Clinical Trials in Critical Care Presented at Kidney Week 2021

By Karen Blum

Recent clinical trials in fluid therapies, COVID-19 treatment, and sepsis management were presented at Kidney Week 2021 to keep nephrologists up to date in critical care medicine: The Balanced Solutions in Intensive Care Study (BaSICS) trial (1, 2) of balanced solutions versus 0.9% saline in critically ill patients; the Efficacy and Safety of Baricitinib for the Treatment of Hospitalized Adults with COVID-19 (COV-BARRIER) trial (3); and the Vitamin C, Thiamine, and Steroids in Sepsis (VICTAS) trial (4) of vitamin C, thiamine, and hydrocortisone on ventilator- and vasopressor-free days in sepsis.

BaSICS
There has been much debate over several decades regarding the use of fluids in the intensive care unit (ICU). Although saline solution has remained the primary fluid over time, recent evidence from observational and randomized controlled trials suggests that the administration of balanced crystalloids results in better outcomes such as reduced mortality and acute kidney injury (AKI). Additionally, infusion rate has been commonly neglected as an aspect of fluid therapy delivery in randomized controlled trials. BaSICS, published as two reports in the Journal of the American Medical Association (JAMA) (1, 2), compared the effects of each fluid type as well as two different infusion speeds.

BaSICS enrolled 11,052 patients in 75 ICUs across Brazil. Participants were randomized to receive either Plasma-Lyte or 0.9% saline and then further randomized to receive these fluids at either 333 mL/hour or 999 mL/hour. Patients included in the study were admitted to an ICU and required at least 1 L of fluid expansion. They also were not expected to be discharged the next day and had at least one risk factor for AKI, such as age over 65 or presence of sepsis.

Baseline characteristics were similar. The mean age of participants was 61, 44% were women, 50% required mechanical ventilation, and acute kidney injury was present in 30% of patients with a Kidney Disease: Improving Global Outcomes (KDIGO) score of 1 or greater at the time of enrollment. Sixty percent were hypertensive, and 44% required some means of mechanical ventilation. The study found no difference in 90-day mortality rates between those who received balanced solution (26.4%) and saline (27.2%). There also was no difference in 90-day mortality rates between those who received slower infusion (26.6%) and faster infusion (27.0%). Furthermore, there were no significant differences found in any of the secondary endpoints related to AKI with need for kidney replacement therapy or AKI with KDIGO scores of 2 or higher on day 3 or 7.

Therefore, the findings do not support the use of balanced solution over normal saline or a slower infusion rate, said M. Elizabeth Wilcox, MD, PhD, an associate professor of medicine at the University of Toronto and a staff intensivist with University Health Network. There may be harm for traumatic brain injury patients with the administration of balanced solution, but further study is required, she said.

COV-BARRIER
Some patients with COVID-19 develop intense, hyperinflammatory states leading to multiorgan failure and ICU admission. Baricitinib, a selective JAK1/JAK2 inhibitor with a known anti-inflammatory profile, was identified as a potential intervention for the treatment of COVID-19. Since then, several small cohort studies have provided some evidence of clinical improvement with its use, Wilcox said.

COV-BARRIER was a phase 3, randomized, double-blind controlled trial that enrolled 1525 patients with COVID-19 and at least one elevated inflammatory marker at 101 centers across 12 countries. Patients were randomized to receive either standard-of-care therapy, including dexamethasone, or 4 mg of baricitinib daily for up to 14 days or until hospital discharge. Follow-up was conducted 28 and 60 days after the last dose of the study drug.

The median patient age was 56, and 37% were women. Approximately 88%-90% of patients required supplemental oxygen, noninvasive ventilation, or high-flow oxygen delivered by nasal cannula. All participants had at least one preexisting comorbid condition.

Twenty-eight percent of patients in the baricitinib group and 31% of patients in the control group progressed to the primary composite endpoint of receiving high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or death at 28 days. All-cause mortality was reduced at 28 days (8% vs. 13%) and at 60 days (10% vs. 15%) for the baricitinib group. Additionally, the frequency of serious adverse events, including infections and venous thromboembolism, was similar between groups.

Results suggest that baricitinib reduces both 28- and 60-day mortality when given in addition to standard of care.

“This has very important implications in terms of it being a possible treatment option to reduce overall deaths in the context of a global burden of mortality during a pandemic,” Wilcox said.

A dose-adjuring study may be of use, she said, as would potentially using a loading dose to prevent rapid progression events.

VICTAS
Despite hundreds of pharmacologic agents and bundled approaches to care for sepsis studied, approximately one-third of patients hospitalized do not survive their diagnosis, Wilcox said. In 2017, the combination of hydrocortisone, vitamin C, and thiamine (HAT) received attention because of its potential effect on reducing mortality rate in the intervention group and a 37.8% mortality rate in the control group at 180 days. These results were consistent with recent randomized studies finding no greater effectiveness of HAT as compared to placebo, but they also confirmed that HAT is safe for this patient population, Wilcox said.

“Underpowered trials fail to provide certainty in their conclusions,” she said. “Therefore, it really isn’t going to be able to settle the debate over HAT treatment in sepsis. Another study may or may not be funded to answer that question.”

References