

# Biomarkers in urinary tract infections – which ones are suitable for diagnostics and follow-up?

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## Abstract

**Introduction:** Urinary tract infections (UTIs) are one of the most common infections worldwide. Under special circumstances, clinicians must rely on laboratory findings, which might have a weak predicting value, misguiding the practitioners and leading to incorrect diagnosis and overuse of antibiotics. Therefore, there is an urgent need for reliable biomarkers in UTIs.

**Methods:** We performed a literature search for biomarkers used in UTIs from January 1999 until May 2020. We used “urinary tract infection” and “biomarker” as the main key words in the PubMed, Medline and Cochrane databases. After peer review, we excluded the duplicates and identified the suitable articles, from which we collected the data and divided the available biomarkers into 5 groups: i) conventional markers; ii) promising, thoroughly studied biomarkers; iii) promising biomarkers that need further studies; iv) biomarkers of unknown significance; v) controversial, not useful markers.

**Results:** We found 131 articles, mostly from the paediatric population. Neutrophil gelatinase-associated lipocalin (NGAL) and interleukins (IL) have a leading role in diagnosing and differentiating UTIs based on a lot of observational, comparative trials. Heparin Binding Protein (HBP), Lactoferrin (LF), Heat-Shock Protein-70 (HSP-70), Human Defensin-5 (HD-5), Lipopolysaccharide Binding Protein (LBP) and mass spectrometry studies are promising, but confirming data are lacking. The measurable components of the innate immune system and local host cell response could be appropriate biomarkers, but their significance is currently unknown.

**Conclusions:** Conventional biomarkers for UTIs have low specificity. The use of urinary NGAL and interleukins could improve the sensitivity and specificity of laboratory diagnosis of UTIs.

**Keywords:** biomarker, urinary tract infection

## Summary of findings

1. Conventional biomarkers (pyuria, nitrite, proteinuria, CRP, PCT) have weak accuracy in general for diagnosis and differential diagnosis for UTIs.
2. The urothelium is an interactive immunological structure that produces an enormous quantity of molecules during the host-pathogene interaction. All of these molecules can form a subject for further research as a potential biomarker for UTIs.
3. Most data is collected on NGAL and interleukins, but their role is not exclusive in diagnostics considering the limiting factors and the lack of well-designed, confirming studies.
4. There are studies with at least 50 or more other biomarkers with either promising or controversial outcomes on their clinical usefulness, which we present briefly.
5. Not only for diagnosis but also for etiologic diagnosis there is a novel technology (NMR-spectrometry) with convincing, but few studies.
6. None of the presented biomarkers can render an exceptional or exclusive role in the field of diagnostics, thus further research is needed to identify suitable, reliable and easily measurable biomarkers.

# 1 Introduction

Urinary tract infections (UTIs) are amongst the most common infections worldwide. The diagnosis is based on symptoms, laboratory and imaging findings depending on the clinical manifestation. In this article, we will use the terminology as defined by the European Urological Association (EAU) in their guideline. For details, see [Table 1](#).

Table 1: Notions and definitions used in the article

Notion	Synonyme	Definition
Urinary tract infection	UTI, symptomatic (s)-UTI	Collective name for lower or upper urinary tract infections; diagnosis is based on typical symptoms and positive urine culture with a single microorganism in significant amount of clone forming units
Uncomplicated cystitis	Lower urinary tract infection (l-UTI), cystitis	Acute, sporadic or recurrent cystitis limited to non-pregnant women with no known relevant anatomical and functional abnormalities within the urinary tract or comorbidities
Uncomplicated pyelonephritis	Upper or febrile urinary tract infection, acute pyelonephritis (APN)	Pyelonephritis is suggested by fever (>38°C), chills, flank pain, nausea, vomiting, or costovertebral angle tenderness, with or without the typical symptoms of cystitis
Urosepsis	Febrile urinary tract infection (f-UTI)	Life-threatening organ dysfunction caused by a dysregulated host response to infection originating from the urinary tract and/or male genital organs
Asymptomatic bacteriuria	ABU	Urinary growth of bacteria in an asymptomatic individual that corresponds to a commensal colonization

Non-febrile, symptomatic lower UTIs react with local mucosal responses; febrile UTIs (f-UTIs)/acute pyelonephritis (APN) have an added significance to systemic host response; patients with asymptomatic bacteriuria (ABU) normally have no or only a discrete host response. Although these approaches provide an appropriate diagnosis in the majority of cases, their diagnostic accuracy or clinical usability can be limited in some situations, including UTIs in infants and in patients with neurogenic conditions or continuous catheterization.

Unfortunately, the widely used conventional biomarkers, including C-reactive protein (CRP), urine nitrite, leukocyte esterase, pyuria, and proteinuria, have a low sensitivity and specificity for predicting or differentiating UTIs, leading to over- or undertreatment. According to a retrospective pediatric study – analyzing 1,186 subjects, using these conventional diagnostic tools, 43% of the patients are overtreated, and 13% are undertreated, leading to recurrent infections, antibiotic resistance or kidney damage [1]. Thus, the need for a suitable, specific, easily measurable, widely available and quick biomarker for UTIs is in the focus of interest.

The search for the potential markers exploded when specific functions of the urothelium were described. The epithelial cells in bladder mucosa are not only a barrier, but also an active, responsive structure. During inflammatory setting, it produces cytokines in order to eliminate the microbial threat [2]. In this process, every produced molecule has its own role, forming a subject for identifying a suitable biomarker.

## 2 Methods

A literature search for biomarkers used in UTIs from January 1999 until May 2020 was performed. We used “urinary tract infections” and “biomarker” as the main key words in the PubMed, Medline and Cochrane databases. After reviewing, a total of 226 publications were identified, which were screened by title and abstract. Excluding the duplicates, we included 168 articles for full paper selection. Due to lacking data or weak study design, we excluded another 37, thus in the end, a total of 131 articles were included into this paper. Based on the results, we divided the available biomarkers into 5 groups:

1. conventional markers;
2. promising, thoroughly studied biomarkers;
3. promising biomarkers that need further studies;
4. biomarkers of unknown significance;
5. controversial, not useful markers.

Under the term “promising biomarkers”, we understand those markers that performed remarkable results on a scientific or on a statistical basis. For detailed information, see [Table 2](#).

Table 2: Identified studies on different biomarkers

Biomarkers		Number of studies
Conventional biomarkers		30
Promising, thoroughly studied markers	Cytokine	29
	NGAL	22
Promising markers that need further studies	HBP	5
	Spectrometry	6
	Lactoferrin	3
	BMP-2 + CysC	2
	MMP-9	1
	LBP	1
	HNP-1,-3 + HD-5	1
Biomarkers of unknown significance		33
Controversial/not useful markers		10

*BMP-2: bone morphogenic protein-2, CysC: cystatin-C,*

*HBP: heparin binding protein,*

*HD-5: human defensin-5,*

*HNP-1,-3: human neutrophil peptides-1,-3,*

*LBP: lipopolysaccharide binding protein,*

*MMP-9: matrix metalloprotease-9,*

*NGAL: neutrophil gelatinase-associated lipocalin.*

*Note: 131 articles were analyzed. The total number of studies mentioned in Table 2 is 141, because some studies deal with more than one marker.*

## 3 Results

Out of the 131 articles, 70 articles were on children, 49 on adults. The remaining 12 articles were either basic research or reviews. 55 studies operated with patient numbers over 50. In 30 articles, we found data on conventional biomarkers (CRP, procalcitonin (PCT), pyuria, nitrite etc.). These studies were either comparative with novel biomarkers or comparative with other conventional biomarkers. We did not deal with the latter ones, because our primary target was to identify and analyze novel biomarkers.

### 3.1 Conventional markers

In this category, we selected those markers that have been in clinical use from the beginning of laboratory diagnostics of UTIs.

Based on a retrospective study analyzing 1,223 cases, pyuria's negative predictive value (NPV) is 75%, and the positive predictive value (PPV) is 40% in UTIs. Neither centrifugation nor staining the samples add any diagnostic advantage [3]. According to a review by Averbek et al., a nitrite test is also a surrogate marker. However, its sensitivity is only 35–57%, but PPV is high with 96%. Combining pyuria with nitrite indicates 67% of the culture-positive cases [4]. Considering that proteinuria can occur in a series of other disease with a varying ratio of the excreted proteins, it is a non-specific marker of UTIs [5]. Lower UTIs induce the local immune system. It is obvious that acute phase proteins like CRP or PCT do not markedly elevate in serum. Based on a Cochrane meta-analysis, CRP has a sensitivity of 94%, and a specificity of 39%, indicating APN with the cut-off value of 2 mg/dl [6]. In a large, prospective study among children, PCT had 86% sensitivity and 89% specificity in detecting APN using 1.3 ng/ml as cut-off value [7].

### 3.2 Promising, thoroughly studied biomarkers

#### 3.2.1 Neutrophil gelatinase-associated lipocalin (NGAL)

We identified 49 articles on the following biomarkers, where studies with larger patient numbers (above 50 subjects) and/or with specific, well-defined, statistically proven outcomes were available. In specific patient groups, more difficult to study, as neurogenic bladder disorder and elderly patients with ABU, studies with smaller patient groups were also considered.

NGAL is an acute-phase protein [8], [9]. It was first observed in acute kidney injury affecting the proximal tubuli [10], [11]. It has a far-reaching effect on immune processes and has a direct bacteriostatic effect by blocking the siderophores on the Gram-negative bacterial wall [12]. NGAL levels elevate after 12 hours of the infection and reach their peak within 3 days [13]. Its secretion shows a variation by age and gender, but differences are small, thus there is no need for standardization [14]. NGAL excretion is independent from glomerular filtration, thus standardization for creatinine is not necessary [15]. Table 3 summarizes the results of studies on NGAL.

Table 3: Urinary and serum NGAL for predicting UTI and differentiating infections

		Cut-off value	Sensitivity	Specificity	Study population	Disease	Aim	References
Urine NGAL	1	42.2 ng/ml	–	–	84 children – infants	f-UTI	Diagnosis of f-UTI	Krzemien et al. 2017 [47]
	2	39.0 ng/ml	–	–	54 children	UTI	Diagnosis of UTI	Krzemien et al. 2019 [48]
	3	–	90%	91%	422 children – infants	UTI	Diagnosis of UTI	Jung et al. 2018 [13]
	4	39.1 ng/ml	97%	95%	260 children – infants	UTI	Diagnosis of UTI	Lubell et al. 2017 [49]
	5	5.75 ng/ml	–	–	812 children	UTI	Diagnosis of UTI	Kim et al. 2014 [8]
	6	23.9 ng/ml	98%	100%	100 adults	UTI	Diagnosis of UTI	Price et al. 2017 [50]
	7	23.9 ng/ml	82%	83%	73 children	UTI	Diagnosis of UTI	Yim et al. 2014 [51]

	8	276 ng/mg (/CRN)	76%	90%	73 children	UTI	Diagnosis of UTI	Yim et al. 2014 [51]
	9	20 ng/ml	97%	76%	89 children	UTI	Diagnosis of UTI	Yilmaz et al. 2009 [9]
	10	20.4 ng/ml	64%	92%	134 children	UTI	Diagnosis of UTI	Arambasic et al. 2016 [52]
	11	29.4 ng/ml	92.5%	90%	134 children	APN	Diagnosis of APN	Arambasic et al. 2016 [52]
	12	73 ng/ml	75%	73%	89 children	APN	Diagnosis of APN	Yilmaz et al. 2009 [9]
	13	290 ng/mg (/CRN)	90%	63%	89 children	APN	Diagnosis of APN	Yilmaz et al. 2009 [9]
	14	229 ng/ml	83%	86%	201 children + neurogenic bladder	ABU/UTI	Distinguishing ABU from UTI	Forster et al. 2018 [53]
	15	38.5 ng/ml	87%	78%	134 children	APN/UTI	Distinguishing APN from UTI	Arambasic et al. 2016 [52]
	16	23.9 ng/ml	98%	100%	100 adults	UTI	Diagnosis of UTI	Price et al. 2017 [50]
<b>Serum NGAL</b>	1	62.25 ng/ml	–	–	812 children	UTI	Diagnosis UTI	Kim et al. 2014 [8]
	2	267 pg/l	72%	71%	64 children – infants	f-UTI	Predicting kidney damage	Yun et al. 2018 [54]

APN: acute pyelonephritis, ABU: asymptomatic bacteriuria, CIC: clean intermittent catheterization, CRN: creatinine, f-UTI: febrile urinary tract infection, NGAL: neutrophil gelatinase-associated lipocalin, UTI: urinary tract infection

Based on the results, urinary NGAL can be a suitable marker for diagnosing UTIs in children and in adults. Although serum NGAL elevates during UTIs as well, referring to the listed data, urinary NGAL seems to be a more sensitive marker for predicting UTIs. For differential diagnosis of upper from lower UTIs, NGAL also could be a useful marker. Although the difference between the two groups was not significant in every study, a remarkable disparity could be observed between these groups [16]. Urine NGAL (U-NGAL) could be used for monitoring as well, because its level correlates with the duration of infection [17].

### 3.2.2 Cytokines

During the host cell-pathogen interaction, a cytokine burst occurs in order to recruit the cells of the innate immune system and enhance the defense against pathogens. In UTIs, cytokines are mainly produced locally in the uroepithelial cell lining of the bladder and secreted into the urine. Generally, creatinine correlation of the cytokine content to compensate for different dilutions of the urine is not considered necessary [18]. Mostly, interleukin 1-beta (IL-1B), interleukin-6 (IL-6) and interleukin-8 (IL-8) are studied. IL-1B could be a promising marker for differentiation between upper and lower UTIs [19]. Studies performed on different cytokines are shown in Table 4.

Table 4: Diagnostic and differential diagnostic value of IL-1B, IL-6, IL-8

		Cut-off value	Sensitivity	Specificity	Study population	Disease	Aim	References
<b>Urinary IL-1B</b>	1	6.9 pg/ml	97%	59%	443 children	UTI	Distinguishing u-UTI from l-UTI	Nanda et al. 2009 [19]
	2	150 pg/mg (/CRN)	79%	88%	75 children	UTI	Diagnosing APN	Sheu et al. 2007 [55]
<b>Serum IL-1B</b>	1	6.9 pg/ml	27%	90%	79 children	UTI	Distinguishing u-UTI from l-UTI	Mahyar et al. 2015 [56]
<b>Urinary IL-6</b>	1	30 pg/ml	52%	92%	390 adults	UTI	Diagnosing UTI	Kjölvmark et al. 2014 [57]
	2	30 pg/ml	38%	82%	134 adults – elderly	UTI	Distinguishing ABU from UTI	Kjölvmark et al. 2016 [58]
	3	30 pg/ml	80%	82%	134 adults – elderly	UTI	Distinguishing ABU from APN	Kjölvmark et al. 2016 [58]
	4	30 pg/ml	59%	84%	134 adults – elderly	UTI	Distinguishing ABU from UTI	Kjölvmark et al. 2016 [58]
	5	600 pg/mg (/CRN)	81%	96%	60 adults – elderly	UTI	Distinguishing ABU from UTI	Rodhe et al. 2009 [59]
	6	25 pg/ml	77%	93%	37 adults + residual urine	UTI	Distinguishing ABU from UTI	Sundén et al. 2017 [60]
	7	25 pg/ml	57%	80%	35 adults – elderly	UTI	Distinguishing ABU from UTI	Sundén et al. 2016 [61]
<b>Urinary IL-8</b>	1	200 pg/ml	93%	90%	264 children	UTI	Diagnosing UTI	Rao et al. 2001 [62]
	2	5 pg/ml	88%	69%	59 children – infants	VUR	Diagnosing VUR	Galanakis et al. 2006 [63]
	3	200 pg/ml	54%	89%	37 adults – elderly	UTI	Distinguishing ABU from UTI	Sundén et al. 2017 [60]
<b>Serum IL-8</b>	1	8 pg/ml	70%	32%	80 children	UTI	Diagnosing UTI	Mahyar et al. 2015 [56]

APN: acute pyelonephritis, ABU: asymptomatic bacteriuria, CRN: creatinine, f-UTI: febrile urinary tract infection, IL-1B: interleukin-1 beta, IL-6: interleukin-6, IL-8: interleukin-8, l-UTI: lower urinary tract infection, s-UTI: symptomatic urinary tract infection, u-UTI: upper urinary tract infection, UTI: urinary tract infection, VUR: vesico-ureteral reflux

IL-6 and IL-8 are expressed rapidly after getting into contact with pathogens. IL-6 not only recruits immune cells, but also initiates gene cascades in order to produce antimicrobial peptides [20]. Due to its key role, it can be a predictor for UTIs and a marker of differentiation.

IL-8 has a central role in all inflammatory processes. Although its elevated concentration is observed in UTIs and can be a predictor of acute pyelonephritis, its specificity is low. It raises in every kind of congenital urinary anomaly, except antenatal renal pelvic dilatation. Thus, IL-8 is not suitable for diagnosing UTIs when an anatomical disorder is present [21].

In a recent observational study, 466 patients were enrolled. It turned out that measuring IL-8 in urine along with serum CRP and neutrophil-lymphocyte ratio (NLR) could indicate the pathogen among adults with type 2 diabetes mellitus. According to the authors, lower levels of CRP (median value: 33 mg/dl), higher levels of NLR (over 3.5) and higher levels of urine IL-8 (uIL-8) (median: 2,120 pg/ml) refer to extended spectrum beta-lactamase (ESBL) producing *Escherichia coli* infection. The opposite findings (median CRP under 39.8 mg/dl, NLR under 3.5, uIL-8 median 668 pg/ml) could indicate the presence of UTIs caused by ESBL producing *Klebsiella pneumoniae*. Increased NLR and IL-8 not only refers to the etiology, but also indicates the occurrence of renal damage. Among the aforementioned markers, NLR had the strongest predictive value for diagnosing UTIs caused by ESBL producing *E. coli* with 88% sensitivity, 73% specificity, 93% PPV and 24% NPV [22].

Using cytokines for diagnosing UTIs is limited by their low specificity. Elevated levels can be seen in a variety of other diseases, where the immune system is activated for a shorter or longer period [23]. A promising solution for this is to find cytokine combinations for a specific disease and develop cytokine pattern studies [24].

### 3.3 Promising biomarkers that need further studies

In this category, we listed biomarkers that have promising results, but due to small numbers of studies, data is lacking about their actual usefulness.

#### 3.3.1 Heparin binding protein (HBP)

HBP is released from activated neutrophils. HBP has a multiple role in inflammation [25]. On the one hand, it induces macromolecular efflux in endothels, thus responsible for swelling and edema forming. On the other hand, it is chemo-attractant and activates monocytes and macrophages [26], [27]. In UTIs, it has an excellent value not only in predicting, but also in differentiating upper from lower UTIs. For studies on HBP, see Table 5.

Table 5: Studies on HBP

		Cut-off value	Sensitivity	Specificity	Study population	Disease	Aim	References
Urinary HBP	1	32 ng/ml	93%	90%	78 children	UTI	Diagnosing UTI	Kjölvmárk et al. 2012 [64]
	2	30 pg/ml	89%	89%	390 adults	UTI	Diagnosing UTI	Kjölvmárk et al. 2014 [57]
	3	30 pg/ml	93%	–	390 adults	UTI	Distinguishing ABU from UTI	Kjölvmárk et al. 2014 [58]
	4	30 ng/ml	92%	33%	134 adults – elderly	UTI	Distinguishing ABU from cystitis	Kjölvmárk et al. 2016 [58]
	5	30 ng/ml	100%	33%	134 adults – elderly	UTI	Distinguishing ABU from u-UTI	Kjölvmárk et al. 2016 [58]
	6	30 ng/ml	96%	33%	134 adults – elderly	UTI	Distinguishing ABU from l-UTI	Kjölvmárk et al. 2016 [58]

APN: acute pyelonephritis, ABU: asymptomatic bacteriuria, HBP: heparin binding protein, l-UTI: lower urinary tract infection, s-UTI: symptomatic urinary tract infection, UTI: urinary tract infection, u-UTI: upper urinary tract infection

### 3.3.2 Matrix metalloprotease-9 (MMP-9)

MMP-9 is a metalloprotease enzyme with a specific role in degradation of extracellular matrix components. During UTIs, MMP-9 often occurs in complex with NGAL [28]. Hatipoglu et al. measured the MMP-9/NGAL complex level in 145 childrens' urine [29]. They found 98% sensitivity and 97% specificity with the cut-off value of 0.08 ng/mg for predicting the diagnosis of UTIs. It could be a better indicator than NGAL alone. Due to the high sensitivity and specificity, it could be used for distinguishing ABU from UTIs. Thanks to its kinetics, it is suitable for monitoring as well [29].

### 3.3.3 Human neutrophil peptides-1,-3 (HNP-1,-3), human defensin-5 (HD-5)

Alpha defensins originate from white blood cells and epithelial cells. In a recent, observational, non-comparative study, using the cut-off values of 174 pg/mg for HD-5 and 383 µg/mg for HNP-1, the sensitivity was 86% and the specificity was 88% for predicting urine culture positivity among 199 children with UTIs [30]. There is a lack of further studies to determine the actual usefulness of these two markers.

### 3.3.4 H1-nuclear magnetic resonance (H1-NMR) spectrometry

H1-NMR spectrometry is a novel laboratory method for detecting metabolites in various samples with limited accessibility. Most human diseases have characteristic modifications in the metabolite profile of fluids prior and during the development of clinical symptoms [31].

Searching a discriminative marker for bacterial UTIs, acetic acid occurred. Using 0.03 mmol/mmol as cut-off, it has 91% sensitivity and 95% specificity for predicting bacterial UTIs.

Trimethylamine (TMA) is a natural metabolite of *E. coli* activity. With measuring the TMA/CRN ratio, the presence of an *E.coli* infection can be determined with 97% specificity and 66% sensitivity using the 0.0117 mmol/mmol value as cut-off. Results were based on analyzing 133 urine samples [31].

6-hydroxynicotinic acid (6-OHNA) is a metabolite of nicotinic acid, which is a metabolite of the *Pseudomonas aeruginosa* and *Klebsiella* species. With this method, etiological diagnosis could be made. Results were based on 30 samples [32].

### 3.3.5 Lactoferrin (LF)

Lactoferrin is a stable iron-binding protein that circulates in serum. Using the 200 ng/ml as a cut-off, its specificity is 89% and its sensitivity 93% for distinguishing between ABU and UTIs [33]. These results originate from a comparative, observational study among adults. Although the study population was over 100 people, no one has confirmed the results ever since.

### 3.3.6 Heat shock protein-70 (HSP-70)

HSPs upregulate during infection. For predicting UTIs, its sensitivity and specificity was 100% using the 158 µg/ml as cut-off in a prospective, comparative, observational study among 40 children with febrile UTIs [34].

### 3.3.7 Bone morphogenic protein-2 (BMP-2) and cystatin C (CysC)

BMP-2 has a role in organ regeneration. Its level significantly increases in urinary stone formation and in infections.

Cystatin C is an endogenous biomarker for renal damage. It has a predictive value in diagnosing APN in children (cut-off: 1.08 mg/dl, sensitivity 58%, specificity 87%). According to a single, small observational study (45 patients), both markers have high values in diagnosing UTIs and predicting stone formation. Using 44 pg/ml as cut-off value for urinary BMP-2 for predicting UTIs has 92% sensitivity, 80% specificity and 86% accuracy. For urine CysC, the sensitivity was 85%, specificity 91% and accuracy 88%, using 525 ng/ml as cut-off [35].



### 3.3.8 Lipopolysaccharide-binding protein (LBP)

LBP is an acute phase protein. In a single, observational study among children, LBP had a sensitivity of 96%, and a specificity of 100% with an undetermined cut-off value [36]. Although the study population was over 100 children, data is lacking about its exact usefulness.

### 3.4 Biomarkers of unknown significance

In this category, we listed biomarkers that are elevated during UTIs, but there is insufficient information about their clinical usefulness (Table 6).

Table 6: Summary of biomarkers of unknown significance

Biomarker	Field	Study population	Results	References
CA19-9	UTI, ureteral stone disease, UPJO	100 children	Serum level raises	Kajbafzadeh et al. 2010 [65], 2020 [66]
MCP-1	Xantogranulomatous pyelonephritis, UPJO	Single case report in a child	Significant elevation in histologic samples	Bartoli et al. 2007 [67]
TLR-4	r-UTI	19 adults	Expression is lower in histologic samples compared to healthy people	Ragnarsdottir et al. 2010 [68]
TLR-2	UTI, multiple sclerosis	–	Expression of soluble form raises in infections and in shubs	Hossain et al. 2018 [69]
NGF	Multiple urological disease including UTIs, OAB etc.	–	Expression raises; potentially responsible for irritable symptoms	Kuo et al. 2012 [70]
CD14, CD44, prostaglandin E2, cellulose, secretory IgA, 8-oxodG, YKL-40, E-cadherin, total antioxidant capacity	UTI	–	Expression raises in serum and in urine	Chien et. al. 2014 [71] Kim et al. 2018 [72] Deo et al. 2004 [73] Antypas et al. 2018 [74] Forster et al. 2019 [40] Becerir et al. 2019 [75] Cuzzolin et al. 2001 [76] Karananou et al. 2016 [77]

CA19-9: carboanhydrate antigene 19-9, MCP-1: monocyte chemotactic protein-1, NGF: nerve growth factor, OAB: overactive bladder syndrome, r-UTI: recurrent urinary tract infection, TLR-2, -4: toll-like receptor-2, -4, UPJO: uretero-pelvic junction obstruction, UTI: urinary tract infection

### 3.5 Controversial, not useful markers

Under controversial biomarkers, we listed molecules where studies reported contradictory results regarding their usefulness for diagnosis or differential diagnosis of UTIs. The common feature in these studies were the small populations included.

Useless markers are not suitable for diagnosis or differential diagnosis in UTIs. Mostly, these biomarkers do not correlate with the course of the disease, or the measurement is technically too complicated for daily application.

The following markers were either not useful for predicting UTIs or not practical: copeptin, KIM-1, ATP, TREM-1, apolipoprotein D, alpha amylase 2B, non-secretory ribonuclease, fibronectin, elastase, etc. [17], [37], [38], [39], [40].

Controversial data on their usefulness can be found for the following biomarkers: Beta-2-microglobulin, pentraxin-3, prosaposin, Tamm-Horsfall Protein, Arginin-Vasopressin [37], [41], [42].

## 4 Discussion

UTIs are common infections in every age group. Under special circumstances, timely diagnosis might be challenging. In these situations, clinicians must decide on laboratory findings, which have a weak accuracy in general. As seen in the details, none of the aforementioned biomarkers can predict the presence of a UTI exclusively. Thus, the interest turns to novel markers, specifically in special patients populations, for example children, who cannot describe their symptoms reliably, or among patients with constant catheterization, who have asymptomatic bacteriuria with or without specific symptoms referring to infection. In these cases, measuring the severity of the immune response could be a suitable alternative to decide about the need of antibiotic treatment. In addition, the diagnostic accuracy of biomarkers can probably only be determined when combined with a detailed and standardized scoring of subjective symptoms along severity indexing and individual risk ratification. For this reason, using validated questionnaires, for example the Acute Cystitis Symptom Score questionnaire [43], [44], could allow stratification of different clinical scenarios in combination with novel biomarkers in the future.

There are specific difficulties in each patient population in which UTI biomarkers are needed, but unfortunately, the patient groups with the highest need for a biomarker are also the ones that are most difficult to study. Not only symptom scoring is difficult; when ABU is frequent, the host response differentiation is obstructed. Furthermore, the comparator, ideally intraindividual comparison before and after a UTI episode, is commonly replaced by matched controls. In our literature search, we found that approximately one third of the articles were on NGAL or on cytokines. Considering that cytokines are key components of the local host-cell response, these are promising biomarkers for differentiating upper from lower UTIs – especially IL-6 and IL-8 [18], [21]. Furthermore, they might be useful in measuring the level of local immune response during uncomplicated lower UTIs, which can help the decision about non-antibiotic treatment [45].

NGAL also has a potential in the diagnosis of UTIs with high sensitivity and specificity. However, an important limitation is that it is a common marker of kidney injury, thus acute or chronic disease and other potential conditions that are yet unknown can elevate its level along with an infectious disease. In this field, further observations are needed [16].

Most of the published data on biomarkers focus on children. There were examples when the context were proven for adults as well, thus we believe that further findings should be valid for adults too. However, due to a lack of studies, the probative value is still missing [16]. Another weakness of the literature search is the lack of data on men, as well as on other forms of UTIs.

Finding suitable biomarkers for UTIs has limitations: The immune system is constantly influenced by varying conditions (chronic, metabolic or malignant disease, intercurrent infections etc.) which may influence the expression of biomarkers. Further research could include a search for bacterial metabolites or volatile organic compounds in urine [31], [44]. The amount of the novel biomarkers is enormous. Therefore, we here focused on those that have promising results or were studied in larger quantities. The cut-off values varied in a wide range in the different studies. The production of these molecules may vary by the severity of the symptoms, the activation of the immune system, anatomic anomalies etc. In order to determine precise cut-off values, a meta-analysis should be performed. However, due to the large number of variables involved, it is uncertain whether such an analysis could be conducted successfully.

## 5 Further research

Each of the biomarkers discussed above needs to be investigated and validated further in well designed clinical studies to determine their clinical usefulness for diagnosis and treatment outcome in patients with different categories of UTI, including uncomplicated and complicated UTI and urosepsis.

## 6 Conclusion

Since the diagnostic accuracy and clinical usability of traditional biomarkers for UTIs in certain clinical settings are limited, there is a need for novel, accurate and widely available biomarkers. Urinary NGAL and interleukins are the most suitable biomarkers that are currently available for clinicians with a potential to improve the sensitivity and specificity of laboratory diagnosis of UTIs.

## Abbreviations

- **6-OHNA:** 6'-hydroxy nicotinic acid
- **8-oxodG:** 8'-hydroxy-2'-deoxyguanine
- **ABU:** Asymptomatic bacteriuria
- **APN:** Acute pyelonephritis
- **ATP:** Adenosine triphosphate
- **BMP-2:** Bone morphogenic protein-2
- **CA19-9:** Carboanhydrate antigene 19-9
- **CAP37:** Cationic antimicrobial protein of 37 kd (synonyme for HPB)
- **CD14:** Cluster of differentiation 14
- **CD44:** Cluster of differentiation 44
- **CIC:** Clean intermittent catheterisation
- **CRN:** Creatinine
- **CRP:** C-reactive protein
- **CysC:** Cystatin C
- **ESBL:** Extended spectrum beta lactamase
- **H1-NMR:** H1-nuclear magnetic resonance
- **HBP:** Heparin binding protein
- **HD-5:** Human defensin-5
- **HNP-1:** Human neutrophil peptide-1
- **HNP-3:** Human neutrophil peptide-3
- **HSP-70:** Heat shock protein-70
- **IL:** Interleukin
- **IL-1B:** Interleukin-1 beta
- **IL-6:** Interleukin-6
- **IL-8:** Interleukin-8
- **LBP:** Lipopolisaccharide binding protein
- **LF:** Lactoferrin
- **I-UTI:** Lower urinary tract infection
- **NGAL:** Neutrophil gelatinase-associated lipocalin
- **NLR:** Neutrophil-lymphocyte Ratio
- **NPV:** Negative predictive value
- **MCP-1:** Monocyte chemotactic protein-1
- **MMP-9:** Matrix metalloprotease-9
- **PCT:** Procalcitonin
- **PGE2:** Prostaglandin-E2
- **PPV:** Positive predictive value
- **sIL-1B:** Serum interleukin 1 beta
- **sIL-6:** Serum interleukin-6
- **sIL-8:** Serum interleukin-8
- **s-NGAL:** Serum neutrophil gelatinase-associated lipocalin
- **s-UTI:** Symptomatic urinary tract infection

- **TAC:** Total antioxidant capacity
- **TMA:** Trimethylamine
- **TLR:** Toll-like receptor
- **TREM-1:** Triggering receptor expressed on myeloid cells-1
- **uIL-1B:** Urinary interleukin-1 beta
- **uIL-6:** Urinary interleukin-6
- **uIL-8:** Urinary IL-8
- **u-NGAL:** Urinary neutrophil gelatinase-associated lipocalin
- **UPJO:** Uretero-pelvic junction obstruction
- **UTI:** Urinary tract infection
- **u-UTI:** Upper urinary tract infection
- **YKL-40:** Tyrosine (Y) – lysine (K) – leucin (L) of 40 kDa
- **VUR:** Vesico-ureteral reflux

## Note

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## Competing interests

The authors declare that they have no competing interests.

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