

Review

What is chronic urinary tract infection? A systematic review

Janni Søvsø Hjelmager^{1†}, Karin Andersen^{2†}, Thomas Emil Andersen^{1,3} and Kristian Stærk^{1,3} ¹Research Unit of Clinical Microbiology, University of Southern Denmark, ²Department of Urology, and ³Department of Clinical Microbiology, Odense University Hospital, Odense, Denmark

†J.S.H. and K. A. contributed equally to this work.

Objective

To define 'chronic' urinary tract infection (UTI) by reviewing current published research that employs this term.

Methods

We systematically searched Medline and Embase for studies covering all aspects of human UTI. For comparison, current urological and infectious disease guidelines were also reviewed.

Results

The electronic search yielded a total of 2175 articles, of which 154 were eventually included for data extraction. Of these, six studies presented a definition of chronic UTI within the text. The definitions were highly incongruent among studies and often identical to the current definition of 'recurrent' UTI.

Conclusion

Chronic UTI is an undefined term, which has nevertheless been increasingly used in the past 15 years. Chronic UTI does not represent a distinct clinical or microbiological condition that justifies its use as medical diagnosis.

Keywords

urinary tract infection, chronic urinary tract infection, bladder infection, recurrent urinary tract infection, urological guidelines, disease definition, unresolved urinary tract infection, recalcitrant urinary tract infection

Introduction

Urinary tract infection (UTI) is one of the most common infectious diseases in humans [1]. UTIs mostly affect women, and 25% of sexually active young women will experience a recurrent infection within 6 months. The number of recurrences is even higher in postmenopausal women [1]. Up to half of these women will further experience multiple episodes of UTI [2,3]. The term 'recurrent UTI' is used to describe the condition in such patients and is clearly defined in clinical guidelines as more than two episodes of UTI within 6 months, or more than three episodes within a year, documented by the presence of over 10^3 colony forming units/mL in the urine [4,5].

'Chronic UTI' is another term occasionally used in published studies to describe a condition characterised by multiple UTIs [6]. In recent years, this term has gained increasing popularity in patient-organised interest groups. Most notably,

the NHS (the UK medical and healthcare service) recently updated its official advice, now recognising chronic UTI as a distinct condition, following pressure from campaigners [7]. Specifically, the NHS recommends that patients with chronic UTI should be referred to a specialist [8]. However, there is no clear description of the term, its aetiology, or its clinical condition, making these recommendations difficult to follow. Currently, the use of the term chronic UTI creates confusion among patients, clinical doctors and researchers in UTI. For chronic UTI to gain acceptance in clinical guidelines, a clear definition is necessary to facilitate the diagnosis and treatment of patients with UTIs.

The aim of this systematic review was to examine the definition and usage of the term chronic UTI in scientific publications. This investigation involved reviewing current published research. Additionally, current urological and infectious disease guidelines were examined to evaluate how the term is employed in clinical recommendations.

Methods

The method used in this systematic review was designed and planned according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocol guidelines [9,10]. The protocol was appropriately registered with the PROSPERO International Prospective Register of Systematic Reviews (ID: CRD42022370592). Our search strategy was developed in collaboration with an information specialist, affiliated to the library of the University of Southern Denmark, Odense, Denmark.

A comprehensive systematic search was conducted in Embase and Medline, covering all available years. The search strategy involved a combination of keyword searches (Medical Subject Headings [MeSH]) using terms such as 'chronic disease' and 'urinary tract infection' as well as free-text searches including 'chronic urinary tract infection' or 'cystitis' or 'bladder infection'. This search strategy was implemented using OVID, combining searches across Embase and Medline databases:

1. Chronic disease/
2. Urinary tract infection/
3. 1 and 2
4. (chronic adj1 (urinary tract infection* or cystitis* or bladder infection)).mp.
5. 3 or 4
6. 5 use medall
7. Use emczd
8. 6 or 7
9. Remove duplicates from 8
10. Limit 9 to English language

The search was conducted on 7 October 2022, and we included all studies published in the English language before this date. The literature search results were uploaded to Covidence for initial screening and data extraction.

Screening

The initial title/abstract screening for eligibility was conducted independently by two reviewers, J.S.H. and K.S. We included studies covering all aspects of human UTI, provided the following terms were mentioned in the title or abstract: chronic urinary tract infection, chronic pyelonephritis, chronic renal infection, chronic kidney infection, chronic bladder infection, or chronic infection of the urinary tract. Studies using animal models of human UTI were also included. However, studies focusing on veterinarian disease (i.e., not modelling human disease) were excluded. Additionally, studies regarding chronic inflammation of the bladder (i.e., chronic cystitis) were included only if they could be related to an infectious aetiology based on the title or abstract. Cancer and other non-infectious conditions of

cystitis were not considered. Disagreements were resolved through discussion between the reviewers.

Given the expected high number of potential studies resulting from our broad search, we limited the data extraction to 300 studies randomly selected using Microsoft Excel (Version 2309 Build 16.0.16827.20278).

Data Extraction

Data extraction was carried out by one reviewer and subsequently validated by the other reviewer. This process involved screening the full-text files of the included studies as follows:

1. Studies not using 'chronic' in connection to UTI, pyelonephritis, renal infection, kidney infection or bladder infection were excluded;
2. The definition was extracted from studies that defined chronic UTI;
3. Publication year was extracted.

Deviation from the PROSPERO Protocol

Following the initial screening, we conducted a second screen of the included studies to exclude the term chronic cystitis, as it was difficult to distinguish between infectious and non-infectious cystitis. The latter represents a pathological tissue inflammation of non-bacterial origin.

Review of Clinical Guidelines

The international guidelines from 11 urological or infectious disease societies were reviewed (Table 1). The guidelines were searched for the following terms: chronic urinary tract infection, recurrent urinary tract infection, persistent urinary tract infection, and complicated urinary tract infection.

Table 1 Review of clinical guidelines.

Guidelines	Abbreviation
European Association of Urology	EAU
American Urological Association	AUA
Canadian Urological Association	CUA
Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction	SUFU
National Institute for Health and Care	NICE
Urological Association of Asia	UAA
Asian Association of Urinary Tract Infection and Sexually Transmitted Infection	AAUS
International Continence Society	ICS
South African Urological Association	SAUA
Government of South Australia	SA Health
European Society of Clinical Microbiology and Infectious Diseases	ESCMID
<i>The AUA, CUA and SUFU use the same guideline for UTI.</i>	

Results

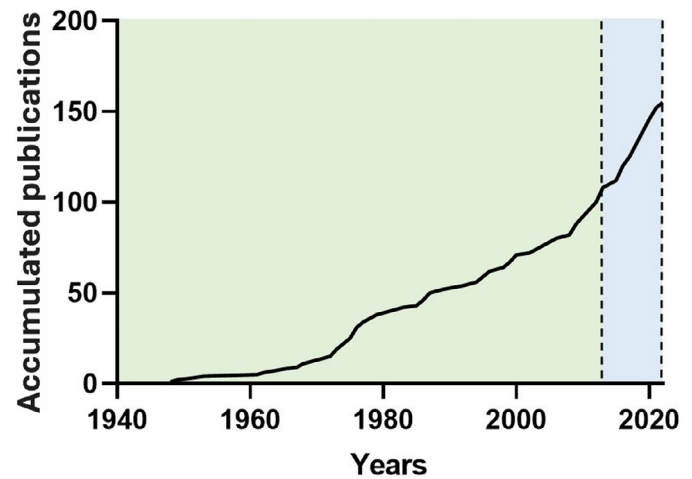
Search Findings

From the electronic literature search, 2175 potential studies were identified (Fig. 1). After abstract and title screening, 561 relevant studies were included, of which 300 were randomly chosen for full-text search. Among, these, 146 were excluded as they were not searchable, not retrievable, or were non-English language publications. Eventually, 154 articles were deemed suitable for data extraction in the final analysis. During the full-text screening, one article was excluded as 'chronic UTI' did not appear in the article. Additionally, in 35 articles, chronic UTI was only mentioned in the abstract, title, or reference.

From 2009 to 2022 an increase in the use of chronic UTI in published articles was observed, with an average of 5.6 articles per year mentioning this term compared to 1.4 in the preceding period (1948–2008; Fig. 2).

Overall, six of the 154 included articles defined chronic UTI, accounting for less than 4%. These definitions are summarised in Table 2. Of the six studies, three did not

Fig. 2 Summary of the use of the term 'chronic UTI' from 1948 to 2022, presented as accumulated publications per year. From 2009 to 2022 (blue shading), the use of 'chronic UTI' increased 4.1-fold.



provide a definition distinguishable from recurrent UTI based on international clinical guidelines [6,11,12]. Other definitions found in our search were unclear and defined the term

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the systematic search.

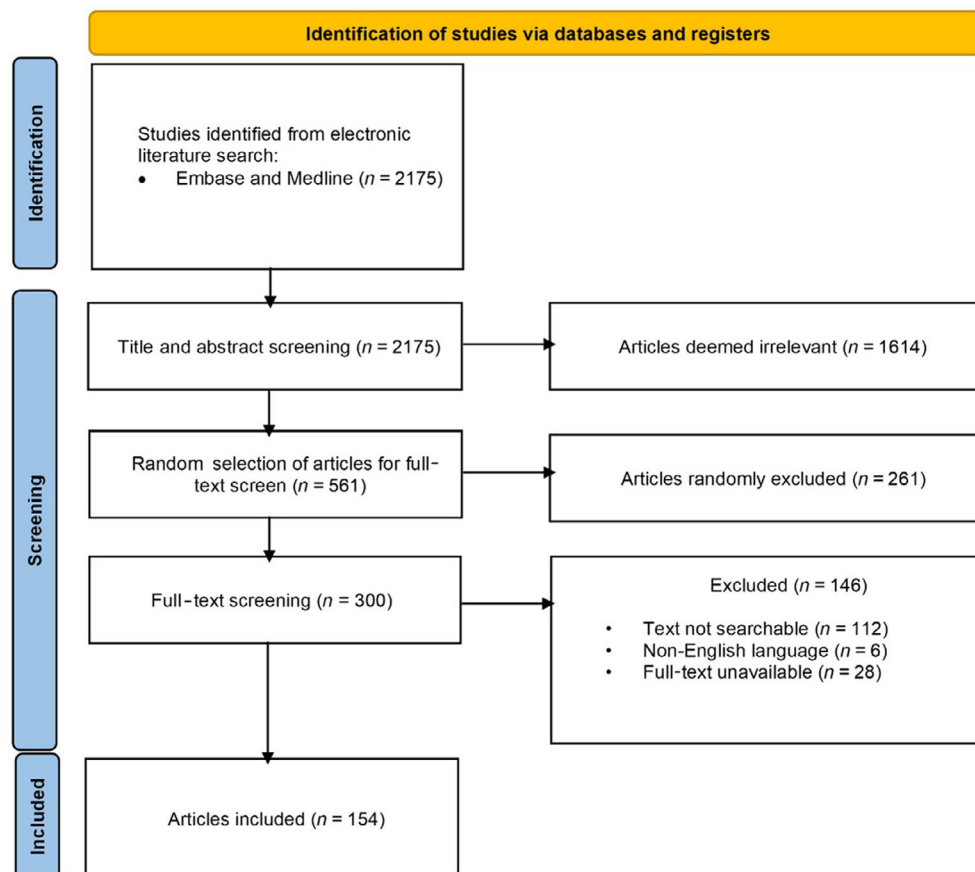


Table 2 Definition of chronic UTI.

Reference	Term	Definition
Arnold et al. [11]	Chronic urinary tract infection	'Chronic' was defined as three or more infections within a 12-month period
Hannan et al. [13]	Chronic bladder infection	'Chronic bladder infection is common and can be either latent, in the form of the quiescent intracellular reservoir, or active in the form of asymptomatic bacteriuria (ASB/ABU) or chronic cystitis'
Hugosson et al. [14]	Chronic urinary tract infection	'Patients with chronic urinary tract infections may either have a true persistent (unresolved) bacteriuria or recurrent reinfections'
Jarvis et al. [15]	Chronic urinary tract infection	'Chronic infection is defined by severe pyuria and persistent bacteriuria' (in relation to mice)
Kalager et al. [12]	Chronic urinary tract infection	'They (patients) all had a history of chronic urinary tract infection with symptoms of cystitis or cystopyelitis four to six times annually'
Zhu et al. [6]	Chronic urinary tract infection	'In some patients, chronic UTI or recurrent UTI (≥ 2 UTI over 6 months or 3 UTI over 12 months) develop. The mechanisms of chronic UTI could be related with intracellular reservoir formation shown in C57BL/6 mice'

vaguely. Most of the definitions failed to delineate how chronic UTI differs from recurrent UTI or to specify the duration of bacteriuria that should be considered 'persistent'. Two studies describe chronic UTI in relation to intracellular bacterial reservoirs in the bladder epithelium, namely, quiescent intracellular reservoirs (QIRs) or intracellular bacterial communities (IBCs), indicating that reservoir formation may be a prerequisite for UTI chronicity. Zhu et al. [6] drew parallels between chronic UTI and recurrent UTI, suggesting a potential link to intracellular reservoirs. Hannan et al. [13] suggest that asymptomatic conditions, such as latent QIRs or asymptomatic bacteriuria, may be considered chronic UTI. However, these proposed definitions lack consistency in several aspects, apart from the presence of persistent bacteriuria (either symptomatic or asymptomatic) and the existence of intracellular bladder reservoirs. Additionally, there were no indications regarding the temporal duration required for the condition to be classified as chronic.

Clinical Guidelines

The findings from international clinical guidelines are presented in Table 3. Chronic UTI was mentioned in one guideline paper (Urological Association of Asia) in relation to catheter-associated UTI, but not specifically defined: 'CA-ASB [catheter-associated asymptomatic bacteriuria] is defined as

chronic urinary tract infection without the manifestation of symptoms (Evidence level A)'.

Recurrent UTI was defined in seven guideline papers, while complicated UTI was defined in five guideline papers (Table 3). One guideline paper mentioned the term 'persistent UTI' but did not define the condition (Table 3). Notably, two guidelines did not include any section on UTI.

Discussion

In this study, we conducted a systematic review of 154 articles, aiming to investigate the use and definition of the term 'chronic UTI'. We found that the term chronic UTI has been increasingly used in scientific publications over the past 15 years. However, only six of 154 publications, or < 4%, provided a definition of this term, and these definitions lacked congruence. Some of the definitions refer to the hypothesis that reservoir formation (QIR and IBC) may be a prerequisite for UTI chronicity.

Intracellular colonisation and bacterial reservoir formation in the bladder originate from studies in mice. In these animals, uropathogenic *Escherichia coli* invade superficial umbrella cells to form IBCs or the transitional epithelium, forming QIRs. These intracellular colonies may survive antibiotic treatment, facilitating later re-emergence and infection of the murine bladder [16–19]. In 2007, Rosen et al. [17] observed intracellular bacteria within exfoliated cells in the urine samples from women with acute UTI, and bladder biopsies from patients with recurrent UTI have shown evidence of tissue-resident bacteria [20]. Together, these studies suggest that a similar pathogenic mechanism may also occur in humans.

The NHS in the UK recently updated their information on UTI to include a section on chronic UTI. The NHS describes chronic UTI as a condition that does not respond to standard short-term courses of antibiotic treatment. Furthermore, the NHS suggests that chronic UTI may be caused by bacteria entering the bladder lining intracellularly, resulting in chronic, long-term UTI. This intracellular presence may then cause urine diagnostic tests to yield false negatives, as intracellular bacteria are not culturable from urine specimens or fall below standard thresholds of significant bacteriuria [8]. This discussion has raised questions about whether patients experiencing longstanding LUTS may have undetected intracellular bacterial reservoirs causing chronic UTI [21]. Elliot et al. [22] investigated the mid-stream urine and bladder biopsies from 33 patients with symptoms of urinary tract disturbance suggesting an infective origin. They found 16 patients with 'sterile' urine, but culture-positive biopsy samples were detected in eight of these patients, and bacteria were observed on the urothelium of 14 patients using scanning electron microscope. Swamy et al. [21] conducted a study involving a substantial cohort of women with

Table 3 Clinical guidelines.

Guidelines	Year	Recurrent UTI	Persistent UTI	Chronic UTI	Complicated UTI	Name of the guideline
EAU	2023	X	/	/	X	Urological infections
AUA	2022	X	/	/	X	Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline (2022)
CUA	2022	X	/	/	X	=//=
SUFU	2022	X	/	/	X	=//=
UAA	2021	/	/	Mentioned but not specified	/	Guidelines for Infection Control in the Urological Field, including Urinary Tract Management
UAA-AAUS	2017	X	X	/	/	Summary of the UAA-AAUS guidelines for urinary tract infections
NICE	2018–2022	X	/	/	/	2022 exceptional surveillance of urinary tract infection (recurrent): antimicrobial prescribing (NICE guideline NG112)
ICS						No guidelines of UTI
SAUA						Guidelines not available
SA Health	2022	X	/	/	/	
ESCMID	2021	/	/	/	X	

X, denotes the term was identified; /, that the term was not identified.

CUA, Canadian Urological Association; EAU, European Association of Urology; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; ICS, International Continence Society; NICE, National Institute for Health and Care Excellence; SA Health, South Australia Health; SAUA, South African Urological Association; SUFU, Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction; UAA-AAUS, Urological Association of Asia–Asian Association of Urinary Tract Infection and Sexually Transmitted Infection.

longstanding LUTS. Their investigation revealed that conventional diagnostic methods, such as dipsticks or urine culture count, were inadequate. Long-term antibiotic treatment resulted in a notable reduction of LUTS symptoms observed among the patients [21]. These findings suggest that patients diagnosed with LUTS may also have an underlying UTI and that QIRs and IBCs could exist in humans. The effectiveness of long-term antibiotics in this patient group is speculated to be explained by complete eradication of (i) dormant bacterial reservoirs in the deeper layers of the bladder mucosa, where cell turnover is slow, and (ii) biofilm-associated bacteria with reduced metabolism and cell division [21]. However, the benefits of long-term antibiotics are reported in case series and lack randomised controlled trials.

In a recent study by Advani et al. [23] the same diagnostic uncertainty is described for patients with acute symptoms and the authors state that labelling the diagnostic uncertainty will lead to improved communication between teams in addition to nuanced and patient-focused treatment approaches.

If intracellular bacterial reservoirs exist in humans, the possibility of uropathogens coexisting within bladder cells and entering a cycle of UTI flares, similar to the herpes simplex virus, may be considered [24]. In such cases, it may be appropriate to employ the term ‘chronic infection’. Currently, however, the causal relation between intracellular reservoirs and recurrent UTI has not been convincingly demonstrated in humans [17]. Moreover, recent findings from an experimental pig model of UTI suggest that the intracellular pathogenesis observed in mice is not recapitulated in larger

mammals [25]. Currently, the uncertainties regarding intracellular colonisation and recurrent UTI in humans warrant further investigation before adopting this as a criterion for a medical term such as chronic UTI.

Over the past couple of decades, urologists, microbiologists, and infectious disease specialists have primarily focused on emphasising the need to distinguish between symptomatic infections – such as UTIs – and the colonisation or presence of bacteria without clinical impact, referred to as bacteriuria or asymptomatic bacteriuria. Additionally, the discovery of the urogenital microbiome, whose clinical significance is not yet fully understood, has further highlighted the importance of this differentiation. This focus is crucial as it aligns with recommendations and efforts to minimise antibiotic use, thereby reducing the risk of increasing bacterial resistance.

Patient-organised interest groups emphasise the ‘chronic’ aspects of conditions to advocate for improved management, which is certainly beneficial but also poses a risk of promoting the overuse of antimicrobial drugs. Providing patients with thorough education and information is essential for achieving a balanced approach to management.

It is important to emphasise that no international guidelines currently recognise or use the term chronic UTI. With this in mind, the medical community should limit their terminology to a few clear and relevant definitions and avoid using poorly defined terms that may lead to confusion or misinterpretation. Chronic UTI is an example of such a term, along with other unclear terms such as pseudo-UTI and

subclinical UTI among others, as discussed by Advani et al. [23].

As clinicians, it is crucial to communicate effectively with patients. Our role as professional caregivers involves clarifying the distinction between a single UTI and recurrent UTI. Use of consistent language to educate patients about their condition improves understanding and treatment. Furthermore, if patients encounter the term in published literature but find it unrecognised by clinicians as a legitimate diagnosis, it could result in misunderstanding and concern.

We observed a significant 4.1-fold increase in the use of the term chronic UTI from 2009 onwards compared to the preceding 70 years. This increase may be associated with the study by Rosen et al. on intracellular pathogenesis, increasing the awareness of its potential role in chronic UTI [17]. Despite the significantly increased use of the term chronic UTI, there remains a lack of terminological consensus to describe this condition. 'Chronic UTI' is often used interchangeably with 'chronic cystitis'. The term chronic cystitis can be misleading, as it does not always denote inflammation caused by bacteria, but also refers to a non-infectious pathological condition in the bladder tissue [17]. The linguistic ambiguity of chronic cystitis also led us to exclude this as a search term in our screening. This decision represents a limitation as it may have resulted in the exclusion of relevant studies from our review. Our study was also limited by the difficulties in accessing searchable articles, leading to the exclusion of 112 out of 300 potential articles. Additionally, our study was limited by searching only two major databases (Embase and Medline). Two databases is a relatively low number compared to the standard approach in systematic reviews that typically involves searching at least two or more databases [26]. During our pilot search, we found an overwhelming number of hits that fell within our criteria; therefore, we decided only to include the two largest databases, Medline and Embase. Further relevant studies would likely have been identified if additional databases were searched, or supplementary search methods were used.

In conclusion, the term chronic UTI has been increasingly used over the past 15 years, yet it lacks a clear definition and pathological causality. Clinically, the condition is characterised by frequent episodes of UTI or flares of bladder-associated symptoms of bacterial origin. However, the term is not clinically relevant or necessary, given that the definition of recurrent UTI already covers this patient group. The authors conclude that, at present, chronic UTI does not represent a distinct clinical condition that justifies its use as a medical diagnosis. The use of the term chronic UTI should be avoided, as it creates confusion among clinicians, researchers and patient groups.

Disclosure of Interests

The authors have nothing to declare.

Funding

The study was supported by postdoctorate funds from the Department of Clinical Research, University of Southern Denmark, Denmark.

References

- 1 Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. *Infect Dis Clin N Am* 2014; 28: 1–13
- 2 McLellan LK, Hunstad DA. Urinary tract infection: pathogenesis and outlook. *Trends Mol Med* 2016; 22: 946–57
- 3 Anger J, Lee U, Ackerman AL et al. Recurrent uncomplicated urinary tract infections in women: AUA/CUA/SUFU guideline. *J Urol* 2019; 202: 282–9
- 4 Aydin A, Ahmed K, Zaman I, Khan MS, Dasgupta P. Recurrent urinary tract infections in women. *Int Urogynecol J* 2015; 26: 795–804
- 5 The Guideline Uroweb. <https://uroweb.org/guidelines/urological-infections/chapter/the-guideline>
- 6 Zhu K, Hill WG, Li F, Shi B, Chai TC. Early increased urinary IL-2 and IL-10 levels were associated with development of chronic UTI in a murine model. *Urology* 2020; 141: 188.e1–188.e6
- 7 <https://www.nhs.uk/conditions/urinary-tract-infections-utis/>
- 8 NHS. Urinary tract infections (UTIs). National Health Service. <https://www.nhs.uk/conditions/urinary-tract-infections-utis/>
- 9 Shamseer L, Moher D, Clarke M et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015; 350: g7647
- 10 Moher D, Shamseer L, Clarke M et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; 4: 1
- 11 Arnold LD, Bachmann GA, Rosen R, Kelly S, Rhoads GG. Vulvodynia: characteristics and associations with comorbidities and quality of life. *Obstet Gynecol* 2006; 107: 617–24
- 12 Kalager T, Boe E, Digranes A, Hoisaether P, Solberg CO. Pivmecillinam treatment of chronic urinary tract infection. *Infection* 1978; 6: 21–2
- 13 Hannan TJ, Totsika M, Mansfield KJ, Moore KH, Schembri MA, Hultgren SJ. Host-pathogen checkpoints and population bottlenecks in persistent and intracellular uropathogenic *Escherichia coli* bladder infection. *FEMS Microbiol Rev* 2012; 36: 616–48
- 14 Hugosson J, Grenabo L, Hedelin H, Lincoln Pettersson KS. Chronic urinary tract infection and renal stones. *Scand J Urol Nephrol* 1989; 23: 61–6
- 15 Jarvis C, Han Z, Kalas V et al. Antivirulence Isoquinolone Mannosides: optimization of the Biaryl aglycone for FimH lectin binding affinity and efficacy in the treatment of chronic UTI. *ChemMedChem* 2016; 11: 367–73
- 16 Justice SS, Hung C, Theriot JA et al. Differentiation and developmental pathways of uropathogenic *Escherichia coli* in urinary tract pathogenesis. *Proc Natl Acad Sci USA* 2004; 101: 1333–8
- 17 Rosen DA, Hooton TM, Stamm WE, Humphrey PA, Hultgren SJ. Detection of intracellular bacterial communities in human urinary tract infection. *PLoS Med* 2007; 4: e329
- 18 Anderson GG, Palermo JJ, Schilling JD, Roth R, Heuser J, Hultgren SJ. Intracellular bacterial biofilm-like pods in urinary tract infections. *Science* 2003; 301: 105–7

- 19 Mulvey MA, Schilling JD, Martinez JJ, Hultgren SJ. Bad bugs and beleaguered bladders: interplay between uropathogenic *Escherichia coli* and innate host defenses. *Proc Natl Acad Sci USA* 2000; 97: 8829–35
- 20 De Nisco NJ, Neugent M, Mull J et al. Direct detection of tissue-resident bacteria and chronic inflammation in the Bladder Wall of postmenopausal women with recurrent urinary tract infection. *J Mol Biol* 2019; 431: 4368–79
- 21 Swamy S, Barcella W, De Iorio M et al. Recalcitrant chronic bladder pain and recurrent cystitis but negative urinalysis: what should we do? *Int Urogynecol J* 2018; 29: 1035–43
- 22 Elliott TS, Reed L, Slack RC, Bishop MC. Bacteriology and ultrastructure of the bladder in patients with urinary tract infections. *J Infect* 1985; 11: 191–9
- 23 Advani SD, Turner NA, North R et al. Proposing the “continuum of UTI” for a nuanced approach to diagnosis and Management of Urinary Tract Infections. *J Urol* 2024; 211: 690–8
- 24 Brugha R, Keersmaekers K, Renton A, Meheus A. Genital herpes infection: a review. *Int J Epidemiol* 1997; 26: 698–709
- 25 Stærk K, Grønnemose RB, Palarasah Y, Lund L, Andersen TE. Intracellular uropathogenic *Escherichia coli* are undetectable in urinary bladders after oral mecillinam treatment: an experimental study in a pig model of cystitis. *Microb Pathog* 2022; 173: 105817
- 26 Ewald H, Klerings I, Wagner G et al. Searching two or more databases decreased the risk of missing relevant studies: a meta-research study. *J Clin Epidemiol* 2022; 149: 154–64

Correspondence: Kristian Stærk, Research Unit of Clinical Microbiology, University of Southern Denmark, J.B. Winsløws Vej 21, 5000 Odense, Denmark.
e-mail: kristian.staerk@rsyd.dk

Abbreviations: IBC, intracellular bacterial community; QIR, quiescent intracellular reservoir.