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Diagnosis and Treatment of Acute Kidney Injury in Pediatrics

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Opinion statement

The term *acute kidney injury* (AKI) has replaced the outdated term acute renal failure throughout the literature and clinical practice. The term "injury" highlights the spectrum of organ injury that may occur and reflects the fact that even small changes in serum creatinine (rise of 0.3 mg/dL) can be associated with adverse outcomes. A major advance in the field of AKI research has been the development of standardized staged definitions of AKI that allow for comparison of incidence, prevalence, and outcomes across studies. The Kidney Disease: Improving Global Outcomes (KDIGO) AKI definition represents the most recent consensus definition which is currently recommended for use in pediatric populations. Utilization of standard AKI definitions has made it clear that AKI occurs often in hospitalized patients and is associated with adverse short-term and long-term outcomes (hospital length of stay, mortality, subsequent chronic kidney disease). Awareness of the impact of AKI has resulted in increased efforts to understand, diagnose, prevent, and manage AKI earlier in the course of illness. While attempts at finding a treatment for AKI have been unsuccessful, largely due to the lack of sensitivity of the primary biomarker, serum creatinine, there have been many major advances in this field over the last 15 years.

The development of novel biomarkers to predict the development of AKI in a timely manner and improve diagnostic accuracy is being pioneered by pediatric AKI researchers. The development of risk stratification scores (renal angina) and functional bedside tests (furosemide stress test) is enhancing our use of these biomarkers and our ability to predict those patients most likely to develop severe AKI. The recognition of the impact of fluid overload on mortality and hospital length of stay in patients with severe AKI has prompted more timely and frequent use of renal replacement therapy in critically ill children. Finally, we are recognizing that children who suffer AKI are at long-term risk for the development of chronic kidney disease and warrant follow-up.

Introduction

Acute kidney injury (AKI) is described as a sudden impairment in kidney function that results in decreased glomerular filtration rate, an inability to maintain fluid balance and electrolyte homeostasis, and an inability to handle waste products. There have been a number of major advances in the field of AKI research over the last 15 years thanks to growing recognition that even small changes in kidney function, previously thought to be of little consequence, can have a significant impact on short-term (hospital length of stay, mortality) and long-term outcomes (development of chronic kidney disease). Though a treatment for AKI remains elusive, much work has been done in the way we approach, diagnose, and manage AKI. The purpose of this review is to highlight the major advances in definition, epidemiology, outcomes, novel biomarker development, clinical awareness, and clinical care that have occurred recently in the field of pediatric AKI.

The definition of AKI: speaking the same language

The term acute kidney injury has replaced the dated "all or nothing" concept of acute renal failure [1, 2]. The term "injury" highlights the spectrum of organ injury that may occur and the evolving nature of these events; clinicians are thus prompted to recognize and intervene early in the course of AKI rather than waiting until organ failure [3]. The operational definition of AKI has evolved from more than 35 divergent definitions to the modern definition. The development of standardized, multidimensional, staged AKI definitions has revolutionized our understanding of the epidemiology and impact of AKI on outcomes and our ability to interpret data across studies in a meaningful way. These systems define AKI according to stage of severity based on graded changes in serum creatinine (or estimated creatinine clearance) from a defined baseline and/or urine output. The evolution in the definition of AKI began in 2004 when the Acute Dialysis Quality Initiative proposed the RIFLE criteria, which included three stages of AKI: risk, injury, and failure and two outcomes: loss and end-stage kidney disease [4]. In 2007, a pediatric version of the RIFLE criteria, the *pediatric* RIFLE (pRIFLE) was developed and validated based on changes in estimated creatinine clearance [5]. Based upon the observations that even small (0.3 mg/dl) increases in creatinine were associated with increased in-hospital morbidity and mortality, the Acute Kidney Injury Network (AKIN) definition was proposed in 2007 [3]. In order to harmonize the subtle differences in these definitions, the Kidney Disease: Improving Global Outcomes (KDIGO) AKI definition has been put forth [6••]. In pediatric patients, the KDIGO AKI definition and staging should be utilized to define AKI for clinical and research purposes (Table 1) [2, 6••].

Table 1. The kidney disease: improving global outcomes (KDIGO) AKI definition

Stage	Change in serum creatinine[a]	Urine output
I	Increase 0.3 mg/dL[b] or increased 150–200 %[c]	<0.5 mL/kg/h for 6 h
II	Increase ≥200–300 %	<0.5 mL/kg/h for ≥12 h
III	Increase ≥300 %, serum creatinine ≥4 mg/dL or dialysis or estimated glomerular filtration rate <35 mL/min/1.73 m^2 for those <18yo	<0.3 mL/kg/h for 24 h or anuria for 12 h

[a]From baseline creatinine
[b]Change over 48 h
[c]Change over 7 days

Advances in clinical awareness: understanding the epidemiology and impact of AKI on outcomes

The utilization of standardized definitions of AKI has allowed for the publication of updated epidemiologic studies highlighting the shift in underlying AKI etiologies. In developing countries, infection and primary renal diseases remain the most common causes of AKI [7–9]. In developed countries, while primary renal disease still accounts for a majority of AKI cases in otherwise healthy children, the etiology of AKI in hospitalized children is often multifactorial and reflective of comorbid conditions (e.g., bone marrow transplantation, need for extracorporeal membrane oxygenation) [10–14]. Most importantly, in each of these populations, AKI has been shown to be common and associated with adverse outcomes. We will review the incidence and outcomes associated with AKI in recent studies of some exemplar populations.

Among critically ill pediatric patient populations, the incidence of AKI is 10–25 % [12–14] and can be as high as 82 % in certain high risk populations, such as those that are mechanically ventilated [5]. These studies have shown an association between AKI and adverse outcomes including prolonged mechanical ventilation, longer intensive care unit (ICU) stays, and increased risk of mortality. For example, Alkandari et al. demonstrated an association between AKI and increased mortality (OR 3.7) that was independent of severity of illness in a cohort of 2106 patients; similar findings were reported by Selewski et al. (OR 3.4) in a cohort of 3009 critically ill children [13, 14].

Children with congenital heart disease represent one of the most extensively studied pediatric populations at risk for AKI. The incidence in this population is high ranging from 30 to 52 %, with neonates representing the most vulnerable subpopulation with an incidence approaching 60 % [15–18]. Post-cardiac surgery AKI is associated with increased risk of in-hospital mortality, duration of intensive care unit stay and overall hospitalization, time to extubation, and need for inotropic support. Several risk factors for the development of AKI in these patients have been identified including prolonged cardiopulmonary bypass time, complexity of surgical repair, degree of hypothermia, circulatory arrest, and postoperative low cardiac output syndromes [16, 18, 19].

Nephrotoxic medication exposure represents an important AKI risk factor, one that is potentially modifiable. Aminoglycosides represent one of the most potentially nephrotoxic medications in widespread use in hospitals: Zappitelli

and colleagues reported a 20 % incidence of AKI among children with ≥5 days of aminoglycoside exposure [20]. Misurac et al. showed that non-steroidal anti-inflammatory drugs (NSAID) induced AKI accounted for 2.7 % of the episodes of AKI over an 11-year period even when used at recommended dosages. The presence of volume depletion at the time of NSAID use was a major risk factor for higher degree of injury. Patients <5 years of age were more likely to need dialysis, intensive care unit admission, and longer hospital stays. Cost estimates for the care of children with NSAID-associated AKI approached $400,000 over an 11-year period [21]. Similarly, in a study of non-critically ill children, Moffett and Goldstein demonstrated that the use of three or more nephrotoxic medications had higher rates of AKI, longer hospital stays, and double the hospital costs ($82,600 vs. $48,300) [22].

Awareness of the significant impact of nephrotoxic medication exposure on the development of AKI, worse outcomes, and increased hospital costs has led to efforts to improve monitoring in these patients at the hospital level. Quality improvement initiatives aimed at nephrotoxic medication exposure screening and AKI detection using electronic medical record surveillance are ongoing and have shown early success. Goldstein et al. reported one such system that utilized the electronic medical record to identify patients at risk of AKI (intravenous aminoglycosides ≥3 days or ≥3 nephrotoxic medications) in a near real-time manner using a multi-disciplinary approach including pharmacy support. The system then triggers more diligent renal function monitoring (daily creatinine measures). The authors demonstrated feasibility of the implementation of such a system at an institutional level; their efforts resulted in a 42 % reduction in AKI intensity [23•].

Advances in novel biomarkers: moving beyond serum creatinine and urine output

Over the past decade, there have been extraordinary advances in the understanding of the diagnosis, epidemiology, and impact of AKI on outcomes in hospitalized patients. Despite these advances, there have not been any successful trials that have demonstrated effective treatment for or amelioration of AKI. In fact, current therapies are limited to supportive care including providing nutritional support, limiting nephrotoxic medications, insuring adequate renal perfusion, and managing sequelae of AKI (fluid overload, electrolyte abnormalities, uremia) [24•]. Failure to develop successful interventions in AKI is in large part related to the reliance on serum creatinine as our primary AKI biomarker. The limitations of serum creatinine have been well described and include a delay in rise of as much as 48 h *after* the injury and an inability to distinguish between functional changes and structural damage. These limitations have hampered the ability of clinicians and researchers to recognize AKI early enough to intervene in a meaningful way. As a result, there has been a significant amount of research to identify novel biomarkers of function and damage, measured in both urine and plasma, to discriminate more effectively the mechanism and timing of injury, especially when multiple biomarkers are used in combination [25].

The development of novel biomarkers to predict the development of AKI in a timely manner is essential to improving outcomes in children with AKI. It is important to distinguish these novel AKI biomarkers from functional biomarkers such as serum creatinine and cystatin C. Novel biomarkers classically include those that detect damage; some of these include urine neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin 18 (IL-18), liver fatty acid binding protein, and others [26]. These have been extensively studied in children undergoing congenital heart surgery and cardiopulmonary bypass [27–29]. In these studies, the biomarkers rose between 2 and 12 h after cardiopulmonary bypass and successfully predicted AKI, as defined by rise in serum creatinine, at 48 h following surgery [27]. These biomarkers are still undergoing rigorous testing and validation before they will be ready for widespread use in clinical care. In addition, while these biomarkers and others have successfully predicted AKI in at-risk populations, their predictive abilities have suffered when they are utilized non-selectively. As a result, there have been calls to improve pre-test probability by testing biomarkers only in "at risk" populations identified by clinical parameters (i.e., the concept of "renal angina") as is described below [24•, 30].

Advances in our understanding of pathophysiology and AKI diagnosis: moving beyond pre-renal, intrinsic renal, and post-renal

A key to investigating the cause of AKI includes an understanding of the common etiologies in a particular patient population and a systematic, ordered approach to the diagnosis. A commonly utilized system for identifying AKI etiologies is to categorize potential insults as pre-renal, intrinsic, and post-renal. Even though this framework is easy to use, it is important to remember that this approach is an oversimplification of AKI pathophysiology. AKI is a clinically heterogeneous condition that involves multiple inflammatory, immunologic, cellular injury, adaptive, and autoregulatory pathways such that not all AKI events, even those within the same anatomic category, have the same underlying mechanism of injury [31]. The anatomic approach is thus imprecise in its ability to describe adequately the nature of the injury and hence the appropriate therapeutic intervention [32]. For instance, not all patients with "pre-renal" AKI—such as some patients with congestive heart failure or nephrotic syndrome—should receive aggressive volume resuscitation. While this remains an evolving area of research, a modern approach to AKI likely involves the incorporation of risk stratification, functional bedside tests, and a combination of functional and damage biomarkers.

As a result of the limitations of current biomarkers in terms of precision, timeliness, and prognostic ability, Basu et al. proposed the use of a collection of clinical risk factors and signs of kidney disease as a framework for identifying and stratifying patients most at risk for developing AKI. This concept emerged as "renal angina" and is analogous to the process of assessing the risk for myocardial infarction in a patient presenting with chest pain [24•, 26]. Clinical risk factors include those that are known to be associated with increased AKI risk

(e.g., mechanical ventilation, bone marrow transplantation); these are combined with clinical and laboratory evidence of kidney injury (e.g., fluid overload and changes in serum creatinine) to provide a framework for stratifying patients into moderate-risk, high-risk, and very-high-risk categories. Thus, a patient who recently underwent bone marrow transplantation and is now intubated, receiving vasopressor medications and demonstrating 10 % fluid overload would require smaller changes in serum creatinine or urine output to be considered at very high risk for AKI than would an otherwise healthy patient receiving nephrotoxic medications for an infection [30]. The renal angina construct is outlined in Tables 2 and 3 is calculated by multiplying risk * injury yielding a score of 1–40.

Basu et al. recently published the first study describing the derivation and validation of the renal angina index using four separate cohorts of critically ill children at two separate institutions [33••]. The renal angina index in the first 8 h of PICU admission was able to predict stage 2 or 3 AKI successfully at 72 h of ICU admission. A renal angina index score of ≥8 was defined as renal angina positive. The renal angina index performed better than severity of illness scores and KDIGO AKI stage at admission. Most importantly, patients who did not have signs of renal angina had a negative predictive value of >92 % for the development of severe AKI on day 3. The authors suggest that the renal angina index can be utilized to identify patients who would benefit from further testing, such as with novel biomarkers. Utilizing such a schema, Basu et al. showed that in critically ill children with sepsis novel AKI biomarkers had poor discrimination when utilized alone, but when added to the renal angina index their ability to predict severe AKI improved significantly [34]. The Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology in critically ill children (AWARE) study is a multicenter prospective observational cohort study that will seek to further validate this concept in critically ill children from over 32 institutions [35]. The purpose of this project is to develop a rich description of pediatric AKI epidemiology in the largest cohort of its kind as well as provide further validation of the renal angina index and its prognostic and diagnostic abilities.

Another avenue of active research prompted by the lack of timely biomarkers is the development of a bedside test of kidney function using diuretics. Chawla et al. have proposed the "furosemide stress test (FST)" as a simple, functional bedside test to help predict a patient's likelihood for progressing to severe AKI and consequent need for renal replacement therapy [36]. A one-time dose of furosemide, 1.5 or 1 mg/kg dose if furosemide naïve, is given, and urine output is monitored for the next 6 h. The authors found that patients who were more likely to progress to AKI stage 3 had significantly less urine output following furosemide administration (urine volume <200 mls in adult

Table 2. Renal angina index—risk

Patient characteristic	Score
Sepsis or ICU admission	1
Stem-cell transplant or Solid organ transplant	3
Mechanical ventilation and ionotropic support	5

Table 3. Renal angina index—injury

Decrease in creatinine clearance	Percent fluid overload	Score
No change	≤5	1
0–24.99 %	5–9.99	2
25–49.99 %	10 to 14.99	4
≥50 %	≥15	8

patients) after 2 h. A recent follow-up study showed this functional test may be as good if not better than individual biomarkers (e.g., urine NGAL, IL-18, KIM-1, and others) in its ability to predict progression to AKI stage 3 [37]. These studies were conducted in a sample of adult patients and would require further validation in pediatric studies. However, this maneuver could be applied easily to children with AKI. In practice, those who do not have a good urinary response to furosemide should be monitored more closely and have a lower threshold for initiating renal replacement therapy rather than waiting a little longer for renal recovery.

Prevention and treatment of AKI

As stated above, in lieu of definitive AKI treatments, supportive care remains the mainstay of treatment. Below, we will review several medications that have been studied as treatments and/or preventative measures for AKI, as well as key aspects of supportive care.

A number of therapies have been studied as potential interventions for AKI including diuretics, dopamine, fenoldopam, theophylline/aminophylline, and rasburicase. Furosemide is one of the most extensively utilized and studied of these agents. Furosemide may augment urine output in some patients, but has been not been shown to prevent the development of AKI or ameliorate its course [6••, 38]. Dopamine, an endogenous catecholamine, has been of interest in the prevention and treatment of AKI because of its vasodilatory effects on the renal vasculature via the dopamine-1 and -2 receptors and its ability to enhance renal blood flow. Despite showing promise in animal models, dopamine has also not been shown to be of benefit in the prevention or treatment of AKI in several controlled trials [39]. Fenoldopam is a highly selective dopamine type 1 receptor agonist that preferentially dilates the renal and splanchnic vasculature. Fenoldopam has demonstrated some modest benefit in a small, single-center study of infants undergoing cardiopulmonary bypass for congenital heart disease repair and warrants further study [40].

Recently theophylline/aminophylline and rasburicase have shown promise in small single center studies as measures that may prevent the development of or progression to severe AKI in select patient populations. Theophylline and aminophylline act by inhibiting adenosine-induced vasoconstriction. Theophylline has been shown to prevent the development of AKI in asphyxiated newborns [41–43]. Theophylline has not been extensively studied in critically ill children with AKI. Aminophylline has shown promise in children who suffer AKI following cardiac surgery, where it was associated with improved renal excretory function and urine output [44]. A randomized double

blinded trial of aminophylline in children undergoing cardiopulmonary bypass recently concluded. In addition, uric acid because of its multiple deleterious effects on renal function has received attention as a novel therapeutic target in AKI. Rasburicase is a recombinant urate oxidase that catalyzes the conversion of uric acid to allantoin. This drug has been utilized extensively to treat hyperuricemia and thus help to prevent AKI in the context of tumor lysis syndrome. Several recent case reports have shown successful use of rasburicase in the treatment of AKI associated with severe hyperuricemia in newborns and in pediatric patients with hemolytic uremic syndrome and rhabdomyolysis [45–47]. Additional study is needed before firm recommendations regarding the use of these therapies can be made.

Until we have proven preventative or interventional treatments, care of children with AKI involves the employment of measures to prevent worsening kidney injury and minimize sequelae such as fluid overload and electrolyte abnormalities. A multidisciplinary approach is critical. For example, children with AKI have reduced drug clearance and are at higher risk for additional nephrotoxic medication-associated injury. Thus, daily evaluation of patient medication lists and dosages by a team of clinicians and pharmacists with expertise in AKI management should be utilized to optimize medication management. Similarly, children with AKI have changes in their electrolyte handling, especially potassium and phosphorus homeostasis, and in their volume requirements. These changes may vary from patient to patient depending on the mechanism of injury and level of residual urine output. Moreover, AKI represents a catabolic state, particularly in critically ill patients. Recent studies have shown that critically ill children with AKI are underfed with regard to protein and energy [48]. As a result, the comprehensive care of children with AKI, particularly the critically ill, should involve a dietician in order to optimize nutritional status. The inability to provide adequate nutrition or maintain metabolic control these are indications for more aggressive interventions including renal replacement therapy (RRT).

Advances in the care of the patient with severe AKI: recognizing the impact of fluid overload and utilizing renal replacement therapy

Over the past decade, RRT has transitioned from a therapy used as a "last-ditch effort" for patients in renal failure to a timely therapy directed at supporting the patient with kidney injury by *preventing* worsening outcomes and *facilitating* renal recovery. Depending on a center's expertise and resources, a variety of RRT modalities may be used including peritoneal dialysis (PD), intermittent hemodialysis (IHD), and continuous renal replacement therapy (CRRT) [49]. PD is often the modality of choice in smaller patients, especially critically ill neonates, as it is technically easier to implement without need for vascular access or large extracorporeal circuits. IHD is favored for use in children with intoxications or inborn errors in metabolism. Over the last 30 years, CRRT has become the modality of choice for providing RRT in critically ill children [50] because of its ability to provide slower and more controlled fluid removal that avoids the large fluid shifts that may occur with other modalities.

The indications for RRT include uremia (typically BUN >100 mg/dL), electrolyte abnormalities (particularly potassium and acidosis), inability to provide adequate nutrition, and fluid overload. Fluid overload currently represents one of the most common indications for initiation of RRT in critically ill children and warrants further discussion. The pediatric literature has been at the forefront of identifying the impact of fluid overload on mortality in critically ill children [51–53, 54••, 55, 56]. These observational studies suggest that fluid overload 10–20 % represents a critical point for intervention with RRT. Using data from the Prospective Pediatric CRRT Registry, a multi-center study at 13 sites, Sutherland et al. showed that children who had >20 % fluid overload at the time of CRRT initiation had increased mortality (OR 8.5) [54••]. The deleterious effects of fluid overload have been demonstrated in other critically ill pediatric populations not receiving CRRT as well, including those requiring mechanical ventilation, in those following heart surgery, and those with shock [57•, 58–60]. The American College of Critical Care Medicine now includes guidelines for addressing fluid balance in pediatric and neonatal patients with septic shock who amass >10 % volume overload during initial resuscitation [61]. RRT should be considered in patients who are fluid overloaded, especially if they have escalating ventilatory requirements, restricted nutrition, and need for large volumes of medications or blood products.

Wide acceptance of CRRT as an early therapy in critically ill children and neonates has been hampered by technical challenges of providing this therapy using equipment that was designed for adults but adapted for children. This is especially true for neonates and small infants. One of the most exciting new advances in the field of neonatal AKI has been the recent development of CRRT machines and systems designed specifically with the smallest of patients in mind. CRRT systems such as CARPEDIEM® (Cardio-Renal Pediatric Dialysis Emergency Machine) and NIDUS® (Newcastle Infant Dialysis and Ultrafiltration System) have smaller extracorporeal volumes, lower required blood flows and ability to interface with smaller vascular catheters, making them ideal for use with small infants [62, 63]. These machines are already in use outside the USA and show great promise; we are currently awaiting clinical trials for approval of these machines or use in the USA.

Future directions: understanding the long-term implications of AKI and increasing awareness of the issue

Previously, it was assumed that those who survive an episode of AKI would recover without long-term sequelae; however, follow-up data from children and adults who have suffered an AKI event suggests that survivors are at risk of developing chronic kidney disease (CKD) [64••, 65, 66]. Coca et al. recently showed that adults who experience an episode of AKI have an increased risk of developing CKD with a hazard ratio of 8.8 (95 % CI 3.1–25.5) [66].

Although the pediatric literature on the long-term effects of AKI is not as robust as that in adults, there is growing evidence that pediatric patients are also at risk of developing CKD following AKI events. In a prospective cohort study of children who experienced AKI in a tertiary center PICU, 10 % of children developed CKD within 1 to 3 years, with an additional 50 % of patients "at risk" for developing CKD [64••]. In a retrospective cohort study of oncology patients exposed to a nephrotoxic medication, 70 % of patients who had an AKI event developed reduced eGFR, hyperfiltration, proteinuria, or hypertension within 6 months of that episode [67]. Finally, a recent meta-analysis evaluating the long-term outcomes of AKI in children has confirmed an increased risk of proteinuria, hypertension, and GFR <90 mL/min/1.73 m^2 following an episode of AKI [65]. From this data, it has become clear that children who have had an episode of AKI warrant follow-up.

The KDIGO guidelines include expert opinion about follow-up for adult patients after an episode of AKI. These patients should be seen by their primary physician within 3 months of the event. If signs of CKD (e.g., hypertension, proteinuria, elevated serum creatinine) are present, the referral to a specialist is necessary. While these recommendations are likely pertinent to children, currently there is not enough firm evidence to develop evidence-based practices. General pediatricians should consider children who have suffered AKI at increased risk and monitor blood pressure with consideration of further testing on a case by case basis.

To answer questions about appropriate long-term follow-up and many other issues pertaining to pediatric AKI, large longitudinal multi-center studies are needed. Pediatric AKI research has typically been hampered by small sample sizes and single-center studies that are often retrospective in design. The Assessment of Worldwide AKI, Renal Angina and Epidemiology (AWARE) study represents a major effort in this area. Initial data from this project are expected soon and will undoubtedly move the field of pediatric AKI much further into the future.

Conclusion

While the care of children who suffer AKI episodes is still hampered by the lack of a definitive "cure," there have been many major advances in the field of pediatric AKI, both in the laboratory and at the bedside. Standardized definitions have allowed for better identification of AKI in patients and comparison of data across studies. The development of more sensitive and specific AKI biomarkers is under way and will likely revolutionize our ability to intervene early enough in the course to develop and re-test previously proposed treatments and improve outcomes. The development of clinical frameworks like the renal angina score allows for earlier recognition of AKI at the bedside using a more robust combination of clinical signs and symptoms as well as functional and damage biomarkers. Our understanding of the impact of fluid overload is prompting earlier intervention and more effective utilization of renal replacement therapy. Above all, there is growing awareness of the scope of the problem and the impact of AKI on both short- and long-term outcomes. The development of a large, collaborative networks such as that for AWARE represents a major step forward in our ability to answer important questions in this field.

Compliance with Ethical Standards

Conflict of Interest

Jennifer G. Jetton declares that she has no conflict of interest. Erika T. Rhone declares that she has no conflict of interest. Matthew W. Harer declares that he has no conflict of interest. Jennifer R. Charlton declares that she has no conflict of interest. David T. Selewski declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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