Iatrogenesis Imperfecta Medicamentosa: Adverse Drug Events in Dialysis Patients are Associated with Higher Resource Utilization and Mortality

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Polypharmacy among patients on dialysis is notorious, with a median pill burden calculated at 19 in a study from 2009 [1]. Although these drugs are prescribed with good intentions, adverse drug events (ADEs) are common and take a great toll on patients on dialysis [2].

In this issue of the *American Journal of Nephrology*, Chan et al. [3] publish new insights into the magnitude of serious ADEs affecting patients on dialysis. The study examines 5 years' worth of data from the Nationwide Emergency Department Sample (NEDS). NEDS is a database that contains data on discharges from emergency departments of a nationally representative sample of nearly 1000 hospitals across 33 states [4]. It was developed for the Healthcare Cost and Utilization Project sponsored by the Agency for Healthcare Research and Quality [4]. The NEDS database includes information on emergency department visits, hospital admissions, discharges to skilled nursing facilities, and in-hospital mortality, among other data elements [4]. For this study, dialysis status and diag-

nosis of ADE in the emergency department were identified by specific ICD-9 codes that are captured within the NEDS database [3].

The authors used propensity matching to identify a group of control patients who were not on dialysis, but who were as likely as cases to have been on dialysis based on a model that took into account diabetes, hypertension, and heart failure status among other variables [3]. The authors then compared cases of dialysis patients who experienced an ADE with propensity-matched controls to determine any differences in a number of outcomes that relate to resource use and mortality [3]. The study results suggest that upward of 1 in every 12 dialysis patients presenting to an emergency department do so as a result of an ADE [3]. This represents a 10-fold increase in the rate of ADE visits as compared with those who are not on dialysis [3]. The magnitude of this finding diminished after propensity matching, implying it is at least partially confounded by the effects of unmeasured comorbidity and

socioeconomic status [3]. Results of the propensity-matched analysis revealed that patients on dialysis have an increased risk of being admitted after presenting with an ADE, as compared with their propensity-matched non-dialysis counterparts [3]. In addition, the present study also demonstrated increased resource utilization such as increased hospital length of stay and increased frequency of discharge to a skilled nursing facility [3]. Of more concern is that the authors found a 3-fold increased risk of dying while in hospital among those who are on dialysis [3].

Perhaps not surprisingly, the majority of emergency department visits for ADEs among dialysis patients were attributed to medications that affected blood constituents, with this signal almost certainly being driven by oral anticoagulant use. The authors point out that the study period coincided with the market release of direct oral anticoagulants (DOACs), which are being used with increasing frequency despite the lack of safety data from randomized trials in dialysis patients [3, 5]. Recently, Mavrakanas et al. [6] have shed light on the pharmacokinetics of apixaban in patients on hemodialysis, and clinical trials are now actively recruiting in an effort to inform the safe use of DOACs in dialysis patients [7]. Aside from DOACs, the safe use of traditional oral vitamin K antagonists in hemodialysis patients has been an ongoing topic of controversy. A recent meta-analysis showed that warfarin use was associated with a non-significant trend toward intracranial hemorrhage (CI for adjusted hazards ratio of [0.93–4]) [8]. Moreover, ADEs in patients taking warfarin are likely to be inversely related to time in therapeutic range, a measure which is notoriously poor among patients on hemodialysis [9].

The results of Chan et al. [3] study appear striking, and the use of a nationally representative database is an exceptional strength of this paper in that it allows for immediate generalizability. However, several important limitations should be noted. Firstly, this database study is subject to the usual concerns related to retrospective observational administrative data. Despite propensity matching, residual confounding may have still introduced bias. Additionally, the NEDS database does not contain hospital admission diagnoses, nor does it contain the granularity needed to elucidate the reasons for prolonged hospital length of stay. The database also does not reliably distinguish those who are being discharged to a skilled nursing facility because of a new loss of autonomy from those who already lived in a nursing home. Finally, reliance on ICD-9 codes without access to clinical data for direct review may have introduced information bias. De-

spite these concerns, the possibility of a 3-fold increased risk of mortality related to ADEs in patients on dialysis is sufficient cause for pause and reflection.

What should be done to mitigate the risks posed by medications to patients on dialysis? Individual case review by a dedicated dialysis pharmacist has been shown to reduce hospitalizations [10]. Decision support tools that reliably reduce the risk of ADEs may be useful adjuncts worth developing for the dialysis population. One such tool has already been developed in the non-dialysis chronic kidney disease (CKD) population [11]; the risk score takes into account 8 readily available variables and has been used to predict ADEs among hospitalized patients with CKD in a study [11]. Unfortunately, this decision support tool has yet to be externally validated, nor is it applicable to patients on dialysis.

Given that the authors identified oral anticoagulants as the most frequent driver of ADEs resulting in emergency department visits and hospitalization, perhaps it is this area where we should concentrate our initial improvement efforts. A recent KDIGO controversy report suggested that “for all CKD patients on anticoagulant therapy, annual re-evaluation of treatment goals and discussion of pros and cons of anticoagulant therapy should be considered” [12]. Reassessment and deprescription of oral anticoagulation should be considered in situations where the risk of ADE exceeds expected benefit. Routine reporting of calculated time in therapeutic range for those taking warfarin, including the frequency of dangerous supratherapeutic values, may further inform the risk of remaining on warfarin at annual review. For those who are to remain on anticoagulation, recruitment into the RENAL-AF or a similar randomized trial should be encouraged.

Improvement strategies to reduce the risk of ADEs should not be limited to the domain of anticoagulation. For example, medication-related hypoglycemia in patients with diabetes in their first year of dialysis is exceptionally common, affecting 10% of patients who initiate hemodialysis, and 7.6% of those who initiate peritoneal dialysis [13].

In summary, the authors make the case that ADEs may pose a threat of increased proportion and significant magnitude in patients on dialysis. Strategies to help identify patients at high risk for ADEs should be an ongoing focus for quality improvement in the dialysis unit.

Disclosure Statement

None.

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