

To Err Is Human: Lessons from Patient Safety Research for Transplant Care

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The unrelenting tide of biomedical innovation has influenced kidney transplant care in profound ways, causing major overall improvement. The incidence of acute graft rejection has dropped precipitously, thereby changing the “natural history” of a renal allograft. As acute graft rejection rates continue to decrease, many had expected that long-term graft survival would subsequently increase; however, this has not been the case. Although researchers have amassed a growing body of literature over the last decade examining immunosuppressive regimens, histologic diagnoses, and ever more sensitive biochemical markers of impending rejection, the problem persists. In this issue of *CJASN*, Taber *et al.* examine long-term graft rejection through a different lens by reporting on adverse events and their consequences among a cohort of patients in the years after transplantation (1).

Over the same period that transplant care has been improving, patient safety research has also made advances. The first large study, the 1999 Harvard Medical Practice Study, reported that one third of adverse events are amenable to advances in medical science and that two thirds of adverse events appear “potentially preventable” through the application of patient safety techniques. Biomedical research typically focuses on the first group, paying little attention to the second group of adverse events caused by medical errors and iatrogenic harm (2). Taber *et al.* study potentially preventable adverse events in order to characterize them, determine their downstream effects, and eventually design strategies to eradicate them.

The study is a *post hoc* analysis of a prospective randomized comparative efficacy trial comparing two induction regimens for adult kidney transplant patients. The trial enrolled 200 patients between the ages of 18 and 75 years who received a solitary kidney transplant. Patients were followed for an average of 2.5 years. For the purposes of determining downstream effects of medication errors, the population was divided into two groups based on whether the patient experienced a clinically significant medication error (CSME). Categorization was based on the presence of a medication error that was both severe (according to a previously validated severity scale) and that contributed to a hospitalization. The authors sought to examine the characteristics of patients who experienced a

CSME, as well as the downstream effects on long-term graft survival, healthcare utilization, and cost.

One of the major findings was that the 3-year graft failure rate was significantly higher in the CSME group compared with the non-CSME group. The authors looked for a difference in graft failure rate in patients who experienced acute rejection compared with those who did not, and they found no difference. Those patients who experienced a CSME were more likely to be readmitted. The median rate was one readmission in the CSME group versus zero in the non-CSME group, and the CSME group had higher associated costs. Over two thirds of patients experienced medication errors over the course of the study and about half involved immunosuppressive regimens. Patients who experienced a CSME had a higher rate of drug interactions outside of their immunosuppressive regimens than did patients who did not experience a CSME.

The authors found that five of six patients experienced an adverse drug reaction (ADR). All of the patients in the CSME group experienced one or more ADRs. Acute rejection was categorized as an ADR, and there was a significantly higher rate of acute rejection in the CSME group.

Several limitations must be addressed when interpreting these results. First, the design of the randomized trial had assigned patients to two different induction regimens, introducing bias to this *post hoc* analysis. Table 2 by Taber *et al.* shows that patients taking IL-2 receptor antagonists were more highly represented in the CSME group (1); however, we cannot determine whether this is a confounder of the relationship between CSMEs and graft survival. A second limitation is that the authors categorize episodes of acute rejection as ADRs, which is not in concordance with standard patient safety research definitions. CSMEs related to immunosuppressive regimens could cause acute rejection. Therefore, ADRs and episodes of acute rejection should be examined as potential confounders or mediators of the relationship between CSMEs and graft survival.

Despite these limitations, the study’s main findings suggest that adverse events, including medication errors and ADRs, are prevalent in this population and have downstream effects on clinical outcomes. These adverse events are not amenable to advances in science, but can be prevented through implementation of patient

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safety techniques that focus especially on ensuring reliability and reducing the likelihood of errors (2). Perhaps the long-term graft survival conundrum can be addressed through this approach.

To illustrate how such techniques may be useful, we begin with the systems theory of causation. This theory is one of several theories of accident causation that are applied across industries. By applying the systems theory to healthcare, proponents remove blame from individuals and instead focus attention on the system as a whole (3). After patient safety techniques are applied to a system, the system makes it harder for errors to occur and easier for the system to detect errors that do occur before harm occurs (4).

Physicians, who are trained to take personal responsibility for patient welfare, often question the basic tenets of the systems theory, or believe that adverse events are so specific to the individual case that deep examination is not fruitful. An example of the importance of examining adverse events is the history of patient safety techniques as applied to adverse drug events (ADEs). A familiar example of the benefit of patient safety techniques is the clinical technology that physicians use today to order medications. These computer systems were designed after patient safety researchers analyzed ADEs. In one study of hospitalized patients, researchers found that the majority of ADEs were related to medication errors (5). A subsequent research study showed that about half of the medication errors were related to medication orders and about a third of the errors were related to medication administration (6). These studies led to computerized provider order entry for physicians and point-of-care medication administration systems for nurses.

In the case of immunosuppressive regimens, monitoring medication levels presents its own hazards. Poor clinical outcomes may occur if the levels are not drawn when indicated or appropriate adjustments are not made in response to the levels. Patient safety techniques were applied to drug level monitoring for vancomycin and researchers determined that there were four reasons for mistimed levels: (1) unclear provider orders, (2) scheduling levels to be drawn with morning laboratory tests, (3) lack of communication between providers, and (4) failure to adjust the blood draw in relation to the previous dose (7). The study failed to improve patient safety using computers, but another study on antiepileptic drug monitoring showed a significant effect of computer alerts on unnecessary testing (8). Therefore, patient safety techniques should be applied to drug level monitoring for immunosuppressive regimens in order to design systems-level solutions.

All types of adverse events resulting from immunosuppressive regimens should be studied with patient safety techniques, including ADRs, which are broadly defined as unintended outcomes when drugs are given at doses used for prophylaxis or therapy. A more actionable definition of ADRs breaks them into three types: intrinsic reactions as a result of the primary or secondary pharmacologic activity of the drug (dose dependent); idiosyncratic immunologic or allergic reactions; and withdrawal reactions that occur after discontinuation of the drug (9). Patient safety researchers have studied ADRs and have proposed several systems-level solutions. Drugs that have a high risk of intrinsic reactions or withdrawal reactions can be highlighted for prescribers. Alerts can also be programmed for a specific

patient who has had an idiosyncratic reaction in the past in order to prevent future idiosyncratic reactions to the same drug or members of the same class of drugs. Finally, over the long term, patient safety research guides pharmacologic advances in safer drugs (10). Therefore, even if adverse events appear to be too specific to an individual patient to be prevented at the systems level, they should still be scrutinized for potential preventability.

Importantly, this study by Taber *et al.* identified medication errors in two thirds of the patients. Of these errors, one sixth were prescribing errors and one sixth were pharmacy errors. As we have demonstrated, systems-level approaches can decrease prescribing and pharmacy errors. Each error should be examined further to identify patterns. Interventions can then be designed to prevent medication errors from happening and to prevent errors that do happen from becoming CSMEs. Notably, the majority of medication errors (over two thirds) were characterized as patient-induced. There are many interventions that have been proven to improve medication adherence, including more thorough patient counseling and simplified dosing regimens (11). The most pressing reason to further characterize the patient-induced errors is to develop new patient safety techniques specific to patients who are receiving immunosuppressive regimens.

The results of the study by Taber *et al.* (1) have the potential to substantially improve transplant care. By viewing patient outcomes through the lens of adverse events, Taber and colleagues have tapped a rich tradition of systems-level solutions. Because graft rejection is a downstream effect of CSMEs, there is great potential to decrease morbidity, mortality, and accompanying costs. It is imperative that these medication errors be further characterized and that systems-level solutions are implemented to improve long-term graft survival.

Disclosures

D.W.B. reports the following unrelated conflicts: he is a coinventor on patent 6029138 held by Brigham and Women's Hospital on the use of decision support software for medical management, licensed to Medicalis Corporation. He holds a minority equity position in the privately held company Medicalis, which develops web-based decision support for radiology test ordering. He serves on the board for SEA Medical Systems, which makes intravenous pump technology. He is on the clinical advisory board for Zynx Inc, which develops evidence-based algorithms, and Patient Safety Systems, which provides a set of approaches to help hospitals improve safety. He consults for EarlySense, which makes patient safety monitoring systems. He consults for QPID, which makes query tools.

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