Epidemiology and Diagnosis of Acute Kidney Injury

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Summary: The development of recent standardized definitions of acute kidney injury (AKI) has allowed us to begin understanding pediatric AKI epidemiology and risk factors and to stratify outcome by AKI severity. AKI incidence will vary with illness severity of the population studied and definition type, ranging from less than 1% when need for dialysis is used to 82% when less conservative definitions (such as ≥1.5 times baseline serum creatinine) are used to define AKI. The most common AKI causes are secondary, such as sepsis, nephrotoxic medication, and ischemia, each leading to acute tubular necrosis (ATN). Children undergoing cardiopulmonary bypass surgery, stem cell transplantation, or with multiple organ dysfunction syndrome are at high risk for these events. A key feature in diagnosis and management includes identifying the presence of ATN versus a reversible hypovolemic state because patients with ATN may quickly develop fluid overload with overaggressive fluid therapy, requiring dialytic removal. Despite advances in acute pediatric dialysis therapy and in overall care of critically ill children, severe AKI still is associated with a high mortality rate, necessitating more research in early AKI identification and therapeutic trials.

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The clinical cases presented by Symons and Picca in this issue are common scenarios encountered by pediatric nephrologists describing patients at high risk of developing acute kidney injury (AKI). AKI denotes the abrupt onset of renal dysfunction resulting from injurious endogenous or exogenous processes, leading to the inability to regulate acid and electrolyte balance, and excrete wastes and fluid; glomerular filtration rate (GFR) decreases, characterized clinically by the body’s accumulation of serum creatinine (SCr). Severe AKI is life-threatening. However, recent evidence suggests that even a small SCr increase is a risk factor for mortality and costs in hospitalized patients.

When faced with clinical situations such as those described in the cases, the nephrologist’s role is to diagnose the presence of AKI, identify the modifiable and nonmodifiable risk factors, followed by patient-specific management. To achieve these goals and provide optimal care, the nephrologist must understand the following: (1) how to define AKI, (2) the disease epidemiology, (3) the possible etiologies in the setting of a specific illness, and (4) the laboratory investigations necessary to diagnose AKI severity. This article focuses on AKI definition and diagnosis, and outlines the causes and epidemiology of AKI, with subsequent application to the clinical cases. This article does not address case 4 since infants with inborn errors of metabolism usually do not experience AKI and the factors important to guide provision of renal replacement therapy are discussed in the article by Picca et al in this issue (p. 477).

EPIDEMIOLOGY

A consistent definition is required to discuss the epidemiology of any disease with validity. Until recently, studies describing AKI epidemiology have used a wide variety of definitions (Table 1), ranging from mild changes in SCr level and
urine output to the need for renal replacement therapy (RRT), which has greatly hampered our ability to discuss AKI epidemiology. Several factors, ranging from type of AKI definition to SCr assay used, affect the estimate of AKI incidence, independent of AKI disease. Understanding these factors allows for a more refined interpretation of the AKI epidemiologic literature.
Definition and Study Population Characteristics

AKI incidence is generally less than 1% when RRT requirement defines AKI. However, a requirement for RRT provision is the most strict AKI definition. Reported AKI incidence increases when less strict AKI definitions are used, such as doubling of SCr. Study population characteristics also will influence the estimate of AKI incidence; studies including more severely ill patients will show a higher rate of AKI development. Two recent prospective pediatric AKI studies show the influence of these factors. In the first study, almost all patients admitted to the pediatric intensive care unit (PICU) were eligible for enrollment and AKI was defined as SCr level doubling. In the second study, only patients receiving invasive mechanical ventilation and vasopressors were included and AKI was defined as a 1.5 times or greater SCr increase. Both population and definition characteristics in the latter study led to a higher estimate of AKI incidence (82% versus 4.5%) than in the former. However, the actual occurrence of AKI in each ICU may not have truly differed. AKI ascertainment merely differed in relation to the study population and AKI definition.

Serum Creatinine Level and Estimated Baseline Renal Function

Currently, AKI generally is defined by changes in SCr level, reflecting changes in GFR. For many reasons, SCr level is an inaccurate marker of GFR and a late marker of AKI. Serum creatinine concentrations are highly affected by muscle mass, which not only changes with age and height of a child, but also with changes in muscle mass associated with hospitalization-associated malnutrition. As GFR decreases acutely, SCr secretion by the renal tubules will increase, leading to falsely low SCr values that may not capture AKI occurrence. Despite these problems, acute SCr change is the reference standard, albeit imperfect, by which epidemiologic AKI studies are based.

Another potential problem in interpreting findings of AKI epidemiologic studies is the issue surrounding baseline renal function. Almost every study estimates baseline renal function in a different way. If a lower estimate of baseline SCr is used to detect acute changes in SCr, then the estimated incidence of AKI will be higher; when a more conservative or higher estimate of baseline SCr is used, then AKI incidence will clearly be lower. In 2008, we examined the effect of using different methods for defining baseline renal function and found that the incidence and severity distribution of AKI are highly affected by how baseline renal function is defined.

Risk, Injury, Failure, Loss, End-Stage Kidney Disease Criteria

A consistent, multidimensional AKI definition represents an important strategy to account for interstudy differences and interpretation of AKI epidemiologic studies. The Acute Dialysis Quality Initiative recently proposed the Risk, Injury, Failure, Loss, End-Stage Renal Disease (RIFLE) criteria for defining AKI. The RIFLE criteria stratify AKI from mild (RIFLE R [risk]: ≥50% SCr level increase from baseline) to severe (RIFLE F [failure]: ≥3 × baseline SCr level) based on changes in SCr level or urine output. A few adult studies have shown that the presence of AKI by RIFLE is a risk factor for mortality in hospitalized adults. We defined AKI using pediatric-modified RIFLE (pRIFLE) criteria (shown in Table 2), and found that AKI occurred in 82% of the most critically ill children admitted to the PICU. AKI defined by these criteria was an independent risk factor for mortality and increased hospital length of stay. Although the pRIFLE criteria are not currently applicable in the clinical setting for medical decision making, they provide a multidimensional research tool to assist with AKI descriptive and outcome studies and also allows clinicians and researchers to speak the same language when discussing the presence of AKI. AKI definition is still an evolving area of research. A more recent modification of the RIFLE criteria was proposed by the Acute Kidney Injury Network (the AKIN criteria staging system), however, this definition has not been evaluated in children. Further epidemiologic research using these definitions in children will contribute to understanding the true incidence of mild to severe AKI in a wide
range of geographic and diagnostic patient populations.

**Cystatin C**

Cystatin C (CysC) is a protease inhibitor produced at a constant rate by nucleated cells, which may be an alternative to SCr to define the presence of AKI. Serum levels are stable with age, muscle mass, diet, and physical activity, and principle excretion is by GFR with no tubular secretion, and it is degraded by proximal tubular cells; all of these attributes are ideal qualities for a marker of GFR. Although CysC is more diagnostic of renal dysfunction than SCr in patients with CKD, patients with CKD have relatively stable renal function, thus CysC cannot be assumed to be a better marker of acute changes in GFR. CysC kinetic studies have suggested that its serum concentrations may achieve a steady state sooner than SCr with acute GFR changes. Early clinical studies in critically ill adults and children undergoing cardiopulmonary bypass surgery suggest that CysC increases 1 to 2 days before SCr does with AKI, but this is still controversial, requiring further research.

**ETIOLOGY AND RISK FACTORS**

The discussion thus far has focused on appropriate interpretation of epidemiologic AKI studies based on AKI definition. Recognition of disease etiology is a crucial component to the understanding of AKI disease epidemiology. Table 3 lists AKI causes commonly seen in children. Different reports reveal different AKI causes depending on the specific population studied. Prevalent causes of AKI are sepsis, the use of nephrotoxic medication, and renal ischemia caused by several disease states in critically ill patients. In fact, most AKI in the critical care setting is caused by secondary renal injury rather than primary renal disease (such as glomerulonephritis or hemolytic-uremic syndrome). Although each of these conditions cause AKI via different mechanisms, they lead to a final common pathway of acute tubular necrosis (ATN), characterized by renal tubular cell death, as depicted in Figure 1.

Specific patient populations who are at higher risk of developing AKI have been studied in some detail. Patients receiving stem cell transplants are at substantial risk of developing AKI for several reasons, including the extensive use of nephrotoxic medications, veno-occlusive disease in association with hepatorenal syndrome, the high incidence of sepsis, and tumor lysis syndrome. Because of the large amounts of fluid received during their treatment, these patients are also at particularly high risk of developing substantial fluid overload. Patients undergoing cardiopulmonary bypass (CPB) are also at risk of postoperative AKI. The pathophysiology of AKI in this setting is mostly ischemia associated with the bypass procedure. The incidence of AKI, defined by SCr level doubling, in the CPB population ranges from approximately 6% to 30%, depending on the case series and AKI definition used.

**Table 2. pRIFLE Criteria**

<table>
<thead>
<tr>
<th></th>
<th>Estimated Creatinine Clearance</th>
<th>Urine Output</th>
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<tbody>
<tr>
<td>Risk</td>
<td>Decrease by 25%</td>
<td>&lt;0.5 mL/kg/h for 8 hours</td>
</tr>
<tr>
<td>Injury</td>
<td>Decrease by 50%</td>
<td>&lt;0.5 mL/kg/h for 16 hours</td>
</tr>
<tr>
<td>Failure</td>
<td>Decrease by 75% or eCrCl &lt;35 mL/min/1.73 m²</td>
<td>&lt;0.3 mL/kg/h for 24 hours or anuric for 12 hours</td>
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<tr>
<td>Loss</td>
<td>Persistent failure &gt;4 weeks</td>
<td></td>
</tr>
<tr>
<td>End stage</td>
<td>End-stage renal disease (persistent failure &gt;3 mo)</td>
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Data from Akcan-Arikan et al.
an important etiology, such as nephrotoxic medication use in the patient treated for a cystic fibrosis exacerbation or a patient presenting to the emergency room with gross hematuria and hypertension. Nonetheless, identification of all potential AKI causes is crucial to provide appropriate recommendations for diagnosis and avoidance of further kidney injury.

Renal hypoperfusion events will be extremely common in the critical care unit and in patients undergoing stem cell transplants, resulting from excessive blood loss, sepsis with capillary leak, cardiac dysfunction, vomiting, inadequate fluid replacement, and burns. Therefore, a detailed fluid balance history is necessary to determine the extent to which renal hypoperfusion may be contributing to the AKI episode. Additionally, a fluid balance history is invaluable to evaluate whether a positive fluid balance is occurring, which may suggest more severe AKI. If available, serial weights are useful for the assessment of progressively positive fluid balance. Detailed medication history will elucidate whether medication-induced nephrotoxicity (eg, aminoglycosides, amphotericin-B, chemotherapeutic agents, angiotensin converting enzyme inhibitors, or calcineurin inhibitors) may be contributing to the current AKI episode.

Estimating baseline kidney function will help determine the severity of kidney injury, and can be assessed by reviewing previously drawn SCr levels over the previous 3 to 6 months to determine a patient’s true baseline SCr level. If baseline SCr levels are unavailable, baseline kidney function can be estimated by assuming a normal estimated creatinine clearance by the Schwartz formula\(^49\) and back-calculating SCr level or by using age- and sex-based SCr normative values.\(^13\)

The physical examination can provide evidence of the cause of AKI. A rash or arthritis may suggest vasculitis or remarkable ascites or jaundice may suggest hepatorenal syndrome. Low blood pressure and poor perfusion will strongly suggest ischemic ATN. The physical examination also helps to evaluate the severity of fluid overload associated with AKI. Fluid overload has been shown to be associated with mortality at initiation of continuous RRT, independent of illness severity\(^50,51\) and with mortal-

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**Table 3. Causes of Pediatric AKI**

<table>
<thead>
<tr>
<th>Renal hypoperfusion</th>
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<tr>
<td>Low intravascular volume</td>
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<tr>
<td>Hemorrhage/bleeding: postoperative, trauma</td>
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<tr>
<td>Severe dehydration</td>
</tr>
<tr>
<td>Third-space losses: sepsis and capillary leak, burns, trauma, hypoalbuminemia (nephrotic syndrome/liver disease)</td>
</tr>
</tbody>
</table>

| Decreased effective circulating volume |
| Cardiac dysfunction: congestive heart failure, cardiac tamponade/pericarditis, sepsis-associated cardiac dysfunction |
| Renal artery obstruction: stenosis, mass |
| Sepsis-associated diffuse vasodilation |

<table>
<thead>
<tr>
<th>Diseases of renal tissue</th>
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<tbody>
<tr>
<td>Glomerular</td>
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<td>Glomerulonephritis</td>
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<table>
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<tr>
<th>Vascular</th>
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<tbody>
<tr>
<td>Hemolytic uremic syndrome: infectious, drug-induced (calcineurin inhibitors), genetic</td>
</tr>
<tr>
<td>Vascular injury: cortical necrosis, renal vein/artery thrombosis, disseminated intravascular coagulation, thrombotic disease, malignant hypertension</td>
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<tr>
<th>Interstitial</th>
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<tr>
<td>Acute interstitial nephritis: drug-induced, infectious, immune-mediated</td>
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<tr>
<td>Infection/pyelonephritis</td>
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<th>Tubular</th>
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<tr>
<td>ATN: hypoxic/ischemic injury, drug-induced, exogenous toxins (metals, venom, illicit drugs, ethylene glycol, methanol), endogenous toxins (rhabdomyolysis, hemolysis, tumor lysis syndrome)</td>
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<td>Tumor lysis syndrome</td>
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<th>Urinary tract obstruction</th>
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<tr>
<td>Urethral obstruction: posterior urethral valves in neonates; urinary catheter obstruction</td>
</tr>
<tr>
<td>Obstruction of solitary kidney urinary tract: congenital (ureteral-pelvic junction, ureteral stenosis, ureterovesical junction, mass), stones, mass</td>
</tr>
<tr>
<td>Bilateral ureteral obstruction: mass, stones</td>
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</table>
ity in children with AKI after stem cell transplantation. Some patients, particularly those with severe capillary leak as seen with septic shock or stem cell transplantation, may have only mild to moderate increases in SCr but in association with severe fluid overload requiring dialytic removal. The following formula can assist in determining the extent of severity of fluid overload: 

\[
\text{Fluid in (L) } / \text{ICU admission} - \text{Fluid out (L) from ICU admission)} / \text{ICU admission weight in kg} \times 100\%.
\]

Correlating changes in oxygen needs with changes in fluid balance may help determine the extent to which fluid overload is impeding adequate oxygenation and ventilation.

Laboratory investigation can help elucidate AKI causes as well as evaluate severity, as shown in Figure 2. Urine examination helps to rule out evidence of glomerulonephritis (hematuria, red blood cell casts, white blood cell casts) and to evaluate for proteinuria, particularly in patients with low serum albumin levels. Patients with ATN may have granular or muddy brown casts.

A common diagnostic dilemma occurs when patients present with an increase in SCr level associated with evidence of renal hypoperfusion, as shown in Figure 3. Some patients simply require fluid administration to return SCr
concentrations to baseline values and may not have true tubular injury. In these patients, reduction in GFR is adaptive to offset the reduction in intravascular volume. However, when renal hypoperfusion is severe, ATN can develop and overly aggressive fluid administration may contribute or lead to fluid overload and respiratory compromise. Calculating the fractional excretion of sodium or urea can be used to help differentiate between increases in SCr level caused by simple renal hypoperfusion versus ATN: (Urine sodium × SCr/serum sodium × urine creatinine) × 100.

The fractional excretion of urea is calculated similarly. Sodium and urea fractional excretion should be low (<1% for sodium and <35% for urea) with fluid-responsive increases in SCr level (prerenal AKI), whereas with ATN, fractional excretion will be higher (>2% for sodium and >35% for urea). The fractional excretion of urea may be less affected by diuretic use. Increases in levels of blood urea nitrogen out of proportion to SCr also may indicate renal hypoperfusion as an important contributing factor to AKI, however, it is important to remember that blood urea nitrogen levels can be increased in states of gastrointestinal bleeding and catabolism (such as corticosteroid use) and does not rule out the presence of ATN.

Figure 2. Laboratory investigation of AKI. Proposed laboratory evaluation of acute SCr increase, beginning with an estimation of baseline kidney function and followed by directed evaluation of urinary, blood, and imaging tests. AIN, acute interstitial nephritis; HUS, hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura; MODS, multiple organ dysfunction syndrome.

Figure 3. Common clinical scenario of a patient with increased SCr level. Clinical scenario whereupon the SCr level increases and whether the cause is reversible renal hypoperfusion or ATN is not known. The patient with ATN is at risk of developing fluid overload with overaggressive fluid therapy.
OUTCOME

Children with AKI requiring RRT, particularly infants and those with multiple organ dysfunction, have a high mortality rate, ranging from 30% to 70%. However, mild pediatric AKI also may be associated with mortality, independent of illness severity. Additional research is needed to determine the strength of the association between milder forms of AKI and mortality. Of particular interest is the long-term renal outcome of patients who have hospital-acquired AKI. Early work by Askenazi et al revealed that up to 60% of children who had hospital-acquired AKI had some form of renal abnormality at the 3- to 5-year follow-up evaluation, defined as hematuria, hypertension, microalbuminuria, low GFR, or high GFR. Another pediatric study showed that 30% of children who underwent bone marrow transplant available for follow-up evaluation displayed reduced GFR at 1 year. Similar findings were confirmed by other investigators in similar populations.

RETURN TO CLINICAL CASES

Clinical Case 1: Sepsis/Multiple Organ Dysfunction Syndrome

This clinical scenario describes a child with septic shock who required large amounts of fluid resuscitation and vasopressors to maintain minimally acceptable blood pressure. There is little doubt, given the increase in SCr level, that this patient has AKI. His SCr initially was 1 mg/dL, increased to 1.6 mg/dL, and finally increased to 2.8 mg/dL. If we assume that his baseline SCr was 1 mg/dL, then he had an approximate tripling of his SCr level, which equates to an approximate 75% reduction in GFR. By using the pRIFLE criteria, this patient has RIFLE F (failure) AKI. His baseline SCr level was most likely even less than 1 mg/dL, given that he already was ill on arrival to the PICU and average SCr concentrations for a boy his age are closer to approximately 0.7 to 0.8 mg/dL. Thus, he suffered a significant reduction in GFR, most likely exceeding a 75% reduction. We can identify several risk factors including the presence of sepsis with likely multiple organ dysfunction, very low blood pressure with renal hypoperfusion, and the use of high doses of vasopressor medication, suggesting that this child has at least moderate to severe ATN. Another clue to the presence of significant ATN was that his SCr concentration did not improve with administration of intravenous fluids; rather, he developed worsening fluid overload. A urinalysis may reveal granular casts and a fractional excretion of sodium study will be greater than 1% to 2%. It would be important to measure his serum calcium, potassium, and phosphorous levels to help assess the severity of ATN, which may require dialysis for metabolic reasons. Calculation of the patient’s fluid overload status revealed: (Total fluid in – out from admission)/weight × 100 = (15.08L − 2.3L)/52 × 100 = 24.6% fluid overload.

This extreme fluid overload occurred despite adequate urine output (1.2 mL/kg/h), displaying a common flawed practice of interpreting absolute urine output without an assessment of net fluid balance. Moreover, his chest radiograph findings and oxygenation status likely were affected by the severe excess amount of fluid he has accumulated, in addition to acute respiratory distress syndrome.

In summary, based on knowledge of how AKI is defined, on the risk factors of AKI, and on methods of assessing AKI severity, we can conclude that this child has severe ATN (attaining the worst acute pRIFLE stratum) caused by severe acute renal hypoperfusion and sepsis, causing an acute (>75%) reduction in his GFR, resulting in severe fluid overload. Based on his clinical situation and his likely need for RRT, he is at high risk of mortality.

Clinical Case 2: AKI After Stem Cell Transplantation

Based on studies of the risk factors and most common causes of AKI, this patient who underwent hematopoietic stem cell transplantation is at risk of developing AKI posttransplant via several mechanisms. The diagnosis of AKI was first made by estimating her baseline SCr value (which we will assume is approximately 0.7 mg/dL, although likely was lower given her age and sex), assessing the rate of increase and peak value of her most recent SCr, which was 2.6 mg/dL. Thus her SCr concentration more than
tripled, signifying a greater than 75% reduction in her GFR. Next, specific AKI causes and risk factors must be identified. These include stem cell transplantation alone, the use of total body irradiation (although this usually contributes to renal dysfunction later), and the presence of graft-versus-host disease, which may be associated with veno-occlusive disease-associated renal dysfunction. In addition, this patient is receiving multiple nephrotoxic medications, including aminoglycosides (toxic to the proximal tubule), amphotericin B (causing distal tubular toxicity and reduction in GFR), and tacrolimus (which causes a reduction in GFR, tubular toxicity, and also may cause a thrombotic thrombocytopenic purpura clinical picture). She also may have sepsis associated with a fever of unknown origin, which may or may not be contributing to her acute renal dysfunction. In addition, it is worthy to note that the increase in SCr is unresponsive to fluid, highly suggesting the presence of ATN. Nevertheless, a fractional excretion of urea test was performed (because she is receiving diuretics and a fractional excretion of sodium study is unreliable) and was found to be greater than 35%. Because of the concern of thrombotic thrombocytopenic purpura secondary to tacrolimus, hemoglobin and platelets and a blood smear for schizocytes also are requested. Despite the extreme acute reduction in GFR, her urine output did not initially decrease substantially; however, this was not unexpected because aminoglycoside and amphotericin-induced nephrotoxicity often are associated with nonoliguric AKI. Because of her high fluid needs and progressive relative reduction in urine output, her fluid overload status has increased substantially at approximately 11%. Given her respiratory status, her obvious substantial AKI, and the acute increase in fluid overload, specific management is necessary.

Clinical Case 3: CPB

This clinical case describes an infant with congenital heart disease who has undergone multiple potentially injurious events to the kidney. Initially, the child had a severe episode of renal hypoperfusion after the first surgical intervention, requiring high doses of vasopressor medications. It is important to note that SCr concentration may only increase substantially 24 to 72 hours after the injurious event, even though ATN is present. Shortly after this event, the child underwent CPB surgery. This procedure is associated with direct ischemia to the kidney as well as inflammatory reactions to extracorporeal circulation. Based on previous studies of children undergoing CPB surgery, this infant had an at least 10% risk of developing SCR level doubling, even without the prior ischemic events. Not surprisingly, the patient developed AKI with a SCr increase from 0.3 to 0.9 mg/dL and the lack of substantial increased urine output after the dose of furosemide suggests the presence of ATN. The combination of fluid requirements, an open chest requiring eventual closure, and significant AKI should direct the team to perform RRT for fluid removal.

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