25 – Infections of Upper and Lower Urinary Tract

Speaker: Barbara Trautner, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Urinary Tract Infections

Barbara W. Trautner, MD, PhD
Professor of Medicine
Baylor College of Medicine

6/21/2022

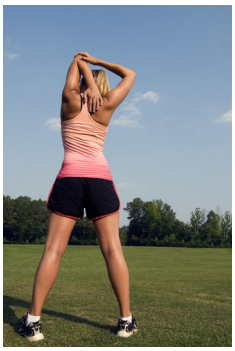
IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

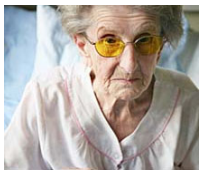
Disclosures of Financial Relationships with Relevant Commercial Interests

- Genentech for COVID-related research

Topics to cover

- Acute cystitis in women
- Asymptomatic bacteriuria
  - Pregnant women
  - Renal transplant
  - Pre-operative screening
- Catheter-associated UTI
- Urosepsis and worse
  - Emphysematous pyelonephritis
  - Emphysematous cystitis
  - Xanthogranulomatous pyelonephritis





UTI differs in different populations

UTI is not the same entity in these different populations
Symptoms and management differ

UTI Question #1

A 24-year-old woman is evaluated for cystitis symptoms of 3 days' duration. She reports no fever, chills, flank pain, or vaginal discharge. She had similar symptoms three months ago and was treated with trimethoprim-sulfamethoxazole, with relief of symptoms.

On physical examination, vital signs and other findings are unremarkable.

On microscopic urinalysis, leukocytes are too numerous to count, erythrocyte count is 10/hpf, 4+ bacteria are present, and rare squamous epithelial cells are seen. Urine pregnancy test is negative.

Which of the following is the most appropriate management?

A. Nitrofurantoin
B. Bactrim
C. Fosfomycin
D. Ciprofloxacin
E. Ibuprofen

Current IDSA UTI Guidelines*

*update in progress

These guidelines cover:

- Uncomplicated cystitis
- Uncomplicated pyelonephritis
- Premenopausal women
- Primarily outpatients

IDSA GUIDELINES

International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases

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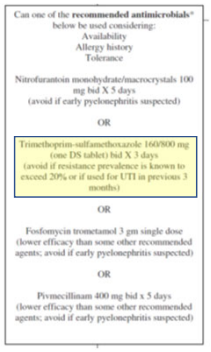
IDSA Cystitis Guidelines (2010)

First-line agents
- Nitrofurantoin
- Trimethoprim-sulfamethoxazole
- Fosfomycin

Alternative choices
- Fluoroquinolones
- Beta-lactams



How long do you treat acute cystitis?

First line choices (5, 3, 1)
- Nitrofurantoin X 5
- Trimethoprim/sulfamethoxazole X 3
- Fosfomycin X1

IDSA Guidelines on Uncomplicated Cystitis, 2010

JAMA Network

From: **Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women: A Randomized Clinical Trial**

JAMA. 2018;319(17):1781-1789. doi:10.1001/jama.2018.3627

Table 3. Clinical and Microbiologic Outcomes

Clinical and Bacteriologic Outcome	No./Total No. (%) Nitrofurantoin (n = 255)	Fosfomycin (n = 258)	Difference, % (95% CI)	*P* Value[a]
Primary Outcome				
Clinical response at 28 d[b]				
Clinical resolution	171/244 (70)	139/241 (58)	12 (4-21)	.004
Clinical failure	66/244 (27)	94/241 (39)		
Indeterminate	7/244 (3)	8/241 (3)		
Missing[c]	11 (4)	17 (7)		

Clinical and microbiological response to 5 days of nitrofurantoin was better than to single dose fosfomycin

Nitrofurantoin: Clinical use

- Interferes with several aspects of bacterial metabolism
- *E. coli* resistance uncommon
- Great for *E. coli* cystitis and prophylaxis
- Inadequate levels in tissue and blood
- Dyes urine yellow
- Intrinsic resistance in *Pseudomonas, Proteus, Serratia*
- Resistance frequent in *Klebsiella* and *Enterobacter*
- Renal excretion but OK to use if GFR >30 mL/min

Cunha et al, Eur J Clin Microbiol Infect Dis 2017; 36(7)
Singh, CMAJ 2015; 187(9)
AGS Beers Criteria 2019

Nitrofurantoin Adverse Events

- Pulmonary toxicity--RARE
  - Acute: reversible hypersensitivity reaction
  - Chronic: persistent pulmonary fibrosis
    - Dose dependent?
    - Favors use of lowest possible dose/less frequent dosing for chronic prophylaxis
- Hepatitis—RARE
- Nausea—common
  - Worse with micro- (QID) than macro-crystalline (BID) formulation

Santos, JAGS 2016, PMID: 27100576

Fosfomycin: Mechanism and Susceptibility Testing

- Inhibits peptidoglycan synthesis
- Requires uptake into the bacterial cell via transporter
- Susceptibility testing
  - G6PD must be present
  - MIC breakpoints standardized ONLY for urinary *E. coli*
  - Requires disk diffusion
- Registered in US in 1996 to treat cystitis caused by *E. coli* and *E. faecalis*
- IV form available in Europe but not United States
- Variable susceptibility in *Klebsiella*, *Pseudomonas*
- Resistant: *Acinetobacter*
- Resistance: mainly loss of uptake, some inactivation

Silver, Cold Spring Harbor Perspectives in Medicine 2017

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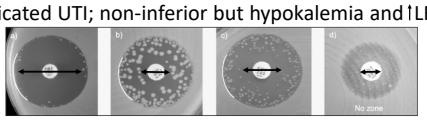
Fosfomycin: Clinical use for UTI

- High levels in urine for over 24 hours
- Single 3 gm dose for cystitis
- Developing niche for ESBL- and KPC- Enterobacteriaceae
  - 3gm every 48-72 hours
- ZEUS trial: IV fosfomycin versus piperacillin-tazobactam for complicated UTI; non-inferior but hypokalemia and ↑LFTs



Photos from eucast.org; arrows (↔) reflect CLSI recommendations

Potential harms of quinolones: FDA warnings

- Dysglycemia
- Tendon rupture/damage
- Interstitial nephritis
- Neuropathy
- Diarrhea—with or without *C. diff*
- Aortic aneurysms?
- Arrhythmias

FDA WARNING

Safety Announcement

[05-12-2016] The U.S. Food and Drug Administration is advising that the serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.

"Treatment" of Cystitis with NSAIDS

- Randomized double-blind trial of diclofenac versus norfloxacin
- 253 women with symptoms of uncomplicated cystitis
  - 73% culture positive
  - 70% of organisms sensitive to norfloxacin
- Norfloxacin was superior to diclofenac for
  - Symptom resolution at 3 days (80% versus 54%)
  - Time to resolution of symptoms (2 versus 4 days)
  - Pyelonephritis prevention (0 cases versus 6, or 5%)

Kronenberg et al, BMJ 2017

UTI Question #1

A 24-year-old woman is evaluated for cystitis symptoms of 3 days' duration. She reports no fever, chills, flank pain, or vaginal discharge. She had similar symptoms two months ago and was treated with trimethoprim-sulfamethoxazole, with relief of symptoms.

On physical examination, vital signs and other findings are unremarkable.

On microscopic urinalysis, leukocytes are too numerous to count, erythrocyte count is 10/hpf, 4+ bacteria are present, and rare squamous epithelial cells are seen. Urine pregnancy test is negative.

Which of the following is the most appropriate management?

A. Nitrofurantoin-best choice for uncomplicated cystitis when TMP/SMX not an option
B. Bactrim (or TMP/SMX)—she had this recently, so may now have resistance
C. Fosfomycin—would be fine, not commonly used in US and may cost more
D. Ciprofloxacin—avoid when other options available
E. Ibuprofen—slower to relieve symptoms and less effective at preventing pyelonephritis

UTI Question #2

A 69-year-old woman comes in for an annual checkup. No change in her baseline health status. When she coughs or sneezes, she notes slight leakage of urine. Her medical history is significant for three vaginal births, and she has well-controlled hypertension.

Her BMI is 30. Her vital signs and other physical examination findings are normal.

On dipstick urinalysis, urine is yellow and with a bad smell, specific gravity is 1.010, pH is 7.0, and moderate leukocyte esterase and nitrites are present; the urinalysis is negative for blood or glucose but 2+ for bacteria.

Which of the following is the most appropriate management?

A. Nitrofurantoin
B. Ciprofloxacin
C. Cystoscopy
D. Urine culture and sensitivities
E. No further infectious workup

Prevalence of Asymptomatic Bacteriuria

Population	Prevalence, %
Children	
Boys	<1
Girls	1–2
Healthy women	
Premenopausal	1.0–5.0
Pregnant	1.9–9.5
Postmenopausal (age 50–70 y)	2.8–8.6
Persons with diabetes	
Women	10.8–16
Men	0.7–11
Elderly persons in the community (age >70 y)	
Women	10.8–16
Men	3.6–19
Elderly persons in a long-term care facility	
Women	25–50
Men	15–50
Persons with spinal cord injury	
Intermittent catheter use	23–69
Sphincterotomy/condom catheter	57
Persons with kidney transplant	
First month posttransplant	23–24
1 mo–1 y post-transplant	10–17
>1 y post-transplant	2–9
Persons with indwelling catheter use	
Short-term	3%–5%/day catheter
Long-term	100

Nicolle et al, IDSA Guidelines for Asymptomatic Bacteriuria, Clin Inf Dis 2019

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Guidelines on Screening for ASB in Pregnant Women

Agency	Year	Recommended?	Strength?	When?	How?	Desired Outcomes
IDSA (United States)	2019	Yes	Strong	12-16 weeks	Culture	Decreased pyelonephritis, decreased low birth weight Possible decrease in preterm labor
CTFPHC (Canadian)	2018	Yes	Weak	1st trimester	Culture	Decreased pyelonephritis, decreased low birth weight
USPSTF (United States)	2019	Yes	Grade B	12-16 weeks or first prenatal visit	Culture	Decreased pyelonephritis, decreased low birth weight

Treatment of ASB and Cystitis During Pregnancy

Antibiotic	Dose	Duration	Notes
Nitrofurantoin	100 mg orally every 12 hours	Five to seven days	Does not achieve therapeutic levels in the kidneys so should not be used if pyelonephritis is suspected. Avoid use during the first trimester and at term if other options are available.
Amoxicillin	500 mg orally every 8 hours or 875 mg orally every 12 hours	Five to seven days	Resistance may limit its utility among gram-negative pathogens.
Amoxicillin-clavulanate	500 mg orally every 8 hours or 875 mg orally every 12 hours	Five to seven days	
Cephalexin	500 mg orally every 6 hours	Five to seven days	
Cefpodoxime	100 mg orally every 12 hours	Five to seven days	
Fosfomycin	3 g orally as single dose		Does not achieve therapeutic levels in the kidneys so should not be used if pyelonephritis is suspected.
Trimethoprim-sulfamethoxazole	800/160 mg (one double strength tablet) every 12 hours	Three days	Avoid during the first trimester and at term.

The durations listed in the table are based on data from studies conducted in both nonpregnant and pregnant women.

UpToDate®

Treatment should be culture based
Group B strep bacteriuria calls for prophylaxis at delivery

UpToDate 2022, Hooton and Gupta

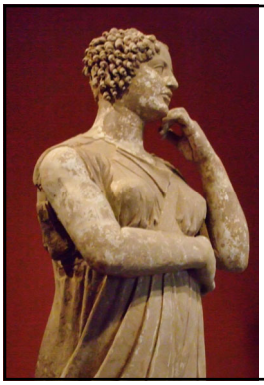
IDSA Guidelines on ASB 2019

Screening and Treatment Indicated

- ✓ Pregnant women
- ✓ Prior to urologic surgery with mucosal trauma
  - Pre-operative urine culture recommended
  - Treat with 1-2 doses of antibiotics shortly prior to surgery

Screening and Treatment Discouraged

- X Infants and children
- X Non-pregnant women
- X Functionally-impaired older adults
- X Diabetic adults
- X Patients >1 month from kidney transplant
- X Neutropenic patients
- X Patients with solid organ transplant
- X Persons with spinal cord injury
- X Patients with indwelling catheters
- X Prior to non-urologic surgery



Mythbusting: Which of the following is true?

A. A change in urine color is an indication for a urine culture
B. Bad smelling urine is suggestive of a UTI
C. Sediment in the urine means we should change the catheter
D. The level of pyuria helps in diagnosis of catheter-associated UTI
E. Beets can turn urine red

UTI Question #3

A 75-year-old man is seen in the pre-operative clinic. He is scheduled to undergo cystoscopy and possible biopsy for persistent hematuria. He is also scheduled for elective left total knee replacement, shortly after the urinary procedure. Other than the hematuria, he denies urinary-specific symptoms. He underwent kidney transplantation 3 years earlier, related to complications of diabetes.

On physical examination, vital signs are normal. His left knee has an effusion but is not red or excessively painful. No change in his baseline creatinine clearance.

On urinalysis, leukocyte count is 10/hpf, erythrocyte count is 100/hpf, 4+ bacteria are present, and no squamous epithelial cells are seen. Urine culture grew >10,000-<100,000 colony-forming units of *Klebsiella pneumoniae*.

Kidney ultrasonography is unremarkable.

Which of the following is the primary indication for antimicrobial therapy in this patient?

A. Cystoscopy and biopsy
B. Diabetes mellitus
C. Kidney transplant
D. Knee prosthesis placement

Preoperative screening for ASB

New(ish) evidence!

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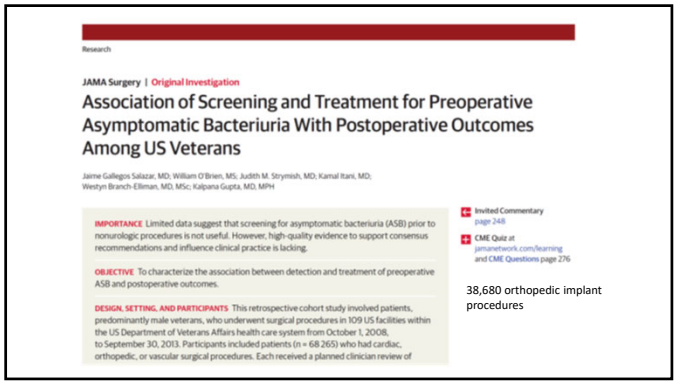

Research

JAMA Surgery | Original Investigation

Association of Screening and Treatment for Preoperative Asymptomatic Bacteriuria With Postoperative Outcomes Among US Veterans

Jaime Gallegos Salazar, MD; William O'Brien, MS; Judith M. Strymish, MD; Kamal Itani, MD; Westyn Branch-Elliman, MD, MSc; Kalpana Gupta, MD, MPH

IMPORTANCE Limited data suggest that screening for asymptomatic bacteriuria (ASB) prior to nonurologic procedures is not useful. However, high-quality evidence to support consensus recommendations and influence clinical practice is lacking.

OBJECTIVE To characterize the association between detection and treatment of preoperative ASB and postoperative outcomes.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study involved patients, predominantly male veterans, who underwent surgical procedures in 109 US facilities within the US Department of Veterans Affairs health care system from October 1, 2008, to September 30, 2013. Participants included patients (n = 68 265) who had cardiac, orthopedic, or vascular surgical procedures. Each received a planned clinician review of

Invited Commentary page 248

CME Quiz at jamanetwork.com/learning and CME Questions page 276

38,680 orthopedic implant procedures

Preoperative Screening for ASB: Key Findings

- Of 17,749 preoperative urine cultures
  - 755 positive
  - 617 were ASB
- ASB did not increase odds of surgical site infection (SSI)
- In 2 cases the urinary organism matched the organism causing SSI (*Staph aureus*)
- ASB was associated with an increased risk of UTI
- Treatment of ASB
  - Not associated with lower risk of surgical site infection
  - Not associated with lower odds of UTI

UTI Question #4

A 46-year-old man is admitted to the hospital for urgent repair of aortic dissection. An indwelling urinary catheter is inserted prior to surgery. Endovascular aortic aneurysm repair is successful, and he is transferred to the surgical intensive care unit. He has underlying diabetes and systolic heart failure.

In addition to removing the urinary catheter as soon as possible, which of the following will decrease this patient's risk of catheter-associated urinary tract infection?

A. Daily cleansing of the meatal area of the catheter with antiseptics
B. Routine catheter change every 3 days
C. Screening for and treatment of bacteriuria
D. Keeping the collecting bag below the level of the bladder
E. Use of antiseptic- or antibiotic-coated urinary catheters

CAUTI prevention

- Do remove the urinary catheters when possible
  - Only indwelling Foleys count for CAUTI metrics
  - ALL types of urinary catheters are associated with bacteriuria
- Don't culture the urine in asymptomatic patients
- Do follow aseptic insertion
- Do ensure uninterrupted drainage
  - No tugging
  - No kinking
  - No reflux due to elevated drainage bag
- Don't routinely irrigate the bladder, exchange the catheter, or use antimicrobial catheters

https://www.cdc.gov/infectioncontrol/guidelines/cauti/

UTI Question #5

A 78-year-old woman is transferred to the surgical ICU after undergoing repair of a urethral diverticulum. The procedure was performed under spinal anesthesia, but difficulties with hypotension during the procedure led to her receiving 2L of IV fluids. She has underlying CHF and renal insufficiency. She arrives in the ICU with an indwelling Foley catheter, placed during the procedure. Prior to the procedure, she had limited mobility and urinary incontinence. She has a stage 1 sacral ulcer (redness but no skin breakdown).

Which of the following is **NOT** an appropriate reason to leave her indwelling catheter in place?

A. Assessment of her urinary output
B. Urinary retention from the spinal anesthesia
C. Management of incontinence
D. Recent surgery on the urethra

Indications for indwelling Foley catheters

Appropriate

- Monitor urine output in critically ill patients
- Acute urinary retention
- Certain surgical procedures (urologic, long duration, large volume shifts)
- Prolonged immobilization from fracture/trauma
- Healing open pressure ulcer
- End of life comfort

Inappropriate

- Prevention of pressure ulcers
- Management of incontinence
- Urine culture collection
  - (use in and out if needed)

https://www.cdc.gov/infectioncontrol/pdf/guidelines/cauti-guidelines-H.pdf

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UTI Question #6

68-year-old diabetic man with CHF, vascular disease, BPH presented with 2 days of vomiting, abdominal pain, and confusion.

Vital signs: T 99.9 BP 47/39, HR 110, RR 22

Physical exam: patient was obtunded but appeared to have tenderness in the epigastric area

Labs: WBC 23.7 (94% segs), platelets 96K; Creatinine 3.1 (from 1.7 baseline)

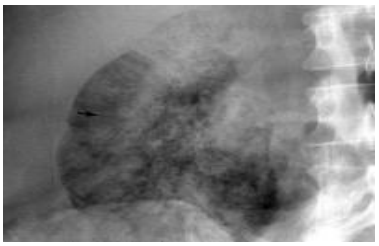
UA: WBC 250, RBC too numerous to count, no bacteria

Troponin 7.2, EKG with ST elevations; HgB A1c 10.5

He was admitted to the CCU and initiated on therapy for an ST elevation myocardial infarction. His blood pressure was labile, and he required pressor support. He required intubation. On hospital day 2, his blood cultures grew 4/4 bottles of *Klebsiella pneumoniae*.

The next slide shows an abdominal radiography (KUB) that had been performed at admission.

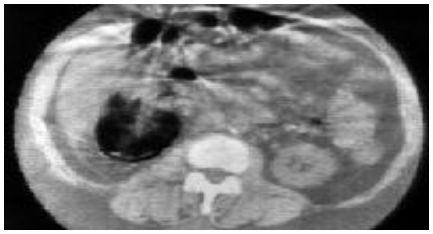
KUB X-Ray of Abdomen



What would you order next?

A. Abdominal ultrasound
B. Abdominal CT
C. Nasogastric tube
D. Stool for *C. diff* testing

Answer: Abdominal CT



Emphysematous pyelonephritis: CT showing gas within the renal parenchyma is definitive

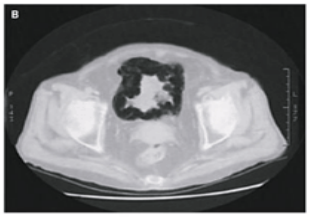
Clinical course of case #6

- Percutaneous drainage of the right kidney
- Renal drainage grew *Klebsiella*
- After weeks in the ICU was stable enough for nephrectomy
- 9 months later had then CABG

Diagnosis and management of emphysematous pyelonephritis

- 95% of cases in patients with diabetes (poorly controlled)
- Negative prognostic factors: shock, impaired consciousness, thrombocytopenia, renal failure
- Organisms: *E. coli, Klebsiella, Proteus*
- Diagnosis often delayed
- Differential: renal abscess, papillary necrosis
- Radiological diagnosis
- **Managed initially by drainage**—percutaneous nephrostomy or ureteral stent
- Nephrectomy for non-responders, severe cases

Kamei, J Infection and Chemotherapy 2021



Emphysematous cystitis

Asada, NEJM 2003;349: 258

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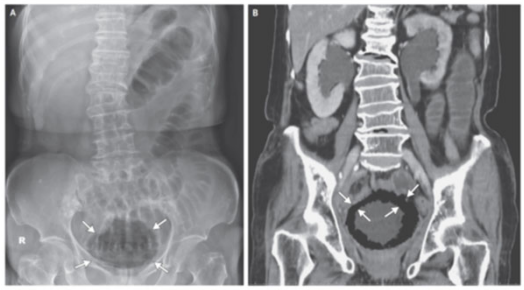
Emphysematous Cystitis



Tzou, NEJM 2016: 375; 18

Diagnosis and management of emphysematous cystitis

- Female predilection
- Most cases in diabetics
- Commonly caused by *E. coli, Klebsiella* (*Candida* reported)
- Organisms produce gas in the bladder wall and lumen
- Can present with lower abdominal pain
- Diagnosed radiologically
- Relieve bladder obstruction if present
- Typically responds well to **medical management**

UTI Question #7

57-year-old man with spinal cord injury (T12) and a chronic indwelling urinary catheter. Two years prior he had a fever, and his blood grew *S. aureus* and *Pseudomonas*. Urine grew lactose negative GNR and gram-positive organisms.

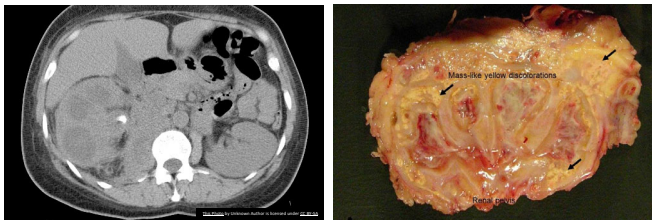
One year prior, he again had a fever, and his blood grew *Serratia, E. coli,* and *Pseudomonas*. Urine grew *Serratia* and *Pseudomonas*.

Both times he was treated with appropriate antibiotics, with resolution of fever and stabilization.

He has had many urine cultures, all of which grew multiple urinary pathogens.

Prior to entry in a research protocol, he had a screening abdominal ultrasound, which showed a hypoechoic mass in right kidney. In addition to CT scan, what will be the definitive therapy:

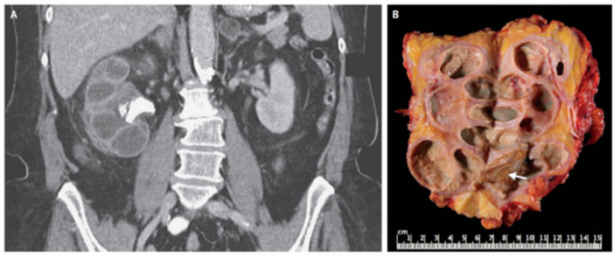
A. Renal biopsy
B. 3-6 months of antibiotics based on current urine culture
C. Percutaneous drainage
D. Nephrectomy



Xanthogranulomatous pyelonephritis

https://www.auanet.org/education/auauniversity/education-products-and-resources/pathology-for-urologists/kidney/inflammatory/necrotic-renal-lesions/xanthogranulomatous-pyelonephritis

Xanthogranulomatous Pyelonephritis



Bear paw sign

Marinacci, New England Journal of Medicine 2018; 378:10

Xanthogranulomatous pyelonephritis

- Chronic polymicrobial infection of renal parenchyma
- Often starts with stone/obstruction
- Frequently insidious and mistaken for tumor
- Renal tissue is destroyed and replaced by granulomatous tissue
- Yellow from the foam cells (macrophages) full of lipids
- **Requires nephrectomy** plus antibiotics

- Our patient underwent right nephrectomy, with finding of a variegated tan-white mass, large amount of inflammatory reaction, purulence in right renal fossa

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To Re-Cap

- Acute cystitis in women-nitrofurantoin
- Asymptomatic bacteriuria
  - Pregnant women-screen and treat
  - Renal transplant-do **not** screen or treat
  - Pre-operative screening-**not** indicated unless urologic surgery
- Catheter-associated UTI—ensure unobstructed drainage
- Urosepsis and worse
  - Emphysematous pyelonephritis-drainage
  - Emphysematous cystitis-medical management
  - Xanthogranulomatous pyelonephritis-removal

Is everything clear now?

- trautner@bcm.edu
- @bwtrautner