BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL
Mass General Brigham

Urinary Tract infections Update for Hospital Medicine

SIGAL YAWETZ, MD

No Relevant Financial Disclosures

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UTI for Hospital Medicine

- General principals in diagnosis and management of cystitis
  - When to test, what tests, when to treat empirically
- Facing drug resistance: empiric and targeted antibiotic choices
  - Empiric and culture guided antibiotics in UTI syndromes
  - New, revived and last resort antibiotics
- Antibiotic choice and duration in febrile and bacteremic UTI syndromes
- Approach to asymptomatic bacteriuria and funguria
- Consultation and imaging in febrile UTI and pyelonephritis

39F, morbid obesity, no other significant PMH, visiting from out of state. Admitted for 36h for DVT complicating COVID. Did not have a Foley catheter.

Calls 2h after discharge forgot to mention a 3-day history of dysuria and urinary urgency prior to admission; now more severe. No fever, nausea, vomiting, flank pain.

Has occasional cystitis 1-2 per year which are treated with antibiotics.

No primary care in area and requests an antibiotic.

Your choice?

Case one ?

A. "Sorry-can't help"
B. Needs an urgent care visit
C. Send empiric antibiotics to a local pharmacy
D. Ask to come in for dipstick before antibiotics
E. Order outpatient UA and culture before antibiotics

Simple (afebrile or uncomplicated) Cystitis - what if we ignore it?

Natural History of Untreated Simple Cystitis in Young cis-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)

Wigton, *et al*., J Gen Int Med 14:491 (1999)

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

Testing for Simple Cystitis in Women

PROS

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

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

Testing for Simple Cystitis in Women

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]

PROS

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

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 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 lower: ~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 poor: ~20%.
  - False negative: low (10^2-10^5/mL) colony counts
  - non nitrite producer: *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 (89.7–90.4)	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 (8.4–16.9)	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 (22.8–38.2)	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 (51.4–61.3)	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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Poor

Excellent

Kayalp et al. Clinical biochemistry 2013 (46) 1285

Diagnostic Options - Culture

Why Culture?

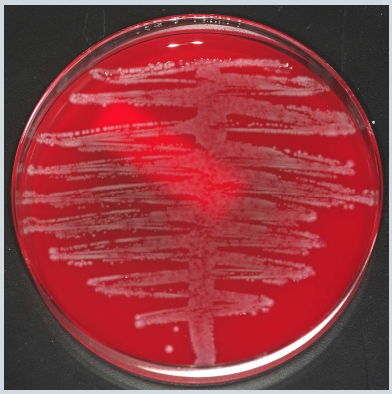
- Confirms diagnosis (significant bacteriuria, >100,000 CFU/mL*?)
- Identifies causative organism
- Provides susceptibility testing to tailor therapy accordingly
  - Helps find narrowest agent
  - Assures no resistance

*CFU=colony forming units

What percent of young women with simple cystitis (frequency, urgency, 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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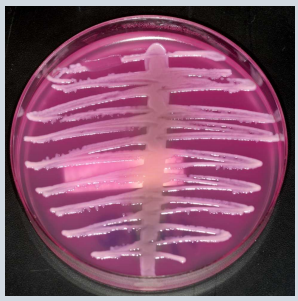
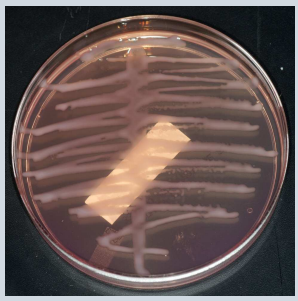




What about the other 50%?

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
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

What changes after menopause?

Diversity of organism

Gupta *CID* 2001(33): 89

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

For simple or uncomplicated cystitis in [young?] women reasonable to focus on symptom-based empiric therapy based on local resistance trends in *E. coli* (and common uropathogens) and local practitioners' experience

Obtain a culture when resistance is suspected or known, non-response to therapy

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 *E. coli*'s resistance rates <20%

Fosfomycin 3 gm x1

(Pivmecillinam 40omg twice daily x 5 days

Not recommended

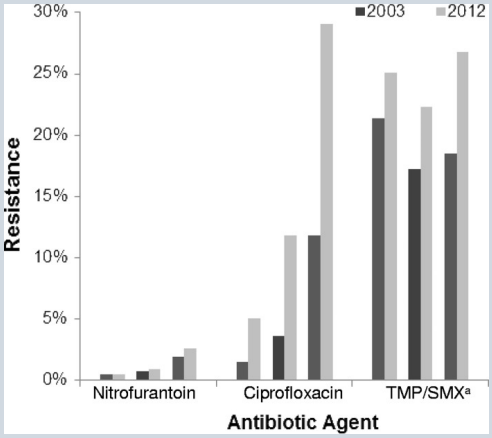
Fluoroquinolones 3 days

β-lactams

Clin Infect Dis 2011 Mar 1;52(5):e103-20

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%).

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

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%**
- Fosfomycin 3 gm x1
- (Pivmecillinam 40omg 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

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

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  - **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

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)

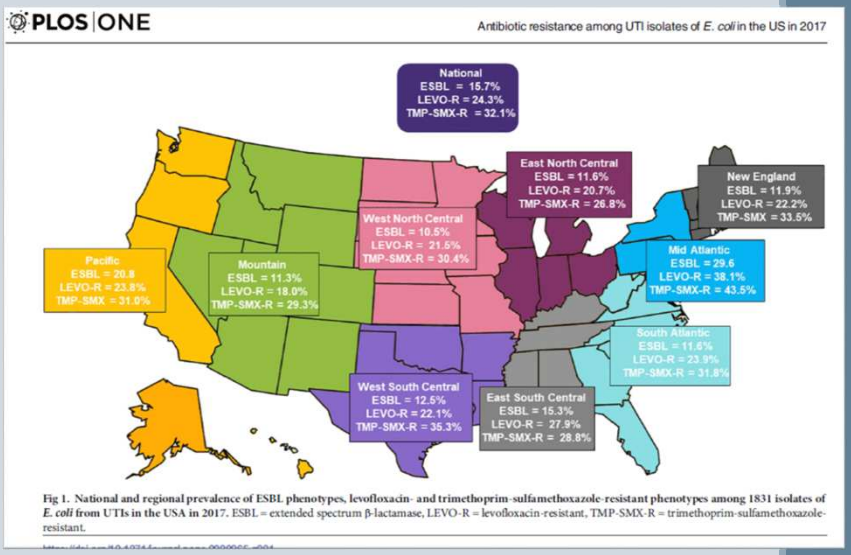

Fig 1. National and regional prevalence of ESBL phenotypes, levofloxacin- and trimethoprim-sulfamethoxazole-resistant phenotypes among 1831 isolates of *E. coli* from UTIs in the USA in 2017. ESBL = extended spectrum β-lactamase, LEVO-R = levofloxacin-resistant, TMP-SMX-R = trimethoprim-sulfamethoxazole-resistant.

National trends in urinary E. coli susceptibilities

Who's at risk for resistant organisms

- Geography/locale
  - community rates of drug resistance *in E coli* higher in the US than Canada, in Spain than other European countries, high in Mexico, Israel, India) but not well documented in many areas.
- Recent stay at a healthcare facility
- Recent antibiotic use, e.g. FQ, broad beta lactam, trim/sulfa
- History of multi-drug resistant organism (… to be continued)
- Also, always obtain culture for patients at high risk of complications from treatment failure
  - E.g. pregnant, abnormal urinary tract, immunosuppression, renal transplant, recurrent febrile UTI/pyelo) – no longer acute simple cystitis

Stapleton J. *Antimicrob chemother*, 2020 *64;* Walker et al. CID 2016. 63:960; Sanchez et al. *J Antimicrob Chemother* 2014; 69 :325

48F, MS, takes 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. You suspect cystitis

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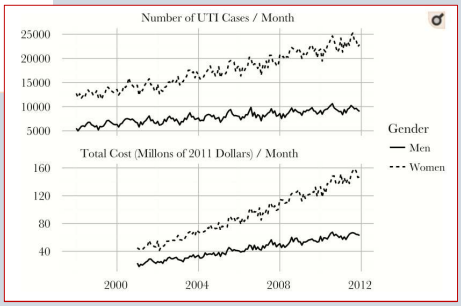
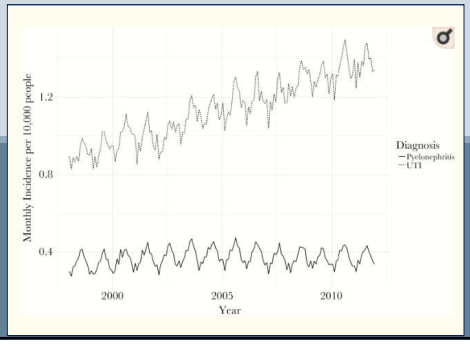
Open Forum Infect Dis. 2017 Winter; 4(1): ofw281.
Published online 2017 Feb 24. doi: 10.1093/ofid/ofw281
PMCID: PMC5414046
PMID: 28480273

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]

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





Nitrofurantoin

Only one indication: **afebrile (uncomplicated) 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


Lucas et al. ID week. 2017

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 susceptible – overestimated?
- 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 in USA limited to *E coli* and *Enterococcus*
- **Sometimes $$$$,** prior auth, discounts, waivers

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 coveragre ,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)

Not all resistance is acquired
Intrinsic resistance in Enterobacteriaceae

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

R = resistant

EUCAST expert rules in antimicrobial susceptibility testi ng

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

https://www.eucast.org/expert_rules_and_expected_phenotypes

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

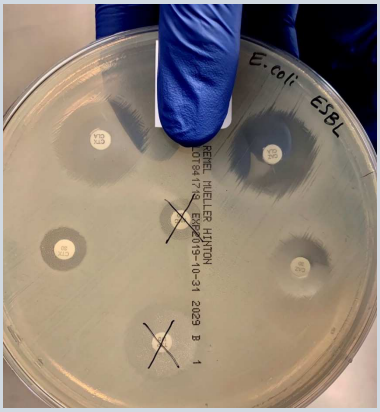
Know you local antibiogram: BWH antibiogram, all isolates, 2020

Common resistance mechanisms in UTI
Extended Spectrum Beta-Lactamase (ESBL) Producing Bacteria

Group of enzymes conferring resistance to most beta lactams including third generation cephalosporins and aztreonam

Plasmid mediated

Hospital, environmental, animal, and food contamination



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

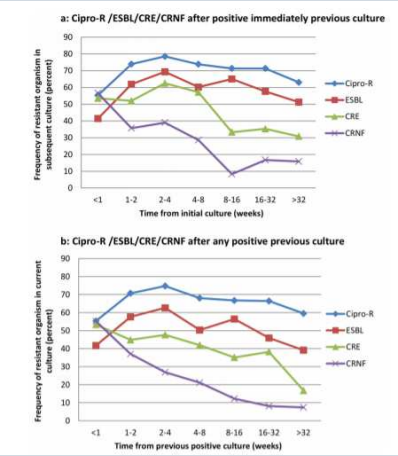
19,546 urine cultures from 4,409 inpatients with UTI, and a previous resistant urinary isolate

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



Antimicrobial agents and chemotherapy 2016; 60: 4717-4721

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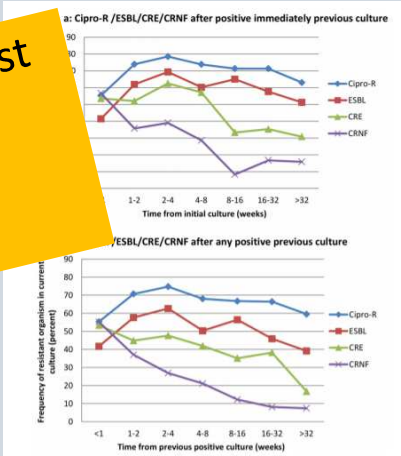
Prior resistant isolates may persist and can / should be used guide antibiotic choice while culture pending



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AmpC - Ambler Class C gene carriers

- Typically, chromosomally encoded
- Inducible in SPiCE-M (or SPACE ESCPM) organisms
  - Before induction organism appears susceptible to third-generation cephalosporins
  - Exposure to β-lactams → Amp C production → β-lactam resistance induced while on therapy (in ~ 20%)
  - Mostly a concern when source control can't be rapidly achieved rapidly / biofilm a concern (in UTI: stones, stents, catheters)
- Not inducible in *E. coli*
- Carbapenems more reliable if susceptible
- Cefepime may still be a reliable option

Serratia marcescens

Providencia stuartii

*I*ndole positive *Proteus (*not mirabilis)

Acinetobacter

Citrobacter spp.

Enterobacter spp.

Morganella morganii

MDRO Oral Options

When oral options adequate for syndrome and susceptible : use oral
- nitrofurantoin (simple cystitis), TMP/SXT, amox/clav, cefpodoxime, FQ, fosfomycin

As de-escalation: febrile UTI, on broad/IV, good response, source control achieved: transition to targeted oral therapy adequate for syndrome to complete course
- nitrofurantoin or fosfomycin may not be appropriate as step-down for pyelonephritis/bacteremia

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

Tetracyclines for UTI? 😟
- not stable in urine, hepatically cleared - if feasible chose alternatives
- typically, not in bacteremia
- when considered, tetracycline has higher urinary clearance, doxycycline used for prostatitis, urethritis

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

Suggestions for Empiric ABX for Febrile or Hospitalized UTI

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 pan 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, carbapenem, or pip-tazo (if previously susceptible). **CALL ID**. Consider two agents until susceptibility known

For home discharge after improvement **if no oral options**:
- Ertapenem: once daily, narrower spectrum than other carbapenems (e.g., no *Enterococcus, Acinetobacter, Pseudomonas* coverage)
- Continuous infusions or daily pump infusions may allow home dosing

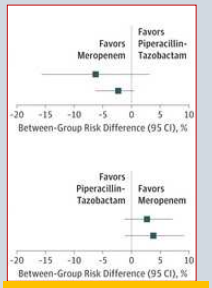
Pallet & Hand. J Antimicrob Chemother 2010; 65s3: s25-33

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

Observational, pyelonephritis

"Last Resort" Antibiotics

Ceftolozane-tazobactam
- MDR *Pseudomonas aeruginosa*

Ceftazidime-avibactam
- Some MDR GNR & *Pseudomonas aeruginosa*
- Some carbapenem-resistant Enterobacteriaceae (CRE, KPC)
  - Not active against NDM-1 CRE

Cefiderocol
- new cephalosporin transported using ba iron-transport system

Imipenem-relebactam
- ESBL, KPC, PsA

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 antibiotics for febrile or bacteremic complicated UTI
Short (7 days) versus long ABX course (10-14 days)?

Acute febrile UTI/pyelonephritis: clinical response + source control?

recent data support shorter (5-7d FQ, 7d other) vs longer courses (10-14 days)

- Most acute pyelonephritis shorter duration studies looked at FQ
- Who may require longer? foreign body (catheters, stones), severe sepsis, immunosuppression, prostatitis (acute or chronic), CKD
- Most short vs. long studies: excluded catheterized patients; *E coli* dominated
- One very recent study in men showed 7 days to be inferior to 14 (Lafaurie, *CID, 2023* https://doi.org/10.1093/cid/ciad070)

Bacteremic UTI: 7d may be adequate if source control achieved, clinical response by d3-5, effective (achieving good urine and blood levels) ABX available

This approaches emphasizes stewardship

Short vs. long, GNR bacteremia:

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

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

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

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 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
- 28d recurrence of sx similar (≈12%)
- No patients progressed to febrile or upper UTI
- Incidence of adverse events similar
- Conclusion: for **afebrile cystitis** 7 days likely sufficient if using cipro or TMP/SXT

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

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: relapsing cystitis episodes, after adequate therapy, same isolate, short interval
- 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 1-3 days with good success

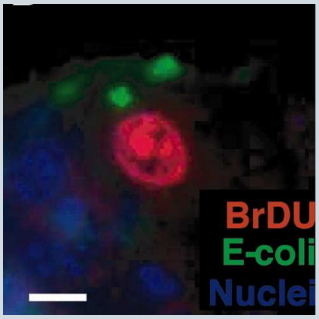
Karaiskos. *J Antimicrob Chemother* 2019

Not all relapse / symptom persistence is prostatitis

Possible reasons for persistent UTI symptoms in men and women

- Persistence in bladder epithelium
- 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)

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

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 **before TURP & other urologic procedures** where mucosal injuries may occur

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

Screening and treatment for ASB before non-urologic surgery

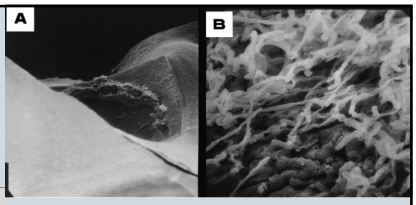
Joint arthroplasty: common prac[illegible]te lack of prospective evidence (observational data sugges[illegible]tween ASB and prosthetic joint infection[PJI])

NOT INDICATED

Cardiac Surgery: le[illegible] 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



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 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

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

UTI and Asymptomatic bacteriuria in older adults (a topic that should have its own talk)

Asymptomatic bacteriuria **very common** in elderly men & women (16%-50% in studies, higher if catheterized)

Older adults with or without bacteriuria often have irritative lower tract urinary symptoms (urgency, incontinence, even dysuria)

Nonspecific symptoms (malaise, weakness, altered mental status/delirium) are common and often attributed to clinical UTI if concomitant bacteriuria present

Diagnosing symptomatic UTI -- a significant challenge in the frail elderly; guidelines not validated and not adhered to; overtreatment common

- Suggested sx: fever, worsening of baseline lower tract sx, upper tract sx
- Practice stewardship: decide on threshold to treat; stop treatment if alternative explanation

Imaging, Urology, Urogynecology, and ID 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, Urology, Urogynecology, and ID consultation in UTI

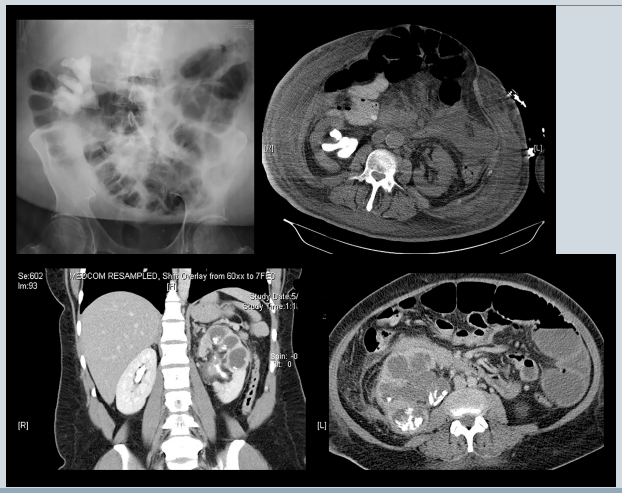
Imaging should be guided by **clinical questions/picture:**

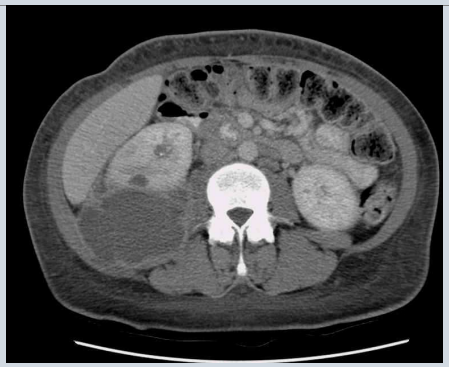
- urgent imaging if obstructed/lack of source control suspected in febrile/septic patient
- non urgent imaging if suspicion for anatomic / functional abnormality / surgically or IR correctable disease OR
- delayed / inadequate response to adequate therapy (e.g. 48-72h)

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





Take Home Points

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Most funguria requires no treatment. A few have invasive disease by candida or another fungal organism

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Some febrile UTI, including bacteremic, could be treated with 7 days of ABX and oral step-down therapy

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