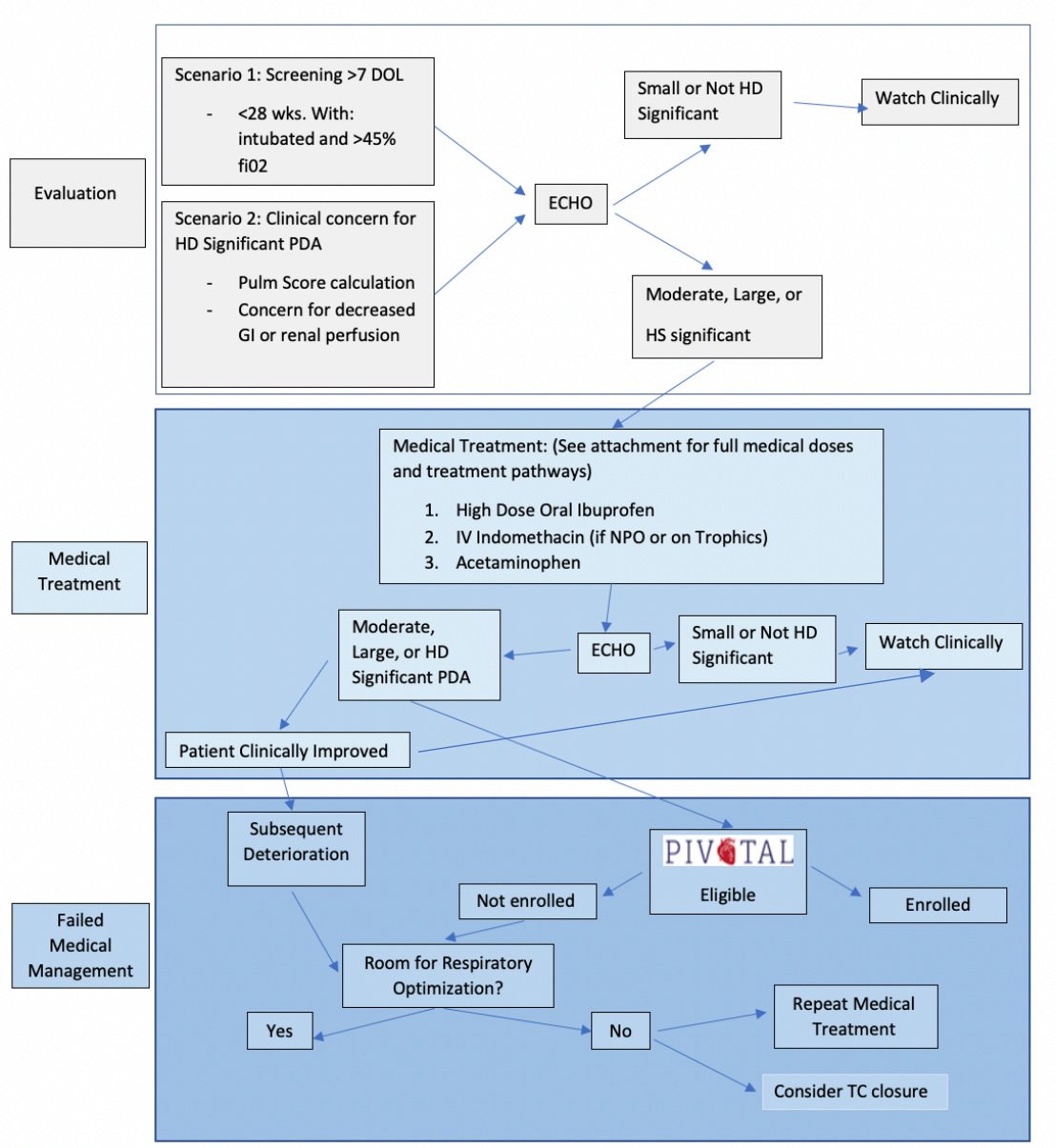
UC DAVIS HEALTH | CHILDREN'S HOSPITAL

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)(Resp support) + (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)(Respiratory support) + (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 × Fi02) + Medication (Weighted Sum)

Respiratory support	Fi02	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 FIO_2. Table adapted from ref [11]

- Example 1: intubated on FIO_2 0.25 and caffeine has score of (2.5)(0.25) + 0.05 = 0.675
- Example 2: CPAP on 30% O_2 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 FIO_2 that is equal to the administered FIO_2 (using the appendix tables from ref [13]). Therefore a 1.2 kg baby on 4 L/min on 40% O_2 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 (RSO_2) to determine hemodynamic significance of the PDA or the effects of indomethacin and surgical ligation on RSO_2 [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% O_2

(3) patients on HFNC ≥ 4 L/min and ≥ 45% O_2) 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:
    - If tolerating feeds, may consider continuing current feeding plan
    - 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 FiO_2 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 × min(1, L/min per kg). The table is adapted from equations 3 and 4 in ref 14. Benaron and Benitz[14] 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 FIO_2 equals the nasal cannula oxygen concentration.)

TABLE A2. Calculation of Effective FIO_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

References:

1. Bixler GM, Powers GC, Clark RH, Walker MW, Tolia VN: **Changes in the Diagnosis and Management of Patent Ductus Arteriosus from 2006 to 2015 in United States Neonatal Intensive Care Units**. *J Pediatr* 2017, **189**:105-112.
2. Benitz WE, Committee on Fetus and Newborn AeAoP: **Patent Ductus Arteriosus in Preterm Infants**. *Pediatrics* 2016, **137**(1).
3. Bose CL, Laughon M: **Treatment to prevent patency of the ductus arteriosus: beneficial or harmful?** *J Pediatr* 2006, **148**(6):713-714.
4. Garcia AV, Lukish J: **Minimally Invasive Patent Ductus Arteriosus Ligation**. *Clin Perinatol* 2017, **44**(4):763-771.
5. Sathanandam S, Balduf K, Chilakala S, Washington K, Allen K, Knott-Craig C, Rush Waller B, Philip R: **Role of Transcatheter patent ductus arteriosus closure in extremely low birth weight infants**. *Catheter Cardiovasc Interv* 2018.
6. Sathanandam S, Justino H, Waller BR, Radtke W, Qureshi AM: **Initial clinical experience with the Medtronic Micro Vascular Plug™ in transcatheter occlusion of PDAs in extremely premature infants**. *Catheter Cardiovasc Interv* 2017, **89**(6):1051-1058.
7. Morville P, Douchin S, Bouvaist H, Dauphin C: **Transcatheter occlusion of the patent ductus arteriosus in premature infants weighing less than 1200 g**. *Arch Dis Child Fetal Neonatal Ed* 2018, **103**(3):F198-F201.
8. Morville P, Akhavi A: **Transcatheter closure of hemodynamic significant patent ductus arteriosus in 32 premature infants by amplatzer ductal occluder additional size-ADOIIAS**. *Catheter Cardiovasc Interv* 2017, **90**(4):612-617.
9. Zahn EM, Peck D, Phillips A, Nevin P, Basaker K, Simmons C, McRae ME, Early T, Garg R: **Transcatheter Closure of Patent Ductus Arteriosus in Extremely Premature Newborns: Early Results and Midterm Follow-Up**. *JACC Cardiovasc Interv* 2016, **9**(23):2429-2437.
10. Zahn EM, Nevin P, Simmons C, Garg R: **A novel technique for transcatheter patent ductus arteriosus closure in extremely preterm infants using commercially available technology**. *Catheter Cardiovasc Interv* 2015, **85**(2):240-248.
11. Rodríguez Ogando A, Planelles Asensio I, de la Blanca ARS, Ballesteros Tejerizo F, Sánchez Luna M, Gil Jaurena JM, Medrano López C, Zunzunegui Martínez JL: **Surgical Ligation Versus Percutaneous Closure of Patent Ductus Arteriosus in Very Low-Weight Preterm Infants: Which are the Real Benefits of the Percutaneous Approach?** *Pediatr Cardiol* 2018, **39**(2):398-410.
12. **Supplemental Therapeutic Oxygen for Prethreshold Retinopathy Of Prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes**. *Pediatrics* 2000, **105**(2):295-310.
13. Madan A, Brozanski BS, Cole CH, Oden NL, Cohen G, Phelps DL: **A pulmonary score for assessing the severity of neonatal chronic lung disease**. *Pediatrics* 2005, **115**(4):e450-457.
14. Weisz DE, McNamara PJ, El-Khuffash A: **Cardiac biomarkers and haemodynamically**

significant patent ductus arteriosus in preterm infants. *Early Hum Dev* 2017, **105**:41-47.

15. Underwood MA, Milstein JM, Sherman MP: **Near-infrared spectroscopy as a screening tool for patent ductus arteriosus in extremely low birth weight infants**. *Neonatology* 2007, **91**(2):134-139.
16. Lemmers PM, Toet MC, van Bel F: **Impact of patent ductus arteriosus and subsequent therapy with indomethacin on cerebral oxygenation in preterm infants**. *Pediatrics* 2008, **121**(1):142-147.
17. Vanderhaegen J, De Smet D, Meyns B, Van De Velde M, Van Huffel S, Naulaers G: **Surgical closure of the patent ductus arteriosus and its effect on the cerebral tissue oxygenation**. *Acta Paediatr* 2008, **97**(12):1640-1644.
18. Meier SD, Eble BK, Stapleton GE, Morales DL, Chang AC, Andropoulos DB: **Mesenteric oxyhemoglobin desaturation improves with patent ductus arteriosus ligation**. *J Perinatol* 2006, **26**(9):562-564.
19. van der Laan ME, Roofthooft MT, Fries MW, Berger RM, Schat TE, van Zoonen AG, Tanis JC, Bos AF, Kooi EM: **A Hemodynamically Significant Patent Ductus Arteriosus Does Not Affect Cerebral or Renal Tissue Oxygenation in Preterm Infants**. *Neonatology* 2016, **110**(2):141-147.
20. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, Hanna BD, Rosenzweig EB, Raj JU, Cornfield D *et al*: **Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society**. *Circulation* 2015, **132**(21):2037-2099.

Medical Legal Disclaimer:

Welcome to the UC Davis Health, Department of Pediatrics, Clinical Practice Guidelines Website. All health and health-related information contained within the Site is intended chiefly for use as a resource by the Department's clinical staff and trainees in the course and scope of their approved functions/activities (although it may be accessible by others via the internet). This Site is not intended to be used as a substitute for the exercise of independent professional judgment. These clinical pathways are intended to be a guide for practitioners and may need to be adapted for each specific patient based on the practitioner's professional judgment, consideration of any unique circumstances, the needs of each patient and their family, and/or the availability of various resources at the health care institution where the patient is located. Efforts are made to ensure that the material within this Site is accurate and timely but is provided without warranty for quality or accuracy. The Regents of the University of California; University of California, Davis; University of California, Davis, Health nor any other contributing author is responsible for any errors or omissions in any information provided or the results obtained from the use of such information. Some pages within this Site, for the convenience of users, are linked to or may refer to websites not managed by UC Davis Health. UC Davis Health does not control or take responsibility for the content of these websites, and the views and opinions of the documents in this Site do not imply endorsement or credibility of the service, information or product offered through the linked sites by UC Davis Health. UC Davis Health provides limited personal permission to use the Site. This Site is limited in that you may not:

- Use, download or print material from this site for commercial use such as selling, creating course packets, or posting information on another website.
- Change or delete propriety notices from material downloaded or printed from it. · Post or transmit any unlawful, threatening, libelous, defamatory, obscene, scandalous, inflammatory, pornographic, or profane material, any propriety information belonging to others or any material that could be deemed as or encourage criminal activity, give rise to civil liability, or otherwise violate the law.
- Use the Site in a manner contrary to any applicable law.

You should assume that everything you see or read on this Site is copyrighted by University of California or others unless otherwise noted. You may download information from this Site as long as it is not used for commercial purposes, and you retain the proprietary notices. You may not use, modify, make multiple copies, or distribute or transmit the contents of this Site for public or commercial purposes without the express consent of UC Davis Health.