RJCCN Case Report
KIDNEY DISEASE

Urinary Ammonium: A Renewed Compass for Renal and Extra-Renal Disorders, a Case Series

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Keywords. urinary electrolytes, ammonium, KING, renal transplant, chronic renal failure

Introduction. Assessment of urinary ammonium (uNH_4^+) describes one of the kidney's most important physiological functions, yet direct measurement is not routinely available. Historically, urine anion gap has been used as a surrogate for uNH_4^+, although this approach is unreliable, particularly in patients with chronic kidney disease. The ability to directly measure uNH_4^+ may therefore provide clinically relevant diagnostic and therapeutic information.
Case Series. In this case series, we present three clinical cases illustrating the utility of uNH_4^+ measurement, now available as a bedside point-of-care measurement (KING, Kures®). These include comparison between a dysfunctional native kidney and a recovering transplanted graft, and the differential diagnosis of a-lactic metabolic acidosis in two distinct clinical settings. Across cases, uNH_4^+ provided timely physiological insight into tubular function, supporting diagnosis and recovery assessment beyond traditional markers.
Conclusions. These observations underscore the importance of distinguishing tubular from glomerular function and complement traditional markers in renal assessment.

RJCCN 2026; 2(3):216-21
www.rjccn.org
DOI: 10.66224/rjccn.2.3.39

INTRODUCTION

In December 2021, 174 American nephrologists signed a petition addressed to Directors of Clinical Laboratories, requesting that urinary ammonium (uNH_4^+) be made a readily available test nationwide. The petition was reported in *Kidney News*, [1] and was first disseminated via Twitter.

The nephrologists who signed the petition argued that estimating uNH_4^+ using the urine anion gap (UAG) is less accurate than direct uNH_4^+ measurement. They consider uNH_4^+ valuable *"not only in the diagnosis of renal tubular acidosis but also in managing acidosis in progressive [chronic kidney disease] CKD and in evaluating and treating patients with kidney stones, where it will give us clues about the acid load the patients consume."*

The ability to measure uNH_4^+ in routine care and to have this information readily available may provide clinically relevant diagnostic and therapeutic information across several specialties, particularly for assessing acid-base disorders and managing CKD. NH_4^+ (Figure 1) plays a fundamental role in renal tubule handling of acid-base regulation. Ammonium is primary produced in the proximal tubule through the catabolism of glutamine catabolism, where glutamine is metabolized via glutaminase and glutamate dehydrogenase. This process produces two molecules of NH_4^+ and

Please cite this article as: Titherington LM, Romagnoli S, Caironi P. Urinary Ammonium: A Renewed Compass for Renal and Extra-Renal Disorders, a Case Series. RJCCN. 2026;2(3):216-21.

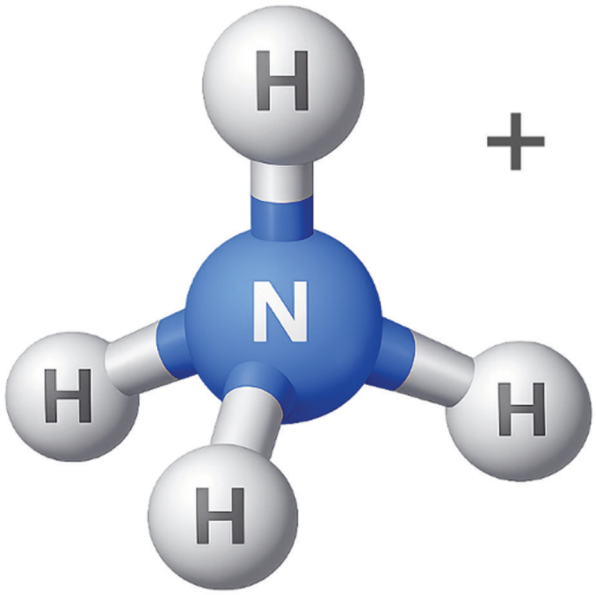

Figure 1. Ammonium molecule represented in graphic form.

alpha-ketoglutarate. The alpha-ketoglutarate is then further metabolised into two molecules HCO_3^- which are absorbed into the blood while the NH_4^+ is secreted into the lumen. This process is enhanced in metabolic acidosis.

From a diagnostic standpoint, direct measurement of uNH_4^+ allows differentiation between metabolic acidosis of either renal or extrarenal origin (See Table 1 for reference ranges). In metabolic acidosis, low uNH_4^+ excretion indicates impaired renal urine acidification, whereas high excretion reflects an appropriate renal response to an extrarenal acid load.[2,3] From a therapeutic perspective, measuring uNH_4^+ enables early identification of patients with CKD at risk of progression, even in the absence of overt acidosis, allowing consideration of alkalizing therapies before clinical acidosis develops.[4,5]

The use of UAG to estimate uNH_4^+ has proven unreliable, particularly in patients with CKD[2,5,6] (Figures 2 and 3). In hospitalized patients, multiple pathological and iatrogenic factors, including underlying disease, diuretics, fluid therapy and other treatments, may independently influence urinary electrolyte excretion and UAG, regardless of acid-base status. Additionally, alterations of unmeasured ions may further limit the reliability of UAG-based uNH_4 estimation.[7]

In response to the nephrologists' petition, an Italian company, Kures® (Milan, Italy) developed the KING® system (Kidney Instant monitoring), which enables direct measurement of uNH_4^+, either from a single random urine sample or through quasi-continuous monitoring at minimum interval of 10 minutes[8]. Access to point-of-care uNH_4^+ measurement could transform the way we assess renal function assessment by enabling us to differentiate between the glomerular and tubular components.[9]

In this article, we present three case reports illustrating a series of clinically applicable uses of this instrument. These examples highlight the clinical utility of uNH_4^+ and its use in evaluating tubular function.

CASE SERIES

Case 1: Comparing a Dysfunctional Kidney with a Successfully Transplanted Kidney, The Basics

The first case describes a 69-year-old female patient who underwent renal transplant for end-stage CKD of unknown origin. On post-operative day 5, there was an abrupt reduction of urine output, which was accompanied by a decrease in uNH_4^+, coinciding with the development of graft hydronephrosis. A nephrostomy was placed, and uNH_4^+ concentration measured from

uNH_4^+ Reference Range and Clinical Interpretation[2, 5,12]

Spot uNH4+	uNH4+excretion	Interpretation	Clinical Implications
< 5, mEq/L	< 20, mEq/d	Low	Alkaline diet, respiratory and metabolic alkalosis, impaired renal acidification (may indicate renal tubular acidosis or CKD).
5 to 30, mEq/L	20 to 40, mEq/d	Normal	Normal renal acid excretion in healthy adults.
> 30, mEq/L	> 40, mEq/d	High	Increased plasma acid load and urine excretion, chronic diarrhoea, high protein intake, or infection with urease-producing bacteria.

Note. Please note that spot urinary ammonium concentrations should be strictly interpreted in the context of the patient's overall clinical and biochemical profile. Serial measurements and longitudinal trends provide greater clinical insight than isolated values. Moreover, the measured "concentration" strictly depends on urine volume, which may physiologically range from 500 mL up to 10 to 15 L/d, depending on water balance regulation. Single spot uNH_4^+ values should therefore be interpreted with caution, whereas longitudinal assessment may better capture changes in NH_4^+ excretion over time.

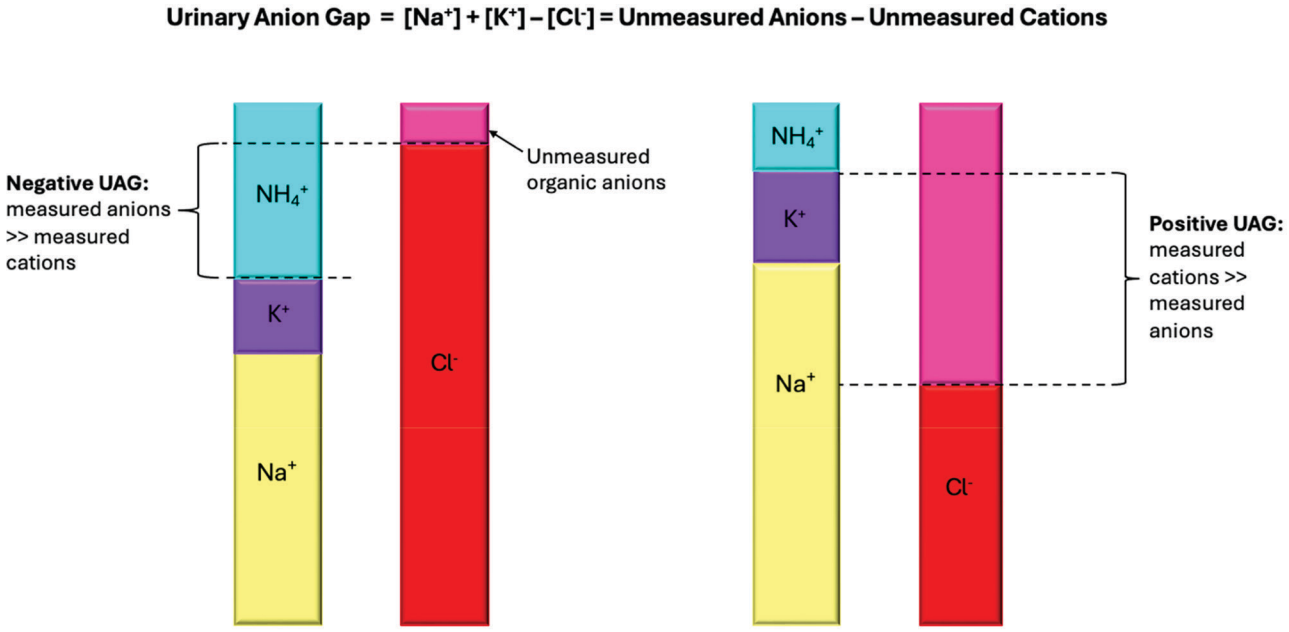

Figure 2. Limitations of the Urine Anion Gap (UAG) as a Surrogate for Urinary NH_4+ Excretion
(Since most urinary NH_4^+ is excreted as NH_4Cl, increased urinary Cl^- generally reflects enhanced NH_4^+ excretion, whereas low urinary Cl^- suggests reduced NH_4^+ elimination. However, several important limitations must be considered. The presence of excess unmeasured anions may lead to over- or underestimation of NH_4^+. The UAG does not account for NH_4^+ excretion with non-chloride anions (e.g., ketoacids or other organic anions). Polyuria and urine pH > 6.5 may alter the relationship between NH_4^+ and Cl^-. Dietary factors, including potassium or sodium salts containing non-chloride anions, can further confound interpretation[6]. In chronic kidney disease, the correlation between UAG and directly measured urinary NH_4^+ becomes unreliable.[2,7])

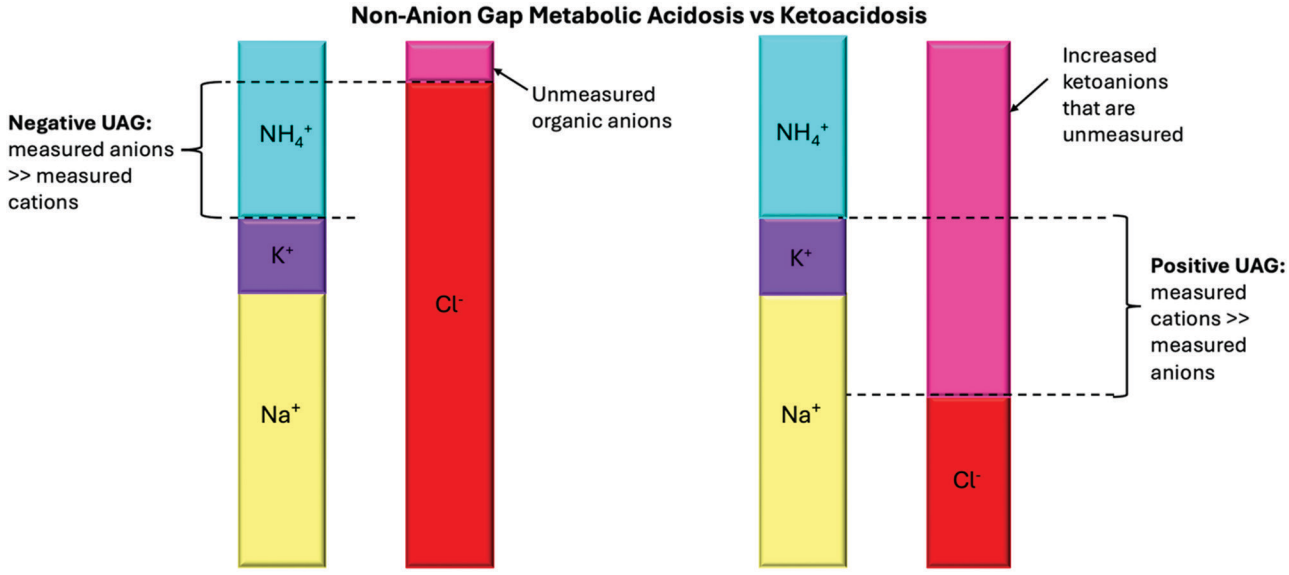

Figure 3. Reduced Reliability of the Urine Anion Gap in Metabolic Ketoacidosis
(In metabolic ketoacidosis, if renal function is preserved, urinary NH_4^+ excretion appropriately increases; however, the accompanying anion differs from chloride. Rather than being excreted as NH_4Cl, NH_4^+ is primarily excreted with β-hydroxybutyrate$^-$ and acetoacetate$^-$. In this setting, urinary Na^+ and K^+ remain relatively unchanged, NH_4^+ increases but is not included in the UAG calculation, Cl^- remains normal or may decrease, and ketoanions rise but are likewise unmeasured. Consequently, when applying the formula $[Na^+] + [K^+] - [Cl^-]$, the UAG may appear positive or only minimally negative, substantially underestimating true urinary NH_4^+ excretion.[2,7])

the nephrostomy urine (originating from the transplanted kidney) was substantially higher than that measured from the urinary catheter (originating from the native kidneys) on post-operative day 10 (25.0 vs. 4.7 mEq/L), supporting recovery of tubular function in the graft (Figure 4).

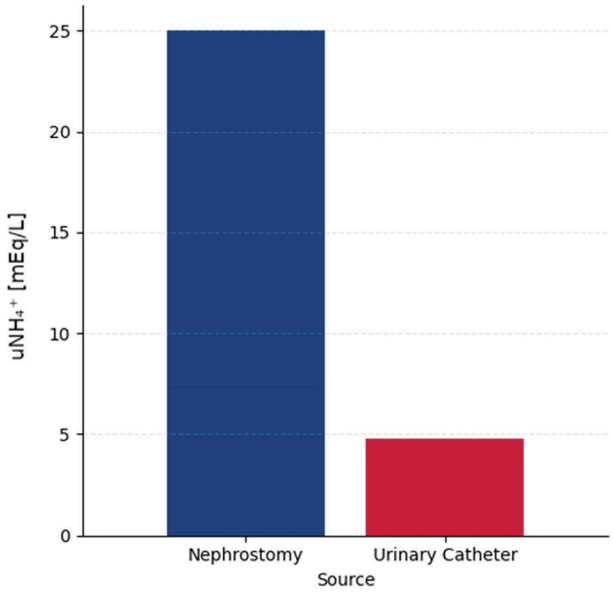

Figure 4. Comparison of Urinary Ammonium (uNH$_4^+$) Concentrations From Nephrostomy and Urinary Catheter in a Renal Transplant Recipient
(On post-operative day 10, uNH$_4^+$ measured from the nephrostomy (reflecting the transplanted kidney) was markedly higher than that from the urinary catheter (reflecting native kidneys) (25.0 vs. 4.7 mEq/L), indicating preserved tubular ammonium excretion and functional recovery of the graft.)

The differing concentrations of uNH$_4^+$ from the transplanted and native kidney demonstrates the physiology of renal compensation when there is adequate tubular function. Notably, despite the acute functional impairment, serum creatinine continued to decline and failed to reflect this deterioration (Figure 5), underscoring its limitation as a predominantly glomerular marker. In contrast, serial uNH$_4^+$ measurements promptly tracked both injury and recovery, suggesting a potential role for daily uNH$_4^+$ monitoring in the assessment of renal tubular function following transplantation.

Case 2: Differential Diagnosis of a-Lactic Metabolic Acidosis in a Critically Ill Patient

The second case describes a 56-year-old female admitted to the ICU with abdominal sepsis secondary to colonic perforation. The patient presented with a-lactic metabolic acidosis with elevated anion gap (pH = 7.27, $PaCO_2$ = 46 mmHg, lactate = 0.9 mmol/L, SBE = -5.5 mmol/L, AG = 18 mmol/L). The absence of lactic acid and the high AG level strongly suggested renal dysfunction as the likely cause, also considering the clinical presentation of sepsis. In the event of renal dysfunction, the kidneys are unable to reabsorb HCO_3^- and experience a reduced ability to produce and excrete NH_4^+. A urine sample was collected, and the uNH$_4^+$ levels were found to be 43.5 mEq/L, which suggests that ammoniagenesis was preserved. Further laboratory tests revealed the presence of ketoacids (20 mg/dL as urine concentration), prompting a different treatment approach. After appropriate therapy, acid-base balance normalized (pH = 7.43, $PaCO_2$ = 36 mmHg, BE = -0.8 mmol/L, AG = 7.5

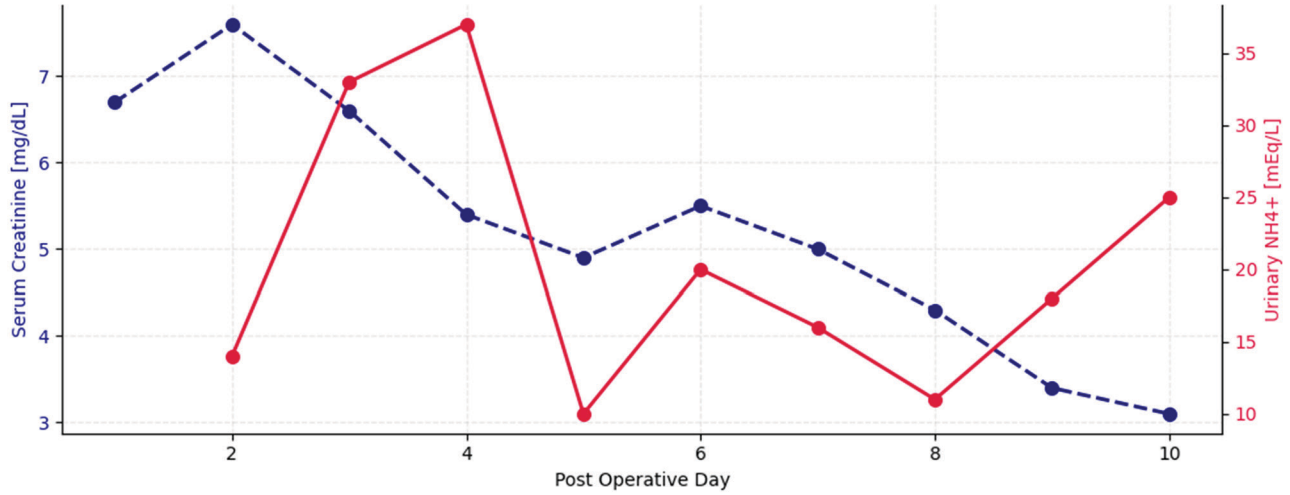

Figure 5. Temporal Evolution of Serum Creatinine and Urinary Ammonium (uNH$_4^+$) Following Renal Transplantation
(Serial measurements over the first 10 post-operative days demonstrate a progressive decline in serum creatinine, indicating improving glomerular function, while uNH$_4^+$ showed an early reduction corresponding with graft hydronephrosis followed by recovery after nephrostomy placement. The divergent trajectories highlight the sensitivity of uNH$_4^+$ to dynamic changes in tubular function that were not immediately reflected by serum creatinine.)

mmol/L). In cases of metabolic acidosis, ruling out a renal cause through a simple measurement of uNH_4^+ can provide valuable and importantly timely information on the underlying aetiology, thereby guiding appropriate treatment. At the same time, early AKI may may not immediately impair ammoniagenesis, making evaluation of trends over time particularly important.

Case 3: Differential Diagnosis of a-Lactic Metabolic Acidosis in a Surgical Patient with Reduced Baseline Renal Reserve

The third case describes a 73-year-old male with a medical history of non-insulin-dependent diabetes mellitus, as well as prior left nephrectomy and right kidney tumour enucleation. The patient underwent a second enucleation of his right kidney. Prior to the surgical procedure, a CT scan with contrast media was performed, resulting in an increase in his serum creatinine from 1.33 to 1.44 mg/dL.

The day of surgery an arterial blood gas analysis was performed and revealed a metabolic acidosis (pH = 7.25, $PaCO_2$ = 44 mmHg, lactate = 0.3 mmol/L, SBE = -8.1 mmol/L, AG = 14 mmol/L). The physicians hypothesised that he had contrast-induced AKI superimposed on CKD. Due to the high risk of exacerbation of CKD, the patient underwent surgical enucleation without renal artery clamping to avoid the potential for ischemia-reperfusion injury. Post-surgery the patient's urine analysis revealed a uNH_4^+ of 29.34 mEq/L, indicating that the residual kidney was attempting to compensate for the metabolic acidosis, likely of non-renal origin. Following the surgical procedure, the patient was transferred to the ICU, where ketone levels were measured and found to be 10 mg/dL. Consequently, a diagnosis of ketoacidosis was established.

DISCUSSION

This descriptive case series provides physiological observations that highlight the potential importance of measuring uNH_4^+ directly. This instrument may assist differential diagnoses and facilitates real-time monitoring of renal tubular function, distinguishing it from glomerular filtration function, which is measured with latency using serum creatinine. Moreover, the assessment of longitudinal trends in uNH_4^+ may also yield valuable information regarding the recovery of AKI, even in conditions of oliguria.

Previous studies have investigated the potential of urine physicochemical profiling to characterize the development of AKI independently of traditional parameters, such as urine output and serum creatinine. For instance, a seminal study by Maciel *et al.* delineated a distinctive urinary physicochemical profile of AKI that was independent of urine output[11]. In this study, AKI was associated with an increase in urinary Strong Ion Difference (uSID) – a different terminology for UAG –, which represents an inverse surrogate of uNH_4^+ excretion. An elevated uSID reflects impaired renal acid excretion, consistent with reduced uNH_4^+ and chloride excretion. Notably, recovery of kidney function was associated with a progressive decrease in uSID, often normalizing earlier than serum creatinine levels. Taken together, these findings once again suggest that uNH_4^+ may serve as a dynamic marker of tubular functional integrity during AKI recovery.

The potential for this concept's application may extend to other domains of critical care, including the assessment of tubular function in patients undergoing renal replacement therapy (RRT). There are currently no large-scale trials investigating the use of uNH_4^+ as a predictor of initiation or weaning from RRT. Nevertheless, in patients with CKD, reduced uNH_4^+ has been independently associated with increased risk of progression to end-stage renal disease requiring chronic dialysis[4]. Based on these observations, we may therefore reason that uNH_4^+ may represent a physiologically relevant marker of tubular functional reserve, with potential utility in future studies aimed at refining assessment of renal recovery and RRT dependency. In addition, a similar line of reasoning may be applied to other, albeit similarly relevant, clinical conditions, such as monitoring renal tubular function in patients with severe ARDS undergoing permissive hypercapnia or in patients with COPD exacerbations, in whom uNH_4^+ assessment may reveal the renal functional reserve to compensate for respiratory acidosis.

Although the potential clinical applications of uNH_4^+ are broad, caution should be exercised when interpreting single measurements. Early or partial acute kidney injury may preserve ammoniagenesis

despite reductions in glomerular filtration rate, and systemic conditions such as sepsis can affect tubular function independently. Therefore, uNH_4^+ values should be considered alongside longitudinal trends in the context of the patient's overall clinical picture.

CONCLUSIONS

Renal function is a multifaceted process involving numerous physiological roles in addition to glomerular filtration. Conceptually, the separation of renal function into glomerular and tubular components may facilitate a more comprehensive assessment of kidney health. Integrating uNH_4^+ with serum creatinine and urine output could offer a simple and clinically feasible approach to assess tubular function, thereby enabling a more global evaluation of renal function.

CONFLICT OF INTEREST AND FUNDING

The authors declare that they have no financial relationships, intellectual property interests, or personal affiliations that could be perceived as influencing the work reported in this manuscript. The device used for urinary ammonium measurement was employed solely for clinical and observational purposes, and no external funding or industry sponsorship was received for this study.

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Received April 2026
Revised May 2026
Accepted June 2026