Retrospective analysis of ESBL (plus) urinary tract infection, taking into consideration its frequency and treatment – own experience

Retrospektywna analiza zakażeń układu moczowego bakteriami ESBL (+) uwzględniająca częstość i sposoby leczenia – doświadczenia ośrodka

Agata Będzichowska [1/], Bolesław Kalicki [1/], Katarzyna Jobs [1/], Agata Wawrzyniak [1/], Agnieszka Lipińska-Opałka [1/], Anna Jung [1/], Sławomir Lewicki [2/], Robert Zdanowski [2/]

[1/] Department of Pediatrics, Pediatric Nephrology and Allergology, Central Clinical Hospital of the Ministry of Defence, Military Institute of Medicine, Warsaw, Poland
[2/] Department of Regenerative Medicine, Military Institute of Hygiene and Epidemiology, Warsaw, Poland

Wprowadzenie. Zakażenia układu moczowego (UTI) są – po infekcjach dróg oddechowych – drugą najczęściej występującą chorobą u dzieci.

Cel. Analiza przypadków zakażeń dróg moczowych u dzieci hospitalizowanych w Klinice Pediatrii, Nefrologii i Alergologii Dziecięcej w ciągu jednego roku, z uwzględnieniem częstotliwości infekcji wywołanych przez patogeny ESBL(+) (wytwarzające beta-laktamazy o szerokim spektrum działania).

Materiały i metody. Przeanalizowane zostały: wiek, płeć, wywiad, objawy kliniczne, wyniki badań laboratoryjnych, przebieg choroby, dobór antybiotyku wg antybiogramu oraz wyniki leczenia.

Wyniki. Spośród wszystkich 1400 dzieci hospitalizowanych w Klinice, odnotowano 88 przypadków UTI (6,3% wszystkich hospitalizacji), z których osiem było o etiologii ESBL (+) (0,6% wszystkich hospitalizacji). Wszystkie te dzieci, u których wykryto w moczu obecność bakterii ESBL(+) w mianie znamiennym, choć raz przed tym epizodem przebywały w szpitalnych oddziałach dziecięcych. Zakażenia pełnoobjawowe rozpoznano u czworga dzieci, natomiast u pozostałych bezobjawowy bakteriomocz. Troje dzieci z zakażeniem ESBL (+) miało wcześniejsze zakażenia dróg moczowych.

Wnioski. Zakażenia patogenami ESBL (+) stanowią znaczący procent zakażeń układu moczowego w obserwowanym materiale; zakażenia spowodowane przez bakterie ESBL(+) obserwowano głównie u dzieci uprzednio hospitalizowanych.

Słowa kluczowe: *zakażenie układu moczowego, bakteriuria, ostre cewkowo-śródmiąższowe zapalenie nerek, patogeny ESBL(+), dzieci*

Introduction. Urinary tract infection (UTI) is the second most common disease in children after respiratory tract infections.

Aim. To analyze UTI cases in children hospitalized in the Department of Pediatrics, Pediatric Nephrology and Allergology during one year, taking into consideration the frequency of ESBL (Extended-Spectrum Beta-Lactamases) infections.

Materials & Methods. Medical documentation data of 1400 patients in 2013 was subjected to a retrospective analysis. Age, gender, history, clinical symptoms, laboratory findings, course of the disease, antibiotic selection according to the antibiogram and outcome were considered.

Results. Of all the children hospitalized in the Department (1400 hospitalizations), 88 UTI cases were reported (6.3% of all hospitalizations). Eight ESBL infections were recorded (0.6% of all hospitalizations). All children had been hospitalized previously. A symptomatic infection was diagnosed in four children. Three children with the infection had a history of urinary tract disease.

Conclusion. The ESBL pathogens represent a significant percentage of UTI in the observed material. UTI caused by the ESBL bacteria was observed primarily in previously hospitalized children.

Key words: *urinary tract infection, bacteriuria, acute tubulointerstitial nephritis, pathogen ESBL(+), children*

© **Hygeia Public Health 2016, 51(1): 51-57**

www.h-ph.pl

Nadesłano: 02.08.2015
Zakwalifikowano do druku: 25.02.2016

Adres do korespondencji / Address for correspondence

dr Sławomir Lewicki
Zakład Medycyny Regeneracyjnej, Wojskowy Instytut Higieny i Epidemiologii
ul. Kozielska 4, 01-163 Warszawa
tel. 261 81 61 08, e-mail: lewickis@gmail.com

Introduction

Epidemiology

Urinary tract infection (UTI) is the second most common disease in children after respiratory tract infections. According to various sources it affects about 8% of girls and 2% of boys under the age of 7 years [1], 1% of full-term and 3% of premature infants [2]. Under the age of 2 years the UTI prevalence is higher in boys (up to 5 times) than in girls. This ratio changes among older children, when UTI affects girls more commonly than boys (from 8 to 10 times) [3].

Classification

Urinary tract infections are a heterogeneous group of diseases covering clinical problems caused by penetration of microorganisms into the urinary tract which normally remains sterile (except for the distal part of urethra). The variety of form and course of UTIs justifies the adoption of standardized terminology [4].

Asymptomatic bacteriuria in children is a condition in which there is a positive urine culture without any changes in urinalysis or clinical examination [3].

UTI can involve the lower or the upper urinary tract. The ureteral orifices to the bladder mark the boundary between the lower and the upper part of the urinary system. Lower UTI in older children is characterized by dysuria (urinary frequency, urinary urgency, suprapubic pain), while there could be no physical exam abnormalities or only mild suprapubic tenderness to palpation in younger children. There may be hematuria in some cases (i.e., in the viral or tuberculous etiology). In urinalysis we can observe pyuria, erythrocyturia and bacteriuria [5-8].

Upper UTI (*pyelonephritis*) typically causes fever, chills, abdominal, back, or flank pain, and costovertebral angle tenderness to percussion on physical exam. There are elevated peripheral inflammatory markers in blood tests; pyuria, microhematuria and bacteriuria in urinalysis and positive urine culture [8].

Etiology

Urinary tracts infections (similarly in children and adults) are caused mostly by gram-negative *Enterobacteriaceae*, especially *E. coli*, responsible for approximately 80-90% of the first episodes of infection in outpatient conditions. In 30% of boys UTIs are caused by *Proteus mirabilis* or *Proteus vulgaris* (these pathogens physiologically dwell under the foreskin). In newborns, more frequently than in other groups, UTI can be caused by *Klebsiella* sp. In adolescents, as in adults, the most common gram-positive bacteria responsible for UTI is *Staphylococcus saphrophyticus*. Pathogens causing hospital-acquired infections (e.g., *Enterococcus*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *S. epidermidis*, *Haemophilus influenzae*) are frequently observed in children with congenital or functional disorders of the urinary tract. Other microorganisms are quite rarely the cause of UTI in children. Among the viral infections adenovirus can occur, especially as a cause of cystitis. *Candida* species can be observed in patients who recently have received antibiotic therapy [8].

Diagnosis

Because of the heterogenous form of clinical UTI symptoms, in every febrile infant and young child one must suspect UTI and obtain a urinary specimen, even if signs may point elsewhere [8]. It should also be noted that these studies (urinalysis and urine culture) should be carried out simultaneously, and that positive urine culture is insufficient to establish a definitive diagnosis and decision concerning treatment.

It is recommended to collect urine into a container directly during micturition (clean catch urine sample), or if this is impossible, from catheterization or suprapubic bladder aspiration [9].

An increased number of leukocytes in the urinalysis (pyuria) is one of the main UTI symptoms. It is usually defined as greater than 10 white blood cells per high-power field (WBC/HPF) in a centrifuged specimen for girls and 5 WBC/HPF for boys. There also may be a small proteinuria or hematuria in the urinalysis (over 5-10 erythrocytes in the field of view) [1-3, 7].

Among the "quick" tests the greatest value have those that evaluate the presence of leukocyte esterase and nitrite in the urine specimen [10].

Due to the high risk of false-positive and false-negative results, in every child who is considered to have UTI a urine culture is necessary for confirmation and appropriate therapy [11-13]. The definition of quantitative urine culture is the presence of equal or more than 100.000 colony-forming units (CFU)/mL in a single, clean-catch, voided urine specimen [14].

Treatment

Urinary tract infections in children under 24 months should be treated as a tubulo-interstitial nephritis [15]. In older children therapy depends on clinical symptoms. Second- and third-generation cephalosporins, amoxicillin with clavulanic acid and trimethoprim/sulfamethoxazole (over 6 weeks of age) are most often used in the UTI treatment in pediatric patients [16, 17]. The first-generation cephalosporins may be used alternatively. Oral pharmacotherapy is mostly carried out for 7-10 days, to 14 days in cases of complicated UTI. Children under 3 months, with clinical signs of urosepsis (systemic infection derived

from the urinary tract), dehydrated, unable to take oral medication, should be hospitalized [17-19].

Imaging studies and prevention

In every child with UTI ultrasonography (USG) should be performed. Cystourethrography or DMSA scintigraphy is recommended in children with abnormal renal ultrasound, micturition dysfunction or recurrent UTI. According to some authors, this form of diagnosis should be considered also in children after an episode of tubulo-interstitial nephritis which occurred under 3 years of age, in boys regardless of age and in patients with UTI and positive family history of vesico-ureteral reflux. Routine, prophylactic antimicrobial treatment is not recommended in children after a first UTI episode. However, such treatment should be considered in children at risk of severe or recurrent infections (the youngest infants, children with congenital urinary tract abnormalities and recurrent UTI) [10].

Characteristics of ESBL(+) bacteria

The ESBL enzymes (Extended-Spectrum Beta-Lactamases) decompose antibiotics containing β-lactam ring. The bacterial strains which are capable of their synthesis are classified as alert pathogens. They are often characterized by multi-drug resistance, which leads to difficulties in selection of effective antibiotic treatment [20].

The rising trend in the number of infections caused by strains of gram-negative antibiotic-resistant β-lactam is observed. This is due to the fact that β-lactam antibiotics were often used in the past (last decade of XX century). Their overuse quickly led to new resistance mechanisms. One of them was production of β-lactamase with an extended-spectrum [21-24].

Strains of ESBL(+) usually are associated with hospital infections. The ESBL enzymes are produced mainly by the hospital spectrum of pathogenic bacteria of the *Enterobacteriaceae* family, but also by non-hospital strains of *E. coli*. Actually they are also the cause of community-acquired infections, especially UTI [14, 25].

Carbapenems (imipenem, meropenem) are the drugs of choice in the treatment of severe infections caused by strains of ESBL(+) [26].

Penicillin with inhibitors (amoxicillin/clavulonian acid, ampicillin/sulbactam, piperacillin/tazobactam) and cephalosporins, which reach high urine concentrations (a condition MIC<1 u/m), can be also used in the treatment of such kinds of UTIs [24].

Another possibility are: fluoroquinolones, aminoglycosides, nitrofurans, cotrimoxazole [16, 24, 27-30].

Aim

To assess the number and course of UTI, including the role of ESBL(+) alarm pathogens, in patients treated for one year in the Department of Pediatrics, Pediatric Nephrology and Allergology, at the Central Clinical Hospital of the Ministry of Defense, Military Institute of Medicine, Warsaw, Poland.

Materials and methods

Materials

The medical documentation data of 1400 patients hospitalized in our Department of Pediatrics, Pediatric Nephrology and Allergology in 2013 was subjected to a retrospective analysis.

Methods

Records of patients diagnosed with UTI were separated among the documentation of all hospitalized children. Urinalysis, urine cultures, clinical symptoms and treatment were analyzed.

Cases of ESBL(+) bacterial infections were subjected to a detailed analysis. Age, gender, history, clinical symptoms, laboratory findings (especially the bacteriological test), course of the disease, antibiotic selection according to the antibiogram and outcome were considered. A correlation between the presence of ESBL bacteria in the urine sample and clinical status and indicators of inflammation was also included. The children meeting the UTI criteria and asymptomatic carriers were separated.

Identification of the isolates was performed by an automated system for identification VITEK2. All the strains were classified as ESBL(+) by the method of double discs.

Results

Of all the children hospitalized in the Department of Pediatrics, Pediatric Nephrology and Allergology in 2013 (1400 hospitalizations), 88 UTI cases were reported (6.3% of all hospitalizations), of which 28 infections (32%) concerned boys, while 60 infections (68%) were observed in girls. Infections were observed in 18 boys under one year of age, which accounted for 64% of all infections in boys. The number of UTIs was 10 in boys over 1 year of age (36%). In girls the opposite trend was observed. The number of infection in girls under 1 year of age was 12 (20% of the total amount of infection in females), in older girls 48 (80%).

Eight ESBL(+) infections were recorded in the Department in 2013. All cases concerned UTI (9% of the total number of UTIs). This constitutes 0.6% of all hospitalizations (Table I).

Table I. Data of patients with ESBL(+) pathogens isolated from urine
Tabela I. Dane pacjentów od których izolowane były z moczu patogeny ESBL(+)

Age /Wiek	Gender /Płeć	Hospitalization /Hospitalizacja	Medical history data /Dane z wywiadu lekarskiego	Urinalysis result /Badanie ogólne moczu	Urine culture result /Wyniki posiewu moczu (cfu/ml)	Antibiogram (sensitivity) /Wrażliwość na antybiotyki	Treatment /Leczenie	Note /Klasyfikacja
1 month /miesiąc	M /M	next /następna	dilation of renal pelvis and calyces, cough /poszerzenie układu kielichowo-miedniczkowego, kaszel	correct (no pyurie) /prawidłowe (bez ropomoczu)	*E. coli* 10^5 ESBL(+)	Amikacin, Gentamicin, Ertapenem, Imipenem	CU	AB
11 year /rok	F /K	next /następna	recurrent UTI, nocturnal enuresis and during daytime, kidney asymmetry /moczenie nocne i dzienne, asymetria wielkości nerek	leukocytes: cover the field of view /leukocyty: pokrywają pole widzenia	*E. coli* 10^5 ESBL(+)	Amikacin, Imipenem, Ertapenem	Amikacin	SI
2 year /rok	F /K	next /następna	fever, pyuria, two T/S doses /gorączka, ropomocz, dwie dawki T/S	leukocytes: cover the field of view /leukocyty: pokrywają pola widzenia	*E. coli* 10^5 ESBL(+)	Amikacin, Ciprofloxacin, Norfloxacin, Imipenem, T/S	Ceftriaxone T/S	SI
2 month /miesiąc	M /M	next /następna	fever, weakness, vomiting, pyuria /gorączka, osłabienie, wymioty, ropomocz	leukocytes /leukocyty 15-20	*E. coli* 10^5 ESBL(+)	Amikacin, Gentamicin, Imipenem	Cefuroxime Amikacin	SI
2 year /rok	F /K	next /następna	recurrent UTI, oliguria, low-grade fever /nawracające UTI, skąpomocz, stany podgorączkowe	leukocytes /leukocyty20-25	*E. coli* 10^5 ESBL(+)	Amikacin, Gentamicin, Ertapenem, Imipenem	Cefuroxime Amikacin	SI
9 year /rok	F /K	next /następna	recurrent UTI, hipercalciuria /nawracające UTI, hiperkalciuria	correct /prawidłowe	*E. coli* 10^5 ESBL(+)	Amikacin, Gentamicin, Ertapenem, Imipenem, T/S	CU	AB
3 year /rok	M /M	next /następna	nephrotic syndrome /zespół nerczycowy	correct /prawidłowe	*K. pneumoniae* $>10^5$ ESBL(+)	Amikacin, Ertapenem, Imipenem	CU	AB
1 month /miesiąc	M /M	next /następna	urosepsis in anamnesis /urosepsa w wywiadzie	correct /prawidłowe	*K. pneumoniae* $>10^5$ ESBL(+)	Amikacin, Ciprofloxacin, Imipenem	CU	AB

T/S – Trimetoprim /Sulfamethoxazole; SI – Symptomatic infection /Zakażenie objawowe; AB – Asymptomatic bacteriuria – no changes in urine analysis and absence of clinical signs /Bezobjawowa bakteriuria – bez zmian w analizie moczu i brak objawów klinicznych; CU – recommended check-ups, decision to treat was taken depending on individual indications /Zalecane badania kontrolne, leczenie zostało podjęte w zależności od indywidualnych wskazań

Alert pathogen infection occurred in 4 girls and 4 boys. It was isolated in three infants and five children over 1 year of age. Of all the ESBL(+) uropathogens *K. pneumoniae* was isolated twice and *E. coli* six times.

The symptomatic infection (positive urine culture, abnormalities in urine analysis and clinical symptoms) was diagnosed in four children (three girls and one boy). In other children the asymptomatic bacteriuria was diagnosed (based on a positive urine culture without accompanying changes in urine analysis and clinical symptoms). In these cases, urine culture was performed because of a history related to other urinary tract disorders (dilation of the renal pelvis and calyces, recurrent UTI, hypercalciuria, nephrotic syndrome, urosepsis in anamnesis). In these patients a repeated urinalysis and urine culture were recommended.

Three children with infection had a history of urinary tract disease. All of 8 children diagnosed with ESBL(+) bacteriuria had been hospitalized in different places previously.

Alert uropathogens were isolated in three children under 1 year of age (boys only) – asymptomatic bacteriuria twice, acute pyelonephritis once.

In each case ESBL(+) was sensitive to aminoglycosides. Sensitivity to fluorochinolones, carbapenems and cotrimoxazole was also recorded. In all these cases the treatment was based on antibiograms. All children treated with antibiotics were discharged from the Department in good general condition.

There was no need to use carbapenems in any case. Carbapenems are the drugs of choice for severe ESBL(+) infections. Aminoglycosides were used in three cases. Trimpetoprim/sulfamethoxazole was used once. Cephalosporins were used as empiric therapy before we obtained the results of urine culture. They are acceptable in the treatment of UTI by ESBL(+) pathogens, because they achieve high urine concentrations.

In the analyzed period there were no serious complications or death due to the ESBL(+) infection. There were no migrations of ESBL strains from patient to patient.

Summary of results

Infection caused by ESBL(+) pathogens in the Department of Pediatrics, Pediatric Nephrology and Allergology, at the Central Clinical Hospital of the Ministry of Defense, Military Institute of Medicine in 2013 accounted for 9% of UTIs and 0.6% of all hospitalizations. All infections concerned urinary tract. None of the children required treatment with carbapenems. Therapy based on cephalosporins and aminoglicosides was successful in each case.

Discussion

Infections caused by gram-negative *Enterobacteriaceae* are serious clinical and therapeutic problems. The most common mechanism of resistance to beta-lactam antibiotics, among gram-negative bacteria of the *Enterobacteriaceae* family, is the production of extended-spectrum beta-lactamase [29].

ESBLs are enzymes that hydrolyze all penicillins, cephalosporins (except cefamycine) and monobactams (aztreonam). Their activity is normally inhibited by clavulanic acid, sulbactam and tazobactam. The location of genes encoding ESBL on plasmids may lead to the development of strains resistant to antibiotics, of which resistance genes are also on plasmids (aminoglycosides, co-trimoxazole, tetracycline, chloramphenicol) [14, 31].

The rapid development of resistance mechanisms of ESBL(+) bacteria limits the therapeutic possibilities and increases the cost of treatment. The spread of ESBL producing strains is an epidemiological risk for patients (prolongation of hospital stay, higher mortality, difficult therapy) and for hospitals (the use of expensive antibiotics) [24, 29, 30].

Authors of papers, analyzing the results of microbiological tests in terms of isolation of alarm pathogens frequency, observed a significant increase in percentage of isolation of ESBL(+) strains over the last 20 years [22, 23, 26, 32, 33].

A multicenter study carried out in Spain in 2000 (GEIH-BLEE Project 2000) and 2006 (GEIH-project BLEE, 2006) showed a significant increase in the proportion of ESBL(+) infections. In 2006, the strains of ESBL(+) *E. coli* constituted 4.04% and *K. pneumoniae* 5.04% among all isolated pathogens. Symptomatic infections were successively 36% and 18%. Positive cultures were obtained mostly from urine (77% *E. coli*, 48.2% *K. pneumoniae*), and infected wounds (8.6% *E. coli*, 14.8% *K. pneumoniae*). There was an eightfold increase in ESBL(+) infections with *E. coli* and a twofold increase in ESBL(+) infections with *K. pneumoniae* in relation to the research conducted in 2000 [34].

An analysis of microbiological tests performed by Samet et al. in patients of all Departments of Hospital in Gdańsk (Poland) conducted in 2001-2003 showed that the frequency of isolation of ESBL(+) did not change significantly during the period, and ranged from 3 to 4.5%. However, in 1999 this incidence was 1.6%, while in 2001 – 3.2%. The authors of the study suspect that these results may be caused by hospitalizations of asymptomatic carriers. The isolation concerned mainly *E. coli* and *K. pneumoniae*. Most of such pathogens were isolated in the pediatric and internal departments [23].

Prospective studies conducted by Vijayakanthi et al. [35] in the neonatal population in India (the Department of Pediatrics and Neonatology and the Department of Microbiology at the Postgraduate Institute of Medical Education and Research and associated Dr. Ram Manohar Lohia Hospital, New Delhi, India) in the period of December 2009-November 2010 concerned children with suspected systemic infection. Of the 150 observed children in eight the ESBL(+) isolates were found, which accounted for 5.3% of positive cultures. *Klebsiella* was the most frequently isolated strain (60%), *E. coli* was found in 30% of cases, *Pseudomonas* – in 10%.

Other authors in their study conducted in 2002-2005 in the Department of Pathology of Infants and Hemostatic Disorders, at the Medical University of Gdańsk confirmed a similar epidemiological situation on Polish territory. ESBL-positive strains were isolated from 128 patients, with an average of 32 infections per year, which was 9.06% of all analyzed infections. Infection of the urinary tract was found in 19 cases (14.8%). *Klebsiella pneumoniae*, isolated from 61 patients (45%), was the dominant strain. Next were *E. coli* (44 patients, 32.3%), *K. oxytoca* (13 patients, 9.5%). Most strains were isolated from faeces and rectal swabs (59%) and from urine (25%). Active infection caused by ESBL-positive strains was diagnosed in 31 children (24%) [24].

The problem of bacterial ESBL(+) infection in the Pediatrics, Nephrology and Allergology Department of the Military Medical Institute in Warsaw in 2013 concerned 9% of patients hospitalized due to UTI (the incidence did not differ significantly from the data available in the literature [22-24]. Half of the children with isolated alarm uropathogen were only asymptomatic carriers. The children were not treated (urine culture was obtained after discharge). It was recommended to perform the control urine culture. In case of re-cultured alert pathogens, treatment should be considered. Carrier state of ESBL strains was most commonly associated with previous long-term stays in hospitals, which was observed also in the described group of patients [29, 30].

Asymptomatic bacteriuria should not be treated. The exceptions are: newborns and infants with immune deficiency, children with vesicoureteral reflux or other defects hindering the outflow of urine, children after kidney transplantation and before urological procedures. Treatment should be considered individually, because antibiotic therapy may promote antibiotic resistance and predispose to symptomatic infection [36, 37].

Urinary system was a reservoir of alert pathogens in each case. Therefore, a group of nephrological patients should be subject to an increased epidemiological vigilance. This is in accordance with the literature data [24, 34]. The epidemiological surveillance of colonized patients is essential to the local epidemic prevention. Noteworthy, all analyzed children were already hospitalized at children's wards. Seven of eight patients had a history of urinary tract disease.

The sensitivity of all isolated alert strains to aminoglycosides in the analyzed group was good news in the light of decreasing sensitivity to antibiotics noted worldwide.

Conclusions

1. The ESBL(+) pathogens represent a significant percentage of UTI in the observed material.
2. Urinary tract infections caused by the ESBL(+) bacteria are observed, as far as our material is concerned, primarily in previously hospitalized children.
3. Each bacterial ESBL(+) infection requires cooperation between clinicians, microbiologists and hospital epidemiologists. This allows for an early detection of epidemics and the implementation of appropriate proceedings.

Piśmiennictwo / References

1. Hellström A, Hanson E, Hansson S, et al. Association between urinary symptoms at 7 years old and previous urinary tract infection. Arch Dis Child 1991, 66: 232-234.
2. Salvatore S. Urinary tract infections in woman. Eur J Obstet Gynecol Reprod Biol 2011, 156(2): 131-136.
3. Litwin M, Antoniewicz J, Gastoł P. Zakażenia układu moczowego. [w:] Podręcznik do Państwowego Egzaminu Lekarskiego i egzaminu specjalizacyjnego. Szubert A (red). Urban and Partner, Wrocław 2005: 679-683.
4. Jodal U, Hansson S. Urinary tract infection. [in:] Pediatric Nephrology. Holliday M, Barret TM, Avner ED (eds). Wiliams and Wilkins, Philadelphia 1994: 952-962.
5. Dohil R, Roberts E, Jones KV, Jenkins HR. Constipation and reversible urinary tract abnormalities. Arch Dis Child 1994, 70(1): 56-57.
6. Monga M, Roberts JA. The possible role of granulocyte elastase in renal damage from acute pyelonephritis. Pediatr Nephrol 1995, 9(5): 583-586.
7. Riedasch G, Heck P, Rauterberg E, Ritz E. Does low urinary sIgA predispose to urinary tract infection. Kidney Int 1983, 23(5): 759-763.
8. Sieniawska M. Rola pediatry pierwszego kontaktu w opiece nad dzieckiem przewlekle chorym. Odcinek 8: Nawracające zakażenia układu moczowego. Med Prakt Pediatr 2000, 10: 130-136.
9. Nicolle LE, Bradley S, Colgan R, et al. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis 2005, 40(5): 643-654.
10. Williams GJ, Hodson EH, Isaacs D, Craig JC. Diagnosis and management of urinary tract infection in children. J Paediatr Child Health 2012, 48(4): 296-301.
11. Committee on Quality Improvement, Subcommittee on Urinary Tract Infection. Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. Pediatrics 1999, 103(4): 843-852.
12. Guidelines for the management of acute urinary tract infection in childhood. Report of a working group of the Research Unit, Royal College of Physicians. J R Coll Physicians Lond 1991, 25(1): 36-42.
13. Williams GJ, Macaskill P, Chan SF, et al. Absolute and relative accuracy of rapid urine tests for urinary tract infection in children: a meta-analysis. Lancet Infect Dis 2010, 10(4): 240-250.
14. Baraniak A. Mechanizmy oporności bakterii na antybiotyki β-laktamowe. Aktualności Narodowego Programu Ochrony Antybiotyków 2011, 1(2): 1-6.
15. Saadeh SA, Mattoo TK. Managing urinary tract infections. Pediatr Nephrol 2011, 26(11): 1967-1976.
16. Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics 2011, 128(3): 595-610.
17. Ammenti A, Cataldi L, Chimenz R, et al. Italian Society of Pediatric Nephrology. Febrile urinary tract infections in young children: recommendations for the diagnosis, treatment and follow-up. Acta Paediatr 2012, 101(5): 451-457.
18. Lichtenberger P, Hooton TM. Antimicrobial prophylaxis in women with recurrent urinary tract infections. Int J Antimicrob Agents 2011, 38 Suppl: 36-41.
19. Salo J, Ikäheimo R, Tapiainen T, Uhari M. Childhood urinary tract infections as a cause of chronic kidney disease. Pediatrics 2011, 128(5): 840-847.
20. Abraham E, Chain E. An enzyme from bacteria able to destroy penicillin. Nature 1940, 146: 837-837.
21. Emery CL, Weymouth LA. Detection and clinical significance of extended-spectrum beta-lactamases in a tertiary-care medical center. J Clin Microbiol 1997, 35(8): 2061-2067.

22. Samet A, Bronk M, Czarniak E i wsp. Drobnoustroje w próbkach materiałów klinicznych od pacjentów Szpitala Klinicznego Nr 1 w Gdańsku z lat 1997-1999. Prz Epidemiol 2000, 54(3/4): 305-313.
23. Samet A, Bronk M, Naumiuk L i wsp. Analiza wyników diagnostycznych badań mikrobiologicznych u pacjentów Szpitala klinicznego w Gdańsku, w latach 2001-2003. Prz Epidemiol 2005, 59(4): 881-890.
24. Wierzba J, Rybak B, Bronk M i wsp. Nosicielstwo i zakażenia pałeczkami z rodziny Enterobacteriaceae wytwarzających szeroko spektralne beta-laktamazy ESBL u pacjentów Oddziału Niemowlęcego Kliniki Pediatrii, Hematologii, Onkologii i Endokrynologii Gdańskiego Uniwersytetu Medycznego w latach 2002-2005. Ann Acad Med Gedan 2009, 39: 155-162.
25. Gniadkowski M, Żabicka D, Hryniewicz W. Rekomendacje doboru testów do oznaczania wrażliwości bakterii na antybiotyki i chemioterapeutyki 2009. Oznaczanie wrażliwości pałeczek Gram-ujemnych. Krajowy Ośrodek Referencyjny ds. Lekowrażliwości Drobnoustrojów. http://www.korld.edu.pl/pdf/02-Rek2009-Paleczki_z_rodziny_Enterobacteriaceae.pdf (12.12.2014).
26. Paterson DL. Recommendation for treatment of severe infections caused by Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLs). Clin Microbiol Infect 2000, 6(9): 460-463.
27. Dzierżanowska D. Lekooporne szczepy szpitalne. [w:] Poradnik antybiotykoterapii w Instytucie Pomnik – Centrum Zdrowia dziecka. Dzierżanowska D (red). Media Press, Łódź 2010: 14-16.
28. Hryniewicz W, Ozorowski T. Szpitalna lista antybiotyków. Propozycja kierowana do szpitali. Narodowy Instytut Leków, Warszawa 2011. http://www.antybiotyki.edu.pl/pdf/szpitalna/szpitalna-lista-antyb-20110617.pdf (12.12.2014).
29. Kamińska W. Problemy narastania oporności drobnoustrojów powodujących zakażenia układu moczowego. Zakażenia 2005, 3: 36-42.
30. Romaniszyn D. Pałeczki Gram(-) w zakażeniach szpitalnych. Zakażenia 2005, 5: 28-31.
31. Rzewuska M. Antybiotykowość Gram-ujemnych pałeczek wytwarzających beta-laktamazy. Życie Weter 2009, 84(3): 199-205.
32. Peña C, Gudiol C, Tubau F, et al. Risk-factors for acquisition of extended-spectrum beta-lactamase-producing Escherichia coli among hospitalized patients. Clin Microbiol Infect 2006, 12(3): 279-284.
33. Sękowska A, Janicka G, Kłyszejko C, et al. Resistance of Klebsiella pneumoniae strains producing and not producing ESBL (extended-spectrum beta-lactamase) type enzymes to selected non-beta-lactam antibiotics. Med Sci Monit 2002, 8(3): BR100-104.
34. Angel Díaz M, Ramón Hernández J, Martínez-Martínez L, et al. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae in Spanish hospitals: 2nd multicenter study (GEIH-BLEE project, 2006). Enferm Infecc Microbiol Clin 2009, 27(9): 503-510.
35. Vijayakanthi N, Bahl D, Kaur N, et al. Frequency and Characteristics of Infections Caused by Extended-Spectrum Beta-Lactamase-Producing Organisms in Neonates: A Prospective Cohort Study. Biomed Res Int 2013, 756209.
36. Cardiff-Oxford Bacteriuria Study Group. Sequelae of covert bacteriuria in schoolgirls: a four-year follow-up-study. Lancet 1978, 311, 8070: 889-893.
37. Verrier Jones K, Asscher AW, Verrier Jones ER, et al. Glomerular filtration rate in schoolgirls with covert bacteriuria. Br Med J (Clin Res Ed) 1982, 285(6351): 1307-1310.