Vessel Plus

Review

Pharmacologic therapies for the low cardiac output syndrome in children after cardiac surgery: evidence of their efficacy and trends in their use

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Abstract

The low cardiac output syndrome describes the phenomenon of the reduction of cardiac output that can occur following cardiac surgery requiring cardiopulmonary bypass. If unrecognized or untreated, this condition can result in significant morbidity and mortality. Along with non-pharmacologic therapies, pharmacologic agents used to help manage the low cardiac output syndrome include catecholamine inotropes, inodilators, systemic vasodilators, pulmonary vasodilators, and other classes of medications. We summarize the rationale and key evidence supporting the use of these therapies in children. In addition, utilizing provider surveys and registry reviews, we describe the current trends in the use of these medications and the variation demonstrated between providers and centers. Given the heterogeneous etiology of low cardiac output syndrome, successful management requires that pharmacologic therapies be tailored to the physiologic derangements of each patient.

Keywords: Cardiac surgery, low cardiac output syndrome, pediatrics, cardiac critical care

INTRODUCTION

The low cardiac output syndrome (LCOS) is generally described as the self-limited reduction of cardiac output that can occur in the first 24 h after cardiac surgeries requiring cardiopulmonary bypass (CPB). Although there is no strict, unified definition, the phenomenon is well recognized and described. The result

is an imbalance of oxygen delivery and oxygen consumption at the cellular level that may lead to oxygen debt and organ dysfunction. If unrecognized or untreated, this condition can result in significant morbidity and mortality[1].

Along with considerable advances in cardiac surgery and CPB over the past decades, the prevention and management of LCOS have evolved to include a vast array of pharmacologic and non-pharmacologic strategies to restore the balance between oxygen delivery and demand. Pharmacologic therapies for LCOS have generally included catecholamine inotropes, inodilators, and systemic vasodilators. In addition, various other medications have been used to manage LCOS in the postoperative period but are less commonly used. Finally, for medically refractory LCOS, mechanical circulatory support can be deployed. In this review for *Vessel Plus*, we hope to summarize high-level evidence (randomized control trials, meta-analyses, systematic reviews) supporting the use of these pharmacologic therapies to manage LCOS and to utilize extensive surveys and registry reviews to describe current trends in their use.

Pathophysiology

The LCOS is the result of multiple pathophysiologic processes that complicate cardiac surgery requiring CPB. Individual patient characteristics, pre-operative state, intraoperative management, residual anatomic lesions, abnormalities in rhythm, and the inherent inflammatory nature of CPB all contribute to the derangements in systemic and pulmonary vascular resistances, cardiac output, oxygen delivery, and alterations in oxygen demand and metabolism [Figure 1].

Pathologic alterations in cardiac loading conditions are the physiologic basis leading to the low cardiac output state. According to the Frank-Starling mechanism, diminished preload from hypovolemia, inflammation, or elevated filling pressures lead to reduced stroke volume. Respiratory abnormalities from pleural effusions, pneumothorax, or elevated airway pressure from mechanical ventilation have a deleterious effect on ventricular filling. Associated elevations in right ventricular afterload can complicate post-operative patient management, especially in those with right ventricular hypertrophy or dysfunction. Changes in pulmonary vascular resistance (PVR), systemic vascular resistance (SVR) after CPB, and specifically systemic hypertension, can decrease cardiac output after surgery. Furthermore, CPB stimulates vasopressin release, which increases SVR and can be deleterious to a dysfunctional systemic ventricle all leading to LCOS.

The exposure of blood to foreign antigens during CPB, along with hypothermia, myocardial ischemia, and reperfusion injury, can cause profound systemic inflammation[2,3]. Specifically, there are elevations in pro-inflammatory cytokines and activation of complement[4]. These are all associated with LCOS, increased ventilator time, and adverse neurologic outcomes[5,6]. In addition, there is also a hypermetabolic and catabolic state after surgery driving increased oxygen demand. Detailed reviews of the pathophysiology of LCOS have recently been well described by Epting *et al.*[7] and Bautista-Hernandez *et al.*[8].

Incidence

Parr and colleagues first described LCOS in 1975 when they observed patients with a cardiac index less than $2 L/min/m^2$ in approximately 25% of patients after congenital heart surgery requiring CPB[9]. In the decades to follow, similar estimates of LCOS incidence in children were obtained by Wernovsky *et al.*[10] and Hoffman *et al.*[11]. However, a more recent study by Du *et al.*[12] found a LCOS incidence of ~10% with a contemporary cohort of 8660 children treated at a single center. In this study, independent risk factors for LCOS development included age, CPB time, residual shunts, outflow tract obstruction for either the left ventricle (LV) or right ventricle (RV), and tricuspid and mitral regurgitation. These risk factors and other clinical parameters have been used to develop LCOS scoring systems to assess LCOS severity[13]. Therefore,
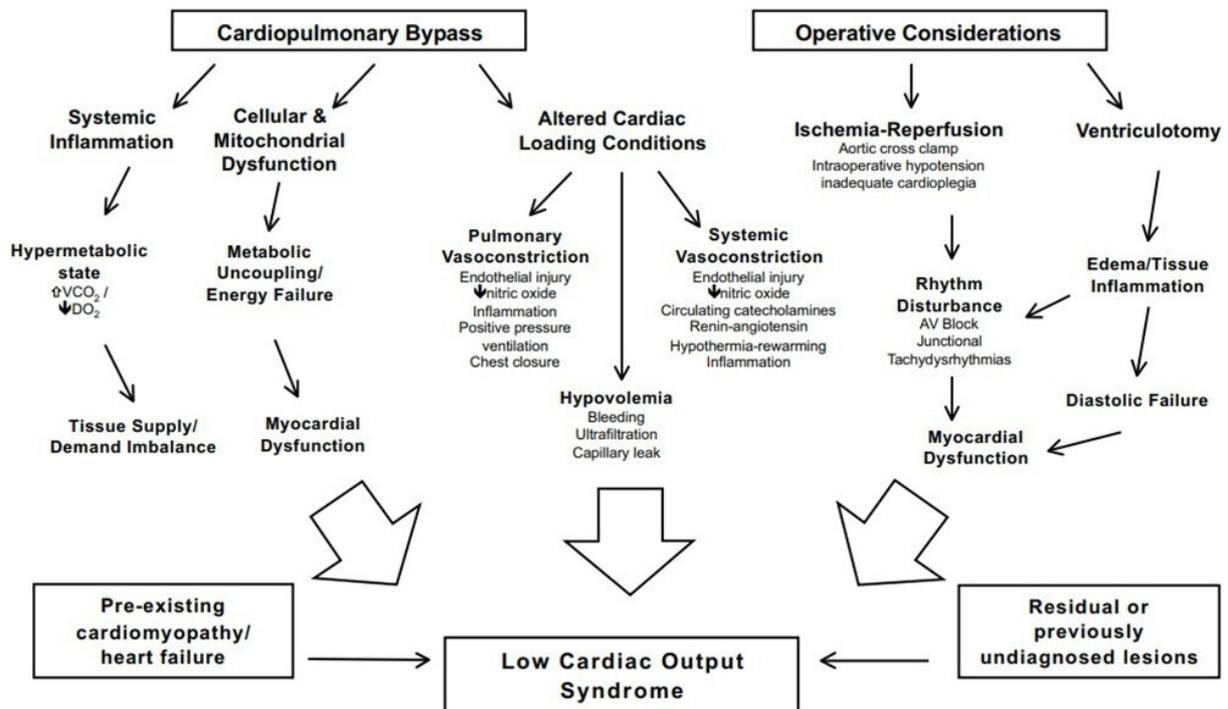
Figure 1. Perioperative factors leading to LCOS. Factors drivern by exposure to CPB (i.e., systemic inflammation, cellular & mitochondrial dysfunction, altered loading conditions) and those influenced by cardiac surgery (i.e., ischemia, ventriculotomy) are noted schematically contributing to LCOS. Reused with permission from Epting *et al.*[7] from Bentham Science Pulishers LTD. LCOS: Low cardiac output syndrome; CPB: cardiopulmonary bypass.

it is important to recognize and treat LCOS, as treatment may mitigate the associated morbidity and mortality after cardiac surgery[9]. Increased severity of LCOS has been specifically associated with increased duration of mechanical ventilation, intensive care unit (ICU) length of stay (LOS), and hospital LOS[13].

THERAPEUTIC OPTIONS FOR THE LOW CARDIAC OUTPUT SYNDROME

The fundamental principle guiding the management of LCOS is the maintenance of an appropriate balance between tissue oxygen delivery and demand. There exists a wide range of both invasive and non-invasive methods of monitoring patients for the development of LCOS and oxygen debt, and a detailed description is outside the scope of this article. However, once recognized, the general approach to LCOS management includes using means to increase oxygen delivery while reducing oxygen demand [Figure 2]. The pharmacologic augmentation of cardiac output is the most common method to improve oxygen delivery. Therapeutic agents that increase heart rate, improve contractility, or decrease afterload are commonly used. Optimizing preload to the heart is often the first-line approach, utilizing the Frank-Starling mechanism to improve stroke volume and cardiac output. Furthermore, maintaining atrioventricular synchrony and augmenting heart rate, either by pharmacologic therapies or temporary pacing, can also increase cardiac output and oxygen delivery. Normormthermia, mechanical ventilation, and sedation, with or without neuromuscular blockade, are common means in which to minimize patient effort and decrease oxygen demands. Although many simultaneous methods to manage LCOS are often deployed, we will summarize the evidence that supports the use of certain pharmacologic therapies and review trends in their utilization in the management of LCOS.
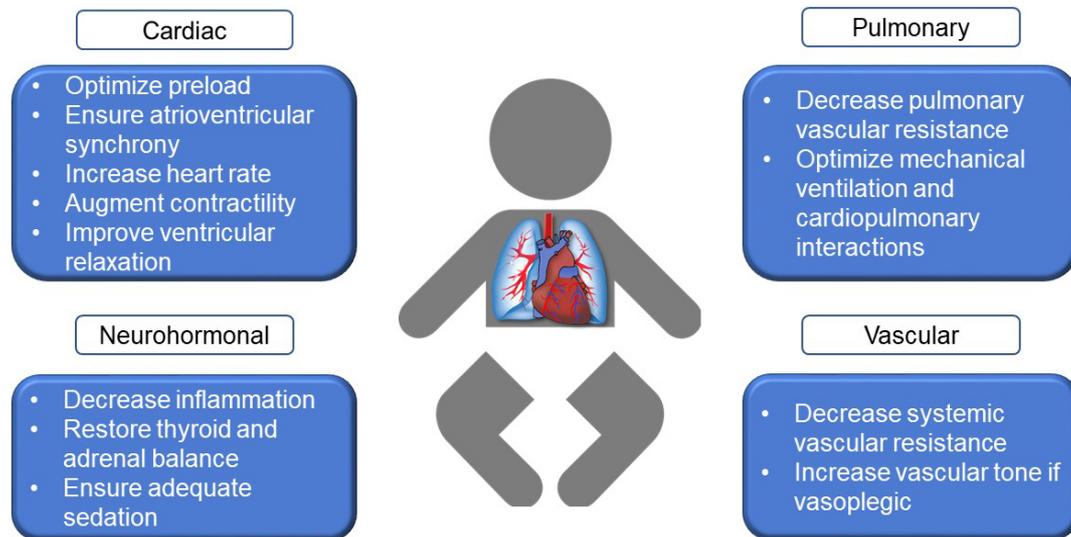
Cardiac
- Optimize preload
- Ensure atrioventricular synchrony
- Increase heart rate
- Augment contractility
- Improve ventricular relaxation

Pulmonary
- Decrease pulmonary vascular resistance
- Optimize mechanical ventilation and cardiopulmonary interactions

Neurohormonal
- Decrease inflammation
- Restore thyroid and adrenal balance
- Ensure adequate sedation

Vascular
- Decrease systemic vascular resistance
- Increase vascular tone if vasoplegic

Figure 2. Management strategies for the treatment of low cardiac output syndrome.

Catecholaminergic inotropes

Catecholaminergic inotropes such as epinephrine, dopamine, and dobutamine have long been used in the cardiac intensive care unit as pharmacologic means to manage LCOS by augmenting cardiac output. They predominantly activate β-1, β-2, α-1, and dopaminergic receptors. β-1 stimulation increases contractility through the binding of the actin-myosin complex with troponin C and enhances chronotropy through calcium channel activation. β-2 stimulation leads to increased calcium uptake by the sarcoplasmic reticulum leading to vasodilation. Activation of α-1 receptors on arterial vasculature results in smooth muscle contraction and increases in SVR. The relative affinity of the different catecholamines for the adrenergic receptors are dose-dependent, vary from drug to drug, and thus are employed to meet specific physiologic goals. In general, these agents increase contractility and stroke volume and are widely available. However, the adverse effects of catecholamines are relatively universal in their resultant tachycardia, raised ventricular end-diastolic pressures, and increased myocardial oxygen demand. Furthermore, the elevation of the SVR, PVR, or provocation of tachyarrhythmias by these agents can inadvertently cause or exacerbate LCOS. In a recent survey of cardiac intensivists, epinephrine and dopamine were the most common agents in this class used to prevent or treat LCOS, and these medications are most commonly started while on or coming off CPB[14]. However, in a recent Pediatric Health Information System (PHIS) database review of over 43,000 cardiac surgeries in children, the frequency of use of catecholaminergic inotropes has decreased in the past ten years[15]. This is likely due to our better understanding of LCOS and the more recent emphasis on reducing RV and LV afterload as alternative means to improve oxygen delivery.

Inodilators

Inodilators are medications that have inotropic and lusitropic effects on the myocardium and vasodilatory effects on the systemic, pulmonary, and coronary vasculature. Milrinone and levosimendan are the most commonly used medications in this category. Levosimendan, a calcium sensitizer, binds troponin C, increasing its affinity for calcium and increases inotropy without increasing myocardial oxygen demand. Its effects are independent of β-adrenergic receptors, and thus its use has a minimal incidence of arrhythmias. The most commonly reported side effects are headache, hypotension, and hypokalemia. The efficacy and safety of levosimendan are well reported in adults, but the pediatric literature is sparse and is limited to observational studies, registry studies, and few randomized control trials (RCT). In a study of 40 infants undergoing surgery with CPB managed with either levosimendan or milrinone, Lechner *et al.*[16]

demonstrated that the levosimendan group had improvements in cardiac output and cardiac index. However, inotropic score, lactate levels, and ICU LOS were unchanged between groups. Using post-operative lactate as a surrogate marker of cardiac output, Momeni *et al.*[17] describe equal efficacy of milrinone and levosimendan in a cohort of 41 children following cardiac surgery; however, because of the high cost and lack of Food and Drug Association approval, levosimendan is not at this time widely used for the management of LCOS in the United States[14].

Milrinone has been studied extensively in children after surgery requiring CPB. Milrinone inhibits phosphodiesterase type 3 leading to an increasing concentration of intracellular cAMP, resulting in increased myocardial contractility. It also accelerates the removal of calcium from the cytosol, allowing more time for myocardial relaxation, thus its lusitropic effect. In addition, its effect on cGMP in the peripheral and coronary smooth muscle cells leads to smooth muscle vasodilation. These simultaneous changes improve myocardial performance without increasing myocardial oxygen demand, and thus milrinone has many advantageous properties. Many studies have reported the positive hemodynamic effects of milrinone in children after cardiac surgery. Most importantly, in the double-blind, placebo-controlled RCT PRIMACORP study, Hoffman *et al.*[11] demonstrated that high dose milrinone significantly reduced LCOS incidence without increases in adverse events. Since that landmark study, milrinone has become a widely used pharmacologic agent to prevent and treat LCOS in children. However, a 2015 Cochrane review concluded there was insufficient evidence of the effectiveness of prophylactic milrinone in preventing death or LCOS in children undergoing surgery for congenital heart disease[18]. Nonetheless, in a recent Pediatric Cardiac Intensive Care Society (PCICS) provider survey, 97% of respondents stated their center routinely uses milrinone to prevent or treat LCOS after CPB[14].

Systemic vasodilators

The purpose of using systemic vasodilators in managing LCOS is to increase stroke volume, cardiac output, and delivery of oxygen to the tissues while decreasing myocardial oxygen demand. Several medications in this class have been trialed in the treatment of LCOS, including systemic nitric oxide donors, natriuretic peptides, and α-antagonists. Sodium nitroprusside releases nitric oxide from vascular endothelial cells leading to systemic vasodilation. Appelbaum *et al.*[19] first described the use of nitroprusside after cardiac surgery and found a 17% increase in cardiac index. Similarly, the nitro-vasodilator nitroglycerine activates cGMP leading to vasodilation of the systemic arterioles and venules. However, due to its preferential effects on the venodilatory properties, it has been found to be less effective in vasodilation compared to nitroprusside[20]. The selective calcium channel blocker nicardipine has also been found to be safe and effective when treating postoperative systemic hypertension, even in children < 6 months of age[21]. Nesiritide, a recombinant form of brain natriuretic peptide, induces smooth muscle relaxation and mitigates the effect of vasopression, leading to vasodilation and promoting diuresis. Although initial adult studies of nesiritide use were associated with improved outcomes after cardiac surgery, subsequent more robust studies and a pooled analysis of RCTs failed to do so[22-24]. Phenoxybenzamine has also been used to block α-1 and α-2 receptors, relax the smooth muscle of systemic vasculature and increase cardiac output. Tweddell *et al.*[25] demonstrated an association between improved mortality and the use of phenoxybenzamine in infants with hypoplastic left heart syndrome after stage 1 palliation, thought to be attributed to reduced SVR, reduced fluctuation in systemic venous and arterial saturation, and improved balance of pulmonary to systemic ratio and delivery of oxygen. However, according to an international survey by Roeleveld and de Klerk[14], pure systemic vasodilators are not often used as first-line therapy for LCOS, except for patients with single ventricle circulation, where nitroprusside is the most commonly used agent.

Pulmonary vasodilators

Increases in PVR after CPB are one of the pathophysiologic mechanisms believed to contribute to LCOS development, and children with preoperative left-sided obstructive lesions and those with left to right shunts are at higher risk of elevated PVR following bypass. Cardiopulmonary bypass causes inflammation that inhibits nitric oxide production and increases the production of endothelin-1. Thus, inhaled nitric oxide (iNO) and its precursors have been trialed to treat or prevent LCOS. Inhaled nitric oxide is a selective pulmonary vasodilator with little effect on the systemic vasculature. Miller *et al.*[26] performed a prospective, double-blind RCT of iNO in 124 infants at risk for pulmonary hypertension (PH) and found that iNO reduced indexed PVR, number of PH crises, and proportion of patients mechanically ventilated at 7 days. In addition, a recent RCT of prophylactic iNO demonstrated a reduction in the incidence of LCOS and the need for ECMO, most markedly seen in children < 2 years of age, and after highly complex surgeries[27]. Another pulmonary vasodilator, the aerosolized prostacyclin iloprost, and iNO were found to be comparable in increasing cardiac output and decreasing pulmonary artery pressures[28]. However, in a study by Wong *et al.*[29] reviewing the PHIS database, of 1678 surgeries performed on patients with known PH, iNO was used only 11.6% of the time, and its use was associated with increased cost and LOS, with no improvement in mortality. Citrulline, a precursor to nitric oxide, has also been trialed to reduce LCOS incidence and improve outcomes but has not been shown to decrease PH episodes significantly[30]. Other inhaled agents such as sildenafil, milrinone, and prostaglandin have also been used for PH but less frequently for LCOS. At this time, there is insufficient data to support the routine use of pulmonary vasodilators such as iNO, as a Cochrane systematic review did not find differences in mortality or many secondary outcomes with its use[31]. However, to better investigate the utility of iNO to increase survival and ventilator-free days after CPB, the multicenter, randomized, double-blind NITric trial is currently underway[32].

ADJUNCTIVE THERAPIES FOR THE LOW CARDIAC OUTPUT SYNDROME
Corticosteroids

Cardiopulmonary bypass is known to cause an inflammatory cascade that is believed to contribute to LCOS and postoperative morbidity. Hence, anti-inflammatory therapy with corticosteroids has been extensively studied for those undergoing cardiac surgery requiring CPB[33,34]. In addition, several studies have investigated the cellular mechanisms whereby corticosteroid supplementation may be beneficial[34,35]. However, a recent meta-analysis of 17 RCTs and 848 pediatric patients by Li *et al.*[36] in 2020 concluded that children receiving corticosteroids did not have a reduction in all-cause mortality compared to controls. They did have a significant reduction in vasoinotropic score but had no significant improvement in other secondary outcomes such as ICU LOS, duration of mechanical ventilation, serum lactate, or incidence of LCOS, among others. A recent two-center RCT also failed to show a significant overall benefit in a mortality-morbidity composite index but did similarly demonstrate a reduction in vasoactive requirements[37]. However, despite the results of this recent meta-analysis and several RCTs, a survey of 188 PCICS members from 85 centers found that 94% of survey respondents reported that they sometimes or always administer corticosteroids for patients with moderate or severe LCOS, with hydrocortisone being the most commonly used agent[38]. To better understand the utility of corticosteroids for children undergoing cardiac surgery with CPB, the currently ongoing multicenter, placebo-controlled STRESS trial is investigating the efficacy and safety of methylprednisolone administration and its association with major outcomes, including mortality, morbidity, and ventilator time[39].

Thyroid hormone replacement

Another class of medication that has been trialed in the management of LCOS over the past few decades is thyroid hormone replacement therapy. It has been shown that triiodothyronine (T3) levels decrease in infants and children after CPB[40]. Given the important role of thyroid hormone in metabolism, it was

postulated that T3 repletion could improve patient outcomes after cardiac surgery. In a pilot RCT performed by Mackie *et al.*[41], continuous T3 infusions were associated with a significant reduction in the time to negative fluid balance, without significant increases in cardiac index. In the OTICC RCT of 208 patients under three years of age, the incidence of LCOS was lower in those receiving the oral T3 group compared to placebo[42]. The more comprehensive TRICC RCT included 193 children under two years of age undergoing surgery with CPB. Although overall, there was no significant difference in time to extubation between the T3 replacement and placebo groups, subgroup analysis demonstrated improved time to extubation and extubation success rate for children less than five months of age receiving T3[43]. Similar improvements with T3 administration in children less than five months of age were found by Marwali *et al.*[44]. However, in a 2019 meta-analysis by Flores *et al.*[45], although there was a significant reduction in the mean inotropic score for those receiving some form of T3, there was no difference in any other significant outcomes, including ventilator time, ICU LOS, hospital LOS, or mortality.

Vasopressin and norepinephrine
Vasopressin and norepinephrine have been used in the management of patients with LCOS and vasoplegia. Although increases in SVR can lead to a decrease in cardiac output, they can be used to maintain adequate perfusion pressures for vital organs such as the brain and kidneys. The use of arginine vasopressin, the stimulant of the V1 receptor, has been shown to decrease the need for fluid resuscitation and inotropic support. However, it has not been found to be associated with significant improvements in major outcomes like ICU LOS or duration of mechanical ventilation[46]. Interestingly, for patients undergoing the Fontan procedure, transpulmonary gradient and chest tube drainage were significantly lower in the vasopressin group compared to placebo[47]. Norepinephrine has been used for patients with LCOS and low systemic vascular resistance, but less commonly than epinephrine and vasopressin[48]. Finally, in a recent review of the PHIS database by Loomba and Flores[15], while the use of catecholaminergic inotropes and vasopressors after cardiac surgery have decreased over the past ten years, the use of vasopressin has increased.

Extracorporeal life support
There is, unfortunately, a subpopulation of children who experience prolonged or severe LCOS refractory to medical management who may require short or long-term mechanical circulatory support (MCS). Early recognition of the failure of medical management for LCOS is important so that MCS can more safely be deployed prior to cardiac arrest. Extracorporeal membrane oxygenation is a commonly used and widely available therapy for prolonged or medically refractory LCOS[49]. A 2014 analysis of the Society for Thoracic Surgeons database found that 2.4% of all surgical patients are placed on postoperative MCS, and 95% of the cases utilized extracorporeal membrane oxygenation as the MCS strategy[50]. Unfortunately for those needing postoperative MCS, the mortality remains dauntingly high, with rates up to ~65%[51].

CONCLUSION

The management of low cardiac output syndrome after pediatric cardiac surgery is evolving, and new pharmacologic therapies continue to emerge with ongoing research. At this time, there is insufficient evidence to support a single pharmacologic agent as the universal best therapy for the prevention or treatment of low cardiac output syndrome. Database reviews and surveys demonstrate that milrinone, epinephrine, and dopamine are the most commonly used pharmacologic therapies, but there remains substantial provider and center variability in the approach towards the management of these patients. Therefore, rigorous multicenter studies with granular data are needed to help providers tailor specific pharmacologic therapies to best support each critically ill child.

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