ANTIMICROBIAL SUSCEPTIBILITY PATTERNS OF *ESCHERICHIA COLI* IN CHILDREN AND ADULTS WITH URINARY TRACT INFECTIONS

WZORCE LEKOWRAŻLIWOŚCI *ESCHERICHIA COLI* U DZIECI I DOROSŁYCH Z ZAKAŻENIEM UKŁADU MOCZOWEGO

Yaroslav O. Mykhalko
DEPARTMENT OF THERAPY AND FAMILY MEDICINE, FACULTY OF POSTGRADUATE EDUCATION AND PRE-UNIVERSITY TRAINING, UZHHOROD NATIONAL UNIVERSITY, UZHHOROD, UKRAINE

ABSTRACT

Introduction: Urinary tract infections (UTIs) are common pathology in children and adults that is caused mainly by Gram-negative bacteria among which *Escherichia coli* plays an outstanding role. UTIs treatment demands empiric antibiotic therapy and knowing of antimicrobial local susceptibility and resistance patterns is crucial for making a decision about an agent for the first line therapy.

The aim of this study was to evaluate the local susceptibility patterns of uropathogenic *E. coli* isolates to antibiotics in patients with UTIs.

Materials and methods: A total of 129 E. coli isolates obtained from 44 children (under the age of 18) and 85 adults with community-acquired UTIs were included in this retrospective study during January and December 2017. Antimicrobial susceptibility testing to17 antimicrobials was performed using disc diffusion method on Mueller-Hinton agar. Statistical analyses were performed using Microsoft Excel 2010 and Statistica 10 software. 95% confidence intervals (CI) for proportions were determined using the Agresti-Coull method. P-values were obtained using two-tailed Fisher's exact test. The difference was considered to be statistically significant if $p<0.05$.

Results: *E. coli* was highly susceptible to levofloxacin and gatifloxacin (93.18% [95% CI 81.11-98.32%] for each) with the lowest susceptibility to amoxicillin/clavulanic acid (2.27%, 95% CI 0.00-12.89%) in children. Susceptibility to the tested cephalosporins ranged from 34.09% (cefuroxime, 95% CI 21.82-48.92%) to 65.91% (cefepime, 95% CI 51.08-78.18%). In adults the highest susceptibility was to gatifloxacin and ceftriaxone (80.00% [95% CI 70.19-87.22%] for both) and the lowest one to amoxicillin/clavulanic acid (2.35%, 95% CI 0.14-8.68%).

Conclusions: Aminopenicillins are not suitable for UTIs treatment unless susceptibility is confirmed by testing. Fluoroquinolones cannot be used for the empirical treatment either of complicated or uncomplicated pyelonephritis in adults. Cefotaxime and ceftriaxone can be recommended for initial treatment of complicated UTIs in adults. The efficacy of cephalosporins in children is doubtful due to high local resistance rates.

KEY WORDS: urinary tract infections, *E. coli*, antibiotics, susceptibility, resistance.

Wiad Lek 2018, 71, 2 cz. I, 306-310

INTRODUCTION

Urinary tract infections (UTIs) are among the most common bacterial infections in children and adults with high annual incidence [1,2]. The prevalence varies depending on age, sex, race and other circumstances [3,4]. UTIs are included in the list of common clinical conditions for which antibiotic therapy reduces the risk of mortality and antimicrobials are considered as the most effective agents in treatment. This pathology is caused mainly by Gram-negative bacteria and Escherichia coli (*E. coli*) plays an outstanding role. In majority of cases antibiotics are prescribed empirically and many circumstances must be taken into account for successful treatment. On the other hand, antimicrobial resistance is constantly increasing and become be a global public health threat [5,6]. That's why information about local resistance rates is crucial for successful empirical treatment of infectious diseases and UTIs in particular. For instance, in European Association of Urology Guidelines on Urological Infections is indicated that a fluoroquinolone can be recommended as first-line therapy if the local resistance rate of *E. coli* is still < 10%. In another case initial empirical therapy with an aminoglycoside or carbapenem has to be considered [7].

THE AIM

The aim of this study was to evaluate the local susceptibility patterns of uropathogenic *E. coli* isolates to antibiotics in patients with UTIs.

MATERIALS AND METHODS

A total of 182 urine samples obtained from children (under the age of 18) and adults with community-acquired UTIs

Table I. The prevalence of pathogens in patients with UTIs, % (95% CI)

	Children, n=58	Adults, n=124	p-value
E. cloacae	0.00 (0.00-7.43)	4.84 (2.02-10.37)	p>0.05
E. coli	75.86 (63.36-85.15)	68.55 (59.90-76.08)	p>0.05
E. faecalis	6.90 (2.24-16.91)	4.03 (1.49-9.34)	p>0.05
K. pneumoniae	0.00 (0.00-7.43)	5.65 (2.56-11.39)	p>0.05
P. aeruginosa	3.45 (0.27-12.41)	2.42 (0.51-7.18)	p>0.05
P. mirabilis	3.45 (0.27-12.41)	2.42 (0.51-7.18)	p>0.05
P. vulgaris	1.72 (0.00-10.01)	1.61 (0.08-6.06)	p>0.05
S. aureus	1.72 (0.00-10.01)	4.03 (1.49-9.34)	p>0.05
S. epidermidis	5.17 (1.21-14.70)	5.65 (2.56-11.39)	p>0.05
S. pneumoniae	0.00(0.00-7.43)	0.81 (0.00-4.87)	p>0.05
Str. pyogenes	1.72 (0.00-10.01)	0.00 (0.00-3.61)	p>0.05

Table II. *E. coli* antibiotic susceptibility patterns to aminopenicillins, % (95% CI)

Antibiotic		Children, n=44	Adults, n=85	p-value
Ampicillin	S	25.00 (14.43-39.59)	22.35 (14.37-32.37)	p>0.05
	I	6.82 (1.68-18.89)	5.88 (2.22-13.36)	p>0.05
	R	68.18 (53.37-80.07)	71.76 (61.37-80.28)	p>0.05
Ampicillin/sulbactam	S	36.36 (23.74-51.17)	28.24 (19.72-38.63)	p>0.05
	I	4.55 (0.42-15.97)	10.59 (5.46-19.12)	p>0.05
	R	59.09 (44.39-72.33)	61.18 (50.54-70.85)	p>0.05
Amoxicillin/clavulanic acid	S	2.27 (0.00-12.89)	2.35 (0.14-8.68)	p>0.05
	I	6.82 (1.68-18.89)	5.88 (2.22-13.36)	p>0.05
	R	90.91 (78.29-96.96)	91.76 (83.71-96.21)	p>0.05

Where:
S – susceptibility; I – intermediate resistance; R - resistance

were studied. All patients were treated in medical facilities of Uzhhorod, Ukraine, between January and December 2017. Pathogenic bacterial isolates were identified by cultural and biochemical methods following standard procedures. 129 *E. coli* isolates were included in this retrospective study and selected for further analysis. Antimicrobial susceptibility testing was performed using disc diffusion method on Mueller-Hinton agar. Depending on the diameter of the inhibition zone bacteria were categorized as susceptible (S), intermediate resistant (I) and resistant (R) to antimicrobials. The following discs with antibiotics were used: ampicillin (10 μg), ampicillin/sulbactam (10/10 μg), amoxicillin/clavulanic acid (20/10 μg), cefazolin (30 μg), cefuroxime (30 μg), cefotaxime (30 μg), ceftazidime (30 μg), cefoperazone (75 μg), ceftriaxone (30 μg), cefepime (30 μg), nalidixic acid (30 μg), pipemidic acid (20 μg), ciprofloxacin (5 μg), ofloxacin (5 μg), norfloxacin (10 μg), levofloxacin (5 μg), gatifloxacin (5 μg). Microbiological testing of isolates was performed in microbiological department of the clinical laboratory of Uzhhorod central city clinical hospital and microbiological department of the clinical laboratory of Public institution "Uzhhorod district hospital".

Statistical analyses were performed using Microsoft Excel 2010 and Statistica 10 software. 95% confidence intervals (CI) for proportions were determined using the Agresti-Coull method. P-values were obtained using two-tailed Fisher's exact test. The difference was considered to be statistically significant if $p<0.05$.

RESULTS

E. coli was isolated in majority of studied urine samples. It was responsible for 44 (75.86%, 95% CI: 63.36-85.15%) UTI cases in children followed by E. faecalis (6.90%) and S. epidermidis (5.17%). The prevalence of other pathogens (P. aeruginosa, Proteus spp., S. aureus, S. epidermidis and Str. pyogenes) all together was 12.06% (95% CI: 5.67-23.18%). In adults E. coli was present in 85 (68.55%, 95% CI: 59.90-76.08%) specimens followed by K. pneumoniae and S. epidermidis (5.65% for both). In 20.16% (95% CI: 13.99-28.13%) of adults UTI was caused by other bacteria (E. cloacae, E. faecalis, P. aeruginosa, Proteus spp., S. aureus and S. pneumoniae). It is worse to notice that E. cloacae, K. pneumoniae and S. pneumoniae were not found in children while S. pyogenes was absent in adults (Table I).

Table III. E. coli antibiotic susceptibility patterns to cephalosporins, % (95% CI)

Antibiotic		Children, n=44	Adults, n=85	p-value
Cefazolin	S	45.45 (31.70-59.94)	62.35 (51.72-71.92)	p>0.05
	I	4.55 (0.42-15.97)	3.53 (0.78-10.30)	p>0.05
	R	50.00 (35.88-64.17)	34.12 (24.90-44.71)	p>0.05
Cefuroxime	S	34.09 (21.82-48.92)	36.47 (27.01-47.10)	p>0.05
	I	9.09 (3.04-21.71)	16.47 (9.95-25.90)	p>0.05
	R	56.82 (42.21-70.33)	47.06 (36.81-57.57)	p>0.05
Cefotaxime	S	54.55 (40.06-68.30)	70.59 (60.14-79.25)	p>0.05
	I	2.27 (0.00-12.89)	12.94 (7.21-21.87)	p>0.05
	R	43.18 (29.67-57.79)	16.47 (9.95-25.90)*	p=0.001
Ceftazidime	S	56.82 (42.21-70.33)	76.47 (66.36-84.29)*	p=0.027
	I	6.82 (1.68-18.89)	7.06 (2.99-14.84)	p>0.05
	R	36.36 (23.74-51.17)	16.47 (9.95-25.90)*	p=0.016
Cefoperazone	S	56.82 (42.21-70.33)	74.12 (63.85-82.30)	p>0.05
	I	6.82 (1.68-18.89)	8.24 (3.79-16.29)	p>0.05
	R	36.36 (23.74-51.17)	17.65 (10.88-27.21)*	p=0.029
Ceftriaxone	S	59.09 (44.39-72.33)	80.00 (70.19-87.22)*	p=0.021
	I	6.82 (1.68-18.89)	8.24 (3.79-16.29)	p>0.05
	R	34.09 (21.82-48.92)	11.76 (6.33-20.51)*	p=0.004
Cefepime	S	65.91 (51.08-78.18)	78.82 (68.90-86.25)	p>0.05
	I	6.82 (1.68-18.89)	3.53 (0.78-10.30)	p>0.05
	R	27.27 (16.23-41.97)	17.65 (10.88-27.21)	p>0.05

Where:
S – susceptibility; I – intermediate resistance; R – resistance; * - the difference was statistically significant when compared children and adults

E. coli susceptibility to the tested aminopenicillins was low both in children and adults (Table II). The lowest *E. coli* susceptibility was detected to amoxicillin/clavulanic acid (2.27% and 2.35% in children and adults respectively, p>0.05) while the highest was to ampicillin/sulbactam (36.36% and 28.24% in children and adults respectively, p>0.05).

In majority of cases *E. coli* strains were highly resistant to amoxicillin/clavulanic acid (90.91% and 91.76% in children and adults respectively, p>0.05) and less resistant to ampicillin and ampicillin/sulbactam (68.18%, 59.09% and 71.76%, 61.18% in children and adults respectively, p>0.05).

Intermediate resistance of the investigated pathogens to the tested aminopenicillins was low with no significant difference between children and adults (>0.05).

The analysis of *E. coli* susceptibility to cephalosporins showed that in pediatric population it was the highest to cefepime (65.91%) and the lowest to cefuroxime (34.09%). In adults the highest susceptibility of isolated strains was detected to ceftriaxone (80.00%) while the lowest to cefuroxime (36.47%). In children susceptibility to all other tested cephalosporins was almost the same and varied from 45.45% to 59.09%. In adults it was higher and varied from 62.35% to 78.82% (Table III).

The resistance of *E. coli* isolates was the highest to cefuroxime (56.82% and 47.06% in children and adults respectively, p>0.05) followed by cefazolin (50.00% and 34.12% in children and adults respectively, p>0.05). The minimal *E. coli* resistance rate was detected to cefepime (27.27%) in pediatric patients and to ceftriaxone (11.36%) in adult.

Both in children and adults intermediate resistance of *E. coli* strains was low and did not exceed 10%. Only to cefuroxime and cefotaxime in adult patients intermediate resistance was > 10% (16.47% and 12.94% respectively) and higher than in pediatric population but the difference was not statistically significant (p>0.05).

E. coli strains isolated from children's urine specimens showed high susceptibility rates to quinolones in majority of cases. Among seven tested quinolones it was the highest to gatifloxacin and levofloxacin (93.18% for each) and the lowest to pipemidic acid (77.27%). *E. coli* susceptibility patterns to the tested antimicrobials in adults were lower in general if compared with pediatric patients. The highest susceptibility was detected to gatifloxacin (80.00%) while the lowest one was to nalidixic acid (58.82%). Susceptibility rates to other quinolones varied from 81.82% to 88.64% in children and from 62.35% to 72.94% in adults (Table IV).

E. coli antimicrobial resistance to the tested quinolones was found to be the highest to pipemidic acid followed by nalidixic acid (22.73% and 18.18% respectively) in children

Table IV. *E. coli* antibiotic susceptibility patterns to quinolones, % (95% CI)

Antibiotic		Children, n=44	Adults, n=85	p-value
Nalidixic acid	S	81.82 (67.78-90.95)	58.82 (48.19-68.69)*	p=0.010
	I	0.00 (0.00-9.58)	2.35 (0.14-8.68)	p>0.05
	R	18.18 (9.25-32.22)	38.82 (29.15-49.46)*	p=0.018
Pipemidic acid	S	77.27 (62.83-87.34)	62.35 (51.72-71.92)	p>0.05
	R	22.73 (12.66-37.17)	37.65 (28.08-48.28)	p>0.05
Ciprofloxacin	S	88.64 (75.57-95.50)	69.41 (58.92-78.23)*	p=0.017
	I	4.55 (0.42-15.97)	14.12 (8.11-23.23)	p>0.05
	R	6.82 (1.68-18.89)	16.47 (9.95-25.90)	p>0.05
Ofloxacin	S	86.36 (72.91-93.98)	72.94 (62.61-81.29)	p>0.05
	I	4.55 (0.42-15.97)	3.53 (0.78-10.30)	p>0.05
	R	9.09 (3.04-21.71)	23.53 (15.71-33.64)	p>0.05
Norfloxacin	S	86.36 (72.91-93.98)	69.41 (58.92-78.23)	p>0.05
	I	4.55 (0.42-15.97)	8.24 (3.79-16.29)	p>0.05
	R	9.09 (3.04-21.71)	22.35 (14.73-32.37)	p>0.05
Levofloxacin	S	93.18 (81.11-98.32)	72.94 (62.61-81.29)*	p=0.006
	I	0.00 (0.00-9.58)	7.06 (2.99-14.84)	p>0.05
	R	6.82 (1.68-18.89)	20.00 (12.78-29.81)	p>0.05
Gatifloxacin	S	93.18 (81.11-98.32)	80.00 (70.19-87.22)	p>0.05
	I	4.55 (0.42-15.97)	3.53 (0.78-10.30)	p>0.05
	R	2.27 (0.00-12.89)	16.47 (9.95-25.90)*	p=0.019

Where:
S – susceptibility; I – intermediate resistance; R – resistance; * - the difference was statistically significant when compared children and adults

Resistance to fluoroquinolones did not exceed 10% and was the lowest to gatifloxacin (2.27%). In contrast, in adults resistance rates to quinolones exceeded 20% threshold in majority of cases. It was also the highest to nalidixic acid and pipemidic acid (38.82% and 37.65% respectively) while the lowest one to ciprofloxacin and gatifloxacin (16.47% for each).

Intermediate resistance levels to the tested quinolones did not exceed 5% in pediatric patients and 10% in adult. Only to ciprofloxacin it was 14.12% in adults. It is remarkable that *E. coli* strains intermediate resistant to levofloxacin and nalidixic acid were not found in tested specimens obtained from children.

DISCUSSION

E. coli is known to be the most common cause of UTIs. The prevalence of this uropathogen in etiological structure varies in wide ranges [8-11]. In studied population group E. coli was also found to be responsible for majority of UTIs cases in both children and adults. Despite this bacterium was detected more often in children than in adults (78.86% and 68.55% respectively) the difference was not statistically significant and the structure of UTIs causative agents was the same in both age groups (p>0.05). The prevalence of other pathogens was 24.14% (95% CI: 14.85-36.64%) in children and 31.45% (95% CI: 23.92-40.10%) in adults with no statistical significance (p>0.05).

The analysis of *E. coli* susceptibility patterns to aminopenicillins showed that it was extremely low in both studied age groups. It is remarkable that susceptibility to amoxicillin/clavulanic acid was the lowest and did not exceed 3% while the resistance was detected in more than 90% of cases. Taking into account low *E. coli* susceptibility and high resistance rates to the tested aminopenicillins these antimicrobials cannot be recommended for the empiric treatment of UTIs neither in adults nor in pediatric patients.

Cephalosporins are widely used for UTIs treatment in routine clinical practice. These antimicrobials are recommended for initial empirical treatment of complicated UTIs (cefodizime, cefotaxime, ceftriaxone) in adults if local resistance pattern is still < 20%. Cefoperazone and ceftazidime are also recommended for empirical treatment in case of initial failure, or for severe cases. For uncomplicated pyelonephritis cephalosporins are considered as alternatives to fluoroquinolones for initial empirical antimicrobial therapy [7].

In pediatrics third generation cephalosporins are also recommended both for severe and simple UTIs [12,13].

But, because of the increasing resistance to these agents and high rate of extended-spectrum beta-lactamase production their efficacy is of concern [14,15].

In our study *E. coli* susceptibility rates to the tested cephalosporins were quite low mainly due to high resistance. But, to cefotaxime and ceftriaxone *E. coli* resistance did not exceed 20% threshold so these antibiotics can be recommended for initial empirical treatment of complicated UTIs in adults. In general, resistance rates to the tested cephalosporins were significantly higher in children when compared with adult patients and exceeded 30% in majority of cases. This can be explained by wide usage of cephalosporins in pediatrics.

While fluorinated quinolones are recommended as a first-line therapy for UTIs in adults [7] its usage advisability in pediatrics is disputable mainly due to adverse effects. It is considered that these antibiotics must be avoided or limited in children because of the potential risk of cartilage damage and growth [7,16,17].

In a present study the analysis of *E. coli* resistance patterns to quinolones showed that it was higher to non-fluorinated agents in children and adults if compare with fluorinated. While resistance to all tested fluoroquinolones exceeded 20% in adults, in pediatric patients it was less than 10%. It's notable that in children *E. coli* susceptibility to quinolones was generally higher if compare with adult patients. But this difference was statistically significant only for nalidixic acid, ciprofloxacin and levofloxacin ($p<0.05$). Obtained data confirmed high activity of fluoroquinolones against uropatogenic *E. coli* strains in pediatric population. On the other hand, their efficacy as a first-line therapy for UTIs in adults questionable because of unfavorable resistance patterns.

CONCLUSIONS

E. coli was the most common uropathogen responsible for the UTIs development. Because of the high local resistance aminopenicillins are not suitable for UTIs treatment unless susceptibility is confirmed by testing. Fluoroquinolones cannot be used for the empirical treatment neither of complicated nor uncomplicated pyelonephritis in adults because resistance rates are >20%. More investigations are needed to evaluate safety of quinolones in pediatric population because these agents showed favorable *E. coli* susceptibility pattern and may be useful in this group of patients. Cefotaxime and ceftriaxone can be recommended for initial empirical treatment of complicated UTIs in adults as the local *E. coli* resistance did not exceed 20% threshold. The efficacy of cephalosporins for the empirical UTIs treatment in children is doubtful due to high local resistance rates.

REFERENCES

1. Barisic Z, Babic-Erceg A, Borzic E et al. Urinary tract infections in South Croatia: aetiology and antimicrobial resistance. Int J Antimicrob Agents 2003;22 (2):61–64.
2. Ronald AR, Nicolle LE, Stamm E et al. Urinary tract infection in adults: research priorities and strategies. Int J Antimicrob Agents 2001;17:343–348
3. Shaikh N, Morone NE, Bost JE et al. Prevalence of urinary tract infection in childhood: a meta-analysis. Pediatr Infect Dis J. 2008; 27(4): 302-308.
4. Nicolle LE. Urinary tract infections in special populations: diabetes, renal transplant, HIV infection, and spinal cord injury. Infect Dis Clin North Am. 2014;28(1):91-104.
5. World Health Organization. Antimicrobial resistance: Global report on surveillance 2014. Available:http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf?ua=1.
6. Woolhouse M, Waugh C, Perry MR et al. Global disease burden due to antibiotic resistance – state of the evidence. Journal of Global Health. 2016;6(1):010306.
7. M. Grabe, R. Bartoletti, T.E. Bjerklund Johansen et al. European Association of Urology Guidelines on Urological Infections 2015. Available: http://uroweb.org/guideline/urological-infections/
8. Aguinaga A1, Gil-Setas A, Mazón Ramos A et al. Uncomplicated urinary tract infections. Antimicrobial susceptibility study in Navarre. An Sist Sanit Navar. 2018;0(0):59989 [Epub ahead of print].
9. Rizwan M, Akhtar M, Najmi AK et al. Escherichia coli and Klebsiella pneumoniae Sensitivity/Resistance Pattern Towards Antimicrobial Agents in Primary and Simple Urinary Tract Infection Patients Visiting University Hospital of Jamia Hamdard New Delhi. Drug Res (Stuttg). 2018. doi: 10.1055/a-0576-0079. [Epub ahead of print]
10. Córdoba G, Holm A, Hansen F et al. Prevalence of antimicrobial resistant Escherichia coli from patients with suspected urinary tract infection in primary care, Denmark. BMC Infect Dis. 2017;17(1):670.
11. Ayelign B, Abebe B, Shibeshi A et al. Bacterial isolates and their antimicrobial susceptibility patterns among pediatric patients with urinary tract infections. Turk J Urol. 2018;44(1):62-69.
12. Erol B, Culpan M, Caskurlu H et al. Changes in antimicrobial resistance and demographics of UTIs in pediatric patients in a single institution over a 6-year period. J Pediatr Urol. 2018. pii: S1477-5131(18)30008-1. doi: 10.1016/j.jpurol.2017.12.002. [Epub ahead of print]
13. Roberts KB, Downs SM, Finnell SM et al. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. / Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management. Pediatrics. 2011;128(3):595-610.
14. Delbet JD, Lorrot M, Ulinski T. An update on new antibiotic prophylaxis and treatment for urinary tract infections in children. Expert Opin Pharmacother. 2017;18(15):1619-1625.
15. Pouladfar G, Basiratnia M, Anvarinejad M. The antibiotic susceptibility patterns of uropathogens among children with urinary tract infection in Shiraz. Medicine (Baltimore). 2017;96(37):e7834.
16. Principi N, Esposito S. Appropriate use of fluoroquinolones in children. Int J Antimicrob Agents. 2015;45(4):341-346.
17. González M C, Rosales C R, Pavez D et al. Safety of fluoroquinolones: risks usually forgotten for the clinician. Rev Chilena Infectol. 2017;34(6):577-582.

ADDRESS FOR CORRESPONDENCE
Yaroslav O. Mykhalko
148, Sobranetska str., Uzhhorod 88000, Ukraine.
tel: +38 0312 66 46 94
e-mail: yaroslav.myhalko@uzhnu.edu.ua

Received: 20.02.2018
Accepted: 10.04.2018

TOM LXXI, 2018, Nr 2 cz I

cena 30 zł
(w tym VAT)

Wiadomości Lekarskie

ISSN 0043-5147

Czasopismo Polskiego Towarzystwa Lekarskiego

Rok założenia 1928

CZASOPISMO INDEKSOWANE W PUBMED/MEDLINE, EBSCO, INDEX COPERNICUS oraz MNiSW (11 pkt), SCOPUS
I POLSKIEJ BIBLIOGRAFII LEKARSKIEJ

SPIS TREŚCI

PRACE ORYGINALNE / ORIGINAL ARTICLES