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Massive and disproportionate elevation of blood urea nitrogen in acute azotemia

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Abstract. In renal failure, blood urea nitrogen and serum creatinine usually rise in tandem; the normal BUN : Cr ratio is 10–15 : 1. Disproportionate rises in BUN : Cr (> 20 : 1) often imply pre-renal azotemia but may be caused by increased protein catabolism or an excessive protein load. In this study we looked at intensive care patients who acutely developed markedly increased BUN (≥ 100 mg/dL) with only modest elevation of Cr (≤ 5 mg/dL) for possible causes of the disproportionate azotemia. There were 19 such cases collected over 6 months, nine women and ten men, with mean age 69.2 ± 4.4 years (13/19 > 75 years). Peak BUN was 156 ± 11 mg/dL; peak Cr 4.3 ± 0.5 mg/dL. Eleven patients expired. Mean serum albumin at the time of consultation was 2.7 ± 0.2 g/dL; mean total lymphocyte count 1.0 ± 0.1/mm^3. Of possible factors causing the azotemia, nine patients had documented hypovolemia; eight had congestive heart failure; six were in septic or hypovolemic shock, and two received high-dose steroids. As contributing factors, eight patients had Salb < 2.5 g/dL; eight were given a high protein intake ≥ 100 g/d; two had HIV, and two others had gastrointestinal bleeding. Infection was present in 14 patients; seven had sepsis (bacteremia with hypotension). All patients had at least one of these factors present and 16/19 had two or more. Fractional Na excretion was < 1% (consistent with pre-renal azotemia) in only four of the 11 patients in whom it was measured. We conclude that severely disproportionate BUN : Cr is frequently multifactorial and is most common in the elderly, perhaps due to their lower muscle mass, and in ICU patients given a high protein intake. It is often not indicative of uncomplicated renal hypoperfusion, although low renal perfusion (hypovolemia, shock, or heart failure) is common. Mortality is high due to the severe illnesses, especially infection, worsened by decreased renal function and hypercatabolic state.

Key words: Acute renal failure, Blood urea nitrogen, Elderly, Septicemia

Introduction

In renal failure, BUN and serum creatinine (Cr) usually rise proportionally. The normal ratio of blood urea nitrogen (BUN) : serum creatinine (Cr) is 10–15 : 1 [1]. A BUN : Cr ratio > 20 : 1 often implies pre-renal azotemia [2]. However, a high ratio may also be caused by gastrointestinal bleeding or increased protein catabolism or intake. We often see patients with marked acute elevations of BUN and relatively modest rises in Cr. The purpose of this study was to look at the clinical patterns of patients with severe acute azotemia and disproportionate rise in BUN to learn what factors characterize this phenomenon.

Methods

We looked prospectively over a 6-month period at all patients in the medical intensive care unit (ICU) who developed azotemia leading to BUN ≥ 100 mg/dL with only modest Cr elevations (≤ 5.0 mg/dL). We selected this level of BUN to avoid ambiguous levels (e.g. BUN 25, Cr 1.2) that span 'normal' and 'pre-renal'. The patients' records were evaluated for possible causes of the azotemia, including hypovolemia, cardiac failure, shock, and corticosteroid administration. A patient was considered to have hypovolemia if there was improvement in the azotemia after administration of intravenous saline.

Table 1. Characteristics of patients with disproportionate BUN : CR

Age	69.2 ± 4.4 years
Mean BUN	156 ± 11 mg/dL
Mean Cr	4.3 ± 0.5 mg/dL
Hypovolemia	9/19
CHF	8/19
Shock	6/19
High-dose Steroids	2/19
Diabetics	7/19
Mortality	11/19

Table 2. Factors contributing to disproportionate BUN : CR

Serum albumin < 2.5	8/19
Protein intake ≥ 100 g/day	9/19
Protein intake ≥ 1.5 g/kg body weight	6/19
HIV	2/19
Gastrointestinal bleeding	2/19
Infection	14/19
Sepsis	7/19

Table 3. Disproportionate BUN : CR ratio surviving vs. expiring patients

	SURVIVED	*EXPIRED*	*p*
Age (years)	*72.6 + 6.7*	*66.7 + 6.1*	*NS*
Receiving diuretics	*2/8*	*1/11*	*NS*
BUN (mg/dL)	131 ± 13	139 ± 11	NS
Cr (mg/dL)	3.5 ± 0.3	3.7 ± 0.3	NS
Dialyzed	*2/8*	*1/11*	*NS*
Vasopressors required	*0/8*	*3/11*	*NS*
Albumin (g/dL)	2.8 ± 0.3	2.9 ± 0.2	NS
Total Lymphocyte Count	1.56 ± 0.40	0.93 ± 0.14	0.09
Sepsis	1/8	6/11	0.07
Hypovolemia	6/8	3/11*	0.05

We then looked for any factors that might have contributed to the disproportion between BUN and Cr. We also assessed protein intake/day, HIV status, gastrointestinal bleeding, infection, and bacteremia. Mortality was recorded and fractional Na excretion (FE_{Na}) measured. Comparisons between those who survived and those who died were made, using either Student's t-test or Fisher's exact test, as appropriate. Group data are presented as mean ± SEM.

Results

We found 19 patients with disproportionate BUN : Cr. Ten were men; nine were women. As shown in Table 1, they tended to be elderly, with mean age 69.2 ± 4.4 years (range 21–87 years); 13/19 (68.2%) were older than 70. The mean age of medical ICU patients at our hospital during a typical month was 57.5 ± 1.8 years. Hypovolemia was present in 47%, and 42% had congestive heart failure. Six patients (32%) were in septic or hypovolemic shock. Only two of the patients were receiving high-dose glucocorticosteroids. Seven of the patients were diabetic.

Contributing factors to the disproportionate rise in BUN are shown in Table 2. Infection was the most common, involving 14 of the 19 patients. Seven of these patients met the criteria for sepsis (bacteremia and hypotension). In eight patients the serum albumin was < 2.5 g/dL. Nine of the patients were receiving 100 or more grams of protein or amino acids/day; in six of these patients this represented 1.5 grams of protein/kg body weight or more. Only two patients had HIV, and two had gastrointestinal bleeding. All patients had at least one of these factors, and 16/19 had two or more. FE_{Na} was measured in 11 of the patients; it was > 1% in all but four, only one of whom had been on a diuretic. All of the four patients with the low FE_{Na} expired.

Table 3 compares the eight patients who survived long enough to leave the ICU with the 11 who expired. There were no demonstrable differences between the groups with regard to the level of azotemia or serum albumin at the time of consultation. Seventy-five per cent of the survivors had hypovolemia, compared to 27% of those who expired, a significant difference (p = 0.05). Mean total lymphocyte count was higher in the survivors, but this trend was not significant due to low power (p = 0.09). A greater proportion of patients who expired had sepsis (55% compared to 13%), but this difference also did not reach statistical significance (p = 0.07).

None of the eight surviving patients was on a ventilator, compared to one of the 11 who expired. Only three patients: two of the survivors and one who expired had received diuretics. Two of the eight survivors and one of those who expired were dialyzed. None of those who survived and only three of the patients who expired received vasopressors. These differences were not statistically significant (Table 3).

Discussion

Our findings indicate that acute disproportionate BUN : Cr usually occurs in elderly, severely ill patients. The phenomenon is nearly always multifactorial, with sepsis or cardiac failure accompanied by shock being the major causes, often worsened by hypercatabolism, which reflects advanced underlying pathology. An additional cause of the excessively high BUN might be that in these sick patients there was continued production of antidiuretic hormone, which increases renal medullary reabsorption of urea [3]. In addition, antidiuretic hormone has been shown to stimulate hepatic ureagenesis [4]. Of interest is that the FE_{Na} is frequently elevated, even in those patients with hypovolemia. This may be due to osmotic diuresis from the excess urea. In chronic renal failure sodium and water excretion was found to be related to 24-hour urea excretion [5].

We previously reported [6] that visceral proteins correlate with survival in acute renal failure. In this study we found no difference in serum albumin levels between those who survived and those who died (Table 2). This may reflect the long half-life of albumin ($\sim$10 days). In contrast, the trend in differences in total lymphocyte counts and sepsis between survivors and non-survivors suggests that these parameters may be more sensitive indicators of the severity of the underlying pathology than serum albumin.

Severely disproportionate BUN : Cr is often multifactorial and is most common in elderly ICU patients. Only six of the 19 patients with this disproportion were younger than 70 years. One cause of this is likely to be these patients' lower muscle mass. Another is a relatively high protein intake. Our regular hospital diet gives 100 g protein/day, which may be too much for patients with lower body weights. Ishibashi et al. [6] recently found that 1–1.2 g of protein/kg body weight is probably optimal in intensive care patients and that higher protein intakes are probably excessive. Animal studies show that high protein intakes can actually exacerbate ischemic renal tubular injury [8].

We conclude that a high BUN : Cr is often not indicative of simple pre-renal azotemia uncomplicated by renal injury, although low renal perfusion (hypovolemia, shock, or heart failure) is often present. Disproportionate BUN : Cr, if BUN $>$ 100 mg/dL, is often associated with high fractional excretion of Na even when there is hypovolemia. Mortality is high due to the severity of the underlying illness and the patients' age (although there was no difference in mean age between the survivors and those who died in the ICU (Table 3)). Survival is likely to be worsened by the decreased renal function and by any hypercatabolic state. Correctable hypovolemia, when present, portends better survival. Not surprisingly, sepsis and lower total lymphocyte count tend to be associated with poorer survival.

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