

Amoxicillin/clavulanate for the treatment of uncomplicated cystitis in women: a historical perspective

Original article Hooton TM *et al.* (2005) Amoxicillin-clavulanate vs ciprofloxacin for the treatment of uncomplicated cystitis in women: a randomized trial. *JAMA* 293: 949–955

SYNOPSIS

KEYWORDS amoxicillin/clavulanate, ciprofloxacin, cystitis, resistance, urinary tract infection

BACKGROUND

Trimethoprim/sulfamethoxazole and fluoroquinolone antibiotics are highly effective in the treatment of acute cystitis, but increasing resistance to these antimicrobials has prompted calls for alternative treatment strategies.

OBJECTIVE

To compare the efficacy of a short course of amoxicillin/clavulanate to that of ciprofloxacin in the treatment of acute uncomplicated cystitis in women.

DESIGN AND INTERVENTION

Between July 1998 and May 2002, women aged 18–45 years with dysuria, frequency, and/or urgency were enrolled in a single-blind, randomized trial. Exclusion criteria included pregnancy, evidence of pyelonephritis, urinary tract abnormality, and recent use of systemic or vaginal topical antimicrobials. After an initial assessment, patients were randomized to receive amoxicillin/clavulanate 500 mg/125 mg twice daily or ciprofloxacin 250 mg twice daily, each for 3 days. Patients were evaluated every 2 weeks for 4 months, or until treatment for symptomatic persistent or recurrent urinary tract infection (UTI) was required. At initial and follow-up assessments, urine and vaginal specimens were analyzed for the presence of uropathogens and for antimicrobial susceptibilities. Only women with at least 10^2 colony-forming units (CFU) of uropathogens per ml of urine at the time of enrollment and who completed at least one follow-up evaluation were included in the analysis.

OUTCOME MEASURES

The primary endpoint was clinical cure, defined as the absence of persistent or recurrent UTI symptoms. Secondary endpoints were microbiologic cure (asymptomatic women with urine cultures of $<10^5$ CFU/ml, or symptomatic women with urine cultures of $<10^2$ CFU/ml) and vaginal colonization with *Escherichia coli*.

RESULTS

Of 370 women enrolled in the study, 322 were eligible for analysis, 99% of whom took at least five of the six prescribed doses. Median age for both treatment groups was 22 years (range 18–45 years). Median follow-up was 103 days (range 2–125 days). Overall, 93 (58%) of 160 women treated with amoxicillin/clavulanate were clinically cured, compared with 124 (77%) of 162 women treated with ciprofloxacin ($P < 0.001$). Even among women infected with strains susceptible to amoxicillin/clavulanate, this combination was inferior to ciprofloxacin: 65 (60%) of 109 women taking amoxicillin/clavulanate were clinically cured, compared with 114 (77%) of 149 women taking ciprofloxacin ($P = 0.004$). Persistent and recurrent UTIs occurred in 8 and 59 women in the amoxicillin/clavulanate group, and in 1 and 37 women in the ciprofloxacin group, respectively. At 2 weeks post-treatment, 118 (76%) of 156 women treated with amoxicillin/clavulanate had a microbiologic cure, compared with 153 (95%) of 161 women treated with ciprofloxacin ($P < 0.001$). Vaginal colonization with *E. coli* occurred in 58 (45%) of 151 women treated with amoxicillin/clavulanate, compared with 16 (10%) of 153 women treated with ciprofloxacin ($P < 0.001$).

CONCLUSION

In women with acute uncomplicated cystitis, including those infected with susceptible strains, a 3-day regimen of amoxicillin/clavulanate is less effective than ciprofloxacin.

COMMENTARY

J Curtis Nickel

One hundred years ago, simple cystitis was not perceived by physicians to be such a big problem. Patients did suffer, but if they had no complicating factors and did not develop an upper tract infection or sepsis, they eventually recovered (despite physicians' ministrations), and frequent recurrences seemed to be rare.¹ With the introduction of antibiotics, it was firmly believed that UTIs would become a historical footnote.² Sulfanilamide, introduced in 1937, was an effective treatment for acute cystitis, and ushered in the era of antimicrobial therapy for UTIs. Side effects and bacterial resistance, however, restricted its usefulness and eventually that of its successors (e.g. sulfisoxazole). Penicillin, introduced in 1947, was the miracle cure for many infectious diseases, but was ineffective against most UTI organisms. The first truly effective antibacterial therapy for uncomplicated cystitis, nitrofurantoin, became available in 1953. In 1962 nalidixic acid, the prototype of the new quinolone class of antibiotics, was introduced. Several antimicrobials for UTIs became available in the 1970s, including β -lactams (e.g. ampicillin and amoxicillin) and the combination of trimethoprim/sulfamethoxazole. The widespread use of ampicillin and amoxicillin in the 1970s and 1980s led to the emergence of resistance, and trimethoprim/sulfamethoxazole became the empiric therapy of choice. Increased use of trimethoprim/sulfamethoxazole, however, has resulted in increasing levels of resistance among UTI organisms in recent years.³ In the later 1980s and 1990s, the newly introduced fluoroquinolones (norfloxacin, ciprofloxacin, ofloxacin and levofloxacin) became the most promising option for empiric treatment of UTIs in the era of increasing widespread resistance to trimethoprim/sulfamethoxazole and amoxicillin.

However, as noted in the present study by Hooton *et al.*, widespread use of these agents is promoting fluoroquinolone resistance. The authors speculated that amoxicillin/clavulanate could provide an alternative to trimethoprim/sulfamethoxazole, allowing the fluoroquinolones to be spared for more serious and antimicrobial-resistant UTIs. In a well-designed, randomized, single-blind trial in premenopausal women with symptoms of acute uncomplicated cystitis

confirmed with urine culture, the authors noted clinical and microbiologic cure rates at the 2-week follow-up visit of only 58% and 76%, respectively, with amoxicillin/clavulanate, compared with 77% and 95%, respectively, with ciprofloxacin. They further noted that even in women infected with strains susceptible to amoxicillin/clavulanate, this drug combination was not as effective as ciprofloxacin.

This study was a well-intentioned effort to find an alternative to trimethoprim/sulfamethoxazole in order to spare fluoroquinolones; unfortunately it seems that amoxicillin/clavulanate is not the answer. Although the perception remains that overall global resistance rates to the fluoroquinolones remain low, exceptions such as Spain and Portugal indicate that this situation will not continue. History will undoubtedly teach us another lesson: namely, that widespread use of fluoroquinolones for uncomplicated UTIs will eventually render this important class of antimicrobials ineffective. At present, there are few alternatives in the pipeline. A quinolone-sparing strategy must be recommended for uncomplicated cystitis.⁴ Trimethoprim/sulfamethoxazole or trimethoprim alone remain the agents of choice for uncomplicated cystitis in most parts of North America. When these agents cannot be used because of resistance, drug allergy, or patient intolerance, nitrofurantoin remains the most suitable alternative. It is unlikely that we will want to go back to pre-antibiotic, expectant management of uncomplicated cystitis; therefore, history teaches us the importance of the physician's role in the stewardship of antimicrobials in the management of uncomplicated UTIs.

References

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Acknowledgments

The synopsis was written by Sandra Michelmore, Associate Editor, Nature Clinical Practice.

Competing interests

The author declared competing interests; go to the article online for details.

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Received 19 May 2005

Accepted 28 June 2005

www.nature.com/clinicalpractice
doi:10.1038/ncpuro0253

PRACTICE POINT

Physicians electing empiric therapy for uncomplicated cystitis should consider quinolone-sparing alternatives, or we will lose another excellent class of antimicrobial agents