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Is combination antimicrobial therapy required for urinary tract infection in children?

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This retrospective study examined the characteristics of 338 pediatric patients presenting with a first episode of symptomatic urinary tract infection at Taichung Veterans General Hospital from November 1996 to December 2001. *Escherichia coli* was the most common pathogen (72.5%), followed by *Proteus mirabilis* (8.3%), *Enterococcus* (5.6%), and *Klebsiella pneumoniae* (4.7%). They were more susceptible to first-generation cephalosporin in comparison with other first-line antimicrobial agents such as trimethoprim/sulfamethoxazole, ampicillin, and gentamicin. Two hundred and eighty-seven (84.9%) of the 338 patients were divided into 3 groups according to the type of antibiotic treatment received, and the susceptibility rate and the averaged day of defervescence after effective antibiotic therapy were compared among the groups. Group 1 consisted of those patients treated with cefazolin or cephalexin alone (95%, 2.1 days); Group 2, cefazolin plus gentamicin (88.9%, 2.8 days); and Group 3, ampicillin plus gentamicin (76.1%, 2.3 days). A total of 38 (13.2%) cases from the 3 antibiotic groups did not respond to empiric antibiotics. For non-susceptible infections, when the antibiotic regimen was switched from cefazolin plus gentamicin to ampicillin alone, only 4 (20%) strains became susceptible, compared with 10 strains (62.5%) becoming susceptible after switching from ampicillin plus gentamicin to cefazolin alone ($p<0.01$). The results indicated that first-generation cephalosporin alone is an appropriate treatment for pediatric cases of community-acquired urinary tract infection and suggest that antimicrobial combinations should be reserved for serious or critical cases.

Key words: Antibiotic combination, defervescence, effective antibiotic therapy, urinary tract infection,

Urinary tract infection (UTI) is a common disease in children, with a total prevalence of approximately 5% [1-2]. Early recognition and appropriate antimicrobial treatment can prevent progression to acute pyelonephritis, which frequently leads to renal scarring and subsequent hypertension or renal insufficiency. It has been demonstrated that approximately 13% to 15% of end-stage renal disease is related to childhood UTI that was frequently unrecognized and undertreated [3]. In Taiwan, combinations of ampicillin plus gentamicin, or cefazolin plus gentamicin are often empirically prescribed to treat UTI for hospitalized children. In recent years, however, antimicrobial resistance has increased markedly in Taiwan, especially of the leading UTI pathogen, *Escherichia coli*. This retrospective study evaluated the effectiveness of first-line antimicrobial agents, prescribed alone or in combination, for the treatment of a first episode of hospitalized children with community-acquired UTI.

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Materials and Methods

A total of 338 children admitted for a first episode of symptomatic UTI to Taichung Veterans General Hospital (TVGH), a 1200-bed medical center in central Taiwan, during the period from November 1996 through December 2001 were included in this study. Their ages ranged from 7 days to 14.8 years. The charts of the patients were reviewed. The clinical features, laboratory data, causative organisms, antibiotic-administration schedule, and averaged day of defervescence after effective antibiotic therapy (ADDAEAT) were collected and analyzed. Symptomatic UTI was defined as signs of acute illness (such as fever, poor appetite, poor

activity, abdominal pain, and/or dysuria) together with a positive urine culture yielding at least one organism by suprapubic puncture, transurethral catheterization ($\geq 10^4$ colony-forming units [CFU]/mL), or midstream or urine-bag collection using the clean catch method ($\geq 10^5$ CFU/mL) [2-4,6]. Cases of asymptomatic bacteriuria, mixed culture (≥2 organisms), and recurrent or nosocomial UTI were excluded. *Lactobacillus* sp., *Corynebacterium* sp., α-hemolytic streptococci, and coagulase-negative staphylococci were not regarded as pathogens. The susceptibility tests of the causative isolates were performed according to National Committee for Clinical Laboratory Standards guidelines for antimicrobial disc diffusion tests [7,8] and the concentration of the antimicrobial agent achieved in the serum rather than in the urine.

To compare the susceptibility rates and ADDAEAT for different antimicrobial agents, 287 of the 338 patients were divided into 3 antimicrobial-regimen groups: Group 1, cefazolin or cephalexin alone; Group 2, cefazolin plus gentamicin; and Group 3, ampicillin plus gentamicin. To compare the ADDAEAT, Groups 2 and 3 were further divided into 2 subgroups according to susceptibility to one or both of the antibiotics. Patients with concomitant diseases, such as bronchopneumonia, acute enterocolitis, and an ADDAEAT of 5 days or more were excluded. Susceptibility to antimicrobial combinations was defined as sensitivity of the isolated bacteria to at least one drug. Non-susceptibility to antimicrobial combinations was defined as resistance to both agents, or to one with intermediate resistance to the other. Chi-square test and Z-test were used for statistical analysis. A p value less than 0.05 was considered statistically significant.

Results

The mean age of the 338 children enrolled in this study was 21.3 months (range, 7 days-14.8 years). There were 222 (65.7%) boys and 116 (34.3%) girls, with a male/female ratio of 1.9:1. Urine sampling consisted of either transurethral catheterization or suprapubic puncture (278 cases; 82.3%), or clean-midstream capture or urine-bag collection (60 cases; 17.7%). Pathogens in order of prevalence (Table 1) were *E. coli* (245 cases; 72.5%), *Proteus mirabilis* (28 cases; 8.3%), *Enterococcus* (19 cases; 5.6%), and *Klebsiella pneumoniae* (16 cases; 4.7%). Drug susceptibility to first-line antibiotics for the causative organisms *E. coli*, *P. mirabilis*, and *K. pneumoniae* was also reviewed (Table 2), with the highest rates demonstrated for cefazolin and the lowest for ampicillin (86.5, 85.7, and 68.7%; and 24.1, 32.1, and 0%, respectively). *K. pneumoniae* was less susceptible to most antibiotics including the third-generation drugs, cephalosporin and amikacin. Resistance to cephalosporins was observed for 7 isolates of *E. coli* and 4 of *K. pneumoniae*, with amikacin resistance also demonstrated for 5 of these 11 isolates. Forty patients from the 3 studied antibiotic-treatment groups were treated with cefazolin or cefalexin alone (Group 1; 11.8%), 180 with cefazolin plus gentamicin (Group 2; 53.3%), and 67 with ampicillin plus gentamicin (Group 3; 19.8%). The total drug susceptibility rate for all 3 antibiotic-treatment

Table 1. Pathogens isolated in children with urinary tract infection

Microorganism	No. of isolates n = 338 (%)
Escherichia coli	245 (72.5)
Proteus mirabilis	28 (8.3)
Enterococcus spp.	19 (5.6)
Klebsiella pneumoniae	16 (4.7)
Morganella morganii	10 (3.0)
Citrobacter spp.	6 (1.8)
Enterobacter spp.	5 (1.5)
Pseudomonas aeruginosa	4 (1.2)
Others[a]	5 (1.5)

[a]Including *Klebsiella oxytoca* (4) and *Proteus vulgaris* (1).

Table 2. Antimicrobial susceptibility of causative organisms by disk diffusion test in children urinary tract infections

Antimicrobial agent	Susceptibility rate (%)		
	E. coli (n = 245)	*P. mirabilis* (n = 28)	*K. pneumoniae* (n = 16)
Cefazolin	86.5	85.7	68.7
Gentamicin	78.0	78.6	56.2
Trimethoprim/Sulfamethoxazole	48.6	35.7	62.5
Ampicillin	24.1	32.1	0.0
Cefmetazole	97.6	100.0	81.2
Amoxillin/Clavulanate	82.9	100.0	75.0
Ampicillin/Sulbactam	76.3	100.0	50.0
Ceftazidime	96.7	100.0	81.2
Ceftriaxone	96.7	100.0	75.0
Cefotaxime	96.3	100.0	81.2
Amikacin	99.2	100.0	75.0

groups was 86.8%, with analogous individual rates for Groups 1, 2, and 3 of 95%, 88.9%, and 76.1%, respectively (p=0.008). The average ADDAEAT for the 3 antibiotic groups was 2.7 days (range, 0-9), while the individual ADDAEATs for Groups 1, 2 and 3 were 2.1, 2.8, and 2.3 days, respectively (p=0.0757). One-hundred-and-two episodes of infections from the 2 susceptible subgroups were susceptible to both agents (S+S), with 41 from Group 2 susceptible to either (S+R/S+I; ADDAEAT 2.7 and 3.1 days, respectively [p= 0.0293]). In addition, the ADDAEATs for the S+S (n = 13) and S+R/S+I (n = 33) subgroups in Group 3 were 1.9 and 2.4 days, respectively (p=0.7243; Table 3).

In total, 38 (13.2%) episodes of infections in the 3 antibiotic groups were not susceptible to empiric antibiotics. Seventeen (44.7%) of the 38 cases became afebrile before being switched to effective antibiotics, with 2.4 days the averaged day of defervescence. When treatment of the non-susceptible infections in Group 2 was switched to ampicillin alone, only 4 (20%) isolates, all of which were *Enterococcus*, became susceptible. By contrast, when Group 3 treatments were switched to cefazolin alone, 10 (62.5%) strains became susceptible, with 8 (80%) of these identified as *E. coli* (p=0.0093; Table 4).

Discussion

E. coli remains the most common pathogen of pediatric UTI, responsible for 75% to 90% of first infections [5, 6,9], with *K. pneumoniae* next in order of prevalence [10-12]. The causative organisms and related drug susceptibility rates in this study were very different from those of previous Taiwan reports [11,12]. Lower *E. coli* incidence (72.5%) and decreased antimicrobial susceptibility for the 4th most common organism, *K. pneumoniae*, were found (Tables 1 and 2). The main treatment goals for UTI are elimination of the bacterial infection, prevention of urosepsis, and reduction of the likelihood of renal damage. When the results of urine culture and susceptibility studies are not available, known patterns of antibiotic sensitivity for the community should be considered before initiation of empiric antibiotic therapy. Typically, adequate antimicrobial therapy results in rapid clinical improvement within 24 to 48 h [13,14], a finding consistent with the overall ADDAEAT (2.7 days) determined in this study. Of the 310 episodes of febrile UTIs, 36 (11.6%) of the patients experienced prolonged fever after use of appropriate antibiotics, defined as time to defervescence of 5 days or more after admission. Eleven cases were excluded because of associated severe underlying disease or concomitant diseases, such as bronchopneumonia and salmonellosis. Of the remaining 25 (76%) cases with prolonged fever, invasive infections, such as bacteremia (n = 3) and acute pyelonephritis (n = 16), may have played important roles. Further, *in vivo*, antibiotics are sometimes effective even when drug resistance has been demonstrated in disc sensitivity tests. This may be due to higher concentration of the drug in urine than in disc [3,13], or to the influence of nonantibiotic therapies, such as fluid hydration or administration of antipyretic drugs. We found that some patients became afebrile even though the infections were not susceptible to the administered antimicrobial agents. A total of 38 patients were initially treated with antibiotics which proved to be non-susceptible, with 17 (44.7%) of them becoming afebrile before being switched to effective antibiotics. The averaged day of defervescence was 2.4 days.

Trimethoprim/sulfamethoxazole is recommended as a primary drug for outpatient treatment of UTI, with parenteral antibiotics, such as the ampicillin-gentamicin combination, recommended for hospitalized children in some textbooks [5,13]. As the incidence of tri-

Table 3. The susceptibility rate and the ADDAEAT for 3 different antibiotic combinations

Antibiotic (Group)	No. of cases (%)	No. of susceptible cases (%)[a]	ADDAEAT (No. of cases)	ADDAEAT (No. of cases)	
				S + S	S + I/R
Cefazolin or cephalexin alone (1)	40 (11.8)	38 (95.0)[b]	2.1[c] (14)		
Cefazolin + gentamicin (2)	180 (53.3)	160 (88.9)[b]	2.8[c] (144)	2.7[d] (103)	3.1[d] (41)
Ampicillin + gentamicin (3)	67 (19.8)	51 (76.1)[b]	2.3[c] (46)	1.9[e] (13) μL	2.4[e] (33)
Total	287 (84.9)	249 (86.8)	2.7[c] (204)		

Abbreviations: ADDAEAT = averaged day of defervescence after effective antibiotic therapy; S = susceptible; R = resistant; I = intermediate resistant

[a]Susceptibility to antimicrobial combinations: susceptible to at least one drug.

[b]p<0.01.

[c]p=0.0757.

[d]p<0.05.

[e]p=0.7243.

Table 4. Susceptibility rate of the non-susceptible infections when the antibiotic combinations were switched to ampicillin or cefazolin

Antibiotic	No. of non-susceptible case[a]	No. of susceptible case (%) when NSAG → C NSCG → A	Organism of successful switching (%)
Cefazolin or cephalexin alone	2	0 (0.0)	-
Cefazolin + gentamicin	20	4 (20.0)[b]	*Enterococcus* (100.0)
Ampicillin + gentamicin	16	10 (62.5)[b]	*E. coli* (80.0)

Abbreviations: NSAG = non-susceptible ampicillin plus gentamicin; NSCG = non-susceptible cefazolin plus gentamicin; C = cefazolin; A = ampicillin

[a]Non-susceptibility to antimicrobial combinations: resistance to both agents, or to one with intermediate resistance to the other.

[b]p=0.0093.

methoprim/sulfamethoxazole or ampicillin-resistant *E. coli* has increased in Taiwan in recent years [6], neither drug should be considered for primary treatment of UTI. It has been suggested that the combination of first-generation cephalosporin plus aminoglycosides is the treatment of choice for hospitalized children with UTI in Taiwan [15]. Further, combination therapy with these 2 classes of agents is the most frequently prescribed UTI treatment for children admitted to TVGH. A high antimicrobial susceptibility to combined treatment was demonstrated in Group 2 and 3 patients (211/247; 85.4%). The combination of ampicillin plus gentamicin was used most frequently for infants younger than 3 months (67/338; 19.8%), while cefazolin plus gentamicin was most frequently administered to affected infants 3 months of age or older (180/338; 53.3%).

The findings of this study suggest that administration of antimicrobial combinations to treat pediatric cases of UTI is unnecessary when a first-generation cephalosporin can be used instead. In addition to the potential ototoxicity and nephrotoxicity associated with aminoglycoside treatment and the related economic considerations, the following data from this study support the choice of first-generation cephalosporin alone for empiric treatment of pediatric UTI cases: 1) *E. coli*, *P. mirabilis*, and *K. pneumoniae* were more susceptible to first-generation cephalosporin (mean susceptibility rate, 85.4%) than to other first-line antimicrobial agents, such as trimethoprim/sulfamethoxazole, ampicillin, and gentamicin (Table 2); 2) high susceptibility rate (95%) and relatively short ADDAEAT (2.1 days; Table 3) were demonstrated for Group 1 (single-agent treatment); 3) when the antibiotic regimens for non-susceptible infections in Groups 3 and 2 were switched to cefazolin or ampicillin alone, respectively, higher success rates were noted (62.5% and 20%, respectively [p=0.0093]; Table 4).

In conclusion, the antibiotic resistance of *E. coli* and other enteric bacteria is increasing in Taiwan. At present, however, a first-generation cephalosporin remains satisfactory as the primary drug for treatment of children with UTI. This may be due to the high sensitivity of *E. coli* to this agent (86.5%), and the scarcity of highly resistant strains (7/245 isolates; 2.9%). This study indicated that a first-generation cephalosporin alone is adequate to treat community-acquired UTI, and that empiric antimicrobial-combination therapy should be reserved for serious or critical cases. These findings are not conclusive, however, and further trials are essential. Exclusive administration of first-generation cephalosporin offers an effective treatment for pediatric cases of community-acquired UTI, with lower cost and incidence of side effects, and similar efficacy in comparison to its combination with an aminoglycoside.

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