

Microbial Threshold Guidelines for UTI Diagnosis: A Scoping Systematic Review

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Abstract: Given the growing impact of antimicrobial resistance, improvements in diagnosis and treatment of the most common outpatient infection, urinary tract infection (UTI), are of great interest to stakeholders. Regulatory authorities have long accepted a microbial threshold of 10^5 CFU/mL as the standard for diagnosing UTI based on standard urine cultures. However, microbial thresholds considered clinically relevant remain in dispute. The aim of this systematic scoping review is to assess the evidence supporting a threshold of 10^5 CFU/mL, to review microbial threshold guidelines, and highlight knowledge gaps in the diagnosis of UTI. A total of 36 guidelines containing 144 recommendations were identified with 64% of guidelines ($n = 23$) and 58% of recommendations ($n = 83$) published in the last six years (2016–2023). Recommendations have changed over time and across variables including the geographical location of the guideline, urine specimen collection method, patient sex, and category of UTI. Guidelines uniformly agreed with suprapubic needle specimen collection; however, there was no consensus for midstream collected urine samples. Guideline microbial thresholds for clinical UTI diagnosis were higher for women at average risk (10^5 CFU/mL) than for men (10^2 to 10^5 CFU/mL) and high-risk patients (10^2 to 10^4 CFU/mL). Guidelines relied heavily on 48 research articles from 20 author teams published between 1956 and 2019 and recommendations frequently cited 23 research articles by 15 author teams published between 1956 and 2013. Evidence supporting 10^5 CFU/mL threshold originated in the mid-1950s from 4 research articles, whereas 18 frequently cited peer-reviewed publications focused their research on the clinical relevance of lower thresholds (10^1 to $<10^5$ CFU/mL). This review demonstrates a lack of consensus for urine culture microbial threshold recommendations for the clinical diagnosis of UTI. Guidelines are primarily based upon sparse and dated evidence. Additional research is needed to inform clinically meaningful diagnostic microbial thresholds in the diagnosis of UTI.

Keywords: urinary tract infection, guideline, microbial, diagnostic threshold, uropathogen, scoping systematic review

Introduction

Urinary tract infections (UTIs) are one of the most common infections affecting persons of all ages.¹ Approximately 20–30% of these UTIs are nosocomial, with the remainder being community-acquired.¹ In 2019, prior to the global pandemic, nearly 30.9 million UTI events were reported from US households, resulting in \$11.45 billion in expenditures.² Considering inpatient UTI treatment and worldwide data, the actual cost of UTI, including healthcare costs, lost wages, and morbidity and mortality, are substantial.^{2–8} Given the prevalence and high costs of UTIs, and the growing impact of antimicrobial resistance worldwide, improvements in diagnosis and treatment are of great interest to stakeholders, including clinicians and patients, reimbursement organizations, and policymakers. Many US regulatory agencies believe there are clinically accepted microbial thresholds, based on standard urine culture (SUC) results, for diagnosing or surveying UTIs.^{9,10} However, clinically accepted microbial thresholds for diagnosing UTI from SUC results are subject to vigorous debate.^{11–13}

UTIs are classified clinically as either uncomplicated (uUTI) or complicated (cUTI). By traditional definitions, uUTIs occur in individuals who do not have any additional risk factors predisposing them to complications.⁸ In contrast, cUTIs

are associated with factors that predispose the individual to a higher likelihood of treatment failure and poor outcomes, such as persistence, recurrence, or increasing severity of the UTI such as sepsis requiring hospitalization and/or resulting morbidity and mortality.^{6,14} These predisposing factors can include structural and functional abnormalities of the urinary tract (eg, obstruction or retention, catheter or foreign body, renal tract calculi, pelvic radiation and surgical alterations), metabolic (eg, diabetes, renal impairment), or immunologic (eg, medical or inherited immune suppression). Likewise, certain patient populations, including the elderly and pregnant patients, are at a higher risk for complications related to UTIs, including sepsis and preterm delivery, respectively. Those with multidrug resistance and recurrent UTI (two symptomatic episodes within six months or at least three symptomatic episodes within 12 months) are also more complicated to diagnose and treat. Additionally, in men, all UTIs are considered cUTIs because of the inherent protective factors normally found in the male urinary tract anatomy.

Newer definitions of uUTI and cUTI, termed “acute simple cystitis” and “acute complicated UTI”, are based on the presumed extent of infection and the severity of illness.¹⁵ Infections confined to the bladder define simple cystitis, whereas signs and symptoms indicating upper urinary tract involvement thus spread beyond the bladder define acute complicated UTI. This schema was developed because it more accurately reflects clinical practice and antimicrobial stewardship principles in infectious disease. This is especially relevant for patients with UTI in the presence of traditional complicating factors who may not show signs of systemic infection but are considered to represent cases of cUTI using the traditional classification system and thus automatically receive longer therapy with more broad spectrum agents. At the same time, patients with traditional complicating factors are recognized as having a higher risk of upper tract and/or systemic infection and are thus monitored more closely, with a low threshold for escalating to management as cases of acute cUTI. For the purpose of this review, guideline descriptions of UTI recommendations satisfying either the traditional or the newer definition were considered a cUTI (Table 1).

We developed a scoping systematic review protocol, a priori, to review the available guideline information and the evidence referenced to justify the recommendations. This review aimed to identify a “generally accepted threshold” level for positive SUC categorized by UTI classification (eg, uUTI or cUTI), region, year, specimen collection method, diagnosis, and patient sex. Since the clinical diagnosis of simple cystitis is frequently based on a positive chemical urine dipstick result, without requiring microscopy or species identification, the importance of standardizing thresholds is most important for cUTI, where bacterial identification and antibiotic sensitivity reporting are important in the treatment

Table 1 cUTI Definition Used for Classification in This Review

Risk Factors and Examples of cUTI	References
* UTIs in the elderly due to increased risk associated with comorbidities and immunocompromised state	Sabih A, Leslie SW. <i>Complicated Urinary Tract Infections</i> . [Updated 2023 Jan 18]. In: <i>StatPearls</i> [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Available from: https://www.ncbi.nlm.nih.gov/books/NBK436013/ Accessed June 5, 2023. ¹⁴
* UTIs in patients with anatomic or functional pathology affecting the urinary tract, such as obstruction, hydronephrosis, renal tract calculi, or colovesical fistula	
* UTIs in patients with an immune-compromised state, such as steroid use, post-chemotherapy, diabetes, or HIV	
* UTIs in males	
* UTIs occurring after instrumentation, nephrostomy tubes, ureteric stents, suprapubic tubes, or Foley catheters	
* UTIs in renal transplant patients	
* UTIs in patients with impaired renal function	
* UTIs following prostatectomy or radiotherapy	

(Continued)

Table 1 (Continued).

Risk Factors and Examples of cUTI	References
* UTIs in patients with a history of recurrent UTIs	Wagenlehner FME, Johansen TEB, Cai T et al. Epidemiology, definition and treatment of complicated urinary tract infections. <i>Nat Rev Urol.</i> 2020;17(10):586–600. ⁶
* Recurrent UTIs defined as at least two symptomatic episodes within six months or at least three symptomatic episodes within 12 months	Medina M, Castillo-Pino E. An introduction to the epidemiology and burden of urinary tract infections. <i>Ther Adv Urology.</i> 2019;11:1756287219832172. ³
* UTIs caused by atypical microorganisms or multi-drug-resistant microorganisms. Typical UTI-causing microorganisms include <i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , several species within the Enterobacteriaceae family (<i>Proteus</i> and <i>Klebsiella</i>), and a few gram-positive bacteria, such as <i>Staphylococcus saprophyticus</i> and <i>Enterococcus faecalis</i> , as well as fungi, such as <i>Candida</i> species	Price TK, Hilt EE, Dune TJ, Mueller ER, Wolfe AJ, Brubaker L. Urine trouble: should we think differently about UTI? <i>Int Urogynecol J.</i> 2018;29(2):205–210. ¹⁶
* UTIs that have possibly extended beyond the bladder (ie, UTI with fever or other systemic symptoms, suspected or documented pyelonephritis, and UTI with sepsis or bacteremia)	Gupta K. Acute complicated urinary tract infection (including pyelonephritis) in adults. [Updated 2023 May]. In: <i>UpToDate</i> [Internet]. The Netherlands: Wolters Kluwer. Available from: https://www.uptodate.com/contents/acute-complicated-urinary-tract-infection-including-pyelonephritis-in-adults Accessed June 5, 2023. ¹⁵

algorithm.^{11,17} Thus, we also aimed to determine if consensus recommendations exist, to highlight knowledge gaps in the laboratory diagnosis of UTI, and evaluate for consistency between current clinical guidelines and practice for adult UTI diagnosis, especially for cUTI.

Materials and Methods

Protocol

A microbiologist/immunologist (LKSP) with experience in literature searches and systematic reviews developed an a priori protocol using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) and PRISMA extension guides.^{18,19} The research team discussed, revised, and finalized the protocol before conducting the literature search for clinical guidance and practice documents for microbial thresholds for UTI diagnosis based on SUC. The final review protocol was not registered with PROSPERO (<https://www.crd.york.ac.uk/PROSPERO>) because this register does not currently include scoping reviews. The authors will share the final protocol upon request.

Eligibility Criteria

Clinical guidance documents were defined as publications that inform clinicians of suggested or required microbial thresholds, with or without other conditions, used to determine if a human patient has a UTI. Clinical guidance documents, clinical practice guidelines, consensus statements, or similar records regarding UTI diagnosis with microbial thresholds for positive SUC were considered eligible. For this scoping review, both peer-reviewed published documents and “gray” guidance documents not published through the peer-review process were eligible for inclusion if they were considered final at the time of publication or posting.^{18,20} Examples of non-peer-reviewed guidelines include guidelines published on professional society websites and government-issued guidance documents. A thirty-year time period was selected to provide adequate internet access availability and determine what if any changes occurred over time. Files were collected from any geographical region but were required to be in English, published from January 1992 through January 2023, and focused on adults. Records that focused on asymptomatic bacteriuria were excluded. Only symptomatic UTI recommendations were collected if a publication included symptomatic and asymptomatic UTI microbial threshold guidance.

Information Sources

Multiple information sources for clinical guidance documents were searched to find as many eligible records as possible. Published and “gray” guidance documents were searched for in electronic databases and on key stakeholder websites in areas of 1) urology, urogynecology, infectious disease, epidemiology, and microbiology societies, 2) regulatory or governing agencies, 3) clinical diagnostic laboratory societies, and 4) other potential stakeholders, such as certifying clinical or laboratory agencies. All potentially relevant supplementary documents cited in the retrieved documents were also acquired. The PROSPERO and Cochrane Reviews registry searches were conducted on January 24, 2023, and the PubMed search on January 25, 2023. The supplemental citation and organizational website searches were completed on February 9, 2023. Three authors were contacted for out-of-print records but did not respond.

Search Strategy

The search strategy developed for this review used the population, intervention, control, and outcome (PICO) and peer review of electronic search strategies (PRESS) checklists to ensure the strategy was appropriate for this systematic scoping review.²¹ The draft Boolean search strategy employed to search peer review published journal databases included medical subject headings (MeSH) terms and parameters for ((UTI OR “urinary tract infection” OR bacteriuria) AND (guidelines OR consensus OR evaluation OR surveillance) NOT (pediatric OR child)) to determine the type of literature returned. Additional refined searches ran a variety of additional term items such as (diagnostic OR diagnosis OR definition), (threshold OR cutoff), (“colony forming unit” OR colony OR CFU OR “urine culture”), (microbial OR microbe OR bacteria), etc., to calibrate the search parameters. This calibration process was tailored using five documents, one of which was not a guidance document, from different sources, years, regions, and abstract styles. Once the search parameters retrieved the test guidance documents, the calibration was complete. The final calibrated parameter search is in Table 2. Applied filters for the English language, human species, and years (1992–2023) defined limits on the search. Internet searches for guidance documents included a similar keyword strategy and met the same inclusion and exclusion criteria as the database searches.

Study Records

Final search results were exported to Microsoft Excel (Redmond, WA), a searchable electronic database. Each search was stored as an individual file to maintain its integrity as a source document.

Selection of Source Evidence

Removal of duplicates using digital object identifier (DOI), publication dates, and author list occurred prior to screening. Two reviewers (LKSP and DW) independently screened each record using identical screening forms containing the reference data and a link to the abstract. The reviewers screened for uniqueness and for eligibility based on the abstract. Using the screening form, reviewers documented any relevant comments, if the record was eligible for further review, the reason for exclusion, or if additional information was required. The screening files were combined and sorted for

Table 2 Final Calibrated Parameter Search for This Review

Parameter Search for Guidelines containing Diagnostic Microbial Thresholds for Urinary Tract Infection
((guidelines [Title/Abstract] OR consensus [Title/Abstract] OR evaluation [Title/Abstract] OR surveillance [Title/Abstract] OR perspective [Title/Abstract] OR recommendation [Title/Abstract]) NOT (pediatric [Title/Abstract] OR children[Title/Abstract] OR child [Title/Abstract]) AND (infection[Title/Abstract]) AND (“urinary tract” [All Fields]) AND (diagnosis [MeSH Terms] OR diagnosis [All Fields] OR diagnostic [All Fields] OR diagnostical [All Fields] OR diagnostically[All Fields] OR diagnostics[All Fields] OR diagnosable [All Fields] OR diagnosi [All Fields] OR diagnosis [MeSH Terms] OR diagnosis [All Fields] OR diagnose [All Fields] OR diagnosed [All Fields] OR diagnoses [All Fields] OR diagnosing[All Fields] OR diagnosis [MeSH Subheading] OR definite [All Fields] OR definitely [All Fields] OR definition [All Fields] OR definitional[All Fields] OR definitions [All Fields] OR definitive [All Fields] OR definitively[All Fields] AND (review [Publication Type] OR ‘review literature as topic’ [MeSH Terms] OR review [All Fields]) AND (humans [MeSH Terms]) AND (english [Language]) AND (1992/01/01:2023/01/31[Date – Publication]))

examination. The reviewers discussed all preliminary eligibility screening discrepancies, and the final decision was documented in the combined reviewer screening file. Papers with preliminary screening discrepancies were ordered and read in full by both reviewers.

Data Charting

Prior to drafting the systematic review protocol, researchers developed and refined a charting form based on previously identified guidelines. Once finalized, the charting form could capture all potentially pertinent information.

The two reviewers shared each record and the Excel charting form electronically via Zoom screen (San Jose, CA). The reviewers worked in tandem and agreed upon data extraction from the record prior to charting the data and saving. Any discrepancies were discussed and the guideline in question was re-read by the reviewers, and data were cited and discussed prior to inclusion or exclusion in the charting file. The charting file format was not revised during the review, and once complete, the data set was locked and dated.

Data Items

Data variables extracted verbatim included type of UTI, microbial threshold, first author, publication year, information source, and publication URL. Other data variables summarized included additional conditions used with the microbial threshold to validate a UTI diagnosis, specimen collection method, patient sex, type of patient (ie, spinal cord injury, institutionalized, etc.), and geographical region. Patient sex was categorized as “both” when not explicitly mentioned in the record. The current definition of uncomplicated versus complicated UTI enabled the sorting of UTI as a separate classification system for data simplification.^{6,14,15} For this study, a UTI was considered complicated when the individual had one or more risk factors that predispose the individual to a higher treatment failure or poor outcomes or possibly extended beyond the bladder, see Table 1.^{3,6,14–16} In addition, for this review, catheter associated UTI (CAUTI), a subset of cUTI, was determined by either guideline author designation or by guideline descriptors indicating catheterization and the presence of symptoms or signs compatible with UTI with no other identified source of infection along with positive microbial identification. Data for cUTI and uUTI were included; however, this review focused primarily on the diagnostic microbial thresholds for non-CAUTI cUTI.

Critical Appraisal of Individual Sources of Evidence

Since all clinical guidance documents were presumed to be based on the best evidence, the reviewers did not perform a critical appraisal of the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) Scale as part of the eligibility criteria.²² A review of the evidence cited by guidelines was conducted to determine which references were most frequently used to justify microbial threshold recommendations.

Synthesis of Results

Key variable data were grouped and summarized by text, table, and figures. The level of the microbial threshold recommended for UTI diagnosis was the priority outcome. Secondary priorities included the number of guidelines, geographic location, changes in recommendations over time, and changes in other key variables.

Results

Summary of Quantity and Basic Characteristics of the Guidelines Included in the Review

Of the 10,312 initial results, 833 met inclusion criteria for screening. Two reviewers independently conducted abstract screenings resulting in 229 records selected for retrieval, 129 from databases and 100 from elsewhere. From these, one from the databases and ten from elsewhere, a total of 11 could not be retrieved due to lack of public accessibility or citation not available for purchase or review. Thirty papers could not be assessed by the reviewers using only abstracts and were included in the retrieval total for full review. Reviewers completed protocol eligibility assessments and excluded another 182 (112 from the databases set and 70 from elsewhere). The reasons for exclusion were that the document was not a guideline (n = 36), the document was a duplicate (n = 24), the document contained no microbial thresholds for UTI diagnosis (n = 109), the

microbial thresholds were for surveillance rather than diagnosis ($n = 6$), or the document was in a language other than English ($n = 7$). Only six guidelines required additional scrutiny by the reviewers to determine recommendation eligibility. The eligibility assessment resulted in the final inclusion of 16 records from databases and registries and 20 records from organizational websites and citation searches for uUTI and cUTI guidelines (Figure 1).¹⁸

A total of 36 eligible guidelines and 144 microbial threshold clinical recommendations from over 30 years were collected.^{1,9,12,13,23–54} All microbial threshold recommendations specifically mentioned patient symptoms as part of the condition being diagnosed. The signs and symptoms collected for each recommendation resulted in a large variety of both broad and vague sets of conditions accompanying each threshold. There were 21 guidelines with 47 specific uUTI microbial threshold recommendations, whereas cUTIs had 29 guidelines and 97 recommendations. The cUTI recommendations were subdivided into 22 CAUTI recommendations and 75 other non-CAUTI recommendations. Only 14 guidelines had recommendations for both uUTI and cUTIs and 2 guidelines were dedicated to CAUTI. Three guidelines discussed candiduria thresholds. Details of the 75 recommendations for cUTI diagnostic microbial thresholds, excluding CAUTI recommendations, can be found in [Supplemental Table 1](#). Recommendation details for uUTI and CAUTI can be found in [Supplemental Information](#) pages, [Supplemental Figures 1](#) and [2](#), [Supplemental Tables 2](#) and [3](#).

Lack of Microbial Threshold Consensus Between and Within Geographical Regions

Microbial threshold consensus was lacking for cUTIs within and between geographical regions, see [Figure 2](#). No guidelines with microbial thresholds in English originated from the Middle East region. A single guideline from South America and two guidelines from Australia could not provide a consensus microbial threshold recommendation. Three guidelines containing 11 recommendations came from the Asian region. North America had 12 guidance documents with 40 cUTI recommendations, whereas Europe had 9 with 21 recommendations. Both regions recommended at least five different microbial thresholds (range: None to 10^5 CFU/mL) for a variety of cUTI conditions and collection methods. See [Supplemental Table 1](#) for more guideline specific details.

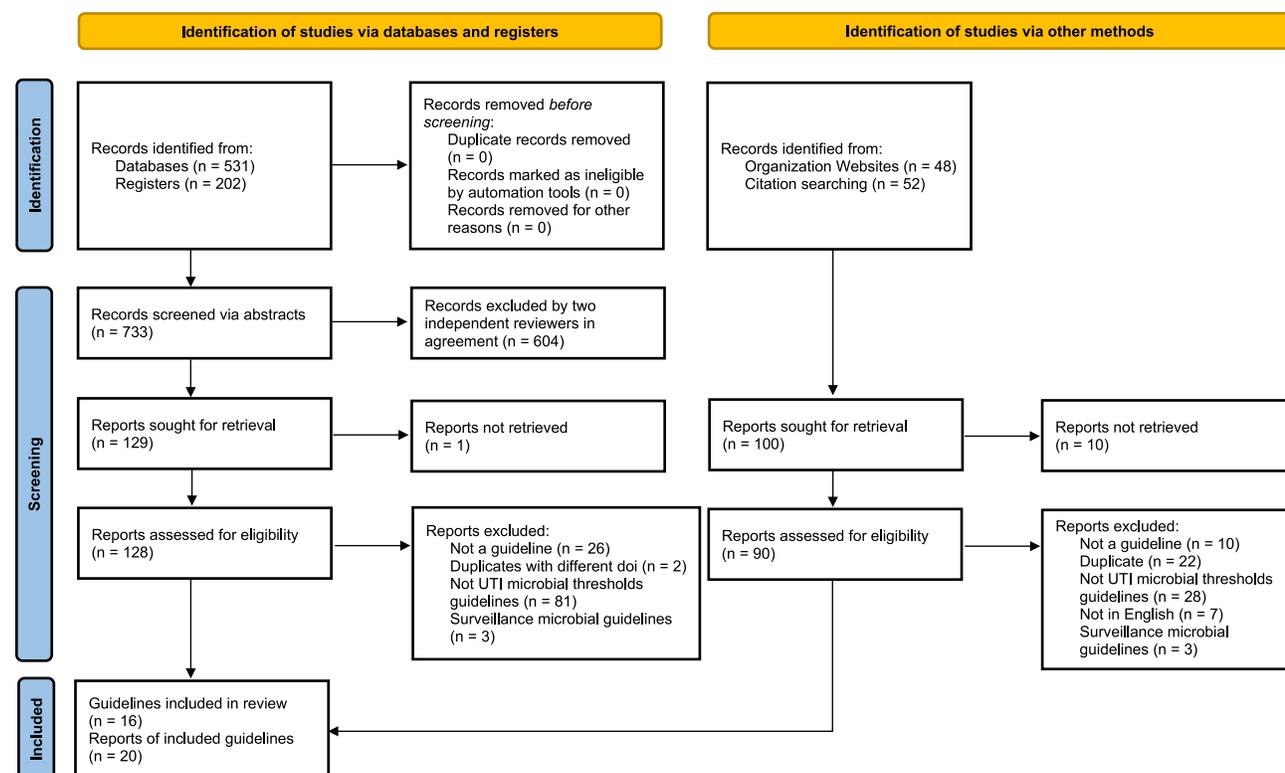


Figure 1 PRISMA flow diagram for this UTI guideline scoping review.

Notes: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. Creative Commons. For more information, visit: <http://www.prisma-statement.org/>.

Complicated UTI Diagnostic Microbial Threshold Recommendations by Geographical Region

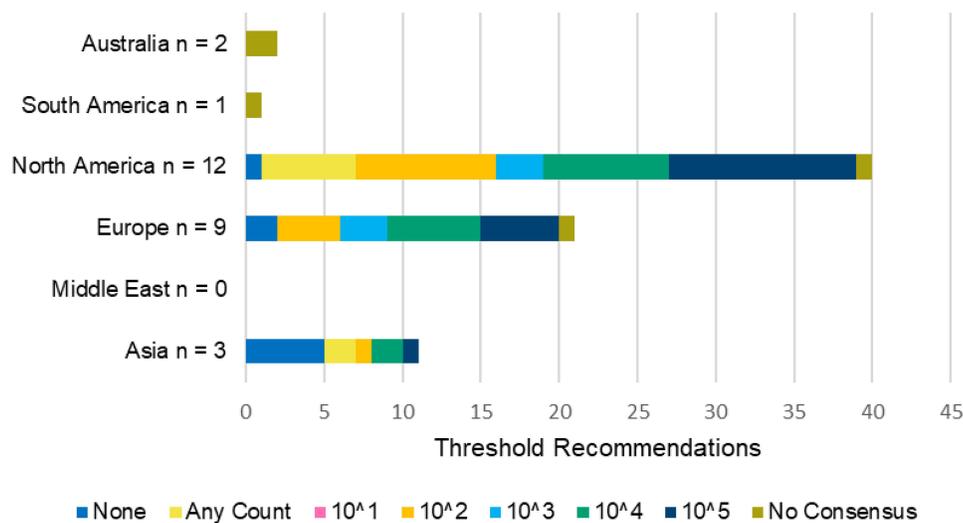


Figure 2 Complicated UTI (cUTI) microbial threshold recommendations by geographical region; CAUTI not included. The vertical axes indicate the region and number of guidelines. The horizontal axes indicate the number of recommendations. Guidelines often included more than one recommendation. Microbial thresholds in CFU/mL are indicated by color (none = navy blue, any count = yellow, 10¹ = pink, 10² = orange, 10³ = light blue, 10⁴ = green, 10⁵ = Oxford blue, and no consensus = khaki). Definition of cUTI used is outlined in Table 1.

Bacterial Threshold for cUTI Changes Over the 30-Year Period

Guidelines and recommendations were evaluated by quartiles to thoroughly view potential changes over time (Figure 3). Each quartile period showed a range of multiple threshold levels. More guidelines for cUTI were published in the most recent period, from 2016 to 2023 (n = 17), than in the prior 24 years combined, from 1992 to 2015 (n = 10). Guidelines from 2016 to 2023 contained 44 recommendations ranging from any count to 10⁵ CFU/mL to no consensus. The largest change in recommendations to 10² and 10³ was observed during this period. The 1992–1999 quartile had the second most

Complicated UTI Diagnostic Microbial Threshold Recommendations Over Time

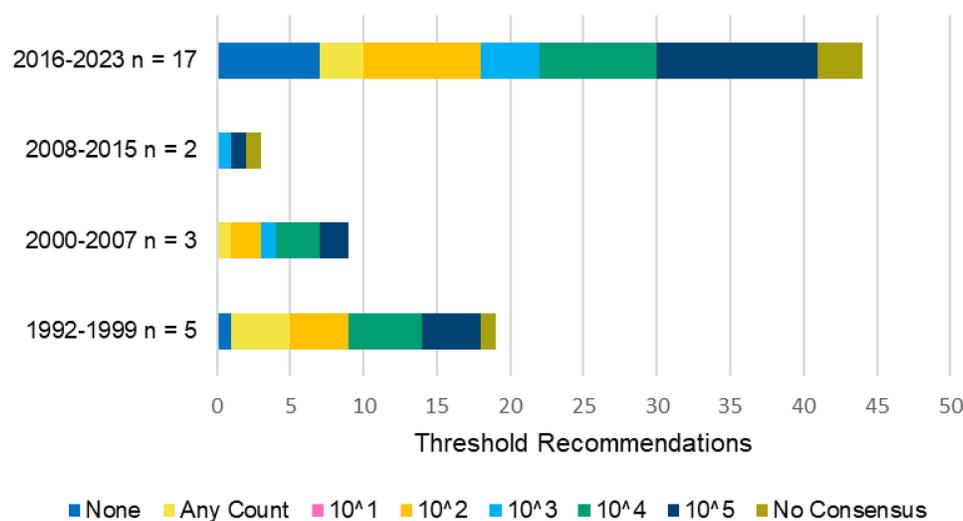


Figure 3 Complicated UTI (cUTI) diagnostic microbial threshold recommendations by time period; CAUTI not included. The vertical axes indicate the eight-year time periods and the number of guidelines. The horizontal axes indicate the total recommendations from all guidelines. Microbial thresholds in CFU/mL are indicated by color (none = navy blue, any count = yellow, 10¹ = pink, 10² = orange, 10³ = light blue, 10⁴ = green, 10⁵ = Oxford blue, and no consensus = khaki).

published guidelines ($n = 5$) and contained 19 recommendations with the same range of thresholds as more recent publications. The fewest publications occurred from 2008 to 2015, two guidelines with three recommendations, and from 2000 to 2007, three guidelines with nine recommendations. During the 30-year period, there were five cUTI recommendations that were unable to provide a consensus recommendation.

Differences in Bacterial Thresholds for Different cUTI Diagnoses

The analysis focused on unspecified cUTI (other) diagnosis as well as two specific diagnoses within the cUTI category, pyelonephritis and recurrent UTI (rUTI). Recommended microbial thresholds for cUTI diagnoses have become more varied over time (Figure 4). Recurrent UTIs (rUTI) and pyelonephritis had large shifts in recommendations in the last 15 years including no threshold, 10^2 , 10^3 , 10^5 CFU/mL, and unable to provide a recommendation. The diagnosis thresholds for pyelonephritis cUTI for the first 15 years recommended 10^4 CFU/mL ($n = 3$). More recent guidelines, 2008–2023, published 11 recommendations; five (45.5%) used 10^4 and three (27.3%) used 10^5 CFU/mL. Three others suggested no threshold, 10^2 CFU/mL, or were unable to provide a recommendation for pyelonephritis. Eight guidelines on “other” cUTI diagnoses published 23 recommendations from 1992 to 2007. Similarly, ten guidelines from 2008 to 2023 provided 23 “other” cUTI recommendations. The recommendations from these two time periods lacked consensus but were most similar across time. The biggest shift between the two 15-year periods was the increased recommendations of None (1992–2007 $n = 0$ versus 2008–2023 $n = 5$, 18.5%). Both the first and the last 15-year periods each had one guideline unable to provide a consensus threshold recommendation.

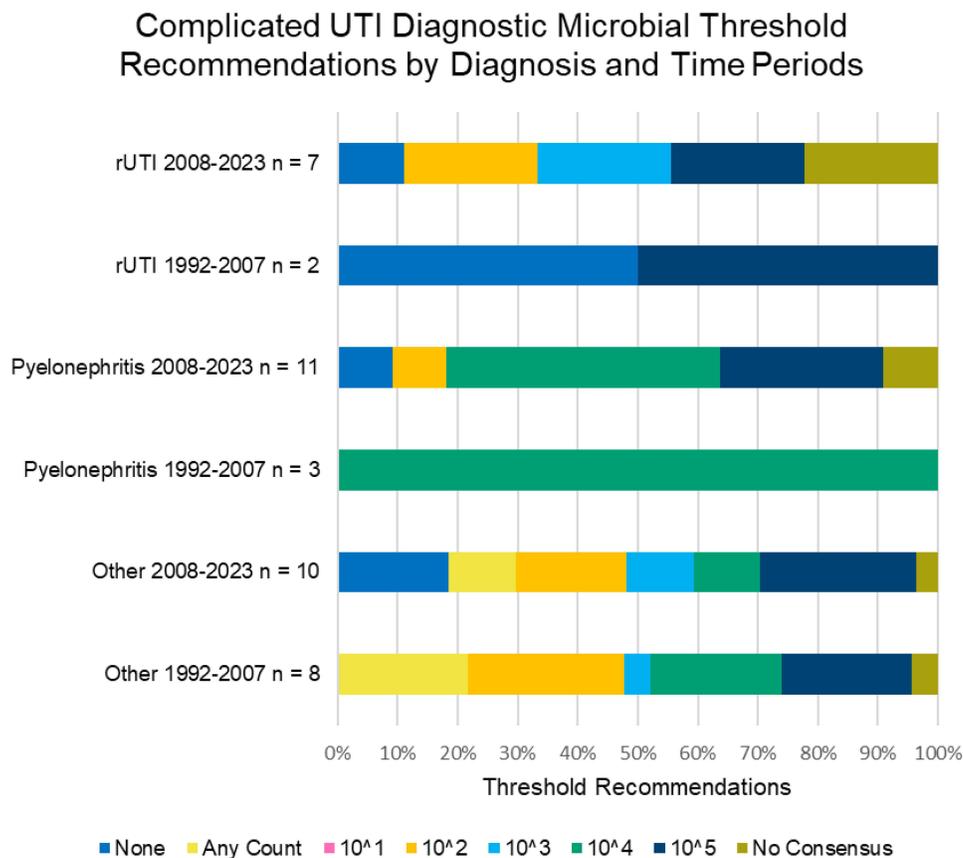


Figure 4 Complicated UTI (cUTI) Diagnostic Microbial Threshold Recommendations by Diagnosis; CAUTI not included - Comparison Between Older and Newer Guidelines. The vertical axes indicate the number of guidelines per diagnosis group/time period. The horizontal axes indicate the percent of the total recommendations for that diagnosis group/time period. Microbial thresholds in CFU/mL are indicated by color (none = navy blue, any count = yellow, 10^1 = pink, 10^2 = orange, 10^3 = light blue, 10^4 = green, 10^5 = Oxford blue, and no consensus = khaki). rUTI = recurrent Urinary Tract Infection.

Bacterial Thresholds Differ Based on Urine Specimen Collection Method

Many guidance documents specified distinct diagnostic thresholds for different specimen collection methods (Figure 5). All four guidelines with recommendations for the suprapubic needle aspirate collection method agreed that any microbial count was clinically relevant for cUTI diagnosis. The four guidelines with recommendations for the intermittent catheterization method agreed on a CFU/mL threshold of 10^2 CFU/mL. Of the seven guideline recommendations for the indwelling catheter collection method, three (43%) were for any count, two (28.5%) were 10^2 , and two (28.5%) were 10^5 CFU/mL. For the in-and-out catheterization method, five guidelines contained seven recommendations, four for 10^2 , two for 10^4 CFU/mL, and one for any count. For this review, the midstream category included guidelines for clean catch, voided, and those that did not specify collection details since this method is the most commonly used. Midstream collection had 27 guidelines with 39 recommendations. The majority of these recommended 10^4 ($n = 11$, 28%) and 10^5 CFU/mL ($n = 13$, 33%).

Bacterial Thresholds for cUTI Differ by Biological Sex

To better understand how patient sex influenced recommendations, we focused on the midstream collection method because it had the largest number of available guideline data points. Recommendations for cUTI and cystitis were stratified by sex and risk (Figure 6). Diagnosis of cUTI cystitis specific to women resulted in one guideline recommendation for a threshold of 10^5 CFU/mL. No guideline recommendations specific to women at additional risk (ie, spinal cord injury (SCI)) were found. Six guideline recommendations specific to men not at additional risk lacked consensus but tended to have lower threshold recommendations with the majority suggesting 10^3 ($n = 3$, 50%) and 10^4 CFU/mL ($n = 2$, 33.3%). Three guidelines for men at high risk for SCI ($n = 2$) and for solid organ transplant ($n = 1$) had 2 recommendations for 10^4 and one each for 10^2 and 10^5 CFU/mL. Of the seven guidelines for diagnosis of average risk patients that did not specify sex, 6 (86%) recommended 10^5 CFU/mL. High-risk patients without specified sex had seven guidelines covering solid organ transplant ($n = 3$), SCI ($n = 2$), intensive care unit (ICU, $n = 1$),

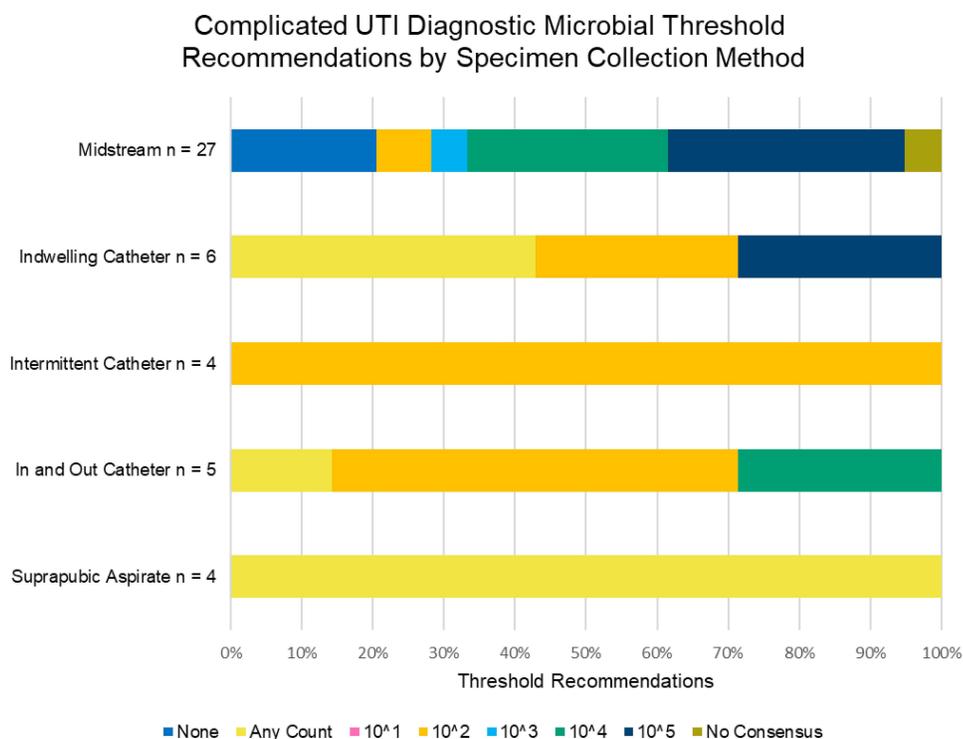


Figure 5 Complicated UTI (cUTI) diagnostic microbial threshold recommendations by specimen collection method; CAUTI not included. The vertical axes indicate the collection method and number of guidelines. The horizontal axes indicate the percent of the total recommendations for each collection method. Microbial thresholds in CFU/mL are indicated by color (none = navy blue, any count = yellow, 10^1 = pink, 10^2 = orange, 10^3 = light blue, 10^4 = green, 10^5 = Oxford blue, and no consensus = khaki). The "indwelling catheter" collection method includes collection via indwelling suprapubic catheter.

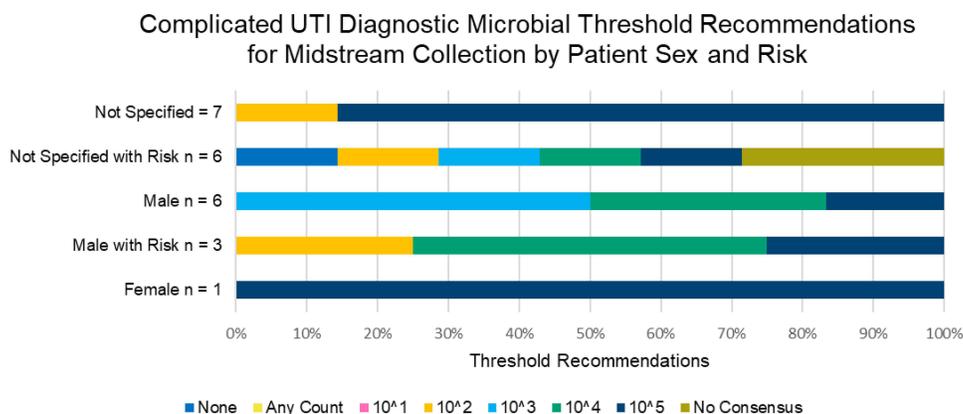


Figure 6 Complicated UTI (cUTI) Midstream Specimen Diagnostic Microbial Threshold Recommendations by Sex and Risk for Cystitis. The vertical axes indicate the sex-risk group and number of guidelines. The horizontal axes indicate the percent of the total recommendations for each group. Microbial thresholds in CFU/mL are indicated by color (none = navy blue, any count = yellow, 10^1 = pink, 10^2 = orange, 10^3 = light blue, 10^4 = green, 10^5 = Oxford blue, and no consensus = khaki). High risk patients in the at risk categories included solid organ transplant, spinal cord injury, intensive care unit, and long-term care patients.

and long-term care (LTC, $n = 1$) analyzed. The recommended thresholds lacked consensus but leaned toward using no or low thresholds as diagnostically important with the exception of the LTC recommendation of 10^5 CFU/mL.

References Cited by the Guidelines as Supporting Evidence for Thresholds

A review of the evidence cited in the guidelines as justification for the microbial recommendations relied heavily on 20 author teams with 48 research articles published between 1956 and 2019.^{26,51,54–99} Of these, 23 papers written by 15 author teams between 1956 and 2013 were the most frequently cited references in the reviewed guidelines.^{26,51,54,55,57,58,60–62,64–67,76–78,81,84–86,88–91} Table 3 details the most frequently cited author teams and their publications. The two most frequently cited references (Hooton et al and Stamm et al)^{58,62} indicated that low bacterial quantification thresholds of 10^2 CFU/mL were highly predictive of UTI in symptomatic patients. In fact, of the 23 references most frequently cited by guidelines, 17 focused on the clinical impact of lower bacterial quantification thresholds (10^1 to $<10^5$ CFU/mL) in symptomatic patients. The four most frequently cited references (Kass and Savage et al)^{64–66,90} justifying the use of 10^5 CFU/mL as a threshold are based on research results in pregnant and pyelonephritis patients published 1956–1967. Guidelines cited other literature as justification for microbial threshold recommendations; however, none of these citations were used by guidelines analyzed in this study.

Discussion

This systematic scoping review demonstrates a lack of consensus across globally reported guidelines relating to clinically relevant thresholds for SUC-based UTI diagnosis. This lack of consensus for both uUTI and cUTI has persisted over 30 years despite the increased number of published guidelines in the last decade. While the most common microbial threshold for symptomatic cUTI recommended in guidelines was 10^5 CFU/mL for voided urine specimens, roughly 67% of guidelines recommended lower thresholds. Guidelines were universally in agreement that a threshold of any bacterial growth should be considered a UTI and treated when considering suprapubic aspirate and $\geq 10^2$ CFU/mL for intermittent catheterization; however, guidelines varied widely when considering indwelling or in-and-out catheterization, voided midstream collections and based on sex or patient risk stratification. In this review, we identified twice as many overall cUTI recommendations for $<10^5$ CFU/mL as those advocating for $\geq 10^5$ CFU/mL. When considering the feasibility of recommendations for the use of lower diagnostic microbial thresholds ($<10^5$ CFU/mL), it is important to consider that not all laboratory techniques can grow low threshold cultures and most do not quantify or report these lower threshold results.^{13,16,23,100–102} While all guidelines reviewed included patient symptoms in the diagnostic criteria, many also included “positive” urinalysis results, such as white blood cell count in the urine, as part of the diagnostic criteria, further increasing variability. The variability in these reports highlights an urgent need for future investigation and standardization of urine testing methods, diagnostic thresholds and clinical definitions of UTI.

Table 3 Quality of Evidence – References Most Frequently Cited as Justification in the Guidelines

Publication/Author Team	Summary	Cited	Total Citations in Study Guidelines
Hooton, Roberts, Cox, Stapleton ⁵⁸	<i>Escherichia coli</i> in midstream urine was highly predictive of acute cystitis even at very low counts (10^2 CFU/mL).	7	18
Hooton, Bradley, Cardenas, Colgan, Geerlings, Rice, Saint, Schaeffer, Tambayh, Tenke, Nicolle ²⁶	2009 IDSA guidelines on diagnosis, prevention, and treatment of CAUTI recommend that in symptomatic patients with indwelling or intermittent catheterization a UTI is present if $\geq 10^3$ CFU/mL of 1 or more bacterial species grow midstream within 48 hours of catheter removal.	6	
Hooton ⁵⁷	The traditional criterion for a positive culture of voided urine (10^5 CFU/mL) is insensitive for bladder infection, and 30 to 50% of women with cystitis have colony counts of 10^2 to 10^4 CFU/mL in voided urine.	2	
Hooton, Stamm ⁵⁵	Overview of the diagnosis and treatment of uncomplicated urinary tract infections in women and men. Microbial threshold level of 10^2 CFU/mL in acute uUTI cystitis and to 10^4 CFU/mL in pyelonephritis are diagnostically more specific and sensitive than the traditional 10^5 CFU/mL cutoff.	2	
Stamm, Counts, Running, Fihn, Turck, Holmes ⁶²	In symptomatic women, 10^2 CFU/mL of coliforms in midstream urine had a high predictive value.	8	14
Stamm, Wagner, Amsel, Alexander, Turck, Counts, Holmes ⁶⁰	Bacteriuria of greater than or equal to 10^5 CFU/mL may be an insensitive diagnostic criterion when applied to symptomatic lower urinary tract infection in voided, catheter, and suprapubic urine.	3	
Stamm, Hooton ⁶¹	Antibiotic treatments and diagnostic criteria, including microbial thresholds, for different types of UTIs are distinct.	2	
Kass ⁶⁴	In approximately 95% of pyelonephritis patients, 10^5 CFU/mL were cultured from voided or catheterized urine.	5	12
Kass ^{66,67}	In most cases, $>10^5$ CFU/mL in urine collected via catheterization indicates the presence of true bacteriuria, that is, of actual multiplication of bacteria within the urinary tract, in pregnancy. Conversely, bacterial colony counts $<10^5$ CFU/mL usually represent contamination upon the collection of the specimen. (Originally published by Kass 1956 ⁶⁶ and reprinted in 2002 ⁶⁷)	4	
Kass ⁶⁵	Based on the $>10^5$ CFU/mL threshold*, 6–7% of pregnant women have bacteriuria in voided urine specimens which leads to pyelonephritis in 40% of those women. *this threshold is based on evidence from a prior publication by Kass ⁶⁶	2	

(Continued)

Table 3 (Continued).

Publication/Author Team	Summary	Cited	Total Citations in Study Guidelines
Nicolle, Ronald, Gupta, Bradley, Colgan, DeMuri, Drekonja, Eckert, Geerlings, Köves, Hooton, Juthani-Mehta, Knight, Saint, Schaeffer, Trautner, Wullt, Siemieniuk, Rice, Schaeffer ^{68–75}	*	1	8
Kunin, White, Hua ⁷⁸ Kunin ⁷⁷	<i>E. coli</i> and <i>Staphylococcus saprophyticus</i> were associated with urinary symptoms and pyuria at 10^2 – 10^4 CFU/mL in clean-catch midstream urine specimens. As bacterial counts increased, so did symptoms and pyuria. Authors concluded this may be an early phase of UTI. Using a clean, freshly voided urine specimen, UTI patients will usually have counts of $>10^5$ CFU/mL of uropathogens. Contamination with commensal microorganisms is usually associated with counts of $<10^3$ CFU/mL. Counts of 10^3 to 10^5 CFU/mL are significant when combined with symptoms and pyuria. Certain bacterial species grow slowly and an appropriate range for significant bacteriuria with these organisms may reach counts of only 10^4 to 10^5 CFU/mL. The tubercle bacillus and systemic fungi grow poorly in urine and are considered significant at any count. Fastidious bacteria require special culture media and will not be detected by routine cultures.	4 2	7
Stark, Maki ⁷⁶	Patients with indwelling catheters that cultured $<10^5$ CFU/mL typically grew $>10^5$ CFU/mL within 3 days of first culture. Concluded catheterized patients are highly susceptible to UTI and low microbial concentrations may be clinically and epidemiologically important.	6	6
Rubin, Shapiro, Andriole, Davis, Stamm ⁵¹	For clinical trial patients testing UTI antimicrobial therapy, proposed using microbial levels of $\geq 10^3$ CFU/mL for acute uncomplicated cystitis, $\geq 10^4$ CFU/mL for pyelonephritis and UTI in men, and $\geq 10^5$ CFU/mL for complicated UTI, in midstream urine specimens, for enrollment.	4	5
Doherty, NIDRR ⁵⁴	Spinal cord injury patients with signs or symptoms should be considered as having a UTI when $\geq 10^2$ CFU/mL is cultured from a catheter-derived specimen, or $\geq 10^4$ CFU/mL is cultured from clean void specimens obtained from males using condom devices. Any detectable count cultured from urine specimens taken from an indwelling catheter should be considered a UTI.	4	4
Sobel ⁸¹	Diagnostic and clinical criteria for candiduria have not been established.	2	4

Lipsky, Ireton, Fihn, Hackett, Berger ⁸⁴	Urine specimens from suprapubic aspiration or urethral catheterization had excellent agreement to clean catch midstream and uncleansed first void specimens. A threshold of $\geq 10^3$ CFU/mL in men is a good criterion for UTI.	3	3
Giesen, Cousins, Dimitrov, van de Laar, Fahey ⁸⁵	A systematic review showed predicting UTI using symptoms with diagnostic thresholds of 10^2 , 10^3 , and 10^5 CFU/mL in clean-catch or catheterized urine specimens were most sensitive at lower microbial levels to rule in presence of a UTI.	3	3
Epp, Larochelle ⁸⁶	10^5 CFU/mL from midstream urine specimens is considered the UTI criterion, but 10^3 CFU/mL is more sensitive and acceptable. Women with growth aside from <i>E. coli</i> and/or persistent hematuria should be evaluated under cystoscopy and imaging.	3	3
Roberts ⁸⁸	Significant UTIs may be associated with counts of $<10^5$ CFU/mL, especially in patients with no other source of infection.	2	3
Hovellius, Mardh, Bygren ⁸⁹	In this study, UTIs with <i>Staphylococcus saprophyticus</i> had a recurrence again in $>50\%$ of subjects, most of whom also had renal associated symptoms. The demonstration of <i>S. saprophyticus</i> in voided urine specimens, even in counts of $<10^4$ bacteria per mL may be a significant finding.	2	2
Savage, Hajj, Kass ⁹⁰	Use of 10^5 CFU/mL in pregnant women may be linked to early labor and delivery.	2	2
Gribble, McCallum, Schechter ⁹¹	The traditional $\geq 10^5$ CFU/mL diagnostic threshold for UTI had an unacceptably low sensitivity for spinal cord injury patients compared to suprapubic aspirations. For gram-positive bacteria, $\geq 10^1$ and $\geq 10^2$ CFU/mL had good sensitivity and specificity. For gram-negative bacteria, $\geq 10^1$ was ideal, but $\geq 10^2$ CFU/mL was sufficient for urine specimens from suprapubic aspiration.	2	2
Platt, Polk, Murdock, Rosner ^{92,93}	*	1	2
Johnson, Stamm ^{94,95}	*	1	2
Naber, Schito, Botto, Palou, Mazzei, Fünfstück, Hofstetter, Brühl, Hoyme ^{96,97}	*	1	2
Fihn, Johnson, Stamm ^{98,99}	*	1	2

Note: *There is no summary because multiple articles were cited only once but came from a frequently cited author and team.

When examining the primary evidence used to justify these guidelines, we found that almost two-thirds (64%) of the 36 guidelines and 144 recommendations were published between 2016 and 2023, yet the evidence cited to justify the recommendations relied heavily on 23 research articles published between 1956 and 2013. This highlights a lack of contemporary research in the area of UTI diagnosis and appropriate treatment thresholds. Although commonly cited, much of the published literature may not be universally generalizable as individual studies include variable populations including asymptomatic, pyelonephritis, or pregnant patients.^{64–66,90} The urine culture threshold of 10^5 CFU/mL suggested in these papers was indicative that significant bacteria were present and unlikely to represent any contamination found in low microbial growth. However, at some point, a UTI positive urine culture of 10^5 CFU/mL became the standard diagnostic threshold, even though the authors specifically stated true bacteriuria could occur at much lower thresholds.^{58,60,67} Over 80% of the most heavily cited publications focus their results on the clinical relevance of lower thresholds (10^1 to $<10^5$ CFU/mL), which account for the individual characteristics of uropathogens and patients and do not specifically recommend a 10^5 CFU/mL threshold.

Traditionally, a UTI is considered complicated when the individual has one or more risk factors that predispose the individual to a higher treatment failure or poor outcomes. A new definition classifies cUTIs as those that have possibly extended beyond the bladder as cUTI.¹⁵ In this review, UTIs satisfying either definition were defined as cUTI. Sensibly, the recommendations for cUTI diagnosis were influenced by specific diagnosis and trended toward lower threshold recommendations over time. The number and variety of recommended thresholds for cUTI diagnosis also increased over time. Threshold recommendations for diagnosis in men tended to be lower than recommendations for the diagnosis of women or no specified sex, reflecting considerations for the relatively protective arrangement of the male urethral anatomy. High-risk patient groups, such as ICU patients, transplant recipients, and patients with SCI also tended to have lower overall microbial threshold recommendations. This lack of a one-size-fits-all consensus threshold for cUTI diagnosis is unsurprising, given the variety of patient risk factors and prognoses associated with differing cUTI diagnoses. We identified a general trending shift in threshold recommendations for any cUTI diagnosis toward a lower ($<10^5$ CFU/mL) threshold since 2008. However, the most recent guidelines, published since 2016, were still highly inconsistent, with recommendations ranging from any count to 10^5 CFU/mL.

Though the recommended diagnostic microbial thresholds for non-CAUTI catheter-based urine specimens varied, a majority of recommendations for indwelling, in-and-out catheterization, and intermittent catheterization set 10^2 CFU/mL as a diagnostic threshold. Suprapubic aspirate urine specimen collection method guidelines unanimously agreed that any microbial count was diagnostic for a cUTI. Since this method draws directly from the bladder via a needle puncture in the abdomen, it is the most invasive, but the least prone to contamination thus this consensus finding is in alignment with the low potential for contamination. In contrast, midstream clean catch specimens are non-invasive, but more susceptible to contamination from the genitourinary anatomy and the environment. Importantly, recommendations for midstream clean catch, which is the most common specimen collection method in clinical use, were inconsistent, with no one threshold reaching a majority recommendation. This variability highlights the need for standard terminology and descriptions of techniques for urine collection in future UTI research.

Ultimately, we conclude that it is essential to keep the intended use in mind when both designing and implementing recommendations for diagnostic microbial thresholds. A single one-size-fits-all threshold for SUC-based UTI diagnosis does not exist and would not be practical. Clinically relevant thresholds for a pyelonephritis patient are and should be different than those of a spinal cord injury because of patient risk factors.^{1,87,91} Likewise, a standard positive SUC-based urine culture diagnostic threshold (ie, $\geq 10^5$ CFU/mL) is unlikely to equal the clinically relevant threshold which is frequently much lower at 10^1 , 10^2 , or 10^3 CFU/mL.^{23,58,62,76} Different bacterial species may have lower clinically relevant thresholds because of their characteristics (ie, virulence, adherence, fastidiousness, etc.).^{16,103,104} *S. saprophyticus* is one such example in which the diagnostic threshold may be important at $\geq 10^2$ – 10^3 CFU/mL.^{43,78,89} Relatively little research has been done verifying if cUTI uropathogens are similar to uUTI ones and at what microbial thresholds these microbes become clinically relevant.

If a clinician is not provided with timely diagnostic test results based on accurate and reliable thresholds, the patient may be undertreated, overtreated, or treated with an inappropriate antimicrobial.^{45,100,105} As antimicrobial resistance continues to rise, this is a valid and urgent concern.^{100–102,105,106} In an effort to adhere to antibiotic stewardship recommendations, clinical reports discourage empiric antibiotic therapy prior to final SUC susceptibility results.^{45,107}

Unfortunately, SUC can take up to 72 hours to result and often fail to identify polymicrobial and fastidious microbial infections.¹⁰¹ However, better diagnostic accuracy and prompt treatment can resolve the infection avoiding empiric therapy, inappropriate dosing or repeat courses of antimicrobials.^{13,85,100–102} The majority of the literature supports *E. coli* as the primary causative bacterium in acute cystitis.^{62,65} Use of SUC to semi-quantitate classic uropathogens in a specimen can provide evidence to help diagnose an active UTI; however, SUC has a few disadvantages. Culturing with SUC methods uses specific selective media which results in cultivating easy to grow microbes like *E. coli* but not non-*E. coli* pathogens and fastidious microbes.^{16,85,101,108,109} Improvement in methodologies for the accurate identification and quantification of uropathogens is needed.^{85,104} Novel techniques with improved accuracy compared to SUC methods may represent an opportunity to refine and modernize the diagnosis and treatment algorithms for UTI.^{101,109–111} As more information about the urinary microbiome is discovered due to advanced in culture-independent technologies, such as polymerase chain reaction and next generation sequencing, better diagnostic microbial thresholds may be ascertained.^{112–114}

Strengths of this study include its rigorous design, comprehensive review of the literature and focus on cUTI, the most significant populations at risk for serious sequelae related to missed diagnosis. Inherent limitations include that many guidelines included both uUTI and CAUTI or failed to clearly define UTI diagnosis, collection method, and/or populations included. For the purposes of this review, guidelines for CAUTI and uUTI are summarized in [Supplemental Tables 2 and 3](#). While typically included under the umbrella of cUTI, CAUTIs represent a unique situation in which UTIs have a known cause, namely a foreign body within the urinary tract. As such, the diagnosis and management of CAUTI is more uniform with most microbial threshold recommendations being 10³ CFU/mL. Additionally, because uUTI is often diagnosed without culture, we elected not to combine threshold guidelines in the primary results. However, data are available in [Supplementary Materials](#). Additionally, we did not include reviews of asymptomatic bacteriuria or screening guidelines. The guidelines and recommendations examined in this review focus on symptomatic patients and that best clinical practices for preventing antimicrobial resistance indicate that asymptomatic bacteriuria should not be treated.⁷⁵ An additional inherent limitation is that some guidelines cited surveillance thresholds as justification for clinical diagnostic threshold, but these two different thresholds should not be confused and are not interchangeable.^{115,116} Lastly, most UTI guidelines analyzed originated from the USA and Europe. While this review limited guidelines to those published in the English language, fewer than 50 additional abstracts were identified when the language filter was removed. It is not known how many of these would have been eligible for review if written in English.

Based on the knowledge gaps we identified in this scoping review, we call for future research efforts to:

- Develop a consensus and validate UTI definitions, symptoms, and diagnoses
- Improve clarity and consistency of diagnostic and clinical guidelines
- Determine what clinically relevant uropathogens exist and whether they differ for uUTI, cUTI, and CAUTI
- Develop relevant, evidence-based, and individual microbial quantification thresholds for clinical use

These goals may be difficult or impossible to achieve with SUC-based techniques, due to its limitations in identifying non-classical uropathogens, such as slow-growing, fastidious, or anaerobic microbes.^{108,117} Culture-independent tests, such as molecular tests, may provide a more comprehensive microbial landscape of the patients' urine to help physicians make more educated treatment decisions and help establish the thresholds described above. Overall, a more uniform consensus on diagnostic microbial threshold recommendations should lead to better clinical care and reduce inappropriate antimicrobial exposure.

Conclusion

Clinical microbial threshold guidelines for diagnosing UTI impact patient care. Many US regulatory agencies believe there are clinically accepted thresholds for determining whether a UTI exists based on SUC results. However, this scoping review demonstrates that SUC-based microbial threshold recommendations have inconsistencies and that additional evidence is needed to identify a gold standard in the diagnosis of true bacterial infection of the urinary tract.

Abbreviations

UTI, urinary tract infection; cUTI, complicated UTI; uUTI, uncomplicated UTI; rUTI, recurrent UTI; CAUTI, catheter associated UTI; SUC, standard urine culture; CFU, colony forming unit; PRISMA-P, preferred reporting items for systematic reviews and meta-analysis protocols; PICO, population, intervention, control, and outcome; PRESS, peer review of electronic search strategies; MeSH, medical subject headings; GRADE, grading of recommendations, assessment, development, and evaluations scale.

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