Eur J Clin Microbiol Infect Dis (2005) 24: 233–235
DOI 10.1007/s10096-005-1301-2

BRIEF REPORT

M. Fritzsche · R. A. Ammann · S. Droz · M. G. Bianchetti · C. Aebi

Changes in antimicrobial resistance of *Escherichia coli* causing urinary tract infections in hospitalized children

Published online: 17 March 2005
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Urinary tract infections (UTI) are among the most common bacterial infections of childhood. Rapid recognition and appropriate antimicrobial therapy relieve symptoms and prevent renal damage [1]. Since therapy for suspected UTI is usually initiated before the responsible organism and its susceptibility to antimicrobial agents are known, the rational choice of an antibiotic relies on local epidemiologic data. In infants and young children without a known urinary tract malformation, *Escherichia coli* is responsible for the vast majority of episodes [2, 3]. Recent studies suggest that in these patients intravenous antibiotic therapy for acute pyelonephritis may no longer be warranted, and that most patients can be treated safely with oral third-generation cephalosporins [3, 4]. However, since outpatient oral therapy for acute pyelonephritis requires certainty that the drug used is active against the expected pathogens, this trend is somewhat at odds with the increasing antimicrobial resistance detected among isolates of *Escherichia coli* in recent years [5–7]. The aim of the retrospective study reported here was to investigate changes in the antimicrobial resistance of *Escherichia coli* causing acute pyelonephritis in children hospitalized with a UTI during 2 decades.

Two study periods were chosen for investigation. The first period from 1980 to 1991 was based on reference data provided by a previous study conducted by one of the present authors (M.G.B.) at the same study site [8]. A power analysis based on this study's data gave us a comparator group size of 150 patients to detect a 10% difference in resistance to amoxicillin-clavulanate (power, 80%; α level, 5%) between the *Escherichia coli* isolates examined in the first period [8] compared with those obtained during a second, more recent, study period. Thus, the duration of the second study period was set to allow for the inclusion of 150 patients <16 years of age who were diagnosed and hospitalized most recently with their first UTI. The duration of this period consequently extended from 1 January 2000 to 31 December 2003.

Inclusion criteria were identical in both periods and consisted of (i) significant *Escherichia coli* bacteriuria, defined as $\geq 10^5$ colony forming units/ml of bag-collected or midstream urine or $\geq 10^4$ colony forming units/ml of urine obtained by transurethral catheterization, and (ii) severe or moderate UTI defined by clinical criteria. Severe UTI was recorded if at least one of the following four criteria were present: (i) *Escherichia coli* bacteremia, (ii) urinary leukocyte casts, (iii) sonography findings characteristic for pyelonephritis, (iv) serum creatinine >50 µmol/l above the age-related upper limit of the normal range. Moderate UTI required at least three of the following criteria for diagnosis: (i) age <1 year, (ii) costovertebral angle tenderness, (iii) C-reactive protein >30 mg/l or erythrocyte sedimentation rate >30 mm/h, (iv) peripheral leukocyte count $>15.0\times10^9$/l, (v) left-shift with >12% band forms. Exclusion criteria included a history of previous UTI, known urinary tract malformation, neurogenic bladder dysfunction, renoparenchymal disorders, immunodeficiency or recent transurethral catheterization prior to that used in the present episode.

Urine specimens were transported to the laboratory using BD Vacutainer tubes (BD Vacutainer, C&S Kit, Franklin Lakes, NJ, USA). Standard techniques were used for culture and identification of *Escherichia coli*. Susceptibility testing was performed using the disk diffusion technique according to the guidelines of the National Committee of Clinical Laboratory Standards. Organisms with intermediate susceptibility were considered sensitive. Comparisons between the study periods were made using the two-tailed

M. Fritzsche · R. A. Ammann · C. Aebi (✉)
Department of Pediatrics and Institute for Infectious Diseases,
University of Bern,
3010 Bern, Switzerland
e-mail: christoph.aebi@insel.ch
Tel.: +41-31-6329487
Fax: +41-31-6329468

S. Droz
Institute for Infectious Diseases, University of Bern,
3010 Bern, Switzerland

M. G. Bianchetti
Ospedale San Giovanni,
6500 Bellinzona, Switzerland

source: https://doi.org/10.7892/boris.117497 | downloaded: 12.10.2024

Table 1 Comparison of antimicrobial resistance in *Escherichia coli* isolates obtained from Swiss children hospitalized with acute urinary tract infection during two study periods

Antimicrobial agent	No. (%) of resistant isolates		*p* value
	1980–1991 [8] (*n*=203)	2000–2003 (*n*=151)	
Ampicillin	67 (33)	78 (51)	<0.001
Amoxicillin-clavulanate	30 (17)	17 (11)	0.16
Cotrimoxazole	32 (16)	38 (25)	0.031
Cephalothin	nt	25 (17)	–
Cefuroxime	nt	2 (1.3)	–
Cefuroxime-axetil	nt	2 (1.3)	–
Ceftriaxone	nt	0 (0)	–

nt, not tested

Fisher exact test. Statistical significance was defined as a *p* value of <0.05.

In the first (1980–1991) [8] and second (2000–2003) study periods, 203 and 151 patients, respectively, were compared. There were no statistically significant differences in age (median age, 6 months [range, 1 week–15 years] vs. 11 months [1 week–12 years]), gender (female, 53% vs. 66%), and proportion of severe vs. moderate UTI (36% vs. 28%) between the first and second study periods, respectively. More detailed data on urinary findings were available for cases in the second study period as follows. Ninety (60%) patients had specimens collected by bag, 36 (24%) by catheterization, and 25 (17%) by mid-stream voiding collection. In 25 (17%) specimens, a second bacterial pathogen was isolated. Thirteen (9%) patients had been treated with an oral antibiotic at the time of hospital admission.

Table 1 lists the rates of *Escherichia coli* resistance found during both study periods. Resistance to ampicillin and cotrimoxazole increased significantly. The decrease in resistance to amoxicillin-clavulanate was not significant. Of the 38 strains that demonstrated resistance to cotrimoxazole in the second study period, 36 (95%), 12 (32%), and 11 (29%) were also resistant to ampicillin, amoxicillin-clavulanate, and cephalothin, respectively. Forty-seven (31%) isolates were resistant to at least two of the antibiotics tested, and 19 (13%) were resistant to at least three agents.

In comparison with previous reports [5–6], this study covers an extended observation period and care was taken to ensure that *Escherichia coli* isolates originated from patients with comparable clinical disease, i.e., community-acquired UTI with a high likelihood of renal involvement in previously healthy children. Since standard management of febrile UTI in Switzerland entails hospitalization, our findings are representative of all febrile UTI episodes occurring in this study area during the two study periods.

Previous studies have mostly reported susceptibility data without considering clinical data in detail. Our major findings are consistent with those of recent pediatric studies from the UK [5], Israel [6], and Germany [7], and they demonstrate a statistically significant increase in resistance to ampicillin and cotrimoxazole over 2 decades but maintenance of full susceptibility to second- and third-generation cephalosporins. While few data from Switzerland are available for comparison, one hospital-based study from Zurich showed lower rates of ampicillin resistance (44%) but higher rates of amoxicillin-clavulanate (33%) and cotrimoxazole (42%) resistance in children [9]. Among UTI isolates from Swiss women in 2000 substantially lower rates of resistance were detected (ampicillin, 27%; amoxicillin-clavulanate, 2.5%; cotrimoxazole, 19%) [10]. The truly unexpected finding in our study was the decrease in resistance to amoxicillin-clavulanate, since resistance rates are known to be influenced by local preferences in the use of antibiotics [11] and sales of pediatric formulations of amoxicillin-clavulanate in Switzerland have continuously risen over the past decade. Thus, one would expect an increase in selective pressure as a growing proportion of UTI patients have been previously exposed to this antibiotic.

Our findings have a direct impact on the choice of an antimicrobial agent for the empiric treatment of pediatric UTI in Switzerland. Amoxicillin should no longer be used. In a child with cystitis (i.e., who is afebrile and has a normal C-reactive protein level), amoxicillin-clavulanate and cotrimoxazole can still be used for first-line therapy. However, physicians electing to treat febrile UTI orally should use a second- or third-generation cephalosporin in order to avoid treatment failure caused by antimicrobial resistance. Using ceftriaxone as a marker, third-generation cephalosporins were found to be fully susceptible (Table 1), and comparative clinical studies have documented their efficacy in the oral therapy of infants and children with acute pyelonephritis [2, 3].

It is possible that our data overestimate the overall rates of resistance in the community for a number of reasons. First, our analysis of hospitalized children may be biased towards higher rates of resistance compared with those found for patients treated in an outpatient setting, even though only 9% of our patients had received oral antibiotic therapy at the time of hospital admission. Second, urinary pathogens causing mild UTI, which were excluded from our study, may show lower rates of resistance. Antimicrobial resistance in the group of patients with moderate UTI, however, was not significantly different from that in the group with severe UTI (data not shown). Third, the impact of in vitro resistance on clinical outcome is not clear. Since drugs such as β-lactam agents and cotrimoxazole reach high urinary concentrations for prolonged periods of time, it is possible that in vitro findings do not accurately predict treatment failure. However, existing data for UTI in adults suggest that infection with resistant organisms may adversely affect clinical outcome [12].

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