Regulation or Autonomy in Transplantation: A Debate

Kidneys are at risk during and after liver transplantation. How can they be better protected? The prescription for intraoperative care is simple to state, if difficult to achieve.

“The bottom line is that if we avoid hypotension, avoid severe blood loss, and avoid reperfusion injury, the kidney will be fine,” said Michael Ramsay, MD, chief of service for the department of anesthesiology and pain management at Baylor University Medical Center in Dallas, in a forum held in Boston at the American Transplant Congress. “But the question is, how do you do that?”

To give a sense of the scope of the problem, Ramsay said that at his own center, acute renal dysfunction occurs in as many as 78 percent of patients intraoperatively. “So it happens, and it happens because of all the rigors we have to put the patients through during transplantation.” Factors that increase the risk of renal injury include preexisting renal impairment, hemodynamic instability, perioperative bleeding, inflammation, and abdominal compartment syndrome.

Changes in operative technique may or may not have helped. The “piggyback” technique is typically used to preserve the patient’s own vena cava while controlling blood flow during transplantation, and it has largely supplanted the older technique of venovenous bypass. The latter technique “is controversial, and is used less these days,” Ramsay said. He noted that a recent analysis of clinical trials in one center where these options were used concluded that piggyback alone resulted in less these days,” Ramsay said. He noted that a recent analysis of clinical trials in one center where these options were used concluded that piggyback alone resulted in less and not every transplant program matches the best centers in the level of patient care it is provided.

Given the tension between the benefits of innovation and the costs of poor outcomes, what is the proper role of regulation? That was the topic of debate between Thomas Hamilton, director of survey and Medicaid Services (CMS), and Dorry Segev, MD, PhD, associate professor of surgery at Johns Hopkins University, speaking at the American Transplant Congress held in Boston in June.

“When there is a high level of complexity, and a high degree of trust is required, these are environments that make regulation less useful. That is true of the banking of living grafts,” which accumulate during its explantation, hitting the heart when flow is restored through the implanted liver. It occurs in about 25 percent of liver transplant recipients. The risk can be reduced by flushing the graft out with saline before the anastomosis. “There is actually less data, and at the present time, none are ready for use.”

In the search for such a predictive marker, Levitsky and colleagues are first looking retrospectively using serial collections of plasma, and comparing those who experience chronic kidney disease after transplantation with those whose long-term renal function is stable. Ultimately, he said, this might help determine whether a liver transplant patient would be better off with a simultaneous kidney transplant.

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Debate
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Will We Ever Know the Long-term Consequences for a Living Kidney Donor?

A family member, a loved one, or just a Good Samaritan who contemplates donating a kidney naturally wants to know what the effect may be on him or her long-term health. Although many studies have attempted to address this pressing question, there are few first-rate data according to researchers speaking at the American Transplant Congress in Boston. And although several new studies are under way to address the deficiencies of the past, even these studies are rife with problems, and definitive results may not be available for years, if ever. “We need better data on this,” according to Amir Garg, MD, PhD, of London Health Sciences Center in Ontario, “but there are many challenges to getting it.”

“It is only in the last 10 years that there has been enough activity to support large, long-term studies,” he said. Even still, many studies have been of questionable utility. Single-center studies tend to have uniform data but are too small to enable meaningful conclusions. In the area of living donor surveys tend to suffer from a high degree of variability in practices between centers, especially across international borders. retrospective studies have the potential for selection bias, whereas prospective studies, including ones self, one's friends, family members, or colleagues.

Finally, he said, the appropriate level of risk may not be captured, leading the center to appear to have worse outcomes than it actually does, given the risks. “One ability to predict outcomes in transplantation, based on the data we’ve collected, is just not very good at all.” But barely better than a coin toss, he said.

Table 2: Adverse Cardiovascular Outcomes in Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Time Period of Trial</th>
<th>NIRS (N = 1265)</th>
<th>CHOIR (N = 1432)</th>
<th>TREAT (N = 4088)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with CKD on dialysis who had a pre-specified, prospective analysis of a composite safety endpoint consisting of death, myocardial infarction, stroke, or serious adverse events of congestive heart failure, unstable angina or arrhythmia</td>
<td>10.0 (9.5, 10.4)</td>
<td>11.8 (11.3, 12.3)</td>
<td>12.5 (12.0, 12.9)</td>
</tr>
<tr>
<td>Patients with chronic kidney disease not on dialysis</td>
<td>10.0 (9.5, 10.4)</td>
<td>11.8 (11.3, 12.3)</td>
<td>12.5 (12.0, 12.9)</td>
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<tr>
<th>Relative Risk</th>
<th>All-cause mortality, MI, hospitalization for CHF, or stroke</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio</td>
<td>1.28 (1.06 – 1.56)</td>
<td>1.34 (1.03 – 1.74)</td>
<td>1.05 (0.94 – 1.17)</td>
</tr>
<tr>
<td>Relative Risk (95% CI)</td>
<td>All-cause mortality</td>
<td>MI, hospitalization for CHF, stroke</td>
<td>All-cause mortality, MI, hospitalization for CHF, stroke, or death</td>
</tr>
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</table>

Patients with Chronic Kidney Disease Not on Dialysis

OMONTYS is not indicated and is not recommended for use in patients with anemia due to chronic kidney disease (CKD) in adult patients on dialysis.

Adverse events associated with the use of ESAs in patients with CKD are generally similar to those observed in patients with end-stage renal disease, but may be at a higher incidence and severity.

In controlled clinical trials of ESAs in patients with CKD compared to placebo, the most common adverse events reported were:

- Headache
- Hypertension
- Fatigue
- Memory loss
- Sleep disturbance

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The safety and efficacy of OMONTYS have not been established in patients with anemia due to chronic kidney disease. Results from clinical trials of ESAs in patients with anemia due to cancer therapy showed decreased locoregional control, progression-free survival and/or decreased overall survival. The findings were observed in clinical trials of other ESAs administered to patients with breast cancer receiving chemotherapy, advanced head and neck cancer receiving radiation therapy, lymphoid malignancy, cervical cancer, non-small cell lung cancer, and with various malignancies who were not receiving chemotherapy or radiotherapy.

Hypertension

OMONTYS is contraindicated in patients with hypertension. Appropriate control hypertension prior to initiation of therapy and dietary restrictions.

Lack of Response to OMONTYS

For lack or loss of hemoglobin response to OMONTYS, initiate a search for other causes for lack or loss of response. Evaluate the patient for anemia and anemia due to chronic kidney disease. In the absence of antibodies to peginesatide, follow dosing recommendations for management of patients with an insufficient hemoglobin response to OMONTYS therapy.

Dosage Management

Patients may require adjustments in their dosage prescriptions after initiation of OMONTYS therapy. Patients receiving OMONTYS may require increased anticoagulation with heparin to prevent clotting of the extracorporeal circuit during hemodialysis.

Laboratory Monitoring

Evaluate transferrin saturation and serum ferritin prior to and during OMONTYS treatment. Administer supplemental iron therapy when serum ferritin is less than 100 mcg/mL, or when serum transferrin saturation is less than 20%. The majority of patients with CKD may require supplemental iron during the course of therapy.