

Urinary Tract Infections for Hospital Medicine

Current Strategies and Common Questions in the Management

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Conflicts

None (commercial)

Editorial:

IDSA UTI guidelines expert panel

UTI topic editor, DynaMed

OBJECTIVES

General Principles in diagnosis and management of urinary tract infections

- UTI syndrome definitions
- When to test, what tests to order
- Empiric therapy versus test-guided treatment choices

Challenges in diagnosis and management of urinary tract infections in the Hospital

- Multi-drug resistance organisms (MDRO)
- Antibiotic allergies
- Complicated and bacteremic UTI syndromes - antibiotic choice and duration
- Inpatient to outpatient transition
- UTI and prostatitis in men
- Catheter and instrument associated Urinary tract infections
- Asymptomatic bacteriuria and funguria – when to test and when to treat?

Role of imaging and consultation

Case one

47F, BMI 34.2, prediabetes (A1C 6.1), not pregnant, no other significant PMH, no medications, admitted with a pulmonary embolus following a 13-hour flight. On ROS reports a 3-day history of dysuria and urinary urgency. Prior similar episodes, ~once per year.

No fever, nausea, vomiting, flank pain

No recent hospitalization or antibiotics except malaria prophylaxis for her trip

Simple cystitis
AKA uncomplicated UTI

Classic lower tract symptoms
(dysuria, urgency, frequency)

No upper tract symptoms or fever

Evolving new Definition of uUTI and cUTI

TRADITIONAL DEFINITION	EVOLVING DEFINITION
Uncomplicated UTI Acute cystitis in healthy, non-pregnant young (premenopausal?) woman without diabetes or urologic abnormalities	Uncomplicated UTI Simple cystitis in men and women (assumes no fever)
Acute Pyelonephritis	Complicated UTI Everything else. <u>Examples:</u> <ul style="list-style-type: none"> - Pyelonephritis - Prostatitis - Fever or systemic toxicity - Bacteremia or sepsis - Obstruction
Complicated UTI Everything else	



Case one – simple, community acquired, “outpatient” cystitis what to do?

47F, BMI 34.2, prediabetes (A1C 6.1), not pregnant, no other significant PMH, no medications, admitted with a pulmonary embolus following a fall. She reports a 3-day history of dysuria, urgency, and suprapubic pain. Similar episodes, ~once per year.

No fever

No recent
prophylaxis

47F with simple
cystitis

Survey
(no one correct
answer)

No upper tract symptoms or fever

- Treat the PE, UTI sx may go away
- Empiric antibiotic therapy, test if no response
- Test and treat empirically while awaiting culture
- Test and await culture to treat

Simple (afebrile or uncomplicated) Cystitis - what if we ignore it? Natural History of Untreated Simple Cystitis (young, normal GU tract)

- Episodes resolve at 2-4 weeks in ~40-50%
 - may account for some of response rate reported in antibiotic trials
- Majority (~70%) clear bacteriuria eventually (weeks to months)
- Progression to pyelonephritis or renal failure rare, if normal GU tract anatomy and function

Wigton, *et al.*, J Gen Int Med, 1999
Hooton, Infect Dis Clin North Am 2003, Hooton, CID, 2004, Christiaens, Br J Gen Pract. 2002, Falagas, J of Infection, 2009



Table 3. Symptomatic and bacteriological effect of nitrofurantoin versus placebo (CFU/ml or more on inclusion, n = 56).

	Nitrofurantoin (Day 1, n = 29)	Placebo (Day 1, n = 27)
Day 3 — bacteriology: (nitrofurantoin n = 26, placebo n = 25; symptoms: nitrofurantoin n = 25, placebo n = 25 ^c)		
Bacteriological cure	21 (81)	5 (20)
Symptomatic cure or improvement	20 (80)	11 (44)
Day 7 — bacteriology: (nitrofurantoin n = 23, placebo n = 22; symptoms: nitrofurantoin n = 24, placebo n = 24)		
Bacteriological cure	17 (74)	9 (41)
Symptomatic cure or improvement	21 (88)	13 (54)

Testing for Simple Cystitis in Women with simple (outpatient) cystitis

PROS

Diagnostic accuracy: sensitivity if only 1 symptom ~50% (dysuria a bit higher)

A negative urinalysis can exclude a UTI

Resistance on the rise — tailor antibiotic to organism

Societal / environmental and personal costs of antibiotic overuse



Testing for Simple Cystitis in Women with simple (outpatient) cystitis

CONS

Sensitivity of symptom-triad for cystitis (healthy non-pregnant cis-woman) ~96%

Causative organisms predictable

Most respond clinically to a standard empiric antibiotic course

Cost of visit and tests

- Several phone triage studies show it's a cost-effective approach ¹⁻²

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A negative urinalysis can exclude a UTI

Resistance in the community on the rise – tailor antibiotic to organism

Societal / environmental and personal costs of antibiotic overuse



1. Fenwick. Brit J Gen Practice, 50: 635 (2000)
2. Saint, et al., Am J Med, 106: 636 (1999)

Non-culture Diagnostic Options

Looking for evidence of inflammation

Pyuria



≥10 WBC/mL in midstream urine (≥ 5 in a sediment of spun urine)



Pyuria is present in almost all acute cystitis

Sensitivity high: ~90%



Pyuria without acute cystitis is common

Specificity low: ~70%



Dipstick leukocyte esterase – rapid screening test for pyuria

Sensitivity (for detecting >10WBC/mL): 75-96%

Specificity for pyuria 94-98%

Non-Culture Diagnostic Options

Looking for evidence of Bacteriuria

Nitrite (positive helpful, negative not)

- Sensitivity poor: ~20%
 - False negative: low (10^2 - 10^5 /mL) colony counts
 - Non-producers of nitrite: *Enterococci*, *S. saprophyticus*, *Acinetobacter*, dilute urine
- Specificity for bacteriuria high: ~95% (GOOD)
 - false positives are rare

Kuijper, *et al.* Eur. J. Clin. Micro Infect Dis 22; 228 (2003)



Urinalysis, Positive and Negative Predictive Values for positive culture (by age group)

Table 1
Diagnostic performance of test strips and sediment microscopy in all subjects and different age groups

Test	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
LE				
All	71.0 (67.6-74.2)	83.6 (83.2-84.2)	9.2 (8.5-10.0)	99.3 (99.1-99.4)
0-1	63.7 (53.6-73.0)	68.8 (67.5-70.0)	4.0 (3.1-5.0)	98.9 (98.5-99.3)
2-17	65.7 (58.7-72.2)	88.6 (88.1-89.0)	5.3 (4.4-6.3)	99.6 (99.5-99.7)
18-69	77.0 (71.3-82.0)	80.8 (79.8-81.8)	14.6 (12.8-16.6)	98.8 (98.5-99.1)
≥70	72.4 (65.6-78.5)	66.0 (62.0-69.8)	42.1 (36.8-47.5)	87.5 (84.0-90.4)
Nitrite				
All	17.7 (15.0-20.6)	90.1 (89.7-90.5)	4.0 (3.4-4.7)	97.9 (97.7-98.2)
0-1	6.9 (2.8-13.6)	90.1 (89.2-90.9)	1.4 (0.6-2.8)	98.0 (97.5-98.3)
2-17	21.9 (16.4-28.3)	97.3 (97.1-97.5)	7.4 (5.4-9.8)	99.1 (99.1-99.1)
18-69	19.9 (15.2-25.4)	68.1 (66.9-69.2)	7.6 (1.9-3.4)	95.2 (94.5-95.8)
≥70	16.1 (11.3-21.9)	60.1 (56.0-64.1)	12.1 (8.4-16.7)	62.7 (63.3-71.7)
Bacteriuria				
All	78.8 (75.7-81.6)	97.8 (97.6-97.9)	45.4 (42.7-48.1)	99.5 (99.4-99.5)
0-1	43.1 (33.4-53.3)	98.0 (97.5-98.3)	30.1 (22.8-38.0)	98.8 (98.2-99.1)
2-17	72.6 (65.9-78.7)	98.3 (98.2-98.5)	29.8 (25.8-34.5)	99.7 (99.6-99.8)
18-69	91.8 (87.7-94.9)	97.0 (96.5-97.4)	56.4 (51.4-61.2)	99.6 (99.4-99.8)
≥70	86.4 (80.9-90.9)	84.4 (81.2-87.2)	65.4 (59.3-71.4)	94.8 (92.5-96.5)
WBC				
All	68.2 (64.8-71.5)	87.8 (87.5-88.2)	11.7 (10.7-12.8)	99.2 (99.0-99.3)
0-1	49.0 (39.0-59.1)	81.9 (80.9-83.0)	5.2 (3.9-6.8)	98.8 (98.4-99.1)
2-17	41.8 (34.9-48.9)	90.3 (89.8-90.7)	4.0 (3.2-4.9)	99.4 (99.3-99.5)
18-69	84.0 (78.9-88.3)	85.6 (84.7-86.5)	20.0 (17.6-22.5)	96.2 (96.3-96.4)
≥70	84.4 (78.6-89.2)	76.0 (72.3-79.4)	54.6 (48.8-60.2)	93.5 (90.3-95.5)



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Poor

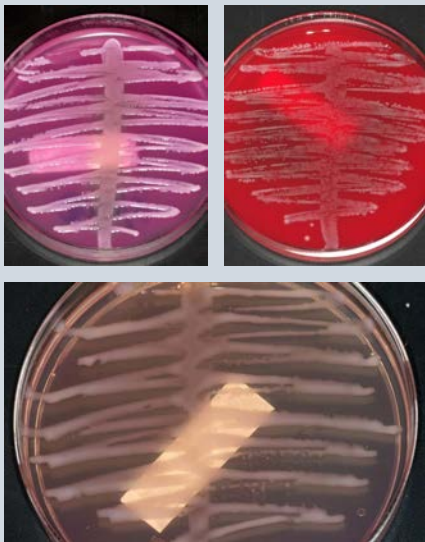
Excellent



Diagnostic Options – Culture and Susceptibilities

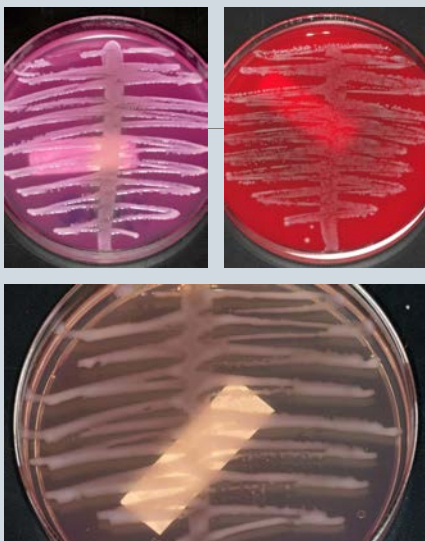
Why Culture?

- Confirms diagnosis (significant bacteriuria, >100,000 CFU/mL*)
- Identifies causative organism
- Provides susceptibility testing to tailor therapy accordingly
 - Helps find narrowest agent
 - Assures no resistance



What percent of young women with simple cystitis (frequency, urgency, or dysuria) have $>10^5$ CFU/ mL of a single uropathogen in the urine?

- A. 85%
- B. 65%
- C. 50%
- D. 33%
- E. 25%



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- B. 65%
- C. **50%**
- D. 33%
- E. 25%



What about the other 50%?

Most have “acute urethral syndrome”

If therapy delayed ~2d – 48% will have $>10^5$ (early presenters)

10^2 - 10^5 CFU 95% sensitive & 85% specific for UTI

Studies in young women: 10^2 cfu of GNR (e.g. *E. coli*) predictive of UTI (compared to catheterized urine)

Some have “symptomatic abacteriuria” e.g. urethritis (GC/chlamdia /mycoplasma / trichomonas / other), genital herpes vaginitis, non-infectious process



Stamm, et al. *NEJM*; 1980 303: 409

Hooten et. Al. *NEJM*; 2013 369:20

Simple cystitis in postmenopausal women Is it truly [much more] complicated?

Table 1. Distribution of uropathogens that cause urinary tract infections in women.

Uropathogen	Frequency among women, by age group, % ^a	
	15–50 years of age	>50 years of age
<i>Escherichia coli</i>	72	53
<i>Klebsiella</i> species	6	12
<i>Proteus</i> species	4	6
<i>Enterobacter</i> species	2	2
<i>Pseudomonas aeruginosa</i>	1	4
Other gram-negative rod	2	4
<i>Enterococcus</i> species	5	12
<i>Staphylococcus aureus</i>	2	2
<i>Staphylococcus saprophyticus</i>	2	0.2
Coagulase-negative staphylococci	3	2
Other	1	3

What changes after menopause?

Diversity of organism

Gupta *CID* 2001(33): 89



IDSA / International Guidelines (2010) Empiric Treatment of Acute Uncomplicated Cystitis

Recommended

Nitrofurantoin macrocrystals 100mg twice daily x 5 days

TMP/SMX DS twice daily x 3 days
if community *E. coli*'s resistance rate <20%

Fosfomycin 3 gm x1

Pivmecillinam 400 mg twice daily x 5 days*

Not recommended

Fluoroquinolones 3 days

β -lactams

Resistance higher (not just to TMP/SXT)

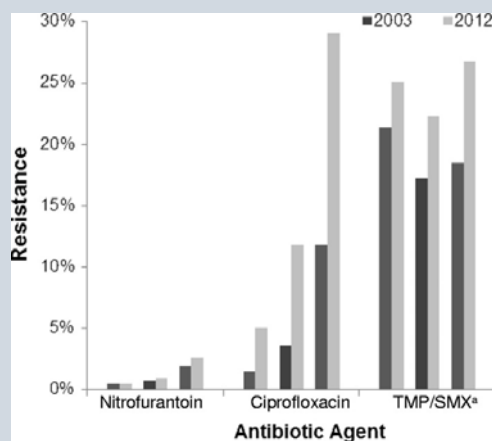
Efficacy in some recent studies lower

Nitrofurantoin and fosfomycin NOT RECOMMENDED if early pyelonephritis suspected

- When diagnosis in question – urinalysis with reflex culture
- When resistance a concern – culture (may start empiric antibiotic while waiting)

Antibiotic Resistance among Urinary Isolates from Female Outpatients in the United States in 2003 and 2012

Sanchez et al [Antimicrob Agents Chemother](#). 2016 May; 60(5): 2680–2683



Surveillance Network USA

Urinary isolates from female outpatients 2012 (*n* = 305,749) *E. coli* in 64.9%

E. coli resistance to nitrofurantoin low (<3%) across all age groups.

E. coli resistance to ciprofloxacin was high among adults (11.8%) and elderly outpatients (29.1%).



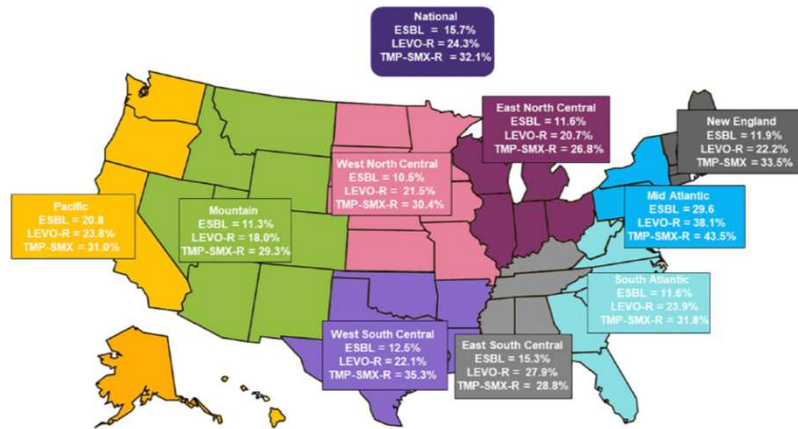


Fig 1. National and regional prevalence of ESBL phenotypes, levofloxacin- and trimethoprim-sulfamethoxazole-resistant phenotypes among 1831 isolates of *E. coli* from UTIs in the USA in 2017. ESBL = extended spectrum β -lactamase, LEVO-R = levofloxacin-resistant, TMP-SMX-R = trimethoprim-sulfamethoxazole-resistant.

National trends in urinary *E. coli* susceptibilities

Fosfomycin (3-g x1) or Nitrofurantoin (100 mg thrice daily x 5 days) for UTI

93% completed trial, 73% + baseline culture

Resistance to both agents low for *E. coli*

Klebsiella and *Proteus* resistance rates higher

Clinical Resolution 28d ($P < .004$, $.001$ for *E. coli*)

- Nitrofurantoin 70% (*E. coli* 78%)
- Fosfomycin 58% (*E. coli* 50%)

Micro Resolution 28d

- Nitrofurantoin 74% (*E. coli* 84%)
- Fosfomycin 63% (*E. coli* 59%)

- Methodologic problems: open label, lots of LTF, positive cultures at baseline not required (27% did not have)
- Response rates lower than other studies for both arms
- Nitrofurantoin dose 100 mg TID (in US 100 mg BID)

48F, MS, takes ocrelizumab (B cell depleting agent), neurogenic bladder, CIC. Has h/o recurrent UTI. Childhood allergy to amoxicillin (rash). Admitted for meropenem therapy for MDR E coli cystitis.

SX: malaise, dysuria, "bladder spasms", leg spasms, low back discomfort, no flank pain, no nausea or systemic toxicity.

UA: >182W, nitrites.

Cx: "ESBL" producing *E. coli*.

Susceptible: amox/clav, pip/tazo, meropenem, imipenem.

Resistant: trimethoprim/sulfa, FQ, aminoglycosides.

Which of the following is correct

?

- A. Oral fosfomycin is adequate if susceptible
- B. Oral nitrofurantoin adequate if susceptible
- C. Amox/clav adequate after test dose or skin test
- D. Once daily IV ertapenem
- E. All of the above



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Definition: afebrile,
(catheter-
associated) cystitis
with MDR organism
in a patient with
abnormal bladder
function

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PMCID: PMC5414046
PMID: 28480273

The Increase in Hospitalizations for Urinary Tract Infections and the Associated Costs in the United States, 1998–2011

Jacob E. Simmering,¹ Fan Tang,² Joseph E. Cavanaugh,³ Linnea A. Polgreen,⁴ and Philip M. Polgreen^{2,5}

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1998 to 2011:
108,672,713
hospital
admissions in the
NIS

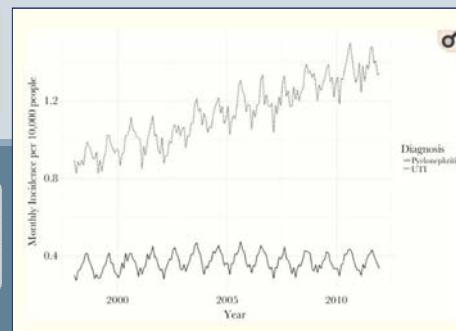
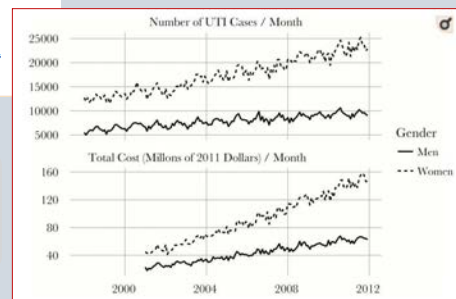
- 960,516 for UTIs in adults

UTI
hospitalizations

- Increasing over time
- Seasonal, peaking in summer

Severity of UTI
admissions

- Decreasing
- Suggesting patients previously treated as outpatients may now be admitted due to increasing resistance



UTI with Multidrug Resistant Organisms (MDRO)

- MDRO: resistance to ≥ 1 antibiotic classes (prior definition 3 or more classes)
- Risk factors for MDRO
 - Urinary MDRO in the past
 - Recent stay at healthcare facility (hospital, LTAC)
 - Travel to areas with high rate of resistance (remember case 1?)
- Rates of both healthcare and community associated MDRO UTI on the rise:
 - Before 2003 most ESBL producing Enterobacteriaceae were health-care associated *Klebsiella*
 - Since 2003 steady increase in highly resistant and ESBL- producing *E. coli* in community associated UTI
 - Many retain susceptibility to fosfomycin and nitrofurantoin

* ESBL: Extended spectrum beta lactamase producing Enterobacteriaceae

Walker et al. CID 2016; 63:960

Sanchez et al. J Antimicrob Chemother 2014; 69 :325

EUCAST expert rules in antimicrobial susceptibility testing

Not all resistance is acquired Intrinsic resistance in Enterobacteriaceae

Rule no.	Organisms	Ampicillin	Amoxicillin-clavulanate	Ticarcillin	Piperacillin	Cefazolin	Cefoxitin	Cefamandole	Cefuroxime	Aminoglycosides	Tetracyclines/tigecycline	Polymyxin B/Colistin	Nitrofurantoin
1.1	<i>Citrobacter koseri</i>	R		R	R								
1.2	<i>Citrobacter freundii</i>	R	R			R	R						
1.3	<i>Enterobacter cloacae</i>	R	R			R	R						
1.4	<i>Enterobacter aerogenes</i>	R	R			R	R						
1.5	<i>Escherichia hermannii</i>	R		R									
1.6	<i>Hafnia alvei</i>	R	R		R								
1.7	<i>Klebsiella spp.</i>	R		R									
1.8	<i>Morganella morganii</i>	R	R			R			R		R	R	R
1.9	<i>Proteus mirabilis</i>											R	R
1.10	<i>Proteus vulgaris</i>	R				R		R	R		R	R	R
1.11	<i>Proteus penneri</i>	R				R		R	R		R	R	R
1.12	<i>Providencia rettgeri</i>	R	R			R					R	R	R
1.13	<i>Providencia stuartii</i>	R	R			R				Note ²	R	R	R
1.14	<i>Serratia marcescens</i>	R	R					R	R	Note ²		R	R
1.15	<i>Yersinia enterocolitica</i>	R	R	R		R	R	R					
1.16	<i>Yersinia pseudotuberculosis</i>											R	

R = resistant

<https://www.scinapse.io/papers/2102217986>

https://www.eucast.org/expert_rules_and_expected_phenotypes

Know your local antibiogram BWH antibiogram, 2023

All isolates:

Gram Negative Rods	#	AMP	AMC	TZP	FOX	CRO	CAZ	FEP	CIP	LVX	GEN	TOB	AMK	MEM	SXT	TET	NIT
<i>Citrobacter freundii</i> [^]	167	R	R	79	R	72	73	97	93	92	96	95	99	99	92	89	*97
<i>Citrobacter koseri</i>	146	R	98	99	94	100	98	100	99	99	100	100	100	100	100	99	*97
<i>Enterobacter cloacae</i> [^]	373	R	R	74	R	71	73	97	89	85	97	94	99	99	86	85	*35
<i>Escherichia coli</i> [^]	5682	58	86	97	93	92	94	98	81	76	91	91	99	99	76	76	*98
<i>Klebsiella aerogenes</i> [^]	224	R	R	85	R	85	84	99	96	93	100	100	100	100	98	97	*13
<i>Klebsiella oxytoca</i>	270	R	92	93	96	90	93	96	94	94	96	96	100	99	94	94	*86
<i>Klebsiella pneumoniae</i>	1269	R	91	93	93	88	88	96	84	82	94	93	99	99	85	78	*27
<i>Morganella morganii</i>	97	R	95	46	88	84	100	90	90	97	97	100	100	88	74	R	
<i>Proteus mirabilis</i>	634	79	---	99	97	99	99	88	88	88	93	95	99	100	83	R	R
<i>Proteus vulgaris</i> [^]	32	R	R	100	100	81	100	100	100	97	100	100	100	100	91	R	R
<i>Serratia marcescens</i>	206	R	R	99	R	95	97	99	91	89	98	92	100	99	98	29	R

[^] *Citrobacter freundii*, *Enterobacter cloacae*, *Klebsiella aerogenes*, and *Proteus vulgaris* may develop resistance during prolonged therapy with third-generation cephalosporins
^{*} Not all isolates were tested for susceptibility, nitrofurantoin results are based off of urinary isolates only
^{^^} Fosfomycin susceptibility only reported for *E. coli* urinary isolates (99% in 2023, n=4938)

ICU:

Gram Negative Rods	#	AMP	AMC	TZP	FOX	CRO	CAZ	FEP	CIP	LVX	GEN	AMK	TOB	MEM	SXT	TET	NIT
<i>Enterobacter cloacae</i> [^]	39	R	R	38	R	31	33	95	74	72	90	97	79	97	72	67	****
<i>Escherichia coli</i>	93	54	77	92	88	80	85	90	67	61	89	99	88	100	70	71	*96
<i>Klebsiella pneumoniae</i>	68	R	76	84	90	66	69	81	69	66	79	100	81	99	68	66	****
<i>Proteus mirabilis</i>	22	64*	---	100*	95*	91*	100*	95*	64*	64*	82*	95*	82*	100*	77*	R	R
<i>Serratia marcescens</i>	26	R	R	96*	R	92*	92*	96*	85*	85*	92*	100*	88*	96*	96*	38*	R

MDRO UTI – using oral options

Patient able to take oral medicine

An effective oral option for the syndrome is available (e.g. cystitis)

- nitrofurantoin (simple cystitis), TMP/SXT, amox/clav, cefpodoxime, FQ, fosfomycin

Step down (or up ☺) /deescalation: cUTI or febrile UTI on parenteral therapy, showing clinical improvement, source control achieved

- nitrofurantoin or fosfomycin may not be appropriate as step-down for pyelonephritis/bacteremia

Confirm allergies, consider [graded?] challenge or skin test based on history

Oral tetracyclines for UTI?

- not stable in urine, hepatically cleared - if feasible chose alternatives
- typically, not used bacteremia

Nitrofurantoin

Only one indication: **afebrile (simple) cystitis**

IDSA guidelines dose 100 mg PO BID (some countries TID)

Broad, resistance rates remain **low** (1-3% MDR *E.coli*)

Barriers/limitations to use:

- Tissue concentrations low: **not** for systemic/deep tissue infection (blood stream, kidney, prostate)
- GFR: **PDR: do not use at CrCl <60 ml/min** (insufficient renal excretion, toxicity)
 - 2015 Beers criteria revision: **more liberal CrCl threshold in elderly** (<30 rather than <60 mL/min) if short term (≤7 days)
- Side Effects
 - More common in elderly, with renal impairment
 - common: nausea (8%) & headache (6%)
 - less common but more serious: hepatitis, neuropathy
 - Rare, idiosyncratic, but serious: **interstitial lung disease / pulmonary fibrosis**

J Am Geriatr Soc 63:2227–2246, 2015

Fosfomycin

Phosphonic acid, inhibits bacterial cell wall synthesis

- FDA approval and lab testing: **E. coli and E. faecalis** uncomplicated cystitis

Susceptibility in urinary isolates (overestimated?):

- ~90.6% of *Enterococci*, 90-94% of *Enterobacteriaceae* (~95% *E. coli*, 90-95% *Klebsiella*), 89.7% PsA
Interpretation of susceptibility varies

Response rates 3g single dose: 78%-83% (58% in a recent study)

Complicated cystitis: may repeat dose every 24-72 hours x 2-4 doses (or more)

Barriers/limitations to use:

- not routinely tested for
- Testing guidelines/approval in USA limited to *E coli* and *Enterococcus*
- **\$\$\$**, prior auth

Hirsch. *Int J Antimicrob Agents* 2015; 46 :642
Liu. *J Microbiol Immunol Infect* 2011; 44:364

Fluoroquinolones in UTI

Historically *E coli* resistance <10%, recently ~ 17% in community, 40% in some countries

For GNR in UTI: cipro preferred

- levofloxacin/moxifloxacin add atypical/respiratory coverage ,moxifloxacin loses PsA

Notable advantages:

- Bioavailability, tissue penetration (prostate, abscesses, kidney), tolerability, bactericidal, inexpensive, broad
- Shorter oral courses

Barriers/limitations to use:

- Connective tissue damage
 - tendinopathy /tendon rupture/ aneurysms/retinal detachment (age>60 Aj RR 3), QT prolongation/arrythmia, neuropsychiatric side effects/neuropathy, emerging resistance, hypoglycemia, teratogenic
- Stewardship: C. difficile and MRSA selection
- Drug interactions (Mg, Fe, Ca, Al decrease absorption)

Should we use prior microbiological susceptibility data from the patient or the community to select empiric therapy in the hospital?

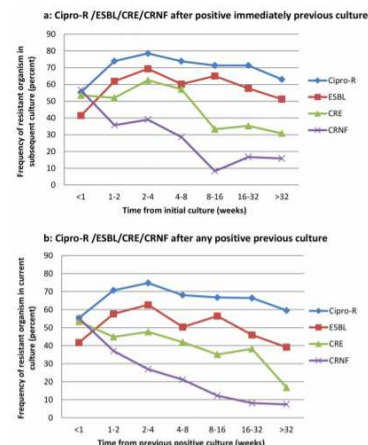
19,546 urine cultures from 4,409 **inpatients** with UTI, and a **previous resistant urinary isolate**

Resistant rates **high**: cipro 47.7%, ESBL 31.9%, CRE 1.7%, CRNF 2.6% *

A previous cultures with resistance was **highly predictive** of a repeat resistant organism with the same phenotype

While the association declined over time, it remained significant at 6m and still high for nearly 2 years

* ESBL: Extended spectrum beta lactamase producing *Enterobacteriaceae*, CRE: Carbapenem R *Enterobacteriaceae*, CRNF: carbapenem-resistant non-fermenter



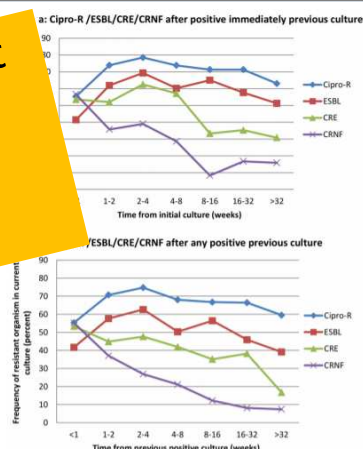
Should we use prior microbiological susceptibility data from the patient or the community to select empiric therapy in the hospital?

19,546 urine cultures from 4,409 inpatients with UTI, and a previous resistant urinary isolate

Resistant rates high: cipro 45%, ESBL 1.7%, CRNF 2.6%

A previous resistant isolate may persist and can / should be used guide antibiotic choice while culture pending

* ESBL: Extended spectrum beta lactamase producing *Enterobacteriaceae*, CRE: Carbapenem R *Enterobacteriaceae*, CRNF: carbapenem-resistant non-fermenter



Antimicrobial agents and chemotherapy 2016; 60: 4717-4721

Same MDR organism, different patient

75M, with frequent relapses or *E. coli* UTI, admitted to initiate IV meropenem for presumed **chronic prostatitis** with MDR *E. coli*, then transfer to the home hospital service for a long course

UA: >182W, nitrites.

Cx: "ESBL" producing *E. coli*.

Susceptible: amox/clav, pip/tazo, meropenem, imipenem.

Not checked: Ertapenem

Resistant: trimethoprim/sulfa, FQ, aminoglycosides.

Which of the following is adequate (may chose more than one correct answer)

- A. Oral fosfomycin is adequate if susceptible
- B. Oral nitrofurantoin is adequate if susceptible
- C. Amox/clav may be given after a test dose or skin test
- D. Once daily ertapenem is likely adequate



Cystitis in Men Therapeutic Dilemmas

- Treatment duration - 7 Versus 14 days?
 - Men with afebrile cystitis (VA study): 272 men (69Y median age) randomized within 7d of starting cipro or TMP/SXT to stop at 7d or continue for 14d. Symptom resolution not significantly different ($\approx 92\%$). 28d recurrence of sx similar ($\approx 12\%$). No patients progressed to febrile or upper UTI
 - Men with febrile UTI (French trial): 282 men with, FQ use. Treatment success higher in 14-day group compared to 7-day group
 - For simple afebrile cystitis, without evidence of prostatitis, 7 days likely adequate
- Are antimicrobials penetrating prostate preferred for simple cystitis?
 - Possibly, but not addressed in above trials

Drekonja DM et al. JAMA 2021 Jul 27; 326:324
Lafaurie M et al, CID 2023 June 15; 2154-2162

Bacterial Prostatitis - General principals

Acute prostatitis

- Acute onset, typically febrile, lower tract urinary symptoms and pelvic or rectal pain/tenderness

Chronic prostatitis

- Indolent
- Typical presentation: short interval relapses of cystitis episodes, after adequate therapy, with same isolate
- Treatment duration: 6-12 weeks

Antibiotics for prostatitis:

- Small, non-protein-bound, lipid-soluble, non-ionized, alkaline, penetrate prostate well
- Standard: TMP/SXT or FQ such as Cipro – good penetration.
- Doxycycline or azithromycin penetrate well
- Beta lactams penetrate less well (challenge in some gram-positive infections)
- Recent study of chronic prostatitis used fosfomycin every 1-2 days for 6-12 days with good success (Karaikos. *J Antimicrob Chemother* 2019; 74(5):1430-1437)

Same MDR organism, different patient

75M, with frequent relapses of *E. coli* UTI, admitted to initiate IV meropenem for presumed **chronic prostatitis** with MDR *E. coli*, then transfer to the home hospital service for a long course

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Resistant: trimethoprim/sulfa, FQ, aminoglycosides.

Which of the following is adequate (may chose more than one correct answer)

- A. Oral fosfomycin is adequate if susceptible ✓
- B. Oral nitrofurantoin is adequate if susceptible ✗
- C. Amox/clav may be given after a test dose or skin test **+/-** as in MAYBE
- D. Once daily ertapenem is likely adequate ✓

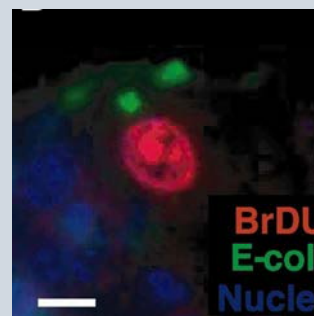


Not all relapse / symptom persistence is prostatitis

Possible reasons for persistent UTI symptoms in men and women

- Persistence in bladder epithelium (urothelium)
- Failure to eradicate vaginal carriage
- Unsuspected upper tract infection (rare)
- Structural abnormalities (uncommon for cystitis)
- Antibiotic resistance (intrinsic or acquired)
- Reinfection
- Symptoms not due to cystitis (common in elderly)

E. coli can survive inside bladder epithelial cells in a quiescent, antibiotic-tolerant, state

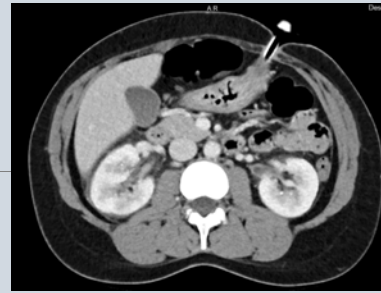


Mysorekar, Proc Natl Acad Sci 103: 14170 (2006)



59F with stress incontinence, normal PVR, several prior episodes of cystitis, all with *E. coli*. Takes methenamine, vitamin C, vaginal estrogen, cranberry, and d-mannose for UTI prevention. Cystitis episodes are typically treated with 7 days of nitrofurantoin; last 3 ago. No prior pyelonephritis or urosepsis episodes. No recent travel or hospitalization. No recent antibiotic except for UTI. No h/o kidney stones.

Component	8/23/24 2335
Ref Range & Units	
WBC	>182 ^
<10 /hpf	
RBC	19 ^
0 - 2 /hpf	
BACTERIA	3+ !
None /hpf	
SQUAMOUS CELLS	Trace !
None /hpf	
HYALINE CAST	0-2
0 - 2 /hpf	
TRANSITIONAL EPITH	None



Admitted from the ER for a 2-day h/o acute onset fever, chills, progressive R > L flank pain. Temp 101.9, HR 102, BP 105/60, UA with 3+ leuk esterase, +blood, bacteria, + nitrite. She feels better after fluid bolus and acetaminophen and HR down to 88.

Allergies

- Penicillin - hives (pos skin test)
- Ceftriaxone - lip swelling and SOB
- TMP/Sulfa - lip swelling and skin erythroderm



Prior Isolates all with this *E. coli*

Susceptibility

	Escherichia coli	
	KIRBY BAUER DISK DIFFUSION METHOD	MIC METHOD
Amikacin		<=2 Susceptible
Amoxicillin + Clavulanate		<=2 Susceptible
Ampicillin		<=2 Susceptible
Cefazolin		<=4 Susceptible
Cefepime		<=1 Susceptible
Cefoxitin		<=4 Susceptible
Ceftazidime		<=1 Susceptible
Ceftriaxone		<=1 Susceptible
Ciprofloxacin		<=0.25 Susceptible
Ertapenem		<=0.5 Susceptible
Fosfomycin	19 Susceptible	
Gentamicin		<=1 Susceptible
Levofloxacin		<=0.12 Susceptible
Meropenem		<=0.25 Susceptible
Nitrofurantoin		<=16 Susceptible
Piperacillin-tazobactam		<=4 Susceptible
Tetracycline		<=1 Susceptible
Tobramycin		<=1 Susceptible
Trimethoprim/sulfamethoxazole		<=20 Susceptible

Febrile Pyelonephritis without What empiric treatment would you give

1. Oral Fosfomycin
2. Fluoroquinolone (IV/PO as tolerated)
3. IV aztreonam
4. IV ceftriaxone with desensitization
5. IV ertapenem
6. IV amikacin x1 dose awaiting results

Definition: febrile pyelonephritis, no obstruction, no shock, no MDR risk, multiple antibiotic allergies



Empiric ABX for Febrile or Hospitalized UTI

Use prior patient history and hospital antibiogram/local resistance to modify these suggestions

No sepsis/ no shock/no resistance risk: ceftriaxone (or 4th gen cephalosporin), cipro/levofloxacin (if no recent use), pip/tazo (?consider amp/sulbactam or trim/sulfa if recent culture susceptible)

***Pseudomonas aeruginosa*:** cefepime, ceftazidime, or piperacillin-tazobactam if previously susceptible

MDRO/ESBL Enterobacteriaceae: carbapenem (or pip/tazo) – favor carbapenem for shock
◦ Ertapenem versus meropenem: different spectrum, time dependent/pk/pD in critical illness

Concern for **SPICE organism/AMP-C**, sick: carbapenem (or cefepime when appropriate)

Severe pen beta-lactam allergy -> ?aztreonam (call ID/allergy)

Suspected **gram-positive cocci**: vancomycin, ?linezolid (not renally cleared) or daptomycin (no PNA)

Septic, sick, high resistance risk, empiric: advanced generation cephalosporin (cefepime), carbapenem, or pip-tazo (if previously susceptible). **CALL ID.** Consider two agents until susceptibility known

Pyelonephritis case continues...

Patient treated with IV cipro given vomiting. Fever, nausea and vomiting resolve within 36 hours. Urine culture with same pan-susceptible *E coli*. Antibiotics changed to oral cipro.

HOW LONG WILL YOU TREAT?



Duration of antibiotics for Pyelonephritis and Acute Febrile UTI Short (7d) vs long (10-14d)

Uncomplicated pyelonephritis: data support short (5-7d FQ, 7d other) as good as long (10-14 days)

- ❖ Most studies *E coli* dominant and excluded catheterized patients
- ❖ Most studies looked at FQ for shorter durations
- ❖ Who may require longer?
 - ❖ Some examples: foreign body (catheters, stones), obstruction, severe sepsis, immunosuppression, slow to respond, pregnant, abscess

For Febrile UTI without bacteremia or pyelonephritis

- ❖ Data limited
- ❖ French Study in men suggested 14d better than 7d (acute prostatitis?) Lafaurie, CID, 2023 <https://doi.org/10.1093/cid/ciad070>
 - ❖ possibly longer courses for prostatitis
- ❖ Clinical response + source control should guide decision on duration

Case continues

On day-3, she's ready for discharge on oral cipro. Right before discharge blood cultures from admission with growth of GNR. Rapid detection identifies *E coli* without ESBL. Repeat blood cultures drawn.

Patient without fever, improving symptoms. Tolerating oral therapy. What would you suggest:

1. Stop oral cipro, begin IV ertapenem or aztreonam awaiting susceptibilities of blood isolate
2. Stop oral cipro, begin IV cipro, await repeat blood cultures to confirm culture clearance
3. Continue oral cipro and send the patient home, extend therapy to 14 days
4. Continue oral cipro and send the patient home to complete 7 days as planned



Duration of antibiotics for Bacteremic UTI Short (7d) vs long (10-14d)

Turjeman et al. "Duration of antibiotic treatment for Gram-negative bacteremia-Systematic review and individual participant data (IPD) meta analysis." *EClinicalMedicine (Lancet discovery Science)* 2003

	Yahav et al. (2019)	von Dach et al. (2020)	Molina et al. (2022)
(Continued from previous page)			
Bacteremia type			
Bacteremia only	30/604 (5%)	37/351 (11%)	33/747 (4%)
Relapsing bacteremia	3/604 (0.5%)	4/351 (1.1%)	4/747 (0.5%)
Other	23/604 (4%)	45/351 (13%)	46/747 (6%)
Enterobacteriaceae			
Non-relapsing bacteremia	5/154 (3%)	None	None
Other ^a	1/154 (0.6%)	12/150 (8%)	None
Recurrent bacteremia (previous 60 days)	NR	NR	NR
Mortality (n/total)	10/764 (1.3%)	48/704 (6.8%)	43/1048 (4.1%)

Table 1. Baseline characteristics of included trials

Variable	Yahav et al.		von Dach et al.		Molina et al.		Mantel-Haenszel OR (95% CI)	Breslow-Day P value
	7 days (n = 306)	14 days (n = 298)	7 days (n = 169)	14 days (n = 165)	7 days (n = 117)	14 days (n = 122)		
90-d mortality	36 (11.8)	32 (10.7)	14 (8.3)	9 (5.5)	10 (8.5)	15 (11.8)	1.08 (0.73-1.58)	0.41
30-d mortality	16 (5.2)	12 (4.0)	6 (3.6)	4 (2.4)	4 (3.4)	8 (6.3)	1.08 (0.62-1.91)	0.40
Relapse of bacteremia -30d	8 (2.6)	8 (2.7)	2 (1.2)	3 (1.8)	7 (5.9)	6 (4.7)	1.00 (0.50-1.97)	0.82
Readmissions -30d	74 (24.2)	79 (26.5)	14 (8.3)	9 (5.5)	11 (9.2)	12 (9.3)	0.98 (0.73-1.33)	0.49
Hospital length of stay, Median (IQR)	1 (0-4)	1 (0-4)	4 (1.3-10)	4 (2-11)	4 (0-9)	3 (0-5)	-	0.21*
Duration of antibiotic therapy, Median (IQR)	5 (4-13)	12 (10-16)	7 (6-9)	13 (9-14)	7 (7-14)	14 (14-16)	-	0.39*
Local supportive complications 90d	16 (5.2)	10 (3.4)	2 (1.2)	1 (0.6)	-	-	1.62 (0.76-3.47)	0.87
Distant complications 90d	2 (0.7)	1 (0.3)	0 (0.0)	0 (0.0)	-	-	2.00 (0.18-22.08)	-
Emergence of resistance to study antibiotic -90d	33 (10.8)	29 (9.7)	3 (1.8)	0 (0.0)	-	-	1.23 (0.74-2.04)	0.11
Diarrhea	18 (5.9)	24 (8.1)	-	-	2 (1.7)	3 (2.3)	0.73 (0.40-1.33)	1.00
<i>Clostridioides difficile</i> infection	2 (0.7)	2 (0.7)	2 (1.2)	4 (2.4)	-	-	0.65 (0.18-2.31)	0.60
Rash	2 (0.7)	4 (1.3)	-	-	1 (0.8)	4 (3.1)	0.37 (0.10-1.41)	0.67
Acute kidney injury	14 (4.6)	12 (4.0)	-	-	3 (2.5)	1 (0.8)	1.33 (0.64-2.77)	0.37

Data are presented as no. (%). OR - odds ratios; CI - confidence interval; IQR - interquartile range. *P value by General linear models.

all variables, fixed-effect meta-analysis model, Mantel-Haenszel method. Homogeneity

Interpretation For patients hemodynamically stable and afebrile at 48 h prior to discontinuation, seven days of antibiotic therapy for *enterobacteriales* bacteremia result in similar outcomes as 14 days, in terms of mortality, relapse, length of hospital stay, complications of infection, resistance emergence, and adverse events. These results apply for any adult age group, gender, source of infection, immune status, and hemodynamic status on presentation.

Short vs. long, GNR bacteremia:

Yahav. CID. 2019 69:1091 | von Dach JAMA. 2020; 323: 2160 | Molina Clin Microbiol Infect. 2022; 28: 550-557

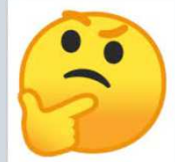
Duration of antibiotics for Bacteremic UTI Short (7d) vs long (10-14d) Summary

- ❖ Bacteremic UTI (AKA urosepsis with bacteremia)
 - ❖ Short courses of 7 days likely adequate when source control achieved, clinical response by d3-5, effective agent confirmed, no other "complicating factors"
 - ❖ Longer therapy may be needed if slow response, "complicating factors (e.g. obstruction, abscess, slow response, incomplete source control, pregnancy, prostatitis)
 - ❖ Step down to oral therapy reasonable if source control achieved, and adequate oral abx available
 - ❖ nitrofurantoin or fosfomycin not appropriate as step-down for pyelonephritis/bacteremia/prostatitis
- ❖ This approach emphasizes stewardship

Board review question 2 (x6)

Patients below is asymptomatic.

Urine sediment: 50 WBC Urine culture: >100,000 cfu of ciprofloxacin R E. coli. Whom will you given antibiotics for? What duration?



32, pregnant, first prenatal visit

48, new diagnosis of diabetes, A1C 14.2%, glucose 396, malodorous urine

36, quadriplegic man, chronic indwelling Foley, LTAC, cloudy urine, leg spasm

62, pre-op eval for a transurethral resection of prostate (TURP)

78 R THR 2016, L THR 2018, simple cystoscopy

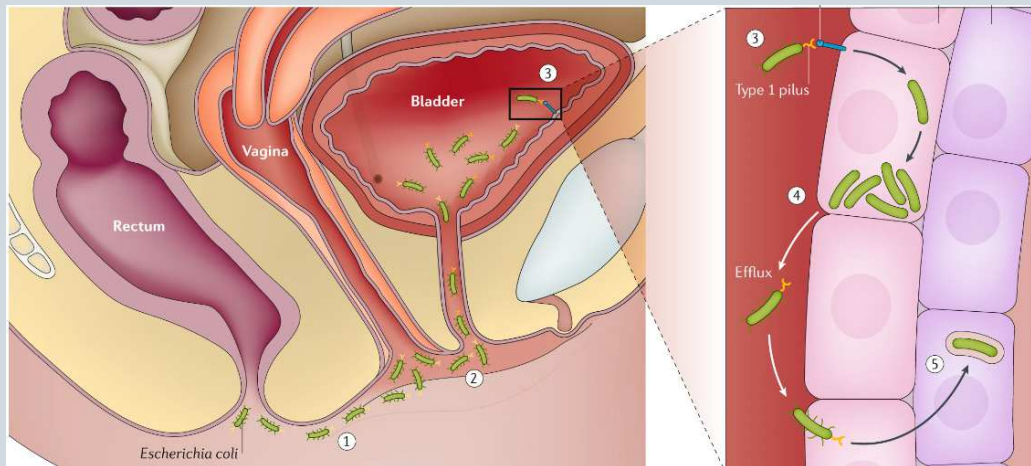
68F, stones, recurrent urosepsis, for stent exchange, nephrostomy exchange, possible lithotripsy, culture always positive

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48, new diagnosis of diabetes, A1C 14.2%, glucose 396, malodorous urine	x
36, quadriplegic man, chronic indwelling Foley, LTAC, cloudy urine, leg spasm	x
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78 R THR 2016, L THR 2018, simple cystoscopy	x
68F, stones, recurrent urosepsis, for stent exchange, nephrostomy exchange, possible lithotripsy, culture always positive	+



UTI pathogenesis

Understanding colonization and Clinical Infection



Asymptomatic Bacteriuria

Bacteriuria in a person without symptoms of a urinary tract infection

Screening (and treatment) for asymptomatic bacteriuria is recommended for:

- **Pregnant** at least once, and if positive “periodically”
 - Many, but not all studies, link untreated bacteriuria to preterm birth, low birth weight, perinatal mortality and bacterial sepsis
- For patients **urologic procedures** where mucosal injuries may occur (e.g. TURP, cystoscopy with biopsy)



2019: <https://www.idsociety.org/practice-guideline/asymptomatic-bacteriuria>

Screening and treatment for ASB before non-urologic surgery

Joint arthroplasty: common practice despite lack of prospective evidence (observational data suggest association between ASB and prosthetic joint infection[PJI])

Cardiac Surgery: less available data, but no prospective data to support treating ASB for this indication

NOT INDICATED



Clin Infect Dis (2017) 64 (6): 806, *Clin Infect Dis* 2014; 59 :41; *Clin Orthop Relat Res* 2013; 471:3822

Candida UTI

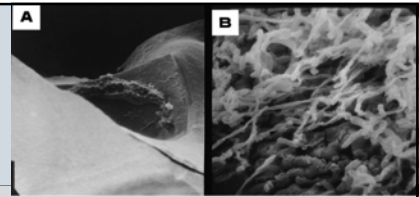
Most commonly **catheter colonizer or vaginal contaminant**

Adheres well to plastics, less well to bladder epithelium (promoted by *E. coli* and *Klebsiella*) – majority are hospitalized patients on antibiotics – not symptomatic - no treatment needed

◦ **Possible Exclusions:**

- retrograde upper tract infection, obstruction, fungal balls
- Systemic infection suspected: think fungemia with seeding of urinary tract (get blood cultures)
- Convincing urinary symptoms and no alternative explanation

Fluconazole preferred but echinocandins and liposomal amphotericin would work as well



Not all yeast is *Candida*; other fungal forms and molds should raise concern for disseminated infection



Catheter-associated UTI (CA-UTI) and Bacteriuria

The presence, absence, or degree of pyuria should not be used to differentiate CA-ASB from CA-UTI – may be irritative

Diagnosis should be made clinically

- Fever, most common, but without localizing findings a challenge to interpret; attribute only when other causes excluded

Consider prostatitis in symptomatic men with chronic catheters

Focus on **prevention**

Treatment of catheter associated UTI (not urinary sepsis):

- 7 days for most (10-14 if delayed response)
- 3 days may be considered in a young woman whose catheter was removed
- Remove or replace catheters at the onset of therapy (especially if in place for >14 days)



Inpatient consultation in UTI

Most outpatient/inpatient UTI don't warrant referral for urologic or urogynaecology evaluation or consultation with urology

- yield low for recurrent cystitis or a single pyelonephritis episode
- postvoid residual measurement simple and helpful
 - especially when neurogenic bladder or pelvic floor dysfunction suspected

ID can help with outpatient prevention, inpatient and outpatient antibiotic stewardship, antibiotic step-down and oral transition, antibiotic management in septic patients or suspected MDRO, or patients with complications

Urology (and IR) can help in source control, relieving obstruction (obstructed UTI/pyelonephritis a **medical emergency**), inpatient and outpatient evaluation & management of reversible causes



Imaging in UTI

Difficult to make a unified recommendation

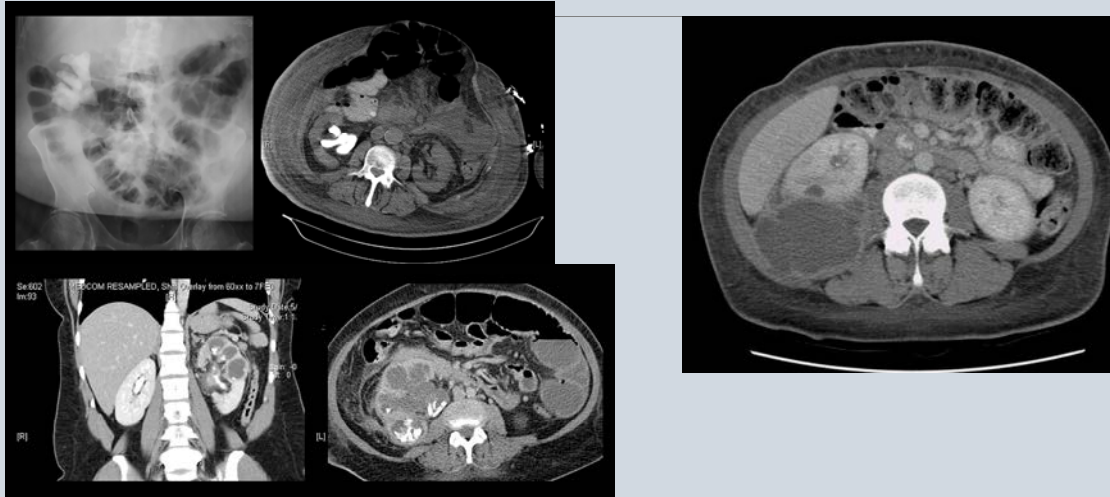
Imaging should be guided by **clinical questions/picture**:

- urgent imaging if obstruction/lack of source control suspected in febrile/septic patient
- non urgent imaging if suspicion for anatomic / functional abnormality / surgical or IR correctable disease OR
- Image if delayed / inadequate response to adequate therapy (e.g. 48-72h)

CT abdomen and pelvis usually imaging of choice (for stone non-contrast CT)

- ultrasound in some cases
- potential indications: persistent hematuria, pelvic floor dysfunction, history of GU surgery or trauma, prior pelvic disease, suspected stones or fistula, poor response after 48h+ in pyelonephritis, early relapse of infection
- <https://acsearch.acr.org/> - pyelonephritis

Selected Imaging in patients with treatment failure



Takeaways / summary

- A negative urinalysis has excellent negative predictive value for a clinically significant urinary infection (possible exclusions: obstruction, neutropenia)
- Community and hospital drug resistance on the rise (know community data and assess individual history and risk factors)
- Some cUTI, including bacteremic, may be treated with a short (7d) course
 - must demonstrate clinical improvement + source control and have no complications
 - step down to adequate oral therapy okay
- Indications to treat asymptomatic bacteriuria are narrow (pregnancy, urologic procedures)
- For rUTI prevention prioritizes stewardship - begin with non antibiotic approaches
 - Just touched on – mostly outpatient issue
- Imaging or urology consultations should be guided by a clinical suspicion for a treatable finding or need for source control intervention

and...

ID is always happy to
help with evaluation
and management

