Patent Ductus Arteriosus
To Treat or Not to Treat

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Patent Ductus Arteriosus (PDA)

- Helps the blood to bypass the lungs in the fetal life
- Normally closes within 72 hours after birth
- Persistent patency of the ductus arteriosus following birth is inversely related to gestational age.
- May cause significant problems if remains patent, especially in premature infants
Fetal Circulation
Embryology

 ♥ The sixth embryonic aortic arch develops in the 5th week

 ♥ Left: proximal LPA & **PDA**
 ♥ Right: proximal MPA and RPA

 ♥ Some ductal muscle strands snare the descending aorta, causing coarctaion, or ensnare the proximal pulmonary artery causing stenosis of the LPA
Closure of PDA

♥ In full-term newborns:
  ♥ Functional closure occurs in ~ 90% of within 48-72 hours.
  ♥ Anatomic closure occurs within two weeks.
  ♥ Closure occurs by 2-6 months in >95% of infants

♥ In preterm newborns: ~ 60% of preterm newborns <28 weeks will have persistent DA

♥ Prevalence: 0.138 – 0.8 per 1000 live births

♥ Conditions associated with persistent DA:
  ♥ Prematurity
  ♥ Maternal Rubella
  ♥ Children born at high altitudes
Factors Affecting DA Patency

During fetal life:
- Prostaglandins produced by the placenta
- Prostaglandins and nitric oxide-like vasodilators produced by the ductus
- Low PaO2 level

Postnatal period:
- Increased production of local vasoconstrictors (e.g. endothelin)
- High PaO2 level
- Removal of prostaglandins (produced by placenta)
- Increased lung metabolism of prostaglandins due to increased pulmonary flow
- Decrease in the number of prostaglandin E2 receptors in the ductal wall
- Degenerative changes cause fibrosis forming the ligamentum arteriosum

- Infections may increase the release of prostaglandins (6-ketoprostaglandin F1) and tumor necrosis factors, and increase the risk of late ductal opening and closure failure
Developmental Factors Affecting the Hemodynamics of the PDA

- PDA + rds
- PDA + RDS
- RDS (±pda)

“RDS” by WEIGHT

1200 gm

ALVEOLAR DEVELOPMENT

PDA

PULMONARY ARTERIES
Clinical Diagnosis

- I-IV/VI Crescendo systolic/continuous murmur “machinery” at LUSB
- Apical mid-diastolic rumble (with significant shunt)
- Hyperactive precordium
- S2: normal/ single and loud
- Bounding pulses due to diastolic runoff
- Wide pulse pressure

- CXR: Cardiomegaly & increase PVMs
- EKG: LAE, LVH, BVH/RVH
Why Clinical Evaluation of PDA in Premature infants is Limited?

♥ Ventilator dependant
♥ Silent PDA
♥ Systolic ejection murmur
♥ Lack of bounding pulses
  ♥ PVR equal or near SVR
  ♥ Lack of enough myocardial reserve to compensate for the rapid runoff
♥ Helpful tools:
  ♥ CXR (cardiomegaly and increase PVMs)
  ♥ Ventilator dependency
  ♥ Echocardiogram
PDA Physiology
ECHOCARDIOGRAM

♥ The most reliable non-invasive diagnostic tool

♥ What to look for?
  ♥ Associated structural abnormalities
  ♥ Size of PDA
  ♥ The secondary effects of volume overload from increased left to right shunting
    ♥ Left atrial and ventricular enlargement
    ♥ LV systolic function
    ♥ Left atrial-to-aortic root ratio of >1.3
  ♥ Estimation of pulmonary artery pressures by measuring Doppler velocities of PDA flow and tricuspid regurgitant jet
Echocardiographic Criteria for Symptomatic PDA

1. Ductal diameter >1.5 mm in the first 30 hours after delivery
2. Left atrial/aortic root ratio >1.4
3. Pulsatile transductal flow (Vmax) <1.8 m/sec
4. Reverse end-diastolic flow in the descending aorta/mesenteric artery*

*Although no study to date has shown a correlation between PDA and NEC, reverse end-diastolic flow in the descending aorta is a definite risk factor for NEC.
Echo Findings
Risks of PDA

- Congestive heart failure
- Pulmonary hemorrhage
- Metabolic acidosis
- Failure to thrive
- Recurrent pneumonias
- Infective endocarditis (0.45% per year)
- Calcification
- Aneurysm formation
- Long term: Pulmonary vascular obstructive disease (PVOD) or Eisenmenger syndrome
Risks of PDA

- Prolonged exposure to a symptomatic PDA has been shown to increase morbidity
- Strongly implicate but no direct link
- **Bronchopulmonary dysplasia (BPD)**
  - N=1460 patients, PDA was identified as a risk factor for BPD with an odds ratio of 1.9
    *(Marshal DD et al, Pediatrics, 1999;104;1345-50)*
- **Necrotizing enterocolitis (NEC)**
  - Evidence for decreased splanchnic and renal blood flow by ultrasound
  - No link between PDA and NEC or feeding intolerance in an epidemiologic study
Respiratory Failure as a Result of PDA in Preterm Infants

- Underdeveloped alveoli in addition to surfactant deficiency
- Less well developed pulmonary lymphatic system
- A relatively larger PDA compared to aortic diameter
- Lower PVR due to less muscle in the pulmonary vascular bed permits relatively larger pulmonary blood flow
- The presence of poor lung compliance in these infants aggravates any existing RDS
- Diastolic runoff which steals significant blood flow from vessels distal to the duct such as the gut.

- Surfactant used in preterm infants to prevent RDS reduces pulmonary vascular resistance and increases left to right shunting across the ductus. However, surfactant does not delay closure of the ductus arteriosus per se
Management

- The ability of a premature infant to tolerate a PDA may be inversely proportional to gestational age.
- Conservative
  - Fluid restriction
- Non-pharmacological
  - Surgical ligation
  - Trans-catheter closure
- Pharmacological
  - Furosemide/Thiazides
  - Cyclo-oxygenase inhibitors (COX)
    - Indomethacin
    - Ibuprofen
Conservative Treatment

Small prospective study for one year based on retrospective analysis (n=30)

- ≤ 30 wks gestation, ventilated and required surfactant therapy
- ECHO done 48-72 hours after birth
- Hemodynamically significant PDA (≥1.4 mm)
- Conservative treatment: fluid restriction (130 ml/kg/day beyond day 3), lower Ti and high PEEP (4,5)
- Persistent PDA or remaining on ventilator were treated surgically

**Results:** 94% ductal closure rate without Rx

Vanhaesebrouck S. et al, BMJ, online publication, 2007
Diuretic Therapy

♥ Furosemide is a prostaglandin agonist, but does not interfere with PDA closure
♥ Dosage: 1mg/kg given IV/PO
♥ Consider thiazides for long-term use
♥ Helps the lungs clear fluid and thereby improves the patient’s ability to tolerate the PDA
♥ Avoid dehydration
♥ Long-term side effects:
  ♥ Hypocalcemia
  ♥ Hypokalemia
  ♥ Metabolic alkalosis and carbon dioxide retention that can be misinterpreted as worsening of cardiopulmonary disease leading to an apparent increase in ventilator support.
Indomethacin

♥ Cyclo-oxygenase inhibitor (COX)
♥ It was first approved by FDA for closure of PDA in 1985
♥ Dosage: 0.1-0.2 mg/kg IV over 30 minutes (q12 hr for 3 doses) followed by 1mg/kg Furosemide
♥ May not be effective after 10 days of life
♥ Its administration is quite variable
♥ *Three primary strategies:*
  ♥ Prophylactic within 24 hours of life
  ♥ Before or at early onset of clinical symptoms
  ♥ After the development of clinical symptoms
♥ Prenatal exposure may affect postnatal responsiveness and surgical ligation may be necessary
♥ *Side effects:* transient oliguria and altered renal function; decrease in cerebral, mesenteric, and renal blood flow; NEC or gastrointestinal perforation; and altered platelet function
Indomethacin Contraindications

- Active bleeding
- Necrotizing enterocolitis (NEC)
- Creatinine ≥ 2mg/dl
- Urine output < 0.6 ml/kg/hr
- Platelet count < 50K
- Active and untreated infection
- Known GI or renal anomaly
Indomethacin Prophylaxis for Preterm Infants

Two multicenter randomized controlled trials (RCTs) in premature infants:

- Ment et al, 1994 (recommends prophylaxis)
- TIPP, 2001 (does not recommend prophylaxis)

Clyman RI et al, J Pediatr 2007;150:46-50
Trial of Indomethacin Prophylaxis in Preterms (TIPP)

1202 ELBW within 6 hrs of age to INDO (0.1 mg/kg/dose q24hrs X3 doses) or placebo (normal saline)

Primary outcome: death or neurosensory impairment at 18 months.

Secondary outcomes: BPD, pulmonary hemorrhage, NEC, ROP, hydrocephalus requiring a VP shunt

Results:

- Decreased incident of symptomatic PDA by 50% but did not reduce incident of BPD (O2 requirement at 36 weeks PMA)
  - 24% vs. 50% (placebo), p < 0.001
- Reduced incident of severe IVH
  - 9% vs. 13% (placebo), p = 0.02
431 patients (600-1250gms) randomized to placebo or INDO (0.1mg/kg/dose q12hrs X3 doses)

Objective: low dose INDO decreases the severity and incidence of IVH

Results:

12% IVH (INDO) vs. 18%, p=0.03
1 pt with grade IV IVH (INDO) vs. 10, p=0.01
Ductal closure for INDO group on D1 to D5 was 81% to 10% while closure for placebo group was 91% to 34%, p<0.001

Ment LR et al., Pediatrics 1994;93:543-50
Increased white matter injury in infants who received prolonged INDO treatment (>4 days) 

(TIPP) study showed no improvement in rate of survival without neurosensory impairment at 18 months. However, long term neurodevelopmental outcome is still being investigated. 
Conclusions

❤ Indomethacin prophylaxis has no significant impact on the incidence of NEC, CLD, ROP, death, or neuro-developmental impairment.

❤ No difference in duration of oxygen dependency, CLD or mortality between no PSI use vs. PSI use prior to ligation

❤ More than one course of PSI prior to surgical ligation trends to increased oxygen dependence (119 days, Vs. 85.5) but not statistically significant
Ibuprofen Vs. Indomethacin

- Ibuprofen is as effective as indomethacin in treating PDA in preterm infants *(NeoProfen loading dose is 10mg/kg IV followed by two doses of 5mg/kg each, after 24 and 48 hours)*
- First approved by FDA in 2006 (2001 in Europe)
- 11 studies (n=620 patients)
- No statistically difference in treatment effect for any outcome (primary or secondary)
- Ibuprofen has fewer negative effects on urine output, cerebral and mesentric blood flow
- Ibuprofen may displace bilirubin from albumin binding sites at higher concentrations
- *Ibuprofen may be associated with increased risk of CLD (O2 requirement at 28 days)*

Surgical Ligation

- For those who are not candidates for, or failed, medical therapy

- In a randomized, controlled trial of prophylactic surgical ligation of PDA, the incidence of NEC decreased from 30% to 8%, however, it had no significant effect on other outcome measures like death, BPD, ROP, and IVH

- Left lateral thoracotomy (standard) with ligation in the OR or at the bedside

- Video-assisted thoracoscopic surgery (VATS)
Surgical Ligation... Complications

- Wound infection
- Chylothorax
- Pneumothorax
- Intra-operative bleeding
- Hypothermia
- Lateral laryngeal nerve injury (vocal cord palsy)
- Phrenic nerve injury
- Thoracic scoliosis
Outcomes of PDA ligation

♥ Population: N=197, mean GA 27wks, BW 957gms, 16 days of life

♥ Outcomes:
  ♥ survival at 30 days post-op (83%)
  ♥ days to extubation (27 days)
  ♥ wean from supplemental oxygen (60 days)
  ♥ Only 22% survived to discharge without CLD
  ♥ Early extubation (within 10 days of ligation): only 30%

♥ Conclusion: Most patients do not experience the anticipated rapid improvements in cardiorespiratory status and will develop CLD

Is Surgical Ligation of PDA Necessary?

❤️ Australian experience of conservative management
❤️ Retrospective study
❤️ 252 patients (EGA <28 wks)
❤️ Three groups:
  ❤️ Group 1: no PDA, n=154
  ❤️ Group 2: significant PDA which closed with medical Rx, n=65;
  ❤️ Group 3: significant PDA which did not close with medical Rx, n=33

❤️ Significant PDA defined as LA to Aortic root ratio >1.4 or ductal diameter of 1.5 mm with a left to right shunt by ECHO or clinically if ECHO is not available

Brooks JM et al., Arch Dis Child Fetal Neonatal Ed 2005; 90:F235-239
Medical treatment included fluid restriction, diuretics, and up to 3 courses of indomethacin (2 different dosing regimen used)

Outcomes assessed:
- CLD (Oxygen or resp. support at 36 wks EGA)
- IVH (grade III or IV)
- Proven NEC
- Duration of hospital stay
- Ventilatory support
- Survival with or without CLD

Brooks JM et al., Arch Dis Child Fetal Neonatal Ed 2005; 90:F235-239
Results

- Increased mortality with a PDA after medical treatment than closed PDA or PDA not treated with Indo.
- No difference in incidence of CLD, NEC, death, IVH, duration of O2 therapy, or hospital stay.

Brooks JM et al., Arch Dis Child Fetal Neonatal Ed 2005; 90:F235-239
PDA Ligation... Initial Treatment

- **Gersony WM. et al, J Pediatr 1983; 102:895-906**
  - Randomized, prospective
  - Compared to Indomethacin treatment
  - 154 infants
  - No statistically significant difference in mortality, BPD, NEC, sepsis, or IVH
  - Increased incidence of pneumothorax, ROP, and grade III IVH

  - Randomized prospective
  - Compared to conservative management (no INDO)
  - Indication for ligation was pulmonary-to-systemic flow ratio >3 or dependence on the ventilator with a large shunt
  - N=84 infants, < 1000 grams
  - Ligation occurred within 24 hours of birth regardless symptoms
  - Decreased incidence of NEC but no difference in mortality, CLD, ROP, or IVH
PDA Ligation After Medical Therapy

♥ Retrospective case review
♥ 87 infants
♥ Determine mortality and morbidity following PDA ligation and whether PSI use prior to ligation affects outcome

♥ Results:
- CLD 77%; IVH 26%; NEC 26%; ROP 27%

♥ Mortality:
- 2% at 7 days, 8% at 30 days, and 20% >30 days
  (CLD, pulmonary interstitial emphysema, bronchiolitis, cor pulmonale)

Lee CL et al, BMC Pediatrics, 2006 May 11, 6:15
Out of the neonatal period, cardiac catheterization with coil occlusion of the PDA has become the standard practice.

Difficult to close in preterm infants.

- Large short PDA
- Risk of obstructing the descending aorta or left pulmonary artery, which are small caliber vessels in neonates.

Coil vs. Amplatzer ductal occluder device
The Nit-Occlud® Spiral Coil System

- Made of Nitinol
- Radiopaque
- MRI compatible
- Delivery through 4F/5F
- Repositionable prior to release
- Coil is premounted on the delivery system
- Fits all PDA types and sizes up to 6 mm
Angiography
The AMPLATZER® Duct Occluder for PDA

Made of a Nitinol wire mesh that is shaped into a cylindrical plug shape with a collar to secure the Duct Occluder in the PDA, with polyester fabric inserts designed to help close the hole and provide a foundation for growth of tissue over the occluder after placement.
Summary

❤️ Most PDAs will close spontaneously but may have a higher mortality risk if remains open after treatment
❤️ Indomethacin and Ibuprofen can close PDAs, reduce the need for PDA ligation, and may reduce the incidence of severe IVH
❤️ No significant difference in mortality, BPD, NEC, length of hospital stay, and ROP between no treatment and prostaglandin inhibitor use
Summary

❤ Surgical ligation has low mortality, but has not been shown to reduce the incidence of CLD, or duration of stay. (May decrease NEC)
❤ Prophylactic PDA ligation vs. prostaglandin inhibition has not been studied extensively
❤ Conservative treatment of PDAs has not been extensively studied
There is no consensus as to what is the best time and optimal management strategy among high-risk preterm infants.