

Protocol for Echocardiography Screening of Extremely Low Birth Weight Infants in the Transitional Period

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Rationale. The transitional period represents a high-risk period for extremely premature infants because it is characterized by dramatic changes in cardiorespiratory physiology, attributable to either the natural history of illness or necessary life saving treatments during this period, which may be variably tolerated. In addition, the preterm germinal matrix is highly vulnerable to dramatic changes in ambient physiology which may lead to acute hemorrhage. Recent observational studies have demonstrated that severe intraventricular hemorrhage (IVH) is preceded by an initial period of low cardiac output followed by augmentation in left ventricular output; therefore, it has been hypothesized that ischemia-reperfusion injury is a plausible mechanism by which IVH occurs^{1, 2}. The presence of a hemodynamically significant ductus arteriosus in the transitional period has been associated with a rapid augmentation of left ventricular output and may, therefore play a role in creating the ambient conditions which are high risk for IVH. The presence of a large PDA on day 3 is associated with a two-fold increased risk of mortality and six-fold increased risk of IVH.³ The reduction in grade III/IV IVH following prophylactic indomethacin therapy lends additional support to this argument.⁴ The lack of improvement in neurodevelopmental outcome may relate to unintended PDA closure in the setting of pulmonary hypertension or heart dysfunction, or the administration of indomethacin to patients where natural PDA closure occurs. In these situations, the risk-benefit profile is shifted towards the adverse effects of treatment. Data from the Epipage study demonstrated that centers which practiced early screening echocardiography and targeted PDA treatment had lower mortality.⁵ Comprehensive evaluation of PDA shunt volume during the first 72 hours of life enables earlier identification of patients at greatest risk of chronic lung disease and adverse outcome.⁶

Early diagnosis and therapy may also modify the risk of other physiological disturbances. Patent ductus arteriosus is associated with increased pulmonary blood flow⁵ and patients treated with targeted indomethacin for a persistent large ductus arteriosus at 6h postnatal age has been associated with a lower risk of pulmonary hemorrhage.^{7, 8} Additionally, persistent ductal shunt during the first postnatal week has been associated with abnormal cardiac adaptation^{9, 10}, impaired mesenteric tissue oxygenation with limited ability to increase post-prandial blood flow¹¹ and impaired pulmonary compliance.¹² Several neonatal morbidities have been associated with prolonged ductal shunt including chronic lung disease¹³ and necrotizing enterocolitis.^{14, 15}

Aim. The aim of this quality improvement guideline is to provide a systematic approach to the diagnosis and therapy of patent ductus arteriosus during the transitional period.

Qualifying Neonates. All preterm infants born < 27 week's gestation [inborn or outborn] qualify for a targeted neonatal echocardiogram and simultaneous head ultrasound between 18 and 36h postnatal age. The duration of the evaluation will be ~20 minutes. A report will be generated including an assessment of myocardial performance, pulmonary and systemic blood flow and ductal shunt (if applicable). A comprehensive set of recommendations for hemodynamic management will be provided and may be implemented at the discretion of the treating physician. Ductal treatment using acetaminophen 15mg/kg Q6h PO or IV acetaminophen 0.2/0.1/0.1 mg/kg x 3 days followed by re-evaluation will be recommended if:

- Ductal diameter is > 1.5mm AND
- Predominant (>90%) left-to-right transductal flow AND
- PDA shunt volume score is ≥ 6

Table 1: PDA shunt volume score

	0 points	1 point	2 points
Mitral E (cm/s)	< 45	45-80	>80
IVRT (ms)	>50	30-50	<30
PV D wave (cm/s)	<0.3	0.3-0.5	>0.5
LA:Ao	<1.3	1.3-2.2	>2.2
LVO (ml/min/kg)	<250	250-430	>430
Descending aortic flow AND/OR celiac/middle cerebral artery	Forward		Reversed

Adapted from ^{16,17}

Contra-indications

1. Moderate-severe left or right ventricular dysfunction
2. Echocardiography consistent with acute pulmonary hypertension
3. No contra-indication to Acetaminophen treatment
4. Congenital Heart Disease

Pre-existing intraventricular hemorrhage does not disqualify neonates from Tylenol therapy for a hemodynamically significant ductus as reduction in shunt may modulate the extent of the injury and may, theoretically, have other benefits such as on chronic lung disease.

Concurrent Management. Ductal shunt is dependent on multiple factors as governed by Poiseuille’s law which determines the volume of flow through a tube. Poiseuille’s Law is:

$$\text{Flow} = \frac{\pi P r^4}{8 \eta l}$$

P is the pressure gradient across the tube (the difference between systemic and pulmonary arterial pressure), r is the diameter of the tube, η is the viscosity of the fluid (determined, in part, by cellular components of blood – RBCs, platelets) and l is the length of the tube. Shunt through the ductus arteriosus may, therefore, be modulated by optimizing these factors.

The pressure gradient may be optimized by creating ambient conditions whereby pulmonary vascular resistance is maintained sufficiently low to ensure oxygenation but sufficiently high to limit the volume of pulmonary blood flow across the ductus arteriosus. This can be done in the following ways:

- Avoid nitric oxide administration in the setting of a significant ductus; infants already on iNO at the time of screening should be weaned off iNO over 12h and echo assessment repeated prior to Tylenol therapy to ensure no residual pulmonary hypertension.
- Maintain permissive hypercapnia [CO₂ target 50-60]
- Avoid excessively high saturations and minimize exogenous oxygen administration
- Use PEEP to tamponade flow

Additionally, there is some evidence to suggest that platelet count may influence efficacy of pharmacologic therapy.^{18, 19} Anemia should also be avoided as low oxygen carrying capacity is associated with increased cardiac output (hence greater flow through the ductus provided the pressure gradient remains unchanged) and lower blood viscosity which may both exacerbate shunt.

Fluid restriction is not recommended as a method of modulating shunt. Its efficacy is limited and lower overall fluid intake leads to lower cardiac output which is associated with a greater risk of compromised post-ductal circulation without change in shunt.²⁰ Diuretics, particularly furosemide, are not recommended in the setting of a hemodynamically significant ductus arteriosus for the same reason as fluid restriction. Additionally, one of the downstream actions of furosemide is the upregulation of prostaglandin E production in the kidney and its release into circulation.²¹ This may have a negative impact on the efficacy of ductal

closure strategies and has been associated with both increased risk of persistent ductal shunt and re-manifestation of the ductus arteriosus after previously documented functional closure.²²

Management of Mild Cardiac Dysfunction. Identification of cardiac dysfunction on screening echocardiography should be considered within the clinical context. Mild cardiac dysfunction without clinical symptoms may not require treatment. If treatment is clinically indicated, dobutamine at a starting dose of 2.5-5mcg/kg/min is the recommended first line agent. Low starting dose is suggested to avoid the risk of rapid augmentation in cardiac output and associated risk of reperfusion injury. There is no evidence to suggest interaction between hydrocortisone and acetaminophen and therefore concurrent hydrocortisone should be at the discretion of the attending physician.

Monitoring for Morbidities. The incidence of spontaneous intestinal perforation will be tracked and compared to a historical cohort. An increase in the rate of spontaneous intestinal perforation by > 25% over the 6-month period following the implementation of this guideline will prompt a thorough review of all extremely preterm infant morbidities/mortality during the period of time following this practice change as compared to a historical cohort including intraventricular hemorrhage, retinopathy of prematurity, patent ductus arteriosus ligation and chronic lung disease. All patients will be screened for intraventricular hemorrhage at the time of echocardiography and concerning findings will be reported to the clinical team. A formal head ultrasound will be recommended to document any abnormal or suspect findings on screening exam.

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