Beyond the cloudiness in urinary tract infection: definitions, diagnostics, and strategies for prevention

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Chapter 3

A reference standard for urinary tract infection research: a multidisciplinary Delphi consensus study

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Abstract

The absence of a consensus-based reference standard for urinary tract infection (UTI) research adversely affects the internal and external validity of diagnostic and therapeutic studies. This hinders the accumulation of evidence for a disease that imposes a significant burden on patients and society, particularly in an era of increasing antimicrobial resistance. We conducted a three-round Delphi study involving an international, multidisciplinary panel of UTI experts (n = 46), and achieved a high degree of consensus (94%) on the final reference standard. New-onset dysuria, frequency and urgency were considered major symptoms, and non-specific symptoms in older patients were not deemed indicative of UTI. The reference standard distinguishes between UTI with and without systemic involvement, abandoning the term 'complicated UTI'. Moreover, different levels of pyuria were incorporated in the reference standard, encouraging quantification of pyuria in studies conducted in all healthcare settings. The traditional bacteriuria threshold (10^5 colony-forming units (CFU)/mL) was lowered to 10^4 CFU/mL. This new reference standard can be used for UTI research across many patient populations and has the potential to increase homogeneity between studies.

Introduction

Urinary tract infection (UTI) is one of the most common bacterial infections in the community. [1] Its high incidence and recurrence rate lead to a decreased quality of life, excessive healthcare costs, and significant use of antimicrobials. [1, 2] UTI diagnosis is commonly based on a combination of symptoms and signs, pyuria, and culture results. Current UTI research primarily focuses on improving diagnostics and developing novel therapeutic and prophylactic modalities, such as new antimicrobials and vaccines. [3, 4] However, UTI studies are impeded by the lack of a consensus-based reference standard for UTI. The absence of a reference standard has several consequences. Firstly, it introduces bias into estimates of diagnostic accuracy and efficacy (also known as verification bias), affecting the internal validity of a study. [5] Secondly, if different criteria are used across studies, results cannot be readily compared, compromising the external validity of a study. These drawbacks are particularly relevant in the context of growing antimicrobial resistance, in which reliable efficacy and safety data on novel antimicrobials for UTI are crucial. Moreover, from an ethical standpoint, it is vital to ensure consistent treatment of study participants and patients, as well as accurate reporting of study findings.

Although several proposed definitions exist, they are limited in their ability to be used in the majority of UTI studies. Centers for Disease Control and Prevention guidelines were primarily formulated for surveillance of nosocomial and catheter-associated UTI, and the revised McGeer criteria were designed for studies in long-term care facilities, limiting their applicability. [6, 7] The European Medicines Agency (EMA) and Food and Drug Administration (FDA) have published guidelines for the development and approval of drugs for the treatment of uncomplicated and complicated UTI, including acute pyelonephritis. [8-10] However, these guidelines apply different symptom criteria, and definitions of complicated UTI are not uniform. Moreover, the EMA guideline does not specify a minimum number of symptoms, and the FDA guideline does not provide a pyuria threshold for uncomplicated UTI, leaving room for interpretation. Furthermore, it is unclear which research methodology was employed in the development of these guidelines. Prior to this study, we performed a systematic review evaluating recently published UTI studies, which demonstrated low adherence to FDA and EMA guidelines. [11] Researchers more frequently defined UTI based on their own criteria or clinical practice guidelines, leading to heterogeneous UTI definitions across studies. These findings underscore the necessity for a multidisciplinary-

supported reference standard for UTI, developed specifically for research purposes. Consequently, the primary aim of this study was to achieve consensus on a reference standard for UTI, applicable to adult women and men, including older patients, who participate in studies focusing on bacterial UTI, excluding those related to indwelling catheters.

Methods

Study design

In order to gain consensus on a reference standard, a Delphi study was conducted and reported following CREDES recommendations. [12] The Delphi method has four main characteristics: an expert panel is questioned about the issue of interest, the process is anonymous to reduce the effect of dominant personalities, the questionnaires are iterative in nature, and the design of the subsequent rounds is informed by a summary of the group response of the previous round. [13] The Delphi method was chosen over other consensus methods (e.g. the nominal group technique) because it offers the advantage of not being limited by geographical and temporal constraints. [14] We planned a minimum of three rounds, with the possibility of additional rounds, depending on the level of consensus. Data was collected using REDCap. [15] An overview of the study design is provided in the Supplementary Material (see **Supplementary Figure 1**), which will be discussed in detail below. This study was registered at ClinicalTrials.gov (ID NCT05365906).

Core group and expert panel

Based on their publication record and clinical expertise, UTI experts were invited by the principal investigators (M.P.B., S.P.C., M.M.C.L.) to be part of the research team, henceforth described as the core group. All core group members who were contacted (via email) agreed to participate. As the primary users of the research reference standard will include researchers from multiple specialties and countries, we ensured multidisciplinary and multinational representation in the core group. The core group consisted of 11 experts from the following countries: the Netherlands (n = 6), the United States (n = 2), the United Kingdom (n = 1), Germany (n = 1), and Hungary (n = 1) and a moderator (M.P.B.). Primary specialties represented in the core group were infectious diseases (n = 4), geriatric medicine (n = 2), urology (n = 2), primary care (n = 1), emergency medicine (n = 1), and microbiology (n = 1); some experts also had secondary specialties. Since the core group members were tasked with designing and interpreting the questionnaire

rounds, as well as constructing the reference standard, a separate expert panel was invited to participate in the Delphi questionnaire and feedback rounds. The core group proposed experts from their respective specialties, and geographical and gender equity were encouraged. There were no specific exclusion criteria for expert panellists. Experts were invited through an email containing an explanation of study objectives, the required effort, outputs, and rewards (an acknowledgement of study participation at publication). The identities of the expert panellists who participated were known exclusively to the core group. Consent to participate in the Delphi surveys was assumed if the surveys were completed and returned. Expert panellists could withdraw at any time.

Expert panel size

In the literature, Delphi panel size varies between ten to several hundred participants. [13] Small panels may not provide a representative range of judgments on the topic at hand, while large panels may lead to low response rates and a significant amount of missing data. In case of a homogenous background of Delphi panellists, around ten to fifteen subjects are usually sufficient. [16] Given the multidisciplinary nature of our expert panel, we aimed to include a minimum of 40 expert panel participants.

Delphi round 1 (R1)

Based on signs, symptoms, and diagnostic tests listed in two previous studies, the core group prepared a questionnaire for the expert panel containing 48 items (see **Supplementary Figure 2**). [11, 17] We clarified the purpose of the questionnaire and structured it into five categories: signs and symptoms (20 items), urinalysis (six items), microbiology (ten items), items focused on ruling out UTI (five items), and items addressing systemic involvement (seven items). We used the RAND/UCLA Appropriateness Method [18] to determine the expert panel's assessment of the degree to which each item indicated UTI, using a Likert scale ranging from 1 (‘not at all indicative’) to 9 (‘very indicative’). An item was deemed (1) indicative of UTI in case of a panel median ≥ 6·5, without disagreement, (2) not indicative of UTI in case of a panel median of ≤ 3·5, without disagreement, and (3) uncertain if the panel median lay in between indicative and not indicative, or any median with disagreement. Disagreement was considered to occur if both extremes of the Likert scale (1–3 and 7–9) contained more than a third of responses. [18] If disagreement occurred in > 20% of items, we planned to repeat this questionnaire round for

the items that met disagreement criteria, after which no further iterations were planned, as R1 primarily served to facilitate the core group in constructing the reference standard and differences in perspectives concerning the topic were considered valuable input.

The questionnaire explicitly stated that signs and symptoms should be graded based on recent onset, and that items should be graded for UTI in general, unless a specific patient population or anatomic site (i.e. cystitis or pyelonephritis) was mentioned. In the signs/symptoms, urinalysis, and microbiology categories, we included additional questions to inquire whether experts would modify their ratings based on the sex (assigned at birth) and age (≥ 65 years) of the patient in question. Per category, experts were given the opportunity to provide extra comments justifying their grading, but they could not add new items. Moreover, we collected data on specialty, country of practice and years working in the field post-training. This questionnaire was pilot tested for content and clarity by three independent infectious diseases specialists.

Development of reference standard and case vignettes

Median scores and expert panel comments (organised thematically by their content) were presented to the core group in an online meeting in June 2022. Based on R1 results and available literature, a reference standard was drafted by the principal investigators. A scoring system was incorporated into the reference standard to reflect that each individual item carried a different weight in its contribution to UTI diagnosis. This draft version was then discussed with all members of the core group in two additional online meetings in July 2022. All core group members participated in at least one online meeting to provide their input for the development of the reference standard. Minutes of group discussions and adjustments to the reference standard were sent to core group members so that additional comments could be provided via email. Disagreements were resolved through discussion and a draft version of the reference standard had to be agreed upon by all core group members before initiation of Delphi round 2 (R2). Rather than solely assessing consensus on the reference standard through expert panel grading in R2 and Delphi round 3 (R3), alignment between the reference standard (scoring system) and the expert panel's interpretation of a set of case vignettes was evaluated. The core group designed ten case vignettes, incorporating various combinations of lower urinary tract and systemic signs and symptoms, pyuria, and urine culture results. The case vignettes included different age groups, sexes,

and health care settings. Cases could be graded as 'definite UTI', 'probable UTI', 'possible UTI', or 'no UTI', analogous to the four UTI categories of the reference standard (based on the scoring system). These categories were chosen to reflect the degrees of certainty in the diagnosis of UTI. To ensure clarity and proper wording, case descriptions were pilot tested by three independent physicians.

Delphi round 2 and 3 (R2 and R3)

In R2, the expert panel first graded the case vignettes, and for each case, experts were given the opportunity to justify their grading. Next, a draft version of the reference standard was presented to the expert panel. Per domain of the reference standard (symptoms and signs, systemic criteria, pyuria, and culture results), experts could indicate their agreement or disagreement with a 'yes' or 'no' answer. In case of disagreement, experts were requested to provide a rationale. Furthermore, overall agreement with the reference standard was assessed through a five-point Likert scale ranging from 1 ('strongly disagree') to 5 ('strongly agree'), and additional comments were encouraged. R2 results were discussed in two online core group meetings in September and October 2022. Based on these results and an additional literature review, adjustments were made to the reference standard. Adjustments had to be agreed upon by all core group members before R3 could be initiated. In R3, a summary of the expert panel grading from R2 was presented, and experts were asked to regrade the same ten case vignettes. Subsequently, the experts regraded the adjusted reference standard, which was presented alongside a description of how the expert panel comments had been addressed. Consensus was defined a priori as a minimum of 80% of experts voting 'agree' or 'strongly agree' and none of the experts voting 'disagree'. If consensus was not reached after R3, subsequent rounds were planned until consensus was reached.

Results

Of the 62 experts who were invited to be a part of the expert panel, 46 (74%) agreed to partake. Two experts declined participation due to either retirement or time constraints, but both suggested alternates. Reasons for non-participation of the other invited experts were unknown. Expert panel characteristics are detailed in **Table 1**. Experts were located in various countries in Europe and North America and had been practicing as a specialist for a median of 13 years (IQR 8 – 20). Three Delphi questionnaire rounds were conducted between April 2022 and December 2022. Response rates were 100%, 87%, and 80% for R1, R2, and R3, respectively.

Complete questionnaires for all three rounds can be found in the Supplementary Material.

Table 1: Expert panel characteristics.

Expert panel characteristics	n = 46
Primary specialty n (%)	
Infectious diseases	13 (28)
Urology	9 (20)
Microbiology	7 (15)
Geriatrics	6 (13)
Family medicine	6 (13)
Emergency medicine	5 (11)
Country of practice n (%)	
United States	14 (30)
The Netherlands	13 (28)
Germany	5 (11)
United Kingdom	3 (7)
Sweden	3 (7)
Belgium	3 (7)
Norway	2 (4)
Canada	1 (2)
Spain	1 (2)
Switzerland	1 (2)
Years working in the field post-training median (IQR)	13 (8 – 20)

One expert panellist was a primary care physician in training but had extensive research and clinical UTI experience and was thus included in the expert panel. Three of the included experts had secondary specialties: general surgery (n = 1), epidemiology (n = 1) and general internal medicine (n = 1).

Delphi round 1

None of the 48 items in R1 met our predefined disagreement criterion. As such, this round was not repeated. Median expert panel ratings and respective interquartile ranges are shown in **Supplementary Figure 2**. In total, 19 of 48 items (40%) were deemed indicative of UTI, 9 of 48 items (19%) were rated 'not indicative', and 20 of 48 items (42%) were of uncertain value. Regarding symptoms and signs, new-onset dysuria, urgency, frequency and symptom recognition (i.e. patient recognises symptoms as UTI) were voted most indicative of UTI, with a high degree of consensus (IQR ≤ 2). Twenty-one of 46 experts (46%) would change their grading if it concerned an older patient, for which the most cited reasons

were: altered symptom presentation (e.g. a higher rate of non-specific symptoms such as delirium and malaise) (n = 11), and decreased specificity of lower urinary tract symptoms due to pre-existing symptoms (n = 3). Thirty-six experts (78%) would not change their grading for male patients.

All pyuria and nitrite items related to older patients were deemed less indicative of UTI than for younger patients, although experts added that their grading would primarily depend on symptom presentation (n = 7), and quality of the urine sample (n = 4). For microbiology items, isolation of the same pathogen from blood and urine cultures received the highest panel median. Regarding the colony-forming units per mL (CFU/mL) threshold for significant bacteriuria, ≥ 10^4 CFU/mL was considered indicative of UTI. Half of the experts who provided additional comments suggested lower (10^2 to 10^4) thresholds for CFU/mL, particularly if *Escherichia coli* was isolated. Seventeen experts (37%) would lower the threshold for urine samples obtained through single 'in-out' urinary catheterisation. Moreover, median scores for items ruling out UTI were highest for the absence of symptoms (in cystitis), pyuria or bacteriuria (without pretreatment). All systemic items other than hypothermia were graded to be useful for differentiating upper from lower UTI, although their low specificity was noted.

Delphi round 2 and adjustments to reference standard

Case vignette results and expert panel comments to each case are shown in the Supplementary Material (see **Supplementary Tables 1 and 2**). For all ten cases, the majority vote aligned with the UTI category as determined by the reference standard. Overall agreement with the drafted reference standard in R2 was 78% (29/37) (see **Supplementary Figure 3**). Per domain, agreement was 82% for symptoms and signs, 70% for systemic criteria, and 68% each for pyuria and culture results. Based on expert panel feedback several changes were made to the reference standard after R2. In the symptoms and signs domain, suprapubic pain, perineal pain (or prostate tenderness on examination) and flank pain (or costovertebral angle tenderness) were moved from major to minor symptoms. Moreover, the option of two minor symptoms was added to the 2-point category. In the systemic criteria domain, an elevated white blood cell (WBC) count was added as a criterion and the C-reactive protein (CRP) cut-off was lowered. Leukocyte esterase was removed from the pyuria domain and new units (cells per high-power field) were added. In the culture domain, the CFU/mL threshold for *Escherichia coli* (10^2 CFU/mL) was adjusted to 10^3, the maximum number of

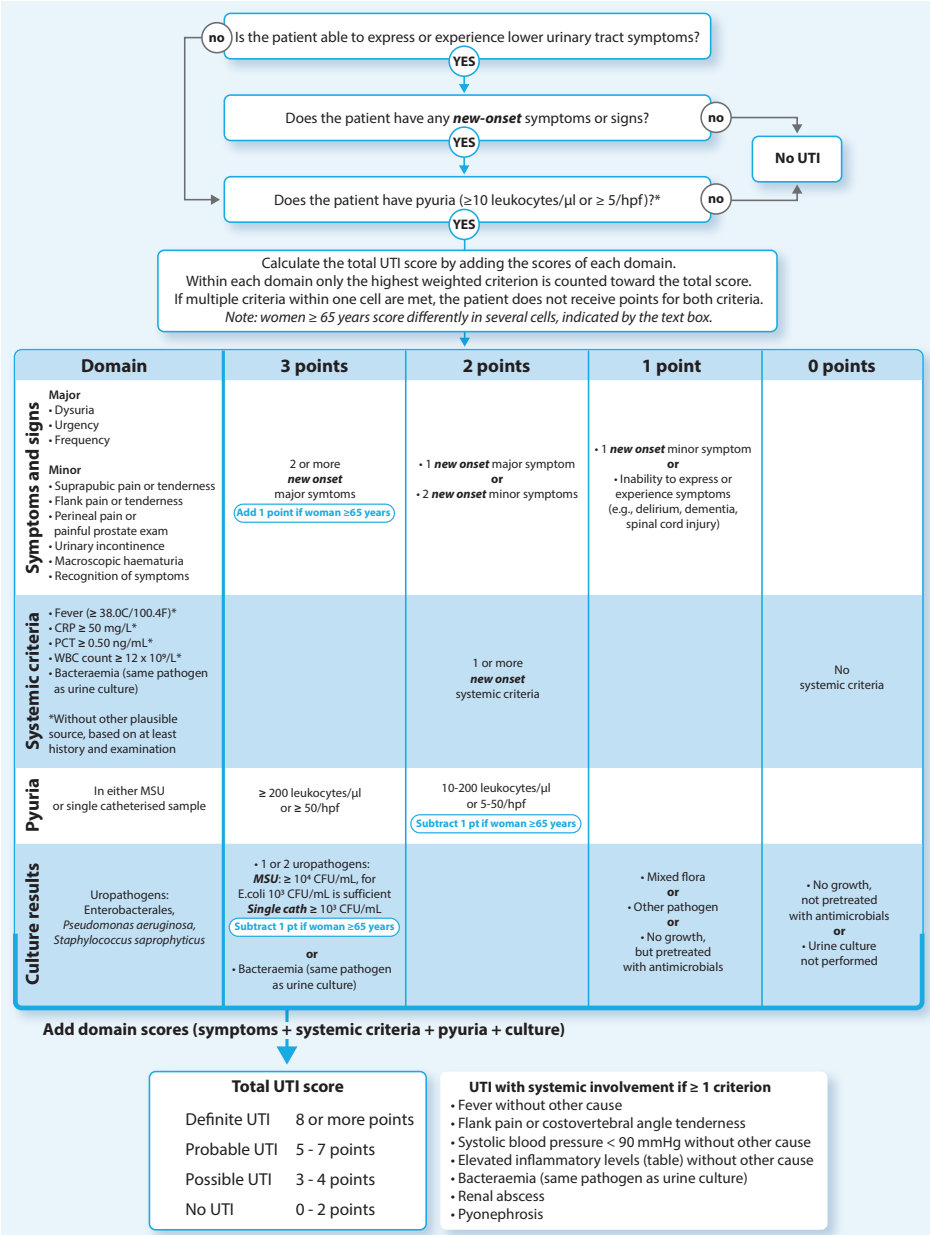

Figure 1: Research reference standard for urinary tract infections. * Pyuria must be quantified, a leukocyte esterase result (urine dipstick) is insufficient. In case of obstructive uropathy or absolute neutropenia, pyuria may be absent and the total UTI score may be calculated. Abbreviations: UTI = urinary tract infection, CRP = C-reactive protein, PCT = procalcitonin, WBC = white blood cell, MSU = midstream urine, CFU = colony-forming units, hpf = high-power field.

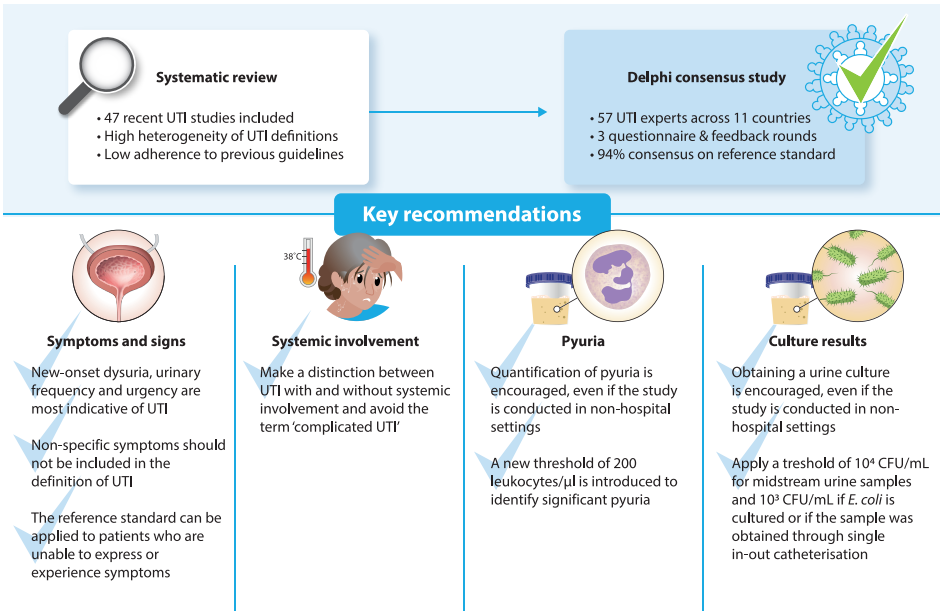

Figure 2: Summary of study findings. Abbreviations: UTI = urinary tract infection, CFU = colony-forming units

uropathogens in the 3-point category was increased to two, nitrites were removed, and *Staphylococcus aureus* was removed from the list of typical uropathogens. Final UTI score categories remained the same.

Delphi round 3

Displaying expert panel interpretation of the case vignettes from R2 led to an increased level of agreement among experts for all ten cases in R3, as shown in **Supplementary Table 1**. Consensus was reached regarding the adjusted reference standard, with 31/33 experts (94%) either agreeing or strongly agreeing with it, while no one disagreed (**Supplementary Figure 3**). The final reference standard is presented in **Figure 1** and key recommendations are summarised in **Figure 2**.

Discussion

In this international Delphi study, we systematically addressed all issues relating to UTI diagnosis and nomenclature and achieved consensus on a reference standard designed specifically for research purposes. By including a broad range

of stakeholders, we incorporated viewpoints from different medical specialties to increase applicability and endorsement across major specialties that frequently encounter UTI.

Signs and symptoms

In the symptoms and signs domain, dysuria, urgency and frequency were chosen as major symptoms, as these symptoms received the highest median scores in R1. This decision was supported by findings from a systematic review showing that these symptoms were most often used in study definitions for UTI. [11] Given that co-occurrence of two lower urinary tract symptoms increases the likelihood of UTI, and these symptoms are not 100% specific for UTI if present alone (e.g. overactive bladder, genitourinary syndrome of menopause), the core group decided to award most points if two or more major symptoms were present. [19] The value of symptom recognition was most debated, as some experts feared that (older) patients would wrongfully attribute symptoms to a UTI based on prior misdiagnosis. However, based on a high median score in R1 and findings by Gupta et al. [20] showing that premenopausal women can accurately self-diagnose UTI, symptom recognition was left in as a minor criterion. Although some expert panellists commented that older patients more frequently present with non-specific symptoms, all non-specific symptoms in R1 received low median scores. This finding is in line with the clinical decision tool for suspected UTI in frail older adults developed through a consensus study by van Buul et al. [17], in which non-specific symptoms, regardless of urinalysis results, do not warrant empirical antimicrobial treatment. Furthermore, another Delphi study, which specifically addressed diagnostic stewardship in the context of ordering urine cultures, classified these nonspecific symptoms as inappropriate justifications for requesting such cultures. [21] The core group believed that older adults who are unable to reliably communicate symptoms (e.g. due to delirium or dementia) should not be excluded from the reference standard, as this population is disproportionately affected by UTI, and a reference standard is vital for research in this population. Considering R1 results and the high background prevalence of asymptomatic pyuria and bacteriuria in this population (especially in women ≥ 65 years), the core group decided to deduct points in pyuria and culture domains for women in this age group. [22-24] Consequently, an older woman with pyuria and bacteriuria, who is unable to communicate symptoms, can only achieve a

classification of 'possible UTI' at best. To offset this deduction, women ≥ 65 years with two major symptoms are granted an additional point.

Systemic criteria

Regarding systemic criteria, core group discussions and expert panel comments focused on the available evidence and cut-off values of the included inflammatory parameters (CRP ≥ 50 mg/L, procalcitonin ≥ 0·50 ng/mL and WBC count ≥ 12 x 10^9/L). Although inflammatory parameter levels are dynamic and depend on the moment of measurement, and thresholds are chosen based on whether high specificity or sensitivity is preferred, the core group felt it was important to provide cut-off values to ensure uniformity. Acknowledging the limited evidence for the included inflammatory parameters regarding UTI with systemic involvement, we chose cut-offs by extrapolating data from studies investigating UTI-related bloodstream infection (BSI) and sepsis. Procalcitonin ≥ 0·50 ng/mL had a sensitivity of 82% and specificity of 66% for BSI in a study with 581 adults with febrile UTI. [25] In a recently published cohort study containing a subset of nearly 15000 adults with presumed UTI, procalcitonin ≥ 0·50 ng/mL showed a sensitivity of 78% and a specificity of 61% for BSI. [26] In an emergency department study involving 160 patients with acute pyelonephritis, sensitivity and specificity of WBC count > 12 x 10^9/L (threshold used in the Surviving Sepsis Campaign guideline) and CRP > 40 mg/L were 58% and 82%, and 76% and 95%, respectively. [27] To further increase specificity, we state that no other plausible source must be present, based on at least history and examination. The core group decided to abandon the term 'complicated UTI' and instead to make a distinction between UTI with and without systemic involvement. We recently showed that 'complicated UTI' definitions are heterogeneous (based on both host factors and systemic involvement), which leads to disparities between studies and hampers the interpretation of their results for different clinical phenotypes. [11] A distinction based solely on clinical phenotype would align more with clinical practice and would facilitate UTI studies evaluating new antimicrobials to include only patients from the target population.

Pyuria

Given that the absence of pyuria, when quantified, rules out UTI (at least in symptomatic women with confirmed bacteriuria) and expert panel grading in R1, the core group agreed that pyuria, albeit with a low threshold, should be an 'entry

criterion' of the reference standard. [28, 29] An exception to this pyuria rule was made for patients with complete obstructive uropathy or absolute neutropenia, in whom pyuria may be absent. [30] Recently, we showed that the most widely used pyuria cut-off (> 10 leukocytes/µl) has a low specificity for UTI in women ≥ 65 years, as asymptomatic bacteriuria is prevalent and is usually accompanied by intermediate degrees of pyuria. [31] As a cut-off of 200 leukocytes/µl increased the specificity to 86%, while maintaining a high sensitivity (89%), the core group incorporated these degrees of pyuria into the reference standard. An important modification to this domain after R2 was the removal of urine dipstick items (leukocyte esterase and nitrites) from the reference standard. Van den Broek et al. [32] show that leukocyte esterase results correlate poorly with absolute degrees of pyuria. Moreover, the core group believed that, at least in research studies, pyuria should be quantified to ensure the validity of the test results, improve comparability between studies and allow for better distinction from asymptomatic bacteriuria. However, quantification of pyuria may not be feasible in every research setting, such as primary and long-term care settings. Since UTI is frequently encountered in these healthcare settings and given the potential benefits of high-quality and standardised UTI research in primary and long-term care, the core group included a supplementary version of the reference standard, in which urine dipstick items are incorporated (see **Supplementary Figure 4**).

Culture results

During expert panel rounds, there was clear support for a threshold of 10^4 CFU/mL for 'significant' bacteriuria, which is lower than the threshold used in FDA and EMA guidelines.[8-10] The traditional threshold of 10^5 CFU/mL was also not supported in the aforementioned Delphi study on urine culture ordering, as it could lead to undertreatment of symptomatic patients with lower colony counts, and inappropriate treatment of asymptomatic patients with higher colony counts. [21] Moreover, the majority of current UTI studies included in our systematic review used thresholds below 10^5 CFU/mL. [11] Based on evidence supporting lower colony counts in symptomatic women with *Escherichia coli* bacteriuria, a threshold of 10^3 CFU/mL specifically for *Escherichia coli* was incorporated into the reference standard, as it is the causative pathogen in approximately 80% of cases. [28, 29, 33] In both systemic criteria and culture domains, points are awarded for bacteraemia (if pathogen matches urine culture results), as the core group felt that this finding represented the strongest evidence of UTI, and a maximum number

of points (5 points) should be given. Based on the study by Hooton et al. [28], enterococci and group B streptococci were not included in the typical uropathogen list (and their score was limited to 1 point). However, if enterococci and group B streptococci grow alongside a typical uropathogen, 3 points are still awarded for the typical uropathogen.

Strengths and limitations

Strengths of our study include using a well-described consensus methodology, the inclusion of experts from multiple relevant specialties and different countries, and requiring a high level of consensus (which was defined a priori). Decisions for the reference standard were not solely based on expert opinion, but also on best available evidence. Given that UTI diagnosis involves many factors, there is no single definitive test, and in clinical practice there are degrees of certainty when diagnosing UTI, we included a scoring system to reflect this, i.e. by including possible, probable, and definite UTI categories. There are several limitations to be noted. As a result of the multifaceted nature of UTI diagnosis, the reference standard does possess a certain level of complexity. However, accuracy was considered more important than simplicity, as the scoring system could be incorporated into a syntax, and this reference standard was not intended to be a clinical decision tool. Another limitation is that our reference standard does not apply to catheter-associated UTI. As symptom presentation and interpretation of urinalysis and culture results is even more challenging in this population, the core group believed that a separate reference standard should be developed for catheter-associated UTI studies. Moreover, a limitation of R1 specifically is that items were graded in isolation, while UTI diagnosis is usually based on many different factors, which might have influenced expert grading. Also, the expert panel consisted only of European and North American experts, and as such, the perspective of low-middle income countries is not represented. Finally, the question remains how a research reference standard can be validated in absence of an existing consensus-based reference standard for UTI. The partial validation that was carried out in our study by comparing case vignette interpretations to reference standard results could be repeated with a larger set of cases and blinded experts. [34] Ultimately, the true value of the reference standard will be determined by whether future UTI studies will adhere to the reference standard and whether this will lead to increased homogeneity between UTI studies.

In conclusion, we have established a consensus-based reference standard for UTI studies, which is supported by experts from multiple countries and medical specialties. This reference standard addresses a significant gap in UTI-related research and has the potential to improve both the internal and external validity of future UTI studies and facilitate accumulation of knowledge and evidence for a disease that imposes a substantial burden on individual patients and society as a whole.

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Author contributions

Conceptualisation (M.P.B., S.P.C., C.S., T.N.P., C.N., L.M., J.M.C., S.E.G., B.K., F.W., M.K., M.M.C.L., L.G.V.), methodology (M.P.B., S.P.C., M.K., M.M.C.L.), data collection, curation and analysis (M.P.B.), writing – original draft preparation (M.P.B., M.M.C.L.), writing – review and editing (S.P.C., C.S., T.N.P., C.N., L.M., J.M.C., S.E.G., B.K., F.W., M.K., M.M.C.L., L.G.V.), supervision (S.P.C., M.M.C.L., L.G.V.). Two authors (M.P.B. and M.M.C.L.) have directly accessed and verified the underlying data reported in the manuscript. All authors have read and agreed to the final version of the manuscript.

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Conflicts of interest

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Disclaimer

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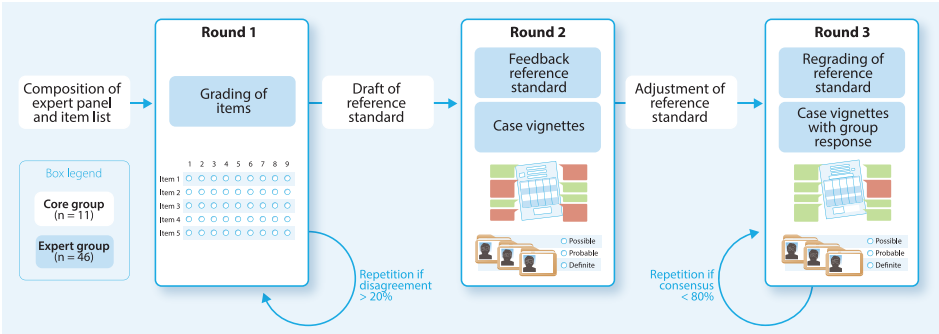
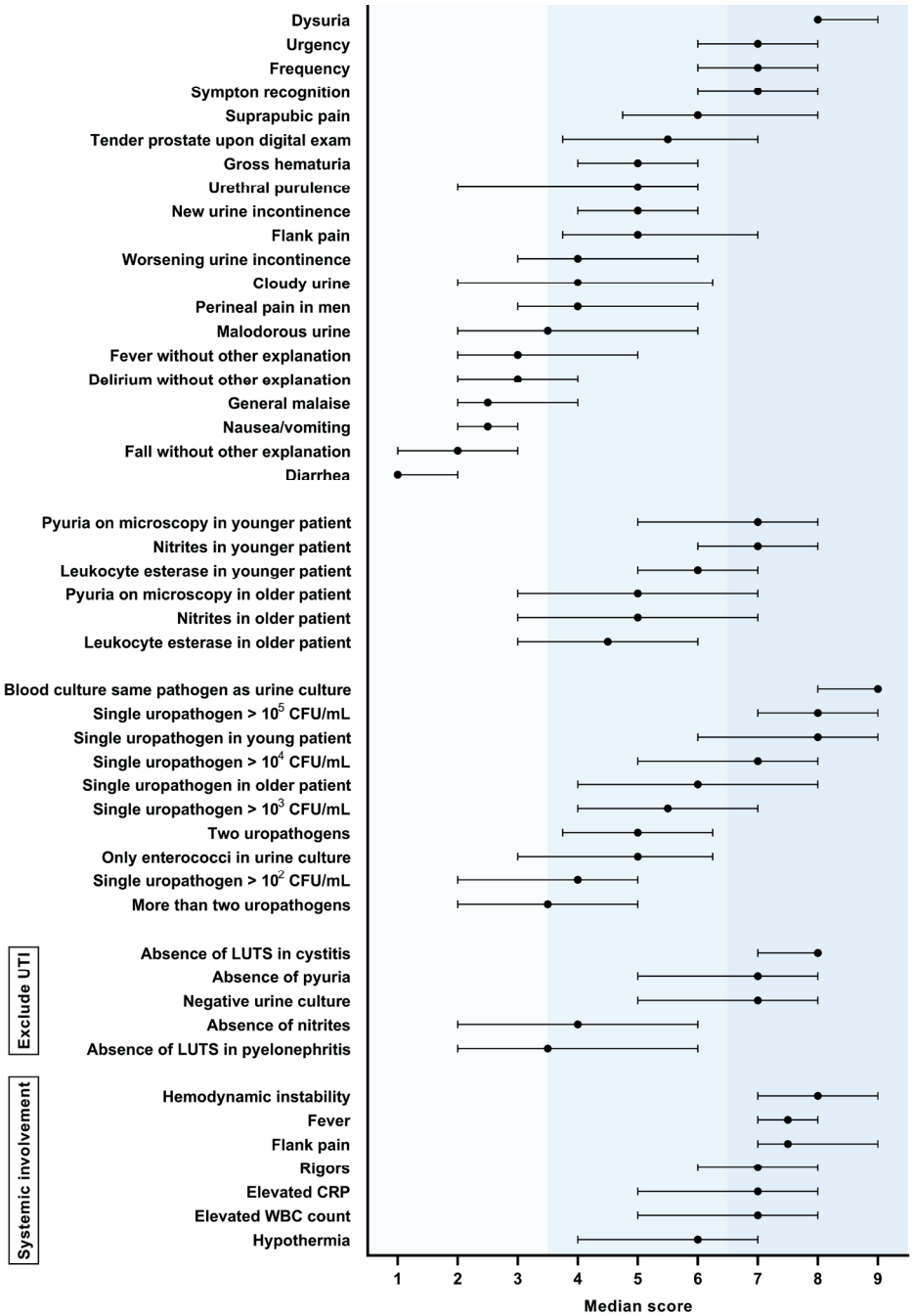
Supplement

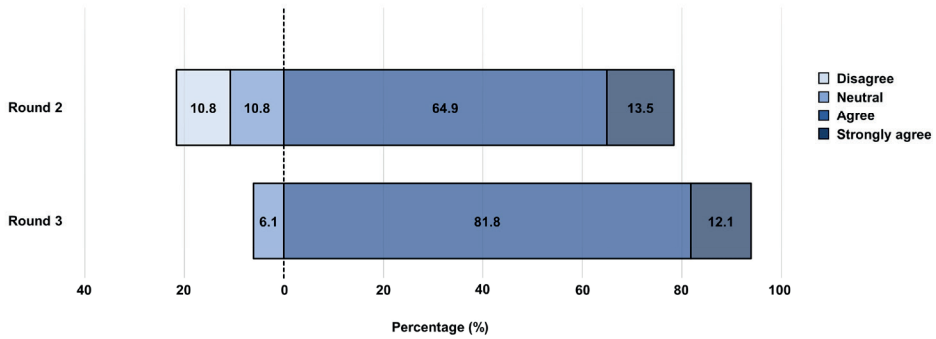


Supplementary Figure 1: Overview of the study design. The core group prepared a questionnaire for the expert group comprising 48 items related to urinary tract infection (UTI) diagnosis. In round 1, the expert panel assigned a value to each item on a Likert scale, ranging from 1 ('not at all indicative of UTI') to 9 ('highly indicative of UTI'). If disagreement (definition according to RAND/UCLA Appropriateness Method) occurred in more than 20% of the items, we planned to conduct another round. Based on the results of round 1 and the available evidence, the core group developed a reference standard. In round 2, consensus was assessed in two ways: experts were asked to rate a set of case vignettes (to evaluate alignment with the reference standard) and provide direct feedback on the initial version of the reference standard. In round 3, experts re-evaluated the same case vignettes and the revised reference standard. If consensus (defined as a minimum of 80% of experts voting 'agree' or 'strongly agree' and none of the experts voting 'disagree') was not reached after round 3, further rounds were planned until consensus was achieved.

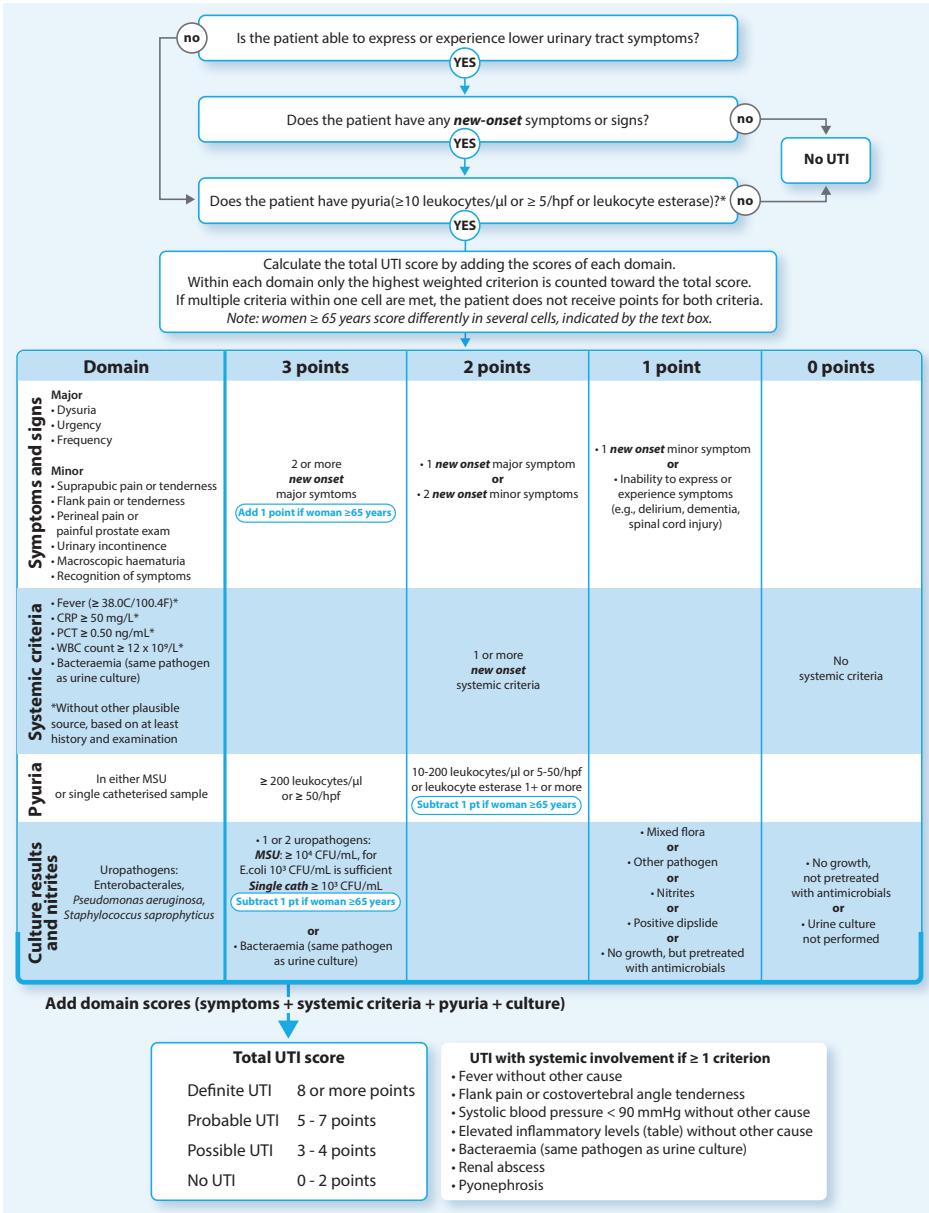


Supplementary Figure 2: Delphi round 1 results. Per item, median scores (represented by the dot) and interquartile ranges are shown. An item was deemed indicative of urinary tract infection (UTI) in case of a panel median ≥ 6·5 (blue panel) without disagreement, not indicative of UTI in case

of a panel median of ≤ 3·5 (white panel) without disagreement, and uncertain if the panel median lay in between indicative and not indicative (light blue panel), or any median with disagreement. Disagreement (both extremes of the Likert scale containing more than a third of responses) did not occur. For the 'exclude UTI' items, a high median score indicates that the item rules out UTI. Abbreviations: CFU = colony-forming units, LUTS = lower urinary tract symptoms; CRP = C-reactive protein; WBC = white blood cell



Supplementary Figure 3: Likert plot of reference standard consensus in Delphi rounds 2 and 3. The 5-point Likert scale ranged from 'strongly disagree' to 'strongly agree'. None of the experts voted for 'strongly disagree'. Experts who neither disagreed nor agreed with the reference standard are depicted as 'neutral'. The proportion of experts voting for each Likert option is displayed in the corresponding bar. Consensus was defined a priori as a minimum of 80% of experts voting 'agree' or 'strongly agree' and none of the experts voting 'disagree'



Supplementary Figure 4: Research reference standard for urinary tract infections – supplement. * In case of obstructive uropathy or absolute neutropenia, pyuria may be absent and the total UTI score may be calculated. Of note: obtaining a urine sample is of utmost importance in all study populations and settings. If no urine can be obtained (neither midstream nor through single catheterization) the total UTI score may be calculated, but this should be mentioned in your study limitations. Abbreviations: UTI = urinary tract infection, CRP = C-reactive protein, PCT = procalcitonin, WBC = white blood cell, MSU = midstream urine, CFU = colony-forming units.

Supplementary Table 1: Concordance between case vignette results and reference standard.

Case (abbreviated)	Ref. standard	Round	Definite	Probable	Possible	No UTI
F25, at GP, new-onset dysuria and frequency, no fever, dipstick positive for LE and nitrites, no urine culture performed.	Probable	2	19 (48)	20 (50)	1 (3)	0
		3	16 (43)	21 (57)	0	0
F80, at LTCF, ADL dependent, refuses morning care because 'she just does not feel like it', no history of cognitive impairment, no signs of delirium, no flank pain, no LUTS, no fever, dipstick positive for LE and nitrites, urine culture *E. coli* > 10^5 CFU/mL.	No UTI	2	3 (8)	7 (18)	12 (30)	18 (45)
		3	1 (3)	3 (8)	10 (27)	23 (62)
M70, at ED, history of BPH, new-onset urgency and frequency, fever, CRP 150 mg/L, urine microscopy 800 leukocytes/µl (> 50 leukocytes/hpf), urine and blood culture *K. pneumoniae* > 10^5 CFU/mL.	Definite	2	37 (93)	2 (5)	1 (3)	0
		3	37 (100)	0	0	0
M85, at home, history of MCI, signs of delirium over the last day, incoherent answers when questioned about LUTS, fever present, no apparent source of infection upon examination, no urine sample due to aggression	Possible	2	0	5 (13)	34 (85)	1 (3)
		3	1 (3)	1 (3)	35 (95)	0
F70, at outpatient clinic, new-onset urinary incontinence and urgency, no other LUTS, no flank pain, no fever, urine microscopy no leukocytes, urine culture mixed flora.	No UTI	2	0	1 (3)	11 (28)	28 (70)
		3	0	1 (3)	6 (16)	30 (81)
F20, at ED, new-onset flank pain and dysuria, no other LUTS, fever is present, CRP 100 mg/L, urine microscopy 500 leukocytes/µl, urine culture *E. coli* > 10^4 CFU/mL, blood culture no growth.	Definite	2	31 (78)	6 (15)	2 (5)	1 (3)
		3	35 (95)	1 (3)	1 (3)	0
F75, at GP, new-onset frequency, no other LUTS, no flank pain, no fever, urine dipstick positive for LE, no nitrites, urine culture *E. faecalis* > 10^4 CFU/mL.	Possible	2	5 (13)	9 (23)	19 (48)	7 (18)
		3	3 (8)	3 (8)	25 (68)	6 (16)

Supplementary Table 1: Continued

Case (abbreviated)	Ref. standard	Round	Definite	Probable	Possible	No UTI
F45, calls GP, dysuria and suprapubic pain, started one day prior, no other LUTS, no fever, no flank pain, took one dose of oral fosfomycin a day ago as patient recognised symptoms, urine dipstick positive for LE, no nitrites, urine culture no growth.	Probable	2	6 (15)	28 (70)	5 (13)	1 (3)
		3	1 (3)	31 (84)	4 (11)	1 (3)
F85, at outpatient clinic, new-onset gross haematuria, oral anticoagulant use, no other LUTS, no flank pain, no fever, urine microscopy 50 leukocytes/µl and 1500 erythrocytes/µl, urine culture *E. coli* and *P. aeruginosa* both > 10^4 CFU/mL.	Possible	2	2 (5)	5 (13)	17 (43)	16 (40)
		3	0	0	22 (60)	15 (41)
F75, at GP, new-onset dysuria, frequency and urgency, no flank pain, no fever, urine dipstick positive for LE and nitrites, urine culture shows mixed flora.	Probable	2	5 (13)	22 (55)	12 (30)	1 (3)
		3	3 (8)	25 (68)	9 (24)	0

All values are n (%). In round 2, 40 experts answered all case vignettes, blinded to the reference standard and group results. In round 3, 37/40 experts (93%) regraded the same case vignettes after having seen group results of round 2. To evaluate alignment between the reference standard and case vignettes in which urine dipsticks were used, we applied the supplementary reference standard. Abbreviations: UTI = urinary tract infection, F = female, M = male, GP = general practitioner, LE = leukocyte esterase, LTCF = long-term care facility, ADL = activities of daily living, LUTS = lower urinary tract symptoms, CFU = colony-forming units, ED = emergency department, BPH = benign prostatic hyperplasia, CRP = C-reactive protein, MCI = mild cognitive impairment.

Supplementary Table 2: Delphi round 2 expert panel comments.

Case number	Expert panel comments
1	• Urine culture result required for definite diagnosis (n = 6) • Could also be sexually transmitted infection or Candidiasis (n = 5)
2	• This is a clear case of asymptomatic bacteriuria (n = 9) • I would wait and see how symptoms develop (n = 3) • Non-specific symptoms are indicative of UTI (n = 3) • Further testing is required/other infections should be ruled out (n = 2)
3	• No remarkable comments
4	• Evaluation of other causes is necessary/source unclear (n = 7) • Delirium and fever are likely UTI (n = 6)
5	• No UTI because of absence of pyuria (n = 3) • New-onset symptoms could be UTI (n = 3) • Would repeat urine culture (n = 3)
6	• Likely pyelonephritis (n = 5) • Further imaging is needed, renal stone (n = 2) • Symptoms more important than bacterial count (n = 2)
7	• Could also be overactive bladder/rule out other cause (n = 5) • Enterococci can be uropathogens (n = 2) • Sample quality (epithelial cells) should be provided (n = 1)
8	• Urine culture probably negative due to pretreatment (n = 10) • Symptom recognition is most important here (n = 2)
9	• Could be bladder cancer/stones, needs cystoscopy (n = 9) • Probably ASB (n = 3) • Would treat because of haematuria (n = 1)
10	• Contaminated specimen, new culture needed (n = 6)

Abbreviations: UTI = urinary tract infection, ASB = asymptomatic bacteriuria