Renal Function in the Elderly

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Introduction

Structural and functional changes occur within the renal parenchyma with advancing age [1, 2]. These changes have been well characterized and allow the elaboration of estimation formulae that are ubiquitous in electronic medical records and laboratory profiles [3]. Understanding how these predictable changes in structure and function impact laboratory profiling, medication dosing, nutritional support, fluid prescription, and decisions regarding renal support techniques for acute kidney injury or acute renal failure are essential for clinicians who care for injured or ill elderly patients.

Renal Biomass and Aging

Advancing age predictably reduces both renal size and functional biomass. Parenchymal loss involved both the cortex and medulla but appears to spare the collecting tubules and renal pelvis [1]. Biomass reduction also involves lean body mass, and there are well-chronicled reductions in muscle mass and proportionate increases in adipose mass in health; of course, disproportionate increases in adipose mass are observed in the clinically severely obese. Nonetheless, reduced lean body mass reduces the measured serum creatinine (Scr) with advancing age [4, 5]. The reduction in Scr from reduced lean body mass renders interpretation of Scr with reduced renal biomass difficult to interpret during critical illness.

Reduced renal biomass limits the ability to clear creatinine. Thus, an individual with reduced lean body mass may have a normal Scr as creatinine is less readily cleared. Alternatively, an elderly individual with a low Scr likely has severe protein-calorie malnutrition as the only way to have a low Scr is to have severely reduced lean body mass in the setting of reduced renal clearance ability. Since fluid resuscitation may also acutely dilute Scr, knowledge of an individual's baseline Scr is essential, as assumptions regarding renal function are fraught with peril when renal function is not normal [6, 7]. Furthermore, using published estimates of renal function such as Cockroft-Gault that is based on gender, age, ideal weight, and a measured Scr is likely inaccurate during acute illness.

Since Scr is also a reflection of plasma volume, thirst may exert a strong influence on the evaluation of renal function. Thirst sensing is reduced in the elderly [8, 9]. Reduced thirst sensation is likely related to reduced hindbrain visceral sensory flow receptor competency, impaired lamina terminalis (osmoreceptor region that resides in the wall of the third ventricle that lacks a blood-brain barrier) responsivity, reduced angiotensin II elaboration (related to reduced renal biomass), cultural norms, and psychogenic influences [8, 10–12]. Additionally, the cingulate cortex is involved in thirst sensing and may be impaired with aging, especially in the setting of stroke [13, 14]. Hypertension also decreases thirst via baroreceptor-mediated reductions in the renin-angiotensin system. Both economic hardship and illnesses such as Alzheimer's and dementia may significantly impair medication compliance, allowing hypertension to exist unchecked. Hormonal influences either support (orexin) or retard (atrial natriuretic peptide, glucagon-like peptide-1) thirst, and their elaboration may be impacted by age [15, 16]. Furthermore, as advancing age reduces mobility through chronic illness including major axial joint arthritis, cerebrovascular accidents, dementia, and Alzheimer's, the ability to satisfy perceived thirst may

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be reduced as well. Therefore, the elderly individual hosts multiple competing influences that generally reduce thirst sensation and thirst satisfaction.

These influences generally leave the acutely or ill elderly patient poorly equipped to manage intravascular volume deficits related to infection, vasodilatation, or hemorrhage. The clinician should be aware that the elderly may present with a volume deficit that includes the intravascular and intracellular as well as extravascular/extracellular spaces due to impaired thirst sensing and satisfaction. Therefore, the resuscitative fluid prescription may be larger than anticipated. Additionally, hypotension may occur earlier than anticipated due to reduced intravascular volume and the reduced ability to compensate for vasodilating influences such as sepsis, severe sepsis, or septic shock. Such knowledge may also inform clinicians with regard to the timing of fluids as opposed to vasopressors.

Evaluation of Renal Function

The principal means of evaluating renal function in clinical practice are as follows: urinalysis and urine microscopy, BUN, Scr, BUN/Scr ratio, urine electrolytes, fractional excretion of sodium (FE_{Na}) or urea (FEUN), 24-h creatinine clearance ($CrCl_{24}$), eGFR, and urinary biomarkers. A detailed discussion regarding the use of urine microscopy is outside of the scope of this chapter.

Urinalysis

This simple bedside assay is rather useful in a variety of fashions. Regarding renal function, assessment of urine specific gravity and pH is helpful in the context of plasma osmolarity and pH. One must determine whether the renal response is appropriate or inappropriate for a given state. One expects that an intact renal system would preserve the ability to both concentrate and dilute urine in an appropriate fashion. For example, an individual with dehydration should not have dilute urine.

Similarly, an impaired renal biomass would lose the ability to concentrate or dilute urine. Such a condition is identified in the post-ATN kidney where the kidney functions as a "pass-through" mechanism with the tonicity of urine approximating that of plasma. Urine in this state generally has a specific gravity of 1.010 and establishes a condition known as isosthenuria. Individuals with "high output renal failure" have such a condition and must be evaluated for unexpected dehydration.

Injured kidneys may shed casts of the tubular system, and these are readily apparent on microscopic examination of urine from such patients; renal tubular epithelial cells may also be readily identified. Similarly, renal inflammation may recruit WBC that are also noted – but are identified generally in the absence of bacteria – when bacteria are present, cystitis and pyelonephritis must also be considered and are aided by urine culture and evaluation of the clinical circumstance. Urine casts may be useful in differentiating ATN from prerenal azotemia in that ATN generally demonstrates renal tubular cell casts, granular casts, and muddy brown or mixed cellular casts. In contradistinction, those with intravascular volume deficit-associated AKI generally demonstrate either no casts or hyaline or fine granular casts. A scoring system to help differentiate these two has been articulated as well [2].

BUN, Scr, and BUN/Scr Ratio

The paired evaluation of blood urea nitrogen (BUN) with Scr is well entrenched in modern medicine. This evaluation tool may be valid prior to medical therapy, but hospital-based therapy may render interpretation difficult or misleading. For instance, nutritional supplementation may artificially raise the BUN while not impacting the Scr establishing a ratio that exceeds the classic cutoff of 20:1 that purportedly indicates prerenal azotemia. In the elderly, reductions in lean body mass may artificially depress the Scr leading to the inappropriate diagnosis of dehydration when it is not present. Alternatively, an increase in Scr from both decreased lean body mass and renal biomass may elevate the Scr impeding the diagnosis of dehydration when it is truly present. Accordingly, in the elderly, the BUN/Scr ratio as well as their individual values may be less reliable than in their more youthful counterparts.

Urine Electrolytes

One modality to aid in the evaluation of renal function as well as plasma volume is the assessment of urine electrolytes. It is important to recognize that there are no fixed normal concentrations as they will change with both dietary intake and the volume of generated urine. In particular, the urinary sodium (UNa) has excellent fidelity in illuminating the renal response to the patient's intravascular volume status and mean arterial pressure. In the absence of a diuretic, a low UNa (<20 mEq/L) indicates intravascular volume depletion, and a high UNa (>40 mEq/L) indicates the absence of depletion [17]. Note that a high UNa does not indicate whether there is any additional volume-recruitable cardiac performance to be garnered. Other electrolytes may be assessed including potassium and chloride but are of less utility in general practice than UNa.

Fractional Excretion of Sodium (FE_{Na}) or Urea Nitrogen (FEUN)

These measures purport to better enable the clinician to determine whether there is intravascular volume depletion or an intrarenal condition such as acute tubular necrosis (ATN) by creating a ratio of U_{Na}, urinary creatinine, plasma sodium, and plasma creatinine such that

$$Fe_{Na} = \left(U_{Na} \times P_{Cr} / U_{Cr} \times P_{Na}\right) \times 100$$

In general, Fe_{Na} is <1 % with plasma volume depletion, congestive heart failure, and acute glomerulonephritis but is >1 % with bilateral ureteric obstruction and ATN; values commonly exceed 3 % with ATN [18]. Fe_{Na} validity is degraded by the presampling administration of diuretics [19]. In that case, the FEUN may be more useful as urea excretion is believed to be more dependent on passive forces but is controversial [19–21].

The FEUN may be calculated in a fashion similar to that of Fe_{Na} where FEUN is represented by the formula

$$\text{FEUN} = \left(U_{Ur} \times P_{Cr} / U_{Cr} \times P_{Ur}\right) \times 100$$

A FEUN <35 % is consistent with the diagnosis of decreased plasma volume [21, 22]. In some studies, FEUN outperforms FE_{Na} in differentiating between acute renal failure due to prerenal azotemia and that due to ATN.

24-Hour Creatinine Clearance ($CrCl_{24}$)

This measure is perhaps the most sensitive indicator of renal function in that it relies on a 24-h collection of urine that is kept on ice to prevent degradation. The 24-h nature of this test accounts for any diurnal or therapy-driven variations in clearance that would be inherent to a spot or 2-h assessment [23]. This assay also allows the clinician to determine whether the patient's native renal function exceeds or fails to reach the clearance that can be achieved by intermittent or continuous renal replacement therapy. The major disadvantage is the time required for collection and the need to keep the entire volume of urine on ice.

eGFR

This ubiquitous measure accompanies every laboratory profile that measures Scr and is accompanied by descriptors of age, gender, and race but does not require height and weight [24]. The currently reported eGFR is derived from multiple studies to replace the eGFR derived from the modified diet in renal disease (MDRD) calculation in patients where the actual GFR exceeds 60 mL/min per 1.73 m^2 body surface area [25]. The original MDRD calculation employs age, creatinine, albumin, urea, gender, and ethnicity in its calculation; a 4-variable modification also exists [25]. The eGFR calculation is represented by

$$\begin{aligned} GFR = {} & 141 \times \min\left(Scr/\kappa, 1\right)\alpha \times \max\left(Scr/\kappa, 1\right) \\ & -1.209 \times 0.993 Age \times 1.018\left[\text{if female}\right] \\ & \times 1.159\left[\text{if black}\right] \end{aligned}$$

where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1 [26].

This test is primarily used as a screening tool to readily follow the trend in renal function and will be useful over time as the patient ages. Cutoffs for eGFR have been articulated to help categorize the stage of renal failure (3, 5, through); stages 1 and 2 are applied to renal function estimates when there is a structural abnormality that is present – otherwise an eGFR of 60–89 is not considered abnormal [26]. eGFR is inaccurate in multiple conditions including but not limited to acute renal failure, age <18, pregnancy, edematous states, severe protein-calorie malnutrition, muscle-wasting diseases, critical illness, and following extremity amputation [27, 28].

Urinary Biomarkers

Since Scr and the measures explored above are insensitive and inaccurate in determining early AKI to perhaps enable early therapy that might change the seemingly invariant mortality rate associated with this injury, a more sensitive marker would be ideal in clinical practice. A variety of biomarkers including kidney injury molecule-1 (KIM-1), N-acetyl-β-D-glucosaminidase (NAG), trefoil factor 3, cyanuric acid, cystatin C, monocyte chemotactic peptide-1, netrin-1, and IL-18 have been proposed as sensitive indicators of renal injury or failure. Only urinary neutrophil gelatinase-associated lipocalin (NGAL) has been made commercially available for clinical application [29, 30]. NGAL, a 25 kDa protein that is covalently bound to gelatinase, is measurable in both urine and plasma with similar performance profile for either measurement source. Of note, sepsis-associated AKI patients have been noted to have higher urinary NGAL levels compared to those with AKI from other causes [31]. NGAL concentrations increase in parallel with RIFLE stage, further validating its use in AKI determination [32]. NGAL outperforms other potential biomarkers as it is both induced/upregulated in terms of concentration and filtered and reabsorbed leading to vast increases in the concentration of the biomarker compared to most others; cystatin C is similarly filtered and reabsorbed but is not induced/upregulated [33].

Limitations in Renal Function Assessment

Recall that the kidney has multiple functions that span, in part, regulation of salt and water concentration, blood pressure, red blood cell production, as well as nitrogenous metabolic product and waste clearance. In general, clinicians only regularly assess those related to salt and water clearance, with a lesser assessment (indirectly) of nitrogenous metabolic product and waste handling. Less frequently, in-depth assessments are undertaken (including, on rare occasion, renal blood flow), but there is little assessment, if ever, in the clinical arena of hormone function (endocrine, autocrine, or paracrine). Similarly, renal replacement therapy is generally limited to nonhormonal functions as well. Thus, assessment of renal function is limited at best.

Epidemiology of Acute Kidney Injury and Acute Renal Failure

An accurate analysis of the epidemiology of acute kidney injury and acute renal failure is hampered by the wide variety of definitions that describe each of these entities. For example, acute renal failure in many clinical investigations has been defined as a doubling of baseline Scr, a Scr >2.0, the need for renal replacement therapy (based on clinician determination, not a proscribed protocol), tripling of Scr, as well as a function of changes in urine flow that is not necessarily coupled with a change in Scr. As a result, comparing across studies is difficult. Further complicating analysis is the fact that the term AKI is relatively new and many patients who were previously labeled as having ARF actually had stage 3 AKI instead [34]. In a related fashion, many terms are used in the literature and describe the same process including acute or chronic renal insufficiency, compromise, or failure. Of course, an acute renal injury may also be a structural injury as a result of trauma. The increased use of CT scans in a wide variety of medical and surgical conditions may also influence the epidemiology of AKI and ARF by increasing the at-risk population to contrast and the well-described radiocontrast nephropathy (RCN) that may follow, especially in elderly patients with concomitant dehydration and diabetes; RCN is more properly termed contrast-induced AKI [35]. The incidence of AKI has increased in recent years as has the survival rate of geriatric patients with renal insults [36]. New nephrotoxic medications, including immunosuppressives and chemotherapeutic agents, impact the number of patients who are at risk for and develop AKI or ARF [37–39]. Thus, the epidemiology of these two entities should be anticipated to be in flux, especially as the population ages [40]. Global access to and delivery of certain diagnostics and therapeutics may establish a geographically biased epidemiology for AKI and ARF as well. Thus, AKI and ARF may occur with disparate frequency in developed compared to developing nations.

Data on AKI and ARF epidemiology does exist for specific hospital domains, including most commonly the intensive care unit. In a fashion similar to that of sepsis and acute lung injury/acute respiratory distress syndrome, the incidence of AKI that does not require renal replacement therapy (RRT) is estimated to be 2000–3000 per million population per year [41]. In contrast, the estimates for AKI that does require RRT are vastly less at 200–300 per million population per year. In order to put these numbers into perspective, 4–5 % of intensive care unit patients receive RRT, and as many as 66 % of intensive care unit patients will develop RIFLE classification-defined AKI [41]. In-hospital mortality strongly correlates with the maximum RIFLE class suffered during that episode of care, as well as with progression through each RIFLE stage of risk, injury, and failure [41, 42]. Despite therapy, RRT-requiring AKI carries a 50–60 % mortality rate with up to one in five sustaining permanent dialysis-dependent renal failure [41].

Certain patient populations may have a higher than population-expected risk for AKI, including those suffering from sepsis or injury. In a large cohort of nearly 10,000 injured patients, the crude AKI incidence was 18.1 % with a greater than twofold increased mortality rate; advanced age, female gender, increased number of comorbid illnesses, and a greater illness severity all increased AKI risk [42]. Similarly, in a study of greater than 120,000 patients, septic patients 27.8 % had a sepsis-related diagnosis; 42.1 % of septic patients developed AKI [43]. Sepsis-associated AKI patients were generally more ill, hypotensive, tachycardic, and demonstrated lower PaO_2/FIO_2 ratio and greater leukocytosis compared to those with AKI of non-septic etiologies. Increased ICU and hospital mortality as well as ICU length of stay were also observed in those with sepsis-associated AKI across all RIFLE categories [43]. These data have important implications for the elderly as they are well represented in the critically ill and injured patient populations. Specific efforts should be pursued at mitigating known risk factors to reduce the incidence and downstream sequelae of AKI in the elderly after critical injury or illness. In particular, AKI predisposes to chronic kidney disease, and the elderly with reduced GFR appear to be at greater risk for this progression than age-matched counterparts with normal GFR [36].

Etiology of Acute Kidney Injury and Acute Renal Failure

The etiology of AKI is complex and multifactorial [44]. Multiple etiologies for the genesis of AKI have been proposed, including, but not limited to, vasoconstriction, leukostasis, venous hypertension, apoptosis, and a disordered

humoral factor milieu including hormones, growth factors, receptors, and intracellular signaling mechanisms. Therefore, multiple etiologies may lead to AKI or ARF. Most AKI appears to be a toxic phenomenon rather than purely a volume-based issue. This observation is easily understood as the contrast-induced (CI) AKI that occurs in the well-perfused and volume-loaded patient. Therefore, AKI may also not respond to plasma volume expansion with regard to hastening resolution. Seemingly paradoxically, AKI may be worsened by excess volume loading as the excess salt and water (and likely starch in patients with sepsis) may lead to renal parenchymal edema and distorted organ pressure-volume relationships. It should be noted that in light of the 6S trial [45], starch use for patients with sepsis has been sharply curtailed and eliminated in many care locations. Instead, albumin and crystalloid use may be accelerated.

Both intra-abdominal hypertension and the abdominal compartment syndrome are increasingly cited as etiologies for AKI and ARF [46]. Several detailed investigations into these entities have been published for the interested reader [47, 48]. Of note, specific mention is made of intrarenal compartment syndrome that may result from renal parenchymal edema (tissue edema and venous hypertension) that may be only incompletely relieved (tissue edema persists) even after abdominal decompression. Thus, AKI may not dramatically or completely improve despite relief of the abdominal compartment syndrome. It is, however, clear that the renal structural and functional changes detailed above place the elderly patient at increased risk for AKI regardless of the cause [49]. Nonetheless, acute kidney injury and acute renal failure all directly impact acid-base homeostasis.

Molecular Underpinnings of AKI

Common themes in AKI include inflammation, altered microcirculation, and bioenergetics adaptive responses. However, the interplay of these elements was not very clear. Using the paradigm of sepsis as a foundation for understanding AKI has led to improved clarity with regard to the molecular events that underpin AKI [50]. In sepsis, damage mediated by pathogen-associated molecular patterns (DAMPs, PAMPs) as well as a host of cytokines circulate and are filtered by the glomerulus. These molecular messengers interact with dendritic cells and neutrophils to augment inflammation. The net effect is to create sluggish peritubular capillary flow that disrupts the microcirculation, increases the exposure time to inflammatory mediators, and activates the endothelium. This local inflammatory cascade also leads to paracrine signaling of the distal tubule, most notably by tumor necrosis factor-alpha (TNF-α) and alarmins, further exacerbating tubular dysfunction. The overall effect is to create S2 segment tubular cell dysfunction that is underpinned by three events: (1) uncoupled respiration leading to oxidant damage, (2) mitophagy, and (3) cell cycle arrest. In sum, these events create a septic AKI phenotype that is focused on survival and decreased energy utilization during a period of extreme stress. It is important to note that while overall renal blood flow may increase during the period of AKI when serum creatinine is elevated, microcirculatory derangements may still lead to cell dysoxia [51].

Strong Ions, Acute Kidney Injury, and Acute Renal Failure

While acid-base balance has been traditionally taught using the Henderson-Hasselbalch approach, it is occasionally unwieldy as it is logarithmically based and requires the six "Bostonian rules" to account for chronicity and to provide correction of the derived data [52]. Recognizing that the human body is complex, this scheme works well in the clinical circumstance. An alternative to the imprecision of the Henderson-Hasselbalch approach has been articulated by Peter Stewart in 1983 that is termed the "strong ion" approach [53]. Strong ions are cations and anions dissociated from their ionic partners in an aqueous milieu in the physiologic pH range. This approach equates plasma ionic charge with pH through the influence of charge of water dissociation. A complete exploration of the intricacies of this approach is beyond the scope of this chapter. The interested reader is referred to one of several thorough reviews on this topic [54–57]. Nonetheless, this approach provides a concise framework to both teach acid-base physiology and be a platform from which to prescribe appropriate fluid therapy.

In the strong ion approach, rendering the net plasma charge more positive is an alkalinizing influence, and reducing the net plasma positive charge is acidifying. Therefore, fluids may be categorized based on charge difference relative to human plasma and their anticipated impact on pH (Table 4.1). Appropriate fluid selection is aided by understanding the patient's pre-fluid infusion pH. By way of example, if a patient has preexisting metabolic acidosis that is due to lactate from hypoperfusion, the choice of fluid may be irrelevant as plasma volume expansion should correct perfusion defects and result in lactic acid metabolism. However, if the acidosis is from organ failure, infusing an acidifying solution such as 0.9 % NSS may be maladaptive. Similarly, if the patient is metabolically alkalotic, then an acidifying solution is an intelligent approach and is well embraced in the concept of a chloride-responsive alkalosis; 0.9 % NSS is the most acidifying solution in common use and provides a gross excess of chloride relative to plasma. This approach has been used in a variety of settings including those focused specifically on the geriatric patient with excellent outcomes [58].

Table 4.1 Commercially available fluids and impact on acid-base balance

Fluid	Na	K	Cl	Lactate	Ca	Mg	Acetate	Gluconate	pH	pH impact
0.9% NSS	154	0	154	0	0	0	0	0	5.0	Acidify
Lactated Ringer's	130	4	110	28	3	0	0	0	6.5	Alkalinize
Normosol-R	140	5	98	0		3	27	23	7.4	None
Plasmalyte-A	140	5	98	0		3	27	23	7.4	None
5% albumin	154 (130–160)	<1	154 (130–160)	0	0	0	0	0	6.4–7.4	Acidify in large volume

The strong ion approach has also been evaluated in terms of outcome prediction. The presence of unmeasured ions, a specific entity that is readily ascertained by that approach, correlates with increased mortality risk in diverse patient populations. These populations include those with major vascular injury, unselected but significantly injured patients, as well as pediatric patients [59–62]. Moreover, the fluid selected for resuscitation may drive unmeasured ion generation [63]. Unmeasured ions are known to accompany a host of critical illnesses including injury, renal failure, hepatic failure, and following cardiopulmonary bypass [55, 64–66]. Outcome modeling using this approach has not been specifically undertaken in the elderly, but offers a potentially fertile domain for future investigation.

Conclusions

Predictable changes in renal function are expected with aging. The clinician should be cognizant of these expected changes as they may directly impact the evaluation of renal function, medication dosing, fluid selection, and the management of acute kidney injury and acute renal failure. Recognizing that acute kidney injury may be both a toxic process and a flow-dependent process that has molecular underpinnings including cell cycle arrest and unexpectedly high flow during the injury phase may curtail some of the common practice of plasma volume expansion for patients with AKI. The articulation of renal biomarkers may better enable the bedside clinician to accurately identify elderly patients with a clinically inapparent renal injury and initiate therapy or protective strategies in an earlier time frame than was traditionally possible. Each of these aspects will be aided by an expanded understanding of the molecular events that drive renal aging and acute kidney injury.

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