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Oliguria: an earlier and accurate biomarker of acute kidney injury?

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In the context of the critically ill patient, the onset of consistent oliguria is an ominous sign that requires immediate attention. Without intervention, intermittent oliguria may turn into persistent oliguria or evolve to acute kidney injury (AKI), with severe associated morbidity and mortality. Whether the addition of urine output to the serum creatinine criteria permits earlier and more specific detection of AKI is controversial, but current evidence supports its importance in early diagnosis and management.

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In medical and surgical practice, oliguria is usually seen as an ominous sign. Based on the need to eliminate at least 300 mosmol/d in maximally concentrated urine (1200 mosmol/kg), oliguria is classically defined as a diuresis of less than 400 ml/d (15 ml/h, 0.2–0.3 ml/kg/h).[1] In practice, oliguria is usually defined as diuresis less than 0.5 ml/kg/h, especially in the perioperative period.

In a recent study,[2] Bouchard and collaborators showed the implications of fluid overload, emphasizing the need to weigh patients daily and to collect accurate intake-and-output data. Now, the same group of authors (Macedo *et al.*,[3] this issue) delves into hour-to-hour urine collections to answer two questions: (1) is oliguria a biomarker associated with important outcomes, such as acute kidney injury (AKI) and increased morbidity and mortality, and (2) will more accurate measures of diuresis permit earlier AKI diagnosis?

Analysis was performed in a cohort of 317 critically ill surgical patients from a prospective observational study on AKI. After screening on intensive care unit admission, all patients were included unless they had AKI by Acute Kidney Injury Network (AKIN) criteria[4] or serum creatinine (SCr) greater than 177 μmol/l for 3 days or less, had preexisting chronic kidney disease stage 5, were on chronic dialysis, or had a functioning renal transplant, liver cirrhosis, or severe anemia.

Data were collected between intensive care unit admission and discharge; admission SCr was considered the reference value. Daily and cumulative fluid balance was computed, but detailed fluid or diuretic administration was not recorded. Overall, the authors showed that the addition of the oliguria criterion was associated with increased patient morbidity and mortality, increased the incidence, and provided earlier diagnosis of AKI.

Analysis of the data showed poor sensitivity and positive predictive value, which worsened as the oliguric interval lengthened from 6 to 24 h: as a screening test, oliguria is a poor marker. Conversely, specificity and negative predictive value were high when the more strict measures of oliguria (diuresis < 0.5 ml/kg/h every hour for 6 h) were used: when patients show persistent, consistent oliguria for 6 hours or more, significant renal injury is likely. This key observation introduces the concept that urine output data can be measured in 6-h blocks without loss of specificity. This study also introduces the original concept of type A and type B oliguria (with and without concomitant increase in SCr, respectively), which in this study are independent of diuretic use. These constructs may facilitate future studies distinguishing prerenal from established AKI.

Because it is not unicausal, one can hardly expect oliguria to be a highly specific or sensitive sole marker of parenchymal ischemic injury. Multiple mechanisms[5] can potentially cause oliguria in this context (Figure 1), including overall reduction and regional intrarenal redistribution of blood flow; glomerular injury or altered intraglomerular hemodynamics; impaired tissue oxygenation causing preferential ischemia to the S_3 segment of the proximal convoluted tubule and the thick ascending loop of Henle; loss of osmolar gradient, interstitial edema, or inflammation; and tubular or lower urinary tract obstruction. The paper by Macedo *et al.*[3] confirms that oliguria is a marker, but establishing the mechanism will require much additional study.

Regardless of the mechanism, this paper shows that AKI diagnosis made on the basis of oliguria has survival implications. Mortality is higher both for patients with oliguria and elevated creatinine (type A) and for patients with isolated oliguria (type B) when compared with non-oliguric AKI or non-AKI patients. The increased area under the curve for mortality when the urine output criterion is added to the SCr criterion is important and contradicts previous studies.[6,7] Furthermore, these results improve on the findings of Cruz *et al.*,[8] who found a marginal independent mortality prediction on the basis of oliguria alone. The association of increasing mortality with longer-lasting or recurrent oliguria suggests the presence of a dose–effect relationship between the severity of renal injury and mortality.

As Macedo *et al.*[3] discuss, the apparently earlier detection of AKI by oliguria than by SCr may be caused by the unavailability of every-12-hour data on SCr. Therefore, if we intend to achieve earlier AKI diagnosis, daily SCr measurements are not good enough. Undoubtedly, the same will be true for the newer biomarkers currently being developed. Just as we have accepted the need to measure troponin repeatedly at much shorter intervals to diagnose acute

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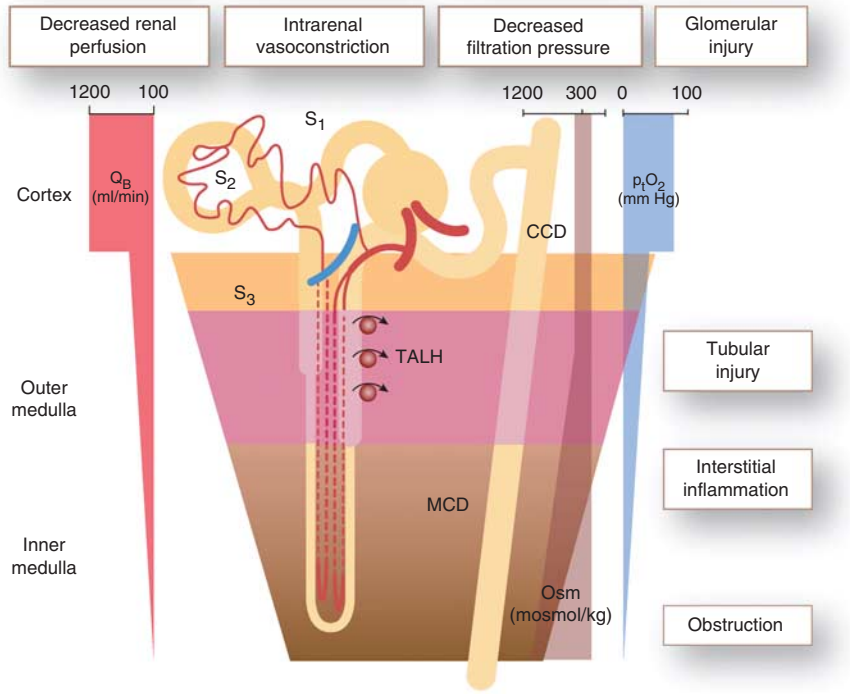

Figure 1 | Mechanisms of oliguria and acute kidney injury. Multiple mechanisms can potentially cause oliguria in the acutely injured kidney. Regional intrarenal differences in blood flow and redistribution; glomerular injury or altered intraglomerular hemodynamics; impaired tissue oxygenation causing preferential ischemia to the S_3 segment of the proximal convoluted tubule and the oxygen-avid thick ascending loop of Henle; loss of osmolar gradient, interstitial edema, or inflammation; and tubular or lower urinary tract obstruction can precipitate oliguria. CCD and MCD, cortical and medullary collecting ducts; Osm, osmolality; p_tO_2, tissue partial pressure of oxygen; Q_B, renal blood flow; S_1–S_3, segments of the proximal convoluted tubule; TALH, thick ascending loop of Henle.

myocardial ischemia, there should be no difficulty for the medical community in accepting this premise.

Similarly, if oliguria will be used for earlier, accurate diagnosis of AKI, 12- or 24-h intervals are not acceptable: the marker is specific when oliguria is consistently low, hour to hour over a 6-h period. Macedo *et al.*[3] show that the gains in sensitivity are associated with clinically significant increases in morbidity (need for renal replacement therapy) and mortality, demanding lesser complacency with episodes of discontinuous oliguria over 6-h intervals. If diuresis decreases transiently, this study says, pay attention to the patient; ascertain whether the oliguria, even if not yet accompanied by an increase in SCr, is due to reversible, addressable reasons. Timely correction of volume contraction or hemodynamic instability is simple, may avoid progression to more ominous persistent oliguria, and is probably effective. The study by Macedo *et al.*[3] emphasizes that, very probably, early thorough evaluation of the clinical situation will lead to timely changes in patient management resulting in avoidance of established AKI. We have achieved little in our efforts to decrease the catastrophic morbidity and mortality of established AKI: we need to focus on early avoidance of the problem. The issue that clouds such important findings is that, from the data provided, it is unclear 'what else is going on with' these patients and what is the relationship between oliguria, fluid status, and treatment (especially diuretics).

Fortunately, the installation of increasingly accurate data collection systems in the intensive care unit, and the possibility of automated analysis of variables such as oliguria and its correlation with myriad other variables, will increasingly allow recognition of the problem at a much earlier phase, when intervention is associated with the greatest benefit at a lesser cost. For sure, such possibilities will permit us to recognize paradigms we cannot even envision at this time.

Predictably, patients with more severe comorbidities and more severe acute disease develop higher-stage AKI by AKIN criteria (progressing from 6-h oliguria to AKIN stage 3). Not surprisingly, patients fulfilling oliguria and SCr criteria are sicker. Conversely, the surprisingly low mortality of the sample (5.6% overall, 1.3% non-AKI and 9.5% AKI) makes the general application of these findings more difficult, when one considers the usually much higher mortalities seen among critically ill surgical patients with multiple organ dysfunctions. The exclusion of patients with AKI on admission probably influences the results.

It appears that non-oliguric patients with AKI (defined by SCr) and oliguric patients without an increase in SCr are very similar in their comorbidities and severity of acute disease, and few evolve to AKIN stage 3. Moreover, when defined by oliguria, AKIN stages 1 and 2 are not associated with increased mortality in this population except when the oliguria lasts more than 24 hours (AKIN stage 3), and by then, very few patients are left without an increase in SCr. The question arises of whether at least some of the oliguric patients without an increase in SCr actually do have AKI, or whether they are oliguric for some other reason (for example, volume contraction or congestive heart failure). The question has important implications because such situations have very disparate effects on SCr concentration,[9] the former increasing and the latter diluting SCr, as recently shown by this same group of authors.[10] In the absence of concurrent data on fluid status and medications (especially diuretics), it is difficult to interpret the actual meaning of isolated oliguria. Conversely, the demonstration by multivariable analysis that oliguric AKI is significantly and independently associated with greater mortality when controlled by the degree of fluid overload lends support to the relevance of the identification of AKI by this criterion.

Similar concerns apply to the use of the need for renal replacement therapy as an end point. In the absence of clear predefined timing and starting criteria, heterogeneity in the decision-making process increases the risk of significant confounding.

The findings in the paper by Macedo *et al.*[3] show that oliguria is more ominous than we

previously thought: it is an important early biomarker in its own right. Now we will have to work harder: oliguria should be seen in the context of early and frequent measurement of known and upcoming biomarkers, and in relationship with the overall fluid status of the patient. Enriched with that information, we must continue to devise novel strategies of early AKI management.

DISCLOSURE
The author declared no competing interests.

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Glomerular diseases associated with hematopoietic neoplasms: an expanding spectrum

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Once thought to be limited mainly to lesions involving deposition of monoclonal paraproteins, glomerular diseases associated with hematologic neoplasms now include forms in which manifestations are probably mediated through cytokines or chemokines. Said *et al.* studied one such lesion, myeloproliferative neoplasm-related glomerulopathy, and found it to be a late complication of these neoplasms, with a generally poor renal outcome. Whether earlier recognition of glomerular diseases associated with hematopoietic neoplasms can result in more effective treatment remains an important question.

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Hematologic malignancies have long been linked with glomerular disorders, and the list of such associations is continually expanding (Table 1), although the pathogenic mechanisms underlying a number of these glomerular lesions remain unclear. The most well-recognized and well-established associations between hematologic and glomerular disorders are those involving plasma-cell dyscrasias, in which the monoclonal paraprotein or a product derived from it is deposited in the glomeruli, resulting initially in proteinuria and later, with increasing deposition of the abnormal protein, in renal insufficiency. The spectrum of monoclonal immunoglobulin deposition disease (MIDD) has been reviewed,[1] and our understanding of the amyloidogenic properties of certain light chains is increasing.[2] Of course, renal involvement in MIDD and AL amyloidosis is not limited to glomeruli, although their progression often involves worsening glomerular pathology. Immunotactoid glomerulopathy, a rare lesion characterized by deposits within glomerular capillaries and mesangial areas that have a microtubular structure by electron microscopy, has emerged as another form of glomerular deposition disease associated with hematologic neoplasms. Glomerular deposits in immunotactoid glomerulopathy are frequently monoclonal, although the underlying hematologic disease is most often a low-grade B-cell neoplasm rather than a plasma-cell dyscrasia. This frequent association with B-cell neoplasms and the presence of monoclonal IgG within the glomerular deposits represent features that distinguish immunotactoid glomerulopathy from the morphologically related lesion of fibrillary glomerulonephritis, which is only rarely associated with hematologic neoplasms and typically has polyclonal glomerular IgG deposits.[3]

Deposition of monoclonal proteins in the context of hematologic neoplasms may also produce a pattern of proliferative glomerulonephritis (GN) that must be distinguished from type I membranoproliferative GN (MPGN) and other forms of proliferative GN (Table 1). Cryoglobulinemic GN due to monoclonal, type I cryoglobulins is rare but has a morphologic pattern similar to that of the more commonly seen cryoglobulinemic GN with type III cryoglobulins, usually related to hepatitis C.[4] Unlike type I cryoglobulinemic GN, the more recently described proliferative GN with monoclonal IgG deposits is only infrequently associated with an underlying lymphoma or leukemia and is often seen in the absence of a detectable serum or urine paraprotein. However, this latter form of GN typically has an MPGN-type pattern, albeit without the intracapillary pseudothrombi and annular substructure of the deposits often seen in cryoglobulinemic GN.[5] It should also be remembered that intermediate- and

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