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NEPHROLOGY - REVIEW

Acute tubular necrosis and pre-renal acute kidney injury: utility of urine microscopy in their evaluation- a systematic review

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Abstract
Background Urine microscopy with examination of the urine sediment examination provides useful diagnostic information about the histology of the kidneys. While most nephrologists use urine microscopy to assess for the presence of glomerular diseases, they are less apt to use this diagnostic test when pre-renal acute kidney injury (AKI) or acute tubular necrosis (ATN) is clinically suspected. More often, tests such as fractional excretion of sodium (FeNa) and fractional excretion of urea (FeUrea) are used to differentiate these two causes of acute kidney injury.
Design and Methods A systematic search of Medline and the Cochrane Database, with no language restrictions, for studies in humans on urine microscopy with sediment examination for the differential diagnosis or risk stratification of acute kidney injury published between January 1960 and February 2009 was undertaken.
Results Based on the limited available data on urine microscopy reviewed in this paper, this test has merit in hospitalized patients with acute kidney injury to differentiate between pre-renal acute kidney injury and acute tubular necrosis. The presence and number of renal tubular epithelial cells and renal tubular epithelial cell casts and/or granular casts in the urine sediment appear beneficial in the diagnosis of ATN and may be useful in predicting more severe kidney damage that is reflected by non-recovery of AKI and need for dialysis.
Conclusions Urine microscopy and urine sediment examination is widely available, easy to perform, and inexpensive. The clinical utility of urine microscopy in the differential diagnosis and prediction of outcome in AKI may be increased by using a simple urinary scoring system based on the number of renal tubular epithelial cells and renal tubular epithelial cell/granular casts.

Keywords Acute kidney injury · Urine microscopy · Acute tubular necrosis · Pre-renal azotemia · Granular casts · Renal tubular cells

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Introduction

Acute kidney injury (AKI), defined as an abrupt decline in kidney functions, is a relatively frequent complication and an independent predictor of poor outcomes in hospitalized patients [1, 2]. In fact, AKI occurs in 5–35% of all hospitalized patients and is independently associated with a 2- to 5-fold increased risk of death [3–5]. In view of the common occurrence

of AKI and its associated poor outcomes, it is critical that potentially reversible AKI is early recognized to allow for appropriate and timely interventions [6, 7].

As pre-renal AKI (pre-renal azotemia) and acute tubular necrosis (ATN) are the most common causes of AKI in hospitalized patients, and therapies and outcomes for these forms of AKI differ significantly, early clinical differentiation is desirable [8, 9]. The recognition of AKI is based primarily on clinical history, physical examination, and certain laboratory measurements. Blood urea nitrogen (BUN), serum creatinine, and urine output are traditionally used to diagnose AKI, but they do not provide insight into the cause of AKI and cannot distinguish between pre-renal AKI and ATN. In the absence of renal biopsy, which is not typically performed in these settings, the differentiation of these two conditions is based on urinary biochemistry and derived indices such as urinary sodium concentration (UNa), fractional excretion of sodium (FeNa), and fractional excretion of urea nitrogen (FeUrea). However, there are limited data concerning the diagnostic strength of these tests in differentiating these two major forms of hospital-acquired AKI [10, 11].

Since the discovery of microscopic elements in the urine in the 19th century, urinalysis has been an essential diagnostic tool in kidney disease [12]. Urine microscopy with urine sediment examination by an experienced nephrologist often provides useful diagnostic information about the histologic state of the kidneys [13, 14]. While most nephrologists use urine microscopy to assess for the presence of glomerular diseases or acute interstitial nephritis, they are less apt to use this diagnostic test when pre-renal AKI or ATN is clinically suspected. More often, tests such as FeNa and FeUrea are used to differentiate pre-renal AKI from ATN.

The purpose of the current study was to critically review the current literature on the role of urine microscopy and urine sediment examination in the differential diagnosis and outcome prediction of AKI in hospitalized patients.

Methods

Search strategy

We systematically searched Medline and the Cochrane Database, with no language restrictions, for studies in humans on urine microscopy with sediment examination for the differential diagnosis or risk stratification of AKI, published between January 1960 and February 2009. The key words urine sediment, urinalysis, acute renal failure, acute kidney injury, acute tubular necrosis, pre-renal azotemia, urinary casts, urine microscopy, renal tubular epithelial cells, granular casts, hyaline casts, renal tubular epithelial cell casts with their synonyms and equivalent Medical Subject Heading (MeSH) terms were used. The searches were performed in coordination with an information specialist. One member of the research team assessed abstracts and full articles. We scrutinized the reference lists of the identified reports, reviews, meta-analyses, and other relevant publications, and the related articles' functions in MEDLINE were used to find additional pertinent studies.

Selection criteria

Since there were no randomized controlled trials, observational cross-sectional studies, case reports, case series, and letters were reviewed and included. Studies on non-dialysis-requiring subjects where the role of urine microscopy with sediment examination for the differential diagnosis or severity of AKI from either ATN or pre-renal AKI were investigated. Two investigators (MK and BK) independently assessed the eligibility of each study.

Data extraction and quality assessment

Reports from all eligible studies were evaluated for appropriateness for inclusion without prior consideration of results. We used information concerning study design, patient characteristics, and risk estimates including their 95% confidence interval (CI) either with the number of urinary casts or expressed as cast scoring system defined by the studies.

Two independent reviewers (MK, BK) performed quality assessment, and any uncertainties in the relevant studies were subsequently discussed with other team members. Reviewers assessed study quality according to guidelines outlined by Hayden et al. [15]. Studies were graded as good quality if they met 5 to 6 criteria, fair if they met 3 to 4 criteria, and poor if they met 2 or fewer criteria.

Data analysis

A standardized framework was used by two independent reviewers (MK, BK) to assess the quality of included studies whose usefulness may have been comprised due to heterogeneity of populations, outcome measures and intervention methods, and to a paucity of studies. There was no disagreement between reviewers. Data were extracted for the latest period of follow-up reported. As none of the studies on urine microscopy were sufficiently homogenous to undertake meta-analysis, the findings were synthesized in a narrative review. Effect sizes and indicators of statistical significance or CI are given where these were reported.

Results

Search results

Of 447 citations, 5 studies were eligible for inclusion [16–21] and they are described in Table 1. Two of those studies were specifically restricted to patients with sepsis [20, 21]. Figure 1 shows our search and selection process.

Study results

All studies showed that urine sediment examination is a valuable diagnostic tool for differential diagnosis of AKI. Marcussen et al. tested cytodiagnostic urine microscopy to determine its utility in the differential diagnosis of AKI in 51 patients with AKI [17]. In their study, 34 patients with ATN of either ischemic or toxic origin had a higher number of collecting duct cells and a higher total number of urinary casts than the 17 non-ATN patients. Moreover, 12 patients requiring dialysis had a greater number of urinary casts (granular, waxy, leukocytic, and broad casts) and renal tubular cells (particularly necrotic cells) than the 39 patients who did not require dialysis. They found that these urinary findings had a significant positive correlation with the magnitude of rise of serum creatinine concentration [16]. They concluded that an increased number of renal tubular cells is associated with ATN, and the presence of an increased number of urinary casts is associated with increased risk for dialysis requirement.

Chawla et al. developed a simple, reliable AKI cast scoring index (CSI) to grade the renal tubular epithelial (RTE) cell and granular casts present on urine microscopy in order to standardize urinary microscopy in a study with 48 patients with AKI due to ATN [17]. The scoring system was graded as follows: Grade 1- no evidence of RTE cell casts or granular casts; Grade 2- rare RTE cell casts and granular casts; Grade 3- many RTE cell casts and granular casts; and Grade 4- sheets of muddy brown granular casts. Three nephrologists were blinded to grade the urine sediment from 30 patients with ATN using the AKI CSI. Subsequently, the AKI CSI was tested in another 18 patients with ATN to determine whether the score could predict lack of renal recovery. The rate of non-renal recovery in these 18 patients was 61.1%, and the patients that did not recover had a higher AKI CSI when compared with patients that recovered renal function (2.55 ± 0.93 vs. 1.57 ± 0.79, $p = 0.04$). ROC area under the curve for AKI CSI to diagnose non-renal recovery was 0.79. This small study suggests that a standardized AKI CSI has the potential to incorporate urinary cast analysis into the progressing field of AKI diagnostics and predict more severe AKI [17].

We recently published a cross-sectional study that supports the utility of urine microscopy in differentiating pre-renal AKI from ATN. The utility of the number of granular casts and urinary scoring system (Table 2) for the diagnosis of ATN is studied [18]. In our cohort of 267 patients, 125 (47%) had a final diagnosis of ATN, and 106 (40%) had pre-renal AKI. Thirty-six (13%) patients with other causes of AKI were excluded. Importantly, the ability of the pre-urine microscopy diagnosis to distinguish ATN from pre-renal AKI was fair (sensitivity− 0.76; specificity− 0.86; positive LR− 5.75) using the final diagnosis as the gold standard. Likelihood ratios (LR) for both ATN and pre-renal AKI from the results of microscopic examination (number of RTE cells and granular casts) by final clinical diagnosis were calculated. A urine microscopy score of ≥ 2 versus a score of 2 was associated with a 74-fold increase in the odds of a final diagnosis of ATN. The LR for both pre-renal azotemia and ATN were calculated for the various categories of granular cast number in the urine sediment (Table 3). Thus, urine microscopy on the day of nephrology consultation is a valuable diagnostic tool for strengthening the probability of a diagnosis of ATN. The presence of granular casts and employment of a urinary

Table 1 Characteristics of the studies

Author (year)	Clinical setting	Aims	Conclusions	Limitations
Marcussen[16] 1995	51 patients with AKI	To investigate the role of the number and type of renal and other cells, and casts in differential diagnosis of AKI	Cytodiagnostic urinalysis may be valuable in addition to other tests in the evaluation of patients with AKI	1. Small study population 2. Although significantly more cells and casts were found in ATN, a substantial number were also seen in pre-renal AKI and in the other non-ATN etiologies 3. They did not control for urine osmolarity and pH, which may affect the formation and stability of urinary casts
Chawla[17] 2008	48 patients with AKI due to ATN	To develop a simple AKI CSI that can grade the level of RTE casts and granular casts in urine sediment in ATN	1. A standardized AKI CSI has the potential to incorporate urinary cast analysis into AKI diagnostics 2. The AKI CSI may be useful in predicting renal outcomes in ATN	1. Small study population 2. They did not assess the samples in each patient at the same time of the day 3. The cellular elements may have deteriorated between viewings 4. The number of reviewers and the variation in the reviewer's training were relatively limited 5. Focused on hospitalized patients with ATN
Perazella[18] 2008	267 patients with AKI	To determine the performance of urinary sediment examination for differentiation of hospital-acquired AKI due to either ATN or pre-renal AKI	1.Urine sediment examination is useful for diagnosis of ATN versus pre-renal AKI 2. A urine sediment score > 2 is an extremely strong predictor of ATN	1. They did not capture the causes of AKI 2. They did not obtain biopsies from patients to verify true ATN in patients with AKI sustained for 48 h 3. They could not evaluate inter-observer variability 4. Microscopists were not blinded to the diagnosis 5. Focused on hospitalized patients with AKI
Gay[19] 1987	31 episodes of AKI in children with sepsis	To examine the correlation of clinical, biological and ultrasound data with urine sediment in septic children with AKI	Urine microscopy correlated well with these AKI parameters and is valuable in the setting of AKI	1. Small study population 2. Focused on ATN in children with sepsis 3. Urine microscopy performed within 5 days of AKI episode 4. No information on types of cells or casts 5. No information on observer training or inter-observer variability 6. Microscopists not blinded to the diagnosis
Graber[20] 1991	65 consecutive inpatients with sepsis and AKI due to ATN	To examine urine sediment findings in ATN in patients with sepsis	Urine microscopy in ATN-demonstrated "bubble cells", RTE cells, and granular casts is seen in the majority of patients with ATN	1. Small study population 2. Focused on sepsis-induced ATN 3. They did not report the type of casts 4. No information on observer training or inter-observer variability 5. Microscopists not blinded to the diagnosis

ATN acute tubular necrosis, *AKI* acute kidney injury, *RTE* renal tubular epithelial, *CSI* cast scoring index

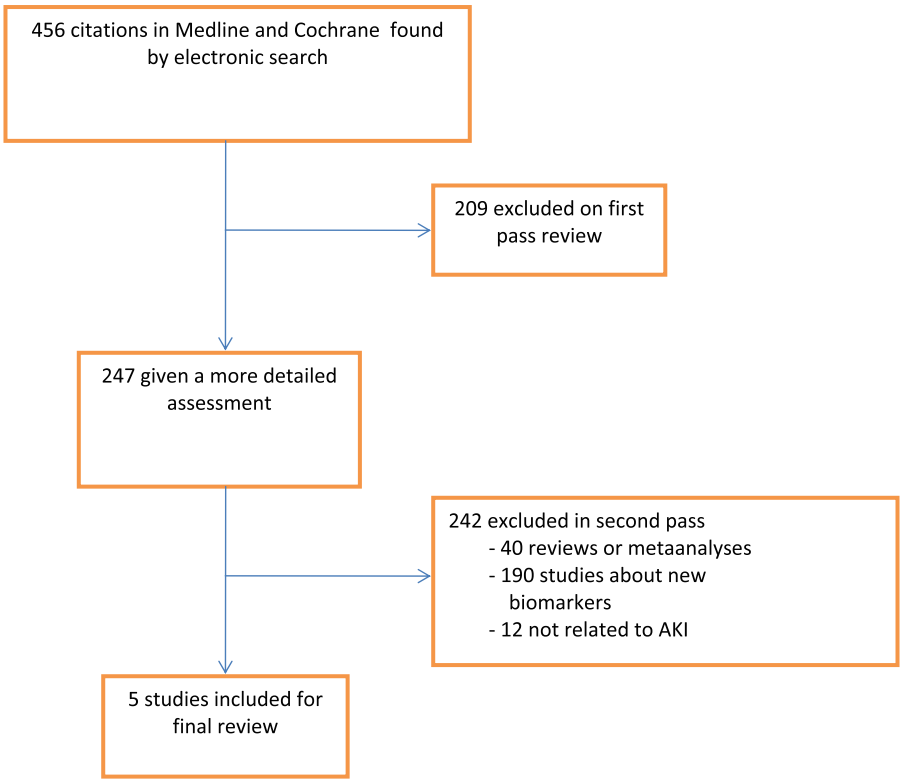

Fig. 1 Search strategy utilized

Table 2 Scoring system based on number of granular casts and RTE cells

Score	Description
1	0 RTE cells and granular casts 0
2	0 RTE cells and granular casts 1–5; or 1–5 RTE cells and granular casts 0
3	1–5 RTE cells and granular casts 1–5; or 0 RTE cells and granular casts 6–10; or 6–20 RTE cells and granular casts 0

RTE renal tubular epithelial cells (per high powered field); granular casts (per low powered field)

Table 3 LR for diagnoses of ATN and pre-renal azotemia based on the number of granular casts present in the urinary sediment

Granular Casts/LPF	LR (ATN)	LR (Pre-renal Azotemia)
0	0.23	4.35
1–5	2.97	0.34
6–10	9.68	0.10

ATN acute tubular necrosis, *LR* likelihood ratio

scoring system can differentiate ATN from pre-renal AKI. Further studies are warranted to better elucidate the role of RTE cells, granular casts, and urinary scoring system in the diagnosis and prognosis of AKI, in particular ATN and pre-renal AKI.

Urinary Microscopy in septic acute kidney injury

Although RTE cells, hematuria, pyuria, muddy brown granular casts and/or RTE cell casts are reported in septic AKI, normal urinary sediment is also described in some cases [19]. There are 2 studies that examine the utility of urine microscopy in the differential diagnosis of AKI in patients with sepsis. Gay et al. examined the urine sediment in 31 episodes of AKI in children [20]. The first urine sediment examination was performed 5 days after the onset of AKI. In 10% of the urine samples, the sediment was normal, while 26% had hematuria. The causes of AKI were sepsis, nephrotoxic agents, hemolytic-uremic syndrome, nephritic syndrome, hemodynamic instability (presumed ischemia), and obstruction. They found a good

correlation between clinical, biological, and ultrasonographic data in 28 cases (90%). Although they did not provide details about the urinary casts in this study, they concluded that urinary sediment examination is valuable in the interpretation of tubular, interstitial or tubulointerstitial lesions in the setting of AKI [20].

Graber et al. evaluated the urinary sediment of 65 patients with renal insufficiency after excluding cases due to pre- or post-renal factors [21]. In patients with ATN, the urine sediment contained large cells with a single nucleus, which appeared to contain one or more fluid-filled vesicles, which they defined as "bubble cells". In most patients with ATN, the urine sediment also contained "normal" appearing RTE cells, muddy brown granular casts, and oval fat bodies. In ATN cases, RTE cells and muddy brown casts were noted in 76% and 62%, respectively, of urine sediments. The authors concluded that urinary sediment evaluation may be helpful in diagnosis of ATN, and these "bubble cells" require more careful study [21].

Discussion

Based on the limited available data on urine microscopy and urine sediment examination reviewed, this widely available and inexpensive test has merit in hospitalized patients with AKI to differentiate between pre-renal AKI and ATN. The presence and number of RTE cells and RTE cell casts and/or granular casts in the urine sediment appear beneficial in the diagnosis of ATN and may be useful in predicting more severe kidney damage that is reflected by non-recovery of AKI and need for dialysis. Moreover, a urinary sediment scoring system based on the number of RTE cells and RTE cell/granular casts is useful in the evaluation of AKI.

The studies reviewed in this paper are generally small, single-center studies that are limited by a number of flaws. Yet, they do provide a relatively consistent conclusion–there is benefit to performing urine microscopy in hospitalized patients with AKI. Two studies support a role of urine microscopy in the differentiation of ATN from either pre-renal AKI [18] or patients with AKI not due to ATN [16]. The paper by Perazella et al. [18] utilizes a urinary sediment scoring system, which reliably differentiates the two common causes of hospital-induced AKI. Two studies support the utility of urinary microscopy in predicting more severe ATN as defined by non-recovery of AKI or need for dialysis, in one of these studies, a CSI was validated and employed [17]. One study examined only ATN cases after excluding pre- and post-renal causes of AKI and found that RTE cells and muddy brown granular casts, as well as bizarre "bubble cells" were present in the urine sediment of a majority of patients [21]. One study did not provide details about the types of cells/casts identified in the urine sediment [20], while one study did not describe the causes of AKI but broke them into ATN versus non-ATN [16]. The authors, however, state that a correlation of urinary findings with clinical and histologic findings was present [20].

The major limitations of the studies included in this review include the following: 1) primarily hospitalized patients with ATN were included; 2) the diagnostic value of urine microscopy was not compared with other diagnostic methods; 3) the studies are small, single-center studies; 4) there is no accepted number of urinary cells or casts (or urinary scoring system) for differential diagnosis of AKI; 5) unclear or no blinding of urinary microscopy readers (except for one study); and 6) intra- and inter-observer variability for microscopic evaluation of urine sediment was not assessed in all studies.

The current interest in urine microscopy and urine sediment examination in the diagnosis and prognosis of pre-renal AKI and ATN is likely related to a few factors. First, these two diagnoses account for the majority of hospitalized AKI. Second, differentiation of ATN from pre-renal AKI would likely change the subsequent care of patients. For example, diagnosis of pre-renal AKI would allow aggressive volume repletion (true volume depletion) or use of other interventions such as vasopressors and inotropic agents to improve renal perfusion (cardiorenal syndrome). In contrast, diagnosis of ATN would prompt removal of nephrotoxins and attention to supportive care. In this regard, judicious fluid administration to correct blood pressure in such patients without over-repletion, which could promote non-cardiac pulmonary edema, would be facilitated. Excessive fluid administration can produce many adverse physiologic effects that in turn cause respiratory distress and increased morbidity and mortality. Fourth, if urine microscopy and a urinary score can provide prognostic information, this would be an extremely important addition to the clinical armamentarium.

The ability to stratify AKI risk at the time of nephrology consultation will allow the clinician to more confidently predict the probable clinical scenario for the consultant, nursing staff, and health care team, as well as for the patient and family. Finally, urine microscopy is appealing as a diagnostic test in that it is widely available, easy to perform following appropriate training, inexpensive, and provides excellent discrimination. This makes for a desirable clinical test for nephrologists, especially as more hospitals move toward automated urine microscopy, which has limited ability to identify urinary casts.

With the availability of tests such as the FeNa and FeUrea, urine microscopy is less often used to differentiate ATN from pre-renal AKI [22]. Studies have shown their ability to reliably discriminate these two causes of AKI; however, these tests have flaws that limit their utility in this setting. First, FeNa was only validated in oliguric patients [23], which make up only a part of the AKI population. Also, there are several clinical scenarios of ATN where a low FeNa (less than 1%) is present. These include sepsis, contrast nephropathy, myoglobulinuric ATN, and several causes of non-oliguric ATN [24, 25]. Furthermore, diuretic agents and bicarbonaturia (vomiting, nasogastric suction) often increase urinary sodium and the FeNa despite the presence of pre-renal AKI [26]. To try to overcome this issue, the FeUrea has been employed to differentiate ATN from pre-renal AKI. Early studies found a low FeUrea ($< 35\%$) in the setting of diuretic use to be a more sensitive and specific index than FeNa in differentiation of pre-renal AKI from ATN, especially if diuretics have been administered [27]. However, subsequent examination of FeUrea has found the test to lack in both sensitivity and specificity for these two causes of AKI [28]. For instance, in osmotic diuresis or in usage of osmotic diuretics such as mannitol or acetazolamide, the proximal tubular absorption of salt and water is impaired and thus increased FeUrea is expected despite renal hypoperfusion [29].

Finally, the era of novel biomarkers has arrived, and many of these have shown great potential in the evaluation of AKI. Although not currently available, several novel urinary biomarkers are elevated in patients with ATN and not pre-renal AKI [30–32]. The prognostic abilities of these biomarkers in AKI are conflicting. Some studies demonstrate that urinary cystatin C, alpha-1 microglobulin, *N*-acetyl-β-D-glucosaminidase (NAG), and retinol-binding protein have fairly strong ability to predict severe AKI (AUC 0.81–0.92) [33, 34]. However, neutrophil gelatinase-associated lipocalin [NGAL], interleukin [IL]-18, and kidney injury molecule [KIM]-1) have shown both good and poor ability to predict length of AKI, need for dialysis, or in-hospital death across studies [35–39]. Some of these biomarkers have AUCs < 0.7 for prediction of severe AKI [34, 36].

In reality, the best approach to the evaluation of patients with hospital-acquired AKI who are suffering from either ATN or pre-renal AKI may be to combine the available tests. For example, following recognition of AKI, urinalysis and urine microscopy should be obtained. Searching for RTE cells, RTE cell casts and granular casts would point toward ATN rather than pre-renal AKI. In oliguric patients, measuring FeNa may add further information, unless they are on diuretics or have a urinary pH > 6.0, when a FeUrea may be more reliable. Using an AKI cast scoring index [17] or urinary scoring system [18] may help to further differentiate ATN from pre-renal AKI and provide prognostic information. In the future, perhaps the combination of urine sediment plus novel biomarkers will improve the accuracy in differentiating the cause of AKI and predicting the outcomes of AKI.

In conclusion, urine microscopy and urine sediment examination is widely available, easy to perform, and inexpensive. The clinical utility of urine microscopy in the differential diagnosis and prediction of outcomes in AKI may be increased by using a simple urinary scoring system. Since intra- and inter-observer reliability is a potential limitation, nephrology training programs should make a concerted effort to guarantee competency in the preparation and interpretation of urine microscopy [14]. This is even more critical going forward as many laboratories are employing automated technology to examine the urine [40, 41], since the reliability of the automated systems for detection of casts is poor. Furthermore, nephrologists are superior in interpreting the urine sediment findings compared to laboratory personnel [42]. Finally, it is time to conduct a well-designed, multi-center, prospective study to assess the composite value of urine microscopy with other diagnostic methods (including novel biomarkers) for differentiating ATN vs. pre-renal AKI and for risk stratification of AKI.

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