

Structured patient interview to assess clinical outcomes in complicated urinary tract infections in the APEKS-cUTI study: pilot investigation

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Ther Adv Infectious Dis
2021, Vol. 8: 1–10
DOI: 10.1177/
20499361211058257
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Abstract

Background: The APEKS-cUTI study demonstrated the non-inferiority of cefiderocol to imipenem–cilastatin in the primary endpoint of the composite of clinical and microbiological outcome in patients with complicated urinary tract infections (cUTIs). We piloted a structured patient interview (SPI) to evaluate clinical outcomes based on patient-reported symptoms while conducting this pivotal randomized, double-blind, phase-2 study. The objectives were to assess the value of the SPI, using its performance relative to physician assessment, and also to strengthen the value of patient-reported measures in conducting clinical trials for cUTI treatment.

Methods: In addition to the protocol-defined clinical and microbiological outcomes, patients randomized in the APEKS-cUTI study were interviewed by the investigator or qualified study personnel at screening/baseline, early assessment (EA), end of treatment (EOT), test of cure (TOC), and follow-up (FUP). The 14-element questionnaire graded cUTI symptoms as absent or present, and if present, as mild, moderate, or severe. Changes in post-baseline symptoms based on patients' responses were rated by the interviewer. The overall clinical outcome was evaluated based on the responses provided by patients at each time point.

Results: Among the 371 patients in the modified intention-to-treat population, the rate of SPI completion in each treatment arm exceeded 90% at each time point. SPI-assessed clinical cure rates were 89.7% in the cefiderocol arm and 84.9% in the imipenem–cilastatin arm. There was substantial agreement between SPI evaluation and investigator global assessment of clinical outcome at TOC and FUP, with lower agreement at EA and EOT.

Conclusion: This analysis suggests that patient-reported symptoms can be effectively captured in hospitalized patients with cUTI in a clinical trial setting. Development of a validated patient-reported outcome for use in such a setting is warranted.

Registration: NCT02321800 (registered on 22 December 2014).

Keywords: cefiderocol, clinical outcome, complicated urinary tract infections, patient reported outcomes, structured patient interview

Received: 24 May 2021; revised manuscript accepted: 20 October 2021.

Introduction

Achieving quality of care for patients is one of the goals of health care and measuring outcomes that include health circumstances relevant to the

patient is an important part of this assessment.¹ As such, there is a drive to incorporate standardized, validated outcome measures, including patient-reported outcome (PRO) measures,

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across the management of medical conditions.² PROs can provide direct evidence of treatment benefit in terms of how patients feel or function³ and a better overall treatment experience for patients,⁴ and they can help with reimbursement justification for medical interventions.³ PROs can also improve patient adherence and self-monitoring, enhance patient–physician discussions^{5,6} and facilitate sponsor–regulatory authority discussions regarding treatment benefit or risks that are consistent with clinical response in clinical trials.^{7–9} Furthermore, PROs can increase the efficiency and relevance of clinical trials.³ The value of PROs is recognized by the US Food and Drug Administration (FDA) which, in 2009, published guidelines to encourage the development of high-quality PROs with defined endpoints capable of providing evidence meeting clinical trial objectives.⁷

However, the availability of validated PROs varies not just across therapeutic areas but also within them. Urinary tract infections (UTIs) are a case in point. They are among the most common bacterial infections, with about 50–60% of adult women experiencing at least one UTI in their lifetime, most of which are uncomplicated. In US women, 250,000 uncomplicated UTI (uUTI) cases/year progress to the kidneys (pyelonephritis), at which point they may be considered complicated UTIs (cUTIs), and approximately 7% of these cases require hospital treatment.¹⁰ The frequency of UTIs increases with age, with a doubling in incidence rates in women 65 years or above.^{11–13} Complicated UTIs, including acute pyelonephritis, are associated with a greater morbidity and mortality risk in men compared with women.¹⁴ Current FDA drug development guidance for cUTIs recommends the inclusion of a structured assessment of the patient-reported symptoms at baseline and at the trial endpoint;^{8,15} however, unlike for uUTIs,^{16,17} no standardized tools have been developed for patients with cUTIs.

The APEKS-cUTI trial was a pivotal phase-2 randomized study that demonstrated the non-inferiority of cefiderocol, a novel siderophore cephalosporin, to imipenem–cilastatin in hospitalized patients with cUTIs at risk of multidrug-resistant (MDR) Gram-negative bacterial infections.¹⁸ In an effort to comply with the FDA recommendations^{8,15} and in the absence of a standardized PRO, the study also pilot tested a

structured patient interview (SPI) as a way of gaining an insight into patient perspectives of their symptoms and observing how SPI-assessed symptoms relate to clinicians' global assessments of clinical outcomes. We report here on the structure and implementation of the SPI in this population of hospitalized patients with cUTIs.

Methods

Ethics and consent

The APEKS-cUTI study was conducted in accordance with all appropriate regulatory requirements and following protocol approval by the Institutional Review Board/Institutional Ethics Committees (Supplementary Table 1). The study complied with current International Conference on Harmonization Good Clinical Practice standards, all appropriate patient privacy requirements, and the ethical principles outlined in the Declaration of Helsinki. All patients, or their legal representatives, gave written informed consent prior to enrollment.

APEKS-cUTI study design

The APEKS-cUTI study was a randomized (2:1), multicenter, phase-2, double-blind, parallel-group, non-inferiority study between cefiderocol and imipenem–cilastatin for the treatment of cUTIs caused by Gram-negative uropathogens in adult patients at risk of MDR infections (NCT02321800).¹⁸ Briefly, between February 5, 2015, and August 16, 2016, adults ≥ 18 years admitted to hospital with a clinical diagnosis of cUTI (with or without pyelonephritis) or acute uncomplicated pyelonephritis and meeting FDA diagnostic criteria for cUTI, including intravenous treatment requirement, were enrolled.¹⁸ None of the patients had uncomplicated UTI, commonly referred to as acute cystitis. Exclusion criteria included >2 uropathogens in baseline urine culture, a fungal UTI, presence of carbapenem-resistant pathogens, or creatinine clearance <20 mL/min. Patients received cefiderocol (2 g) or imipenem–cilastatin (1 g/1 g) *via* intravenous infusion over 1 hour, every 8 hours, for 7–14 days. The primary objective of the study was to compare the composite outcome (clinical response and microbiological eradication) at test of cure (TOC) achieved using cefiderocol or imipenem–cilastatin. Clinical outcome was based on the investigator's evaluation of patient's clinical

Table 1. Structured patient interview used to evaluate patient-reported symptoms.

Symptoms:	Is the symptom present?	If yes, enter severity
Feeling feverish	<input type="checkbox"/> YES <input type="checkbox"/> NO	<input type="checkbox"/> MILD <input type="checkbox"/> MODERATE <input type="checkbox"/> SEVERE
Shaking/chills	<input type="checkbox"/> YES <input type="checkbox"/> NO	<input type="checkbox"/> MILD <input type="checkbox"/> MODERATE <input type="checkbox"/> SEVERE
Malaise	<input type="checkbox"/> YES <input type="checkbox"/> NO	<input type="checkbox"/> MILD <input type="checkbox"/> MODERATE <input type="checkbox"/> SEVERE
Frequency of urination	<input type="checkbox"/> YES <input type="checkbox"/> NO	<input type="checkbox"/> MILD <input type="checkbox"/> MODERATE <input type="checkbox"/> SEVERE
Urgency of urination	<input type="checkbox"/> YES <input type="checkbox"/> NO	<input type="checkbox"/> MILD <input type="checkbox"/> MODERATE <input type="checkbox"/> SEVERE
Dysuria (painful urination)	<input type="checkbox"/> YES <input type="checkbox"/> NO	<input type="checkbox"/> MILD <input type="checkbox"/> MODERATE <input type="checkbox"/> SEVERE
Urinary incontinence	<input type="checkbox"/> YES <input type="checkbox"/> NO	<input type="checkbox"/> MILD <input type="checkbox"/> MODERATE <input type="checkbox"/> SEVERE
Cloudy or change in color of urine	<input type="checkbox"/> YES <input type="checkbox"/> NO	<input type="checkbox"/> MILD <input type="checkbox"/> MODERATE <input type="checkbox"/> SEVERE
Nausea	<input type="checkbox"/> YES <input type="checkbox"/> NO	<input type="checkbox"/> MILD <input type="checkbox"/> MODERATE <input type="checkbox"/> SEVERE
Vomiting	<input type="checkbox"/> YES <input type="checkbox"/> NO	<input type="checkbox"/> MILD <input type="checkbox"/> MODERATE <input type="checkbox"/> SEVERE
Pain above the pubic bone	<input type="checkbox"/> YES <input type="checkbox"/> NO	<input type="checkbox"/> MILD <input type="checkbox"/> MODERATE <input type="checkbox"/> SEVERE
Abdominal pain	<input type="checkbox"/> YES <input type="checkbox"/> NO	<input type="checkbox"/> MILD <input type="checkbox"/> MODERATE <input type="checkbox"/> SEVERE
Flank/back/costovertebral angle pain or tenderness	<input type="checkbox"/> YES <input type="checkbox"/> NO	<input type="checkbox"/> MILD <input type="checkbox"/> MODERATE <input type="checkbox"/> SEVERE
Back pain	<input type="checkbox"/> YES <input type="checkbox"/> NO	<input type="checkbox"/> MILD <input type="checkbox"/> MODERATE <input type="checkbox"/> SEVERE
Other ^a specify: _____	<input type="checkbox"/> YES <input type="checkbox"/> NO	<input type="checkbox"/> MILD <input type="checkbox"/> MODERATE <input type="checkbox"/> SEVERE

^aOnly if considered by the investigator to be related to complicated urinary tract infection.

signs as well as symptoms, with response defined as resolution or improvement of cUTI symptoms present at study entry and the absence of new symptoms.¹⁸ Clinical and microbiological responses were evaluated at early assessment (EA; 4 ± 1 day after start of treatment), end of therapy (EOT; 7–14 days), TOC (7 ± 2 days after EOT), and follow-up (FUP; 14 days after EOT) visits. Full details of the study design and the results of primary and secondary outcomes are published elsewhere.¹⁸

SPI

Patient-reported UTI symptoms were captured on paper by an interviewer, as described below, using a sponsor-developed SPI based on a 14-element questionnaire (Table 1) administered at baseline screening (Day –2 to Day 1 prior to randomization), at Day 1 of treatment and then again at EA, EOT, TOC, and FUP (Table 2). In the event that screening and Day 1 occurred on

the same day, which was the most frequent sequence of events, only one interview was required. Interviews were conducted one-to-one with the patient by the physician investigator or qualified study personnel, all of whom had received relevant interview training and written instructions, including the importance of avoiding leading questions. If possible, the same interviewer was used for a given patient at each visit. The symptom questionnaire was available in relevant language translations, and interviews were conducted in the local language or that most appropriate for the patient. The interview questions were not fully scripted, and interviewers were allowed to use their discretion in phrasing questions in local language; however, no leading questions were used to prompt patients. The ability of patients to answer questions was assessed at each visit. Only patients who were alert, oriented, and considered by the investigator to be capable of answering symptoms questions were interviewed at any given time point. If patients were

Table 2. Interviewer reporting of post-baseline patient-reported symptoms.

Symptoms	Severity	
Symptoms:	Symptoms findings (since the last visit)	If finding was 2–5, then enter severity ^a
For each of the 14 pre-specified symptoms:	<input type="checkbox"/> 0 – Not present at last assessment	<input type="checkbox"/> MILD
Feeling feverish	<input type="checkbox"/> 1 – Resolved or returned to the state before the UTI	<input type="checkbox"/> MODERATE
Shaking/chills	<input type="checkbox"/> 2 – Not present at baseline/last assessment but new onset	<input type="checkbox"/> SEVERE
Malaise	<input type="checkbox"/> 3 – Continuing and increased since the last assessment	
Frequency of urination	<input type="checkbox"/> 4 – Continuing but decreased since the last assessment	
Urgency of urination	<input type="checkbox"/> 5 – Continuing and no change since the last assessment	
Dysuria (painful urination)		
Urinary incontinence		
Cloudy or change in color of urine		
Nausea		
Vomiting		
Pain above the pubic bone		
Abdominal pain		
Flank/back/ costovertebral angle pain or tenderness		
Back pain		
Other ^b		

UTI, urinary tract infection.
^aBased on the investigators' clinical judgment, not pre-defined criteria for infection severity.
^bIf recorded at baseline visit or if considered by the investigator to be a new symptom related to complicated urinary tract infection at any visit.

confused and/or unable to answer questions and their responses were considered by the investigator to be unreliable, the inability to conduct the interview was recorded and the interview could be attempted again at a later visit.

The SPI was developed by the sponsor and evaluated the presence of 14 pre-defined symptoms (Yes/No) noted in the medical literature as being associated with cUTI, including five designated as core symptoms by the FDA cUTI trials recommendations (i.e. dysuria, urinary frequency, urinary urgency, suprapubic pain, and flank pain)⁸ and their severity (Table 1). Additional symptoms included infection-related symptoms, which are not specific for cUTI, such as fever, chills, malaise, nausea, vomiting, and pain in various locations (Table 1). Severity was defined as follows: mild—present but not debilitating; moderate: present—somewhat debilitating; and severe—present, very debilitating. Any symptoms outside the defined categories, or new symptoms identified at post-baseline visits, were recorded only if they were judged by the investigator as being clearly related to the cUTI. In the event

that the investigator suspected a new cUTI, whether it was a superinfection during study treatment or a new infection following completion of study treatment up to the FUP visit, the investigator was to complete an unscheduled patient visit, including administration of an unscheduled SPI. Following completion of each interview, the interviewer rated the change in patient-reported symptoms from the last visit using the following criteria: 0—not present at last assessment; 1—resolved or returned to the status before the diagnosis of cUTI; 2—not present at baseline/last assessment but new onset; 3—continuing and increased since the last assessment; 4—continuing but decreased since the last assessment; and 5—continuing and no change since the last assessment.

Comparison of clinical outcome assessments between investigators' global assessments and SPI

The clinical outcomes assessed at TOC between investigators' global assessments (used as the primary endpoint in the trial) and the SPI were

Table 3. Definitions of investigator-associated clinical and microbiological responses.

Definitions	
Clinical response	Assessed by the investigator as resolution or improvement in core clinical signs and symptoms of cUTI present at baseline and no new symptom emerged, or return to pre-infection baseline.
Clinical failure	No apparent response to therapy, persistence of signs and/or symptoms of cUTI infection, or reappearance of signs and/or symptoms that were present at an earlier visit.
Indeterminate clinical response	Observed when the clinical response could not be determined due to the patient being lost to follow-up.
Microbiological eradication	Eradication of baseline Gram-negative pathogen by quantitative microbiological assessment (i.e., urine culture of the causative pathogen growing at $\geq 10^5$ CFU/mL at baseline was reduced to $< 10^4$ CFU/mL).
Microbiological failure	Persistence of baseline Gram-negative pathogen by quantitative microbiological assessment (i.e., urine culture of the causative pathogen growing at $\geq 10^5$ CFU/mL at baseline grew at $\geq 10^4$ CFU/mL).
Indeterminate microbiological response	No urine culture was taken or a urine culture that could not be interpreted for any reason.
CFU, colony-forming unit; cUTI, complicated urinary tract infection.	

compared. Investigator-assessed clinical outcome is defined in Table 3. For the SPI, in accordance with FDA guidance,⁸ clinical outcome involved assessment of the following core cUTI symptoms (dysuria, urinary frequency, urinary urgency, suprapubic pain, and flank pain) and was defined as: clinical response—resolution or improvement of all baseline symptoms at TOC; clinical failure—no resolution or improvement of some baseline symptoms at TOC; indeterminate—missing symptoms information either at baseline or TOC. Resolution of baseline symptoms associated with anatomic abnormalities predisposing to cUTI, such as those associated with the presence of an indwelling urinary catheter, was not required for the patient to be considered a successful responder.

Statistical analysis

Pooled clinical outcomes across treatment arms were combined with microbiological outcomes to obtain composite endpoints for investigator-assessed and patient-reported symptoms in the SPI. In the case of a missing TOC (FUP) assessment, if the patient was a treatment failure on or

after the EOT assessment, the treatment failure was carried forward; otherwise, he or she was imputed as indeterminate. Patients receiving rescue therapy were considered to be clinical failures. Agreement between investigator global and SPI post-baseline outcomes were expressed by the kappa coefficient (κ) as: 0–0.2, slight; 0.2–0.4, fair; 0.4–0.6, moderate; 0.6–0.8, substantial; and 0.8–1.0, almost perfect.¹⁹ The analysis was performed in the microbiological (modified) intention-to-treat population (mITT; all randomized patients who received at least one dose of study drug (ITT) and had a baseline UTI causative Gram-negative bacterial uropathogen on culture of urine or blood), which was also the primary efficacy analysis population, as well as in the ITT population.¹⁸

Results

As reported in the primary publication, of the 452 patients randomized across 67 hospitals in 15 countries, 448 received treatment (300 in the cefiderocol arm and 148 in the imipenem–cilastatin arm). The mITT population comprised 371 patients (252 in the cefiderocol arm and 119

patients in the imipenem–cilastatin arm). In this population, severe disease (as determined according to an investigator’s clinical judgment) was reported for 19.8% (50/252) of patients in the cefiderocol arm and 16.8% (20/119) in the imipenem–cilastatin arm and approximately 24% of patients in each arm were ≥ 75 years old (61/252 for cefiderocol and 29/119 for imipenem–cilastatin).

At each time point, over 90% of patients completed the SPI in both the cefiderocol and imipenem–cilastatin arms; nearly all patients completed the SPI at EA (99.2% (250/252) and 98.3% (117/119) and EOT (99.2% (250/252) and 99.2% (118/119) with rates of 95.2% (240/252) and 92.4% (110/119) at TOC, and 92.9% (234/252) and 90.8% (108/119) at FUP, respectively.

Clinical cure rates according to SPI patient responses were 89.7% (226/252) in the cefiderocol arm and 84.9% (101/119) in the imipenem–cilastatin arm (adjusted treatment difference: 4.96%; 95% confidence interval (CI): –2.48, 12.39) at TOC. There was substantial agreement between SPI evaluation and investigator global assessment for clinical outcomes at TOC and FUP (Table 4, Supplementary Table 2). The agreement at EA and EOT was somewhat lower than that at TOC and FUP. The composite of clinical response according to patient responses and microbiological response at TOC was achieved by 71.8% patients (181/252) in the cefiderocol arm and 55.5% (66/119) in the imipenem–cilastatin arm (adjusted treatment difference: 16.95%; 95% CI: 6.59, 27.32).

Changes in individual symptoms per visit based on the SPI are shown in Supplementary Table 3. The most frequent patient-reported symptoms were feeling feverish, chills, painful urination, and suprapubic, back, or flank pain. The greatest change in symptoms occurred by the EA visit, indicating a rapid response to treatments in the most common acute symptoms. There was no difference in response trends between treatment arms.

Discussion

The results from this analysis show that elicitation of responses from patients about their

symptoms was achieved effectively using an SPI in a population of hospitalized patients with cUTI at risk of MDR infection. Completion rates of the SPI were high at all visits, ranging from nearly all patients (98.3–99.2%) at EA and EOT, through 92.4–95.2% at TOC, and remaining above 90% at FUP (90.8–92.9%).

Clinical cure rates at TOC based on the SPI responses were achieved in a very high proportion of patients in the cefiderocol (90%) and imipenem–cilastatin (85%) arms, respectively. These SPI-based investigator-assessed patient-reported results for clinical cure agreed substantially with the investigator-assessed global clinical responses. At the EA and EOT visits, investigators’ assessments showed improvement of patients’ symptoms, although some symptoms may still have been present, which may explain the lower degree of agreement. Particularly at EOT, the numbers of clinical failures assessed by the investigator and the SPI were very small, and the disagreement in clinical failures resulted in a lower kappa coefficient. Using the SPI clinical response, the composite endpoint at TOC was achieved in 72% of patients in the cefiderocol arm and 56% in the imipenem–cilastatin arm, which was very similar to the primary efficacy analysis of the study (cefiderocol 73% and imipenem–cilastatin 54%).¹⁸ The difference in composite response was mainly determined by the difference in microbiological eradication between the two treatments.

There is no validated PRO measure available for utilization in clinical studies of patients with cUTI. Since the initial reports of PRO use in 1976, a few PRO measures have been developed (and/or validated) for uncomplicated UTIs,^{20,21} such as the Acute Cystitis Symptom Score (ACSS) and the UTI Symptoms Assessment Questionnaire (UTISA).^{16,17} The RECAPTURE phase-3 trial in cUTIs did incorporate the collection of data on patient-reported symptoms, but it used the Patient Symptom Assessment Questionnaire (PSAQ), which was designed for uUTI; the content and construction validity for cUTI remain unclear.²² This questionnaire contained five UTI symptom-related questions with severity ratings comparable to those used in the SPI described in this study. In the PSAQ, patients compared their current symptoms with baseline and without relation to previous post-baseline visits. Patient response was algorithmically

Table 4. Agreement between investigator-assessed clinical outcome and structured patient interview-assessed clinical outcome at each time point in the microbiological intention-to-treat population.

Time point–investigator assessment, <i>N</i> = 371	Clinical outcome by SPI, ^a <i>N</i> = 371				Kappa coefficient (κ)
	Clinical cure, <i>n</i> (%)	Clinical failure, <i>n</i> (%)	Relapse, <i>n</i> (%)	Indeterminate ^b <i>n</i> (%)	
Early assessment					
• Clinical cure	284 (76.5)	52 (14.0)		0	0.267
• Clinical failure	15 (4.0)	16 (4.3)		2 (0.5)	
• Indeterminate ^c	0	0		2 (0.5)	
End of treatment					
• Clinical cure	354 (95.4)	11 (3.0)		0	0.287
• Clinical failure	3 (0.8)	1 (0.3)		0	
• Indeterminate ^c	0	0		2 (0.5)	
Test of cure					
• Clinical cure	322 (86.8)	8 (2.2)		0	0.820
• Clinical failure	5 (1.3)	17 (4.6)		0	
• Indeterminate ^c	0	1 (0.3)		18 (4.9)	
Follow-up					
• Clinical cure	279 (75.2)	8 (2.2)	4 (1.1)	0	0.766
• Clinical failure	2 (0.5)	29 (7.8)	1 (0.3)	0	
• Relapse	14 (3.8)	0	10 (2.7)	0	
• Indeterminate ^c	2 (0.5)	0	0	22 (5.9)	

cUTI, complicated urinary tract infection; FUP, follow-up; SPI, structured patient interview; TOC, test-of-cure.
^aClinical outcome based on patient-reported symptoms was assessed by symptom resolution that included core symptoms of cUTI (dysuria, urinary frequency, urinary urgency, suprapubic pain, and flank pain).
Clinical cure: resolution or improvement of all the core baseline symptoms at TOC.
Clinical failure: no resolution or improvement of some core baseline symptoms at TOC.
^bIndeterminate: any core symptoms missing at either baseline or TOC.
^cIndeterminate: lost to follow-up such that a determination of clinical response (success or failure) cannot be made.
Relapse: signs and/or symptoms of cUTI that were absent at TOC reappear at FUP.

transcribed at each assessment following form completion. This contrasted with the SPI used in APEKS-cUTI, which used interview-led questions and relied on the interviewer, not the patient, to rate symptom change from the previous assessment.

The findings from this analysis provide much-needed preliminary information regarding the feasibility and practicability of collecting patient-reported symptom data from hospitalized patients

with cUTIs in clinical trials. Adherence to responding to questions was high even in hospitalized patients, being greater than 90% at all assessments. The authors recognize that the high levels of compliance achieved with the questionnaire in this analysis may be due partly to the fact that it was interviewer led, thereby relieving the patient of the onus of self-reporting. However, high levels of adherence have been noted in the use of other PROs in the hospitalized setting²³ and in older patients.²⁴

The SPI used in APEKS-cUTI was not a validated PRO instrument, nor did it aim to validate any prior PRO developed in UTI studies. The development and validation of such a tool requires an iterative process involving rigorous qualitative research^{25,26} and interpretation of response by patients using patient-based anchors, such as return to usual state of health. As such, we acknowledge that there are a variety of methodological limitations that may constrain the more detailed interpretation possible with a PRO. As the SPI was not validated, it is possible that some terms, such as malaise and fever, were open to interpretation by patients, thereby obscuring the capture of conclusive information. Indeed, fever has been shown to encompass a wide variety of themes or symptoms (e.g. chills, warmth, sweating, headache, and weakness).²⁷ Imprecise terminology can also lead to double counting of symptoms that are specified on the form but also subsumed under another category (e.g. chills, which are also recognized as an element of fever). The use of double-barreled questions (e.g. shaking/chills) could have created uncertainty regarding which symptom the patient is responding to (i.e. shaking, chills or both). Thus, the authors acknowledge that the current pilot SPI questionnaire lacks construct validity.²⁷ Finally, bias may have been introduced by the use of a non-standardized script and by potential word changes when translating the questionnaire into different languages.

Several international clinical practice guidelines are available for the selection of the most appropriate antibiotic treatment for patients with acute pyelonephritis and cUTI, including those who are at risk of being infected with MDR pathogens or extended-spectrum beta-lactamase-expressing bacteria.^{28–30} A broader range of antibiotic options is now available for the treatment of cUTIs following the approval of ceftazidime–avibactam, ceftolozane–tazobactam, meropenem–vaborbactam, imipenem–cilastatin–relebactam, plazomicin, and cefiderocol, although their place in current management remains unclear.³¹ Future use of PROs in clinical practice, as well as in clinical trials, may help to guide better selection of therapy, as standardization of questions may decrease measurement error. Electronic data capture from home can allow patients to be followed without office visits and may improve real-world evidence and post-marketing evaluations of therapies for cUTI.

Conclusion

The results of this pilot study of an SPI used within the APEKS-cUTI trial demonstrate that patient-reported symptoms can be effectively captured and recorded in a clinical trial setting in hospitalized patients with cUTI and that they have value in assessing treatment benefit from the patient's point of view. There was a strong agreement between the SPI evaluation and investigators' assessments of clinical response. The patient-reported symptoms points helped investigators to better evaluate treatment effects and adverse effects. Further development of validated PROs for cUTIs are needed to better inform clinical trials and patient care.

Acknowledgements

The authors thank Dr John Powers for his critical review of the manuscript. Editorial support was provided by Adrienn Kis and Joanne Shrewsbury-Gee, Highfield, Oxford, United Kingdom, sponsored by Shionogi & Co., Ltd., Osaka, Japan.

Authors' note

Data included in the manuscript were presented in part at IDWeek 2019 (Portsmouth S, *et al.* Structured Patient Interview in Complicated Urinary Tract Infections to Assess Clinical Outcomes versus Investigator's Evaluation in the APEKS-cUTI Study. IDWeek 2019; Poster 1473. Washington DC, October 2–5, 2019; Open Forum Infectious Diseases, Volume 6, Issue Supplement_2, October 2019, Pages S537, <https://doi.org/10.1093/ofid/ofz360.1337>).

Authors' contributions

SP was the medical lead and monitor for the study, was involved in data curation, formal data analysis and validation. RE was involved in the conceptualization of the study, methodology and data curation. KT was involved in formal data analysis, data curation, and validation. GT was involved in data interpretation. TDN was involved in the conceptualization of the study, methodology, data curation, formal data analysis, and validation. All authors contributed to the writing and reviewing of the original draft manuscript and approval of the final version.

Data availability

Data presented in this paper can be shared with external investigators, researchers at reasonable request from Shionogi via the following website: <https://clinicalstudydatarequest.com/>.

Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: SP, TDN, and KT had been employees of Shionogi at the time the study was conducted. RE is a consultant for Shionogi and has received consultancy fees. GT is a former consultant for Shionogi and has received consultancy fees. All authors had full access to the study data.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The study was funded by Shionogi & Co., Ltd., Osaka, Japan.

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Supplemental Material

Supplemental material for this article is available online.

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