Amoxicillin Therapy of Acute Urinary Infections in Adults


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Fifty-two patients, 48 females and 4 males, with suspected urinary infection were treated with amoxicillin. Twenty-two females with presumed bladder infection were treated with amoxicillin, 250 mg three times a day for 7 days; 26 females and 4 males with presumed renal infection were treated with amoxicillin, 500 mg three times a day for 14 days. Five patients were immediate treatment failures, with positive urine cultures during therapy. All five patients had been infected with amoxicillin-resistant urinary pathogens. Three patients, treated as for bladder infections, reinfected during 6 weeks of follow-up, and only one relapsed. Two patients, treated as for renal infections, reinfected, whereas four relapsed. During therapy, amoxicillin-susceptible gram-negative rods were eradicated from the periurethral area in all but one patient. Of 28 patients studied, 19 acquired a predominant growth of either resistant aerobic gram-negative rods or Candida albicans from periurethral cultures. Our findings suggest that these two regimens of amoxicillin achieve satisfactory cure rates in urinary infection, but both regimens significantly alter the normal periurethral flora.

The hydroxylation of the phenyl side chain of ampicillin has resulted in amoxicillin, a penicillin with an antibacterial spectrum similar to ampicillin but more completely absorbed after oral administration (11). Several studies have reported the use of this agent in the treatment of urinary infection (3, 5, 6, 10). However, the optimal duration and dose of therapy to eradicate infection is undetermined. This report concerns itself with an evaluation of two different regimens in patients with acute urinary infection: (i) a "low-dose" regimen of 250 mg three times a day for 1 week in women with probable bladder infection, and (ii) a "high-dose" regimen of 500 mg three times a day for 2 weeks in patients with probable renal infection.

MATERIALS AND METHODS

Patient selection. Fifty-two adults, 48 females and 4 males, were studied. All patients gave verbal informed consent to be included in the study. Most patients were first seen with acute urinary symptoms at the Emergency Room or Primary Health Care Unit of the Health Sciences Centre, and amoxicillin treatment was begun immediately after urine cultures and periurethral swabs were obtained. No patient was known to have renal calculi or urological disease that would compromise successful therapy with an antimicrobial agent. All the patients had normal renal function, with a serum creatinine of less than 1.5 mg/100 ml. Patients with a previous history of untoward reaction to any of the penicillins were excluded from participation in the study. Pregnant patients were also excluded. Twenty-six females with a history of fever, chills, and flank pain, with costovertebral angle tenderness, symptoms and signs indicative of upper urinary tract infection were given amoxicillin 500 mg three times a day for 14 days; patients without these findings but with frequency, dysuria, and suprapubic pain were given amoxicillin 250 mg three times a day for 7 days. All four male patients had upper urinary tract symptoms and were treated with the high-dose 2-week course. Six women had less acute bladder symptoms and, after two positive urine cultures, their infections were treated as bladder infections with the low-dose one-week regimen.

To assess the immediate response to therapy, patients were requested to return at the end of 1 week of therapy and at 2 and 6 weeks after therapy to determine drug efficacy in the cure of infection. At each visit, the patient was specifically questioned about side effects and symptoms of infection, and a urine culture was obtained.

A modified Fairley bladder wash-out procedure was performed in nine women to localize the site of infection with greater accuracy (2). Unfortunately, most patients had to be treated at the time when they were first seen with acute symptoms, and no localization procedures were carried out.

Collection of specimens. Periurethral specimens were collected at each visit from female patients, with the patient on the examining table in the lithotomy position. A research nurse wearing sterile gloves spread the labia apart exposing the urethral meatus. With a cotton-tipped applicator, a specimen
was collected by a circular motion around the entire urethra. The swab was inserted into a screw-capped glass tube containing 5 ml of physiological saline. Finally, a clean, voided midstream urine specimen was collected.

Bacteriological techniques. The tube containing the periurethral swab was blended in a Vortex mixer at high speed for 1 min, and portions of 0.001 and 0.01 ml of the suspension and the urine were inoculated onto sheep blood agar, MacConkey agar, and chocolate agar. After 24 h of incubation at 37°C, colony counts were determined on all organisms isolated from the swab and urine. Susceptibility tests were performed on all urinary pathogens with a single disk diffusion method with an inoculum of 5 \times 10^{5} \text{organisms per ml on Mueller-Hinton agar} \text{(1). Minimum inhibitory concentrations (MICs) of amoxicillin were determined on Mueller-Hinton agar with the Steers replicator device and an inoculum of 10^{5} \text{organisms per ml (8). Susceptible organisms had an MIC of } 50 \text{ } \mu\text{g of amoxicillin per ml. Actually, all but one were susceptible to 6.25 } \mu\text{g or less per ml. Resistant organisms were not inhibited by 100 } \mu\text{g of amoxicillin per ml. All Escherichia coli isolates from periurethral and urine specimens were serotyped with antisera to the O somatic antigens (4).}

Bacteriuria was defined as the presence of more than 100,000 organisms per ml of urine in a single clean, voided midstream urine in 30 patients who developed acute urinary symptoms and by two cultures positive for over 100,000 organisms of the same species in 12 patients with less severe symptoms.

RESULTS

The results of therapy are summarized in Table 1. Nineteen of the 22 females entered in the "low-dose bladder study" had bacterial urinary infection. In retrospect, three patients with symptoms considered to be due to bacterial cystitis had a negative urine culture, and Trichomonas vaginalis infection was subsequently found in one and moniliasis was observed in the other two. These patients were then treated appropriately and were not included further in the study. Four of the 19 patients were infected with organisms resistant to amoxicillin. Three of these patients were immediate treatment failures, since the organisms persisted during therapy, and two patients had continuing symptoms. Infection recurred in four patients either during or within 6 weeks of completing amoxicillin therapy. One patient with a Streptococcus faecalis urinary infection had a relapse with the same organism within 1 week after therapy. Three patients reinfeeted, each with an organism resistant to amoxicillin. Six weeks after completion of low-dose amoxicillin therapy, 11 of the 19 patients were free of bacteriuria without additional therapy. Of the 15 patients infected with susceptible organisms, 11 (73%) were cured at 6 weeks.

Six patients in the low-dose study group had untoward effects. Two patients developed symptomatic moniliasis, and four had mild gastrointestinal symptoms. However, none of these patients discontinued therapy.

After initial evaluation, 26 female patients were entered into the study under the upper tract infection category and were treated with 2 weeks of amoxicillin, 500 mg three times a day. Unfortunately, seven of these patients had negative cultures. This included two patients who, in retrospect, were seen to be ill with acute pelvic inflammatory disease. In one, Neisseria
gonorrhoeae was isolated from a cervical culture. Both patients improved on amoxicillin but are not included in the evaluation of therapeutc efficacy. No specific diagnoses were made in the other five patients to account for their symptoms. Five of these 19 patients had upper tract infection by the bladder wash-out technique. Two of the 19 were infected with amoxicillin-resistant organisms, and in both instances the organism persisted during therapy. Five patients who initially responded to therapy, with negative urine cultures during therapy, failed to return for follow-up. Of the 12 patients with susceptible organisms who did return, four relapsed within 2 weeks of completing therapy with the initial infecting organism. In three of these patients, E. coli, and, in one, Proteus mirabilis, was the infecting pathogen. After relapse, two of these four patients were given a 6-week course of amoxicillin, 1.5 g/day. One was cured with this course of therapy and one again had a relapse with the same serotype of E. coli. Two patients reinfected with an amoxicillin-resistant Klebsiella sp. during the 6 weeks of follow-up. Of the 14 females with adequate follow-up, initially treated with 2 weeks of amoxicillin, 500 mg three times a day, six were free of bacteriuria without additional therapy at 6 weeks after completion of therapy.

All patients with amoxicillin-susceptible organisms responded satisfactorily to therapy, with rapid improvement in upper tract symptoms. Five patients with an elevated temperature at the onset of therapy became afebrile within 48 h.

Five patients had side effects on the high-dose regimen. One patient had urticaria, one had severe nausea and vomiting with epigastric distress, two had vulvar pruritis, and one noted soft stools. The patient with urticaria and the patient with epigastric distress both discontinued taking amoxicillin before completion of therapy.

Four male patients with amoxicillin-susceptible E. coli urinary infection were treated for 14 days with 500 mg three times a day. All four tolerated the medication well and had negative urine cultures during therapy. After discontinuation of therapy, two patients relapsed with their initial infecting strain, and two remained free of infection during 6 weeks of follow-up.

Organisms resistant to ampicillin, as determined by the Bauer-Kirby (1) high-content single disk diffusion technique, had an amoxicillin MIC of 50 µg or more per ml. Five of the six patients with amoxicillin-resistant organisms in this study had persistent positive cultures during therapy and were immediate therapeutic failures.

Paired periurethral swabs were obtained before treatment and at the completion of therapy from 28 patients. Eight of 15 treated with the low-dose regimen and 5 of 13 treated with the high-dose regimen had positive periurethral cultures before therapy, with the same gram-negative rod present in the voided urine culture.

Table 2 summarizes the results of the periurethral swabs at the completion of therapy. In every instance, susceptible Enterobacteriaceae disappeared from the perineum during high-dose therapy and persisted in only one patient during low-dose therapy. Eight of the 15 patients on the low-dose regimen acquired amoxicillin-resistant enteric pathogens or C. albicans. Two patients acquired resistant E. coli, and four acquired resistant Klebsiella sp. Eleven of the 13 patients on the high-dose regimen were colonized during therapy with resistant gram-negative organisms. The amoxicillin-resistant organisms appearing during therapy always differed in either species or serotype from the pretherapy susceptible periurethral organisms. All five patients who reinfe{c}ted during or within 6 weeks of completion of therapy became reinfected with amoxicillin-resistant organisms present on periurethral cultures at the time of or before their recurrence.

DISCUSSION

This study confirms the efficacy of amoxicillin in the treatment of urinary infection in females infected with susceptible organisms. The patient population in this study consisted, for the most part, of acutely symptomatic, healthy females with normal renal function and no underlying urological disease. Although localization of infection on clinical criteria is fraught with error, we have found that 78% of women with upper tract symptoms have organisms emanating from their upper tracts (2). Localization by the bladder wash-out technique cannot be carried out routinely in acutely ill patients, and the test for the detection of antibody-coated bacteria (9) only became available in our hospital after this study was completed. Most acutely ill patients are treated for renal or bladder infection solely on the basis of clinical parameters.

Earlier studies from this center have shown that a short therapeutic regimen is adequate to cure proven bladder infections in the majority of females (7). In this study, a 1-week low-dose oral amoxicillin regimen eradicated the infection in 13 of 14 patients with susceptible patho-
Table 2. Enterobacterial and candidal periurethral colonization during amoxicillin therapy

<table>
<thead>
<tr>
<th>Determination</th>
<th>Amoxicillin dose (three times a day)</th>
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<tbody>
<tr>
<td></td>
<td>250 mg for 7 days</td>
</tr>
<tr>
<td>No enterobacterial or candidal colonization prior to or during therapy</td>
<td>3</td>
</tr>
<tr>
<td>Periurethral culture negative pretherapy but positive during therapy with resistant Enterobacteriaceae or Candida</td>
<td>4</td>
</tr>
<tr>
<td>Resistant E. coli</td>
<td>1</td>
</tr>
<tr>
<td>Resistant Klebsiella sp.</td>
<td>1</td>
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<tr>
<td>Resistant Klebsiella sp. and C. albicans</td>
<td>1</td>
</tr>
<tr>
<td>C. albicans</td>
<td>1</td>
</tr>
<tr>
<td>Periurethral culture positive for susceptible Enterobacteriaceae pretherapy which were eliminated and replaced with resistant organisms</td>
<td>4</td>
</tr>
<tr>
<td>Resistant E. coli</td>
<td>1</td>
</tr>
<tr>
<td>Resistant E. coli and Klebsiella sp.</td>
<td>0</td>
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<tr>
<td>Resistant Klebsiella sp.</td>
<td>2</td>
</tr>
<tr>
<td>C. albicans</td>
<td>1</td>
</tr>
<tr>
<td>Periurethral culture positive for Enterobacteriaceae pretherapy which were eliminated and not replaced</td>
<td>2</td>
</tr>
<tr>
<td>Susceptible Enterobacteriaceae present before therapy persisted throughout therapy</td>
<td>1</td>
</tr>
<tr>
<td>Resistant Enterobacteriaceae present before therapy persisted throughout therapy</td>
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gens and presumed bladder infections. A longer duration or a higher dose of amoxicillin would not have provided any additional benefit to these 13 patients.

A two-week course of 1.5 g of amoxicillin per day eradicated infection in 8 of 12 adequately followed patients who were infected with susceptible strains that were presumed to originate in the upper urinary tract. It is our impression from ongoing studies that about 75% of patients with acute uncomplicated upper tract infection are cured by a 2-week course of an oral antimicrobial agent if the infecting organism is susceptible and cultures during therapy are negative. The numbers are too small in the present group to conclude that amoxicillin differs from other oral agents.

Four of the 48 women treated with amoxicillin complained of vulvar pruritus, and in every instance, C. albicans was present on culture. One patient developed an urticarial rash, one had severe epigastric distress, and five noted soft, frequent stools. Without careful double-blind prospective studies, this level of drug intolerance cannot be said to be different from that associated with ampicillin.

Although superinfection with resistant organisms is a recognized complication of antimicrobial chemotherapy, only recently has their role in predisposing the urinary tract to resistant reinfections received serious study. Alteration of the colonic and periurethral flora precedes recurrence with resistant organisms (12). An optimal therapeutic regimen should cure the target infection with little disruption of bacterial ecology. We hypothesized that low-dose therapy for 1 week with a well-absorbed oral antimicrobial agent excreted unchanged in the urine would cure bladder infections without altering periurethral flora. Although amoxicillin eradicated the infection in 13 of 14 women with susceptible pathogens and lower tract symptoms, it altered the periurethral flora and predisposed to reinfections with resistant Enterobacteriaceae. Further studies with smaller doses and shorter duration are needed to determine optimal therapy for bladder infections in women.

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LITERATURE CITED


