Antimicrobial Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women

2010 Clinical Practice Guidelines by the Infectious Diseases Society of America and the European Society for Clinical Microbiology and Infectious Diseases

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IDSA GUIDELINES

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

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Clinical Practice Guidelines, CID 2011; 52:e103-20

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Infectious Diseases Society of America – European Society for Clinical Microbiology and Infectious Diseases Uncomplicated UTI Guideline

Co-Sponsoring Organizations:

- Association of Medical Microbiology and Infectious Diseases - Canada
- American College of Obstetricians and Gynecologists (ACOG)
- Society of Academic Emergency Medicine (SAEM)
- American Urological Association (AUA)
- European Society of Clinical Microbiology and Infectious Diseases (ESCMID)

Specialties represented:

infectious diseases, microbiology, internal medicine, family medicine (primary care), urology, OB-GYN, emergency med

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Goals and Scope

- Update the 1999 IDSA uncomplicated UTI guideline
- Time period examined: 1997-2008
- Population addressed: healthy, premenopausal, nonpregnant women with uncomplicated cystitis or pyelonephritis
- The guidelines do not address complicated UTI (including those with anatomical or voiding abnormalities, or co-morbidities), recurrent UTI, or UTI in men or children

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Overview

- Uncomplicated UTI – cystitis and pyelonephritis
- Scope
  - Major Recommendations
  - Controversies/Limitations

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Literature Review and Analysis

- Study Inclusion Criteria: Randomized clinical trial involving women with acute cystitis or pyelo by symptoms published in English since 1998.
- Exclusion Criteria: mixed populations (>10% men/complicated UTI)
- Outcomes Evaluated: Clinical and Bacterial
  - Early (first visit post-treatment, typically occurring at 0-7 days after the last dose of the antimicrobial)
  - Late (last visit post-treatment, typically occurring at 30 – 45 days after the last dose of the antimicrobial)
  - Adverse side effects

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Case

- A 35-yo woman who presents with 2 days of burning on urination and today noticed some blood in her urine
  - married; monogamous
  - no h/o STDs; contracepts with OCP
  - had a UTI last year

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What additional information do you need to diagnose a UTI?

a. Ask her if symptoms are similar to previous episode
b. Ask her if she has vaginal discharge
c. You need a urine culture to make the diagnosis
d. All the above are needed
e. Only 1 and 2 are needed

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Diagnosis of Acute Uncomplicated Cystitis

- Bent et al—women with symptoms of UTI, no vaginal discharge, had > 90% probability of acute cystitis
  - Do not need to do a urinalysis
  - Do not need a urine culture

Bent S, et al. JAMA. 2002;287(20):2701-2710.

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Algorithm

- Woman with symptoms of UTI (acute onset dysuria, frequency, or urgency)
  - No complicating conditions (if pregnant, known voiding abnormalities, co-morbid conditions -> complicated UTI)
  - No back pain (if present -> consider pyelonephritis)
  - No vaginal discharge (if present -> consider STD)
  - → then > 90% probability of acute cystitis
  - If hx not clear → dipstick
    - positive → 80% cystitis (consider tx for UTI)
    - negative → 20% cystitis (dipstick not very specific so 1/5th of these cases might still have real UTI – consider urine cx, close f/u, other diagnoses)

Bent S, et al. JAMA. 2002;287(20):2701-2710

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Culture vs. No Culture

- Complicated UTI: Anatomic, functional or metabolic abnormality of the urinary tract
  - Women—pregnant, bladder outlet obstruction
  - Men—eg, voiding dysfunction due to prostatic disorders
  - Diabetes, immunocompromised, post-menopausal, elderly
  - Catheter, calculi, neurogenic bladder
- h/o Multi-drug resistance
- Pyelonephritis (even if uncomplicated)

Get a urine culture; start empiric antibiotics; tailor therapy based on culture

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You diagnose acute cystitis. Which is a 2010 IDSA Guideline recommended agent for treatment of acute uncomplicated cystitis?

a. Ciprofloxacin
b. Nitrofurantoin
c. Ampicillin
d. Cephalexin

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The Starting Point

- Cystitis: Trimethoprim-sulfamethoxazole (T-S) is standard choice (A1)
  - Fluoroquinolones (A1)
    - Nitrofurantoin, Fosfomycin (B1)
    - β –lactams, including pivmecillinam1 (E1)
- Pyelonephritis: oral FQ x 14 days (A1)
  - T-S, if known to be susceptible
  - Amox/clav if Gram Stain shows gram postive cocci

Pivmecillinam is not available in the United States

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Changes in the Landscape Since the 1999 Guidelines

- Increasing antimicrobial resistance rates
- Increased reporting of clinical outcomes
- Inclusion in of uropathogens resistant to the study drugs in clinical trials (previously excluded)
- New antibiotics and disappearance of others from market
- Increased appreciation of the importance of “collateral damage”

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Collateral Damage

"Collateral damage" is a term used to refer to ecological adverse effects of antibiotic therapy;

- the selection of drug-resistant organisms
- unwanted development of colonization or infection with multidrug-resistant organisms

Paterson DL. 2004; 38 Suppl 4:S341-S345.

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Today

"There is no single best agent for treatment of acute uncomplicated cystitis (AUC)"

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What is the Optimal Treatment for AUC?

Recommended antimicrobials

- Nitrofurantoin 100 mg bid X 5 days (AI)
- Trimethoprim-sulfamethoxazole 160/800 mg (one DS tablet) bid X 3 days (avoid if resistance prevalence is known to exceed 20% or if used for UTI in previous 3 months) (AI)
- Fosfomycin2 3 gm single dose (lower efficacy than some other recommended agents; avoid if pyelonephritis suspected) (AI)
- Pivmecillinam3 400 mg bid x 5 days (lower efficacy than some other recommended agents; avoid if pyelonephritis suspected) (AI)

Absence of fever, flank pain, or other suspicion for pyelonephritis; able to take po, 2. Only approved for *E coli;* 3. Not available in the US

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Grading System

Strength of recommendation

A Good evidence to support a recommendation for or against use

B Moderate evidence to support a recommendation for or against use

C Poor evidence to support a recommendation

Quality of evidence

I Evidence from ≥ 1 properly randomized, controlled trial

II Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from > 1 center); from multiple time-series; or from dramatic results from uncontrolled experiments

III Evidence from opinions of respected authorities; based on clinical experience, descriptive studies, or reports of expert committees.

Source: The periodic health examination. Canadian Task Force on the Periodic Health Examination. Health Canada, 1979. Adapted and reproduced with the permission of the Minister of Public Works and Government Services, Canada, 2009

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Rating Scales

- Quality of evidence scale
  - Most choices are a level I (Evidence from >1 RCT)
- Strength of recommendation
  - Efficacy
  - Safety/tolerability
  - Prevalence of resistance
  - Promotion of resistance/collateral damage

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Overview of Antibiotic Profiles for AUC

Antibiotic	Efficacy	Safety	Resistant Prevalence	Collateral Damage
NTF	93% (84-95%)	Good	Low	Low
T-S	93% (90-100%)	Good	Intermed. (varies)	Poss
Fosfomycin	91%	Good	Low	Low

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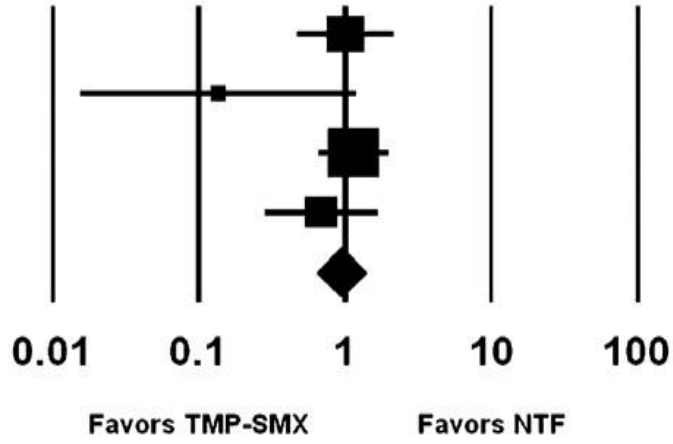
Acute uncomplicated Cystitis
Meta-analysis: T-S vs. Nitrofunantoin

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Gupta 2007	1.015	0.483	2.133	0.039	0.969
Hooton 1995	0.137	0.016	1.195	-1.799	0.072
Spencer 1994	1.155	0.667	1.999	0.513	0.608
Iravani 1999	0.697	0.290	1.674	-0.809	0.419
	0.943	0.640	1.390	-0.297	0.767

Statistics for each study

Odds ratio and 95% CI



Gupta K et al. Clin Infect Dis. 2011;52:e103–e120

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You diagnose acute cystitis. What is a 2010 IDSA Guideline recommended agent for treatment of AUC?

a. Ciprofloxacin
b. Nitrofurantoin
c. Ampicillin
d. Cephalexin

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Fluoroquinolones (FQ)

- No longer available:
  - Gatifloxacin and Sparfloxacin: Henry, Naber, Richards
- New Formulation:
  - Ciprofloxacin XR vs. ciprofloxaicn bid: Henry, Fourcroy
- Differing doses, durations:
  - Ciprofloxacin bid x 3 days vs. 7 days: Vogel
  - Norfloxacin 400 vs. 800: Pimentel
  - Ciprofloxacin vs. Norfloxacin: Auguer
- FQ vs. other:
  - Ciprofloxacin vs. Amox/clav: Hooton
  - Norfloxacin vs. Pivmecillinam: Nicolle
  - Ciprofloxacin vs. NTF vs. T-S: Iravani

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β-lactams

	Cure Rates Bacterial, Clinical	
Kavatha	Cefpodoxime 98	T-S 100
Nicolle	Pivmecillinam 75, 82	Norfloxacin 91, 88
Hooton	Amox-clav 73, 58	Cipro 94, 77
Leigh	Ceflaclor 80, 93	Cefdinir 85, 91
Ferry	Pivmecillinam 84-93, 55-64	Placebo 34, 25

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Overview of Antibiotic Profiles for AUC

Antibiotic	Efficacy	Safety	Resistant Prevalence	Collateral Damage
NTF	93% (84-95%)	Good	Low	Low
T-S	93% (90-100%)	Good	Intermed. (varies)	Poss
Fosfomycin	91%	Good	Low	Low
Pivmecillinam	55-82%	Good	Low	Low
FQs	90% (85-98%)	Good	Intermed. (varies)	Prob.
B-lactams	89% (79-98%)	Fair	Intermed. (varies)	Prob.

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Alternative Treatments for AUC

- The fluoroquinolones, ofloxacin, ciprofloxacin, and levofloxacin, in 3-day regimens are highly efficacious (A-I) but have a propensity for collateral damage and should be reserved for important uses other than acute cystitis, and thus should be considered alternative antimicrobials for acute cystitis (A-III).
- β-lactam agents including amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil in 3- to 7-day regimens are appropriate choices for therapy when other recommended agents cannot be used (B-I).
- Other β-lactams, such as cephalexin, are less well studied but may also be appropriate in certain settings (B-III). The β-lactams generally have inferior efficacy and more adverse effects compared to other UTI antimicrobials (B-I).

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A Tweet

"What IDSA fails to recognize in their new UTI guidelines is that nitrofurantoin is about 40x more costly than TMP/SMX"

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Our Response to the Tweet

"We (IDSA) do in fact recognize that cost plays an important role in decision making about antimicrobials, and it is one of several factors that we think should go into a decision about choice. T/S is not right for everyone due to allergy or concern about resistance; cipro is not right for everyone due to concerns about collateral damage; and NF, while more expensive, is effective and has very little collateral damage. Fosfomycin also has little collateral damage, but it is not as effective and is also an expensive agent."

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Optimizing Treatment of AUC

*The choice between these agents should be individualized and based on patient allergy and compliance history, local practice patterns, local community resistance prevalence, availability, cost, and patient and provider threshold for failure

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You are new in town and don't know the local prevalence of resistance to the drugs you are considering.
The best course of action would be:

a. Do a Pub-med search
b. Consult your local hospital antibiogram
c. Ask the patient
d. Get a urine culture

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The Conundrum

- Most of us don't know our local resistance rates
- Hospital antibiograms often not stratified by gender/location/other clinical data
- Laboratory surveys based on passive surveillance biased by urine cultures obtained from women who may have been sicker, failed initial regimen, or have RF for resistance
- Active surveillance not done in the US

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Trimethoprim-sulfamethoxazole may no longer be acceptable for treatment of AUC in the U.S.

Table 1. Annual Rates of Resistance in Urinary *Escherichia coli* Isolates to Select Antimicrobials Among Outpatient Women of Childbearing Age (16–45 y), 2000–2010

Drug	Total isolates 2000–2010	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	Total change 2000–2010[a]
TMP-SMX	667648	17.5	16.9	16.7	17	17.3	17.7	18.3	18.8	19.7	19.6	20.8	3.3
Ciprofloxacin	592555	1.2	1.4	1.9	2.4	2.9	4.1	5.4	6.2	7.2	7	7.1	5.9
Nitrofurantoin	646516	0.5	0.5	0.5	0.5	0.4	0.4	0.6	0.6	0.6	0.6	0.5	0
Amox-Clav	255728	3.7	3.3	4.3	3.6	3	3.6	4.7	6.7	7.6	4.4	4	0.3
Ampicillin	657246	39.7	38.9	38.8	38.4	37.4	38	38.8	39	39.6	39.6	40.2	0.5
Cephalothin	170561	12	14.1	12.5	12	11.5	14.9	15.3	13.4	12.8	11.7	12.2	0.2

Sanchez et al, CID 2011; Letter to Editor in response to UTI GL

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Managing Uncomplicated UTI – Making Sense out of Resistance Data CID 2011

- Passive surveillance systems have inherent selection bias
- Prospective, systematic, active surveillance of uncomplicated uropathogens at the local practice and/or health care system levels is essential to inform empirical antimicrobial decisions for acute cystitis
- Focused examination of clinical failure rates with empiric regimens for uncomplicated cystitis patients can also be informative

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What is True Community-Acquired Urinary Tract Infection? Comparison of Pathogens Identified in Urine from Routine Outpatient Specimens and from Community Clinics in a Prospective Study

- There are data to support the wide variation in rates obtained from laboratories compared with rates from patients with acute cystitis who would normally not have urine cultures performed.
- The difference in rates for
  - TS: (27% higher in lab survey)
  - FQ: (18% higher in lab survey)
  - Cefuroxime (14% higher in lab survey)
  - NTF: no significant difference

T. Y. Ti Eur J Clin Microbiol Infect Dis (2003)

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Predictors of Resistance in AUC

- Most data is for T-S; some for FQ
  - Exposure in past 3 months
  - Travel to endemic area
  - Previous MDR

➢ Ask your patient!

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Your patient tells you she took T-S 6 weeks ago for a skin infection. She also remembers having a difficult to treat bacteria previously

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The previous UTI was due to an ESBL-producer, you should consider prescribing:

- Ciprofloxacin
- Fosfomycin
- Cefuroxime
- Hold off on antibiotics; check-in with her in 2 days

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Fosfomycin

- Phosphonic acid derivative
- Inhibits cell wall synthesis
- Oral sachet - for uncomplicated cystitis
- Also IV formulation (Germany, France, Spain, Italy, Japan) --- but data for use in non-UTI conditions sparse

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Fosfomycin

- Active against wide spectrum of GP and GN organisms, including ESBL, VRE,
  - Resistance is chromosomally encoded rather than plasmid – little cross-reactivity with R to other agents
- Clinical cure 83% = cipro x 5 days (81%) for AUC in Turkey (Ceran et al, J Infect Chem, 2010)
- Fosfomycin Ca+ tablet 500 mg tid x 2 days = fosfomycin trometamol 1 gm sachet (Matsumoto et al, J Infect Chemo 2010)
- Meta-analysis: Fosfomycin = comparators (Falagas et al. J Antimicrob Chemo 2010)

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Fosfomycin - limitations

- Availability limited (FDA approved in US but not widely used)
- Inferior efficacy in some studies (medical letter)
- Not tested or reported in most clinical labs
  - Breakpoints vary by study
- Increased use → increasing resistance (Oteo et al, J Antimicrob Chemo 2010)

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PLACEBO for AUC

- Clinical cure can be achieved in 25%–42% of women
- Associated with prolongation of symptoms as well as a small risk of progression to pyelonephritis (1/38; Christiaens et al)

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PLACEBO for AUC

Antibiotics vs. placebo in the treatment of women with uncomplicated cystitis: a meta-analysis of randomized controlled trials.

Falagas ME, et al. J Infection 2009;58:91-102

- 5 RCT in uncomplicated cystitis reviewed:
- Antibiotics superior to placebo
- Cure: OR=4.67, 95% CI = 2.34-9.35
- Micro eradication: OR=10.67, 95% CI=2.96-38.43
- Adverse events: OR=1.64, 95% CI=1.10-2.44

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The Debate over Efficacy vs. Collateral Damage

- Only pertains to cystitis
  - not for more invasive or serious diseases
- Minimal risk of progression to tissue invasion or sepsis
  - spontaneous resolution may attenuate differences in clinical outcomes when a drug with 80% efficacy is compared with one with 95% efficacy
- AUC is one of the most common indications for antimicrobial exposure in an otherwise healthy population
  - very small increments in collateral damage repeated many times may in aggregate magnify the impact

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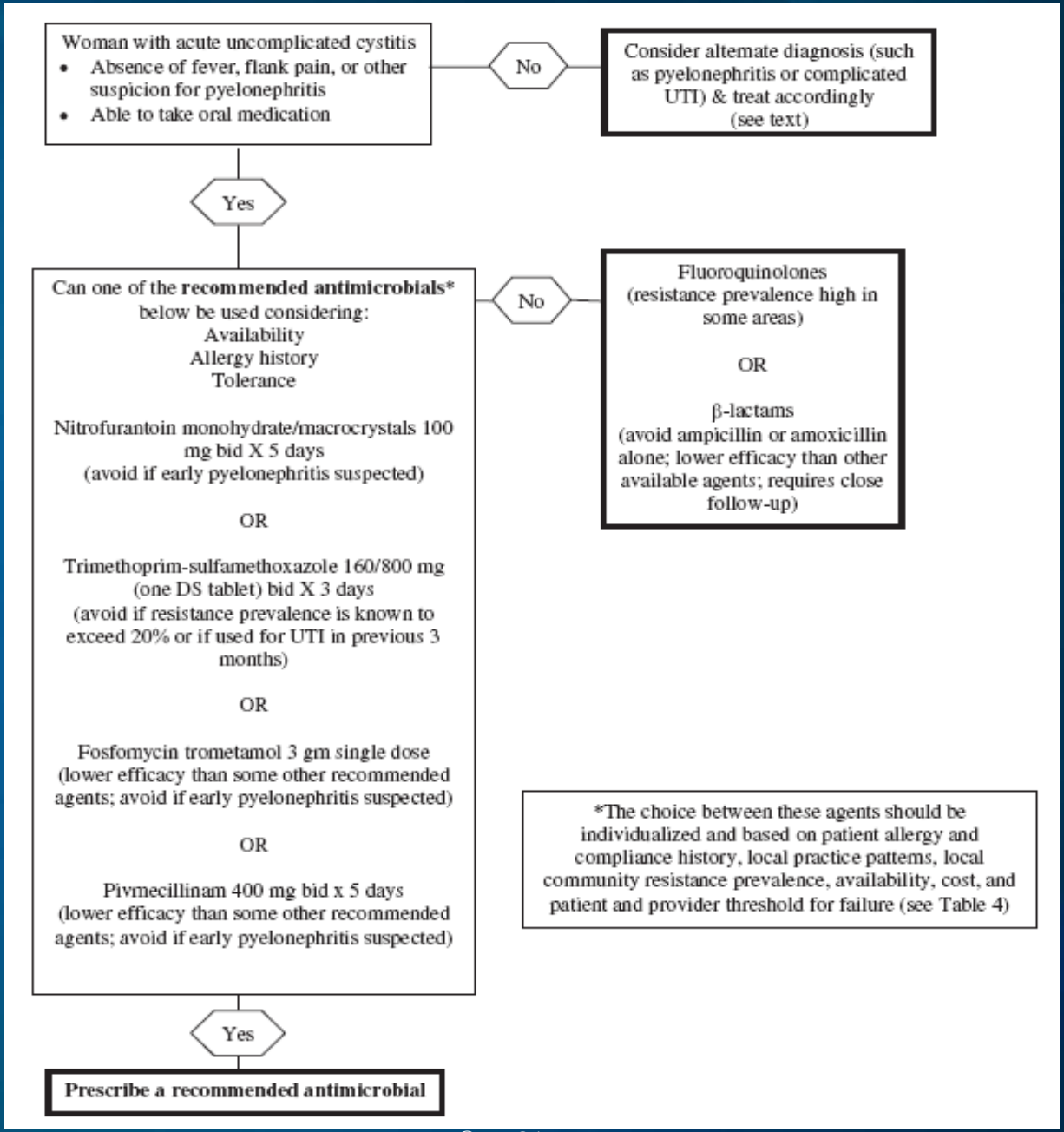
Woman with acute uncomplicated cystitis
• Absence of fever, flank pain, or other suspicion for pyelonephritis
• Able to take oral medication
No
Consider alternate diagnosis (such as pyelonephritis or complicated UTI) & treat accordingly (see text)
Yes
Can one of the recommended antimicrobials* below be used considering:
Availability
Allergy history
Tolerance
Nitrofurantoin monohydrate/macrocrystals 100 mg bid X 5 days
(avoid if early pyelonephritis suspected)
OR
Trimethoprim-sulfamethoxazole 160/800 mg (one DS tablet) bid X 3 days
(avoid if resistance prevalence is known to exceed 20% or if used for UTI in previous 3 months)
OR
Fosfomycin trometamol 3 gm single dose
(lower efficacy than some other recommended agents; avoid if early pyelonephritis suspected)
OR
Pivmecillinam 400 mg bid x 5 days
(lower efficacy than some other recommended agents; avoid if early pyelonephritis suspected)
No
Fluoroquinolones
(resistance prevalence high in some areas)
OR
β-lactams
(avoid ampicillin or amoxicillin alone; lower efficacy than other available agents; requires close follow-up)
*The choice between these agents should be individualized and based on patient allergy and compliance history, local practice patterns, local community resistance prevalence, availability, cost, and patient and provider threshold for failure (see Table 4)
Yes
Prescribe a recommended antimicrobial

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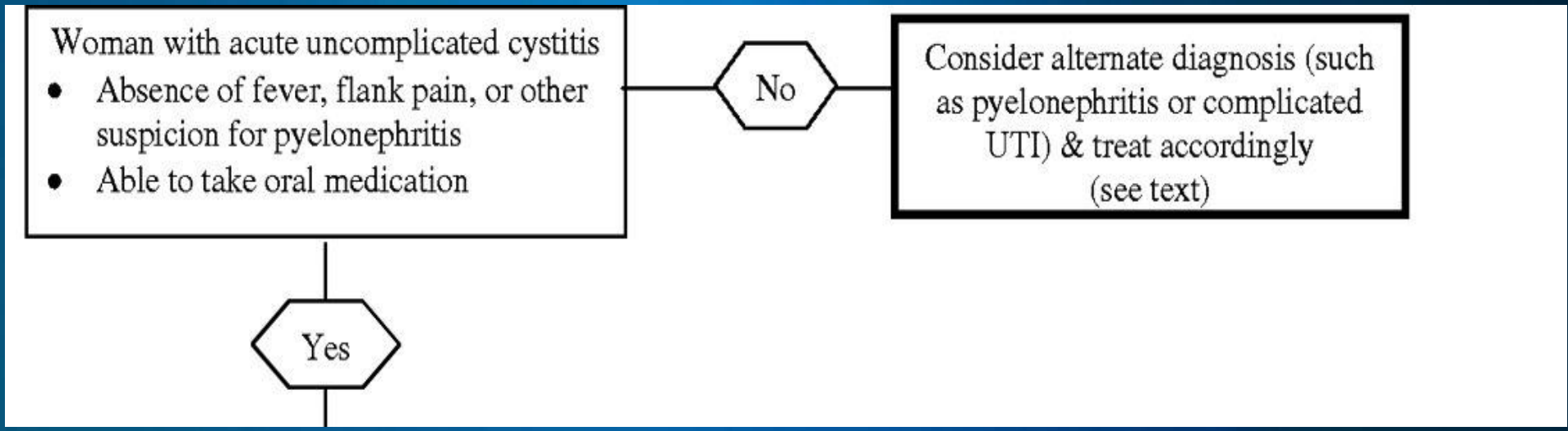
Acute Uncomplicated Cystitis

Approach to choosing an optimal antimicrobial agent for empirical treatment of acute uncomplicated cystitis.



Gupta K et al. Clin Infect Dis. 2011;52:e103–e120

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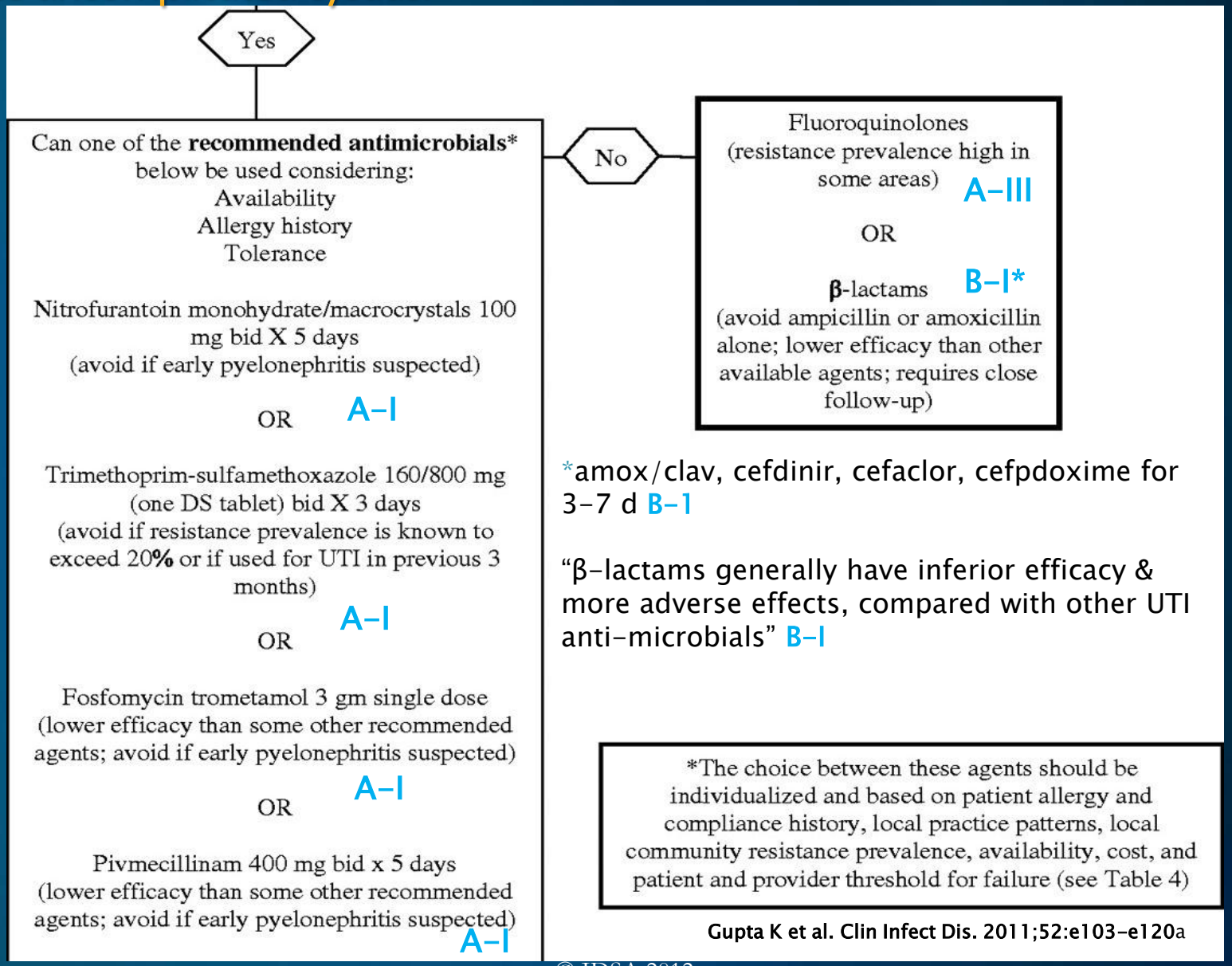
Approach to choosing an optimal antimicrobial agent for empirical treatment of acute uncomplicated cystitis.



Gupta K et al. Clin Infect Dis. 2011;52:e103–e120a

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On further questioning, your patient admits to some lower back pain and now has some chills. Her temperature is 100.5 and she has mild L CVAT What is a Guideline-recommended agent for pyelonephritis?

a. Ciprofloxacin for 7 days
b. Fosfomycin for 7 days
c. Cefpodoxime for 7 days
d. Bactrim DS for 10 days

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Pyelonephritis

- Oral ciprofloxacin (500 mg twice daily) for 7 days, with or without an initial 400-mg dose of intravenous ciprofloxacin, is an appropriate choice for therapy in patients not requiring hospitalization (A-I)
  - where the prevalence of resistance of community uropathogens to fluoroquinolones is not known to exceed 10%
- A once-daily oral fluoroquinolone, including ciprofloxacin (1000 mg extended release for 7 days) or levofloxacin (750 mg for 5 days)(B-II)

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When is Intravenous Administration Indicated?

- Obvious clinical criteria (Nausea/vomiting; sepsis)
- Initial therapy for borderline patient who is probably going home with an oral regimen
- Resistance to FQ and T-S
  - An initial 1-time intravenous dose of a long-acting parenteral antimicrobial, such as 1 g of ceftriaxone (B-III) or a consolidated 24-h dose of an aminoglycoside, is recommended (B-III)

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The Threshold Debate

- T-S: The threshold of 20% as the resistance prevalence at which the agent is no longer recommended for empirical treatment of acute cystitis is based on expert opinion derived from clinical, in vitro, and mathematical modeling studies (B-III).
- FQ: Data are insufficient to make a recommendation about what fluoroquinolone resistance level requires an alternative agent in conjunction with or to replace a fluoroquinolone for treatment of pyelonephritis.

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Pyelonephritis

- Oral trimethoprim-sulfamethoxazole DS twice daily for 14 days is effective for treatment of acute uncomplicated pyelonephritis if the uropathogen is known to be susceptible (AI).
  - If susceptibility is not known and trimethoprim-sulfamethoxazole is used, an initial intravenous one gram dose of ceftriaxone is recommended (BII)
- Oral β-lactam agents are less effective than other available agents (BIII). Initial intravenous dose of a long-acting parenteral antimicrobial is recommended (CTX BII; AG BIII)

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Panel Members:

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IDSA Guidelines

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It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situation. IDSA considers adherence to its guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

The full practice guideline and additional resources are available at: www.idsociety.org/IDSA_Practice_Guidelines/

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