GUIDELINES FROM THE INFECTIOUS DISEASES SOCIETY OF AMERICA

Guidelines for Antimicrobial Treatment of Uncomplicated Acute Bacterial Cystitis and Acute Pyelonephritis in Women

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This is part of the series of practice guidelines commissioned by the Infectious Diseases Society of America (IDSA) through its Practice Guidelines Committee. The purpose of this guideline is to provide assistance to clinicians in the diagnosis and treatment of two specific types of urinary tract infections (UTIs): uncomplicated, acute, symptomatic bacterial cystitis and acute pyelonephritis in women. The guideline does not contain recommendations for asymptomatic bacteriuria, complicated UTIs, Foley catheter–associated infections, UTIs in men or children, or prostatitis. The targeted providers are internists and family practitioners. The targeted groups are immunocompetent women. Criteria are specified for determining whether the inpatient or outpatient setting is appropriate for treatment. Differences from other guidelines written on this topic include use of laboratory criteria for diagnosis and approach to antimicrobial therapy. Panel members represented experts in adult infectious diseases and urology. The guidelines are evidence-based. A standard ranking system is used for the strength of the recommendation and the quality of the evidence cited in the literature reviewed. The document has been subjected to external review by peer reviewers as well as by the Practice Guidelines Committee and was approved by the IDSA Council, the sponsor and supporter of the guideline. The American Urologic Association and the European Society of Clinical Microbiology and Infectious Diseases have endorsed it. An executive summary and tables highlight the major recommendations. Performance measures are described to aid in monitoring compliance with the guideline. The guideline will be listed on the IDSA home page at http://www.idsociety.org It will be evaluated for updating in 2 years.

—Peter A. Gross, MD for the IDSA Practice Guidelines Committee

Executive Summary

Objective: To develop evidence-based guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women.

Options: Many antimicrobial regimens comprising different drugs, doses, schedules, and durations have been used to treat these common bacterial infections. Only a few of these regimens have been directly compared in adequately designed studies.

Outcomes: We evaluated three end points for each regimen: frequency of eradication of initial bacteriuria, recurrent bacteriuria, and adverse effects.

Evidence: We identified articles by Medline searches and supplemented them with papers referenced in their bibliographies and those of reviews, monographs, and textbooks. Two authors read each article in English that appeared to meet a priori inclusion and exclusion criteria and completed a data form for each article. All authors reviewed articles meeting inclusion and exclusion criteria, and pertinent data were sorted into tables. Prospective, randomized, controlled trials were accepted for analysis and assessed individually, if of sufficient size. Trials of comparable agents were consolidated by use of meta-analytic techniques. Searches, reviews, and tables were completed in 1997; analyses and writing were done in 1998.

Received 17 March 1999; revised 17 May 1999.

This guideline is part of a series of updated or new guidelines from the IDSA that will appear in *CID.*

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Clinical Infectious Diseases 1999;29:745–58

1058–4838/99/2904–0002$03.00

Recommendations:

Acute uncomplicated bacterial cystitis. In otherwise healthy adult nonpregnant women with acute uncomplicated bacterial cystitis, single-dose therapy is generally less effective than the same antimicrobial used for longer durations (A,I). However, most antimicrobials given for 3 days are as effective as the same antimicrobial given for a longer duration (A,I).

Trimethoprim-sulfamethoxazole for 3 days should be considered the current standard therapy (A,I). Trimethoprim alone (A,II) and ofloxacin (A,I) are equivalent to trimethoprim-sulfamethoxazole; other fluoroquinolones, such as norfloxacin, ciprofloxacin, and fleroxacin, are probably of similar effectiveness (A,II). Fluoroquinolones are more expensive than trimethoprim-sulfamethoxazole and trimethoprim, and, to postpone emergence of resistance to these drugs, we do not recommend them as initial empirical therapy except in communities with high rates of resistance (i.e., >10%–20%) to trimethoprim-sulfamethoxazole or trimethoprim among uropathogens. When given for 3 days, β-lactams as a group are less effective than the foregoing drugs (E,I). Nitrofurantoin and fosfomycin may become more useful as resistance to trimethoprim-sulfamethoxazole and trimethoprim increase (B,I).

Acute pyelonephritis. The few properly designed trials for management of acute pyelonephritis are several years old, precluding recommendations firmly based on recent evidence. For young nonpregnant women with normal urinary tracts presenting with an episode of acute pyelonephritis, 14 days of antimicrobial therapy is appropriate (A,I); courses of highly active agents as short as 7 days may be sufficient for mild or moderate cases (B,I). Mild cases can be managed with oral medications (A,II), and we recommend an oral fluoroquinolone (A,II) or, if the organism is known to be susceptible, trimethoprim-sulfamethoxazole (B,II). If a gram-positive bacterium is the likely causative organism, amoxicillin or amoxicillin/clavulanic acid may be used alone (B,III). Patients with more severe cases of acute pyelonephritis should be hospitalized (A,II) and treated with a parenteral fluoroquinolone, an aminoglycoside with or without ampicillin, or an extended-spectrum cephalosporin with or without an aminoglycoside (B,III); if gram-positive cocci are causative, we recommend ampicillin/sulbactam with or without an aminoglycoside as therapy (B,III). With improvement, the patient's regimen can be changed to an oral antimicrobial to which the organism is susceptible to complete the course of therapy (B,III).

These guidelines are based on antimicrobial susceptibilities reported in the late 1990s, which are changing over time and vary geographically; thus, we recommend that communities periodically reassess susceptibility of uropathogens to commonly used antibiotics. *Validation:* This manuscript was reviewed by infectious disease specialists and urologists interested in urinary tract infections (see Acknowledgments), and many of their comments have been incorporated. The conclusions were presented at the 1998 meeting of the Infectious Diseases Society of America. *Sponsors:* This process was sponsored by the Infectious Diseases Society of America and endorsed by the American Urological Association.

Introduction

Symptomatic urinary tract infections (UTIs) are among the most common of bacterial infections. Their magnitude can be judged either by visits to physicians, estimated as high as 8,000,000 per year in the United States (mostly for cystitis) [1], or by admission to hospitals, estimated at >100,000 per year (mostly for acute pyelonephritis) [2, 3]. A variety of antimicrobial regimens comprising different drugs, doses, schedules, and durations have been used to treat UTIs. Thus, the Infectious Diseases Society of America (IDSA) convened a committee to systematically review this topic and develop guidelines for the antimicrobial treatment of acute uncomplicated bacterial cystitis and acute pyelonephritis in women.

Methods

Two separate reviews and analyses were done, one for cystitis and one for pyelonephritis. For each, the review began with a Medline search making use of key words such as "cystitis," "urinary tract infection," "UTI," "acute pyelonephritis," and "kidney infection." These articles were supplemented with others obtained from their bibliographies and from reviews, monographs, and textbooks. Only articles in English could be reliably reviewed. The abstracts of all articles were read, and articles that appeared to meet a priori inclusion and exclusion criteria were obtained and read by two committee members who each completed a data form for each article. Discrepancies were discussed by the two reviewers until resolved. All articles meeting inclusion and exclusion criteria were distributed to all reviewers, and pertinent data were sorted into tables for analyses.

Acute uncomplicated bacterial cystitis. We reviewed studies of women with acute bacterial cystitis, which was characterized as dysuria, frequency, and/or urgency confirmed by the presence of bacteriuria in adult nonpregnant women with apparently normal urinary tracts. We excluded articles if they did not include a clinical description of the UTI or the patient population and if we could not remove from analysis pregnant patients, those who were <12 years of age, or those with complicated UTIs (urinary catheterization, renal transplantation, or urologic abnormalities). Articles were also excluded if >2% of patients had fever and/or flank pain or asymptomatic bacteriuria or were men. Also excluded were studies of UTIs in selected patient groups with a specific medical illness, such as diabetes mellitus. Inclusion criteria required the article to state that all patients had "cystitis," "uncomplicated UTI," or one or

Table 1. Categories reflecting the strength of each recommendation and grades reflecting the quality of evidence on which recommendations are based.

Category or grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for or against use
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from at least one properly randomized, controlled trial
II	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), from multiple time-series studies, or from dramatic results in uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

NOTE. Adapted from [6].

more of dysuria, frequency, and urgency; were "women," "adult females," or females ⩾12 years of age; had a quantitative urine culture yielding $\geqslant 10^2$ cfu of a uropathogen/mL; were assigned to oral antimicrobial regimens by prospective randomization; and had at least one follow-up visit for microbiological assessment after antimicrobial therapy.

Data collection included antimicrobial type, dose, and duration; type of patient population; definition of bacteriuria; whether the study was blinded or not; and whether patients were excluded because of resistant organisms. We collected data for one primary and two secondary end points. The primary end point was eradication of initial bacteriuria, which we assessed at the follow-up visit closest to 7 days after the end of therapy. A secondary end point was recurrent bacteriuria. Because of different definitions of relapse (with the initial infecting organism) and reinfection (with a different organism) among the articles, we consolidated these into one category: recurrent bacteriuria, that is, documentation of eradication of the initial infecting bacteria followed by a new episode of bacteriuria within 6 weeks after the end of therapy. Another secondary end point was adverse effects, usually assessed on or before the 7-day follow-up visit, which, when possible, we defined as all new symptoms or signs, not just those thought by the investigators to be "probably related" to the antimicrobials.

Acute uncomplicated pyelonephritis. Except for flank pain and/or fever, exclusion criteria were similar to those used for acute cystitis. Inclusion criteria required statements that each patient had "acute pyelonephritis," "kidney infection," "febrile UTI," or flank pain (and/or tenderness) and/or fever. Patients had to be "women," "adult females," or females ⩾15 years of age and had to have at least one follow-up visit after antimicrobial therapy for microbiological assessment. Because of the dearth of papers anticipated in this category, two differences from the cystitis inclusion criteria were that bacteriologic documentation, although required, was not required to be quantitative, and randomized antimicrobial assignment was not required for initial review. Data collection and assessment were similar to those for cystitis.

Statistics. The relative effect of one antimicrobial compared with that of another was estimated by the risk difference: the difference in the observed probabilities of end point events. For meta-analyses of multiple studies of the same comparison, the risk differences were pooled by use of a random effects model [4]. A two-tailed P value, pertaining to the pooled risk difference, was derived from this procedure. The Q statistic was used to test for homogeneity of effect sizes [4]. If the Q statistic for the primary objective of the meta-analysis, that is, comparison of initial eradication rates, revealed significant heterogeneity ($P < .05$), meta-analysis was not used. A normal approximation (Z) test (two-tailed) was used to evaluate the statistical significance of risk differences for individual studies.

As with other IDSA guidelines [5], our recommendations were classified by strength and by quality of evidence (table 1) [6]. A prepublication draft was circulated to 27 selected experts

Table 2. Meta-analyses of studies examining the duration of treatment with trimethoprim-sulfamethoxazole for acute uncomplicated cystitis.

Comparison, parameter [reference]	Short-term therapy	Longer-term therapy	P value
Single-dose vs. ⩾7 d [7–13]			
Eradication	416/480 (87)	438/466 (94)	.014
Recurrence	61/353 (17)	47/360 (13)	NS
Adverse effects	46/430 (11)	121/432 (28)	<.001
3 d vs. ⩾7 d [9, 14]			
Eradication	161/174 (93)	166/176 (94)	NS
Recurrence	34/176 (19)	21/175 (12)	.053
Adverse effects	52/297 (18)	88/298 (30)	.057

NOTE. Data are no. with parameter/total (%). NS = not significant, i.e., >.05.

in the UTI field, and 26 returned comments, some of which were incorporated in subsequent manuscript revisions.

Results

Acute Uncomplicated Bacterial Cystitis

Of the several thousand titles and abstracts screened, 337 articles were identified that possibly met our criteria and were copied and reviewed by two reviewers. Of these, 76 indeed did meet exclusion and inclusion criteria for the analysis. Of the 76, 53 used $\geq 10^5$ cfu/mL as the quantitative break point for diagnosis of bacteriuria, 11 used $\geq 10^4$, 3 used $\geq 10^3$, 8 used $\geq 10^2$, and 1 accepted any organisms found by suprapubic aspiration of bladder urine. Some used lower concentrations for diagnosis of UTI caused by *Staphylococcus saprophyticus* than for that caused by *Escherichia coli.* All were randomized, as required by inclusion criteria, and 32 were double-blinded. Fifty-five trials did not exclude from analysis patients infected with organisms resistant to one or more of the trial antimicrobials.

Trimethoprim-sulfamethoxazole. This was the most common antimicrobial studied. Of the 76 reports, 30 included trimethoprim-sulfamethoxazole and another examined trimethoprim/sulfadiazine. Seven trials compared trimethoprim-sulfamethoxazole as single-dose therapy vs. longer durations of therapy [7–13]. Table 2 demonstrates that trimethoprim-sulfamethoxazole was significantly less effective as single-dose therapy than as multiday therapy in eradicating initial bacteriuria (87% vs. 94%; $P = .014$); there were no significant differences in rates of recurrence. Five of the seven studies investigated adverse effects; these reports, each independently and by meta-analysis as a group, revealed significantly lower incidences of adverse effects with single-dose therapy than with multiday therapy (meta-analysis, 11% vs. 28%; $P < .001$).

Two studies compared 3 days of trimethoprim-sulfamethoxazole with longer durations [9, 14]. Meta-analysis revealed that 3-day therapy with trimethoprim-sulfamethoxazole yielded eradication rates equivalent to those seen with therapy given for 7 or 10 days (table 2). However, there tended to be an increased recurrence rate with the 3-day trimethoprim-sulfamethoxazole therapy (19% vs. 12%; $P = .053$). This was counterbalanced by a trend toward a higher incidence of adverse effects with the longer durations (18% vs. 30%; $P = .057$).

On the basis of the high frequency of trimethoprim-sulfamethoxazole use among the studies meeting our criteria, its choice by many experts as standard therapy for uncomplicated cystitis in women [15–17], and its success in eradicating initial bacteriuria (average of 93% in the studies included herein), we used trimethoprim-sulfamethoxazole treatment for ≥ 3 days as the standard against which other antimicrobials were compared. The use of trimethoprim-sulfamethoxazole as a standard also allowed us to conduct a power analysis that defined the sample size needed to permit individual assessment of single trials, as well as to judge the power of meta-analyses. To detect a difference of $\geq 7\%$ compared with the 93% eradication rate for trimethoprim-sulfamethoxazole, 135 women were needed in each study group (80% power). In studies of ≥ 135 patients per group, if the rate of an end point in one group was not significantly different from that in the other group, we defined the groups as being equivalent in rates of that end point.

Table 3. Meta-analyses of studies examining the duration of treatment with trimethoprim and comparison of trimethoprim (TMP) with trimethoprim-sulfamethoxazole (TMP-SMZ) for acute uncomplicated cystitis.

Comparison, parameter [reference]	Single-dose therapy	≥5 d	*P* value
Single-dose vs. ≥5 d [18–20]			
Eradication	201/243 (83)	230/247 (93)	<.001
Recurrence	18/178 (10)	13/169 (8)	NS
Adverse effects	35/270 (13)	53/283 (19)	NS
	TMP, 7 d	TMP-SMZ, 7 d	
TMP vs. TMP-SMZ [21, 22]			
Eradication	185/210 (88)	112/128 (88)	NS
Recurrence	ND	ND	—
Adverse effects	28/179 (16)	28/181 (15)	NS

NOTE. Data are no. with parameter/total (%). ND = not determined; NS = not significant, i.e., >.05.

Below, we first discuss trials that sought optimal durations of an antimicrobial for treatment of acute bacterial cystitis; next, trials that compared the antimicrobial with trimethoprim-sulfamethoxazole as a standard; and, finally, trials that examined the antimicrobial against drugs that in other studies were proven comparable to trimethoprim-sulfamethoxazole.

Trimethoprim. Nine of the trials that met our criteria included trimethoprim in at least one arm. Three studies compared trimethoprim as single-dose therapy with longer durations [18–20]. A meta-analysis of these revealed that single-dose therapy was less effective in eradicating bacteriuria than was therapy lasting for ≥5 days (83% vs. 93%; $P < .001$) (table 3). One study showed significantly fewer side effects with the single dose of trimethoprim [18], but the meta-analysis that included this trial did not show a significant difference ($P = .53$ with a Q statistic of 5.84, indicating a trend toward heterogeneity of the rate of side effects; $P = .054$).

Only one small study compared trimethoprim for 3 days vs. a longer duration (10 days) [23]. The eradication rates were similar, but the size of the trial was insufficient to demonstrate a significant difference; nevertheless, the trial did reveal that the longer duration of therapy was associated with a significantly higher incidence of adverse effects (3 [6%] of 50 vs. 12 [19%] of 64; $P = .032$).

Trimethoprim alone has been compared with trimethoprim-sulfamethoxazole, each given for 7 days, in two trials [21, 22];

Table 4. Studies examining the duration of therapy with fluoroquinolones for acute uncomplicated cystitis.

Drug and comparison, parameter [reference]	Shorter-term	Longer-term	*P* value
Norfloxacin, SDT vs. 3 or 7 d [24, 25]*			
Eradication	107/130 (82)	127/133 (95)	<.001
Recurrence	36/127 (28)	18/130 (14)	.007
Adverse effects	29/169 (17)	45/157 (29)	NS
Ciprofloxacin, SDT vs. 7 d [26]			
Eradication	95/107 (89)	102/103 (99)	.001
Recurrence	7/87 (8)	6/95 (6)	NS
Adverse effects	24/145 (17)	16/146 (11)	NS
Fleroxacin, SDT vs. 7 d [27]			
Eradication	151/172 (88)	173/180 (96)	.004
Recurrence	9/48 (19)	11/66 (17)	NS
Adverse effects	94/316 (30)	97/321 (30)	NS
Norfloxacin, 3 vs. 7 d [28, 29]*			
Eradication	346/356 (97)	331/337 (98)	NS
Recurrence	57/357 (16)	29/343 (8)	.018
Adverse effects	74/436 (17)	80/437 (18)	NS
Ciprofloxacin, 3 vs. 5 or 7 d [26]			
Eradication	340/359 (95)	241/255 (95)	NS
Recurrence	40/289 (14)	38/206 (18)	NS
Adverse effects	119/515 (23)	62/362 (17)	NS
Lomefloxacin, 3 vs. 7 d [30]			
Eradication	180/196 (92)	190/194 (98)	.006
Recurrence	22/194 (11)	30/194 (15)	NS
Adverse effects	57/228 (25)	73/235 (31)	NS

NOTE. Data are no. with parameter/total (%). NS = not significant, i.e., >.05; SDT = single-dose therapy.
* Meta-analysis.

the meta-analysis was of sufficient power to demonstrate an equivalent rate of eradication of initial bacteriuria and of adverse effects (table 3). In neither study was the incidence of recurrent bacteriuria investigated.

Fluoroquinolones. Thirty-eight reports provided data on 40 trials with a fluoroquinolone in at least one arm. Among these, six studies compared single-dose therapy with longer durations. Four of these, of norfloxacin, ciprofloxacin, and fleroxacin* [24–27], individually revealed significantly lower eradications with single-dose therapy than with longer durations (table 4). However, when all six studies were combined into a meta-analysis, significant heterogeneity was revealed. This heterogeneity was contributed primarily by two small studies [31, 32] that had high rates of eradication attained by use of single-dose therapy with ofloxacin (42/45, 93%) and pefloxacin* (32/32, 100%).

Four studies compared therapy with a fluoroquinolone for 3 days vs. a longer duration (table 4). For norfloxacin [28, 29], 3-day therapy was equivalent to 7-day therapy in eradication of initial bacteriuria and in adverse effects. Although recurrence rates with norfloxacin given for 3 days were significantly higher than 7-day therapy ($P = .018$), both were relatively low (16% vs. 8%). Ciprofloxacin given for 3 days yielded rates of eradication, recurrence, and adverse effects equivalent to those found for 5- or 7-day therapies [26]. Lomefloxacin given for 3 days yielded a high eradication rate (92%); however, it was lower than the eradication rate for 7-day therapy (98%; $P = .006$) [30].

Among the fluoroquinolone trials that met our criteria and were individually of sufficient size or could be combined into meta-analyses, only ofloxacin has been compared with trimethoprim-sulfamethoxazole at the same durations of use. These two antimicrobials had equivalent rates both of eradication and of adverse effects (table 5) [31, 33, 34]. One of the three studies [34] demonstrated a significantly lower rate of recurrent bacteriuria with ofloxacin than with trimethoprim-sulfamethoxazole. However, this was not found in the two other studies, and meta-analysis of the three yielded no difference in the rate of recurrent infections but did in heterogeneity of these rates (Q statistic of 8.29; $P = .015$).

Studies comparing fluoroquinolones are also outlined in table 5. Ciprofloxacin given for 3 days appeared to be equivalent to norfloxacin given for 7 days [26]. Two other fluoro-

Table 5. Comparative studies of fluoroquinolones for treatment of acute uncomplicated cystitis.

Reference, parameter	Ofloxacin, ⩾3 d	TMP-SMZ, ⩾3 d	*P* value
[28, 33, 34]*			
Eradication	241/253 (95)	183/191 (96)	NS
Recurrence	18/240 (8)	16/184 (9)	NS
Adverse effects	65/277 (23)	55/221 (25)	NS
	Ciprofloxacin, 3 d	Norfloxacin, 7 d	
[26]			
Eradication	142/149 (95)	135/141 (96)	NS
Recurrence	19/126 (15)	13/112 (12)	NS
Adverse effects	45/211 (21)	37/213 (17)	NS
	Fleroxacin, 7 d	Ciprofloxacin, 7 d	
[27]			
Eradication	173/180 (96)	196/204 (96)	NS
Recurrence	11/66 (17)	8/63 (13)	NS
Adverse effects	97/321 (30)	84/324 (26)	NS
	Lomefloxacin, 3 and 7 d	Norfloxacin, 3 and 7 d	
[32, 35]*			
Eradication	251/256 (98)	241/248 (97)	NS
Recurrence	36/254 (14)	32/251 (13)	NS
Adverse effects	113/319 (35)	72/303 (24)	<.001

NOTE. Data are no. with parameter/total (%). NS = not significant, i.e., >.05; TMP-SMZ = trimethoprim-sulfamethoxazole.
* Meta-analysis.

* Not available in the United States as of this writing.

Table 6. Comparative studies of single-dose therapy (SDT) with pefloxacin and with rufloxacin for acute uncomplicated cystitis.

Reference, parameter	Pefloxacin SDT	TMP-SMZ, ⩾5 d	*P* value
[36, 37]*			
Eradication	199/206 (97)	202/211 (96)	NS
Recurrence	11/203 (5)	15/209 (7)	NS
Adverse effects	33/206 (16)	33/211 (16)	NS
	Rufloxacin SDT	Pefloxacin SDT	
[38]			
Eradication	158/165 (96)	171/178 (96)	NS
Recurrence	31/165 (19)	35/178 (20)	NS
Adverse effects	42/218 (19)	40/228 (18)	NS
	Pefloxacin SDT	Norfloxacin, 5 d	
[39]			
Eradication	69/75 (92)	72/75 (96)	NS
Recurrence	14/67 (21)	18/73 (25)	NS
Adverse effects	39/98 (40)	23/101 (23)	.008
	Rufloxacin SDT	Norfloxacin, 3 d	
[40]			
Eradication	77/82 (94)	73/74 (99)	NS
Recurrence	3/64 (5)	2/54 (4)	NS
Adverse effects	21/103 (20)	12/100 (12)	NS

NOTE. Data are no. with parameter/total (%). TMP-SMZ = trimethoprim-sulfamethoxazole.

* Meta-analysis.

quinolones were compared with either ciprofloxacin or norfloxacin. Fleroxacin was equivalent to ciprofloxacin for 7-day therapy [27]. Lomefloxacin, while equivalent to norfloxacin in eradication and recurrences, was associated with a significantly higher incidence of adverse effects (35% vs. 24%; $P < .001$) [30, 35].

Two more recently released fluoroquinolones with longer half-lives, pefloxacin and rufloxacin,* have been studied predominantly as single-dose therapy. A small underpowered study compared single-dose therapy and 3-day therapy with pefloxacin and did not demonstrate a difference between the regimens [32]. In two studies, single-dose therapy with pefloxacin was compared with 5- or 7-day treatment with trimethoprim-sulfamethoxazole and demonstrated equivalent rates of eradication, recurrent bacteriuria, and side effects [36, 37] (table 6). Subsequently, in a single large study, rufloxacin and pefloxacin each as single-dose therapy were compared and found to be equivalent [38]. These studies of single-dose pefloxacin yielded rates of adverse effects of 15%–18%. However, a moderate-sized study of single-dose therapy with pefloxacin vs. 5-day therapy with norfloxacin yielded an adverse effect rate for pefloxacin of 40%, which was significantly higher than that for norfloxacin (23%) [39]. Additionally, rufloxacin had significantly more adverse effects on the CNS than did pefloxacin [38] or norfloxacin [40].

Nitrofurantoin. Only three studies of nitrofurantoin met our criteria. One compared nitrofurantoin single-dose therapy with a 10-day regimen; this was of insufficient power to show a difference in eradication rates but did show a significantly higher rate of adverse effects with the longer-term therapy (4 [4%] of 104 vs. 15 [13%] of 114; $P = .011$) [41]. Two studies compared nitrofurantoin preparations with trimethoprim-sulfamethoxazole. In a small study, nitrofurantoin in macrocrystal form given q.i.d. was compared with trimethoprim-sulfamethoxazole given b.i.d., each for 3 days. The nitrofurantoin preparation had a significantly lower eradication rate: 32 of 38 vs. 39 of 40 ($P = .038$) [42]. A larger, but still underpowered, study of 7 days of therapy with nitrofurantoin monohydrate macrocrystals, trimethoprim-sulfamethoxazole, or trimethoprim, all at b.i.d. dosage, revealed similar rates of eradication and adverse effects among the three antimicrobials, but eradication rates for all three were low (77%–83%) [21].

β-lactams. β-lactams were studied in 26 reports that met our criteria. Six studies compared β-lactams as single-dose therapy with longer durations of therapy and showed that single-dose therapy was significantly less effective at eradication than was multiday therapy (four studies were of treatment for ⩾10 days), although significantly fewer patients had side effects with single-dose therapy (table 7) [43–48]. The only study of adequate size that compared a β-lactam antimicrobial given for 3 days vs. longer durations was for pivmecillinam* [49]; 3 days was equivalent to 7 days of therapy in eradication of initial bacteriuria, although the shorter treatment was associated with an increased incidence of recurrence ($P = .04$).

Only three trials of various β-lactams vs. adequate comparators were useful (table 7). One moderate-sized trial compared 3-day therapy with each of two β-lactam antimicrobials, cefadroxil and amoxicillin, vs. trimethoprim-sulfamethoxazole [42]. Although only of low power, the study revealed that trimethoprim-sulfamethoxazole was more effective in eradication of bacteriuria than was amoxicillin ($P = .05$). The study was insufficiently powerful to demonstrate that the similarity between trimethoprim-sulfamethoxazole and cefadroxil eradication rates was meaningful, but the rate of recurrence with cefadroxil was higher, although not quite significantly so ($P = .063$). Another small study examined 3-day therapy with amoxicillin vs. trimethoprim/sulfadiazine* [50]. This trial demonstrated a significantly lower eradication rate with amoxicillin ($P = .004$) and a higher rate of recurrent bacteriuria that was not quite significant ($P = .085$). Finally, a Swedish study compared 5-day therapy with the β-lactam ritipenem acoxil* vs. norfloxacin [51]. The β-lactam yielded a significantly lower eradication rate ($P < .001$) and a higher rate of adverse effects ($P = .001$).

Fosfomycin. Fosfomycin trometamol has been approved for use as single-dose therapy for treatment of acute uncom-

Table 7. Duration-of-therapy and comparative studies of β-lactams for treatment of acute uncomplicated cystitis.

Reference, parameter	Various, SDT	Various, ⩾3 d		*P* value
[43–48]*				
Eradication	225/293 (77)	227/264 (86)		.004
Recurrence	28/147 (19)	14/119 (12)		NS
Adverse effects	25/271 (9)	44/253 (17)		.024
	Pivmecillinam, 3 d	Pivmecillinam, 7 d		
[49]				
Eradication	138/151 (91)	139/148 (94)		NS
Recurrence	15/121 (12)	6/119 (5)		.04
Adverse effects	17/174 (10)	18/171 (11)		NS
	Amoxicillin, 3 d	Cefadroxil, 3 d	TMP-SMZ, 3 d	
[42]				
Eradication	37/43† (86)	37/37 (100)	39/40† (98)	
Recurrence	8/42 (19)	11/32‡ (34)	6/39‡ (15)	
Adverse effects	13/52 (25)	12/40 (30)	16/46 (35)	
	Amoxicillin, 3 d	TMP/sulfadiazine, 3 d		
[50]				
Eradication	59/67 (88)	76/76 (100)		.004
Recurrence	19/64 (30)	13/75 (17)		.085
Adverse effects	16/107 (15)	9/107 (8)		NS
	Ritipenem acoxil, 5 d	Norfloxacin, 5 d		
[51]				
Eradication	73/114 (64)	97/109 (89)		<.001
Recurrence	ND	ND		—
Adverse effects	42/140 (30)	19/138 (14)		.001

NOTE. Data are no. with parameter/total (%). ND = not determined; SDT = single-dose therapy; SMZ = sulfamethoxazole; TMP = trimethoprim.

* Meta-analysis.

† $P = .05$.

‡ $P = .063$.

plicated cystitis. Although eight trials examining fosfomycin met our criteria, none compared single-dose therapy vs. longer durations of the same drug, and six were not useful because either they were too small or compared fosfomycin against inappropriate comparator regimens, such as other antimicrobials as single-dose therapy [52–57]. In the two useful trials, fosfomycin single-dose therapy was compared with norfloxacin for 5 or 7 days [58, 59]. Although a meta-analysis of these two trials yielded inadequate power to distinguish differences in eradication rates, it showed a significantly higher rate of adverse effects with single-dose fosfomycin (table 8).

Examination of two of the six trials initially excluded for the reasons noted above is instructive. In one of these studies [54], fosfomycin as single-dose therapy was compared with ofloxacin and trimethoprim-sulfamethoxazole, each also given as single-dose therapy; fosfomycin was significantly less effective in eradicating initial bacteriuria than was ofloxacin (135 [70%] of 194 vs. 92 [86%] of 107; $P < .001$). In the other [57], fosfomycin as single-dose therapy was significantly less effective than was the quinolone pipemidic acid* for 5 days (84% vs. 93%; $P = .018$) (table 8). Finally, although not meeting our criteria because they are unpublished, data presented to the U.S. Food and Drug Administration Anti-Infective Drugs Advisory Committee [60] indicated that among a total of >1,000 patients, single-dose therapy with fosfomycin was significantly less effective in eradicating bacteriuria (77%–82%) than was trimethoprim-sulfamethoxazole for 10 days or ciprofloxacin for 7 days (98% each).

Additional comments. Although not among the primary objectives of this study, two observations are of note. First, several studies suggested that older women tended to have lower bacteriuria eradication rates [24, 29, 61]. Second, infections with *S. saprophyticus,* commonly a distant second to *E. coli* in incidence among UTIs in women of childbearing age,

Table 8. Comparative studies of fosfomycin treatment for acute uncomplicated cystitis.

Trial [reference], parameter	Fosfomycin SDT	Comparator	*P* value
Fosfomycin SDT vs. norfloxacin, ≥5 d [58, 59]*			
Eradication	91/94 (97)	74/80 (93)	NS
Recurrence	26/85 (31)	22/76 (29)	NS
Adverse effects	29/112 (26)	12/109 (11)	.004
Fosfomycin SDT vs. pipemidic acid, 5 d [57]			
Eradication	123/146 (84)	133/143 (93)	.018
Recurrence	9/122 (7)	8/122 (7)	NS
Adverse effects	25/144 (17)	21/144 (15)	NS

NOTE. Data are no. with parameter/total (%). NS = not significant, i.e., >.05; SDT = single-dose therapy.
* Meta-analysis.

tended to be eradicated less frequently with 3-day than with longer therapy in some studies, particularly of fluoroquinolones [28–30]. Consequently, prudence might suggest that cystitis in older women or caused by *S. saprophyticus* might be better managed by longer courses of antimicrobials, for example, 7 days.

Not all of the 76 articles meeting our criteria have been discussed herein. Those that do not appear in the text or tables were not useful in our assessment because of inappropriate comparators or insufficient power and/or because they were not amenable to meta-analysis.

Acute Pyelonephritis

Studies of antimicrobial treatment of acute uncomplicated pyelonephritis that met our criteria were uncommon. Of several hundred articles screened by title and abstract, only 42 appeared relevant, and of these, only nine met our inclusion and exclusion criteria.

Of these nine, five were prospective, randomized, controlled trials [62–66]. However, one randomized patients to two durations of therapy and used a variety of antimicrobial regimens [62]. Thus, only four randomized, controlled trials of antimicrobial agents could be adequately reviewed. We derived two conclusions from these studies. The first is that trimethoprim-sulfamethoxazole is preferred over ampicillin. There are at least two reasons for this. The first is a relatively high prevalence of organisms causing acute pyelonephritis that are resistant to ampicillin [63, 64]. The second is that even for susceptible organisms, there is a significantly increased recurrence rate in patients given ampicillin compared with those given trimethoprim-sulfamethoxazole [64]; Ode et al. [65] and Jernelius et al. [66], in their studies of duration of treatment with ampicillin or ampicillin-like compounds, also found high recurrence rates with these β-lactams.

The second conclusion is that 2 weeks of therapy for acute uncomplicated pyelonephritis appears to be adequate for the majority of women. Stamm et al. [64] demonstrated that treatment of mild acute uncomplicated pyelonephritis with trimethoprim-sulfamethoxazole or ampicillin for 2 weeks was similar to 6 weeks of therapy with these agents. Jernelius et al. [66] studied pivampicillin* plus pivmecillinam* as a combination given for 1 week or 3 weeks. At follow-up after 3–4 weeks, only 6 of the 14 patients receiving 1-week therapy remained free of bacteriuria, compared with 14 of the 16 who had received 3 weeks of therapy ($P = .014$). These data suggest that 2 weeks of treatment yields results similar to those of 6 weeks of treatment and, at least with this β-lactam combination, 1 week of therapy is less effective than 3 weeks. Additionally, although not in controlled trials of duration, Johnson et al. [63] and Ward et al. [67] demonstrated high cure rates with 2 weeks and a mean of 11 days, respectively, of therapy.

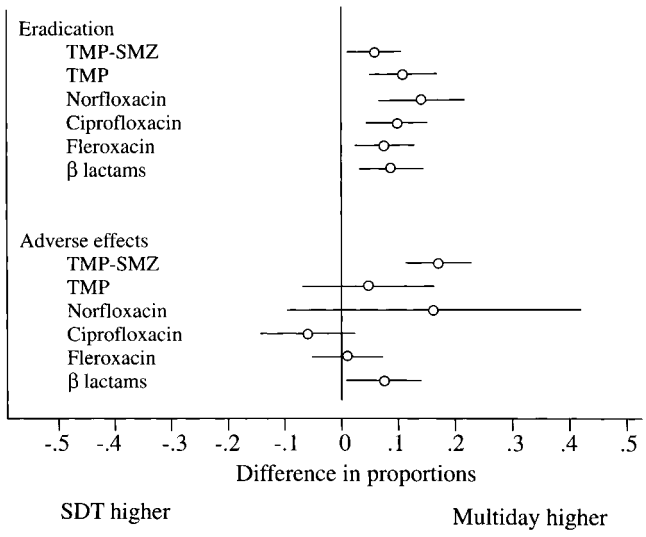

Figure 1. Single-dose therapy (SDT) vs. multiday therapy for uncomplicated cystitis: differences in proportions of patients experiencing eradication and adverse effects, with 95% confidence intervals. SMZ = sulfamethoxazole; TMP = trimethoprim. These plots represent data from respective tables. Note that meta-analyses of separate studies pool differences by a weighting procedure (see Methods); therefore, the plotted risk differences may not agree exactly with those derived from the proportions in the tables.

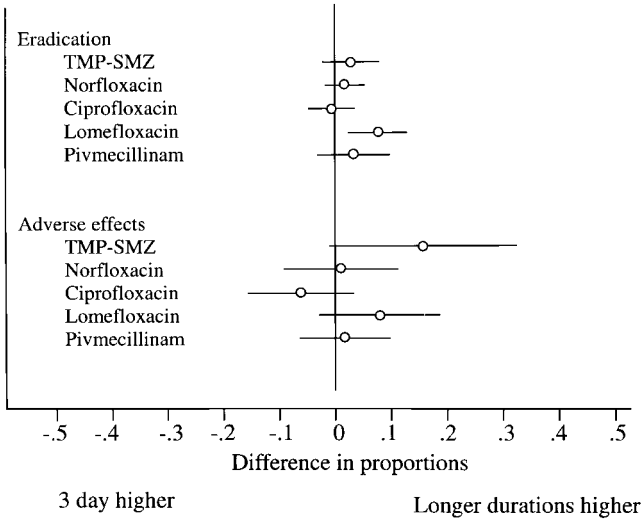

Figure 2. Three-day vs. longer-duration therapy for uncomplicated cystitis: differences in proportions of patients experiencing eradication and adverse effects, with 95% confidence intervals. SMZ = sulfamethoxazole; TMP = trimethoprim. These plots represent data from respective tables. Note that meta-analyses of separate studies pool differences by a weighting procedure (see Methods); therefore, the plotted risk differences may not agree exactly with those derived from the proportions in the tables.

Taken together, these data suggest that 10–14 days is a sufficient duration of therapy for acute pyelonephritis.

It should be noted, however, that some experienced clinicians have successfully treated cases of acute pyelonephritis with 5- to 7-day therapy with aminoglycosides, β-lactams, or fluoroquinolones [68, 69]. These latter findings must be reconciled with those of Jernelius et al. [66], however, and controlled trials examining shorter durations of therapy with highly active agents for acute uncomplicated pyelonephritis are thus needed [69].

Discussion

Acute Uncomplicated Cystitis

Single-dose therapy. Interest in single-dose therapy for treatment of acute cystitis [70] is evident from the fact that 50 of the 76 reports assessed herein included single-dose therapy as at least one arm. However, this systematic review revealed that single-dose therapy was significantly less effective in eradicating initial bacteriuria than were longer durations of treatment with trimethoprim-sulfamethoxazole, trimethoprim, norfloxacin, ciprofloxacin, fleroxacin, and, as a group, β-lactam antimicrobials (figure 1). In no reviewed study was single-dose therapy found to be significantly better in eradicating initial bacteriuria than was a longer duration with the same antimicrobial. Indeed, in no trial nor meta-analysis of sufficient power was single-dose therapy found to be even equivalent to longer durations of the same antimicrobial. This finding is consistent with two previous systematic reviews [71, 72].

Nevertheless, although not adequately tested against longer durations, three antimicrobials have recently emerged as possible candidates for single-dose therapy. Two are fluoroquinolones, pefloxacin and rufloxacin. Single-dose therapy with pefloxacin was tested against multiday trimethoprim-sulfamethoxazole and appeared promising; single-dose therapy with rufloxacin in a single large study was shown to be equivalent to single-dose therapy with pefloxacin. However, rates of adverse effects of these agents require definition by further studies.

The third antimicrobial of interest for single-dose therapy was fosfomycin trometamol. However, no trial meeting our criteria compared single-dose vs. longer durations of therapy with fosfomycin, and only two trials included an appropriate control. A meta-analysis of these two trials, while still of insufficient power to distinguish differences in eradication rates, demonstrated a significantly higher incidence of adverse effects with fosfomycin than with norfloxacin. Furthermore, two other studies demonstrated significantly lower rates of eradication of initial bacteriuria by fosfomycin single-dose therapy than by ofloxacin single-dose therapy and than by multiday pipemidic acid.* Finally, large but unpublished studies suggest that single-dose therapy with fosfomycin is less effective than multiday therapy with either trimethoprim-sulfamethoxazole or ciprofloxacin.

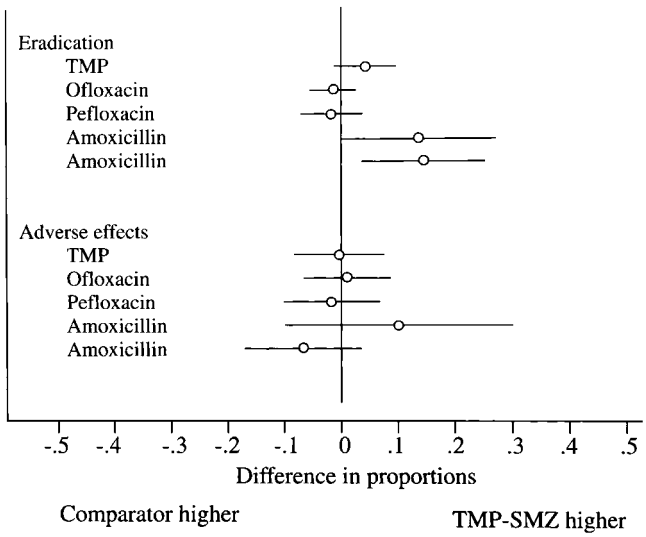

Figure 3. Comparison of various antibiotics with trimethoprim-sulfamethoxazole (TMP-SMZ) at the same durations of therapy for uncomplicated cystitis: differences in proportions of patients experiencing eradication and adverse effects, with 95% confidence intervals. These plots represent data from respective tables. Note that meta-analyses of separate studies pool differences by a weighting procedure (see Methods); therefore, the plotted risk differences may not agree exactly with those derived from the proportions in the tables.

Three-day therapy. Unlike single-dose therapy, 3 days of therapy is equivalent in efficacy to longer durations in studies of sufficient power for trimethoprim-sulfamethoxazole, norfloxacin (although an increased incidence of recurrences was noted), and ciprofloxacin (figure 2). Although lomefloxacin when given for 3 days had a 92% eradication rate, this was significantly lower than the 98% eradication rate for 7 days of therapy (however, lomefloxacin may be less appealing than other fluoroquinolones because of a significantly higher rate of adverse effects than seen with norfloxacin at equivalent durations). Among our assessed trials, the only β-lactam studied in this way was pivmecillinam, for which 3-day therapy was equivalent to 7 days of therapy in rates of eradication and adverse effects but yielded significantly higher recurrence rates.

If trimethoprim-sulfamethoxazole at ⩾3 days is the standard of therapy, other antimicrobials shown to be equivalent to trimethoprim-sulfamethoxazole include trimethoprim and ofloxacin when used in the same durations and pefloxacin when used as single-dose therapy (figure 3).

Fluoroquinolones. It is unfortunate that of fluoroquinolones, only ofloxacin and pefloxacin were tested against trimethoprim-sulfamethoxazole in studies of acceptable design and/or size. However, perhaps one can extrapolate useful information by analyzing a series of comparative studies. Pefloxacin single-dose therapy appears to be equivalent to trimethoprim-sulfamethoxazole therapy of ⩾5 days. Rufloxacin is equivalent to pefloxacin and both pefloxacin and rufloxacin as single-dose therapy appear to be similar to norfloxacin as multiday therapy in eradication of initial bacteriuria (although norfloxacin has fewer adverse effects). Therefore, norfloxacin for 3 or 5 days may be similar to trimethoprim-sulfamethoxazole for 5 days. Norfloxacin for 7 days is equivalent to ciprofloxacin for 3 days, and 7 days of ciprofloxacin is equivalent to fleroxacin. Lomefloxacin is equivalent to norfloxacin in eradication and recurrence but has more adverse effects.

Therefore, of the fluoroquinolones, the following may be equivalent or similar to ⩾3 days of trimethoprim-sulfamethoxazole in eradication of initial bacteriuria, recurrence, and adverse effects: ofloxacin, norfloxacin, ciprofloxacin, and fleroxacin. Pefloxacin single-dose therapy, rufloxacin single-dose therapy, and lomefloxacin at ⩾3 days may have higher rates of adverse effects than does norfloxacin.

β-lactams. Most of the β-lactams appear to be less effective than trimethoprim-sulfamethoxazole, trimethoprim, and the fluoroquinolones in eradication of initial bacteriuria and may yield increased incidences of recurrences and of adverse effects. Among the 26 trials in which a β-lactam was included in at least one arm, in only one did the β-lactam yield significantly greater rates of eradication of initial bacteriuria than did the non-β-lactam comparator: 3-day cefadroxil vs. 3-day macrodantin [42]. In the other trials, the β-lactams tended to be less effective in eradication of initial bacteriuria or in prevention of recurrence than were the non-β-lactam comparators. This is similar to the conclusions reached in other reviews [71]. The reasons for the relatively poor performance of β-lactams in treating symptomatic cystitis, particularly compared to their usefulness in other situations, is not completely clear. One reason may be that many β-lactams are rapidly excreted and the time during which significant drug concentrations are present in urine is short. Another is that β-lactams are relatively ineffective in clearing gram-negative rods from the vaginal and colonic flora, thus possibly predisposing to recurrence [73].

Nitrofurantoin. Unfortunately, nitrofurantoin as therapy for UTI has been studied infrequently in well-designed trials; assessment is further confounded by the use of different preparations. A small study found that 3-day treatment with nitrofurantoin macrocrystals was significantly less effective than 3-day treatment with trimethoprim-sulfamethoxazole in eradicating initial bacteriuria. A larger study, but of insufficient power, suggested that 7-day nitrofurantoin monohydrate macrocrystals was similar to 7-day trimethoprim and trimethoprim-sulfamethoxazole in eradication of initial bacteriuria, although rates were low for all three antimicrobials. We conclude that 3 days is too short a duration for nitrofurantoin treatment, that nitrofurantoin for 7 days may or may not be similar in effectiveness to trimethoprim and trimethoprim-sulfamethoxazole, and that this venerable urinary tract antimicrobial needs to be studied against current standard therapies in larger trials.

Recommendations. For susceptible organisms, trimethoprim-sulfamethoxazole double-strength given for 3 days is highly effective therapy for uncomplicated bacterial cystitis in adult nonpregnant women (A,I). Trimethoprim alone is equivalent to trimethoprim-sulfamethoxazole, at least for 7 days of therapy (A,I); thus, although not clearly documented in clinical trials, we conclude that with 3 days of therapy, trimethoprim is similar to trimethoprim-sulfamethoxazole (A,II). Intuitively, we recognize the likelihood that trimethoprim alone when compared in large populations against trimethoprim-sulfamethoxazole would have a lower incidence of side effects. Among the fluoroquinolones used for multiday therapies, ofloxacin is equivalent to trimethoprim-sulfamethoxazole (A,I), and norfloxacin (A,II), ciprofloxacin (A,II), and fleroxacin (A,II) are similar to trimethoprim-sulfamethoxazole. Other recently introduced fluoroquinolones are probably as effective (B,II), but some may have different incidences of side effects; furthermore, for those with broader antimicrobial spectra, widespread use for UTI and resulting emergence of resistance may limit their usefulness for respiratory, polymicrobial, and other non-urinary infections.

For uncomplicated cystitis, one should expect that ⩾90% of patients will experience eradication of bacteriuria and a low risk of recurrence and that treated patients will have an acceptably low risk of adverse effects if given treatment for 3 days with trimethoprim-sulfamethoxazole; with trimethoprim; or with the fluoroquinolones, ofloxacin, norfloxacin, ciprofloxa-

cin, or fleroxacin. For empirical treatment of acute uncomplicated cystitis, we recommend trimethoprim-sulfamethoxazole or trimethoprim in areas where the prevalence of resistance to these drugs among *E. coli* strains causing cystitis is <20%; other students of UTI suggest a threshold as low as 10%. Increasing resistance to these drugs among strains causing cystitis may soon limit their usefulness. The fluoroquinolones as a group are highly effective in treating cystitis, but because of their utility in treating complicated UTIs and prostatitis, which would be compromised if widespread use led to increased resistance, and because of their expense, we do not recommend these universally as first-line empirical therapy for uncomplicated cystitis. The fluoroquinolones could be used, however, in areas where the prevalence of resistance to trimethoprim and trimethoprim-sulfamethoxazole among uropathogens is high. Other options include nitrofurantoin, perhaps as 7-day therapy, and fosfomycin single-dose therapy (B,I); each of these requires further study. Although useful in other types of infections, β-lactams as a group are less effective in treatment of cystitis than are trimethoprim-sulfamethoxazole, trimethoprim, and the fluoroquinolones (E,I).

Acute Pyelonephritis

For decades, the traditional therapy for patients with acute uncomplicated pyelonephritis was hospitalization and treatment with intravenous antimicrobials for up to 6 weeks. More recent studies suggest that most young healthy women with acute pyelonephritis and uncomplicated urinary tracts will have a satisfactory outcome with 2 weeks of antimicrobial therapy [74, 75] (A,I). Some have advocated therapy lasting for 5–7 days [68, 69, 76], especially for mild to moderate pyelonephritis (B,I). Furthermore, accumulating data support the notion that not all and perhaps none of the therapy must be delivered iv [74, 75, 77, 78] (A,II). A woman who has a mild case of acute pyelonephritis (i.e., low-grade fever and a normal or slightly elevated peripheral leukocyte count without nausea or vomiting) and is compliant with therapy can be treated with oral antimicrobials on an outpatient basis. For empirical therapy, we recommend an oral fluoroquinolone (A,II). If the organism is known to be susceptible, oral trimethoprim-sulfamethoxazole provides an alternative (B,II). Many physicians administer a single parenteral dose of antimicrobial (ceftriaxone, gentamicin, or a fluoroquinolone) before initiating oral therapy [75, 79] (B,III). If a gram-positive organism is causative, we recommend the use of amoxicillin or amoxicillin/clavulanic acid (B,III). A useful option for some patients may be admission to a 12- to 24-hour observation unit of an emergency department where the response to initial therapy with a parenteral agent can be monitored [79] (B,II).

If a patient at the time of presentation is sufficiently ill to require hospitalization (high fever, high white blood cell count, vomiting, dehydration, or evidence of sepsis) or fails to improve during an initial outpatient treatment period, she should be admitted to a hospital and treated with iv antimicrobials (A,II). We recommend use of a parenteral fluoroquinolone, an aminoglycoside with or without ampicillin, or an extended-spectrum cephalosporin with or without an aminoglycoside (B,III). If gram-positive cocci are causative, we would use instead ampicillin/sulbactam with or without an aminoglycoside (B,III). After clinical improvement, as measured by resolution of fever (usually at 48–72 hours), we suggest changing to an oral regimen with agents active against the infecting organism and recommend fluoroquinolone compounds or trimethoprim-sulfamethoxazole (and for gram-positive organisms, amoxicillin or amoxicillin/clavulanic acid) (B,III).

Antimicrobial Susceptibility Profiles

We believe that these recommendations are appropriate for infections in the late 1990s in most communities in the United States. However, the clinician should be aware of current antimicrobial susceptibility patterns for *E. coli* and other uropathogens in the local community. Unfortunately, this information may become increasingly difficult to obtain because of the trend toward treating episodes of acute cystitis without obtaining cultures of urine [15, 16]. For cases of acute pyelonephritis, because of the potential severity of the infection, we strongly advocate culture of urine and susceptibility testing of isolated organisms [15, 16].

Data from bacteria isolated from the urine of patients with cystitis and pyelonephritis in Seattle are instructive [80]. In >4,000 isolates from women with acute uncomplicated cystitis seen at a health maintenance organization, the prevalence of resistance to trimethoprim-sulfamethoxazole, trimethoprim, and amoxicillin significantly increased over the period 1992–1996. Of greatest concern, the prevalence of resistance to trimethoprim-sulfamethoxazole was ⩾18% in 1996 [80]. Resistance to fluoroquinolones and nitrofurantoin among *E. coli* strains causing cystitis was <1% throughout the study period. Among 50 strains causing acute uncomplicated pyelonephritis in college women, resistance to trimethoprim-sulfamethoxazole was 30% [81]. These data indicate that routine mechanisms must be established in communities to assess antimicrobial susceptibility of uropathogens and that standard regimens for empirical therapy must be reassessed periodically in light of changing susceptibility patterns.

Indications and Performance Measures

Uncomplicated acute bacterial cystitis in women. The indicator, in areas where the prevalence of resistance to trimethoprim-sulfamethoxazole and to trimethoprim is <20%, is that uncomplicated acute bacterial cystitis should be treated for 3 days with trimethoprim-sulfamethoxazole or trimethoprim. The performance measure would be the rate of

compliance with this A,I recommendation. The denominator would be all otherwise healthy adult nonpregnant women with symptoms of frequency, urgency, and/or dysuria and with $\geqslant 10^2$ cfu of bacteria/mL of urine. The numerator would be the number of such women treated with oral trimethoprim-sulfamethoxazole or trimethoprim for 3 days.

Uncomplicated acute pyelonephritis in women. The indicator is that otherwise healthy young women with acute pyelonephritis should be treated for 7–14 days, mostly with oral antibiotics. The performance measure would be degree of compliance with this B,I recommendation. The denominator would be all young otherwise healthy nonpregnant women with normal urinary tracts presenting with flank pain and/or fever and with $\geqslant 10^2$ cfu of bacteria/mL of urine. The numerator would be the number of such women treated for 7–14 days, either totally with oral antibiotics or with oral antibiotics following improvement with initial parenteral antibiotics.

Suggestions for Future Studies

We reviewed treatment studies of one of the most common bacterial infections in humans, acute bacterial cystitis in otherwise healthy women. However, our criteria to insure study rigor, developed a priori, excluded the great majority of reports. The usual reason for rejection was that the study populations included not only women with uncomplicated cystitis but also men as well as persons with asymptomatic bacteriuria, fever, or flank pain or complicated urinary tract infections. Although we recognize that many of these studies were designed by pharmaceutical firms seeking regulatory approval for their drugs, we suggest that future investigations be reported to allow separate analyses of adult, nonpregnant women with normal urinary tracts who are experiencing dysuria, frequency, and/or urgency in the absence of fever or flank pain. The design should be that of a prospective, double-blind, randomized trial using as the control agent one of the antimicrobials recommended here; numerators and denominators for recurrences should be easily discernible. Analyses should include an intent-to-treat approach that includes not only patients with uropathogens subsequently found to be susceptible but also those with organisms resistant to the study drug(s). Outcome measures should be not only bacteriologic but also clinical symptoms; at least a 4-week evaluation should be conducted. These suggestions are consistent with the guidelines developed by the IDSA and the U.S. Food and Drug Administration [82].

Our recommendations regarding the treatment of acute pyelonephritis are limited by the relative paucity of appropriate studies. Controlled trials examining management of acute pyelonephritis are few, and many of the available studies are weakened by participation of heterogeneous populations, including men and patients with complicated urinary tracts. We suggest that more attention be devoted not only to trials of therapy for acute pyelonephritis but also to presentation of data in a manner allowing analyses of relatively homogeneous populations, such as women with uncomplicated urinary tracts.

Additional types of studies would enhance our understanding of optimal management of uncomplicated UTIs. Antimicrobial resistance patterns will continue to change, implying that properly designed studies performed in a timely fashion will be necessary to maintain currency. These trials should include not only newly introduced agents but also extant antimicrobials, to gauge their relative importance; examples of the latter may be nitrofurantoin and fosfomycin. Studies also would be helpful that focus on specific subsegments, such as the elderly and those with UTIs due to enterococci or *S. saprophyticus.*

Acknowledgments

We would like to acknowledge the superb administrative and typing skills of Linda Horne and the library research performed by Theresa Jackson and Deborah Bills. The following persons reviewed the manuscript and did not have substantive disagreements with its conclusions or recommendations: Vincent T. Andriole, Michel G. Bergeron, Stacy J. Childs, Clair E. Cox, Stephan D. Fihn, Ellie J. C. Goldstein, J.M.T. Hamilton-Miller, Godfrey K. Harding, Donald Kaye, Calvin M. Kunin, Leonard Leibovici, Benjamin A. Lipsky, William M. McCormack, Kurt G. Naber, J. Curtis Nickel, Lindsay E. Nicolle, S. Ragnar Norrby, Lawrence L. Pelletier, Jr., Raul Raz, Allan R. Ronald, Robert H. Rubin, Thomas A. Russo, Charles V. Sanders, Jack D. Sobel, Russell W. Steele, and Gary E. Stein.

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