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

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Part I

Defining UTI

Chapter 2

Definitions of urinary tract infection in current research: a systematic review

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Abstract

Defining urinary tract infection (UTI) is complex, as numerous clinical and diagnostic parameters are involved. In this systematic review we aimed to gain insight into how UTI is defined across current studies. We included 47 studies, published between January 2019 and May 2022, investigating therapeutic or prophylactic interventions in adult patients with UTI. Signs and symptoms, pyuria and a positive urine culture were required in 85%, 28% and 55% of study definitions, respectively. Five studies (11%) required all three categories for the diagnosis of UTI. Thresholds for significant bacteriuria varied from 10^3 to 10^5 colony-forming units/mL. None of the 12 studies including acute cystitis and 2/12 (17%) defining acute pyelonephritis used identical definitions. Complicated UTI was defined by both host factors and systemic involvement in 9/14 (64%) studies. In conclusion, UTI definitions are heterogeneous across recent studies, highlighting the need for a consensus-based, research reference standard for UTI.

Introduction

Urinary tract infection (UTI) refers to a plethora of clinical phenotypes, including cystitis, pyelonephritis, prostatitis, urosepsis, and catheter-associated UTI (CA-UTI). [1, 2] In both clinical practice and in research, the diagnosis of UTI is based on a multitude of clinical signs and symptoms and diagnostic tests. Signs and symptoms can be further subdivided into (1) lower urinary tract symptoms (LUTS), such as dysuria, frequency, and urgency, (2) systemic signs and symptoms, such as fever, and (3) non-specific signs and symptoms, such as nausea and malaise. Commonly used diagnostic tests include urine dipstick for determining the presence of leukocyte esterase and nitrites, microscopy or flowcytometry for quantification of pyuria, and urine and blood cultures.

When defining and diagnosing UTI, numerous combinations of signs, symptoms and outcomes of diagnostic tests are possible, and this diversity is reflected in various research guidelines. For drug development and approval purposes, the European Medicines Agency (EMA) [3] and Food and Drug Administration (FDA) [4, 5] have developed guidelines for clinical trials evaluating antimicrobials for the treatment of UTI, summarised in **Table 1**. These guidelines provide definitions for uncomplicated UTI, complicated UTI, and acute pyelonephritis. McGeer et al. [6] have developed research guidelines for studies in long-term care facilities (LTCF). Clinical practice guidelines include the Infectious Diseases Society of America (currently being updated) [7] and European Association of Urology guidelines [8]. It is important to distinguish between research guidelines and clinical practice guidelines as the latter are meant for treatment recommendations, and the definitions in these clinical guidelines are generally based on often-limited diagnostic information available when assessing a patient in the clinical, near-patient setting.

While the aforementioned research guidelines overlap in the sense that they all include a combination of symptoms and evidence of pyuria and/or bacteriuria in the definition of UTI, they also differ. For instance, none of these guidelines include the same set (or minimum number) of symptoms for the diagnosis of UTI. Moreover, the definition of complicated UTI is variable, and either based on systemic signs and symptoms or the presence of host factors predisposing the patient to a complicated clinical course (e.g. functional or anatomical abnormalities of the urinary tract).

Table 1: EMA and FDA definitions of uncomplicated and complicated UTI

Category	EMA – uUTI	FDA – uUTI	EMA – cUTI	FDA – cUTI
Symptoms	A minimum number of symptoms, such as frequency, urgency, and dysuria.	≥ 2: dysuria, frequency, urgency, suprapubic pain (note: lower abdominal discomfort is also mentioned in another section of the guidance document) Patients should **not** have signs or symptoms of systemic illness such as fever > 38°C, shaking chills or other manifestations suggestive of cUTI	A minimum number of signs/ symptoms compatible with an ongoing process in the urinary tract, such as flank or pelvic pain, CVA tenderness, dysuria, frequency or urgency	≥ 2: chills or rigors or warmth associated with fever (>38°C), flank or pelvic pain, dysuria or frequency or urgency, CVA tenderness (note: malaise is also mentioned in another section of the guidance document)
Host factors	Female patients	Female patients with normal anatomy of the urinary tract	≥ 1: indwelling catheter, urinary retention, obstruction, neurogenic bladder. AP is mentioned separately from cUTI, but it is not further defined	≥ 1: indwelling urinary catheter, neurogenic bladder, obstructive uropathy, azotemia caused by intrinsic renal disease, urinary retention (including retention caused by BPH). AP is a subset of cUTI regardless of underlying abnormalities of the urinary tract
Pyuria	> 10 leukocytes/ mm^3	'A microscopic evaluation for pyuria or dipstick analysis for leukocytes, nitrites or a catalase test should be performed'	> 10 leukocytes/ mm^3	Urine dipstick positive for leukocyte esterase **or** > 10 leukocytes/ mm^3
Bacteriuria	> 10^5 CFU/mL of a single relevant pathogen	≥ 10^5 CFU/mL of a single species of bacteria	> 10^5 CFU/mL of a single, or no more than two relevant pathogens	≥ 10^5 CFU/mL of a single species of bacteria

In the EMA guidelines bacteriuria definitions were mentioned in the description of the microbiological intention-to-treat population. In the FDA guidelines, they were also mentioned separately, under clinical microbiology considerations. Abbreviations: EMA = European Medicines Agency, FDA = Food and Drug Administration, uUTI = uncomplicated UTI, cUTI = complicated UTI, CVA = costovertebral angle, AP = acute pyelonephritis, CFU = colony-forming units

It is probable that this wide range of possible definitions and different research guidelines pose problems for researchers conducting studies with patients with UTI. A uniform research definition increases homogeneity between studies, which is important for the interpretation, synthesis and comparability of results, and mitigates the risk of misclassification bias. This is especially relevant in an era of rising antimicrobial resistance, in which novel antimicrobials are being investigated in large randomised controlled trials. The aim of this systematic review is to evaluate how UTI is defined in current studies, and to what extent these definitions differ between studies.

Methods

This systematic review was conducted in accordance with the *Preferred Reporting Items for Systematic reviews and Meta-analyses* (PRISMA) 2020 guidelines [9].

Eligibility criteria

Studies published between January 2019 and May 2022, investigating any therapeutic or prophylactic intervention in adults with (recurrent) UTI were eligible for inclusion. Given the fact that definitions tend to change over time, this time frame was chosen to reflect the most recent consensus. In addition, updated FDA and EMA guidelines were published in 2019. We excluded studies concerning only prostatitis, catheter-associated UTI (CA-UTI), pericatheter or perioperative prophylaxis or ASB. Studies investigating patients with spinal cord injury or neurogenic bladder were also excluded, because separate UTI definitions are mostly used for patients who are unable to experience (or have altered perception of) LUTS. Finally, we excluded systematic reviews, meta-analyses, and studies published in non-English language journals

Search strategy

Multiple electronic databases (PubMed, Embase, Web of Science and the Cochrane library) were searched on May 16th, 2022. Our search strategy was constructed by a research librarian and was based on a PICO-style approach. We applied language and publication year filters as described above and used an 'article type' type filter for clinical trials. The complete search strategy is provided in the **Supplement**.

Data extraction and analysis

Covidence software was used for screening and data extraction. References were imported and duplicates were removed. Title and abstract screening, full-text screening and data extraction were performed by two independent reviewers (M.P.B., R.M.H.J.). In case of disagreement, a third researcher was consulted (M.M.C.L.) and a final decision was based on consensus.

For each study, the following data were collected: study design, setting, population, intervention, and the type of UTI under investigation. Criteria for the definition of UTI were subdivided into three categories: signs and symptoms, urinalysis and urine culture. For each of these categories, we assessed whether they were required or conditionally required (i.e. dependent on the presence of other categories) for the diagnosis of UTI. If categories were not mentioned, or if they were only required for a secondary outcome or definition, they were considered as not required. Definitions were derived from eligibility criteria, unless definitions were explicitly stated elsewhere. For signs and symptoms, additional data were collected on minimum number of symptoms and symptom specification (e.g. if fever and frequency were further defined). Moreover, we recorded which symptoms were part of the definition of acute cystitis, acute pyelonephritis and UTI if a clinical phenotype was not mentioned (henceforth described as 'UTI – phenotype not specified'). For the urinalysis category, we extracted which methods were used for determining pyuria, which cut-off values were applied, and whether nitrites were part of the UTI definition. Regarding the urine culture category, we recorded the cut-off value for CFU/mL and the maximum number of uropathogens. For all three categories, we assessed whether study definitions met FDA and EMA guideline requirements. Concerning complicated UTI, we collected the same components of the definition as described above, but we also assessed whether the definition was based on host factors, systemic involvement, or a combination of both. Finally, we compared definitions between studies, stratified per UTI type. No risk of bias assessment was performed as we studied definitions instead of outcomes. Data are summarised as proportions.

Results

Study selection and study characteristics

The study selection process is summarised in a PRISMA flowchart (**Figure 1**). We screened 348 reports published between January 2019 and May 2022. Studies that were excluded during title and abstract screening (n = 290) mainly involved

patients with CA-UTI or conditions other than UTI (e.g. interstitial cystitis), or investigated pericatheter or perioperative prophylaxis. During full-text screening, seven non-English articles and secondary analyses of articles already included in the study using our search criteria, were excluded. A total of 47 randomised controlled trials and cohort studies with a median of 145 participants were included. [10–56]

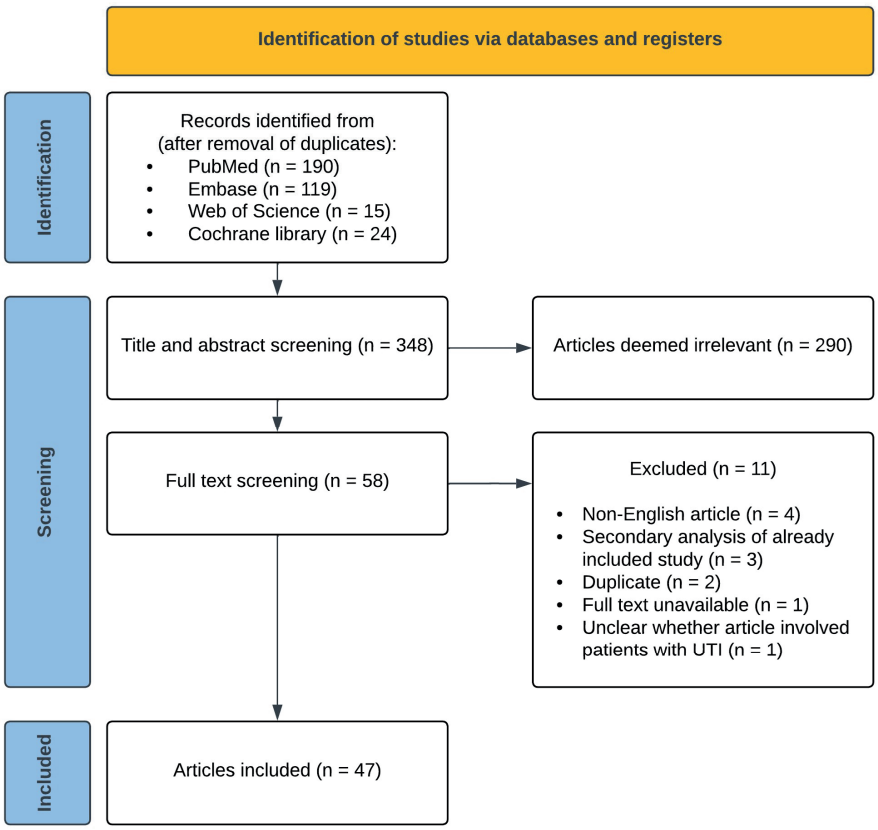

Figure 1: PRISMA flowchart of the study selection process. Abbreviations: UTI = urinary tract infection.

Thirty-one studies (66%) investigated antimicrobials for the treatment of UTI, and 15 (32%) evaluated antimicrobial prophylaxis for recurrent UTI. Sixteen studies (34%) only included women, four studies (9%) only included men, and 27 studies (57%) included both. Participants were hospitalised in 25 studies (53%)

and treated through an outpatient or primary care clinic in 22 studies (47%). None of the included studies were conducted in long-term care facilities. Twelve studies (26%) included acute cystitis, 16 (34%) included acute pyelonephritis and 13 (28%) included 'UTI – phenotype not specified'. A table containing details of all included studies is provided in **Supplementary Table 1**.

UTI definition and heterogeneity

Table 2 shows how UTI was defined across the included studies. In 11 studies (23%) the definition consisted of only signs and symptoms, in 16 studies (34%) the definition consisted of both signs and symptoms and a positive urine culture, and in 5 studies (11%) all three components (signs and symptoms, the presence of pyuria and a positive urine culture) were required for the diagnosis of UTI. None of the studies investigating acute cystitis (n = 12) or 'UTI – phenotype not specified' (n = 13) included the same set of symptoms and diagnostic criteria in their definition. Of the studies defining acute pyelonephritis, two (17%) used identical definitions.

Signs and symptoms

Signs and symptoms were required for the diagnosis of UTI in 40 studies (85%). Of these, 34 (85%) specified signs and symptoms in the definition. The different signs and symptoms that were included in the definition of acute cystitis, acute pyelonephritis and 'UTI – phenotype not specified' are highlighted in **Table 3**. FDA guidelines [4] require a minimum of two of the following symptoms for patients with uncomplicated UTI: dysuria, urgency, frequency and suprapubic pain. Two out of 12 studies (17%) met these criteria. Flank pain and/or costovertebral angle tenderness, fever, nausea and/or vomiting, and dysuria were most often included in the definition of acute pyelonephritis. Frequency was not further specified in any study. Perineal and/or prostate pain was part of the definition in 3/31 (10%) studies involving men. A specific temperature cut-off for fever was defined in 7/17 (65%) studies that included fever in the definition of UTI.

Table 2: Categories of UTI definition.

Categories of UTI definition (n = 47)	n (%)
Signs and symptoms	
Required	40 (85)
Conditionally required	1 (2)
Not required	6 (13)
Signs and symptoms specified	34/40 (85)
Minimum number of symptoms specified	24/40 (60)
Pyuria	
Required	13 (28)
Conditionally required	4 (9)
Not required	30 (64)
Method of establishing pyuria specified	14/17 (82)
Dipstick only	2 (14)
Quantification only	4 (29)
Both methods allowed	8 (57)
Cut-off for pyuria specified	12/12 (100)
> 5 leukocytes/hpf	2 (17)
> 10 leukocytes/µl or > 10 leukocytes/hpf	10 (83)
Urine culture	
Required	26 (55)
Conditionally required	1 (2)
Not required	20 (43)
Cut-off for CFU/mL specified	19/27 (70)
> 10^3 CFU/mL	8 (42)
> 10^4 CFU/mL	4 (21)
> 10^5 CFU/mL	7 (37)
Maximum number of uropathogens specified	4/27 (15)
Urine collection method specified	12/47 (26)

If categories were not mentioned, they were considered as not required. Definitions were derived from eligibility criteria, unless definitions were explicitly stated elsewhere. Percentages may not add up to 100 due to rounding. Abbreviations: UTI = urinary tract infection, hpf = high-power field, CFU = colony-forming units

Table 3: Symptoms and signs in different types of UTI.

Symptoms & signs	Acute cystitis (n = 12)	Acute pyelonephritis (n = 16)*	UTI – phenotype not specified (n = 13)
Dysuria	9 (75)	8 (50)	9 (69)
Urgency	9 (75)	6 (38)	7 (54)
Frequency	9 (75)	7 (44)	6 (46)
Suprapubic pain	5 (42)	0	6 (46)
Macroscopic haematuria	4 (33)	0	4 (31)
Lower abdominal pain	2 (17)	0	1 (8)
Perineal/prostate pain	1 (8)	0	2 (15)
Pelvic pain	0	2 (13)	1 (8)
Flank pain or CVA tenderness	1 (8)	12 (75)	2 (15)
New urinary incontinence	0	0	1 (8)
Worsening incontinence	0	0	1 (8)
Fever	0	12 (75)	2 (15)
Chills or rigors	0	7 (44)	0
Nausea or vomiting	0	8 (50)	0
Symptoms not specified	3 (25)	4 (25)	2 (15)

*This included all studies investigating acute pyelonephritis, either alone or in conjunction with other types of UTI. All symptoms and signs are shown as n (%). Other symptoms mentioned in studies focusing on acute cystitis or 'UTI – phenotype not specified' were: vesical tenesmus (n = 1), malodorous and/or cloudy urine (n = 1), hypogastric pain (n = 1), and nocturia (n = 1). Additional criteria for the definition of acute pyelonephritis not mentioned in the table: elevated serum inflammatory parameters (n = 1), signs of pyelonephritis on ultrasound or computed tomography (n = 1), and hypotension (n =1). Abbreviations: UTI = urinary tract infection, CVA = costovertebral angle.

Urinalysis and urine culture

The presence of pyuria was required for the diagnosis of UTI in 13/47 (28%) studies, while both FDA and EMA guidelines [3-5] require pyuria in their definition of UTI. A cut-off for pyuria was specified in 12 studies, of which 10 (83%) applied a cut-off value of > 10 leukocytes/µl or > 10 leukocytes/high-power field. None of the included studies required the presence of nitrites for the diagnosis of UTI, although they were conditionally required in three studies (6%). A positive urine culture was mandatory for UTI diagnosis in 26/47 (55%) studies, of which 12 (55%) were conducted in the primary care or outpatient setting and 14 (56%) involved hospitalised patients. Of the 19 studies that mentioned a cut-off value for CFU/mL, 8 (42%) used a cut-off of 10^3 CFU/mL. Out of all studies, 7 (15%) required a positive urine culture with at least 10^5 CFU/mL, complying with EMA and FDA guidelines. [3-5]

Complicated UTI

We included 14 studies that defined complicated UTI. Three (21%) based their definition on complicating host factors only, one (7%) on systemic involvement only, and nine (64%) on both host factors and systemic involvement. The various host factors included in the definition are provided in **Table 4**. Male sex was considered a complicating factor in two studies (17%).

Table 4: Definition of complicated UTI.

Complicated UTI (n = 14)	n (%)
How is complicated UTI defined?	
Both host factors and systemic involvement	9 (64)
Only host factors	3 (21)
Only systemic involvement	1 (7)
Complicated UTI not further defined	1 (7)
Which host factors are part of complicated UTI criteria?*	
Obstructive uropathy	11 (92)
Functional or anatomical abnormalities of the urinary tract	10 (83)
Indwelling catheter or nephrostomy tube	9 (75)
Intrinsic renal disease	8 (67)
Urinary retention in men due to BPH	5 (42)
Urinary retention in general	3 (25)
Male sex (regardless of urinary retention)	2 (17)
Diabetes mellitus	2 (17)
Systemic lupus erythematosus	2 (17)
Pregnancy	1 (8)
Immunocompromised state	1 (8)
Kidney transplant recipient	1 (8)

*Host factors were specified in n = 12 studies, this was used as the denominator for the proportions. For the purpose of this table, systemic involvement was defined as the presence of fever and/or rigors in the criteria for diagnosis of complicated UTI. Abbreviations: UTI = urinary tract infection, BPH = benign prostatic hyperplasia

Discussion

In this systematic review we demonstrate that UTI definitions used in current research studies are highly heterogeneous in terms of clinical signs and diagnostic tests. In addition, few studies met symptom, pyuria and urine culture criteria mentioned in existing research guidelines.

Signs and symptoms

The presence of signs and symptoms was required in the majority of UTI definitions used in the included studies. As symptoms and signs remain the cornerstone of UTI diagnosis, it is noteworthy that 15% of studies did not require signs and symptoms for the diagnosis of UTI and an even greater number of studies did not specify which symptoms and signs needed to be present. Defining specific symptoms may help to mitigate the risk of misclassification. Symptom specification is especially relevant in studies involving older patients with UTI, given the high background prevalence of asymptomatic bacteriuria and pyuria. [57–59] Most of the studies that did clarify which symptoms were part of the UTI definition included classic UTI-associated symptoms, such as dysuria, frequency and urgency. However, we also found a broad variety of non-specific manifestations, particularly in studies that did not define the UTI phenotype under investigation. Regardless of the unclear clinical relevance of non-specific symptoms in UTI, this diversity of symptoms contributes to heterogeneity between studies, which is supported by our finding that few of the included studies used the same set of symptoms to define UTI. Furthermore, in over a third of the included reports, a minimum number of symptoms (for diagnosis) was not mentioned. Given the fact that even classic LUTS are not 100% specific for UTI, and probability of UTI increases when a combination of symptoms is present, a minimum number of symptoms should be specified. [60]

Pyuria and bacteriuria

Interestingly, less than a third of included studies required the presence of pyuria in the definition of UTI. With the exception of patients with absolute neutropenia and complete obstructive uropathy, pyuria is present in virtually all symptomatic patients with bacteriuria, and its absence has a high negative predictive value for UTI. [61–63] In the included studies, pyuria was rarely quantified and thresholds for significant pyuria were low. A recent study has shown that low pyuria cut-offs should be avoided in older women, as the specificity for UTI is very low in this population. [64] Moreover, studies used different units of measurement interchangeably (i.e. identical thresholds were applied for cells per µl and hpf), while results are influenced by different (pre)analytical procedures and previous studies have shown a µl/hpf ratio of 5:1. [65] Be that as it may, quantification of pyuria in UTI studies should be encouraged, and pyuria should be included in the definition of UTI to reduce the risk of misclassification.

As growth of a uropathogen supports the diagnosis of UTI in a symptomatic patient, it is surprising that a positive urine culture was not part of the UTI definition in approximately half of the included studies. Even though urine cultures are not always required in a clinical setting (e.g. in primary care), we believe that culture confirmation should at least be encouraged in a research setting. Furthermore, we found that studies used varying cut-offs for significant bacteriuria, ranging from 10^3 to 10^5 CFU/mL, while EMA and FDA guidelines both recommend a threshold of 10^5 CFU/mL. The question remains whether this is the optimal cut-off [66]: colony-counts as low as 10^2 CFU/mL in midstream urine have been found in symptomatic premenopausal women with *E. coli* bacteriuria. [61, 62]

Complicated UTI

Studies differed widely in their definition of complicated UTI. Since the majority of studies defined complicated UTI based on both complicating host factors and systemic involvement, different clinical phenotypes were included in each study. This not only contributes further to disparities between studies, it also affects the applicability of study results. Moreover, the aforementioned heterogeneity is compounded by the fact that host factors are very diverse in themselves and there is no consensus about which host factors should be included in the definition of complicated UTI. As astutely phrased by James Johnson [67], "it may be time to find a different term than complicated UTI for UTIs that occur in patients with underlying predisposing factors, since this term seems hopelessly mired in ambiguity." Johansen et al. [68] have proposed a UTI classification system for clinical and research purposes based on clinical phenotype, severity, host factors and pathogen susceptibility. However, this classification system was not used by any of the included studies in our review. In the Netherlands, the primary care guidelines for UTI have already made a distinction between a UTI in a complicated host versus UTI with systemic involvement. [69]

Existing research guidelines

We found that few studies met symptom, pyuria and urine culture criteria mentioned in FDA and EMA guidelines. [3-5] In addition, we identified that studies more frequently based UTI definitions on clinical practice guidelines. The use of clinical practice guidelines in the place of research guidelines seems inappropriate, as clinical guidelines are less stringent than research guidelines, and they base empirical treatment recommendations on limited diagnostic information. Taken together, our findings imply that a widely accepted, consensus-based gold

standard for the diagnosis of UTI is lacking, and is much needed in the field of UTI research.

Strengths and limitations

Strengths of this systematic review include our comprehensive search strategy, including multiple electronic databases, and extracting data from supplemental material, as UTI definitions were frequently only mentioned in a supplemental protocol. Our study has several limitations. For some of the included therapeutic studies, eligibility criteria served as a proxy for the UTI definition, if a definition was not mentioned separately. This might have contributed to additional heterogeneity. For instance, prophylactic studies including patients with recurrent UTI more frequently provided separate UTI definitions, since these often served as outcome measures. Also, some heterogeneity might be explained by the fact that we included studies that investigated different UTI phenotypes. However, this effect was mitigated by evaluating different UTI phenotypes separately. Another limitation is that we filtered our search strategy on publication date and study type. While expanding the time period would have provided more data, it would not reflect the most recent consensus and would likely have contributed to further heterogeneity, as these studies were published before the FDA and EMA guidance documents. Furthermore, including more observational studies most likely would not have reduced heterogeneity, as these are presumably less likely to follow FDA and EMA guidelines for drug approval. Since we did not find any recent studies that were conducted in long-term care facilities, and we excluded studies regarding CA-UTI and UTI in spinal cord injury patients, it is unclear how heterogeneous definitions are in these areas. Defining UTI might be even more challenging for these populations and settings.

Conclusions

In conclusion, UTI definitions differ widely across recent therapeutic and interventional studies. An international consensus-based reference standard is needed to reduce misclassification bias within studies and heterogeneity between studies. To avoid ambiguity, such a reference standard should veer away from the term ‘complicated UTI’ and instead categorise UTI based on systemic involvement, as these are different entities with different treatments. Based on results of this systematic review, our group has initiated an international consensus study to construct a UTI reference standard for research purposes.

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Author contributions

Conceptualisation and methodology M.P.B., R.M.H.J., S.P.C., L.G.V., M.M.C.L.; screening and data extraction M.P.B., R.M.H.J.; data analysis M.P.B.; writing – original draft preparation M.P.B., R.M.H.J; writing – review and editing M.P.B, R.M.H.J., C.S, T.N.P., C.N, L.M, J.M.C, S.E.G, B.K., F.W., S.P.C, L.G.V., M.M.C.L.; supervision M.M.C.L., S.P.C, and L.G.V. All authors have read and agreed to the final version of the manuscript.

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Conflicts of interest

None of the authors have an association that might pose a conflict of interest regarding this manuscript.

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Supplement

Search strategy

Search date: May 16th, 2022

Number of articles per electronic database:

- **PubMed**: 308 – after removal of comments, editorials and letter: 294 – after applying publication year filter (2019 and more recent): 190
- **Embase**: 327 – 161 unique articles – after applying publication year filter: 119
- **Web of Science**: 165 – 17 unique articles – after applying publication year filter: 15
- **Cochrane library** (published trials only): 241 – 40 unique – after applying publication year filter: 24

Search strategy per electronic database:

PubMed

http://www.ncbi.nlm.nih.gov/pubmed?otool=leiden

((("Anti-Bacterial Agents"[Mesh] OR "Anti-Bacterial Agents"[Pharmacological Action] OR "Anti-Bacterial Agents"[tw] OR "Anti-Bacterial Agent"[tw] OR "Antibacterial Agents"[tw] OR "Antibacterial Agent"[tw] OR "antibiotic"[tw] OR "antibiotics"[tw] OR "anti biotic"[tw] OR "anti biotics"[tw] OR "Fluoroquinolones"[Mesh] OR "Fluoroquinolones"[tw] OR "Fluoroquinolone"[tw] OR "Ciprofloxacin"[tw] OR "Enoxacin"[tw] OR "Enrofloxacin"[tw] OR "Fleroxacin"[tw] OR "Gatifloxacin"[tw] OR "Gemifloxacin"[tw] OR "Levofloxacin"[tw] OR "Moxifloxacin"[tw] OR "Norfloxacin"[tw] OR "Ofloxacin"[tw] OR "Pefloxacin"[tw] OR "Fosfomycin"[Mesh] OR "Fosfomycin"[tw] OR "Phosphomycin"[tw] OR "Phosphonomycin"[tw] OR "Monuril"[tw] OR "Cephalosporins"[Mesh] OR "Cephalosporins"[tw] OR "Cephalosporin"[tw] OR "Cefaclor"[tw] OR "Cefadroxil"[tw] OR "Cefamandole"[tw] OR "Cefatrizine"[tw] OR "Cefazolin"[tw] OR "Cefdinir"[tw] OR "Cefepime"[tw] OR "Cefixime"[tw] OR "Cefmenoxime"[tw] OR "Cefmetazole"[tw] OR "Cefonicid"[tw] OR "Cefoperazone"[tw] OR "Cefotaxime"[tw] OR "Cefotetan"[tw] OR "Cefotiam"[tw] OR "Cefoxitin"[tw] OR "Cefsulodin"[tw] OR "Ceftazidime"[tw] OR "Ceftibuten"[tw] OR "Ceftizoxime"[tw] OR "Ceftriaxone"[tw] OR "Cefuroxime"[tw] OR "Cephacetrile"[tw] OR "Cephalexin"[tw] OR "Cephaloglycin"[tw] OR "Cephaloridine"[tw] OR "Cephalothin"[tw] OR "Cephamycins"[tw] OR "Cephapirin"[tw] OR "Cephradine"[tw] OR "Carbapenems"[Mesh] OR "Carbapenems"[tw] OR "Carbapenem"[tw] OR "Doripenem"[tw] OR "Ertapenem"[tw] OR "Thienamycins"[tw] OR "Imipenem"[tw] OR "Meropenem"[tw] OR "Aminoglycosides"[mesh:noexp] OR "Gentamicins"[mesh] OR "Tobramycin"[Mesh] OR "Aminoglycosides"[tw] OR "aminoglycoside"[tw] OR "gentamycin"[tw] OR "Gentamycins"[tw] OR "Gentamicin"[tw] OR "Gentamicins"[tw] OR "Sisomicin"[tw] OR "Netilmicin"[tw] OR "tobramycin"[tw] OR "Tobramycins"[tw] OR "Vaccinium macrocarpon"[Mesh] OR "Vaccinium macrocarpon"[tw] OR "cranberry"[tw] OR "cranberries"[tw] OR "cranberr*"[tw] OR "Methenamine"[Mesh] OR "Methenamine"[tw] OR "Hexamine"[tw] OR "Hexamethylenetetramine"[tw] OR "Urotropin"[tw] OR "Aminoform"[tw]

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Broader search:

((("Anti-Bacterial Agents"[Mesh] OR "Anti-Bacterial Agents"[Pharmacological Action] OR "Anti-Bacterial Agents"[tw] OR "Anti-Bacterial Agent"[tw] OR "Antibacterial Agents"[tw] OR "Antibacterial Agent"[tw] OR "antibiotic"[tw] OR "antibiotics"[tw] OR "anti biotic"[tw] OR "anti biotics"[tw] OR "Fluoroquinolones"[Mesh] OR "Fluoroquinolones"[tw] OR "Fluoroquinolone"[tw] OR "Ciprofloxacin"[tw] OR "Enoxacin"[tw] OR "Enrofloxacin"[tw] OR "Fleroxacin"[tw] OR "Gatifloxacin"[tw] OR "Gemifloxacin"[tw] OR "Levofloxacin"[tw] OR "Moxifloxacin"[tw] OR "Norfloxacin"[tw] OR "Ofloxacin"[tw] OR "Pefloxacin"[tw] OR "Fosfomycin"[Mesh] OR "Fosfomycin"[tw] OR "Phosphomycin"[tw] OR "Phosphonomycin"[tw] OR "Monuril"[tw] OR "Cephalosporins"[Mesh] OR "Cephalosporins"[tw] OR "Cephalosporin"[tw] OR "Cefaclor"[tw] OR "Cefadroxil"[tw] OR "Cefamandole"[tw] OR "Cefatrizine"[tw] OR "Cefazolin"[tw] OR "Cefdinir"[tw] OR "Cefepime"[tw] OR "Cefixime"[tw] OR "Cefmenoxime"[tw] OR "Cefmetazole"[tw] OR "Cefonicid"[tw] OR "Cefoperazone"[tw] OR "Cefotaxime"[tw] OR "Cefotetan"[tw] OR "Cefotiam"[tw] OR "Cefoxitin"[tw] OR "Cefsulodin"[tw] OR "Ceftazidime"[tw] OR "Ceftibuten"[tw] OR "Ceftizoxime"[tw] OR "Ceftriaxone"[tw] OR "Cefuroxime"[tw] OR "Cephacetrile"[tw] OR "Cephalexin"[tw] OR "Cephaloglycin"[tw] OR "Cephaloridine"[tw] OR "Cephalothin"[tw] OR "Cephamycins"[tw] OR "Cephapirin"[tw] OR "Cephradine"[tw] OR "Carbapenems"[Mesh] OR "Carbapenems"[tw] OR "Carbapenem"[tw] OR "Doripenem"[tw] OR "Ertapenem"[tw] OR "Thienamycins"[tw] OR "Imipenem"[tw] OR "Meropenem"[tw] OR "Vaccinium macrocarpon"[Mesh] OR "Vaccinium macrocarpon"[tw] OR "cranberry"[tw] OR "cranberries"[tw] OR "cranberr*"[tw] OR "Methenamine"[Mesh] OR "Methenamine"[tw] OR "Hexamine"[tw] OR "Hexamethylenetetramine"[tw] OR "Urotropin"[tw] OR "Aminoform"[tw]

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Embase

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Web of Science

http://isiknowledge.com/wos ((TI=("Antibiotic agent" OR "Anti-Bacterial Agents" OR "Anti-Bacterial Agent" OR "Antibacterial Agents" OR "Antibacterial Agent" OR "antibiotic" OR "antibiotics" OR "anti biotic" OR "anti biotics" OR "quinolone derivative" OR "Fluoroquinolones" OR "Fluoroquinolone" OR "Ciprofloxacin" OR "Enoxacin" OR "Enrofloxacin" OR "Fleroxacin" OR "Gatifloxacin" OR "Gemifloxacin" OR "Levofloxacin" OR "Moxifloxacin" OR "Norfloxacin" OR "Ofloxacin" OR "Pefloxacin" OR "Fosfomycin" OR "Fosfomycin" OR "Phosphomycin" OR "Phosphonomycin" OR "Monuril" OR "Cephalosporin Derivative" OR "Cephalosporins" OR "Cephalosporin" OR "Cefaclor" OR "Cefadroxil" OR "Cefamandole" OR "Cefatrizine" OR "Cefazolin" OR "Cefdinir" OR "Cefepime" OR "Cefixime" OR "Cefmenoxime" OR "Cefmetazole" OR "Cefonicid" OR "Cefoperazone" OR "Cefotaxime" OR "Cefotetan" OR "Cefotiam" OR "Cefoxitin" OR "Cefsulodin" OR "Ceftazidime" OR "Ceftibuten" OR "Ceftizoxime" OR "Ceftriaxone" OR "Cefuroxime" OR "Cephacetrile" OR "Cephalexin" OR "Cephaloglycin" OR "Cephaloridine" OR "Cephalothin" OR "Cephamycins" OR "Cephapirin" OR "Cephradine" OR "Carbapenems" OR "Carbapenems" OR "Carbapenem" OR "Doripenem" OR "Ertapenem" OR "Thienamycins" OR "Imipenem" OR "Meropenem" OR "Aminoglycoside" OR "Aminoglycoside Antibiotic agent" OR "Gentamicin" OR "Tobramycin" OR "Aminoglycosides" OR "aminoglycoside" OR "gentamycin" OR "Gentamycins" OR "Gentamicin" OR "Gentamicins" OR "Sisomicin" OR "Netilmicin" OR "tobramycin" OR "Tobramycins" OR "cranberry extract" OR "cranberry" OR "cranberry juice" OR "Vaccinium macrocarpon" OR "cranberry" OR "cranberries" OR "cranberr*" OR "Methenamine" OR "Methenamine" OR "Hexamine" OR

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AND py=(2017 OR 2018 OR 2019 OR 2020 OR 2021 OR 2022 OR 2023)

NOT DT=(meeting abstract))

Supplementary Table 1: Overview of included studies.

Study	Design & setting	Intervention	Population	Type of UTI	Refers to guideline	Symptoms	Acute pyelonephritis	Complicated UTI	Pyuria	Positive urine culture & cut-off
Aloush 2019	Experimental (n = 171) Hospital	Therapeutic – oral antimicrobial	Both women and men	UTI – phenotype not specified	Yes, CDC guideline	Required	–	–	Not required	Required, cut-off 10^5 CFU/mL
Arakawa 2019	Experimental (n = 115) Hospital	Therapeutic – intravenous antimicrobial	Both women and men	Multiple types of UTI including complicated UTI	No	Required	Regarded as subset of complicated UTI, and defined separately	Based on both host factors and systemic involvement	Required, > 10 leukocytes/µl	Required, cut-off 10^5 CFU/mL
Babar 2021	Experimental (n = 145) Primary care or outpatient	Prophylactic – cranberry	Women	UTI – phenotype not specified	Yes, IDSA clinical practice guideline	Required	–	–	Not required	Not required
Boel 2020	Observational (n = 1129) Hospital	Therapeutic – intravenous antimicrobial	Both women and men	Bacteraemic / febrile UTI	No	Not required	–	–	Not required	Required, cut-off 10^3 CFU/mL
Botros 2021	Experimental (n = 92) Primary care or outpatient	Prophylactic – methenamine	Women	UTI – phenotype not specified	Yes, EAU guideline	Required	–	–	Not required	Required, cut-off 10^3 CFU/mL

Supplementary Table 1: Continued

Study	Design & setting	Intervention	Population	Type of UTI	Refers to guideline	Symptoms	Acute pyelonephritis	Complicated UTI	Pyuria	Positive urine culture & cut-off
Bruyère 2019	Experimental (n = 85) Primary care or outpatient	Prophylactic – cranberry	Women	UTI – phenotype not specified	No	Required	–	–	Not required	Required, cut-off 10^5 CFU/mL
Costache 2019	Experimental (n = 40) Primary care or outpatient	Therapeutic – other	Both women and men	Acute cystitis	No	Required	–	–	Not required	Required, cut-off 10^3 CFU/mL
Diebold 2021	Experimental (n = 78) Primary care or outpatient	Prophylactic – other	Women	Acute cystitis	No	Required	–	–	Not required	Not required
Drekonja 2021	Experimental (n = 272) Primary care or outpatient	Therapeutic – oral antimicrobial	Men	Acute cystitis	No	Required	–	–	Not required	Not required
Eckburg 2022	Experimental (n = 1372) Hospital	Therapeutic – oral antimicrobial	Both women and men	Complicated UTI	Yes, FDA guideline	Required	Not regarded as subset of complicated UTI, and defined separately	Based on both host factors and systemic involvement	Required, either positive leukocyte esterase or > 10 leukocytes per hpf or mm^3	Not required

Supplementary Table 1: Continued

Study	Design & setting	Intervention	Population	Type of UTI	Refers to guideline	Symptoms	Acute pyelonephritis	Complicated UTI	Pyuria	Positive urine culture & cut-off
Edlund 2022	Experimental (n = 152) Hospital	Therapeutic – intravenous antimicrobial	Both women and men	Complicated UTI	No	Required	Not regarded as subset of complicated UTI, and defined separately	Based on host factors only	Required, positive leukocyte esterase	Not required
El Nekidy 2021	Observational (n = 85) Hospital	Therapeutic – intravenous antimicrobial	Both women and men	UTI - phenotype not specified	No	Required	-	-	Not required	Required, no cut-off specified
Ferrante 2019	Experimental (n = 35) Primary care or outpatient	Prophylactic – other	Women	UTI - phenotype not specified	No	Required	-	-	Not required	Required, no cut-off specified
Gama 2020	Experimental (n = 272) Primary care or outpatient	Prophylactic – methenamine	Both women and men	UTI - phenotype not specified	No	Required	-	-	Not required	Not required
Gamble 2022	Observational (n = 153) Hospital	Therapeutic – oral antimicrobial	Both women and men	Multiple types of UTI including complicated UTI	Yes, EAU guideline	Not required	Not regarded as subset of complicated UTI, and defined separately	Based on host factors only	Not required	Required, no cut-off specified

Supplementary Table 1: Continued

Study	Design & setting	Intervention	Population	Type of UTI	Refers to guideline	Symptoms	Acute pyelonephritis	Complicated UTI	Pyuria	Positive urine culture & cut-off
Gágyor 2021	Experimental (n = 398) Primary care or outpatient	Prophylactic – other	Women	Acute cystitis	No	Required	-	-	Not required	Not required
Harding 2022	Experimental (n = 240) Primary care or outpatient	Prophylactic – methenamine	Women	UTI - phenotype not specified	Yes, Public Health England (clinical practice guideline)	Required	-	-	Not required	Not required
Jansaker 2019	Experimental (n = 368) Primary care or outpatient	Therapeutic – oral antimicrobial	Women	Acute cystitis	No	Required			Not required	Not required
Kaye 2019	Experimental (n = 456) Hospital	Therapeutic – intravenous antimicrobial	Both women and men	Complicated UTI	No	Required	Not regarded as subset of complicated UTI, and defined separately	Based on both host factors and systemic involvement	Required, either positive leukocyte esterase or > 10 leukocytes per hpf	Not required

Supplementary Table 1: Continued

Study	Design & setting	Intervention	Population	Type of UTI	Refers to guideline	Symptoms	Acute pyelonephritis	Complicated UTI	Pyuria	Positive urine culture & cut-off
Kohno 2021	Experimental (n = 83) Hospital	Therapeutic – intravenous antimicrobial	Both women and men	Complicated UTI	No	Required	Regarded as subset of complicated UTI, and defined separately	Based on both host factors and systemic involvement	Required, either positive leukocyte esterase or > 10 leukocytes per hpf or mm^3	Required, cut-off 10^5 CFU/mL
Koradia 2019	Experimental (n = 81) Primary care or outpatient	Prophylactic – cranberry	Women	Acute cystitis	Yes, EAU guideline	Required	-	-	Not required	Required, cut-off 10^3 CFU/mL
Li 2021	Experimental (n = 208) Primary care or outpatient	Therapeutic – oral antimicrobial	Both women and men	Multiple types of UTI including complicated UTI	No	Required	Only complicated UTI is investigated, acute pyelonephritis is not mentioned	Based on both host factors and systemic involvement	Required, > 10 leukocytes/µl or > 5 per hpf	Required, cut-off 10^5 CFU/mL

Supplementary Table 1: Continued

Study	Design & setting	Intervention	Population	Type of UTI	Refers to guideline	Symptoms	Acute pyelonephritis	Complicated UTI	Pyuria	Positive urine culture & cut-off
Lojanapiwat 2019	Experimental (n = 289) Hospital	Therapeutic – oral antimicrobial	Both women and men	Complicated UTI	No	Required	Regarded as subset of complicated UTI, and defined separately	Based on both host factors and systemic involvement	Conditionally required	Not required
Mir 2019	Experimental (n = 230) Hospital	Therapeutic – intravenous antimicrobial	Both women and men	Complicated UTI	Yes, FDA guideline	Required	Regarded as subset of complicated UTI, but not defined separately	Based on both host factors and systemic involvement	Not required	Required, cut-off 10^5 CFU/mL
Mirzaei 2019	Experimental (n = 30) Primary care or outpatient	Prophylactic – other	Women	Acute cystitis	No	Required	-	-	Not required	Required, cut-off 10^3 CFU/mL
Montelin 2019	Observational (n = 171) Primary care or outpatient	Therapeutic – oral antimicrobial	Men	Acute cystitis	No	Required	-	-	Not required	Required, cut-off 10^3 CFU/mL

Supplementary Table 1: Continued

Study	Design & setting	Intervention	Population	Type of UTI	Refers to guideline	Symptoms	Acute pyelonephritis	Complicated UTI	Pyuria	Positive urine culture & cut-off
Nestler 2021	Experimental (n = 173) Primary care or outpatient	Prophylactic – other	Women	UTI - phenotype not specified	No	Required	-	-	Not required	Required, cut-off 10^3 CFU/mL
Overcash 2020	Experimental (n = 22) Hospital	Therapeutic – oral antimicrobial	Women	Acute cystitis	No	Required	-	-	Conditionally required, either positive leukocyte esterase or at least 10 leukocytes/ mm^3	Not required
Overcash 2019	Experimental (n = 31) Hospital	Therapeutic – oral antimicrobial	Women	Acute cystitis	Yes, FDA guideline	Required	-	-	Required, positive leukocyte esterase	Not required
Pierotti 2020	Observational (n = 306) Hospital	Therapeutic – intravenous antimicrobial	Both women and men	Bacteraemic / febrile UTI	No	Not required	-	-	Not required	Not required
Radulescu 2020	Experimental (n = 120) Primary care or outpatient	Prophylactic – cranberry	Women	Acute cystitis	Yes, EAU guideline	Required	-	-	Not required	Not required

Supplementary Table 1: Continued

Study	Design & setting	Intervention	Population	Type of UTI	Refers to guideline	Symptoms	Acute pyelonephritis	Complicated UTI	Pyuria	Positive urine culture & cut-off
Ryanto 2019	Observational (n = 152) Hospital	Therapeutic – intravenous antimicrobial	Both women and men	Multiple types of UTI including complicated UTI	No	Not required	Acute pyelonephritis is mentioned, but not defined	Complicated UTI is mentioned, but not defined	Not required	Not required
Safwat 2019	Experimental (n = 389) Primary care or outpatient	Prophylactic – other	Men	UTI – phenotype not specified	No	Not required	–	–	Not required	Required, no cut-off specified
Sagan 2020	Experimental (n = 80) Hospital	Therapeutic – intravenous antimicrobial	Both women and men	Complicated UTI	No	Required	Not regarded as subset of complicated UTI, and defined separately	Based on host factors only	Required, either positive leukocyte esterase or > 10 leukocytes per mm^3 or hpf	Not required
Sashidhar 2022	Experimental (n = 50) Primary care or outpatient	Therapeutic – oral antimicrobial	Both women and men	Acute cystitis	No	Required	–	–	Required, method not specified	Not required
Senard 2020	Observational (n = 50) Hospital	Therapeutic – intravenous antimicrobial	Men	Bacteraemic / febrile UTI	Yes, French clinical practice guideline	Required	–	–	Not required	Required, no cut-off specified

Supplementary Table 1: Continued

Study	Design & setting	Intervention	Population	Type of UTI	Refers to guideline	Symptoms	Acute pyelonephritis	Complicated UTI	Pyuria	Positive urine culture & cut-off
Sharara 2020	Observational (n = 186) Hospital	Therapeutic – intravenous antimicrobial	Both women and men	Acute pyelonephritis	No	Required	Defined separately, not mentioned whether part of complicated UTI	-	Required, > 10 leukocytes per hpf	Required, cut-off 50000 CFU/mL
Sojo-Dorado 2022	Experimental (n = 143) Hospital	Therapeutic – intravenous antimicrobial	Both women and men	Bacteraemic / febrile UTI	No	Conditionally required	-	-	Conditionally required, either positive leukocyte esterase or > 10 leukocytes/mm^3	Required, no cut-off specified
Sorli 2019	Observational (n = 33) Hospital	Therapeutic – intravenous antimicrobial	Both women and men	Multiple types of UTI, including acute pyelonephritis	Yes, CDC guideline	Required	Defined separately, not mentioned whether part of complicated UTI	-	Not required	Required, cut-off 10^5 CFU/mL

Supplementary Table 1: Continued

Study	Design & setting	Intervention	Population	Type of UTI	Refers to guideline	Symptoms	Acute pyelonephritis	Complicated UTI	Pyuria	Positive urine culture & cut-off
Stalenhoef 2019	Experimental (n = 63) Primary care or outpatient	Prophylactic – antimicrobial	Both women and men	UTI – phenotype not specified	No	Required	-	-	Required, method not specified	Required, cut-off 10^3 CFU/mL
Tehrani 2021	Experimental (n = 59) Hospital	Therapeutic – oral antimicrobial	Both women and men	Acute pyelonephritis	No	Required	Defined separately, not mentioned whether part of complicated UTI	-	Required, > 10 leukocytes per hpf	Not required
Ten Doesschate 2019	Observational (n = 40) Primary care or outpatient	Therapeutic – oral antimicrobial	Both women and men	Multiple types of UTI including bacteraemic / febrile UTI	No	Required	-	-	Not required	Required, cut-off 10^4 CFU/mL
Ten Doesschate 2021	Experimental (n = 97) Hospital	Therapeutic – oral antimicrobial	Women	Complicated UTI	No	Required	Regarded as subset of complicated UTI, but not defined separately	Febrile UTI is considered a complicated UTI	Not required	Required, cut-off 10^4 CFU/mL

Supplementary Table 1: Continued

Study	Design & setting	Intervention	Population	Type of UTI	Refers to guideline	Symptoms	Acute pyelonephritis	Complicated UTI	Pyuria	Positive urine culture & cut-off
Tseng 2020	Experimental (n = 26) Primary care or outpatient	Prophylactic – other	Women	UTI – phenotype not specified	No	Required	–	–	Conditionally required, either positive leukocyte esterase or > 5 cells/hpf	Conditionally required, cut-off 10^4 CFU/mL
Tullos 2020	Observational (n = 180) Hospital	Therapeutic – intravenous antimicrobial	Both women and men	UTI – phenotype not specified	No	Not required	–	–	Not required	Required, no cut-off specified
Wagenlehner 2019	Experimental (n = 609) Hospital	Therapeutic – intravenous antimicrobial	Both women and men	Complicated UTI	Yes, FDA guideline	Required	Regarded as subset of complicated UTI, and defined separately	Based on both host factors and systemic involvement	Required, either positive leukocyte esterase or > 10 leukocytes per hpf	Not required
Wald-Dickler 2022	Observational (n = 322) Hospital	Therapeutic – oral antimicrobial	Both women and men	Complicated UTI	No	Required	Regarded as subset of complicated UTI, but not defined separately	Based on both host factors and systemic involvement	Not required	Required, no cut-off specified

Abbreviations: UTI = urinary tract infection, CFU = colony-forming units; CDC = Centers for Disease Control and Prevention; IDSA = Infectious Diseases Society of America; EAU = European Association of Urology; FDA = Food and Drug Administration; hpf = high-power field.