

Department of Paediatric Nephrology, Skubiszewski Medical University of Lublin

MAŁGORZATA ZAJĄCZKOWSKA, ZOFIA ZINKIEWICZ,  
BEATA BIENIAŚ, LESZEK PIECHUTA, IRENA SZAJNER-MILART,  
MAREK MAJEWSKI

*Recurrent urinary tract infections – uropathogen incidence  
and drug sensitivity*

Urinary tract infection (UTI) is one of the most common infectious diseases in infants and young children. Over the last few decades enormous progress has been made in the understanding of the pathogenesis and the natural history of UTI in children, which makes a rapid diagnostic intervention, identification of risk factors and an adequate early and causative treatment possible.

Recurrent UTI occur usually in children with anatomical and/or functional urinary tract abnormalities, such as vesicoureteral reflux (VUR) or neurogenic bladder dysfunction (NBD). Those children are particularly susceptible to permanent renal damage with progressing renal scarring and hypertension that in consequence may lead to chronic renal failure (1). Acute, bacterial UTI accompanied by fever requires immediate causative treatment. This is particularly important in children under 5 years of age in whom the healing processes of renal inflammatory foci lead to scars formation. In the absence of bacteriological evaluation of UTI, its therapy must be empirical. In empirical treatment of UTI, it would be desirable to base the choice of an antibiotic on the results of drug sensitivity studies of pathogens occurring in a particular area.

The aim of the study was the retrospective analysis of the results of drug sensitivity studies of bacterial species cultured from 681 urinary specimens collected from children with recurrent UTI in the period from 1997 to 2001. The incidences of particular uropathogens were also analyzed. In addition, an attempt to estimate the incidence of reinfections due to different bacteria and relapses resulting from persistence of infection was made.

MATERIAL AND METHODS

The study comprised case records of 79 children (12 boys and 67 girls) aged 0–18 years (the mean 8.7 +/- 0.4) with recurrent UTI treated in 1997–2001 in the Department of Pediatric Nephrology and/or in pediatric nephrology outpatient units, Children's University Hospital, Lublin. The study comprised only those children in whom recurrences of UTI occurred at least four times over the 5-year period of the follow-up.

In boys, UTI was observed most commonly in the first three years of life. In older boys, the age distribution was rather uncharacteristic, probably because of too small number of cases. In girls, the age distribution of UTI was more uniform. The highest incidence was observed in the first two years of life and in the ninth and tenth year of age.

Factors that predispose to UTI were detected in 73 (92.4%) children. They included VUR, other anatomical abnormalities (renal duplication, urethral or ureteral obstruction), NBD after the menigomyelocele surgery and urolithiasis, and were detected in 30 (38%), 17 (21.5%), 18 (22.8%) and three (3.8%) children, respectively. The coexistence of predisposing factors was frequently observed. In 23 (29.1%) patients, in addition to those with NBD, nocturnal enuresis and/or diurnal urinary incontinence was observed. In three (3.8%) children, recurrences of UTI were diagnosed in the course of glomerulopathies (including 2 nephrotic syndromes), in one (1.3%) child UTI recurred despite the absence of recognizable risk factors and two patients with recurrent UTI had nocturnal enuresis. Children with VUR were the most numerous group. In 23 (29.1%) children, VUR was the basic pathology, and in seven (8.9%) patients, it was secondary to NBD. VUR of grade I<sup>o</sup>–III<sup>o</sup> and VUR of grade IV<sup>o</sup>–V<sup>o</sup> were detected in 17/30 (57%) and 13/30 (43%) children, respectively. In 55 patients urodynamics (Fig. 1) was performed. In all children with NBD, functional abnormalities of the lower urinary tract were detected. In 18 children functional abnormalities coexisted with other risk factors (VUR and other anatomical abnormalities). Isolated functional abnormalities of the lower urinary tract without anatomical defects were detected in 12 (15.2%) children. A contractile detrusor, neurogenic detrusor overactivity and detrusor-sphincter dyssynergy were diagnosed in 69.2%, 23.9% and 23.1% of children with NBD, respectively. Idiopathic detrusor overactivity and dysfunction of urethra were disclosed in 70% and 53.3% out of 37 children without NBD, respectively.

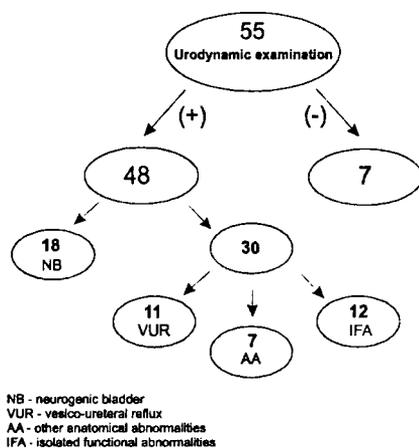


Fig. 1. Urodynamic examinations in particular groups of children

For further analysis the studied children were divided into five groups: the group A – 18 children with NBD, the group B – 23 children with VUR ( without NBD), the group C – 17 children with other anatomical abnormalities, the group D – 12 children with isolated functional abnormalities, and the group E – three children with urolithiasis. The allocation into particular groups was based on the most significant predisposing factor. Children from the group E were excluded from comparative analysis concerning bacterial drug sensitivity (too small number of patients). The bacteriologic evaluation of urinary specimens were performed in Children’s University Hospital.

In the absence of genetic data of the invading bacteria, the differentiation between reinfections and relapses was based on etiologic variability or different drug sensitivity of causative agents of particular infection episodes.

## RESULTS

The analysis of pathogens cultured from 681 urinary specimens revealed that *Escherichia coli* was the most common invading agent. It was much more frequently observed in girls (60.6%) than in boys (36.5%). The second most common invading agent was *Proteus spp.* In boys, it was isolated three times more frequently than in girls (36.5% and 12.4%, respectively). *Pseudomonas aeruginosa* and *Klebsiella spp.* were also detected more frequently in boys than in girls (Table 1). *Enterobacter spp.* was cultured in none of the boys, whereas in girls, the presence of this pathogen was detected in 39 (6.7%) urinary specimens.

Table 1. Pathogens isolated from urine samples in the children with recurrent UTIs

	total	girls	boys
<i>E.coli</i>	388 (57%)	351 (60.6%)	37 (36.5%)
<i>Proteus spp.</i>	106 (15.6%)	72 (12.4%)	34 (33.5%)
<i>Pseudomonas aerug.</i>	62 (9.1%)	50 (8.6%)	12 (11.6%)
<i>Klebsiella spp.</i>	44 (6.5%)	31 (5.4%)	13 (12.7%)
<i>Enterobacter</i>	39 (5.7%)	39 (6.7%)	-
<i>Enterococcus</i>	29 (4.2%)	25 (4.3%)	4 (3.9%)
<i>Staphylococcus epid.</i>	9 (1.3%)	9 (1.6%)	-
<i>Citrobacter</i>	1 (0.15%)	1 (0.2%)	-
<i>Edwardsiella</i>	1 (0.15%)	1 (0.2%)	-
<i>Morganella</i>	1 (0.15%)	-	1 (0.9%)
<i>Neisseria</i>	1 (0.15%)	-	1 (0.9%)

In 18 children with NBD, *Proteus spp.* (20.8%), *Pseudomonas aeruginosa* (17.1%) and *Klebsiella spp.* (12.0%) were isolated more frequently than in patients from other risk groups. In those children, *Escherichia coli* (45.4%) was cultured much more rarely than in patients from other risk groups (Fig. 2).

In 23 children with VUR, *Enterobacter spp.* (18.3%) was relatively frequently isolated and *Pseudomonas aeruginosa* (12.4%) – somewhat more frequently as compared with children from other risk groups. In 17 children with other anatomical abnormalities, *Escherichia coli* (71.9%) and *Proteus spp.* (18.8%) were most commonly isolated organisms. *Escherichia coli* (73.9%) was the most frequent pathogen in 12 children with isolated functional abnormalities. In those children, *Pseudomonas aeruginosa* and *Enterobacter spp.* were not isolated (Fig. 2). Drug sensitivity of most frequently isolated bacteria is presented in Table 2. It should be emphasized that the sensitivity of isolated *Escherichia coli* to cotrimoxazole (60%) was surprisingly low. The sensitivity of cultured *Klebsiella spp.* to cotrimoxazole (62.8%) was somewhat higher than that of *Escherichia coli*. The sensitivity of the remaining bacterial species to cotrimoxazole varied from 2.4% to 37.0%. The very low sensitivity to ampicillin was observed (*Escherichia coli* – 5%, *Proteus spp.* – 50% and *Enterococcus spp.* – 73.6%). The sensitivity to amoxicillin-clavulanic acid was satisfactory for *Escherichia coli* (80.0%), *Klebsiella spp.* (82.5%) and *Enterococcus spp.* (87.0%), but it was considerably lower for *Enterobacter spp.* (43.6%) and *Proteus spp.* (57.5%) (Table 2).

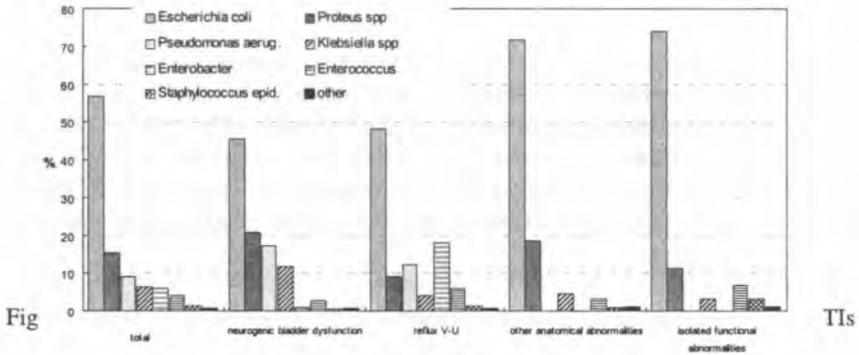


Table 2. Drug sensitivity of the most frequent uropathogens isolated from urine samples in children with recurrent UTIs

<i>E. coli</i>		<i>Proteus spp.</i>		<i>Pseudomonas aerug.</i>	
drug	sensitivity (%)	drug	sensitivity (%)	drug	sensitivity (%)
ceftriaxone	97.2	norfloxacin	100.0	norfloxacin	98.3
pefloxacyn	95.8	aztreonam	85.7	aztreonam	96.6
netilmicin	95.6	pefloxacyn	84.0	netilmicin	88.5
cefuroxime	90.3	nitrofurantoin	74.8	ceftazydym	87.8
amoks. z kwas. klaw.	89.5	nalidixic acid	74.7	amikacin	82.8
nitrofurantoin	89.4	netilmicin	70.0	azlocillin	82.7
nalidixic acid	80.0	ceftriaxone	68.5	piperacillin	75.0
piperacillin	73.4	piperacillin	68.4	carbenicillin	72.5
cotrimoxazole	60.0	amoxicillin+clav.ac.	57.5	ceftriaxone	68.3
doxycilin	59.4	ceftazydym	57.1	cotrimoxazole	10.0
ampicillin	5.0	cefuroxime	54.4	cefuroxime	6.6
		ampicillin	50.0	nalidixic acid	3.2
		cotrimoxazole	37.0	doxycilin	1.7
		doxycilin	9.0		
<i>Klebsiella spp.</i>		<i>Enterobacter</i>		<i>Enterococcus</i>	
drug	sensitivity (%)	drug	sensitivity (%)	drug	sensitivity (%)
ceftriaxone	90.9	netilmicin	97.6	nitrofurantoin	95.4
netilmicin	82.9	ceftriaxone	95.0	amoxicillin+clav.ac.	87.0
amoxicillin+clav.ac.	82.5	nitrofurantoin	90.0	azlocillin	84.0
piperacillin	65.1	piperacillin	73.7	netilmicin	82.6
cotrimoxazole	62.8	cefuroxime	72.5	ampicillin	73.6
pefloxacyn	58.8	amoxicillin+clav.ac.	43.6	penicillin	66.7
nitrofurantoin	58.2	pefloxacyn	36.1	doxycilin	54.5
cefuroxime	56.1	nalidixic acid	10.2	cotrimoxazole	36.3
nalidixic acid	47.6	cotrimoxazole	2.4		

--- sensitivity  $\geq 80.0\%$

The drug sensitivity of bacteria isolated from children predisposed to recurrent UTI due to anatomical and/or functional abnormalities of the urinary tract did not show significant differences as compared with the general drug sensitivity. An attempt to estimate the drug sensitivity of cultured bacterial species in the particular years of observation showed low sensitivity to cotrimoxazole which varied from 43.4% to 51.4% and a significant decrease in sensitivity to amikacin, ceftazidime and carbenicillin over the last two years (Fig. 3).

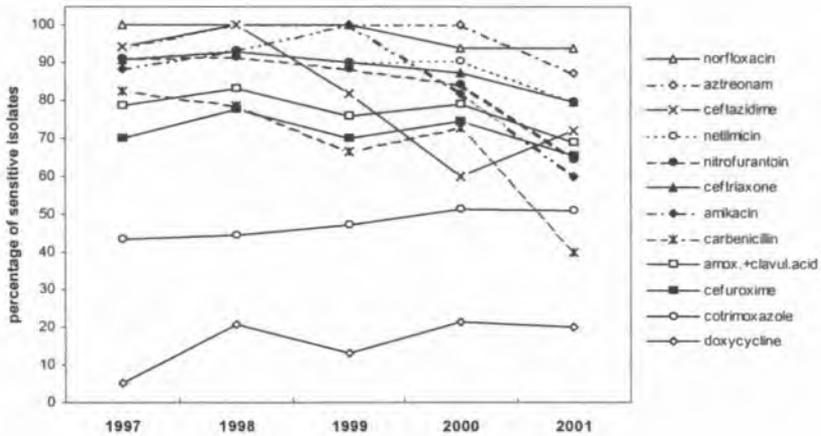


Fig. 3. Drug sensitivity of all uropathogens isolated from urine samples in the children with recurrent UTIs in particular years

A number of recurrences of UTI per patient a year was also calculated. The recurrences of UTI occurred most frequently in children with NBD – 4.3 infections per patient a year. A number of recurrences of UTI in children with VUR, other anatomical abnormalities and isolated functional abnormalities were 3.7, 3.2 and 3.0, respectively.

Taking into account bacterial species cultured from urinary specimens and their drug sensitivity, the infection episodes were classified as reinfections and relapses in 74.7% and 25.3% of children, respectively. The lowest number of relapses was observed in children with VUR and the highest one – in those with other anatomical abnormalities (Fig. 4), but the difference was not statistically significant. This could be a result of the difficulties in formation of homogeneous groups of patients. For example, in children with NBD often VUR was diagnosed.

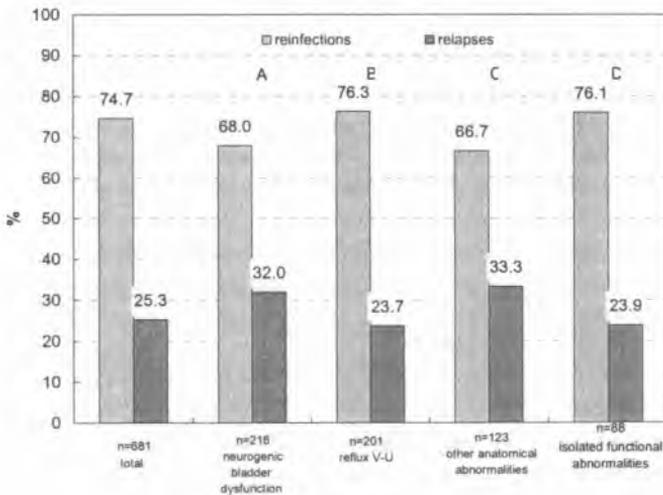


Fig. 4. Reinfections and recurrences of urinary tract infection of the examined children in relation to predisposing factors

In children with NBD, considerable etiologic variability of particular infection episodes was observed. In 10 (55.6%) children with NBD, the number of different bacterial species per one patient varied from 4 to 6 over 5-year period of follow-up, whereas in other children predisposed to recurrent UTI, the number of different bacterial species per one patient did not exceed 4. The phenomenon of etiologic variability of particular infection episodes was observed in eight (34.8%), two (11.8%) and three (25.0%) children with VUR, other anatomical abnormalities and isolated functional abnormalities, respectively.

## DISCUSSION

Predisposition to recurrent UTI is determined by many factors. They include: age of a patient, status of local and native immunity, coexisting systemic disease, anatomical and/or functional abnormalities, virulence of pathogen, method of treatment of the first and the following episodes of infections and duration of treatment. Factors predisposing to recurrent UTI often coexist with one another and sometimes are difficult to detect. The study comprised 79 children aged 0–18 years with recurrent UTI. Significant preponderance of girls and typical patient's age distribution are consistent with other studies (2, 15).

In our study, the incidence of risk factors for recurrent UTI was much more higher as compared with the data from literature. This was the result of the selection of patients. The study comprised only those in whom recurrences of UTI occurred at least four times over the 5-year period of the follow-up. Only one patient had no recognizable risk factors. In infants and young children, even one episode of UTI may entail the risk of recurrence of infection that may be relapse resulting from bacteria persistence or reinfection due to different bacteria. In our study, reinfections occurred much more frequently than relapses. The incidence of reinfection was approximately 80%. Children with the urinary obstructive abnormalities of anatomical and/or functional origin or with urolithiasis were particularly predisposed to relapses (11, 14). In our study, the mean incidence of relapses was 25.3%. In children with NBD and anatomical abnormalities, the incidences of relapses were 32.0% and 33.3%, respectively.

The analysis of pathogens cultured from urinary specimens showed that *Escherichia coli* was the dominant invading agent. *Escherichia coli* was cultured from 57.0% of urinary specimens. It was more frequently detected in girls (60.6%) than in boys (36.5%) while *Proteus mirabilis* was more frequently cultured in boys (33.5%) than in girls (12.4%). The third most common uropathogen was *Pseudomonas aeruginosa*. *Klebsiella spp.*, *Enterobacter spp.* and *Enterococcus spp.* were other invading bacteria (Table 1). In uncomplicated ITU or in acute pyelonephritis, the predictability of spectrum of causative bacteria is relatively high. *Escherichia coli* still remains the most common uropathogen. It is a causative agent of UTI in 78%–80% of cases (2, 9, 15). However, in children with recurrent UTI and predisposing factors, *Escherichia coli* is cultured less commonly (30%–60%). In those children, *Proteus spp.*, *Klebsiella spp.* and *Pseudomonas aeruginosa* are more common invading bacteria than *Escherichia coli*. In some studies, *Proteus spp.* is uncommon causative agent of UTI in boys (5, 8, 12). This may be a result of ritual or therapeutic circumcision which eliminates the colonization of subpreputial area by *Proteus spp.* or other bacteria (7). The study disclosed the low drug sensitivity of isolated strains of *Proteus spp.*, many of which showed multidrug resistance. The isolated strains of *Proteus spp.* displayed sensitivity only to streptomycin and fluoroquinolones. A phenomenon of much higher drug resistance of strains of *Proteus spp.* was also observed by Kamińska et al. (4).

The bacteriological evaluation of children predisposed to recurrent UTI due to anatomical and/or functional abnormalities showed that in patients with NBD, *Proteus spp.*, *Pseudomonas aeruginosa*, and *Klebsiella spp.* were, in comparison with other ones, much more frequently isolated. In those patients, the most considerable etiologic variability of particular infection episodes and the highest

number of infection episodes per child in each year of observation were noted. Ronald (9) drew attention to the fact that in children with NBD treating with clean intermittent catheterization, infections caused by *Pseudomonas aeruginosa* and *Candida spp.* occurred much more frequently than in other ones. Favourable outcome of UTI depends directly on the time of introduction of etiotropic treatment. This statement is of special importance in young children aged under 5–6 years in whom the highest rate of progression of permanent renal damage is observed. Therefore, clinical diagnosis of UTI should always be confirmed by bacteriological evaluation. However, in the first 24–48 hours and sometimes for a longer period, the treatment must be empirical. Taking into account the possibility of serious complications of insufficiently effective empirical therapy, the introduction of a highly effective drug with consideration for the low risk of its side-effects is justified. In those situations, the knowledge of uropathogens specific for particular region and their drug sensitivity is very helpful.

The results of our drug sensitivity studies showed that the dominant uropathogen, *Escherichia coli*, displayed relatively low sensitivity to cotrimoxazole (60%) and very low sensitivity to ampicillin (5%). The decrease in sensitivity of *Escherichia coli* to cotrimoxazole and amoxicillin was also observed by other authors (3, 6, 9, 12). American Academy of Pediatrics recommends to use cotrimoxazole, ampicillin and other drugs as first-line drugs in empirical therapy of uncomplicated UTI provided that resistance to those drugs does not exceed 20% (3, 10). If resistance to the drug is higher, the use of other drugs should be considered. Drugs with sensitivity lower than 80% are not indicated in empirical therapy. Our study showed that in children over 5 years of age with uncomplicated UTI, the use of nitrofurantoin may be considered (2, 12). Nitrofurantoin is easily absorbed from the digestive system, it has no impact on patient's own bowel flora and achieves high concentration in the urine. Nitrofurantoin is effective in infections caused by *Escherichia coli*, *Enterococcus spp.* and *Enterobacter spp.* while *Pseudomonas aeruginosa*, *Klebsiella spp.* and numerous strains of *Proteus spp.* are usually resistant to the drug. In younger children or in serious, febrile infections, the first-line drugs are second- and third-generation cephalosporins, aminoglycosides or a combination of cephalosporins and aminoglycosides. If necessary, after obtaining complete bacteriological evaluation, the initial treatment should be modified. The adequate treatment is especially important in children with VUR or obstructive abnormalities of anatomical and/or functional origin. Those children are at higher risk for acute pyelonephritis with renal scarring (10) and for development of chronic renal failure later in life (13). The long-term observations of children with renal scars which are the consequence of acute pyelonephritis suggest that even unilateral renal scars may result in serious complications including a decrease in renal mass and glomerular filtration rate and elevation of diastolic blood pressure (10).

## CONCLUSIONS

1. The bacteriological evaluation of children with UTI showed that *Escherichia coli* was the dominant uropathogen. *Proteus spp.*, *Pseudomonas aeruginosa*, *Klebsiella spp.*, *Enterobacter spp.*, *Enterococcus spp.* and *Staphylococcus epidermidis* were other bacteria invading the urinary tract. It should be emphasized that *Proteus spp.* occurred almost three times more frequently in boys than in girls.

2. The bacteriological evaluation of children predisposed to UTI due to anatomical and/or functional abnormalities revealed that infections in those with NBD and VUR were characterized by the most considerable etiologic variability and most frequently required the use of broad-spectrum antibiotics.

3. The low sensitivity of *Escherichia coli* to ampicillin and cotrimoxazole eliminates those drugs from empirical therapy. The use of other drugs, to which

resistance does not exceed 20%, should be considered. In each case of UTI, it is mandatory to identify the invading agent and, if necessary, to modify initial empirical treatment.

4. The high percentage of functional abnormalities in the studied children suggests the necessity for performing urodynamics in each case of UTI, even in the absence of positive history of dysfunctional voiding. Recognition of urodynamic disorder associated with UTI requires introduction of adequate additional treatment.

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#### SUMMARY

The aim of the study was the retrospective analysis of the results of the drug sensitivity studies of bacterial species cultured from 681 urinary specimens collected from 79 children (12 boys and 67 girls) aged 0–18 years with recurrent urinary tract infection in a period from 1997 to 2001. Factors predisposing to recurrent urinary tract infections and the incidences of particular uropathogens were

also analyzed. *Escherichia coli* (57.3%), *Proteus spp.* (15.6%) and *Pseudomonas aeruginosa* (9.1%) were the most frequent isolated pathogens. Reinfections and relapses of urinary tract infections were observed in 74.7% and 25.3% of the children, respectively. In some children etiologic variability of particular infection episodes were observed. In the majority of the children infection episodes were caused by one or two bacterial species and new infections differed from previous ones only in drug sensitivity. In 30 children vesicoureteral reflux was detected. Other anatomical abnormalities of urinary tract were revealed in 17 children. In 18 children, neurogenic bladder dysfunction was diagnosed. Urodynamics disclosed functional abnormalities in 48/55 children.

#### Nawracające zakażenia układu moczowego (NZUM) u dzieci – lekowrażliwość izolowanych patogenów

Celem pracy było przesledzenie rodzaju bakterii i ich wrażliwości na stosowane leki w przebiegu nawrotów choroby lub ponownego zakażenia (reinfekcji), z uwzględnieniem współistniejących czynników ryzyka. Badania przeprowadzono u 79 dzieci z NZUM, w tym 85% dziewcząt i 15% chłopców w wieku 0–18 lat. Wśród badanych dzieci u 30 stwierdzono obecność odpływów pęcherzowo-moczowodowych (OPM), u 17 inne wady anatomiczne, u 18 pęcherz neurogeny (PN). Zaburzenia czynnościowe dolnych dróg moczowych w wywiadzie, poza PN, występowały u 23 dzieci. Badania urodynamiczne wykazały obecność zmian u 48/55 dzieci. Najczęściej stwierdzano idiopatyczną nadaktywność wypieracza, dysfunkcję cewki moczowej i zespół parć naglących. Znamienną bakteriurię stwierdzono w 681 posiewach moczu. Analiza posiewów z uwzględnieniem rodzaju patogenów i ich lekowrażliwości pozwoliła zakwalifikować 74,7% epizodów zakażenia jako reinfekcje, a 25,3% jako nawroty zakażenia. U części dzieci stwierdzono dużą różnorodność i zmienność etiologiczną zakażeń. U większości powtarzające się epizody zakażeń dotyczyły jednego lub dwóch rodzajów bakterii, a nowe zakażenia różniły się tylko odmienną wrażliwością na antybiotyki.