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DISCLOSURES

None.

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See related article, “Inhibition of Histone Deacetylase Expands the Renal Progenitor Cell Population,” on pages 794–802.

Variations in Mortality among Hospitalizations for Acute Kidney Injury

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Health insurance, setting of care, geography, and primary disease all affect mortality among various populations in the United States.^{1,2} If medical care for these different populations were truly comparable, then we might expect similar mortality outcomes and attribute differences to random variation. Unfortunately, population-to-population variations in mortality are frequently observed and persist even after controlling for individual patient characteristics. This suggests potentially remediable differences in the content, organization, and delivery of health care may be important in shaping true variation.^{3–6} Such modifiable differences in health care–related mortality, if they exist, warrant special attention as clinical and public health problems.

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This conceptual framework should be familiar to nephrologists. The national ESRD surveillance system, comprising the ESRD Networks and the US Renal Data System, consistently reports the likelihood of receiving a kidney transplant, mortality in hemodialysis patients, or incident ESRD differ in a non-random manner among patient groups, among geographic areas, and over time.⁷ Variations in patient care associated with these outcomes are reported as well,⁸ and interventions during the past 15 years to reduce variations in providing hemodialysis have substantially reduced mortality among patients with ESRD.^{9–11}

An important question is the extent to which this conceptual framework extends to other aspects of clinical nephrology. One area in which new ideas are being piloted is in pre-ESRD care for stage 4 chronic kidney disease (CKD). The Centers for Medicare and Medicaid Services recently piloted surveillance and quality improvement activities to test the applicability of reducing variations in care in earlier stages of CKD among primary care physicians.¹² If surveillance data can be used to direct targeted interventions to improve the care of patients with earlier stages of CKD, then nephrologists may be able to translate evidence-based clinical practice guidelines into better outcomes for kidney disease.

Another potential application of this conceptual framework comes from an important report in this issue of *JASN*. James *et al.*¹³ examine the mortality of patients who were treated in hospitals for acute kidney injury (AKI) regarding variations in time and place. They use an annual sample of hospitalizations, the Nationwide Inpatient Sample, designed in part to track and analyze national trends in health care quality and outcomes, to address two simple questions: Does mortality among patients who are hospitalized for AKI vary between weekday and weekend admissions, and does mortality risk for AKI vary by hospital size? They found patients who were admitted with a diagnosis of primary AKI on weekends experienced 7% greater mortality. This increased weekend risk was substantially greater in smaller (17% increase) compared with larger (7%) hospitals, a 45% relative risk differential.

A frequent concern about reported variations in mortality rates such as those reported by James *et al.*¹³ is that selection of study participants; errors in measuring either the outcome or group membership; and failure to account for disease severity, comorbidities, and other patient attributes may bias observed results. The authors' treatment of these issues is instructive and provides unexpected insight into hospital admissions for AKI.

They used a nationally representative sample of admissions to US hospitals, readily available to researchers, to reduce selection bias and increase the applicability of their results to the practicing nephrologist. In-hospital mortality was recorded in the same data source, reducing the likelihood that patients who met their AKI diagnosis in either high- or low-mortality hospitals were systematically excluded from the analyses. The authors used a validated, claims-based algorithm to ensure that each case of AKI was based on comparable documentation. Admissions were categorized as being for either primary and

secondary AKI on the basis of the discharge diagnosis listed as the main cause for hospitalization. James *et al.*¹³ also reduced heterogeneity among the populations being compared across time and place by focusing their analyses on the remaining 22% of patients with primary AKI.

These steps substantially reduce but do not preclude the possibility that measurement bias may occur absent standard diagnostic criteria for AKI.¹⁴ Hospital-to-hospital variations in AKI documentation might have been further reduced, however, if more precise diagnostic criteria were available. In particular, identifying the type of injury that led to AKI,¹⁵ which is highly uneven and influences mortality, might have affected the data on day of the week or hospital size, and this issue might contribute to some of the mortality differences; however, information about the cause of injury is not reflected by the current *International Classification of Diseases, Ninth Revision* codes for acute renal failure (584.5, 584.6, 584.7, 584.8, and 584.9), which depend instead on the presumed location of injury, tubular necrosis, renal cortical necrosis, medullary (papillary) necrosis, other specified pathologic lesion in kidney, and unspecified causes.¹⁶

The reported mortality comparisons might also have been biased if differences in the severity of AKI and other patient attributes associated with increased risk for death varied during the week or among hospitals. They account for this possibility by controlling for age, gender, race, and comorbid conditions. Ideally, had the relevant information been available in the database, risk stratification criteria for AKI such as the recently published Risk, Injury, Failure, Loss, ESRD (RIFLE) criteria that is based on changes in urine output and serum creatinine could have further controlled for differences in the severity of renal injury.^{17–19} This issue is important, because it is evident that even minor AKI confers increased risk for both short- and long-term mortality.^{20–23}

What then are we to make of the conclusion of this well-designed study that weekend admissions characterized by either primary or secondary AKI associate with increased risk for death that is greater in small compared with large hospitals? These data do need replication, as is true of any single report, and as noted by the authors' further explanatory studies. Notably, these results raise the important question of identifying potentially modifiable risk factors that contribute to mortality differences.

James *et al.*¹³ suggest a reasonable hypothesis that increased weekend mortality reflects delayed recognition and treatment among patients with AKI as a result of the limited resources, particularly timely initiation of nephrology consultation and hemodialysis. These two possibilities warrant close scrutiny and comment. That delayed hemodialysis may contribute to variations in AKI-related mortality reflects the assumption that renal replacement therapy plays a substantial role in the care of patients who are admitted with AKI.

The data in this study, which reveal an unexpected picture of hospitalizations for AKI, suggest otherwise. The frequencies of hemodialysis care on the weekend (8.4%) and weekday (8.9%) were unexpectedly low and nearly the same. Although

we are not provided dialysis rates individually for primary and secondary AKI, it is evident that for the overwhelming majority of these patients, someone determined that dialysis was not necessary. The overall low dialysis rates for both weekend and weekday AKI admissions suggest that although delayed initiation of renal replacement therapy may contribute to the increased weekend mortality, it may not be the sole or even major explanatory factor.

What of the second possibility, that failure of timely nephrology referral contributes to increased weekend mortality? As discussed by the authors,¹³ the impact of “nephrology consultation and the provision (and timing of) renal replacement therapy” on patient mortality is not currently supported by evidence—the notion being “hypothetical” in their words. Furthermore, a contrarian might argue if $\geq 90\%$ of patients who are admitted with AKI do not require hemodialysis, then what added benefit is derived from a nephrology consultation?

The process similar to that used in ESRD to improve hemodialysis care may be relevant in addressing the nondialytic contribution of nephrology care for AKI. The methods for producing evidence-based practice guidelines for nephrology care in AKI is well advanced,²⁴ and the clinical practice guidelines similar to those used in ESRD are being published (<http://www.renal.org/Clinical/GuidelinesSection/AcuteKidneyInjury.aspx>). Although the current guidelines appropriately focus mainly on dialysis therapy in AKI, current AKI guidelines do suggest nondialytic contributions to the care of patients who are admitted to the hospital for AKI.²⁵ Attributes of this care include timely nephrology consultation, appropriate assignment of cause and severity and need for dialysis, nondialytic management of volume, attention to antisepsis measures, metabolic control, adjustment of drug dosing, and modification of nutritional support. An international Kidney Disease: Improving Global Outcomes (KDIGO) working group is currently developing international AKI guidelines that address nondialytic nephrology care in more detail.²⁶

If an evidence database supporting the role of these or other variations in nephrology care for patients with AKI can be developed²⁷ and translated into quality indicators,²⁸ similar to those for hemodialysis practice, then it would be possible to draw inferences about their contribution to weekday-to-weekend and hospital-to-hospital variability in mortality of patients with AKI. In turn, this information could be used to address variations in care.²⁹

DISCLOSURES

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See related article, “Weekend Hospital Admission, Acute Kidney Injury, and Mortality,” on pages 845–851.

Pulling the Trigger in Atypical Hemolytic Uremic Syndrome: The Role of Pregnancy

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In the past 15 years, our understanding of the molecular mechanisms that predispose to atypical hemolytic uremic syndrome (aHUS) has increased dramatically.¹ A series of studies established that dysregulation of the alternative complement pathway plays a significant role in the pathogenesis of disease in the majority of patients.^{1,2} Mutations in both complement regulators (factor H, factor I, and membrane co-factor protein) and activators (C3 and factor B) have been described in both familial and sporadic forms. In addition, factor H autoantibodies, which impair the activity of factor H, and mutations in the gene encoding thrombomodulin are now known.^{3,4}

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More than one family member is affected in approximately 10% of patients with aHUS. The study of such families reveals a higher prevalence of the aforementioned mutations and indicates that not every individual who carries a mutation manifests the disease.⁵ The rate of nonpenetrance is approximately 50%, and it has been shown that naturally occurring variability in single-nucleotide polymorphisms and haplotype blocks of the *CFH* and *CD46* genes encoding factor H and membrane co-factor protein, respectively, increase susceptibility to disease. Moreover, multiple concurrent factors such as single-nucleotide polymorphisms, mutations, and autoantibodies may be necessary for disease to manifest in individual families.⁶

Some event almost always triggers the disease in the majority of patients. aHUS typically presents in childhood, and a history of a preceding nondiarrheal viral infection is common. This is also true of adults and in females of childbearing age the phenotype of aHUS can present late in pregnancy or soon after delivery;⁷ pregnancy may be the trigger in 10% of all patients with aHUS.⁸

Fakhouri *et al.*⁹ in their article in this issue of *JASN* provide us with substantial additional information that will be enlightening to all those who are interested in this condition. They confirm in female adults that aHUS associates with pregnancy in 20% of patients, and, in the majority, this occurs postpartum. Complement abnormalities were found in 86% of these patients; this is the highest prevalence reported in any subgroup of aHUS to date. The prognosis for such patients in the 1970s was extremely poor, with a mortality rate of approximately 55%, and of those who survived, approximately 50% required long-term dialysis.¹⁰ Mortality has improved since then, but Fakhouri *et al.* indicate that 76% of patients develop ESRD despite receiving plasma exchange. The prognosis for renal transplantation in these patients is equally gloomy, especially in those who are known to have a factor H mutation, 80% of whom will lose an allograft to recurrent disease within 2 years of transplantation,¹¹ although liver-kidney transplants may do better.¹²

With the poor prognosis for these patients and their seeming resistance to plasma exchange, are there any other therapeutic maneuvers that might benefit management? Anecdotal reports suggest that the C5 mAb eculizumab may be an effective form of treatment for aHUS,¹³ and the results of clinical trials currently being undertaken with this agent are awaited eagerly. If eculizumab proves to be effective, then could it be used in pregnancy or postpartum? Recent reports of patients with paroxysmal nocturnal hemoglobinuria showed no adverse effects when used in pregnancy,¹⁴ and, in particular, there is no evidence the drug crosses the placenta or is present in breast milk.

What is it about pregnancy, particularly the postpartum period, that increases susceptibility to aHUS? That complement plays a pivotal role in the pathophysiology of pregnancy is well established.¹⁵ In particular, complement-mediated placental damage is prevented by trophoblast expression of the complement regulators known as decay-accelerating factor,