



Review

Asymptomatic Bacteriuria or Urinary Tract Infection? New and Old Biomarkers

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Abstract: Urinary tract infections (UTIs) are among the most common infective disease in the adult population. UTI diagnosis is based essentially on the presence of lower urinary tract symptoms (e.g., dysuria, urgency, and frequency) and the evidence of bacteriuria (by dipstick testing and/or urine culture). UTI diagnosis is not always easy because symptoms can be vague, or patient basal conditions can interfere negatively with the diagnostic process, whereas urine culture is still ongoing. In those cases, the differential diagnosis among UTIs and asymptomatic bacteriuria (ABU) may be challenging, while the clinician has to decide whether to start an antibiotic treatment shortly. The purpose of the present review is to analyze the biomarkers that could help in UTI diagnosis. Some biomarkers, such as procalcitonin, interleukin-6, neutrophil gelatinase-associated lipocalin, chemokines, lactoferrin, and bone morphogenetic protein-2, seem promising in UTI diagnosis, while other biomarkers failed to show any utility. Whereas a single biomarker was not enough, a combination of biomarkers could have more chances to help in the diagnosis.

Keywords: urinary tract infections; asymptomatic bacteriuria; biomarker



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1. Introduction

Urinary tract infections (UTIs) are among the most common infections in the adult population [1]. In non-pregnant healthy women, the diagnosis of UTI is straightforward, based on urinary symptoms, such as dysuria, frequency, and urgency in the absence of vaginal discharge [2]. In such patients, urine culture is not recommended to diagnose UTI, not improving the diagnosis accuracy of the clinical assessment [3]. In other cases, including recurrent UTIs (more than two episodes in the last six months or more than three UTIs in one year), male gender, pregnant women, patients with relevant anatomical/functional abnormalities of the urinary tract, immunocompromised patients, indwelling urinary catheters, renal diseases, and diabetes mellitus, the urine culture has a pivotal role in the diagnosis of UTIs [2]. Therefore, in cases such as complicated UTIs and recurrent UTIs, the presence of urinary symptoms and the detection of a pathogen by urine culture impact antibiotic treatment. In co-morbid patients and the elderly, UTI symptoms could be atypical or related to other conditions. For example, in patients with a cognitive impairment, it is not easy to determine the presence of lower urinary tract symptoms (LUTS), whereas in those patients with prostatic enlargement, non-infectious urethritis, bladder dysfunction, bladder tumors, and distal ureteric stone, LUTS could be present without concomitant UTIs. Finally, the results of urine cultures are not immediately available and could take 1–3 days. In this scenario, the diagnosis and the related antibiotic treatment can be a challenge. An inappropriate antibiotic therapy increases the risk of antibiotic resistance [4], and it is a financial burden for the community [5]. Conversely, a delay of an appropriate treatment could impact patient conditions, considering that mortality rates due to urosepsis can be as high as 16% [6]. Consequently, there is a strong need for biomarkers able to ease the clinical diagnosis of UTIs. The purpose of the present review is to assess the role of biomarkers in

the diagnosis of UTIs. Specifically, we focus on the uncertain diagnosis when the symptoms are vague or difficult to interpret, evaluating the biomarkers that can help to discriminate between asymptomatic bacteriuria and UTIs.

2. Search Strategy

We performed a non-systematic literature search using the following strategy on Pubmed and Scopus in September 2021. Specifically, we searched for the terms “Urinary tract infection” and “biomarker” in the Pubmed Mesh Resources. Moreover, we performed a free text search in Pubmed and Scopus adopting the following search terms: “Procalcitonin”, “Interleukin 6”, “Neutrophil Gelatinase associated Lipocalin”, “Proadenomedullin”, “adenosine-5-triphosphate”, “Tamm-Horsfall protein”, “Bone morphogenetic protein-2”, “beta2-Microglobulin”, and “lactoferrin”. Finally, we restricted our results by adopting the following limits: “English” language and “adults”. We screened all the abstracts to identify all the relevant studies. Appendix A shows the details for every biomarker term.

3. Results and Discussion

3.1. Procalcitonin

Procalcitonin (PCT) is a precursor of the hormone calcitonin and belongs to acute phase reactants. In inflammatory conditions, PCT levels increase significantly. Specifically, PCT increases during bacterial infections and seems to provide supplemental information in the diagnosis of some bacterial infections, such as respiratory tract infection and urosepsis [7]. Furthermore, PCT levels correlate to bacterial load, and consequentially its levels decrease with the improvement in clinical conditions. Such peculiarities provide prognostic information in patients with infections, suggesting the management of bacterial infection, especially in septic disease [7]. On the other hand, two recent meta-analyses in children disputed this promising ability in UTI diagnosis, showing little accuracy for cystitis (AUC around 0.71 in ROC curve) [8,9], and limited evidence supports its utility in pyelonephritis diagnosis [10]. Consequently, PCT could not be recommended in clinical practice as a predictive marker of cystitis or pyelonephritis in children.

Table 1 summarizes the characteristics and the main results of the five studies evaluating the role of PCT in the diagnosis of UTIs.

Table 1. Procalcitonin diagnostic value in UTIs, in a target population of adults.

Study Reference	Type of Study	Type of Patients	Number of Cases/Number Of Controls	Results	Findings
Rothe K. et al. 2020 [11]	Retrospective analysis	Adults with bacteriuria admitted to the emergency department	128 UTIs/55 ABU	PCT (Cut-off = 0.25 ng/mL) NPV 0.962	Negative PCT could be useful to identify ABU
Li Y.-M. et al. 2020 [12]	Prospective case-control study	Adult admitted to the stroke unit department	35 UTIs/151 controls	PCT 0.09 (0.05–0.15)* in UTI vs. 0.06 (0.03–0.1)* in Controls OR = 2.25 <i>p</i> = 0.726	Despite the increase in PCT level in UTIs, PCT fails as independent predictor of UTIs
Levine A.R. et al. 2018 [13]	Retrospective analysis	Adults admitted to the emergency department	48 UTIs/245 controls	AUC 0.717 (<i>p</i> < 0.001) PCT (Cut-off = 0.25 ng/mL): NPV 0.91	Negative PCT was a strong predictor of absence of UTIs and may be useful in the antibiotic management

Table 1. Cont.

Study Reference	Type of Study	Type of Patients	Number of Cases/Number Of Controls	Results	Findings
Iftimie S. et al. 2016 [14]	Prospective case-control study	Adults with recent urine catheter removal	42 ACI/100 healthy subjects	PCT (pg/L): 36.5 (1–570.3)'' no ACI vs. 51.7 (1.4–1269.1)'' ACI, $p = 0.15$. AUC 0.57	PCT showed considerable degree of overlap between groups (controls, urine catheter removal with and without acute concomitant infection), a low diagnostic accuracy.
Masajtis-Zagajewska A. et al. 2015 [15]	Prospective study	Adults admitted to hospital with LUTS	45 UTIs/24 healthy subjects	PCT (ng/mL): 3.7 (± 15.3) * in UTI vs. 0.06 (± 0.02) * in Controls, $p < 0.001$. AUC U-UTIs 0.94 (0.845–0.993)'', AUC L-UTIs 0.505 (0.185–0.575)''	PCT seems a promising biomarker in the diagnosis of U-UTIs, but showed its weakness in the diagnosis of L-UTIs.

ABU: asymptomatic bacteriuria; NPV: negative predictive value; AUC: area under curve; ACI: acute concomitant infection; LUTS: lower urinary tract symptoms; U-UTIs: upper urinary tract infections. (*) variable represented as mean (\pm standard deviation), (') variable represented as median (interquartile range), (') variable represented as median (95% confidence interval).

Specifically, the evaluated trials showed the good negative predictive value of PCT in UTIs diagnosis [11,13]. This aspect is relevant in clinical practice because a PCT value < 0.25 ng/mL suggests the low likelihood of having UTIs. Thus, negative PCT supported general practitioners in the decision to wait for urine culture results or follow-up patient conditions before administering empirical antibiotic treatments. Conversely, high PCT levels at the moment of the clinical onset of a suspicious UTI are not a sensible marker for the diagnosis of UTIs. However, an elevated PCT should be evaluated carefully by the clinicians, especially in fragile people, because its value accurately predicts the presence of bacteraemia and bacterial load [16] and seems correlated to disease severity [14,15], regardless of the origin of the primary infection. Finally, three studies showed low accuracy and neglectable PCT changes in lower UTIs [12,14,15]. Those results suggest a marginal role of PCT during lower UTIs and seem congruent with the idea that PCT increases significantly during bacteremia.

3.2. Interleukin-6

Interleukin-6 (IL-6) is a cytokine and participates in different biological activities, including immunoregulation, inflammation, and oncogenesis. In an acute-phase reaction, IL-6 levels increase quickly in response to inflammation and infective stimuli [17]. For example, during a septic episode, IL-6 concentration can arise by 100 times over the basal concentration, which in healthy people is under 5 pg/mL [18].

Table 2 summarizes the characteristics and the main results of the 11 studies evaluating the role of IL-6 in the diagnosis of UTIs.

Table 2. Serum and urine interleukin-6 diagnostic value in UTIs, with a target population of adults.

Study Reference	Type of Study	Type of Patients	Number of Cases/Number of Controls	Results	Finding
Gill K. et al. 2021 [19]	Prospective, blind, observational cohort study	Adult women with OAS symptoms	24 patients with OAB and 22 asymptomatic control subjects	The differences between patients and controls in urine u-IL-6 ($F = 49.0$, $p < 0.001$). u-IL-6 levels were predicted by bacteriuria ($p = 0.024$), and pyuria count ($p < 0.001$), but not by pain ($p = 0.93$), LUTS score ($p = 0.658$), and urgency ($p = 0.31$)	In OAB urinary u-IL-6 was associated with pyuria and bacterial growth, suggesting its potential role in chronic disease
Li Y.-M. et al. 2020 [12]	Prospective case-control study	Adult admitted to the stroke unit department	35 UTI/151 controls	IL-6 (pg/mL): 4.49 (2.53–11) [^] in UTI vs. 3.23 (2–4.49) [^] in Controls $p = 0.03$ OR = 1.175 $p = 0.047$	IL-6 increases significantly during UTI, and seems an independent predictor marker of UTI
Gadalla A.A.H. et al. 2019 [20]	Case-control study	Adult women with at least one symptom	79 UTI/104 no UTI	U-IL-6 (ng/L): 0.5 (0–2.7) [^] in no UTI 1.1 (0–3.1) [^] in UTI	No significant change in U-IL-6 between symptomatic woman with and without UTIs
Kjölvmárk C. et al. 2016 [21]	Prospective case-control study	Elderly (≥ 80 years old) assisted in a nurse home residence.	49 UTI/38 ABU	U-IL-6 150 (4–630) [^] in UTI vs. 4 (4–13) [^] in ABU $p < 0.01$. U-IL-6 > 30 pg/mL PPV and NPV of L-UTI were, respectively, 0.56 and 0.68. PPV and NPV of U-UTI were 0.74 and 0.87, respectively.	U-IL-6 increases significantly during UTI. U-IL-6 seems clinically useful to discriminate ABU from U-UTI, while its utility seems inconsistent in the discrimination between ABU and L-UTI
Sunden F. and Wullt B. 2016 [22]	Prospective case-control study	Adult assisted in a nurse home residence.	22 UTI/35 ABU	U-IL-6 (ng/L) 227 (17–1400) [^] in UTI vs. 30 (8–86) [^] in ABU	U-IL-6 increases significantly in UTIs
Van der Starre et al. 2015 [23]	Case-control study	Adults with LUTS and fever	46 bacteraemic UTI/45 No bacteraemic UTI/45 controls	u-IL-6 (pg/umol) was higher in UTIs ($p < 0.001$). No significant difference was found between bacteraemic and no bacteraemic UTI patients ($p = 0.21$)	u-IL-6 levels are different between controls and UTI patients, although it does not distinguish bacteraemia status
Masajtis-Zagajewska A. et al. 2015 [15]	Prospective study	Adults with LUTS admitted to hospital, and adult healthy subjects	45 UTI/32 U-UTI/24 controls	IL-6 (pg/mL): 84.8 (± 67) in U-UTI vs. 3.1 (± 1.6) [*] in controls, $p < 0.001$ 22.5 (± 1.6) in L-UTI vs. 3.1 (± 1.6) [*] in controls, $p < 0.001$ 84.8 (± 67) in U-UTI vs. 22.5 (± 1.6) [*] in controls, $p < 0.001$	IL-6 seems a promising biomarker to assess UTI diagnosis. This preliminary study suggested IL-6 levels could discriminate between U and L-UTI. Limits: the comparison with healthy people could overestimate its ability in doubtful cases

Table 2. Cont.

Study Reference	Type of Study	Type of Patients	Number of Cases/Number of Controls	Results	Finding
Sundvall P.D. et al. 2014 [24]	Cross sectional study	Elderly (≥ 65 years) assisted in a nurse home residence.	135 positive urine culture/286 negative urine culture	U-IL-6 (ng/L) 2.5 (1–5.7) [^] in positive urine culture vs. 1.3 (0.6–2.8) [^] in negative urine culture $p < 0.001$	In positive urine cultures, U-IL-6 was significantly higher than in negative urine cultures, but the study did not intercept any significant relationship with the symptoms
Grönberg-Hernández J. et al. 2011 [25]	Placebo-controlled study	Adults, who received therapeutic inoculation with <i>E. coli</i> 83972	23 patients, 223 bacteriuric urine samples 68 sterile urine samples	u-IL-6 (ng/L): 5.5(± 1) [^] in ABU 3.2(± 0.5) [^] in sterile urine, $p = 0.3$	No significant difference in u-IL-6 between the patients who developed ABU and those who did not.
Rodhe N. et al. 2009 [11]	Case-control study	Elderly (≥ 80 years old)	16 L-UTI/24 ABU/20 controls	U-IL-6 (ng/mL): 54.7 (10.7–443) ^{^^} in L-UTI vs. 14.4 (7.1–37.4) ^{^^} in ABU 11.7 (5.6–69.1) ^{^^} in controls. Sensitivity: 0.88 (60–98)'' Specificity: 0.96 (77–100)''	U-IL-6 can improve the diagnostic process of UTI
Ciszek M. et al. 2006 [26]	Prospective case-control study	Kidney transplant recipients with bacteriuria	5 UTI/22 ABU/25 controls	U-IL-6 (pg/mg creatinine): 3.92 (0.22–17.33) ^{^^} in ABU 15.71 (3.6–246.95) ^{^^} in UTIs 2.54 (0.34–78.41) ^{^^} in control	No significant difference was detected in U-IL-6 levels between ABU patients and controls, while its levels increase significantly in UTI patients
Olszyna D.P. et al. 2001 [27]	Case-control study	Adults who received a urinary catheter	10 UTIs patients/20 no-UTI patients	u-IL-6 value in UTIs and in non UTIs not reported	u-IL-6 is released in the urine of postoperative patients who have a urinary catheter, irrespective of the presence of a UTI.
Nicolle L.E. et al. 1993 [28]	Prospective case-control study	Elderly (≥ 65 years) assisted in a nurse home residence.	51 ABU/34 Fever no UTI/9 UTI	u-IL-6 was detected in 43% of asymptomatic subjects and in 78% of UTI patients	U-IL-6 was identified more frequently in bacteriuric specimen.
Ko Y.C. et al. 1993 [29]	Case-control study	Adults with LUTS	113 UTI patients/74 no UTI patients/20 healthy subjects	u-IL-6 (pg/mL): 92.5 (± 43.3) [^] in UTI vs undetectable in control group	u-IL-6 seems to increase in UTI

ABU = asymptomatic bacteriuria; LUTS = lower urinary tract symptoms; U-UTIs = upper urinary tract infection; OAB = over acting bladder; NPV = negative predictive value; PPV = positive predictive value; AUC = area under curve; OR = odds ratio. (*) variable represented as mean (\pm standard deviation), (') variable represented as median (interquartile range), (^^) variable represented as median (min–max), (') variable represented as median (95% confidence interval).

UTIs induce a significant increase in serum IL-6, and its level could differentiate lower and upper UTIs. Unfortunately, only two small studies evaluated this aspect and in two different clinical settings [15,21]

Urine IL-6 was explored by eleven small studies [11,12,15,19–23,26–28], usually performed in the elderly. Not all studies suggested a significant increase in urine IL-6 during UTIs, and the studies were too heterogenous to obtain a univocal recommendation. Currently, some studies have shown a significant increase in urine IL-6 in the case of pyelonephritis and bacteremia [15,21]; others suggested a significant increase also in lower UTIs [11,22–26,29]; others concluded there are no significant differences in urine IL-6 be-

tween UTIs and asymptomatic bacteriuria [20,21,27,28]. Probably, urine IL-6 increases proportionally to inflammatory status related to urinary infection. This hypothesis could explain the heterogeneity in the results among the studies, which evaluated urine IL-6 levels in a different clinical setting of UTI.

Finally, only two studies evaluated its accuracy [11,21], and only one [21] proposed a possible cut-off for urine IL-6 level in the diagnosis of UTIs. Therefore, there is insufficient evidence to support its use as UTI predictor in clinical practice. Although considering those results promising, new studies should be performed to estimate its actual accuracy in UTI diagnosis.

3.3. Neutrophil Gelatinase-Associated Lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL) is a 21-kD protein of the lipocalin superfamily. During bacterial infections, NGAL is secreted by neutrophils to limit bacterial growth. Specifically, NGAL binds bacterial siderophores limiting the iron supply and consequently the bacterial cellular process. Furthermore, NGAL seems to promote differentiation of renal epithelial cells and its predictive value in acute kidney injury has been proven in recent years [30].

Table 3 shows the characteristics and the main results of the four studies evaluating the role of urine NGAL value in the diagnosis of UTIs.

Table 3. Urine NGAL diagnostic value in UTIs; target population: adults.

Study Reference	Type of Study	Type of Patients	Number of Cases/Number of Controls	Results	Finding
Gadalla A.A.H. et al. 2019 [20]	Case-control study	Adult women with at least one symptom	79 UTI/104 no UTI	u-NGAL (ng/mL): 5.5 (0–5.9) [~] in UTIs 4.5 (0–5.9) [~] in No UTIs Combined to other immunological biomarkers: AUC 0.81 (0.68–0.94) [~] PPV 0.82 (0.55–0.95) [~] NPV 0.76 (0.58–0.88) [~]	The use of u-NGAL associated with other immunological biomarkers (CXCL8, MMP9, IL1 β) seems a good predictor of UTIs.
Price J.R. et al. 2017 [31]	Prospective case-control study	Adult women with LUTS	50 UTI/50 healthy subjects	u-NGAL (ng/mL): 88.9 (40.7–193.4) [^] in UTIs vs 3.6 (2.5–8.1) [^] in controls, $p < 0.001$ AUC for UTIs = 0.973 Cut-off 23.9 ng/mL: Sensitivity 98%, Specificity 100%	u-NGAL in women seems to have an excellent accuracy to detect UTIs, showing a better AUC compared with u-leukocytis (AUC 0.84) and u-nitrates (AUC 0.6927)
Urbschat A. et al. 2014 [32]	Prospective case-control study	Adults with LUTS with or without fever	30 U-UTIs/29 L-UTIs/38 healthy subjects	u-NGAL (ng/mL): 111.07 (± 114.29) [*] in U-UTI vs. 47.78 (± 58.6) [*] in healthy subjects, $p < 0.01$ 100.61 (± 95.38) [*] in L-UTI vs. 47.78 (± 58.6) [*] in healthy subjects, $p < 0.05$ 111.07 (± 114.29) [*] in U-UTI vs. 100.61 (± 95.38) [*] in L-UTI, $p = \text{NS}$	u-NGAL increases significantly in UTIs. However, NGAL levels do not allow to discriminate between U-UTI and L-UTI
Decavele A.S. et al. 2011 [33]	Prospective case-control study	Adults admitted to hospital and outpatients	110 UTI/104 controls	u-NGAL (ng/mL) and leukocyturia: $\rho = 0.518$, $p < 0.001$ u-NGAL (ng/mL) and urinary bacterial count: $\rho = 0.243$, $p < 0.001$	The authors suggested the correction of u-NGAL levels considering leukocyturia in the urine

LUTS = lower urinary tract symptoms; L-UTI = urinary tract infection; U-UTIs = upper urinary tract infection; CXCL8 = Chemokines; MMP9 = matrix metalloproteinase-9; IL1 β = interleukin1 β ; ED = emergency department; NPV = negative predictive value; PPV = positive predictive value; AUC = area under curve. (*) variable represented as mean (\pm standard deviation), (^) variable represented as median (interquartile range), (~) variable represented as median (min–max), (") variable represented as median (95% confidence interval).

The first reports about urine NGAL accuracy in UTI diagnosis seem promising, especially in women. Specifically, Price et al. showed how u-NGAL has excellent accuracy in UTI diagnosis in a cohort of 100 women, 50 adult women with UTIs and 50 healthy adult women [31]. However, in our opinion, such remarkable results are related to the nature of the control group (constituted by healthy women), which can magnify the difference with UTI women and the accuracy of uNGAL as a biomarker of UTIs. Moreover, Gadalla et al. showed how u-NGAL performance could be implemented by combining its use with other immunological biomarkers (IL-8, IL-1alfa, and matrix metalloproteinase-8), even comparing symptomatic women with UTIs and without UTIs [20].

Nevertheless, currently, the number of studies and the number of patients enrolled do not allow to suggest its clinical use in UTI diagnosis.

3.4. Urinary Adenosine-5'-Triphosphate

Urinary adenosine-5'-triphosphate (ATP) is an organic compound that has the primary role to provide energy in many biological intracellular processes. Specifically, during UTIs, ATP release in a urine sample is increased by inflammatory cells and bacteria [34]. Consequently, its detection in the urine could be a useful biomarker of the infective process.

Table 4 summarizes the characteristics and the main results of the three studies evaluating the role of urine ATP levels in the diagnosis of UTIs.

Table 4. Urine ATP diagnostic value in UTIs; target population: adults.

Study Reference	Type of Study	Type of Patients	Number of Cases/Number of Controls	Results	Finding
Gill K. et al. 2015 [35]	Prospective cross-sectional observational study	Adults with LUTS	340 LUTS/75 healthy subjects	AUC = 0.6	U-ATP is an unconvincing clinical diagnostic marker.
Lundin A. et al. 1989 [36]	Case-control study	Adult women with LUTS	753 women with positive urine culture/373 women with no diagnostic urine culture	NPV = 0.91 PPV = 0.93	A low ATP value seems to exclude UTI, while a high ATP value suggests UTI diagnosis. Limit: the ATP test is too complicated to become widely accepted.
Hallander H.O. et al. 1986 [37]	Case-control study	Adults with LUTS	136 bacteriuric patients/645 no-bacteriuric patients	Sensitivity 0.9, Specificity 0.94, PPV 0.76, NPV 0.98 to detect bacteriuria Sensitivity 0.7, Specificity 0.89, PPV 0.91, NPV 0.99 to detect positive urine culture	u-ATP levels predicts a positive urine culture. Better diagnostic efficiency can be obtained in combination with other tests, such as the nitrite and dipslide test.

LUTS = lower urinary tract symptoms; NPV = negative predictive value; PPV = positive predictive value; AUC = area under curve.

These studies have ambiguous results. Specifically, whereas older studies suggested a good performance of ATP as a surrogate marker of bacteriuria [36,37], the latest reports failed to prove its utility as a surrogate marker of UTIs [35]. Likely, these inconclusive results could be related to differences in the methods of ATP analysis and the clinical setting.

3.5. Proadrenomedullin

Proadrenomedullin (proADM) plays an important role in the inflammation and infective process and showed a good performance as a new biomarker in septic disease [38]. Whereas some studies evaluated proADM impact in the treatment management of UTIs [39–41], no study evaluated its possible role in the discrimination between UTIs and ABU.

3.6. Beta2-Microglobulin

Beta2-microglobulin (β 2-M) is a protein with a molecular weight of 11.8 KD, passes easily through the glomerular membrane and is almost completely reabsorbed and metabolized by the tubules. Urine β 2-M increases during tubular damage and, consequently, it could be a sensitive marker of upper UTIs.

Table 5 summarizes the characteristics and the main results of the four studies evaluating the role of urine β 2-M as a biomarker of UTIs.

Table 5. Urine β 2-M diagnostic value in UTIs, target population adults.

Study Reference	Type of Study	Type of Patients	Number of Cases/Number of Controls	Results	Finding
Sandberg T. et al. 1986 [42]	Prospective case-control study	Adults Women with LUTS with or without fever	105 U-UTIs 32 L-UTIs 12 patients with fever of non-renal origin	67% of U-UTI were associated with β 2-M \geq 50 mg/mol creatinine, only 6% of L-UTIs has β 2-M \geq 50 mg/mol creatinine	An increased β 2-M \geq 50 mg/mol creatinine is associated with pyelonephritis but not with cystitis
Schardijn G. et al. 1984 [43]	Prospective case-control study	Adults with LUTS	19 U-UTIs/15 L-UTIs/44 controls	β 2-M (ug/die): 8509 (4890–60,000)** in U-UTIs 162 (33–308)** in L-UTI 110 (33–361)** in controls	Not significant to improve UTI diagnosis, likely useful to suggest U-UTIs
Mengoli C. et al. 1982 [44]	Case-control study	Adults with bacteriuria	19 U-UTIs/15 L-UTIs and ABU	β 2-M (ug/die): 1471 (\pm 320)* in U-UTIs 71 (\pm 14)* in L-UTIs e ABU	Not significant to improve UTI diagnosis, likely useful to suggest U-UTIs
Schardijn G. et al. 1979 [45]	Prospective case-control study	Adults with LUTS	10 U-UTIs/14 L-UTIs/20 controls	β 2-M (ug/die): 3249 (624–9500)** in U-UTIs 170 (33–325)** in L-UTIs 112 (33–363)** in controls	Not significant to improve UTI diagnosis, likely useful to suggest U-UTIs

LUTS = lower urinary tract symptoms; ABU = asymptomatic bacteriuria; L-UTIs = lower urinary tract infections; U-UTIs = upper urinary tract infection. (*) variable represented as mean (\pm standard deviation), (**) variable represented as mean (min–max).

All the studies on β 2-M were published before 1986. All the studies focused on the ability of β 2-M to discriminate between upper and lower UTIs [42–45]. As expected, no significant difference was found between lower UTIs and ABU. Consequently, its use in the diagnosis of UTIs should not be suggested.

3.7. Chemokines

Chemokines (ChKs) are small cytokines secreted by cells that induce directional movement of specific cell populations, such as leukocytes, endothelial and epithelial cells, to inflamed tissues. There are four different subgroups of ChK: CXC, CC, C, and CX3C. Specifically, CXCs are potent neutrophil/natural killer activators, while CC induce chemotaxis of T cell and monocytes.

Table 6 summarizes the characteristics and the main results of the eight studies evaluating the role of ChKs as a biomarker of UTIs.

Table 6. Serum and urine chemokines diagnostic value in UTIs; target population: adults.

Study Reference	Type of Study	Type of Patients	Number of Cases/Number of Controls	Results	Finding
Gadalla A.A.H. et al. 2019 [20]	Case-control study	Adult women with at least one symptom	79 UTI/104 no UTI	u-CxCL8 (): 2 (0–3.9)^ in No-UTI 3.1 (0.8–4.6)^ Combined with other immunological biomarkers: AUC 0.81 (0.68–0.94)'' PPV 0.82 (0.55–0.95)'' NPV 0.76 (0.58–0.88)''	The use of u- CxCL8 associated with other urinary immunological biomarkers (NGAL, MMP9, and IL1 β) seems a good predictor of UTIs.
Tyagi P. et al. 2016 [46]	Prospective case-control study	Adults	62 UTI patients/ 59 OAB patients/ 26 Control	u-CXCL1 (target 20 pg/mL): AUC 0.71 Sensibility 0.5968, Specificity 0.8877. u-CXCL8 (target 20 pg/mL): AUC 0.71 Sensibility 0.6538, Specificity 0.7097. u-CXCL10 (target 20 pg/mL): AUC 0.54 Sensibility 0.3864, Specificity 0.6271.	Significant elevation in u-CXCL-1, u-CXCL-8, and u-CXCL-10 together were seen in UTIs relative to OAB and asymptomatic controls. Urinary chemokines highlight molecular differences in the overlapping symptoms of UTIs and OAB.
Iftimie S. et al. 2016 [14]	Prospective case-control study	Adults with recent urine catheter removal	42 ACI patients/100 healthy subjects	u-CCL2 (pg/L): 209.71 (115.7–357.2)^ NO ACI vs. 183.3 (104.6–329.5)^, $p = 0.295$. AUC 0.55	u-CCL2 showed considerable degree of overlap between the groups (controls, urine catheter removal with and without acute concomitant infection), and a low diagnostic accuracy.
Rodhe N. et al. 2009 [11]	Case-control study	Elderly (≥ 80 years old)	16 L-UTI/24 ABU/20 controls	u-CXCL-1 (>150 pg/mg Creat): sensitivity 0.69, specificity 0.79 u-CXCL-8 (> 285 pg/mg Creat): sensitivity 0.63, specificity 0.96	u-CXCL-1 and u-CXCL-8 were highly increased in patients with L-UTI. The measurement of u-CXCL-1 and u-CXCL-8 can improve the diagnostic process of UTIs.
Hawn T.R. et al. 2009 [47]	Cross-sectional study	Adult women with and without a history of recurrent L-UTIs and U-UTIs	391 women with ABU/731 without ABU	u-CXCL-8 (pg/mL): 26.6/32.5/32.5^ in negative u-WCB vs. 568/912.4/1578.3^ in positive u-WCB ($p < 0.0001$) u-CXCL-6 (pg/mL): 16.1/20.2/43.6^ in negative u-WCB vs. 48.9/153.3/289.5^ in positive u-WCB ($p = 0.007$)	The urinary levels of u-CXCL-8 and u-CXCL-6 were associated with higher neutrophil levels
Godaly G. et al. 2007 [48]	Prospective case-control study	Adults	29 <i>E.coli</i> UTIs/ 27 healthy subjects	u-CXCL-1 0.214 (0.0–7.4)^ u-CXCL-5 0.16 (0.0–1.8)^ u-CXCL-8 6.123 (0.062–652)^ u-CXCL-10 3.611 (0.0–34.2)^ u-CCL-2 0.445 (0.0–19.2)^ u-CCL-5 0.73 In UTI group. u-CXCL-1, u-CXCL-5, u-CXCL-8, u-CVCL-10, u-CCL-2, u-CCL-5 NO detected in healthy group	A complex CXC and CC chemokine response was detected in patient urine, with a significant influence of the fimbrial type

Table 6. Cont.

Study Reference	Type of Study	Type of Patients	Number of Cases/Number of Controls	Results	Finding
Ciszek M. et al. 2006 [26]	Prospective case-control study	Kidney transplant recipients with bacteriuria	5 UTIs/22 ABU/25 controls	u-CXCL-8 (pg/mg creatinine): 33.492 (2.97–129.749) ^{^^} in ABU vs. 2.97(2.97–44.164) ^{^^} in Control, $p < 0.01$, 146.801 (24.646–2114.254) ^{^^} in UTIs vs. 2.97(2.97–44.164) ^{^^} in Control, $p < 0.001$	A significant difference was detected in u-CXCL-8 levels between ABU patients and controls ($p < 0.01$), while its levels increase significantly in UTIs ($p < 0.001$)
Olszyna D.P. et al. 2001 [27]	Case-control study	Adults who received a urinary catheter	10 UTI patients/20 no UTI patients	CXCL-8 value not reported	CXCL-8 is released in the urine of postoperative patients who had a urinary catheter, and was significantly higher in patients who developed UTIs ($p < 0.01$)

ABU = asymptomatic bacteriuria; LUTS = lower urine tract symptoms; L-UTIs = lower urinary tract infections; U-UTIs = upper urinary tract infection; OAB = over acting bladder; NPV = negative predictive value; PPV = positive predictive value; AUC = area under curve; OR = odds ratio. (°) variable represented as median (interquartile range), (°°) variable represented as median (min–max), (°°°) variable represented as median/75th percentiles/90th percentiles.

Unfortunately, the studies are not consistent in the results, and their use in clinical practice cannot be recommended considering the little accuracy of urine Chks in UTI diagnosis. Nevertheless, the studies on CXCL-8, known as well as IL-8, showed a significant increase in the urine during UTIs [11,20,26,27,48] and good specificity [20,46]. Currently, CXCL-8 is the most promising chemokines in UTI diagnosis and should be studied in depth in future research, especially in combination with other biomarkers.

3.8. Bone Morphogenetic Protein-2

Bone morphogenetic protein-2 (BMP-2) is known for its important role in the development of bone and cartilage, but it seems to participate in the paracrine and autocrine action of organ regeneration [49]. Only one study investigated its role in UTI diagnosis and showed a significant increase in its serum levels in UTIs [50]. A cut-off point of 44 pg/mL was shown to have accuracy as high as 86% in detecting UTIs. Unfortunately, we failed to identify other studies corroborating such findings, and the number of the cases and controls included in this study was too limited to suggest its use in clinical practice without further validation.

3.9. Secretory Immunoglobulin A

Secretory immunoglobulin A (S-IgA) is the major immunoglobulin isotype in external secretions of mucosal epithelia and the first line of local immunological defence. In UTIs, S-IgA was shown to inhibit the *Escherichia coli* adhesion to urinary epithelial cells [51].

Table 7 summarizes the characteristics and the main results of the two studies evaluating the role of s-IgA in the diagnosis of UTIs.

Although the results showed a significant increase in the biomarker during UTIs, its clinical use could not be suggested considering the quality of the studies and the limited number of cases.

Table 7. Urine sIgA diagnostic value in UTIs; target population: adults.

Study Reference	Type of Study	Type of Patients	Number of Cases/Number of Controls	Results	Finding
Deo S.S. et al. 2004 [51]	Case-control study	Adults and children	17 adults with UTIs/10 adult as controls	sIgA (ug/mL): 80(± 48)* in UTI 5.2(± 0.73)* in controls, $p < 0.001$	sIgA increased significantly in adults with UTIs, although in children with UTIs, sIgA increase was the highest
Floege J. et al. 1990 [52]	Case-control study	Adult women	Group A: 10 recurrent asymptomatic UTIs Group B: 8 recurrent asymptomatic UTIs with urinary tract abnormality Group C: 4 recurrent symptomatic UTIs Group D: 5 selective IgA deficiency 68 controls	sIgA value not reported	sIgA increased significantly in women with UTIs regardless of a recurrent UTI history.

(*) variable represented as mean (± standard deviation).

3.10. Lactoferrin

Lactoferrin (LF) is a multifunctional 80 KD glycoprotein of the transferrin family. Its primary biological role is antimicrobial activity, interfering with bacteria growth by free iron sequester [53].

Table 8 summarizes the characteristics and the main results of the two studies evaluating the role LF in the diagnosis of UTIs.

Table 8. Urine lactoferrin diagnostic value in UTIs; target population: adults.

Study Reference	Type of Study	Type of Patients	Number of Cases/Number of Controls	Results	Finding
Gill K. et al. 2021 [35]	Prospective, blind, observational cohort study	Adult women	24 patients with OAB and 22 asymptomatic control subjects	The differences between patients and controls in urine lactoferrin ($F = 228.5$ $p < 0.001$). Lactoferrin levels were predicted by LUTS score ($p = 0.003$), urgency ($p = 0.011$) and pyuria count ($p < 0.001$), but not by pain ($p = 0.62$) and bacteriuria ($p = 0.79$)	In OAB patients, urinary lactoferrin was associated with pyuria and its symptoms
Arao S. et al. 1999 [53]	Case-control study	Adults	60 UTIs 28 no UTIs	LF (cut-off > 200 ng/mL): Sensitivity = 0.95, Specificity = 0.929, PPV = 0.96, NPV = 0.897, Accuracy = 0.94	LF measured by IC test strip provided a useful tool for the rapid and simple detection of UTIs

LUTS = lower urinary tract symptoms; OAB = over active bladder; NPV = negative predictive value; PPV = positive predictive value.

Arao S. et al. (1999) suggested that LF levels > 200 ng/mL were associated with accuracy as high as 94% in the diagnosis of UTIs [53]. In the other report, Gill et al. showed the potential role of LF in the patients with overactive bladder syndrome to identify UTIs not diagnosed by standard urine cultures [42], but the findings of the study seem to be inclusive, and the conclusions are not fully supported by the data presented. Likely, more studies about the role of LF in UTI diagnosis are necessary to suggest its use in clinical practice.

4. Conclusions

Serum biomarkers showed their weakness in UTI diagnosis considering the limited positive predictive value. Although their use in clinical practice could be helpful to exclude upper UTIs and evaluate the severity of the infectious disease, few studies assess the

reliability of serum markers in UTI diagnosis. Urine biomarkers are simple to collect and could be a precious help in uncertain UTI diagnoses. Unfortunately, their clinical use in this context cannot be suggested considering the current evidence (such as contradictory results, low number of patients, the different clinical settings and the different definitions of UTIs). Future studies in this field should focus on u-NGAL, u-IL-6, u-CXCL-8 and LF, which currently seems the most promising biomarker in UTI diagnosis.

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Appendix A

Table A1. Research Strategy for Each Term.

Term	Results	Filters Applied: English, Adult	Selected Items
"Urinary" AND "Tract" AND "Infection"	70,452	Not applied	Not applied
"Procalcitonin"	7444	Not applied	Not applied
"Interleukin-6"	95,463	Not applied	Not applied
"Neutrophil Gelatinase-Associated Lipocalin"	5276	Not applied	Not applied
"Adenosine-5'-Triphosphate"	120,102	Not applied	Not applied
"Proadrenomedullin"	665	Not applied	Not applied
"beta2-Microglobulin"	12,627	Not applied	Not applied
"Chemokine"	121,862	Not applied	Not applied
"Bone morphogenetic protein-2"	10,112	Not applied	Not applied
"Secretory" AND "Immunoglobulin A"	6463	Not applied	Not applied
"Lactoferrin"	9144	Not applied	Not applied
"Urinary" AND "Tract" AND "Infection" AND "Procalcitonin"	221	57	7
"Urinary" AND "Tract" AND "Infection" AND "Interleukin-6"	204	48	10
"Urinary" AND "Tract" AND "Infection" AND "Neutrophil Gelatinase-Associated Lipocalin"	83	16	4
"Urinary" AND "Tract" AND "Infection" AND "Adenosine-5'-Triphosphate"	44	6	2
"Urinary" AND "Tract" AND "Infection" AND "Proadrenomedullin"	10	5	0
"Urinary" AND "Tract" AND "Infection" AND "beta2-Microglobulin"	68	28	4
"Urinary" AND "Tract" AND "Infection" AND "Chemokine"	229	53	8
"Urinary" AND "Tract" AND "Infection" AND "Bone morphogenetic protein-2"	6	3	1
"Urinary" AND "Tract" AND "Infection" AND "Secretory Immunoglobulin A"	68	20	2
"Urinary" AND "Tract" AND "Infection" AND "Lactoferrin"	33	3	2

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