Clinica Chimica Acta 471 (2017) 286–291

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Invited critical review

New markers of urinary tract infection

Anna Masajtis-Zagajewska, Michal Nowicki*

Department of Nephrology, Hypertension and Kidney Transplantation, Medical University of Lodz, Central University Hospital and Teaching Center, Pomorska 251, 92-213 Lodz, Poland

ARTICLE INFO

Keywords:
Urinary tract infection
Acute pyelonephritis
Inflammation, biomarkers

ABSTRACT

Urinary tract infection (UTI) is the most common bacterial infection independent of age. It is also one of the most common causes of hospitalizations for infections among elderly people and the most common indication for antibiotic prescriptions in primary care. Both diagnostics and management of lower and upper urinary tract infections provide challenges in clinical practice due to their high prevalence and recurrence, and worldwide increase of antibiotic resistance. The clinical symptoms of UTI are often uncharacteristic or asymptomatic. The accurate diagnosis and early treatment are crucial due to risk of septicaemia and long-term consequences. Currently the diagnosis of urinary tract infection is based on the presence of clinical symptoms in combination with the results of nitrite strip test indicating the presence of bacteria in urine and semi-quantitative measurement of white blood cells count in urine. Although urine culture is the gold standard in UTI diagnostics it is both time-consuming and costly. Searching for novel biomarkers of UTI has attracted much attention in recent years. The article reviews several promising serum and urine biomarkers of UTI such as leukocyte esterase, C-reactive protein, procalcitonin, interleukins, elastase alpha (1)-proteinase inhibitor, lactofferin, secretory immunoglobulin A, heparin-binding protein, xanthine oxidase, myeloperoxidase, soluble triggering receptor expressed on myeloid cells-1, α-1 microglobulin (α1Mg) and tetrazolium nitroblue test (TNB).

1. Introduction

Urinary tract infection (UTI) is the most common infection of bacterial etiology across all age groups. It is also one of the most common causes of hospitalisation for infection among elderly people [1] and the most common cause of antibiotics prescriptions in a primary care. UTI also constitutes over 30% of all infectious complications in patients after kidney transplantation [2]. Diagnostics and effective treatment of both lower and upper urinary tract infections still provide significant challenges for clinical practice due to their frequent appearance, recurrence and a worldwide increase of antibiotic resistance. (See Table 1.)

UTIs may give uncharacteristic symptoms or they could be asymptomatic or dominated by the symptoms of kidney abscess and urosepsis with associated kidney failure that may even lead to death. Pyelonephritis and kidney scaring develop in approximately 50% children with feverish urinary tract infection. The worst clinical course is frequently observed in immunocompromised patients. However, if an adequate therapy is early initiated, overall prognosis is good. An accurate diagnosis and early treatment are crucial also due to a risk of long-term consequences, including chronic kidney disease [3,4].

The location of the infection, i.e. an involvement of the lower or upper urinary tract need to be quickly established but that is not always possible based on clinical symptoms [5–7]. Typically, lower UTI (L-UTI) manifests with dysuria, frequent and difficult or painful urination. In most cases clinical symptoms of upper UTI (U-UTI) are dominated by fever, shivering and side pain [8].

The choice of therapy is dependent on the location of the infection, its severity and a type of pathogen. The duration of therapy recommended for uncomplicated UTI is shorter compared to complicated UTI that involves the kidneys [9]. U-UTI requires therapy with an antibiotic well-penetrating into the kidney parenchyma.

Currently the diagnosis of urinary tract infection is primarily based on the presence of symptoms in combination with the results of fast diagnostic nitrite strip test indicating the presence of bacteria in urine and semi-quantitative measurement of white blood cells count in urine. However, the primary diagnosis is connected with relatively high rate of errors in comparison with the gold standard that is the urine culture [10–15]. That often leads to unnecessary administration of antibiotics and risk of their adverse events and the development of antibiotic resistance [16,17].

Urine test and urine culture are standard methods in the diagnostics of UTI. Although urine culture remains the gold standard of UTI diagnostics it is time-consuming and costly [18]. Taking into consideration

* Corresponding author.
E-mail address: nefro@wp.pl (M. Nowicki).

http://dx.doi.org/10.1016/j.cca.2017.06.003
Received 2 February 2017; Received in revised form 4 June 2017; Accepted 4 June 2017
Available online 13 June 2017

Table 1
Novel biomarkers of urinary tract infections.

Candidate biomarker	Reference	Study population	UTI location	Biological material for measurement	Comments
Leukocyte esterase (LE) and nitrite test	Nys S [21] Koeijers JJ [22] Mambatta K [69] Semeniuk H [70] Juthani-Mehta M [23]	Adults - 1993 Adults – 422 Adults - 635 Adults - 479 Adults – 101	Lower UTI and upper UTI	Urine	The sensitivity of the nitrite test (36%–57%) was shown to be lower than that of the LE test (72%–94%) among most female populations, whereas the specificity of the nitrite test was higher (75%–95% vs. 9%–83%). The combination of the urine LE test with the urinary nitrite test provides an excellent screen for establishing the presence of UTI. Most commercially available urine test strips (dipsticks) allow screening for both. However, the presence of one or both of these biomarkers does not help differentiating between UTI and asymptomatic bacteriuria
Procalcitonin (PCT)	Benador N [27] Gurgoze MK [28] Pecile P [31] Sugimoto K [71] Belhadj-Tahar H [72] Nikfar R [73]	Children - 80 Children – 76 Children - 100 Adults - 68 Children - 183 Children – 100	Upper UTI Upper UTI Upper UTI Lower and upper UTI Upper UTI Upper UTI	Serum	PCT has a good diagnostic accuracy and an interesting clinical value for APN, with a sensitivity and a specificity ranging from 58% to 94.1% and 36.4 to 93.6%, respectively. Serum procalcitonin is a sensitive marker to predict parenchymal damage and it determination is useful in clinical settings, Serial PCT measurement could also be used to follow-up the effect of treatment and to establish prognosis and renal damage.
Elastase alpha (1)-proteinase inhibitor (*E*-alpha(1)-PI)	Fretzayas A [46]	Children – 83 patients	Lower UTI and upper UTI	Urine and plasma	Elevated levels of E-alpha(1)-PI in urine seem to be a useful tool for the diagnosis of UTI in neonates. Plasma E-alpha(1)-PI is a sensitivite but not a specific marker for the detection of acute pyelonephritis. Urinary E-alpha(1)-PI levels cannot be used for this purpose.
Lactofferin (LF)	Arao S [47]	Adults – 88 patients	Lower UTI and upper UTI	Urine	Urinary LF is a sensitive marker and provide a useful tool for the simple and rapid diagnosis of UTI
Secretory immunoglobulin A (sIgA)	Deo SS [48]	Children – 68 patients, Adult – 17	Lower UTI and upper UTI	Urine	Presence of sIgA correlated with UTI in children and adults and seems to be directed to the infective agent and can also be used to identify the type of infection.
	Floege J [74]	Adults – 68 patients	Asymptomatic and acute UTI	Urine	
	Sudha S [75]	Children – 68 patients, Adult – 17	Lower UTI and upper UTI	Urine	
Heparin-Binding Protein (HBP)	Kjolvmark [55]	Adults – 390 patients	Lower UTI and upper UTI	Urine	U-HBP is the best diagnostic marker for UTI and could also discriminate between cystitis and pyelonephritis. The sensitivity and specificity for HBP in urine as a marker for UTI were 89.2% and 89.9%, respectively.
	Kjolvmark [56]	Children – 78	Lower UTI and upper UTI	Urine	U-HBP can be helpful guidance in the management of children with suspected UTI
Xanthine oxidase (XO)	Ciragil P [58]	Children and adults – 549 patients	Bacteriuria	Urine	Sensitivity in diagnosis Of UTI – 100%, specificity – 100%. This marker will be useful in early diagnosis UTI
Myeloperoxidase (MPO)	Ciragil P [58]	Children and adults – 549 patients	Bacteriuria	Urine	Sensitivity in diagnosis of UTI – 87%, specificity – 100%. This marker will be useful in early diagnosis UTI
Soluble triggering receptor expressed on myeloid cells-1 (TREM1)	Determann RM [65]	Adults – 70 patients	Lower – 55 patients, upper – 15 patients	Urine	This marker is reliable biological marker for bacterial infection but may not be sufficient for detection of urinary tract infection due to its low sensitivity.
A-1 microglobulin (α1Mg) and α1Mg/creatinine ratio	Mantur M [62] Everaert K [67]	Children – 86 patients Adults – 483 patients	Upper	Urine	Noninvasive and cost effective strategy with diagnostic capability for urinary tract disorders such as early recognition damages during pyelonephritis