Strategies to control the emerging bacterial antibiotic resistance in urology

Ph.D. Thesis

/Short version/

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1. INTRODUCTION

The antibiotic era provided us safety versus pathogenic bacteria since generations. The modern medicine highly depends on antibiotics. As a result, the widespread use of antibiotics has led to a rapid increase in bacterial resistance. If we do not find a solution, the increase of bacterial resistance is going to lead to catastrophic consequences from medical, scientific and economical point of view [1]. Without immediate interference, by the year 2050, the expected number of deaths from infections caused by multiresistant bacteria would outgrow the number of deaths from cancer, reaching 10 million people per year worldwide . Nevertheless, in the last twenty years the research and the funding on stopping the spread of multidrug-resistant pathogens decreased and our actions are already delayed by 20 years. This means we need prudent clinical practice and further research [2].

To find a solution, the stewardship antibiotic programs have been organized [3]. They aim to develop and implement coordinated, international strategies to increase the efficiency of antibiotic treatment and tackle antibiotic resistance. The main strategies have been systematically summarised within the O'Neill report [2]. According to the report, surveillance, adherence to guidelines, prudent antibiotic consumption, development of new, rapid diagnostic procedures, catheter types, research on new therapeutic modalities, application of non-antibiotic treatment modalities are essential strategies for delaying the increase of antimicrobial resistance.

2. AIMS

The aim of this thesis is to demonstrate our results on surveillance and cystitis diagnostic research.

I. Surveillance

With surveillance (Papers I-II) we aimed to evaluate the bacterial spectrum and antimicrobial resistance of uropathogens cultured from urine samples within the last 14 years at the Department of Urology in Jahn Ferenc South Pest Hospital.

II. Cystitis diagnostic research

At first, we aimed to introduce a practical diagnostic tool on acute uncomplicated cystitis (AUC) for Hungarian physicians and scientists by the development of the Hungarian version of the Acute Cystitis Symptom Score (ACSS) questionnaire (Paper III). Furthermore using our data we performed the clinical diagnostic validation of the Hungarian version for its possible use as a research tool in clinical trials (Paper IV).

Next, we performed the comprehensive international analysis of the ACSS as a diagnostic and follow-up tool for research on acute cystisis using the data obtained during the validation of the different language versions of the ACSS (Paper V).

3. MATERIALS AND METHODS

3.1. Methods of surveillance

All urine samples taken from inpatients between 2004 to 2017 at the Department of Urology in Jahn Ferenc South Pest Hospital were retrospectively analyzed. To calculate the trends of antibiotic resistance and positive urine culture numbers the Cochran–Armitage test was used. $P < 0.05$ was considered significant. The culturing and susceptibility tests were performed by the central laboratory of the hospital complying with the actual international guidelines (CLSI and EUCAST) [4, 5]. We compared our results with the latest available international data from the Global Prevalence Study on Infections in Urology (GPIU) study (2003-2010) [6, 7]. 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

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

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 [8].

The translation and validation of the ACSS into Hungarian language were performed in line with the Linguistic Validation Manual for Patient-Reported Outcomes (PRO) Instruments Guidelines [9]. 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 [8].

The study was performed between 2015 and 2016 in the urological outpatient clinic of Jahn Ferenc South Pest Hospital. Females aged ≥18 years old diagnosed with AUC were enrolled as "Patients" along with healthy women as "Controls". The diagnosis and treatment was made in accordance with the European Association of Urology (EAU) Guidelines by the treating physician in agreement with the investigators [10]. Besides the standard urological examinations, the patients were also invited to fill in the ACSS questionnaire (Part A). 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 were asked to fill out the Part B of the questionnaire.

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

In this non-interventional, case-control study we aimed to reassess the diagnostic values of the ACSS in comparison with the latest Food and Drug Administration (FDA) and European Medicines Agency (EMA) draft guidelines for the diagnosis of AUC [11, 12].

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. The diagnosis made by the treating physician was taken as a reference. The statistical analysis included dichotomization of the responses, calculation of sensitivity, specificity, predictive values, medians and means and further diagnostic values. A p-value of <0.05 was considered statistically significant.

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

The ACSS was tested 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

[11, 12]. For data mining the same database was used as in the previous study. One hundred thirty-four female patients with diagnosed AUC and having sufficient data on follow-up visits were included in the current analysis. The follow-up "visits" were grouped depending on the time difference between the first diagnostic and the follow-up visits.

To determine clinical cure, 8 different thresholds were defined and weighted against each other (Table 1). The "G" and "H" criteria were adopted from the draft FDA and EMA guidelines (FDA: dysuria, urinary frequency, urinary urgency, and suprapubic pain; EMA: frequency, urgency, and dysuria), the rest were related to the ACSS items.

Table 1. 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. The rate of *Enterococcus faecalis* has significantly increased (from 15% in 2004 to 26% in 2017, p<0,0001). The occurance of other bacteria including *K. pneumoniae* and *P. aeruginosa* remained under 10%.

4.1.2. List of the most relevant resistance results

- ***Fluoroquinolones:*** ciprofloxacin resistance in *E. coli* has significantly increased from 19% (25/130) to 25% during the 14 years (p=0.039). In the case of *E. faecalis* the resistance to ciprofloxacin consistently remained above 47%, while for levofloxacin it ranged between 30-42%.
- ***Penicillins:*** Resistance to ampicillin remained stable in the case of *E. coli* (2004: 57%, 2017: 54%), *E. faecalis* (between 0-2%), and *K. pneumoniae* (100%). Against amoxicillin/clavulanic acid resistance of *E. coli* varied between 6% and 35%. The resistance of *K. pneumoniae* versus amoxicillin/clavulanic acid increased significantly (p<0.0001) from 17% to 62%.
- ***Carbapenems:*** In *E. coli, K. Pneumoniae, E. faecalis,* and *P. mirabilis* no resistance was observed to imipenem, meropenem, and ertapenem during the examined years.
- ***Cephalosporins:*** The resistance of *E. coli* to cefuroxime slightly but not significantly increased from 8% to 14% (p=0.741). In *E. coli* the resistance to ceftriaxone significantly increased 1%→12% (p<0.0001) by the end of the studied period. The resistance of *E. coli* to cefepime increased from 1% in 2004 to 8% in 2012 (p<0.0001).
- ***Aminoglycosides:*** 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).
- ***Sulfamethoxazole/trimethoprim:*** 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).
- ***Nitrofurantoin:*** In *E. coli,* the resistance did not rise above 2%, whereas in *K. pneumoniae* and *P. mirabilis* it reached 100%.
- ***Multidrug-resistant (MDR) species:*** The incidence of MDR bacteria (MRSA, VRE, MRAB, Gram-negatives) significantly increased (p=0.008) from 8% (23/279) in 2013 to 14% (42/305) in 2015. 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 rate of ESBL-positive strains among *K. pneumoniae* varied between 24% (7/29) to

33% (10/30). In the last six years, 6% (7/110) to 9% (12/129) of the cultured *E. coli* strains were ESBL-positive, with an exceptional peak of 15% (16/108) in 2011.

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 1. 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.

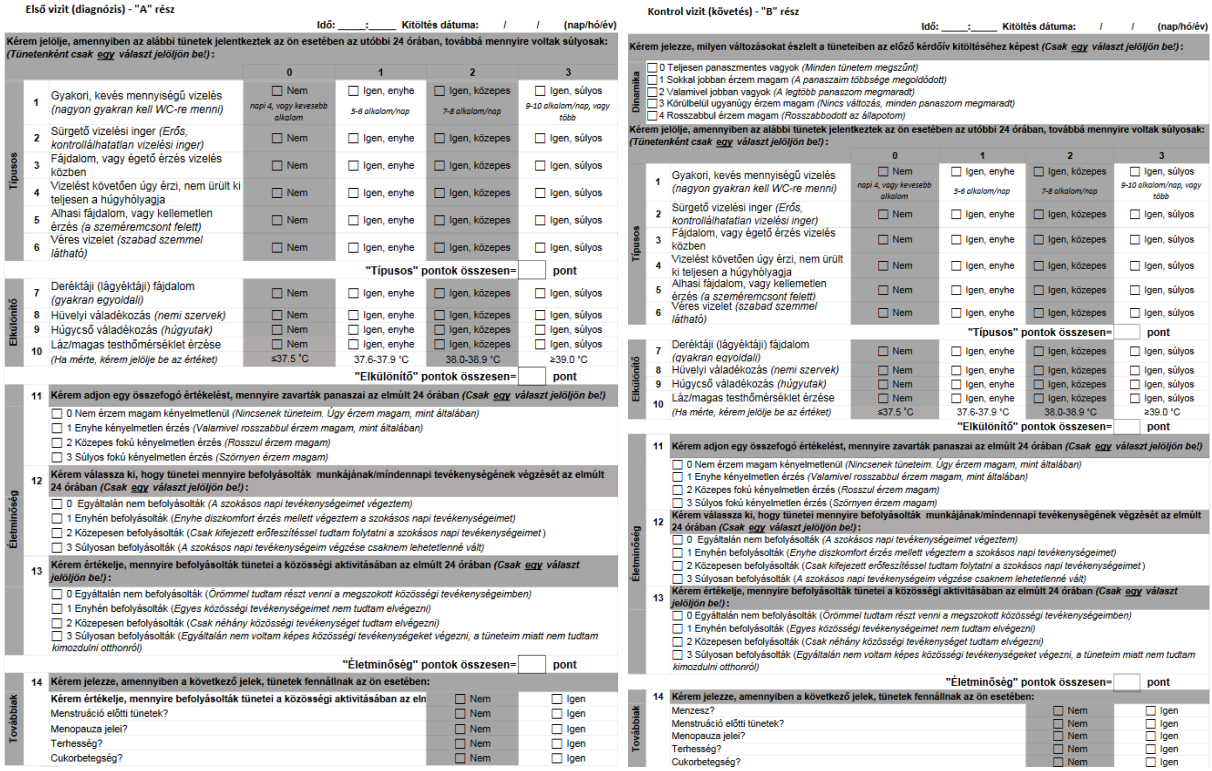

Figure 1. The Hungarian version of the ACSS questionnaire

4.2.2. Clinical diagnostic validation of the Hungarian ACSS

Thirty-seven 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 representative sign for AUC was painful urination, which was observed in 78% of the patients. The study found significant differences between the two groups in each domain of the

questionnaire. For prediction of AUC at cut-off score 6 of „Typical" domain, the positive and negative predictive values (PPV, NPV) were 96,55% and 92,31%, the sensitivity and specificity were 90% and 97%, respectively.

Seventy-four percent of the patients came back for test of cure (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 subanalysis of various possibilities to differentiate between treatment success and non-success found 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 (success 87%, non-success 13%).

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

Out of 916 patients 517 were selected for this comprehensive analysis (from the 68 Hungarian patients, 16 were enrolled), based on having sufficient information concerning questionnaire data and urinalysis. The age of the participants ranged between 15 to 87 years (mean 34). 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 vs 1, respectively ($p<0.001$). The scored severity of the "Typical" symptoms also differed significantly between the Patients and Controls: median 10 vs 1, respectively ($p<0.001$).

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 sensitivity, specificity (average [95% CI]) and further diagnostic values of the different proposed approaches for diagnosing AUC are demonstrated in Table 2. The differences in diagnostic values between the three diagnostic approaches were statistically not significant ($p>0.05$).

Table 2. 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.

The first and the follow-up evaluations were carried out at a maximum time difference of 29 days. Significant difference was found between the visits regarding the average summary scores of the "Typical" domain ($p<0.05$). 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.

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.

Discrimination of clinical cure:

Results of the eight different predetermined thresholds to define cure were analyzed at the different follow-up visits. 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 10-29 days from the first 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. This means we need coordinated and prudent clinical practice and further research. To find a solution, antibiotic stewardship programs have been organized [3]. The O'Neill report systematically summarizes the most important and actual options to tackle down the antibiotic resistance [2]. 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. Outside the topic of the thesis we applied several aspects of stewardship programs during our scientific work, including education, adherence to guidelines and proper antibiotic use, avoidance of antibiotic use, non-antibiotic prophylaxis and treatment, catheter research, research on possible uropathogens and participation in the international surveillance. This thesis focuses on the local surveillance and cystitis diagnostic research.

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 to build up and improve our antibiotic treatment strategies [13]. Surveillance is the first primary step to prudent antibiotic use and lays the foundation for the strategies against the increasing antibiotic resistance [2, 14].

In the first part of our research (Papers I-II), we aimed to surveil the local resistance patterns of uropathogens from urine collected at the Department of Urology in Jahn Ferenc South Pest Hospital between 2004-2017. 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, type of urogenital infections, risk factors, and antibiotic consumption in urological departments since 2003 [15].

In our department about half of the cultured bacteria were *E. coli* which was close to the rate of 55% found in Southern European countries [6, 7]. 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.

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.

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. 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 [16].

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. 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 [17]. At our department, resistance to carbapenems of most pathogens was minimal. 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 of its toxicity. It resulted in acceptably low resistance rates in the case of most bacteria (especially in *E. coli* it remained below 7%).

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). 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.

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 contributes to an enormous amount of antibiotic prescriptions is AUC. There are several non-antibiotic prophylactic [10, 18, 19] and therapeutic [20-22] modalities available to replace antibiotic treatment of AUC, however almost none of them are supported by high-quality, standardized, well-designed research. The further research requires reliable tools for: a) diagnosis and establishing inclusion criteria for 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 [23].

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

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. Additionally we tested the clinical use, the diagnostic accuracy of the Hungarian 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 diagnostic accuracy indicates 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.

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 [8, 11, 12]. 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 analysis revealed that 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

Patient-Reported Outcome Measures (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. The different domains of the ACSS could be used alone or in combinations for this purpose. In Paper V our aim was to discuss the benefits of the ACSS as a PROM instrument by analysing the data from the clinical validation studies of the ACSS in different languages.

Our results show that not noly the presence but also the severity of the symptoms is relevant for assessment of the medical condition. By symptom scoring the ACSS does not only increase the diagnostic accuracy but provides a more detailed monitoring of the condition during follow-up [11, 24]. The assessment of QoL is an important criterion for PROMs [25]. The findings of the QoL assessment were closely linked to the symptom scoring, but it seems that for some patients the normalisation of their QoL takes somewhat longer than the resolution of their symptoms. The patients' own judgement of the overall outcome is documented in the "Dynamics" domain of the ACSS. 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.

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. 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.

6. CONCLUSIONS

6.1. Surveillance

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 narrow-spectrum antibiotics such as sulfamethoxazole/trimethoprim, nitrofurantoin or fosfomycin 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.

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.

6.2. Cystitis diagnostic research

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

As a part of an international team, we successfully performed the translation and linguistic validation of the ACSS in Hungarian language. The clinical diagnostic tests on the Hungarian version of the ACSS suggest that the questionnaire can be used for diagnosis and monitoring of the clinical condition.

The Hungarian ACSS is now available as an accurate, fast and cost-effective diagnostic tool in clinical practice. It 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.

6.2.2. International assessment of the ACSS as a diagnostic tool

The comprehensive assessment of the ACSS as a diagnostic tool using the international data confirmed that the ACSS is an accurate, transparent standardized method for diagnosis. It is especially important for patient inclusion in clinical research.

6.2.3. Evaluation of the ACSS as a follow-up instrument

The analysis revealed that 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. Such tool can be used in clinical trials as a standardized method for follow-up and monitoring 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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Publications serving as the basis for the Ph.D. thesis

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