Strategies to control the emerging bacterial antibiotic resistance in urology

Ph.D. Thesis

Magyar András M.D.

Szeged

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Department of Urology, Jahn Ferenc South Pest Hospital

Supervisor: Prof. Péter Tenke, M.D., Ph.D. DSc.

Co-supervisor: Dr. Béla Köves, MD., Ph.D.

The University of Szeged, Doctoral School of Clinical Medicine

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Publications serving as a basis for the Ph.D. thesis

I. **Magyar A**, Köves B, Nagy K, Dobák A, Arthanareeswaran VKA, Bálint P, et al. Spectrum and antibiotic resistance of uropathogens between 2004 and 2015 in a tertiary care hospital in Hungary. J Med Microbiol. 2017;66(6):788-797. **IF: 2.156**

II. **Magyar A**, Dobák A, Bálint P, Arthanareeswaran VKA; Nagy K, Póth S, et al. Húgyúti kórokozók spektrumának és antibiotikum-rezisztenciájának változása osztályunkon 2004 és 2017 között. Magyar Urológia. 2018;30(3):96-104.

III. **Magyar A**, Alidjanov JF, Pilatz A, Nagy K, Arthanareeswaran VKA, Póth S, et al. The role of the acute cystitis symptom score questionnaire for research and antimicrobial stewardship. Validation of the Hungarian version. Cent European J Urol. 2018;71(1):134-141.

IV. Alidjanov JF, Naber KG, Pilatz A, Radzhabov A, Zamuddinov M, **Magyar A**, et al. Evaluation of the draft guidelines proposed by EMA and FDA for the clinical diagnosis of acute uncomplicated cystitis in women. World journal of urology. World J Urol. 2020;38(1):63-72. **IF: 3.217**

V. Alidjanov JF, Naber KG, Pilatz A, Radzhabov A, Zamuddinov M, **Magyar A**, et al. Additional assessment of Acute Cystitis Symptom Score questionnaire for patient-reported outcome measure in female patients with acute uncomplicated cystitis: part II. World J Urol. 2020;38(8):1977-1988. **IF: 3.217**

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XVI. **Magyar A**, Arthanareeswaran VKA, Soós L, Nagy K, Dobák A, et al. Does micropattern (sharklet) on urinary catheter surface reduce urinary tract infections? Results from phase I randomized open label interventional trial. European Urology Supplements. 2017;16(3):146-148.

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XXI. **Magyar A**, Köves B, Tenke P. Osztályunkon középsugaras, és katéteres pozitív vizeletmintákból nyert baktériumok, továbbá azok antibiotikum érzékenysége 2010-2012 között. Uroonkológia 2013;10(1):18.

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List of Abbrevations

ACSS	Acute Cystitis Symptom Score
AUC	Acute uncomplicated cystitis
CI	Confidence interval
CLSI	Clinical and Laboratory Standards Institute
DOR	Diagnostic odds ratio
E. coli	*Escherichia coli*
E. faecalis	*Enterococcus faecalis*
EAU	European Association of Urology
ESIU	European Association of Urology, Section of Infections in Urology
EMA	European Medicines Agency
ESBL	Extended-spectrum beta-lactamase
ESCMID	European Society for Microbiology and Infectious Diseases
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	Food and Drug Administration
GPIU	Global Prevalence Study on Infections in Urology
IDSA	Infectious Diseases Society of America
IQR	Interquartile range
K. pneumoniae	*Klebsiella pneumoniae*
LR	Likelyhood ratio
MDR	Multidrug-resistance
MRAB	Multidrug-resistant *Acinetobacter baumannii*
MRSA	Methicillin-resistant *Staphylococcus aureus*
NPV	Negative predictive value
P. aeruginosa	*Pseudomonas aeruginosa*
P. mirabilis	*Proteus mirabilis*
PPV	Positive predictive value
PRO	Patient-Reported Outcomes
PROM	Patient-Reported Outcome Measure
QoL	Quality of Life
SD	Standard deviation
ToC	Test of Cure
UK	United Kingdom
UTI	Urinary tract infection
VRE	Vancomycin-resistant Enterococci

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1. INTRODUCTION

1.1. Background

Since the second half of the 20th century the widespread use of antibiotics in healthcare, agriculture, and environment has led to a rapid increase in resistance of bacteria to antibiotics. Today it has become such a severe global issue that the WHO has listed it among the most dangerous threats to mankind. According to a case study from 2011-2012, 91 000 deaths are related to healthcare-associated infections in the European Union yearly. Of these, 15 000 can be attributed to healthcare-associated urinary tract infections [1]. Another study revealed that multidrug-resistant bacteria (resistant to more than three unrelated antibiotic groups) are responsible for 25 000 deaths in the European Union every year, which is higher than the number of deaths caused by HIV/AIDS, Parkinson's disease, or suicide. The cost expenses on multidrug-resistant bacteria exceed 1.5 billion Euros per year [2].

Without immediate interference the antimicrobial resistance is going to lead to devastating consequences from a medical, scientific, and also economical point of view [3]. The spread of resistant strains soon will result in the deficit of antibiotic agents to treat patients, and the chance of successful empirical antibiotic treatment will notably decrease. As a result morbidity and mortality would largely increase. By 2050, the expected mortality from infections caused by multidrug-resistant bacteria would outgrow the number of deaths caused by cancer, reaching 10 million people per year worldwide [3, 4].

Despite the obvious threat, in the last twenty years research and funding on the subject decreased, as an increasing number of companies have abandoned antiinfective research [5]. New antibiotics with novel actions will not be available in the near future [2]. As a result, our actions against the increasing resistance are already delayed by 20 years. It is inevitable to initiate intense research and implement global strategies in order to delay the spread of bacterial resistance to antibiotics and gain time for the development of new antibiotics effective against the actual multidrug-resistant bacteria. Moreover, implementation of non-antibiotic measures should replace antibiotic treatment whenever reasonably possible.

1.2. Stewardship programs

Positive news is that the international cooperation has already begun. Antibiotic stewardship programs have been developed to set coordinated strategies for reducing antimicrobial resistance [6]. Recently the government of the United Kingdom (UK) has initiated the Fleming fund investing 375 million USD in surveillance of resistance in emerging countries, and further Chinese and UK collaboration is expected with the Global Innovation Fund. In 2014 the government of the UK conducted a massive investigation to reveal the most effective and affordable methods to tackle down the antibiotic resistance. As a result, the strategies of the stewardship programs have been summarized and published within the O'Neill report [4]. The most important methods are listed in Table 1. They emphasize, that the cause of the increasing resistance is multifactorial, and so should be the solution. The main strategies are based both on prudent antibiotic use and further research [7]. At first, we need to cut the unnecessary antibiotic consumption. With proper antibiotic use we can delay the development of the resistance in our clinical practice, while enhancing patient health outcomes at the same time. Whereas, further research should focus on the development of new antibiotics and alternative non-antibiotic treatment methods. For early recognition of whether antibiotic treatment is indicated or not, development of new rapid diagnostic methods is required.

Table 1. Methods to tackle down resistance according to the O'Neill report [4]

I. Prudent antibiotic use in practice	**II. Further scientific research**
a) Public awareness, education	f) Novel antibiotics
b) Avoidance in agriculture	g) Non-antibiotic treatment
c) Avoidance in medicine	h) Rapid diagnostic procedures
d) Local and global surveillance	i) Novel catheters
e) Adherence to the guidelines	j) International coalition on research and action

***a) Public awareness, education*:** Education on the proper infection control, sanitation, and hygiene is crucial. The population, the workers in the agriculture and the medical personnel should be aware regarding the consequences of excessive antibiotic consumption. We need to change the widespread belief that infections generally require antibiotic treatment.

***b) Avoidance in agriculture*:** The amount of antibiotics utilized in livestock is vast and often includes medicines also used in humans. In the USA over 70% of the total volume of the antibiotics defined as medically important for humans by the FDA (Food and Drug Administration) are sold for use in animals [4]. It is mandatory to change the uncontrolled antibiotic usage policy in the agriculture.

***c) Avoidance in medicine*:** Knowledge on when to omit the use of antibiotics is crucial. Treatment of asymptomatic bacteruria should be limited only to surgical prophylaxis or during pregnancy [8]. Furthermore, we need to avoid the use of broad-spectrum antibiotics whenever reasonably possible. The excessive use of antibiotics with broad-spectrum of action leads to the disruption of the patients' normal flora and results in the development of further opportunistic infections.

***d) Local and global surveillance*:** The local antibiotic policies have substantial impact on the resistance, therefore it may vary depending on the geographic region and change with time [9]. Continuous local and global surveillance serves as the basis for building up the optimal strategies for empirical antibiotic treatment and surgical prophylaxis.

***e) Adherence to the guidelines*:** Besides providing detailed recommendations for the treatment of UTIs, the guidelines help in choosing the appropriate antibiotics for prophylaxis in different types of urologic surgical procedures. A study revealed that adherence to the European Association of Urology (EAU) Guidelines on surgical prophylaxis could reduce the overall use of antibiotics, without increasing the rate of postoperative infections, and also being cost-effective [10].

***f) Proper use and development of novel antibiotics*:** There are a few novel antibiotics available to manage infections with multidrug-resistant (MDR) bacteria. Ceftazidime/Avibactam, a new beta-lactamase inhibitor could be used versus ESBL- (Extended-spectrum beta-lactamase) and carbapenemase-positive pathogens. A combination of Ceftolozan/Tazobactam is effective versus ESBL-producing Enterobacteriaceae. [11]. We need to save these last-resort antibiotics for patients with more severe infections, such as urosepsis, and only if the classic antibiotics can not be recommended [7]. We should invest resources into further research on new antibiotics, other therapeutic modalities, and vaccines. However, it is an expensive and lengthy process, thus we need to gain time by following the principles of the antibiotic stewardship programs worldwide [4].

***g) Research on non-antibiotic treatment modalities*:** The emergence of antibiotic resistant bacteria has increased the need for searching alternatives to antibiotic treatment and preventive measures [4, 7]. We will discuss its importance in details later.

***h) Introduction and development of diagnostic tools and procedures for clinical use and research*:** In clinical practice early diagnosis can improve patient health outcomes. Slow diagnostic technology should be replaced by new rapid diagnostic methods. By implementation of fast, accurate and reliable diagnostic means we could reduce the amount of antibiotic subscription and decrease the prolonged use of broad-spectrum antibiotics. The time factor is especially crucial in sepsis, where any latency increases mortality. Dipstick tests, flow cytometry, PCR, and other amplification techniques could provide early susceptibility results. There are some new quick diagnostic methods under development. The isothermal microcalorimetry is a promising technology to show the growth rate of bacteria by measuring the heat exertion of bacteria. It will be able to reveal whether the bacteria is resistant to the applied empirical antibiotic treatment in the patient or not [12, 13]. We also require simple, fast and cost-effective diagnostic tools to diagnose less severe, but very frequent infectious diseases such as acute uncomplicated cystitis (AUC). Recently, the Acute Cystitis Symptom Score questionnaire (ACSS) has been introduced [14]. The ACSS is a diagnostic tool, that allows an accurate evaluation of the different symptoms of AUC by assignment of numeric scores to their severity based on the patients' feedback. It can be used for diagnostics, but also important for further research on non-antibiotic drugs, as it could provide objective follow-up and comparison on the efficiency of different treatment modalities.

***i) Research on novel catheters*:** Each time a urinary catheter is placed, microbes adhere to its surface and produce a matrix of extracellular polymeric substances. This so-called biofilm provides protection to pathogens against antibiotics and the immune system. Within the biofilm most of bacteria survive the treatment as it prevents the antibiotics from reaching them. As a result, the slow, reduced antibiotic exposure promotes the selection of resistant bacteria [15]. Several catheter modifications have been proposed aiming to decrease the biofilm formation, however none of the strategies tested until now proved to be useful in this regard [16].

***j) International coalition on research and action*:** Since the spread of bacterial resistance to antibiotics is a global problem, only locally it can not be resolved. Implementation of well-coordinated strategies with international cooperation is essential [17].

1.3. The situation in urology

Urology plays a unique and important role in the development of antimicrobial resistance. In urologic departments resistance patterns may significantly differ from other hospital units for several reasons [18].

1) A substantial proportion urologic visits are due to infections and many of the patients are treated with recurrent UTIs;

2) The presence of urological complicating factors, such as stones, foreign bodies, anatomic abnormalities sustain persistent and complicated UTIs;

3) In patients hospitalized at urologic departments an increased proportion of urine culture samples is expected to be positive;

4) Different antibiotics are being used at each department to treat different types of infections.

1.3.1. Surveillance

In Hungarian hospitals urologic departments generally do not perform monitoring on antibiotic resistance of uropathogens, and therefore there is no such data available from urologic patients. As a result, the empiric treatment of UTIs is done almost blindly as we do not have sufficient information for providing the best proper empirical treatment for our urologic patients.

The best approximate of resistance status is provided by the National Centre of Epidemiology, which summarises resistance profiles in Hungarian hospitals up to year 2017. However, the surveillance has substantial limits as not all important antibiotics are listed, the definitions of resistance are not standardized, and no information can be gained regarding the situation in urologic departments (neither summarised, nor data separated by regions) [19].

There are some cumulate European surveillance data available [17, 20], however, almost none of them has performed the assessment of urologic patients separately. The only ongoing international, multicentre surveillance study focusing on urologic departments is The Global Prevalence of Infections in Urology (GPIU) [21, 22]. However, the latest results of international urological surveillance from the GPIU study need to be updated.

1.3.2. Antiinfective research

Not only the surveillance is insufficient. AUC is one of the most frequent infectious diseases in urology and contributes to an enormous amount of antibiotic consumption. In all cases of AUC, antibiotic treatment is still the standard treatment. Nevertheless, it is clear by now that in the future, the treatment of cystitis should highly rely on non-antibiotic treatment modalities. High-quality research on non-antibiotic therapeutic modalities is, however, stagnating. There were several studies conducted aiming to evaluate the efficiency of different non-antibiotic drugs, but none of them were standardized, and no objective diagnostic and follow-up and cure criteria were established [8]. Until recently, there was no reliable tool available to compare the different non-antibiotic treatment modalities.

For all these reasons we need to implement the antibiotic stewardship programs in Hungarian urological practice. First of all, we have to surveil the bacterial resistance in urologic departments, and adjust our local antibiotic treatment strategies accordingly. We also need to place a greater emphasis ont he research of alternative non-antibiotic treatment modalities both in Hungary and on the international level.

2. AIMS

The main objective of our scientific work was to present and highlight the importance of the most recent and relevant strategies for reducing the emergence of bacterial resistance to antibiotics, and to introduce these fundamental strategies into the Hungarian urological practice and research. The aim of this thesis is to demonstrate our results on surveillance and cystitis diagnostic research in details.

I. Surveillance

With surveillance we aimed to evaluate the bacterial spectrum and antibiotic resistance of uropathogens cultured from urine samples within the last 14 years at the Department of Urology in Jahn Ferenc South Pest Hospital.

Our specific objectives were to:

I/1. Evaluate the spectrum of the most common uropathogens (Papers I-II)

I/2. Assess the antimicrobial resistance patterns of the predominant bacteria (Papers I-II) and estimate the rate of multidrug-resistant bacteria (Paper I)

I/3. Compare the results with the international data (Paper I)
I/4. Develop a local antibiotic treatment strategy based on the results (Papers I-II)

II. Cystitis diagnostic research

At first, we aimed to introduce a practical diagnostic tool on AUC for Hungarian physicians and scientists by the development of the Hungarian version of the ACSS questionnaire. Furthermore, using the data obtained with the Hungarian version of the questionnaire we performed a clinical diagnostic validation of the Hungarian version for its possible use as a research tool in clinical trials.

Next, we performed the comprehensive international analysis of the ACSS as a diagnostic tool for research on acute cystisis using the data obtained during the validation of the different language versions of the ACSS.

Our specific objectives were to:

II/1. Perform the translation and linguistic validation of the Hungarian ACSS (Paper III)
II/2. Conduct the clinical diagnostic validation of the Hungarian ACSS (Paper III)
II/3. Internationally evaluate the diagnostic accuracy of the ACSS (Paper IV)
II/4. Further assess its ability to be used as a follow-up instrument (Paper V)

3. MATERIALS AND METHODS

3.1. Methods of surveillance

The current study was conducted at the Department of Urology in Jahn Ferenc South Pest Hospital, a tertiary care hospital in Budapest, Hungary. All mid-stream urine samples and also urine collected from catheterized patients or during urinary tract puncture, taken from inpatients between January 2004 to December 2017, were retrospectively analyzed. In Paper I we summarised our results from the period of 2004-2015 in English, while Paper II is considered as its update with the latest data from 2016-2017. Paper II was written in Hungarian in order to provide surveillance data for Hungarian practitioners.

The urine samples were taken from patients having UTI as well as asymptomatic patients not having UTI (urine cultures taken preoperatively).

Because of the absence of an electronic database before 2010, limited data was transferred from the microbiology laboratory. Based on the microbiologist's decision, mostly due to economic reasons, in some cases, resistance to all antibiotics was not measured. Missing data in table cells are marked as N.D. (not determined).

The improvement of our electronic computer system in 2010 allowed us to perform data mining in depth. To eliminate duplicate results, only one species per year per patient with an identical antibiogram was included in the statistical analysis. To calculate the trends of antibiotic resistance and positive urine culture numbers, the Cochran–Armitage trend test was used. $P < 0.05$ was considered significant. Only the five most prevalent species present in >5% of the bacterial spectrum and their resistance patterns were analyzed in this study. In the cases of low numbers and high fluctuation of data, we displayed the mean occurrences of resistant isolates during consecutive years.

3.1.1. Culture and antimicrobial susceptibility

The urine samples were collected in boric acid containers and sent to the microbiology laboratory for the identification of the bacteria. The culturing and susceptibility testing was performed by the central laboratory of the hospital complying with the actual international guidelines. In 2011 the laboratory shifted from Clinical and Laboratory Standards Institute (CLSI) Performance Standards for Antimicrobial Susceptibility Testing [23] to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) system [24]. The changes in methods or antibiotics used for screening the resistance profile throughout the years were not relevant. The resistant bacterial isolates were described in accordance with the European Committee on Antimicrobial Susceptibility Testing–EUCAST MIC breakpoint tables [24].

3.1.2. Multidrug-resistant species

Data on multidrug-resistance (MDR) was gained from the report of our hospital to the Hungarian National Nosocomial Surveillance System (National Epidemiology Centre) [19]. The results on ESBL-producing organisms were available from 2010-2015, while for other MDR species data between 2013-2015 could be evaluated. Species meeting the following criteria were considered MDR: vancomycin-resistant *Enterococcus faecalis* and *faecium*

(VRE), ESBL-producing or carbapenem-resistant *Enterobacteriaceae*, MDR *Pseudomonas aeruginosa* (susceptible to ≤2 of the following antibiotics: piperacillin/tazobactam, ceftazidime, cefepime, imipenem, meropenem, ciprofloxacin, gentamicin, tobramycin, amikacin), carbapenem-resistant *Acinetobacter baumannii* and different types of MDR *Staphylococcus aureus*, including methicillin-resistant *Staphylococcus aureus* (MRSA). *Klebsiella pneumoniae* strains which were able to hydrolyze third-generation cephalosporins, but could be inhibited by clavulanic acid (in vitro) were considered ESBL-positive. However, isolates resistant to third-generation cephalosporins yet sensitive to fourth-generation cephalosporins were not considered as ESBL-producing organisms.

3.1.3. Comparison with the international results

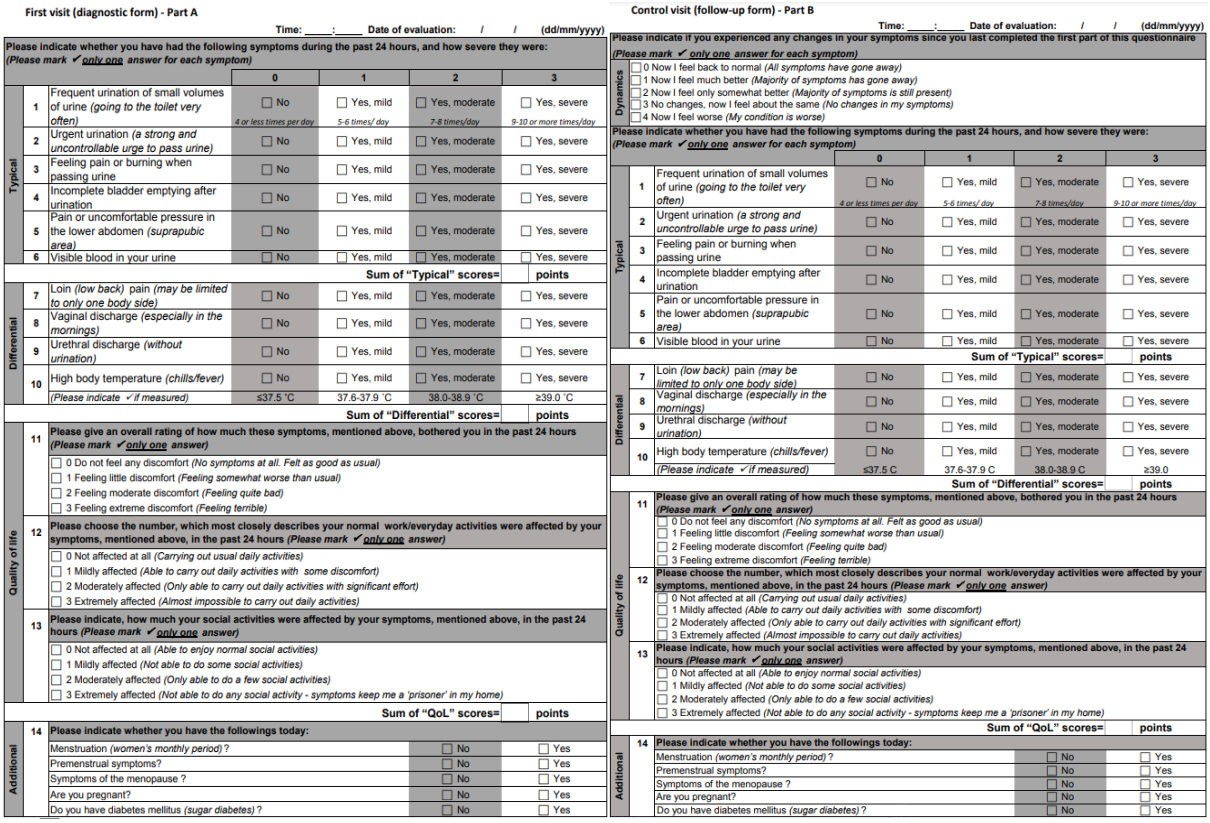
We compared our results from the period of 2004-2017 with the latest available data of the GPIU study from 2003-2010 [21, 25].

3.1.4. Development of a local antibiotic use strategy

The results were evaluated regarding the spectrum, resistance patterns and their dynamics in order to improve our local antibiotic use strategy.

3.2. Methods of the cystitis diagnostic research

The ACSS questionnaire is a diagnostic tool for AUC, that allows an accurate symptom evaluation by assignment of numeric scores to their severity based on the patients' feedback. The ACSS is composed of a diagnostic and a follow-up form (A and B part). Each form consists of four domains. The first domain focuses on typical symptoms, the second contains questions for differential diagnosis, the third evaluates the quality of life (QoL), and the fourth domain aims to assess additional relevant medical conditions. Furthermore, the B part of the questionnaire also includes a „Dynamics" domain, which registers the overall clinical outcome reported by the patient [26]. The UK English version of the ACSS is demonstrated in Figure 1.



First visit (diagnostic form) - Part A

Time: ____:____ Date of evaluation: / / (dd/mm/yyyy)

Please indicate whether you have had the following symptoms during the past 24 hours, and how severe they were:
(Please mark ✔only one answer for each symptom)

			0	1	2	3
Typical	1	Frequent urination of small volumes of urine *(going to the toilet very often)*	☐ No *4 or less times per day*	☐ Yes, mild *5-6 times/ day*	☐ Yes, moderate *7-8 times/day*	☐ Yes, severe *9-10 or more times/day*
	2	Urgent urination *(a strong and uncontrollable urge to pass urine)*	☐ No	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
	3	Feeling pain or burning when passing urine	☐ No	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
	4	Incomplete bladder emptying after urination	☐ No	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
	5	Pain or uncomfortable pressure in the lower abdomen *(suprapubic area)*	☐ No	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
	6	Visible blood in your urine	☐ No	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
					Sum of "Typical" scores=	**points**
Differential	7	Loin *(low back)* pain *(may be limited to only one body side)*	☐ No	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
	8	Vaginal discharge *(especially in the mornings)*	☐ No	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
	9	Urethral discharge *(without urination)*	☐ No	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
	10	High body temperature *(chills/fever)*	☐ No	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
		(Please indicate ✓if measured)	≤37.5 °C	37.6-37.9 °C	38.0-38.9 °C	≥39.0 °C
					Sum of "Differential" scores=	**points**

Quality of life	11	**Please give an overall rating of how much these symptoms, mentioned above, bothered you in the past 24 hours** *(Please mark ✔only one answer)* ☐ 0 Do not feel any discomfort *(No symptoms at all. Felt as good as usual)* ☐ 1 Feeling little discomfort *(Feeling somewhat worse than usual)* ☐ 2 Feeling moderate discomfort *(Feeling quite bad)* ☐ 3 Feeling extreme discomfort *(Feeling terrible)*
	12	**Please choose the number, which most closely describes your normal work/everyday activities were affected by your symptoms, mentioned above, in the past 24 hours** *(Please mark ✔only one answer)* ☐ 0 Not affected at all *(Carrying out usual daily activities)* ☐ 1 Mildly affected *(Able to carry out daily activities with some discomfort)* ☐ 2 Moderately affected *(Only able to carry out daily activities with significant effort)* ☐ 3 Extremely affected *(Almost impossible to carry out daily activities)*
	13	**Please indicate, how much your social activities were affected by your symptoms, mentioned above, in the past 24 hours** *(Please mark ✔only one answer)* ☐ 0 Not affected at all *(Able to enjoy normal social activities)* ☐ 1 Mildly affected *(Not able to do some social activities)* ☐ 2 Moderately affected *(Only able to do a few social activities)* ☐ 3 Extremely affected *(Not able to do any social activity - symptoms keep me a 'prisoner' in my home)*
		Sum of "QoL" scores= **points**

Additional	14	**Please indicate whether you have the followings today:**		
		Menstruation *(women's monthly period)* ?	☐ No	☐ Yes
		Premenstrual symptoms?	☐ No	☐ Yes
		Symptoms of the menopause ?	☐ No	☐ Yes
		Are you pregnant?	☐ No	☐ Yes
		Do you have diabetes mellitus *(sugar diabetes)* ?	☐ No	☐ Yes

Control visit (follow-up form) - Part B

Time: ____:____ Date of evaluation: / / (dd/mm/yyyy)

Please indicate if you experienced any changes in your symptoms since you last completed the first part of this questionnaire
(Please mark ✔ only one answer for each symptom)

Dynamics
- ☐ 0 Now I feel back to normal *(All symptoms have gone away)*
- ☐ 1 Now I feel much better *(Majority of symptoms has gone away)*
- ☐ 2 Now I feel only somewhat better *(Majority of symptoms is still present)*
- ☐ 3 No changes, now I feel about the same *(No changes in my symptoms)*
- ☐ 4 Now I feel worse *(My condition is worse)*

Please indicate whether you have had the following symptoms during the past 24 hours, and how severe they were:
(Please mark ✔only one answer for each symptom)

			0	1	2	3
Typical	1	Frequent urination of small volumes of urine *(going to the toilet very often)*	☐ No *4 or less times per day*	☐ Yes, mild *5-6 times/ day*	☐ Yes, moderate *7-8 times/day*	☐ Yes, severe *9-10 or more times/day*
	2	Urgent urination *(a strong and uncontrollable urge to pass urine)*	☐ No	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
	3	Feeling pain or burning when passing urine	☐ No	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
	4	Incomplete bladder emptying after urination	☐ No	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
	5	Pain or uncomfortable pressure in the lower abdomen *(suprapubic area)*	☐ No	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
	6	Visible blood in your urine	☐ No	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
					Sum of "Typical" scores=	**points**
Differential	7	Loin *(low back)* pain *(may be limited to only one body side)*	☐ No	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
	8	Vaginal discharge *(especially in the mornings)*	☐ No	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
	9	Urethral discharge *(without urination)*	☐ No	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
	10	High body temperature *(chills/fever)*	☐ No	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
		(Please indicate ✓if measured)	≤37.5 C	37.6-37.9 C	38.0-38.9 C	≥39.0
					Sum of "Differential" scores=	**points**

Quality of life	11	**Please give an overall rating of how much these symptoms, mentioned above, bothered you in the past 24 hours** *(Please mark ✔only one answer)* ☐ 0 Do not feel any discomfort *(No symptoms at all. Felt as good as usual)* ☐ 1 Feeling little discomfort *(Feeling somewhat worse than usual)* ☐ 2 Feeling moderate discomfort *(Feeling quite bad)* ☐ 3 Feeling extreme discomfort *(Feeling terrible)*
	12	**Please choose the number, which most closely describes your normal work/everyday activities were affected by your symptoms, mentioned above, in the past 24 hours** *(Please mark ✔only one answer)* ☐ 0 Not affected at all *(Carrying out usual daily activities)* ☐ 1 Mildly affected *(Able to carry out daily activities with some discomfort)* ☐ 2 Moderately affected *(Only able to carry out daily activities with significant effort)* ☐ 3 Extremely affected *(Almost impossible to carry out daily activities)*
	13	**Please indicate, how much your social activities were affected by your symptoms, mentioned above, in the past 24 hours** *(Please mark ✔only one answer)* ☐ 0 Not affected at all *(Able to enjoy normal social activities)* ☐ 1 Mildly affected *(Not able to do some social activities)* ☐ 2 Moderately affected *(Only able to do a few social activities)* ☐ 3 Extremely affected *(Not able to do any social activity - symptoms keep me a 'prisoner' in my home)*
		Sum of "QoL" scores= **points**

Additional	14	**Please indicate whether you have the followings today:**		
		Menstruation *(women's monthly period)* ?	☐ No	☐ Yes
		Premenstrual symptoms?	☐ No	☐ Yes
		Symptoms of the menopause ?	☐ No	☐ Yes
		Are you pregnant?	☐ No	☐ Yes
		Do you have diabetes mellitus *(sugar diabetes)* ?	☐ No	☐ Yes

Figure 1. The English version of the ACSS questionnaire

3.2.1. The translation and linguistic validation of the Hungarian Acute Cystitis Symptom Score (Paper III)

The translation and validation of the Hungarian version of the ACSS were performed in line with the Linguistic Validation Manual for Patient-Reported Outcomes (PRO) Instruments Guidelines [27]. The validated Russian version of the ACSS was taken as a source, with the English version as a reference to create the corrected Hungarian version [26]. The process is demonstrated in Figure 2.

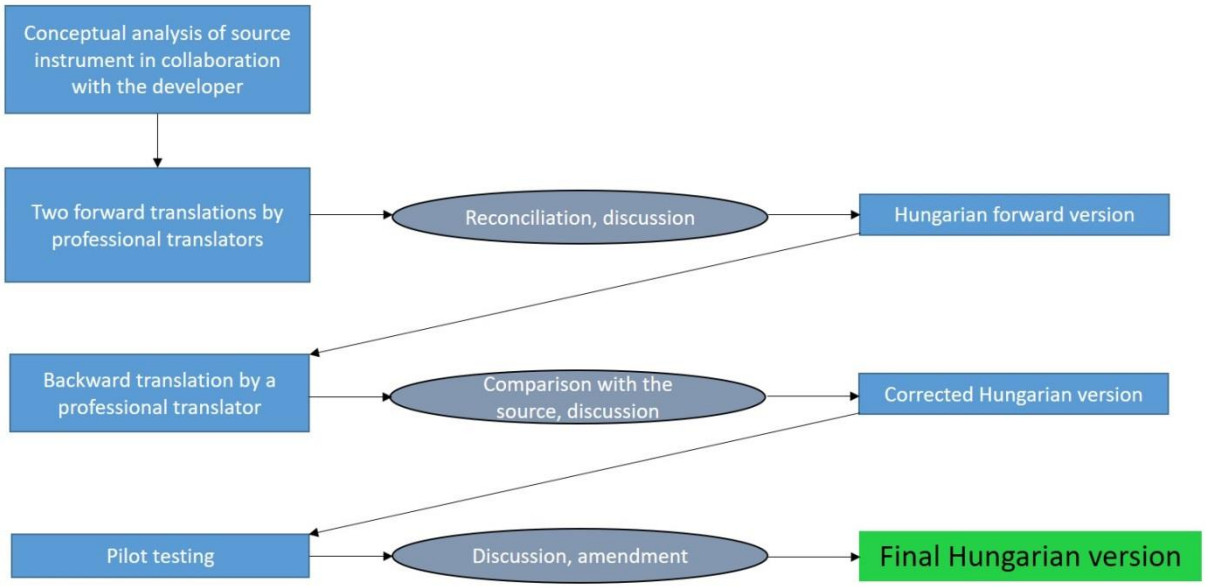


Figure 2. Diagram of the process of the translation and linguistic validation

A pilot test of the corrected provisional Hungarian version of the ACSS was carried out in 6 female respondents who had experienced AUC in their history at least once. The notes of the patients were then discussed, and the final version of the questionnaire was created.

3.2.2. Clinical diagnostic validation of the Hungarian version

3.2.2.1. Recruitment, data acquisition

The study was performed between September 2015 and February 2016 in the urological outpatient clinic of Jahn Ferenc South Pest Educational Hospital. Females aged ≥18 years old diagnosed with AUC were enrolled as "Patients" along with healthy women as "Controls". The diagnosis was made in accordance with the EAU guidelines by the treating physician in agreement with the investigators [8]. Besides the standard urological examinations, the patients were also invited to fill in the ACSS questionnaire (Part A). The treatment was also performed in accordance with the actual EAU guidelines. In addition, the patients were advised to come for a test of cure (ToC) visit after finishing the prescribed therapy. On the ToC visit they filled out Part B of the questionnaire. All results were registered using the latest version of a specific client software (e-USQOLAT) [28].

3.2.2.2. Statistical analysis

Data obtained from the ACSS survey were analyzed by the same statician using similar methodology published in previous ACSS validation studies with other languages [14, 29-33].

Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 21.0. IBM, GmbH, Ehningen, Germany) was used for the calculations. The analysis involved calculations of the ordinary descriptive statistical values (average values such as means and medians), evaluation of predictive values and responsiveness (sensitivity, specificity). Differences between variables were measured using standard deviations and 95% confidence intervals (95% CI). Statistical significance of differences was evaluated using p-value. Substantive significance was estimated via effect size calculation by correlation coefficient (rho) and Cohen's d. The statistical power was assessed using Wilks' lambda. Treatment success and non-success rates were defined using individual criteria. The definitions along with the results are presented in Table 11.

3.2.2.3. Approval of the ethical committee

The research was performed in accordance with the ethical standards of the 1964 Helsinki declaration. It was approved by the Local Ethical Committee of the institute and the national Medical Research Council (ETT-TUKEB) on 24th February 2015 (Approval number: 34/2015.–6423/2015/EKU). Before enrollment, all participants were asked to sign a written patient informed consent.

3.2.3. International assessment of the ACSS as a diagnostic tool (Paper IV)

For the clinical diagnosis of patients with AUC, the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have proposed "draft" guidelines for further discussion: a) Adult-adolescent females with pyuria (WBC ≥ 10/μL) and at least two of the following signs or symptoms of **dysuria, urinary frequency, urinary urgency, and suprapubic pain** (FDA) [34]; b) Female patients with documented pyuria (WBC ≥ 10/μL) and having a minimum number of symptoms such as **frequency, urgency, and dysuria** (EMA) [35].

In this non-interventional, case-control study we aimed to reassess the diagnostic values of these proposed draft guidelines using the Acute Cystitis Symptom Score (ACSS) and to evaluate its diagnostic accuracy in comparison with the latest FDA and EMA draft guidelines for the diagnosis of AUC. The data of 916 female respondents derived from the database obtained during the previous international multi-center validation studies were analysed. Results from the "Typical" domain of the ACSS were used in this study, since all information

essential for our purpose, concerning symptomatology, can be found on this domain. In the recent analysis the diagnosis made by the treating physician was taken as a reference. The decision was made based on the history and the results of the laboratory findings in accordance with the national and international standards and guidelines [8, 36, 37].

The diagnostic value of the ACSS at a cut-off score of 6 was calculated and compared with the diagnostic approaches proposed by the EMA and FDA. The statistical analysis was performed by a professional statistician. The data processing included dichotomization of variables for assessment of the diagnostic values. In the case of diagnostic criteria proposed by the FDA and EMA, the responses of the “Typical” domain were dichotomized as “Positive” or “Negative”, depending on the presence or absence of the symptoms. While in the case of the ACSS the summary of the symptom score from the “Typical” domain was relevant for the calculations. Sensitivity, specificity, positive and negative likelihood ratios (+LR and −LR, respectively), positive and negative predictive values (PPV and NPV respectively), Youden’s J-index, diagnostic odds ratio (DOR) were then calculated. ROC-curve analysis was used for the assessment of the area under the curve. A p-value of <0.05 was considered statistically significant.

3.2.4. Evaluation of the ACSS as a follow-up instrument (Paper V)

Paper V can be considered as the second part of Paper IV. In this publication the ACSS was tested further to reveal its use as a patient reported outcome measure (PROM) instrument for clinical studies as compared to the recently published FDA and EMA guidelines [34, 35]. For data mining the same database was used as in the previous study. One hundred thirty-four cases of female patients with diagnosed AUC and having sufficient data on follow-up visits, were included in the current analysis. The patients were selected according to the following inclusion criteria: 1) a summary score of “Typical” domain of 6 and more; 2) at least one follow-up evaluation after the baseline visit; 3) no missing values in the ACSS questionnaire data. The diagnosis of AUC was made by the treating physician. The treatment was performed in accordance with the national and international urological guidelines [7, 8]. Only the outcome, but not the treatment modalities, were taken into consideration in the analysis of this non-interventional study. The follow-up "visits" were grouped depending on the time difference between the first diagnostic and the follow-up visits. Data collected using both Part A and B of

the ACSS questionnaire were analyzed in this study. The results from the "Typical", "QoL", and “Dynamic” domains of the ACSS were compared with the latest criteria for the diagnosis and overall clinical assessment proposed by the FDA and EMA [34, 35]. Depending on the presence and absence of the symptoms and their severity, the items were dichotomized as positive or negative. In the „Dynamics” domain, the dichotomized responses "yes I feel normal" and "yes I feel much better" were considered as resolution of symptoms.

To determine clinical cure, 8 different thresholds were defined and weighted against each other (Table 2). The "G" and "H" criteria were adopted from the draft FDA and EMA guidelines, the rest were related to the ACSS items. Clinical cure was considered only in patients with no visible blood in the urine.

Table 2. The eight predetermined thresholds for evaluation of clinical cure at the outcome

A	A summary score of the “Typical” domain up to 5 AND no visible blood in the urine
B	A summary score of the “Typical” domain up to 4 AND no visible blood in the urine
C	A summary score of the “Typical” domain up to 5 AND no “Typical” item > 1 (mild) AND no visible blood in the urine
D	A summary score of the “Typical” domain up to 4 AND no “Typical” item > 1 (mild) AND no visible blood in the urine
E	A summary score of the “Typical” domain up to 5 AND no “Typical” item > 1 (mild) AND no visible blood in the urine AND no “QoL” item > 1
F	A summary score of the “Typical” domain up to 4 AND no “Typical” item > 1 AND no visible blood in the urine AND no “QoL” item > 1
G	A summary score of the four FDA symptoms up to 4 AND no score > 1 (mild) AND no visible blood in the urine
H	A summary score of the three EMA symptoms up to 3 AND no score > 1 (mild) AND no visible blood in the urine

4. RESULTS

4.1. Results of surveillance (Papers I-II)

4.1.1. Bacterial spectrum

During the 14-year-long period, a total of 3 513 urine cultures showing a significant presence of uropathogens were analyzed. *Escherichia coli* was the most prevalent pathogen in the entire study period. It averaged about 48% of the samples, with the highest percentage of 56% in 2008, and the lowest of 39% in 2016. The rate of *Enterococcus faecalis* has significantly increased (from 15% in 2004 to 26% in 2017, p<0,0001). The prevalence of *K. pneumoniae* did not vary during the years, with an average of 11% (p=0.797). The percentage of *P. aeruginosa* showed a slight increase (p=0.044), while the prevalence of *Proteus mirabilis*

remained constant (p=0.382). However, the rate of both bacteria remained under 10%. The spectrum of the cultured bacteria in our department is shown in Figure 3.

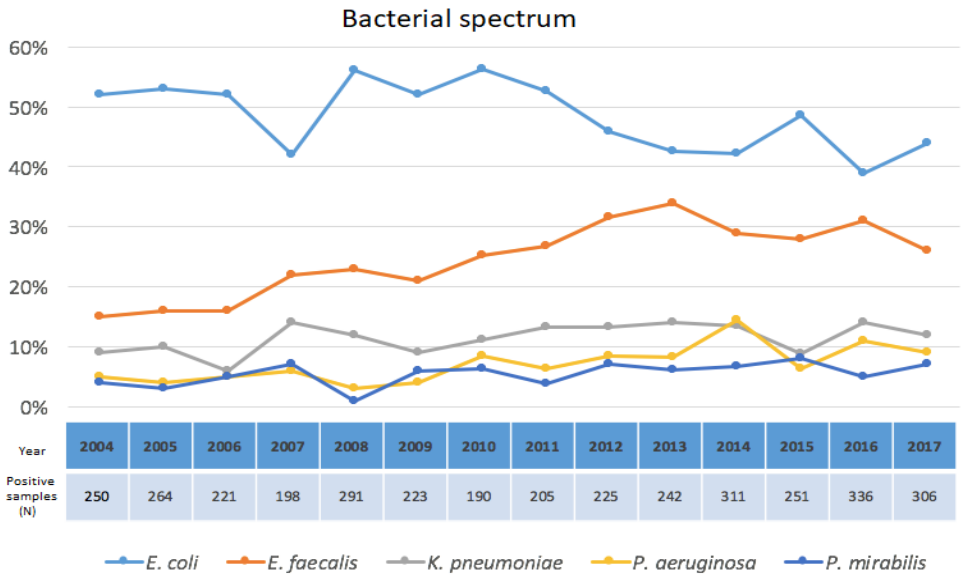


Figure 3. The prevalence of five most commonly cultured bacteria in 3 513 urine samples

4.1.2. Resistance patterns

4.1.2.1. Fluoroquinolones (Table 3)

The ciprofloxacin resistance in *E. coli* has significantly increased from 19% (25/130) to 25% during the 14 years (p=0.039), while in *K. pneumoniae* it was varying between 26% to 59%. In the case of *E. faecalis* the resistance to ciprofloxacin consistently remained above 47%, while for levofloxacin it ranged between 30-42%. The resistance of *P. aeruginosa* versus ciprofloxacin and levofloxacin showed a decreasing tendency during the studied years. However, the decrease was not statistically significant: in the case of ciprofloxacin: 38%→15% (p=0.086), while in levofloxacin: 38%→19% (p=0.09). Resistance against ciprofloxacin in *P. mirabilis* varied between 10% and 44%.

Table 3. Resistance rates against fluoroquinolones (ciprofloxacin and levofloxacin) between 2004 and 2017

Ciprofloxacin resistance											Levofloxacin resistance					
Year	*E. coli*		*E. faecalis*		*K. pneumoniae*		*P. aeruginosa*		*P. mirabilis*		*E. coli*		*E. faecalis*		*P. aeruginosa*	
	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)
2004	19	(25/130)	100	(38/38)	ND		38	(5/13)	ND		0	(0/22)	ND		38	(5/13)
2005	18	(25/140)	100	(42/42)	ND		27	(3/11)	ND		0	(0/12)	ND		40	(4/10)
2006	22	(25/115)	97	(34/35)	ND		36	(4/11)	ND		14	(1/7)	ND		40	(4/10)
2007	27	(22/83)	100	(44/44)	ND		33	(4/12)	ND		12	(2/17)	ND		33	(4/12)
2008	15	(24/156)	52	(34/66)	34	(11/32)	14	(1/7)	50	(2/4)	12	(2/17)	ND		17	(1/6)
2009	24	(28/116)	96	(45/47)	30	(6/20)	22	(2/9)	38	(5/13)	9	(1/11)	ND		25	(2/8)
2010	22	(24/107)	47	(22/47)	29	(6/21)	19	(3/16)	33	(4/12)	0	(0/13)	ND		13	(2/15)
2011	32	(34/108)	56	(31/55)	26	(7/27)	15	(2/13)	13	(1/8)	0	(0/15)	ND		15	(2/13)
2012	24	(25/103)	50	(9/18)	59	(17/29)	16	(3/19)	44	(7/16)	0	(0/25)	ND		38	(6/16)
2013	22	(23/103)	ND		32	(11/34)	5	(1/20)	13	(2/15)	ND		ND		5	(1/20)
2014	25	(33/131)	ND		29	(12/42)	22	(10/45)	19	(4/21)	ND		41	(24/59)	22	(10/45)
2015	25	(31/122)	ND		50	(11/22)	13	(2/16)	10	(2/20)	ND		40	(26/65)	19	(3/16)
2016	24	(31/131)	ND		49	(24/49)	26	(10/38)	24	(4/17)	ND		42	(42/100)	28	(10/35)
2017	25	(33/131)	ND		51	(19/37)	15	(4/27)	21	(4/19)	ND		30	(22/73)	19	(5/27)

ND = not determined

4.1.2.2. Penicillin derivatives (Table 4)

Resistance to ampicillin remained stable in the case of *E. coli* (2004: 57%, 2017: 54%), *E. faecalis* (between 0-2%), and *K. pneumoniae* (100%). In *P. mirabilis* it showed a statistically significant increase (p=0.007) from 20% to 40% until 2015, however afterwards a slight decrease could be detected.

Against amoxicillin/clavulanic acid resistance of *E. coli* varied between 6% and 35%. The resistance of *K. pneumoniae* increased significantly (p<0.0001) from 17% to 62%. Resistance to amoxicillin/clavulanic acid in *P. mirabilis* mostly remained under 10%.

Table 4. Resistance rates against penicillin derivates (ampicillin and amoxicillin/clavulanic acid) between 2004 and 2017

Ampicillin resistance									Amoxicillin/clavulanic acid resistance					
Year	*E. coli*		*E. faecalis*		*K. pneumoniae*		*P. mirabilis*		*E. coli*		*K. pneumoniae*		*P. mirabilis*	
	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)
2004	57	(74/130)	0	(0/38)	100	(23/23)	20	(2/10)	23	(30/130)	17	(4/23)	10	(1/10)
2005	40	(56/140)	0	(0/42)	88	(23/26)	25	(2/8)	14	(20/140)	19	(5/26)	0	(0/8)
2006	53	(61/115)	0	(0/35)	100	(13/13)	18	(2/11)	28	(32/115)	23	(3/13)	9	(1/11)
2007	48	(40/83)	2	(1/44)	100	(28/28)	21	(3/14)	18	(15/83)	14	(4/28)	7	(1/14)
2008	49	(76/156)	0	(0/66)	100	(33/33)	50	(2/4)	6	(10/156)	6	(2/33)	25	(1/4)
2009	52	(60/116)	0	(0/47)	100	(20/20)	23	(3/13)	19	(22/116)	15	(3/20)	8	(1/13)
2010	67	(72/107)	0	(0/47)	100	(21/21)	33	(4/12)	17	(18/107)	33	(7/21)	0	(0/12)
2011	57	(61/107)	2	(1/55)	100	(27/27)	38	(3/8)	23	(25/107)	26	(7/27)	13	(1/8)
2012	52	(53/103)	0	(0/71)	100	(29/29)	44	(7/16)	15	(15/103)	57	(17/30)	0	(0/16)
2013	45	(46/103)	1	(1/82)	100	(34/34)	53	(8/15)	14	(14/103)	47	(16/34)	7	(1/15)
2014	60	(78/131)	0	(0/90)	100	(42/42)	52	(11/21)	35	(46/131)	38	(16/42)	19	(4/21)
2015	54	(66/122)	0	(0/70)	100	(22/22)	40	(8/20)	28	(34/122)	59	(13/22)	5	(1/20)
2016	54	(71/132)	2	(2/105)	100	(49/49)	35	(6/17)	18	(24/132)	53	(26/49)	6	(1/17)
2017	54	(72/133)	0	(0/79)	100	(37/37)	32	(6/19)	26	(35/133)	62	(23/37)	11	(2/19)

4.1.2.3. Carbapenems (Table 5)

In *E. coli, K. Pneumoniae*, *E. faecalis*, and *P. mirabilis*, no resistance was observed to imipenem, meropenem, and ertapenem during the examined years. The resistance of *P. aeruginosa*, however, showed a significant increase (p=0.004) versus imipenem, from 6% in 2010 to 19% in 2017.

Table 5. Resistance rates against imipenem between 2008 and 2017

Imipenem resistance

Year	*E. coli*		*E. faecalis*		*K. pneumoniae*		*P. aeruginosa*		*P. mirabilis*	
	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)
2008	0	(0/156)		ND	0	(0/33)	0	(0/7)	25	(1/4)
2009	0	(0/116)		ND	0	(0/20)	0	(0/9)	15	(2/13)
2010	0	(0/107)		ND	0	(0/21)	6	(1/16)	0	(0/12)
2011	0	(0/108)		ND	0	(0/27)	15	(2/13)	0	(0/8)
2012	0	(0/101)	0	(0/14)	0	(0/30)	5	(1/19)	0	(0/16)
2013	0	(0/103)	0	(0/9)	0	(0/32)	5	(1/20)	0	(0/15)
2014	0	(0/131)	0	(0/10)	0	(0/42)	16	(7/45)	0	(0/21)
2015	0	(0/122)	0	(0/49)	0	(0/22)	27	(4/15)	0	(0/19)
2016	0	(0/132)	1	(1/105)	0	(0/49)	26	(10/38)	0	(0/2)
2017	0	(0/132)	0	(0/78)	0	(0/36)	19	(5/27)		ND

ND – not determined

4.1.2.4. Cephalosporins (Table 6)

The resistance of *E. coli* to cefuroxime slightly but not significantly increased from 8% to 14% (p=0.741). Resistance to cefuroxime in *K. pneumoniae* fluctuated between 24% and 60%. In *P. mirabilis*, resistance to cefuroxime did not increase above 8%.

In the case of *E. coli* resistance to cefixime remained under 14%, while in *P. mirabilis* basically no resistant strain was detected (except in 2017, where a 16% resistance rate was observed). In *K. pneumoniae*, resistance to cefixime increased from 2010: 29% to 2017: 51%, however, the change was not statistically significant (p=0.075).

In *E. coli* resistance to ceftriaxone significantly increased from 1%→12% (p<0.0001) by the end of the studied period, while in *K. pneumoniae* the resistance rates varied between 24% and 57%. The cultured *P. mirabilis* strains did not show resistance to ceftriaxone and ceftazidime. Resistance to ceftazidime in the case of *P. aeruginosa* ranged between 0% to 16%.

The resistance of *E. coli* to cefepime increased from 1% in 2004 to 8% in 2012 (p<0.0001). In 2012 resistance of *K. pneumoniae* to cefepime reached 40%. As for *P. aeruginosa* and *P. mirabilis* the resistance to cefepime decreased from 15% to 4% and from 10% to 0% respectively, however, the changes were statistically not significant (p=0.45 and p=0.331).

Table 6. Resistance rates against cephalosporins (cefuroxime, ceftriaxone, cefixime, ceftazidime and cefepime) between 2004 and 2017

Cefuroxime resistance							Ceftriaxone resistance						Cefixime resistance					
Year	*E. coli*		*K. pneumoniae*		*P. mirabilis*		*E. coli*		*K. pneumoniae*		*P. mirabilis*		*E. coli*		*K. pneumoniae*		*P. mirabilis*	
	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)
2004	8	(9/107)	29	(6/21)	8	(1/12)	1	(1/129)	0	(0/23)	0	(0/10)		ND		ND		ND
2005	18	(19/108)	30	(8/27)	0	(0/8)	0	(0/140)	4	(1/26)	0	(0/8)		ND		ND		ND
2006	8	(8/103)	60	(18/30)	6	(1/16)	1	(1/115)	0	(0/13)	9	(1/11)		ND		ND		ND
2007	7	(7/103)	32	(11/34)	0	(0/15)	2	(2/83)	0	(0/28)	0	(0/14)		ND		ND		ND
2008	10	(13/131)	24	(10/42)	0	(0/21)	0	(0/156)	0	(0/33)	0	(0/4)	0	(0/1)		ND	0	(0/4)
2009	12	(15/122)	50	(11/22)	0	(0/20)	5	(6/115)	0	(0/20)	0	(0/13)	4	(5/116)		ND	0	(0/13)
2010	8	(9/107)	29	(6/21)	8	(1/12)	9	(9/106)	29	(6/21)	0	(0/12)	8	(8/106)	29	(6/21)	0	(0/12)
2011	18	(19/108)	30	(8/27)	0	(0/8)	16	(17/108)	26	(7/27)	0	(0/8)	14	(15/106)	26	(7/27)	0	(0/8)
2012	8	(8/103)	60	(18/30)	6	(1/16)	6	(6/103)	57	(17/30)	0	(0/16)	7	(2/25)	57	(17/30)	0	(0/16)
2013	7	(7/103)	32	(11/34)	0	(0/15)	7	(7/103)	32	(11/34)	0	(0/15)	7	(7/101)	32	(11/34)	0	(0/15)
2014	10	(13/131)	24	(10/42)	0	(0/21)	9	(12/131)	24	(10/42)	0	(0/21)	9	(11/128)	24	(10/42)	0	(0/20)
2015	12	(15/122)	50	(11/22)	0	(0/20)	8	(10/122)	46	(10/22)	0	(0/20)	10	(12/122)	48	(10/21)	0	(0/20)
2016	10	(13/132)	43	(21/49)	0	(0/17)	8	(10/122)	43	(21/49)	0	(0/17)	10	(13/131)	44	(21/48)	0	(0/17)
2017	14	(18/132)	58	(21/36)	0	(0/19)	12	(16/133)	51	(19/37)	0	(0/19)	12	(16/133)	51	(19/37)	16	(3/19)

Ceftazidime resistance									Cefepime resistance							
Year	*E. coli*		*K. pneumoniae*		*P. aeruginosa*		*P. mirabilis*		*E. coli*		*K. pneumoniae*		*P. aeruginosa*		*P. mirabilis*	
	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)
2004		ND		ND		ND		ND	1	(1/129)	0	(0/23)	15	(2/13)	10	(1/10)
2005		ND		ND		ND		ND	0	(0/139)	0	(0/26)	9	(1/11)	0	(0/8)
2006		ND		ND		ND		ND	2	(2/114)	0	(0/13)	9	(1/11)	9	(1/11)
2007		ND		ND		ND		ND	2	(2/83)	0	(0/28)	0	(0/12)	0	(0/14)
2008	0	(0/156)	0	(0/33)	0	(0/7)	0	(0/4)	0	(0/156)	0	(0/33)	0	(0/7)	0	(0/4)
2009	5	(6/116)	15	(3/20)	11	(1/9)	0	(0/13)	7	(8/116)	0	(0/20)	11	(1/9)	15	(2/13)
2010	9	(9/106)	29	(6/21)	13	(2/16)	0	(0/12)	8	(8/106)	29	(6/21)	13	(2/16)	0	(0/12)
2011	16	(17/108)	26	(7/27)	8	(1/13)	0	(0/8)	16	(17/108)	26	(7/27)	8	(1/13)	0	(0/8)
2012	6	(6/100)	59	(17/29)	16	(3/19)	0	(0/16)	8	(8/103)	40	(4/10)	12	(2/17)	0	(0/16)
2013	7	(7/103)	32	(11/34)	0	(0/20)	0	(0/15)		ND	33	(4/12)	0	(0/20)		ND
2014	9	(11/129)	22	(9/41)	13	(6/45)	0	(0/21)		ND	100	(1/1)	7	(3/45)		ND
2015	8	(10/122)	46	(10/22)	6	(1/16)	0	(0/20)		ND		ND	6	(1/16)		ND
2016	8	(10/132)	43	(21/49)	16	(6/38)	0	(0/17)		ND		ND	9	(3/35)		ND
2017	12	(16/133)	51	(19/37)	11	(3/27)	0	(0/19)		ND		ND	4	(1/25)		ND

ND – not determined

4.1.2.5. Aminoglycosides (Table 7)

Resistance of *E. coli* to gentamicin remained bellow 7%, furthermore, decreasing resistance rates could be observed in *E. faecalis (*from 100% to 48%), in *P. aeruginosa (*from 31% to 7%) and in *P. mirabilis (*from 30% to 12%). The changes were statistically significant ($p<0.0001$, $p=0.013$, $p=0.002$ respectively). However, the resistance of *K. pneumoniae* to gentamicin significantly increased ($p<0.0001$) from 0% to 37%.

The resistance rate of *E. coli* to amikacin has also decreased (2004: 4% →2011: 0%). The decline was statistically significant (p=0,003). The resistance of *P. aeruginosa* did not surpass 6% in the last 11 years, while in *K. pneumoniae* and *P. mirabilis* no resistance was found to amikacin.

Table 7. Resistance rates against aminoglycosides (gentamicin and amikacin) between 2004 and 2017

	Gentamicin resistance										Amikacin resistance							
Year	*E. coli*		*E. faecalis*		*K. pneumoniae*		*P. aeruginosa*		*P. mirabilis*		*E. coli*		*K. pneumoniae*		*P. aeruginosa*		*P. mirabilis*	
	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)
2004	6	(8/130)	100	(38/38)	0	(0/23)	31	(4/13)	30	(3/10)	4	(5/130)		ND	0	(0/13)		ND
2005	7	(10/140)	100	(42/42)	4	(1/26)	36	(4/11)	38	(3/8)	3	(4/140)		ND	0	(0/11)		ND
2006	4	(5/115)	100	(35/35)	0	(0/13)	45	(5/11)	45	(5/11)	1	(1/115)		ND	18	(2/11)		ND
2007	5	(4/83)	100	(44/44)	4	(1/28)	33	(4/12)	29	(4/14)	7	(6/83)		ND	0	(0/12)		ND
2008	0	(0/156)	53	(35/66)	0	(0/33)	0	(0/7)	25	(1/4)	0	(0/7)	0	(0/2	0	(0/7)	0	(0/1)
2009	4	(5/116)	100	(47/47)	0	(0/20)	22	(2/9)	15	(2/13)	0	(0/116)	0	(0/20)	0	(0/9)	0	(0/13)
2010	4	(4/107)	38	(18/47)	24	(5/21)	0	(0/16)	8	(1/12)	0	(0/107)	0	(0/21)	0	(0/16)	0	(0/12)
2011	3	(3/108)	38	(21/55)	30	(8/27)	15	(2/13)	0	(0/8)	0	(0/108)	0	(0/27)	0	(0/13)	0	(0/8)
2012	1	(1/72)	53	(38/71)	36	(10/28)	21	(4/19)	6	(1/16)	0	(0/21)	10	(1/10)	0	(0/19)	0	(0/5)
2013	2	(2/103)	44	(36/82)	21	(7/34)	5	(1/20)	20	(3/15)	0	(0/1)	0	(0/3)	5	(1/20)	0	(0/4)
2014	5	(6/131)	50	(45/90)	2	(1/42)	18	(8/45)	14	(3/21)	0	(0/3)	0	(0/1)	2	(1/45)	0	(0/1)
2015	6	(7/122)	50	(35/70)	36	(8/22)	13	(2/16)	15	(3/20)	0	(0/1)	0	(0/1)	6	(1/16)	0	(0/2)
2016	6	(8/132)	49	(51/105)	25	(12/49)	21	(8/38)	0	(0/17)	0	(0/1)	0	(0/1)	3	(1/37)		ND
2017	2	(2/133)	48	(38/79)	32	(12/37)	7	(2/27)	12	(2/17)		ND		ND	0	(0/25)		ND

ND – not determined

4.1.2.6. Sulfamethoxazole/trimethoprim (Table 8)

In *E. coli*, resistance rates ranged between 19% and 35%, while in the case of *K. pneumoniae*, it has significantly increased from 13% in 2004 to 44% in 2017 ($p<0.0001$).

4.1.2.7. Nitrofurantoin (Table 8)

In *E. coli*, the resistance did not rise above 2%, whereas in *K. pneumoniae* and *P. mirabilis* it reached 100%.

Table 8. Resistance rates against sulfamethoxazole/trimethoprim and nitrofurantoin between 2004 and 2017

	Sulfamethoxazole/trimethoprim resistance								Nitrofurantoin resistance							
Year	*E. coli*		*E. faecalis*		*K. pneumoniae*		*P. mirabilis*		*E. coli*		*E. faecalis*		*K. pneumoniae*		*P. mirabilis*	
	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)
2004	19	(24/128)	13	(5/38)	13	(3/23)	20	(2/10)	2	(3/129)	0	(0/38)		ND		ND
2005	19	(27/140)	24	(10/42)	15	(4/26)	38	(3/8)	1	(1/140)	5	(2/42)		ND		ND
2006	24	(28/115)	29	(10/35)	8	(1/13)	27	(3/11)	2	(2/115)	0	(0/35)		ND		ND
2007	29	(24/82)	32	(14/44)	4	(1/28)	29	(4/14)	2	(2/82)	2	(1/44)		ND		ND
2008	26	(41/156)	33	(22/66)	21	(7/33)	50	(2/4)	1	(1/153)	0	(0/66)	18	(6/33)	100	(4/4)
2009	28	(33/116)	23	(11/47)	6	(1/16)	33	(4/12)	2	(2/116)	2	(1/45)	47	(9/19)	100	(13/13)
2010	30	(31/105)		ND	16	(3/19)	33	(4/12)	1	(1/106)	0	(0/46)	71	(15/21)	100	(12/12)
2011	31	(32/102)		ND	22	(6/27)	57	(4/7)	0	(0/55)	0	(0/18)	31	(4/13)	100	(4/4)
2012	23	(23/102)		ND	63	(19/30)	63	(10/16)	0	(0/65)	0	(0/46)	90	(18/20)	100	(9/9)
2013	19	(18/95)		ND	28	(9/32)	29	(4/14)	1	(1/100)	0	(0/81)	91	(31/34)	100	(15/15)
2014	25	(33/131)		ND	14	(6/42)	33	(7/21)	0	(0/128)	0	(0/89)	100	(41/41)	100	(20/20)
2015	19	(22/118)		ND	36	(8/22)	50	(8/16)	0	(0/121)	0	(0/70)	100	(21/21)	100	(20/20)
2016	32	(42/132)		ND	49	(24/49)	24	(4/17)	0	(0/131)	1	(1/103)	100	(48/48)	100	(17/17)
2017	27	(34/127)		ND	44	(16/36)	47	(9/19)	0	(0/128)	0	(0/79)	100	(37/37)	100	(18/18)

ND – not determined

4.1.2.8. Fosfomycin

Fosfomycin resistance was tested between 2010 and 2012 for *E. coli*, *K. pneumoniae* and *P. mirabilis*. Relatively low resistance rates were found: 0% to 5% in *E. coli*, 0% to 15% in *K. pneumoniae* and 0% to 14% in *P. mirabilis*:).

4.1.2.9. Polymixin, Vancomycin, Tobramycin, Piperacillin/tazobactam

No resistance to polymixin was observed in *E. coli*, *K. pneumoniae*, and *P. aeruginosa*, whereas in *P. mirabilis* strains the resistance was practically 100%.

In the case of *E. faecalis*, no vancomycin resistance was found during the whole study period. *P. aeruginosa* showed 0-8% resistance to colistin, 0-16% to tobramycin, while for piperacillin/tazobactam, its resistance reached 12% in 2017.

4.1.3. Multidrug-resistant species

The incidence of MDR bacteria significantly increased (p=0.008) from 8% (23/279) to 14% (42/305). Table 9(a) presents combined data on all MDR species since 2013.

No significant increase in ESBL-positive cases was observed between 2010 to 2015 (in ESBL-producing *E. coli*: p=0.96; *K. pneumoniae*: p=0.791). The results are presented in Table 9(b).

The rate of ESBL-positive strains among *K. pneumoniae* varied between 24% (7/29) to 33% (10/30). An exceptional peak of 60% (18/30) was observed in 2012.

In the last six years, 6% (7/110) to 9% (12/129) of cultured *E. coli* strains were ESBL-positive, with a highest rate of 15% (16/108) in 2011.

Table 9. Multidrug-resistant species (MDR MRSA, VRE, MRAB, Gram-negative and ESBL-positive species) between 2010/2013 and 2015

(a) MDR species

Year	MRSA		VRE		MRAB		Gram-negatives*		All	
	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)
2013	31	(4/13)	0	(0/85)	100	(1/1)	10	(18/180)	8	(23/279)
2014	40	(2/5)	0	(0/91)	25	(1/4)	9	(23/248)	7	(26/348)
2015	80	(8/10)	0	(0/82)	100	(2/2)	15	(32/211)	14	(42/305)

(b) ESBL-producing species

Year	*Escherichia coli*		*Klebsiella pneumoniae*	
	%	(*n*/*N*)	%	(*n*/*N*)
2010	6	(7/110)	27	(6/22)
2011	15	(16/108)	24	(7/29)
2012	6	(6/103)	60	(18/30)
2013	6	(6/105)	32	(11/34)
2014	9	(12/131)	24	(10/42)
2015	9	(12/129)	33	(10/30)

4.1.4. Comparison with the international results

According to the results from the GPIU [21, 25], the most frequent pathogens in our region were *E. coli* (36%) and *Enterococcus species* (14%)[25]. In our department about the half of the cultured bacteria were *E. coli*.

In the GPIU study the average resistance of *E. coli* to ciprofloxacin was 45% which did not change significantly with time. In our department, however, the resistance to ciprofloxacin in *E. coli* has increased from 19% to 25% (p=0.039).

In the GPIU study the global resistance rate of all uropathogens versus ciprofloxacin rose over 50%, while according to our data only *E. faecalis* and *K. pneumoniae* could reach that level.

Both the GPIU study and our analysis found a high rate of resistance in the case of *K. pneumoniae* versus ciprofloxacin and cephalosporins. In our department the rate of ciprofloxacin resistant *K. pneumoniae* was ranging between 26-59%, while in the GPIU it reached 57% on average. The resistance of *K. pneumoniae* to cefuroxime in our department varied between 24-60%, while in the GPIU study it ranged from 46 to 81%.

4.1.5. Development of the local antibiotic use strategy

Based on our data we can not recommend the use of fluoroquinolones for empirical treatment of UTIs in our region. Carbapenems are safe, however should be saved for the treatment severe infections. In less severe UTIs sulfamethoxazole/trimethoprim, fosfomycin, and nitrofurantoin are good options, while the use of cephalosporins should be limited. Gentamicin may be considered if intravenous antibiotic treatment is indicated.

When selecting antibiotics for empirical treatment in the presence of urinary tract foreign bodies, the high rate of *E. faecalis (*reaching 26%) should be taken into account.

4.2. Results of the cystitis diagnostic research

4.2.1. Translation and linguistic validation of the Hungarian ACSS (Paper III)

The questionnaire: the translated and validated Hungarian version of the ACSS is shown in Figure 4.

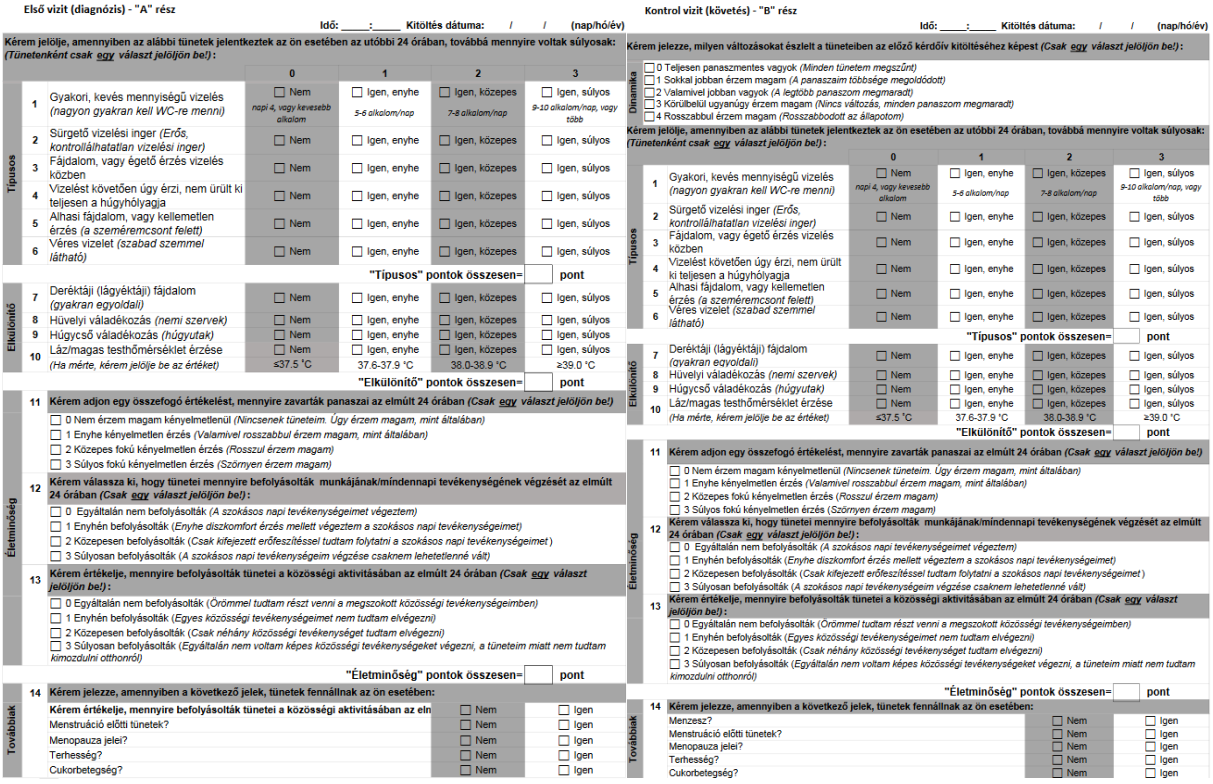


Figure 4. The Hungarian version of the ACSS questionnaire

Pilot test: the pilot test revealed that all six patients had found the Hungarian version of the ACSS to be understandable and the scale to be adequate and clear in that they could not have answered it more than one way. The feedback from the patients confirmed that the validation study might proceed.

4.2.2. Clinical diagnostic validation of the Hungarian ACSS

Demography: 37 healthy Controls and 31 Patients with AUC were included in the study. The mean age of the participants was 48 (19-85) for Controls and 42 for AUC Patients (18-78).

The most important results of the statistical analysis including statistical power and effect size analysis are presented in Table 10.

Table 10. Differences in scores of the different domains of the ACSS between groups of Patients and Controls and comparison between two visits

Typical scores	Controls	Patients	P value	Cohen's d/effect-size r (power)	Patients' Visit 1	Patients' Visit 2	P value	Cohen's d/effect-size r (power)
Number	37	31			23	23		
Range	0 to 9	3 to 16	<0.0001	3.20/0.85 (1.00)	6 to 16	0 to 9	<0.0001	3.52/0.87 (1.00)
Mean ±SD	0.84 ±1.79	9.42 ±3.33			9.86 ±2.89	1.05 ±2.04		
95% CI for Mean	0.24 to 1.43	8.20 to 10.64			8.54 to 11.17	0.12 to 1.97		
Median	0	10.00			10.00	0.00		
0.25 percentile	0	6.00			7.00	0.00		
0.75 percentile	1	11.00			11.00	1.25		
Differential scores	Controls	Patients	P value	Cohen's d/effect-size r (power)	Patients' Visit 1	Patients' Visit 2	P value	Cohen's d/effect-size r (power)
Range	0 to 2	0 to 5	<0.0001	0.94/0.43 (0.98)	0 to 4	0 to 2	0.021	0.65/0.31 (0.74)
Mean ±SD	0.11 ±0.46	1.03 ±1.30			0.86 ±1.11	0.29 ±0.56		
95% CI for Mean	-0.04 to 0.26	0.55 to 1.51			0.35 to 1.36	0.03 to 0.54		
Median	0	1.00			1.00	0.00		
0.25 percentile	0	0.00			0.00	0.00		
0.75 percentile	0	2.00			2.00	0.25		
Quality of Life (QoL) scores	Controls	Patients	P value	Cohen's d/effect-size r (power)	Patients' Visit 1	Patients' Visit 2	P value	Cohen's d/effect-size r (power)
Range	0 to 8	0 to 9	<0.0001	2.14/0.73 (1.00)	0 to 8	0 to 6	<0.0001	2.06/0.77 (1.00)
Mean ±SD	0.84 ±1.74	4.94 ±2.08			4.95 ±2.20	1.05 ±1.53		
95% CI for Mean	0.26 to 1.42	4.17 to 5.70			3.95 to 5.95	0.35 to 1.75		
Median	0	5.00			6.00	0.00		
0.25 percentile	0	6.00			3.00	0.00		
0.75 percentile	0.50	6.00			6.00	2.00		
Typical+QoL scores	Controls	Patients	P value	Cohen's d/effect-size r (power)	Patients' Visit 1	Patients' Visit 2	P value	Cohen's d/effect-size r (power)
Range	0 to 13	6 to 25	<0.0001	3.08/0.84 (1.00)	6 to 22	0 to 12	<0.0001	3.38/0.86 (1.00)
Mean ±SD	1.68 ±3.18	14.35 ±4.86			14.81 ±4.40	2.10 ±2.98		
95% CI for Mean	0.62 to 2.74	12.57 to 16.14			12.81 to 16.81	0.74 to 3.45		
Median	0	15.00			15.00	1.00		
0.25 percentile	0	10.00			11.00	0.00		
0.75 percentile	2.50	17.00			17.00	3.00		

Comparative analysis: The study found significant differences between the two groups in each domain of the questionnaire (Table 10). The findings from the comparative analysis of the typical symptom scores between the two groups are demonstrated in Figure 5.

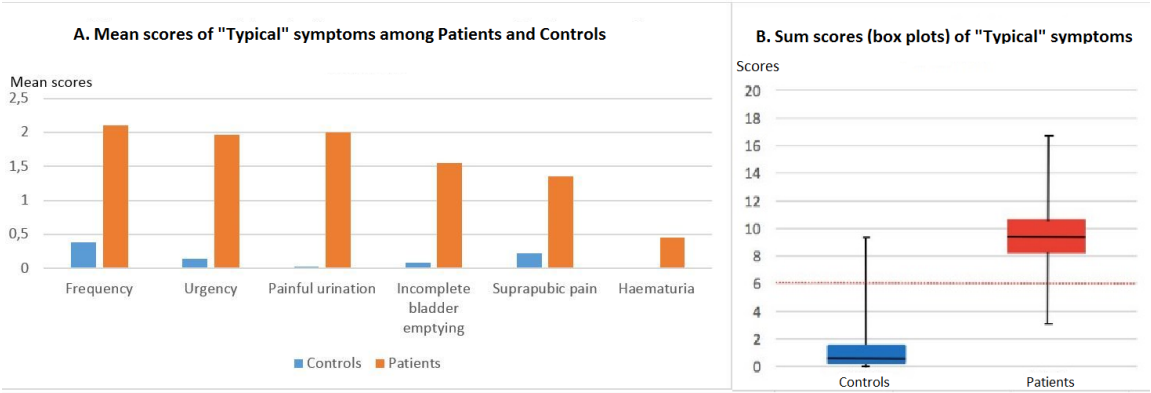


Figure 5. A: Mean score comparison of typical symptoms between Patients and Controls; **B:** Sum scores (box-and-whisker plots) of "Typical" symptoms among Patients and Controls with cut-off line

The most representative sign for AUC was painful urination, which was observed in 78% of the patients. For the prediction of AUC at cut-off score 6 of „Typical" domain, PPV and NPV were 96,55% and 92,31%, sensitivity and specificity were 90% and 97%, respectively.

Follow-up comparison: 74% of the patients came back for ToC visit, which was at day 15 on average. Sixty-one percent of the patients felt back to normal, and 30% felt much better. The results from comparative analysis of the ACSS scores between the two visits are demonstrated in Table 10.

The subanalysis of various possibilities to differentiate between treatment success and non-success is presented in Table 11. It can be seen that the „Typical" domain at a cut-off score of 4 or lower, is reliable to assess the effectiveness of the therapy, at the ToC visits.

Table 11. Rates of treatment success using different individual criteria

Mode	Domain(s)	Definition of Success (Scores)	Success N (%)	Non-Success N (%)
1	Dynamics	≤1	21 (91.3%)	2 (8.7%)
2	Main symptoms[a]	≤3, but no item >1 (mild)	20 (87%)	3 (13%)
3	Typicals	≤4, but no item >1 (mild)	20 (87%)	3 (13%)
4	QoL	≤3, but no item >1 (mild)	22 (95.7%)	1 (4.3%)
5	Typicals+QoL	≤7, but no item >1 (mild)	20 (87%)	3 (13%)
6	Typicals/ QoL	≤4/≤3, but no item >1 (mild)	20 (87%)	3 (13%)

[a] MAIN SYMPTOMS include TYPICALS 1–3 only: frequency, urgency, painful urination; QoL – Quality of Life; N – number

4.2.3. International assessment of the ACSS as a diagnostic tool (Paper IV)

Study population: Out of 916 patients 517 were enrolled for this comprehensive analysis. From the 68 Hungarian patients, 16 were selected in the analysis, based on having sufficient data for inclusion. The age of the participants ranged between 15 to 87 years (mean 34). There were no considerable demographic differences between the two groups. The numbers of Controls and Patients were 232 and 285 accordingly.

General assessment of the symptoms to reveal the diagnostic accuracy of the ACSS: The number of cases with positive "Typical" symptoms differed significantly between the Patients and Controls: median 5 (IQR of 0–3) vs 1 (IQR of 4–6), respectively ($p<0.001$; Figure 6). The scored severity of the "Typical" symptoms also differed significantly between the Patients and Controls: median 10 (IQR of 7-13) vs 1 (IQR of 0-4), respectively ($p<0.001$; Figure 7).

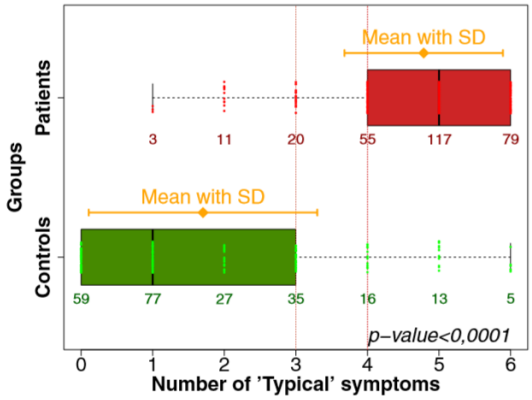


Figure 6. Boxplot diagram (IQR, range, mean±SD) on number of the ACSS typical symptoms in respondents (patients with AUC, Controls without AUC)

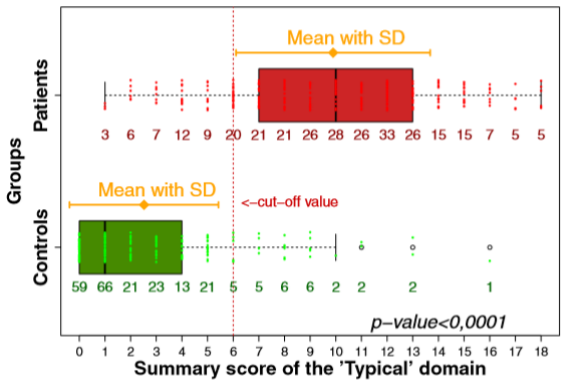


Figure 7. Boxplot diagram (IQR, range, mean±SD) on the summary score of the six ACSS typical symptoms in respondents (patients with AUC, controls without AUC)

The most common symptom was urinary frequency in both groups. Its prevalence was 72.92% for the entire study population, 47.84% among Controls, and 93.33% among Patients. Among the urinary frequency positive cases, most of the Controls had “mild” symptoms (81/111=72.97%), whereas the majority of Patients (189/266=71.05%) suffered from “moderate” or “severe” urinary frequency. The Youden’s index of the six ACSS typical symptoms according to presence and severity in the study population is presented in Figure 8. It can be seen that not only the presence of the symptoms but also their severity is important for the diagnosis.

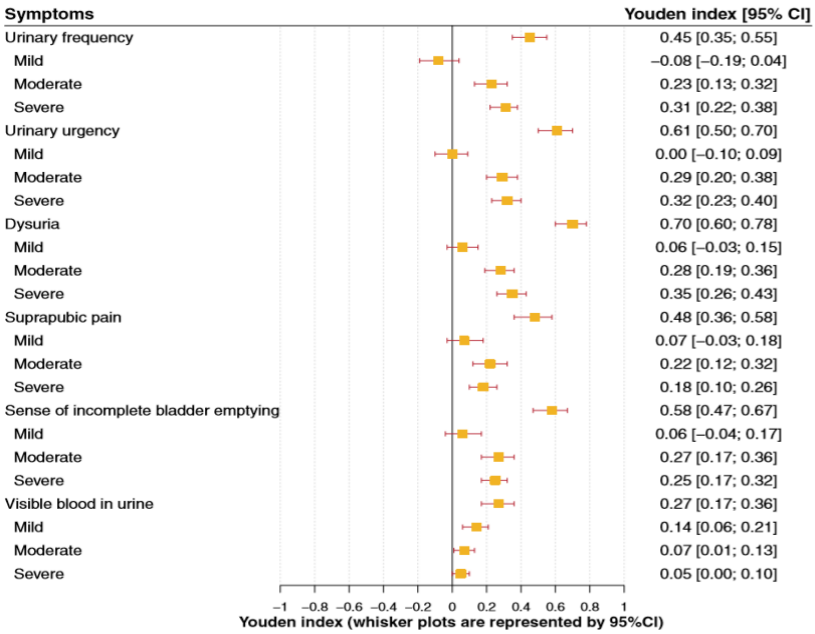


Figure 8. Youden’s index of the six ACSS typical symptoms according to presence and severity in the study population (patients with AUC and controls without AUC)

The sensitivity, specificity (average [95% CI]) and further diagnostic values of the different proposed approaches for diagnosing AUC are demonstrated in Table 12. The differences in diagnostic values between the three diagnostic approaches were statistically not significant ($p>0.05$).

Our data also show that if the cut-off value of the ACSS is combined with positive pyuria, then the sensitivity and specificity change to 0.73 [0.67; 0.78] and 0.96 [0.93; 0.98], respectively. Pyuria by itself had already a reasonable sensitivity [0.85 (0.80; 0.89)] and specificity [0.72 (0.66; 0.78)].

Table 12. Diagnostic accuracy of the different proposed approaches for acute cystitis. Average value [95% confidence interval]. PPV=positive predictive value, NPV=negative predictive value, +LR and –LR=positive and negative likelihood ratio, DOR= diagnostic odds ratio

Diagnostic criteria	Sensitivity	Specificity	PPV	NPV	+LR	-LR	DOR	Yourden's J index	Area-under-curve
Draft approach by EMA	0.84 [0.79; 0.88]	0.83 [0.77; 0.87]	0.86 [0.81; 0.90]	0.81 [0.75; 0.86]	4.88 [3.67; 6.50]	0.19 [0.14; 0.25]	25.60 [16.06; 40.81]	0.67 [0.57; 0.76]	0.83 [0.80; 0.87]
Draft approach by FDA	0.83 [0.78; 0.87]	0.88 [0.84; 0.92]	0.90 [0.85; 0.93]	0.81 [0.76; 0.86]	7.15 [4.99; 10.23]	0.19 [0.15; 0.25]	37.49 [22.57; 62.26]	0.71 [0.62; 0.80]	0.85 [0.82; 0.88]
ACSS at cut-off value of 6	0.87 [0.83; 0.91]	0.88 [0.83; 0.91]	0.90 [0.85; 0.93]	0.85 [0.79; 0.89]	6.96 [4.94; 9.81]	0.15 [0.11; 0.20]	46.92 [27.89; 78.94]	0.75 [0.65; 0.82]	0.87 [0.84; 090]

4.2.4. Evaluation of the ACSS as a follow-up instrument (Paper V)

One hundred thirty-four patients were selected for the analysis giving a total of 236 visits. Their mean age was 36 years. Summary scores of "Typical" domain of ACSS cathegorised based on the time difference between the baseline and follow-up visits are demonstrated in Figure 9.

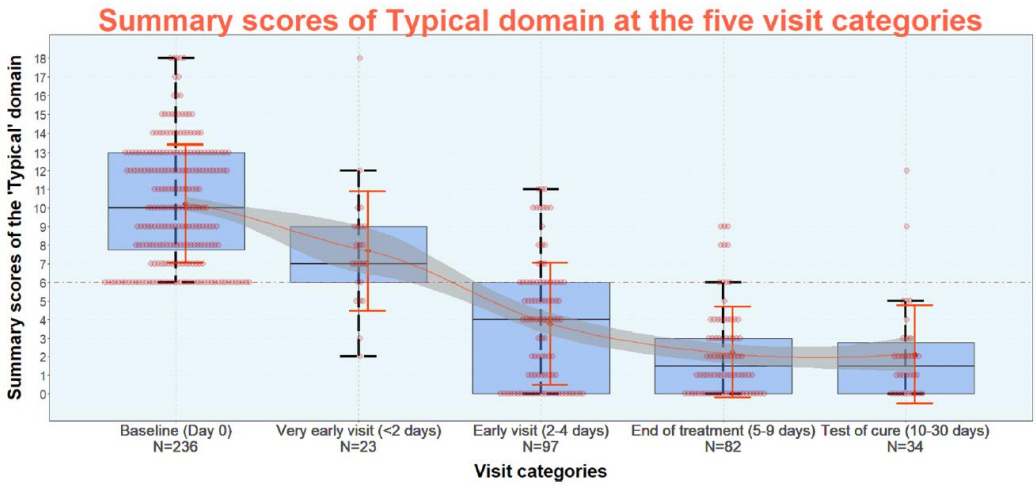


Figure 9. Summary scores of "Typical" domain of ACSS at diagnostics of acute uncomplicated cystitis (AC) in women (baseline) and at the four different follow-up visit categories. Note: red dots represent cases, orange diamonds represent mean scores, orange error bars represent standard deviations, orange line illustrates the symptomatic "course" of AC, grey "strip" around the orange line represents standard error of a mean

The "baseline" and "follow-up" evaluations were carried out at a maximum time difference of 29 days. Significant difference was found between all visit categories regarding the average

summary scores of the "Typical" domain ($p< 0.05$), except between those at end-of-therapy and ToC evaluations ($p=0.71$). At Baseline visit severe dysuria, urgency and frequency were reported by the 50%, 39% and 31% of the patients accordingly. By the ToC visit these rates reduced to 0%, 3% and 3% accordingly. Although the number of cases with positive symptoms, and the severity of the symptoms decreased over the observation time, a relatively high proportion of cases of at least mild symptoms remained even up to ToC visit. At ToC visit 35% of the patients still had mild dysuria, frequency and urgency, while 18% and 15% of the patients experienced incomplete bladder emptying and suprapubic pain.

At the Baseline visit haematuria was found only in 34.75% of the cases, and it decreased to a mere 5.88% at ToC visit.

The symptoms of AUC affected QoL in almost all cases (96.6–98.7%). Although the moderate and severe cases were reduced during follow-up, about one-third of patients still claimed at the least mild impact on their QoL.

Table 13. Overall changes (ACSS "Dynamics") from baseline visit at the four follow-up visit categories

ACSS (Dynamics) N of cases	Feeling normal (n, %)	Much better (n, %)	Somewhat better (n, %)	No changes (n, %)	Feeling worse (n, %)
Visit 2, N=23	0 (0.0%)	1 (4.4%)	12 (52.2%)	9 (39.1%)	1 (4.4%)
Visit 3, N=97	17 (17.5%)	39 (40.2%)	31 (32.0%)	9 (9.3%)	1 (1.0%)
Visit 4, N=82	24 (29.3%)	40 (48.8%)	12 (14.6%)	3 (3.7%)	3 (3.7%)
Visit 5, N=34	14 (41.2%)	10 (29.4%)	10 (29.4%)	0 (0.0%)	0 (0.0%)

Visit 2 (very early, Day <2); visit 3 (early, Day 2-4); visit 4 (end of treatment, Day 5-9); visit 5 (test of cure, Day 10-30)

Discrimination of clinical cure: In the "Dynamics" domain, the number of participants responding "back to normal" or "much better" have increased over the follow-up time, however, a notable number of respondents (10-31%) stated "somewhat better" (Table 13).

Therefore, it is not evident how "clinical cure" should be defined using the "Dynamics" domain by itself. Moreover, differenciating between "feeling much better" and "feeling somewhat better" would result in too low "clinical cure" rates, which would not reflect the clinical experience in patients with AUC.

Results of the eight different predetermined thresholds to define cure were analyzed at the different follow-up visits (Table 2). Six were related to ACSS items (A-F) and one adapted each to FDA and EMA criteria (G and H). The severity of symptoms in combination with or without

QoL items provided fairly comparable rates of “clinical cure”. By the Test of Cure visit, the treatment success and non-success rates in the cases of C, G and H criteria were 82,35% and 17,65%. While in the case of criteria E, 79,41% and 17,65% success and non-succes rates were calculated, respectively. Of the different thresholds tested, a summary score of the typical symptoms of ≤5 with no symptom scoring >1, without visible blood in urine, with or without including QoL issues was favoured (C and E).

5. DISCUSSION

Antimicrobial resistance caused by the widespread use of antibiotics is a growing worldwide problem, which may lead to catastrophic consequences. To find a solution, antibiotic stewardship programs have been organized. They aim to develop and implement systematic, coordinated, international strategies to increase the efficiency of antibiotic treatment, stop the increase of antibiotic resistance by reducing the overuse and misuse of antimicrobial agents, guiding proper infection control and monitoring [7, 8]. The O'Neill report systematically summarizes the most important and actual options to tackle down the antibiotic resistance [4]. The report highlights that the reason for the increasing resistance is multifactorial, so should be the solution, as several strategies should be implemented all at once. This means we need coordinated and prudent clinical practice and further research. The main strategies are listed in Table 1. Following the O'Neill points as a guide, we aimed to improve and enhance the war against bacterial resistance by introducing the antibiotic stewardship strategies into the Hungarian urological clinical practice and research. This thesis focuses on surveillance and cystitis diagnostic research. Outside the topic of the thesis we applied several further aspects of stewardship programs we will discuss later.

5.1. Surveillance

Monitoring of the most prevalent bacteria and their resistance plays an important role in delaying the development of resistance, since it provides essential information for practitioners and researchers to build up and improve their proper antibiotic treatment strategies [38]. This knowledge gives the opportunity to limit the use of broad-spectrum antibiotics without compromising safety. Application of narrower spectrum antibiotics results in lower collateral damage and on long term it helps to preserve the broad-spectrum antibiotics for more severe

infections. For these reasons surveillance is the first primary step to prudent antibiotic use and lays the foundation for the strategies against the increasing antibiotic resistance [2, 4].

In the first part of our research, we aimed to surveil the local resistance patterns of uropathogens from urine collected at the Department of Urology in Jahn Ferenc South Pest Hospital. Our hospital is responsible for a population of up to 1 050 000 in Budapest and its surrounding area. In Paper I we summarized the data from the period of 2004-2015 in an international journal, while in Paper II we extended the research up to 2017 and published the data in a Hungarian journal for the Hungarian public. We compared our results with the international data from the GPIU study and used this information to advance the antibiotic treatment strategy in our region.

The GPIU study provides data on antibiotic resistance, types of urogenital infections, risk factors, and antibiotic consumption in urological departments since 2003 [22]. More than 20 000 patients have been screened and more than 2000 patients are currently listed in this database.

5.1.1. Bacterial spectrum

The GPIU study revealed that in Northern Europe, the region Hungary was part of [21], between 2003 and 2010 the most frequent pathogens were *E. coli* (36%) and *Enterococcus species* (14%)[25]. In our department, however, about half of the cultured bacteria were *E. coli* which was closer to the rate of 55% found in Southern European countries. Over the years the percentage of *E. coli* slightly decreased. While in the case of *E. faecalis*, the second most frequent pathogen, an increasing trend was observed. The increase may be contributed to the widespread use of urinary foreign bodies and endourological practice. In 2017 the rate of *E. faecalis* reached 26% which is a significant number and should be taken into account when selecting antibiotics for empirical treatment while foreign bodies are present in the urinary tract.

5.1.2. Resistance patterns

The results from the GPIU study are controversial as the survey could not confirm obvious increase in the antibicrobial resistance among uropathogens against most antibiotics between

2003-2010. In our department, however, we could observe significant increase in the resistance against several antimicrobials.

The resistance to ciprofloxacin in *Escherichia coli* has increased from 19% to 25% during the 14 years long study period (p=0.039). Even though these rates are better than the results from the GPIU study, they are still too high for empirical treatment. *K. pneumoniae* shown even higher resistance versus ciprofloxacin, ranging between 26-59%. These results were in line with the international data. *E. faecalis* was resistant to ciprofloxacin and levofloxacin in more than 47% and 30% of the cases, respectively, while in the case *P. aeruginosa* a decreasing trend could be observed. In 2017 the resistance of *P. aeruginosa* to ciprofloxacin has dropped to 15%, however, this decrease was not statistically significant. Our results confirm that fluoroquinolones can no longer be recommended for empirical treatment of UTIs in our region. Moreover, in 2019 the European Commission implemented significant regulations on the use of fluoroquinolones due to their disabling and potentially long-term side effects [39].

In the case of cephalosporins, resistance of *E. coli* did not exceed the rate of 20%. This may be attributed to our restrictive antimicrobial use policy against the presctiption of cephalosporins and fluoroquinolones. Despite that, a significant increase of resistance was observed in the case of *E. coli* against ceftriaxone. By 2017 it reached a rate of 12% ($p<0.0001$) breaching the recommended 10% limit for empirical treatment. In accordance with the international data, resistance rates of *K. pneumoniae* against cephalosporins was very high. Even in the case of cefepime which is a fourth-generation cephalosporin its resistance reached 40% in 2012. We came to the conclusion that if the presence of MDR bacteria or Gram-positive bacteria such as *E. faecalis* are not suspected, cephalosporins may be safely used for empirical treatment of UTIs.

The international data also warns us of the spread of carbapenem-resistant bacteria [40]. At our department, resistance to carbapenems of most pathogens was minimal, with the exception of *P. aeruginosa* which shown a significant increase (p=0.004) from 6% in 2010 to 19% in 2017.

Based on our results sulfamethoxazole/trimethoprim, fosfomycin, and nitrofurantoin can still replace fluoroquinolones and cephalosporins in less severe cases. Generally, we used gentamicin less frequently in our department because its toxicity. It resulted in acceptably low

resistance rates in the case of most bacteria (especially in *E. coli* it remained below 7%), however in *K. pneumoniae* the resistance significantly increased.

5.1.3. Multidrug-resistance

The data available on the MDR species was limited. Generally, in line with international trends, the rate of MDR species found at our department increased significantly (p=0.008) from 8% in 2013 to 14% in 2015. We found a notably high rate of MDR ESBL-positive *K. pneumoniae* strains (24-33% of the cultured *K. pneumoniae* strains, with an exceptional peak of 60% in 2012), which could explain the high resistance rates of *K. pneumoniae* to cephalosporins mentioned above. The incidence of ESBL-producing *E. coli* varied between 6 to 15%. With the concurrent lack of new antimicrobial agent development, the increasing rate of MDR bacteria is a major concern. According to the GPIU study, 9% of the hospitalized patients in urological departments develop nosocomial UTIs due mostly to MDR bacteria. Therefore prescribers must be aware of MDR uropathogens when choosing antibiotic agent for empirical treatment of nosocomial UTIs.

It is also important that during antibiotic treatment collateral damage should always be taken in consideration. Other than increasing the rate of antimicrobial resistance, antibiotic groups with broad spectrum of activity such as fluoroquinolones or cephalosporins, may lead to severe *Clostridium difficile* infections [41].

The data from our surveillance can be used to improve the antibiotic treatment strategy in our region, and provides useful information for practitionnaires from other parts of Hungary as well. However, we strongly recommend that every urologic department should perform regular monitoring on their local antibiotic resistance profiles, as the results may vary geographically and with time.

5.2. Cystitis diagnostic research

The alarming results of our surveillance support the importance of further urological antiinfective research. One of the most important fields of UTI, which largely contributes to the development of resistance, is AUC. The reason for this is that AUC is one of the most frequent infections, affects most of the women, and leads to an enormous amount of antibiotic prescriptions. However, there are serious deficiencies regarding the diagnostics, treatment,

prevention and research on AUC, which increases the amount of unnecessary antibiotic consumption even further [8, 42, 43].

Diagnosis: In spite of the numerous publications, there is still no generally accepted strategy regarding the clinical diagnosis of AUC, which also means a significant limitation to defining inclusion criteria for clinical trials [34-36]. The updated guidelines of the Infectious Diseases Society of America (IDSA) and the European Society for Microbiology and Infectious Diseases (ESCMID) mainly consist of recommendations regarding the treatment but not the objective diagnosis of AUC.

For diagnosis in clinical practice or in studies neither the urinanalysis nor the microbiology can be considered as a standard criterion on their own. The contamination of the urine sample, especially in female patients is not uncommon. The count of significant bacteriuria is also questionable and depends on different factors, including the timing of the sample collection or the amount of water intake. Also the mistaken belief that the urine should be considered as sterile has fallen [44]. Not the results of the urine analysis should be treated but the symptoms. It is extremely important, as treatment of asymptomatic bacteruria is justified exclusively in selected cases (before specific urologic surgeries or during pregnancy). The correct evaluation of the symptoms is the only reliable method to diagnose AUC, and not even the laboratory analysis can replace it. The common upper respiratory tract infections are a great example where the diagnosis and treatment are naturally based on the symptoms and not the laboratory tests [45, 46].

Recently, the FDA and EMA have suggested criteria for the standardized diagnosis of AUC in their guidelines, however, they consider only the presence of the symptoms but ignore their severity. The symptoms requested by FDA and EMA are usually typical, but not exclusive for AUC. Also earlier studies revealed that if the symptoms appear in mild form, their presence can not differentiate between patients with AUC and healthy controls accurately [47]. The severity of the symptoms may be of greater importance for an accurate diagnosis of acute cystisis than just their presence or absence.

Research: It is of utmost importance to enhance the research on prophylaxis, diagnostics and treatment of AUC. There are several non-antibiotic prophylactic [8, 43, 48] and therapeutic [49-51] modalities available to replace antibiotic treatment of AUC, however almost none of them are supported by high quality, standardized, well-designed research.

The foremost reason for the stagnation of the research is the lacking of reliable tools for: a) diagnosis and establishing inclusion criteria for the studies; b) monitoring treatment efficiency; c) linear comparison of different antibiotic and non-antibiotic treatment modalities; d) defining the cure in clinical trials e) long-term follow-up.

Recently, the European Association of Urology, Section of Infections in Urology (EAU-ESIU) group for cystitis research has introduced the Acute Cystitis Symptom Score questionnaire (ACSS), which has the potential to satisfy these requirements [14].

In the second part of our research, in cooperation with an international scientific group, we conducted research on a new diagnostic tool, the Acute Cystitis Symptom Score (ACSS) [14] which opens a possibility to decrease the antibiotic consumption during the treatment of AUC.

5.2.1. The translation, linguistic and clinical diagnostic validation of the Hungarian Acute Cystitis Symptom Score

Until now, there was no such cystitis questionnaire available in Hungary. In order to be able to conduct further good quality research on AUC in our country, and elevate the Hungarian cystitis research to the international level, the development of a Hungarian version of the ACSS questionnaire was essential.

In Paper III our objective was to overcome the language barriers of further cystitis research by translation, linguistic and clinical diagnostic validation of the Hungarian version. The data collected during the study later contributed to further international testing of the questionnaire, which included the results obtained using all the versions of the ACSS validated in different languages. Additionally we tested the clinical use, the diagnostic accuracy of the Hungarian questionnaire with the Hungarian data, which we considered as a preliminary verification for further international testing of the ACSS.

The translation and linguistic validation was performed successfully. The study revealed that the Hungarian ACSS is well designed, and the questions are clear and understandable.

The clinical diagnostic validation process has revealed excellent values of predictive ability and responsiveness for diagnosis of AUC. At cut-off score 6 of the „Typical” domain, PPV and NPV were 96,55%, and 92,31%, sensitivity and specificity were 90% and 97%, respectively. These results show that the „Typical” domain can be perfectly used to confirm or exclude AUC.

The high sensitivity and specificity of the ACSS and the clear difference in the ACSS scores between the control and patient groups indicate that the questionnaire can describe the dynamics of the clinical condition as well. The subanalysis of the data performed in order to assess the effectiveness of the therapy using various combinations of different domains has shown the same rates of treatment success and non-success for each combination. To describe success we suggest to use „Typical" domain at a score of ≤4, but no item >1, as it shows excellent predictive values for diagnosis as well. This criteria can also be used in combination with the assessment of QoL.

The preliminary clinical diagnostic tests of the ACSS using the data of the Hungarian patients with AUC suggest that the questionnaire can be used for accurate diagnosis and monitoring of the clinical condition. With the Hungarian ACSS now we can join to international studies that rely on the use of ACSS. Using the methodology desribed in the paper we strongly recommend the translation and validation of the ACSS into other languages as well in order to be able to initiate coordinated international research on AUC.

5.2.2. Assessment of the ACSS as a diagnostic tool for clinical studies

The international cooperation using all the linguistic versions of the ACSS resulted in an extensive database that made it possible to perform a large-scale global testing of the ACSS [26, 34, 35]. The data obtained from the Hungarian patients significantly contributed to the following studies. The objective of the conclusive analysis was to assess the value of ACSS as a possible instrument for international research on AUC.

In Paper IV, we evaluated the diagnostic accuracy of ACSS in comparison with the latest criteria proposed by FDA and EMA draft guidelines for the diagnosis of AUC. The current research can be also considered as a verification study for the FDA and EMA guidelines as the ACSS includes the symptoms listed by the FDA and EMA as well. The analysis revealed that there was a strong correlation between the symptoms of the "Typical" domain and the diagnosis of acute cystisis. Even without urinalysis, the diagnostic value of the ACSS at a cut-off value of 6 was at least as favorable as the draft proposals by FDA and EMA. The differences in diagnostic values between the three diagnostic approaches were statistically not significant ($p>0.05$). Therefore, this threshold can be recommended as a diagnostic criteria of AUC in epidemiological and interventional studies as well as in clinical use.

5.2.3. Evaluation of the ACSS as a follow-up instrument for clinical trials

In Paper V our aim was to discuss the benefits of the ACSS as a Patient-Reported Outcome Measure (PROM) instrument by analysing the data from the clinical validation studies of the ACSS in different languages. According to the FDA, a PROM is any report on the status of a patient's health condition that directly comes from the patient. PROMs are widely used in medical product clinical trials to measure and compare the efficiency of different treatment modalities, note the risks and benefits of the treatment. During the development of ACSS the patients were involved in the progress, shared their experiences, which is a basic requirement for PROMs [52]. The different domains of the ACSS could be used alone or in combinations for this purpose.

„Typical" domain: besides registering the presence of the symptoms suggested by the FDA and EMA, the ACSS is also capable of scoring them by adding numerical values to their severity. Symptom scoring does not only increase the diagnostic accuracy but provides a more detailed monitoring of the condition during follow-up [34, 47].

In our analysis, as expected, the severity of the symptoms correlated with the time between the diagnosis and the follow-up visit after the treatment. However, the complete elimination of all symptoms was not found in all patients, even though most of them (up to 88%) were considered clinically cured. At ToC visit 35% of the patients still experienced mild forms of dysuria, frequency and urgency. It confirms the observations of our previous studies that the presence but also the severity of the symptoms is relevant for assessment of the medical condition. A detailed evaluation and registering the resolution of specific symptoms is also important for recognising other pathologies. For example, if visible blood in the urine persists, further investigation is indicated in order to exclude bladder cancer.

„QoL" domain: With the ACSS patients are interviewed of their personal experiences, the impact of the disease on their QoL, daily life and work and social life. The assessment of the QoL is an important criterion for PROMs [52]. The findings of the QoL assessment were closely linked to the symptom scoring, but it seems that for some patients, normalisation of their QoL takes somewhat longer than the resolution of their symptoms.

„Dynamics" domain: The patients' own judgement of the overall outcome is documented in the "Dynamics" domain of the ACSS. It consists of five grades of outcome: Feeling normal, Much better, Somewhat better, No changes, Worse. The number of patients answering "Feeling

normal" or "Much better" has increased over follow-up time, however, there was still a notable proportion of patients reporting "Somewhat better", which is hard to interpret. Although the "Dynamics" domain of the ACSS perfectly reveals the patients' experience on the dynamics of the disease, it does not provide detailed information on symptoms' changes and severity. The domain can be used for general assessment of the symptoms after treatment in clinical practice, however, for well-designed clinical trials, a more refined definition of clinical outcome would be expident.

Defining clinical cure: It has become evident that in studies focusing on the treatment of AUC, the dismissal of bacteriuria can not be considered as a major criterion for cure anymore. Detailed evaluation of the symptoms is required. However, unfortunately, the guidelines for outcome assessment by FDA and EMA, are not very well defined.

Due to the draft FDA guidelines, “clinical response” is considered as the resolution of the symptoms of UTI.

While, according to the EMA the clinical outcome can be described as a cure, failure, or indeterminate. The EMA suggests that the cure should be defined as i) complete resolution of clinical signs and symptoms and ii) sufficient improvement or return to baseline status such that no further antibacterial therapy is required for the index infection. What is sufficient improvement or resolution of symptoms is not clarified.

Neither the „Dynamics” domain of the ACSS is sensitive enough for accurate outcome assessment. It would be expedient to find a threshold in the ACSS below which a patient may be considered clinically cured.

Evaluation of the symptoms found at diagnosis and their changes could describe the outcome more efficiently. For diagnosis, the FDA proposed to use four symptoms (dysuria, urinary frequency, urgency, and suprapubic pain), while the EMA suggested to assess only three signs (frequency, urgency, and dysuria). The “Typical” domain of the ACSS also includes these symptoms.

Using the diagnostic (“Typical”) symptoms in combination with or without measurement of QoL issues we attempted to find the most advantageous method to define clinical cure in comparison with the diagnostic definitions proposed by the FDA and EMA guidelines. The positive achievement of “clinical cure” was tested by the eight predefined thresholds. Six of them were related to the ACSS items, one was adapted to the FDA criteria and one to the EMA.

Based on our results the favored two thresholds most appropriate for PROM instrument are:

1) a summary score of the “Typical” domain up to 5 AND no item > 1 (mild) AND no visible blood in the urine
2) a summary score of the “Typical” domain up to 5 AND no item > 1 (mild) AND no visible blood in the urine AND no “QoL” item > 1

The results of treatment success and non-cuccess using these tresholds were comparable to those obtained using the definitions adapted from the FDA and EMA. Since the symptoms proposed by the FDA and EMA for evaluation of AUC are also included into the ACSS, the questionnaire can be used as an instrument for this purpose.

5.3. Further aspects of the stewardship programs

Apart from **surveillance** and **cystitis diagnostic research** our scientific work consisted of applying several other elements of the O'Neill report. The associated papers are listed in “Publications directly related to the subject of the Ph.D. thesis” section. **1) Education:** in order to promote the use of these strategies in clinical practice we performed regular reports on our latest surveillance results, discussed the issue of the increasing resistance, its causes, and possible solutions at Hungarian and international urological meetings. **2) Adherence to guidelines and proper antibiotic use:** we accomplished the translation of the US and European Guidelines on Urological Infections. **3) Non-antibiotic prophylaxis and treatment, avoidance of antibiotic use:** as a part of our research on AUC we discussed the latest non-antibiotic preventive and therapeutic means, including the use of immunoprophylaxis and combined phytotherapy through several publications. **4) Catheter research:** as a part of our research on the antimicrobial resistance and management of catheter-associated UTIs we analyzed a novel catheter type (Sharklet) which in contrast with the previous chemical catheter modifications, utilizes the alteration of the physical attributes of the catheter surface. Using electromicroscopy we revealed that the special micropattern can significantly decrease the rate of biofilm formation on the modified catheter surface. **5) Research on possible uropathogens:** additionally we managed to confirm that *Actinotignum schaalii*, a newly recognized pathogen, is able to cause urological infections. Using the MALDI-ToF technology we successfully isolated the bacteria from a urine sample of a patient suffering from lower urinary tract infection. The case report is recently being prepared for publication [53, 54]. **6) Participation**

in the international surveillance: we are annually collecting Hungarian data for the GPIU study, also contacted and recruited other urologic departments from all over the country. Then by joining to the GPIU study group we are now actively participating in the processing of the international surveillance data.

5.4. Opportunity for further research

It has become evident that we need to place more emphasis on the anti-infective research as infections can be even much more alarming than the oncologic diseases. The COVID-19 outbreak has reminded us of the true importance of infectology. Without having cure, a pandemic from a microorganism of even a relatively low fatality rate can cause enormous damage to the economy, not mentioning its healthcare aspects. Moreover, as a result of the pandemic, the role of telemedicine has also largely increased. The ACSS can be used for self-diagnosis or diagnosing by telephone.

5.4.1. Further surveillance

The results of international urological surveillance from the GPIU study are only published until 2010. When the latest data will be published, we will be able to compare the results with our recent data, which might reveal useful information regarding the efficacy of our antibiotic treatment strategy.

5.4.2. Further research on acute uncomplicated cystitis (AUC)

In the era of increasing resistance, the practice to treat AUC with antibiotics regardless of its severity should be changed. It is clear by now that in the future treatment of AUC should highly rely on non-antibiotic modalities [2, 42]. With the implementation of symptom scoring we expect a huge breakthrough in the research on non-antibiotic treatment of AUC. The ACSS has already been used in a phase III clinical trial to assess the efficiency of a combined phytotherapy in AUC [55], where the non-antibiotic approach shown comparable results to antibiotic treatment. We also started using the Hungarian version combined with urine inflammatory markers in order to determine patient groups who could profit the most from symptomatic or non-antibiotic treatment.

6. CONCLUSIONS

6.1. Surveillance

1. During the studied period about the half of the cultured bacteria were *E. coli*, however a significant increase in the rate of *E. faecalis* was observed, which may be contributed to the increasing rate of endourological procedures. The same tendancy can be observed in the international data. The increased rate of *E. faecalis* should be taken into account when selecting antibiotics for empirical treatment while foreign bodies are present in the urinary tract.
2. In our region we observed a significant increase in the resistance of the predominant bacteria against most of the antibiotics. Our results were slightly better when compared to the international data, which means we can still use narrower spectrum antibiotics such as aminoglycosides or cephalosporins and save carbapenems for severe infections. However, based on our results, the use of fluoroquinolones cannot be recommended for empirical treatment of UTIs.
3. The increase in the rate of MDR species is a major concern. Prescribers must be aware of MDR uropathogens when choosing antibiotic agent for empirical treatment of nosocomial UTIs.
4. The data from our surveillance allowed us develop a local antibiotic treatment strategy in our department and its surrounding area. The results provide helpful information to improve the antibiotic treatment strategy in other parts of Hungary as well, however, we strongly recommend that every urologic department should perform regular monitoring on their local antibiotic resistance profiles.

6.2. Cystitis diagnostic research

1. As a part of an international team, we performed the translation, linguistic and clinical diagnostic validation of the ACSS in order to develop the Hungarian version of the questionnaire. As a result, the ACSS is now available for Hungarian urologists, gynecologists and general practitioners as an accurate, fast and cost-effective diagnostic tool in clinical practice. The ACSS may decrease the costs in primary care by emitting urine analysis, or can be used for self-diagnosis and telemedicine making it beneficial for the global healthcare system.

2. The most important advantage of the ACSS is that it can be recommended for international epidemiological and interventional studies on AUC.

The assessment of the ACSS as a diagnostic tool confirmed that the Hungarian ACSS, along with the other language verisions of the ACSS, can now be safely used in clinical research as an accurate, transparent standardized method for diagnosis, and patient inclusion.

3. The evaluation of the ACSS as a tool for PROMs revealed that the additional information gained by symptom scoring is especially important for longitudinal evaluation of the condition. The ACSS can reliably assess the possible changes of the symptoms after therapy, their bothersomeness, and effect on the QoL, impacts on daily and social activities. Therefore, it can be used in clinical trials as a standardized method for follow-up and monitoring of the efficiency of the applied treatment. In the future it could be used for the comparison of different antibiotic and non-antibiotic treatment modalities.

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I.

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Spectrum and antibiotic resistance of uropathogens between 2004 and 2015 in a tertiary care hospital in Hungary

András Magyar,[1,*] Béla Köves,[1] Károly Nagy,[1] András Dobák,[2] Vinodh Kumar Adithyaa Arthanareeswaran,[1] Péter Bálint,[1] Florian Wagenlehner[3] and Péter Tenke[1]

Abstract

Purpose. Surveillance of the bacterial spectrum and antibiotic-resistance patterns of locally occurring uropathogens is essential to serve as a basis for empirical treatment of urinary tract infections (UTIs), as antibiotic-resistance rates may vary geographically with significant differences between countries and regions, and with time.

Methodology. We retrospectively analysed all urine samples taken in the department of urology in a tertiary care hospital in Hungary from January 2004 to December 2015.

Results/Key findings. The five most commonly occurring bacteria were *Escherichia coli*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Proteus mirabilis*. Resistance of *Escherichia coli* to ciprofloxacin increased significantly from 19 to 25 %. Although the resistance of *Escherichia coli* against cephalosporins showed an increasing trend, it still remained generally low. However, resistance rates of *K. pneumoniae* to cephalosporins were very high, reaching 60 %, due to the high rate of extended-spectrum-β-lactamase-positive *Klebsiella* strains. We observed a significant increase in the rate of carbapenem-resistant *Pseudomonas aeruginosa*.

Conclusion. Fluoroquinolones cannot be recommended for empirical treatment in our region. Cephalosporins can be a good empirical choice for treating Gram-negative UTIs, but should be avoided when multi-drug resistant (MDR) bacteria are suspected. Increases in the rate of carbapenem-resistant *Pseudomonas aeruginosa*, and in the general rate of MDR bacteria, are both a very alarming trend. We recommend practising prudent antibiotic policy, preferably using antibiotics with the narrowest possible spectrum.

INTRODUCTION

The use of antibiotics in healthcare inevitably leads to increasing antimicrobial resistance, with local antibiotic policies having a strong impact on resistance patterns [1]. In order to enhance patient health outcomes and reduce the emergence of resistance to antibiotics, coordinated strategies are needed [2–4]. It is essential to carry out surveillance of the bacterial spectrum and resistance to antibiotics of locally occurring uropathogens that could serve as a basis for empirical treatment of urinary tract infections (UTIs) and for surgical prophylaxis, as antibiotic-resistance rates may vary geographically, with significant differences between countries and regions, and with time [5]. The aim of this retrospective analysis was to assess the changes in the spectrum of bacteria cultured from urine samples of patients in Jahn Ferenc South Pest Teaching Hospital, Department of Urologyand to compare the annual change in bacterial antibiotic resistance.

METHODS

All urine samples (mid-stream urine, urine collected from catheterized patients and urine collected during urinary tract puncture) taken for any reason (including samples from patients having UTIs, as well as urine cultures taken preoperatively from asymptomatic patients not having UTIs) from inpatients in the department of urology in a tertiary care hospital in Hungary from January 2004 to December 2015 were retrospectively analysed. The Cochran–Armitage test was used to study the trends of antibiotic resistance and positive urine culture numbers. $P<0.05$ was considered significant.

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Author affiliations: [1]Department of Urology, Jahn Ferenc South Pest Teaching Hospital, 1 Koves Street, 1204 Budapest, Hungary; [2]Corden International, 1 Piheno Street, 1525 Budapest, Hungary; [3]Department of Urology, Pediatric Urology and Andrology, Justus-Liebig-University, Giessen, Germany.

***Correspondence:** András Magyar, magyara@gmail.com

Keywords: antibiotic resistance; uropathogens; bacterial spectrum.

Abbreviations: ESBL, extended-spectrum-β-lactamase; GPIU, Global Prevalence of Infections in Urology; MDR, multi-drug resistant; MRSA, meticillin-resistant *Staphylococcus aureus*; UTI, urinary tract infection; VRE, vancomycin resistant *Enterococcus faecalis* and *Enterococcus faecium*.

To eliminate duplicate results, only one species per year per patient with an identical antibiogram was included in the statistical analysis. To describe the changes in resistance and bacterial spectrum, we used the following methods and simplifications: (1) resistance rates were discussed per antibiotic; (2) for presenting the changes in bacterial spectrum and resistance rates on tables and figures, we decided to include only the five most prevalent species present in >5 % of the bacterial spectrum; (3) in the cases of low numbers and high fluctuation of data, we displayed the mean occurrences of resistant isolates during consecutive years; (4) until 2010, we had limited data transferred from Corden International, microbiology laboratory, Budapestdue to the absence of an electronic database; therefore, missing data in table cells were marked as ND (not determined). The ND mark was also used in the cases of data not being determined based on the microbiologist's decision, mostly due to economic reasons.

From 2010, the improvement of our electronic computer system gave us the opportunity to perform data mining in depth. In order to evaluate the reason for increasing *Klebsiella pneumoniae* resistance, we were able to separate the extended-spectrum-β-lactamase (ESBL)-producing strains. Organisms that were able to hydrolyse third-generation cephalosporins, but could be inhibited by clavulanic acid (*in vitro*), were considered ESBL positive. However, isolates resistant to third-generation cephalosporins, yet sensitive to fourth-generation cephalosporins, were not considered as ESBL-producing organisms.

Culturing methods

For identification of the bacteria, the urine samples were collected in boric acid containers and sent to the microbiology laboratory. The inoculation of the pathogens was performed using a 0.01 ml loop into BD Brilliance UTI agar. After incubation at 37 °C for 16–18 h in a normal atmosphere thermostat, the colonies were inoculated into Oxoid-Columbia blood or MacConkey agar (Oxoid). For identification of the micro-organisms, we used the BD Phoenix automated system (BD Biosciences) or ENTEROtest 16 kit (Lachema). There was no relevant change in methods nor antibiotics used for screening the resistance profile throughout the years. Until 2011, antibiotic-susceptibility testing was performed using the BD Phoenix automated system or Mueller–Hinton agar with the disc diffusion method in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines [6], then we shifted to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards [7]. To determine MICs, the BD Phoenix automated system or Liofilchem MIC strips were used. After incubation, the isolates were classified as susceptible, intermediate and resistant according to the EUCAST MIC breakpoint tables [7]. In accordance with the international standards, *Enterobacteriaceae* were considered resistant to fosfomycin, colistin and tigecycline with MIC concentrations exceeding 32, 2 and 2 mg l^{-1}, respectively.

Multi-drug resistant (MDR) species

Data for MDR species were gained from the report of Jahn Ferenc South Pest Teaching Hospitalto the Hungarian National Nosocomial Surveillance System (National Epidemiology Centre) [8]. In the report, species meeting the following criteria were considered MDR: vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* (VRE), ESBL-producing or carbapenem-resistant *Enterobacteriaceae,* MDR *Pseudomonas aeruginosa* (susceptible to $\leq$2 of the following antibiotics: piperacillin/tazobactam, ceftazidime, cefepime, imipenem, meropenem, ciprofloxacin, gentamicin, tobramycin, amikacin), carbapenem-resistant *Acinetobacter baumannii*, and different types of MDR *Staphylococcus aureus* including meticillin-resistant *S. aureus* (MRSA).

RESULTS

Bacterial spectrum

A total of 2871 urine cultures showing a significant presence of uropathogens was analysed during the 12-year-long period. The yearly number of positive cultures did not vary significantly (mean 240 positive samples, P=0.271). The spectrum of cultured bacteria in Jahn Ferenc South Pest Teaching Hospital, Department of Urology is shown in Fig. 1. The bacterial spectrum in the urine cultures of hospitalized patients was fairly constant over the years. *Escherichia coli* was the most frequent species in the whole study period. It averaged about 50 % of the samples, with a highest percentage of 56 % in 2008 and 2010, and a lowest of 42 % in 2007 and 2014. *Enterococcus faecalis* showed a significant increasing tendency (from 15 % in 2004 to 28 % in 2015, P<0.0001). The prevalence of *K. pneumoniae* remained fairly constant during the years, with a mean of 11 %. The percentage of *Pseudomonas aeruginosa* and *Proteus mirabilis* showed a slight increase, but remained lower than 10 %, except for *Pseudomonas aeruginosa* in 2014, when it reached 14 %.

Resistance patterns

The resistance rates for the antibiotics are summarized in Tables 1–6.

Fluoroquinolones (Table 1)

Ciprofloxacin resistance in *Escherichia coli* showed a significant increase from 19 % (25/130) to 25 % (31/122) during the 12 years (P=0.021). In *K. pneumoniae*, resistance patterns against ciprofloxacin and norfloxacin fluctuated, varying between 26 % (7/27) to 59 % (17/29). In the case of *Enterococcus faecalis*, resistance to ciprofloxacin was above 47 % (22/47) and to levofloxacin exceeding 40 % (26/65). *Pseudomonas aeruginosa* showed variable, but significantly decreasing resistance to ciprofloxacin from 38 % (5/13) to 13 % (2/16), P=0.025, and levofloxacin, from 38 % (5/13) to 19 % (3/16), during the studied years (P=0.032). Resistance of *Proteus mirabilis* against ciprofloxacin varied between 10 % (2/20) and 44 % (7/16) in the second half of the studied period.

Penicillin derivatives (Table 2)

Ampicillin resistance remained constant in the case of *Escherichia coli*, 57 % (74/130) to 54 % (66/122); *Enterococcus*

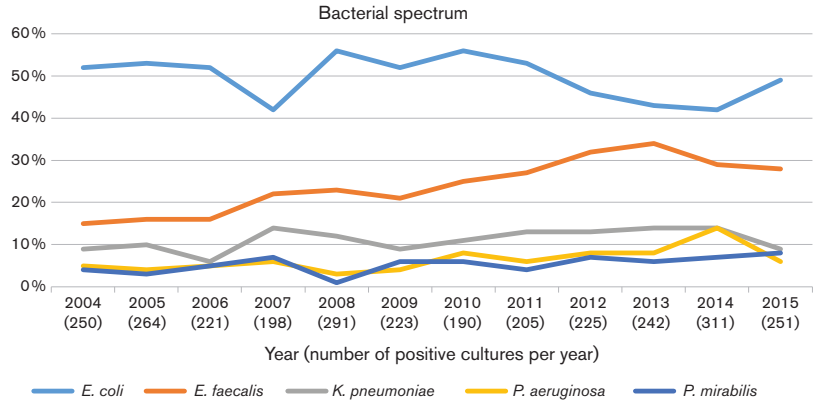

Fig. 1. The prevalence of the five most commonly cultured bacteria in the 2871 urine samples.

faecalis, 0 % (0/70); and *K. pneumoniae*, 100 % (22/22); and showed statistically significant increase (P=0.007) in the case of *Proteus mirabilis* from 20 % (2/10) to 40 % (8/20), peaking in 2013 with 53 % (8/15).

Resistance of *Escherichia coli* against amoxicillin/clavulanic acid varied between 6 % (10/156) and 35 % (46/131). Resistance of *K. pneumoniae* showed significant increase (P<0.0001) from 17 % (4/23) to 59 % (13/22). Regarding *Proteus mirabilis*, resistance to amoxicillin/clavulanic acid reached 19 % (4/21) in 2014, but mostly remained under 10 % (1/10).

Carbapenems (Table 3)

No resistance developed to imipenem, meropenem and ertapenem in *Escherichia coli*, *K. pneumoniae*, *Enterococcus faecalis* and *Proteus mirabilis* during the examined years. *Pseudomonas aeruginosa* showed resistance rates with significant increasing tendency (P=0.026) versus imipenem, from 6 % (1/16) in 2010 to 27 % (4/15) in 2015; however, the increase from 0 % (0/16) to 19 % (3/16) in the case of meropenem was not significant (P=0.075) in the second half of the studied period.

Cephalosporins (Table 4)

Cephalosporin resistance was evaluated only for Gram-negative pathogens. Resistance to cefuroxime in *Escherichia coli* increased slightly but not significantly (P=0.88) from 8 % (9/107) to 12 % (15/122), peaking in 2011 at 18 % (19/108). In *K. pneumoniae,* resistance to cefuroxime varied between 24 % (10/42) and 60 % (18/30), and in *Proteus mirabilis* it was under 8 % (1/12).

Cefixime resistance in *Escherichia coli* remained under 14 % (15/106) and in *Proteus mirabilis* it was 0 % (0/20 in 2015). The resistance rate in *K. pneumoniae* showed a non-significant increase (P=0.765) from 29 % (6/21) to 48 % (10/21).

In the case of ceftriaxone and ceftazidime, *Escherichia coli* showed a slight but significant increase in resistance during the study years, from 1 % (1/129) to 8 % (10/122), and 0 % (0/156) to 8 % (10/122), respectively (P<0.0001 and P=0.015, respectively). In *K. pneumoniae,* resistance rates against ceftriaxone fluctuated between 24 % (10/42) and 57 % (17/30) in the second half of the period. No ceftriaxone and ceftazidime resistant *Proteus mirabilis* strain was cultured. *Pseudomonas aeruginosa* showed resistance to ceftazidime ranging from 0 % (0/20) to 16 % (3/19).

Cefepime resistance in *Escherichia coli* increased significantly (P<0.0001) from 1 % (1/129) to 8 % (8/103). The resistance level of *K. pneumoniae* reached 40 % (4/10) in 2012. Resistance rates found in the case of *Pseudomonas aeruginosa* and *Proteus mirabilis* for cefepime decreased from 15 % (2/13) to 6 % (1/16), and from 10% (1/10) to 0 % (0/16), respectively; however, the changes were statistically not significant (P=0.446 and P=0.331, respectively).

Aminoglycosides (Table 5)

Gentamicin resistance remained under 7 % (10/140) in *Escherichia coli*. The resistance rates significantly decreased from 100 % (38/38) to 50 % (35/70) in *Enterococcus faecalis* (P<0.0001), 31 % (4/13) to 13 % (2/16) in *Pseudomonas aeruginosa* (P=0.011), and 30 % (3/10) to 15 % (3/20) in *Proteus mirabilis* (P=0.013), while in *K. pneumoniae* a significant increase (P<0.0001) was observed from 0 % (0/23) to 36 % (8/22).

Resistance to amikacin in *Escherichia coli* decreased significantly (P=0.003). In 2004, the resistance rate was 4 % (5/130), while in 2011, which was the last year that it was tested in larger numbers, the rate was 0 % (0/108). Resistance of *Pseudomonas aeruginosa* was 6 % (1/16) in 2015. In the last year of testing, no resistance to amikacin was found in *K. pneumoniae* and *Proteus mirabilis* cultures.

Sulfamethoxazole/trimethoprim (Table 6a)

Resistance to sulfamethoxazole/trimethoprim in *Escherichia coli* ranged between 19 % (22/118 in 2015) and 31 % (32/102), which peaked in 2011. Resistance rates in *K. pneumoniae* significantly increased (P=0.001) from 13 % (3/23) in 2004 to 36 % (8/22) in 2015, with a peak of 63 % (19/30) in

Table 1. Resistance rates against fluoroquinolones

The table shows the resistance rates against ciprofloxacin, levofloxacin and norfloxacin between 2004 and 2015. ND, Not determined

(a) Ciprofloxacin resistance											Levofloxacin resistance					
Year	*Escherichia coli*		*Enterococcus faecalis*		*Klebsiella pneumoniae*		*Pseudomonas aeruginosa*		*Proteus mirabilis*		*Escherichia coli*		*Enterococcus faecalis*		*Pseudomonas aeruginosa*	
	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)
2004	19	(25/130)	100	(38/38)		ND	38	(5/13)		ND	0	(0/22)		ND	38	(5/13)
2005	18	(25/140)	100	(42/42)		ND	27	(3/11)		ND	0	(0/12)		ND	40	(4/10)
2006	22	(25/115)	97	(34/35)		ND	36	(4/11)		ND	14	(1/7)		ND	40	(4/10)
2007	27	(22/83)	100	(44/44)		ND	33	(4/12)		ND	12	(2/17)		ND	33	(4/12)
2008	15	(24/156)	52	(34/66)	34	(11/32)	14	(1/7)	50	(2/4)	12	(2/17)		ND	17	(1/6)
2009	24	(28/116)	96	(45/47)	30	(6/20)	22	(2/9)	38	(5/13)	9	(1/11)		ND	25	(2/8)
2010	22	(24/107)	47	(22/47)	29	(6/21)	19	(3/16)	33	(4/12)	0	(0/13)		ND	13	(2/15)
2011	31	(34/108)	56	(31/55)	26	(7/27)	15	(2/13)	13	(1/8)	0	(0/15)		ND	15	(2/13)
2012	24	(25/103)	50	(9/18)	59	(17/29)	16	(3/19)	44	(7/16)	0	(0/25)		ND	38	(6/16)
2013	22	(23/103)		ND	32	(11/34)	5	(1/20)	13	(2/15)		ND		ND	5	(1/20)
2014	25	(33/131)		ND	29	(12/42)	22	(10/45)	19	(4/21)		ND	41	(24/59)	22	(10/45)
2015	25	(31/122)		ND	50	(11/22)	13	(2/16)	10	(2/20)		ND	40	(26/65)	19	(3/16)

(b) Norfloxacin resistance						
Year	*Escherichia coli*		*Klebsiella pneumoniae*		*Proteus mirabilis*	
	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)
2008	14	(22/153)	36	(12/33)	50	(2/4)
2009	18	(21/116)	35	(7/20)	46	(6/13)
2010	22	(24/107)	29	(6/21)	33	(4/12)
2011	32	(34/106)	26	(7/27)	13	(1/8)
2012	25	(25/102)	57	(17/30)	44	(7/16)
2013	23	(23/102)	32	(11/34)	13	(2/15)
2014	25	(32/128)	29	(12/42)	20	(4/20)
2015	25	(31/122)	48	(10/21)	10	(2/20)

Table 2. Resistance rates against penicillin derivates

The table shows the resistance rates against ampicillin and amoxicillin/clavulanic acid between 2004 and 2015.

Year	Ampicillin resistance								Amoxicillin/clavulanic acid resistance					
	E. coli		*Enterococcus faecalis*		*Klebsiella pneumoniae*		*Proteus mirabilis*		*Escherichia coli*		*Klebsiella pneumoniae*		*Proteus mirabilis*	
	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)
2004	57	(74/130)	0	(0/38)	100	(23/23)	20	(2/10)	23	(30/130)	17	(4/23)	10	(1/10)
2005	40	(56/140)	0	(0/42)	88	(23/26)	25	(2/8)	14	(20/140)	19	(5/26)	0	(0/8)
2006	53	(61/115)	0	(0/35)	100	(13/13)	18	(2/11)	28	(32/115)	23	(3/13)	9	(1/11)
2007	48	(40/83)	2	(1/44)	100	(28/28)	21	(3/14)	18	(15/83)	14	(4/28)	7	(1/14)
2008	49	(76/156)	0	(0/66)	100	(33/33)	50	(2/4)	6	(10/156)	6	(2/33)	25	(1/4)
2009	52	(60/116)	0	(0/47)	100	(20/20)	23	(3/13)	19	(22/116)	15	(3/20)	8	(1/13)
2010	67	(72/107)	0	(0/47)	100	(21/21)	33	(4/12)	17	(18/107)	33	(7/21)	0	(0/12)
2011	57	(61/107)	2	(1/55)	100	(27/27)	38	(3/8)	23	(25/107)	26	(7/27)	13	(1/8)
2012	52	(53/103)	0	(0/71)	100	(29/29)	44	(7/16)	15	(15/103)	57	(17/30)	0	(0/16)
2013	45	(46/103)	1	(1/82)	100	(34/34)	53	(8/15)	14	(14/103)	47	(16/34)	7	(1/15)
2014	60	(78/131)	0	(0/90)	100	(42/42)	52	(11/21)	35	(46/131)	38	(16/42)	19	(4/21)
2015	54	(66/122)	0	(0/70)	100	(22/22)	40	(8/20)	28	(34/122)	59	(13/22)	5	(1/20)

Table 3. Resistance rates against carbapenems

The table shows the resistance rates against imipenem, meropenem and ertapenem between 2008 and 2015.

(a) Imipenem resistance

Year	*Escherichia coli*		*Enterococcus faecalis*		*Klebsiella pneumoniae*		*Pseudomonas aeruginosa*		*Proteus mirabilis*	
	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)
2008	0	(0/156)		ND	0	(0/33)	0	(0/7)	25	(1/4)
2009	0	(0/116)		ND	0	(0/20)	0	(0/9)	15	(2/13)
2010	0	(0/107)		ND	0	(0/21)	6	(1/16)	0	(0/12)
2011	0	(0/108)		ND	0	(0/27)	15	(2/13)	0	(0/8)
2012	0	(0/101)	0	(0/14)	0	(0/30)	5	(1/19)	0	(0/16)
2013	0	(0/103)	0	(0/9)	0	(0/32)	5	(1/20)	0	(0/15)
2014	0	(0/131)	0	(0/10)	0	(0/42)	16	(7/45)	0	(0/21)
2015	0	(0/122)	0	(0/49)	0	(0/22)	27	(4/15)	0	(0/19)

(b) Meropenem resistance

Ertapenem resistance

Year	*Escherichia coli*		*Klebsiella pneumoniae*		*Pseudomonas aeruginosa*		*Proteus mirabilis*		*Escherichia coli*		*Klebsiella pneumoniae*		*Proteus mirabilis*	
	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)
2010	0	(0/85)	0	(0/16)	0	(0/16)	0	(0/12)	0	(0/107)	0	(0/21)	0	(0/12)
2011	0	(0/108)	0	(0/22)	15	(2/13)	0	(0/8)	0	(0/108)	0	(0/27)	0	(0/8)
2012	0	(0/75)	0	(0/20)	5	(1/19)	0	(0/11)	0	(0/103)	0	(0/30)	0	(0/16)
2013	0	(0/99)	0	(0/31)	0	(0/20)	0	(0/15)	0	(0/103)	0	(0/34)	0	(0/15)
2014	0	(0/131)	0	(0/41)	16	(7/45)	0	(0/21)	0	(0/131)	0	(0/42)	0	(0/21)
2015	0	(0/121)	0	(0/22)	19	(3/16)	0	(0/19)	0	(0/122)	0	(0/22)	0	(0/20)

ND, Not determined.

2012. In the case of *Proteus mirabilis*, resistance rates ranged between 20 % (2/10) and 63 % (10/16).

Nitrofurantoin (Table 6a)

Resistance to nitrofurantoin in *Escherichia coli* remained below 2 % (3/129). *K. pneumoniae* and *Proteus mirabilis* were 100 % (21/21 and 20/20, respectively) resistant to nitrofurantoin in 2015.

Fosfomycin (Table 6b)

Fosfomycin was tested in the laboratory between 2010 and 2012. We found relatively low resistance rates for *Escherichia coli*, 0 % (0/102) to 5 % (1/20); *K. pneumoniae*, 0 % (0/7) to 15 % (3/20); and *Proteus mirabilis*, 0 % (0/4) to 14 % (1/7).

Polymyxin B (Table 6b)

Resistance to polymyxin B was 95 % (19/20) to 100 % (21/21) in *Proteus mirabilis*, and 0 % in *Escherichia coli, K. pneumoniae* and *Pseudomonas aeruginosa*, between 2010 and 2015 (in 2015 the rates were 0/122, 0/22 and 0/16, respectively).

Additional data

In *Pseudomonas aeruginosa*, resistance to colistin ranged between 0 % (0/16) and 8 % (1/13), and to tobramycin between 0 % (0/16) and 16 % (7/45). Piperacillin/tazobactam was tested with *Pseudomonas aeruginosa* with the highest rate of resistance in 2014 : 11 % (5/45). In *Enterococcus faecalis*, tigecycline and vancomycin resistances remained at 0 % (0/70 in 2015), but the tetracycline resistance level was high and ranged from 87 % (41/47) to 94 % (17/18).

MDR species (Table 7)

Combined data on all MDR species is available only from 2013 and is presented in Table 7(a). During this period, the rate of MDR bacteria showed a significant (P=0.008) increase from 8 % (23/279) to 14 % (42/305).

ESBL-producing *K. pneumoniae* and *Escherichia coli* (Table 7b)

About 24 % (7/29) to 33 % (10/30) of cultured *K. pneumoniae* were ESBL positive since 2010, with an exceptional peak of 60 % (18/30) in 2012. The rate of ESBL-positive *Escherichia coli* varied between 6 % (7/110) to 9 % (12/129) in the last 6 years, but in 2011 it reached 15 % (16/108). The increase of ESBL-positive cases from 2010 to 2015 was not significant (in ESBL-producing *Escherichia coli*, P=0.96; *K. pneumoniae*, P=0.791).

DISCUSSION

The optimal treatment of hospitalized patients requires knowledge of the antimicrobial-resistance patterns of the most frequent uropathogens. It is extremely important to carry out surveillance of the regional and local spectrum of

Table 4. Resistance rates against cephalosporines

The table shows the resistance rates against cefamandole, cefuroxime, ceftriaxone, cefixime, ceftazidime and cefepime between 2004 and 2015.

(a) Cefamandole resistance							Cefuroxime resistance					
Year	*Escherichia coli*		*Klebsiella pneumoniae*		*Proteus mirabilis*		*Escherichia coli*		*Klebsiella pneumoniae*		*Proteus mirabilis*	
	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)
2004	4	(5/130)	4	(1/23)	0	(0/10)	8	(9/107)	29	(6/21)	8	(1/12)
2005	5	(7/140)	8	(2/26)	13	(1/8)	18	(19/108)	30	(8/27)	0	(0/8)
2006	16	(18/115)	0	(0/13)	18	(2/11)	8	(8/103)	60	(18/30)	6	(1/16)
2007	4	(3/83)	4	(1/28)	21	(3/14)	7	(7/103)	32	(11/34)	0	(0/15)
2008	0	(0/156)	3	(1/33)	0	(0/4)	10	(13/131)	24	(10/42)	0	(0/21)
2009	7	(8/116)	5	(1/20)	8	(1/13)	12	(15/122)	50	(11/22)	0	(0/20)
2010	7	(7/107)	0	(0/21)	0	(0/12)	ND		ND		ND	

(b) Ceftriaxone resistance							Cefixime resistance					
Year	*Escherichia coli*		*Klebsiella pneumoniae*		*Proteus mirabilis*		*Escherichia coli*		*Klebsiella pneumoniae*		*Proteus mirabilis*	
	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)
2004	1	(1/129)	0	(0/23)	0	(0/10)	ND		ND		ND	
2005	0	(0/140)	4	(1/26)	0	(0/8)	ND		ND		ND	
2006	1	(1/115)	0	(0/13)	9	(1/11)	ND		ND		ND	
2007	2	(2/83)	0	(0/28)	0	(0/14)	ND		ND		ND	
2008	0	(0/156)	0	(0/33)	0	(0/4)	0	(0/1)	ND		0	(0/4)
2009	5	(6/115)	0	(0/20)	0	(0/13)	4	(5/116)	ND		0	(0/13)
2010	9	(9/106)	29	(6/21)	0	(0/12)	8	(8/106)	29	(6/21)	0	(0/12)
2011	16	(17/108)	26	(7/27)	0	(0/8)	14	(15/106)	26	(7/27)	0	(0/8)
2012	6	(6/103)	57	(17/30)	0	(0/16)	7	(2/25)	57	(17/30)	0	(0/16)
2013	7	(7/103)	32	(11/34)	0	(0/15)	7	(7/101)	32	(11/34)	0	(0/15)
2014	9	(12/131)	24	(10/42)	0	(0/21)	9	(11/128)	24	(10/42)	0	(0/20)
2015	8	(10/122)	46	(10/22)	0	(0/20)	10	(12/122)	48	(10/21)	0	(0/20)

(c) Ceftazidime resistance									Cefepime resistance					
Year	*Escherichia coli*		*Klebsiella pneumoniae*		*Pseudomonas aeruginosa*		*Proteus mirabilis*		*Escherichia coli*		*Klebsiella pneumoniae*		*Pseudomonas aeruginosa*		*Proteus mirabilis*	
	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)
2004	ND		ND		ND		ND		1	(1/129)	0	(0/23)	15	(2/13)	10	(1/10)
2005	ND		ND		ND		ND		0	(0/139)	0	(0/26)	9	(1/11)	0	(0/8)
2006	ND		ND		ND		ND		2	(2/114)	0	(0/13)	9	(1/11)	9	(1/11)
2007	ND		ND		ND		ND		2	(2/83)	0	(0/28)	0	(0/12)	0	(0/14)
2008	0	(0/156)	0	(0/33)	0	(0/7)	0	(0/4)	0	(0/156)	0	(0/33)	0	(0/7)	0	(0/4)
2009	5	(6/116)	15	(3/20)	11	(1/9)	0	(0/13)	7	(8/116)	0	(0/20)	11	(1/9)	15	(2/13)
2010	9	(9/106)	29	(6/21)	13	(2/16)	0	(0/12)	8	(8/106)	29	(6/21)	13	(2/16)	0	(0/12)
2011	16	(17/108)	26	(7/27)	8	(1/13)	0	(0/8)	16	(17/108)	26	(7/27)	8	(1/13)	0	(0/8)
2012	6	(6/100)	59	(17/29)	16	(3/19)	0	(0/16)	8	(8/103)	40	(4/10)	12	(2/17)	0	(0/16)
2013	7	(7/103)	32	(11/34)	0	(0/20)	0	(0/15)	ND		33	(4/12)	0	(0/20)	ND	
2014	9	(11/129)	22	(9/41)	13	(6/45)	0	(0/21)	ND		100	(1/1)	7	(3/45)	ND	
2015	8	(10/122)	46	(10/22)	6	(1/16)	0	(0/20)	ND		ND		6	(1/16)	ND	

ND, Not determined.

Table 5. Resistance rates against aminoglycosides

The table shows the resistance rates against gentamicin and amikacin between 2004 and 2015.

Gentamicin resistance											Amikacin resistance							
Year	*Escherichia coli*		*Enterococcus faecalis*		*Klebsiella pneumoniae*		*Pseudomonas aeruginosa*		*Proteus mirabilis*		*Escherichia coli*		*Klebsiella pneumoniae*		*Pseudomonas aeruginosa*		*Proteus mirabilis*	
	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)
2004	6	(8/130)	100	(38/38)	0	(0/23)	31	(4/13)	30	(3/10)	4	(5/130)		ND	0	(0/13)		ND
2005	7	(10/140)	100	(42/42)	4	(1/26)	36	(4/11)	38	(3/8)	3	(4/140)		ND	0	(0/11)		ND
2006	4	(5/115)	100	(35/35)	0	(0/13)	45	(5/11)	45	(5/11)	1	(1/115)		ND	18	(2/11)		ND
2007	5	(4/83)	100	(44/44)	4	(1/28)	33	(4/12)	29	(4/14)	7	(6/83)		ND	0	(0/12)		ND
2008	0	(0/156)	53	(35/66)	0	(0/33)	0	(0/7)	25	(1/4)	0	(0/7)	0	(0/2)	0	(0/7)	0	(0/1)
2009	4	(5/116)	100	(47/47)	0	(0/20)	22	(2/9)	15	(2/13)	0	(0/116)	0	(0/20)	0	(0/9)	0	(0/13)
2010	4	(4/107)	38	(18/47)	24	(5/21)	0	(0/16)	8	(1/12)	0	(0/107)	0	(0/21)	0	(0/16)	0	(0/12)
2011	3	(3/108)	38	(21/55)	30	(8/27)	15	(2/13)	0	(0/8)	0	(0/108)	0	(0/27)	0	(0/13)	0	(0/8)
2012	1	(1/72)	53	(38/71)	36	(10/28)	21	(4/19)	6	(1/16)	0	(0/21)	10	(1/10)	0	(0/19)	0	(0/5)
2013	2	(2/103)	44	(36/82)	21	(7/34)	5	(1/20)	20	(3/15)	0	(0/1)	0	(0/3)	5	(1/20)	0	(0/4)
2014	5	(6/131)	50	(45/90)	2	(1/42)	18	(8/45)	14	(3/21)	0	(0/3)	0	(0/1)	2	(1/45)	0	(0/1)
2015	6	(7/122)	50	(35/70)	36	(8/22)	13	(2/16)	15	(3/20)	0	(0/1)	0	(0/1)	6	(1/16)	0	(0/2)

ND, Not determined.

the most commonly occurring bacteria and antimicrobial-resistance rates during empirical treatment [9, 10].

The Global Prevalence of Infections in Urology (GPIU) study is an annual worldwide-performed point prevalence study intended to create surveillance data on antibiotic resistance, type of urogenital infections and risk factors, and data on antibiotic consumption in urological departments. According to the results of the GPIU study between 2003 and 2010, the most frequently occurring bacteria in Northern Europe (the region Hungary is part of) were *Escherichia coli* (36 %) and *Enterococcus* species (14 %) [11]. In Jahn Ferenc South Pest Teaching Hospital, Department of Urology, about half of the cultured bacteria were *Escherichia coli*. This percentage is higher than in Northern European countries as a whole and is closer to the *Escherichia coli* rate found in Southern European countries (55 %), and shows a slight decrease over the years. We found *Enterococcus faecalis* to be the second most frequently occurring species, and the prevalence has significantly increased during the years to 28 %. This increasing trend may be explained by the more widespread use of urinary foreign bodies and endourological practices, and should be considered when selecting antibiotics for empirical treatment.

International data on resistance rates concerning hospitalized urological patients are controversial. In the 2003–2010 GPIU study, no obvious increase in resistance for most antimicrobials was observed. However, Jahn Ferenc South Pest Teaching Hospital, Department of Urologyshowed a significant increasing trend in the resistance to some antimicrobials.

Resistance of *Escherichia coli* to ciprofloxacin increased significantly from 19 to 25 %. Although these rates are lower than the rates found in the GPIU study, they are still considered too high for empirical treatment. Resistance of *K. pneumoniae* to ciprofloxacin was also high, ranging between 26 and 50 %, in accordance with the international data. Resistance of *Enterococcus faecalis* against ciprofloxacin and levofloxacin was higher than 50 and 40 %, respectively, while regarding *Pseudomonas aeruginosa* resistance against ciprofloxacin reached a mean of 22 %. Based on these data, the use of fluoroquinolones cannot be recommended for empirical treatment of UTIs in our region.

For all cephalosporins, resistance in *Escherichia coli* remained under 20 %. This may be attributed to a change in our antimicrobial policy, which aimed to reduce the usage of cephalosporins and fluoroquinolones. Despite that, a significant increase of resistance was observed in the case of *Escherichia coli* against ceftriaxone ($P<0.0001$), ceftazidime ($P=0.015$) and cefepime ($P<0.0001$), up to 8 %. However, these three resistance rates above are still below the 10 % limit for empirical treatment. Resistance rates of *K. pneumoniae* against cephalosporins were very high, reaching 60 %. Resistance to cefepime, a fourth-generation cephalosporin, reached 40 % in 2012. These data are in accordance with the international trends. These high resistance rates for *K. pneumoniae* can be explained by the high percentage of MDR ESBL-positive *K. pneumoniae* strains in the last few years. Therefore, cephalosporins can be a good empirical choice for treating Gram-negative UTIs, but should be avoided in settings where MDR bacteria are suspected. Since *Enterococcus faecalis* is considered to be resistant to cephalosporins, relatively high rates of *Enterococcus faecalis* need to be taken into account in the case of empirical treatment, especially if a foreign body is placed or found in the urinary tract. It is a surprising fact that *Proteus mirabilis* was 100 % susceptible

Table 6. Resistance rates against sulfamethoxazole/trimethoprim, nitrofurantoin, polymyxin B and fosfomycin

The table shows the resistance rates against sulfamethoxazole/trimethoprim, nitrofurantoin, polymyxin B and fosfomycin between 2004 and 2015.

(a) Sulfamethoxazole/trimethoprim resistance									Nitrofurantoin resistance							
Year	*Escherichia coli*		*Enterococcus faecalis*		*Klebsiella pneumoniae*		*Proteus mirabilis*		*Escherichia coli*		*Enterococcus faecalis*		*Klebsiella pneumoniae*		*Proteus mirabilis*	
	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)
2004	19	(24/128)	13	(5/38)	13	(3/23)	20	(2/10)	2	(3/129)	0	(0/38)	ND		ND	
2005	19	(27/140)	24	(10/42)	15	(4/26)	38	(3/8)	1	(1/140)	5	(2/42)	ND		ND	
2006	24	(28/115)	29	(10/35)	8	(1/13)	27	(3/11)	2	(2/115)	0	(0/35)	ND		ND	
2007	29	(24/82)	32	(14/44)	4	(1/28)	29	(4/14)	2	(2/82)	2	(1/44)	ND		ND	
2008	26	(41/156)	33	(22/66)	21	(7/33)	50	(2/4)	1	(1/153)	0	(0/66)	18	(6/33)	100	(4/4)
2009	28	(33/116)	23	(11/47)	6	(1/16)	33	(4/12)	2	(2/116)	2	(1/45)	47	(9/19)	100	(13/13)
2010	30	(31/105)	ND		16	(3/19)	33	(4/12)	1	(1/106)	0	(0/46)	71	(15/21)	100	(12/12)
2011	31	(32/102)	ND		22	(6/27)	57	(4/7)	0	(0/55)	0	(0/18)	31	(4/13)	100	(4/4)
2012	23	(23/102)	ND		63	(19/30)	63	(10/16)	0	(0/65)	0	(0/46)	90	(18/20)	100	(9/9)
2013	19	(18/95)	ND		28	(9/32)	29	(4/14)	1	(1/100)	0	(0/81)	91	(31/34)	100	(15/15)
2014	25	(33/131)	ND		14	(6/42)	33	(7/21)	0	(0/128)	0	(0/89)	100	(41/41)	100	(20/20)
2015	19	(22/118)	ND		36	(8/22)	50	(8/16)	0	(0/121)	0	(0/70)	100	(21/21)	100	(20/20)

(b) Polymyxin B resistance									Fosfomycin resistance					
Year	*Escherichia coli*		*Klebsiella pneumoniae*		*Pseudomonas aeruginosa*		*Proteus mirabilis*		*Escherichia coli*		*Klebsiella pneumoniae*		*Proteus mirabilis*	
	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)
2010	0	(0/107)	0	(0/21)	0	(0/16)	100	(12/12)	0	(0/102)	15	(3/20)	9	(1/11)
2011	0	(0/108)	0	(0/27)	0	(0/13)	100	(8/8)	0	(0/90)	4	(1/23)	14	(1/7)
2012	0	(0/75)	0	(0/18)	0	(0/12)	100	(11/11)	5	(1/20)	0	(0/7)	0	(0/4)
2013	0	(0/103)	0	(0/34)	0	(0/20)	100	(15/15)		ND		ND		ND
2014	0	(0/131)	0	(0/41)	0	(0/45)	100	(21/21)		ND		ND		ND
2015	0	(0/122)	0	(0/22)	0	(0/16)	95	(19/20)		ND		ND		ND

ND, Not determined.

to ceftriaxone and ceftazidime over a period of 12 years, which can be explained by the low number of *Proteus mirabilis*-positive cultures (mean 13 samples per year).

Although most pathogens showed none to minimal resistance against carbapenems, the highly significant increase in the case of *Pseudomonas aeruginosa* (from 6 % to 27 % for imipenem, P=0.026) is alarming. The GPIU study and other international studies also found the worldwide spread of carbapenem-resistant bacteria in urological departments a considerable problem [12].

Resistance against sulfamethoxazole/trimethoprim, fosfomycin and nitrofurantoin was acceptable in the case of the most frequent bacteria (except for MDR *K. pneumoniae*) despite the fact that these antibiotics were used more frequently in the last few years to reduce the usage of fluoroquinolones and cephalosporins, at least in the less severe, uncomplicated cases. Therefore, they may still be effectively used to replace fluoroquinolones in non-empirical therapy of uncomplicated lower UTIs.

The use of gentamicin is generally less frequent in Jahn Ferenc South Pest Teaching Hospital, Department of Urology, due to its toxicity. Resistance was, therefore, acceptably low, except in *K. pneumoniae* where we found significantly increasing rates.

We observed a significant increase in the rate of MDR species from 8 to 14 %, (P=0.008). This is in line with the international trends. Since 2010, 24–33 % of cultured *K. pneumoniae* strains were ESBL positive. In 2012, the rate was even higher, reaching 60 %. The rate of ESBL-resistant *Escherichia coli* varied between 6 to 9 % in the last 6 years, but in 2011 it reached 15 %. The increase of MDR bacteria, especially the increasing antimicrobial resistance of *K. pneumoniae*, with the concurrent lack of novel antimicrobial agent development is alarming. The GPIU study found that 9 % of the patients hospitalized in urological clinics developed nosocomial UTIs, due mostly to MDR uropathogens. Therefore, in the case of a nosocomial UTI, empiric antibiotic treatment should be aimed against these MDR

Table 7. MDR species

The table shows the rate of MDR MRSA, VRE, multiresistant *A. baumannii* (MRAB) and Gram-negatives, and the rate of ESBL-positive species between 2010 and 2015.

(a) MDR species

Year	MRSA		VRE		MRAB		Gram-negatives*		All	
	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)	%	(*n*/*N*)
2013	31	(4/13)	0	(0/85)	100	(1/1)	10	(18/180)	8	(23/279)
2014	40	(2/5)	0	(0/91)	25	(1/4)	9	(23/248)	7	(26/348)
2015	80	(8/10)	0	(0/82)	100	(2/2)	15	(32/211)	14	(42/305)

(b) ESBL-producing species

Year	*Escherichia coli*		*Klebsiella pneumoniae*	
	%	(*n*/*N*)	%	(*n*/*N*)
2010	6	(7/110)	27	(6/22)
2011	15	(16/108)	24	(7/29)
2012	6	(6/103)	60	(18/30)
2013	6	(6/105)	32	(11/34)
2014	9	(12/131)	24	(10/42)
2015	9	(12/129)	33	(10/30)

*Including ESBL-producing species.

pathogens (e.g. carbapenems or β–lactams with anti-*Pseudomonas* activity). When choosing antibiotics for UTIs, we also have to consider that many of these antibiotic groups, like fluoroquinolones or cephalosporins, are associated with the increasing incidence of *Clostridium difficile* infections [13].

Limitations

Our study had the following limitations. Until 2010, we had limited data transferred from the microbiology laboratory due to the absence of an electronic database. Since 2010, the incorporation of a computer system gave us the opportunity to analyse more data. As the presented data is based on the analysis of microbiological samples without clinical background information, the rate of asymptomatic bacteriuria or symptomatic UTI could not be calculated, which could introduce biases. Our analysis contained urine samples taken from catheterized patients, which might introduce bias to the interpretation of the results. In some cases, the culture was taken after several days of hospital exposure, reflecting a possible change in the collected bacteria toward hospital-acquired flora. Some antibiotics were not routinely tested by the microbiology laboratory; therefore, they were not included in our analysis. Available data for multi-drug resistance was based on criteria for the official Hungarian national nosocomial infection surveillance, which does not always match the international criteria. The statistical significance of changes in some cases, due to low numbers of bacteria, could not be measured correctly. Since *K. pneumoniae* is naturally resistant to ampicillin, the reported resistance rate of 88 % in 2005 (Table 2) is considered to be incorrect.

Conclusion

Since the local pathogen profile and antimicrobial susceptibility may vary geographically and temporally, knowledge of the local bacterial spectrum and susceptibility patterns is mandatory for the correct empiric treatment of UTIs. The surveillance of antimicrobial use is necessary for establishing an appropriate infection control program and antibiotic policy. We recommend decreasing unnecessary usage of fluoroquinolones and cephalosporins in our region, and recommend instead the prescription of antimicrobials with low potencies for collateral damage, especially in less severe cases.

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Conflicts of interest
The authors declare that there are no conflicts of interest.

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II.

Húgyúti kórokozók spektrumának és antibiotikum-rezisztenciájának változása osztályunkon 2004 és 2017 között

Magyar András dr.[1], Dobák András dr.[2], Bálint Péter dr.[1], Vinodh Kumar Adithyaa Arthanareeswaran dr.[3], Nagy Károly dr.[1], Póth Sándor dr.[1], Bata Anikó dr.[1], Tenke Péter dr.[1], Köves Béla dr.[1]

[1]Jahn Ferenc Dél-pesti Kórház és Rendelőintézet, Urológiai Osztály, Budapest (osztályvezető: Tenke Péter dr.)

[2]Corden International, Budapest

[3]Lipcsei Egyetem, Urológiai Klinika, Németország (igazgató: Jens-Uwe Stolzenburg dr.)

Levelezési cím:
Dr. Magyar András
1076 Budapest, Thököly út 21. III/28.
E-mail: magyara@gmail.com
Tel.: +36 31 783-9686

ÖSSZEFOGLALÁS

Bevezetés: A húgyúti fertőzések empirikus kezelése során elengedhetetlen a helyi rezisztenciaviszonyok és az előforduló baktériumok spektrumának ismerete, hiszen ezek földrajzilag és időben is jelentős változatosságot mutathatnak. Célunk az osztályunkon vett vizeletmintákból nyert kórokozók előfordulásának és a leggyakoribb kórokozók antibiotikum-rezisztenciájának évente történő felmérése.

Anyag és módszerek: Osztályunkon minden középsugaras és katéteres vizeletmintából kitenyészett kórokozót és azok antibiotikum-rezisztenciáját rögzítettük 2004 és 2017 között. A bakteriális spektrum és rezisztenciaváltozások statisztikai analízise során a Cochran–Armitage-tesztet alkalmaztuk ($p<0,05$).

Eredmények: Összesen 3513 vizeletmintában igazolódott szignifikáns mennyiségű kórokozó. A leggyakoribb két kórokozó az *Escherichia coli* és az *Enterococcus faecalis* voltak. Az *E. coli* ciprofloxacin rezisztenciája szignifikánsan nőtt a vizsgálati időszakban, elérte a 25%-ot, míg cefalosporinokkal szemben az *E. coli* rezisztenciája 20% alatt maradt.

Következtetések: Súlyos húgyúti fertőzések empirikus kezelésére a fluorokinolonok alkalmazása nem javasolt régiónkban. A cefalosporinok Gram-negatív fertőzések esetén empirikusan biztonsággal alkalmazhatók, viszont kerülendők multirezisztens kórokozók gyanúja esetén. Minden osztály számára javasoljuk a kórokozók spektrumának, illetve érzékenységének évenként történő feltérképezését.

KULCSSZAVAK

ANTIBIOTIKUM, REZISZTENCIA, UROPATOGÉNEK, BAKTERIÁLIS SPEKTRUM

Changes In The Bacteial Spectrum And Antibiotic Resistance Pattern Of Uropathogens At Our Department Between 2004 And 2017

SUMMARY

Objective: Since bacterial antibiotic resistance rates may vary with significant differences between countries and regions, as well as change over time, yearly surveillance of the bacterial spectrum and antibiotic-resistance patterns of locally occurring uropathogens is essential to serve as a basis for empirical treatment of urinary tract infections (UTIs). The objective of our study was to investigate the changes in the bacterial spectrum and the antibiotic resistance rates of uropathogens cultured from urine samples collected at our department.

Material and methods: All urine samples taken at our department, from 2004 to 2017 were retrospectively analyzed. The significance rates of the annual changes were calculated using Cochran-Armitage test ($p<0.05$).

Results: A total of 3513 urine cultures showed significant presence of pathogens. *Escherichia coli* and *Enterococcus faecalis* were the most frequently isolated bacteria. Resistance of *E. coli* to ciprofloxacin has increased significantly, reaching a rate of 25%, while in the case of cephalosporines, resistance of *E. coli* remained under 20%.

Conclusion: For empirical treatment fluoroquinolones can be no longer recommended in our region. Gram-negative UTIs can be safely treated with cephalosporines, however, they should be avoided if multi-drug resistant bacteria are suspected. Surveillance and monitoring of the bacterial resistance patterns is recommended for all institutions.

KEYWORDS

ANTIBIOTICS, RESISTANCE, UROPATHOGENS, BACTERIAL SPECTRUM

Bevezetés

Az antibiotikumok széles körű alkalmazása a baktériumok rezisztenciájának fokozatos növekedéséhez vezet. Ahhoz, hogy ezt a folyamatot elkerülhessük, illetve lelassítsuk, ezáltal javítva az antibiotikum-kezelések eredményességét, összehangolt nemzetközi stratégiák kidolgozása és széles körű alkalmazása szükséges (1–3).
Egy adott kórképért felelős baktériumok aránya és rezisztenciája időben változhat és földrajzilag is jelentős eltérést mutathat, mivel a helyi antibiotikum-kezelési stratégiák jelentősen befolyásolják a baktériumok antibiotikum-rezisztenciájának alakulását az adott régióban. Ezért alapvetően fontos a helyi rezisztenciaviszonyok időszakos felmérése az urológiai gyakorlatban, mivel ezek ismeretén alapul a húgyúti fertőzések eredményes empirikus kezelése és a sebészeti antibiotikum-profilaxis megtervezése (4, 5). Retrospektív vizsgálatunknak az volt a célja, hogy felmérjük a Jahn Ferenc Dél-pesti Kórház és Rendelőintézet Urológiai osztályán vett vizeletmintákból kitenyészett kórokozók előfordulását és antibiotikum-rezisztenciáját, továbbá megvizsgáljuk azok időbeli változását. A régebbi, 2004–2015 közötti eredményeinket előzőleg angol nyelven közöltük (6). Célunk a legfrissebb, 2016–2017-ben felmért adatok közzététele, továbbá a korábbi adataink bemutatása a magyar közönség részére.

Anyag és módszerek

A Jahn Ferenc Kórház és Rendelőintézet Urológiai Osztályán minden osztályon levett vizelettenyésztés-eredményt rögzítettük a 2004 és 2017 közötti időszakban. Ide tartoztak a középsugaras, katéteres és punkció során vett vizeletminták vizsgálatainak eredményei egyaránt. A mintákat húgyúti fertőzések miatt, illetve a műtéti előkészítés részeként adták le a betegek. A bakteriális spektrum- és rezisztenciaváltozásait a Cochran–Armitage-teszt segítségével vizsgáltuk (szignifikancia küszöb: $p<0,05$). Az adatok kielemzése során a következő módszereket és egyszerűsítéseket alkalmaztuk:

1. a rezisztenciaarányok antibiotikumonként kerültek feltüntetésre;
2. a leggyakoribb 5 baktérium antibiotikum-rezisztenciáját és időbeli változását vizsgáltuk, amelyek a minták több mint 5%-ában jelen voltak;
3. azokban az években, ahol kevés esetszámot észleltünk, az ebből adódó kiugrásokat a legközelebbi éves adatok átlagának kiszámításával küszöböltük ki;
4. a 2010-ig gyűjtött adatok korlátozott mennyiségben voltak elérhetőek a számítógépes rendszer akkori hiánya miatt;
5. az adatok hiányosságát a táblázatok celláiban N.M. (nincs meghatározva) jelzéssel láttuk el, amelybe a mikrobiológus döntése alapján nem vizsgált esetek is beletartoznak.

A 2010-ben bevezetett számítógépes rendszer az adatok sokkal részletesebb, pontosabb elemzését tette lehetővé.

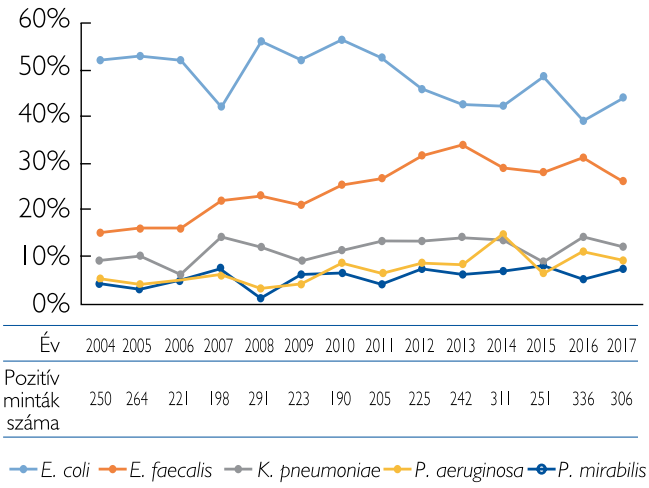
Tenyésztéses módszerek

A vizeletminták bórsavas tartályokban kerültek átszállításra a mikrobiológiai laboratóriumba.
A baktériumokat 0,01 ml-es kaccsal oltották BD Brilliance UTI agar táptalajra. Az inkubáció 37 °C-on történt, 16-18 órán keresztül, hagyományos termosztátban. Ezt követően a baktériumkolóniák Oxoid-Columbia blood, illetve MacConkey agar táptalajra (Oxoid) kerültek leoltásra. A baktériumok azonosításához BD Phoenix automatizált rendszert (BD Biosciences), vagy ENTEROtest 16 kit-et alkalmaztak (Lachema). A vizelettenyésztés módszertana érdemben nem változott az évek során. 2011-ig a baktériumok antibiotikum-érzékenységét BD Phoenix automatizált rendszer, vagy Mueller–Hinton-agar segítvégével vizsgálták a Clinical and Laboratory Standards Institute (CLSI) irányelvek tükrében (7). 2011-től az European Committee on Antimicrobial Susceptibility Testing (EUCAST) standardoknak megfelelően végezték a vizsgálatokat (8). A MIC-értékek megállapítását BD Phoenix automatizált rendszer, vagy Liofilchem MIC-csíkok segítségével végezték. Az inkubálást követően az izolátumokat az EUCAST MIC-határérték táblázatoknak megfelelően a következő kategóriákba sorolták: érzékeny, mérsékelten érzékeny, rezisztens (8).

Eredmények

Bakteriális spektrum

A vizsgált 14 éves időszakban összesen 3513 vizeletmintában igazolódott szignifikáns mennyiségű kórokozó. A kitenyészett baktériumok spektrumának időbeli változása az *1. ábrán* látható. A bakteriális spektrumban az évek során érdemi változás nem történt. A vizsgálati időszakban a leggyakoribb kórokozónak az *Escherichia coli* bizonyult, az esetek 48%-ában tenyészett ki. A legmagasabb értéket 2008-ban érte el, ekkor



1. ÁBRA: A LEGGYAKORIBB BAKTÉRIUMOK: AZ OSZTÁLYUNKON LEVETT VIZELETMINTÁKBÓL KITENYÉSZETT BAKTÉRIUMOK SPEKTRUMÁNAK IDŐBELI VÁLTOZÁSA A 2004–2017 KÖZÖTTI IDŐSZAKBAN

az esetek 56%-ában fordult elő, míg a legalacsonyabb érték 2016-ban volt mérhető: 39%. Az *Enterococcus faecalis* gyakorisága szignifikánsan növekedett a vizsgálati időszakban: a 2004-ben észlelt 15%-ról 2017-re 26%-ra nőtt (p<0,0001). A Klebsiella pneumoniae átlagosan 11% körüli előfordulása érdemben nem változott az évek során (p=0,797). A Pseudomonas aeruginosa aránya enyhén emelkedett (p=0,044), míg a Proteus mirabilis aránya nem változott (p=0,382), de mindkettő előfordulási aránya többnyire 10% alatt maradt.

Rezisztenciaviszonyok

A baktériumok antibiotikum-rezisztencia arányainak összesítése az *1–6. táblázatokban* látható.

Fluorokinolonok *(1. táblázat)*

Tizennégy év alatt az *E. coli* ciprofloxacin rezisztenciája szignifikánsan, 19%-ról 25%-ra nőtt (p=0,039). A K. pneumoniae ciprofloxacin és norfloxacin rezisztenciája 26% és 59% között ingadozott. Az *E. faecalis* esetén a ciprofloxacin-rezisztencia végig magasabb volt, mint 47%, míg a levofloxacin-rezisztencia 30-42% közötti értékeket mutatott. A *P. aeruginosa* rezisztenciája ciprofloxacinnal és levofloxacinnal szemben csökkenő tendenciát mutatott, ami azonban nem volt szignifikáns: ciprofloxacin vonatkozásában 38%-ról 15%-ra (p=0,086), míg levofloxacin esetében 38%-ról 19%-ra csökkent (p=0,09). A *P. mirabilis* ciprofloxacin rezisztenciája 10% és 44% között ingadozott a vizsgálati időszakban.

Penicillinszármazékok *(2. táblázat)*

Az *E. coli* esetében az ampicillinrezisztencia érdemben nem változott: 2004-ben 57%-ot, 2017-ben 54%-ot mutatott. Az *E. faecalis* ampicillin rezisztenciája sem nőtt, 0% és 2% között mozgott. A *K. pneumoniae* rezisztenciája szintén változatlan, 100% maradt. A *P. mirabilis* esetében ugyanakkor az ampicillinrezisztencia 2015-ig szignifikánsan emelkedett 20%-ról 40%-ra (p=0,007), majd az ezt követő években csökkenő tendenciát mutatott. Az *E. coli* amoxicillin/clavulánsav rezisztenciája 6% és 35% között ingadozott. A *K. pneumoniae* esetén pedig szignifikánsan nőtt 17%-ról 62%-ra (p<0,0001). Amoxicillin/clavulánsavval szemben a P. *mirabilis* rezisztenciája az évek döntő többségében 10% alatti értékeket mutatott.

Karbapenemek *(3. táblázat)*

Imipenem, meropenem és ertapenem vonatkozásában nem észleltünk számottevő mennyiségű rezisztens *E. coli, K. pneumoniae, E. faecalis* és *P. mirabilis* törzset a vizsgálati időszakban. A *P. aeruginosa* ugyanakkor jelentős rezisztencianövekedést mutatott imipenemmel szemben, míg 2010-ben 6%, 2017-ben már 19%-os értéket mértünk (p=0,004).

1. TÁBLÁZAT: REZISZTENCIA FLUOROKINOLONOKKAL SZEMBEN: A LEGGYAKORIBB KÓROKOZÓK CIPROFLOXACIN, LEVOFLOXACIN ÉS NORFLOXACIN REZISZTENCIÁJA 2004 ÉS 2017 KÖZÖTT

Ciprofloxacin rezisztencia											Levofloxacin rezisztencia					
Év	E. coli		E. faecalis		K. pneumoniae		P. aeruginosa		P. mirabilis		E. coli		E. faecalis		P. aeruginosa	
	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)
2004	19	(25/130)	100	(38/38)		N.M.	38	(5/13)		N.M.	0	(0/22)		N.M.	38	(5/13)
2005	18	(25/140)	100	(42/42)		N.M.	27	(3/11)		N.M.	0	(0/12)		N.M.	40	(4/10)
2006	22	(25/115)	97	(34/35)		N.M.	36	(4/11)		N.M.	14	(1/7)		N.M.	40	(4/10)
2007	27	(22/83)	100	(44/44)		N.M.	33	(4/12)		N.M.	12	(2/17)		N.M.	33	(4/12)
2008	15	(24/156)	52	(34/66)	34	(11/32)	14	(1/7)	50	(2/4)	12	(2/17)		N.M.	17	(1/6)
2009	24	(28/116)	96	(45/47)	30	(6/20)	22	(2/9)	38	(5/13)	9	(1/11)		N.M.	25	(2/8)
2010	22	(24/107)	47	(22/47)	29	(6/21)	19	(3/16)	33	(4/12)	0	(0/13)		N.M.	13	(2/15)
2011	32	(34/108)	56	(31/55)	26	(7/27)	15	(2/13)	13	(1/8)	0	(0/15)		N.M.	15	(2/13)
2012	24	(25/103)	50	(9/18)	59	(17/29)	16	(3/19)	44	(7/16)	0	(0/25)		N.M.	38	(6/16)
2013	22	(23/103)		N.M.	32	(11/34)	5	(1/20)	13	(2/15)		N.M.		N.M.	5	(1/20)
2014	25	(33/131)		N.M.	29	(12/42)	22	(10/45)	19	(4/21)		N.M.	41	(24/59)	22	(10/45)
2015	25	(31/122)		N.M.	50	(11/22)	13	(2/16)	10	(2/20)		N.M.	40	(26/65)	19	(3/16)
2016	24	(31/131)		N.M.	49	(24/49)	26	(10/38)	24	(4/17)		N.M.	42	(42/100)	28	(10/35)
2017	25	(33/131)		N.M.	51	(19/37)	15	(4/27)	21	(4/19)		N.M.	30	(22/73)	19	(5/27)

Norfloxacin rezisztencia						
Év	E. coli		K. pneumoniae		P. mirabilis	
	%	(n/N)	%	(n/N)	%	(n/N)
2008	14	(22/153)	36	(12/33)	50	(2/4)
2009	18	(21/116)	35	(7/20)	46	(6/13)
2010	22	(24/107)	29	(6/21)	33	(4/12)
2011	32	(34/106)	26	(7/27)	13	(1/8)
2012	25	(25/102)	57	(17/30)	44	(7/16)
2013	23	(23/102)	32	(11/34)	13	(2/15)
2014	25	(32/128)	29	(12/42)	20	(4/20)
2015	25	(31/122)	48	(10/21)	10	(2/20)
2016	24	(31/131)	50	(24/48)	24	(4/17)
2017	25	(33/132)	51	(19/37)	21	(4/19)

N.M. = nincs meghatározva

Cefalosporinok *(4. táblázat)*

E. coli esetében a cefuroximrezisztencia enyhén, nem szignifikáns mértékben emelkedett 8%-ról 14%-ra (p=0,741). A *K. pneumoniae* cefuroxim rezisztenciája 24% és 60% között váltakozott, míg *P. mirabilis* esetén 8%-nál magasabb érték nem volt tapasztalható. A cefixim vonatkozásában az *E. coli* rezisztenciája nem haladta meg a 14%-ot, míg *P. mirabilis* esetében csak 2017-ben találkoztunk rezisztens törzsekkel, az esetek 16%-ában. *K. pneumoniae* esetén statisztikailag nem szignifikáns rezisztencianövekedés volt tapasztalható cefiximmel szemben: 2010-ben 29%-os, míg 2017-ben 51%-os arányt mértünk (p=0,075). Ceftriaxonnal szemben az *E. coli* rezisztenciája szignifikáns emelkedést mutatott. Míg 2004-ben 1% volt, 2017-ig ez az arány 12%-ig emelkedett (p <0,0001). *K. pneumoniae* esetében a ceftriaxon rezisztencia 24% (és 57% között ingadozott a vizsgálati időszak második felében, míg *P. mirabilis* esetében ceftriaxon rezisztenciát nem észleltünk. A *P. aeruginosa* ceftazidim rezisztenciája 0% (0/20) és 16% (3/19) között ingadozott. Az *E. coli* cefepim rezisztenciája szignifikáns növekedést mutatott (p<0,0001). Míg 2004-ben 1%-os, 2012-ben már 8%-os értékeket számoltunk. Cefepimmel szemben a *K. pneumoniae* rezisztenciája 2012-ben elérte a 40%-ot. A *P. aeruginosa* és *P. mirabilis* esetén észlelt rezisztenciaarányok cefepimmel szemben csökkenő tendenciát mutattak. Míg *P. aeruginosa* esetében 15%-ról 4%-ra (p=0,45), *P. mirabilis* vonatkozásában 10%-ról 0%-ra csökkent (p=0,331), bár ezek az változások nem voltak statisztikailag szignifikánsak.

Aminoglikozidok *(5. táblázat)*

A gentamicin-rezisztencia *E. coli* törzsek esetén 7% alatt maradt, miközben *E. faecalis* vonatkozásában szignifikánsan csökkent 100%-ról 48%-ra (p<0,0001). *P. aeruginosa* esetén 31%-ról 7%-ra, míg *P. mirabilis* esetén 30%-ról 12%-ra csökkent (p=0,013 és p=0,002). Csupán a *K. pneumoniae* gentamicin rezisztenciája mutatott szignifikáns, 0%-ról 32%-ra történő emelkedést (p<0,0001).

Az *E. coli* amikacin rezisztenciája szignifikánsan csökkent (p=0,003): míg 2004-ben az arány 4% volt, 2011-ben 0%-os értéket számoltunk. Az ezt követő években mértékét rutinszerűen már nem vizsgáltuk. A *P. aeruginosa* rezisztenciája amikacinnal szemben az utóbbi években nem haladta meg a 6%-ot. *K. pneumoniae* és *P. mirabilis* esetén sem észleltünk jelentős amikacin-rezisztenciát.

Trimetoprim/szulfametoxazol *(6. a táblázat)*

Az *E. coli* esetén számított trimetoprim/szulfametoxazol rezisztencia 19% (2015-ben) és 32% között ingadozott. *K. pneumoniae* vonatkozásában aránya szignifikánsan, a 2004-ben észlelt 13%-ról 2017-ben mért 44%-ra nőtt (p<0,0001). Legmagasabb értékét 2012-ben érte el, ekkor 63%-os rezisztenciaarányt mutatott. *P. mirabilis* esetén a rezisztencia 20% és 63% között mozgott.

Nitrofurantoin *(6. a táblázat)*

Az *E. coli* nitrofurantoin rezisztenciája összességben nem haladta meg a 2%-ot, ezzel szemben a *K. pneumoniae* és *P. mirabilis* esetében elérte a 100%-ot.

Foszfomicin *(6. b táblázat)*

A foszfomicinnel szemben kialakuló rezisztenciát 2010 és 2012 között vizsgáltuk. E. *coli* esetében 0-5%, *K. pneumoniae* vonatkozásában 0-15%, *P. mirabilis* esetén pedig 0-14%-os értékeket kaptunk.

2. TÁBLÁZAT: REZISZTENCIA PENICILLIN SZÁRMAZÉKOKKAL SZEMBEN: A LEGGYAKORIBB KÓROKOZÓK AMPICILLIN ÉS AMOXICILLIN/KLAVULÁNSAV REZISZTENCIÁJA 2004 ÉS 2017 KÖZÖTT

	Ampicillin rezisztencia								Amoxicillin/klavulánsav rezisztencia					
Év	E. coli		E. faecalis		K. pneumoniae		P. mirabilis		E. coli		K. pneumoniae		P. mirabilis	
	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)
2004	57	(74/130)	0	(0/38)	100	(23/23)	20	(2/10)	23	(30/130)	17	(4/23)	10	(1/10)
2005	40	(56/140)	0	(0/42)	88	(23/26)	25	(2/8)	14	(20/140)	19	(5/26)	0	(0/8)
2006	53	(61/115)	0	(0/35)	100	(13/13)	18	(2/11)	28	(32/115)	23	(3/13)	9	(1/11)
2007	48	(40/83)	2	(1/44)	100	(28/28)	21	(3/14)	18	(15/83)	14	(4/28)	7	(1/14)
2008	49	(76/156)	0	(0/66)	100	(33/33)	50	(2/4)	6	(10/156)	6	(2/33)	25	(1/4)
2009	52	(60/116)	0	(0/47)	100	(20/20)	23	(3/13)	19	(22/116)	15	(3/20)	8	(1/13)
2010	67	(72/107)	0	(0/47)	100	(21/21)	33	(4/12)	17	(18/107)	33	(7/21)	0	(0/12)
2011	57	(61/107)	2	(1/55)	100	(27/27)	38	(3/8)	23	(25/107)	26	(7/27)	13	(1/8)
2012	52	(53/103)	0	(0/71)	100	(29/29)	44	(7/16)	15	(15/103)	57	(17/30)	0	(0/16)
2013	45	(46/103)	1	(1/82)	100	(34/34)	53	(8/15)	14	(14/103)	47	(16/34)	7	(1/15)
2014	60	(78/131)	0	(0/90)	100	(42/42)	52	(11/21)	35	(46/131)	38	(16/42)	19	(4/21)
2015	54	(66/122)	0	(0/70)	100	(22/22)	40	(8/20)	28	(34/122)	59	(13/22)	5	(1/20)
2016	54	(71/132)	2	(2/105)	100	(49/49)	35	(6/17)	18	(24/132)	53	(26/49)	6	(1/17)
2017	54	(72/133)	0	(0/79)	100	(37/37)	32	(6/19)	26	(35/133)	62	(23/37)	11	(2/19)

3. TÁBLÁZAT: REZISZTENCIA KARBAPENEMEKKEL SZEMBEN: A LEGGYAKORIBB KÓROKOZÓK IMIPENEM, MEROPENEM ÉS ERTAPENEM REZISZTENCIÁJA 2008 ÉS 2017 KÖZÖTT

Imipenem rezisztencia										
Év	E. coli		E. faecalis		K. pneumoniae		P. aeruginosa		P. mirabilis	
	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)
2008	0	(0/156)	N.M.		0	(0/33)	0	(0/7)	25	(1/4)
2009	0	(0/116)	N.M.		0	(0/20)	0	(0/9)	15	(2/13)
2010	0	(0/107)	N.M.		0	(0/21)	6	(1/16)	0	(0/12)
2011	0	(0/108)	N.M.		0	(0/27)	15	(2/13)	0	(0/8)
2012	0	(0/101)	0	(0/14)	0	(0/30)	5	(1/19)	0	(0/16)
2013	0	(0/103)	0	(0/9)	0	(0/32)	5	(1/20)	0	(0/15)
2014	0	(0/131)	0	(0/10)	0	(0/42)	16	(7/45)	0	(0/21)
2015	0	(0/122)	0	(0/49)	0	(0/22)	27	(4/15)	0	(0/19)
2016	0	(0/132)	1	(1/105)	0	(0/49)	26	(10/38)	0	(0/2)
2017	0	(0/132)	0	(0/78)	0	(0/36)	19	(5/27)		N.M.

Meropenem rezisztencia									Ertapenem rezisztencia					
Év	E. coli		K. pneumoniae		P. aeruginosa		P. mirabilis		E. coli		K. pneumoniae		P. mirabilis	
	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)
2010	0	(0/85)	0	(0/16)	0	(0/16)	0	(0/12)	0	(0/107)	0	(0/21)	0	(0/12)
2011	0	(0/108)	0	(0/22)	15	(2/13)	0	(0/8)	0	(0/108)	0	(0/27)	0	(0/8)
2012	0	(0/75)	0	(0/20)	5	(1/19)	0	(0/11)	0	(0/103)	0	(0/30)	0	(0/16)
2013	0	(0/99)	0	(0/31)	0	(0/20)	0	(0/15)	0	(0/103)	0	(0/34)	0	(0/15)
2014	0	(0/131)	0	(0/41)	16	(7/45)	0	(0/21)	0	(0/131)	0	(0/42)	0	(0/21)
2015	0	(0/121)	0	(0/22)	19	(3/16)	0	(0/19)	0	(0/122)	0	(0/22)	0	(0/20)
2016	0	(0/129)	0	(0/49)	18	(7/38)	0	(0/17)	0	(0/132)	0	(0/49)	0	(0/17)
2017	0	(0/132)	0	(0/36)	15	(4/27)	0	(0/19)	0	(0/133)	0	(0/37)	0	(0/19)

N.M. – nincs meghatározva

Polimixin B *(6. b táblázat)*

E. coli, K. pneumoniae és *P. mirabilis* esetében a vizsgálati időszakban egyáltalán nem észleltünk rezisztenciát Polimixin B-vel szemben, viszont a *P. mirabilis* gyakorlatilag 100%-os rezisztenciát mutatott.

Az *E. faecalis* rezisztenciája vancomycinnel szemben a vizsgálati időszakban végig 0% volt.

A *P. aeruginosa* kolisztin rezisztenciája 0% és 8% között, tobramycin rezisztenciája pedig 0% és 16% között változott, míg piperacillin/tazobactam rezisztenciája 2017-ben elérte a 12%-ot.

Megbeszélés

A hospitalizált betegek húgyúti fertőzéseinek megfelelő kezeléséhez a helyileg előforduló húgyúti kórokozók spektrumának és antibiotikum-rezisztenciájának ismerete szükséges, ezért rendkívül fontos ezen adatok évről évre történő felmérése. Ezen adatok ismerete segítségül szolgálhat a megfelelő antibiotikum kiválasztásakor húgyúti fertőzések empirikus kezelése, illetve sebészeti műtéti profilaxis során (9, 10).

A legnagyobb urológiai nozokomiális infekciókat és bakteriális antibiotikum rezisztenciaviszonyokat felmérő nemzetközi prevalencia vizsgálat a Global Prevalence of Infections in Urology (GPIU) study. Ennek során minden évben világszerte felmérik a rezisztenciaviszonyokat, a nozokomiális húgyúti fertőzések előfordulását, rizikófaktorait és az antibiotikum-kezelési szokásokat. A GPIU legutóbbi 2003–2010-es adatainak összegzése szerint Észak-Európában, ahova Magyarországot is besorolták, a leggyakoribb kórokozó az *Escherichia coli* (36%) és az Enterococcus species (14%) (11). A Jahn Ferenc Dél-pesti Kórház és Rendelőintézet Urológiai Osztályán az esetek körülbelül felében *E. coli* tenyészett ki, amely arány magasabb, mint az észak-európai országokban és inkább megközelíti a dél-európai országokban észlelt 55%-os értéket. Az *E. coli* aránya az évek során csökkenő tendenciát mutat. A második leggyakoribb kórokozó osztályunkon az *Enterococcus faecalis* (2017-ben 26%). Arányának növekedése az endourológiai beavat-

4. TÁBLÁZAT: REZISZTENCIA CEPHALOSPORINOKKAL SZEMBEN: A LEGGYAKORIBB KÓROKOZÓK CEFAMANDOL, CEFUROXIME, CEFTRIAXONE, CEFIXIME, CEFTAZIDIME ÉS CEFEPIME REZISZTENCIÁJA 2004 ÉS 2017 KÖZÖTT

Cefamandol rezisztencia						
Év	E. coli		K. pneumoniae		P. mirabilis	
	%	(n/N)	%	(n/N)	%	(n/N)
2004	4	(5/130)	4	(1/23)	0	(0/10)
2005	5	(7/140)	8	(2/26)	13	(1/8)
2006	16	(18/115)	0	(0/13)	18	(2/11)
2007	4	(3/83)	4	(1/28)	21	(3/14)
2008	0	(0/156)	3	(1/33)	0	(0/4)
2009	7	(8/116)	5	(1/20)	8	(1/13)
2010	7	(7/107)	0	(0/21)	0	(0/12)

Cefuroxim rezisztencia							Ceftriaxon rezisztencia						Cefixim rezisztencia					
Év	E. coli		K. pneumoniae		P. mirabilis		E. coli		K. pneumoniae		P. mirabilis		E. coli		K. pneumoniae		P. mirabilis	
	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)
2004	8	(9/107)	29	(6/21)	8	(1/12)	1	(1/129)	0	(0/23)	0	(0/10)	N.M.		N.M.		N.M.	
2005	18	(19/108)	30	(8/27)	0	(0/8)	0	(0/140)	4	(1/26)	0	(0/8)	N.M.		N.M.		N.M.	
2006	8	(8/103)	60	(18/30)	6	(1/16)	1	(1/115)	0	(0/13)	9	(1/11)	N.M.		N.M.		N.M.	
2007	7	(7/103)	32	(11/34)	0	(0/15)	2	(2/83)	0	(0/28)	0	(0/14)	N.M.		N.M.		N.M.	
2008	10	(13/131)	24	(10/42)	0	(0/21)	0	(0/156)	0	(0/33)	0	(0/4)	0	(0/1)	N.M.		0	(0/4)
2009	12	(15/122)	50	(11/22)	0	(0/20)	5	(6/115)	0	(0/20)	0	(0/13)	4	(5/116)	N.M.		0	(0/13)
2010	8	(9/107)	29	(6/21)	8	(1/12)	9	(9/106)	29	(6/21)	0	(0/12)	8	(8/106)	29	(6/21)	0	(0/12)
2011	18	(19/108)	30	(8/27)	0	(0/8)	16	(17/108)	26	(7/27)	0	(0/8)	14	(15/106)	26	(7/27)	0	(0/8)
2012	8	(8/103)	60	(18/30)	6	(1/16)	6	(6/103)	57	(17/30)	0	(0/16)	7	(2/25)	57	(17/30)	0	(0/16)
2013	7	(7/103)	32	(11/34)	0	(0/15)	7	(7/103)	32	(11/34)	0	(0/15)	7	(7/101)	32	(11/34)	0	(0/15)
2014	10	(13/131)	24	(10/42)	0	(0/21)	9	(12/131)	24	(10/42)	0	(0/21)	9	(11/128)	24	(10/42)	0	(0/20)
2015	12	(15/122)	50	(11/22)	0	(0/20)	8	(10/122)	46	(10/22)	0	(0/20)	10	(12/122)	48	(10/21)	0	(0/20)
2016	10	(13/132)	43	(21/49)	0	(0/17)	8	(10/122)	43	(21/49)	0	(0/17)	10	(13/131)	44	(21/48)	0	(0/17)
2017	14	(18/132)	58	(21/36)	0	(0/19)	12	(16/133)	51	(19/37)	0	(0/19)	12	(16/133)	51	(19/37)	16	(3/19)

Ceftazidim rezisztencia									Cefepim rezisztencia							
Év	E. coli		K. pneumoniae		P. aeruginosa		P. mirabilis		E. coli		K. pneumoniae		P. aeruginosa		P. mirabilis	
	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)
2004	N.M.		N.M.		N.M.		N.M.		1	(1/129)	0	(0/23)	15	(2/13)	10	(1/10)
2005	N.M.		N.M.		N.M.		N.M.		0	(0/139)	0	(0/26)	9	(1/11)	0	(0/8)
2006	N.M.		N.M.		N.M.		N.M.		2	(2/114)	0	(0/13)	9	(1/11)	9	(1/11)
2007	N.M.		N.M.		N.M.		N.M.		2	(2/83)	0	(0/28)	0	(0/12)	0	(0/14)
2008	0	(0/156)	0	(0/33)	0	(0/7)	0	(0/4)	0	(0/156)	0	(0/33)	0	(0/7)	0	(0/4)
2009	5	(6/116)	15	(3/20)	11	(1/9)	0	(0/13)	7	(8/116)	0	(0/20)	11	(1/9)	15	(2/13)
2010	9	(9/106)	29	(6/21)	13	(2/16)	0	(0/12)	8	(8/106)	29	(6/21)	13	(2/16)	0	(0/12)
2011	16	(17/108)	26	(7/27)	8	(1/13)	0	(0/8)	16	(17/108)	26	(7/27)	8	(1/13)	0	(0/8)
2012	6	(6/100)	59	(17/29)	16	(3/19)	0	(0/16)	8	(8/103)	40	(4/10)	12	(2/17)	0	(0/16)
2013	7	(7/103)	32	(11/34)	0	(0/20)	0	(0/15)	N.M.		33	(4/12)	0	(0/20)	N.M.	
2014	9	(11/129)	22	(9/41)	13	(6/45)	0	(0/21)	N.M.		100	(1/1)	7	(3/45)	N.M.	
2015	8	(10/122)	46	(10/22)	6	(1/16)	0	(0/20)	N.M.		N.M.		6	(1/16)	N.M.	
2016	8	(10/132)	43	(21/49)	16	(6/38)	0	(0/17)	N.M.		N.M.		9	(3/35)	N.M.	
2017	12	(16/133)	51	(19/37)	11	(3/27)	0	(0/19)	N.M.		N.M.		4	(1/25)	N.M.	

N.M. – nincs meghatározva

5. TÁBLÁZAT: REZISZTENCIA AMINOGLYCOSIDOKKAL SZEMBEN: LEGGYAKORIBB KÓROKOZÓK GENTAMICIN ÉS AMIKACIN REZISZTENCIÁJA 2004 ÉS 2017 KÖZÖTT

	Gentamicin rezisztencia										Amikacin rezisztencia							
Év	E. coli		E. faecalis		K. pneumoniae		P. aeruginosa		P. mirabilis		E. coli		K. pneumoniae		P. aeruginosa		P. mirabilis	
	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)
2004	6	(8/130)	100	(38/38)	0	(0/23)	31	(4/13)	30	(3/10)	4	(5/130)	N.M.		0	(0/13)	N.M.	
2005	7	(10/140)	100	(42/42)	4	(1/26)	36	(4/11)	38	(3/8)	3	(4/140)	N.M.		0	(0/11)	N.M.	
2006	4	(5/115)	100	(35/35)	0	(0/13)	45	(5/11)	45	(5/11)	1	(1/115)	N.M.		18	(2/11)	N.M.	
2007	5	(4/83)	100	(44/44)	4	(1/28)	33	(4/12)	29	(4/14)	7	(6/83)	N.M.		0	(0/12)	N.M.	
2008	0	(0/156)	53	(35/66)	0	(0/33)	0	(0/7)	25	(1/4)	0	(0/7)	0	(0/2	0	(0/7)	0	(0/1)
2009	4	(5/116)	100	(47/47)	0	(0/20)	22	(2/9)	15	(2/13)	0	(0/116)	0	(0/20)	0	(0/9)	0	(0/13)
2010	4	(4/107)	38	(18/47)	24	(5/21)	0	(0/16)	8	(1/12)	0	(0/107)	0	(0/21)	0	(0/16)	0	(0/12)
2011	3	(3/108)	38	(21/55)	30	(8/27)	15	(2/13)	0	(0/8)	0	(0/108)	0	(0/27)	0	(0/13)	0	(0/8)
2012	1	(1/72)	53	(38/71)	36	(10/28)	21	(4/19)	6	(1/16)	0	(0/21)	10	(1/10)	0	(0/19)	0	(0/5)
2013	2	(2/103)	44	(36/82)	21	(7/34)	5	(1/20)	20	(3/15)	0	(0/1)	0	(0/3)	5	(1/20)	0	(0/4)
2014	5	(6/131)	50	(45/90)	2	(1/42)	18	(8/45)	14	(3/21)	0	(0/3)	0	(0/1)	2	(1/45)	0	(0/1)
2015	6	(7/122)	50	(35/70)	36	(8/22)	13	(2/16)	15	(3/20)	0	(0/1)	0	(0/1)	6	(1/16)	0	(0/2)
2016	6	(8/132)	49	(51/105)	25	(12/49)	21	(8/38)	0	(0/17)	0	(0/1)	0	(0/1)	3	(1/37)		N.M.
2017	2	(2/133)	48	(38/79)	32	(12/37)	7	(2/27)	12	(2/17)		N.M.		N.M.	0	(0/25)		N.M.

N.M. – nincs meghatározva

kozások és húgyúti idegentestek elterjedésével magyarázható, amit figyelembe kell vennünk az antibiotikum-kiválasztáskor empirikus kezelések során.

A bakteriális antibiotikum-rezisztencia tekintetében ellentmondó eredmények születtek. A 2003–2010-es GPIU-vizsgálat során nem észleltek egyértelmű bakteriális rezisztencianövekedést a legtöbb antibiotikummal szemben, míg osztályunkon néhány antibiotikum vonatkozásában szignifikáns rezisztenciaemelkedést tapasztaltunk. Az *E. coli* ciprofloxacin rezisztenciája szignifikánsan nőtt 19%-ról 25%-ra. Bár ezen érzékek alacsonyabbak, mint a GPIU-vizsgálatban észlelt arányok, mégis túl magasak ahhoz, hogy biztonsággal alkalmazzuk őket empirikus kezelés során. A *K. pneumoniae* ciprofloxacin rezisztenciája szintén magasnak bizonyult, 26%-59% között ingadozott, ami megfelel a nemzetközi adatoknak. Az *E. faecalis* ciprofloxacin és levofloxacin rezisztenciája meghaladta az 47%, illetve 30%-ot. A *P. aeruginosa* ciprofloxacin rezisztenciája csökkenő tendenciát mutat, 2017-ben 15%-os értéket ért el, viszont ez az eredmény nem tekinthető statisztikailag szignifikánsnak. Ezen adatok alapján a fluorokinolonok nem javasolhatók többé húgyúti fertőzések empirikus kezelésére régiónkban. A cefalosporinokkal szemben az *E. coli* rezisztenciája 20% alatt maradt. Ennek lehetséges oka a megváltozott antibiotikum-felhasználási stratégiánk, miszerint visszaszorítottuk a fluorokinolonok alkalmazását és csökkentettük a cefalosporinokét. Ennek ellenére, *E. coli* esetében szignifikáns rezisztencianövekedést tapasztaltunk ceftriaxonnal szemben, amely elérte a 12%-ot ($p<0,0001$), ezáltal 2017-re meghaladta az empirikus kezeléshez ajánlott 10%-os küszöböt. A *K. pneumoniae* cefalosporin rezisztenciája igen magasnak bizonyult, ami megfelel a nemzetközi megfigyeléseknek. Negyedik generációs cefalosporinnal, a cefepimmel szemben a *K. pneumoniae* rezisztenciája 2012-ben elérte a 40%-ot. A *K. pneumoniae* magas rezisztenciájának hátterében feltételezhetően a multirezisztens, ESBL-pozitív *K. pneumoniae* arányának növekedése állhat (11). Eredményeink alapján a cefalosporinok jó empirikusan választható antibiotikumoknak tekinthetők Gram-negatív húgyúti fertőzések kezelése során, de kerülendők abban az esetben, ha multirezisztens kórokozó gyanúja felmerül. Mivel az *Enterococcus faecalis* természetes rezisztenciával bír cefalosporinokkal szemben, húgyúti idegen testek jelenlétében a várható magasabb arányát figyelembe kell vennünk az empirikus antibiotikum-választás során. Meglepő tény, hogy nem észleltünk ceftriaxon- és ceftazidim-rezisztenciát a vizsgálati időszakban Proteus mirabilis esetében, ami a viszonylag alacsony Proteus mirabilis izolátumszámmal magyarázható (átlagosan 13-15 minta évente). A legtöbb kórokozó minimális rezisztenciát mutatott karbapenemekkel szemben, ugyanakkor a *P. aeruginosa* szignifikáns ($p=0,004$) rezisztencianövekedése aggodalomra adhat okot. A 2010-ben észlelt 6%-os imipenem rezisztenciája 2017-ben 19%-ra emelkedett. Az urológiai osztályokon világszerte növekvő karbapenem-rezisztenciáról a GPIU-vizsgálat és más nemzetközi vizsgálatok is beszámoltak (12).

A kórokozók többségének trimetoprim/szulfametoxazol, foszfomicin és nitrofurantoin antibiotikumokkal szemben mért rezisztenciája elfogadható mértékű volt az utóbbi években, annak ellenére, hogy ezen antibiotikumokat, gyakrabban alkalmaztuk enyhébb nem komplikált húgyúti fertőzések esetén fluorokinolonok és cefalosporinok helyett. Ezáltal ezek az antibiotikumok továbbra is hatékonyan helyettesíthetik a fluorokinolonokat, különösen nem komplikált alsó húgyúti fertőzések empirikus kezelése során. Gentamicint osztályunkon, toxicitása miatt, igen ritkán alkalmazunk. Ennek megfelelően a baktériumok gentamicin-rezisztenciája elfogadhatóan alacsony

6. TÁBLÁZAT: REZISZTENCIA SULFAMETHOXAZOLE/TRIMETHOPRIM, NITROFURANTOIN, POLIMIXIN B ÉS FOSFOMYCIN ANTIBIOTIKUMOKKAL SZEMBEN: A LEGGYAKORIBB KÓROKOZÓK SULFAMETHOXAZOLE/TRIMETHOPRIM, NITROFURANTOIN, POLIMIXIN B ÉS FOSFOMYCIN REZISZTENCIÁJA 2004 ÉS 2017 KÖZÖTT

Sulfamethoxazole/trimethoprim rezisztencia								
Év	E. coli		E. faecalis		K. pneumoniae		P. mirabilis	
	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)
2004	19	(24/128)	13	(5/38)	13	(3/23)	20	(2/10)
2005	19	(27/140)	24	(10/42)	15	(4/26)	38	(3/8)
2006	24	(28/115)	29	(10/35)	8	(1/13)	27	(3/11)
2007	29	(24/82)	32	(14/44)	4	(1/28)	29	(4/14)
2008	26	(41/156)	33	(22/66)	21	(7/33)	50	(2/4)
2009	28	(33/116)	23	(11/47)	6	(1/16)	33	(4/12)
2010	30	(31/105)	N.M.		16	(3/19)	33	(4/12)
2011	31	(32/102)	N.M.		22	(6/27)	57	(4/7)
2012	23	(23/102)	N.M.		63	(19/30)	63	(10/16)
2013	19	(18/95)	N.M.		28	(9/32)	29	(4/14)
2014	25	(33/131)	N.M.		14	(6/42)	33	(7/21)
2015	19	(22/118)	N.M.		36	(8/22)	50	(8/16)
2016	32	(42/132)	N.M.		49	(24/49)	24	(4/17)
2017	27	(34/127)	N.M.		44	(16/36)	47	(9/19)

Nitrofurantoin rezisztencia								
Év	E. coli		E. faecalis		K. pneumoniae		P. mirabilis	
	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)
2004	2	(3/129)	0	(0/38)	N.M.		N.M.	
2005	1	(1/140)	5	(2/42)	N.M.		N.M.	
2006	2	(2/115)	0	(0/35)	N.M.		N.M.	
2007	2	(2/82)	2	(1/44)	N.M.		N.M.	
2008	1	(1/153)	0	(0/66)	18	(6/33)	100	(4/4)
2009	2	(2/116)	2	(1/45)	47	(9/19)	100	(13/13)
2010	1	(1/106)	0	(0/46)	71	(15/21)	100	(12/12)
2011	0	(0/55)	0	(0/18)	31	(4/13)	100	(4/4)
2012	0	(0/65)	0	(0/46)	90	(18/20)	100	(9/9)
2013	1	(1/100)	0	(0/81)	91	(31/34)	100	(15/15)
2014	0	(0/128)	0	(0/89)	100	(41/41)	100	(20/20)
2015	0	(0/121)	0	(0/70)	100	(21/21)	100	(20/20)
2016	0	(0/131)	1	(1/103)	100	(48/48)	100	(17/17)
2017	0	(0/128)	0	(0/79)	100	(37/37)	100	(18/18)

Polimixin B rezisztencia								
Év	E. coli		K. pneumoniae		P. aeruginosa		P. mirabilis	
	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)
2010	0	(0/107)	0	(0/21)	0	(0/16)	100	(12/12)
2011	0	(0/108)	0	(0/27)	0	(0/13)	100	(8/8)
2012	0	(0/75)	0	(0/18)	0	(0/12)	100	(11/11)
2013	0	(0/103)	0	(0/34)	0	(0/20)	100	(15/15)
2014	0	(0/131)	0	(0/41)	0	(0/45)	100	(21/21)
2015	0	(0/122)	0	(0/22)	0	(0/16)	95	(19/20)
2016	0	(0/132)	0	(0/49)	0	(0/38)	100	(17/17)
2017	0	(0/133)	0	(0/37)	0	(0/27)	100	(19/19)

Fosfomycin rezisztencia						
Év	E. coli		K. pneumoniae		P. mirabilis	
	%	(n/N)	%	(n/N)	%	(n/N)
2010	0	(0/102)	15	(3/20)	9	(1/11)
2011	0	(0/90)	4	(1/23)	14	(1/7)
2012	5	(1/20)	0	(0/7)	0	(0/4)
2013	N.M.		N.M.		N.M.	
2014	N.M.		N.M.		N.M.	
2015	N.M.		N.M.		N.M.	
2016	N.M.		N.M.		N.M.	
2017	N.M.		N.M.		N.M.	

N.M. – nincs meghatározva

szinten maradt, kivéve K. pneumoniae esetén, ahol szignifikánsan emelkedő értékeket mértünk.

A GPIU eredményei alapján a hospitalizált betegek 9%-ánál alakul ki nozokomiális fertőzés. Ilyenkor gyakran multirezisztens kórokozó áll a fertőzés hátterében, amit az empirikus kezelés során, az antibiotikum megválasztásakor figyelembe kell vennünk. Ezért, amennyiben multirezisztens kórokozóra gyanakszunk, törekednünk kell arra, hogy a várható kórokozó érzékenységének megfelelő antibiotikumot válasszuk (pl.: karbapenemek, vagy anti-Pseudomonas aktivitással bíró béta-laktámok). Azt is figyelembe kell vennünk, hogy a legtöbb széles spektrumú antibiotikum, mint a fluorokinolonok és a cefalosporinok összefüggésbe hozhatók a *Clostridium difficile* fertőzések növekvő előfordulásával (13).

A 2010-es évet követő időszakra vonatkozó nemzetközi GPIU-vizsgálatok adatainak feldolgozása jelenleg is zajlik, amelyeknek a saját adatainkkal történő összehasonlítása a későbbiekben hasznos információval szolgálhat az antibiotikum-kezelési stratégiánk hatékonyságát illetően.

Vizsgálatunk korlátai

2010-ig, korlátozott adatmennyiséghez fértünk hozzá a mikrobiológiai laborból a számítógépes rendszer és az elektronikus adatbázis hiánya miatt. A 2010-es évtől kezdve az informatikai rendszer kiépítése jelentősen kiterjesztette az adatok feldolgozásának lehetőségeit. A mikrobiológiai adatgyűjtésből kifolyólag nem állnak rendelkezésre klinikai háttéradatok a tenyésztésekkel kapcsolatban (tünetmentes bakteriuria vagy tünetekkel járó húgyúti fertőzés). Mivel a *K. pneumoniae* természetes rezisztenciával bír ampicillinnel szemben, a 2005-ben észlelt 88%-os rezisztenciaarány tévesnek tekintendő.

Következtetés

Mivel a kórokozók helyi spektruma és antibiotikumokkal szembeni rezisztenciája időben és földrajzi régiónként eltér, a helyi viszonyok felmérése rendkívül fontos, hogy megfelelő empiri-

kus antibiotikum-kezelésben részesítsük a húgyúti fertőzésben szenvedő betegeket. A helyi rezisztenciaviszonyok ismerete megalapozza a megfelelő infekciókontroll és antibiotikum-kezelési stratégia felállítását. Kevésbé súlyos húgyúti fertőzések esetén szükségszerű a fluorokinolonok és cefalosporinok alkalmazásának visszaszorítása, illetve a helyi rezisztenciaviszonyok ismerete alapján, szűkebb spektrumú antibiotikumokkal történő helyettesítése.

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III.

ORIGINAL PAPER

URINARY TRACT INFECTIONS

The role of the Acute Cystitis Symptom Score questionnaire for research and antimicrobial stewardship. Validation of the Hungarian version

András Magyar[1], Jakhongir Alidjanov[2], Adrian Pilatz[2], Károly Nagy[1], Vinodh Kumar Adithyaa Arthanareeswaran[1], Sándor Póth[1], András Bécsi[1], Florian M.E. Wagenlehner[2], Kurt G. Naber[3], Péter Tenke[1], Béla Köves[1]

[1]*Department of Urology, Jahn Ferenc South Pest Teaching Hospital, Köves, Hungary*
[2]*Department of Urology, Pediatric Urology and Andrology, Justus-Liebig-University, Giessen, Germany*
[3]*Technical University of Munich, Munich, Germany*

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Corresponding author
András Magyar
Department of Urology
Jahn Ferenc South Pest Teaching Hospital
1, Köves Street
1204 Budapest, Hungary
magyara@gmail.com

Introduction The Acute Cystitis Symptom Score (ACSS) is a new self-reporting tool to evaluate the symptoms of uncomplicated acute cystitis (AC) in women. The linguistic and clinical validation process of the Hungarian version used in this study may serve as a guide for the validation of the ACSS in other languages.
Material and methods In this prospective cohort study, women with AC (Patients) and those without (Controls) filled in the Hungarian ACSS version, during their visits to physician's office. Statistical analysis included ordinary descriptive values, calculation of reliability, validity, discriminative ability, responsiveness (sensitivity, specificity) and comparative analysis.
Results Thirty-one patients were recruited for validation along with 37 controls. Statistical analyses resulted in excellent values of internal consistency, discriminative ability and validity for diagnosis of AC. At the cut-off at a score of 6 in the 'typical' domain, positive and negative predictive values were 97% and 92%, sensitivity and specificity were 90% and 97%, respectively.
Conclusions The ACSS has demonstrated benefits for diagnosis and patient-reported outcome assessment. It is objective, fast, and cost-effective, and may help to easily confirm the accurate diagnosis of AC. Therefore, it may be especially important for clinical and epidemiological studies on AC in women.

Key Words: cystitis ‹› female ‹› follow-up ‹› genitourinary tract infection ‹› pain ‹› questionnaire

INTRODUCTION

Women, suffering from acute uncomplicated cystitis (AC) represent the vast majority of the cases of the urinary tract infections (UTIs) – the most widespread infectious diseases worldwide [1].
Non-standardised and subjective evaluation of symptoms of AC, inappropriate and prolonged administration of antibiotics, low adherence to international guidelines have led to excessive antibiotic prescription and inevitably to increasing antimicrobial resistance, and unfortunately, the development of novel antimicrobial agents is not expected in the near future [2]. Antibiotic stewardship programs aim to set coordinated strategies to enhance patient health outcomes, decrease the use of broad-spectrum antibiotics and to slow down the increase of antimicrobial resistance [3, 4, 5]. In order to reach these aims, standardised, high-quality investigations of available and future modalities for treatment and prevention of UTIs have to be conducted [5–9].
Clinical studies on UTIs often rely only on patients' self-diagnosis of episodes of AC. The major limitation of current evidence making the results of the studies often unreliable is the use of non-standardised, non-validated methods of self-diagnosis. Therefore,

objective self-diagnosis and self-assessment of outcome are essential, as a basis for comparing the efficacy of different treatment modalities, either of antibiotic and non-antibiotic [10, 11].

The Acute Cystitis Symptom Score (ACSS) was developed under the hypothesis that diagnosis of AC can be made with high probability, based on typical symptomatology, such as frequency, urgency and dysuria, in the absence of vaginal and/or urethral discharge [2]. Uzbek and Russian versions of the ACSS were tested in Uzbek and Russian speaking female populations of the Republic of Uzbekistan. Thereafter, the ACSS was translated into and validated in German and British English languages. The ACSS and its scoring system has demonstrated high values of reliability, validity and discriminative abilities in all studies held in Uzbekistan, Germany and Great Britain [12–16]. The evaluation of the ACSS in other languages, such as Polish, Romanian, Ukrainian, and American English is in preparation.

Our study was designed as a prospective cohort study of the associations between symptomatology and diagnosis of AC, and the assessment of its outcomes in women, with the ACSS used as a standardised tool.

This paper mainly encompasses an internal validation part of the study, which aimed to develop a Hungarian version of the ACSS. The current study may also serve as an example and methodological guide for linguistic and clinical validation of the ACSS in other languages.

MATERIAL AND METHODS

The Acute Cystitis Symptom Score questionnaire

The ACSS contains 18 questions (items), which are divided into 4 domains: 6 items regarding typical acute cystitis symptoms ('Typical' domain), 4 items for differential diagnosis ('Differential' domain), 3 items on quality of life ('QoL' domain) and 5 additional questions regarding other relevant circumstances, such as menses and pregnancy ('Additional' domain). The first 3 domains are designed and scored in a Likert-type scale in order to measure severity of symptoms, while the items of the last domain are designed as dichotomous requiring only simple 'Yes/No' answers.

Translation process

The translation and linguistic validation of the Hungarian version of the ACSS was performed in accordance with the Linguistic Validation Manual for Patient-Reported Outcomes (PRO) Instruments guidelines [17]. The validated Russian version of the ACSS was taken as a source. First, two independent primary, forward translations into the Hungarian language were produced by two professional translators, followed by a consultative meeting between the two primary translators and the local project manager to obtain a consensus 'provisional' version. Then the provisional version was back-translated into the source language by an independent translator, which was compared with the source version of the questionnaire, as a test. This step was followed by pilot testing of the corrected provisional version of the questionnaire. The notes of the patients were then discussed and the final version of the questionnaire was created. The validated British English version was taken into account as a reference before the final Hungarian version was accepted. The process of translation and linguistic validation was published by our workgroup in details earlier [12–16, 18].

Ethical approval

The protocol of the validation process was approved by the Egészségügyi Tudományos Tanács (ETT) TUKEB Medical Research Council, Budapest Hungary on 24th February 2015 (Approval number: 34/2015.–6423/2015/EKU) and the Local Ethical Committee of the tertiary care hospital, where the work was conducted. The research was performed in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Before inclusion into the study, all patients and subjects were requested to sign written patient informed consent.

Pilot test

A pilot test of the translated Hungarian version of the ACSS was carried out in 6 female respondents, of different ages, with different levels of education and belonging to different social groups, who had experienced AC in their history at least once.

Clinical validation study

Recruitment

Female respondents aged 18 years and older, who visited the urological outpatient clinic of a Hungarian tertiary care hospital from September 2015 to February 2016, diagnosed with uncomplicated AC (Patients) were enrolled along with healthy women without AC or any significant urological condition, not visiting the hospital as patients (Controls).

Patient groups

For allocation of the respondents into groups and further analysis of responsiveness, a project supervisor

and two members of the research team were chosen. One of them (A.B.) had access to the case histories and the results of respondents' clinical and laboratory investigations, but was blinded to the results of the questionnaire survey while the second member (A.M.) was blinded to all results of respondents' investigations apart from the ACSS test results and the final diagnosis of the urologist. Based on information given to them, they have made independent diagnostic decisions whether the respondent had or did not have AC. Their decisions were documented and compared by the research supervisor (P.T.). In cases when their opinions coincided true negative (both of them decided that the patient did not have AC) or true positive (both of them decided that patient did have AC), diagnoses were marked. All disagreements were discussed with the project supervisor and a final decision was achieved by consensus. Using this algorithm, respondents were divided into two groups: control group (Controls) and acute cystitis group (Patients).

Examination, data collection

The diagnosis of AC was strictly adjusted to the European Association of Urology Guidelines [2]. The criteria and the examinations performed for the diagnosis of AC in this study are summarised in Table 1.

In addition to the urological examinations, the patients were asked to fill out the ACSS questionnaire (Part A).

Appropriate therapy, for those women who had AC, was prescribed according to European Association of Urology Guidelines [2]. Patients were suggested to come for test-of-cure (TOC) visit after finishing of prescribed therapy. During TOC, they were requested to fill out the 'follow-up' form (Part B) of the ACSS.

All data were recorded into an electronic database via the latest version of a specific client software (e-USQOLAT) [19].

Statistical analysis

Data obtained from ACSS survey were analysed using Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 21.0. IBM, GmbH, Ehningen, Germany). Statistical analysis included ordinary descriptive statistical values (average values such as means and medians, etc.).

Calculations of Cronbach's alpha, split-half reliability and Spearman-Brown prophecy were used for the assessment of internal consistency (reliability analysis) of the Hungarian ACSS [20, 21]. Splitting into halves was performed in dependence of odd end even ordinary numbers of items.

Validity and discriminative ability were evaluated via calculation of responsiveness (sensitivity and specificity), using area under receiver operating characteristic curve (AUC) analysis along with positive and negative likelihood ratios as well as diagnostic odds ratio. Two by two (2x2) tables were used with taking the acute cystitis as an 'exposure', and scores of the ACSS – as an 'outcome'.

Table 1. *Criteria and examinations performed for the diagnosis of acute cystitis*

Examination type	Criteria
Focused medical history exploration and standard urological physical examination (performed under conditions of clinical practice)	• history of lower urinary tract symptoms (dysuria, frequency and urgency, suprapubic pain, hematuria, cloudy/foul smelling urine), exclusion of asymptomatic bacteruria • absence of vaginal discharge or irritation • no risk factors for complicated urinary tract infections • no signs of acute pyelonephritis, absence of fever, systemic symptoms or flank pain
Microscopy of centrifuged urine sediment or urine dipstick test (mid-stream clean catch urine samples)	Sediment examination: at least one of the following conditions had to be true: • 6 or more leucocytes per unit/high power field (HPF) • 100 or more bacteria per unit/HPF • 3 or more red blood cells per unit/HPF in urine sediment OR Urine dipstick test suggesting urinary tract infection (nitrite, leukocyturia, haematuria)
Urine culture (mid-stream clean catch urine samples)	10^3 or more CFU of uropathogens in 1 ml of unspun urine
Additional examinations, if indicated, to exclude other conditions than acute uncomplicated cystitis	In the case of atypical symptoms the physician in charge (expert urologist specialist) decided if additional diagnostic studies were necessary: • kidney and bladder ultrasound • kidney-ureter-bladder x-ray • other clinical and/or instrumental diagnostic procedures and tests

Table 2. *Success and non-success rates using individual criteria*

Mode	Domain(s)	Definition of Success (Scores)	Success N (%)	Non-Success N (%)
1	Dynamics	≤1	21 (91.3%)	2 (8.7%)
2	Main symptoms[a]	≤3, but no item >1 (mild)	20 (87%)	3 (13%)
3	Typicals	≤4, but no item >1 (mild)	20 (87%)	3 (13%)
4	QoL	≤3, but no item >1 (mild)	22 (95.7%)	1 (4.3%)
5	Typicals+QoL	≤7, but no item >1 (mild)	20 (87%)	3 (13%)
6	Typicals/ QoL	≤4/≤3, but no item >1 (mild)	20 (87%)	3 (13%)

[a] MAIN SYMPTOMS include TYPICALS 1–3 only: frequency, urgency, painful urination; QoL – Quality of Life; N – number

Normality of distributions was assessed visually and numerically, using Q-Q plots and Shapiro-Wilk test [22]. Comparative analysis was performed using Mann-Whitney's U (non-parametric) and Student's t (parametric) tests [23, 24]. Differences between variables were measured using standard deviations and 95% confidence intervals (95% CI). Statistical significance of differences was evaluated using P-value; substantive significance was estimated via effect size calculation by correlation coefficient (rho).

Success and non-success rates were defined using individual criteria. The definitions along with the results are presented in Table 2.

Substantive significance was estimated via effect size calculation by correlation coefficient (rho) and Cohen's d. The statistical power of the test between cases (Patients vs Controls) and within cases (Visit 1 vs. Visit 2) for the ACSS domains was assessed using Wilks' lambda.

RESULTS

Translation and linguistic validation

The process of translation and linguistic validation of the ACSS resulted in the final Hungarian ACSS. After approval by hospital authorities, the final version was used for the pilot test. Both the Hungarian and the British English versions of the ACSS are available at the ACSS website [25].

Table 3. *Differences in scores of the different domains of the Acute Cystitis Symptom Score (ACSS) between groups of Patients and Controls and comparison between two visits*

Typical scores	Controls	Patients	P value	Cohen's d/effect-size r (power)	Patients' Visit 1	Patients' Visit 2	P value	Cohen's d/effect-size r (power)
Number	37	31			23	23		
Range	0 to 9	3 to 16	<0.0001	3.20/0.85 (1.00)	6 to 16	0 to 9	<0.0001	3.52/0.87 (1.00)
Mean ±SD	0.84 ±1.79	9.42 ±3.33			9.86 ±2.89	1.05 ±2.04		
95% CI for Mean	0.24 to 1.43	8.20 to 10.64			8.54 to 11.17	0.12 to 1.97		
Median	0	10.00			10.00	0.00		
0.25 percentile	0	6.00			7.00	0.00		
0.75 percentile	1	11.00			11.00	1.25		
Differential scores	Controls	Patients	P value	Cohen's d/effect-size r (power)	Patients' Visit 1	Patients' Visit 2	P value	Cohen's d/effect-size r (power)
Range	0 to 2	0 to 5	<0.0001	0.94/0.43 (0.98)	0 to 4	0 to 2	0.021	0.65/0.31 (0.74)
Mean ±SD	0.11 ±0.46	1.03 ±1.30			0.86 ±1.11	0.29 ±0.56		
95% CI for Mean	-0.04 to 0.26	0.55 to 1.51			0.35 to 1.36	0.03 to 0.54		
Median	0	1.00			1.00	0.00		
0.25 percentile	0	0.00			0.00	0.00		
0.75 percentile	0	2.00			2.00	0.25		
Quality of Life (QoL) scores	Controls	Patients	P value	Cohen's d/effect-size r (power)	Patients' Visit 1	Patients' Visit 2	P value	Cohen's d/effect-size r (power)
Range	0 to 8	0 to 9	<0.0001	2.14/0.73 (1.00)	0 to 8	0 to 6	<0.0001	2.06/0.77 (1.00)
Mean ±SD	0.84 ±1.74	4.94 ±2.08			4.95 ±2.20	1.05 ±1.53		
95% CI for Mean	0.26 to 1.42	4.17 to 5.70			3.95 to 5.95	0.35 to 1.75		
Median	0	5.00			6.00	0.00		
0.25 percentile	0	6.00			3.00	0.00		
0.75 percentile	0.50	6.00			6.00	2.00		
Typical+QoL scores	Controls	Patients	P value	Cohen's d/effect-size r (power)	Patients' Visit 1	Patients' Visit 2	P value	Cohen's d/effect-size r (power)
Range	0 to 13	6 to 25	<0.0001	3.08/0.84 (1.00)	6 to 22	0 to 12	<0.0001	3.38/0.86 (1.00)
Mean ±SD	1.68 ±3.18	14.35 ±4.86			14.81 ±4.40	2.10 ±2.98		
95% CI for Mean	0.62 to 2.74	12.57 to 16.14			12.81 to 16.81	0.74 to 3.45		
Median	0	15.00			15.00	1.00		
0.25 percentile	0	10.00			11.00	0.00		
0.75 percentile	2.50	17.00			17.00	3.00		

Pilot test

All six respondents of the pilot test have found the questionnaire to be understandable, and the scale to be adequate and clear in that they could not have answered it more than one way, what may judge for this Hungarian version of the ACSS to be used as final version for the clinical validation study.

Clinical validation study

Demography

Sixty-eight Hungarian women were recruited for validation. Thirty-seven of them were recognised as having no acute cystitis (Controls), whereas diagnosis of AC was approved in 31. The median (range) age of Controls and Patients was 48 (19–85) and 42 (18–78) years, respectively.

Analysis of reliability

'Typical' domain

Cronbach's α for 'Typical domain was 0.89 (95% CI; 0.84 to 0.93), the correlation between forms was 0.86, the Guttman split half and the Spearman-Brown coefficients were 0.91 and 0.93 respectively.
The mean score achieved by the Controls was 0.84 ±1.79, while Patients achieved 9.42 ±3.33 (p <0.0001, Table 3). Results of comparative analysis of typical symptom scores between Patients and Controls are demonstrated in Figures 1 and 2.
ROC analysis resulted in AUC = 0.99 (95% CI; 0.96 to 1.0; p <0.001). The most representative sign for AC according to our data was painful urination and it was observed in 78% of Patients. It also showed the highest AUC, while 'haematuria' had the lowest.

'Differential' domain

The Cronbach's α value was 0.45 (95% CI; 0.17-0.65). The mean total score, achieved by Patients (1.03 ±1.3) was significantly higher than that achieved by Controls (0.11 ±0.46, p <0.0001) (Table 3). The AUC for this domain was 0.74 (95% CI, 0.6 to 0.87, p = 0.001).

'Quality of Life' domain

The reliability in the category 'quality of life' was high: Cronbach's α was 0.95 (CI 95%; 0.93 to 0.97). Mean total score was 0.84 ±1.74 vs. 4.94 ±2.08 in Controls vs. Patients respectively (p <0.0001, Table 3). The AUC was 0.94 (95% CI: 0.88 to 1.00).

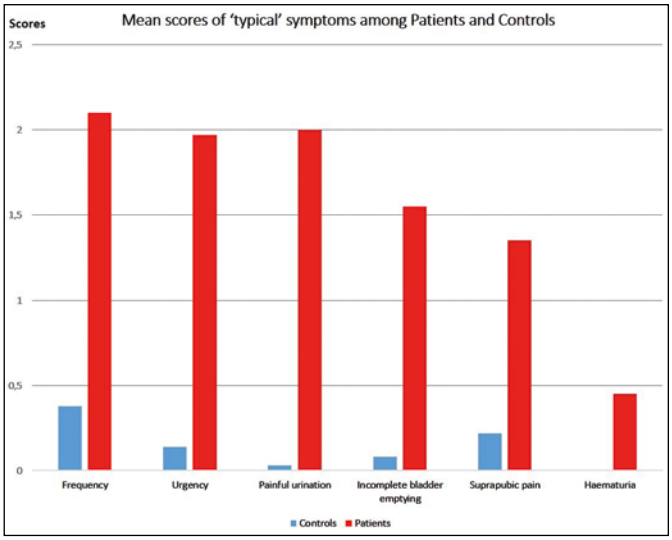

Figure 1. *Mean score comparison of typical symptoms between patients and controls.*

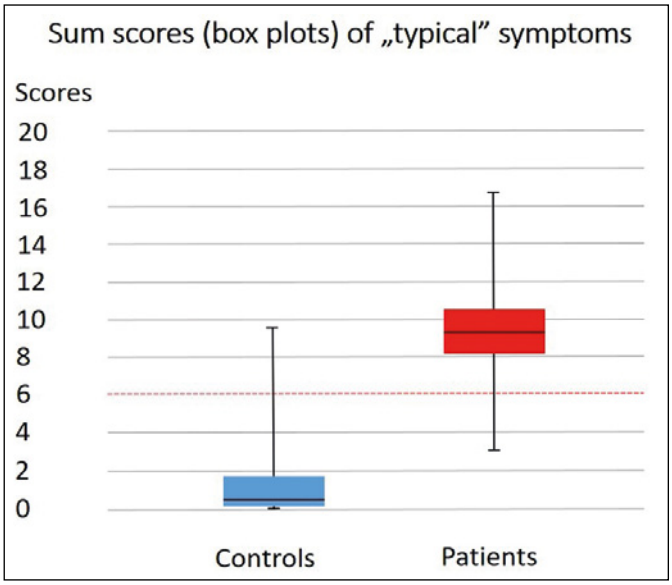

Figure 2. *Sum scores (box-and-whisker plots) of 'typical' symptoms among patients and controls with cut-off line.*

'Typical' and 'Quality of Life' domains

Since the 'QoL' domain consists of three items, it is not reasonable to apply the analysis of split-half reliability for this domain. Therefore, we performed this analysis for combined 'Typical' and 'QoL' domains. The Cronbach's α value for this 'combined domain' (9 items) was 0.93 (CI 95%: 0.91 to 0.96), with 0.92 for the first part and 0.80 – for the second part. Correlation between parts was 0.93, Spearman-Brown coefficient was 0.96, and the Guttman's split-half coefficient was 0.93.

Analysis of validity

For prediction of acute cystitis, at cut-off score 6 of Typical domain, positive and negative predictive values were 96.55% and 92.31%, sensitivity and specificity were 90% and 97%, respectively.

Follow-up visit, comparison between the two visits

Twenty-three (74%) members of the Patients group came back for TOC visit, with 61% patients who felt back to normal and 30% felt much better. The average interval between visits was 15 days. Results of comparative analysis of the ACSS scores between the two visits are presented on Table 3.

Table 2 represents various possibilities to differentiate between success and non-success, using part B of the ACSS (23 Patients treated for AC). Application of four different modalities (main symptoms, Typicals, Typicals + QoL, Typicals/QoL) revealed the same numbers of patients showing success and non-success in 20 (87%) and 3 (13%) of patients, respectively. These results were proven by clinical investigation of mentioned Patients. A very similar pattern was found, when patient-reported outcome was assessed earlier using the Russian and Uzbek versions of the ACSS [13].

Since 'Typical' domain have shown excellent results concerning sensitivity and specificity for diagnosing AC (the cut-off score of 6), it may be reasonable to use the same domain at a score of ≤4, but no item >1 for patient-reported outcome of success of treatment.

Statistical power and effect size analysis

The results of the analysis are presented in Table 3.

DISCUSSION

Emerging antibiotic resistance of uropathogens is a serious and well-known problem. The excessive use of broad-spectrum antibiotics leads to increased bacterial resistance. Development of multi-drug resistant bacteria results in higher rate of therapeutic failure and leads to administration of broader spectrum antibiotics for empirical treatment. Broader spectrum antibiotics, such as carbapenems, fluoroquinolones or cephalosporins, however, should be saved for patients with more severe infections, whereas patients with benign infections like AC should be treated initially with narrow spectrum antibiotics in accordance with the actual guidelines, availability and local patterns of susceptibility [2]. Therefore, fast and unequivocal diagnosis and outcome assessment of uncomplicated AC is extremely important both for clinical and research purposes. It is especially reasonable, since the first Phase 3 studies comparing antibiotic versus non-antibiotic treatment have shown that symptomatic treatment by itself may become an accepted treatment modality in the future [11, 26].

Validated patient questionnaires are becoming increasingly popular in all fields of modern medical practice. Specific questionnaires, such as International Prostate Symptom Score (I-PSS) [27] and the International Index of Erectile Dysfunction (IIEF) [28] – translated and validated in several languages, have become widely used instruments of urological examination, and are inevitable in the course of comparing different treatment strategies. However, up to most recently there has been no widespread validated questionnaire suitable for diagnosis and outcome of AC.

The Acute Cystitis Symptom Score questionnaire was initially reported in 2013. It evaluates patient symptoms, estimates the effect of the disease on quality of life and contributes to differential diagnostics. Originally developed in Uzbekistan in Uzbek language, the ACSS is now already translated and clinically tested in Russian, British English and German languages [12–16, 18]. The ACSS nowadays is filled out by hundreds of female patients suffering from AC and has proved to be valuable in clinical practice and was also included in the updated German guidelines on uncomplicated UTI [29].

The aim of the current study was to perform the linguistic and clinical validation of the Hungarian version of the ACCS. The study revealed that the Hungarian version of ACSS is well-designed and the questions are clear and understandable. The statistical power and effect size analysis revealed, that the number of the respondents and their allocation was appropriate for the validation study. The validation process of the translated Hungarian ACSS version has demonstrated excellent values of internal consistency, discriminative and predictive abilities, and validity for diagnosis of AC in women. Values of interclass correlation were also very good. The analysis of responses and the symptoms showed significant differences between control and AC group in each category. Strong correlation between different categories was observed.

The 'Typical' symptoms were highly specific and almost exhaustive predictors of AC. The leading symptom for AC according to Hungarian data is painful urination, observed in 78% of patients with AC. Cut-off score of 6 of 'Typical' domain can be excellently used to differentiate between cases positive and negative for AC, thanks to high predictive values (96.55% and 92.31%, respectively). As well, 'Typical'

domain, at a cut-off score of 4 or lower, is reliable to assess effectiveness of the therapy, at the test-of-cure visits, either in combination with 'Quality of Life' domain or not.

The current study was performed at a single centre, which may be considered a limitation. This also explains the relatively low number of participants. In addition, 8 of 31 patients did not return for any control visit and therefore did not fill in the second part (control visit) of the ACSS. Nevertheless, the similarity of results of the current study to those of previous studies, may judge that the effect of possible selection bias if any, is however non-significant and the results are representative. Moreover, high sensitivity, specificity, association between laboratory tests and questionnaire results, the clear difference in scores between control group and patient group, all these together suggest, that the questionnaire is able to describe the dynamics of the clinical condition very well.

In our study, we have validated the Hungarian version of the ACSS not only linguistically but also clinically. Thus, the Hungarian ACSS can now be used as an effective tool in the diagnosis and outcome assessment of AC in Hungarian speaking women for clinical and research purposes not only by urologists, but also by gynaecologists and general practitioners in their clinical practice. Methodology of validation, described in this paper, may be used as an example for translation and validation of the ACSS questionnaire into other languages.

CONCLUSIONS

The ACCS is an easy, fast, cost-effective tool and might be used as standardised tool in UTI research and clinical practice. The ACSS provides an objective evaluation of diagnosis and patient-reported outcome assessment, and is therefore, especially important for both analytical and descriptive studies, such as clinical trials and epidemiological studies. For this reason, we recommend to translate and validate the ACSS questionnaire into other languages as well.

CONFLICTS OF INTEREST

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The other authors did not have any conflicts of interest.

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IV.

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TOPIC PAPER

Evaluation of the draft guidelines proposed by EMA and FDA for the clinical diagnosis of acute uncomplicated cystitis in women

Jakhongir F. Alidjanov[1] · Kurt G. Naber[2] · Adrian Pilatz[1] · Abdukhamid Radzhabov[3,4] · Musluhuddin Zamuddinov[5] · András Magyar[6] · Peter Tenke[6] · Florian M. Wagenlehner[1]

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Abstract

Purpose To reassess the diagnostic values of the "draft" guidelines for the clinical diagnosis of acute uncomplicated cystitis (AC), recently proposed by US Food and Drug Administration (FDA) and European Medicines Agency (EMA).

Methods The data of 517 female respondents (patients with acute cystitis and controls) derived from the e-USQOLAT database were analyzed and used for the validation of proposed "draft" guidelines of FDA and EMA, compared to the Acute Cystitis Symptom Score (ACSS) questionnaire. The diagnostic values of the proposals concerning signs, symptoms and their severity were assessed and compared.

Results The six "typical" symptoms of the ACSS were strongly associated with the diagnosis of AC. The number of positive "typical" symptoms differed significantly between patients and controls: median 5 (IQR 4–6) vs 1 (IQR 0–3) respectively. Scored severity of "typical" symptoms also differed significantly between groups of patients and controls: median (IQR) 10 (7–13) vs 1 (0–4), respectively. The best balance between sensitivity and specificity is shown by the ACSS cut-off value of 6 scores and more of the "Typical" domain, followed by an approach proposed by FDA and EMA, justifying ACSS to be used as a diagnostic criterion for the clinical diagnosis of AC.

Conclusions Not only the presence but also the severity of the symptoms is important for an accurate diagnosis of AC. The ACSS, even without urinalysis is at least as favourable as the draft diagnostic proposals by FDA and EMA. The ACSS can be recommended for epidemiological and interventional studies, and allows women to establish self-diagnosis of AC, making the ACSS also cost-effective for healthcare.

Keywords Urinary tract infection · Cystitis · Acute Cystitis Symptom Score · ACSS · Guidelines · Diagnosis

Introduction

Despite numerous publications, there is still no generally accepted strategy regarding the clinical diagnosis of acute uncomplicated cystitis (AC). The updated guidelines of the Infectious Diseases Society of America (IDSA) and the European Society for Microbiology and Infectious Diseases (ESCMID) mainly consist of recommendations about the treatment of AC and not the diagnosis [1]. These guidelines were limited to the treatment of AC and pyelonephritis in premenopausal, non-pregnant women with no known urological abnormalities or comorbidities. In addition, the authors noted that postmenopausal women or those who have well-controlled diabetes mellitus in the absence of urological sequelae may be considered as having uncomplicated UTIs (uUTIs) by some experts, but a discussion of specific management of these groups was outside the scope of the guidelines.

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✉ Jakhongir F. Alidjanov
dr.alidjanov@gmail.com

[1] Department of Urology, Pediatric Urology and Andrology, Justus-Liebig-University, Rudolph-Buchheim Str.7, 35392 Giessen, Germany

[2] Straubing, Germany

[3] Treatment and Diagnostic Center "Olami Tib", J.Rasulov 29 Street., 734060 Dushanbe, Tajikistan

[4] Sankt-Katharinen Hospital, Seckbacher Landstr. 65E, 60389 Frankfurt, Germany

[5] Department of Urology, Madadi Akbar Clinic, Ayni Street 14, Dushanbe, Tajikistan

[6] Department of Urology, Jahn Ferenc South Pest Teaching Hospital, Köves út 1, Budapest 1204, Hungary

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In the last update of these guidelines of the European Association of Urology (EAU) from 2019, AC is defined as acute, sporadic or recurrent cystitis limited to non-pregnant women with no known relevant anatomical and functional abnormalities within the urinary tract or comorbidities [2]. According to the EAU guidelines, the diagnosis of AC can be made with a high probability based on a focused history of lower urinary tract symptoms (dysuria, frequency and urgency) and the absence of vaginal discharge or irritation.

The definition of UTIs in a broader sense is presented in the updated German National Clinical Practice S3 Guideline [3]: UTIs may be classified as uncomplicated in the absence of relevant functional or anatomical abnormalities in the urinary tract, with no relevant renal functional impairment and any relevant concomitant disease that could aggravate the UTIs or condition, which could increase the risk of development of serious complications. Simple cystitis in this regard, may represent no additional health problem for the woman with stable diabetes mellitus, whereas any kind of pyelonephritis, whether earlier defined as uncomplicated or complicated, could interfere with her metabolic balance and could lead to severe complications. It becomes obvious today that a simple general classification of UTIs into uncomplicated and complicated UTIs is far too rough. Therefore, a more differentiated stratification of UTIs with the deeper consideration of risk factors was proposed earlier [4].

Recently, the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have proposed "draft" guidelines for the clinical diagnosis of patients with AC for further discussion:

(a) Adult and, if appropriate, adolescent females with evidence of pyuria (WBC ≥ 10/µL) and at least two of the following signs or symptoms of dysuria, urinary frequency, urinary urgency, and suprapubic pain (FDA) [5];
(b) Female patients with documented pyuria (WBC ≥ 10/µL) and having a minimum number of symptoms such as frequency, urgency and dysuria (EMA) [6].

We aimed to reassess the diagnostic values of these proposed draft guidelines using the Acute Cystitis Symptom Score (ACSS) which was validated in several languages [7–10].

Material and methods

Study design

The current study is designed as a non-interventional, case–control study.

Data acquisition

The e-USQOLAT database, containing the relevant clinical and laboratory data obtained from female respondents (patients with AC and controls without AC) during clinical validation of the ACSS in several countries was selected as a primary source for data mining [11]. All relevant data were acquired from the database at the access date of January 1, 2019.

The "diagnostic Part A" of the ACSS questionnaire, used for diagnostic purposes contains four domains [7]. Since all information essential for our purpose, concerning symptomatology (four symptoms mentioned above, plus two symptoms: "incomplete bladder emptying" and "visible blood in urine") constitutes the "typical" domain of the ACSS, we decided to limit our analysis of the symptoms and their severity to this domain. Analyses of other items and domains of the ACSS are discussed elsewhere [12].

Further information about the questionnaire itself in different languages can be found on the ACSS website (https://www.acss.world).

Data processing

Only cases with sufficient information concerning questionnaire data and urinalysis were selected for further statistical analysis.

The diagnosis concerning the presence or absence of AC, made by the treating physician based on the history and the results of the laboratory findings in accordance with national and/or international standards and guidelines [1–3] was taken as reference. Confirmed diagnosis of AC was considered a positive diagnostic outcome (patients) and the absence of AC was taken as a negative diagnostic outcome (controls), respectively.

The presence of symptoms (positive, negative), symptoms' severity (mild, moderate, severe), and the proposed diagnostic approaches (EMA, FDA, ACSS) were considered for calculation of their diagnostic values.

Presence of pyuria was considered a confounder. Since two different types of urinalyses were performed in different countries (dipsticks with esterase test or microscopy according to Nechiporenko [13]), results of these two methods were unified and labelled, respectively, as "negative", "trace", "small", "moderate" and "large", depending on the number of white blood cells.

Data processing included a procedure of dichotomization of variables for the assessment of diagnostic values. Generally, relative variables were labelled as "0" for "negative"/"not match", and "1" for "positive"/"match".

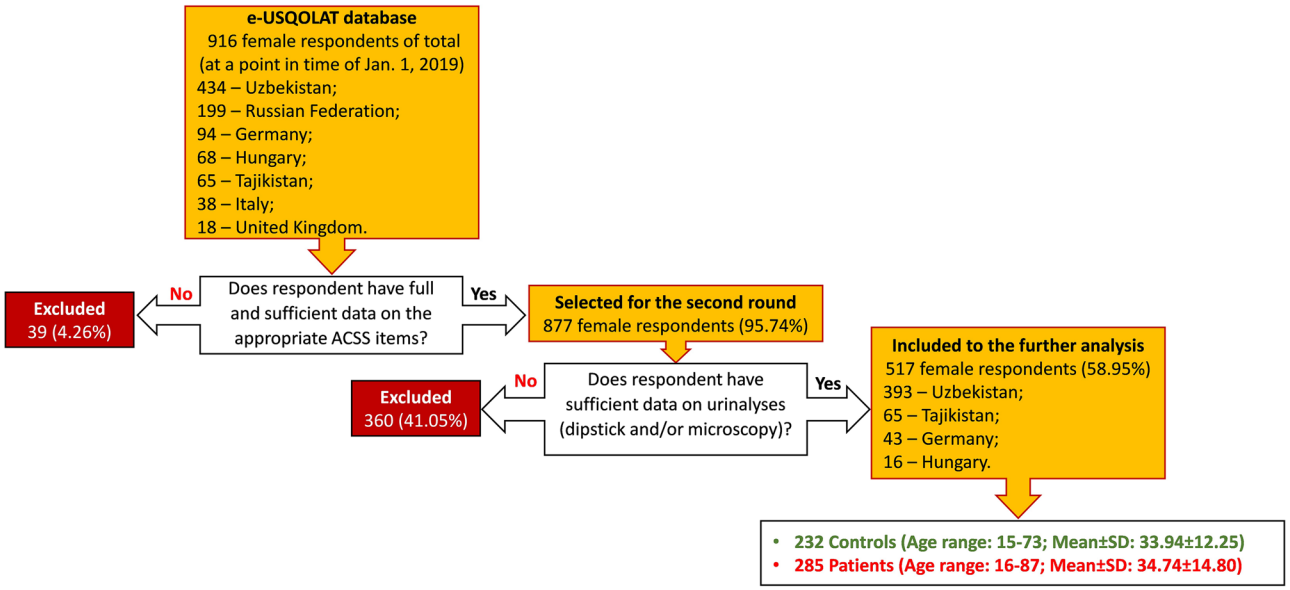

Fig. 1 Flowchart of the selection of the study population

Statistical analysis

Contingency tables were used for the statistical analysis of the bivariate (dichotomized) variables. The diagnostic values of the different proposals regarding the relations of exposure, confounder and the diagnostic outcome were assessed. Values such as sensitivity, specificity, positive and negative likelihood ratios (+ LR and − LR, respectively), Youden's J-index, diagnostic odds ratio (DOR), positive and negative predictive values (PPV and NPV, respectively) were calculated. ROC curve analysis was used for the assessment of area under the curve (AUC). The strength of associations between exposure and a positive diagnostic outcome was measured using Pearson's product-moment correlation coefficient.

Tests of the comparative analyses were performed in dependence of normality and homoscedasticity of distributions which in turn were assessed using dot charts and *Q*–*Q* plots.

For the comparison of independent, homoscedastic and normally distributed variables, Student's two-sided *t* test was used. For normally distributed heteroscedastic independent variables, Welch's two-sided modified *t* test was used. Non-parametric tests were used when parametric tests were considered inappropriate. A *p* value of less than 0.05 was considered statistically significant.

R v.3.5.2 with in-built and additional (third-party) packages was used for the statistical analysis and graphical representation of the results [14–16].

Results

On the access date, the e-USQOLAT database contained information about 911 female respondents from seven different countries (Fig. 1). Respondents are allocated to the groups of patients (with AC) and controls (without AC) according to the final diagnosis of the treating physician.

A total number of 517 respondents from four countries matched all the inclusion criteria and could be selected for further data processing and analysis (Fig. 1). Missing results of urinalysis accounted for the majority of mismatches in the inclusion criteria (360; 39.52% of total). Only 39 of excluded respondents had no sufficient questionnaire data (4.28% of total).

The age of the population included in the study ranged from 15 to 87 years with the following averages: median (interquartile range—IQR) – 30.50 (24.00; 40.00), mean ± SD – 34.38 ± 13.71. The group of controls consisted of 232 (44.87%) respondents with a median age (IQR) – 31.00 (25.00; 40.00), a mean age ± SD - 33.94 ± 12.25, ranging from 15 to 73 years. Two hundred eighty-five (55.13%) respondents in the group of patients had a median age (IQR) of 30.00 (24.00; 41.00), a mean age ± SD – 34.74 ± 14.80, ranging from 18 to 87 years old. The process of selection of the study population and essential demographic data are presented in Fig. 1 and Table 1.

Linear model fit analysis for "diagnostically significant grades" of pyuria revealed values of ≥ 25 WBC/μL for dipstick analysis and > 8000 WBC/mL for urine microscopy according to Nechiporenko [13] to have a statistically significant positive relationship with the diagnosis

Table 1 Demographics of the study population (patients with AC and controls without AC)

	Total $N=517$		Controls $N=232$		Patients $N=285$	
	N	Prevalence among the study population	*N*	Prevalence within the group	*N*	Prevalence within the group
Parameter						
Age						
Young girls (15–21 years old)	73	14.15	31	13.36	42	14.74
First mature age (22–35 years old)	254	49.22	117	50.43	137	48.07
Second mature age (36–55 years old)	134	25.97	63	27.16	71	24.91
Advanced age (56–74 years old)	50	9.69	20	8.62	30	10.53
Old age (≥74 years old)	5	0.97	0	0.00	5	1.75
Language versions of the ACSS filled						
Uzbek (cyr)	294	56.87	140	60.34	154	54.04
Russian	87	16.83	44	18.97	43	15.09
Tajik	58	11.22	21	9.05	37	12.98
German	43	8.32	19	8.19	24	8.42
Uzbek (lat)	19	3.68	4	1.72	15	5.26
Hungarian	16	3.09	4	1.72	12	4.21
Additional conditions at the time of visit						
Pregnancy	58	11.22	27	11.64	31	10.88
Symptoms of the menopause	43	8.32	21	9.05	22	7.72
Menstruation ("monthlies")	46	8.90	19	8.19	27	9.47
Signs of premenstrual syndrome (PMS)	43	8.32	18	7.76	25	8.77
Known sugar diabetes	4	0.77	2	0.86	2	0.70
Pyuria	306	59.19	64	27.59	242	84.91

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of AC: sensitivity – 0.85 [95% CI = 0.80; 0.89], specificity – 0.72 [0.66; 0.78], PPV – 0.79 [0.74;0.84], NPV – 0.80 [0.74; 0.85], crude DOR – 14.77 [9.57; 22.80], Youden index – 0.57 [0.46; 0.67].

The median number of positive symptoms for controls was 1 with IQR of 0–3 and differed significantly non-significant ($p < 0.001$) from that for patients, which was 5 with IQR of 4–6 (Fig. 2).

According to the ACSS data, the most common symptom among the entire study population was urinary frequency (72.92%). It included 47.84% of controls and 93.33% of patients. Whereas the majority of controls experienced "mild" urinary frequency (81/111 = 72.97%), "moderate" or "severe" values of the symptom were more "specific" for the group of patients (189/266 = 71.05%) (Table 2).

Figures 3 and 4, respectively, represent the prevalence, DOR and Youden's index of the six "typical" symptoms and their severity, used in the ACSS questionnaire. All six symptoms had a significant positive association with a positive outcome (PO), i.e. diagnosis of AC. It also was verified that not only the presence of the symptoms but also their severity is important for the diagnosis (Fig. 4). More detailed results of the analysis of different diagnostic values of these

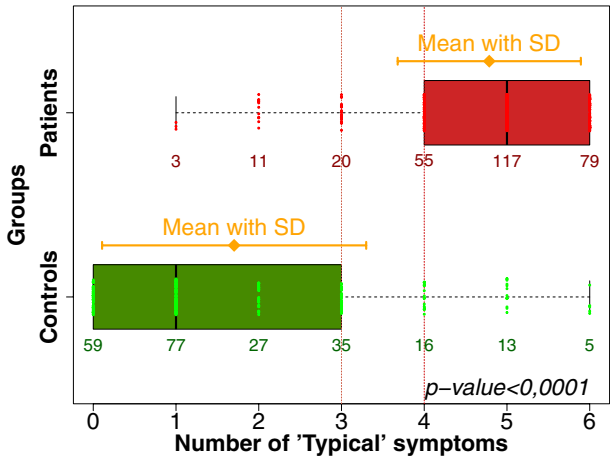

Fig. 2 Boxplots (IQR, range, mean ± SD) of the number of the ACSS typical symptoms in respondents (Patients with AC, Controls without AC)

symptoms and their severity are given in Supplementary Tables 1, 2, 3.

Scoring the symptoms into 0 (no symptom), 1 (mild), 2 (moderate), and 3 (severe) revealed for controls a median

Table 2 ACSS parameters of the study population (patients with AC and controls without AC)s

	Total $N=517$		Controls $N=232$		Patients $N=285$	
	N	Prevalence among study population	*N*	Prevalence within the group	*N*	Prevalence within the group
Urinary frequency	377	72.92	111	47.84	266	93.33
Mild	158	30.56	81	34.91	77	27.02
Moderate	118	22.82	24	10.34	94	32.98
Severe	101	19.54	6	2.59	95	33.33
Urinary urgency	313	60.54	63	27.16	250	87.72
Mild	88	17.02	40	17.24	48	16.84
Moderate	114	22.05	14	6.03	100	35.09
Severe	111	21.47	9	3.88	102	35.79
Dysuria	306	59.19	48	20.69	258	90.53
Mild	83	16.05	29	12.50	54	18.95
Moderate	102	19.73	10	4.31	92	32.28
Severe	121	23.40	9	3.88	112	39.30
Suprapubic pain	319	61.70	82	35.34	237	83.16
Mild	121	23.40	45	19.40	76	26.67
Moderate	124	23.98	27	11.64	97	34.04
Severe	74	14.31	10	4.31	64	22.46
Sense of incomplete bladder emptying	319	61.70	69	29.74	250	87.72
Mild	114	22.05	43	18.53	71	24.91
Moderate	121	23.40	20	8.62	101	35.44
Severe	84	16.25	6	2.59	78	27.37
Visible blood in the urine	125	24.18	22	9.48	103	36.14
Mild	64	12.38	11	4.74	53	18.60
Moderate	37	7.16	7	3.02	30	10.53
Severe	24	4.64	4	1.72	20	7.02

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symptom score of 1 with IQR of 0–4 which significantly differed from that for patients: 10 with IQR of 7–13 ($p<0.001$) (Fig. 5).

ROC curve analysis revealed the largest area under the curve (AUC) for the summary score of the "typical" domain of the ACSS (AUC [95% CI] = 0.93 [0.91; 0.95]), in descending order followed by dysuria (0.85 [0.82; 0.88]), urination urgency (0.85 [0.82; 0.88]), sense of incomplete bladder emptying (0.79 [0.75; 0.83]), suprapubic pain (0.74 [0.70; 0.78]), and visible blood in urine (0.63 [0.60; 0.67]) (Fig. 6).

Sensitivity and specificity (average [95% CI]) for the different proposed approaches of diagnosing AC are the following:

(a) 0.84 [0.79; 0.88] and 0.83 [0.77; 0.87] for the draft approach by EMA[1];
(b) 0.83 [0.78; 0.87] and 0.88 [0.84; 0.92] for the draft approach by FDA[2]; and
(c) 0.87 [0.83; 0.91] and 0.88 [0.83; 0.91] for the cut-off value of the ACSS[3], respectively.

The differences in diagnostic values between these three diagnostic approaches are, however, statistically not significant ($p>0.05$) (Supplementary Tables 2 and 3).

If the cut-off value of the ACSS is combined with positive pyuria, then the specificity and sensitivity change to 0.96 [0.93; 0.98] and 0.73 [0.67; 0.78], respectively.

Pyuria by itself had a reasonable sensitivity (0.85 [0.80; 0.89]) and specificity (0.72 [0.66; 0.78]) (Suppl. Table 2).

The ROC curve analysis of the proposed diagnostic approaches demonstrated the best balance between

[1] A minimum number of symptoms such as frequency, urgency and dysuria AND documented pyuria.

[2] At least two of such symptoms as dysuria, urinary frequency, urinary urgency, and suprapubic pain AND evidence of pyuria.

[3] Summary score of "Typical" domain ≥ 6.

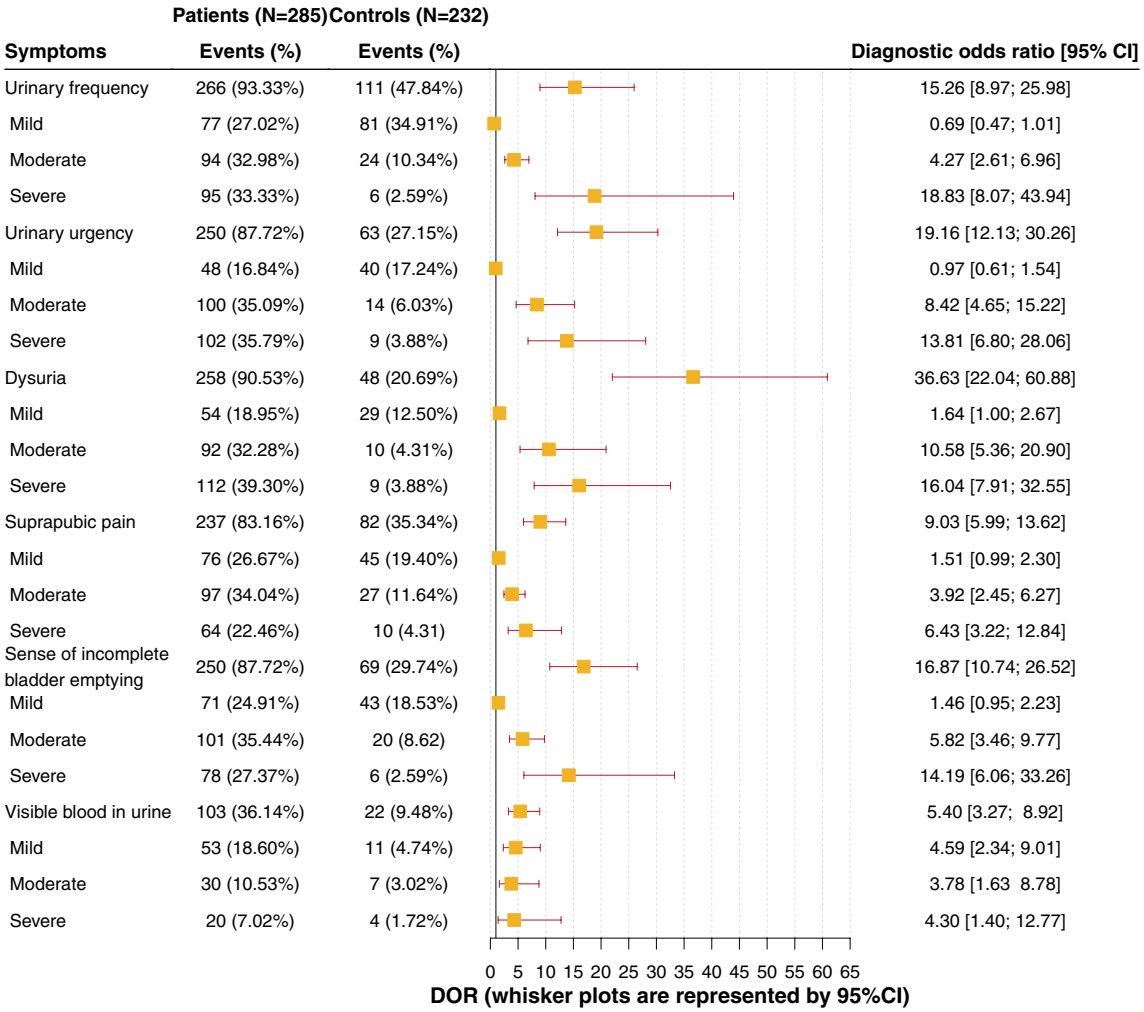

Fig. 3 Prevalence and diagnostic odds ratio (average, 95% CI) of the six ACSS typical symptoms in the study population (patients with AC and controls without AC)

sensitivity and specificity in the following descending order: ACSS cut-off value of ≥ 6 of "typical" domain (AUC [95% CI] of 0.87 [0.84; 0.90]), draft proposal by FDA (0.85 [0.82; 0.88]), and the draft proposal by EMA (0.83 [0.80; 0.87]). However, the differences in AUC between the three mentioned approaches were statistically non-significant ($p > 0.05$).

Diagnostic values of different numbers and scores of symptoms with or without considering pyuria are presented in Supplementary Tables 2 and 3. Graphical representation of the different diagnostic proposals by FDA, EMA, and ACSS is given as Supplementary Figs. 1, 2, 3, 4, 5, 6, 7, 8, 9.

Discussion

Urinary tract infections (UTIs) are among the most widespread infectious diseases in general practice [17], with 80% of cases classified as uUTIs. Although current guidelines recommend antibiotics as the first choice of treatment for the acute phase [2, 18], several prospective randomized, placebo-controlled studies comparing antibiotic and non-antimicrobial symptomatic therapeutic modalities have been performed [19–22]. Results of these studies were compelling enough for the updated German Clinical Guidelines [18] to encourage the use of the non-AB symptomatic treatment in selected cases of acute lower uUTIs with mild-to-moderate symptoms.

Since AC can be considered a benign infection without general risk of aggravation of UTI or serious complications, mainly the clinical diagnosis with or without point of care urinalysis (such as pyuria) and longer term follow-up with

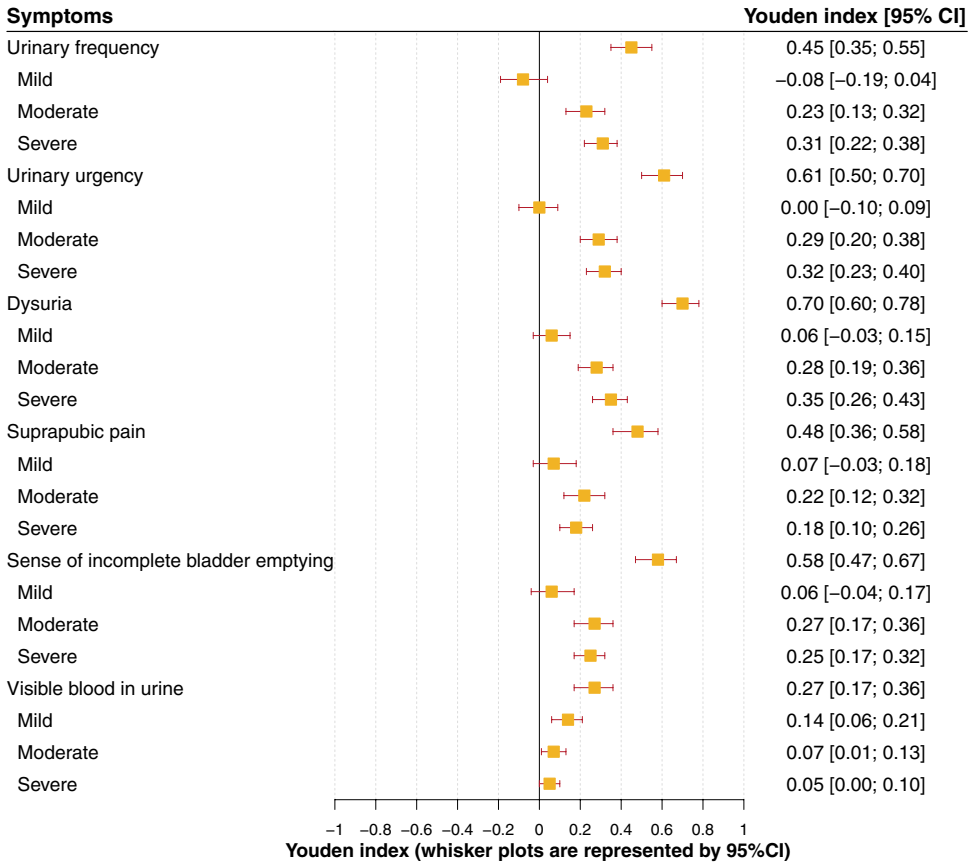

Fig. 4 Youden's index of the six ACSS typical symptoms according to presence and severity in the study population (patients with AC and controls without AC)

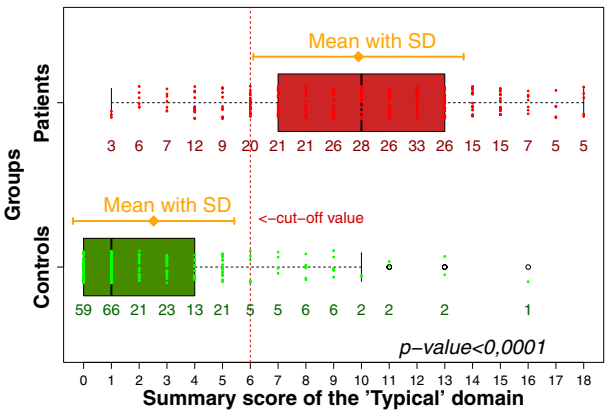

Fig. 5 Boxplots (IQR, range, mean ± SD) of the summary score of the six ACSS typical symptoms in respondents (patients with AC, controls without AC)

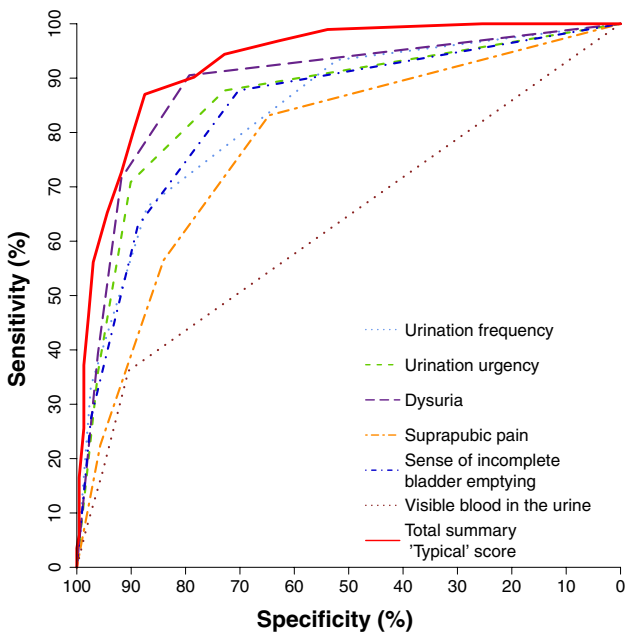

Fig. 6 Receiver operating characteristic (ROC) curves for the six individual typical symptoms and the summary score of the six symptoms proposed by ACSS

patient-reported clinical outcome (e.g. for at least 4 weeks after end of treatment) should become the main inclusion and outcome criteria of future studies. This would also better correspond to the general recommendations and everyday practice, making urine culture unnecessary, with the exception of specific situations, such as (a) suspected pyelonephritis, (b) symptoms not resolving within about 1 week or

recurring within 4 weeks after the completion of treatment; (c) atypical symptoms; (d) pregnancy [2].

Urine culture before and probably after treatment will remain important for epidemiological studies, and for studies including at least one antimicrobial therapy arm. However, the use of any defined significant bacteriuria as post hoc inclusion criterion is at least questionable. Nowadays, it is known that even under normal physiological condition, urine is not sterile [23]. The term "significant bacteriuria" was used in the past to differentiate between infection and contamination of a urine sample collected for analysis. When bladder urine from patients with unquestioned acute pyelonephritis was examined quantitatively, none contained less than 10^5 colony forming units (CFU) of uropathogen per mL [24]. Bacteriuria of $\geq 10^5$ CFU/mL in adults was originally defined significant only for the diagnosis of pyelonephritis. In 1982, Stamm et al. [25] documented that the levels of $\geq 10^5$ CFU/mL of a pathogen in urine have a very high specificity (99%) but a very low sensitivity (51%) for the diagnosis of AC. Bacteriuria of $\geq 10^2$ CFU/mL was suggested by the authors as the best diagnostic criterion (sensitivity, 95%; specificity, 85%). In 2013, Hooton et al. [26] confirmed that *E. coli* identified as low as 10^1–10^2 CFU/mL was sensitive and specific for the diagnosis of AC in symptomatic women. But still, about 20% of these symptomatic female patients were culture "negative" even when being tested for such low counts. Quantitative PCR (qPCR) for *E. coli* and *S. saprophyticus* finally demonstrated that almost all women with symptoms suggestive for UTIs and a "negative" culture still have an infection with *E. coli* [27]. Therefore, according to the German National S3 Guideline, the detection of *E. coli* in symptomatic women is predictive for a bacterial UTI, irrespective of the number of pathogens. In contrast, the presence of Enterococci and group B *Streptococci* in urine is not predictive for UTIs [3].

Hence, the use of a general definition for significant bacteriuria of $\geq 10^5$ CFU/mL as an inclusion criterion, may falsely exclude about half of the patients with a probable diagnosis of AC presented with the same symptoms. Therapeutic consequences drawn from such studies may have to be then restricted for this subgroup of patients. Therefore, we recommend considering all patients included with the same clinical criteria into a study as the main target population. Patients with bacteriuria of $\geq 10^2$ or $\geq 10^3$ CFU/mL, in turn, should then only be considered as microbiologically evaluable patients. The same principles should be applied for outcome criteria, based on patient-reported outcome using a validated questionnaire at least up to 4 weeks after the end of therapy. Consideration of the elimination of bacteriuria as the main study aim is scientifically questionable, due to the findings that asymptomatic bacteriuria may probably be protective against recurrent UTI [28, 29]. It should, however, be registered as additional results of the study.

The analysis of 517 female respondents (patients and controls) has revealed that the diagnostic value of the ACSS cut-off value without urinalysis is at least as favourable as the draft proposals by FDA or by EMA. The most important advantage of the ACSS is that it could be used also in epidemiological studies or for self-diagnosis of the patient without the need for additional laboratory tests, such as urinalysis. For clinical interventional studies, however, the same threshold could be used as an inclusion criterion together with the evidence of pyuria and thus dramatically increasing the specificity.

Although it has been demonstrated that the scoring of the five first typical symptoms in the ACSS questionnaire are not much inferior to the six symptoms, including visible blood, we recommend to include further all six items in the typical domain, because visible hematuria in connection with typical urinary symptoms may be pathognomonic for acute hemorrhagic cystitis. It can also be an important differential sign. If visible hematuria persists after treatment, it needs a further careful investigation of the patient to exclude any other urological disease, such as bladder cancer. The Swiss guidelines have also included a recent onset of hematuria as one of the typical symptoms of AC besides frequency, urgency and dysuria with pyuria and bacteriuria of $\geq 10^2$ CFU/ml [30].

The shortcoming of the study is mainly related to the design as a non-interventional, case–control study.

There are different laboratory methods defining pyuria in different countries. The dichotomized approach allocating pyuria into "significant" and "non-significant" allowed to bring the values together, thus reducing possible biases. The difference between pyuria (WBC $\geq$ 25/µL) tested in the current analysis and pyuria (WBC $\geq$ 10/µL) proposed by FDA and EMA remains open. The ratio of patients and controls in our study is 1:0.81, which is close to the optimal ratio of 1:1.

Because of the non-interventional approach, the study protocol could only be suggestive for the participating physicians, who were asked to follow the national and international guidelines for the diagnosis and treatment of women with AC. Therefore, variations of the management could only be minimized but not completely avoided.

Conclusions

The diagnostic values of the "draft" guidelines proposed by FDA and EMA were compared with the validated ACSS questionnaire. Not only the presence but also the severity of the symptoms (scoring) are important for an accurate diagnosis of AC. It could be shown that the diagnostic value of the ACSS, even without additional urinalysis, is at least

as favorable for the clinical diagnosis of AC as the draft clinical proposals by FDA and EMA. Therefore, the ACSS can be recommended for epidemiological and interventional studies, and allows women for self-diagnosis of AC, which makes the ACSS also cost-effective for healthcare.

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Compliance with ethical standards

Conflicts of Interest Prof. Kurt G. Naber, Prof. Florian M. Wagenlehner, Dr Adrian Pilatz, and Dr Jakhongir Alidjanov are authors and copyright holders of the ACSS questionnaire.

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ORIGINAL ARTICLE

Additional assessment of Acute Cystitis Symptom Score questionnaire for patient-reported outcome measure in female patients with acute uncomplicated cystitis: part II

J. F. Alidjanov[1] · K. G. Naber[2] · A. Pilatz[1] · A. Radzhabov[3,4] · M. Zamuddinov[5] · A. Magyar[6] · P. Tenke[6] · F. M. Wagenlehner[1]

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Abstract

Purpose Since symptomatic, non-antibiotic therapy has become an alternative approach to treat acute cystitis (AC) in women, suitable patient-reported outcome measures (PROM) are urgently needed. The aim of this part II of a larger non-interventional, case–control study was the additional assessment of the ACSS as a suitable PROM.

Methods Data from 134 female patients with diagnosed acute uncomplicated cystitis were included in the current analysis with (1) a summary score of "Typical" domain of 6 and more; (2) at least one follow-up evaluation after the baseline visit; (3) no missing values in the ACSS questionnaire data. Six different predefined thresholds based on the scoring of the ACSS items were evaluated to define "clinical cure", also considering the draft FDA and EMA guidelines.

Results Of the six different thresholds tested, a summary score of the five typical symptoms of 5 and lower with no symptom more than 1 (mild), without visible blood in urine, with or without including QoL issues was favoured, which partially also could be adapted to the draft FDA and EMA guidelines. The overall patient's clinical assessment ("Dynamic" domain) alone was not sensitive enough for a suitable PROM.

Conclusions Scoring of the severity of symptoms is needed not only for diagnosis, but also for PROM to define "clinical cure" of any intervention, which could be combined with QoL issues. Results of the study demonstrated that the ACSS questionnaire has the potential to be used as a suitable PROM and should further be tested in prospective clinical studies.

Keywords Urinary tract infection · Cystitis · Acute cystitis symptom score · ACSS · Guidelines · Patient-reported outcome

Introduction

Although current guidelines recommend the use of antibiotics (ABs) as the first choice of treatment for the acute phase of uncomplicated urinary tract infections (uUTI) [1, 2], several prospective randomized, controlled studies have been performed already comparing antibiotic therapy with symptomatic therapy of uncomplicated acute cystitis (AC) in women [3–6]. These results were compelling enough for the updated German Clinical Guidelines [2] to encourage the use of non-AB symptomatic treatment in selected cases of acute lower uUTIs with mild-to-moderate symptoms. Taking into account the possible protective abilities of asymptomatic bacteriuria against recurrent UTI, it has become obvious that the elimination of bacteriuria cannot be considered anymore the main aim of studies focused on the assessment of the efficacy of non-antibiotic modalities in the treatment of AC [7, 8]. Consequently, suitable and

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✉ J. F. Alidjanov
dr.alidjanov@gmail.com

K. G. Naber
kurt@nabers.de

1 Clinic for Urology, Pediatric Urology and Andrology, Justus Liebig University, Giessen, Germany

2 Department of Urology, Technical University of Munich, Munich, Germany

3 Treatment and Diagnostic Center "Olami Tib", Dushanbe, Tajikistan

4 Sankt-Katharinen Hospital, Frankfurt, Germany

5 Department of Urology, Madadi Akbar Clinic, Dushanbe, Tajikistan

6 Department of Urology, Jahn Ferenc South Pest Teaching Hospital, Budapest, Hungary

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effective patient-reported outcome measures (PROM) are urgently needed.

According to the Food and Drug Administration (FDA) guidance for industry, a PROM is "a means to capture PROM data used to measure treatment benefit or risk in medical product clinical trials". Additional definition of a PROM includes the following: "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else. The outcome can be measured in absolute terms (e.g., the severity of a symptom, sign, or state of a disease) or as a change from a previous measure. In clinical trials, a PROM can be used to measure the effect of a medical intervention on one or more concepts (i.e., the *thing* being measured, such as a symptom or group of symptoms, effects on a particular function or group of functions, or a group of symptoms or functions shown to measure the severity of a health condition)" [9].

The Acute Cystitis Symptom Score (ACSS) was already introduced as a standardized self-reporting diagnostic questionnaire, which has proven its efficacy in the clinical diagnosis of AC in women and in monitoring possible changes after therapy [10–14]. The ACSS has been translated and validated in several languages and is available online (http://www.acss.world/downloads.html). In a smaller, non-interventional study, the ACSS was already evaluated as a PROM [13, 14]. Since the ACSS has now been used in a larger non-interventional, case–control study [15], we aimed to perform an additional assessment of the ACSS as a suitable PROM.

Materials and methods

Study design

The current study was planned as a non-interventional within-subject design and can be considered as part II of the recent publication [15], which mainly analysed the diagnostic values of the ACSS as compared to the recently published draft guidelines of FDA and EMA [16, 17].

Study tool

The ACSS is composed of the "Diagnostic" and "Follow-up" forms (part A and part B). Each of these forms consists of four domains: (1) typical symptoms, (2) differential symptoms, (3) quality of life (QoL), (4) additional medical conditions. Besides the four mentioned domains, the "Follow-up" part B of the ACSS contains the "Dynamics" domain to assess the overall clinical outcome reported by the patient [10].

The "Typical" domain of the ACSS contains six patient-reported items corresponding to (1) urination frequency, (2) urination urgency, (3) burning pain during urination (dysuria), (4) suprapubic pain, (5) incomplete bladder emptying, vi) visible blood in the urine.

The "QoL" domain is composed of three items concerning (1) overall discomfort (bothersomeness) caused by the symptoms and their severity, (2) impact on daily work/activities, and (3) impact on social activities.

The items of the "Typical" and "QoL" domains were scored according to severity: none, mild, moderate, and severe.

The "Differential" domain of the ACSS contains items concerning differential diagnostic considerations, such as female genital infections and upper UTI symptoms. The "Additional" domain contains questions concerning important medical conditions, such as menstruation, premenstrual syndrome (PMS), postmenopause, pregnancy, and diabetes mellitus.

The "Dynamics" domain of the ACSS is composed of five grades concerning overall changes of the symptomatology: Feeling (1) normal (all symptoms have gone away); (2) much better (most of the symptoms has gone away); (3) somewhat better (only some symptoms have gone away); (4) no changes; (5) worse.

The data from both "Diagnostic" and "Follow-up" forms of the ACSS questionnaire were used in this study.

From the draft guidelines proposed by FDA, the four (dysuria, urinary frequency, urinary urgency, and suprapubic pain) or by EMA, the three (frequency, urgency and dysuria) symptoms mentioned in the corresponding draft guidelines—all included also in the ACSS questionnaire—were analysed accordingly [16, 17]. All items were dichotomized (s. below) as "Positive" or "Negative", depending on the presence or absence of the symptom, and their severity was also considered.

Data acquisition

The e-USQOLAT database, containing relevant clinical information and laboratory data of women with and without AC was selected as a primary source for data mining [18]. These data were obtained from female respondents at baseline and follow-up visits during clinical validation of the ACSS in several countries. All relevant data were acquired from the database at its state on the access date of January 1, 2019.

Data processing

Of among 517 female respondents, described in our recent publication [15], we have selected patients with AC according to the diagnosis made by the treating physician with the following inclusion criteria: (1) summary score of "typical symptoms" of 6 and more; (2) at least one follow-up

evaluation after the initial "diagnostic" visit; (3) no missing values in the ACSS questionnaire data, including the "Dynamics" domain of the "follow-up Part B" of the questionnaire (Fig. 1).

Patients were supposed to receive appropriate medical treatment according to the national and international guidelines and therapeutic standards [1, 2, 19]. However, only

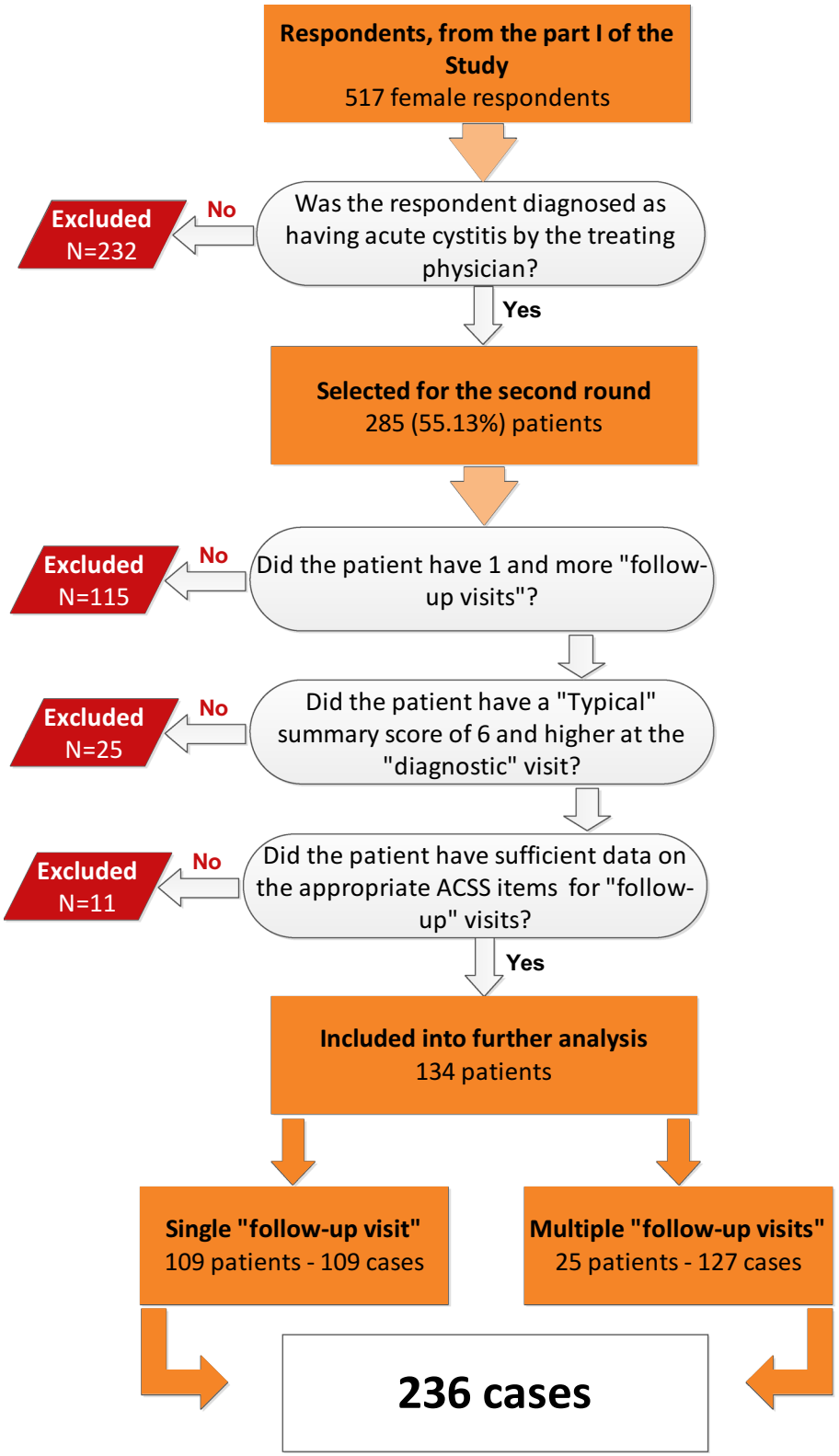

Fig. 1 Flowchart of patients' selection. Part I of the study [15]

outcome and not therapy modalities were included in the further analysis of this non-interventional study.

Patients, who have filled up more than 1 "follow-up Part B" of the ACSS were added as new cases per each available follow-up form (visit). Visits were grouped depending on the time difference between the first diagnostic visit and further "follow-up" evaluation visits.

The "Dynamics" domain of the "follow-up Part B" form of the ACSS was also considered for evaluation of overall clinical outcome determined by the patient. In the purpose of dichotomization, items "Yes I feel normal" and "Yes, I feel much better" were merged and classified as "clinical cure", whereas the three remaining items ("Yes, I feel somewhat better", "No, there are barely any changes", and "Yes, I feel worse") were merged to "failure". The procedures of dichotomization were described previously [15].

In general, relative variables were labelled as "0" for "negative,"/"not match", and "1" for "positive"/"match".

Thresholds and terms

The evaluation terms or "visits" were classified according to the time difference (in days) between the "diagnostic" and "follow-up" evaluations.

To determine meaningful thresholds for clinical cure, typical symptoms, QoL and overall clinical assessments ("Dynamic" domain) were evaluated, combined and/or weighed against each other.

Statistical analysis

Two-by-two contingency tables were used for the statistical analysis of the bivariate (dichotomized) variables, where the thresholds in different times of the evaluation were considered as the test variable (exposure), and efficacy of the therapy was taken as an outcome.

The validity of the predetermined thresholds was evaluated by the assessment of their relations with the overall clinical outcome as reported by the patients in the "Dynamics" domain of the "follow-up" form of the ACSS.

Such values as sensitivity, specificity, positive and likelihood ratios, Youden's J-index, odds ratio (OR), positive and negative predictive values (PPV and NPV respectively), positive and negative likelihood ratios (+LR and −LR respectively) were calculated. ROC-curve analysis was used for the assessment of area under the curve (AUC). The strength of associations between test variables and the outcome was measured using Pearson's product–moment correlation coefficient.

Tests of the comparative analyses were performed in dependence of normality and homoscedasticity of distributions which in turn were assessed using normality tests (Shapiro–Wilk's) [20], histograms and normal Q–Q plots (see Suppl. Figures 1 and 2).

For the comparison of independent, homoscedastic and normally distributed variables, Student's two-sided *t* test was used. For normally distributed heteroscedastic independent variables, Welch's two-sided modified *t* test was used. Non-parametric tests such as Kruskal–Wallis rank-sum test [21] and Wilcoxon/Mann–Whitney rank-sum test for pairwise comparisons [22] were used when parametric tests were considered inappropriate. A p value of less than 0.05 was considered statistically significant.

R v.3.5.2 with in-built and additional packages was used for the statistical analysis and graphical representation of the results [23–26].

Results

Using the criteria described above, 134 patients of among 517 previously selected female respondents [15] were included in the current analysis. The age of the selected patients ranged from 17 to 82 years, with a median (IQR) of 31 (24.00–44.25) and mean (SD) of 36.28 (16.03) years. Of them, 109 filled up at least 1 copy of the "follow-up Part B" form of the ACSS (one "follow-up" visit) after the initial "diagnostic" visit and 25 patients filled up multiple copies at different "follow-up" visits. Altogether, they have formed 236 cases (Fig. 1).

The maximum time difference between "diagnostic" (visit 1) and "follow-up" evaluations (FU visits) was 29 days. According to the time difference, we have classified four terms of the "follow-up" evaluations: (1) Very early evaluation or "Visit 2" (less than 2 days between "diagnostic" and "follow-up" evaluations); (2) Early evaluation or "Visit 3" (2–4 days between "diagnostic" and "follow-up" evaluations); (3) End-of-therapy evaluation or "Visit 4" (5–9 days between "diagnostic" and "follow-up" evaluations), and (4) Test-of-cure evaluation or "Visit 5" (10–30 days between "diagnostic" and "follow-up" evaluations).

Eight different thresholds for evaluation of clinical cure at the outcome were predetermined:

A. A summary score of the "Typical" domain up to 5 AND no visible blood in the urine
B. A summary score of the "Typical" domain up to 4 AND no visible blood in the urine
C. A summary score of the "Typical" domain up to 5 with no item > 1 (mild) AND no visible blood in the urine
D. A summary score of the "Typical" domain up to 4 AND no "Typical" item > 1 (mild) AND no visible blood in the urine

E. A summary score of the "Typical" domain up to 5 AND no "Typical" item > 1 (mild) AND no visible blood in the urine AND no "QoL" item > 1
F. A summary score of the "Typical" domain up to 4 AND no "Typical" item > 1 AND no visible blood in the urine AND no "QoL" item > 1
G. A summary score of the four FDA symptoms up to 4 AND no score > 1 (mild) AND no visible blood in the urine
H. A summary score of the three EMA symptoms up to 3 AND no score > 1 (mild) AND no visible blood in the urine

Six of these thresholds (A–F) are related to the ACSS items, one (G) was adapted to the FDA criteria, considering four symptoms, and one (H) was adapted to the EMA criteria, considering three symptoms, as suggested in the corresponding draft guidelines [16, 17].

Since only 34.75% of patients had visible blood in urine, which decreased to only two patients at visits 4 and 5, we considered a clinical cure for all of the thresholds only for cases with no visible blood as stated by the patient.

At the time of "diagnostic" evaluation (visit 1), median (IQR) of the summary typical score by the patients was 10 (7.75–13.00). On the next day of therapy (very early evaluation/visit 2), it reduced to 7.00 (6.00–9.00). Further reductions were as follows: 4.00 (0.00–6.00) at the early evaluation (visit 3), 1.50 (0.00–3.00) at the end-of-therapy evaluation (visit 4), and 1.50 (0.00–2.75) at the test-of-cure evaluation (visit 5). The average summary scores of the "Typical" domain differed significantly between all evaluation categories ($p < 0.05$), except between those at end-of-therapy and test-of-cure evaluations ($p = 0.71$) (Table 1, Fig. 2).

The severity of the six typical symptoms at visit 1 and the follow-up visits are presented in Table 2. At the "diagnostic" visit 1, five of six typical symptoms were positive in 88.98–97.03% of the cases. Although the percentage of cases with positive symptoms decreased over the observation time (especially starting from visit 3), and the percentages of cases with severe or moderate symptoms decreased

Table 1 Summary scores of "Typical" domain at the five visit categories (mean, SD, median, IQR)

	Cases (*n*)	Sum score of typical domain				
		Mean	SD	Median	IQR	
Visit 1 (diagnostics, Day 0)	236	10.23	3.18	10.00	7.75	13.00
Visit 2 (very early FU, Day < 2)	23	7.70	3.21	7.00	6.00	9.00
Visit 3 (early FU, Day 2–4)	97	3.77	3.29	4.00	0.00	6.00
Visit 4 (end of treatment, Day 5–9)	82	2.26	2.94	1.50	0.00	3.00
Visit 5 (test of cure, Day 10–30)	34	2.12	3.38	1.50	0.00	2.75

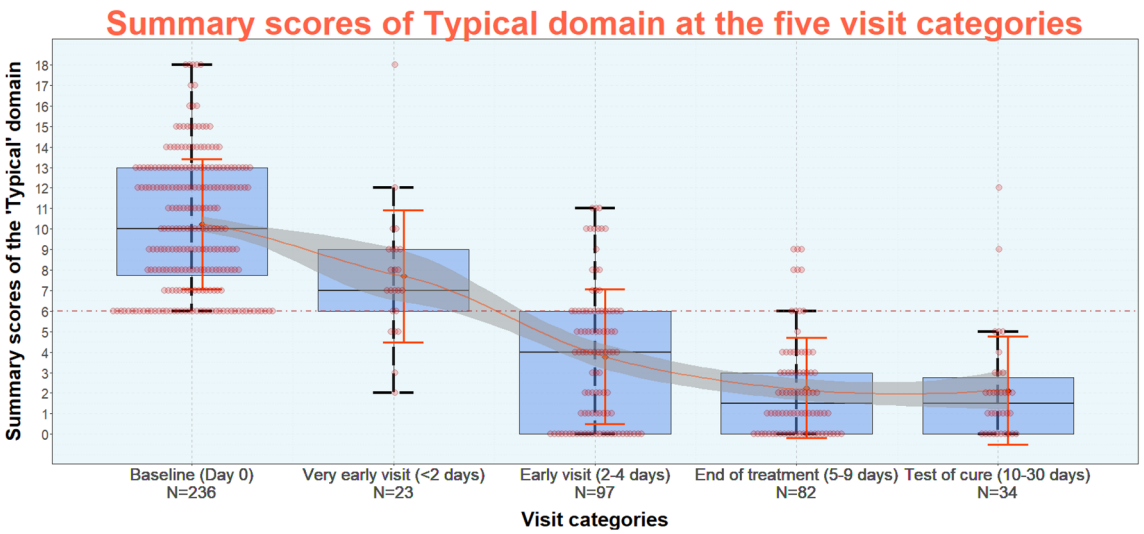

Fig. 2 Summary scores of "Typical" domain of ACSS at diagnostics of acute uncomplicated cystitis (AC) in women (baseline) and at the four different follow-up visit categories: "very early visit", "early visit", "end-of-treatment visit", "test-of-cure visit". *Note* Red dots represent cases, orange diamonds represent mean scores, orange error bars represent standard deviations, orange line illustrates the symptomatic "course" of AC, grey "strip" around the orange line represents standard error of a mean

Table 2 Typical symptoms and their severity claimed by the patients at the five visit categories

Visit 1	Diagnostics (Day 0). *n* of cases = 236			
Typical symptoms	Total (%)	Mild (%)	Moderate (%)	Severe (%)
Urinary frequency	210 (88.98%)	69 (29.24%)	69 (29.24%)	72 (30.51%)
Urinary urgency	220 (93.22%)	40 (16.95%)	88 (37.29%)	92 (38.98%)
Dysuria	229 (97.03%)	38 (16.10%)	72 (30.51%)	119 (50.42%)
Suprapubic pain	196 (83.05%)	62 (26.27%)	83 (35.17%)	51 (21.61%)
Incomplete bladder emptying	218 (92.37%)	62 (26.27%)	89 (37.71%)	67 (28.39%)
Visible blood in urine	82 (34.75%)	43 (18.22%)	21 (8.90%)	18 (7.63%)
Visit 2	Very early FU visit (in less than 2 days). *n* of cases = 23			
Typical symptoms	Total (%)	Mild (%)	Moderate (%)	Severe (%)
Urinary frequency	18 (78.26%)	10 (43.48%)	5 (21.74%)	3 (13.04%)
Urinary urgency	22 (95.65%)	13 (56.52%)	8 (34.78%)	1 (4.35%)
Dysuria	22 (95.65%)	5 (21.74%)	12 (52.17%)	5 (21.74%)
Suprapubic pain	18 (78.26%)	8 (34.78%)	6 (26.09%)	4 (17.39%)
Incomplete bladder emptying	19 (82.61%)	8 (34.78%)	8 (34.78%)	3 (13.04%)
Visible blood in urine	4 (27.39%)	2 (8.70%)	1 (4.35%)	1 (4.35%)
Visit 3	Early FU visit (2–4 days). *n* of cases = 97			
Typical symptoms	Total (%)	Mild (%)	Moderate (%)	Severe (%)
Urinary frequency	42 (43.30%)	28 (28.87%)	12 (12.37%)	2 (2.06%)
Urinary urgency	51 (52.58%)	36 (37.11%)	13 (13.40%)	2 (2.06%)
Dysuria	59 (60.82%)	40 (41.24%)	14 (14.43%)	5 (5.15%)
Suprapubic pain	49 (50.52%)	32 (32.99%)	10 (10.31%)	7 (7.22%)
Incomplete bladder emptying	50 (51.55%)	38 (39.18%)	9 (9.28%)	3 (3.09%)
Visible blood in urine	13 (13.40%)	8 (8.25%)	4 (4.12%)	1 (1.03%)
Visit 4	End-of-treatment FU visit (5–9 days). *n* of cases = 82			
Typical symptoms	Total (%)	Mild (%)	Moderate (%)	Severe (%)
Urinary frequency	24 (29.27%)	16 (19.51%)	7 (8.54%)	1 (1.22%)
Urinary urgency	33 (40.24%)	26 (31.71%)	6 (7.32%)	1 (1.22%)
Dysuria	37 (45.12%)	33 (40.24%)	3 (3.66%)	1 (1.22%)
Suprapubic pain	24 (29.27%)	19 (23.17%)	3 (3.66%)	2 (2.44%)
Incomplete bladder emptying	28 (34.15%)	21 (25.61%)	7 (8.54%)	0 (0.00%)
Visible blood in urine	2 (2.44%)	1 (1.22%)	1 (1.22%)	0 (0.00%)
Visit 5	Test-of-cure visit (10–30 days). *n* of cases = 34			
Typical symptoms	Total (%)	Mild (%)	Moderate (%)	Severe (%)
Urinary frequency	14 (41.28%)	12 (35.29%)	1 (2.94%)	1 (2.94%)
Urinary urgency	14 (41.28%)	12 (35.29%)	1 (2.94%)	1 (2.94%)
Dysuria	15 (44.12%)	12 (35.29%)	3 (8.82%)	0 (0.00%)
Suprapubic pain	6 (17.65%)	5 (14.71%)	1 (2.94%)	0 (0.00%)
Incomplete bladder emptying	8 (23.53%)	6 (17.65%)	1 (2.94%)	1 (2.94%)
Visible blood in urine	2 (5.88%)	2 (5.88%)	0 (0.00%)	0 (0.00%)

significantly, a relatively high proportion of cases of at least mild symptoms remained even up to visit 5. Visible blood in the urine (a pathognomonic symptom of hemorrhagic cystitis) was found only in 34.75% of cases at the "diagnostic" visit 1 and was reduced to only two cases at the visits 4 (2.44%) and 5 (5.88%).

Table 3 represents the results of the assessment of the quality of life (QoL). It can be seen that the symptoms of acute cystitis affect all three indicated categories of QoL

Table 3 Impact on quality of live at the five visit categories

Visit 1	Diagnostic visit (Day 0). *n* of cases = 236			
Impact on quality of life	Total (%)	Mild (%)	Moderate (%)	Severe (%)
Overall discomfort	233 (98.73%)	38 (16.10%)	135 (57.20%)	60 (25.42%)
Work/daily activities	230 (97.46%)	86 (36.44%)	111 (47.03%)	33 (13.98%)
Social activities	228 (96.61%)	100 (42.37%)	89 (37.71%)	39 (16.53%)
Visit 2	Very early FU visit (in less than 2 days). *n* of cases = 23			
Impact on quality of life	Total (%)	Mild (%)	Moderate (%)	Severe (%)
Overall discomfort	18 (78.26%)	10 (43.48%)	5 (21.74%)	3 (13.04%)
Work/daily activities	22 (95.65%)	13 (56.52%)	8 (34.78%)	1 (4.35%)
Social activities	22 (95.65%)	5 (21.74%)	12 (52.17%)	5 (21.74%)
Visit 3	Early FU visit (2–4 days). *n* of cases = 97			
Impact on quality of life	Total (%)	Mild (%)	Moderate (%)	Severe (%)
Overall discomfort	42 (43.30%)	28 (28.87%)	12 (12.37%)	2 (2.06%)
Work/daily activities	51 (52.58%)	36 (37.11%)	13 (13.40%)	2 (2.06%)
Social activities	59 (60.82%)	40 (41.24%)	14 (14.43%)	5 (5.15%)
Visit 4	End-of-treatment FU visit (5–9 days). *n* of cases = 82			
Impact on quality of life	Total (%)	Mild (%)	Moderate (%)	Severe (%)
Overall discomfort	24 (29.27%)	16 (19.51%)	7 (8.54%)	1 (1.22%)
Work/daily activities	33 (40.24%)	26 (31.71%)	6 (7.32%)	1 (1.22%)
Social activities	37 (45.12%)	33 (40.24%)	3 (3.66%)	1 (1.22%)
Visit 5	Test of cure (10–30 days). *n* of cases = 34			
Impact on quality of life	Total (%)	Mild (%)	Moderate (%)	Severe (%)
Overall discomfort	14 (41.18%)	12 (35.29%)	1 (2.94%)	1 (2.94%)
Work/daily activities	14 (41.18%)	12 (35.29%)	1 (2.94%)	1 (2.94%)
Social activities	15 (44.12%)	12 (35.29%)	3 (8.82%)	0 (0.00%)

in almost all the cases (96.6–98.7%). Although the higher rates of severity (moderate, severe) were reduced during follow-up, about one-third of patients still claimed at the least mild impact on their QoL in all three categories.

The percentage of cases with "back to normal" or "much better" in the "Dynamics" domain have increased over the follow-up time, but there was still a noticeable number of the cases stated as "somewhat better" (Table 4). Therefore, it is difficult to decide how "clinical cure" should be defined in the frame of the current study using only the "Dynamics" domain by itself.

In Table 5, the results of the Tables 2–4 are summarized using for the six items of the "Typical" domain and the three items of the "QoL" domain the percentages of cases rating their symptoms and impact on QoL as moderate or severe at visit 1 (diagnostics) and the three follow-up visits (early, end of treatment, test of cure) and the patient's overall clinical assessment ("Dynamics" domain) according two different thresholds at the same three follow-up visits. It can be seen

Table 4 Overall changes (ACSS "Dynamics") from visit 1 at the four follow-up visit categories

ACSS (Dynamics) *n* of cases	Feeling normal (*n*, %)	Much better (*n*, %)	Somewhat better (*n*, %)	No changes (*n*, %)	Feeling worse (*n*, %)
Visit 2 (Day < 2), *n* = 23	0 (0.00%)	1 (4.35%)	12 (52.17%)	9 (39.13%)	1 (4.35%)
Visit 3 (Day 2–4), *n* = 97	17 (17.53%)	39 (40.21%)	31 (31.96%)	9 (9.28%)	1 (1.03%)
Visit 4 (Day 5–9), *n* = 82	24 (29.27%)	40 (48.78%)	12 (14.63%)	3 (3.66)	3 (3.66%)
Visit 5 (Day 10–30), *n* = 34	14 (41.18%)	10 (29.41%)	10 (29.41%)	0 (0.00%)	0 (0.00%)

Visit 2 (very early, Day < 2); visit 3 (early, Day 2–4); visit 4 (end of treatment, Day 5–9); visit 5 (test of cure, Day 10–30)

Table 5 Percentage of cases rating their symptoms and impact on the quality-of-life parameters as moderate and severe at visit 1 (diagnostics) and at three follow-up visits (early, end of treatment, a test of cure) and the patient's overall assessment (Dynamics domain) according to two different thresholds at the same three follow-up visits

	Visit 1 ($n=236$)	Visit 3 ($n=97$)	Visit 4 ($n=82$)	Visit 5 ($n=34$)
Typical symptoms (moderate + severe)				
Urinary frequency	59.75%	14.43%	9.76%	5.88%
Urinary urgency	76.27%	15.46%	8.54%	5.88%
Dysuria	80.93%	19.58%	4.88%	8.82%
Suprapubic pain	86.78%	17.53%	6.10%	2.94%
Incomplete bladder emptying	66.10%	12.37%	8.54%	5.88%
Visible blood in urine	16.53%	4.12%	1.22%	0%
Quality of life (moderate-to-severe impact)				
Overall discomfort	82.62%	14.43%	9.76%	5.98%
Work/daily activities	70.01%	15.46%	8.54%	5.98%
Social activities	54.34%	19.58%	4.88%	0%
Dynamics				
"Somewhat better, no changes, feeling worse"		50.27%	21.95%	29.41%
"No changes, feeling worse"		10.31%	7.32%	0%

that the scoring of the symptoms (except visible blood in urine) and the "QoL" items are decreasing fairly parallel starting from visit 1 to visit 5. As mentioned above, establishing a threshold between "feeling much better" and "feeling somewhat better" would show far too low "clinical cure" rates which are not compatible with clinical experience in patients with AC.

Finally, the results of the eight different predetermined thresholds—six related to ACSS items and one adapted each to FDA and EMA criteria—analysed at the different follow-up visits concerning discrimination of clinical cure depending on the answers of the patients are shown in Table 6. In general, the results demonstrate again that using severity of symptoms combined with or without QoL items fairly comparable rates of "clinical cure" could be obtained.

As a next step, we tested the positive achievement of "clinical cure" rates by the eight thresholds in association to outcome using the "Dynamics" domain considering "clinical cure" as (1) resolution of symptoms (feeling normal) and (2) feeling much better. Due to lack of sufficient cases at the very early visit (< 2 days between "diagnostic" and "follow-up" evaluations), we decided to remove these 23 cases from this kind of evaluation. Thus, 213 cases of the total were included in further analysis.

The ROC-curve analysis of the different thresholds concerning the overall clinical outcome as reported by the patients in the "Dynamics" domain, demonstrated that the comparatively largest AUC (average [95% CI]) was noted for the threshold category B (Summary score of the "Typical" domain up to 4 AND no visible blood in the urine) at the "Early evaluation" (0.83 [0.75; 0.91]). It was as well comparatively larger for other terms of evaluation: 0.78 [0.64; 0.92] and 0.83 [0.65; 1.00] for the "End of treatment" and "Test of cure" evaluations. However, the differences were not statistically significant when compared either with other thresholds or other terms of evaluation (Suppl. Figure 1 a–c, Suppl. Table 1).

Highest value of sensitivity (average [95% CI]) was revealed for the threshold "A" (0.91 [0.85; 0.95]), the highest value of specificity was revealed for the threshold "F" (0.77 [0.65; 0.86]). The most optimal balance between sensitivity and specificity, positive and negative likelihood ratios, also highest Youden index and strongest correlation with the positive outcome ("Success", according to the "Dynamics" domain of the "follow-up part B" form of the ACSS) was found to be for the threshold "D" (Summary score of the "Typical" domain up to 4 AND no "Typical" item > 1 in the absence of the visible blood in the urine): sensitivity (0.88 [0.81–0.92]) and specificity (0.74 [0.62–0.84]) (Suppl. Table 1).

Discussion

Since a PROM is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else, the ACSS questionnaire could be such an instrument for female patients with AC. Besides the "Differential" and "Additional" domains (see above), the ACSS contains three different domains (Typical, QoL, Dynamics), which could be used alone or in combinations for this purpose. In the "Typical" domain, the patient is asked about six symptoms/signs, which she has already scored before, at visit 1, the diagnosis of AC was established. Although the symptoms asked for are usually considered typical for AC, none of the symptoms/signs can, however, be considered exclusive for AC. In earlier studies, it could be demonstrated, that the same symptoms in a mild form do not very well differentiate between patients with AC and controls without AC [12, 17].

Table 6 A number of cases above and below certain breakpoints representing success and non-success at the four follow-up visit categories. Each case with "visible blood in the urine (VBU)" was rated "non-success". (Threshold letters adjusted to supplementary table 1)

Criteria for success and non-success	Yes (*n*, %)	No (*n*, %)
Visit 2 (very early, Day < 2), *n* of cases = 23		
A) summary score of typical domain ≤ 5 scores and "visible blood in urine" = 0	5 (21.74%)	18 (78.26%)
B) summary score of typical domain ≤ 4 scores and "visible blood in urine" = 0	2 (8.70%)	21 (91.3%)
C) summary score of typical domain ≤ 5 scores, no item > 1 and "visible blood in urine" = 0	2 (8.70%)	21 (91.3%)
D) summary score of typical domain ≤ 4 scores, no item > 1 and "visible blood in urine" = 0	2 (8.70%)	21 (91.3%)
E) summary score of typical domain < 5 scores, no item > 1 and no item of QoL > 1 and "visible blood in urine" = 0	1 (4.35%)	22 (95.65%)
F) summary score of typical domain ≤ 4 scores, no item > 1 and no item of QoL > 1 and "visible blood in urine" = 0	1 (4.35%)	22 (95.65%)
G) summary score of 4 FDA symptoms ≤ 4, no item > 1 and "visible blood in urine" = 0	2 (8.70%)	21 (91.3%)
H) summary score of 3 EMA symptoms ≤ 3, no item> 1 and "visible blood in urine" = 0	2 (8.70%)	21 (91.3%)
Visit 3 (early, Day 2–4), *n* of cases = 97		
A) summary score of typical domain ≤ 5 scores and "visible blood in urine" = 0	64 (65.98%)	33 (34.02%)
B) summary score of typical domain < 4 scores and "visible blood in urine" = 0	54 (55.67%)	43 (44.33%)
C) summary score of typical domain ≤ 5 scores, no item > 1 and "visible blood in urine" = 0	55 (56.70%)	42 (43.30%)
D) summary score of typical domain ≤ 4 scores, no item > 1 and "visible blood in urine" = 0	51 (52.58%)	46 (17.42%)
E) summary score of typical domain ≤ 5 scores, no item > 1 and no item of QoL > 1 and "visible blood in urine" = 0	53 (54.64%)	44 (45.36%)
F) summary score of typical domain ≤ 4 scores, no item > 1 and no item of QoL > 1 and "visible blood in urine" = 0	50 (51.55%)	47 (48.45%)
G) summary score of 4 FDA symptoms ≤ 4, no item > 1 and "visible blood in urine" = 0	56 (57.73%)	41 (42.27%)
H) summary score of 3 EMA symptoms ≤ 3, no item > 1 and "visible blood in urine" = 0	59 (60.82%)	38 (39.18%)
Visit 4 (end of treatment, Day 5–9), *n* of cases = 82		
A) summary score of typical domain ≤ 5 scores and "visible blood in urine" = 0	70 (85.37%)	12 (14.63%)
B) summary score of typical domain ≤ 4 scores and "visible blood in urine" = 0	69 (84.15%)	13 (15.85%)
C) summary score of typical domain ≤ 5 scores, no item > 1 and "visible blood in urine" = 0	66 (80.49%)	16 (19.51%)
D) summary score of typical domain ≤ 4 scores, no item > 1 and "visible blood in urine" = 0	66 (80.49%)	16 (19.51%)
E) summary score of typical domain ≤ 5 scores, no item > 1 and no item of QoL > 1 and "visible blood in urine" = 0	60 (73.17%)	22 (26.83%)
F) summary score of typical domain ≤ 4 scores, no item > 1 and no item of QoL > 1 and "visible blood in urine" = 0	60 (73.17%)	22 (26.83%)
G) summary score of 4 FDA symptoms ≤ 4, no item > 1 and "visible blood in urine" = 0	66 (80.49%)	16 (19.51%)
H) summary score of 3 EMA symptoms ≤ 3, no item > 1 and "visible blood in urine" = 0	67 (81.71%)	15 (18.28%)
Visit 5 (test of cure, Day 10–30), *n* of cases = 34		
A) summary score of typical domain ≤ 5 scores and "visible blood in urine" = 0	30 (88.24%)	4 (11.76%)
B) summary score of typical domain ≤ 4 scores and "visible blood in urine" = 0	28 (82.35%)	6 (17.65%)
C) summary score of typical domain ≤ 5 scores, no item > 1 and "visible blood in urine" = 0	28 (82.35%)	6 (17.65%)
D) summary score of typical domain ≤ 4 scores, no item > 1 and "visible blood in urine" = 0	27 (79.41%)	7 (20.59%)
E) summary score of typical domain ≤ 5 scores, no item > 1 and no item of QoL > 1 and "visible blood in urine" = 0	27 (79.41%)	7 (20.59%)
F) summary score of typical domain ≤ 4 scores, no item > 1 and no item of QoL > 1 and "visible blood in urine" = 0	27 (79.41%)	7 (20.59%)
G) summary score of 4 FDA symptoms ≤ 4, no item > 1 and "visible blood in urine" = 0	28 (82.35%)	6 (17.65%)
H) summary score of 3 EMA symptoms ≤ 3, no item > 1 and "visible blood in urine" = 0	28 (82.35%)	6 (17.65%)

Therefore, scoring of the symptoms is necessary to increase the diagnostic value of the so-called "typical" symptoms. The same applies for outcome criteria if symptoms are used for PROM, because the complete elimination of all symptoms cannot always be expected in all patients, although considered clinically cured. By scoring the severity of the symptoms, the threshold of most suitable reduction of symptoms needs to be analysed carefully below which a patient may be considered clinically cured. Therefore, scoring the severity of the symptoms also becomes relevant for PROM.

Although reports of patients concerning symptoms can only be subjective by definition, by answering the same, in the meantime, familiar questionnaire at any follow-up visit, one can at least expect that by scoring the symptoms not only the presence or absence, but also the increasing or decreasing severity of each symptom reported by the patient can be considered as a quasi-objective measure. Nevertheless, the amount of the reported change may still be subjective. Therefore, we do not consider a certain total summary score as a threshold to define "clinical cure", but rather postulate that the symptoms do not exceed a severity of more than mild. Visible blood in urine, however, should become always absent, because persistent visible blood in urine would need further diagnostic steps to exclude serious pathologies, such as bladder cancer.

Besides symptom severity, the patient can also be asked about symptom discomfort (bothersomeness) and impact on daily and social activities (QoL domain) as considered necessary for PRO measures by Holm et al. [27]. Considering the QoL domain in addition, the results are closely related to the results using the symptom scoring system alone, but one gets the impression that for some patients, adjustment of their QoL takes somewhat longer than their awareness of symptom severity reduction.

Finally, in the ACSS, the patient is asked about her overall clinical assessment ("Dynamics" domain), which again considers more a relative change as compared to the situation before the AC has occurred (normal, baseline status) and compared to the situation when the diagnosis was established and any therapeutic intervention has started. The intention to correlate the overall patient's clinical assessment with the reduction of the severity of typical symptoms was, however, not convincing. Unfortunately, we could not test the overall clinical assessments proposed in the draft guidelines by FDA and EMA [16, 17]. According to the draft EMA guidelines, the clinical outcome should be categorised as cure, failure or indeterminate. The cure may be defined as (1) complete resolution of clinical signs and symptoms and/or (2) sufficient improvement or return to baseline status such that no further antibacterial therapy is required for the index infection. According to the draft FDA guidelines, "clinical response" is defined as resolution of the symptoms of uUTI (dysuria, urinary frequency, urinary urgency, suprapubic pain) present at trial entry (and no new symptoms). Using both definitions, one probably will face the same problems, how patients consider "sufficient improvement" (EMA) or "resolution of symptoms" (FDA).

Considering these three different measures (symptoms, discomfort (bothersomeness) and impact on QoL, patient's overall clinical assessment), it may be difficult to agree on the best PROM instrument for defining "clinical cure". Using the ACSS for systematic reasons, we suggest the following two thresholds as the most appropriate for a suitable PROM instrument depending on the requirement not to include or to include QoL issues as strongly requested by Holm et al. [27]: (1) a summary score of the "Typical" domain up to 5 with no item > 1 (mild) AND no visible blood in the urine (threshold C); and (2) a summary score of the "Typical" domain up to 5 AND no "Typical" item > 1 (mild) AND no visible blood in the urine AND no "QoL" item > 1 (threshold E). If the threshold including QoL is used (E), one should consider that obviously "QoL improvement" is stated by some patients later than a reduction of symptoms' severity. Whereas at visit 4 (end of treatment), the discrepancy between threshold C and E still were six cases (in favour of C), at visit 5 (test of cure), the difference was reduced to only one case.

The study has, of course, several limitations. It was a non-interventional study. The final diagnosis and treatment of AC were established by the treating physician according to international and national guidelines and standards. Because of the non-interventional character of the study, the follow-up visits of the patients could also not be defined a priori, but only grouped according to meaningful time intervals representing very early (< 2 days) and early (2–4 days) follow-up visits, end-of-treatment (5–9 days) and test-of-cure visits (> 10 days). Although all patients during the different follow-up categories were part of the cohort at visit 1 (diagnostics), the amount of cohorts during the different follow-up visits may also have differed very much between follow-up visits. Within a follow-up visit category, however, all parameters calculated referred to the same group of patients analysed at the beginning (diagnostic visit) and thus, were comparable.

In summary, the ACSS questionnaire was originally developed for clinical diagnostics and therapeutic outcome in female patients with acute uncomplicated cystitis (AC). During development, patients were interviewed, how they describe best the so-called typical symptoms of AC and their severity during an acute episode of AC and when they felt cured or improved after treatment, which was compared with controls without AC. In addition, the patients and the controls were asked about the impact on their quality of life according to three aspects (bothersomeness of symptoms, impact on daily life and work, impact on social life) and for their own overall clinical assessment after treatment. Therefore, the ACSS questionnaire can also be used as a PROM instrument, because patients were involved in the development, by focus groups and interviews to capture the breadth of symptoms and experiences associated with this particular disease, as requested by Rothrock et al. [28].

Nevertheless, it would be helpful to test the thresholds suggested in the current study to define "clinical cure"

additionally in a prospective study with better-defined follow-up visits of all patients included.

Conclusions

Since non-antibiotic therapy has become an alternative approach to treat AC in women, suitable PRO measures are urgently needed. Although typical symptoms are mainly used for clinical diagnosis and outcome, these symptoms are not exclusively found in AC. Therefore, severity scoring of the symptoms is needed not only for diagnostics, but also for PRO measure to define "clinical cure" of any intervention. The presented data analysis demonstrated that the ACSS questionnaire has the potential to be used as a suitable instrument for PRO in well-designed prospective clinical studies.

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Compliance with ethical standards

Conflict of interest Prof. Kurt G. Naber, Prof. Florian M. Wagenlehner, Dr. Adrian Pilatz, and Dr. Jakhongir Alidjanov are authors and copyright holders of the ACSS questionnaire. Jakhongir Alidjanov declares a personal conflict of interest with Elsevier publishing company due to his personal disagreement with the policy of the company.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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