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Validation of the American English Version of The Acute Cystitis Symptom Score

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Running Title: American English ACSS

Abstract

Background
To develop and validate the American-English version of the self-reporting Acute Cystitis Symptom Score (ACSS), a suitable tool for diagnosis and patient-reported outcome in female patients with acute uncomplicated cystitis (UC).

Methods
After certified translation into American-English and cognitive assessment, the clinical validation of the ACSS was performed as an embedded study in a US phase II trial (ClinicalTrials.gov Identifier: NCT03129295).

Results
A total of 167 female patients with typical symptoms of UC were included in the study following FDA guidance. At Day 1 (diagnosis) the mean(SD) sum score of the six ACSS typical symptoms reached 10.60(2.51). Of 100 patients followed-up last time on Day 5 or 6 (End-of-treatment, EoT), 91 patients showed clinical success according to the favoured ACSS criteria (sum score of typical symptoms 0.98(1.94)). There was no correlation between the severity of symptoms on Day 1 or between clinical success rate at EoT and level of bacteriuria on Day 1.

Conclusion
The American-English ACSS showed high predictive ability and responsiveness, and excellent levels of reliability and validity. It can now be recommended as the new master version in clinical and epidemiological studies, in clinical practice or for self-diagnosis of women with symptoms of UC.

Keywords: Acute Cystitis Symptom Score, ACSS,cystitis, urinary tract infection,female patients, diagnosis, patient-reported outcome

Introduction

Women are significantly more predisposed to urinary tract infections (UTI) than men. Nearly one of three women will have had at least 1 episode of UTI requiring antimicrobial therapy by the age of 24 years and almost one of two women will experience at least one symptomatic UTI during their lifetime [1]. The diagnosis of acute uncomplicated cystitis (UC) can be made with high probability based on a focused history of lower urinary tract symptoms and the absence of vaginal discharge or irritation [2]. Various urinary symptoms have been used to assess the diagnosis and severity of UC in women [3-7], but only a few studies developed a questionnaire to also evaluate the severity and impact on activity impairment [5, 6].

The Acute Cystitis Symptom Score (ACSS) is a simple and self-reporting questionnaire for female patients with UC, allowing to assess not only the presence, but also the severity of typical and differential symptoms, quality of life, and considering additional health conditions and possible changes after therapy [8-10]. The ACSS has proven to be a valuable instrument for clinical studies and medical practice for initial diagnosis, as well as for a patient-reported outcome (PRO) measure allowing to monitor the efficacy of therapy in women, suffering from UC [8-10]. According to the U.S. Food and Drug Administration (FDA) guidance [11] and European Medical Agency (EMA) draft guideline [12], the clinical esponse is important not only for the primary composite efficacy endpoint but also at each fixed time point assessment as a secondary endpoint, meaning that the ACSS could also be used as a well-defined PRO measure instrument. The current study aimed to develop and validate the American English version of the Acute Cystitis Symptom Score (ACSS).

Results

Linguistic validation

After the certified translation from the source language, Russian, into the target language, American English, the ACSS was discussed further and adapted slightly by the Scientific Committee (SC), with the consideration of the FDA recommendations [13]. The cognitive assessment was performed by 10 US physicians and 49 females aged 19-87 years, with American English as their first language, of different races (white 81.6%), of different educational levels (Grade School 2.0%; High School 30.6%; College 55.1%; Postgraduate 12.2%), of different reasons for their doctor visit, and with history (73.5%) or without history (26.5%) of UC [13]. Feedback from these females and physicians were discussed within the SC, and after necessary corrections and an appropriate update, the final version of the ACSS (Fig. 1) was established and used in the US Phase II trial as mentioned above.

Clinical validation at visit 1(diagnosis)

Table 1. Demographics and additional conditions according to ACSS of the US and international group at D1 (visit 1). SD–standard deviation; IQR-interquartile range; PMS–premenstrual syndrome; p1 - Wilcoxon-Mann-Whitney test; p2 - Chi-square test

	US study group	**International study group**	
Patients	**N (%)**	**N (%)**	p^1-value
Total	167 (100%)	237 (100%)	
Range age (years)	17-87	17-87	0.072
Mean age (SD)	36.8 (15.3)	34.6 (15.1)	
Median age (IQR)	32 (25;46)	30 (23;40)	
18-32 years	86 (51.5%)	138 (58.2%)	0.233
33-47 years	43 (25.8%)	50 (21.1%)	
48-62 years	21 (12.6%)	28 (11.8%)	
>62 years	17 (10.2%)	19 (8.0%)	
NA	-	2 (0.8%)	
			p^2-value
Menstruation	19 (11.4%)	25 (10.6%)	0.943
PMS	8 (4.8%)	20 (8.4%	0.201
Menopause	11 (6.6%)	19 (8.0%)	0.676
Pregnancy	0 (0%)	27 (11.4%)	<0.001
Diabetes mellitus	2 (1.2%)	2 (0.8%)	1.000

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Figure 1. American English Acute Cystitis Symptom Score (ACSS) - Questionaire

American English Acute Cystitis Symptom Score (ACSS) - Questionnaire

FIRST VISIT – Part A (diagnostic part)

Time: : Date of evaluation: / / (mm/dd/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 Symptoms	**1**	Frequent urination of small amounts of urine *(going to the toilet very often)*	☐ None *up to 4 times/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 sudden and uncontrollable urge to urinate)*	☐ None	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
	3	Feeling burning pain when urinating	☐ None	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
	4	Feeling incomplete bladder emptying (*Still feel like you need to urinate again after urination*)	☐ None	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
	5	Feeling pain not associated with urination in the lower abdomen (*below the belly button*)	☐ None	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
	6	Blood seen in urine *(without menses)*	☐ None	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
					Sum of "Typical" scores=	**points**
Differential	**7**	Flank pain *(pain in one or both sides of the lower back)*	☐ None	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
	8	Abnormal vaginal discharge *(abnormal amount, color and/or odor)*	☐ None	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
	9	Discharge from the urethra (*urinary opening*) without urination	☐ None	☐ Yes, mild	☐ Yes, moderate	☐ Yes, severe
	10	Feeling high body temperature/fever *Temperature measured* ☐ No ☐ Yes	☐ None ≤99.5°F	☐ Yes, mild 99.6°F-100.2°F	☐ Yes, moderate 100.3°F-102.0°F	☐ Yes, severe ≥102.1 °F
					Sum of "Differential" scores=	**points**
Quality of life	**11**	**Please rate how much discomfort you have experienced because of these symptoms in the past 24 hours *(Please mark only one answer)*:**				
		☐ 0 No discomfort *(No symptoms at all. I feel as good as usual)* ☐ 1 Mild discomfort *(I feel a little worse than usual)* ☐ 2 Moderate discomfort *(I feel much worse than usual)* ☐ 3 Severe discomfort *(I feel terrible)*				
	12	**Please indicate how these symptoms have interfered with your everyday activities/work in the past 24 hours *(Please mark only one answer)*:**				
		☐ 0 Did not interfere at all *(Working as usual on a working day)* ☐ 1 Mildly interfered *(Due to the symptoms, I work slightly less)* ☐ 2 Moderately interfered *(Daily work requires effort)* ☐ 3 Severely interfered *(I almost cannot work)*				
	13	**Please indicate how these symptoms have interfered with your social activities *(visiting people, meeting with friends, etc)* in the past 24 hours *(Please mark only one answer)*:**				
		☐ 0 Did not interfere at all *(My social activities did not change in any way, I live as usual)* ☐ 1 Mildly interfered *(Insignificant decrease in activities)* ☐ 2 Moderately interfered *(Significant decrease. I have to spend more time at home)* ☐ 3 Severely interfered *(It's terrible. I barely left the house)*				
					Sum of "QoL" scores=	**points**
Additional	**14**	**Please indicate whether you have the following at the time of completion of this questionnaire:**				
		1. Menstruation *(Menses)*?			☐ No	☐ Yes
		2. Premenstrual syndrome *(PMS)*?			☐ No	☐ Yes
		3. Signs of menopausal syndrome *(e.g. hot flashes)?*			☐ No	☐ Yes
		4. Pregnancy ?			☐ No	☐ Yes
		5. Known *(diagnosed)* diabetes mellitus *(high sugar)?*			☐ No	☐ Yes

FOLLOW-UP VISIT – Part B (patient-reported outcome)

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

		Please indicate if you experienced any changes in your symptoms since the first time you completed this questionaire
Dynamics	**15**	☐ 0 Yes, I feel great (All symptoms are completely gone) ☐ 1 Yes, I feel much better (Most of the symptoms are gone) ☐ 2 Yes, I feel somewhat better (Only some symptoms are gone) ☐ 3 No, there are barely any changes (I still have about the same symptoms) ☐ 4 Yes, I feel worse (My condition is worse)

All Questions of Part A 1-14 follow here in Part B as well

A total of 167 female patients aged (median, range) 30 (17-87) years with typical symptoms of acute AC at 11 sites were included in the clinical study, which followed the FDA guidance [11]. Demographic characteristics of the US and the international cohorts are provided in Table 1 with a mean (SD) age of 36.8 (15.3) and 34.6 (15.1) years, respectively. Cohorts were homogenous concerning age or additional conditions except for pregnancy because pregnant women were not included in the US study according to FDA guidance [11].

Test of the internal consistency of the items of the ACSS resulted in Cronbach's alpha (95% CI) of 0.89 (0.87; 0.91) for "Typical" domain (r=0.58), 0.46 (0.35; 0.56) for the "Differential" domain (r=0.15), 0.96 (0.95; 0.97) for the "QoL" domain (r=0.88), and 0.90 (0.88; 0.92) for the total questionnaire (r=0.39). Of the 167 patients 162 (97.0%) achieved at Day 1 a sum score of the „Typical" domain (ACSS) of 6 and higher, which shows an excellent agreement between the clinical diagnosis made by the treating physician according to FDA guidance [11] and the patient's symptoms scoring using the ACSS questionnaire [8,9].

Detailed questionnaire data for the US cohort at Day 1 including the severity of symptoms and impact on the quality of life (QoL) are provided in Table 2. About 80%-90% of patients complained of the moderate-to-severe intensity of following symptoms: urinary frequency, urinary urgency, dysuria, and sense of incomplete bladder emptying. Half of the patients had moderate or severe suprapubic pain and about 25% noticed visible blood in the urine (haemorrhagic cystitis) of different intensity. Half of the patients complained of flank pain and about 30% of them noticed at least moderate and severe intensity ("Differential" domain).

Table 2. ACSS data derived from patients of the US group at Day 1 (diagnostics before start of treatment)

ACSS		**Total Patients (N=167; 100%)**	**Symptom Severity (N,%)**				
Do-main	**Q**	**Symptoms**	0 None (N,%)	1 Mild (N,%)	2 Moderate (N,%)	3 Severe (N,%)	2+3 Mod+Sev (N,%)
Typical Symptoms	1	Urinary frequency	3 (1.80%)	18 (10.78%)	82 (49.10%)	64 (38.32%)	146 (87.42%)
	2	Urinary urgency	1 (0.60%)	16 (9.58%)	90 (53.89%)	60 (35.93%)	150 (89.82%)
	3	Dysuria (burning pain when urinating)	12 (7.19%)	22 (13.17%)	76 (45.51%)	57 (34.13%)	133 (79.64%)
	4	Incomplete bladder emptying	3 (1.80%)	17 (10.18%)	96 (57.49%)	51 (30.54%)	147 (88.03%)
	5	Pain in lower abdomen (suprapubic pain)	46 (27.54%)	30 (17.96%)	72 (43.11%)	19 (11.38%)	91 (54.49%)
	6	Visible blood in urine	125 (74.85%)	20 (11.98%)	10 (5.99%)	12 (7.19%)	22 (13.18%)
Differential Symptoms	7	Flank pain	86 (51.50%)	30 (17.96%)	38 (22.75%)	13 (7.78%)	51 (30.53%)
	8	Abnormal vaginal dis-charge	106 (63.47%)	38 (22.75%)	18 (10.78%)	5 (2.99%)	23 (13.77%)
	9	Discharge from the urethra	125 (74.85%)	30 (17.96%)	12 (7.19%)	0 (0.00%)	12 (7.19%)
	10	High body tempera-ture/fever	157 (94.01%)	9 (5.39%)	1 (0.60%)	0 (0.00%)	1 (0.60%)
Quality of Life	11	Discomfort because of symptoms	9 (5.39%)	27 (16.17%)	83 (49.70%)	48 (28.74%)	131 (78.44%)
	12	Interference with eve-ryday activities/work	14 (8.38%)	47 (28.14%)	72 (43.11%)	34 (20.36%)	106 (63.47%)
	13	Interference with social activities	26 (15.57%)	43 (25.75%)	70 (41.92%)	28 (16.77%)	98 (58.69%)

Q = Questions of the ACSS;

Moderate or severe abnormal vaginal and urethral discharges were noted by 14% and 7% of patients respectively, whereas moderate but no severe feeling of fever was indicated by one patient. Concerning the

quality of life 78%, 63%, and 59% of patients complained about moderate or severe general discomfort due to the symptoms, about interference with everyday activities/work or social activities, respectively.

Detailed questionnaire data for the US cohort at Day 1 including the severity of symptoms and impact on the quality of life (QoL) are provided in Table 2. About 80%-90% of patients complained of the moderate-to-severe intensity of following symptoms: urinary frequency, urinary urgency, dysuria, and sense of incomplete bladder emptying. Half of the patients had moderate or severe suprapubic pain and about 25% noticed visible blood in the urine (haemorrhagic cystitis) of different intensity. Half of the patients complained of flank pain and about 30% of them noticed at least moderate and severe intensity ("Differential" domain). Moderate or severe abnormal vaginal and urethral discharges were noted by 14% and 7% of patients respectively, whereas moderate but no severe feeling of fever was indicated by one patient. Concerning the quality of life 78%, 63%, and 59% of patients complained about moderate or severe general discomfort due to the symptoms, about interference with everyday activities/work or social activities, respectively.

The comparison between the US and the international cohort did not show any statistically significant difference in the average number and sum scores of the "Typical" and "Quality of Life" domains, as well as in the sum score of the entire ACSS. The sum score of the "Differential" domain (such items as flank pain, vaginal and urethral discharge and elevated body temperature) was lower for the US cohort compared to international cohort and the difference was statistically significant (*P*=0.003) (Table 3, Suppl. Fig. 1 and 2).

Table 3. ACSS sum scores of typical symptoms, differential symptoms, and quality of life derived from the US and international group on Day 1.

	US Group		**International Group**		
ACSS	**Patients**	**Sum Score**	**Patients**	**Sum Score**	
Domain	N (total)	Mean (SD)	N (total)	Mean (SD)	p-value*
Typical	167	10.60 (2.51)	237	10.12 (3.76)	0.155
Differential	167	1.79 (1.81)	237	2.39 (2.05)	0.003
QoL	167	5.37 (2.34)	237	5.58 (1.92)	0.443
ACSS total	167	17.72 (5.0)	237	18.08 (5.99)	0.314

*Student t-test

There was no significant association between the amount and/or severity of symptoms on Day 1 and level of bacteriuria on Day 1 (Fig. 2).

Patient-reported outcome during and after therapy

Figure 3 represents the summary score of the typical domain of the ACSS on Day 1-6 of the US cohort. The results demonstrated that after high sum scores at Day 1 before treatment (mean 10.6), the following days during treatment the sum scores are reduced quite distinctly and reached almost a plateau on the Days 5 and 6. Therefore we investigated more carefully the 100 patients, who filled in the ACSS questionnaire on Day 1 and the last time either on Days 5 or 6.

Table 4 demonstrates the sum scores of typical symptoms (total and concerning the amount of bacteriuria at Day 1), differential symptoms, and quality of life of the patients in the US cohort at Day 1 (Baseline) and Days 5/6 (EoT). The reduction from Day 1 to end-of-treatment at Days 5/6 was highly significant for all ACSS domains.

Correlation test for the sum scores of the „Typical" domain stratified according to the amount of bacteriuria at Day 1, has proven our hypothesis about the absence of significant relationships between the severity of UC or clinical outcome at EoT and the amount of bacteriuria at the time of the start of the therapy (Table 4).

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Figure 2. Boxplots (IQR, range, mean ± SD) of the number present and sumscore of the six ACSS typical symptoms in the US group versus the 3 categories of bacteriuria at Day 1.

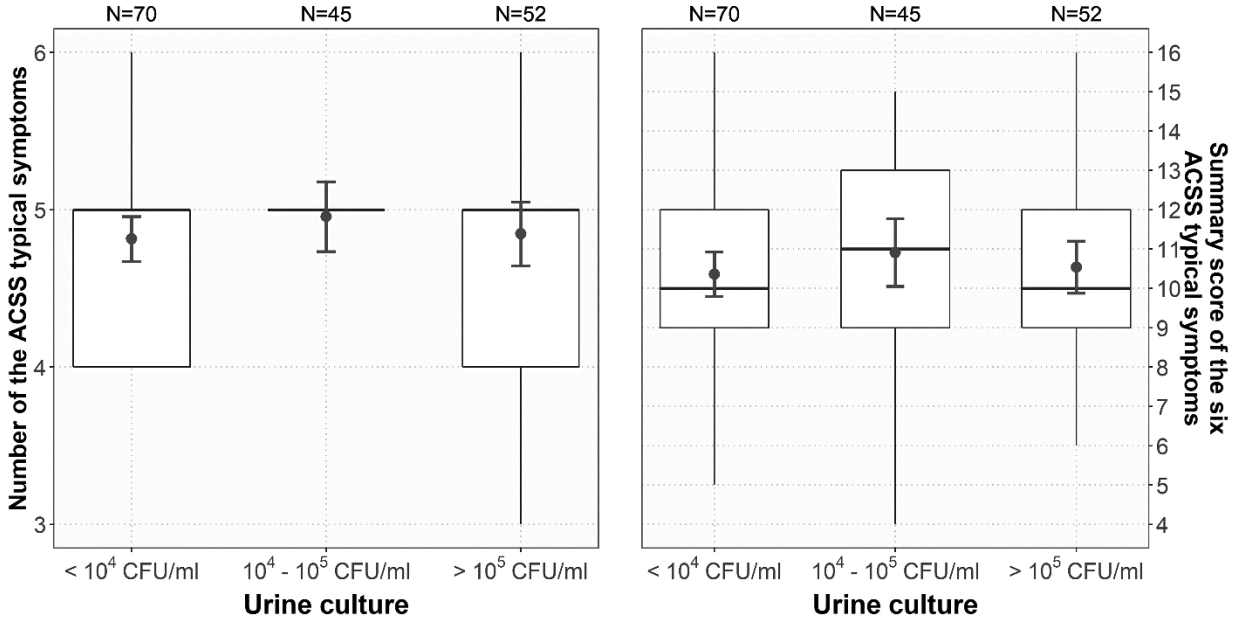

Figure 3. Boxplots (IQR, range, mean ± SD, error of mean) of the sumscore of the six ACSS typical symptoms in the US group on Day 1-6.

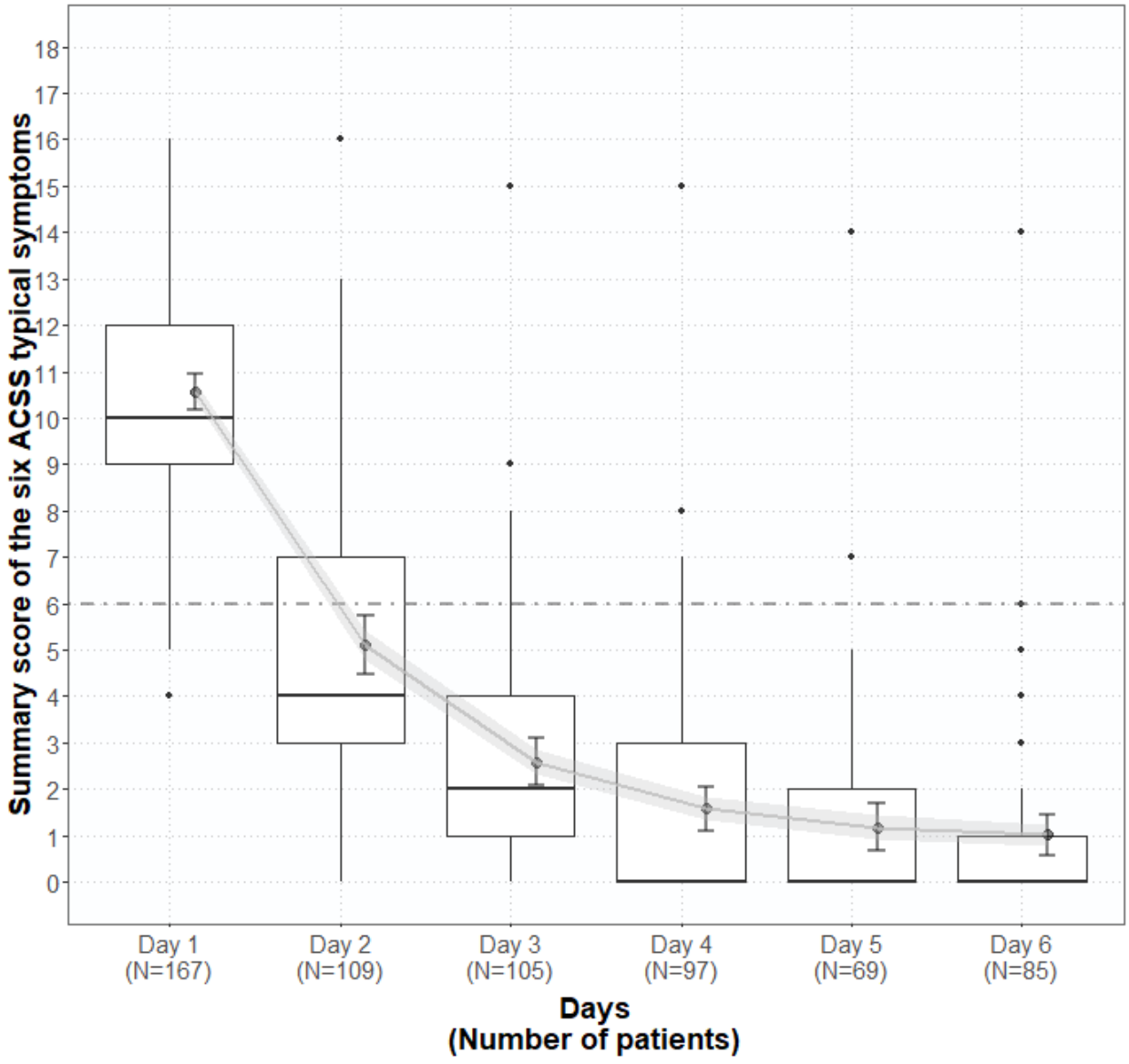

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Table 4. ACSS sum scores of i) typical symptoms in relation to amount of bacteriuria, ii) differential symptoms, and iii) quality of life derived from the same patients of the US group at Day 1 (Diagnostics) and Day 5/6 (End of Therapy). p -paired t-test.

		Day 1 (Diagnostics)			Day 5/6 (End of Therapy)			
ACSS		**Patients**	**Sum Score**		**Patients**	**Sum Score**		
Domain		N (total)	Mean (SD)	Median (IQR)	N (total)	Mean (SD)	Median (IQR)	p-value
Typical	Total	100	10.49 (2.60)	10 (9;12)	100	0.98 (1.94)	0 (0;1)	<0.001
	$<10^4$ CFU/ml	43	10.53 (2.59)	11 (9;12.5)	43	1.49 (2.60)	0 (0;2)	<0.001
	10^4 CFU/ml	29	10.66 (2.93)	11 (9;13)	29	0.48 (1.12)	0 (0:0)	<0.001
	$>10^5$ CFU/ml	28	10.25 (2.29)	10 (9;12)	28	0.71 (1.12)	0 (0;1.3)	<0.001
Differential		100	1.57 (1.74)	1 (0;3)	100	0.34 (0.62)	0 (0;1)	<0.001
QoL		100	5.48 (2.46)	6 (4;7)	100	0.46 (0.93)	0 (0;0)	<0.001
ACSS total		100	17.54 (5.30)	17 (14;22)	100	1.78 (2.82)	0 (0;2)	<0.001

Table 5. ACSS data derived from patients of the US group at Day 1 (diagnostics before the start of treatment) and Day 5/6 (end of treatment)

		Day 1 (Diagnostics)						Day 5/6 (End of Therapy)							0+1 vs 2+3
ACSS		**Total**	**Symptom Severity**					**Total**	**Symptom Severity**						
Domain	Q	N (100 %)	0 None (N,%)	1 Mild (N,%)	2 Moderate (N,%)	3 Severe (N,%)	2+3 Mod/Sev (N,%)	N (100 %)	0 None (N,%)	1 Mild (N,%)	2 Moderate (N,%)	3 Severe (N,%)	2+3 Mod/Sev (N,%)	p^1-value	p^2-value
Typical Symptoms	1	100	2	14	48	36	84	100	75	17	6	2	8	<0.001	<0.001
	2	100	0	10	55	35	90	100	79	19	1	1	2	<0.001	<0.001
	3	100	6	15	44	35	79	100	88	11	0	1	1	<0.001	<0.001
	4	100	3	9	54	34	88	100	90	9	0	1	1	<0.001	<0.001
	5	100	28	19	39	14	53	100	90	10	0	0	0	<0.001	<0.001
	6	100	77	11	7	5	12	100	98	1	1	0	1	<0.001	0.002
Differential Symptoms	7	100	54	21	18	7	25	200	85	13	2	0	2	<0.001	<0.001
	8	100	71	16	10	3	13	100	90	9	1	0	1	<0.001	0.001
	9	100	78	16	6	0	6	100	95	5	0	0	0	<0.001	0.014
	10	100	88	12	0	0	0	100	96	4	0	0	0	0.024	NA
Quality of Life	11	100	7	11	48	34	82	100	76	23	1	0	1	<0.001	<0.001
	12	100	10	26	41	23	64	100	89	11	0	0	0	<0.001	<0.001
	13	100	15	24	45	16	61	100	90	10	0	0	0	<0.001	<0.001

Dynamics	Q – ACSS question; p^1 - Wilcoxon signed ranks test; p^2 - McNemar's chi-square test		**Grading of „Dynamics“**				
			0	1	2	3	4
		100	64	27	7	2	0

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Table 5 shows in more detail the severity of the individual typical and differential symptoms, their impact on each of the quality of life categories and the overall patient's assessment of symptomatic changes (ACSS „Dynamics") at EoT claimed by the same 100 patients of the US study cohort at Day 1 and 5/6 (EoT)

Table 6 shows the number of cases when using certain breakpoints to determine success and non-success at Days 5/6 in the patients of the US (n=100) and international study cohort at Day 5-9 (EoT) (n=82) [10]. Of the five predefined thresholds, the threshold A (Sum score of typical domain ≤5 scores, no item >1 and "visible blood in urine" =0) and D (Sum score of 4 FDA symptoms ≤4, no item >1 and "visible blood in urine" =0) are favoured and showed the same results with a success rate of 91 % in the US and 80% in the international cohort. The higher success rate in the US cohort can probably be explained because all patients were treated by a suitable antibiotic, whereas the non-interventional treatment of the international cohort might have varied considerably.

Table 6. Number of cases using certain ACSS thresholds for clinical success at Day 5/6 in the patients of the US (n=100) and international group at Day 5-9 (end of treatment) (n=82) [10].
Note: each case with any "visible blood in the urine (VBU)" at end of treatment was rated "non-success"

Type	**Thresholds for clinical success**	**American English**	**International**
A	Sum score of typical domain ≤ 5 scores, no item > 1	91 (91%)	66 (80.49%)
B	Sum score of typical domain ≤ 5 scores, no item > 1 and no item of QoL > 1	91 (91%)	60 (73.17%)
C	Dynamics, no item >1	91 (91%)	64 (78.05%)
D	Sum score of the 4 FDA symptoms ≤ 4, no item > 1	91 (91%)	66 (80.49%)
E	Sum score of the 3 EMA symptoms ≤ 3, no item> 1	91 (91%)	67 (81.71%)

4 FDA symptoms (urinary frequency, urinary urgency, dysuria, suprapubic pain)
3 EMA symptoms (urinary frequency, urinary urgency, dysuria)

Validation of the American English ACSS using pre- and posttreatment results
The diagnostic values of the different items and the sum score of the „Typical" domain of the ACSS were tested comparing results obtained by the ACSS before and after treatment.
Figure 4 illustrates that not only the pure presence of typical symptoms but rather severity (scores) increases the diagnostic accuracy as has been shown earlier [7]. Receiver operating characteristic (ROC) curves for each independent item and the sum score of the "Typical" domain demonstrated the best-balanced results for sensitivity (96%, 95%-CI: 90%-99%) and specificity (98%, 95%-CI: 93%-100%) for the sum score of 6 typical symptoms as compared to the individual symptoms. More detailed calculations, such as positive and negative predictive values, positive and negative likelihood ratio, and correlation with a positive outcome (diagnosis of UC) comparing different clinical diagnostic definition are shown in Table 7. Again a sum score of 6 or more of the „Typical" domain (ACSS) showed the most favourable results as compared e.g. for the FDA [11] and EMA [12] inclusion criteria for the clinical diagnosis of UC.

Discussion
The ACSS, validated in several other languages (www.acss.world), could now also be successfully translated and validated in American English as embedded study of a prospective, interventional clinical US phase II trial following FDA guidance in female patients with acute UC.

Psychometric parameters and diagnostic values of the American English ACSS showed good-to-excellent values which were comparable to those of the source language, Russian, and other versions as previously translated and validated in different languages, as well as other results obtained during this study [8-10, 14-18]

Comparing the results obtained by the ACSS for diagnostics of acute UC and EoT showed again, that the diagnostic value depends not only on the presence, but very much also on the severity (scoring) of the symptoms, which may be typical, but not specific for acute UC because some of the symptoms can also be caused by other urological diseases. It also could be shown that for clinical

diagnostics the best balance between sensitivity and specificity can be obtained using a sum score of 6 or higher of all six ACSS typical symptoms as compared to the presence or severity of single symptoms or a selection of 3 or 4 so-called typical symptoms according to the EMA [12] or FDA [11] guidance, respectively, as has been shown earlier as well [8,9,15].

Figure 4. Receiver operating characteristic (ROC) curves and diagnostic odds ratios for the ACSS typical symptoms in 100 patients of the US group comparing the results obtained at Day 1 (diagnostics) and Day 5/6 (end of treatment).

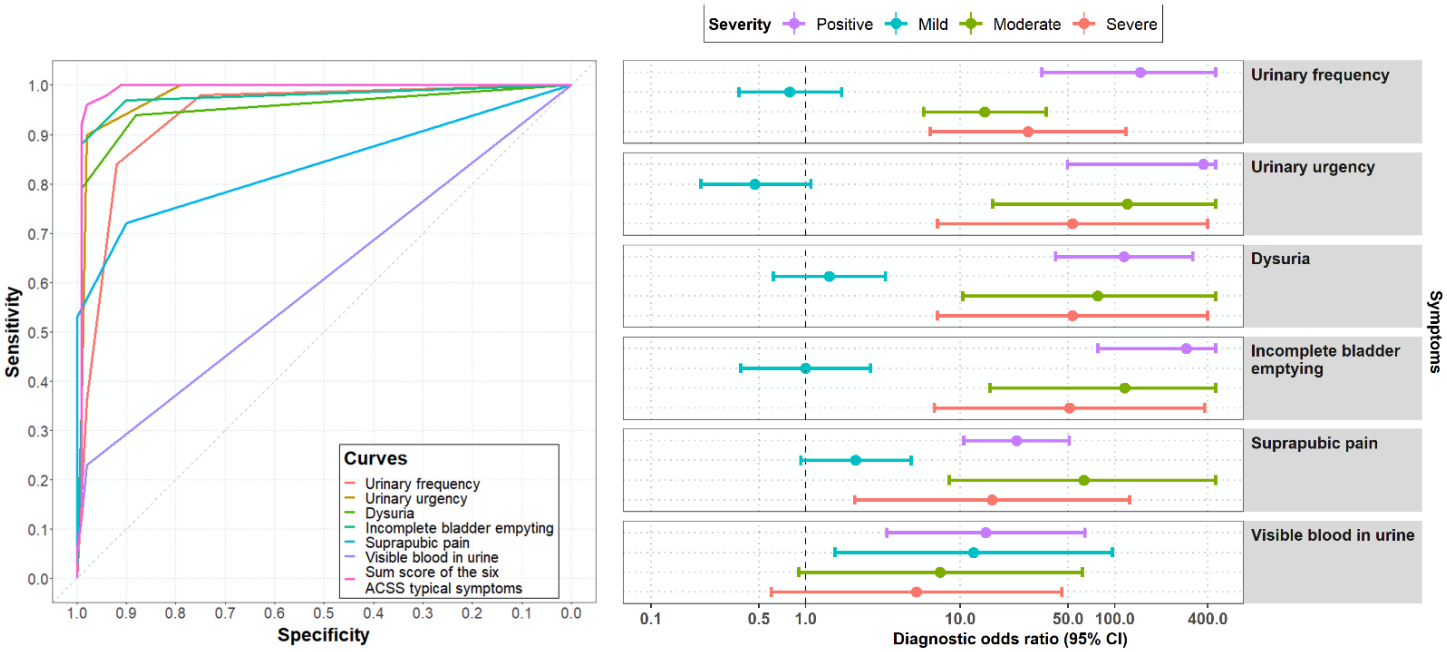

Table 7. Sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratio, and correlation with a positive outcome (PO for diagnosis of cystitis) using different criteria (mean and 95% CI). CI-confidence interval; PPV-positive predictive value, NPV-negative predictive value; +LR - positive likelihood ratio; -LR - negative likelihood ratio; AUC – area under the curve; PO – positive outcome (diagnosis is correct). Main symptoms and 3 EMA symptoms: urinary frequency, urinary urgency, dysuria; 4 FDA symptoms: urinary frequency, urinary urgency, dysuria, suprapubic pain

Criteria	N (%) positive	N (%) negative	Sensitivity	Specificity	PPV	NPV	+LR	-LR	AUC	Correlation with PO
ACSS: typical domain, sum score >=6	96 (96%)	2 (2%)	0.96 (0.90-0.99)	0.98 (0.93-1.00)	0.98 (0.92-1.00)	0.96 (0.90-0.99)	48.00 (12.17-189.38)	0.04 (0.02-0.11)	0.97 (0.95-0.99)	0.94 (0.92-0.95)
ACSS: main symptoms, sum score >=6	77 (77%)	1 (1%)	0.77 (0.68-0.85)	0.99 (0.95-1.00)	0.99 (0.93-1.00)	0.81 (0.73-0.88)	77.00 (10.92-542.88)	0.23 (0.16-0.33)	0.88 (0.84-0.92)	0.78 (0.72-0.83)
FDA: at least 2 positive symptoms of 4	100 (100%)	33 (33%)	1.00 (0.96-1.00)	0.67 (0.57-0.76)	0.75 (0.67-0.82)	1.00 (0.95-1.00)	3.03 (2.29-4.01)	0.00 (0.00-NA)	0.84 (0.79-0.88)	0.71 (0.63-0.77)
EMA: at least 1 positive symptom of 3	100 (100%)	22 (22%)	1.00 (0.96-1.00)	0.78 (0.69-0.86)	0.82 (0.74-0.88)	1.00 (0.95-1.00)	4.55 (3.14-6.57)	0.00 (0.00-NA)	0.89 (0.85-0.93)	0.80 (0.74-0.85)

Using five different reasonable thresholds to differentiate between success and non-success resulted in the same outcome for the US study, but each threshold showed slightly different outcomes in the international group. Nevertheless, the study shows that the ACSS could also be

used as a PRO measure instrument to demonstrate the same or different clinical outcome in prospective, randomized clinical studies comparing different treatment modalities.

By using the ACSS in this US clinical trial it could be shown for the first time that the severity of symptoms and the clinical outcome do not correlate with the level of bacteriuria before treatment. There was no difference for both parameters (severity of symptoms and clinical outcome), whether the urine culture showed 10^5 CFU/ml (as requested by FDA and EMA for microbiological outcome assessment), 10^4 CFU/ml or $<10^4$ CFU/ml.

Since it has been shown in several studies that much lower amounts of bacteriuria are also clinically significant, clinical diagnostics and patient-reported outcome using validated questionnaires should become a priority in women with acute UC, especially when symptomatic treatment modalities are also involved [19-21]. Nevertheless, microbiological investigations should not be neglected, but also considering much lower amounts of bacteriuria by using appropriate laboratory methods.

Material and Methods

Study design

The clinical study was initiated, supported, and designed by Mission Pharmacal Company, San Antonio, TX 78239, USA, as a randomized, double-blind, placebo-controlled, multicenter Phase II trial of the efficacy and safety of MPC-SHRC for the relief of symptoms associated with uncomplicated UTI (ClinicalTrials.gov Identifier: NCT03129295; https://clinicaltrials.gov/ct2/history/NCT03129295?V_1=View) with the ACSS accepted as a study tool. The primary study protocol was approved by the Western Institutional Review Board (WIRB) on July 27, 2017.

The ACSS as a study tool

The ACSS is a 2-part, self-reporting questionnaire (Fig. 1), including the following questions:

i) 6 questions about typical symptoms of UC („Typical“ domain): urinary frequency, urinary urgency, dysuria, incomplete bladder emptying, suprapubic pain, visible blood in the urine.

ii) 4 questions regarding differential diagnosis („Differential“ domain): flank pain, abnormal vaginal discharge, urethral discharge, elevated body temperature/fever.

iii) 3 questions on the quality of life („QoL“ domain): general discomfort, interference with everyday activity/work, interference with social life.

All questions of the domains i-iii are to be answered according to severity (scoring 0-3): no (0), mild (1), moderate (2), severe (3).

iv) 5 questions on additional conditions, which may affect therapy („Additional“ domain): menstruation, premenstrual syndrome, menopause, pregnancy, diabetes mellitus. The answers are yes or no.

v) 5 questions on the patient's assessment of overall symptomatic changes after the baseline visit („Dynamics“ domain). The answers are rated (scored): Feeling normal (0), much better (1), somewhat better (2), barely any change (3), worse (4).

Part A includes the domains i-iv (Typical, Differential, QoL, Additional) and Part B includes the domains v (Dynamics) and i-iv as in Part A.

Linguistic validation of the American English version of the ACSS

The linguistic validation process included 2 stages: 1) The certified translation into American English from original Russian [14, 22, 23] by Mapi Language Services, Lyon, France (Ref.No.16-053816) according to international guidelines with forward and backward translations and consideration of comments from subjects interviewed with American English as a first language [24-26], and 2) cognitive assessment by 10 US physicians, and by 49 US female subjects with and without a history of UC. The whole process was steered by a scientific committee (SC).

Clinical validation

The clinical validation was performed as an embedded study of the above-mentioned Phase II trial following the study protocol, Good Clinical Practice, and Code of Federal Regulations Title 1, Parts 50, 56, and 312. The study consisted of 2 on-site visits: Visit 1 (Day 1) (baseline) and visit 2 (discharge). After the baseline examination, all subjects were randomized to receive either the

investigational drug or placebo QID for 3 days. All randomized subjects received concurrent antibiotic treatment as prescribed by the investigator. Before any study-related activities, written informed consent was signed and personally dated by the subject.

The ACSS was first completed on Day 1 (diagnosis) before therapy and was then completed daily until 48 hours after the end of treatment (EoT). In this side study, the blinding concerning the investigational drug or placebo was maintained. The scores of the ACSS questionnaire in the US study cohort were compared with those obtained in an international cohort of 237 female patients with acute UC from other studies, who have used the ACSS in their native languages (Uzbek, Russian, Tajik, German, Hungarian), and who also fulfilled the FDA guidance [11] concerning requirements for clinical diagnosis of acute UC with at least 2 of the following 4 typical symptoms: urinary frequency, urinary urgency, dysuria, suprapubic pain, and evidence of pyuria in urinalysis [9, 10]. The amount of urine culture (colony forming units/ml) was tested concerning the presence and severity of the ACSS typical symptoms and the clinical outcome at EoT.

Data acquisition and processing
The data of the American English ACSS were retrieved from the US cohort. The ACSS data for the international cohort were retrieved from the e-USQOLAT database as described earlier [9, 10]. Since US cohort consisted of only the patients, the data at Day 1 (Baseline) of the US cohort were used to define the data of positive outcome/“Patients”, and the last data obtained at Days 5 or 6 (EoT) were used to define negative outcome/“Controls” to assess psychometric reliability and diagnostic value of the American English ACSS. The presence of symptoms (positive, negative), symptoms’ severity (mild, moderate, severe), and the proposed diagnostic approaches (FDA, EMA, ACSS) were considered. Data processing included a procedure of dichotomization of variables for the assessment of diagnostic values. Relative variables were labelled as “0” for “negative”/”not match”, and “1”-for “positive”/”match”. as described in detail earlier [9, 10].

Statistical Analysis
Descriptive statistics were presented using mean, standard deviations (SD), confidence intervals (CI), median and interquartile range (IQR). Psychometric reliability was measured by the values of internal consistency of the items in the domain and the entire questionnaire presented by Cronbach’s alpha and strength of association between items and summary score of domains as well as the total score of the ACSS, presented by Pearson’s *r*-coefficient of product-moment correlation. Diagnostic values of the domains and items of the ACSS and diagnostic modalities were assessed by calculation of sensitivity, specificity, positive and negative likelihood ratios, diagnostic odds ratio (DOR) and ROC-curve analysis.
Comparative analysis was performed via paired t-test (for numerical data), Wilcoxon signed ranks test (for ordinal and interval data) and McNemar’s chi-square test (for categorical variables). Pearson's correlation coefficient was used to assess the strength of associations between variables and the outcome, and the interval nature of the outcome variable (e.g. grouped number of CFU of pathogens in urine culture). Statistical significance was set at 0.05.

R v.3.5.2 with in-built and additional packages was used for the statistical analysis and graphical representation of the results [27-30].

Conclusions
The Acute Cystitis Symptom Score (ACSS), a self-reporting questionnaire, has now been translated, linguistically validated and also used the first time clinically embedded in a prospective, interventional US clinical trial performed according to FDA guidance in women with symptoms of uncomplicated UTI. In this study, the American English ACSS showed high values of predictive ability and responsiveness, and excellent levels of reliability and validity for diagnostics of acute UC and as a PRO measure. Therefore the ACSS can now be recommended as a new master version for clinical or epidemiological studies, but also in clinical practice and for self-diagnosis for women with symptoms of acute UC with American English as the first language.

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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.

Translations of the ACSS in other languages are available on the website:
http://www.acss.world/downloads.html

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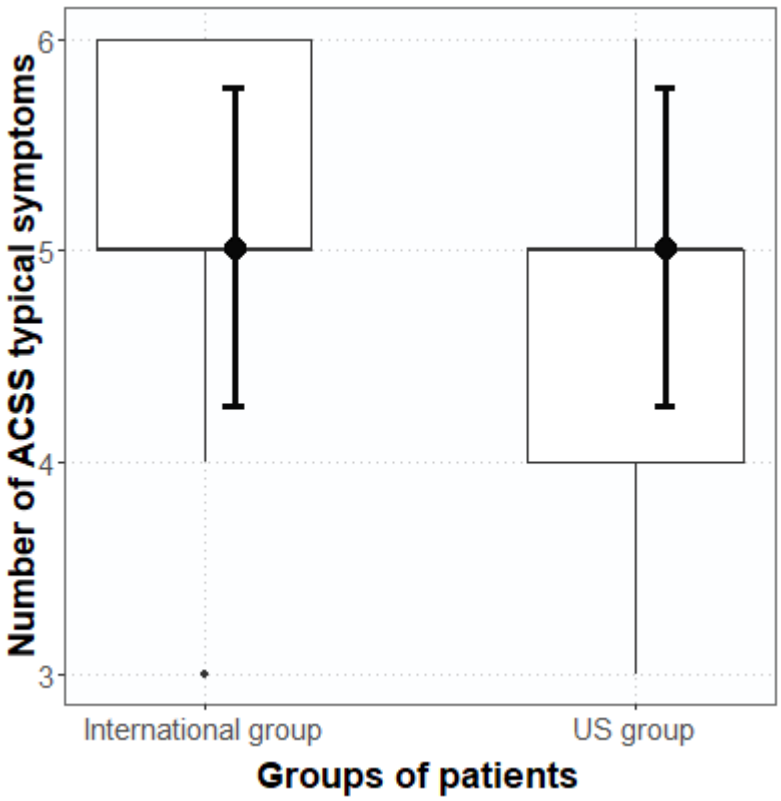
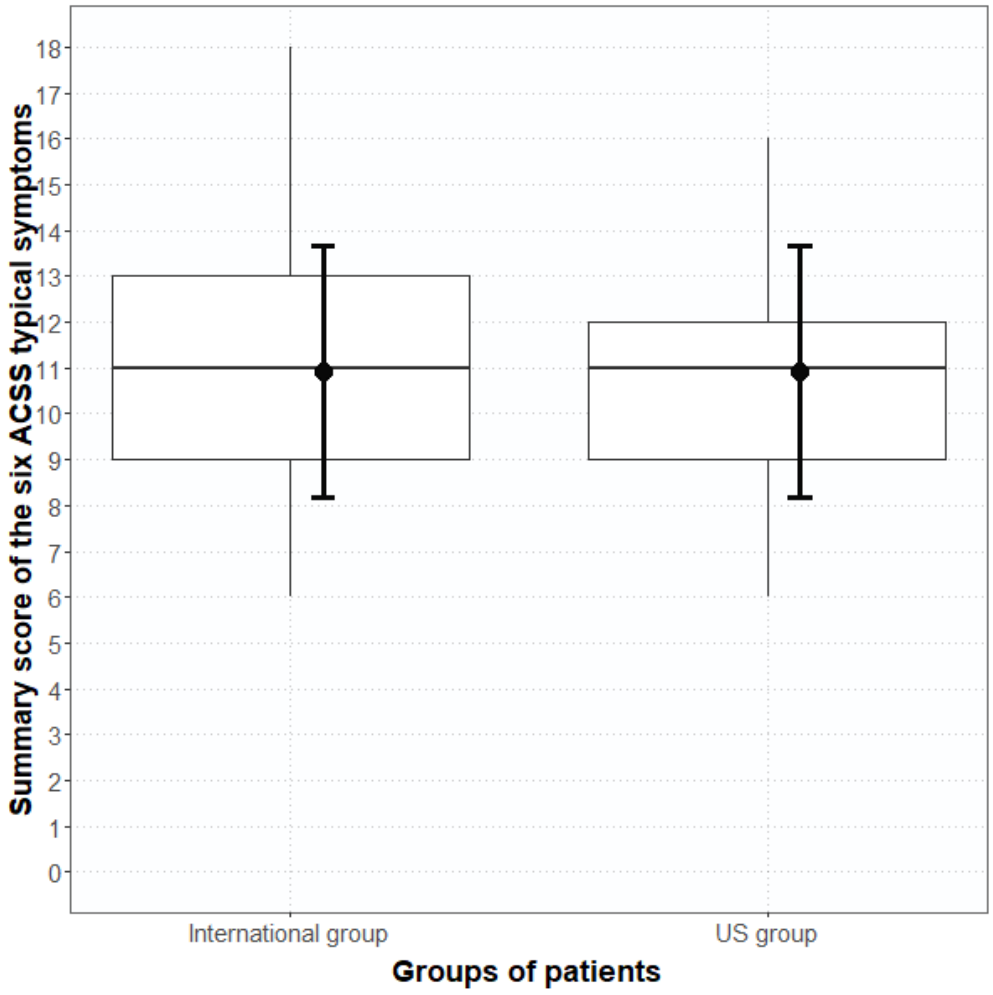
Supplementary Material

Suppl. Figure 1. Boxplots (IQR, range, mean ± SD) of the numbers of ACSS typical symptoms in the US and in the international group



Suppl. Figure 2. Boxplots (IQR, range, mean ± SD) of summary scores of the ACSS typical symptoms in the US and the international group



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Suppl. Figure 3. Boxplots (IQR, range, mean ± SD) of the severity of the six ACSS typical symptoms in the US group versus the 3 categories of bacteriuria at Day 1.