DUCTUS ARTERIOSO PERSISTENTE (DAP)

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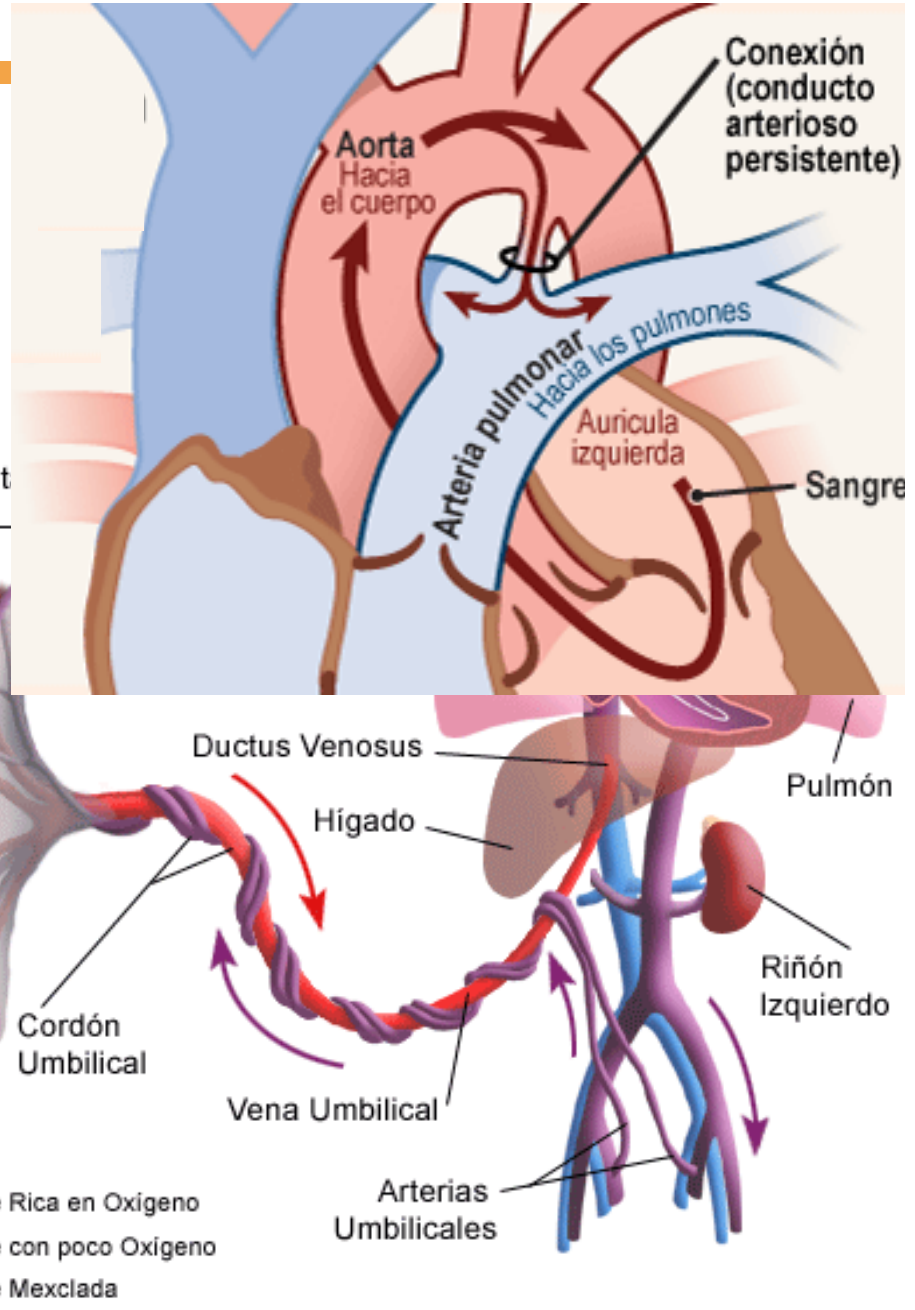
HOJA DE RUTA

- Introducción
- Epidemiología
- Fisiología y Fisiopatología
- Diagnóstico
- Tratamiento
- Conclusiones
- Bibliografía

INTRODUCCIÓN

- **Definición:** vaso sanguíneo que comunica el tronco de la arteria pulmonar con la aorta descendente.
- **Embriológicamente:** porción distal del sexto arco aórtico.
- **Histológicamente:** Túnica media pobre en fibras elásticas y rica en fibras musculares lisas en forma de doble capa helicoidal → contracción y dilatación.

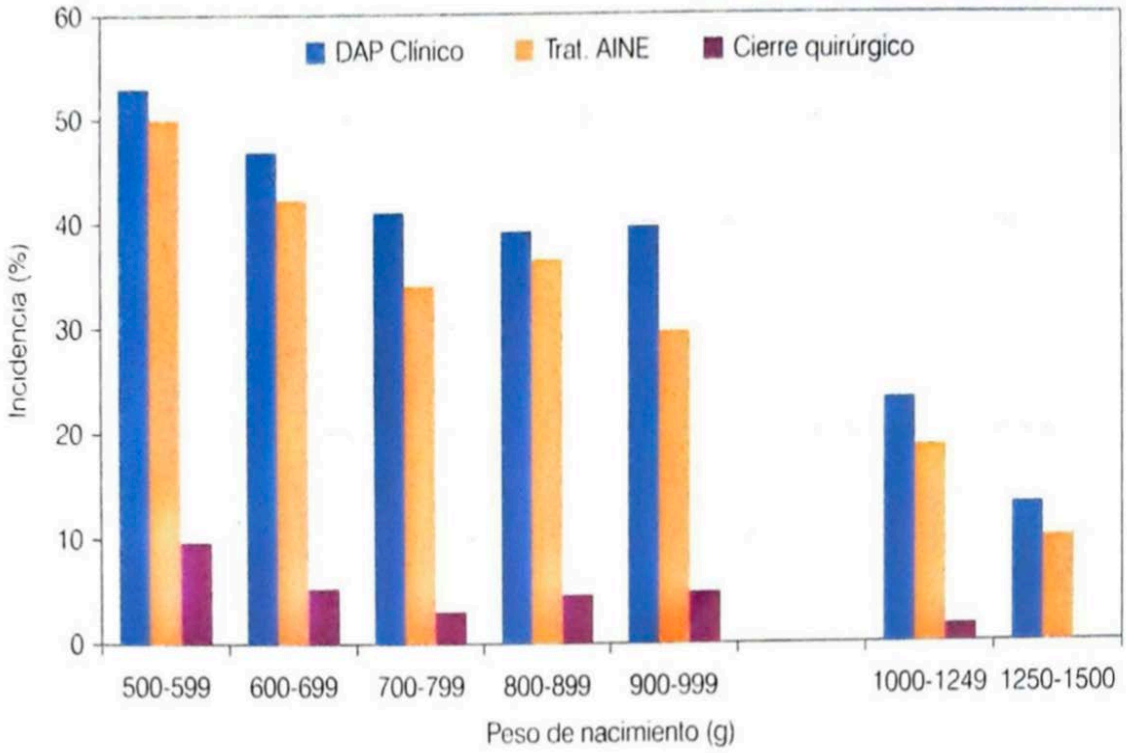


Tapia, J.L., González A. (2018). Cap 46 DAP. Luco M, et al. *Neonatología.* Ed 4°. (p 397-406)

INCIDENCIA

- **Incidencia DAP:** 20-40% <1500 gr y 35-70% <1000 gr.
- Hasta 60-70% puede requerir manejo médico o quirúrgico.
- **Factores de riesgo DAP:**
  - Edad gestacional y PN.
  - SDRA (>EDS).
  - Infecciones.
  - Trombocitopenia.
  - Altura sobre nivel del mar.

Fig 46-1. Incidencia DAP clínico y tratamiento en 1770 RN <1500 gr en 16 unidades de la red Neocosur 2010-2011.



Tapia, J.L., González A. (2018). Cap 46 DAP. Luco M, et al. *Neonatología.* Ed 4°. (p 397-406)

FACTORES QUE INFLUYEN EN DAP

Factors Promoting Postnatal DA Closure	Factors Promoting Preterm DA Patency
Molecular Factors	
Increased O_2 tension Decreased vasodilating prostaglandins Activation of cytochrome P450 Increased endothelin-1 levels Production of isoprostanes (8-iso-PGF2α) Inhibition of potassium channels (K_{ATP}, Kv, BK_{Ca}) Activation of transient receptor potential channels Decrease in intracellular cAMP and/or cGMP levels Angiotensin II Bradykinin Acetylcholine Norepinephrine Activation of RhoA, RhoB, Rock1, and Rock2	Hypoxia Increased nitric oxide signaling Increased prostaglandin signaling
Physiologic Factors	
Decreased pulmonary vascular resistance Increased systemic vascular resistance	Prolonged bidirectional or right-to-left blood flow Low-velocity blood flow
Structural Factors	
Mature contractile smooth muscle cells Prominent intimal cushions Vasa vasorum Zone of ischemia and/or necrosis Platelet adherence to lumen	Thin layer or immature smooth muscle Insufficient intimal cushion development Thrombocytopenia or platelet dysfunction

PEDIATRICS Volume 146, number 5, November 2020:e20201209. State Of the Art Review Article. Patent Ductus Arteriosus of the Preterm Infant.

ALTERACIONES GENÉTICAS ASOCIADAS A DAP

TABLE 1 Genetic Factors Associated With PDA

Human Syndromes (Gene)	Nonsyndromic SNPs (Accession Number)
22q11.2 deletion	Increased Risk of PDA
Char (*TFAP2B*)	*TFAP2B* (rs987237)
Cantu (*ABCC9*, *KCNJ8*)	*TRAF1* (rs1056567)
Noonan (*PTPN11*)	*AGTR1* (rs5186)
Mowat-Wilson (*SMADIP1*)	Decreased Risk of PDA
DiGeorge (*TBX1*)	*PTGIS* (rs493694, rs693649)
Holt-Oram (*TBX5*)	*ESR1* (rs2234693)
Loeys-Dietz (*TGFBR1* and *TGFBR2*)	*IFN-γ* (rs2430561)
Rubinstein-Taybi (*CREBP*)	
Periventricular heterotopia (*FLNA*)	

PDA is associated with several genetic syndromes. Several SNPs have also been associated with cases of nonsyndromic PDA. *ABCC9*, ATP binding cassette subfamily C member 9; *AGTR1*, angiotensin II receptor type 1; *CREBP*, cyclic adenosine monophosphate–response element binding protein; *ESR1*, estrogen receptor 1; *FLNA*, filamin A; *IFN-γ*, interferon-γ *KCNJ8*, potassium inwardly rectifying channel subfamily J member 8; *PTGIS*, prostaglandin I2 synthase; *PTPN11*, protein tyrosine phosphatase nonreceptor type 11; *SMADIP1*, SMAD-interacting protein 1; SNP, single-nucleotide polymorphism; *TBX1*, T-box transcription factor 1; *TBX5*, T-box transcription factor 5; *TFAP2B*, transcription factor AP-2-β; *TGFBR1*, transforming growth factor-β receptor type 1; *TGFBR2*, transforming growth factor-β receptor type 1; *TRAF1*, tumor necrosis factor receptor associated factor 1.

PEDIATRICS Volume 146, number 5, November 2020:e20201209. State Of the Art Review Article. Patent Ductus Arteriosus of the Preterm Infant.

International Journal of *Molecular Sciences*

MDPI

Review

The Association of Patent Ductus Arteriosus with Inflammation: A Narrative Review of the Role of Inflammatory Biomarkers and Treatment Strategy in Premature Infants

Yu-Jen Wei [1,2,†], Rosie Hsu [3,†], Yung-Chieh Lin [1], Tak-Wah Wong [4,5,6], Chung-Dann Kan [7] and Jieh-Neng Wang [1,*]

Método:

- 5883 artículos inicia→ N° 77.

Conclusiones:

- **Corioamnionitis** →proceso inflamatorio fetal → citoquinas y DAP: remodelación vascular o dilatación vasos del conducto.
- **Esteroides prenatales:** ↓ incidencia y gravedad DAP en RN con corioamnionitis.

Table 2. Potential biomarkers involved in PDA pathogenesis.

Biomarker	Potential Pathological or Clinical Role That May Relate to Perinatal Inflammation and PDA
TNF-α	Mediators in the early inflammatory response
IL-1	Mediators in the early inflammatory response Risk of preterm birth
IL-6	Mediators in the early inflammatory response Risk of preterm birth Clinically related to persistent PDA
IL-8, IL-10, MIP-1α	Related to persistent PDA Clinical risk of preterm birth
IL-15	Attenuates smooth muscle cell proliferation Involved in atherogenesis
IL-17	Risk of preterm birth Involved in vascular remodeling and prostaglandin expression Increases platelet aggregation
GDF-15	Related to persistent PDA Associated with tissue hypoxia, inflammation, acute injury, and oxidative stress.
MCP-1	Clinically related to persistent PDA Regulates migration and infiltration of monocytes and macrophages Risk of preterm birth Related to thrombus formation
PGDH	Risk of preterm birth

Yu-Jen Wei, et al. *Int. J. Mol. Sci.* 2022, *23*, 13877.

FISIOLOGÍA

Cierre Funcional

- Vasocontricción DA 1° 48 hrs RNT.
- Vasocontricción 2°↑ PaO2, ↓PG y cambios hemodinámicos.

Cierre Anatómico

- Se completa 2-8 sem.
- Contricción → hipoxia pared ductal → disrrupcion endotelial→ muerte celulas musculares → reacción inflamatoria local → fibrosis y cierre definitivo

Vasocontrictores

- Oxígeno → ↑Ca intracel
- Endotelina 1, catecolaminas

Vasodilatadores

- Prostaglandinas (PGE1-PGI2)

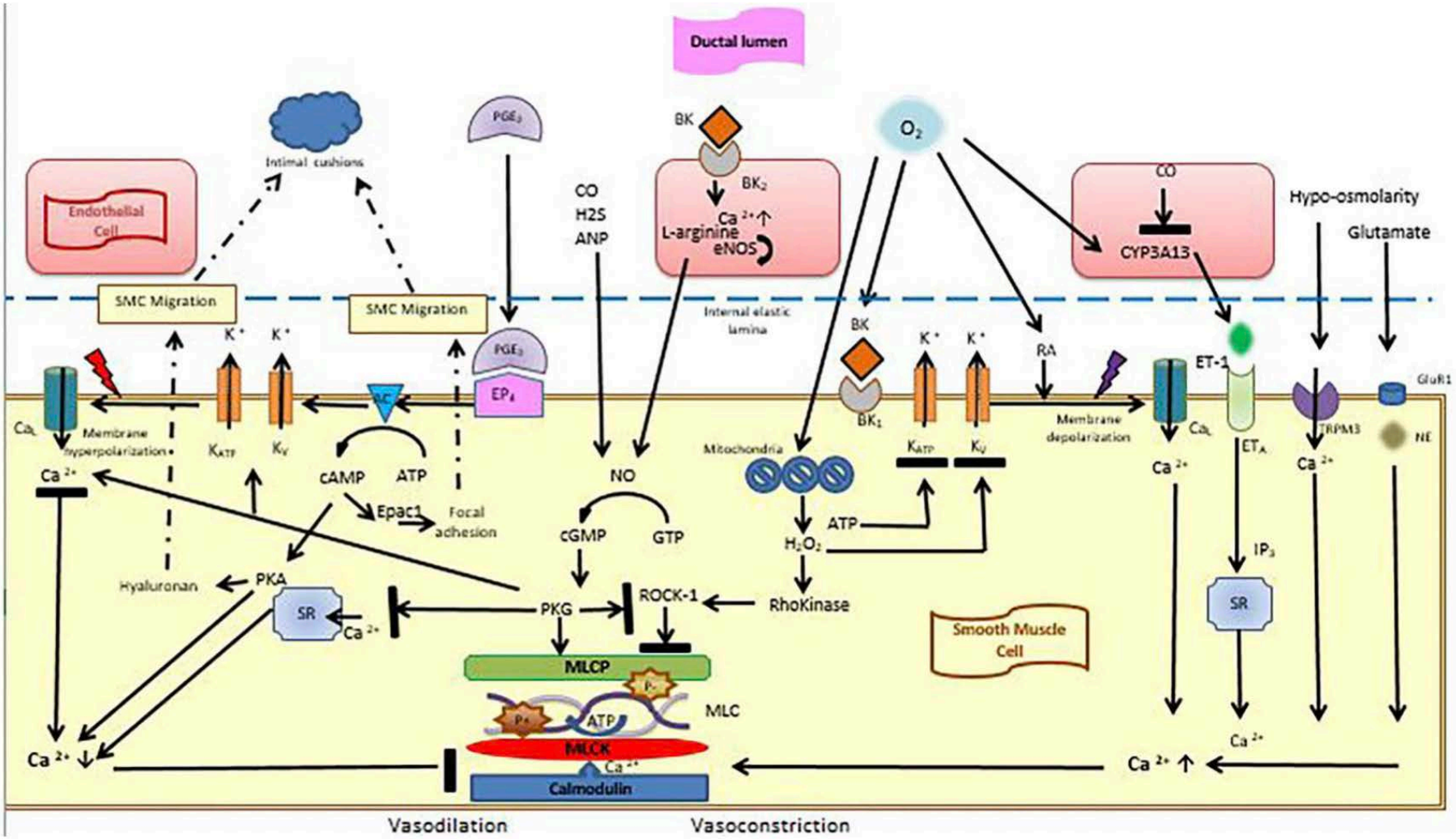
\+

Alta resistencia pulmonar fetal

Circulación fetal→ circulación extrauterina

Tapia, J.L., González A. (2018). Cap 46 DAP. Luco M, et al. *Neonatología.* Ed 4°. (p 397-406)

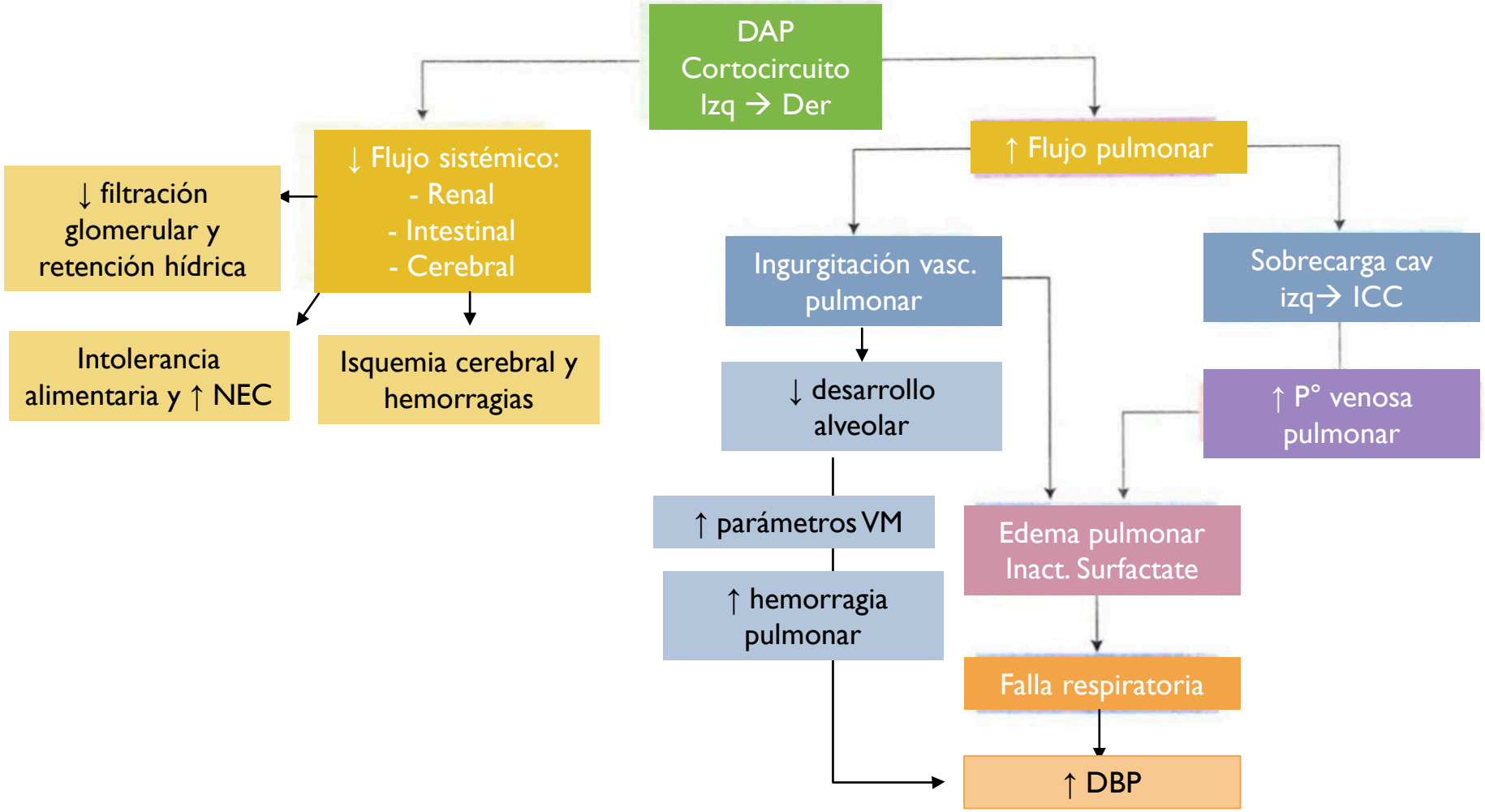
FISIOLOGÍA



Ovalı F (2020) Molecular and Mechanical Mechanisms Regulating Ductus Arteriosus Closure in Preterm Infants. Front. Pediatr. 8:516.

FISIOPATOLOGÍA

Figura 46-2. Esquema de las consecuencias hemodinámicas y respiratorias del DAP y sus interacciones.



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DIAGNÓSTICO:

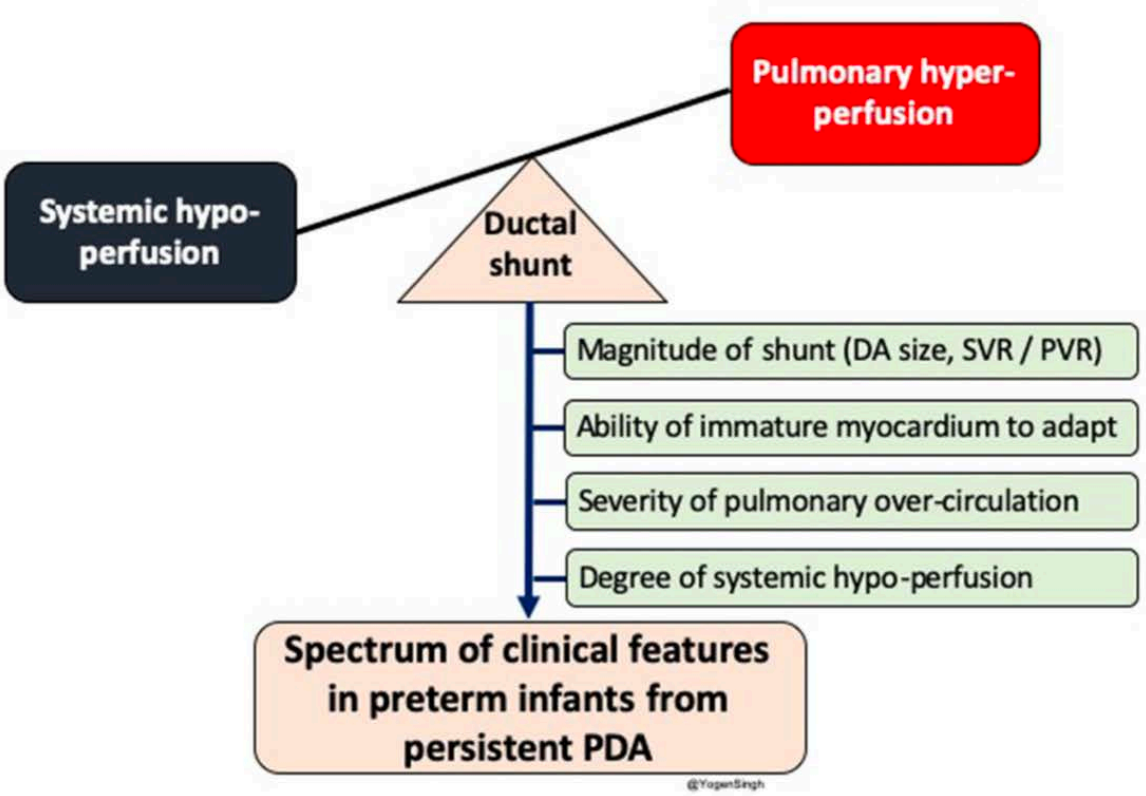


FIGURE 1 | Diagram showing impact of significant left to right shunt across ductal arteriosus (DA) leading to pulmonary over-circulation and systemic hypoperfusion. Spectrum of clinical features in preterm infants depends upon magnitude of ductal shunt, which depends upon DA size and balance between systemic and pulmonary vascular resistance, and inability of immature myocardium to adpat to circulatory disturbance. PDA, patent ductus arteriosus; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.

Singh Y, et al. Front. Pediatr. 8:573627.

DIAGNÓSTICO: CLÍNICO Y MARCADORES BQ…

Triada clínica:

Hipotensión	• Dentro de las 1° 48 hrs.
Soplo sistólico infraclav izq→ dorso	• 2° caída de resistencia vascular pulmonar, con aumento velocidad del cortocircuito por el DA
Precordio Hiperactivo	• Pulsos saltones y taquicardia 2° a compensación del "robo sistémico".

Biomarcadores bioquímicos…

- **Marcadores séricos:** BNP, NT-proBNP y troponina T cardíaca.
- **Marcadores urinarios:** lipocalina asociada a la gelatinasa de neutrófilos y la proteína de unión a ácidos grasos de tipo cardíaco.

Usado para predecir el momento del cierre ductal…

Parkerson S, et al. (2021) Front. Pediatr. 8:590578.
Tapia, J.L., González A. (2018). Cap 46 DAP. Luco M, et al. *Neonatología.* Ed 4°. (p 397-406)

DIAGNÓSTICO: ECOCARDIOGRÁFICO

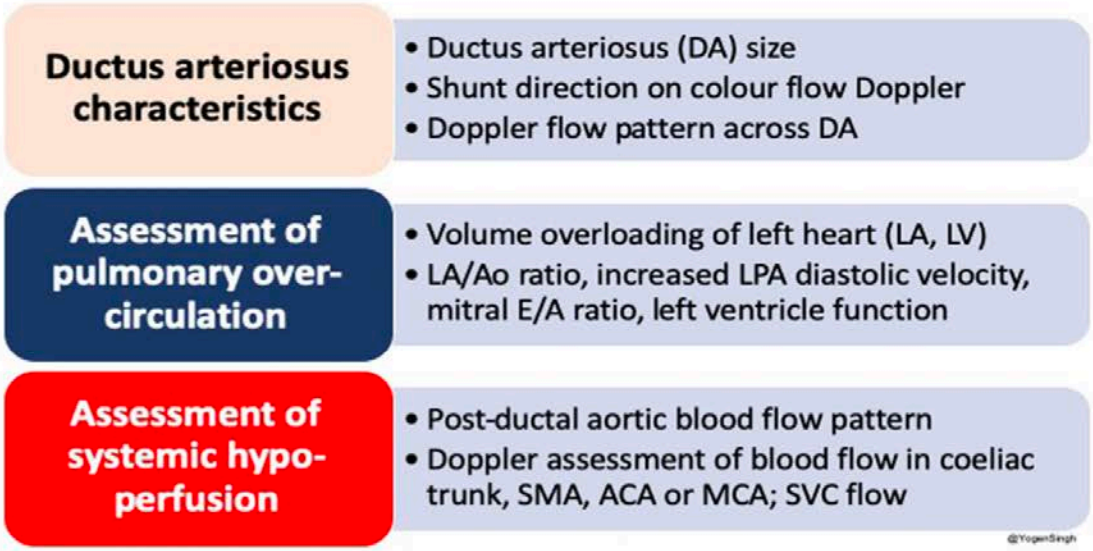


FIGURE 2 | Summary of an approach to echocardiographic assessment of PDA and hemodynamic evaluation; LA, left atrium; LV, left ventricle; DA, ductus arteriosus; Ao, aorta; SMA, superior mesenteric artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; SVC, superior vena cava.

Tabla 46-1. Criterios ecográficos para calificar significación hemodinámica del DAP

	DAP no HS	DAPHS moderado	DAPHS severo
Diámetro ductal (mm)	< 1,5	1,5-3	> 3
Veloc. sistólica pico (m/s)	> 2,5	1,5-2,5	< 1,5
Veloc. diastólica máx en API (m/s)	< 0,2	0,2-0,4	> 0,4
Flujo diastólico Ao descendente	Anterógrado	Ausente	Retrógrado
Relación AI/Ao	< 1,5	1,5-2	> 2

Tapia, J.L., González A. (2018). Cap 46 DAP. Luco M, et al. *Neonatología*. Ed 4°. (p 397-406)
Singh Y, et al. Front. Pediatr. 8:573627.

DIAGNÓSTICO: ECOCARDIO

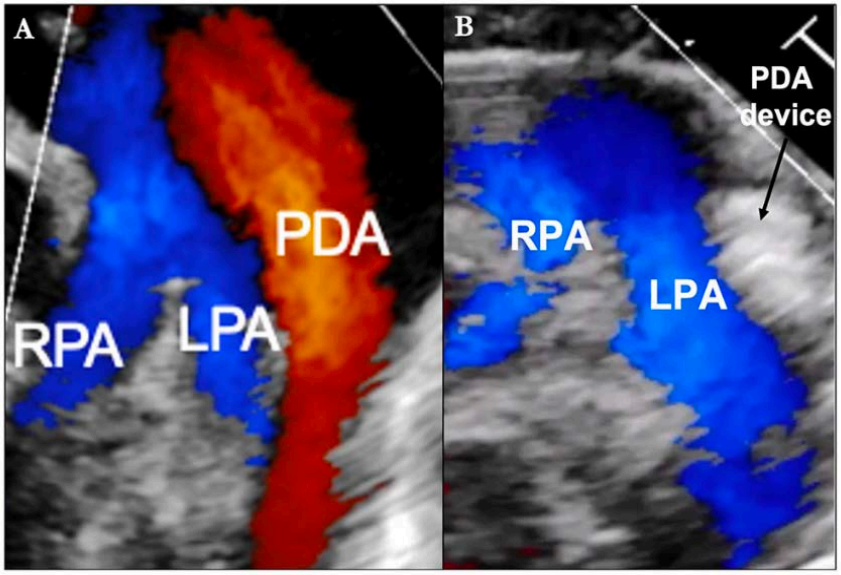
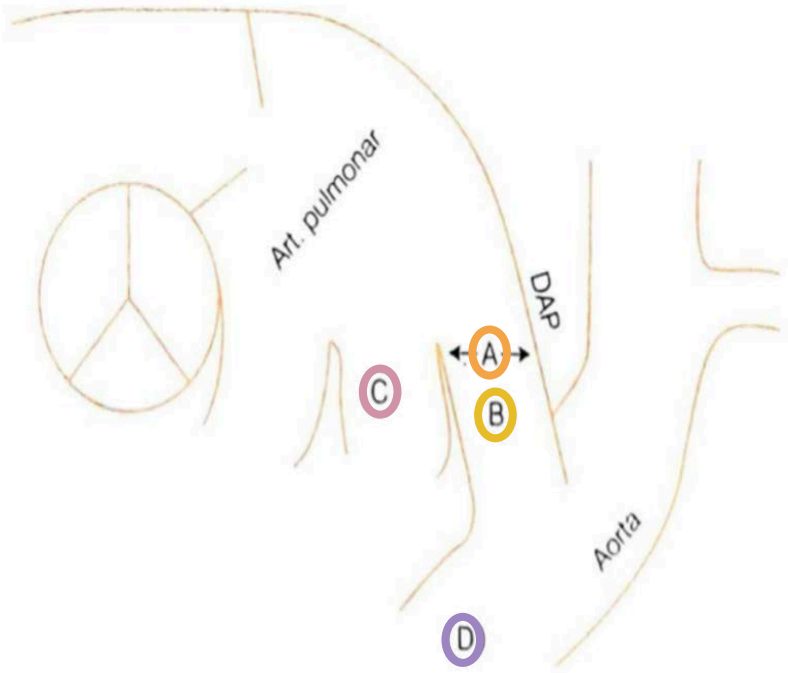


FIGURE 1 | (A) Transthoracic Echocardiogram (parasternal short axis image with color Doppler) demonstrating the relative size of the patent ductus arteriosus (PDA) in comparison to the left pulmonary artery (LPA) and right pulmonary artery (RPA). **(B)** Post-transcatheter PDA closure.

Parkerson S, et al. (2021) Front. Pediatr. 8:590578.

- **A** • Sitio de medición diámetro ductal.
- **B** • Sitio evaluación doppler continuo y velocidad del flujo.
- **C** • Doppler pulsado en Arteria pulmonar izq para cuantificar hiperflujo pulmonar.
- **D** • Doppler pulsado en Ao descedente para cuantificar robo sistémico.



Tapia, J.L., González A. (2018). Cap 46 DAP. Luco M, et al. *Neonatología.* Ed 4°. (p 397-406)

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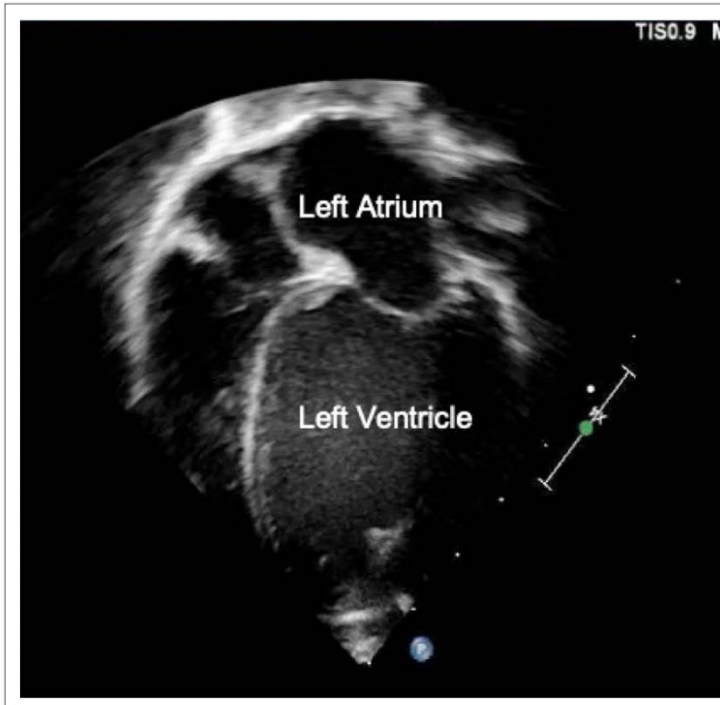
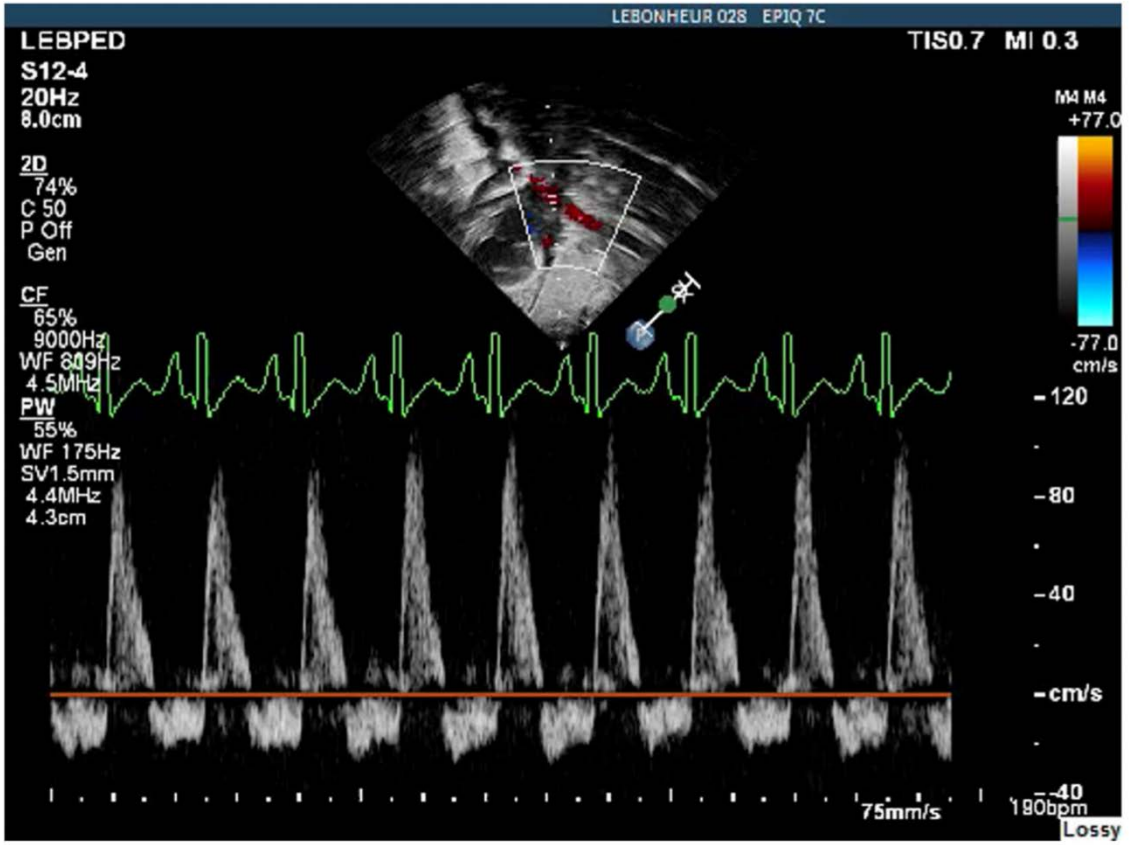


FIGURE 2 | Transthoracic Apical 4-chamber view showing left atrial and ventricular dilation suggestive of a hemodynamically significant PDA.



Abdominal Aorta Doppler pattern showing diastolic flow reversal indicative of a hemodynamically significant PDA.

Parkerson S, et al. (2021) Front. Pediatr. 8:590578.

ACTA PÆDIATRICA
NURTURING THE CHILD

Table 1 Demographic and echocardiographic parameters in infants with different PDA treatment categories

Clinical/ Echocardiographic parameter	All patients n = 60	No treatment n = 33	Medical treatment n = 17	Surgical ligation (with or without preceding medical treatment) n = 9	Difference between treatment groups (p-value)
Gestation (weeks)	25.8 (1.5)	26.7 (1.2)	25.0 (0.8)	24.4 (0.8)	<0.001
Birthweight (g)	817 (190)	909 (190)	734 (98)	666 (115)	<0.001
Sex (M:F)	30:30	16:18	8:9	6:3	0.55
SDS	−0.37 (0.8)	−0.41 (0.8)	−0.27 (0.6)	−0.42 (0.9)	0.81
Antenatal steroids (%)	93	94	100	78	0.09
CRIB II scores	12 (2.9)	11 (3.1)	13 (1.6)	14 (1.4)	<0.001
Invasive ventilation on day 1, n (%)	55 (92)	29 (88)	17 (100)	9 (100)	0.20
Mean airway pressure on day 1, cms	7.7 (1.7)	7.2 (1.6)	8.4 (1.7)	8.2 (1.5)	0.031
Invasive ventilation on day 3, n (%)	39 (65)	15 (46)	16 (94)	8 (89)	0.002
Mean airway pressure on day 3, cms	7.5 (2.3)	7.0 (2.3)	8.7 (2.6)	7.4 (0.5)	0.037
Necrotising enterocolitis, n (%)	12 (20)	7 (21)	3 (18)	2 (22)	1.0
Normal CrUS at 1 week, n (%)	44 (73)	28 (85)	11 (65)	5 (56)	0.16
Day 1 Echocardiographic PDA parameters					
B&W diameter (mm)	1.31 (0.5)	1.30 (0.6)	1.37 (0.5)	1.23 (0.5)	0.83
Colour diameter (mm)	1.37 (0.6)	1.36 (0.7)	1.40 (0.5)	1.37 (0.6)	0.98
V_{max} (m/s)	1.21 (0.7)	1.26 (0.7)	1.11 (0.8)	1.19 (0.6)	0.77
Day 3 Echocardiographic PDA parameters					
B&W diameter (mm)	0.99 (0.8)	0.79 (0.8)	1.40 (0.6)	0.93 (0.6)	0.023
Colour diameter (mm)	1.00 (0.8)	0.76 (0.8)	1.46 (0.7)	0.96 (0.6)	0.007
V_{max} (m/s)	0.93 (0.9)	0.85 (1.0)	1.05 (0.8)	1.01 (0.9)	0.72
Change in echocardiographic PDA parameters between day 1 and day 3					
B&W diameter (mm)	0.35 (0.9)	0.55 (0.9)	−0.02 (0.9)	0.30 (0.8)	0.09
Colour diameter (mm)	0.40 (1.0)	0.63 (0.9)	−0.06 (0.9)	0.40 (0.8)	0.05
V_{max} (m/s)	−0.27 (0.8)	−0.42 (0.6)	−0.16 (0.9)	−0.10 (0.8)	0.60

CRIB = Clinical risk index for babies; CrUS = Cranial ultrasound scan; SDS = Standard deviation scores; PDA = Patent ductus arteriosus; B&W = Black and white. Values are expressed as mean (SD) unless otherwise stated.

DETERMINANTES DEL RIESGO EN DAP

Lower Risk	Determinants of Risk (hsPDA)	Higher Risk
No	**Tachycardia**	Yes
No	**Tachypnea**	Yes
No need for respiratory support or oxygen, stable Spo_2 and Pao_2	**Respiratory support**	Need for invasive or non-invasive respiratory support Worsening respiratory situation (eg, increasing flow and Fio_2 on HFNC; increasing PEEP, PIP and Fio_2 on CPAP; NIV; MV) and frequent desaturations
Abdomen soft, not distended	**Abdominal signs and symptoms**	Abdominal distension, residual feeding volume (other pre-NEC signs)
Not present	**Signs of organ dysfunction**	Renal failure, NEC, impaired NIRS variables
• LA only mildly dilated: LA/Ao ≤ 1,2 (PLAX) • Normal LV size • Normal systolic LV function (LVEF ≥ 55%) • Ductal Diameter ≤ 1 mm (at narrowest ID) • PDA Vmax ≥ 3 m/s (CW Doppler) • Ductal systolic and diastolic left–to–right flow ≥ 2 m/s (continuous) usually indicates narrowing (closing) PDA • Normal mean and diastolic PA flow • ACA RI ≤ 0.75 • No (or only early) diastolic retrograde DAO flow	**Echocardiography, Doppler sonography (cerebral, abdominal)**	• Severe LA dilation: LA/Ao ≥ 1,4 (PLAX) • Severe LV dilation (4C view, PSAX) • Systolic LV dysfunction (LVEF < 50%) • Ductal diameter ≥ 2 to 3 mm (at narrowest ID) or ductal diameter greater than or equal to MPA diameter • PDA Vmax ≤ 2 m/s (CW, unrestrictive) • Ductal left-to–right diastolic flow ≥ 0,5 m/s • Highly elevated mean + diastolic PA flow • Severe PA dilation (eg, LPA > AAO) • ACA RI ≥ 0.9 • Holodiastolic retrograde DAO flow (steal)

PEDIATRICS Volume 146, number 5, November 2020:e20201209. State Of the Art Review Article. Patent Ductus Arteriosus of the Preterm Infant.

TRATAMIENTO

Murmur

Systemic hypotension

Evidence of end-organ hypoperfusion, renal insufficiency, NEC, IVH

Acidosis (lactic, metabolic)

Oxygenation failure

Increased ventilation requirements

Radiologic evidence of cardiomegaly or pulmonary edema

ELGAN (<28 week) and/

or any clinical sypmtomatology

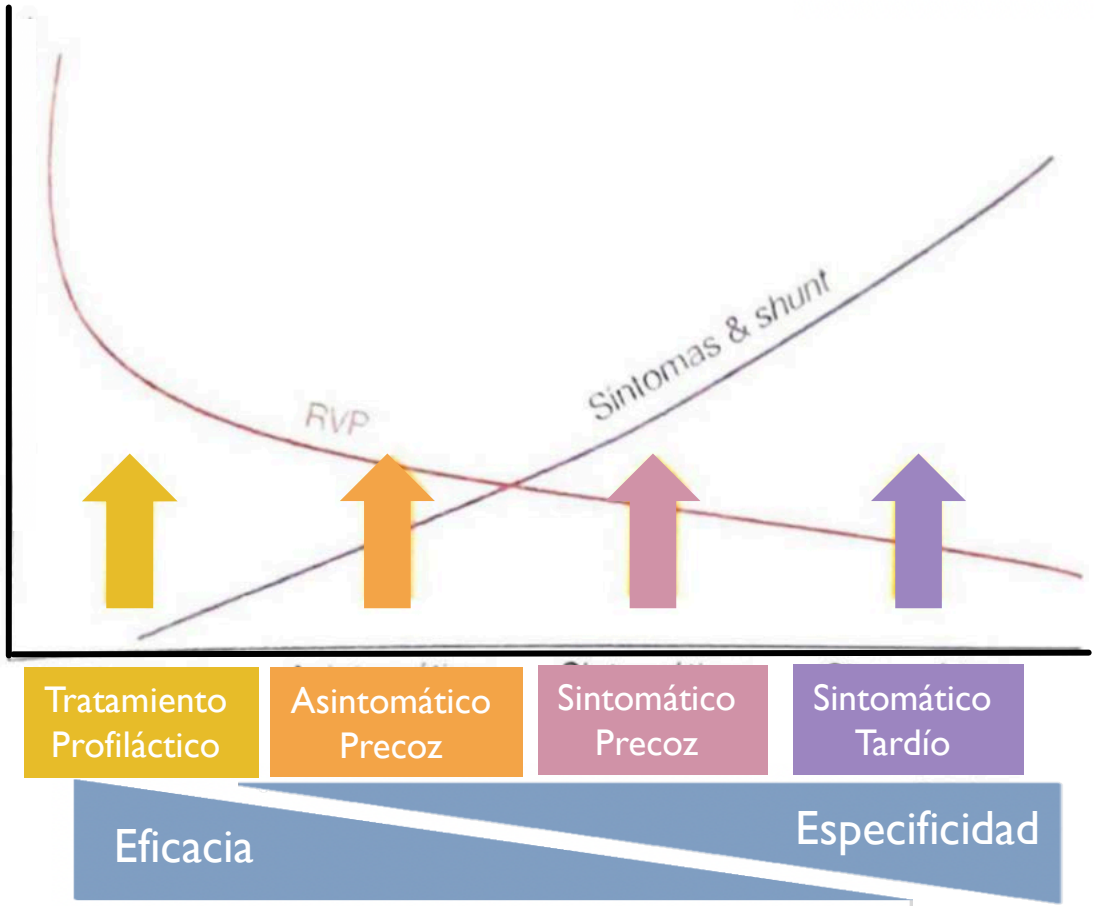
Echo assesment

hsPDA

Follow-up Treatment

Singh Y, et al. Front. Pediatr. 8:573627.

Fig. 46-4. Períodos de tratamiento DAP



Tapia, J.L., González A. (2018). Cap 46 DAP. Luco M, et al. *Neonatología.* Ed 4°. (p 397-406)

TRATAMIENTO: PROFILÁCTICO

Figura 46-5. Esquema de tratamiento profiláctico en el prematuro < 28 semanas.

<28 sem
(evaluar entre las 3-12 hrs)

ECO (+)

Diámetro >2 mm

Si → Tratar

No → No Tratar

ECO (-)

Riesgo HIV severa >30%

Si → Tratar

No → No Tratar

www.neocosur.org

Tapia, J.L., González A. (2018). Cap 46 DAP. Luco M, et al. *Neonatología.* Ed 4°. (p 397-406)

TRATAMIENTO: GENERAL

Ambiente térmico neutro	• Minimizar demanda de oxígeno.
Adecuada oxigenación y apoyo ventilatorio	• PEEP mod-alto para ↓ EPA y consecuencia del shunt por el DAP.
Evitar aporte excesivo líquidos	• Balance para aporte adecuado y evitar restricción líquidos con falla renal 2°.
Hcto >35%	• Mejorar entrega O2 si la perfusión esta limitada.
Evitar uso de furosemida	• Estimula secreción PGE2, con desarrollo DAP.

Tapia, J.L., González A. (2018). Cap 46 DAP. Luco M, et al. *Neonatología.* Ed 4°. (p 397-406)
Waal K., Prasad R., Kluckow M. Seminars in Fetal and Neonatal Medicine 26 (2021) 101219

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ORIGINAL ARTICLES

PDA-TOLERATE Trial: An Exploratory Randomized Controlled Trial of Treatment of Moderate-to-Large Patent Ductus Arteriosus at 1 Week of Age

Ronald I. Clyman, MD[1,2], Melissa Liebowitz, MD[1], Joseph Kaempf, MD[3], Omer Erdeve, MD[4], Ali Bulbul, MD[5],

Diseño:
N° 202 RN <28 sem con DAP mod-grande, 6 y 14 DDV.

- Ensayo controlado randomizado, 2014- 2017

Resultados

- Sin diferencias resultado 1° (ligadura Qx o DAP al alta).
- Sin diferencias resultado 2°: DBP, muerte, y necesidad VM.
- ERT <soporte inotrópico, > retraso alimentación > sepsis tardía y muerte RNPT ≥26 sem.

Table VI. Neonatal outcomes in infants <26 weeks and ≥26 weeks gestation

Outcomes	<26 wk (n = 106) CT group (n = 51)	<26 wk (n = 106) ERT group (n = 55)	<26 wk (n = 106) Risk ratio (95% CI)	≥26 wk (n = 96) CT group (n = 47)	≥26 wk (n = 96) ERT group (n = 49)	≥26 wk (n = 96) Risk ratio (95% CI)
Primary outcome						
Ligation or outpatient PDA follow-up, %	44	31	0.72 (0.43-1.20)	34	32	0.93 (0.52-1.70)
PDA ligation, %	18	15	0.86 (0.36-2.00)	6.4	8.9	1.40 (0.33-5.90)
Outpatient PDA follow-up, %	26	16	0.63 (0.28-1.40)	28	23	0.82 (0.40-1.70)
Secondary outcomes						
NEC, %*	24	18	0.76 (0.36-1.60)	13	13	0.94 (0.33-2.70)
BPD, %	70	62	0.89 (0.66-1.20)	37	36	0.97 (0.56-1.70)
BPD or death, %	75	69	0.93 (0.73-1.20)	38	45	1.20 (0.72-1.90)
Death, %	18	22	1.20 (0.57-2.70)	2.1	16†	7.70 (1.04-59.0)
PDA (moderate/large) 10 d after randomization, %*	80	47‡	0.59 (0.43-0.80)	79	33‡	0.42 (0.27-0.66)
Rescue criteria met, %	80	40‡	0.50 (0.34-0.71)	43	20†	0.47(0.24-0.92)
Received rescue treatment, %	63	23‡	0.36 (0.21-0.62)	34	13†	0.39 (0.17-0.91)
Received furosemide ≥14 d, %*	49	40	0.82 (0.53-1.30)	43	29	0.67 (0.39-1.20)
Days until enteral intake 120 ml/kg/d, median (IQR)*	20 (10-31)	18.5 (11-31)	0.92 (0.85-1.00)¶	6 (3-14)	14† (4.5-19)	2.30 (2.10-2.60)¶
Daily weight gain, g/kg/d, mean ± SD*	21.2 ± 4.6	21.4 ± 4.1	−0.26 (−2.10 to 1.60)¶	24.2 ± 4.2	23.7 ± 5.2	0.59 (−1.40 to 2.60)¶
Days until last gavage feeding, median (IQR)*	88 (74-118)	90 (74-116)	0.96 (0.92-1.00)¶	65 (49-84)	68 (57-84)	1.20 (1.20-1.30)¶
Other exploratory analyses						
Pulmonary hemorrhage, %*	2.0	1.8	0.93 (0.06-14.4)	2.1	2.0	0.96 (0.06-14.9)
sIVH, %	15.7	23.6	0.93 (0.32-2.70)	6.4	12.2	1.4 (0.25-8.20)
PVL (cystic), %	20	13	0.64 (0.26-1.50)	2.1	12	5.8 (0.72-46.0)
ROP (treated), %	30	24	0.81 (0.41-1.60)	2.2	12§	5.5 (0.67-45.0)
Pneumonia, %*	13	7	0.53 (0.16-1.70)	4	8	1.9 (0.37-10.0)
Bacteremia, %*	29	35	1.17 (0.67-2.10)	13	24	1.9 (0.78-4.70)
Bacteremia, CONS, %*	2	7	0.23 (0.03-2.01)	6	0	**
Bacteremia Non-CONS, %*	27	27	0.99 (0.53-1.90)	6	24†	3.8 (1.20-12.7)
Received dopamine ≥3 d, %*	44	22†	0.49 (0.26-0.90)	6.4	4.3	0.67 (0.12-3.80)
Received corticosteroids ≥7 d, %*	53	42	0.79 (0.53-1.20)	21	12	0.58 (0.23-1.50)
Days until discharge, median (IQR)*	103 (91-129)	106 (89-127)	0.98 (0.95-1.00)¶	76 (62-94)	78 (63-97)	1.2 (1.10-1.20)¶

Clyman R., et al. J Pediatr. 2019 Feb;205:41-48.e6.

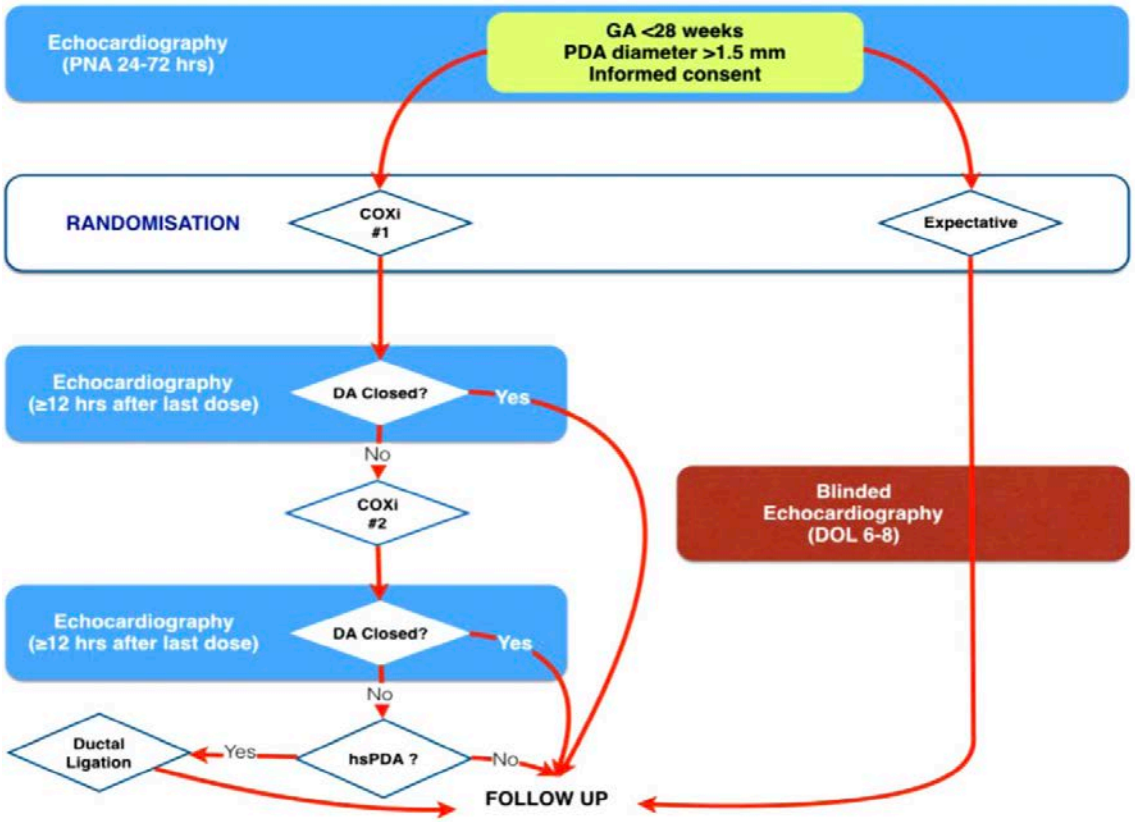
Hundscheid et al. BMC Pediatrics (2018) 18:262
https://doi.org/10.1186/s12887-018-1215-7

BMC Pediatrics

STUDY PROTOCOL Open Access

Early treatment versus expectative management of patent ductus arteriosus in preterm infants: a multicentre, randomised, non-inferiority trial in Europe (BeNeDuctus trial)

Tim Hundscheid[1*], Wes Onland[2], Bart van Overmeire[3], Peter Dijk[4], Anton H. L. C. van Kaam[5], Koen P. Dijkman[6], Elisabeth M. W. Kooi[4], Eduardo Villamor[7], André A. Kroon[8], Remco Visser[9], Daniel C. Vijlbrief[10], Susanne M. de Tollenaer[11], Filip Cools[12], David van Laere[13], Anne-Britt Johansson[14], Catheline Hocq[15], Alexandra Zecic[16], Eddy Adang[17], Rogier Donders[17], Willem de Vries[10], Arno F. J. van Heijst[1] and Willem P. de Boode[1]



Métodos:

- E° multicéntrico, aleatorizado UCIN.
- RNPT < 28 sem con DAP con diámetro > 1,5 mm.
- Tratamiento precoz (24 y 72 h) con COX1 ibuprofeno v/s expectante.

Resultados esperados:

- **Resultado 1°:** mortalidad y/o NEC estadio Bell ≥ IIa, y/o DBP.
- **Resultado 2°:** secuelas a corto plazo insuf. cardiovascular, desarrollo neurológico a los 2 años.

TRATAMIENTO: MÉDICO

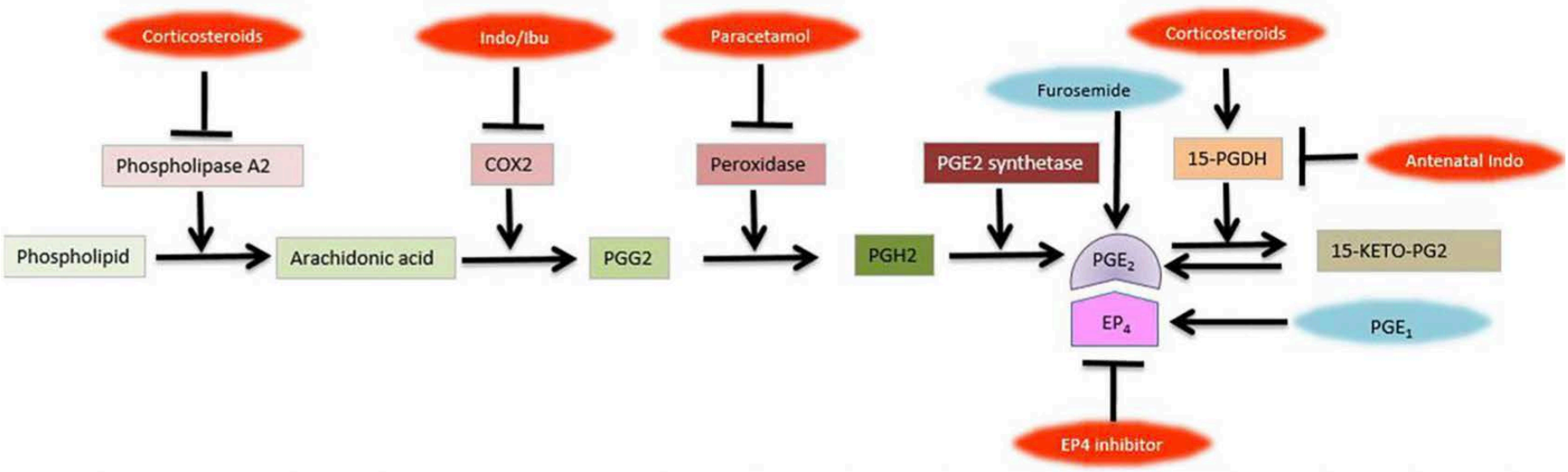


FIGURE 2 | Prostaglandin pathway and metabolism. Inhibitors of various steps are shown in red., COX-1, cyclooxygenase-1; EP4, Prostaglandin receptor 4; Indo, Indomethacin; Ibu, Ibuprofen; PG, prostaglandin; 15-PGDH, 15-hydroxyprostaglandin dehydrogenase; 15-KETO-PG2 (Figure courtesy of Fahri Ovali).

Ovalı F (2020) Molecular and Mechanical Mechanisms Regulating Ductus Arteriosus Closure in Preterm Infants. Front. Pediatr. 8:516.

TRATAMIENTO: MÉDICO

	Dosis	Vía	Contraindicaciones
Indometacina	**<48 hrs:** 0,2 mg/kg inicial. Luego 2 dosis de 0,1 mg/kg cada 12 hrs **2-7 días:** 0,2 mg/kg inicial. Luego 2 dosis de 0,2 mg/kg cada 12 hrs **>7 días:** 0,2 mg/kg inicial. Luego 2 dosis 0,25 mg/kg cada 12 hrs	Endovenosa	Contraindicaciones: BUN>50MG% Crea >1,8 mg/% Plaquetas <50.000 Diátesis hemorrágica NEC *Infusiones deben ser lentas: 2-3 hrs.
Ibuprofeno	10 mg/kg inicial, luego 2 dosis de 5 mg/kg cada 24 hrs	Endovenosa Oral	Precaución si plaquetas <50.000 → > riesgo diátesis hemorrágica
Paracetamol	15 mg/kg/dosis cada 6 hrs por 3-5 días	Endovenosa Oral	No usar en falla hepática. *Control pruebas hepáticas 24-48 hrs.

Tapia, J.L., González A. (2018). Cap 46 DAP. Luco M, et al. *Neonatología.* Ed 4°. (p 397-406)

2017

JPPT | Clinical Investigation

Acetaminophen for Patent Ductus Arteriosus in Extremely Low-Birth-Weight Neonates

Caitlyn M. Luecke, PharmD; Caren J. Liviskie, PharmD; Brandy N. Zeller, PharmD; Zachary A. Vesoulis, MD; and Christopher McPherson, PharmD

MÉTODOS: dosis PCT 15 mg/kg c/ 6 hrs (88 % IV).

- Marcadores fn hepática y renal, soporte respiratorio y morbilidades para describir seguridad del PCT.

RESULTADOS: N° 41 RN → mediana PN 760 g y mediana EG 25 sem.

- 27 RN (66 %) no requirieron más tratamiento → Sin RAM en terapia con PCT.

Table 2. Patient Characteristics of Responders and Non-Responders to Acetaminophen

Table 3. Safety Parameters

Parameter	Baseline	Treatment	p value
Alanine transaminase, units/L, median (IQR)	6 (0–8)	8 (5–13)	0.019
Aspartate transaminase, units/L, median (IQR)	24 (19–30)	25 (19–35)	0.362
Alkaline phosphatase, units/L, median (IQR)	405 (263–604)	381 (328–636)	0.286
Bilirubin, mg/dL, median (IQR)	3.0 (1.6–4.4)	2.8 (1.8–3.8)	0.314
Serum creatinine, mg/dL, median (IQR)	0.6 (0.4–1.0)	0.5 (0.4–0.8)	0.040
Positive end expiratory pressure, mm Hg, median (IQR)	6 (5–7)	6 (5–7)	1
Fraction of inspired oxygen, median (IQR)	0.37 (0.27–0.49)	0.35 (0.26–0.42)	0.131
Any intraventricular hemorrhage, n (%)	19 (46)	19 (46)	1
Grade III/IV intraventricular hemorrhage, n (%)	9 (22)	9 (22)	1
Necrotizing enterocolitis, n (%)	0 (0)	4 (10)	0.13
Spontaneous intestinal perforation, n (%)	7 (17)	8 (20)	1

Luecke CM., et al. J Pediatr Pharmacol Ther 2017;22(6):461–466

JAMA | Original Investigation

2018

Association of Placebo, Indomethacin, Ibuprofen, and Acetaminophen With Closure of Hemodynamically Significant Patent Ductus Arteriosus in Preterm Infants
A Systematic Review and Meta-analysis

Souvik Mitra, MD; Ivan D. Florez, MD, MSc; Maria E. Tamayo, MD, MSc; Lawrence Mbuagbaw, MD, PhD; Thuva Vanniyasingam, MSc; Areti Angeliki Veroniki, PhD; Adriana M. Zea, RD; Yuan Zhang, PhD; Behnam Sadeghirad, PharmD, MPH; Lehana Thabane, PhD

OBJETIVOS

- Calcular probabilidad cierre DAP con comp HDN con intervenciones farmacoterapéuticas y sus RAMS.

FUENTES DE DATOS: MEDLINE, Embase y Cochrane → 2015- 2017.

- ECA RNPT <37 sem tratados con indometacina, ibuprofeno o acetaminofén IV/VO.

RESULTADOS:

- Resultado 1°: cierre del PDA hemodinámicamente significativo
- Resultado 2°: cierre quirúrgico, mortalidad, NEC, y HIV.

RESULTADOS: N° 68 ECA → 4802 RN

- Tasa general cierre DAP: 67,4 %.
- Una dosis alta ibuprofeno VO → probabilidad significativamente > cierre DAP v/s dosis estándar IV.
- Sin diferencias significativas en mortalidad, NEC, HIV v/s placebo.

Souvik Mitra, et al. *JAMA*. 2018;319(12):1221-1238.

Received: 21 April 2021 | Revised: 1 June 2021 | Accepted: 2 June 2021

DOI: 10.1111/apa.15970

2021

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

EBNEO COMMENTARY

Is intravenous paracetamol as effective as ibuprofen in closing haemodynamically significant patent ductus arteriosus after the first treatment course in preterm babies?

Asad Abbas | Matthew Cawsey

Birmingham Women's Hospital, Birmingham, UK

Método: E° controlado aleatorio prospectivo → RN 25+0 y 31+6 sem.

- Objetivo comparar un ciclo de 3 días de paracetamol IV v/s ibuprofeno IV para cerrar hsPDAP.

E° PDA-TOLERATE

- En comparación con la tasa de cierre espontáneo DAP, la razón de probabilidad de cierre ductal inducido por paracetamol fue menor v/s ibuprofeno.
- PCT TTO DAP: < incidencia de trombocitopenia y < RAMS renales y gastrointestinales.

2 RS que compararon PCT v/s ibuprofeno

- Diferencia significativa a favor del paracetamol en niveles creatinina, diuresis, recuento plaquetas, bilirrubina e incidencia hemorragia gastrointestinal.

Abbas A., Matthew Cawsey M. *Acta Paediatrica*. 2021;00:1–2.

TRATAMIENTO: QX

- **Ligadura quirúrgica endoscópica**
  - Menos complicaciones: embolización, trombosis arterial, trauma valv. Tricupidea,
- **Ligadura quirúrgica abierta por toracotomía:** método tradicionalmente utilizado para cierre ductal definitivo → *complicaciones*:
  - Parálisis de las cuerdas vocales.
  - Quilotórax.
  - Síndrome post ligadura.
  - FR independiente de deterioro motor, retraso en el desarrollo y discapacidad funcional de moderada a grave.

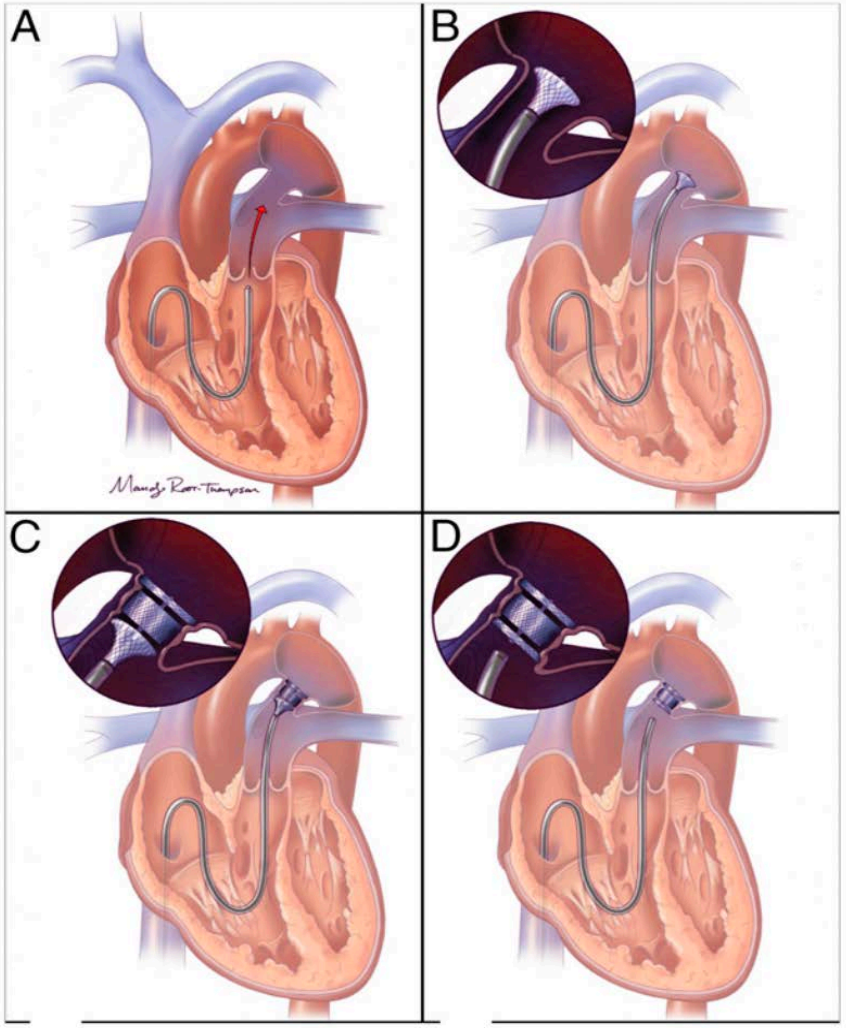


Figure 2. Procedural steps for percutaneous delivery of occlusive devices for patent ductus arteriosus closure. (33)(42) Originally published in Backes, Giesinger, Rivera et al. Percutaneous Closure of the Patent Ductus Arteriosus in Very Low Weight Infants. *Journal of Pediatrics*. 2019;213:219. Mandy Root-Thompson, Medical Illustrator.

Scerbo D., et al. Neoreviews. 2020 Jul;21(7):e469-e478.

CONCLUSIONES

- El DAP corresponde a la persistencia del vaso sanguíneo que comunica el tronco de la arteria pulmonar con la aorta descendente, pudiendo tener consecuencias hemodinámicas negativas.
  - **DBP, NEC, HIV, ICC, AKI.**
- El principal factor de riesgo de la **menor edad gestacional.**
- El diagnóstico del DAP con compromiso hemodinámico se puede realizar a través de:
  - **Triada clínica:** Hipotensión + Soplo infraclav izq + pulsos saltones.
  - **Evaluación ecocardiográfica.**
  - En proceso de evaluación de **marcadores bioquímicos.**
- Existen **discrepancias en los beneficios del tratamiento** (conducta expectante cierre espontáneo), cuando realizarlo (preventivo o sintomático?) y mediante que forma (médico o quirúrgico?)

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