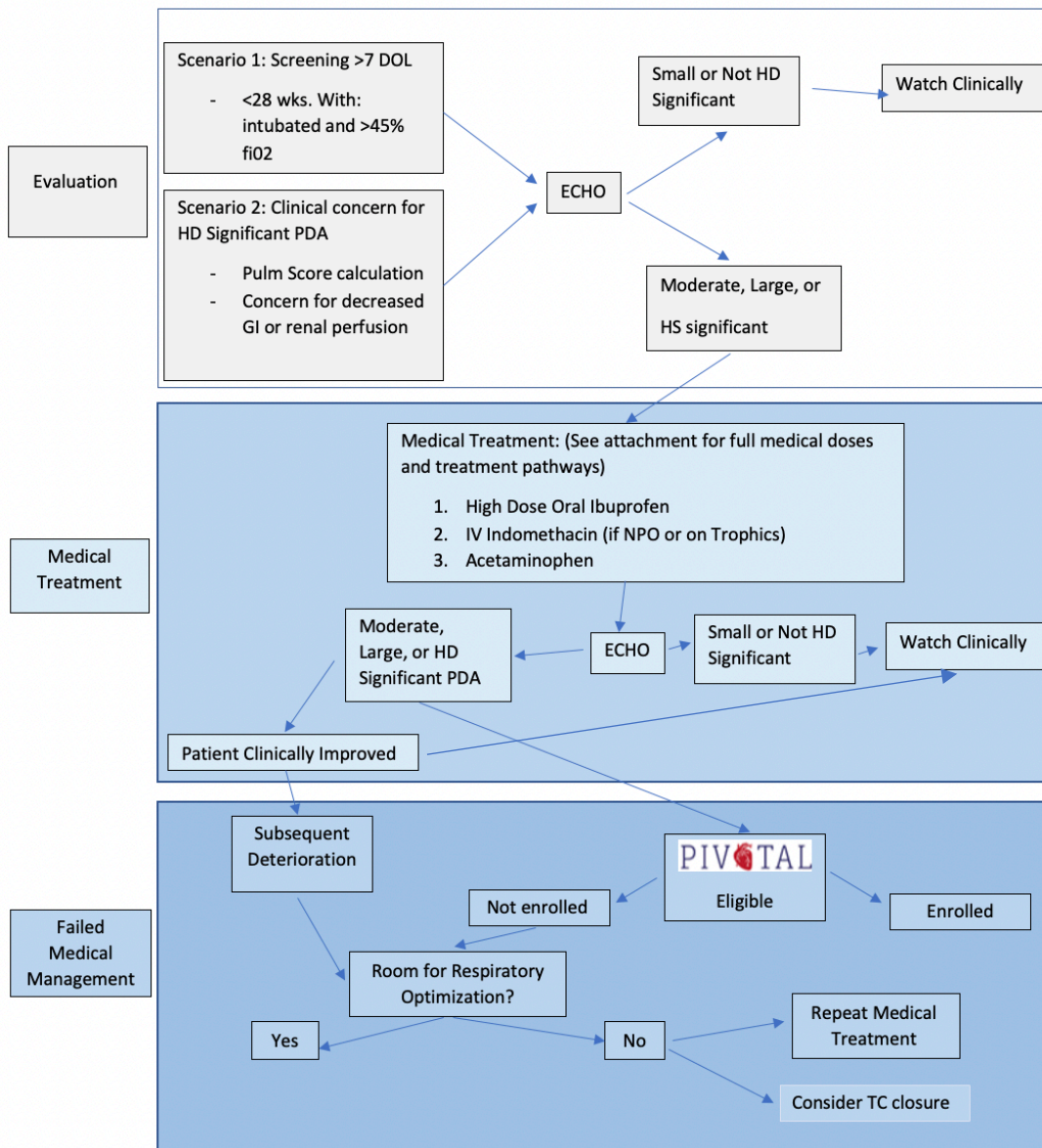


Patent Ductus Arteriosus Management Guideline



Background

The patent ductus arteriosus (PDA) is commonly observed in extremely preterm infants with an incidence as high as 50% [1]. The complications arising from a PDA in preterm infants include pulmonary hemorrhage, congestive heart failure, exacerbation of bronchopulmonary dysplasia and pulmonary hypertension. Since the first reported case of a PDA ligation by Dr. Robert Gross 80 years ago in 1938, PDA closure by medical (prophylactic and therapeutic) and surgical techniques has been in vogue.

The effectiveness of medical therapy is at best 50%–70% (lower for those <32 weeks' gestation), and can lead to transient alterations in renal function, necrotizing enterocolitis (NEC), gastrointestinal perforation and impairment of cerebral blood flow velocity [2, 3].

In recent years, surgical ligation using a minimally invasive thoracoscopic approach has shown fewer surgical complications,[4] while a percutaneous catheter closure by venous access in preterm infants weighing as little as 600 grams show promising treatment options [5-11].

With the advent of small occlusive devices, more and more centers are closing the PDA in extremely low birth weight infants by interventional catheterization techniques. Long-term risks and benefits of this technique are not, yet, known.

In the current protocol, we propose to identify newborns in the NICU at highest morbidity risk from a PDA that may benefit from transcutaneous PDA closure (TCPC).

The pulmonary score and the echocardiogram findings will be the primary determinants of treatment eligibility. Data on biomarkers, regional oxyhemoglobin saturations (by near-infrared spectroscopy [NIRS]) and physical examination will, also, be used to identify and monitor the hemodynamically significant PDA and to assess treatment response.

Pulmonary Hypertension Score Calculation: $(FIO_2)(\text{Resp support}) + (\text{med score})$

Calculating the Pulmonary Score:

- In the STOP-ROP study, a pulmonary score was developed by three neonatologists to evaluate the baseline pulmonary status of the infants at the time of randomization [12]. The score is calculated as:
 - $(FIO_2)(\text{Respiratory support}) + (\text{medication score})$
- where FIO_2 is expressed as a fraction; support = 2.5 if on ventilator, 1.5 if on less invasive ventilation, and 1.0 if on nasal cannula, or no support (Table). A median score of 0.48 has been associated with a higher risk of pulmonary morbidity [13]. A recent retrospective study comparing surgical ligation and TCPC (mean weight 1330 g [range 1000 -1980 g]) has shown a faster improvement in respiratory status using the pulmonary score following TCPC [11].

Formula = (Respiratory support × FiO₂) + Medication (Weighted Sum)

Respiratory support	FiO ₂	Medication (Weighted Sum)
Mechanical ventilation = 2.5 points	0.21–1	Sistemic steroids = 0.2 points
Non-Invasive ventilation (CPAP/BIPAP) = 1.5 points		Regular diuretics or inhaled steroids = 0.1 points.
Nasal cannula or non-oxygen = 1 point		Methylxanthines or intermittent diuretics = 0.05 points

- *See appendix tables in ref [13] to determine effective FIO₂. Table adapted from ref [11]
- Example 1: intubated on FIO₂ 0.25 and caffeine has score of (2.5)(0.25) + 0.05 = 0.675
- Example 2: CPAP on 30% O₂ on diuretics and caffeine yields (1.5)(0.3) + (0.1+0.05) = 0.6
- *any flow > 2 L/min in patient < 2 Kg has an effective FIO₂ that is equal to the administered FIO₂ (using the appendix tables from ref [13]). Therefore a 1.2 kg baby on 4 L/min on 40% O₂ on caffeine yields (1)(0.4) + 0.05 = 0.45

Echocardiographic Findings

UC Davis PDA echo protocol:

- a. Ductal shunt flow, bidirectional or predominantly left to right
- b. LA/Ao ratio ≥ 1.5
- c. Ductal diameter ≥ 1.5 mm
- d. LV dimension index > 2.0 Z score

UC Davis Quantification or Grade of PDA size (assuming normal sized branch pulmonary arteries)

- None - Not detected despite standard imaging
- Trivial - Unable to be measured despite clear 2D / greyscale imaging
 - Only able to see faint left to right color shunt
 - No left heart enlargement
- Small - <33% diameter of branch pulmonary arteries
- Moderate - 33-66% diameter of branch pulmonary arteries
- Large - 66-100% diameter of branch pulmonary arteries

As a general rule of thumb:

1 kg weight and 35 cm length - infant's BSA is 0.1 m ²			
RPA diameter *		LPA diameter *	
Minimum	0.19 cm	Minimum	0.18 cm
Median	0.36 cm	Median	0.35 cm
Maximum	0.53 cm	Maximum	0.52 cm

* Boston z-score regression tables

3.5 kg weight and 50 cm length infant's BSA is 0.22 m ² (average term)			
RPA diameter *		LPA diameter *	
Minimum	0.35 cm	Minimum	0.33 cm
Median	0.53 cm	Median	0.52 cm
Maximum	0.72 cm	Maximum	0.71 cm

* Boston z-score regression tables

Near-Infrared Spectroscopy (NIRS)

There have been inconsistent reports in the literature on the benefits in using regional oxyhemoglobin saturation measurements (RSO₂) to determine hemodynamic significance of the PDA or the effects of indomethacin and surgical ligation on RSO₂ [15-18]. A recent study in extreme premature infants did not show a difference in cerebral and renal NIRS in infants with a closed duct and those with an open duct [19]. Furthermore, retrograde blood flow as demonstrated on echocardiogram did not affect cerebral and renal NIRS measurements [19]. There are currently no studies that have reported the use of NIRS in patients that have had TCPC.

Inclusion Criteria for Considering Medical / Catheter based therapy for PDA:

Infants ≤ 28 weeks gestation and/or ≤ 1250 g are eligible for inclusion.

Infants that have a pulmonary score ≥ 0.5 with

- (1) intubated patient
- (2) patients on less invasive ventilation [NIPPV/NCPAP] receiving ≥ 30% O₂
- (3) patients on HFNC ≥ 4 L/min and ≥ 45% O₂) on post-natal days 5-7 will have a first echocardiographic assessment.

Evidence of a moderate-to-large duct in the setting of a pulmonary score ≥ 0.5 would indicate a hemodynamically significant PDA (hsPDA) and qualify for treatment.

Biomarkers, physical exam findings, need for vasoactive cardiac support and NIRS measurement will provide additional information on severity of the hsPDA and guide treatment option.

Dosage for Medications:

- **High Dose Oral Ibuprofen:** 15-20mg/kg Loading dose followed by 7.5-10mg/kg q24h for 2 additional doses (total 3 doses)*
- **IV Indomethacin:** 0.2mg/kg at 0, 12, 24 and 48h (total 4 doses)*
- **Acetaminophen** if others contraindicated: 15mg/kg q6h x5-7d

*Notes: Consider checking Platelets and Creatinine before initiation of Ibuprofen or Indomethacin. Platelets should be >50 and Creatinine <1.3 to initiate treatment with an NSAID

Feeds:

- PDA's that are NOT hemodynamically Significant: Enteral Feeds as Tolerated
- PDA's that ARE hemodynamically Significant:
 - o If tolerating feeds, may consider continuing current feeding plan
 - o If having feeding intolerance: Recommend not more than Trophic Feeds (10-20ml/kg/day of BM) while on medical therapy or awaiting follow up imaging.

Appendix:

Effective FiO₂ calculations (from Madan et al):

TABLE A1. Factor as a Function of Flow and Weight

Flow, L/min	Weight, kg										
	0.7	1.0	1.25	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.5
0.01	1	1	1	1	1	0	0	0	0	0	0
0.03	4	3	2	2	2	1	1	1	1	1	1
0.06	9	6	5	4	3	2	2	2	2	1	1
0.15	21	15	12	10	8	6	5	4	4	3	3
0.25	36	25	20	17	13	10	8	7	6	6	5
0.50	71	50	40	33	25	20	17	14	13	11	9
0.75	100	75	60	50	38	30	25	21	19	17	14
1.00	100	100	80	67	50	40	33	29	25	22	18
1.25	100	100	100	83	63	50	42	36	31	28	23
1.50	100	100	100	100	75	60	50	43	38	33	27
2.00	100	100	100	100	100	80	67	57	50	44	36
3.00	100	100	100	100	100	100	100	86	75	67	55

Factor = $100 \times \min(1, \text{L/min per kg})$. The table is adapted from equations 3 and 4 in ref 14. Benaron and Benitz¹⁴ assumed that there is a constant nasal flow over the inspiratory cycle and the upper airway does not act as a reservoir. Additional assumptions for STOP-ROP infants include the following: inspiration time = 0.3 seconds; tidal volume = 5 mL/kg body weight. Either inspiration is entirely nasal or cannula flow is low enough so that, in each inspiration, the infant inhales all output from the cannula. (For most STOP-ROP study infants, if flow [L/min] exceeds body weight [kg], then effective FiO₂ equals the nasal cannula oxygen concentration.)

TABLE A2. Calculation of Effective F_{IO_2}

Factor	Oxygen Concentration, %						
	21	22	25	30	40	50	100
0	21	21	21	21	21	21	21
1	21	21	21	21	21	21	22
2	21	21	21	21	21	22	23
3	21	21	21	21	22	22	23
4	21	21	21	21	22	22	24
5	21	21	21	21	22	22	25
6	21	21	21	22	22	23	26
7	21	21	21	22	22	23	27
8	21	21	21	22	23	23	27
9	21	21	21	22	23	24	28
10	21	21	21	22	23	24	29
11	21	21	21	22	23	24	30
12	21	21	21	22	23	24	30
13	21	21	22	22	23	25	31
14	21	21	22	22	24	25	32
15	21	21	22	22	23	25	33
17	21	21	22	23	24	26	34
18	21	21	22	23	24	26	35
19	21	21	22	23	25	27	36
20	21	21	22	23	25	27	37
21	21	21	22	23	25	27	38
22	21	21	22	23	25	27	36
23	21	21	22	23	25	28	39
25	21	21	22	23	25	28	41
27	21	21	22	23	25	29	42
28	21	21	22	24	26	29	43
29	21	21	22	24	27	29	44
30	21	21	22	24	27	30	45
31	21	21	22	24	27	31	47
33	21	21	22	24	27	31	47
36	21	21	22	24	28	31	49
38	21	21	23	24	28	32	51
40	21	21	23	25	29	33	53
42	21	21	23	25	29	33	54
43	21	21	23	25	29	33	55
44	21	21	23	25	29	34	56
50	21	21	23	25	30	35	60
55	21	22	23	26	31	37	64
57	21	22	23	26	32	38	66
60	21	22	23	26	32	38	68
63	21	22	24	27	33	39	71
67	21	22	24	27	34	40	74
71	21	22	24	27	34	42	77
75	21	22	24	28	35	43	80
80	21	22	24	28	36	44	84
83	21	22	24	28	37	45	87
86	21	22	24	29	37	46	89
100	21	22	25	30	40	50	100

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