown by Medina-Bombardó et al. and other studies. The authors conclude that urinalysis with a positive nitrite or moderate pyuria and/or bacteriuria can be used to accurately predict UTI in women.

This does not however eliminate the usefulness of history and physical exam. These are still helpful for identifying at-risk groups and differentiating between asymptomatic bacteriuria and symptomatic UTIs in pregnancy and other differential diagnoses.

History and physical examination should give important information leading towards suspicion of a urinary tract infection, which can be confirmed with laboratory testing.

## Approach to patient management

In the evaluation of the patient, predisposing factors such as diabetes mellitus, frequency of sexual intercourse, new sexual partner, spermicide use, previous or recurrent UTI and low socio-economic status should be pursued in order to guide management (Kodner 2010).

Physical examination is important in complimenting the history. An effort should be made to distinguish between a lower and upper urinary tract infection(Schnarr 2008).

Lower urinary tract symptoms such as dysuria and suprapubic tenderness may occur with pyelonephritis, although these are more common with cystitis. Bimanual palpation may elicit tenderness if cystitis is present(Schnarr 2008).

A patient with pyelonephritis will however generally tend to be sicker than one with cystitis. Thus, a patient with pyelonephritis may be febrile (>38 degrees Celsius), tachycardic, and have renal angle as well as suprapubic tenderness (Schnarr 2008).

Combined with history and relevant investigations, examination should also aim to rule out other differential diagnoses or co-morbid states predisposing to UTI(Kodner 2010).

Fetal status should also be assessed during examination(Schnarr 2008).

Kodner CM, Thomas Gupton EK. Recurrent urinary tract infections in women: diagnosis and management. Am Fam Physician. 2010 Sep 15;82(6):638-43.

Schnarr J, Smaill F. Asymptomatic bacteriuria and symptomatic urinary tract infections in pregnancy. Eur J Clin Invest. 2008 Oct;38 Suppl 2:50-7.



## Approach to patient management: *Urine sample collection, transportation and processing*

Laboratory assessment is invaluable and for this, evaluation of an appropriately-collected urine sample is indispensable.

A urine sample should be collected, stored and transported in a manner as to minimize contamination.

Although for minimizing contamination suprapubic aspiration is the gold standard and straight catheterization is second best, both procedures are invasive and laborious.

The clean-catch midstream technique is non-invasive and yields colony counts that correlate well with samples collected using the other two methods.

Cleansing procedures used in this method have no added benefit, however, and are not recommended in routine practice.

Interpretation of results should bear in mind the collection technique, which should be specified on requisition forms.



## Approach to patient management: *Urine sample collection, transportation and processing*

Samples should be plated within two hours after collection, using calibrated loops, which provide information on the number of colony forming units per milliliter as well as isolated colonies for sensitivity testing.

For routine cultures, blood and McConkey's agars should be used. Owing to the fact that the majority of UTIs in outpatients, unlike in hospitalized patients, are due to aerobic and facultative gram-negative bacteria, selective media for gram-positive media should not be used on samples from these patients, or any patient s for whom gram-positive bacteria are suspected but not documented.

## Urinalysis and dipstick testing

Urinalysis entails assessment of the physical properties of color and odor, as well as a chemical and microscopic assessment of the urine sample. For example, a cloudy sample may indicate pyuria, red for hematuria, while a pungent smell is characteristic of UTI (Simerville 2005).

Of the parameters tested in urinalysis, nitrite accurately predicts the presence of UTI. Presence of **nitrites** in the urine is highly specific of nitrate-reducing gram-positive or gram-negative bacteria in sufficient quantities (>10000/ml) but it is not highly sensitive (Simerville 2005).

**Leukocyte esterase**, produced by neutrophils, may occur in pyuria. Leukocyte casts are more common with pyelonephritis than cystitis. Chlamydia and *Ureaplasma Urolyticum* may be associated with pyuria and negative urine cultures (Simerville 2005).

Negative nitrite and leukocyte esterase can be used to rule out UTI in pregnancy. **Urinalysis results should however be looked at in totality in order to exclude other possible differentials** (Schnarr 2008).

For example, even though there seems to be no causal relationship between asymptomatic UTIs and proteinuria except in patients with underlying complications such as diabetes or nephropathy, in pregnancy, evaluation for serious conditions such as preeclampsia should be pursued (Carter 2006). On the other hand, there is sufficient evidence that symptomatic UTIs cause proteinuria and albuminuria (Carter 2006).

Carter JL, Tomson CRV, Stevens PE, Lamb EJ. Does urinary tract infection cause proteinuria or microalbuminuria? A systematic review. Nephrol Dial Transplant. 2006 Jan 11;21(11):3031-7.

Schnarr J, Smaill F. Asymptomatic bacteriuria and symptomatic urinary tract infections in pregnancy. Eur J Clin Invest. 2008 Oct;38 Suppl 2:50-7.

Simerville JA, Maxted WC, Pahira JJ. Urinalysis: a comprehensive review. Am Fam Physician. 2005 Mar 15;71(6):1153-62.

## Urinalysis and dipstick testing

### *Microscopic urinalysis*

Microscopic examination of a centrifuged urine sediment gives invaluable information. Squamous epithelial cells most commonly indicate a contaminated urine sample, while casts help to localize the pathology, and in this case, leukocyte casts are associated with the kidney as the foci, as in pyelonephritis (Simerville 2005).

Triple phosphate crystals which are colorless with a characteristic “coffin lid” appearance, may be a normal finding but are often associated with alkaline urine and UTI (typically associated with *Proteus* species) (Simerville 2005).

Bacteria may also be evident under the microscope through gram staining, and this is significant if there are more than 5 bacterial cells/high power field, which correlates with 100,000 CFU/ml on culture indicative of UTI, in asymptomatic patients.

Though the gram stain gives immediate results, advising empiric therapy, it is insensitive and hence may not detect bacteriuria in the  $10^2$  -  $10^3$  range. Its use is therefore ideal in patients with acute pyelonephritis, invasive UTI, or where immediate information on the etiology is needed (Wilson 2004).

Simerville JA, Macted WC, Pahira JJ. Urinalysis: a comprehensive review. *Am Fam Physician*. 2005 Mar 15;71(6):1153-62.

Wilson ML, Gaido L. Laboratory diagnosis of urinary tract infections in adult patients. *Clin Infect Dis*. 2004 Apr 15;38(8):1150-8.

## Urine culture

Urine culture with two urine specimens is regarded as the gold standard, with a 95% probability that the woman has bacteriuria if positive, compared to 80% probability if only one urine sample is collected and cultured (Schnarr 2008).

However, culture of two separate specimens is only necessary for outpatients being evaluated for recurrent UTIs, treatment failures, or who have complicated UTIs, or for inpatients who develop UTIs. It is unnecessary for the evaluation of outpatients with uncomplicated UTIs (Wilson 2004) .

A culture is positive if a single bacterial species is isolated in a concentration greater than 100,000 colony forming units per millilitre of urine, from the clean-catch midstream collection of two consecutive urine specimens. For urine collected via bladder catheterisation, the threshold is 100 colony forming units of a single species per millilitre (Meads 2011).

Meads C. Screening for asymptomatic bacteriuria in pregnancy: External review against programme appraisal criteria for the UK National Screening Committee (UK NSC). UK National Screening Committee; 2011.

Schnarr J, Smaill F. Asymptomatic bacteriuria and symptomatic urinary tract infections in pregnancy. *Eur J Clin Invest.* 2008 Oct;38 Suppl 2:50-7.

Wilson ML, Gaido L. Laboratory diagnosis of urinary tract infections in adult patients. *Clin Infect Dis.* 2004 Apr 15;38(8):1150-8.

## Complete blood count, procalcitonin, c-reactive protein and ESR

A complete blood count may only generally indicate the presence of infection on account of elevated white blood cells, but does not localize the infection. Its routine use for uncomplicated UTI is therefore not recommended. In the patient with a complicated UTI, it may be necessary to evaluate for severe infection such as sepsis (Bilir 2013).

Of all these markers of infection, many studies have shown the importance of Procalcitonin in better predicting acute pyelonephritis in UTI than white blood cell counts or C-reactive protein (Leroy 2013).

Though most of these studies have been extensively conducted in children, one small study in pregnant women revealed that procalcitonin was significantly higher in pregnant women with asymptomatic bacteriuria (n=30) than in healthy pregnant women, the control group (n=39). Procalcitonin level was normal despite the higher levels of WBC, ESR and CRP levels in the control group (Bilir 2013).

Bilir F, Akdemir N, Ozden S, Cevrioglu AS, Bilir C. Increased serum procalcitonin levels in pregnant patients with asymptomatic bacteriuria. *Annals of Clinical Microbiology and Antimicrobials*. 2013 Sep 5;12(1):25.

Leroy S, Fernandez-Lopez A, Nikfar R, Romanello C, Bouissou F, Gervais A, Gurgoze MK, Bressan S, Smolkin V, Tuerlinckx D, Stefanidis CJ, Vaos G, Leblond P, Gungor F, Gendrel D, Chalumeau M. Association of procalcitonin with acute pyelonephritis and renal scars in pediatric UTI. *Pediatrics*. 2013 May;131(5):870-9.

## Imaging

*Ultrasonography.* Ultrasonography may be useful for routine indications in pregnancy but not for the assessment of asymptomatic UTIs. It is however useful in pyelonephritis if the etiology is obstructive or an abscess is suspected. Ultrasound can also document kidney size and scarring. Ultrasound-guided percutaneous nephrostomy is indicated for renal abscess.

*CT Scan and MRI.* These are the most precise methods for identifying bacterial interstitial nephritis and micro-abscesses within the kidney, as well as perinephric abscesses, emphysematous pyelonephritis and renal papillary necrosis. Their application is more relevant in the patient with urosepsis.

## Treatment of asymptomatic bacteriuria

Left untreated, asymptomatic bacteriuria can lead to acute pyelonephritis in 30% of the cases. Treatment is also indicated for preventing low birth weight; however, the role of treatment in reducing preterm delivery is questionable (Guinto 2010).

Treatment of any bacteriuria with colony counts  $\geq 100,000$  CFU/mL in pregnancy using appropriate antibiotics is an accepted and recommended strategy (Allen 2012).

For urine collected via bladder catheterisation, the threshold is 100 colony forming units of a single species per milliliter (Meads 2011).

Allen VM, Yudin MH, Bouchard C, Boucher M, Caddy S, Castillo E, Money DM, Murphy KE, Ogilvie G, Paquet C, van Schalkwyk J, Senikas V, Infectious Diseases Committee, Society of Obstetricians and Gynaecologists of Canada. Management of group B streptococcal bacteriuria in pregnancy. *J Obstet Gynaecol Can.* 2012 May;34(5):482-6.

Guinto VT, De Guia B, Festin MR, Dowswell T. Different antibiotic regimens for treating asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev.* 2010;(9):CD007855. .

Meads C. Screening for asymptomatic bacteriuria in pregnancy: External review against programme appraisal criteria for the UK National Screening Committee (UK NSC). UK National Screening Committee; 2011.

## Antibiotic choice for asymptomatic bacteruria

While the causative organisms remain consistent across settings and locations, antibiotic susceptibility and sensitivity patterns may differ from one locality to another, and subject to change over time, depending on resistance patterns (Smaill 2007).

Equally of note is the fact that while susceptibility can be determined in the laboratory, factors such as dosing frequency, duration of treatment, severity of side effects and hence tolerability are important considerations in selecting the optimal treatment regimen. The risk of teratogenicity also limits the use of some antibiotics (Guinto 2010).

Therefore, despite the general agreement on the need for treatment of asymptomatic bacteriuria, evidence on the safest, most effective antibiotic regimen has been lacking. Authors of a Cochrane review recommend that, in treatment of asymptomatic bacteriuria, the antibiotic choice should be made based on factors such as cost, local availability and side effects in the selection of the best treatment option (Guinto 2010).

Antibiotics chosen for asymptomatic bacteriuria and symptomatic UTI should have a good maternal and fetal safety profile, excellent efficacy and low resistance rates in a given population (Schnarr 2008).

Guinto VT, De Guia B, Festin MR, Dowswell T. Different antibiotic regimens for treating asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev.* 2010;(9):CD007855.

Schnarr J, Smaill F. Asymptomatic bacteriuria and symptomatic urinary tract infections in pregnancy. *Eur J Clin Invest.* 2008 Oct;38 Suppl 2:50-7.



## Duration of treatment

In a Cochrane review, comparing the effect of shorter- vs longer duration of treatment, findings suggest that a single-dose regimen may be less effective compared to a seven-day regimen. The authors therefore recommend the use of the standard seven-day regimen as currently no evidence exists comparing three-, four- or five-day regimens with 7-day regimens.

## Treatment regimens for asymptomatic bacteriuria and cystitis in pregnancy

Antibiotics	Duration of therapy	Comments
Nitrofurantoin (Macrobid®) 100 mg	q12 h, 3-5 days	Avoid in G6PD deficiency
Amoxicillin 500 mg	q8 h, 3-5 days	Increasing resistance
Co-amoxicillin/clavulanate	500 mg q12 h, 3-5 days	
Cephalexin (Keflex®) 500 mg	q8 h, 3-5 days	Increasing resistance
Fosfomycin 3 g	Single dose	
Trimethoprim	q12 h, 3-5 days	Avoid trimethoprim in first trimester/term

## Recommendations in treatment of symptomatic UTI

In pregnant women who present symptoms of an UTI, a single urine sample for culture should be taken before empiric antibiotic treatment is started.

Local guidance on bacterial resistance patterns should be sought to aid in the choice of antibiotic for pregnant women. A seven day course of treatment is normally sufficient.

Given the risks of symptomatic bacteriuria in pregnancy, a urine culture should be performed seven days after completion of antibiotic treatment as a test of cure.

Do not prescribe trimethoprim for pregnant women with established folate deficiency, low dietary folate intake, or women taking other folate antagonists.

In women with pyelonephritis whose symptoms are mild and for whom close follow-up is possible, antibiotics can also be given on an outpatient basis.

## Treatment of symptomatic UTI

### Pyelonephritis

The most recent Cochrane review of various antibiotic regimens for the treatment of pyelonephritis found no significant differences relating to cure rates, recurrence, incidence of preterm delivery, admission to neonatal intensive care unit, need for antibiotic change and incidence of prolonged pyrexia for various antibiotic regimens in most of the included studies, except that cefuroxime achieved better cure rates compared to cephadrine (41/52 vs 29/49) and resulted in fewer recurrences (11/52 vs 20/49) (Vazquez 2003).

Based on limited data, it is therefore difficult to identify one particular antibiotic as being superior to the rest. However, evidence on effects of treatment by setting suggest that while outpatient treatment resulted in increased gestational age at delivery, babies born to inpatients had a significantly bigger birthweight (Vazquez 2003).

It is suggested that for pyelonephritis after 24 weeks of gestation, the patient should be put on intravenous antibiotics until they have been fever-free for 48 hours, at which time oral treatment should be instituted, for a duration of 10-14 days (Schnarr 2008).

## Treatment regimens for pyelonephritis in pregnancy

<b>Antibiotics</b>	<b>Dose</b>
Ceftriaxone	1-2 g IV or IM q24 h
Aztreonam	1 g IV q8-12 h
Piperacillin-tazobactam	3.375-4.5 g IV q6 h
Cefepime	1 g IV q12 h
Imipenem-cilastatin	500 mg IV q6 h
Ampicillin +	2 g IV q6 h
Gentamicin	3-5 mg/kg/day IV in 3 divided doses

## Management of Urosepsis

Urosepsis is the severest form of UTI, with the most serious potential adverse outcomes, including death. Treatment is usually continued for 14-21 days and failure to respond to treatment should trigger further evaluation for urinary tract obstruction or abscess, which necessitates drainage. Apart from antibiotic therapy, other measures must be undertaken to avoid the risk of septic shock. These measures include:

Hemodynamic support: The goal is to achieve and maintain adequate tissue perfusion. IV fluids are administered initially and vasopressor medication if IV fluids fail.

Parameters of adequate perfusion include: pulmonary capillary wedge pressure at 12-16 mmHg or central venous pressure at 8-12 cm H<sub>2</sub>O. Urine output rate >0.5 mL/kg/hr; mean arterial blood pressure >65 mmHg (systolic blood >90 mmHg) and a cardiac index of greater than or equal to 4 L/min/ m<sup>2</sup>

Respiratory support: Hypoxemia, hypercapnea, altered sensorium or respiratory muscle fatigue signal the need for ventilatory support.

Metabolic support: In the initial few days, the desired blood glucose levels should be <150mg/dl. Euglycemia is targeted later.

## Notes on specific antibiotic classes and pregnancy

A number of drugs are excreted through the kidneys, making a number of them theoretically useful in treating UTIs based on the potential concentration in the renal system. However, the pregnant state prohibits the use of an antibiotic where safety to the fetus or newborn is a concern. Where the benefits outweigh the risks, the antibiotic can still be used, in the face of no other alternative.

**Trimethoprim and Sulfonamides:** Sulfonamides have the risk of neonatal jaundice if sufficient serum levels are present at the time of delivery.

The addition of trimethoprim increases activity but trimethoprim inhibits folate synthesis, which is crucial for preventing neural tube deformities.

Trimethoprim alone or Trimethoprim sulfamethoxazole (TMP-SMX) combinations should be avoided in the first trimester as well as after 32 weeks gestation.

**Quinolones:** Several studies have not found increased risk of major malformations, fetal musculoskeletal defects, spontaneous abortions, prematurity, intrauterine growth retardation, or postnatal disorders.

## Notes on specific antibiotic classes and pregnancy

**Ampicillin:** semi-synthetic penicillins are particularly active against enterococcus. Ampicillin shows high levels of urinary concentration, hence its continued use even with emerging resistance.

Addition of clavulanic acid, a B-lactamase inhibitor, confers activity against B-lactamase producing E. Coli.

**Cephalosporins:** are considered generally safe to use during pregnancy, but the high protein-binding capacity of ceftriaxone may displace bilirubin if given a day prior to delivery, predisposing neonatal jaundice especially in premature infants.

Cephalexin was associated with major defects in a Michigan Medicaid surveillance study although a Hungarian case-control study did not find teratogenicity.

**Nitrofurantoin:** FDA category B drug. It is specific for urinary tract infections. Avoid in G-6-PD deficiency



## Prevention of recurrent urinary tract infections in pregnancy

Postcoital prophylaxis should be considered in pregnant women with a history of frequent UTIs before the onset of pregnancy, to reduce their risk of UTI (Grabe 2014).

In one Cochrane review, close monitoring and a daily dose of nitrofurantoin combined with high clinic attendance rate was associated with a significant reduction in asymptomatic bacteriuria (Schneeberger 2012).

Apart from pharmacological interventions, non-pharmacological (cranberry products, acupuncture, probiotics and behavioural modifications) interventions have also been used in the past for prevention of recurrent urinary tract infections in pregnancy. However, the best approach is currently not known (Schneeberger 2012).

Grabe M, Bartoletti R, Bjerklund-Johansen TE, Çek HM, Pickard RS, Tenke P, Wagenlehner F, Wullt B. Guidelines on urological infections. European Association of Urology; 2014.

Schneeberger C, Geerlings SE, Middleton P, Crowther CA. Interventions for preventing recurrent urinary tract infection during pregnancy. Cochrane Database Syst Rev. 2012;11:CD009279.

## Summary

Asymptomatic bacteriuria in pregnancy predisposes women to pyelonephritis and cystitis. These urinary tract infections in pregnancy are associated with chorioamnionitis, preeclampsia, low birth weight and neonatal infection.

Screening for bacteriuria with urine culture is recommended early in pregnancy, between 10-16 weeks or at first booking if later.

The use of dipstick testing to screen for bacterial UTI at the first or subsequent antenatal visits is not recommended.

Treatment of any bacteriuria with colony counts  $\geq 100,000$  CFU/mL in pregnancy with appropriate antibiotics is recommended.

Treatment should be based on culture and sensitivity findings, especially for asymptomatic bacteriuria.

For symptomatic UTI, empiric treatment with broad-spectrum antibiotics with activity against E.Coli should be chosen on a background of cost, safety in pregnancy and availability.

Longer duration (7 days) of treatment is better than single dose treatment.

## Implications for future research

- The NICE Clinical Guideline on antenatal care (NICE 2008) includes a recommendation that “RCTs are needed to confirm the beneficial effect of screening for asymptomatic bacteriuria”.
- An economic model on the cost effectiveness of screening for asymptomatic bacteriuria using culture, dipstick and dipslide is required, taking into account the more recent evidence on pyelonephritis and diagnostic accuracy of dipslides.
- Additional studies are needed to investigate other antibiotics or antibiotic combinations and other shorter treatment schedules (three- or five-day regimens) other than penicillins and cephalosporins, in view of emerging drug resistance.
- There is a need for future studies to evaluate the most promising antibiotics, in terms of class, timing, dose, acceptability, and maternal and neonatal outcomes and costs.
- Randomised controlled trials, comparing different pharmacological and non-pharmacological interventions, are necessary to investigate potentially effective interventions to prevent recurrent urinary tract infection (RUTI) in women who are pregnant.

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