

# 21 – Infections of Upper and Lower Urinary Tract Infections

Speaker: Barbara Trautner, MD



## Infections of Upper and Lower Urinary Tract Infections

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### Disclosures of Financial Relationships with Relevant Commercial Interests

- Advisor for PhioGen (past)
- Stockholder in Abbott Laboratories, Bristol Myers Squibb, AbbVie, and Pfizer (past)
- Research funding from Genentech and Peptilomics
- Research funding from STRIVE (Shionogi arm)

### Topics to cover

- Acute cystitis in women
- Recurrent cystitis in women
- Asymptomatic bacteriuria
- Catheter-associated UTI
- Pyelonephritis
- Urosepsis and worse



UTI differs in different populations

UTI is not the same entity in these different populations

### The Great Divide

#### My patient populations

- Men
- Older adults in long-term care
- Persons who require urinary catheters for bladder drainage
- Persons with neurogenic bladders

#### UTI treatment evidence base

- Pre-menopausal women
- Female college students and university staff

### Question #1



#### PREVIEW QUESTION

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. TMP/SMX
- C. Fosfomycin
- D. Ciprofloxacin
- E. Ibuprofen

hpf, high-powered field; TMP/SMX, trimethoprim/sulfamethoxazole

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**Current Infectious Diseases Society of America (IDSA) UTI Guidelines\***

\*update in progress

These guidelines cover:

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

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

**IDSA Cystitis Guidelines (2010)**

Can one of the recommended antimicrobials\* below be used considering:

- Availability
- Allergy history
- Tolerance

Nitrofurantoin monohydrate/macrocrystals 100 mg bid x 5 days (avoid if early pyelonephritis suspected)

OR

Trimethoprim-sulfamethoxazole 160/800 mg (one DS tablet) bid x 3 days (avoid if resistance prevalence is known to exceed 20% or if used for UTI in previous 3 months)

OR

Fosfomycin trometamol 3 gm single dose (lower efficacy than some other recommended agents; avoid if early pyelonephritis suspected)

OR

Pyroecillinam 400 mg bid x 5 days (lower efficacy than some other recommended agents; avoid if early pyelonephritis suspected)

**First-line agents**

- Nitrofurantoin
- Trimethoprim-sulfamethoxazole
- Fosfomycin

**Alternative choices**

- Fluoroquinolones
- Beta-lactams

bid, twice daily; DS, double strength

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

**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

GFR, glomerular filtration rate

**Nitrofurantoin Adverse Events**

- Pulmonary toxicity—RARE
  - Acute: reversible hypersensitivity reaction
  - Subacute or chronic: diffuse pneumonitis
    - 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

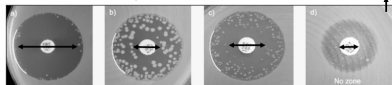


QID, four times daily

Santos, JAGS 2016, PMID: 27100576

**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- Enterobacterales
  - 3gm every 48-72 hours
- IV fosfomycin associated with hypokalemia and elevated LFTs (not approved in United States)



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

CLSI, Clinical and Laboratory Standards Institute; ESBL, extended-spectrum beta-lactamase; IV, intravenous; KPC, Klebsiella pneumoniae carbapenemase; LFT, liver function tests

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## Potential Harms of Quinolones: FDA warnings

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



**Safety Announcement**

[ 09-12-2016 ] 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.

*C. diff, Clostridioides difficile*

## New Oral Drugs in the Pipeline for Cystitis

### FDA approved for uUTI

- Pivmecillinam
  - April 24, 2024
  - In use in Europe and Canada
  - Endorsed in 2010 IDSA guidelines
  - Pro-drug of mecillinam
  - Binds to PBP-2 in Gram-negative cell wall
  - 185 mg tid for 3-7 days
- Use for
  - Enterobacteriales, including ESBL+
  - Staph saprophyticus

### Not FDA approved

- Gepotidacin
- Sulopenem
- Tebipenem



Not for *Pseudomonas*

## Question #2



A 38-year-old woman comes in for recurrent UTI. This is her 3<sup>rd</sup> episode of symptomatic, culture-proven cystitis in the past 12 months. The recurrent UTIs are very inconvenient to her. She notes that her UTI symptoms usually begin within 2 days of sexual intercourse.

You offer an antibiotic prescription to allow her to self-treat when she feels the cystitis symptoms developing, but she travels internationally and would rather completely avoid developing a UTI.

Which of the following is the most appropriate strategy to prevent recurrent UTI in this woman?

- Nitrofurantoin daily for 24 months
- Nitrofurantoin one dose after intercourse for 6 months
- Ciprofloxacin daily for 6 months
- Trimethoprim-sulfamethoxazole twice daily for 6 months
- Cranberry tablets

## Prevention and Management of Recurrent UTI

- Self-treatment coupled with urine collection for culture is an appropriate strategy
- Use the most focused antibiotic and as sparingly as possible
- If the woman's episodes are related to sexual intercourse, one dose of antibiotics after intercourse is an effective strategy
- Guidelines suggest treating daily for 3-12 months
- No clarity on which antibiotic to use, other than to avoid fluoroquinolones given side effects and resistance

Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline (2022)  
<https://www.auanet.org/guidelines-and-quality/guidelines/recurrent-uti>

## Non-antibiotic Strategies to Prevent Recurrent UTI

### Likely helpful (FDA approved)

- Increasing fluid intake
- Vaginal estrogen in post-menopausal women
- Methenamine (?)

### Uncertain benefit (not FDA approved)

- Other behavioral changes
- Cranberry products (?)
- D-mannose
- Probiotics
- Other supplement (liquid or other)

Fluid intake: Hooton TM, et al. *JAMA Intern Med.* 2018  
 Methenamine trials: Harding C, et al. *Health Technol Assess.* 2022  
 Botros C, et al. *Int Urogynecol J.* 2022  
 Systematic review of cranberry products: Williams G, et al. *Cochrane Database Syst Rev.* 2023

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## Audience Response Question #3

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 hypertension and type 2 diabetes mellitus.

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.

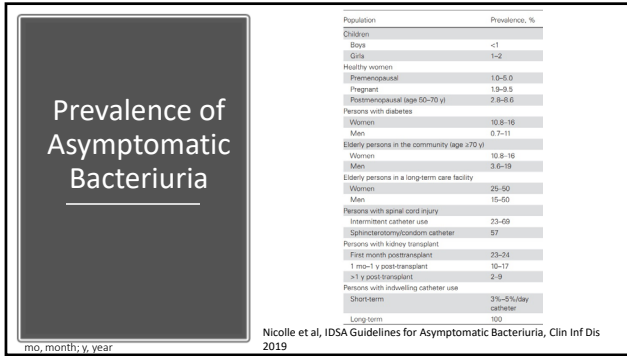
Which of the following is the most appropriate management?


- Nitrofurantoin
- Ciprofloxacin
- Cystoscopy
- Urine culture and sensitivities
- No further infectious workup

BMI, body mass index


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Choosing Wisely  
An initiative of the ABIM Foundation



Five Things Physicians and Patients Should Question

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**Don't treat asymptomatic bacteriuria with antibiotics.**

Inappropriate use of antibiotics to treat asymptomatic bacteriuria (ASB), or a significant number of bacteria in the urine that occurs without symptoms such as burning or frequent urination, is a major contributor to antibiotic overuse in patients. With the exception of pregnant patients, patients undergoing prostate surgery or other invasive urological surgery, and kidney or kidney pancreas organ transplant patients within the first year of receiving the transplant, use of antibiotics to treat ASB is not clinically beneficial and does not improve morbidity or mortality. The presence of a urinary catheter increases the risk of bacteriuria; however, antibiotic use does not decrease the incidence of symptomatic catheter-associated urinary tract infection (CAUTI), and unless there are symptoms referable to the urinary tract or symptoms with no identifiable cause, catheter-associated asymptomatic bacteriuria (CA-ASB) does not require screening and antibiotic therapy. The overtreatment of ASB with antibiotics is not only costly, but can lead to C. difficile infection and the emergence of resistant pathogens, raising issues of patient safety and quality.

### IDSA Guidelines on ASB 2019

<p><b>Screening and Treatment Indicated</b></p> <ul style="list-style-type: none"> <li>✓ Pregnant women</li> <li>✓ Prior to urologic surgery with mucosal trauma             <ul style="list-style-type: none"> <li>• Pre-operative urine culture recommended</li> <li>• Treat with 1-2 doses of antibiotics shortly prior to surgery</li> </ul> </li> </ul>	<p><b>Screening and Treatment Discouraged</b></p> <ul style="list-style-type: none"> <li>X Infants and children</li> <li>X Non-pregnant women</li> <li>X Functionally-impaired older adults</li> <li>X Diabetic adults</li> <li>X Patients &gt;1 month from kidney transplant</li> <li>X Neutropenic patients</li> <li>X Patients with solid organ transplant</li> <li>X Persons with spinal cord injury</li> <li>X Patients with indwelling catheters</li> <li>X Prior to non-urologic surgery</li> </ul>
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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	1 <sup>st</sup> 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

CTFPHC, Canadian Task Force on Preventive Health Care; USPSTF, United States Preventive Services Task Force



### Myth-Busting (True Facts!)

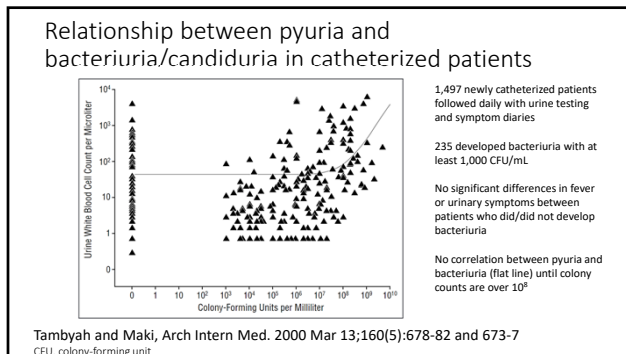
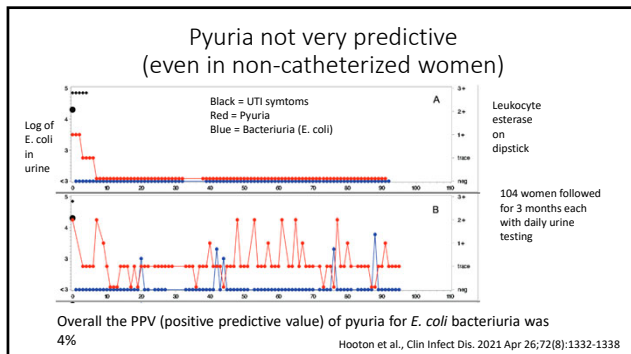
- **Bacteriuria ≠ UTI**
  - Bacteriuria in the urine can be bladder colonization or symptomatic urinary tract infection
- **Pyuria ≠ UTI**
  - The presence of WBC in the urine doesn't help much with diagnosis of UTI
  - Absence of pyuria suggests to look for a non-UTI diagnosis
- **Foul smelling urine ≠ UTI**
- **Sediment or cloudy urine in catheter tubing ≠ UTI**
  - All catheterized bladders develop high level bacteriuria
  - Flushing the catheter to make sure it is patent is a good idea
- **Healthy bladders are not sterile in many people**
- **Take home points:**
  - Order urine tests only in patients with urinary symptoms
  - The best thing you can do with asymptomatic bacteriuria is leave it alone
  - Pyuria is not a reliable marker for UTI
  - Changes in the urine are not reliable markers for UTI



WBC, white blood cell

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### Audience Response Question #4

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?

- Cystoscopy and biopsy
- Diabetes mellitus
- Kidney transplant
- Knee prosthesis placement

### Audience Response Question #5

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?

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

### Audience Response Question #6

A 37-year-old woman with a history of recurrent UTIs developed typical symptoms of urgency, frequency, and dysuria five days ago. On the advice of her close friend, she decided to treat this UTI with a nutritional supplement instead of antibiotics. Symptoms did not resolve, and she developed worsening low back pain. This morning she vomited once. In the office, her temperature is 100.5F, BP 135/70, HR 110, RR 16. She is not currently vomiting and can sip water.

You do not have any prior urine cultures to guide your therapy. Assuming you can manage her as an outpatient, what treatment would you offer?

- Oral trimethoprim-sulfamethoxazole for 5 days
- Oral ciprofloxacin for 14 days
- One dose of ceftriaxone IM plus oral ciprofloxacin for 7 days
- Cephalexin for 7 days
- Nitrofurantoin for 10-14 days

BP, blood pressure; HR, heart rate; IM, intramuscular; RR, respiratory rate

### Management of Pyelonephritis

- Many clinical trials included pyelonephritis with complicated UTI
- Complicated UTI increasingly means urinary tract infection that has spread beyond the bladder (to kidneys, bloodstream)
- Empiric oral therapy
  - Trimethoprim-sulfamethoxazole 7-14 days
  - Fluoroquinolones 5-7 days
  - Consider a one-time dose of IM ceftriaxone or gentamicin while awaiting cultures
  - Oral beta-lactams (cephalosporins, amoxicillin-clavulanate) 10-14 days
- Empiric intravenous therapy
  - IV cephalosporins, piperacillin-tazobactam, carbapenems, fluoroquinolones
- To avoid: nitrofurantoin and fosfomycin

Johnson and Russo, NEJM 2018. 378;1

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## Audience Response Question #7

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)

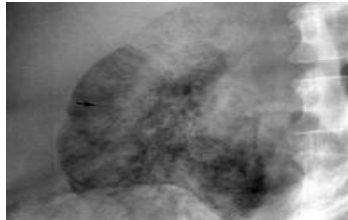
UA: WBC 250, RBC too numerous to count, no bacteria

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.

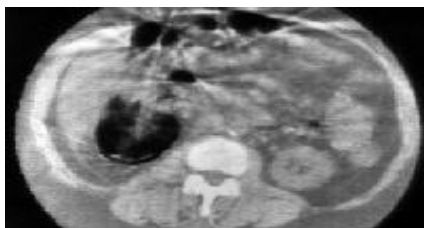
## Audience Response Question #7: X-Ray of Abdomen



What would you order next?

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

## Abdominal CT with Emphysematous Pyelonephritis



CT showing gas within the renal parenchyma

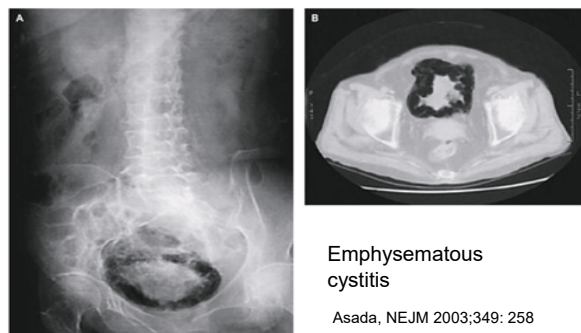
## Clinical course of case #7

- 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 coronary artery bypass surgery

## 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

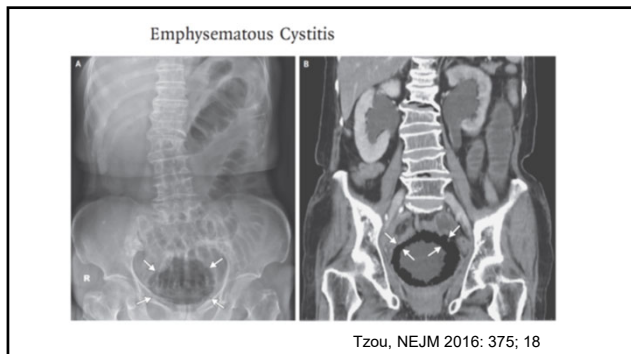


Emphysematous cystitis

Asada, NEJM 2003;349: 258

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## 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**

## Audience Response Question #8

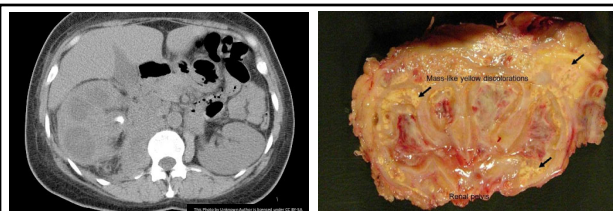
57-year-old man with spinal cord injury (T12) and a chronic indwelling urinary catheter. Two years prior he had a fever, and his blood grew *S. aureus* and *Pseudomonas*. Urine grew lactose negative GNR and gram-positive organisms.

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:

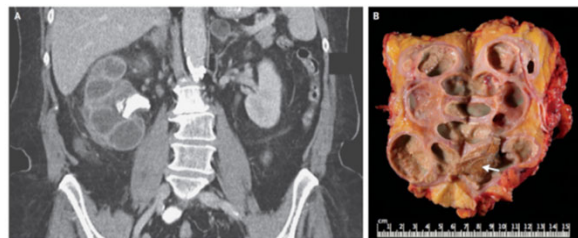
- Renal biopsy
- 3-6 months of antibiotics based on current urine culture
- Percutaneous drainage
- Nephrectomy



## 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 and recurrent cystitis in women—nitrofurantoin
- Asymptomatic bacteriuria
  - Pregnant women—screen and treat
  - Urologic surgery—screen and treat
  - Everyone else—don't test the urine
- Catheter-associated UTI—ensure drainage
- Pyelonephritis—treat with tissue-active agent
- Urosepsis and worse
  - Emphysematous pyelonephritis—drainage
  - Emphysematous cystitis—medical management
  - Xanthogranulomatous pyelonephritis—removal

Is everything clear now?

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