CLINICAL CONSENSUS **EVIDENCE MAP**

SUPPLEMENTAL DIGITAL CONTENT

CLINICAL CONSENSUS NUMBER 5

**Evidence Map**

Urinary Tract Infections in Pregnant Individuals

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| **Asymptomatic Bacteriuria Diagnosis and Treatment** | | |
| **RECOMMENDATION STATEMENTS** | | |
| Diagnosis:  1. Clinicians should screen for asymptomatic bacteriuria (ASB) with a urine culture once at a visit early in prenatal care. There is insufficient evidence to recommend for or against repeat screening during pregnancy after a negative initial culture.  Treatment:  2. Clinicians should prescribe a 5–7-day course of targeted antibiotics to treat asymptomatic bacteriuria with colony counts ≥ 100,000 CFU/mL. There is insufficient evidence to recommend for or against repeat screening after appropriate treatment of an initial episode of ASB. | | |
| **SUPPORTING EVIDENCE** | | |
| **Related Guidelines**  American College of Obstetricians and Gynecologists (ACOG) 2020 Committee Opinion No. 797 Prevention of Group B Streptococcal Early-Onset Disease in Newborns: Regardless of planned mode of birth, all pregnant women should undergo antepartum screening for GBS at 36 0/7–37 6/7 weeks of gestation, unless intrapartum antibiotic prophylaxis for GBS is indicated because of GBS bacteriuria during the pregnancy or because of a history of a previous GBS-infected newborn. This new recommended timing for screening provides a 5-week window for valid culture results that includes births that occur up to a gestational age of at least 41 0/7 weeks.  Infectious Diseases Society of America (IDSA) 2019 Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: In pregnant women, we recommend screening for and treating ASB (strong recommendation, moderate-quality evidence). In pregnant women with ASB, we suggest 4–7 days of antimicrobial treatment rather than a shorter duration (weak recommendation, low-quality evidence).  United States Preventive Services Task Force (USPSTF) 2019 Recommendation Statement: The USPSTF recommends screening pregnant persons for asymptomatic bacteriuria using urine culture. (B recommendation) The USPSTF recommends against screening for asymptomatic bacteriuria in nonpregnant adults. (D recommendation) | | |
| **Category I** | **Category II** | **Category III** |
| Systematic Reviews/Meta-Analyses:  Wang 2020 suggests that single-dose Fosfomycin tromethamine produces equivalent clinical outcomes to comparator antibiotics in terms of clinical efficacy and microbiological efficacy; it is therefore clinically effective and safe for women with uncomplicated urinary tract infection (UTI) and pregnant women with UTI or ASB, and has higher patient compliance  Smaill 2019 antibiotic treatment may be elective in reducing the risk of pyelonephritis in pregnancy, but our confidence in the elect estimate is limited given the low certainty of the evidence; there may be a reduction in preterm birth and low birthweight with antibiotic treatment, consistent with theories about the role of infection in adverse pregnancy outcomes, but again, the confidence in the elect is limited given the low certainty of the evidence  Widmer 2015 a single-dose regimen of antibiotics may be less effective than a short-course (four- to seven-day) regimen, but more evidence is needed from large trials measuring important outcomes, such as cure rate; women with asymptomatic bacteriuria in pregnancy should be treated by the standard regimen of antibiotics until more data become available testing seven-day treatment compared with shorter courses of three- or five-day regimens  Randomized Controlled Trial:  Kazemier 2015 in women with an uncomplicated singleton pregnancy, asymptomatic bacteriuria is not associated with preterm birth; asymptomatic bacteriuria showed a significant association with pyelonephritis, but the absolute risk of pyelonephritis in untreated asymptomatic bacteriuria is low | Kasparek 2021 a hemoglobinopathy trait increased the risk of adverse maternal outcomes but did not increase adverse neonatal outcomes  Langermans 2021 if recommendations remain to screen for  asymptomatic bacteriuria at least once during pregnancy,  this study indicates that the moment of testing (first vs.  second trimester) has no clinical impact on obstetrical  outcomes  O’Leary 2020 there is a high prevalence of positive urine dipstick and contaminated culture in asymptomatic pregnant women; body mass index (BMI) is a risk factor for urine culture contamination and further research into this topic is essential given trends in obesity worldwide  Schneeberger 2018 the overall prevalence of ASB was low in pregnant women with and women without diabetes mellitus (DM) or gestational diabetes mellitus (GDM); neither ASB nor UTI did differ significantly between the groups; study data discourage a routine ASB screen and treat policy in pregnant women with DM or GDM  Schneeberger 2013 in pregnant women, the contamination rate of midstream samples is comparable with the contamination rates of morning and clean-catch samples; the quantity of contaminants varied among the three samples collected by one woman; these results show that more complex, unpractical, and time-consuming morning and clean-catch samples are not superior; therefore, we recommend a midstream sample to assess bacteriuria in pregnant women  McDonnold 2012 majority of cases of pyelonephritis that occur prior to 12 weeks are among women with no prenatal care; although the United States Preventive Services Task Force guidelines advise screening urine culture at 12 to 16 weeks, these findings support initiating screening at an earlier gestational age  Tita 2007 contrary to other recent reports, perinatal mortality and preeclampsia are not increased in carriers of sickle cell trait or hemoglobin C  Hill 2005 the incidence of pyelonephritis has remained low in the era of routine prenatal screening for asymptomatic bacteriuria; first-trimester pyelonephritis accounts for over 1 in 5 antepartum cases; gram-positive uropathogens are found more commonly as pregnancy progresses; maternal complications continue, but poor obstetrical outcomes are rare  Baill 1990 sickle trait was associated with a significant increase in bacteriuria (13.0% vs 9.0%) and pyelonephritis (2.1% vs 1.4%); no difference was seen in birthweight between the two groups | American Academy of Pediatrics (AAP) and ACOG 2017 provides guidelines for perinatal care included organization of perinatal health care, inpatient perinatal care services, quality improvement and patient safety, maternal and neonatal interhospital transfer, pre-pregnancy care, antepartum care, intrapartum care of the mother, postpartum care of the mother, medical and obstetric complications, care of the newborn, neonatal complications and management of high-risk infants, perinatal infections, infection control  Macejko 2007 because pyelonephritis during pregnancy may cause significant morbidity for both the mother and the fetus, proper screening and treatment of bacteriuria, regardless of the presence of symptoms, is necessary to prevent complications |

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| **Urinary Tract Infection Diagnosis and Treatment** | | |
| **RECOMMENDATION STATEMENTS** | | |
| Diagnosis:  3. Clinicians should evaluate patients with symptoms of urinary tract infection with a urine culture. Urinary tract infection should be suspected based on the presence of symptoms, may be supported by a positive urinalysis, and is confirmed by urine culture showing ≥100,000 CFU/mL.  Treatment:  4. Clinicians should treat UTIs in pregnant individuals with a 5-7 day course of a targeted antibiotic. If empiric therapy is started before culture and sensitivity results are available, amoxicillin/ampicillin regimens should be avoided due to high rates of resistance in E. coli to these antibiotics in most areas.  5. There is insufficient evidence to guide management after UTI treatment in pregnancy. Clinicians may consider repeating a urine culture 1-2 weeks after completing treatment for UTI or evaluating only if symptoms recur.  6. There is insufficient evidence to guide management after recurrent UTI in pregnancy. After treating a recurrent acute infection, clinicians may consider initiating antimicrobial urinary suppression for the remainder of the pregnancy, preferably using a lower single daily dose of an antibacterial drug to which the bacterium isolated was susceptible. | | |
| **SUPPORTING EVIDENCE** | | |
| **Related Guidelines**  Brazilian Society of Infectious Diseases (SBI), Brazilian Federation of Gynecology and Obstetrics Associations (FEBRASGO), Brazilian Society of Urology (SBU) and Brazilian Society of Clinical Pathology/Laboratory Medicine (SBPC/ML) 2020 Joint Report: All cases of significant bacteriuria (≥105 CFU/mL in middle stream sample) should be treated with antimicrobials considering safety and susceptibility profile. In women with typical symptoms of cystitis, dipsticks are not necessary for diagnosis. Urine cultures should be collected in pregnant women, recurrent UTI, atypical cases, and if there is suspicion of pyelonephritis. First line antimicrobials for cystitis are Fosfomycin trometamol in a single dose and nitrofurantoin, 100 mg every 6 hours for five days. Second line drugs are cefuroxime or amoxicillin-clavulanate for seven days. During pregnancy, amoxicillin and other cephalosporins may be used, but with a higher chance of therapeutic failure. In recurrent UTI, all episodes should be confirmed by urine culture. Treatment should be initiated only after urine sampling and with the same regimens indicated for isolated episodes. Prophylaxis options of recurrent UTI are behavioral measures, nonantimicrobial and antimicrobial prophylaxis. In pregnant women, options are cephalexin, 250–500 mg and nitrofurantoin, 100 mg (contraindicated after 37 weeks of pregnancy).  American Urological Association (AUA), Canadian Urological Association (CUA), Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) 2019 (Anger 2019) Guideline Recurrent Uncomplicated Urinary Tract Infections in Women: This guideline does not apply to pregnant women. In women who experience UTIs temporally related to sexual activity, antibiotic prophylaxis taken before or after sexual intercourse has been shown to be effective and safe. This use of antibiotics is associated with a significant reduction in recurrence rates.  Society of Obstetricians and Gynaecologists of Canada (SOGC) 2010 Practice Guideline Recurrent urinary tract infection: Pregnant women at risk of recurrent urinary tract infection should  be offered continuous or post-coital prophylaxis with nitrofurantoin or cephalexin, except during the last 4 weeks of pregnancy. (II-1B)  American College of Physicians (ACP) 2001 Best Practice No 167: the laboratory diagnosis of urinary tract infection: The optimal method for screening is urine culture, which should be repeated to exclude contamination. Reagent strip testing only is less effective in identifying those patients who will develop pyelonephritis, but it does offer considerable cost savings. | | |
| **Category I** | **Category II** | **Category III** |
| Systematic Reviews/Meta-Analyses:  Shulz 2022 A total of 1063 women from nine studies were included. The primary outcome was the microbiologic cure attested by urine culture. When compared with the multiple-day use of antibiotics, the single-dose treatment has shown statistically similar results in reaching culture cure (odds ratio 1.02, 95% confidence interval 0.73–1.44).  Emami 2020 increasing resistance rate in UTI-related agents is a risk factor that endangers both mother and fetus; health care providers should consider screening as the radical part of infection control strategies; due to low resistance rate to nitrofurantoin, this drug can be a good choice for UTI treatment in pregnancies, but it should use with caution  Wang 2020 suggests that single-dose Fosfomycin tromethamine produces equivalent clinical outcomes to comparator antibiotics in terms of clinical efficacy and microbiological efficacy; it is therefore clinically effective and safe for women with UTI and pregnant women with UTI or ASB, and has higher patient compliance  Schneeberger 2015 a daily dose of nitrofurantoin and close surveillance has not been shown to prevent recurrent UTI (RUTI) compared with close surveillance alone; a significant reduction of ASB was found in women with a high clinic attendance rate and who received nitrofurantoin and close surveillance; there was limited reporting of both primary and secondary outcomes for both women and infants; no conclusions can be drawn regarding the optimal intervention to prevent RUTI in women who are pregnant; randomized controlled trials comparing different pharmacological and non-pharmacological interventions are necessary to investigate potentially effective interventions to prevent RUTI in women who are pregnant  Vazquez 2011 although antibiotic treatment is effective for the cure of urinary tract infections, there are insufficient data to recommend any specific drug regimen for treatment of symptomatic urinary tract infections during pregnancy; all the antibiotics studied were shown to be very effective in decreasing the incidence of the different outcomes; complications were very rare; all included trials had very small sample sizes to reliably detect important differences between treatments; future studies should evaluate the most promising antibiotics, in terms of class, timing, dose, acceptability, maternal and neonatal outcomes and costs  Albert 2004 continuous antibiotic prophylaxis for 6-12 months reduced the rate of UTI during prophylaxis when compared to placebo; after prophylaxis two studies showed no difference between groups; there were more adverse events in the antibiotic group; one randomized controlled trial compared postcoital versus continuous daily ciprofloxacin and found no significant difference in rates of UTIs, suggesting that postcoital treatment could be offered to woman who have UTI associated with sexual intercourse | Philips 2020 study results do not indicate an increased risk of adverse pregnancy outcome after Fosfomycin exposure during early pregnancy  Mannucci 2019 study data, based on a large number of pregnancies, confirm the safety use of Fosfomycin use in pregnancy  Hansen 2016 first trimester trimethoprim-sulfonamide (TMPSUL) exposure was not associated with a higher risk of the congenital anomalies studied, compared to exposure to penicillin’s and/or cephalosporins, or no exposure to antibacterial  Goldberg 2013 first trimester exposure to nitrofurantoin was not associated with increased risk for total major congenital malformations or with specific malformations  Crider 2009 penicillin’s, erythromycins, and cephalosporins, although used commonly by pregnant women, were not associated with many birth defects; sulfonamides and nitrofurantoin’s were associated with several birth defects, indicating a need for additional scrutiny  Naber 2008 despite wide cross-country variability of bacterial susceptibility/resistance rates to the other antimicrobials tested, Fosfomycin, mecillinam, and nitrofurantoin have preserved their in vitro activity in all countries investigated  Zhanel 2006 study reports higher rates of antibiotic resistance in US versus Canadian outpatient urinary isolates of E. coli and demonstrates the continuing evolution of resistance to antimicrobial agents  Aslan 2003 voiding symptoms during pregnancy are highly prevalent; these symptoms worsen as the pregnancy progresses | Chu 2018 interpreting the probability of urinary tract infection based on symptoms and testing allows for greater accuracy in diagnosis of urinary tract infection, decreasing overtreatment and encouraging antimicrobial stewardship  Glaser 2015 antimicrobial choice in pregnancy should reflect safety for both the mother and the fetus; pregnant patients with cystitis should be treated for 3 to 7 days; these patients should be followed with serial cultures throughout pregnancy, and prophylactic antimicrobial therapy should be considered; pregnant patients with pyelonephritis should initially be admitted for intravenous antimicrobial therapy and receive a total of 7 to 14 days of culture-directed treatment; these patients should be followed with serial cultures throughout pregnancy, and prophylactic antimicrobial therapy should be strongly considered  McCormick 2008 acute cystitis and pyelonephritis demand full assessment and treatment, with early involvement of other specialists in severe or systemic infection; all women should be reviewed to confirm post-treatment urine sterility; empirical antimicrobial treatments will occasionally be required but any decision to treat should be re-evaluated once culture and sensitivity reports are available; when choosing an antimicrobial, the pharmacokinetics and bioavailability of the individual drug in pregnancy must be considered along with the resistance profiles of microorganisms in the local antenatal population; it is also vital to use treatments with an established safety profile and, most importantly, without teratogenetic risks  Lee 2008 existing data indicate that exposure to penicillin’s, cephalosporins, fluoroquinolones, nitrofurantoin, or phenazopyridine during pregnancy is not associated with increased risk of fetal malformations; trimethoprim sulfamethoxazole should be avoided, if possible, during the first trimester of pregnancy because of the antifolate effect associated with neural tube defects  FitzGerald 2007 provides an overview of the lower urinary tract during pregnancy, including considerations of symptoms of urinary frequency; nocturia and incontinence; changes in bladder support; and the occurrence of urinary retention, a urologic emergency  Simerville 2005 a complete urinalysis includes physical, chemical, and microscopic examinations; midstream clean collection is acceptable in most situations, but the specimen should be examined within two hours of collection; cloudy urine often is a result of precipitated phosphate crystals in alkaline urine, but pyuria also can be the cause; a strong odor may be the result of a concentrated specimen rather than a urinary tract infection; dipstick urinalysis is convenient, but false-positive and false-negative results can occur; specific gravity provides a reliable assessment of the patient’s hydration status; microhematuria has a range of causes, from benign to life threatening; glomerular, renal, and urologic causes of microhematuria often can be differentiated by other elements of the urinalysis; although transient proteinuria typically is a benign condition, persistent proteinuria requires further work-up; uncomplicated urinary tract infections diagnosed by positive leukocyte esterase and nitrite tests can be treated without culture |

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| **Pyelonephritis Diagnosis and Treatment** | | |
| **RECOMMENDATION STATEMENTS** | | |
| Diagnosis:  7. Pyelonephritis should be suspected in the presence of fever ≥ 38.0 C and urine studies suggesting UTI, with additional symptoms of upper genitourinary tract infection [such as flank pain or costovertebral angle tenderness] supporting the diagnosis.  Treatment:  8. Clinicians should initially manage pyelonephritis in pregnancy in the inpatient setting. Empiric antibiotic therapy should have adequate renal tissue penetration and be targeted against most likely pathogens. Antibiotic therapy should be adjusted as needed based on urine culture and sensitivity. Parenteral antibiotics should be continued until the patient is clinically improving. Patients should complete a total of 14 days of antibiotic therapy.  9. There is insufficient evidence to guide management after treatment of pyelonephritis in pregnancy. Clinicians may consider suppressive therapy for the remainder of the pregnancy as for recurrent UTI. | | |
| **SUPPORTING EVIDENCE** | | |
| **Category I** | **Category II** | **Category III** |
| Systematic Reviews/Meta-Analyses:  Moradi 2021 the prevalence of E. coli and extended‑spectrum β‑lactamase (ESBL) E. coli is high in pregnant women; the overuse of antibiotics was higher in European and Asian pregnant women than other continents  Vazquez 2011 although antibiotic treatment is effective for the cure of urinary tract infections, there are insufficient data to recommend any specific drug regimen for treatment of symptomatic urinary tract infections during pregnancy; all the antibiotics studied were shown to be very effective in decreasing the incidence of the different outcomes; complications were very rare; all included trials had very small sample sizes to reliably detect important differences between treatments; future studies should evaluate the most promising antibiotics, in terms of class, timing, dose, acceptability, maternal and neonatal outcomes and costs  Randomized Controlled Trials:  Sanchez-Ramos 1995 daily single-dose intravenous ceftriaxone is as effective as multiple-dose cefazolin in the treatment of patients with acute pyelonephritis during pregnancy  Van Dorsten 1987 results suggest that more aggressive management of acute pyelonephritis in pregnancy may be indicated and that suppressive therapy cannot compensate for inappropriate in-hospital management | Denoble 2022 in an age of increasing antibiotic resistance, more than one-half of pregnant women with bacteriuria experience at least 1 infection with an antibiotic-resistant organism; these resistance patterns have a real clinical impact as pregnant women with antibiotic-resistant gram-negative lower urinary tract infections have an estimated 2- to 3-fold increased odds of developing pyelonephritis  Artero 2013 pregnant women with pyelonephritis received inappropriate empirical antimicrobial treatment (IEAT) in a small but significant number of cases; amoxicillin-clavulante and cephalosporines were adequate in most cases; more studies are needed to define the clinical impact of IEAT on prognosis  Rizvi 2011 regular screening should be done for the presence of symptomatic or asymptomatic bacteriuria in pregnancy; for empirical treatment cefoperazone-sulbactum can be recommended, which is a safe drug, covering both gram positive and gram negative organisms and with a good sensitivity  Greer 2008 the patients with ampicillin-resistant organisms were more likely to be older and multiparous; there were no significant differences in hospital course (length of stay, days of antibiotics, extended care unit (ECU) admission, or readmission); patients with ampicillin resistant organisms did not have higher complication rates (anemia, renal dysfunction, respiratory insufficiency, or preterm birth); a majority of uropathogens were ampicillin resistant, but no differences in outcomes were observed in these patients  Melzer 2007 mortality following bacteremia infection caused by ESBL producing E. coli was significantly higher than non-ESBL producing E. coli  Chen 2006 in the management of complicated acute pyelonephritis (APN), routine cultures of blood should be reevaluated  Hill 2005 the incidence of pyelonephritis has remained low in the era of routine prenatal screening for asymptomatic bacteriuria; first-trimester pyelonephritis accounts for over 1 in 5 antepartum cases; gram-positive uropathogens are found more commonly as pregnancy progresses; maternal complications continue, but poor obstetrical outcomes are rare  Wing 1998 there are no significant differences in clinical response to antimicrobial therapy or birth outcomes among subjects treated with ampicillin and gentamicin, cefazolin, or ceftriaxone for acute pyelonephritis in pregnancy before 24 weeks' gestation  Sandberg 1991 results show that long-term low-dose antimicrobial prophylaxis is highly effective in this population at high risk of recurrent acute pyelonephritis  Wing 2014 maternal complications of anemia, septicemia, acute pulmonary insufficiency, and acute renal dysfunction are commonly encountered, and the risk of preterm birth is higher in the obstetric population with pyelonephritis than the baseline obstetric populatio | Glaser 2015 antimicrobial choice in pregnancy should reflect safety for both the mother and the fetus; pregnant patients with cystitis should be treated for 3 to 7 days; these patients should be followed with serial cultures throughout pregnancy, and prophylactic antimicrobial therapy should be considered; pregnant patients with pyelonephritis should initially be admitted for intravenous antimicrobial therapy and receive a total of 7 to 14 days of culture-directed treatment; these patients should be followed with serial cultures throughout pregnancy, and prophylactic antimicrobial therapy should be strongly considered  Jolley 2010 when acute pyelonephritis is diagnosed, conventional treatment includes intravenous fluid and parenteral antibacterial administration; there are limited data by which to assess the superiority of one antibacterial regimen over the other in terms of efficacy, patient acceptance and safety for the developing fetus; however, it is important to consider antimicrobial resistance patterns in the local community when choosing an agent; moreover, there are growing public health concerns regarding antimicrobial resistance to commonly prescribed medications for urinary tract infections in pregnancy; there is a small body of evidence to support the ambulatory treatment of pregnant women with pyelonephritis in the first and early second trimesters, but the majority of women will be managed as inpatients  McCormick 2008 acute cystitis and pyelonephritis demand full assessment and treatment, with early involvement of other specialists in severe or systemic infection; all women should be reviewed to confirm post-treatment urine sterility; empirical antimicrobial treatments will occasionally be required but any decision to treat should be re-evaluated once culture and sensitivity reports are available; when choosing an antimicrobial, the pharmacokinetics and bioavailability of the individual drug in pregnancy must be considered along with the resistance profiles of microorganisms in the local antenatal population; it is also vital to use treatments with an established safety profile and, most importantly, without teratogenetic risks  Mittal 2005 ASB, if left unrecognized and untreated, frequently progresses to pyelonephritis, and is associated with preterm delivery and low birth weight infants; 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  Gilstrap 2001 because the initial antibiotic therapy is empirical, a variety of antimicrobial agents can be used for the treatment of bacteriuria; these drugs include the sulfonamides (500 mg; four times a day), nitrofurantoin (100 mg twice daily), and the cephalosporins (250 mg four times a day); therapy should generally be given for 3 days for the initial infection; longer courses of therapy can be used for recurrent infections; another useful regimen is nitrofurantoin, 100 mg at bedtime for 10 days, or for 21 days for recurrences; single-dose regimens have also been used  Wing 2001 the standard approach to the treatment of acute  pyelonephritis in pregnancy is hospitalization, and  administration of intravenous hydration, antipyretics and parenteral antimicrobial therapy; there is insufficient data to recommend one antibacterial regimen at the current time; ambulatory treatment of acute pyelonephritis in pregnancy beyond 24 weeks’ appears to be limited in its applicability  and is therefore not recommended |