Autologous Creatinine Clearance in a Case of Necrotizing Fasciitis and Anuria

Michael T. Eadon Jay L. Koyner

Section of Nephrology, University of Chicago, Chicago, Ill., USA

Key Words

Necrotizing soft tissue infection • Fasciitis • Acute renal failure • Burn • Debridement

Abstract

Necrotizing fasciitis can present with concomitant acute kidney injury. The etiology of acute kidney injury is often multifactorial; potential sources include volume depletion, abdominal compartment syndrome, rhabdomyolysis, and acute tubular necrosis (which may be related to hemodynamic instability, medications, or sepsis/infection). Kidney injury, defined via changes in serum creatinine, portends increased morbidity and mortality. Thus, it is crucial to accurately diagnose and assess the severity of kidney injury. We present the case of a patient with necrotizing fasciitis who endured 31 consecutive days of complete anuria. His serum creatinine decreased over this interval without the use of extracorporeal hemofiltration or dialysis. The explanation for this novel phenomenon lies in massive daily sero-sanguineous discharge and insensible losses with subsequent volume resuscitation. The patient's own convective clearance was substantial enough to maintain a modest creatinine clearance of 15 ml/min during sustained anuria. Our case emphasizes the importance of employing the creatinine, estimated glomerular filtration rate, and urine output

portions of the Acute Kidney Injury Network (AKIN) or Risk Injury Failure Loss End stage (RIFLE) criteria in assessing the severity of kidney injury. It further reinforces the imperfection in using serum creatinine as a primary measure of glomerular filtration rate.

Copyright © 2012 S. Karger AG, Basel

Case Report

A 56-year-old morbidly obese African-American male with a history of diabetes mellitus (baseline creatinine 0.8 mg/dl) presented to the emergency center with a 5-day history of fevers, chills, and painful swelling of his right anterior proximal thigh. Examination revealed a 12-cm malodorous, firm, erythematous region of the right lower extremity with extension to the groin. He had bullae, crepitus, and a cutaneous tract with exudative drainage. He was diagnosed with a necrotizing soft tissue infection (NSTI) and underwent emergent surgical debridement. During his 91-day hospitalization, the patient underwent 15 surgical explorations and debridements. Skin and soft tissue were excised circumferentially down to exposed muscle from his xyphoid process to just above his right knee (fig. 1a); total body surface area of debridement was 35%. He had considerable insensible losses and massive sero-sanguineous drainage from his wounds. Drainage collection was quantified using an Exu-Dry® dressing and Yankauer suction device (fig. 1b) and averaged 9.9 ± 6.6 (mean $\pm$ SE) liters daily. To maintain adequate blood pressure, the patient received a mean of 21.8 ± 14.0 liters of intravenous lactated Ringer's solution and blood products daily. Despite aggressive

Fig. 1. Skin and soft tissue were excised circumferentially down to exposed muscle (a) with 35% total body surface area of debridement. Massive wound output was collected using an Exu-Dry® dressing (b) and Yankauer suction device.

Fig. 2. Time course for serum creatinine, urine output, and wound output is given. The patient's serum creatinine decreased during sustained anuria, while wound output increased. Dialysis was not initiated until hospital day 85.

volume replacement, he intermittently required vasopressor and inotropic support. He was intubated and ventilated during debridement on hospital day 1 and remained ventilated throughout hospitalization (tracheostomy day 36).

On presentation, his creatinine was elevated to 1.4 mg/dl and returned to baseline with appropriate volume repletion (fig. 2). Serum creatinine kinase was elevated to 664 U/l on admission and gradually returned to normal levels. Throughout the first 4–5 days, urine output remained robust (approx. 2 liters); however, post-debridement hypotension (MAP 53) on day 7 resulted in non-oliguric acute kidney injury (AKI) on hospital days 9–16 (peak creatinine 2.3) with his creatinine returning to 1.1 mg/dl on day 18.

A second episode of AKI followed surgical debridement on day 24, associated with hemodynamic instability. Nephrology was consulted. Urinalysis revealed dense muddy brown casts consistent with acute tubular necrosis. Fractional excretion of sodium

was 3.1%. Renal ultrasound revealed no hydronephrosis with 15-cm kidneys bilaterally. Bladder pressures were measured daily and remained normal (10–15 mm Hg). By day 40, he developed complete anuria (<100 ml urine/24 h), which persisted for 31 days. His peak creatinine was 3.7 mg/dl on day 43.

Surprisingly, his serum creatinine improved despite anuria, typically ranging from 1.2 to 1.9 mg/dl. As volume loss from his wound discharge was thought to contribute to creatinine clearance, wound electrolyte concentrations were obtained and found similar to serum (table 1). A day 60 serum cystatin C was 1.90 mg/l (normal range 0.5–1.0 mg/l) with same-day creatinine of 1.6 mg/dl.

Despite anuria and AKI, the patient was consistently hypokalemic and hypophosphatemic, often requiring intravenous replacement of both. He received high-protein, high-calorie tube feeds; however, his serum albumin declined from 2.9 g/dl to a nadir of 1.9 g/dl. The hospital course was complicated by bacteremia,

Table 1. Total input, output, serum electrolytes and electrolytes from wound discharge are provided (serum and wound values approximated each other)

	Day 60		Day 85	
	serum values	wound values	serum values	wound values
Sodium, mEq/l	140	143	133	134
Potassium, mEq/l	3.3		3.1	
Chloride, mEq/l	100		100	
Bicarbonate, mEq/l	24		21	
Urea nitrogen, mg/dl	28	28	100	104
Creatinine, mg/dl	1.6	1.6	1.6	1.6
Input and output				
Total input, liters	42.6		18.4	
Wound drainage, liters	19.7		8.6	
Urine output, ml	0		79	

fungemia, ventilator-associated pneumonia, persistent respiratory failure, atrial fibrillation with rapid ventricular response, and two episodes of cardiac arrest with successful resuscitation. After 45 days of oligoanuria, hemodialysis was initiated on day 85 for volume removal as the patient had increasing oxygen requirements due to concomitant pulmonary edema and *Pseudomonas/Klebsiella pneumoniae*. On day 91, the patient died of cardiac arrest after a change in his code status to ‘do not resuscitate’.

Discussion

NSTIs frequently present with concomitant AKI. Creatinine on presentation is 52.4% higher in patients with NSTI as compared to matched controls with other soft tissue infections [1]. Mortality with NSTI is variable (6–76%) [2, 3] with a recent large case series of 89 patients demonstrating a rate of 21.3% [2, 3].

The etiology of AKI is often multifactorial in NSTIs with potential sources including hypoperfusion, abdominal compartment syndrome, rhabdomyolysis, and acute tubular necrosis related to hemodynamic instability, medications, or inflammatory milieu (sepsis/infection). Inpatient mortality for critically ill patients with AKI is high with estimates of 60.3% (95% CI 58.0–62.6) [4]. Regardless of its etiology, AKI is associated with increased mortality in the setting of NSTI. In a retrospective single-center cohort study of 166 patients with NSTI over a 5-year period, NSTI with AKI compared to NSTI without AKI conferred an odds ratio of 3.1 for death in multivariate analysis (95% CI 1.1–9.4, $p = 0.03$) [5].

We present the case of a patient with NSTI whose own convective clearance through a large abdominal and lower body wound maintained a modicum of creatinine clearance during sustained anuria. In this unique circumstance, serum creatinine became a deceptive primary determinant of eGFR. Accurate assessment of kidney injury severity is crucial as it impacts prognosis, need for extracorporeal therapy, and medication dosing. The APACHE II score and other indices used in risk stratification of the critically ill employ changes in creatinine as a determinant [6]. Further, increased serum creatinine has been suggested as diagnostic criteria in differentiating NSTIs from non-invasive soft tissue infections such as cellulitis [1, 7]. Through the use of modern standardized AKI criteria which rely on both serum creatinine and urine output [Acute Kidney Injury Network (AKIN) and Risk Injury Failure Loss End stage (RIFLE)], our patient’s diagnosis was never in question; however, refinement of prognosis may have assisted in earlier code status discussions.

As the patient’s serum creatinine improved during complete anuria without extracorporeal hemodialysis or hemofiltration, another mechanism for creatinine clearance must have been present. Loss of muscle mass due to multiple tissue debridements and catabolism during prolonged critical illness inherently decreases serum creatinine. However, we postulate much of the daily creatinine clearance was due to convective clearance in sero-sanguineous discharge across his exposed muscle and fascia. The patient had marked volume losses and daily replacement. The recorded wound volume loss underestimated true volume loss secondary to significant evaporative losses and inconsistencies in recording practices. After initial resuscitation, the fluid replacement goal was to keep input and output (including unmeasured losses) approximately even. His inputs are likely a better measure of true volume loss than the recorded volume loss. On average, replacement input was 21.8 liters daily after onset of anuria. Body weight remained similar from onset of anuria until dialysis initiation, decreasing from 207 to 205 kg over 45 days.

Creatinine clearance is calculated using the formula:

$$\text{Creatinine clearance (ml/min)} = \left[\frac{\text{urine creatinine}}{\text{serum creatinine}} \right] \times \left[\frac{\text{volume (ml)}}{\text{time (min)}} \right]$$

In an analogous exercise, the same was done for our patient’s creatinine clearance due to wound discharge. As shown in table 1, spot fluid and serum creatinine levels were 1.6 mg/dl. The patient’s serum creatinine had only mild day-to-day variance late in his hospital course and spot fluid creatinine was obtained during this period;

thus, it is reasonable to extrapolate his spot clearance to a 24-hour value. Assuming a 21.8-liter volume loss in 24 h (his average replacement need), he would clear 349 mg of creatinine in 24 h. Creatinine clearance would be 15 ml/min. For his age, ethnicity, and creatinine of 1.6 mg/dl, the MDRD eGFR is 55 ml/min. While the MDRD estimate should be applied with caution during AKI, there is a clear discrepancy between the observed serum creatinine of 1.6 mg/dl and the calculated creatinine clearance of 15 ml/min. As above, the patient's loss of muscle mass may account for some of this discrepancy. Further, although the patient's weight was stable, it should have decreased with muscle loss. Thus, a dilutional component exists as well [8].

Wound urea clearance is evaluated in a similar way to creatinine clearance. Serum and wound urea values approximated each other (table 1), again suggesting clearance through wound drainage. However, the patient's serum urea gradually increased to over 100 mg/dl. From day 60 to 85, there was an average increase in serum urea of 3 mg/dl/day. Given the patient's weight of 207 kg, his total body water was approximately 100 liters; thus, his daily increase in total body urea was approximately 3 g. Assuming constant wound urea concentrations over a day, urea clearance ranged between 6 and 23 g daily, with an average of 14.4 g/day. The expected daily input of urea would be the clearance (14.4 g) added to the daily change in total body urea (3 g) or about 17.4 g. This value is similar to his delivered nutrition therapy (at least 100 g protein or 16 g nitrogen daily). Discrepancies lie in the patient's negative nitrogen balance due to catabolic state, daily variation in liters of wound drainage, and daily variation in delivered nutrition.

The application of evidence from burn literature to NSTIs appears relevant as similarities in treatment and complications exist. However, unlike our case, many studies assessing kidney function during recovery from severe burns predominantly note polyuric kidney injury [9–12]. In these polyuric patients, it is not uncommon to see creatinine clearances above 120 ml/min [10, 13]. Calculations of creatinine clearance based on serum creatinine failed to accurately estimate 24-hour urine creatinine clearances in the setting of burns [13, 14]. The contribution of wound fluid creatinine clearance is infrequently discussed; however, Sosa et al. [15] suggest the burn wound acts as an extrarenal site for creatinine loss. Although lacking anuria, their case holds parallels to our own including correlation of serum and fluid electrolytes and an increase in estimated creatinine clearance with significant wound losses.

An evaluation of AKI in the setting of NSTI or burn should exclude the presence of rhabdomyolysis. The incidence of all-cause AKI associated with critical burns is high at 39.1% [16]. However, a 10-year retrospective review of 714 severely burned patients revealed a 1% incidence of rhabdomyolysis [17]. A smaller retrospective study found the incidence of late-onset rhabdomyolysis to be as high as 9% in severely burned patients [18]. Rhabdomyolysis has been described in the setting of skin necrosis associated with injection drug use [19]; however, larger trials and case series are lacking. Assessment of renal function in the setting of rhabdomyolysis may be aided by the determination of cystatin C. Large variations in eGFR calculations between cystatin C and creatinine have been noted during recovery from rhabdomyolysis related AKI [20]. Our patient had an elevated creatinine kinase at the time of admission (664 U/l) which gradually improved over 3 weeks and thus was inconsistent with rhabdomyolysis-associated AKI. Of interest, on hospital day 60, our patient's cystatin C level was higher than his creatinine (1.9 mg/l vs. 1.6 mg/dl, respectively). While neither his cystatin C nor creatinine level are consistent with AKI requiring dialysis, the eGFR estimates based on each are different. The patient's creatinine-based eGFR (MDRD) is 55 ml/min and his cystatin C-based (Dade Behring) estimate is 34 ml/min [21]. A potential explanation may be his history of diabetes, which has been shown to be associated with higher levels of cystatin C compared to serum creatinine [22]. Additionally, the eGFR based on cystatin C is less impacted by the patient's decrease in muscle mass and correlates better with our calculated wound clearance above.

Medication dosing errors are common in the setting of critical illness [23, 24]. In our hospital, eGFR based on the MDRD equation is reported with any serum creatinine level. Despite the safeguards of computerized physician order entry, the patient's renal function was repeatedly overestimated, leading to the overdosing of several medications. A further caveat lies in whether to assess the patient's effective clearance as 0 ml/min for anuria or include the patient's limited creatinine clearance from his wound in dosing. Again drawing from burn literature, several studies suggest increased antibiotic clearance in the setting of massive burns [25–28]. Data suggests antibiotic clearance is correlated with increased creatinine clearance seen in burns; however, the possibility remains that some of the antibiotic is cleared through sero-sanguineous drainage.

In summary, we present the case of a patient with NSTI who endured 31 consecutive days of complete an-

uria. His creatinine decreased over this interval without the use of extracorporeal therapy. Instead, his abdominal and lower extremity wound acted as a non-specific filter and the patient's volume loss and replacement were analogous to continuous hemofiltration. During sustained anuria, he maintained a small measure of creatinine clearance through his massive wound output.

Acknowledgement

This work was supported by National Institute of Health grants T32DK007510, T32GM007019, and K23 DK081616.

References

- Wong CH, Khin LW, Heng KS, Tan KC, Low CO: The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. *Crit Care Med* 2004;32:1535–1541.
- McHenry CR, Piotrowski JJ, Petrinic D, Malangoni MA: Determinants of mortality for necrotizing soft-tissue infections. *Ann Surg* 1995;221:558–565.
- Wong CH, Chang HC, Pasupathy S, Khin LW, Tan JL, Low CO: Necrotizing fasciitis: clinical presentation, microbiology, and determinants of mortality. *J Bone Joint Surg Am* 2003;85-A:1454–1460.
- Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Ronco C: Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA* 2005;294:813–818.
- Anaya DA, McMahon K, Nathens AB, Sullivan SR, Foy H, Bulger E: Predictors of mortality and limb loss in necrotizing soft tissue infections. *Arch Surg* 2005;140:151–158.
- Knaus WA, Draper EA, Wagner DP, Zimmerman JE: Apache II: a severity of disease classification system. *Crit Care Med* 1985;13:818–829.
- Sarani B, Strong M, Pascual J, Schwab CW: Necrotizing fasciitis: current concepts and review of the literature. *J Am Coll Surg* 2009;208:279–288.
- Macedo E, Bouchard J, Soroko SH, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, Mehta RL: Fluid accumulation, recognition and staging of acute kidney injury in critically ill patients. *Crit Care* 2010;14:R82.
- Schiavon M, Di Landro D, Baldo M, De Silvestro G, Chiarelli A: A study of renal damage in seriously burned patients. *Burns Incl Therm Inj* 1988;14:107–112.
- Haynes BW Jr, DeBaakey ME, Denman FR: Renal function studies of severely burned patients; a preliminary report. *Ann Surg* 1951;134:617–625.
- Cameron JS: Disturbances of renal function in burnt patients. *Proc R Soc Med* 1969;62:49–50.
- Planas M, Wachtel T, Frank H, Henderson LW: Characterization of acute renal failure in the burned patient. *Arch Intern Med* 1982;142:2087–2091.
- Conil JM, Georges B, Fourcade O, Seguin T, Lavit M, Samii K, Houin G, Tack I, Saivin S: Assessment of renal function in clinical practice at the bedside of burn patients. *Br J Clin Pharmacol* 2007;63:583–594.
- Lott RS, Uden DL, Wargin WA, Strate RG, Zaske DE: Correlation of predicted versus measured creatinine clearance values in burn patients. *Am J Hosp Pharm* 1978;35:717–720.
- Sosa JL, Ward CG, Hammond JS: The relationship of burn wound fluid to serum creatinine and creatinine clearance. *J Burn Care Rehabil* 1992;13:437–442.
- Mustonen KM, Vuola J: Acute renal failure in intensive care burn patients (ARF in burn patients). *J Burn Care Res* 2008;29:227–237.
- Stollwerck PL, Namdar T, Stang FH, Lange T, Mailander P, Siemers F: Rhabdomyolysis and acute renal failure in severely burned patients. *Burns* 2011;37:240–248.
- Bache SE, Taggart I, Gilhooly C: Late-onset rhabdomyolysis in burn patients in the intensive care unit. *Burns* 2011;37:1241–1247.
- Hengge UR, Beiderlinden M, Otterbach F, Groeben H, Nast-Kolb D, Mehnert WH, Peters J, Schmid KW: 31-year-old injection drug user with massive skin necrosis and shock. *Dermatology* 2003;206:169–171.
- Yap M, Lamarche J, Peguero A, Courville C: Serum cystatin C versus serum creatinine in the estimation of glomerular filtration rate in rhabdomyolysis. *J Ren Care* 2011;37:155–157.
- Larsson A, Malm J, Grubb A, Hansson LO: Calculation of glomerular filtration rate expressed in ml/min from plasma cystatin C values in mg/l. *Scand J Clin Lab Invest* 2004;64:25–30.
- Stevens LA, Schmid CH, Greene T, Li L, Beck GJ, Joffe MM, Froissart M, Kusek JW, Zhang YL, Coresh J, Levey AS: Factors other than glomerular filtration rate affect serum cystatin C levels. *Kidney Int* 2009;75:652–660.
- Colpaert K, Claus B, Somers A, Vandewoude K, Robays H, Decruyenaere J: Impact of computerized physician order entry on medication prescription errors in the intensive care unit: a controlled cross-sectional trial. *Crit Care* 2006;10:R21.
- McCoy AB, Peterson JF, Gadd CS, Danciu I, Waitman LR: A system to improve medication safety in the setting of acute kidney injury: Initial provider response. *AMIA Annu Symp Proc* 2008:1051.
- Loirat P, Rohan J, Baillet A, Beaufils F, David R, Chapman A: Increased glomerular filtration rate in patients with major burns and its effect on the pharmacokinetics of tobramycin. *N Engl J Med* 1978;299:915–919.
- Conil JM, Georges B, Lavit M, Seguin T, Tack I, Samii K, Chabanon G, Houin G, Saivin S: Pharmacokinetics of ceftazidime and cefepime in burn patients: the importance of age and creatinine clearance. *Int J Clin Pharmacol Ther* 2007;45:529–538.
- Weinbren MJ: Pharmacokinetics of antibiotics in burn patients. *J Antimicrob Chemother* 1999;44:319–327.
- Dolton M, Xu H, Cheong E, Maitz P, Kennedy P, Gottlieb T, Buono E, McLachlan AJ: Vancomycin pharmacokinetics in patients with severe burn injuries. *Burns* 2010;36:469–476.