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Factors associated with acute kidney injury or failure in children undergoing cardiopulmonary bypass: a case-controlled study

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Summary

Acute kidney injury (AKI) is a serious complication that occurs commonly following cardiopulmonary bypass (CPB) in infants and children. Underlying risk factors for AKI remain unclear, given changes in CPB practices during recent years. This retrospective, case–control study examined the relationships between patient, perioperative factors, AKI, and kidney failure in children who underwent CPB.

Methods: Cohorts of children with and without AKI were identified from the cardiac perfusion and nephrology consult databases. Demographic, perioperative, and postoperative outcome data were extracted from the databases and from medical records. Children were stratified into groups based on the Acute Dialysis Quality Initiative's RIFLE definitions for acute kidney risk or injury (AKI-RI) and kidney failure.

Results: The study groups included 308 controls (no AKI-RI or failure), 161 with AKI-RI, and 89 with failure. Young age, preoperative need for mechanical ventilation, milrinone, or gentamicin; intraoperative use of milrinone and furosemide; durations of CPB and anesthesia; multiple cross-clamp and transfusion of blood products were significantly associated with AKI or failure. Young age, perioperative use of milrinone, multiple cross-clamps, extracorporeal membrane oxygenation, cardiac failure, neurological complications, sepsis, and failure significantly increased the odds of mortality.

Conclusion: This study identified multiple perioperative risk factors for AKI-RI, failure, and mortality in children undergoing CPB. In addition to commonly known risk factors, perioperative use of milrinone, particularly in young infants, and furosemide were independently predictive of poor renal outcomes in this sample. Findings suggest a need for the development of protocols aimed at renal protection in specific at risk patients.

Introduction

Acute kidney injury (AKI) is a well-known and serious complication following cardiopulmonary bypass (CPB), occurring in as many as 11–17% of infants and children following repair of congenital heart defects (CHD) (1,2). Several factors including young age (3,4), small size (3), complexity of the heart defect (4), and CPB duration (5,6) have previously been identified as risk factors for renal dysfunction in children. However, varying definitions of renal insufficiency, small and/or homogeneous samples, and limited sets of perioperative factors investigated leave a significant gap in our current understanding of this phenomenon. Additionally, several

significant changes in CPB practices have occurred over the past decade, including changes in pump technology, pump prime solutions, use of hemofiltration and modified ultrafiltration (MUF), as well as use of agents such as aprotinin and newer vasoactive substances. While such techniques have resulted in improved hemostasis, hemodynamics, and inflammatory responses during CPB, the impact of such practice changes on the risk for AKI remains unclear. Given the known association between AKI and increased morbidity and mortality in adults and children, particularly in those requiring dialysis (7–10), a greater understanding of associated risk factors may facilitate studies that evaluate interventions targeted at protection of renal function during and following CPB.

The purpose of this retrospective, case–control study was therefore to examine the relationships between multiple perioperative factors, AKI and failure or the need for dialysis in children who underwent CPB and to identify underlying conditions that, if targeted for intervention, may minimize the risk for AKI.

Methods

This retrospective study was approved by the University of Michigan Institutional Review Board with a waiver of informed consent. A nested case–control study design was used to identify the sample taken from all children (birth to <18 years) who underwent CPB for repair of a CHD between 1998 and 2006. A cohort of children was identified from the nephrology consult list over this study period to generate a large sample of children with potential adverse renal outcomes. The control group was identified using a probability sample (i.e., computer-generated, random selection), twice the size of the consultation list, obtained from the cardiac perfusion database over the same period. All duplicate patients (i.e., children who underwent bypass more than once) were excluded, as were children who had chronic renal failure preoperatively or who underwent cardiac transplantation.

Standardized institutional guidelines for pediatric CPB circuit components, pump flows, and cardioplegia were adhered to throughout this study period. Standard anticoagulation was carried out with heparin 400–500 units per kg. A kaolin-ACT (Hemochron Jr.) was utilized, and an ACT of >450 s was obtained before initiation of CPB. Packed red blood cells (PRBCs) were added to the CPB priming solution if the calculated hematocrit (Hct) was $<27\%$ (goal of no $<25\%$). Mannitol ($0.25\ \mathrm{G{\cdot}kg^{-1}}$) was added to all priming solution and given again during re-warming. Steroids were given to all children who underwent circulatory arrest. Nonpulsatile CPB was employed using a roller pump and a microporous hollow fiber membrane oxygenator. Pump flows were weight based and adjusted according to surgeon specifications. Mean arterial pressure during bypass was maintained at 20–50 mmHg depending on the age of the patient except during surgical request for low flow states. Conventional ultrafiltration was used during the re-warming phase of CPB as needed (to increase hematocrit and remove excess volume in the venous reservoir.) Modified ultrafiltration was conducted for 10 min immediately postbypass for all children <15 kg. Use of deep hypothermic circulatory arrest (DHCA) was based on the complexity of the surgical procedure as well as patient weight. Anesthetic care including fluid management, use of inotropes, diuretics, and transfusions, was based on individual patient needs. In general, dopamine was administered to facilitate weaning from CPB. Epinephrine was used to provide inotropic support for neonates and as needed in others. Milrinone was added as needed to reduce afterload, and lastly, vasopressin was added to improve systemic vascular tone.

Electronic and paper medical records, including the preoperative anesthesiology and cardiology medical history and physical examinations, intraoperative anesthesia and perfusion flowsheets, postoperative intensive care unit (ICU) flowsheets, progress and discharge notes, were reviewed for data retrieval. Research assistants blinded to the purpose of the study recorded all data that included: demographics, surgical procedure coded in accordance with the Risk Assessment in Congenital Heart Surgery criteria (RACHS-1) (11), baseline and postoperative laboratory values for the first 3 postoperative days (PODs) (e.g. serum creatinine [SCr] and blood urea nitrogen), CPB and circulatory arrest data, intraoperative times (total anesthetic duration, DHCA time and cross-clamp time) medications (including inotropes, diuretics, gentamicin, aprotinin, etc.), urine output over the first 3 days, and postoperative course (including all complications and mortality).

The outcomes for this study included acute renal failure risk or injury (AKI-RI), kidney failure and death. Postoperative AKI-RI was classified using the Acute Dialysis Quality Initiative's 'RIFLE' criteria (12), recently modified for children (pRIFLE) (13) as: 1.5–2 times increase in SCr from baseline, and/or urine output $<0.5\ \mathrm{ml{\cdot}kg^{-1}}$ per h over any 24-h period during the first 3 PODs. Children who required dialysis (peritoneal or hemodialysis) at any time during their postoperative course were identified with failure. Additional pre- and postoperative conditions, including cardiac failure, neurological complications and

sepsis, were derived from inpatient cardiology and subspecialty notes and discharge summaries.

Statistical analysis was conducted using SPSS software (SPSS Inc., Chicago, IL, USA). Data are presented as n (%) or mean ± standard deviation, as appropriate. Univariate analyses (Student *t* tests or chi square with Fisher's exact tests, as appropriate) were conducted to evaluate the associations between patient, perioperative factors, and renal outcomes groups (AKI-RI or failure vs other children). Significant relationships are presented using odds ratios (OR) and confidence intervals (CI). Several logistic regression models (backward, stepwise) were developed to examine the relationships between preoperative, intraoperative and pertinent postoperative outcomes and the renal outcomes groups. P values < 0.05, corrected as appropriate for unequal variance, were accepted as statistically significant.

Results

One hundred sixty-six of 238 children in the nephrology consult database met study inclusion criteria. Three hundred and twenty-eight children were selected from the balance of 4611 in the perfusion database. The records of the combined groups ($n = 494$) were reviewed. Eight children who died intraoperatively or in the immediate postoperative period (within hours) were excluded from this study, as they had no laboratory values and could not be classified into one of the renal outcomes groups. Following careful review of the records, the final sample was stratified as follows: 308 controls (no AKI-RI or failure), 161 who had AKI-RI during the first 3 POD, and 89 who developed kidney failure during their hospitalization. Characteristics of these samples and the relationships between perioperative factors are described in Table 1. Stepwise, backward logistic regression models were generated to examine factors that were independently associated with the outcomes. The first model regressed the following independent factors on AKI-RI: age, preoperative diuretics, nephrotoxic antibiotics, mechanical ventilation, and milrinone; intraoperative minutes, CPB minutes; multiple cross-clamps; MUF, ultrafiltrate; milrinone, epinephrine, and transfusion. The second included the following factors regressed on kidney failure: age, preoperative diuretics, nephrotoxic antibiotics, mechanical ventilation, milrinone and dobutamine; intraoperative minutes, CPB minutes, multiple cross-clamps, ultrafiltrate; milrinone, epinephrine, and transfusion (Table 2). A third model added an interaction factor between dobutamine and age, as this agent is used more often in younger infants in this setting. This additional factor did not alter findings related to the independent associations for AKI-RI or failure.

Of the children who required dialysis, 27 (30%) had peritoneal dialysis, 43 (48%) were placed on continuous veno-venous hemofiltration (CVVH) or hemodialysis, and 19 (21%) had peritoneal and hemodialysis. There were no differences in age or RACHS-1 score between children with peritoneal vs other dialysis methods. However, hemodialysis was initiated significantly earlier postoperatively compared to peritoneal dialysis (5.3 ± 8.7 vs 9.3 ± 14.8 days; $P = 0.47$). The time to initiation of dialysis ranged from 0 to 61 days after surgery (6 ± 10.6 days), and duration of dialysis in survivors ranged from 1 to 79 days (12.8 ± 18.5 days).

Table 3 displays the relationships between other pertinent postoperative outcomes and renal outcomes. AKI-RI and failure were significantly associated with respiratory, neurologic, cardiovascular, infectious complications, and mortality postoperatively ($P < 0.017$). A significantly greater proportion of children who underwent peritoneal dialysis survived compared to those who required CVVH or hemodialysis (48.1% vs 12.9%, respectively). Factors that were associated with death by univariate analysis were entered into a logistic regression model with backward selection. The following factors were found to be independently associated with mortality: young age (*Wald* 6.3; *Exp(B)* **1.3** [*CI* 1–1.6]; $P = 0.012$), preoperative use of milrinone (4.6; **5.7** [1.2–28]; 0.032), intraoperative use of milrinone (8.6; **4.4** [1.6–11.9]; 0.003), multiple cross-clamps (8.2; **9.1** [2–40.8]; 0.004), extracorporeal membrane oxygenation (ECMO) (21.2; **17** [5.1–56.8]; < 0.001), cardiac failure (12.9; **5.9** [2.2–15.4]; < 0.001), neurological complications (4.5; **3.6** [1.1–11.7]; 0.03) sepsis (11.6; **6** [2.1–16.9]; 0.07), and kidney failure (24.6; **12.8** [4.7–35.1]; < 0.001).

Discussion

This retrospective, cohort study identified multiple preoperative and intraoperative factors associated with renal failure in children undergoing CPB. While several of these factors have been well documented, several previously unreported risk factors have been identified. Perioperative use of certain inotropic agents, diuretics, and gentamicin were found to be independently associated with poor renal outcomes in this setting. Additionally, similar to recent studies in children (14,15), use of aprotinin was not associated with poor outcomes in this sample. These findings identify children at risk for renal failure, which, in turn, may guide future research aimed at reducing risk.

Table 1 Preoperative and intraoperative characteristics of the groups

	Control group *n* = 308	AKI-RI[a] *n* = 161	Kidney failure *n* = 89
Preoperative status			
Age (years)	3.55 ± 5.5	1.45 ± 3.6[b]	1 ± 2.6[b]
Neonate (≤1 month)	156 (51%)	93 (58%)	50 (56%)
Weight (kg)	15.2 ± 20	8.1 ± 12.9[b]	6.7 ± 9.6[b]
Male gender	185 (60%)	89 (55%)	52 (58%)
Baseline creatinine	0.64 ± 0.27	0.55 ± 0.23	0.68 ± 0.65
Baseline blood urea nitrogen	14 ± 9.2	14.6 ± 11.58	18.2 ± 16.1
Baseline hematocrit	41.0 ± 6.2	42.0 ± 6.2	42.3 ± 6.0
Diuretics	150 (49%)	96 (60%) [**1.54**;1, 2.3][b]	58 (65%) [**1.9**; 1.2, 3.1][b]
Gentamicin/vancomycin	43 (14%)	39 (24%) [**1.8**; 1.1, 3][b]	30 (34%) [**3**; 1.8, 5.1][b]
Mechanical ventilation	91 (30%)	75 (47%) [**2**; 1.3, 2.9][b]	45 (51%) [**2.1**; 1.3, 3.4][b]
Inotropic support	76 (25%)	54 (34%)	34 (38%) [**1.8**; 1.1, 2.9][b]
Dopamine	68 (22%)	43 (27%)	26 (29%)
Milrinone	8 (3%)	14 (9%) [**3.8**; 1.5, 9.2][b]	9 (10%) [**3.3**; 1.4, 8][b]
Epinephrine	10 (3%)	6 (4%)	5 (6%)
Vasopressin	1 (<1%)	2 (1%)	1 (1%)
Dobutamine	14 (5%)	11 (7%)	10 (11%) [**2.8**; 1.2, 6.4][b]
ECMO	2 (1%)	4 (3%)	6 (7%) [**9.5**; 2.3, 38.7][b]
Previous cardiac surgery	90 (29%)	42 (26%)	28 (32%)
Intraoperative data			
RACHS-1[c] (11)			
1	13 (4%)	0	0
2	56 (18%)	21 (13%)	10 (11%)
3	113 (37%)	55 (34%)	26 (29%)
4	54 (18%)	36 (22%)	26 (29%)
6	72 (23%)	49 (30%)	27 (30%)
Intraoperative minutes	297.7 ± 74.6	340.5 ± 93.7[b]	351.2 ± 179.5[b]
Cardiopulmonary bypass	69.1 ± 49.1	84.2 ± 70.1[b]	96.8 ± 83.3[b]
minutes	134 (44%)	79 (49%)	44 (49%)
Circulatory arrest *n* (%)	16 ± 21.2	16.6 ± 21.1	17 ± 21.4
Circ arrest minutes	9 (3%)	22 (15%) [**4.4**; 2, 9.4][b]	15 (18%) [**4.1**; 2, 8.6][b]
Multiple cross-clamp	213 (70%)	132 (82%) [**1.9**; 1.2, 3][b]	70 (80%)
Modified ultra filtration	164.1 ± 150.9	250.6 ± 190.8[b]	262.5 ± 221.9[b]
Ultrafiltrate (ml·kg^{-1})	103.2 ± 73.1	105.8; 86.9 ± 58.8	86.9 ± 50.1
Furosemide	35 (11%)	23 (14%)	20 (23%) [**2.3**; 1.3, 4.2][b]
Gentamicin or vancomycin	16 (5%)	6 (4%)	3 (3%)
Aprotinin	248 (81%)	134 (83%)	76 (85%)
Inotropic support	280 (91%)	146 (97%) [**3.1**; 1.2, 8.1][b]	86 (97%)
Dopamine	277 (90%)	148 (92%)	78 (88%)
Milrinone	97 (32%)	87 (54%) [**2.4**; 1.6, 3.5][b]	49 (55%) [**2.1**; 1.3, 3.3][b]
Epinephrine	153 (50%)	116 (72%) [**2.4**; 1.6, 3.6][b]	71 (80%) [**3.4**; 2, 6][b]
Transfusion required	182 (59%)	116 (72%) [**1.7**; 1.2, 2.6][b]	64 (72%) [1.6; 0.96–2.6][b]
PRBC transfused	78 (25%)	64 (40%) [**2.0**; 1.3, 3][b]	38 (43%) [**2.0**; 1.3, 3.2][b]
Platelets or FFP	156 (51%)	108 (67%) [**1.9**; 1.3, 2.9][b]	59 (66%) [**1.6**; 1, 2.7][b]
Hematocrit end of case	38.2 ± 7.7[b]	40.8 ± 7.7[b]	40.9 ± 7.7[b]
Albumin administered	167 (54%)	100 (62%)	57 (64%)

Data presented as mean ± SD or *n* (%) [**odds ratio**; confidence interval], where applicable.

[a]72 children in the AKI-RI group also developed kidney failure.

[b]$P < 0.05$ vs other children.

[c]RACHS-1 scored as previously described as follows: (1) atrial septal defects, coarctation repair, etc.; (2) hemifontan, ventriculo-septal defects; (3) arterial switch, Fontan, mitral valve procedures; (4) aortic arch or truncus procedures, combinations; (6) Norwood.

PRBC, packed red blood cells, FFP, fresh frozen plasma; AKI-RI, acute kidney risk or injury; ECMO, extracorporeal membrane oxygenation; RACHS-1, risk assessment in congenital heart surgery criteria.

Table 2 Perioperative factors independently associated with acute kidney injury and failure (results of multivariate analysis)

	AKI-RI	Failure
Age	9.26; 0.002	NS
Gentamicin preoperative	NS	10.6; 0.001 [**3** (1.6, 5.7)]
Milrinone preoperative	4.1; 0.043 [**3.2** (1.1, 9.1)]	NS
Mechanical ventilation preoperative	4.3; 0.038	3.8; 0.051 [**1.8** (1, 3.3)]
Dobutamine preoperative	NS	3.9; 0.047
Multiple cross-clamp	7.9; 0.005 [**2.8** (1.2, 6.3)]	NS
CPB duration	NS	10.5; 0.001
Ultrafiltrate removed	NS	4.8; 0.028
Anesthesia duration	12.6; <0.001	NS

Data presented as Wald statistic; *P* value with [**Exp B** (Confidence interval)], as appropriate. NS, Not significant; CPB, cardiopulmonary bypass.

Several factors, including young age, small size, and cyanosis have been previously associated with renal failure following CPB in children (4,6,16). Inconsistencies in findings, however, suggest that mediation of these inherent risk factors by multiple perioperative factors, including use of inotropes and other agents, acute inflammation, and poor cardiac function affect renal outcomes in this population (9,17). Data from the present study support a multifactorial relationship between the perioperative course and renal outcomes, with many such factors indicative of low cardiac output states during this period. In fact, children who received preoperative dobutamine and/or milrinone, and intraoperative epinephrine were nearly three times as likely to develop AKI-RI or kidney failure postoperatively. Furthermore, cardiac failure, sepsis, need for ECMO and open chest postoperatively were significantly associated with AKI-RI and failure. Hoffman, *et al.* (18) previously reported that children without preoperative low cardiac output syndrome (LCOS) randomized to receive milrinone immediately after surgery were less likely to develop LCOS and had no difference in creatinine clearance compared to those who received placebo. In contrast, children in the present study setting received milrinone or other inotropes for treatment of LCOS. It may therefore be likely that underlying cardiac failure is the primary factor leading to poor renal outcomes, with inotropes as secondary indicators.

We further found that children with poor renal outcomes were 4–12 times more likely to have received diuretics, gentamicin, and mechanical ventilation preoperatively. Intravenous diuretics are used in our setting to treat oliguria associated with congestive failure, and gentamicin was used to treat fever during septic work-ups. These variables therefore indicate underlying physiologic compromise that may place children at higher risk. Simsic *et al.* (19) reported that newborns who were mechanically ventilated preoperatively had a greater degree of preoperative hemodynamic compromise and higher inotropic scores compared to spontaneously breathing neonates. These risk factors are therefore likely interdependent.

In this sample, children with AKI-RI or failure were equally likely to have received aprotinin compared to controls. Early randomized, controlled trials of aprotinin in children and adults reported no differences in renal outcomes between those who received the agent vs placebo (20,21). In contrast, two retrospective studies in large samples of adults who underwent coronary

Table 3 Relationship between postoperative outcomes, acute renal failure (AKI-RI) and failure*

	Control group *n* = 308	AKI-RI *n* = 161	Failure *n* = 89
Complications			
Respiratory	37 (12%)	43 (27%) [**2.4**; 1.5, 3.9]	24 (27%) [**2**; 1.2, 3.5]
Neurologic	15 (5%)	29 (18%) [**3.8**; 2, 7]	23 (26%) [**5.6**; 3, 10.5]
Sepsis	21 (7%)	40 (25%) [**3.2**; 1.9, 5.3]	35 (41%) [**6.9**; 4, 11.9]
Cardiovascular	102 (33%)	117 (73%) [**4.8**; 3.1, 7.2]	82 (93%) [**21.7**; 9.2, 50.9]
ECMO	5 (2%)	50 (31%) [**8.7**; 4.8, 16]	52 (59%) [**39.4**; 19.9, 77.9]
Low-output cardiac failure	20 (7%)	57 (36%) [**5.6**; 3.4, 9.3]	51 (58%) [**14.2**; 8.2, 24.6]
Chest open after surgery	100 (33%)	83 (52%) [**2**; 1.4, 3]	59 (67%) [**3.8**; 2.4, 6.3]
Additional surgery required	25 (8%)	56 (35%) [**4.6**; 2.8, 7.4]	46 (52%) [**8.8**; 5.2, 14.8]
Death	18 (6%)	68 (42%) [**6.7**; 4.1, 10.8]	68 (76%) [**36.9**; 20, 67.9]

Data presented as *n* (%) [**odds ratio**; confidence interval].

*All comparisons were significant between group vs other children ($P < 0.017$).

AKI-RI, acute kidney risk or injury; ECMO, extracorporeal membrane oxygenation.

artery bypass surgery found an increased risk of renal injury, myocardial infarction, and death in patients who received aprotinin (22,23). These studies led to the withdrawal of the agent from the US market. More recently, two retrospective, case–control studies in children reported no association between the use of aprotinin and renal failure in children (14,15). Szekely *et al.* (24) similarly found that while children who received aprotinin had higher rates of renal dysfunction and failure, when risk adjusted using propensity matching, the independent role of aprotinin in the development of poor renal outcomes was not supported. While transient effects of aprotinin on renal function have been described, the effects on renal function in children remain poorly understood. Further study using a randomized, controlled design in large samples of children is warranted to better evaluate safety in this population.

Several aspects of CPB and surgery, however, have been implicated as risk factors for poor renal outcomes (17). The present study found that prolonged surgery and CPB duration, and multiple cross-clamp during surgery were associated with adverse renal outcomes, a finding similar to earlier studies (5,6). Duration of surgery, bypass, and cross-clamp likely reflects the complexity of the defect and surgical repair. The underlying lesions in these cases, as well as nonpulsatile flow during CPB, may be associated with decreased perfusion states, placing the kidneys at greater risk. In contrast to earlier data (5,6), the use of DHCA was not associated with AKI-RI in the present study. Advances in surgical techniques including completing as much dissection as possible prior to initiation of DHCA have shortened the duration of arrest, thereby reducing the associated risks of circulatory arrest over time. Lastly, the global inflammatory response that correlates with CPB duration (17,25), and to which younger and smaller patients are more susceptible (26), may further contribute to poor renal outcomes. Several techniques commonly used during CPB, including MUF, hemofiltration or use of aprotinin, attenuate the inflammatory response (26). The reduction in inflammatory mediators is transient, and its relationship with postoperative outcomes is unclear. MUF has been shown, however, to decrease the duration of postoperative mechanical ventilation, and improve hemodynamic parameters (26), suggesting improved end-organ perfusion. In the present study, the relationship between the use of these techniques and adverse renal outcomes was not found.

Previous investigators have found a significant association between the lowest hematocrit during CPB and postoperative renal injury in adults (27). Furthermore, these effects on renal injury were worsened if early PRBC transfusions were utilized to correct the low hematocrit (27). While we were unable to demonstrate a similar association between hematocrit and renal injury, we found that transfusion of blood products was significantly associated with but was not an independent predictor of AKI-RI or failure. The relationship between a low hematocrit, transfusion of blood products and renal risk requires further investigation in children undergoing CPB.

The ability to generalize findings from this study may be limited by several methodological issues common to retrospective designs. Firstly, cases were identified from the nephrology consult database, and it remains unknown whether all cases of AKI-RI or failure were included. Also, it remains possible that observed associations are because of the effect of some confounding variable, such as serum glucose levels and other factors, not included in these analyses. In an attempt to identify such confounders, correlations and univariate analyses were initially performed including all patient-related and perioperative factors collected for this study. Lastly, it is well known that there may be significant variability in practices across settings, which limits the ability to generalize findings.

Conclusion

Although this study cannot draw cause and effect relationships, the findings have identified multiple perioperative factors associated with the development of untoward renal outcomes. Young age, multiple cross-clamps and longer intraoperative times were found to be associated with both AKI-RI and failure. The use of milrinone preoperatively and intraoperatively was associated with AKI-RI but not kidney failure, while preoperative ventilation and gentamicin and intraoperative furosemide were associated with kidney failure but not AKI-RI. These findings suggest a complex interrelationship between perioperative factors and poor renal outcomes in children who undergo CPB.

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