



# Urine alpha-1-microglobulin reliability in the diagnosis of pyelonephritis: a systematic review

Anoush Azarfar (MD)<sup>1</sup>, Yalda Ravanshad (MD)<sup>2</sup>, Mohammad Esmaeili (MD)<sup>1</sup>, Fatemeh Ghane Sherbaf (MD)<sup>1</sup>, Mitra Naseri (MD)<sup>1</sup>, Fahime Noferesti (MD)<sup>\*1</sup>

<sup>1</sup>Department of Pediatric, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

<sup>2</sup>Clinical Research Development Unit, Ghaem Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

### ARTICLE INFO

#### Article type

Systematic review article

#### Article history

Received: 7 Jan 2015

Revised: 7 Mar 2015

Accepted: 16 Mar 2015

#### Keywords

Alpha-1-microglobulin

Children

Pyelonephritis

### ABSTRACT

**Introduction:** Pyelonephritis is known as kidney inflammation due to bacterial infection which should be diagnosed and treated promptly. In this article, we decided to systematically review the diagnostic value and reliability of evaluating urine excretion low molecular weight protein alpha-1-microglobulin (A1M).

**Methods:** PubMed and Scopus were searched for the relevant articles about the efficacy of urine alpha-1-microglobulin assays in the diagnosis of pyelonephritis in children. The search strategy was microglobulin AND pyelonephritis. No language and date limitations were included in this review.

**Results:** A total of 16 articles were retrieved from PubMed and 23 articles from Scopus. After studying the abstracts, only 5 articles were selected, which specifically studied the efficacy of alpha-1-microglobulin in the diagnosis of pyelonephritis in children.

**Discussion:** A1M is not an acute phase protein but its concentration alters in several clinical conditions.

**Conclusion:** Evaluating the urine concentration of A1M is a noninvasive and cost effective strategy with the diagnostic capability for urinary tract disorders such as early recognition of tubular damages during pyelonephritis.

Please cite this paper as:

Azarfar A, Ravanshad Y, Esmaeili M, Ghane Sherbaf F, Naseri M, Noferesti F. Urine alpha-1-microglobulin reliability in the diagnosis of pyelonephritis: a systematic review. *Rev Clin Med.* 2015;2(4):174-177.

## Introduction

Acute pyelonephritis (PN) is a serious renal bacterial infection, which is associated with significant morbidity rate and higher incidence rate in women compared to men (1). This bacterial infection involves the lower urinary tract and results in a tubular dysfunction. This serious infection can lead to hospitalization of the majority of cases. Urinary tract is known as a common site of infection and acute pyelonephritis is recognized as the most severe type of urinary tract infection (UTI). High fever, malaise, dehydration, vomiting, stomach pain, irritability, and poor feeding are

proposed as the clinical symptoms and systemic characteristics of this kidney infection. *Escherichia coli* is the major etiological agent in almost 80% of the cases (2). Early recognition and treatment of the infection are indispensable to avoid the late sequelae. Diagnosis and differentiation of pediatric pyelonephritis is a challenging issue. Several diagnostic strategies have been used to assess the kidney involvement in children with urinary tract infections such as urine culture, nuclear imaging dimercaptosuccinic acid (DMSA), renal scan and erythrocyte sedimentation (ESR) and C-re-

**\*Corresponding author:** Fahime Noferesti.

Department of Pediatric, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

**E-mail:** noferestif1@yahoo.com

**Tel:** 09155193677

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

active protein (CRP) measurements as blood inflammation indices (3). In almost 15% of children with acute pyelonephritis, renal parenchymal scarring has been recognized by DMSA scans as a long-term consequence of acute pyelonephritis and associated vesicoureteral reflux, which can eventually lead to other problematic consequences such as hypertension and proteinuria (4).

Evaluating various types of biomarker levels might be also supportive during the detection process of urinary tract infection in children such as urinary matrix metalloproteinase 9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) (5). Low molecular serum proteins are found in urine in an extremely low concentration, however during the damage processes of proximal tubules, these small proteins will be excreted into the urine. Increased levels of urinary alpha-1-microglobulin (A1M), procalcitonin, and chemokine IL-8 have been also suggested to be associated with the incidence of acute urinary tract infection and vesicoureteral reflux (6,7). Nevertheless, the exact role of these biomarkers is not certainly revealed in detecting the pediatric pyelonephritis.

A1M is a low molecular weight protein measured in patients with pyelonephritis as a significant indicator of proximal tubular dysfunction. A specific characteristic of A1M, its stability even in room temperature, made it a good candidate to be studied for the diagnosis of pyelonephritis in children. Sensitivity and specificity of A1M in distinguishing pediatric with pyelonephritis is not sufficiently investigated.

In this paper, we aim to provide a systematic review of articles in PubMed and Scopus, evaluating the prognostic value of alpha-1-microglobulin in detecting the children with pyelonephritis with or without vesicoureteral reflux and renal scarring.

## Methods

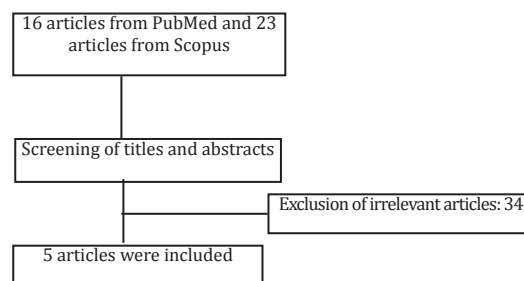
PubMed and Scopus were searched to obtain the relevant articles with the following search terms: acute pyelonephritis AND microglobulin. Last search was done in December 2014. No language and date limitations were included in our search strategy. Children with pyelonephritis or outflow disease of the upper urinary tract were included in our study, while patients with hydronephrosis or renal atrophy, patients without any proven UTI, those with UTI but without fever and patients with high fever of non-renal origin encompassed the exclusion criteria.

## Results

A total of 39 articles were retrieved according to the search strategy (16 articles from PubMed and 23 articles from Scopus). After studying the abstracts of the articles, majority of them were omitted due to the irrelevant renal diseases to the purpose of our study or studying B2-microglobulin. Only five articles were related to the subject of our study (Figure 1).

Applicable information and data of one relevant article written in Russian could not be retrieved due to inaccessibility to the full text of the article. Information regarding studies conducted on pediatrics with pyelonephritis is summarized in Table 1.

**Figure 1.** Flowchart diagram of reviewed articles



**Table 1.** Studies on the diagnostic value of A1M in children with pyelonephritis

Author Year Reference	Study language	Patients	Result	Outcome
Rodriguez 2009 (16)	Spanish	40 patients suspected of acute <sup>1</sup> PN Age: 1-11 years old	Normal ultrasonography scan and glomerular filtration rate	Combined use of urinary biomarkers did not increase the sensitivity of the diagnosis
Puczko-Michalczyk 2008 (17)	Polish	Case group: 23 infants with PN Control group: 30 healthy infant Age: 1-24 weeks	Sensitivity (70.4%) and specificity (56.1%) for <sup>2</sup> A1M	Higher concentration of urine markers in case group compared with control
Everaert 1998 (6)	English	51 patients with PN	Sensitivity of 94% and specificity of 67% for A1M	Urinary A1M/creatinine ratio is a diagnostically useful marker in PN patients
Everaert 1998 (18)	English	44 children over 3 months with PN	Sensitivity of 98% and specificity of 100% for A1M	Pyelonephritis patients have higher urinary A1M

<sup>1</sup>PN: Pyelonephritis; <sup>2</sup>A1M: Alpha-1-microglobulin

## Discussion

Evaluating urinary microproteins is a noninvasive method that might have the diagnostic potential for early detection and differentiation of renal abnormalities.

Based on the literatures, beta 2-microglobulin has been a detecting urinary protein marker or index for many years and a considerable number of studies have investigated its diagnostic features (8-13). However, due to its weak constancy in acid PH, its diagnostic potential is questionable and impaired. In one study, Konda et al. revealed that these markers were not considerably predictive of renal function compared with A1M; however the concentration of beta 2-microglobulin, N-acetyl-beta-D-glucosaminidase, and microalbumin increased in children with reflux neuropathy. A1M can even indicate the presence of unusual renal function in reflux nephropathy in pediatrics before the incidence of proteinuria (14).

In 2000, Mantur et al. revealed that evaluating the urinary A1M/creatinine ratio was a useful means with the diagnostic advantages of proximal tubule damage during pediatric infection of urinary tract with *E. coli* (15). Pyelonephritis is known as a bacterial infection condition, which could result in parenchymal scarring and life-treating consequences.

Nowadays, alpha-1-microglobulin (A1M) as a multifunctional and immunomodulatory protein has shown a wide range of clinical use and has become a considerable alternative test for evaluating tubular function; this might be due to its constancy.

### Diagnostic importance of A1M

Studies on urinary excretion of A1M revealed successful results regarding the capability of this marker in the diagnosis of various urological diseases involved kidneys including patients with reflux and with outflow disease of the upper tract (19).

Due to the lack of specific symptoms in children with urinary tract infection, early diagnosis of pyelonephritis is extremely important. Acute phase of pyelonephritis might occur without any parenchymal inflammatory lesions, which are difficult and time-consuming to be diagnosed especially in children and infants (20). Early detection of bacterial infection and performing the appropriate treatment could reduce the possibility of parenchymal scarring. In normal condition, 99% of filtered low molecular weight proteins are absorbed in tubules, while urine excretion of these proteins is called tubular disease (21).

According to the study of Everaert et al. A1M was proposed as the most effective biomarker in differentiating acute prostatitis from acute pyelo-

nephritis while compared with other biomarkers such as urinary gamma-glutamyltransferase, albumin, creatinine, and immunoglobulin A (IgA) (6). The urine excretion of A1M showed a statistically significant increased due to renal colic and chronic ureteral obstruction in PN patients (6). In this study, age and gender of patients have been investigated as possible risk factors of urinary excretion of A1M. They revealed that there was no relation between PN patients' gender and A1M urinary excretion rate despite of the slight influence of age on A1M urinary excretion. Moreover, it was mentioned that urine production rate significantly increased the urine A1M/creatinine fraction. Immunonephelometry was used to evaluate the concentration of urinary A1M and their results were in concordance with DMSA image outcomes. Everaert et al. showed that in DMSA lesion-positive (acute pyelonephritis) patients, the urinary excretion of A1M was significantly higher compared with DMSA lesion-negative (cystitis) patients who had normal A1M excretion in urine (18). It was even revealed that the excretion of A1M was significantly different in patients with bilateral pyelonephritis compared to those with unilateral pyelonephritis (18).

Currently, checking of inflammatory lesions through Tc-99m dimercaptosuccinic acid (99mTc-DMSA) scintigraphy is considered "gold standard" in acute phase of pyelonephritis. Therefore, DMSA uptake is a marker of pyelonephritis. Assessing the concentration of proximal tubular dysfunction markers can be beneficial in the diagnosis of acute pyelonephritis. The concentration of urine biomarkers has been evaluated and compared with the 99mTc-DMSA results to measure their correlation. Everaert et al. observed a considerably high correlation between urinary A1M concentration and DMSA results. They reported the urinary A1M evaluation as a cheap, quick, and reliable screening method for the diagnosis of acute pyelonephritis and applying the appropriate and necessary antibiotic treatment (18). A1M is a sensitive and specific indicator of acute pyelonephritis and differentiator between upper and lower urinary tract infection. Furthermore, A1M might diagnose the incidence of acute pyelonephritis at the time of hospital admission and before obtaining urine culture results (19). Mentioned studies evaluated the concentration changes of urine biomarkers as a noninvasive and cost effective method; however this method might be very complicated due to the difficult comparisons. In the study of Puczko-Michalczyk, in 2008, nephrometric assay was used for the evaluation of A1M (17). Applying computer-based systems for urine protein differentiation could improve

the quality of test interpretation. According to the study of Gonzalez Rodriguez et al. in 2009, A1M is more sensitive in the diagnosis of acute pyelonephritis compared with other renal diseases (16).

The small number of studies conducted on this issue, especially English language articles, limited the obtained data in this review.

## Conclusion

A1M is not an acute phase protein but its concentration alters in several clinical conditions. Evaluating the urine concentration of A1M is a noninvasive and cost effective strategy with the diagnostic capability for urinary tract disorders such as early recognition of tubular damages during pyelonephritis.

## Acknowledgement

We would like to thank Clinical Research Development Unit of Ghaem Hospital for their assistant in this manuscript.

## Conflict of Interest

The authors declare no conflict of interest.

## References

- Ramakrishnan K, Scheid DC. Diagnosis and management of acute pyelonephritis in adults. *Am Fam Physician*. 2005;71:933-942.
- Stamm WE, Hooton TM. Management of urinary tract infections in adults. *N Engl J Med*. 1993;329:1328-1334.
- Strohmeier Y, Hodson EM, Willis NS, et al. Antibiotics for acute pyelonephritis in children. *Cochrane Database Syst Rev*. 2014;7:CD003772.
- Shaikh N, Ewing AL, Bhatnagar S, et al. Risk of renal scarring in children with a first urinary tract infection: a systematic review. *Pediatrics*. 2010;126:1084-1091.
- Chromek M, Tullus K, Hertting O, et al. Matrix metalloproteinase-9 and tissue inhibitor of metalloproteinases-1 in acute pyelonephritis and renal scarring. *Pediatr Res*. 2003;53:698-705.
- Everaert K, Delanghe J, Vande Wiele C, et al. Urinary alpha 1-microglobulin detects uropathy. A prospective study in 483 urological patients. *Clin Chem Lab Med*. 1998;36:309-315.
- Galanakis E, Bitsori M, Dimitriou H, et al. Urine interleukin-8 as a marker of vesicoureteral reflux in infants. *Pediatrics*. 2006;117:e863-867.
- beta-2 Jantusch BA, Rifai N, Getson P, et al. Urinary N-acetyl-beta-glucosaminidase and beta-2-microglobulin in the diagnosis of urinary tract infection in febrile infants. *Pediatr Infect Dis J*. 1994;13:294-299.
- Beta2 Coppo R, Porcellini MG, Gianoglio B, et al. Glomerular permselectivity to macromolecules in reflux nephropathy: microalbuminuria during acute hyperfiltration due to aminoacid infusion. *Clin Nephrol*. 1993;40:299-307.
- Beta2 Di Pietro A, Proverbio MR, Pescatore L, et al. [Determination of the urinary secretion of beta 2-microglobulin combined with sequential renal scintigraphy using H123 for the early diagnosis of pyelonephritis in children]. *Pediatr Med Chir*. 1986;8:511-513.
- Gekle D, Kult J, Huttig H, et al. beta2-Microglobulin in healthy children and in children with renal diseases (author's transl). *Z Kinderheilkd*. 1975;119:293-298.
- Gekle D, Kult J, Huttig G, et al. Beta 2-microglobulin in the differential diagnosis of glomerular and tubular kidney diseases. *Monatsschr Kinderheilkd*. 1975;123:413-414.
- Ametov AS, Gavriushova LP, Tvorogova TM, et al. Radioimmunological test for beta 2-microglobulin in kidney diseases in children. *Med Radiol (Mosk)*. 1982;27:38-42.
- Konda R, Sakai K, Ota S, et al. Followup study of renal function in children with reflux nephropathy after resolution of vesicoureteral reflux. *J Urol*. 1997;157:975-979.
- Mantur M, Kemona H, Dabrowska M, et al. alpha1-microglobulin as a marker of proximal tubular damage in urinary tract infection in children. *Clin Nephrol*. 2000;53:283-287.
- Gonzalez Rodriguez JD, Canalejo D, Martin Govantes JJ, et al. Proteinuria in urinary infection and acute pyelonephritis in paediatric patients: can it replace scintigraphic studies in diagnostic localisation?. *Nefrologia*. 2009;29:163-169.
- Puczko-Michalczuk A, Zoch-Zwierz W, Wasilewska A, et al. Evaluation of inflammatory and renal injury markers in youngest children with pyelonephritis. *Pol Merkur Lekarski*. 2008;25:451-454.
- Everaert K, Raes A, Hoebek P, et al. Combined use of urinary alpha1-microglobulin and 99mTc DMSA scintigraphy in the diagnosis and follow-up of acute pyelonephritis and cystitis in children. *Eur Urol*. 1998;34:486-91.
- Everaert K, Hoebek P, Delanghe J. A review on urinary proteins in outflow disease of the upper urinary tract. *Clin Chim Acta*. 2000;297:183-189.
- Linné T, Fituri O, Escobar-Billing R, et al. Functional parameters and 99mtechnetium-dimercaptosuccinic acid scan in acute pyelonephritis. *Pediatr Nephrol*. 1994;8:694-699.
- Grubb A. Diagnostic value of analysis of cystatin C and protein HC in biological fluids. *Clin Nephrol*. 1992;38:S20-27.