Feasibility Assessment of a Biomarker-Guided Kidney-Sparing Sepsis Bundle: The Limiting Acute Kidney Injury Progression In Sepsis Trial

Hernando Gómez, MD[1]

Alexander Zarbock, MD[2,3]

Stephen M. Pastores, MD[4]

Gyorgy Frendl, MD[5]

Sven Bercker, MD[6]

Pierre Asfar, MD[7]

Steven A. Conrad, MD[8]

Jaques Creteur, MD[9]

James Miner, MD[10]

Jean Paul Mira, MD[11]

Johan Motsch, MD[12]

Jean-Pierre Quenot, MD[13–15]

Thomas Rimmelé, MD[16]

Peter Rosenberger, MD[17]

Christophe Vinsonneau, MD[18]

Bob Birch, PhD[19]

Fabienne Heskia, MS[20]

Julien Textoris, MD[20,21]

Luca Molinari, MD[22]

Louis M. Guzzi, MD[23]

Claudio Ronco, MD[24]

John A. Kellum, MD[1]

OBJECTIVES: To determine the feasibility, safety, and efficacy of a biomarker-guided implementation of a kidney-sparing sepsis bundle (KSSB) of care in comparison with standard of care (SOC) on clinical outcomes in patients with sepsis.

DESIGN: Adaptive, multicenter, randomized clinical trial.

SETTING: Five University Hospitals in Europe and North America.

PATIENTS: Adult patients, admitted to the ICU with an indwelling urinary catheter and diagnosis of sepsis or septic shock, without acute kidney injury (acute kidney injury) stage 2 or 3 or chronic kidney disease.

INTERVENTIONS: A three-level KSSB based on Kidney Disease: Improving Global Outcomes (KDIGOs) recommendations guided by serial measurements of urinary tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7 used as a combined biomarker [TIMP2]•[IGFBP7].

MEASUREMENTS AND MAIN RESULTS: The trial was stopped for low enrollment related to the COVID-19 pandemic. Nineteen patients enrolled in five sites over 12 months were randomized to the SOC ($n = 8$, 42.0%) or intervention ($n = 11$, 58.0%). The primary outcome was feasibility, and key secondary outcomes were safety and efficacy. Adherence to protocol in patients assigned to the first two levels of KSSB was 15 of 19 (81.8%) and 19 of 19 (100%) but was 1 of 4 (25%) for level 3 KSSB. Serious adverse events were more frequent in the intervention arm (4/11, 36.4%) than in the control arm (1/8, 12.5%), but none were related to study interventions. The secondary efficacy outcome was a composite of death, dialysis, or progression of greater than or equal to 2 stages of acute kidney injury within 72 hours after enrollment and was reached by 3 of 8 (37.5%) patients in the control arm, and 0 of 11 (0%) patients in the intervention arm. In the control arm, two patients experienced progression of acute kidney injury, and one patient died.

CONCLUSIONS: Although the COVID-19 pandemic impeded recruitment, the actual implementation of a therapeutic strategy that deploys a KDIGO-based KSSB of care guided by risk stratification using urinary [TIMP2]•[IGFBP7] seems feasible and appears to be safe in patients with sepsis.

KEY WORDS: acute kidney injury; biomarker; cell cycle arrest; sepsis

S epsis, a dysregulated immune host response to infection that results in life-threatening organ dysfunction (1) affects more than 48 million people every year worldwide and represents ~20% of global deaths (2). Almost two-thirds of patients with its most severe presentation, septic shock, develop acute kidney injury (AKI), and AKI is an independent risk factor for death from sepsis. Indeed, patients with septic shock who develop Kidney Disease: Improving Global Outcomes (KDIGO) stages 2–3 AKI are more than four times more likely to die within 60 days compared with those without AKI (3).

KEY POINTS

Question: Is it feasible and safe to implement a biomarker-guided strategy to deliver Kidney Disease: Improving Global Outcomes (KDIGOs)-based kidney-sparing sepsis bundles (KSSBs) of care in patients with sepsis?

Findings: Protocol adherence was 81.9% for the first two levels of KSSB and 25% for level 3. No serious adverse events were related to study interventions. The composite of death, dialysis, or acute kidney injury progression occurred in 37.5% and 0% of patients in the control and intervention arm.

Meaning: Although the COVID-19 pandemic impeded recruitment, the actual implementation of a therapeutic strategy that deploys a KDIGO-based KSSB of care guided by urinary [TIMP2]•[IGFBP7] may be feasible and appears to be safe in patients with sepsis.

Importantly, this increased risk may be reversible because patients with sepsis who recover from AKI have similar 1-year and 3-year mortality as those without AKI (4, 5). This is in agreement with preclinical (6–9) and clinical (10) data demonstrating that the development of AKI carries far-reaching consequences like remote organ dysfunction (6–9) and susceptibility to infection (7). Together, these data suggest that AKI may be in the causal pathway to death from sepsis and that efforts to reverse sepsis-associated AKI may improve survival. However, there are no proven interventions to reverse or prevent sepsis-associated AKI (11).

The novel urinary biomarkers tissue inhibitor of metalloproteinases-2 (TIMP2) and insulin-like growth factor-binding protein 7 (IGFBP7), provide early warning of kidney tubular stress and anticipate the risk of developing AKI (12–15). An overall risk score of the combination of these biomarkers, [TIMP2]•[IGFBP7], has been validated in critically ill subjects to predict the development of moderate to severe AKI within 12 hours after assessment (12–14), and has been approved by the Federal Drug Administration (FDA) for clinical use since 2014. Importantly, two single-center, randomized clinical studies have used [TIMP2]•[IGFBP7] to guide the implementation of KDIGO bundles in patients after cardiac surgery (PrevAKI) and major noncardiac surgery (bigpAK) demonstrating decreased frequency and

severity of postoperative AKI, and ICU and hospital length of stay (LOS) (16, 17). However, this approach has never been studied in patients with sepsis. The objective of this study was to evaluate the feasibility and safety of a [TIMP2]•[IGFBP7]-guided implementation of a kidney-sparing sepsis bundle (KSSB, intervention arm) and to assess the impact of such strategy on clinical outcomes and resource utilization in comparison to the current standard of care (SOC, control arm). Although recruitment is an essential part of the assessment of feasibility, the consequences of the COVID-19 pandemic on our study preclude us from drawing any meaningful conclusions on recruitment rates. However, we hope that the data we present hereby will contribute to knowledge-building on other key aspects of feasibility, safety, and the implementation of a biomarker-guided therapeutic strategy in sepsis.

MATERIALS AND METHODS

Trial Design, Oversight, and Ethics Statement

Limiting Acute Kidney Injury Progression In Sepsis was designed as an adaptive, multicenter, randomized controlled interventional trial and was sponsored by bioMérieux. The study was conducted in accordance with the provisions of the Declaration of Helsinki (October 2008) and the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice. The protocol and the informed consent form were reviewed and approved by each independent site institutional review board (**supplemental digital content**, http://links.lww.com/CCX/B238). The trial was registered on clinicaltrials.gov (NCT04434209) and the protocol was published ahead of enrollment (18). All patients enrolled in the study signed an informed consent before any study procedures. A steering committee and an independent safety monitoring committee oversaw the trial.

Patients

Patients were eligible for enrollment if they met the following inclusion criteria: age greater than or equal to 21 years; admission to ICU and expected to remain for greater than 48 hours; presence of an indwelling urinary catheter with an expectation for it to remain for greater than 48 hours; a clinical diagnosis of sepsis based on Sepsis-3 definition as having an infection and organ dysfunction defined by an increase in Sequential Organ Failure Assessment score of 2 or more, or septic

shock, defined as vasopressor requirement to maintain a mean arterial pressure of greater than or equal to 65 mm Hg and a serum lactate level greater than 2 mmol/L (> 18 mg/dL) in the absence of hypovolemia. Patients were excluded if they had: history of kidney transplant or any solid organ transplant receiving calcineurin inhibitors; KDIGO stage 2 or 3 AKI at the time of screening or within the past 2 weeks; been receiving dialysis or were in imminent need of dialysis (defined as within 6 hr per attending physician judgment) at the time of enrollment; baseline estimated glomerular filtration rate less than 45 mL/min/1.73 m², calculated using the modification of diet in renal disease study formula based on the SCr measurement obtained at the time closest to enrollment; total bilirubin greater than 4 mg/dL at enrollment; confirmed COVID-19 infection. The complete eligibility criteria have been published (18) and can also be found in **supplementary appendix** (http://links.lww.com/CCX/B238).

Randomization and Treatment

Patients were randomly assigned in a 1:1 ratio to a control arm consisting of the use of local SOC guidelines for diagnostic assessment and treatment or to the intervention arm, consisting of the use of serial [TIMP2]•[IGFBP7] testing to guide the implementation of a KSSB. In the control arm, urine samples for serial [TIMP2]•[IGFBP7] testing were collected, frozen, and shipped to a central laboratory (bioMérieux SA, Marcy l'Etoile, France) for analysis at the following time points: 1) between 6 and 9 hours after the diagnosis of sepsis, 2) between 6 and 9 hours after the first urine sample was collected, and 3) between 12 and 15 hours after the second urine sample was collected. Results of urine samples were not available for clinical decision-making. In the intervention arm, patients underwent [TIMP2]•[IGFBP7] on-site testing at the same time points as the control group. Patients with any [TIMP2]•[IGFBP7] test result of greater than 0.3 were provided one of three levels of kidney KSSBs depending on the quantitative value of the test results obtained at the first time point. The level of the KSSB was then continued or incremented based on subsequent quantitative levels of urinary [TIMP2]•[IGFBP7] and study interventions were continued for a total of 72 hours (**Fig. 1**). The treating clinician had the option to decline the use of any KSSB intervention when they determined it was not in the best interest of the patient.

The three levels of the KSSB interventions were based on KDIGO guidelines (19), have been described in detail (18), and can also be found in supplementary appendix (http://links.lww.com/CCX/B238), but in general consisted of the following: 1) level 1, identification and removal of any nephrotoxic medications, the use of balanced crystalloids, and strict monitoring of daily fluid input and output, 2) level 2, included all interventions in level 1 plus the use of functional hemodynamic monitoring (FHM) to guide fluid and hemodynamic resuscitation, and 3) level 3, included levels 1 and 2, plus the use of hospital resources including consultation with a nephrologist and/or infectious disease specialist, to assess other causes of AKI and evaluate source control and antibiotic coverage.

Outcomes and Follow-up

The primary endpoint was feasibility, assessed by quantifying the adequacy of treatment allocation based on biomarker data and adherence to the study protocol. Two key secondary endpoints were safety and efficacy. Safety was evaluated by monitoring 1) all serious adverse events (SAE), 2) all serious adverse device events (SADE), 3) all serious unanticipated adverse device events (SUADE), and 4) all non-SAEs. Definitions for each category of adverse events can be found in supplementary appendix (http://links.lww.com/CCX/B238). Efficacy was assessed by the occurrence of a composite of death, dialysis (defined as any form of renal replacement therapy [RRT]), or progression of greater than or equal to 2 stages of AKI (stages 0–2/3 or stages 1–3) within 72 hours after enrollment.

Additional major secondary outcomes were the composite efficacy outcome at 48 hours, the rate of occurrence of AKI, death or use of RRT within 72 hours of enrollment, in-hospital and 30-day mortality, renal recovery defined as less than 120% study reference creatinine at the time of hospital discharge or day 60 after enrollment, whichever occurred first, ICU LOS, and RRT, ICU, invasive hemodynamic, and mechanical ventilation-free days. Follow-up was planned for 60 days after enrollment.

STATISTICAL ANALYSIS

We estimated a sample size of 540 patients to detect a 30% reduction in the primary composite endpoint. The statistical analysis plan was published before unblinding the results (18) and further details can also
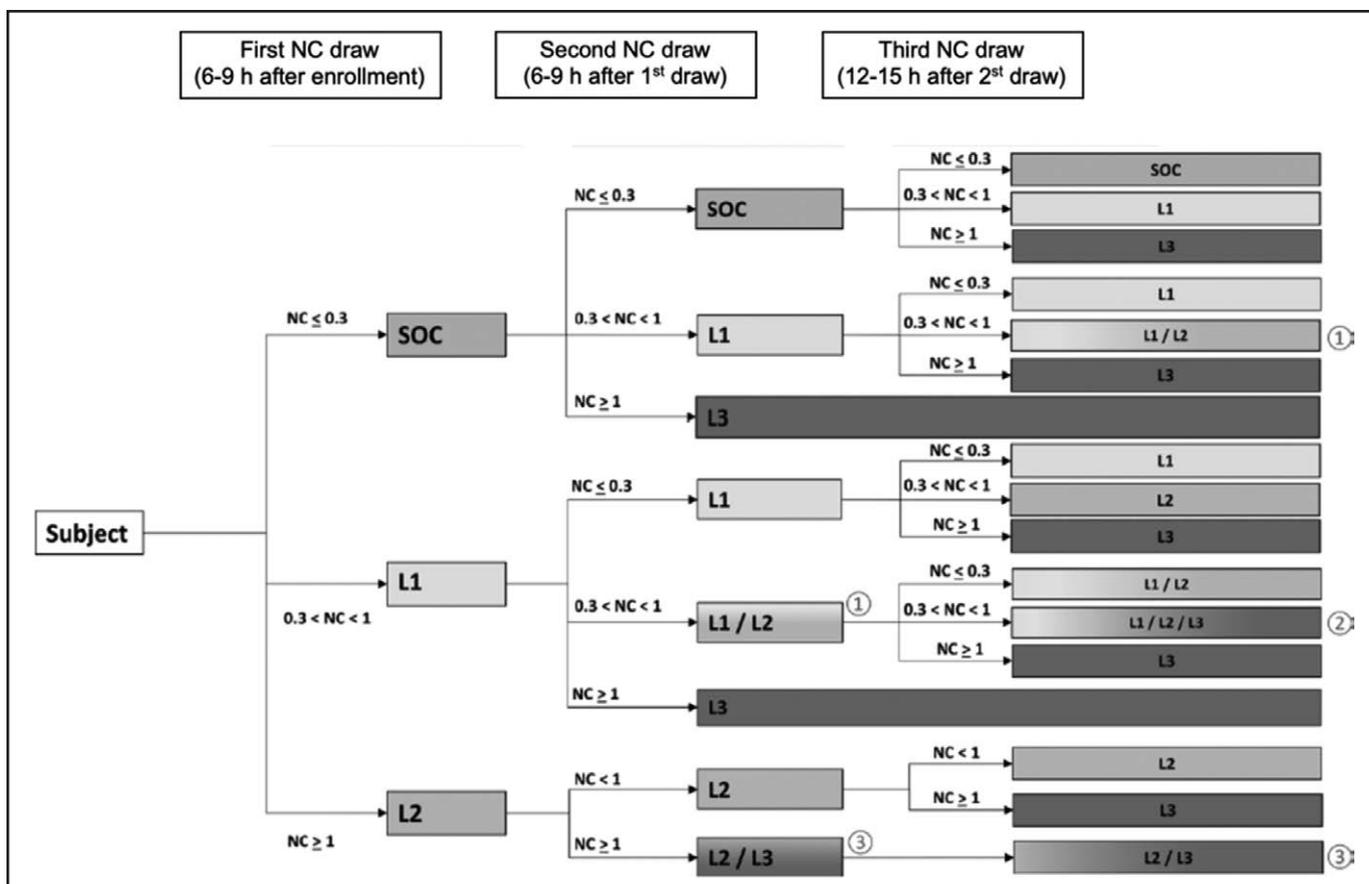
Figure 1. Diagram demonstrating the flow of patients in the study randomized to the treatment group (modified from [18]). Based on the level of urinary [TIMP2]•[IGFBP7], denoted in the figure as "NC" for NephroCheck, patients would be allocated to receiving 1) standard of care (SOC) if the first urinary NC level was below 0.3, 2) level 1 kidney-sparing sepsis bundle (KSSB) if NC was between 0.3 and 1, or 3) level 2 KSSB if NC was greater than 1. Then, 6–9 hr after the first NC, a second NC test would be sent, and patients would be reassigned to either a higher level of KSSB or to stay in their current levels. As a rule, once a patient was at any given KSSB level, the patient would stay at that level or move to a higher level based on NC, but never move to a lower level. Finally, 12 hr after the second NC draw, a third NC would be sent, and patients would be reassigned to the corresponding KSSB level and maintained there for a total of 72 hr (i.e., total time since randomization).

be found in supplementary appendix (http://links.lww.com/CCX/B238). There was no blinding in this study at the site level, but the sponsor and study members were blind to group allocation. Because the study was stopped early, the efficacy analysis was limited to reporting the number and proportion of patients experiencing the primary composite endpoint in each arm.

Safety Analysis

All SAEs, SADEs, SUADEs, and non-SAEs that were definitely, probably, or possibly related to the device or a protocol-related procedure were coded using the Medical Dictionary for Regulatory Activities, Version 23.0, (ICH, Geneva, Switzerland) to classify events under low-level terms and the occurrence rate of occurrence

was reported. SAEs/SADEs/SUADEs were also summarized by their relationship to the study treatment. In addition, mortality was assessed.

Summary statistical analyses were provided for demographics, medical history, and risk factor variables at baseline. Continuous variables were summarized using median values and categorical variables using numbers and percentages. All analyses were conducted using SAS software, version 9.4 (SAS Institute, Inc, Cary, NC). No hypothesis testing was done for efficacy due to the sample size.

RESULTS

The study was stopped prematurely because of unanticipated low enrollment rates due to the COVID-19

pandemic. A total of 19 patients were enrolled across five sites from January 2021 to December 2021, 8 (42.0%) of whom were randomized to control and 11 (58.0%) to the intervention arm. Ten patients (56.2%) were admitted to a medical ICU, and 9 to medical/surgical ICUs. Enrolled patients had a median age of 71 years (range: 52–83), a median weight of 76 kg (range: 60–110); the majority were males (68.4%), of White race (89.5%), had a confirmed infection (89.5%), and had septic shock (94.7%). The source of infection was bacterial, fungal, or yeast in 15 (78.9%), 4 (21.1%), and 3 (15.8%) patients, respectively. Additional demographic information and differences between groups are shown in **Table 1**.

Primary Outcome

Feasibility, Implementation, Protocol Adherence, and Follow-up. All enrolled patients were adequately assigned to the right level of bundled care based on rapid turnover and communication of the results of [TIMP2]•[IGFBP7].

Adherence to the study protocol is summarized in **eTable 1** (http://links.lww.com/CCX/B238). For KSSB level 1, 9 of 11 patients in the intervention group had 1 or more nephrotoxic medications/agents stopped as recommended per protocol. However, 5 of 8 patients in the control group also had nephrotoxic medications discontinued by the treating team. For KSSB level 2, FHM to guide resuscitation was used in 9 of 11 patients in the intervention group, and only in 1 of 8 patients in the control arm. The two patients in the intervention arm who were not resuscitated using FHM never reached the level 2 KSSB bundle based on their biomarker levels. In addition, balanced crystalloid as the only resuscitation fluid was used in 8 of 11 patients in the intervention arm, whereas this was only the case in 3 of 8 patients in the control arm. Although compliance with KSSB levels 1 and 2 was excellent, compliance with level 3 was low, with nephrology and infectious disease consults only ordered in one of four patients in the intervention arm.

Secondary Outcomes

Safety. The proportion of reported SAEs was higher in the intervention arm (4/11, 36.4%) than in the control arm (1/8, 12.5%) (**eTable 2**, http://links.lww.com/CCX/B238). In the intervention arm, SAEs included

cardiac arrest, aspiration, infective endocarditis, and bronchial hemorrhage; the patient in the control group had intestinal ischemia. Although all 5 SAEs were ultimately fatal, none were considered related to study interventions.

There were no vascular or urinary catheter-related infections reported in the first 72 hours after enrollment. Three of 8 patients (37.5%) in the control arm and 2 of 11 (18.2%) patients in the intervention arm were reported to have urinary catheter infections in the period from 72 hours to 30 days after enrollment.

Composite Efficacy Endpoint. The composite efficacy outcome of death, dialysis, or progression of greater than or equal to two stages of AKI within 72 hours after enrollment was reached by 3 of 8 (37.5%) patients in the control arm, and 0 of 11 (0%) patients in the intervention arm (**Table 2**). In the control arm, two patients experienced progression of AKI, and one patient died. No patient required RRT during the 72-hour window. However, one patient in the control arm and three patients in the intervention arm required RRT after the 72-hour window (Table 2).

Additional Secondary Outcomes. Secondary outcomes are summarized in Table 2 and **eTable 3** (http://links.lww.com/CCX/B238). Death, dialysis, or progression of AKI at 48 hr followed the same trend as the composite at 72 hr. The higher occurrence of the composite outcome in the control group was driven by higher number of patients dying and experiencing progression of AKI (Table 2, eTable 3, http://links.lww.com/CCX/B238). Similarly, AKI of any stage occurred more frequently in controls and almost every metric of resource utilization was worse in controls as compared with the intervention group (Table 2, eTable 3, http://links.lww.com/CCX/B238). These differences are only trends and need to be interpreted with caution.

Overall, 18 of 19 patients (94.7%), 7 in the control group, and 11 in the treatment group received at least one protocol-specified nephrotoxic medication or another medication considered by the site investigator to be potentially nephrotoxic. The mean number of nephrotoxic drugs used was 3.5 in the control arm and 3.3 in the intervention arm, with no obvious group differences in the distribution of diverse types of drugs (eTable 1, http://links.lww.com/CCX/B238). Three (37.5%) patients in the control arm and 8 (72.7%) patients in the treatment arm received balanced crystalloids, with volumes of 4,417 ± 1,666 mL

TABLE 1.
Demographics and Baseline Patient Data

Variable	Measure	All Patients	Control	Intervention
Site				
Brigham and Women's Hospital	*n* (%)	1 (5.3%)	0 (0%)	1 (9.1%)
University Hospital of Angers	*n* (%)	1 (5.3%)	1 (12.5%)	0 (0%)
Memorial Sloan Kettering Cancer Center	*n* (%)	2 (10.5%)	0 (0%)	2 (18.2%)
University of Munster	*n* (%)	14 (73.7%)	6 (75.0%)	8 (72.7%)
University of Leipzig	*n* (%)	1 (5.3%)	1 (12.5%)	0 (0%)
Type of ICU				
Combined ICU	*n* (%)	3 (15.8%)	1 (12.5%)	2 (18.2%)
Medical	*n* (%)	10 (52.6%)	6 (75.0%)	4 (36.4%)
Neurologic/neurosurgical	*n* (%)	1 (5.3%)	1 (12.5%)	0 (0%)
Surgical	*n* (%)	5 (26.3%)	0 (0%)	5 (45.5%)
Demographics				
Age	Median (range)	71 (52–83)	71.5 (53–83)	67 (52–81)
Male	*n* (%)	13 (68.4%)	5 (62.5%)	8 (72.7%)
Race				
Unknown	*n* (%)	2 (10.5%)	1 (12.5%)	1 (9.1%)
White	*n* (%)	17 (89.5%)	7 (87.5%)	10 (90.9%)
Baseline medical condition				
Weight	Median (range)	76 (60–110)	72.5 (60–110)	80 (63.5–91.6)
Reference serum creatinine	Median (range)	0.8 (0.5–1.4)	0.8 (0.5–1.3)	0.8 (0.6–1.4)
Admission serum creatinine	Median (range)	1 (0.5–3.7)	1.1 (0.5–1.4)	1 (0.6–3.7)
Enrollment serum creatinine	Median (range)	0.8 (0.5–1.5)	0.8 (0.5–1.4)	0.8 (0.6–1.5)
Acute kidney injury stage				
0	*n* (%)	17 (89.5%)	7 (87.5%)	10 (90.9%)
1	*n* (%)	2 (10.5%)	1 (12.5%)	1 (9.1%)
Medical history				
Diabetes	*n* (%)	4 (21.1%)	3 (37.5%)	1 (9.1%)
Hypertension	*n* (%)	5 (26.3%)	2 (25.0%)	3 (27.3%)
Active cancer treatment	*n* (%)	4 (21.1%)	2 (25.0%)	2 (18.2%)
Sepsis diagnosis				
SOFA score increase	*n* (%)	15 (78.9%)	6 (75.0%)	9 (81.8%)
SOFA score	Median (range)	9.5 (4–15)	10.5 (4–15)	9 (5–15)
Septic shock	*n* (%)	18 (94.7%)	7 (87.5%)	11 (100.0%)
Lactate	Median (range)	1.7 (0.9–9)	1.75 (0.9–2.4)	1.4 (0.9–9)
Confirmed infection	*n* (%)	17 (89.5%)	7 (87.5%)	10 (90.9%)
Bacterial	*n* (%)	15 (78.9%)	7 (87.5%)	8 (72.7%)
Fungal	*n* (%)	4 (21.1%)	2 (25.0%)	2 (18.2%)
Yeast	*n* (%)	3 (15.8%)	0 (0%)	3 (27.3%)

SOFA = Sequential Organ Failure Assessment.

TABLE 2.
Summary of Clinical Outcomes

Endpoint	All	Control	Intervention
Primary endpoint			
Composite at 72 hr (*n*, %)	3/19 (15.7)	3/8 (37.5)	0/11 (0)
Death within 72 hr	1/19 (5.3)	1/8 (12.5)	0/11 (0)
RRT within 72 hr	0/19 (0)	0/8 (0)	0/11 (0)
Progression of AKI within 72 hr	2/19 (10.5)	2/8 (25)	0/11 (0)
Secondary endpoints			
Composite at 48 hr (*n*, %)	1/19 (5.3)	1/8 (12.5)	0/11 (0)
Death within 48 hr	0/19 (0)	0/8 (0)	0/11 (0)
RRT within 48 hr	0/19 (0)	0/8 (0)	0/11 (0)
Progression of AKI within 48 hr	1/19 (5.3)	1/8 (12.5)	0/11 (0)
Mortality			
In-hospital	2/19 (10.5)	1/8 (12.5)	1/11 (9.1)
30 d	3/19 (15.8)	1/8 (12.5)	2/11 (18.2)
AKI			
AKI stage 1 or greater	11/19 (57.9)	7/8 (87.5)	4/11 (36.4)
AKI stage 2/3	4/19 (21.1)	3/8 (37.5)	1/11 (9.1)
Renal recovery (*n*/total of patients with any AKI)	4/19 (21.1)	4/7 (57.1)	0/4 (0)
Resource utilization			
ICU length of stay (mean, SD)		17.4 (12.6)	13.5 (8.2)
ICU-free days (mean, SD)		10.6 (12.1)	14.9 (7.2)
Invasive hemodynamic-free days (mean, SD)		29 (2.6)	22.2 (3.3)
Mechanical ventilation-free days (mean, SD)		15.4 (13.1)	20.9 (9.1)
RRT-free days (mean, SD)		28.4 (4.2)	28.5 (2.7)

AKI = acute kidney injury, RRT = renal replacement therapy.

and 2,088 ± 1,639 mL, respectively. One patient in the control arm (40% glucose) and two in the treatment arm (albumin) received other types of fluids. Eight patients had no bolus fluids recorded following enrollment.

DISCUSSION

During the first 2 years of the COVID-19 pandemic, numerous trials were halted and many never resumed. Unfortunately, the LAPIS trial was a casualty of the pandemic, and the available sample is insufficient to identify or refute an efficacy signal. The decision was made not to include COVID patients for two reasons. First, what we know today about the prevalence, pathophysiology, and characteristics of AKI and the performance of [TIMP2]•[IGFBP7] in COVID patients was largely unknown then. Second, because KSSB bundles were designed for bacterial sepsis and therefore, may not be appropriate for patients with COVID given that the development of AKI during COVID may be influenced by factors that are not considered in these interventions. However, in this study, we report several important findings that can inform future trials. Together with our prior publication (18), this report provides a detailed roadmap for implementation and assessment of the efficacy of an escalating, biomarker-guided, sepsis care bundle to reduce the development of moderate to severe AKI.

There is no question that recruitment for LAPIS was lower than expected and that the effect of the pandemic on our ability to recruit ultimately lead to the premature termination of the study. Although we cannot draw conclusions on potential recruitment outside

of a global pandemic, our results provide important insights into other aspects of feasibility and safety that are directly related to study design. For instance, the investigators identified the tight 6-hour enrollment window as the only potential barrier to enrollment. After a discussion during our last investigators meeting, the window was extended to 12 hours. Despite that a stratified intervention based on the rapid turnover of a biomarker appeared complex, we demonstrated that the collection, processing, and communication of the biomarker results to the treating team was never a barrier to enrollment. Furthermore, the adoption of the proposed interventions by treating physicians was not difficult and adherence to the protocol was high overall, probably because these are therapeutic strategies with which most clinicians are familiar. The only aspect of the implementation of the bundles that failed was KSSB level 3. We submit that this may be more a reflection of local practice, as most patients were enrolled in Europe, where consultations with other services in this context are less frequent than in North America. In fact, the only patient in whom a protocol-mandated consultation with specialists was ordered was enrolled in the United States. The study also provides data to support the idea that the implementation of KDIGO bundles may be safe, as no numerical differences were found in SAEs, SADEs, SAUDEs, or catheter-related infections between groups. Overall, our study serves as "proof of concept" that the implementation of a biomarker-guided protocol to deploy therapeutic interventions is possible in patients with sepsis. Given the extraordinary circumstances of the COVID-19 pandemic where non-COVID research was dramatically impacted, it is important to evaluate feasibility using criteria other than enrollment. LAPIS highlights how focusing only on enrollment may be insufficient, and that the evaluation of other aspects such as barriers to implementation of study procedures, protocol adherence, and limitations to follow-up were as fundamental as being able to enroll patients, yielding very important information for future trials.

Two of the most frequently voiced arguments against the use of AKI biomarkers are that early diagnosis is futile because there are no specific therapies to treat AKI and that KDIGO recommendations are "routinely administered." However, prior trials have shown that the implementation of KDIGO-recommended interventions can decrease the risk of moderate-severe AKI when guided by urinary levels of [TIMP2]•[IGFBP7] in patients undergoing cardiac surgery and major abdominal surgery (16, 17, 20). Our results now provide the first evidence that a biomarker-guided implementation of KSSB based on KDIGO recommendations is feasible and may be beneficial in patients with sepsis. In addition to supporting the strong rationale and mounting evidence for the use of biomarker-guided therapeutic interventions (21), our results also highlight a profound lack of implementation of KDIGO bundles in daily practice reported by others (22), particularly the use of FHM to guide fluid resuscitation. This is an important deficiency because FHM-guided resuscitation in septic patients results in lower net fluid balance, risk of respiratory failure, or AKI requiring RRT (23). In addition, FHM-guided resuscitation is one of the most important measures to prevent AKI in cardiac surgery patients (24). With this in mind and in the absence of specific treatments for AKI, harnessing a strategy that deploys common, recommended, proven, and widely available, yet unused therapies based on the risk stratification of patients using an FDA and Conformite Europeenne-approved biomarker to reduce AKI seems like the easiest, cheapest, most logical next step to improve the care of patients with sepsis.

Our decision to publish the results from this limited dataset was motivated in part by the notion that science should be engaged in knowledge-building. The international critical care research community is large and heterogeneous, and resources and priorities are not equally distributed. It is our hope that by providing transparency into LAPIS, and its successes and failures, we will facilitate advances in one of the most significant complications of sepsis, AKI.

CONCLUSIONS

The effects of the COVID-19 pandemic on the LAPIS study preclude us from making any conclusions about recruitment. However, our data suggest that the actual implementation of a therapeutic strategy that deploys a KDIGO-based, kidney KSSB of care guided by risk stratification using urinary [TIMP2]•[IGFBP7] is feasible and appears to be safe in patients with sepsis and septic shock. Future studies will need to address the efficacy of this strategy to improve clinically relevant outcomes.

ACKNOWLEDGMENTS

1   Program for Critical Care Nephrology, Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA.

2   Department of Anesthesiology, Intensive Care and Pain Medicine, University Hospital Münster, Münster, Germany.

3   Outcomes Research Consortium, Cleveland, OH.

4   Department of Anesthesiology and Critical Care Medicine, Critical Care Center, Memorial Sloan Kettering Cancer Center, New York, NY.

5   Department of Anesthesiology, Surgical ICU Translational Research Center, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

6   Department of Anesthesia and Intensive Care Medicine, University Hospital of Leipzig, Leipzig, Germany.

7   Medical Intensive Care Department, University Hospital of Angers, Angers, France.

8   Departments of Medicine, Emergency Medicine and Pediatrics, Louisiana State University Health Sciences Center, Shreveport, LA.

9   Department of Intensive Care, Cliniques Universitaires de Bruxelles−Hôpital Erasme, Université Libre de Bruxelles, Bruxelles, Belgique.

10 Department of Emergency Medicine, Hennepin Health and University of Minnesota, Minneapolis, MN.

11 Medical Intensive Care Unit, Cochin University Hospital, Groupe Hospitalier Paris Centre, AP-HP, Paris Cite University, Paris, France.

12 Department of Anesthesiology, University Clinics Heidelberg, Heidelberg, Germany.

13 Department of Intensive Care, Burgundy University Hospital, Dijon, France.

14 Lipness Team, INSERM Research Center LNC-UMR1231 and LabEx LipSTIC, University of Burgundy, Dijon, France.

15 INSERM CIC 1432, Clinical Epidemiology, University of Burgundy, Dijon, France.

16 Anesthesiology and Intensive Care Medicine, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France.

17 Department of Anesthesiology and Intensive Care Medicine, Tübingen University Hospital, Hoppe-Seyler-Straße, Tübingen, Germany.

18 Critical Care Unit, Bethune Hospital, Bethune, France.

19 US Data Sciences Department, US Data Sciences bioMerieux Inc, Hazelwood, MO.

20 Global Medical Affairs, bioMérieux, Marcy l'Etoile, France.

21 Service d'Anesthésie et de Réanimation, Hospices Civils de Lyon, Université Claude Bernard Lyon 1, Lyon, France.

22 Department of Translational Medicine, Università del Piemonte Orientale, Novara, Italy.

23 Cardiothoracic and Vascular Intensive Care Medicine, Orlando Regional Medical Center, Orlando, FL.

24 Department of Nephrology, Dialysis and Transplantation, International Renal Research Institute of Vicenza, San Bortolo Hospital, University of Padova, Vicenza, Italy.

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, et al: The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016; 315:801−810

2. Rudd KE, Johnson SC, Agesa KM, et al: Global, regional, and national sepsis incidence and mortality, 1990-2017: Analysis for the Global Burden of Disease Study. *Lancet* 2020; 395:200−211

3. Kellum JA, Chawla LS, Keener C, et al; ProCESS and ProGReSS-AKI Investigators: The effects of alternative resuscitation strategies on acute kidney injury in patients with septic shock. *Am J Respir Crit Care Med* 2016; 193:281−287

4. Fiorentino M, Tohme FA, Wang S, et al: Long-term survival in patients with septic acute kidney injury is strongly influenced by renal recovery. *PLoS One* 2018; 13:e0198269

5. Kellum JA, Sileanu FE, Bihorac A, et al: Recovery after acute kidney injury. *Am J Respir Crit Care Med* 2017; 195:784−791

6. Klein CL, Hoke TS, Fang WF, et al: Interleukin-6 mediates lung injury following ischemic acute kidney injury or bilateral nephrectomy. *Kidney Int* 2008; 74:901−909

7. Faubel S, Shah PB: Immediate consequences of acute kidney injury: The impact of traditional and nontraditional complications on mortality in acute kidney injury. *Adv Chronic Kidney Dis* 2016; 23:179−185

8. Faubel S, Edelstein CL: Mechanisms and mediators of lung injury after acute kidney injury. *Nat Rev Nephrol* 2016; 12:48−60

9. Singbartl K, Bishop JV, Wen X, et al: Differential effects of kidney-lung cross-talk during acute kidney injury and bacterial pneumonia. *Kidney Int* 2011; 80:633−644

10. Perner A, Haase N, Guttormsen AB, et al; 6S Trial Group: Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012; 367:124−134

11. Yende S, Angus DC: Long-term outcomes from sepsis. *Curr Infect Dis Rep* 2007; 9:382−386

12. Kashani K, Al-Khafaji A, Ardiles T, et al: Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care* 2013; 17:R25

13. Hoste EA, McCullough PA, Kashani K, et al; Sapphire Investigators: Derivation and validation of cutoffs for clinical use of cell cycle arrest biomarkers. *Nephrol Dial Transplant* 2014; 29:2054−2061

14. Bihorac A, Chawla LS, Shaw AD, et al: Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication. *Am J Respir Crit Care Med* 2014; 189:932–939

15. Kellum JA, Devarajan P: What can we expect from biomarkers for acute kidney injury? *Biomark Med* 2014; 8:1239–1245

16. Meersch M, Schmidt C, Hoffmeier A, et al: Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: The PrevAKI randomized controlled trial. *Intensive Care Med* 2017; 43:1551–1561

17. Gocze I, Koch M, Renner P, et al: Urinary biomarkers TIMP-2 and IGFBP7 early predict acute kidney injury after major surgery. *PLoS One* 2015; 10:e0120863

18. Molinari L, Heskia F, Peerapornratana S, et al; Sapphire and Protocolized Care for Early Septic Shock (ProCESS) Investigators: Limiting acute kidney injury progression in sepsis: Study protocol and trial simulation. *Crit Care Med* 2021; 49:1706–1716

19. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int* 2012; 2:1–141

20. Zarbock A, Kullmar M, Ostermann M, et al: Prevention of cardiac surgery-associated acute kidney injury by implementing the KDIGO guidelines in high-risk patients identified by biomarkers: The PrevAKI-multicenter randomized controlled trial. *Anesth Analg* 2021; 133:292–302

21. Ronco C, Chawla L, Husain-Syed F, et al: Rationale for sequential extracorporeal therapy (SET) in sepsis. *Crit Care* 2023; 27:50

22. Sadjadi M, Porschen C, von Groote T, et al: Implementation of nephroprotective measures to prevent acute kidney injury in septic patients: A retrospective cohort study [published online ahead of print]. *Anesth Analg* 2023. doi:10.1213/ANE.0000000000006495

23. Douglas IS, Alapat PM, Corl KA, et al: Fluid response evaluation in sepsis hypotension and shock: A randomized clinical trial. *Chest* 2020; 158:1431–1445

24. von Groote TC, Ostermann M, Forni LG, et al; PrevAKI Investigators: The AKI care bundle: All bundle components are created equal-are they? *Intensive Care Med* 2022; 48:242–245