



# Urinary Tract Infections in Pregnancy

- ▶ PAUL J. WENDEL, MD
- ▶ PROFESSOR AND DIRECTOR
- ▶ MATERNAL/FETAL MEDICINE
- ▶ UNIVERSITY OF TENNESSEE HEALTH SCIENCE  
CENTER
- ▶ MEMPHIS, TN

**No disclosures and no conflicts of interest**

**No interest or shareholder of any drug company  
involving the antibiotics we will discuss**



# Background of this lecture

- ▶ ACOG released a clinical consensus publication in August 2023 entitled “Urinary tract infections in pregnant individuals.”
- ▶ Always a medical/legal document.
- ▶ Challenged some of my prior clinical practice.
- ▶ Our goal should always be to stay with school of fish from a standpoint of
  - ▶ Safety
  - ▶ Quality



# Goals of this Presentation

- ▶ Review diagnostic criteria
  - ▶ Asymptomatic bacteriuria
  - ▶ Symptomatic acute cystitis
  - ▶ Pyelonephritis
- ▶ Review Recommendations for treatment of the above diagnosis.
- ▶ Review recommendations for follow up testing after initial infection and diagnosis of ASB or cystitis.
- ▶ Discuss areas “ripe” for inquiry and research in the future.

# How was this consensus developed

- ▶ Convened by the ACOG committee on clinical consensus in obstetrics.
- ▶ Authors
  - ▶ Anna S. Graseck, MD (Generalist @ university of Penn)
  - ▶ Jennifer Thompson MD ( MFM @ Vanderbilt )
  - ▶ Allison Bryant, MD, MPH, (MFM @ Mass General)
  - ▶ Alison Cahill, M.D., MSCI, (MFM @ UT Austin)
  - ▶ Neil Silverman MD (MFM @ UCLA)
  - ▶ Mark Turrentine, MD (Generalist @ Baylor/Houston)

# Literature search performed 2000—present

Cochrane library

Cochrane Registry of controlled trials

EMBase

Pub med

Medline for human only studies in English language

Search terms for medical disparities and implicit bias were incorporated.

Recommendations drafted to promote health equity and reduce disparities.

Each consensus or recommendation required a 2/3 vote for approval and all opinions exceeded the 75 % approval.

## Purpose/Background

- ▶ Urinary tract infections (UTI'S) is one of the most common Perinatal complications in pregnancy (8-10%)
- ▶ Infections represents a spectrum
  - ▶ ASB >Acute cystitis > pyelonephritis
- ▶ The presence of UTIs have been associated with both the PTL and LBW.
- ▶ Serious maternal complications from pyelonephritis are associated with
  - ▶ Sepsis/PTB
  - ▶ DIC
  - ▶ ARDS
  - ▶ Maternal death

# Epidemiology

- ▶ UTIs are classified by the site of infection.
  - ▶ Lower urinary tract (ASB, cystitis)
  - ▶ Upper urinary tract (pyelonephritis)
- ▶ ASB – Seen in 2-10% of pregnancies
- ▶ Acute cystitis 1-2 % of pregnancies
- ▶ Pyelonephritis – 1-2 % of pregnancies
- ▶ 15 % ASB -> 15% cystitis -> 15 % get pyelo -> 15% get sepsis/ARDS



Predisposed  
factors  
increasing the  
incidence of  
UTI's in the  
pregnant vs  
non pregnant  
state

- ▶ Progesterone mediated dilation and relaxation of the internal urethral sphincter and ureters.
- ▶ Mechanical compression of the ureter by the gravid uterus(especially at the pelvic brim)
- ▶ Both lead to
  - ▶ Residual volume in the bladder with stasis
  - ▶ Vesicoureteral reflux
  - ▶ Bacterial colonization
    - ▶ Results in ascending infection

# Asymptomatic Bacteriuria (ASB)

- ▶ Screening for ASB – accepted practice to prevent pyelonephritis
- ▶ Most ASB studies done in 1960-1980
- ▶ Study quality poor and methodology suspect
- ▶ ABx regimens not reflective of today's practice
  - ▶ Since ASB screening/treatment are NOW routine practice > incidence of pyelonephritis has dropped from 20-35 % to 1-4 % of patients with ASB

# Current Practice

- ▶ The after mentioned response shows ASB screenings is effective
- ▶ However, the 2 most recent randomized trials of patients with ASB
  - ▶ The non treatment group only has a pyelonephritis rate of 2.2-2.4%
  - ▶ Suggest that in some populations the baseline rate of Pyelonephritis is lower even without screening/treatment
- ▶ Thus, in 2019 the US preventative services task force downgraded recommendation for ASB
- ▶ Screening from “A” (substantial benefit) to “B” (evidence of only moderate benefit)
- ▶ However, Trials still show consistent association with decrease in pyelonephritis
- ▶ ASB screening in pregnancy still recommended

# ASB Screening in Pregnancy- When and How?

## When?

- ▶ Screening should be performed “at a visit early in prenatal care.”
- ▶ Pyelonephritis is most prevalent in 2<sup>nd</sup> trimester. a significant portion of patients with Pyelonephritis are reported in 1<sup>st</sup> Trimester who were not screened for ASB
- ▶ Prudent to collect urine for screening “early”
- ▶ There is “*insufficient evidence*” to recommend a specific GA at which to screen

# ASB Screening in Pregnancy- When and How?

## How??

- ▶ Routine urine dipstick testing for infection at each visit
  - ▶ “Does not have benefit” and not sufficiently sensitive to detect ASB
- ▶ A midstream urine culture is recommended
  - ▶ Has not been shown to reduce the rate of vaginal bacterial contamination of urine.

# Mid stream and Midstream Clean Catch Urine Specimen

- ▶ commonly have at least moderate levels of contamination
  - ▶ Epithelial cells on gram stain
  - ▶ Mixed flora on culture results
- ▶ 1/3 of all urine cultures by either collection method show growth of skin flora up to 100,000 colony units/ml  $10^5$  cfu/ml
- ▶ No evidence specifically addressing whether to repeat a contaminated sample
- ▶ “Repeated attempts in hopes of avoiding contamination may ultimately be futile”

# ABS Screening

- ▶ After an initial negative urine culture
  - ▶ Additional screening is not indicated because residential risk of pyelo is low.
- ▶ Higher risk populations could be screened more than once
  - ▶ Sickle cell anemia patients have an 40 % increase in positive urine culture compared to hemoglobin A controls but not hemoglobin C patients
  - ▶ Although reasonable to screen sickle cell patients more often, there is “insufficient evidence” specify a frequency

# ASB Screening

- ▶ Patients with diabetes or spinal cord injury should not undergo additional screenings for ABS beyond initial screen
- ▶ There is evidence that the harm of the screening outweigh potential benefits
  - ▶ In the spinal cord patients ASB appears to be protective against symptomatic UTI
  - ▶ Additionally, treatment can precipitate infection and pressure antimicrobial resistance



# Treatment of ASB

- ▶ ASB is clinically significant at colony counts of 100,000 ( $10^5$ ) cfu/ml or higher
  - ▶ Lower counts may represent contamination
  - ▶ Do not require treatment
- ▶ GBS should only be treated if present in  $> 10^5$  cfu/ml
- ▶ Lower colony counts of GBS do not require treatment. Should be noted for an indication for GBS prophylaxis @ delivery

# Treatment of ABS

- ▶ RX should be a 5–7-day course of an antibiotic that has demonstrated efficacy against the most common etiologic bacteria (E.coli, proteus, klebsiella)
- ▶ Normal vaginal flora( lactobacillus, corynebacteria, and coagulase negative staphylococcus **should not be treated.**
- ▶ Duration of treatment is typically 5-7 days
- ▶ Fosfomycin is the only exception to this rule as 1 day treatment
- ▶ 3-day treatment with antibiotics “lack data to support their use.”
  - ▶ Nitrofurantoin - \$ 19.69
  - ▶ Cephalexin - \$ 12.39
  - ▶ Sulfamethoxazole-trimethoprim - \$ 13.51
  - ▶ Fosfomycin - \$ 30.10
  - ▶ Amoxicillin - \$ 16.53
  - ▶ Amoxicillin - Clavulanate - \$ 13.87

**Table 1. Antibiotic Regimens for Treatment of Asymptomatic Bacteriuria and Acute Cystitis**

Antimicrobial	Regimen	Considerations
Nitrofurantoin	100 mg orally every 12 h for 5–7 d	Reasonable to offer in the 1st trimester if no appropriate alternatives are available Avoid as treatment for pyelonephritis due to inability to reach therapeutic levels in the kidney
Cephalexin*	250–500 mg orally every 6 h for 5–7 d	
Sulfamethoxazole-trimethoprim	800/160 mg every 12 h for 5–7 d	Reasonable to offer in the 1st trimester if no appropriate alternatives are available In areas with more than 20% resistance to trimethoprim-sulfamethoxazole, avoid if initiating treatment before culture results are available
Fosfomycin	3 g orally once	Avoid as treatment for pyelonephritis due to inability to reach therapeutic levels in the kidney
Amoxicillin*	500 mg orally every 8 h for 5–7 d 875 mg orally every 12 h for 5–7 d	High degree of resistance; avoid if initiating treatment before culture results are available
Amoxicillin—clavulanate*	500 mg orally every 8 h for 5–7 d 875 mg orally every 12 h for 5–7 d	High degree of resistance; avoid if initiating treatment before culture results are available

\*For patients with a  $\beta$ -lactam allergy for whom other classes of antibiotic are inappropriate, further investigation regarding the severity of allergic reaction is necessary. For patients at low risk for anaphylaxis, treatment with cephalosporins would be appropriate; however, individuals at high risk for anaphylaxis would need to be treated with an alternative regimen.

Modified from:

1. Matuszkiewicz-Rowińska J, Malyszko J, Wieliczko M. Urinary tract infections in pregnancy: old and new unresolved diagnostic and therapeutic problems. Arch Med Sci 2015;11:67–77. doi: 10.5114/aoms.2013.39202
2. Wang T, Wu G, Wang J, Cui Y, Ma J, Zhu Z, Qiu J, Wu J. Comparison of single-dose fosfomycin tromethamine and other antibiotics for lower uncomplicated urinary tract infection in women and asymptomatic bacteriuria in pregnant women: a systematic review and meta-analysis. Int J Antimicrob Agents 2020;56:106018. doi: 10.1016/j.ijantimicag.2020.106018

# Acute Cystitis - Clinical Criteria

- ▶ Differentiated from ASB by “presence of symptoms”
  - ▶ Dysuria
  - ▶ Hematuria
  - ▶ Urinary frequency
  - ▶ Nocturia
- ▶ Clearly overlap with the typical pregnancy symptoms

# Acute cystitis – Diagnostic Criteria

- ▶ Diagnostic studies critical to differentiate from pregnancy symptoms to prevent overtreatment
- ▶ Urinalysis is a useful tool for triage
  - ▶ **Pyuria** > 5 wbc/hpf
  - ▶ **Leukocyte esterase** sensitive - 97% sensitive for UTI but less specific because WBCs could be contaminant
  - ▶ **Nitrates** – most specific finding UTI (94-98%) but not all bacteria produces nitrates
- ▶ If neither nitrates nor leukocyte esterase are present – UTI is unlikely (neg predictive value 78-98%)
- ▶ UTI is **excluded** if dipstick entirely normal

**Table 2. Accuracy of Urinalysis Findings to Predict Culture-Positive Urinary Tract Infection\***

Test	Result	Sensitivity (%)	Specificity (%)	PPV	NPV
Dipstick					
	Leukocyte esterase (+)	72–97	41–86	43–56	82–91
	Nitrites (+)	19–48	92–100	50–83	70–88
	Leukocyte esterase or nitrites (+)	46–100	42–98	52–68	78–98
	Protein at 3+ or higher	96	87	NA	NA
	Protein at 1+ or higher	91–100	65–99	NA	NA
Microscopy					
	More than 5 WBCs/HPF	90–96	47–50	56–59	83–95
	More than 5 RBCs/HPF	18–44	88–89	27	82
	Bacteria (any amount)	46–58	89–94	54–88	77–86

Abbreviations: PPV, positive predictive value; NPV, negative predicative value; NA, not applicable; WBC, white blood cell; HPF, high-power field; RBC, red blood cell.

\*The PPV and NPV for UTI are presented as a range, because they will vary with the prevalence of UTI in the population studied. In populations with a low prevalence of UTI the PPV decreases while the NPV increases.

Modified from Simerville JA, Maxted WC, Panira JJ. Urinalysis: a comprehensive review [published erratum appears in Am Fam Physician 2006;74:1096]. Am Fam Physician 2005;71:1153–62.

## Acute Cystitis - Diagnostics

- ▶ Ideally urine culture should be obtained
  - ▶ Tailoring of antibiotics therapy by sensitivities
- ▶ Threshold colony count to confirm infection is 100,000 ( $10^5$ ) cfu/ml
- ▶ Some authors suggest Rx for colony counts as low 100 ( $10^2$ ) of

Single organism “in the presence of symptoms”

Antibiotic treatment may be started for symptomatic relief with a positive urinalysis and tailored after results of UC sensitivities are resulted

## Acute Cystitis – Treatment / Selection

- ▶ Once diagnosis of cystitis is made, 5 -7 days course of antibiotics is started
- ▶ If empiric therapy is started before sensitives are available
  - ▶ Ampicillin/ amoxicillin
  - ▶ Should be avoided due to high rates of resistance (39-48% are)
- ▶ Once sensitives are available
  - ▶ Use the narrowest practical spectrum antibiotic
- ▶ Treat for appropriate duration (5-7 days)
- ▶ These are essential components of “antibiotic stewardship and optimal clinical care”

## Acute cystitis – Treatment

- ▶ with the appropriate antibiotic choice, treatment is effective
- ▶ However meta-analysis evaluating multiple treatment options found no difference in
  - ▶ Cure rates
  - ▶ Rates of reinfection
  - ▶ Preterm delivery
  - ▶ Need for alternate therapy

# Acute Cystitis – antibiotic selection as first line

- ▶ Nitrofurantoin
  - ▶ Low resistance rates
  - ▶ Effective against many of the typical pathogens common in pregnancy
  - ▶ Concentrated and achieves therapeutic levels in bladders
  - ▶ Nitrofurantoin/ sulfamethoxazole-trimethoprim
    - ▶ Shows some data regarding possible abnormalities if used in the 1<sup>st</sup> trimester and data is mixed and have methodologic limitations
  - ▶ Consensus “nitrofurantoin and trimethoprim are reasonable in 1<sup>st</sup> trimester if no
  - ▶ Nitrofurantoin in G6-PD is contradicted due to hemolytic anemia and pulmonary toxicity



# Acute Cystitis – Duration of Treatment

- ▶ Typical antibiotic course is 5-7 days. There is “insufficient evidence” to recommend 3-day RX in pregnancy
- ▶ However, several studies showed single dose Fosfomycin was effective
- ▶ Meta analysis single dose Fosfomycin
  - ▶ For has similar outcomes to 5-7 regimens
  - ▶ Plus, compliance may be higher (offsets cost)

# Acute Cystitis – Antibiotic Choices

- ▶ Both of nitrofurantoin and Fosfomycin should be avoided if the differential diagnosis includes possible pyelonephritis
- ▶ Neither of these antibiotics have been shown to reach adequate tissue levels within the kidney.

# Acute Cystitis - Test of Cure (TOC)

- ▶ “Insufficient data” to guide management after acute cystitis in pregnancy
- ▶ May obtain culture 1-2 weeks after completion of RX
- ▶ Patient can be monitored for symptoms and only re-culture if symptoms reoccurred.
- ▶ Benefits of either strategy are lacking to make recommendation

# Acute Cytosis in Pregnancy – Recurrent Infection

- ▶ Recurrent UTI – 2 or more UTI's in pregnancy occurs in 4-5 % of pregnancies
- ▶ Little data regarding management in this setting
- ▶ Given the risk of progression to pyelonephritis
  - ▶ Initiation of prophylaxis in nonpregnant population reduced Recurrence rates Compared to placebo in patients with > two infections/ year
- ▶ Prophylaxis (2 strategies )
  - ▶ postcoital taken before or after vaginal intercourse
  - ▶ continuous antibiotics generally at night
- ▶ Common suppressive agents
  - ▶ Nitrofurantoin 100 mg QHS
  - ▶ cephalexin 250-500 mg QHS

# Pyelonephritis - Definition

- ▶ Pyelonephritis – an infection of the kidney that arises from bacteria ascending from bladder to upper urinary tract
- ▶ Differentiating between symptomatic UTI and pyelonephritis is based on abnormal urinalysis with
  - ▶ History – fever ( $\geq 38^{\circ}\text{C}$ , nausea, and vomiting)
  - ▶ PE – (flank pain CVA tenderness)
- ▶ Classic triage
  - ▶ fever, flank pain, pyuria
- ▶ Differential diagnosis includes nephrolithiasis, renal abscess, chorioamnionitis

# Pyelonephritis - Diagnosis

- ▶ Patients suspected of having pyelonephritis should have
  - ▶ Midstream or catheterized urine specimen collected
  - ▶ Urinalysis
  - ▶ Microcopy
  - ▶ Culture and sensitives
- ▶ Urine specimen should be obtained before antibiotics initiated but treatment not delayed waiting on culture results
  - ▶ Blood cultures – “frequently obtained but may not be clinically useful”
  - ▶ Only 21% of BCs positive
    - ▶ Rarely changed clinical management
    - ▶ Bacteriology was concordant between UC and BC
    - ▶ duration of treatment was not affected by bacteremia

# Pyelonephritis

- ▶ One of the most common reasons for hospitalization in pregnancy
- ▶ Untreated pyelonephritis leads to significant obstetric and maternal complications
  - ▶ Preterm labor and delivery
  - ▶ sepsis
  - ▶ Septic shock
  - ▶ ARDS/ Pulmonary edema
  - ▶ Maternal Death
- ▶ Initial management
  - ▶ Aggressive fluid hydration
  - ▶ Intravenous antibiotics

# Pyelonephritis Treatment

- ▶ IV antibiotics should be started immediately
  - ▶ Tailored once microbiology and sensitives return
- ▶ Choice of antibiotics should be individualized based on
  - ▶ Local susceptibility data
  - ▶ Any recent antibiotic use by patient
- ▶ Recent studies evaluated benefits of various antibiotic regimens
  - ▶ No one treatment has been found superior
- ▶ Patients with beta lactam allergy
  - ▶ Further investigation into severity of allergic response
  - ▶ **Low** potential for anaphylaxis
    - ▶ Use of cephalosporin is appropriate
  - ▶ **High** risk of anaphylaxis
    - ▶ Aztreonam is appropriate with ID support/ consultation

**Table 3. Antibiotic Regimens for Treatment of Pyelonephritis**

Antimicrobial	Regimen
Ampicillin + gentamicin	2 g IV every 6 h  1.5 mg/kg IV every 8 h 5 mg/kg IV every 24 h
Ceftriaxone	1 g IV every 24 h
Cefepime	1 g IV every 12 h
Aztreonam (appropriate in patients with $\beta$ -lactam allergy)	1 g IV every 8–12 h

Abbreviation: IV, intravenously.

Data from:

1. Wing DA, Hendershott CM, Debuque L, Millar LK. A randomized trial of three antibiotic regimens for the treatment of pyelonephritis in pregnancy. *Obstet Gynecol* 1998;92:249–53. doi: 10.1016/s0029-7844(98)00156-2
2. Sanchez-Ramos L, McAlpine KJ, Adair CD, Kaunitz AM, Delke I, Briones DK. Pyelonephritis in pregnancy: once-a-day ceftriaxone versus multiple doses of cefazolin. A randomized, double-blind trial. *Am J Obstet Gynecol* 1995;172:129–33. doi: 10.1016/0002-9378(95)90100-0
3. Vazquez JC, Abalos E. Treatments for symptomatic urinary tract infections during pregnancy. *The Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD002256. doi: 10.1002/14651858.CD002256.pub2
4. Glaser AP, Schaeffer AJ. Urinary tract infection and bacteriuria in pregnancy. *Urol Clin North Am* 2015;42:547–60. doi: 10.1016/j.ucl.2015.05.004



# Treatment Pyelonephritis

- ▶ Majority (75-95 %) have clinical improvements (afebrile after 24 hours) within 48-72 hours after starting IV antibiotics
- ▶ Failure to respond within 72 hours
  - ▶ Ensure bacterial resistance not present
  - ▶ Undergo imaging to rule out other urinary tract pathology
- ▶ Resistance is most common cause of treatment failure

# Pyelonephritis Treatment

- ▶ After improvement transition to appropriate antibiotic (based on sensitives) to complete 14-day course
- ▶ Nitrofurantoin/ Fosfomycin are not appropriate agents for oral treatment
  - ▶ only for lower urinary tract
  - ▶ Do not reach therapeutic levels in renal parenchyma
- ▶ Urine culture should be obtained **after completion** of 14 days of antibiotics to ensure no residual infection

# Pyelonephritis Treatment/Resistance

- ▶ Antimicrobial resistant organism
  - ▶ Extended spectrum beta lactamase producing E.coli (ESBL)
  - ▶ Methicillin resistant staphylococci aureus (MRSA)
  - ▶ Both increasing in prevalence
  - ▶ ESBL E.coli now 34% and 37% of klebsiella isolates
  - ▶ MRSA seen in 30 % of staph aureus

One study found an increase maternal mortality in patients with ESBL infections

When resistant organism detected, *“consultation with infections disease specialist may be indicated.”*

# Pyelonephritis – follow up Clinical Management

- ▶ Recurrent pyelonephritis is seen in up to 25% of pregnant pts before delivery
- ▶ Data limited regarding optimal management
- ▶ Small studies support daily suppressive therapy
  - ▶ Nitrofurantoin 100mg QHS
  - ▶ Cephalexin 250-500 mg QHS
  - ▶ For remainder of pregnancy **and** continuing **4-6 weeks postpartum**
  - ▶ Additional monthly urine cultures to screen for recurrence “should be considered” for the duration of pregnancy

# Urinary Tract Infections – Further research needed

- ▶ Timing of maternal screening for ASB
- ▶ Which populations warrant repeat ASB screening
- ▶ Appropriateness for TOC if treated for ASB
- ▶ Is a 3-day course of oral antibiotics appropriate use for ASB
- ▶ efficacy, utility, and dosage of prophylactic antibiotics following recurrent UTI or pyelonephritis
- ▶ Postpartum management/ for the treatment of recurrent UTI or pyelonephritis
- ▶ Recommendations for patients with indwelling catheters

