Urinary Tract infections Update for Hospitalists

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UTI for Hospital Medicine

- General principals in diagnosis and management of UTI
  - When to test, what tests, when to treat empirically
- The problem of drug resistance
  - Time to change testing/empiric ABX guidelines?
- New and revived antibiotics
- Approach to asymptomatic bacteriuria and funguria
- Imaging in febrile UTI/pyelonephritis

*

Case one

39F, morbid obesity, calls back 2h after discharge from a 36h admission for a DVT following COVID. She states she forgot to mention a 3-day history of dysuria and urinary urgency prior to her admission, which are now more severe. She has no primary care provider. No fever, nausea, vomiting, or flank pain. Has occasional UTI 1-2/year. Requests an antibiotic prescription. Did not have a Foley.

What would you do?

A. "Sorry-can't help"
B. Ask her to make an urgent care visit
C. Start empiric antibiotics over the phone
D. Ask her to get dipstick before antibiotics
E. Order outpatient UA and culture before antibiotics

Simple (afebrile) Cystitis - what if you ignore it?

Natural History of Untreated Simple Cystitis in Young Women with a Normal Urinary Tract

- Episode resolution after 2–4 weeks in ~ 50%
  - may account for some of response rate reported in antibiotic trials (especially if R)
- Majority (~70%) w/ simple cystitis clear bacteriuria eventually (weeks to months)
- Progression to pyelonephritis & renal failure rare (if normal GU tract anatomy and function)

Table 3. Symptomatic and bacteriological effect of nitrofurantoin versus placeb 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)

Hooton, Infect Dis Clin North Am 2003
Hooton, CID, 2004
Christiaens, Br J Gen Pract. 2002
Falagas, J of Infection, 2009

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Testing for Simple Cystitis in Women

Pros

- Diagnostic accuracy: sensitivity of only 1 symptom ~50% (dysuria a bit higher)
- A urinalysis can exclude a UTI
- Resistance in the community on the rise – tailor antibiotic to organism
- Societal / environmental and personal costs of antibiotic overuse not measured

Testing for Simple Cystitis in Women

Cons

- Sensitivity of symptoms triad for cystitis in healthy non-pregnant 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

Pros

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- A urinalysis can exclude a UTI
- Resistance in the community on the rise – tailor antibiotic to organism
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Testing for Simple Cystitis in Women

Non-culture Diagnostic Options
Looking for Pyuria

- ≥10 WBC/mL in midstream urine (≥ 5 in a sediment of spun urine)
- Pyuria is present in almost all women with 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 Bacteriuria

Nitrite (positive helpful, negative not)

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

Urine microscopy with **gram stain**

- Labor intensive, messy, poor sensitivity ~50% (can't rule-out)
- Good specificity ~90% (if one dominant organism seen)

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 (89.7–90.4)	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)	99.2 (99.1–99.3)
18–69	19.9 (15.2–25.4)	68.1 (66.9–69.2)	2.6 (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)	67.7 (63.5–71.7)
Bacteriuria				
All	78.8 (75.7–81.6)	97.8 (97.6–97.9)	45.4 (42.7–48.1)	99.5 (99.4–99.6)
0–1	43.1 (33.4–53.3)	98.0 (97.5–98.3)	30.1 (22.8–38.3)	98.8 (98.5–99.1)
2–17	72.6 (65.9–78.7)	98.3 (98.2–98.5)	29.8 (25.8–34.1)	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 (59.3–71.1)	94.8 (92.5–96.5)
WBC				
All	68.2 (64.8–71.5)	87.8 (87.5–88.2)	11.7 (10.7–12.6)	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)	99.2 (98.9–99.4)
≥70	84.4 (78.6–89.2)	76.0 (72.3–79.4)	54.6 (48.8–60.2)	93.5 (90.1–95.5)

Kayalp et al. Clinical biochemistry 2013 (46) 1285

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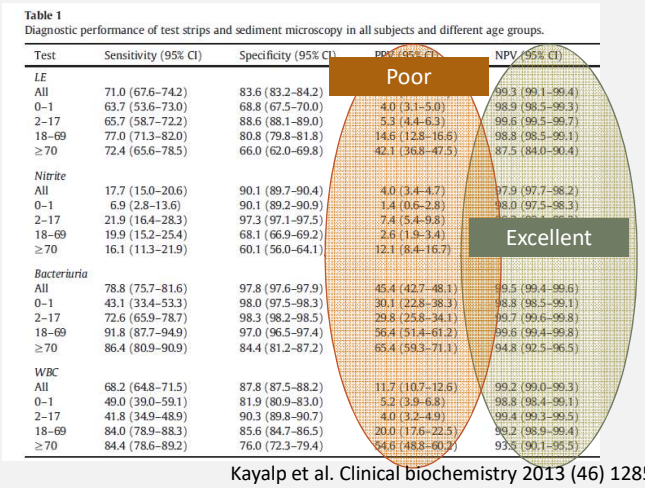

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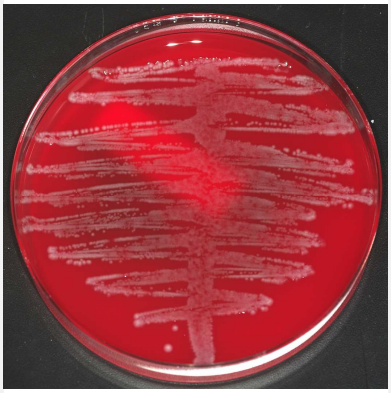
Diagnostic Options Culture

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

- *CFU=colony forming units

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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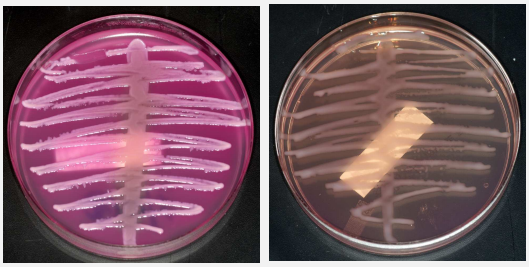

* ~90% for women who have recurrent UTI

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 still 95% sensitive & 85% specific for UTI (comparator: suprapubic aspirate)
- Recent study showed that even 10^2 cfu of *E. coli* are predictive of UTI (comparator cath urine) in young women. Gram positives not predictive
- 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

Survey of Culture Results in Outpatient Urine Samples from US Women

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
Escherichia coli	72	53
Klebsiella species	6	12
Proteus species	4	6
Enterobacter species	2	2
Pseudomonas aeruginosa	1	4
Other gram-negative rod	2	4
Enterococcus species	5	12
Staphylococcus aureus	2	2
Staphylococcus saprophyticus	2	0.2
Coagulase-negative staphylococci	3	2
Other	1	3

Uncomplicated

Complicated

Gupta et. al.
CID 2001(33): 89

Uncomplicated UTIs (simple/afebrile cystitis in [young] women)

Most treatment guidelines and recommendations for simple or uncomplicated cystitis in women focus on symptom-based empiric therapy based on resistance data from the community (local data and local practitioners' experience)

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

Recommended

- Nitrofurantoin macrocrystals 100mg twice daily x 5 days
- TMP/SMX DS twice daily x 3 days

  if *E. coli*'s resistance rates <20%
- Empiric Fosfomycin 3 gm x1
- Pivmecillinam 400 mg twice daily x 5 days

Not recommended

- Fluoroquinolones 3 days
- β-lactams

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

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

- 93% completed trial, 73% + baseline CX
- 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)

JAMA. 2018;319(17):1781-1789

48F, MS on ocrelizumab (B cell depleting agent), neurogenic bladder / CIC. Has h/o recurrent UTI. Childhood allergy to amoxicillin (rash).

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

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D. Once daily ertapenem is likely adequate

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Open Forum Infect Dis. 2017 Winter; 4(1): ofw281.
Published online 2017 Feb 24. doi: 10.1093/ofid/ofw281
PMCID: PMC5414046
PMID: 28480273

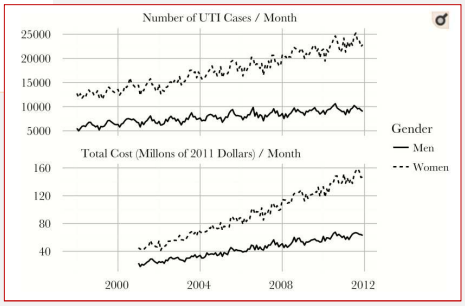
The Increase in Hospitalizations for Urinary Tract Infections and the Associated Costs in the United States, 1998–2011

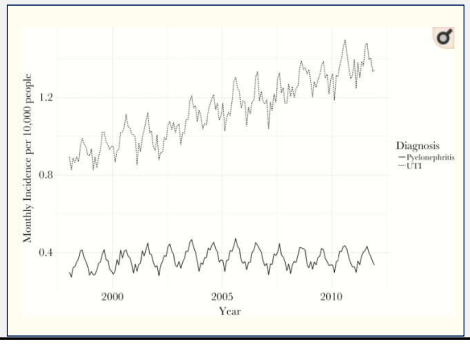
Jacob E. Simmering, [1] Fan Tang, [2] Joseph E. Cavanaugh, [3] Linnea A. Polgreen, [4] and Philip M. Polgreen [5] [6]
Author information ▸ Article notes ▸ Copyright and License information Disclaimer

- 1998 to 2011: 108,672,713 hospital admissions in the NIS
  - 960,516 for UTIs in adults
- Incidence of UTI hospitalization
  - Increasing over time
  - Seasonal, peaking in summer

Severity of UTI admission:

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





Fosfomycin

- Phosphonic acid, inhibits bacterial cell wall synthesis
  - FDA approval *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 susceptible – overestimated?
  - No AST guidelines for most organisms
  - Interpretation of susceptibility varies: different thresholds by regulatory bodies with debate: how to interpret colonies inside zone of clearance
- Response rates 3g dose: 78%-83% (58% in a recent study)
- Complicated cystitis 2-3 doses every other / every third day
- Prostatitis: daily for 6 weeks (wait, what?)
- Barriers: not routinely tested for, CLSI guidelines limited, cost, need for prior auth / waivers

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

Fosfomycin

Occurrence of non-susceptible inner colonies on fosfomycin disk diffusion testing that would confound sensitivity interpretation – rare event

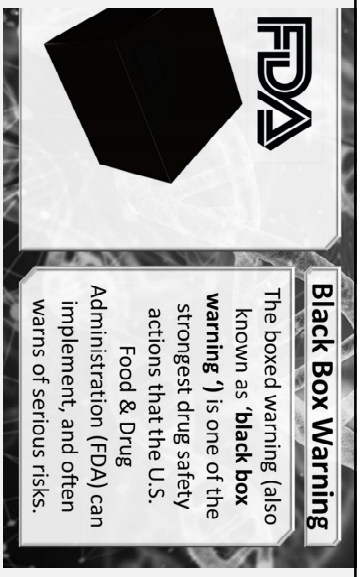
Nitrofurantoin

- Only indication for use: cystitis
- Recommended IDSA guidelines dose 100 mg PO BID, but in some countries TID is the norm
- Resistance rates remain very low (1-1.4% MDR *E.coli)*
- Barriers: tissue drug concentrations low: not effective in systemic or deep tissue infection (e.g. blood stream, kidney, prostate), GFR
- Side Effects
  - More common in elderly and with renal impairment
  - common: nausea (8%) & headache (6%); less common: hepatitis, neuropathy, interstitial lung disease / pulmonary fibrosis
- PDR: do not use at CrCl <60 ml/min
  - Concerns: insufficient renal excretion with renal impairment and toxicity
  - A 2015 Beers criteria revision provided a more liberal CrCl threshold in the elderly (<30 rather than <60 mL/min)
    - This remains controversial
    - Use only for short tem (≤7 days)

J Am Geriatr Soc 63:2227–2246, 2015

Fluoroquinolones in UTI

- For GNR in UTI: cipro generally preferred.
  - levofloxacin/moxifloxacin add atypical +respiratory coverage (e.g. GU *mycoplasma)*
  - Moxifloxacin loses PsA
- Notable advantages:
  - oral bioavailability, tissue penetration (**prostate, abscesses, kidney**), tolerability, bactericidal, inexpensive, broad
- Notable disadvantages:
  - 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
  - Antimicrobial stewardship: *C. difficile* and MRSA selection
- Drug interactions (Mg, Fe, Ca, Al decrease absorption)



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What if 75M, with frequent relapses or *E. coli* UTI, whom you have just decided to treat for **chronic prostatitis**

UA: >182W, nitrites.

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

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

Not checked: Ertapenem

Resistant: trimethoprim/sulfa, FQ, aminoglycosides.

He's directly admitted to medicine for IV meropenem and home hospital or VNA transfer

Which of the following is correct (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 and prostatitis in Men Therapeutic dilemmas

- For afebrile cystitis - how long is long enough? How short is too short?
  - 7 or 14 days? Shorter regimens adequate?
- Are antimicrobials penetrating prostate preferred even for simple cystitis?
- Recent VA study: 272 afebrile 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 (≈92%)
  - Subgroup with positive (77%) or negative (23%) culture also no difference
  - At 28d recurrence of sx similar in both treatment groups (≈12%)
  - No patients progressed to febrile or upper UTI
  - Incidence of adverse events was similar in both treatment groups.
  - Conclusion: for afebrile cystitis 7 days likely sufficient if using cipro or TMP/SXT

Drekonja DM et al. JAMA 2021 Jul 27; 326:324

Chronic Prostatitis with FQ-R TMP/SXT MDRO
Is Fosfomycin an oral option?

- Small, non protein-bound, lipid soluble, non ionized, alkaline
- Standard TMP/SXT or Cipro – good penetration.
- Doxycycline or azithro penetrate well; doxy bacteriostatic, pathogen spectrum limited
- Fosfomycin achieves acceptable prostatic concentration in an inflamed prostate. In health volunteers, therapeutic levels u to 17h after 3g dose.
- Greek study of Fosfomycin 3g q24h x 1 week, then q48h for 6-12w
- 44 patients, 33 FQ-R, 14% Enterococci
  - Cure EOT / 3M / 6M: 82% / 80% / 73%
  - Eradication: 86% EOT / 6m: 86% / 77%
  - Failure 12 patients
  - Side effects: diarrhea: 8 patients (18%). 1 discontinuation, 4 changed to q72h intervals

Karaiskos. *J Antimicrob Chemother* 2019

UTI with Multidrug Resistant Organisms (MDRO)

- MDRO: resistance to ≥ 1 agent in ≥ 3 antibiotic 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
- 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 of those retain susceptibility to fosfomycin and nitrofurantoin

Walker et al. CID 2016. 63:960
Sanchez et al. *J Antimicrob Chemother* 2014; 69 :325

* ESBL: Extended spectrum beta lactamase producing *Enterobacteriaceae*

Intrinsic versus Acquired Resistance

Organism \ Antimicrobial Agent	Ampicillin	Amoxicillin-clavulanate	Ampicillin-sulbactam	Piperacillin	Ticarcillin	Cephalosporins I: Cefazolin, Cephalothin	Cephamycins: Cefoxitin, Cefotetan	Cephalosporin II: Cefuroxime	Imipenem	Tetracyclines	Tigecycline	Nitrofurantoin	Polymyxin B Colistin	Aminoglycosides
Citrobacter freundii	R	R	R			R	R	R						
Citrobacter koseri, **Citrobacter amalonaticus** group[a]	R				R									
Enterobacter cloacae complex[b]	R	R	R			R	R							
Escherichia coli	There is no intrinsic resistance to β-lactams in this organism.													
Escherichia hermannii	R				R									
Hafnia alvei	R	R	R			R	R							
Klebsiella (formerly *Enterobacter*) *aerogenes*	R	R	R			R	R							
Klebsiella pneumoniae, **Klebsiella oxytoca, Klebsiella varificola**	R				R									
Morganella morganii	R	R				R		R	[c]		R	R	R	
Proteus mirabilis	There is no intrinsic resistance to penicillins and cephalosporins in this organism.								[c]	R	R	R	R	
Proteus penneri	R					R		R	[c]	R	R	R	R	
Proteus vulgaris	R					R		R	[c]	R	R	R	R	
Providencia rettgeri	R	R				R			[c]	R	R	R	R	
Providencia stuartii	R	R				R			[c]	R	R	R	R	[d]
***Raoultella* spp.**[e]	R				R									
Salmonella and *Shigella* spp.	There is no intrinsic resistance to β-lactams in these organisms; refer to **WARNING** below for reporting.													
Serratia marcescens	R	R	R			R	R	R				R	R	
Yersinia enterocolitica	R	R			R	R								

National trends in urinary E. coli susceptibilities

PLOS ONE

Antibiotic resistance among UTI isolates of *E. coli* in the US in 2017

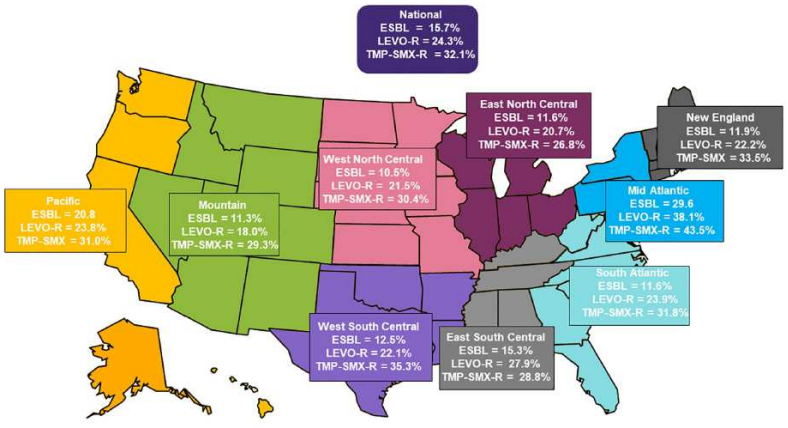


Fig 1. National and regional prevalence of ESBL phenotypes, levofloxacin- and trimethoprim-sulfamethoxazole-resistant phenotypes among 1831 isolates of *E. coli* from UTIs in the USA in 2017. ESBL = extended spectrum β-lactamase, LEVO-R = levofloxacin-resistant, TMP-SMX-R = trimethoprim-sulfamethoxazole-resistant.

(Based on first isolate per patient during the calendar year with antibiotic results)

Gram Negative Rods	#	AMP	AMC	TZP	FOX	CRO	CAZ	FEP	CIP	LVX	GEN	AMK	TOB	MEM	ETP	SXT	TET	NIT
Citrobacter freundii^	135	R	R	84	R	80	82	99	93	87	99	100	96	100	*100	87	88	*95
Citrobacter koseri	108	R	99	99	96	95	96	99	96	94	98	100	98	100	*100	98	97	*79
Enterobacter cloacae^	322	R	R	74	R	70	73	93	93	90	98	100	97	98	*100	90	89	*29
Escherichia coli^^	4882	55	84	97	93	91	94	97	79	74	91	100	92	100	*100	76	74	*97
Klebsiella aerogenes^	158	R	R	89	R	87	88	100	97	95	99	100	99	100	*100	97	96	*9
Klebsiella oxytoca	207	R	94	96	98	95	97	99	94	93	99	100	98	100	*100	95	92	*73
Klebsiella pneumoniae	1048	R	90	94	95	89	91	97	86	83	94	100	93	99	*100	84	79	*27
Morganella morganii^	85	R	R	95	33	87	85	95	84	81	92	100	98	100	*100	81	55	R
Proteus mirabilis	457	81	99	100	98	99	99	99	87	86	93	100	95	100	*99	83	R	R
Serratia marcescens^	161	R	R	98	R	96	99	100	96	96	98	99	91	100	*100	99	22	R

^ *Citrobacter*, *Enterobacter*, *Morganella* and *Serratia* may develop resistance during prolonged therapy with third-generation cephalosporins (derepression of AmpC beta-lactamase)

* 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 2020, n=3352)

^^ 80.6% (3997/4962) of *E. coli* isolates were from a urinary source

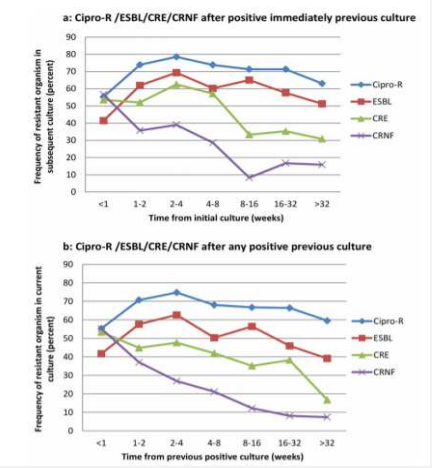
	#	CAZ	FEP	TZP	CIP	LVX	GEN	AMK	TOB	MEM	ATM
Pseudomonas aeruginosa	668	93	92	91	77	69	90	95	95	90	*71

BWH antibiogram, all isolates, 2020

Should we use prior microbiological susceptibility data from the patient to select empiric therapy?

Prior resistant isolates may persist and can be used guide antibiotic choice while culture is pending

- 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 for nearly 2 years

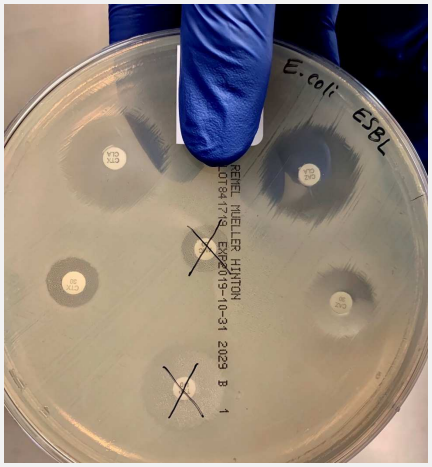


* ESBL: Extended spectrum beta lactamase producing *Enterobacteriaceae,* CRE: Carbapenem R *Enterobacteriaceae*, CRNF: carbapenem-resistant non-fermenter

Antimicrobial agents and chemotherapy 2016; 60: 4717-4721

Extended Spectrum Beta-Lactamase (ESBL) Producing Bacteria

- A group of enzymes conferring resistance to mist beta lactams including third gen cephalosporins and aztrenonam
- Plasmid mediated
- Hospital, environmental, animal, and food contamination

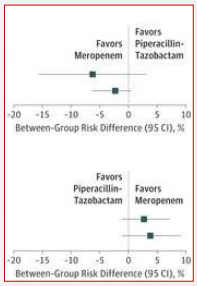


ESBL:
carbapenem or pip/tazo?

JAMA | Original Investigation

Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance
A Randomized Clinical Trial

JAMA September 11, 2018 Volume 320, Number 10



Success

Failure

RCT, bacteremia

Is Piperacillin-Tazobactam Effective for the Treatment of Pyelonephritis Caused by Extended-Spectrum β-Lactamase–Producing Organisms?

Sima L Sharara, Joe Amoah, Zoi D Pana, Patricia J Simner, Sara E Cosgrove, Pranita D Tamma ✉

Clinical Infectious Diseases, ciz1205, https://doi.org/10.1093/cid/ciz1205
Published: 20 December 2019 **Article history** ▾

- No differences in resolution of sx d7 or 30d
- 1 (2%) patient in the TZP arm and 11 (8%) patients in the carbapenem arm had incident carbapenem-resistant organisms within 30 days

Observation, pyelonephritis

AmpC
Ambler Class C gene carriers

- Chromosomally encoded
- Inducible in SPiCE-M (or SPACE ESCPM) organisms: exposure to β-lactams → AmpC production → β-lactam resistance in oftent initially susceptible isolate
- Before induction, could appear to be susceptible to third-generation cephalosporins→ resistance may develop while on therapy (20%)
- Non-inducible in E. coli

Serratia marcescens

Providencia stuartii

Indole positive proteae (not mirabilis)

Acinetobacter

Citrobacter spp.

Enterobacter spp.

Morganella morganii

MDRO Oral Options

- If susceptible, and adequate (e.g. cystitis/prostatitis/stepdown=de-escalation), use **oral agents**: nitrofurantoin (for simple cystitis), TMP/SXT, amox/clav, cefpodoxime, FQ, fosfomycin(?)
  - When **source control achieved → transition to oral therapy** to complete course (MDRO or susceptible organisms, nitrofurantoin not adequate for this indication).
- Confirm charted allergies and consider **skin testing & graded challenge** if unclear allergy history
- Tetracyclines are not stable in urine and are hepatically cleared. Would avoid for cystitis when alternatives.
  - If considered, tetracycline has a higher urinary clearance than doxycycline or minocycline. Doxycycline good to use for prostatitis, urethritis.

Pallet & Hand. J Antimicrob Chemother 2010; 65s3: s25-33

Empiric ABX for Febrile / Hospitalized UTI

- **Non-septic**, no risk factors for resistance: ceftriaxone, ciprofloxacin or levofloxacin, pip/tazo
- Concern for ***Pseudomonas aeruginosa,*** no prior resistance: cefepime, ceftazidime, or piperacillin-tazobactam
- Concern for **multidrug resistant/ESBL Enterobacteriace**: carbapenem (or pip/tazo vs. cefepime if susceptible before, or not septic)
- Concern for **SPICE organism/AMP-C**, sick: cefepime or carbapenem
- **Severe** penicillin allergy -> Aztreonam (call ID/allergy)
- Suspected **gram-positive cocci**: vancomycin, linezolid (not renally cleared), or daptomycin (not for pneumonia)
- **Septic, sick, high resistance risk: CALL ID**. Consider two different agents until susceptibility known.
- **For home discharge** if no oral options:
  - Remember ertapenem is once daily, but narrower spectrum than other carbapenem
  - Continuous infusions or daily pump infusions may allow home dosing

Pallet & Hand. J Antimicrob Chemother 2010; 65s3: s25-33

"Last Resort" Antibiotics

- Ceftolozane-tazobactam (off market)
  - Activity against MDR *Pseudomonas aeruginosa*
- Ceftazidime-avibactam
  - Activity against MDR *Pseudomonas aeruginosa*
  - Activity against some carbapenem-resistant Enterobacteriaceae (CRE)
    - Not active against NDM-1 CRE
- Cefiderocol
  - new cephalosporin transported across the outer membrane by the bacterial iron-transport system
- Imipenem-relebactam
- Colistin
- Polymyxin

GNRs in 2021

	Ceftolozane tazobactam	Ceftazidime avibactam	Meropenem vaborbactam	Imipenem relebactam	Cefiderocol
ESBL	✓	✓	✓	✓	✓
• CTX-M	✓	✓	✓	✓	✓
CRE	×	✓	✓	✓	✓
• KPC	×	✓	✓	✓	✓
• MBL	×	×	×	×	✓
• OXA-48	±	✓	×	×	✓
P. aeruginosa	✓	✓	✓	✓	✓
• CEFTAZ-R	✓	✓	±	✓	✓
• CARB-R	✓	✓	×	✓	✓
A. baumannii	×	×	×	×	✓
• XDR	×	×	×	×	✓

Courtesy Dr. Ryan Shields, PharmD MS UPMC CHANGING MEDICINE

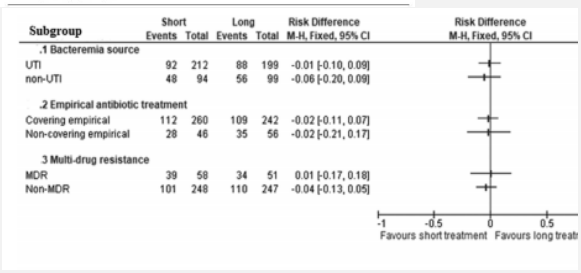
Duration of ABX in sepsis of urinary source

De-escalation and duration

- De-escalation: narrower spectrum, when feasible, once AST back
- Responding to therapy (clinical, lab, cultures cleared) + source controlled: consider shorter duration (7-10 days) and transition to oral therapy when possible

Proof of concept study

Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial



CID 2019:69 (1 October) • Yahav et al

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 year-old women, pregnant at 10w2d, first prenatal visit	
48 year-old woman, new diagnosis of diabetes, Hemoglobin A1C 12, blood glucose 396, malodorous urine	
36 year-old quadriplegic man, chronic indwelling Foley catheter, at a rehabilitation facility, urine cloudy	
62 year-old man, pre-operative evaluation for a transurethral resection of prostate (TURP)	
78 R THR 2016, L THR 2018, needs simple cystoscopy	
68F, stones, recurrent urosepsis, for stent exchange, nephrostomy exchanged or lithotripsy, culture always positive	
86M in LTAC with delirium, no fever	

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Urine sediment: 50 WBC Urine culture: >100,000 cfu of ciprofloxacin R E. coli.
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78 R THR 2016, L THR 2018, needs simple cystoscopy	x
68F, stones, recurrent urosepsis, for stent exchange, nephrostomy exchanged or lithotripsy, culture always positive	+
86M in LTAC with delirium, no fever	x

Asymptomatic Bacteriuria

- Bacteriuria in a patients without symptoms of a urinary tract infection
- Screening (and treatment) for asymptomatic bacteriuria is recommended for:
  - **Pregnant women** 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 **before TURP & other urologic procedures** where mucosal injuries may occur
  - ? Recent (1 month) renal transplantation

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

Screening and treatment for ASB before non-urologic surgery

NOT INDICATED

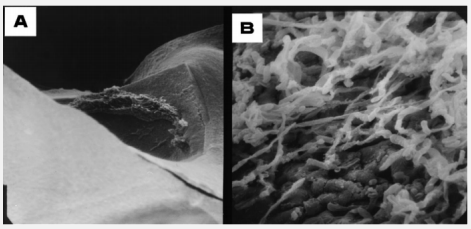
- **Joint arthroplasty**: common practice despite lack of prospective evidence (observational data suggested link between ASB and prosthetic joint infection[PJI])
  - 2 recent prospective RCTs showed that while there may be a link, organisms were discordant (urine and joint), and UTI treatment did not reduce PJI risk
  - Elimination of this practice at one large center had no significant impact on incidence on PJI
- **Cardiac Surgery**: less available data, but no prospective data to support treating ASB for this indication

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

Candida UTI

- Ascending or from blood stream? (blood cx if sick)
- Vaginal contamination, colonization or tissue invasion?
- Catheter associated? Adheres well to plastics, less well to bladder epithelium (promoted by *E. coli* and *Klebsiella)* – majority of hospitalized patients – no treatment needed
- Retrograde upper tract infection? ISO obstruction?
- Fluconazole preferred but echinocandins, liposomal amphotericin 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
- 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 <u>at the onset of therapy</u> (especially if in place for >14 days

Tambyah *Current opinion in infectious diseases* 25.4 (2012): 365
Saint, Sanjay, NEJM (2016): 2111

UTI and Asymptomatic bacteriuria in older adults

- Asymptomatic bacteriuria **very common** in elderly men and women (16%-50% in studies, higher if catheterized)
- Older adults with or without bacteriuria often have on-infectious lower tract urinary symptoms (urgency, incontinence, dysuria)
- Nonspecific symptoms (malaise, weakness, altered mental status/delirium) often attributed to clinical UTI concomitant bacteriuria
- The diagnosis of symptomatic UTI remains a significant challenge in the frail elderly; although guidelines available they are not all validated and not adhered to; overtreatment is common
  - Suggested sx: fever, worsening of baseline lower tract sx, upper tract sx

Imaging in UTI

When does acute pyelonephritis require imaging?

- Goal of imaging: identify complications that require source management: obstruction, abscess/pus, gas (emphysematous)
- Most medical literature recommends against routine imaging in uncomplicated pyelonephritis, unless no improvement 48-72h / clinical concern
- Some urologic guidelines recommend ultrasound to exclude obstruction
- American College of Radiology recommends early imaging for those at complication risks: diabetes or Immunocompromised, history of stones or prior renal surgery, or not responding to therapy

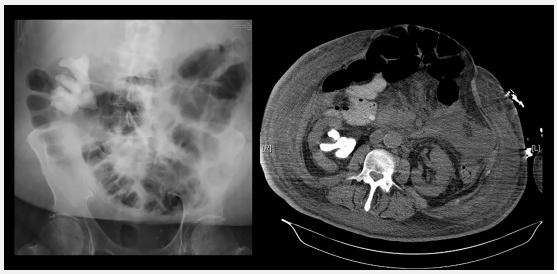
Summary of evidence	LE
Urine culture and antimicrobial susceptibility testing should be performed in all cases of pyelonephritis in addition to urinalysis.	4
A prospective observational cohort study found that radiologic imaging can selectively be applied in adults with febrile UTI without loss of clinically relevant information by using a simple clinical prediction rule.	2b
Additional imaging investigations, such as an unenhanced helical computed tomography should be done if the patient remains febrile after 72 hours of treatment or in patients with suspected complications e.g. sepsis.	4

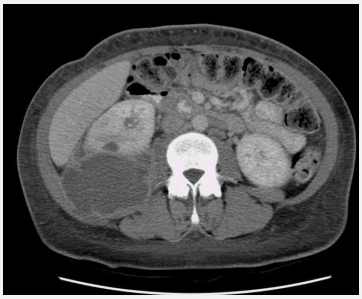
Recommendations	Strength rating
Perform urinalysis (e.g. using a dipstick method), including the assessment of white and red blood cells and nitrite, for routine diagnosis.	Strong
Perform urine culture and antimicrobial susceptibility testing in patients with pyelonephritis.	Strong
Perform imaging of the urinary tract to exclude urgent urological disorders.	Strong

SUMMARY OF RECOMMENDATIONS

- **Variant 1:** Diagnostic imaging is usually not appropriate for initial evaluation of acute pyelonephritis in the uncomplicated patient.
- **Variant 2:** CT abdomen and pelvis with IV contrast or CT abdomen and pelvis without and with IV contrast are usually appropriate for imaging complicated patients in the setting of acute pyelonephritis.

Selected Imaging





Take Home Points

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No consensus on early imaging in febrile UTI, use clinical judgement