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REVIEW

A Review of Prolonged Mechanical Ventilation in Pediatric Cardiac Surgery Patients: Risk Factors and Implications

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Abstract: Congenital heart disease (CHD) is a complex common defect in pediatric patients, and definitive treatment is usually cardiac surgery, especially for diseases with complex aetiology (ie, Critical CHD). While significant success has been reported due to improvement in diagnosis and treatment, the risk of mortality is still relatively higher than in the general population. Advances in surgical and post-surgical clinical management continue to increase survival in pediatric patients. However, mechanical ventilation (MV) during and after post-surgical procedures is linked with potential complications that may drive morbidity and mortality. Standard clinical practice dictates weaning patients off MV within the first 24 hours after surgery. However, various factors may increase the risk of extubation failure (EF), reintubation, and prolonged MV (PMV). Generally, PMV has been linked with increased length of pediatric intensive care unit (PICU) stay, morbidity, and higher risk of post-cardiac surgery mortality. The risk of PMV may be either preexisting (preoperative), perioperative/intraoperative, and/or postoperative, with the tendency to define the clinical course and patient outcomes. Monitoring and understanding the physiological dynamics of these risk factors may provide an opportunity for better and improved clinical management, which may translate into better patient outcomes. This review delves into the risk factors of extubation failure, reintubation, and PMV in pediatric cardiac surgery patients with complex (CHD) and the potential preventative measures to improve patients' outcomes.

Keywords: congenital heart disease, prolonged mechanical ventilation, pediatric, cardiac surgery, risk factors, respiratory care

Introduction

Congenital heart disease (CHD) is an umbrella term that defines a wide array of defects diagnosed at birth and affects the function and structure of the heart. With a prevalence ranging between 8 and 9 per 1000 live births globally, CHD remains the most common congenital disability globally and remains a major global health problem.[1–4] Regionally, the prevalence of CHD in North America was estimated at around 7–12 per 1000 live births with about 8 and 9 cases per 1000 live births in Europe and Asia, respectively. Of these, about 25% of cases are considered critical (CCHD) requiring surgery with the potential for post-surgery complications. Generally, the type of CHD significantly influences the diagnosis, prognosis and clinical management of the disease whereby some defects are linked with higher risk of complications than others.

The various types of CHD are mainly classified into cyanotic and non-cyanotic CHD based on whether the disease is associated with cyanosis (reduction in low blood oxygen level resulting in the skin colour turning bluish) or not. Types of cyanotic CHD includes tricuspid atresia, truncus arteriosus, total anomalous pulmonary venous return (TAPVR), and transposition of Great Arteries (TGA).[5,6] Acyanotic CHD (obstructive lesions) is CHD not linked with reduction in blood oxygen and includes, among others, coarctation of the Aorta, pulmonary stenosis, aortic stenosis, atrial and ventricular septal defects (ASD & VSD).[7] Clinically, cyanotic CHD types are considered more critical, requiring immediate medical intervention including mechanical ventilation and surgery compared with the acyanotic CHD types.[8–10] However,

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cyanotic and acyanotic CHD may be critical depending on the age at presentation and especially complex when diagnosed in neonates.[11]

According to the report by Chobufo et al, 2020, the mortality rate for children with CHD decreased between 1999 and 2020 from 47% to 37%.[12] This may be attributed to early detection and improvement in treatment options as well as success of these management plans. While, the breakthroughs in detection and management have resulted in the majority (up to 90%) of CHD patients surviving well into adulthood, the risk of mortality may be up to 18-fold higher compared with children born without this condition.[13] Specifically, breakthroughs in the diagnosis combined with the development of cutting-edge treatment/management options including catheter interventions, surgical interventions to correct aortic coarctation, defect of the atrioventricular septa, Mustard and Senning atria as well as the development of the arterial switch, Rastelli procedure and the development of single-ventricle Fontan circulation have significantly improved survival in CHD, especially in births from the 1990s.[13–19]

Indeed, since Henry Souttar performed the first cardiac surgery (Mitral Commissurotomy) in 1925, surgical intervention remains one of the definitive management of CHD in pediatric patients.[20] However, the story of cardiac surgery is not a smooth journey, and following 80% mortality rates in patients that underwent this procedure, the consensus was to abandon it due to the high risk-to-benefit ratio. While heart surgery for CHD has advanced significantly over the years (and decades), various challenges still emphasize the need for further research to understand the risk factors for perioperative mortality, especially in pediatric patients with CCHD.

This challenge is significantly enhanced in pediatric patients on mechanical ventilation following surgery for CCHD. Approximately over 50% of pediatric patients undergoing cardiac surgery require MV following a move to the ICU.[21] Mechanical ventilation is required for surgical procedures and to stabilize patients' respiratory status post-surgery, usually after their transfer into the ICU for close monitoring during recovery.[22–24] Generally, while most patients undergoing mechanical ventilation (MV) after cardiac surgery are weaned from the ventilator after a day, extubation failure (EF) may occur in up to 18% of patients and is associated with an increase in the risk of mortality and length of ICU or hospital stay.[25,26] This is especially so in neonates undergoing cardiac surgery for CHD. Thus, EF may increase fragility and fatigue and predispose reintubation, increasing the risk of hypoxemia and cardiopulmonary shutdown/arrest. In addition, reintubation often also means prolonged mechanical ventilation (PMV) with the associated increase in the risk of ventilator-linked infection, trauma, need for further sedation, perioperative morbidity, and mortality.[21,27–29] While postoperative care is optimized to reduce the length of stay in the pediatric ICU (PICU) through fast-track weaning of patients off MV, various factors still complicate weaning off MV. Although recent advancement means up to 97% of pediatric patients survive following cardiac surgery, certain preoperative, perioperative, and postoperative cardiac and extra-cardiac factors have been shown to increase the risk of morbidity and mortality in the subgroup of patients who do not survive. Understanding these challenging factors and how they affect the dynamics of treatment and outcome requires synthesis of current research, especially to delineate the specific benefits of various interventions. Thus, this review presents recent evidence regarding the indications for mechanical ventilation, factors associated with EF during weaning, and consequently, longer dependence on MV and the effect of this on patients' outcomes.

Mechanical Ventilation Management of Pediatric Cardiac Surgery Patients

Pediatric patients undergoing cardiac surgery for CHD are primarily put on MV in the operating theatre, where they are closely monitored for changes in physiological complications. After surgery, the primary approach is quick removal of the respiratory tube from patients (extubation), ideally within the first 24 hours, to preserve usually intact respiratory function, especially when patients' hemodynamic parameters are within the physiological level.[30,31] However, some patients still require postoperative MV with complex clinical needs.

MV for pediatric cardiac surgery can be generally categorized into invasive (IV) and noninvasive (NIV) MV according to patients' postoperative condition. NIV methods include continuous positive airway pressure (CPAP), bilevel positive airway pressure mode (BIPAP), or nasal cannula among patients following cardiac surgery. Generally, the use of NIV is either to prevent respiratory complications following extubation or to manage acute respiratory failure in patients with intact airway integrity.[32] Specifically, the NIV method is preferred as a safer alternative to the IV because it avoids the need for reintubation of patients and the potential complications associated.[33] Indeed, Fernandez Lafever et al investigated the use of NIV in PICU following cardiac surgery of 935 patients and reported an 85% success rate. Specifically, CPAP was reported in this study as the most common NIV method employed, with BIPAP being increasingly used among practitioners.[34] Indeed, other studies have also corroborated these findings, explicitly showing that NIV is portable, safe, and effective in improving peak expiratory flow and reducing the length of PICU stay of pediatric patients following cardiac surgery.[35–39] Another noninvasive technique for oxygenation is the high-flow nasal cannula (HFNC). Indeed, HFNC was reported by Hernández et al to be as effective as other NIV in extubated high-risk adults.[40]

However, in specific patient groups, the use of NIV is contraindicated, for instance, in patients with acute respiratory failure associated with loss of integrity of the airway and airflow. Reintubation (invasive MV) is necessary for these patients to maintain a physiological state. While applicable, reintubation most often means PMV, which has been shown to increase the risk of ventilation-associated infections (eg, pneumonia), lung injury, malnutrition, and ventilator dependence,41[42] which may create a vicious cycle of further EF, longer PICU stay, combined with increased medical cost.[21] Intuitively, NIV is the preferred mode of ventilatory support post-cardiac surgery in the PICU and generally implies a better prognosis.

Risk Factors for Prolonged Mechanical Ventilation and Extubation Failure in Pediatric Cardiac Surgery Patients.

Successful and timely (≤24 hours) weaning of pediatric patients following cardiac surgery for CHD is a preferred clinical management approach. This is because it allows for spontaneous recovery and is associated with increased survival and positive postoperative outcomes.[43,44] However, in some subgroups of patients, it is impossible to disconnect them from MV due to cardiac and noncardiac complications affecting their ability to respirate independently. In such patients, it is necessary to alt weaning and prolong MV and PICU stay. In other patients, MV weaning and extubation may be interrupted due to changes in the patient's condition, resulting in the inability to respirate spontaneously. Extubation failure (EF) describes the need for reintubation within 1–3 days after removal of ventilatory support was initiated. Indeed, EF and the need for re-intubation may contribute to morbidity and prolong patients' dependence on MV, as well as PMV and the associated risks. Indeed, prolonged need for MV generally burdens clinical resources and has been reported to be associated with a significant increase in the risk of in-hospital mortality.[44–46]

Intuitively, most factors reported to be associated with increased risk of EF and PMV, such as open sternum, infection/sepsis, pulmonary hypertension, postoperative cardiac failure/arrest, as well as other factors, may increase the complexity of clinical management. For instance, acute kidney injury, preoperative mechanical ventilation, myocardial dysfunction, and open sternum, among others, were to be associated with prolonged hospital stay over two weeks (14 days) in pediatric cardiac surgery patients.[47] Similarly, in a retrospective analysis of 1566 consecutive adult patients who underwent heart surgery, age, gender, impaired kidney function, arrhythmia, mitral insufficiency, and noncardiac arterial disease, among others, were linked with a prolonged postoperative hospital stay.[48]

In general, the various risk factors for EF and PMV may be classified into those that are preexisting (preoperative), complications during the surgical procedure (perioperative/intraoperative), and/or postoperative factors that occur after surgery when patients are moved into the PICU for recovery (Figure 1, Table 1).

Preoperative Risk Factors

Preoperative factors are preexisting characteristics of patients that may increase the risk of EF and predispose PMV. Various factors have been identified that predispose pediatric patients to EF and prolonged need for MV in the ICU following CHD surgery. For instance, in the study by Alrddadi et al of over 250 pediatric patients who underwent cardiac surgery for CHD, lower age and weight and pulmonary hypertension were reported to be associated with PMV.[49] These findings were confirmed by another study of over 300 pediatric patients, which showed that age (< 12 months), pulmonary hypertension, and incidence of cardiac failure/arrest significantly increased the risk of PMV.[50] Indeed, evidence has further shown that EF is significantly driven by preoperative age, pulmonary hypertension, lower gestational age, and the presence of congestive heart failure, with some of these factors showing cumulative and synergistic effects on patients' extubation success.[51] Relying on the expanding body of evidence, Vida et al have

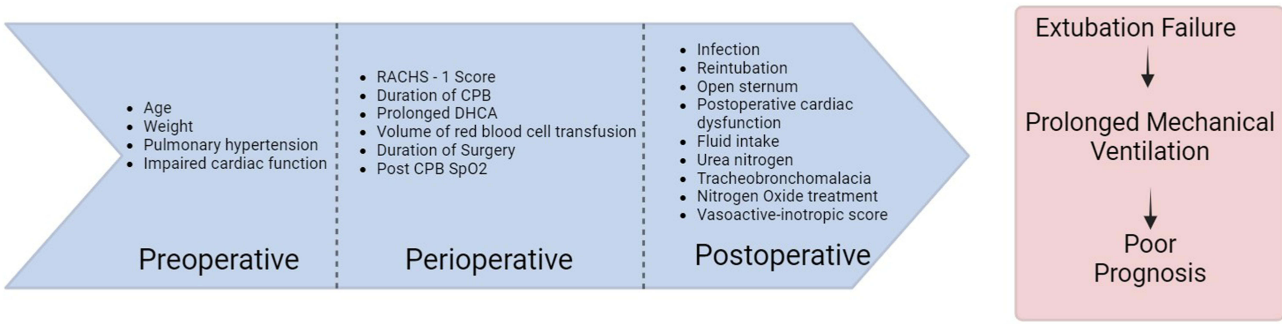

Figure 1 The risk factors of extubation failure and prolonged mechanical ventilation in pediatric cardiac surgery patients that lead to poor prognosis.
Abbreviations: RACHS-1, Risk adjustment for surgery for congenital heart disease (RACHS)-1 score; CPB, Cardiopulmonary Bypass; DHCA, Deep hypothermic circulatory arrest; SpO2, Arterial Oxygen Saturation.

hypothesized that pulmonary arterial hypertension is a contraindication for early or fast-track extubation and MV weaning in pediatric cardiac surgery patients.[52]

Some other preoperative risk factors for PMV that have been reported include the Canadian Cardiac Society and New York Heart Association classes, which are used to, respectively, measure the severity of exertional angina and heart failure in patients with CHD. As a general measure of preexisting cardiac function, these factors have been reported to be associated with patients' MV dynamics following cardiac surgery.[40]

Perioperative/Intraoperative Risk Factors

Events during cardiac surgical procedures can also influence EF, PMV, morbidity, and mortality in pediatric cardiac surgery patients. Specifically, the risk adjustment for surgery for congenital heart disease (RACHS)-1 score, a risk-adjustment tool for assessing the complexity of the surgical procedure for CHD,[53] was reported by Shi et al to be independently associated with PMV in a group of 172 pediatric patients.[54] Further, the duration of cardiopulmonary bypass (CPB), as well as longer cross-clamp time during cardiac surgery, has been reported to be associated with various complications, including increased capillary permeability and intrapulmonary shunt, gas exchange dysfunction, atelectasis, hypoxia, and higher risk of infection,[55–57] all of

Table 1 Risk Factors for Prolonged Mechanical Ventilation and Extubation Failure in Pediatric Cardiac Surgery Patients.

Category	Risk Factors
Preoperative	- Lower age and weight
	- Pulmonary hypertension
	- Congestive heart failure
	- Lower gestational age
	- Severity of exertional angina and heart failure (Canadian Cardiac Society and New York Heart Association classes)
Perioperative	- High RACHS-1 score (Risk Adjustment for Congenital Heart Surgery)
	- Duration of cardiopulmonary bypass (CPB)
	- Longer cross-clamp time
	- Prolonged deep hypothermic circulatory arrest (DHCA)
	- Intraoperative red blood cell transfusion volume
	- Duration of surgical procedure
	- Post-CPB arterial oxygen level

(*Continued*)

Table 1 (Continued).

Category	Risk Factors
Postoperative	- Length of Paediatric Intensive Care Unit (PICU) stay
	- Incidence of infection
	- Reintubation following extubation failure (EF)
	- Open sternum
	- Impaired cardiac function
	- Post-CPB arterial oxygen tension (PaO2/FiO2)
	- Fluid intake within the first 24 hours post-surgery
	- Urea nitrogen
	- Treatment with nitric oxide
	- Tracheobronchomalacia (weakness of the tracheal tissue)
	- Vasoactive-inotropic score (VIS)
	- Postoperative blood lactate levels
	- Dysregulated inflammatory response (sepsis and systemic inflammatory response syndrome)
	- Concomitant genetic defects (eg, Down Syndrome, DiGeorge syndrome, Heterotaxy syndrome)
	- Metabolic and renal dysfunction

which may result in an increased risk of adverse postoperative outcomes.[58] Another risk factor for PMV that has been reported in pediatric cardiac surgery patients is prolonged deep hypothermic circulatory arrest (DHCA).[59] Designed in the 1950s and later introduced into clinical practice by Griepp et al,[60] the DHCA uses hypothermia to protect patients against cerebral damage during CPB.[61] In a study of 381 patients who underwent triple-branched stent graft for acute Type A aortic dissection, DHCA duration was reported by Xie et al to be higher in patients who showed PMV following surgery.[62]

Other factors that have been linked with extended postoperative MV include intraoperative red blood cell transfusion volume, duration of surgical procedure, and post-CPB arterial oxygen level.[62,63]

Postoperative Risk Factors

Aside from preoperative and perioperative factors shown to influence mechanical ventilation dynamics following pediatric cardiac surgery, various postoperative physiological parameters have also been reported to be linked with EF and PMV. Generally, these factors may be cross-over conditions from before surgery (preoperative), perioperative factors that did not resolve or new clinical events with a definitive influence on patients' ventilatory needs (Figure 1). Some factors that have been reported to increase the risk of EF and PMV are PICU (pediatric ICU), length of stay, incidence of infection, reintubation (following EF), open sternum, and impaired cardiac function.[49] Indeed, another factor shown to be postoperatively associated with poorer outcomes is the post-CPB arterial oxygen tension (PaO_2 /FiO_2) and the fluid intake within the first 24 hours post-surgery. Both these variables were reported to be associated with a medium increase in the duration of MV in pediatric cardiac surgery patients admitted to the ICU.[63] Székely et al assessed the risk factors for medium (MMV) and PMV in a population of pediatric cardiac surgery patients at a tertiary hospital in Hungary and reported urea nitrogen, treatment with nitric oxide, and Tracheobronchomalacia (weakness of the tracheal tissue) all independently predictive of PMV.[63] Other postoperative factors reported to be predictive of ventilatory and clinical outcomes include patients' vasoactive-inotropic score (VIS), which is a clinical model that measures the quantity in dosage of pharmacological cardiovascular intervention (vasopressors and inotropic medications) a patient is receiving.[64,65] For instance, VIS measured at the end of cardiac surgery in 250 adult patients with CHD was found in a work by Liu et al to be independently associated with PMV.[66] Further, the postoperative blood level of lactate, which reflects low tissue oxygen, was assessed for its prognostic value in terms of predicting morbidity and mortality in pediatric patients (<12 months old) undergoing cardiac surgery.[67] The predictive value of arterial lactate was further corroborated in pediatric cardiac surgery patients in another study by Alves et al, who reported a significant link between this biomarker and the risk of developing renal, cardiovascular, and respiratory complications.[68] Indeed, it is unclear whether the postoperative lactate level is an unresolved increase that has been extensively reported perioperatively in various studies and which has been significantly linked with increased post-operative morbidity and mortality.[69–72] Further, other factors including dysregulated inflammatory response (sepsis and systemic inflammatory response syndrome), concomitant genetic defects (eg, Down Syndrome, DiGeorge syndrome, heterotaxy syndrome, etc), metabolic and renal dysfunction may further exacerbate extubation failure and PMV.73[74]

Preventing and Treating Extubation Failure and Prolonged Mechanical Ventilation Following Pediatric Cardiac Surgery

While most risk factors for extubation/weaning failure, as well as PMV, are non-modifiable, various approaches have been assessed for their ability to reduce the risks. Specific focus has been placed on using novel perioperative mechanical ventilation methods and various ventilatory weaning strategies to prevent extubation failure and PMV (Figure 2).

Firstly, the use of low-tidal or low-frequency MV during cardiopulmonary bypass has been proposed as an easy and cost-effective technique to prevent PMV in pediatric cardiac surgery patients. Indeed, while various studies have assessed the effect of this technique in said population, current evidence is still inconsistent. For instance, in a survey of 140 pediatric cardiac surgery patients undergoing cardiopulmonary bypass, Padalino et al assessed the effect of low-tidal or low frequency on the length of MV and found no significant improvement or advantages compared with unventilated patients.[58]

Another technique trialed in pediatric patients following cardiac surgery for CHD is the use of spontaneous breathing, where patients in the treatment arm of the clinical trial were put on a continuous positive airway pressure as follows: 10 cmH_2O of pressure support, 5 cmH_2O of positive end-expiratory pressure and <0.5 fractions of inspired oxygen for 2 hours. Control patients were ventilated based on a standard clinical management plan. Extubation failure, defined as the

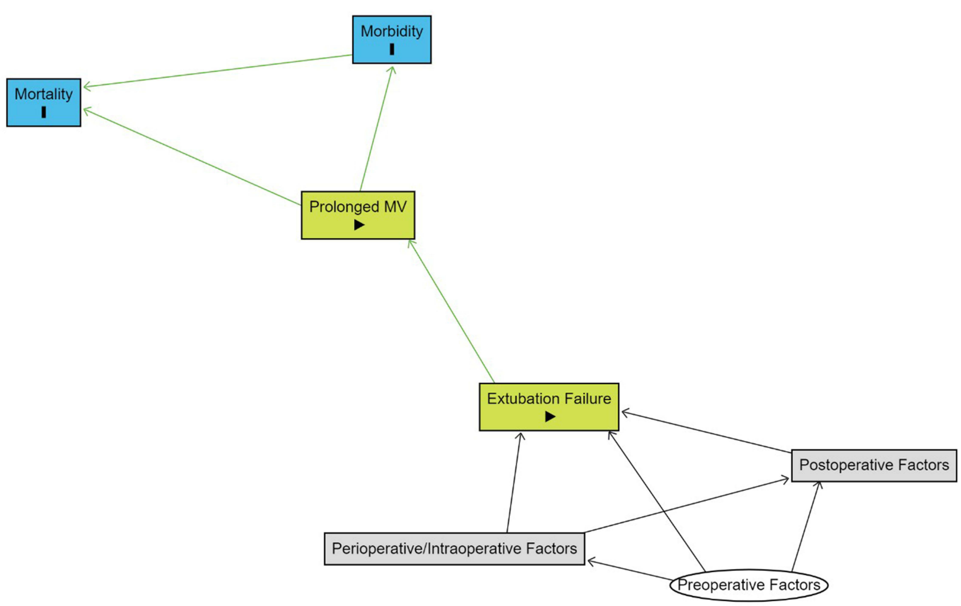

Figure 2 Directed Acyclic Graph (DAG) showing the relationships between the risk factors and patient outcomes (Morbidity and Mortality) in pediatric cardiac surgery patients.

need for reintubation within 48 hours of extubation, was compared within the group. Statistically, authors reported a lower rate of EF and a reduced length of stay in the treatment arm in the pediatric ICU.[75]

In cases where the causes of extubation can be isolated and assessed, specific therapies can be applied to manage EF and prevent PMV. For instance, diuretics and vasodilators may be used to stabilize patients where the cause of EF is cardiac failure before reattempting extubation.[76] Also, prophylactic administration of corticosteroids has been extensively studied as a preventative treatment for EF failure and reintubation in patients under MV.[77,78] Specifically, in a systematic review and meta-analysis of 10 randomized controlled trials including 591 subjects, Kiruma et al reported approximately a 40% reduction in the risk of EF in pediatric patients administered corticosteroids compared with standard care.[79] Indeed, other studies have also shown the benefit of corticosteroids in preventing extubation failure in neonates and adult patients on MV.[80,81] However, due to the reported side effects of corticosteroids,[82] it is crucial to consider the unique physiological parameters of individual patients and put in place a close monitoring protocol for the best outcomes.

Conclusion and Prospect

While fast weaning from mechanical ventilation is the preferred postoperative clinical course for pediatric cardiac surgery patients, extubation failure based on cardiac and noncardiac factors may result in a prolonged need for mechanical ventilation. Although more than 91% of these patients' population still survive following cardiac surgery, clinical complications are widely believed to be predictable, and while not controllable, they could help inform personalized and improved patient care in the future. Specifically, these factors could help inform patients of more appropriate timing for extubation and MV weaning. Also, while various studies have focused on the contributory effect of various associated factors, there is no evidence assessing the cumulative impact of the combination of these factors. Thus, this is a potential area that could be the focus of future research. Another area of potential research outputs is the need to establish causal inference between the risk factors reported in various studies (discussed above) and the incidence of complications (including mechanical ventilation and PMV) as well as risk of mortality. As most studies included are observational involving classic statistical measure of association, it is unclear whether the reported factors really drives the complications. Indeed, causal inference models have been employed in other surgical context[83] and could potentially broaden our understanding of the primary factors driving prognosis, with the potential to develop targeted interventions.[84]

Further, there is a need for unified protocols for MV weaning as well as establishing the timing of extubation to minimize EF and PMV pediatric patients following cardiac surgery for CCHD. Indeed, more work will need to be done to accumulate the required data for such a protocol; thus, becoming a cardiologist is an exciting time. Indeed, based on the history and the journey so far, cardiac surgery for pediatric CHD has developed significantly over the years. Moreover, it is safe to say that there will be more insights in the future as more technological advances in medicine and allied fields are made.

Disclosure

The author reports no conflicts of interest in this work.

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