

What is the Diagnostic Accuracy of Novel Urine Biomarkers for Urinary Tract Infection?

Biomarker Insights
Volume 18: 1–16
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DOI: 10.1177/11772719221144459



George Edwards¹, Anna Seeley², Adam Carter²,
Maia Patrick Smith², Elizabeth LA Cross³, Kathryn Hughes⁴,
Ann Van den Bruel⁵, Martin J Llewelyn³, Jan Y Verbakel^{5,1}
and Gail Hayward¹

¹NIHR Community Healthcare Medtech and IVD Cooperative, Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK. ²Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK. ³Department of Global Health and Infection, Brighton and Sussex Medical School, Falmer, UK. ⁴PRIME Centre Wales, Division of Population Medicine, Cardiff University, Cardiff, UK. ⁵EPI-Centre, Academic Centre for General Practice, KU Leuven, Leuven, Belgium.

ABSTRACT

BACKGROUND: Urinary tract infection (UTI) affects half of women at least once in their lifetime. Current diagnosis involves urinary dipstick and urine culture, yet both methods have modest diagnostic accuracy, and cannot support decision-making in patient populations with high prevalence of asymptomatic bacteriuria, such as older adults. Detecting biomarkers of host response in the urine of hosts has the potential to improve diagnosis.

OBJECTIVES: To synthesise the evidence of the diagnostic accuracy of novel biomarkers for UTI, and of their ability to differentiate UTI from asymptomatic bacteriuria.

DESIGN: A systematic review.

DATA SOURCES AND METHODS: We searched MEDLINE, EMBASE, CINAHL and Web of Science for studies of novel biomarkers for the diagnosis of UTI. We excluded studies assessing biomarkers included in urine dipsticks as these have been well described previously. We included studies of adult patients (≥ 16 years) with a suspected or confirmed urinary tract infection using microscopy and culture as the reference standard. We excluded studies using clinical signs and symptoms, or urine dipstick only as a reference standard. Quality appraisal was performed using QUADAS-2. We summarised our data using point estimates and data accuracy statistics.

RESULTS: We included 37 studies on 4009 adults measuring 66 biomarkers. Study quality was limited by case-control design and study size; only 4 included studies had a prospective cohort design. IL-6 and IL-8 were the most studied biomarkers. We found plausible evidence to suggest that IL-8, IL-6, GRO-a, sTNF-1, sTNF-2 and MCR may benefit from more rigorous evaluation of their potential diagnostic value for UTI.

CONCLUSIONS: There is insufficient evidence to recommend the use of any novel biomarker for UTI diagnosis at present. Further evaluation of the more promising candidates, is needed before they can be recommended for clinical use.

KEYWORDS: Systematic review, biomarkers, infection diagnosis, UTI

RECEIVED: August 1, 2022. **ACCEPTED:** October 31, 2022.

TYPE: Systematic Review

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was funded by the National Institute for Health and Care Research (NIHR) Community Healthcare MedTech and In Vitro Diagnostics Co-operative at Oxford Health NHS Foundation Trust (MIC-2016-018). GE, JV and GH receive funding from the NIHR Community Healthcare MedTech and In Vitro Diagnostics Co-operative at Oxford Health NHS Foundation Trust (MIC-2016-018).

The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

COMPETING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: George Edwards, Nuffield Department of Primary Care Health Sciences, University of Oxford, Woodstock Road, Oxford OX2 6GG, UK. Email: george.edwards@phc.ox.ac.uk

Background

Urinary tract infections (UTIs) are common across all age ranges and healthcare settings, with a lifetime risk of 50% to 60%.¹ They are amongst the most common indications for antibiotics in the USA,² and in England³ where they cost the NHS in the UK £316 million annually in emergency admissions for older adults alone.⁴ Over-treatment of suspected UTI and unnecessary treatment of asymptomatic bacteriuria (ASB) drive antibiotic overuse, and selection for antimicrobial resistance.^{5,6} Receipt of antibiotics for UTI results in carriage of resistant bacteria, which may persist for up to 12 months,⁷ and treatment of ASB

increases the risk of recurrent infection.⁸ Thus current antimicrobial guidelines support prompt but targeted antibiotic prescribing, especially for older, multimorbid or frail patients, reliant on timely and accurate diagnosis of infection.⁹

Diagnosis of UTI is traditionally based on presence of typical symptoms, positive urine dipstick and growth of uropathogenic bacteria on urine culture.¹⁰ Each of these components presents problems. Many patients at risk of UTI may not experience typical symptoms, especially older adults, or those living in residential homes, where 40% of UTIs are incorrectly diagnosed.¹¹ Even in younger women with uncomplicated UTI, the



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specificity of 'typical' symptoms such as dysuria, frequency and urgency is low, ranging from 20% to 45%.¹²

Urine dipstick tests to detect nitrates (presence of bacteria) and leucocytes are quick, simple and readily available across community and hospital settings. Nitrates have moderate specificity for infection (85%–98%)¹³ but are insufficient to rule-out UTI with a sensitivity of 30% to 40%. Presence of leucocyte-esterase is only modestly improves post-test probability of UTI, and is not diagnostic of infection in isolation.^{1,4} Due to the prevalence of ASB, urine dipsticks are unreliable in both older adults and catheterised patients.¹⁴ Accordingly, though widely used, results are commonly discounted in routine clinical practice.¹⁵

There are, too, limitations, in the diagnostic performance of urinary culture. Up to a third of urine cultures are contaminated by skin and/or faecal flora introduced during sampling¹⁶ and this has the potential to both obscure a true infection and give a positive culture result in the absence of infection. Further, cultures typically take 24 to 72 hours to report so it is usually necessary to make an antibiotic prescribing decision before culture results are available and they cannot distinguish infection from asymptomatic bacteriuria, especially in the elderly.¹⁷

Urine biomarkers could aid accuracy of UTI diagnosis and be developed into cheap, rapid point of care tests (POCTs), useful in settings without ready access to laboratory facilities. The last systematic review of urine biomarkers (in 2009) identified interleukins, notably IL-6 and IL-8, as potential candidates, but these had only been evaluated in a small number of studies.¹⁸ Over the last decade there has been a rapid expansion in biomarker technologies but there is insufficient evidence as to how these perform. In this review we therefore aimed to synthesise evidence of urine biomarkers for the diagnosis of UTI. We primarily used urine culture as our reference standard as this is widely used and easily comparable between studies. As a secondary aim we explored how urine biomarkers can distinguish UTI from ASB, given urine culture cannot differentiate these 2 conditions.

Methods

Our review protocol was registered with PROSPERO in November 2019: CRD42019156071.

Search

We searched Medline, Embase, CINAHL and Web of Science from inception until 11th April 2022 for studies with combined Medical Subject Headings and free text search terms in 3 main themes: urinary tract infection (eg, cystitis, UTI, bacteriuria); biomarkers (eg, biomarkers, immunoglobulins); and urine testing (eg, urinalysis, urine*, test*). The full search strategy is available in Supplemental Table 1.

Eligibility

Participants: We included studies of adult patients (≥ 16 years) with a suspected or confirmed urinary tract infection (including

cystitis and pyelonephritis) or bacteriuria. We excluded studies not specifying the ages of included patients, of children under the age of 16, or where data for any patients under the age of 16 could not be disaggregated.

Index tests: We included studies of urine biomarkers. We considered a biomarker to be any substance which can be measured in the urine which may be indicative of medical state.¹⁹ This may arise through a biological or pathogenic process and includes markers of immune response and bacterial activity. This does not include detection of bacteria. We excluded studies of leucocyte esterase and nitrites, as they have been thoroughly studied, have modest test accuracy,^{1,13,14} and are insufficient for making a final diagnosis in clinical practice.^{14,15,20}

Reference standard: We included studies with microscopy and/or culture as a reference standard and we did not specify a threshold for infection after culture as our aim was to offer a wide perspective on the available evidence for novel biomarkers. There is not one agreed threshold level of bacteria for diagnosing all UTIs^{21,22} and microscopy only can be useful for ruling out bacteriuria.²³ We excluded studies using clinical signs and symptoms or dipstick only.

Types of studies: We included prospective cohort studies assessing diagnostic accuracy, cross-sectional studies, and case-control studies with a healthy control group. Although case-control studies risk exaggerating the differences between groups, by excluding cases for which diagnosis is difficult or unclear, and overestimate prevalence (spectrum bias), we included studies with this design as we did not expect to find a large number of cohort studies.

Settings: We did not exclude studies based on their clinical setting.

Selection of studies

The Cochrane Collaboration Covidence platform was used for study screening.²⁴ Two authors (GE, GH, ELAC, KH, AVDB, JV, MPS, AES, AC) screened each study according to prespecified inclusion and exclusion criteria and we resolved disagreements by discussion with a third reviewer. We screened titles and abstracts initially and obtained full texts for potentially relevant studies. We hand searched reference lists in relevant systematic reviews for relevant studies.

Data extraction

We extracted study information, participant characteristics, index test description and process, statistical analysis, and results using a data extraction form designed by GE and piloted by GE, KH and MPS. One author (GE, AC, MPS, KH, AES) chosen at random performed data extraction using a standardised and piloted data extraction form. This was checked by a second author, chosen by availability, for accuracy.

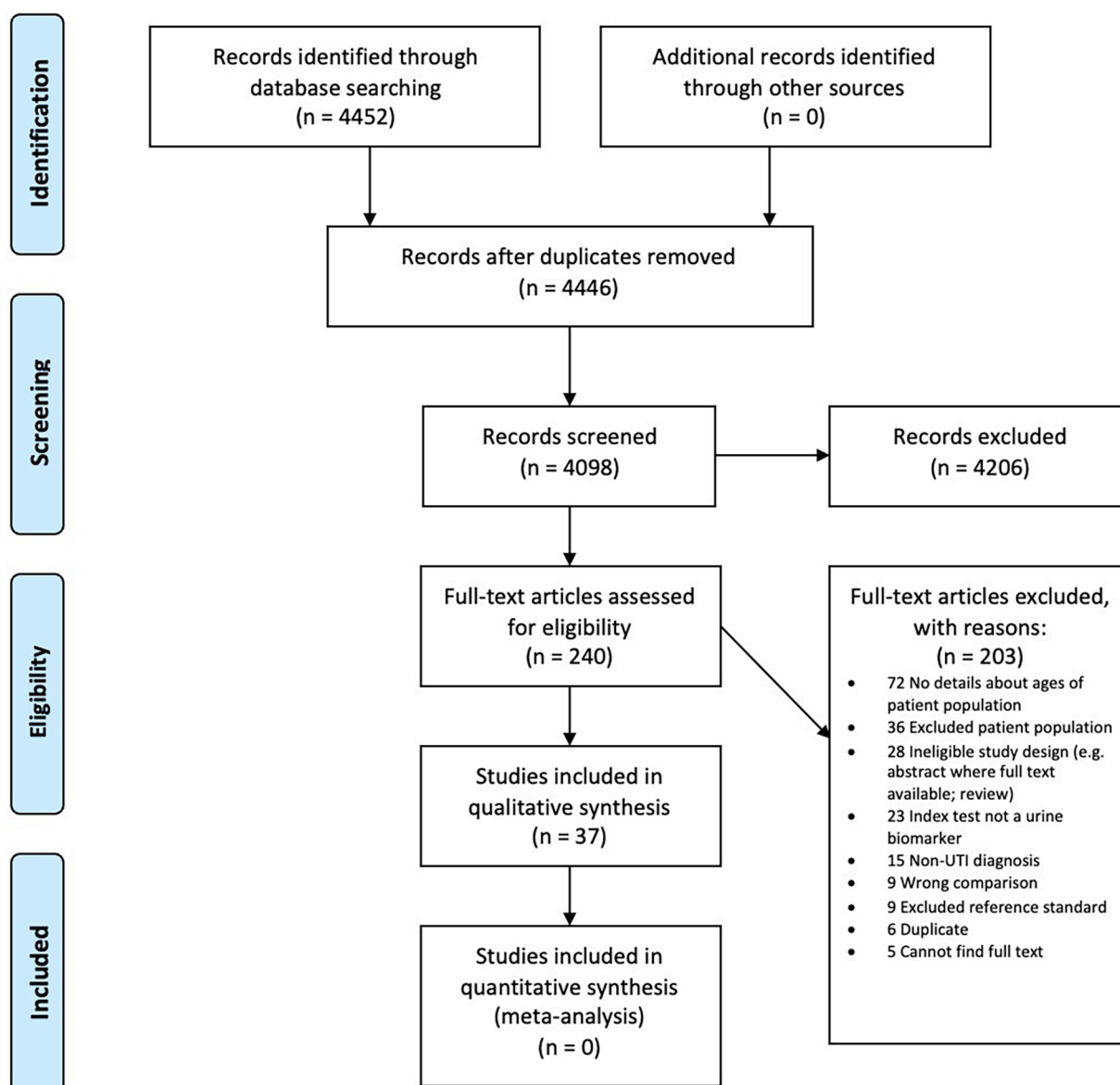


Figure 1. Prisma flow diagram.

Risk of bias assessment

One author (GE, AC, MPS, KH, AES) assessed the risk of bias in the procedures of each included study using an the QUADAS-2 framework.²⁵ This was checked by a second reviewer and any disagreements were resolved through discussion. One author reviewed the appraisal of each included study for consistency.

Analysis

Due to study heterogeneity and a paucity of diagnostic accuracy data we were unable to perform meta-analyses as initially intended. We have summarised our results narratively.

Results

Our database search identified 4446 unique references; we excluded 4206 based on the title and abstract leaving 240 for a

full text review. We included 37 studies in our descriptive analysis (see Figure 1 for PRISMA flowchart). The most common reasons for exclusion were a lack of information about the ages of participants or confirmed inclusion of children. The 37 studies included 4009 adults and measured 66 different biomarkers (see Table 1 and Supplemental Table 2).

Risk of bias assessment

Our risk of bias assessment using the QUADAS-2 tool is presented in Table 2. Overall, we found little high quality prospectively collected evidence. We found 4 studies with a prospective cohort design.²⁶⁻²⁹ In one of these²⁸ we had low concerns in all domains apart from bias in the conduct of the index test as it wasn't clear whether the threshold was pre-specified. This was the only study which recruited a random sample of patients presenting with a suspected UTI.²⁸ We rated one of these

Table 1. Biomarker abbreviations.

BIOMARKER	ABBREVIATION
Alanine aminopeptidase	AAP
Beta-2-Microglobulin	B2M
Chemokine (C-X-C) ligand 2 (also known as monocyte chemoattractant protein 1)	CCL-2
C-X-C motif chemokine ligand 10	CXCL10
C-X-C motif chemokine ligand 5	CXCL5
Epithelial cell–derived neutrophil activating protein	ENA 78
Granulocyte colony-stimulating factor	G-CSF
C-X-C motif chemokine ligand 1	CXCL1 (GRO-a)
Heparin-Binding Protein	HBP
High Mobility Group Box-1	HMGB1
Immunoglobulin (eg, A)	Ig (eg, IgA)
Clinical Isolate Antigen	CIA
Mixed Coliform Antigen	MCA
Interleukin 1	IL-1
Interleukin 1 receptor antagonist	IL-1 RA
Interleukin 1 beta	IL-1B
Matric Metalloproteinase 9	MMP9
Urinary Neutrophil gelatinase-associated lipocalin	uNGAL
Macrophage Migration Inhibitory Factor	MIF
Myeloperoxidase to creatinine ratio	MCR
Myeloperoxidase	MPO
N-nitrosodibutylamine	NBDA
N-nitrosodiethylamine	NDEA
N-nitrosodimethylamine	NDMA
N-nitrosodi-n-propylamine	NDPA
N-nitrosodiphenylamine	NDPhA
Nerve Growth Factor	NGF
N-nitrosomethylethylamine	NMEA
N-nitrosomorpholine	NMOR
N-nitrosopiperidine	NPIP
N-nitrosopyrrolidine	NPYR
Platelet-derived growth factor	PDGF
Soluble IL-1 Receptor	sIL-1R
Soluble IL-6 Receptor	sIL-6R
Soluble tumour necrosis factor receptor (eg, 1 or 2)	sTNFR (eg, sTNFR1)

(Continued)

Table 1. (Continued)

BIOMARKER	ABBREVIATION
Soluble triggering receptor expressed on myeloid cells-1	sTREM-1
Trimethylamine	TMA
Tumour Necrosis Factor Alpha	TNF-alpha
Volatile Organic Compounds	VOCs

studies with a high or medium risk of bias in all domains due to a lack of reporting of the study process.²⁶

Most of our included studies (33/37) had a case-control design. We rated most (26/33) of these studies were rated as having a high risk of bias for patient selection (26/33) and conduct of the index test (31/33) because they either did not use consecutive or random sampling or did not report their sampling method, and the index test was interpreted with knowledge of the results of the reference standard (culture).

Across all studies, we rated the risk of bias due to the conduct or applicability of the reference standard to be low or medium as we excluded studies not using culture and microscopy as a reference standard. We had minimal concern about the applicability of the index tests to our question, which was intentionally broad.

Objective 1: Potential urine biomarkers for the diagnosis of UTI

The diagnostic accuracy of 64 biomarkers compared with urine culture was investigated in 36 studies including 3979 participants. Three biomarkers (MCR, IL-8, IL-6) were evaluated as part of a cohort study, and a further 7 biomarkers were each studied in 3 or more case-control studies (see Tables 3 and 4); the results for these biomarkers are summarised below. Supplemental Tables 2 and 3 detail our findings for the remaining 54 biomarkers which were studied either once or twice in 27 case-control studies. Supplemental Table 4 summarises the biological function of each biomarker.

Myeloperoxidase (MPO) to creatinine ratio (MCR)

One cohort study measured myeloperoxidase (MPO) to creatinine ratio (MCR) (measured in ng MPO to g creatinine) in 253 adult outpatients with suspected UTI.²⁸ In samples which were culture positive for 1 or 2 pathogens, log₂MCR values were higher than those in patients with sterile urine (mean 8.6 ng/g (SD 2.5) vs 5.4 (SD 1.5), $P=.001$). Accordingly an MCR of 194.0 ng/g or above had a sensitivity of 66%, specificity of 95% and PPV of 95% for positive culture.

IL-8

We found 2 cohort studies of catheterised in-patients and 7 case-control studies, conducted in hospital in-patients, out-

Table 2. Quality assessment summary using QUADAS-2 tool. Red = high risk of bias, or high concern of applicability to the research question, Orange = medium risk or concern. Green = low risk or concern.

STUDY	PATIENT SELECTION		INDEX TEST		REFERENCE STANDARD		FLOW AND TIMING
	RISK OF BIAS	APPLICABILITY	RISK OF BIAS	APPLICABILITY	RISK OF BIAS	APPLICABILITY	RISK OF BIAS
<i>Objective 1 only</i>							
Bai et al ²⁸	Low	Low	Medium	Low	Low	Low	Low
Benlier et al ³⁰	High	High	High	Low	Medium	Low	High
Burdorf ³¹	High	High	High	Low	Low	Low	Medium
Deo and Vaidya ³²	High	Medium	High	Low	Medium	Low	Medium
Flores-Figueroa et al ²⁷	Medium	High	Medium	Low	Low	Low	Low
Forster et al ³³	High	High	High	Low	Medium	Low	Medium
Gadalla et al ³⁴	Medium	Low	Medium	Low	Low	Low	Medium
Greenwell et al ³⁵	High	Medium	High	Low	Low	Low	High
Hu et al ³⁶	High	Medium	High	Low	Low	Low	Medium
Jacobson et al ³⁷	High	Medium	High	Low	Low	Low	High
Johnson et al ³⁸	High	Medium	High	Medium	Medium	Medium	High
Kjolvmark et al ³⁹	High	Low	High	Low	Low	Low	High
Lam et al ⁴⁰	High	Low	High	Medium	Low	Low	Medium
Lussu et al ⁴¹	High	Low	High	Medium	Low	Low	High
Nishitani et al ⁴²	High	Low	High	Low	Medium	Low	Medium
Olszyna et al ⁴³	High	Medium	High	Low	Medium	Medium	Medium
Olszyna et al ⁴⁴	High	Medium	High	Low	Medium	Medium	Medium
Olszyna et al ²⁹	Medium	Medium	High	Low	Low	Low	Medium
Price et al ²²	High	Medium	High	Low	Low	Low	Medium
Pupek-Musialik ⁴⁵	High	Low	High	Low	Low	Low	Medium
Sahin et al. ⁴⁶	Medium	Medium	High	Low	Low	Low	High
Sandberg et al ⁴⁷	High	Medium	High	Low	Low	Low	Medium
Short et al ⁴⁸	High	High	High	Low	Low	Low	High
Tyagi et al ⁴⁹	High	Low	High	Medium	Medium	Low	High
Vera et al ⁵⁰	High	Medium	High	Low	Medium	Medium	High
Wu et al ⁵¹	Medium	Low	High	Low	Medium	Medium	Medium
Zhu et al ⁵²	High	Medium	High	Low	Medium	Medium	High
<i>Objectives 1 and 2</i>							
Ciszek et al ⁵³	High	High	High	Low	Low	Low	Medium
Determann et al ⁵⁴	High	Low	Medium	Low	Medium	Low	High
Ethel et al ⁵⁵	Medium	Low	High	Low	Low	Low	Medium
Hedges et al ⁵⁶	High	Medium	High	Low	Low	Medium	Low
Jacobson et al ⁵⁷	High	Medium	High	Low	Low	Low	High
Jacobson et al ⁵⁸	High	Medium	High	Low	Low	Low	High

(Continued)

Table 2. (Continued)

STUDY	PATIENT SELECTION		INDEX TEST		REFERENCE STANDARD		FLOW AND TIMING
	RISK OF BIAS	APPLICABILITY	RISK OF BIAS	APPLICABILITY	RISK OF BIAS	APPLICABILITY	RISK OF BIAS
Kjolvmark et al ⁵⁹	High	Medium	High	Low	Low	Low	High
Rodhe et al ⁶⁰	Medium	Medium	High	Low	Low	Low	Medium
Sundvall et al ⁶¹	Medium	Medium	Low	Low	Medium	Low	Medium
<i>Objective 2 only</i>							
Sunden and Wullt ²⁶	High	Medium	High	Medium	Medium	Medium	High

patients and general practice. Figure 2 displays median IL-8 levels measured for each condition across these studies.

In a cohort study of 16 catheterised in-patients,²⁷ a threshold of 50pg IL-8 per ml of urine was associated with a sensitivity of 97.1% (95% CI 77.1-99.9) and a specificity of 85.3% (95% CI 62.3-95.3) for diagnosing UTI.

In a second cohort study of 165 patients catheterised following major abdominal surgery,²⁹ mean IL-8 concentrations were higher at the point of positive urine culture than baseline, and also higher than in patients without a positive culture. No precise figures were given.

The results from the case-control studies are summarised in Table 3. Urinary IL-8 was between 10 and 36 times higher in samples from patients with pyelonephritis^{37,57} and febrile UTI,⁴⁴ and between 2 and 49.4 times higher in samples from patients with cystitis or a non-specific UTI (ie, a UTI not specified as upper or lower tract) than in those from healthy controls.^{34,49,53,60} One study, including 8 participants with cystitis found similar median urinary IL-8 in cystitis and control groups.⁵⁷

IL-6

We found 1 cohort study, 1 cross-sectional study and 7 case-control studies investigating IL-6, conducted across in-patient, nursing home and primary care populations. See Figure 3 for median IL-6 levels reported in these studies.

In the cohort study, no increase in mean IL-6 the urine of catheterised patients on the day of UTI diagnosis was detected. This study found that urinary IL-6 increased in all patients in the 8 days following catheterisation.²⁹

In the cross-sectional study, urinary IL-6 was found to be higher in nursing home residents with positive urine culture (median concentration of 2.5 ng/l (range 1.0-5.7)) compared with those with negative urine culture 1.3 ng/l (range 0.6-2.8) $P < .001$.

The results from the case-control studies are summarised in Table 3. Three studies found higher level of IL-6 in samples from patients with pyelonephritis than samples from healthy control subjects.^{37,39,57} Six studies compared samples from

patients with cystitis or a non-specific UTI with those from controls.^{39,51,53,57,59,60} In 3 studies, samples from patients were between 3.8 and 37.5 times higher in samples from patients than those from controls.^{53,59,60} The remaining 3 found equivocal results,³⁹ or no difference between groups.^{51,57}

Other biomarkers

We found consistent evidence that biomarkers CXCL-1 and sTNFR types 1 and 2 were elevated in samples from patients with UTI. Three studies found median chemokine (C-X-C Motif) ligand 1 (CXCL-1) to be between 10 and 38 times higher in samples from a mixed population of patients with UTI, cystitis, febrile UTI compared with controls.^{44,49,60} Median levels of sTNFR-1 were between 2 and 10 times higher in samples from patients with pyelonephritis or febrile UTI than in those from healthy controls, whilst median sTNRF-2 was between 3 and 7 times higher.^{37,43,58}

We found consistent evidence that IL-1B and IL-10 biomarkers were not elevated in samples from patients with UTI. We found 3 studies each which demonstrated no elevation of IL-1B^{43,49,60} or IL-10 marker levels in samples from patients with UTI.^{37,43,60}

We found contradictory evidence for 2 biomarkers: secretory IgA (sIgA) and IL1-RA. Two studies found samples from patients with recurrent UTI or UTI not specified as upper or lower tract to have mean levels of sIgA between 3.3 and 40 times higher than healthy controls.^{32,48} Two studies found no difference in mean concentration of urinary sIgA between cystitis and non-specific UTI groups, and controls respectively.^{35,55}

Two studies from the same trial found median IL1-RA concentrations to be 200 times lower ($P < .001$) in patients with UTI than controls, albeit with large ranges. One study found median IL1-RA in samples from patients with UTI to be half ($P < .05$) that of samples from healthy controls.⁴⁹ One study found no differences.⁴³

Objective 2: Biomarkers to distinguish between asymptomatic bacteriuria and UTI

We found 9 studies, including 1058 patients, and evaluating 14 biomarkers for differentiating urine from patients with positive

Table 3. Results for IL-6 and IL-8.

BIOMARKER	STUDIES	POPULATION	MEASURED BIOMARKER (MEDIAN PG/ML AND IQR UNLESS STATED)							STATISTICAL SIGNIFICANCE BETWEEN UTI AND NON-UTI/CONTROL ^a
			UTI	CYSTITIS	PYELONEPHRITIS	FEBRILE UTI	ASB	OAB	NOT UTI	
IL-6	Ciszek et al ⁵³	Patients with stable graft function 12-60 month after kidney transplantation	15.71 (range 3.61-246.95)				3.92 (0.22-17.33)			Median IL-6 pg/mg creatinine higher ($P = .0003$) in UTI compared to ASB and control. No difference between ASB and control.
IL-6	Jacobson et al ³⁷	Patients admitted to hospital with non-obstructive pyelonephritis		44 (no IQR given)					nd	IL-6 was higher in patients with acute pyelonephritis than controls ($P < .001$)
IL-6	Kjølvmark et al (GP Cohort) ³⁹	Patients presenting in primary care with symptoms of UTI, patients presenting to ED with suspected UTI		17 (2-198)	261 (170-606)				1 (1-1)	IL-6 higher in patients with cystitis, and with pyelonephritis than patients without UTI ($P < .01$)
IL-6	Kjølvmark et al (ED Cohort) ³⁹	Patients presenting in primary care with symptoms of UTI, patients presenting to ED with suspected UTI		1 (1-359)	217 (7-719)				1 (1-10)	IL-6 higher in patients with pyelonephritis ($P < .01$) but not cystitis than control patients
IL-6	Kjølvmark et al ⁵⁹	Nursing home residents	150 (4-630)				4 (4-13)		4 (4-8)	Higher in UTI than ASB ($P < .01$), no difference between ASB and no UTI
IL-6	Olszyna et al ²⁹	165 Catheterised patients undergoing major abdominal surgery	no data							IL-6 levels increased in the 2-4 days preceding UTI and a similar increase was found in patients not developing a UTI in the same period.
IL-6	Jacobson et al ⁵⁷	Patients admitted to hospital with pyelonephritis		ND (range ND-90)	44 (range ND-430)		ND (ND-24)		ND	IL-6 higher in patients with pyelonephritis than healthy controls ($P < .001$). No comparison with ASB.
IL-6	Wu et al ⁵¹	Adult patients presenting to a hospital with UTI	5.72 (3.84-9.02)						5.31 (4.32-6.39)	No differences between groups were found.

(Continued)

Table 3. (Continued)

BIOMARKER	STUDIES	POPULATION	MEASURED BIOMARKER (MEDIAN PG/ML AND IQR UNLESS STATED)						STATISTICAL SIGNIFICANCE BETWEEN UTI AND NON-UTI/CONTROL ^a
			UTI	CYSTITIS	PYELONEPHRITIS	FEBRILE UTI	ASB	OAB	
IL-6	Rodhe et al ⁵⁰	Patients aged 80 and above		54.7 (range 10.7-443)			14.4 (7.1-37.4)		11.7 (5.6-69.1) Statistical testing was performed but it was unclear which groups were compared.
IL-6	Hedges et al ⁵⁶	Non-pregnant women			81.2 units/ml (range 0-512)		86.2 units/ml (range 0/190)		No statistical testing reported
IL-6	Sunden et al ²⁶	Patients aged 80 and above	mean 227 ng/L (range 17-1400)				mean 30 ng/l (range 8-86)		Patients with sterile urine or ASB had very low or undetectable levels of urine IL-6. Patients with minor symptoms and not receiving antibiotics had lower levels of IL-6 than patients receiving antibiotics for a suspected UTI ($P < .001$). IL-6 was available to prescribing clinicians.
IL-6	Sundvall et al ⁶¹	Nursing home residents	2.5 ng/L (1.0-5.7)					1.3 ng/L (0.6-2.8)	Urine IL-6 concentration was higher in residents with positive urine culture ($P = .000004$) than in residents with negative urine culture
IL-8	Ciszek et al ⁵³	Patients with stable graft function 12-60 months after kidney transplantation	146.80 (range 24.65-2114.25)				33.49 (2.97-129.75)		Median IL-8 pg/mg creatinine higher ($P < .001$) in UTI in ASB control. IL-8 higher in ASB than control ($P < .0004$)
IL-8	Jacobson et al ⁵⁷	Patients admitted to hospital with pyelonephritis		70 (ND-840)	78 (ND-3700)		93 (ND-270)		IL-8 higher in patients with pyelonephritis than controls ($P < .005$). No comparison made with cystitis or ASB.

(Continued)

Table 3. (Continued)

BIOMARKER	STUDIES	POPULATION	MEASURED BIOMARKER (MEDIAN PG/ML AND IQR UNLESS STATED)							STATISTICAL SIGNIFICANCE BETWEEN UTI AND NON-UTI/CONTROL ^a
			UTI	CYSTITIS	PYELONEPHRITIS	FEBRILE UTI	ASB	OAB	NOT UTI	
IL-8	Flores-Figueroa et al ²⁷	Catheterised hospital patients	309						10	At a threshold of 50 pg/ml, IL-8 was associated with a sensitivity of 97% and a specificity of 85% for diagnosing UTI
IL-8	Gadalla et al ³⁴	Women presenting with UTI symptoms to primary care	8.57 (1.74-24.25)						4 (1-14.92)	No statistically testing performed
IL-8	Jacobson et al ³⁷	Patients admitted to hospital with non-obstructive pyelonephritis			870 (no IQR given)				87 (no IQR given)	IL-8 was higher in patients with acute pyelonephritis than controls ($P < .001$)
IL-8	Olszyna et al ⁴⁴	Patients with suspected gram-negative urosepsis				0.38 ng/ml (range <0.01-3.13)			<0.01 ng/ml (<0.01-0.14)	Patients with urosepsis at admission had higher urinary IL-8 than healthy controls <0.01
IL-8	Olszyna et al ²⁹	165 Catheterised patients undergoing major abdominal surgery	no data						no data	IL-8 was increased in UTI positive patients on the day of positive culture, but not in UTI controls ($P < .01$).
IL-8	Rodhe et al ⁶⁰	Patients aged 80 and above		313 (range 137-550)			69.6 (6.5-809)		14.5 (2.5-50.7)	Statistical difference between groups was unclear.
IL-8	Sunden et al ²⁶	Patients aged 80 and above	mean 2013 ng/L (range 387-3399)				mean 3392 (164-7500)			There was no different in urinary IL-8 levels between Nursing Home residents with UTI and ASB
IL-8	Tyagi et al ⁴⁹	Patients routinely visiting a urology clinic	63.67 (8.8-140.3)					4.70 (0-16.81)	4.45 (0-19.52)	UTI was higher than controls ($P < .01$), and OAB ($P < .001$)

^aStatistical significance included where reported by the authors.

Table 4. Biomarker table for biomarkers to diagnose UTI investigated 3 times or more.

BIO MARKER	STUDIES	POPULATION	MEASURED BIOMARKER (MEDIAN PG/ML AND IQR UNLESS STATED)					STATISTICAL SIGNIFICANCE BETWEEN UTI AND NON-UTI/CONTROL ^a			
			UTI	CYSTITIS	RECURRENT CYSTITIS	PYELONEPHRITIS	FEBRILE UTI	ASB	OAB	CONTROLS	
GRO-a (CXCL1)	Rodhe et al ⁶⁰	Patients aged 80 and above		222 (range 0->6000)				38.0 (0-783)		14.5 (2.5-50.7)	Statistical testing was performed but it was unclear which groups were compared
GRO-a (CXCL1)	Olszyna et al ⁴⁴	Patients with suspected gram- negative urosepsis					0.38ng/ ml (range <0.01- 3.13)			<0.01 (<0.01- 0.14)	Higher in patients with febrile UTI than controls (<i>P</i> < .05)
GRO-a (CXCL1)	Tyagi et al ⁴⁹	Patients routinely visiting a urology clinic	47.14 (2.8- 336.4)						4.70 (0-16.81)	4.48 (0-19.52)	Higher in samples from patients with UTI than controls and OAB (<i>P</i> < .001)
IgA – secretory	Ethel et al ^{55*}	Women (no more details given)	mean 0.045 (±0.04) urinary antibodies to mixed coliform antigen					mean 0.101 (±0.13) urinary antibodies to mixed coliform antigen		mean 0.44 (±0.02) urinary antibodies to mixed coliform antigen	Higher in samples from patients with ASB (<i>P</i> < .01)
IgA – secretory	Deo and Vaidya ³²	Adult patients showing signs of urinary tract infection	mean 80ug/ml (±48)							mean 5.2 (±0.73)	Higher in samples from patients with UTI than those from controls (<i>P</i> < .001)
IgA – secretory	Greenwell et al ³⁵	Adults (no more details given)		1		1				1	No difference between samples from patients with cystitis and controls. Higher in samples from patients with pyelonephritis than controls (<i>P</i> = .012)
IgA – secretory	Short et al ⁴⁸	Catheterised women with recurrent cystitis			mean 0.774 mg/dl creatinine (±0.186)					mean 0.228 mg/dl creatinine (±0.140)	Higher in samples from patient with UTI than controls (<i>P</i> < .001)

(Continued)

Table 4. (Continued)

BIO MARKER	STUDIES	POPULATION	MEASURED BIOMARKER (MEDIAN PG/ML AND IQR UNLESS STATED)							STATISTICAL SIGNIFICANCE BETWEEN UTI AND NON-UTI/CONTROL ^a	
			UTI	CYSTITIS	RECURRENT CYSTITIS	PYELONEPHRITIS	FEBRILE UTI	ASB	OAB		CONTROLS
IL-1 RA	Jacobson et al ⁵⁸	Patients admitted to hospital with non-obstructive pyelonephritis				40 (range nd-43 000)		nd (nd-52)		8400 (700- 76 000)	Lower in patients with pyelonephritis than controls (<i>P</i> < .001). No comparison with ASB
IL-1 RA	Jacobson et al ³⁷	Patients admitted to hospital with non-obstructive pyelonephritis				40 (no IQR given)				8400 (no IQR given)	Lower in patients with pyelonephritis than controls (<i>P</i> < .001).
IL-1 RA	Olszyna et al ⁴³	No detail given					0.67 ng/ml (range 0.10- 26.0)			0.60 (<0.08-3.62)	No differences found
IL-1 RA	Tyagi et al ⁴⁹	Patients routinely visiting a urology clinic	72.08 (28.45- 151.7)						62.03 (33.07- 148.1)	181.9 (40.02- 635.6)	Higher in samples from patients with UTI than controls and OAB (<i>P</i> < .05)
IL-10	Rodhe et al ⁶⁰	Patients aged 80 and above		12.5 (1.4-31.3)				14.6 (5.3-31.6)		9.2 (1.7-16.6)	Statistical testing was performed but it was unclear which groups were compared
IL-10	Jacobson et al ³⁷	Patients admitted to hospital with non-obstructive pyelonephritis				nd				nd	No differences found
IL-10	Olszyna et al ⁴³	No detail given					nd			nd	No differences found
IL-1B	Rodhe et al ⁶⁰	Patients aged 80 and above		97.1 (0-11 500)				62.7 (15.9-153)		57.5 (25.9-186)	Statistical testing was performed but it was unclear which groups were compared

(Continued)

Table 4. (Continued)

BIO MARKER	STUDIES	POPULATION	MEASURED BIOMARKER (MEDIAN PG/ML AND IQR UNLESS STATED)						STATISTICAL SIGNIFICANCE BETWEEN UTI AND NON-UTI/CONTROL ^a		
			UTI	CYSTITIS	RECURRENT CYSTITIS	PYELONEPHRITIS	FEBRILE UTI	ASB		OAB	CONTROLS
IL-1B	Olszyna et al ⁴³	No detail given					nd			nd	No differences found
IL-1B	Tyagi et al ⁴⁹	Patients routinely visiting a urology clinic	1.76 (0.84- 5.26)						0.12 (0.07- 0.23)	0.29 (0.06-2.24)	No differences found
sTNFR1	Jacobson et al ⁵⁸	Patients admitted to hospital with non-obstructive pyelonephritis				2500 (range 334-24 000)		460 (206-1040)		1125 (195-3250)	Higher in patients with pyelonephritis than controls (<i>P</i> < .001). No comparison with ASB.
sTNFR1	Jacobson et al ³⁷	Patients admitted to hospital with non-obstructive pyelonephritis				2500 (no IQR given)				1125 (no IQR given)	Higher in patients with pyelonephritis than controls (<i>P</i> < .001).
sTNFR1	Olszyna et al ⁴³	No detail given					17.55 ng/ml (range <0.04- 25.0)			1.78 (0.4-3.32)	Higher in patients with febrile UTI than controls (<i>P</i> < .001)
sTNFR2	Jacobson et al ⁵⁸	Patients admitted to hospital with non-obstructive pyelonephritis				6300 (940-54 000)		980 (424-3000)		1980 (375-5000)	Higher in patients with pyelonephritis than controls (<i>P</i> < .001). No comparison with ASB.
sTNFR2	Jacobson et al ³⁷	Patients admitted to hospital with non-obstructive pyelonephritis				6300 (no IQR given)				1980 (no IQR given)	Higher in patients with pyelonephritis than controls (<i>P</i> < .001).
sTNFR2	Olszyna et al ⁴³	No detail given					14.96ng/ ml (range <0.02- 50.0)			2.34 (0.5-5.34)	Higher in patients with febrile UTI than controls (<i>P</i> < .001)

^aStatistical significance included where reported by the authors.

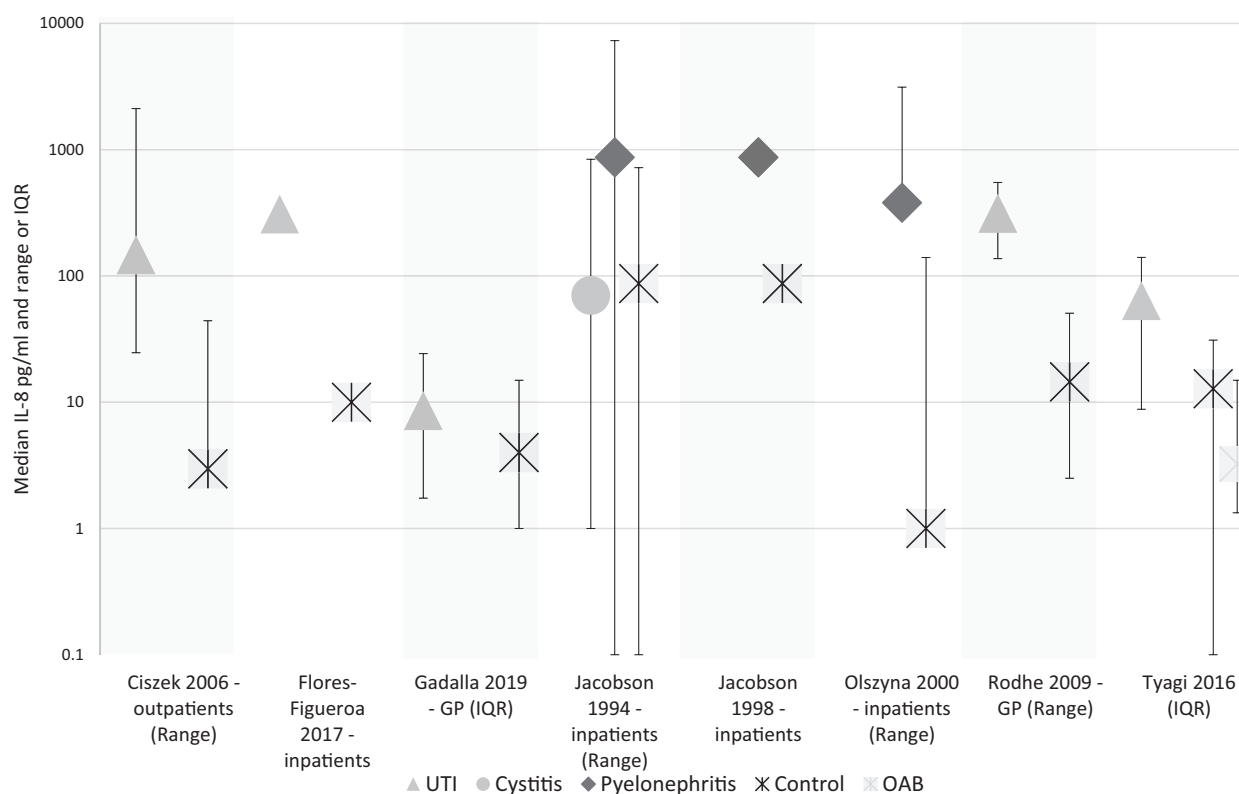


Figure 2. Median IL-8 titre in pg/ml in studies reporting medians. Olszyna et al.²⁹ not shown. Variance shown in the study title.

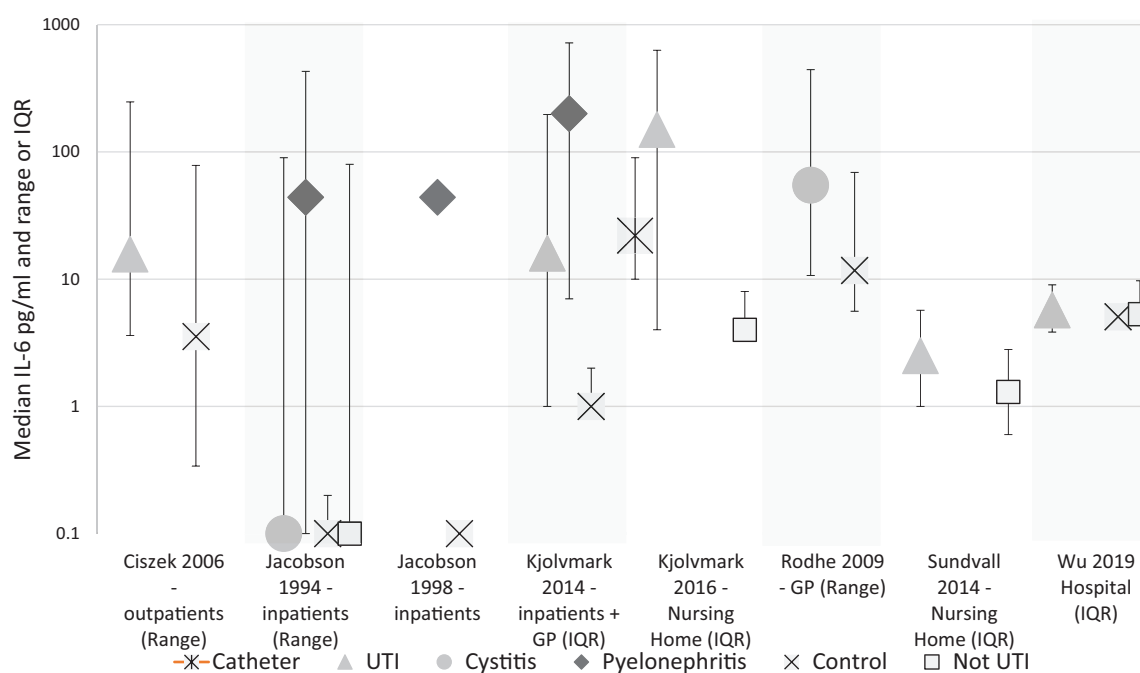


Figure 3. Median IL-6 titre in pg/ml in studies reporting medians. Olszyna et al.²⁹ and Hedges et al.⁵⁶ not shown. Variance shown in study title.

culture and symptoms (UTI) and positive culture and no symptoms (asymptomatic bacteriuria (ASB)) (Tables 3 and 4). One study had a cohort design, whilst the rest had a case-control design. Seven studies compared ASB to a non-specific UTI group^{26,53-55,57,60,61}, 1 study compared ASB to a cystitis and a pyelonephritis group,⁵⁹ and the final study compared

ASB with a pyelonephritis group only.⁵⁶ Fourteen biomarkers were investigated; IL-6 7 times, IL-8 4 times, and the remainder only once.

All of these studies compared biomarker levels in patients with a positive urine culture and symptoms to patients who had a positive urine culture without symptoms. No study attempted

to differentiate UTI and ASB in patients who were unable to report symptoms. In 1 study,²⁶ biomarkers levels were compared between patients with UTI symptoms prescribed antibiotics and those not receiving antibiotics, although the biomarker was made available to clinicians making treatment decisions, meaning there may be an incorporation bias.

IL-8

Four studies analysed IL-8, one of which had a cohort design and sampled a nursing home population.²⁶ The cohort study took monthly urine samples from 35 patients with ASB (defined as 2 consecutive urine samples 4 weeks apart with $\geq 10^5$ CFU/ml of the same pathogen with controlled somatic diseases) and compared levels of both biomarkers before and during episodes of UTI. During ASB, the mean IL-8 concentration in urine was 2013 ng/l (range 387–3999) in comparison to 3392 (164–7500) during UTI. No statistical difference was found.

In one case-control study urine samples from patients with cystitis⁶⁰ had a median concentration of IL-8 4.8 times higher than those from patients with ASB. One study including renal transplant patients with non-specific UTI during follow up demonstrated that those with UTI had a median concentration of IL-8 4.4 times higher than samples from patients with ASB ($P < .001$).⁵³ A study including patients with pyelonephritis and cystitis found that they had comparable IL-8 concentrations to patients with ASB.⁵⁷

IL-6

Six studies analysed IL-6, including one cohort study.²⁶ In the cohort study, the mean IL-6 concentration in urine from patients with ASB was 30 ng/l (range 8–86) in comparison to a mean of 227 (17–1400) during UTI ($P = .017$).

In a second phase of the cohort study, 254 suspected UTIs in 84 patients were analysed using IL-6 testing in combination with a urine culture. Patients with minor symptoms and not receiving antibiotics had lower levels of IL-6 than patients receiving antibiotics for a suspected UTI (point estimates not given) ($P < .0001$).²⁶ At a threshold of 25 ng/ml, urinary IL-6 was associated with a sensitivity of 57%, a specificity of 80%, a PPV of 52% and an NPV of 83% for differentiating treated UTI from ASB.

Two case-control studies found 4⁵³ and 37.5⁵⁹ times higher median urinary IL-6 in samples from patients with non-specific UTI than those with ASB (see Table 3). One study found median IL-6 at 3.8 times the concentration in samples from patients with cystitis compared to those from patients with ASB⁶⁰, whilst another found no difference.⁵⁷ Two studies found no differences in urinary IL-6 between samples from patients with pyelonephritis and those with ASB.^{56,57}

Others

Results from the remaining 12 biomarkers are summarised in Supplemental Table 2. Three biomarkers: uHPB, CXCL-1 and

sTREM-1 were elevated in samples from patients with UTI compared to those with ASB. In the study analysing sTREM-1, 39/70 participants with a UTI (56%) had a urine culture, whilst the remainder we diagnosed with a positive dipstick and bacteria in the urine sediment.

Discussion

We found 37 studies investigating 64 individual urine biomarkers for the diagnosis of UTI. The quality of the available evidence was limited by study design and heterogeneity, but a handful of biomarkers emerged as viable candidates for new diagnostic tests. In 8 studies IL-8 was consistently raised in UTI patients compared to controls, and in 1 study rose 24 hours earlier than a UTI diagnosis was made. CXCL-1 was also markedly higher in samples from patients with UTI compared to those from controls across 3 studies, albeit all were case-control. A singular cohort study suggested MCR may have a good ability to rule-in UTI, but the sensitivity was low. In the majority of studies, IL-6 was also associated with infection compared to controls, and was the only biomarker to consistently demonstrate higher levels in UTI compared to ASB, including in older adults.

The role of specific cytokines in the bladder's response to infection is a major unknown. Interestingly IL-8, IL-6 and CXCL-1 are released by macrophages, the largest resident immune cell population in the bladder, and the urothelium.⁶² Early in pathogenic *E. coli* infection, shedding of superficial urothelial cells helps clear bacteria, but also exposes deeper layers of the urothelium, triggering cytokine release. A delicate balance exists between bacterial clearance and preserving tissue integrity. Taken together, high levels of these cytokines may be early indicators of invasive infection and help differentiate this from asymptomatic bacteruria.

Our results incorporate a major expanse in evidence since a previous systematic review in 2009,¹⁸ which only identified 11 urine biomarkers. The previous review also focused on serum biomarkers, including IL-6, IL-8 and procalcitonin, which cannot differentiate UTI from other sources of infection. The evidence for urinary IL-6 and IL-8 is mirrored in a recent systematic review of febrile children with UTI; urinary IL-6 had a pooled sensitivity of 77% (95% CI 69%–83%) and specificity of 87% (95% CI 86%–92%), and urinary IL-8 had a pooled sensitivity of 87% (95% CI 82%–91%) and specificity of 90% (95% CI 87%–93%).⁶³

Due to the nature and quality of evidence available there are some limitations to our findings. There was virtually no data on diagnostic performance, hence we were unable to perform quantitative analysis, either between biomarkers, or compared to dipstick or culture. The majority of biomarkers were only studied once and the large heterogeneity between study design, population ages and included conditions make comparisons less meaningful. We did not use a pre-specified threshold for number of colony forming units per ml of urine in our reference standard. This reflects the lack of consensus on this threshold internationally.^{21,22} We also included microscopy as a possible, albeit far

from perfect, reference standard, and found one study which used microscopy only as the reference standard for some patients. The diagnostic accuracy of microscopy is unclear due to a lack of specific evidence and its sensitivity may be as low as 50%,⁶⁴ however it may be used to rule out the presence of bacteria. Both choices allowed us to capture the widest range of evidence possible regarding novel biomarkers, but may have reduced comparability of evaluations. Furthermore, most of our included studies had a case-control design increasing the risk of selection and ascertainment bias. All of the studies comparing biomarkers in symptomatic UTI versus ASB used patient-reported conventional UTI symptoms to distinguish between the 2 conditions. This limits the applicability to patients with atypical symptoms, or those who cannot communicate, such as nursing home residents.

Our results are a stepping-stone for future research, in particular prospective, rather than case-control studies. Larger cohort studies could help determine diagnostic performance and thresholds for testing. Our focus would be on settings where near-patient testing has the potential for largest impact, for example, within primary care, where urine dipsticks are usually the only other test available, and delays in receiving urine culture results are longest. Research addressed at how novel biomarkers may differentiate between ASB and UTI need careful design. Currently there is no universal reference standard, and there is also an overlap in patient populations, especially in older adults, as patients with ASB develop active infection. Combined panels of urine biomarkers may also increase diagnostic performance. In one study an algorithm using IL-8 and 3 other biomarkers (MMP9, NGAL and IL-1 β) had a modest ability to rule in infections (positive Likelihood ratio 6.29, 95% CI 2.04-19.36),³⁴ although the diagnostic thresholds used in these algorithms were not specified. Future research may consider the diagnostic value of measuring multiple biomarkers from a single sample, and the added value of this for clinicians. Ultimately, well powered and carefully design randomised trials of urinary biomarkers in practice are needed to establish how they can help identify those patients who would most benefit from antibiotics.

Conclusion

This systematic review provides justification for the further investigation of a number of novel urinary biomarkers, notably CXCL-1, IL-6, IL-8, MCR and the sTNFRs. Primary care based prospective studies are needed to establish diagnostic performance and utility in clinical practice.

Declarations

Ethics approval and consent to participate

Not required.

Consent for publication

All authors have approved the manuscript and consented to its publication.

Author contributions

Conceptualisation (GE, ML, GH), Data Curation (GE, AS), Formal Analysis (GE, AS), Funding Acquisition (GH), Investigation (all authors), Methodology (GE, AVB, JV, GH), Resources (GE, GH), Software (GE), Supervision (GH), Validation (GH), Visualisation (GE, AS), Writing original draft (GE, AS), Writing review and editing (all authors).

Acknowledgements

The authors would like to acknowledge Nia Roberts for performing the literature searches, and Marta Wanat, Marta Santillo, Tomasz Dobryzki, Joe Kang, Barbora Benkova, Nahoko Kasai, and Olga Romanova for helping translate papers not published in English.

Availability of data and materials

Not applicable.

ORCID iD

George Edwards  <https://orcid.org/0000-0002-0048-4178>

Supplemental material

Supplemental material for this article is available online.

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