HOSPITAL UNIVERSITARIO AUSTRAL

Ductus Arterioso Persistente: Manejo actual y nuevas controversias

4° Congreso Argentino de Neonatología
22-24 de Mayo, 2019

Gabriel Musante
gmusante @cas.austral.edu.ar

HOSPITAL UNIVERSITARIO AUSTRAL

Ductus Arterioso Persistente:

Superando la visión dualista ante la incertidumbre

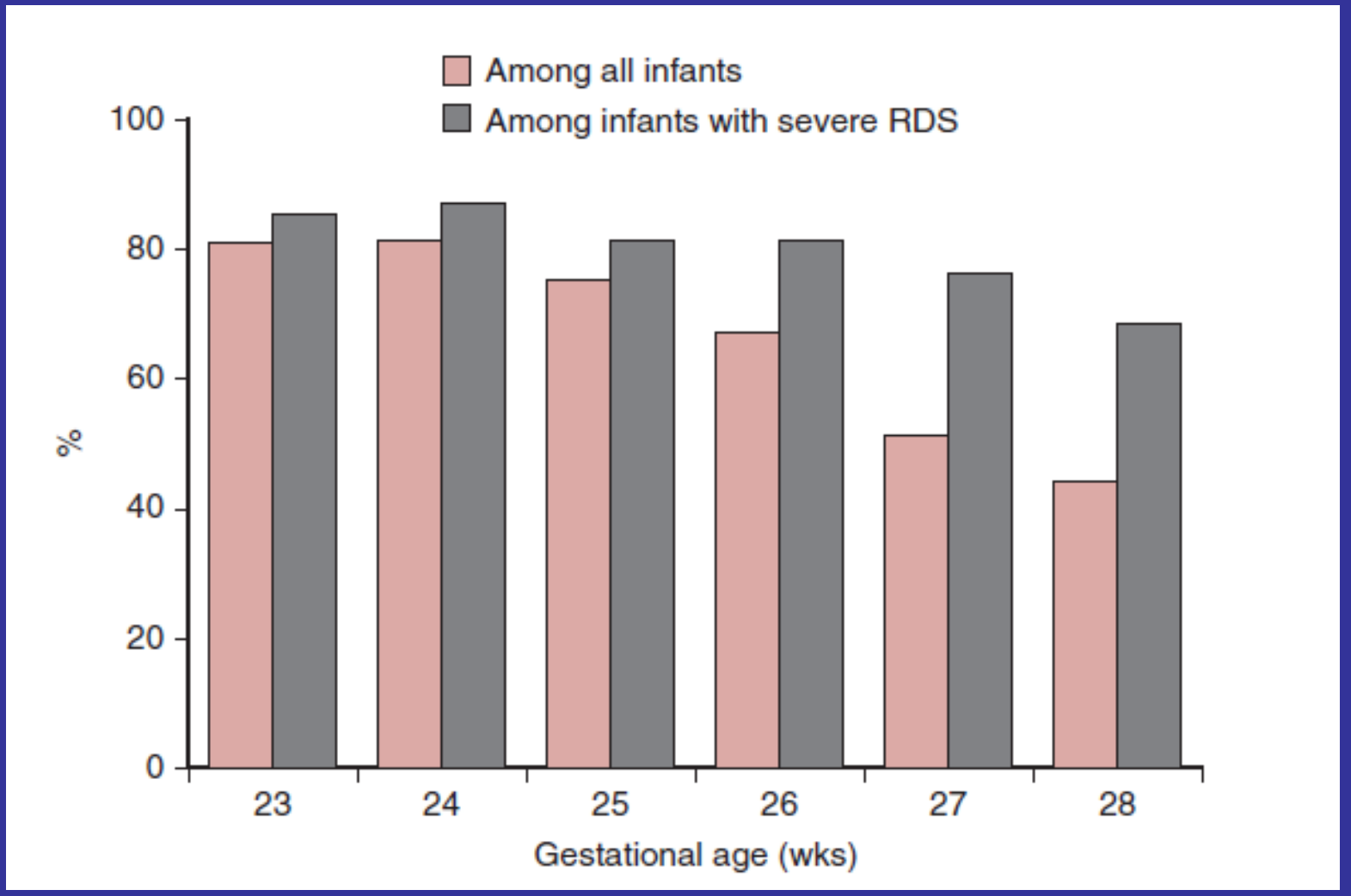
4° Congreso Argentino de Neonatología

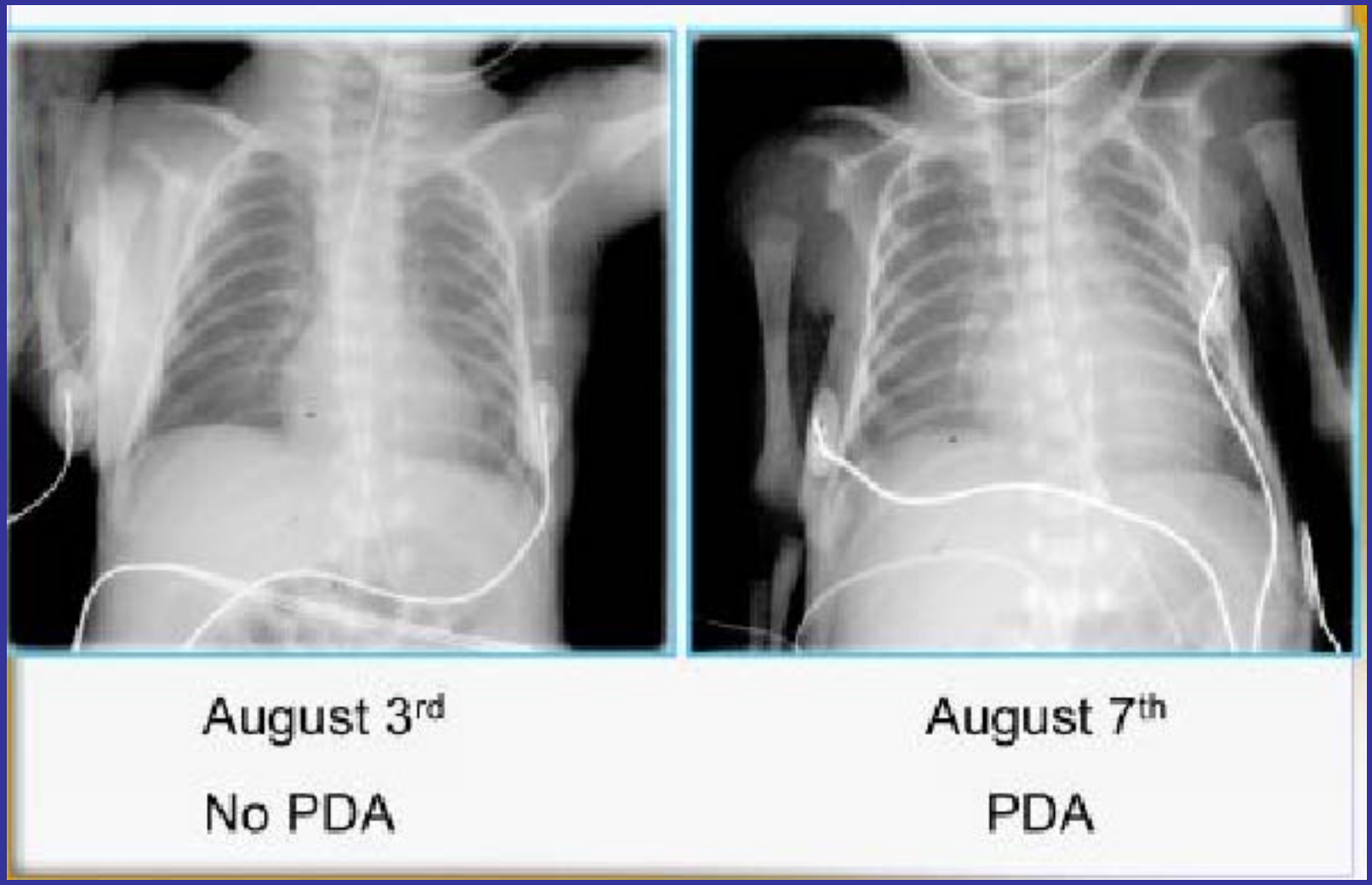
22-24 de Mayo, 2019

Gabriel Musante

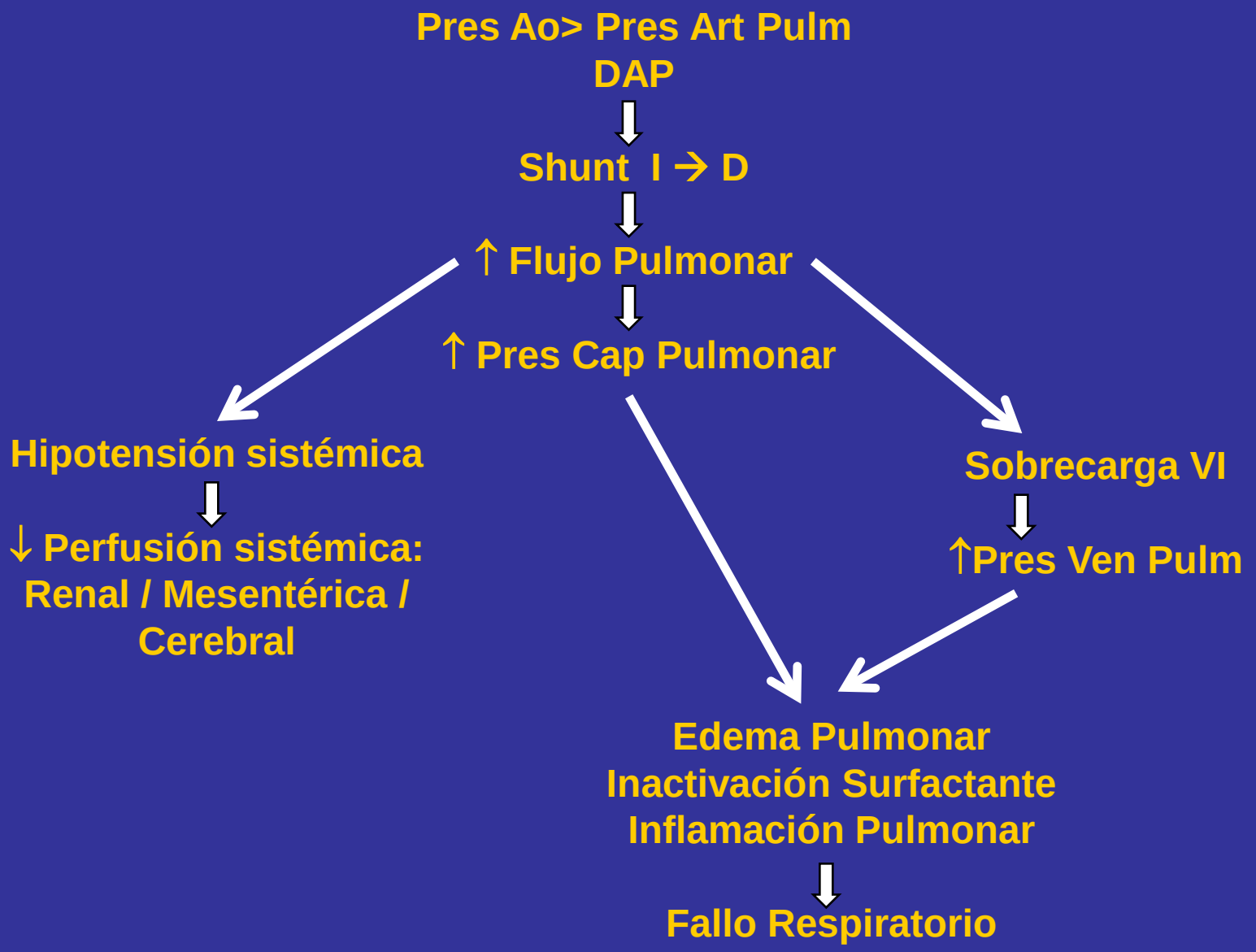
gmusante @cas.austral.edu.ar

Incidencia de DAP en UM–JMMC 2003-2009




August 3rd
No PDA
August 7th
PDA

Consecuencias Cardio-respiratorias del DAP:



Consecuencias Cardio-respiratorias del DAP:

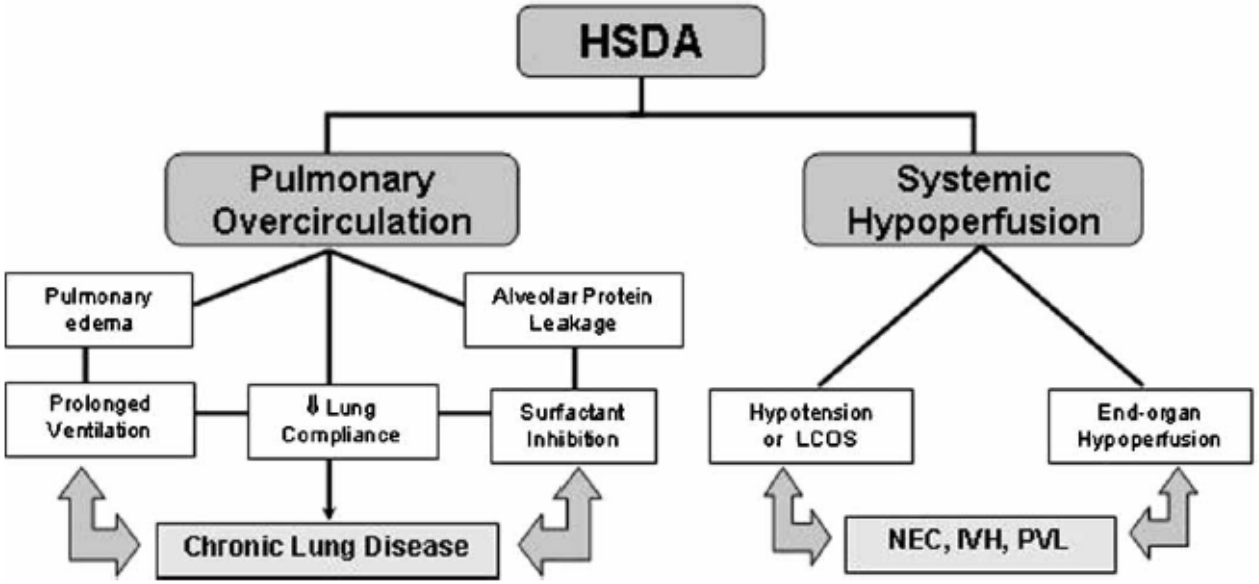


Figure 1. Pathophysiologic consequences of a HSDA. NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; PVL, periventricular leucomalacia; LCOS; low cardiac output syndrome.

HOSPITAL UNIVERSITARIO AUSTRAL

Efecto agudo del DAP sobre función pulmonar:

- Aumento del flujo y volumen sanguíneo pulmonar
- Edema / hemorragia pulmonar
- Disminución de la Compliance
- Aumento de la Resistencia
- ↑ Inflamación
- ↑ PaCO2
- ↓ PaO2

HOSPITAL UNIVERSITARIO AUSTRAL

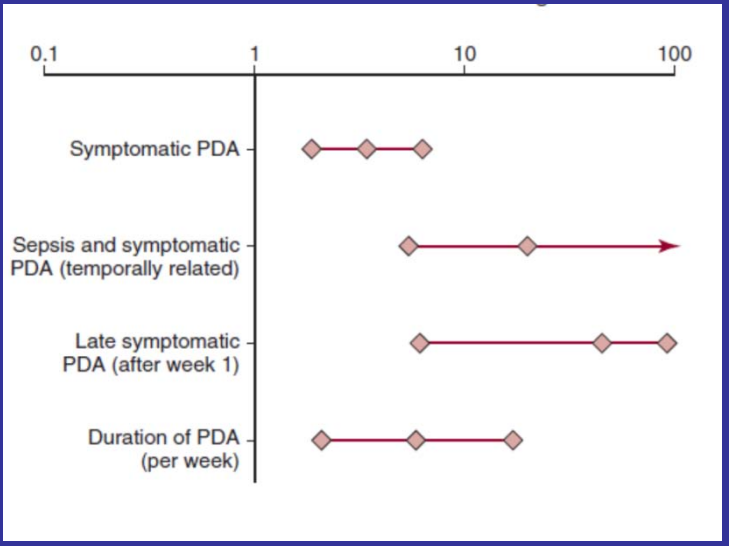
Patent Ductus Arteriosus and Respiratory Outcome in Premature Infants

Eduardo Bancalari[a] Nelson Claure[a] Alvaro Gonzalez[b]

Table 1. Odds ratios for development of BPD by multivariate logistic regression analysis

Factor	Odds ratio for BPD (95% CI)
Symptomatic PDA	6.2 (2.1–18.4)
Sepsis and symptomatic PDA (temporally related)	48.3 (6.3 to >100)
Late symptomatic PDA (after 1st week of life)	21.1 (5.6–80)
Duration of symptomatic PDA (per week)	3.5 (1.9–6.5)

Data are from Rojas et al. [56].



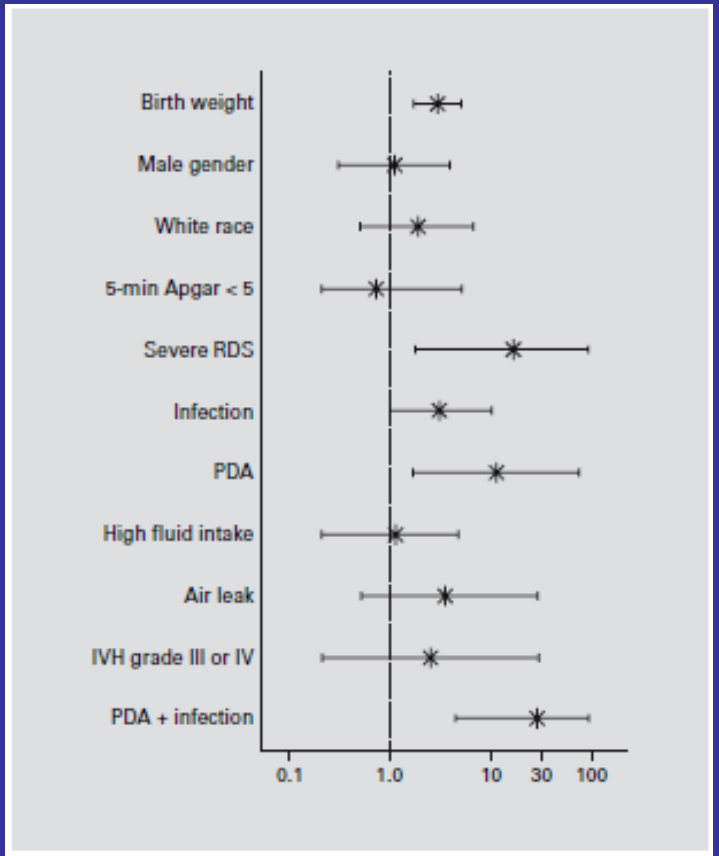
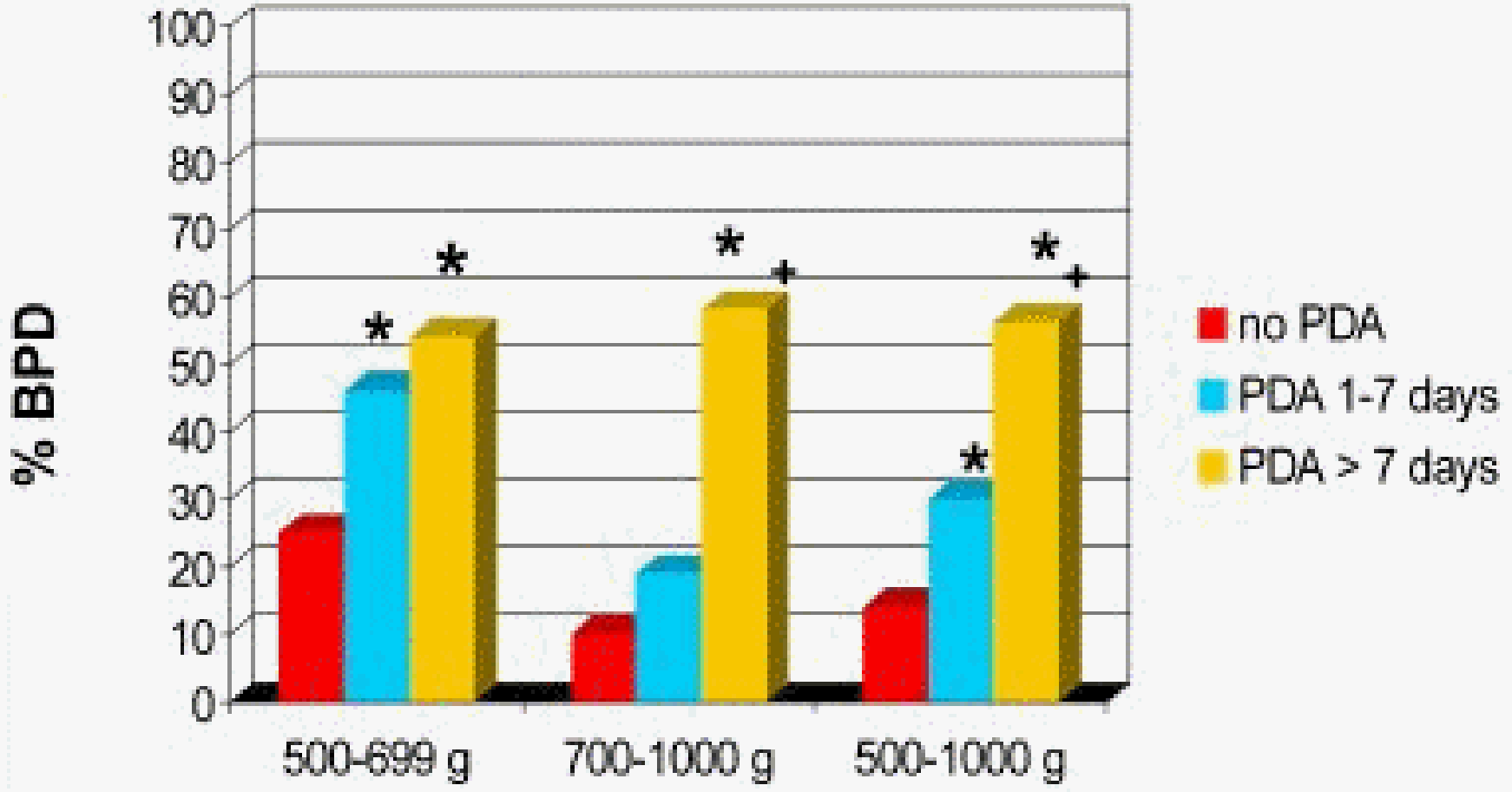


Fig. 2. Odds ratio for development of BPD, from Gonzalez et al. [57].

Biol Neonate 2005;88:192–201

Duration of PDA and Incidence of Severe BPD (O_2 36 weeks PMA)



* p < 0.05 vs no PDA + < 0.05 vs PDA 1- 7 days

Del Moral T,et al Pediatr Res 49:282A,2001

- **Impacto de las intervenciones?**
- Eficacia y seguridad?
- Impacto del manejo conservador?
- Manejo evidencia inconcluyente
- Conducta pendular e ideología - Sesgos
- Fisiopatología / Sentido común
- Estratificación
- Enfoque individualizado?

*Effects of indomethacin in premature infants with patent ductus arteriosus: Results of a national collaborative study**

The Journal of Pediatrics
June 1983

Welton M. Gersony, M.D., George J. Peckham, M.D., R. Curtis Ellison, M.D., Olli S. Miettinen, M.D., Ph.D., and Alexander S. Nadas, M.D.

"…it appears that the preferable treatment in the small premature infant presenting with a hemodynamically significant patent ductus arteriosus is to use indomethacin only after an appropriate course of usual medical therapy fails. With such a strategy, it would be expected that about one third of infants would respond to the usual medical therapy alone and thus not be exposed to the drug. Indomethacin given at such time remains equally efficacious in closing the ductus as when it is given as an adjunct to initial therapy. Surgery is satisfactory backup treatment when indomethacin therapy is unsuccessful. "

PDA MANAGEMENT AND DURATION OF ENDOTRACHEAL INTUBATION

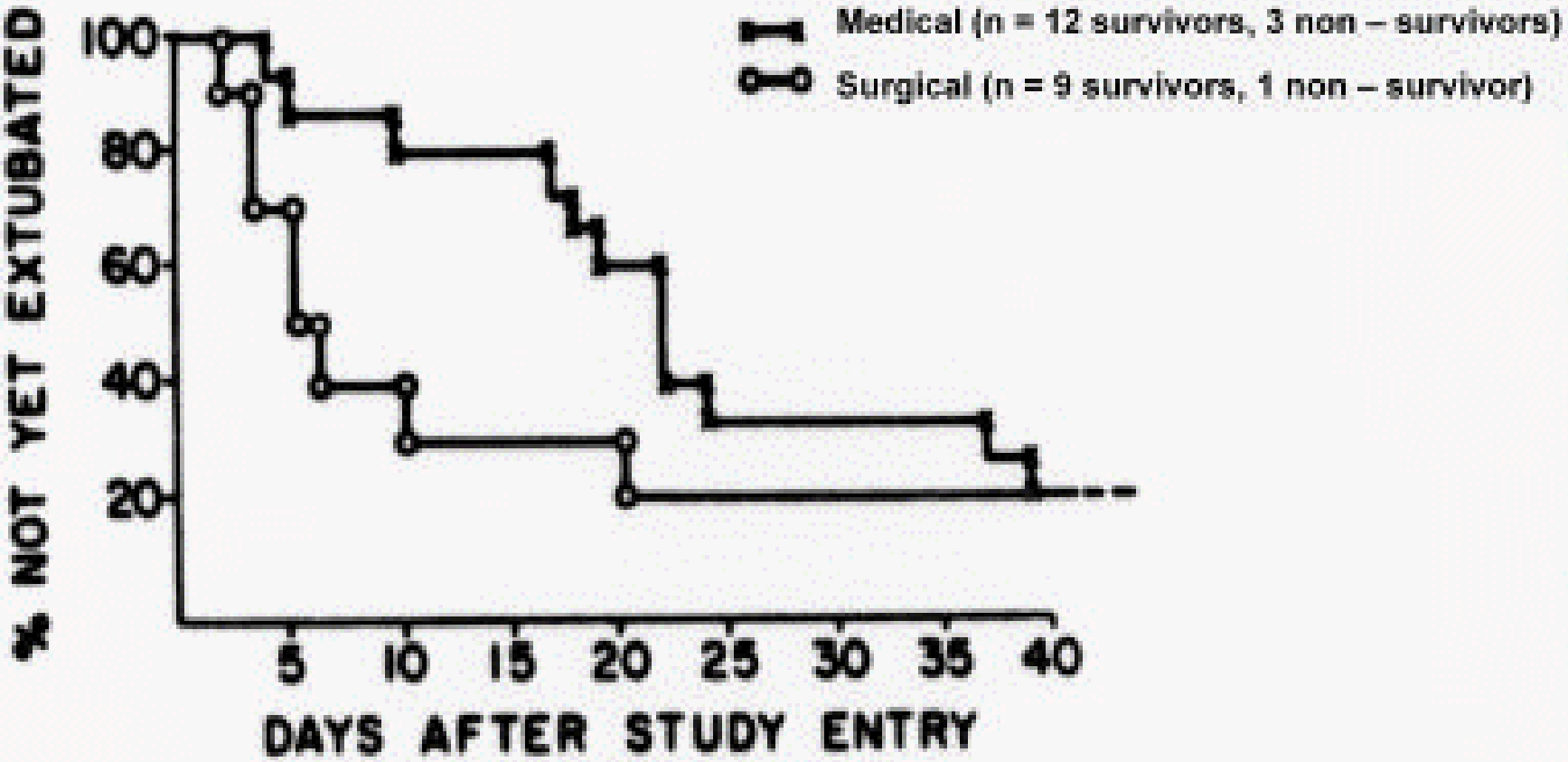


Illustration of mechanical ventilator dependence of the study groups. The patients who died were considered never to have been successfully extubated.

Cotton R, et al: J Pediatr, 93:1978

Early Closure of the patent ductus arteriosus in very low-birth-weight infants: A controlled trial.

	Control		"Early" PDA intervention		
	%	N	%	N	P
Mortality	30.8	4/13	9.1	1/11	0.1
Bronchopulmanary	66.7	8/12	18.2	2/11	<.003
Combined mortality plus BPD	84.6	13	27.3	11	<.002

Merritt et al. J of Pediatr 1981:99, 281

HOSPITAL UNIVERSITARIO AUSTRAL

Patency of the ductus arteriosus in the premature infant: is it pathologic? Should it be treated?

Matthew M. Laughon, Michael A. Simmons and Carl L. Bose

Summary

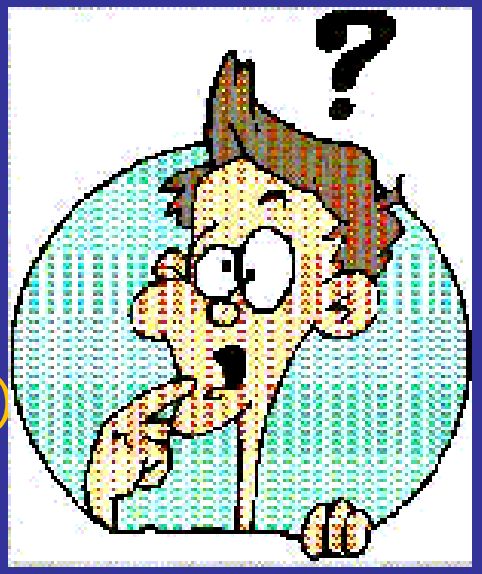
In preterm infants, patency of the ductus arteriosus may represent a normal physiologic adaptation to allow shunting from either systemic-to-pulmonary circulation (*eg*, in the first day of life) or from pulmonary-to-systemic circulation (*eg*, in the presence of severe lung disease). Therapies designed to close the ductus arteriosus are contraindicated in some settings and should not be considered a standard of care at any time until these therapies are proven to decrease long-term clinical morbidities in randomized, placebo-controlled trials.

Current Opinion in Pediatrics 2004, 16:146–151

Problemas:

- Cuando tratarlo?
- Cómo tratarlo?
- En quien tratarlo?
- Para qué tratarlo?

- **Hay que tratarlo?** (!)



Patent Ductus Arteriosus: Evidence for and against Treatment

Ronald I. Clyman, MD
Nancy Chorne, MD
Cardiovascular Research Institute and Department of Pediatrics
University of California San Francisco
San Francisco, CA

The Journal of Pediatrics • March 2007

TREATMENT TO PREVENT PATENCY OF THE DUCTUS ARTERIOSUS: BENEFICIAL OR HARMFUL?

Carl L. Bose, MD
Matthew Laughon, MD, MPH
Division of Neonatal-Perinatal Medicine
Department of Pediatrics
University of North Carolina School of Medicine
Chapel Hill, NC 27599-7596

The Journal of Pediatrics • June 2006

REVIEW ARTICLE

Preterm patent ductus arteriosus: Should we treat it?

Nick Evans

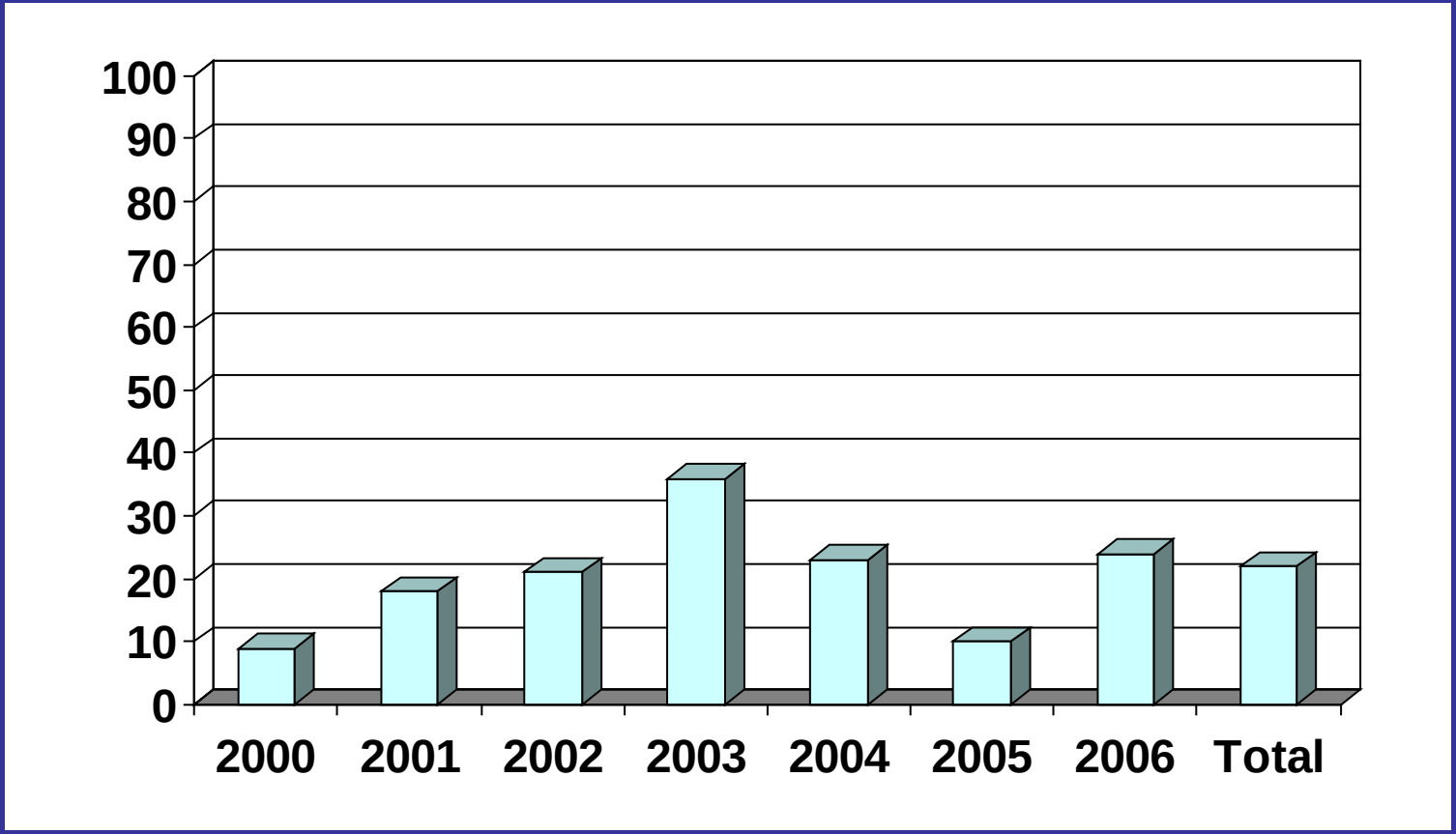
Department of Newborn Care, Royal Prince Alfred Hospital and University of Sydney, Sydney, New South Wales, Australia

Journal of Paediatrics and Child Health **48** (2012) 753–758

PDA ligation at JMH

Year	Births <1000 g	PDA ligation
2002	103	21 (20.3%)
2001	105	25 (23.8%)
2000	94	19 (20.2%)
1999	95	20 (21.0%)
1998	103	23 (22.3%)
Total	**500**	**107 (21.4%)**

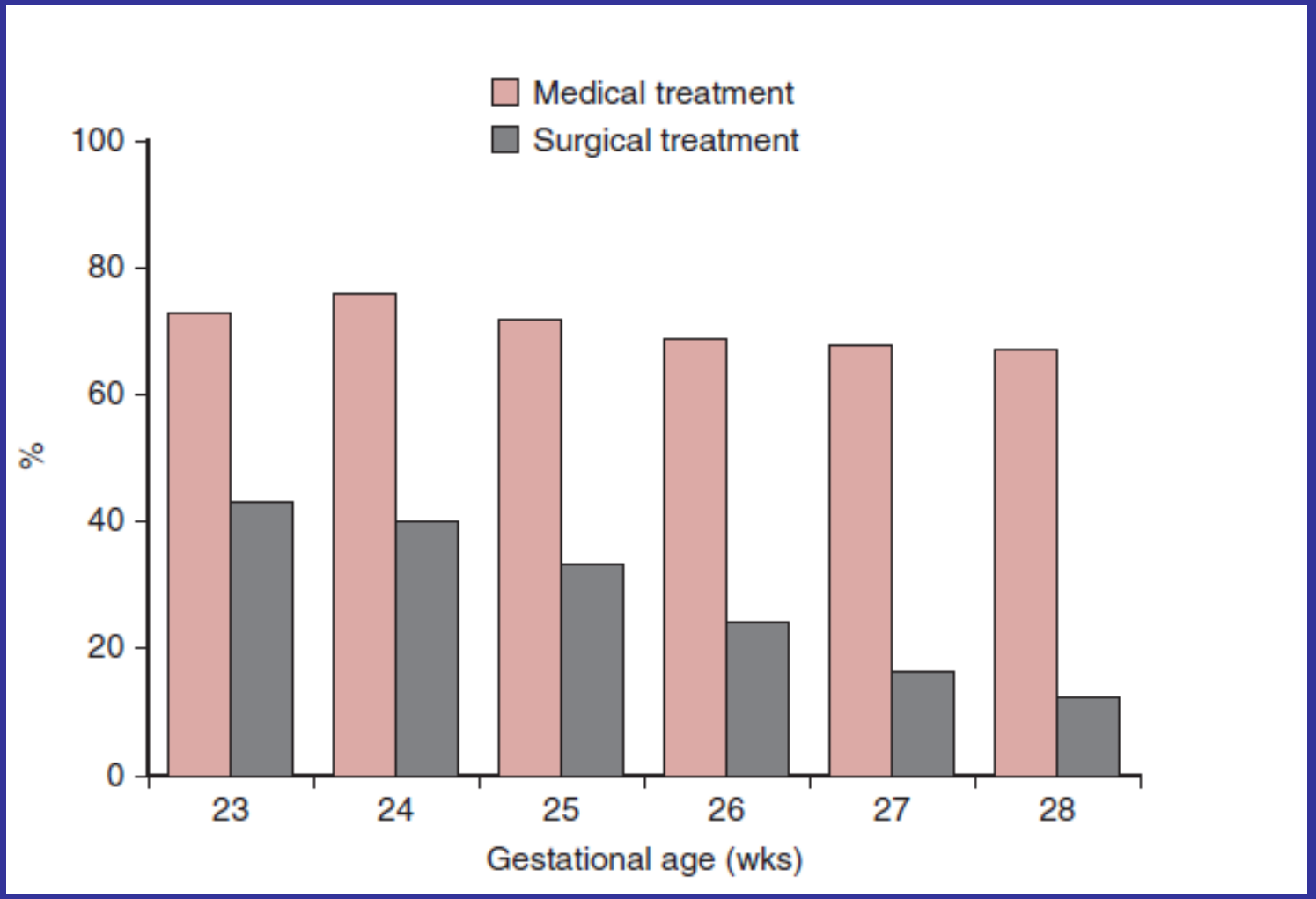
Evolución anual de RNMBP con DAP operado (%)

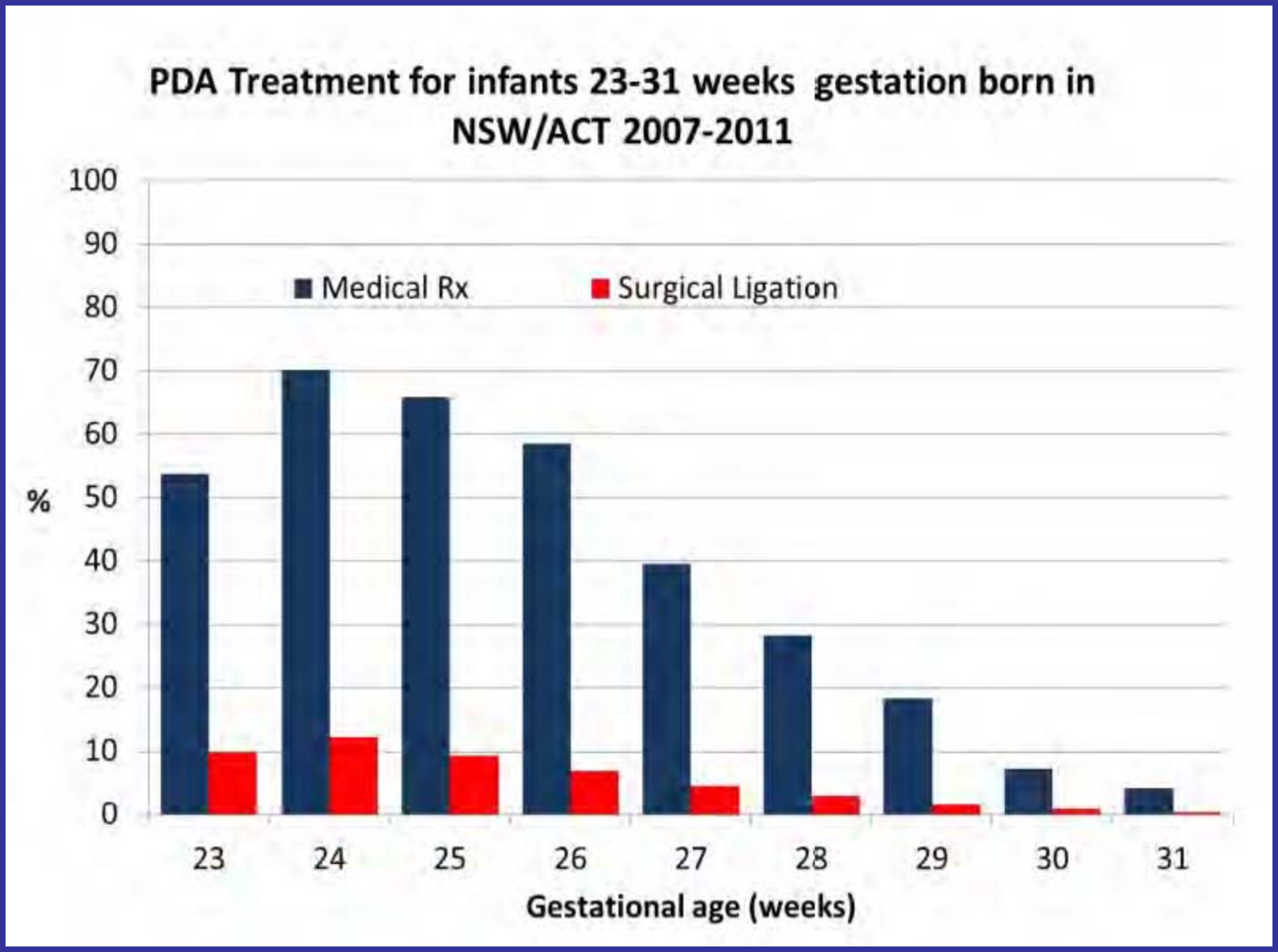


CLINICA Y MATERNIDAD SUIZO ARGENTINA

CyMSA 2000-2006, n=420 RNMBP

Tratamiento del DAP en Red NICHD 2003-2007

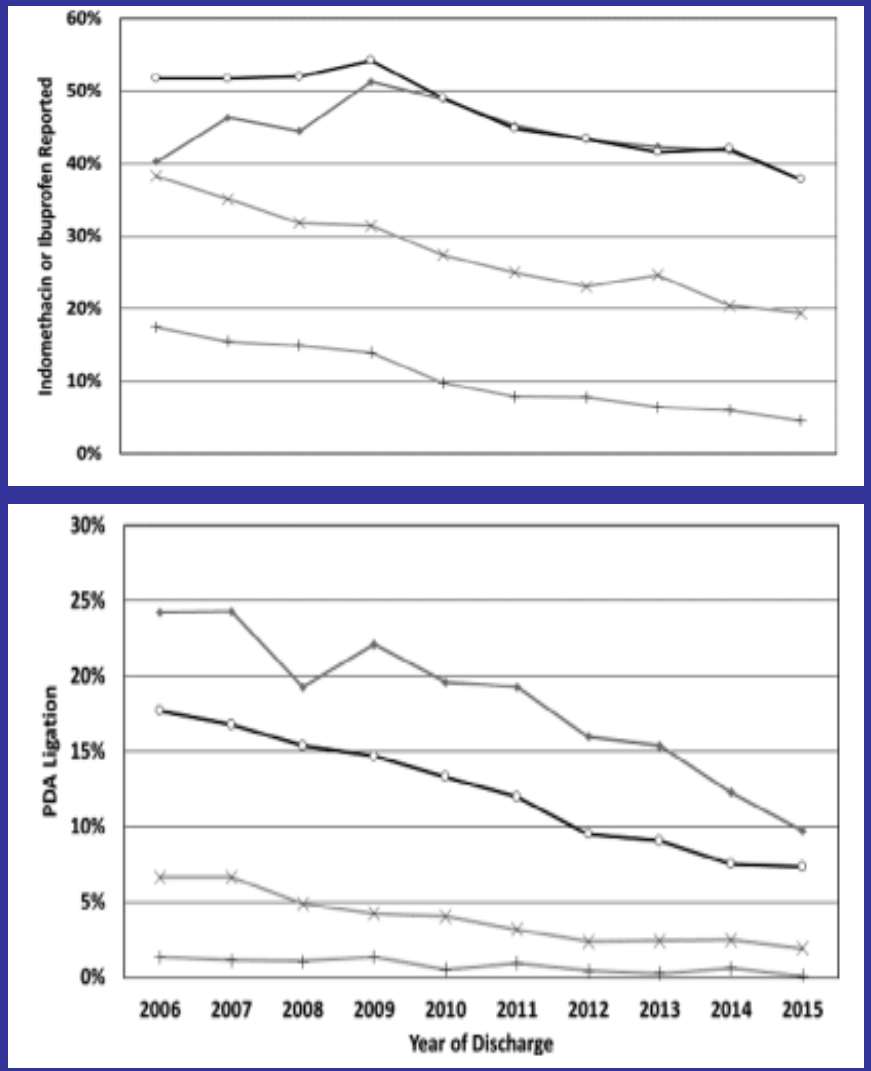



PDA Treatment for infants 23-31 weeks gestation born in NSW/ACT 2007-2011
100
90
80
70
60
50
40
30
20
10
0
%
Medical Rx
Surgical Ligation
23
24
25
26
27
28
29
30
31
Gestational age (weeks)

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Changes in the Diagnosis and Management of Patent Ductus Arteriosus from 2006 to 2015 in United States Neonatal Intensive Care Units

G. Michael Bixler, MD[1], George C. Powers, MD[2], Reese H. Clark, MD[3], M. Whit Walker, MD[4], and Veeral N. Tolia, MD[5]



Neurosensory Impairment after Surgical Closure of Patent Ductus Arteriosus in Extremely Low Birth Weight Infants: Results from the Trial of Indomethacin Prophylaxis in Preterms

NANDKISHOR S. KABRA, MD, BARBARA SCHMIDT, MD, MSC, ROBIN S. ROBERTS, MSC, LEX W. DOYLE, MD, LUANN PAPILE, MD, AVROY FANAROFF, MD, AND THE TRIAL OF INDOMETHACIN PROPHYLAXIS IN PRETERMS (TIPP) INVESTIGATORS*

Objectives To determine whether surgical closure of a patent ductus arteriosus (PDA) is a risk factor for bronchopulmonary dysplasia (BPD), severe retinopathy of prematurity (ROP), and neurosensory impairment in extremely low birth weight (ELBW) infants.

Study design We studied 426 infants with a symptomatic PDA, 110 of whom underwent PDA ligation and 316 of whom received medical therapy only. All infants participated in the multicenter Trial of Indomethacin Prophylaxis in Preterms (TIPP) and were observed to a corrected age of 18 months.

Results Of the 95 infants who survived after PDA ligation, 50 (53%) had neurosensory impairment, compared with 84 of the 245 infants (34%) who survived after receiving only medical therapy (adjusted odds ratio, 1.98; 95% CI, 1.18-3.30; $P = .0093$). BPD (adjusted odds ratio, 1.81; 95% CI, 1.09-3.03; $P = .023$) and severe ROP (adjusted odds ratio, 2.20; 95% CI, 1.19-4.07; $P = .012$) were also more common after surgical PDA closure.

Conclusions PDA ligation may be associated with increased risks of BPD, severe ROP, and neurosensory impairment in ELBW infants. *(J Pediatr 2007;150:229-34)*

Patent Ductus Arteriosus and Its Treatment as Risk Factors for Neonatal and Neurodevelopmental Morbidity

Nancy Chorne, MD[a], Carol Leonard, PhD[a], Robert Piecuch, MD[a], Ronald I. Clyman, MD[a,b]

[a]Department of Pediatrics and [b]Cardiovascular Research Institute, University of California, San Francisco, California

The authors have indicated they have no financial relationships relevant to this article to disclose.

METHODS. A total of 446 infants (<28 weeks' gestation) were treated with the same patent ductus arteriosus care–oriented protocol, and logistic regression analysis was used to examine the effects of several patent ductus arteriosus–related variables (presence of a symptomatic patent ductus arteriosus, the number of indomethacin doses used, the ductus response to indomethacin, and the use of surgical ligation) on the incidence of retinopathy of prematurity, necrotizing enterocolitis, chronic lung disease, death, and neurodevelopmental impairment.

RESULTS. Most of the predictive effects that the presence of a patent ductus arteriosus and its treatment had on neonatal morbidity could be accounted for by the infants' immature gestation. Use of surgical ligation, however, was significantly associated with the development of chronic lung disease and was independent of immature gestation, other patent ductus arteriosus–related variables, or other perinatal and neonatal risk factors known to be associated with chronic lung disease.

Pediatrics, 2007

Patent Ductus Arteriosus and Its Treatment as Risk Factors for Neonatal and Neurodevelopmental Morbidity

Nancy Chorne, MD[a], Carol Leonard, PhD[a], Robert Piecuch, MD[a], Ronald I. Clyman, MD[a,b]

[a]Department of Pediatrics and [b]Cardiovascular Research Institute, University of California, San Francisco, California

The authors have indicated they have no financial relationships relevant to this article to disclose.

TABLE 5 Association Between CLD and PDA-Related Variables: Unadjusted, Adjusted for Gestation, Adjusted for Perinatal/Neonatal Variables, and Adjusted for Gestation and Ligation

PDA-Related Variables	Risk of CLD			
	Model 1: Unadjusted OR (95% CI)	Model 2: Adjusted for Gestational Age, OR (95% CI)	Model 3: Adjusted for Perinatal and Neonatal Factors, OR (95% CI)[a]	Model 4: Adjusted for Gestational Age and Ligation, OR (95% CI)
Indomethacin doses				
Prophylactic doses >3	2.09 (1.26–3.47)[b]	1.69 (1.00–2.86)	1.35 (0.75–2.44)	1.32 (0.71–2.45)
Total doses >3	1.83 (1.13–2.95)[b]	1.44 (.87–2.38)	1.23 (0.70–2.16)	1.02 (0.54–1.94)
Ductus patent after prophylactic indomethacin	2.33 (1.25–4.36)[b]	1.79 (0.93–3.45)	1.54 (0.75–3.18)	1.09 (0.44–2.70)
Symptomatic PDA	2.81 (1.65–4.78)[b]	1.54 (0.90–2.64)	1.55 (0.85–2.81)	0.45 (0.10–2.06)
Ligation	2.14 (1.29–3.55)[b]	1.97 (1.11–3.47)[b]	1.91 (1.02–3.57)[b]	—

CI indicates confidence interval.

[a] Perinatal/neonatal variables included in model 3 of CLD (see Table 2) included the following: gestational age, male gender, preeclampsia, respiratory score, NEC, and sepsis.

[b] $P < .05$.

Pediatrics, 2007

Table 1: Odds ratios for neonatal and neurodevelopmental outcomes for infants with a patent ductus arteriosus treated with surgical ligation compared with medical management

Study	Characteristics	Odds ratios (95% confidence intervals)				
		Death	ROP	CLD	NDI	Death or NDI
Kabra 2007*	426 ELBW infants with symptomatic PDA	0.56	2.20	1.81	1.98	1.55
	PDA ligation (n=110)	(0.29-1.10)	(1.19-4.07)	(1.09-3.03)	(1.18-3.30)	(0.97-2.50)
	Medical treatment only (n=316)					
Madan 2009†	2,838 ELBW infants with PDA and known treatment assignment	0.56	-	2.89	1.58	1.20
	Primary ligation (n=135)	(0.35-0.90)		(2.18-3.84)	(1.27-1.97)	(0.82-1.76)
	Indomethacin only (n=1, 525)					
	Indomethacin and ligation (n=775)					
	No treatment (n=403)					
Clymans 2009‡	Post-hoc analysis of RCT comparing early prophylactic ligation (n=40) vs. delayed selective ligation (n=44) in ELBW infants	0.87	-	5.83	-	-
		(0.36-2.09)		(1.46-23.3)		
Mirea 2012§	Infants with GA≤32 weeks with a PDA.	0.41	1.91	2.30	-	-
	Conservative treatment (n=577)	(0.31-0.54)	(1.51-2.41)	(1.91-2.77)		
	Indomethacin only (n=2,026)					
	Indomethacin and ligation (n=626)					
	Primary ligation (n=327)					

Weisz & McNamara 2014

HOSPITAL UNIVERSITARIO AUSTRAL

ORIGINAL ARTICLE

Is surgical ligation of patent ductus arteriosus necessary? The Western Australian experience of conservative management

J M Brooks, J N Travadi, S K Patole, D A Doherty, K Simmer

Arch Dis Child Fetal Neonatal Ed 2005;**90**:F235–F239. doi: 10.1136/adc.2004.057638

See end of article for authors' affiliations

Correspondence to: Dr Patole, Department of Neonatal Paediatrics, King Edward Memorial Hospital, Bagot Road, Subiaco, Western Australia 6008; Sanjay.Patole@health.wa.gov.au

Accepted August 2004

Background: Surgical ligation of patent ductus arteriosus (PDA) is widely practised in preterm infants despite no clear evidence that this improves outcomes. Geographical isolation meant that ductal ligation was not an option in King Edward Memorial Hospital until recently.

Objective: A retrospective data analysis to test the hypothesis that outcomes of infants with persistent PDA were no worse than those of infants with no significant duct or a duct that closed after medical treatment.

Patients and Methods: A total of 252 infants (gestation ⩽28 weeks) born between 1 January 2000 and 30 June 2002 were divided into three groups: group 1, no significant PDA (n = 154); group 2, significant PDA which closed after medical treatment (n = 65); group 3, significant PDA remaining patent after medical treatment (n = 33). A significant PDA was defined by a left atrium to aortic root ratio of >1.4 or a ductal diameter >1.5 mm with a left to right shunt.

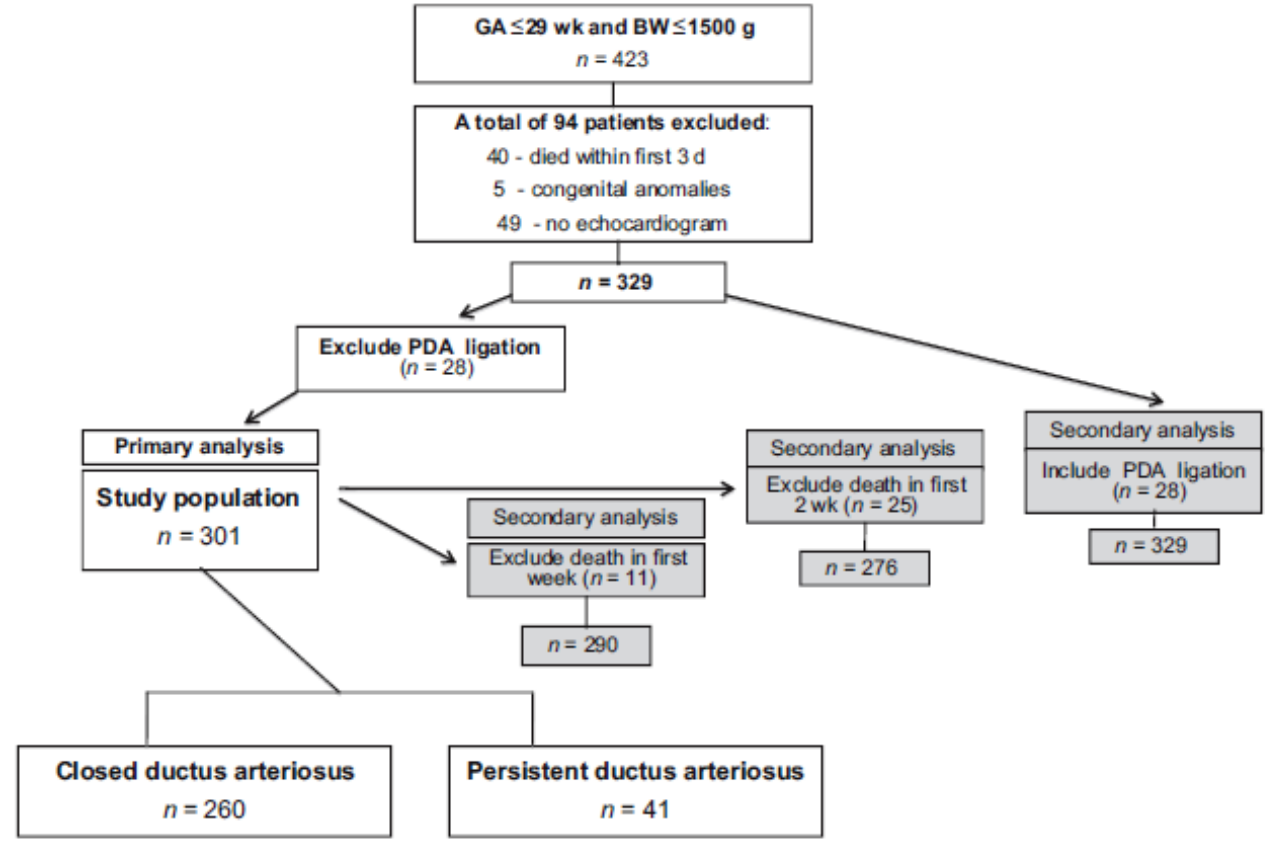
Results: Twenty four (10%) infants died at median (interquartile range) 15.5 (9–35) days. After adjustment for gestational age, relative to group 1, the infants from group 3 were at a 4.02 times increased risk of death (95% confidence interval 1.12 to 14.51). There was no significant difference between groups in the incidence of chronic lung disease, chronic lung disease or death, necrotising enterocolitis, intraventricular haemorrhage, duration of oxygen, or hospital stay.

Conclusion: Mortality was higher in infants with a persistent PDA, but other morbidities were not significantly different. A randomised trial is needed to determine whether surgical ligation will reduce mortality in such infants.

HOSPITAL UNIVERSITARIO AUSTRAL

Failure of Ductus Arteriosus Closure Is Associated With Increased Mortality in Preterm Infants

Shahab Noori, MD[a], Michael McCoy, MS, ARNP[a], Philippe Friedlich, MD, MS, Epi[b], Brianna Bright, MA[a,c], Venugopal Gottipati, MD[a], Istvan Seri, MD, PhD[b], Kris Sekar, MD[a]

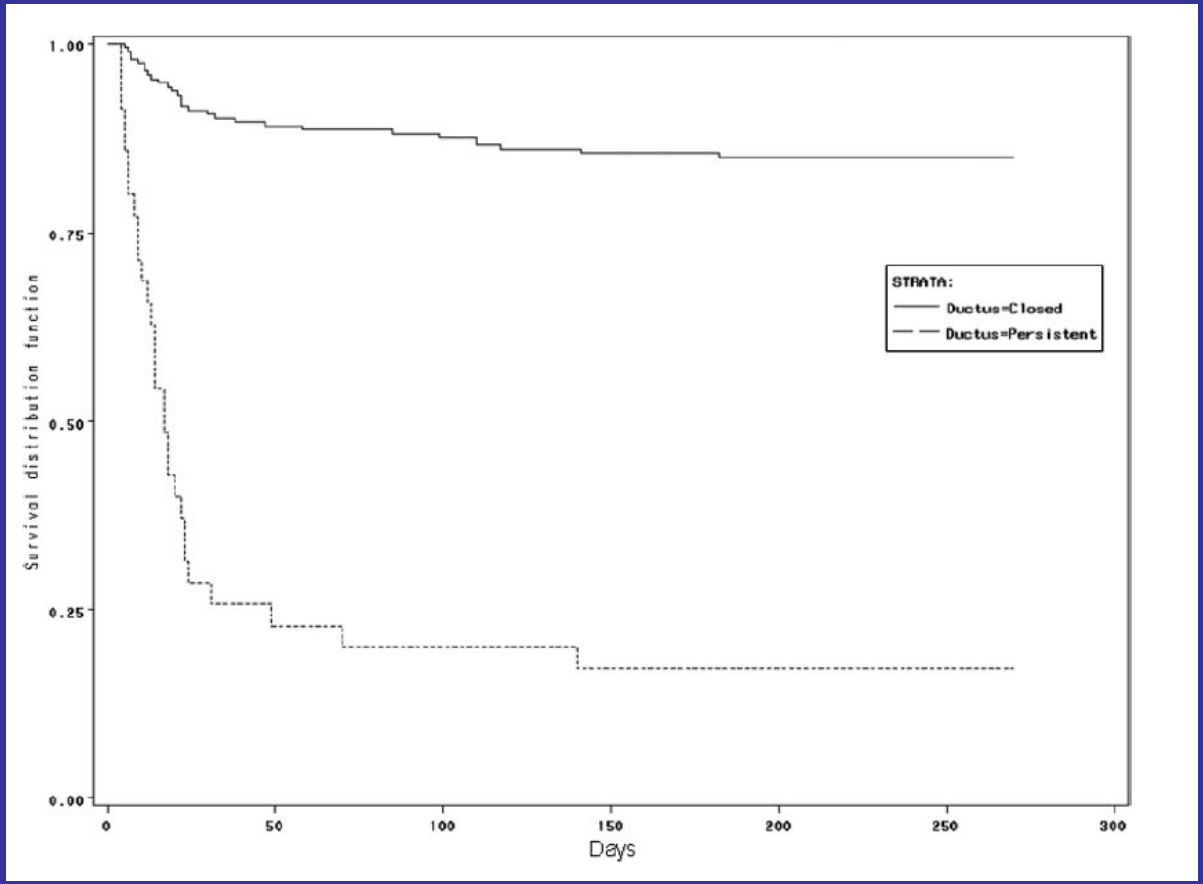


Pediatrics 2009;123:e138–e144

HOSPITAL UNIVERSITARIO AUSTRAL

Failure of Ductus Arteriosus Closure Is Associated With Increased Mortality in Preterm Infants

Shahab Noori, MD[a], Michael McCoy, MS, ARNP[a], Philippe Friedlich, MD, MS, Epi[b], Brianna Bright, MA[a,c], Venugopal Gottipati, MD[a], Istvan Seri, MD, PhD[b], Kris Sekar, MD[a]



OR 16.8 (6.1-46.6)
HR 8.34 (4.3-16.1)

Pediatrics 2009;123:e138–e144

Cierre Quirúrgico

- La asociación con resultados adversos es preocupante pero la eventual causalidad es cuestionable
- Reportes sugieren la eficacia y relativa seguridad del cierre quirúrgico comparada con la persistencia prolongada
- Little 2003, Palder 1987, Trus 1993 y otros en estudios retrospectivos postulan mejores resultados con Cx en los ELBW
- Otros muestran mejor resultado con Cx temprana que tardía (Jaillard 2006, Lee 2006, Vida 2009)
- Estudios en animales son contradictorios
- Se usa menos pero sigue siendo parte del estándar de cuidado de la mayoría
- No está resuelto y quizás los resultados dependan también de factores concurrentes tales como equipo quirúrgico, modalidad anestésica, traslados a otras áreas o centros entre otros.

HOSPITAL UNIVERSITARIO AUSTRAL

Original article

Morbidity and mortality in preterm neonates with patent ductus arteriosus on day 3

Anna Sellmer,[1,2,3] Jesper Vandborg Bjerre,[2] Michael Rahbek Schmidt,[4] Patrick J McNamara,[5] Vibeke Elisabeth Hjortdal,[6] Bente Høst,[2] Bodil Hammer Bech,[7] Tine Brink Henriksen[2,3]

What this study adds

- Presence of a PDA on day 3 of life is associated with increased odds of mortality and severe morbidity in neonates born prior to 28 weeks gestation.
- In neonates born prior to 28 weeks gestation a PDA diameter ≥1.5 mm on day 3 is associated with greater odds of intraventricular haemorrhage, bronchopulmonary dysplasia and mortality or severe morbidity.

Sellmer A, *et al*. *Arch Dis Child Fetal Neonatal Ed* 2013;**98**:F505–F510.

PDA Ligation and Health Outcomes: A Meta-analysis

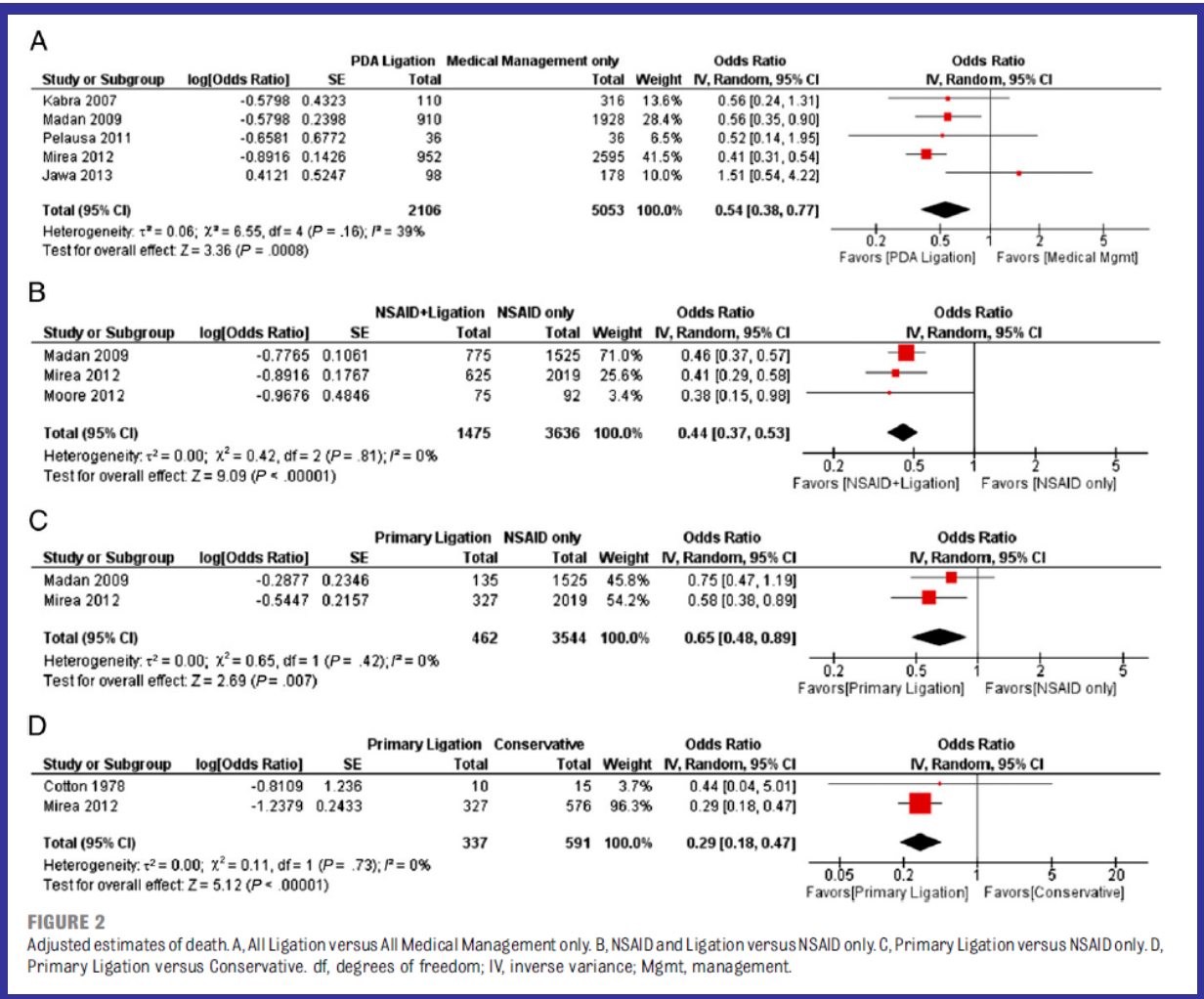


FIGURE 2

Adjusted estimates of death. A, All Ligation versus All Medical Management only. B, NSAID and Ligation versus NSAID only. C, Primary Ligation versus NSAID only. D, Primary Ligation versus Conservative. df, degrees of freedom; IV, inverse variance; Mgmt, management.

CONCLUSIONS: Surgical ligation of PDA is associated with reduced mortality, but surviving infants are at increased risk of NDI. However, there is a lack of studies addressing survival bias and confounding by indication. *Pediatrics* 2014;133:e1024–e1046

Pediatrics 2014;133:e1024–e1046

HOSPITAL UNIVERSITARIO AUSTRAL

Research

JAMA Pediatrics | Original Investigation

Association of Patent Ductus Arteriosus Ligation With Death or Neurodevelopmental Impairment Among Extremely Preterm Infants

Dany E. Weisz, MD, MSc; Lucia Mirea, PhD; Erin Rosenberg, BSc; Maximus Jang, BSc, MD; Linh Ly, MD; Paige T. Church, MD; Edmond Kelly, MD; S. Joseph Kim, MD, PhD; Amish Jain, MD; Patrick J. McNamara, MD, MSc; Prakesh S. Shah, MD, MSc

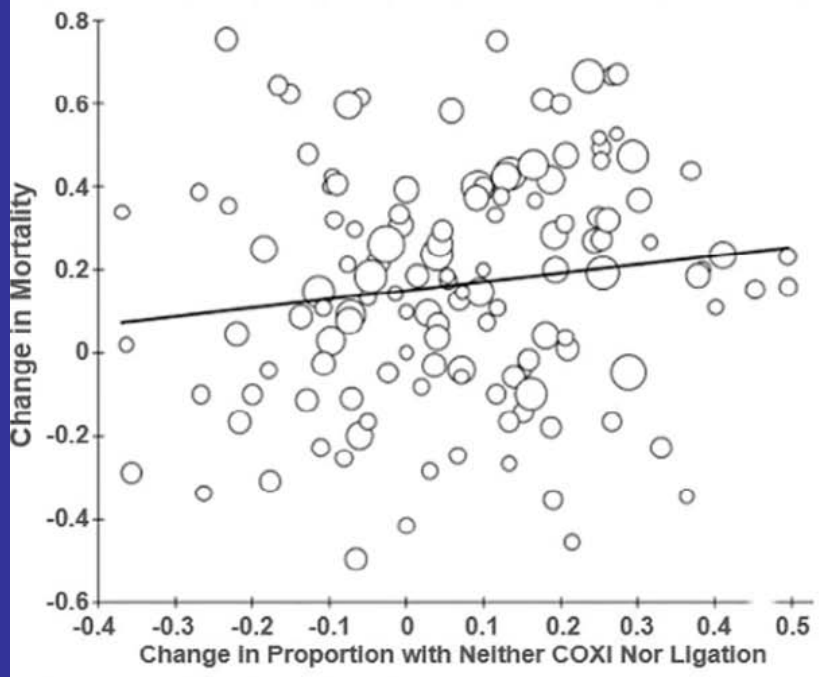
Table 3. Neonatal and Neurodevelopmental Outcomes of Infants Who Underwent Ligation vs Medically Treated Infants[a]

Outcome	No. (%)		Model 1: Crude OR (95% CI)	Model 2: AOR (95% CI)[b] Antenatal/Perinatal Covariates Only	Model 3: AOR (95% CI)[c] Model 2 and Postnatal, Preductal Closure Covariates
	Ligation (n = 184)	Medical Treatment (n = 570)			
Death or moderate-severe neurodevelopmental impairment[d]	110 (59.8)	299 (52.5)	1.24 (0.87-1.77)	0.97 (0.65-1.44)	0.83 (0.52-1.32)
Death before discharge[e]	17 (9.2)	121 (21.2)	0.38 (0.22-0.65)	0.17 (0.09-0.31)	0.09 (0.04-0.21)
Moderate-severe neurodevelopmental impairment	92 (50.0)	174 (30.5)	1.79 (1.22-2.62)	1.64 (1.08-2.51)	1.27 (0.78-2.06)
Chronic lung disease	141 (76.6)	237 (41.6)	3.67 (2.44-5.52)	3.13 (1.96-5.00)	1.36 (0.78-2.39)
Severe retinopathy of prematurity	42 (22.8)	30 (5.3)	4.48 (2.70-7.45)	2.67 (1.52-4.68)	1.61 (0.85-3.06)

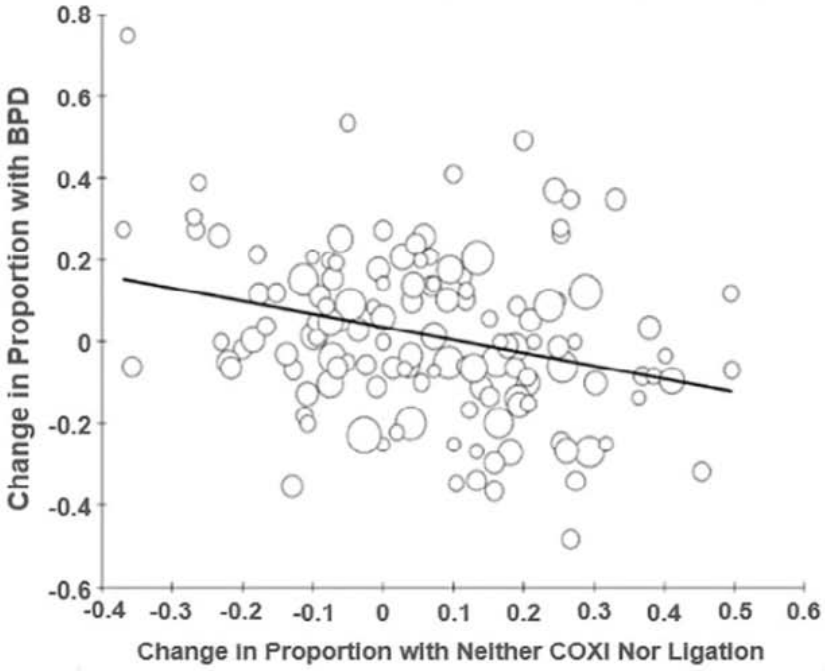
Covariation of Neonatal Intensive Care Unit-Level Patent Ductus Arteriosus Management and In-Neonatal Intensive Care Unit Outcomes Following Preterm Birth

James I. Hagadorn, MD, MSc[1,2], Mihoko V. Bennett, PhD[3,4], Elizabeth A. Brownell, PhD[1,2], Kurlen S. E. Payton, MD[5], William E. Benitz, MD[3], and Henry C. Lee, MD, MS[3,4]

a) No COXI or Ligation versus Mortality



b) No COXI or Ligation versus BPD



Journal of Pediatrics 2018

REVIEW ARTICLE »»

Patent Ductus Arteriosus Ligation and Adverse Outcomes: Causality or Bias?

Dany E. Weisz, Patrick J. McNamara[1,2,3]

Department of Newborn and Developmental Paediatrics, Sunnybrook Health Sciences Centre, [1]Department of Paediatrics, Division of Neonatology, [2]Department of Physiology, University of Toronto, [3]Physiology and Experimental Medicine Program, Hospital for Sick Children Research Institute, Toronto, Canada

Semin Fetal Neonatal Med. 2018 Aug;23(4):255-266. doi: 10.1016/j.siny.2018.03.003. Epub 2018 Mar 7.

Surgical management of a patent ductus arteriosus: Is this still an option?

Weisz DE[1], Giesinger RE[2].

EDITORIAL

Neurodevelopmental Outcomes Following Surgical Ligation for Patent Ductus Arteriosus Among Extremely Preterm Infants
Case Closed?

Elizabeth E. Foglia, MD, MSCE; Barbara Schmidt, MD, MSc

Cierre Quirúrgico y manejo del DAP

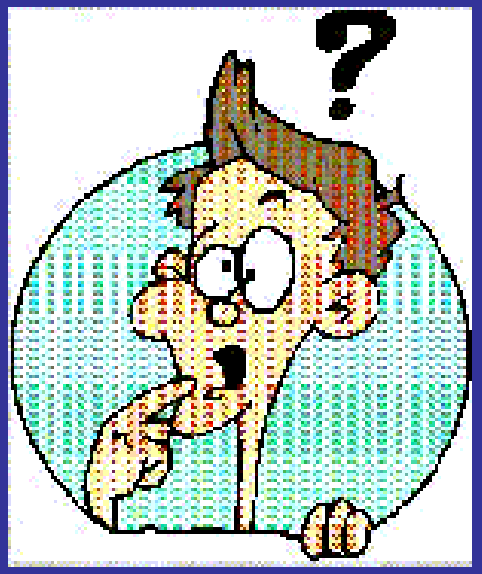
Cont. y otras consideraciones

- Asistimos en los últimos años a una modificación del paradigma
- La literatura disponible sigue siendo no concluyente (sesgos)
- Aprendimos los neonatólogos manejar PT con ductus “abiertos”?
- Debemos re-explicar la fisiopatología neonatal?
- Son iguales todos los pacientes y los ductus?
- Las alternativas a la terapéutica clásica tampoco han sido evaluadas
- La alternativa planteada es no tratarlos? No sería mejor elegir a quien y cuando tratar?
- Debemos esperar el síntoma /daño o anticiparlo?
- Intuimos que tanto la no intervención como la IM como la CX tienen ventajas y desventajas
- Cuál es el camino a seguir?

Problema:

- Cuando tratarlo?
- Cómo tratarlo?
- En quien tratarlo?
- Para qué tratarlo?

- Hay que tratarlo? (!)



Estrategias terapéuticas

1. Profilaxis (indometacina o ibuprofeno)
2. Tratamiento temprano (pre sintomático)
3. Tratamiento del DAP sintomático (temprano y tardío)
4. Tratamiento del DAP con insuf cardíaca
5. Lugar o momento del cierre quirúrgico ?

Evid.-Based Child Health **5**: 416–471 (2010)

[Intervention Review]

Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants

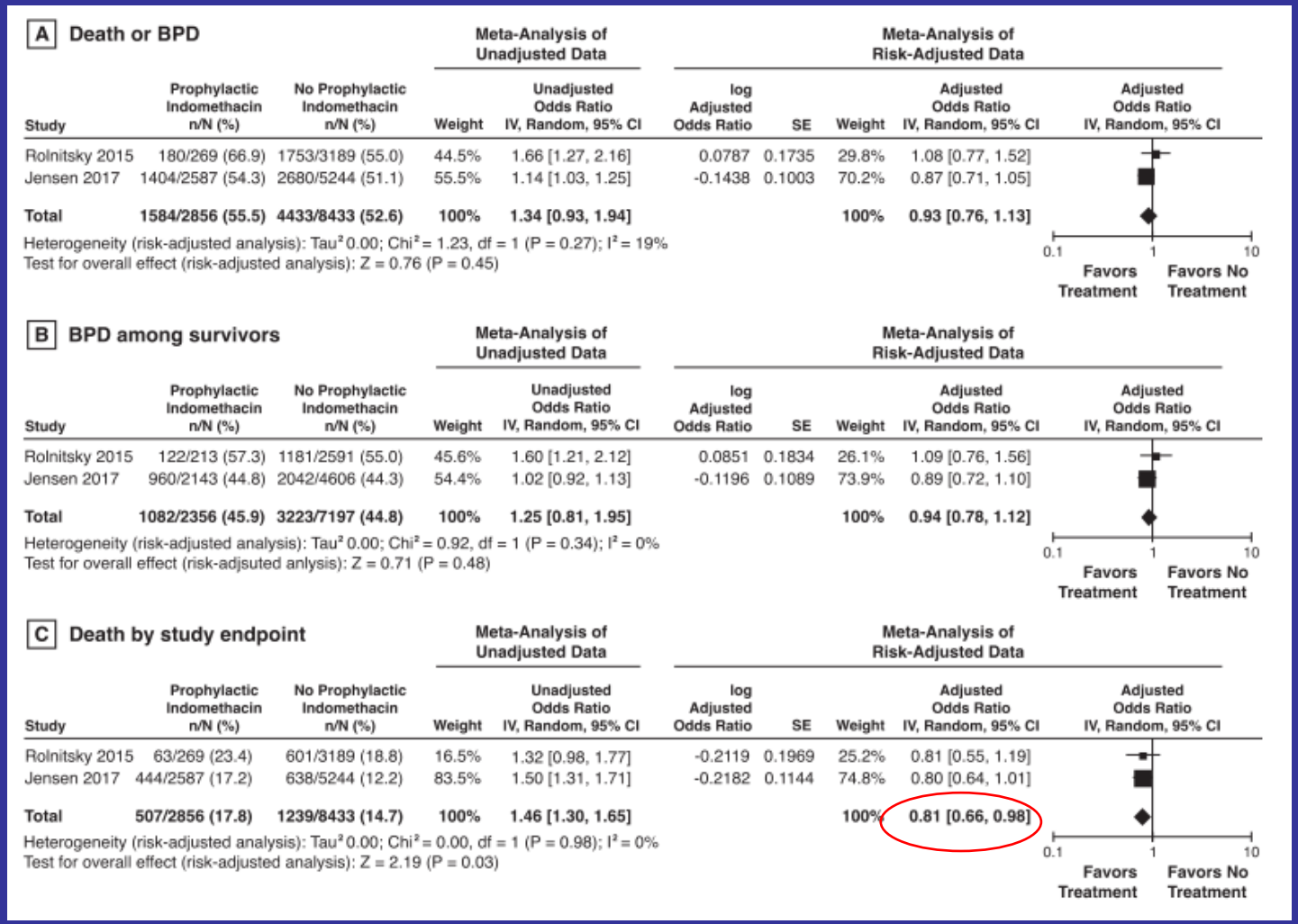
Peter W Fowlie[1], Peter G Davis[2]

Authors' conclusions

Prophylactic treatment with indomethacin has a number of immediate benefits, in particular a reduction in symptomatic patent ductus arteriosus, the need for duct ligation and severe intraventricular haemorrhage. There is no evidence to suggest either benefit or harm in longer term outcomes including neurodevelopment. Depending on clinical circumstances and personal preferences, there may be a role for prophylactic indomethacin in some infants on some neonatal units.

Association between prophylactic indomethacin and death or bronchopulmonary dysplasia: A systematic review and meta-analysis of observational studies

Erik A. Jensen, MD, MSCE, Elizabeth E. Foglia, MD, MSCE, and Barbara Schmidt, MD, MSc*



THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Timing of Patent Ductus Arteriosus Treatment and Respiratory Outcome in Premature Infants: A Double-Blind Randomized Controlled Trial

Ilene R. S. Sosenko, MD, M. Florencia Fajardo, MD, Nelson Claure, MSc, PhD, and Eduardo Bancalari, MD

- RCT Ibuprofeno temprano vs rescate para prevenir DBP
- Outcome 1° # días con O2 en primeros 28d
- PN 500-1250, DAP “leve” y Eco +
- Aleatorizados a IBU vs Placebo recibiendo luego IBU de rescate por DAP hemodinámicamente significativo
- Calculo de tamaño muestral n= 168. Terminado con n=120

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Timing of Patent Ductus Arteriosus Treatment and Respiratory Outcome in Premature Infants: A Double-Blind Randomized Controlled Trial

Ilene R. S. Sosenko, MD, M. Florencia Fajardo, MD, Nelson Claure, MSc, PhD, and Eduardo Bancalari, MD

	IBU temprano n=54	Expectante n= 51
Peso nac	854 g	842 g
EG	26 s	25 s
Tratam c/ Ibu (d)	3d	11d
Nunca Tx (%)	0	49 %
DAP a los 28d (%)	17%	43%
DAPHS	15%	20%
Días O2	21 (14-25)	19 (12-24)
O2 36s (%)	33%	33%
Muerte (%)	7,4%	11,8%
Perf Int (%)	3,7%	7,8%
ECN(%)	5,6%	3,9%
Ligadura (%)	14,8%	19,6%

A randomised placebo-controlled trial of early treatment of the patent ductus arteriosus

Martin Kluckow,[1,2] Michele Jeffery,[1] Andy Gill,[3] Nick Evans[2,4]

- Ductal Echocardiographic Targeting and Early Closure Trial (DETECT)
- Ensayo controlado con placebo en 3 UCIN de Australia (2007-2010)
- <29s - pesquisa con ecocardiografía entre 3-12hs de vida
- Si el ductus era “grande” se aleatorizó a Indo vs placebo
- Resultado principal combinado muerte/ecocerebral “anormal”
- n=92 (44 vs 48) – enrolamiento suspendido x falta de droga
- Sin diferencias en resultado principal (18 vs 19%)
- Hemorragia pulmonar 2 vs 21%
- Menor HIC 4,5 vs 12,5% (NS)
- Uso “open label” de indo 20 vs 40%

Arch Dis Child Fetal Neonatal Ed 2014;**99**:F99–F104

Patent Ductus Arteriosus Management and Outcomes in Japan and Canada: Comparison of Proactive and Selective Approaches

Tetsuya Isayama, MD[1,2] Lucia Mirea, PhD[1,2] Rintaro Mori, FRCPCH, PhD[3] Satoshi Kusuda, MD, PhD[4] Masanori Fujimura, FRCPCH[5] Shoo K. Lee, MBBS, FRCPC, PhD[1,2] Prakesh S. Shah, MD, FRCPC, MSc[1,2]; on behalf of the Neonatal Research Network of Japan and the Canadian Neonatal Network

Conclusion Lower composite mortality/morbidity outcome in Japan versus Canada only among infants with PDA, and association of surgical ligation with higher mortality/morbidity only in Canada, suggest differential PDA management and ligation processes contribute to outcome variation.

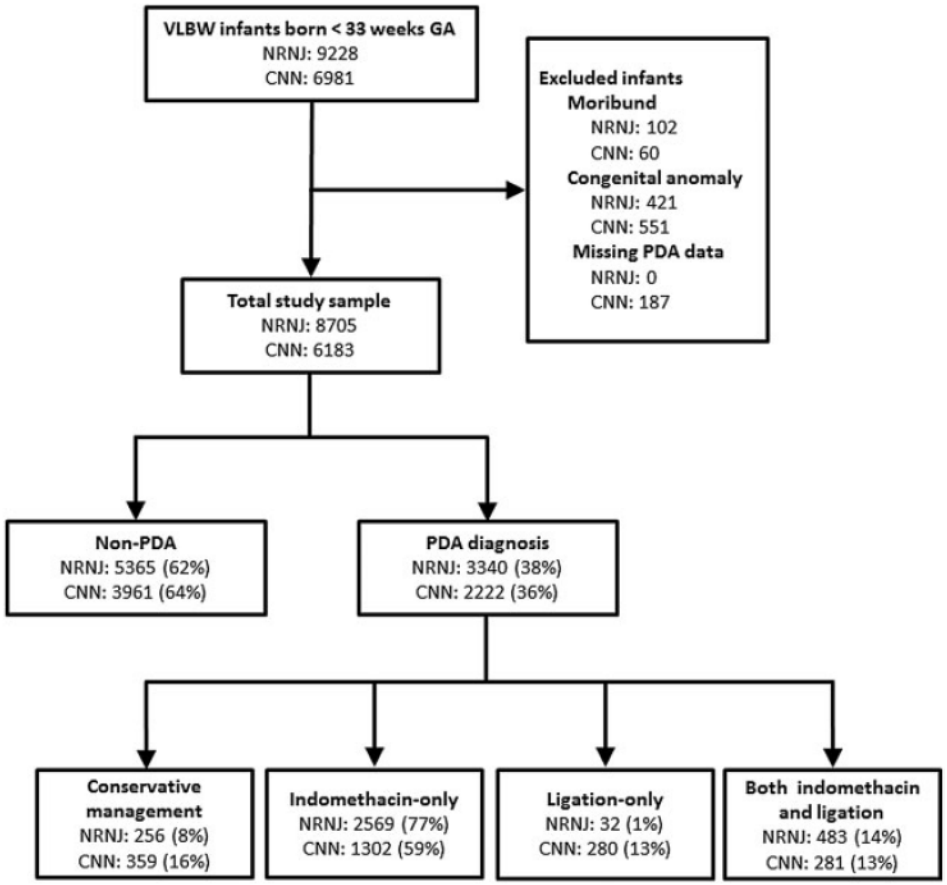


Fig. 1 Study population of VLBW (< 1,500 g) infants born at < 33 weeks' gestational age from the NRNJ and CNN. CNN, Canadian Neonatal Network; GA, gestational age; NRNJ, Neonatal Research Network of Japan; PDA, patent ductus arteriosus; VLBW, very low birth weight.

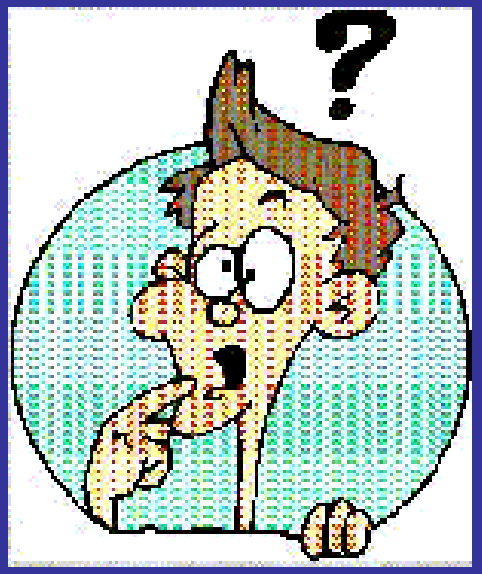
Am J Perinatol 2015

Estudios de tratamiento temprano dirigido

- TRIOCAPI (Francia) n=363 Ibuprofeno
- Baby OSCAR (Reino Unido) n=730 Ibuprofeno
- BeNe Ductus (Paises Bajos) n= 564 Ibuprofeno
- U-PDA (Australia) n= 594 Indometaina/Ibuprofeno

Problema:

- Cuando tratarlo?
- Cómo tratarlo?
- En quien tratarlo?
- Para qué tratarlo?



- Hay que tratarlo? (!)

Predicción del DAP Sintomático

Early echocardiographic prediction of symptomatic patent ductus arteriosus in preterm infants undergoing mechanical ventilation

Martin Kluckow, MBBS, FRACP, and Nick Evans, DM, MRCP

From the Department of Perinatal Medicine, King George Vth Hospital, Royal Prince Alfred Hospitals, Camperdown, Australia

Objective: To identify early echocardiographic markers allowing prediction of subsequent symptomatic patent ductus arteriosus (PDA).
Methods: One hundred sixteen preterm infants (<1500 gm) requiring mechanical ventilation underwent echocardiography at a mean postnatal age of 19 hours (range, 7 to 31 hours). Four potential markers were studied: the left atrial to aortic root ratio, pulsed Doppler measurement of left ventricular output, the minimum diameter of the color Doppler signal within the course of the duct (ductal diameter), and the direction of postductal aortic diastolic flow. Subsequent ductal closure or significant patency (if suspected clinically) was confirmed echocardiographically.
Results: A significant PDA developed in 42 infants (36%). Ductal diameter was the most accurate echocardiographic marker in predicting subsequent significant PDA. With a ductal diameter of 1.5 mm or greater there were 34 true-positive, 11 false-positive, 63 true-negative, and 8 false-negative results, giving a positive likelihood ratio of 5.5 and a negative likelihood ratio of 0.22 for prediction of development of a PDA requiring treatment. The sensitivity was 81% and the specificity was 85%. Only one infant older than 28 weeks of gestational age had a significant PDA, and limiting the analysis to infants younger than 29 weeks of gestation further improved the predictive accuracy of ductal diameter. The positive likelihood ratio was 8.1 and the negative likelihood ratio was 0.19, with a sensitivity of 83% and a specificity of 90%.
Conclusion: Color Doppler measurement of the internal ductal diameter allows early prediction of significant PDA in preterm infants. (J Pediatr 1995;127:774-9)

Predicción del DAP Sintomático

B-Type Natriuretic Peptide Predicts Responses to Indomethacin in Premature Neonates with Patent Ductus Arteriosus

Jong-Hau Hsu, MD, San-Nan Yang, MD, PhD, Hsiu-Lin Chen, MD, Hsing-I. Tseng, MD, Zen-Kong Dai, MD, PhD, and Jiunn-Ren Wu, MD

THE USE OF A BEDSIDE ASSAY FOR PLASMA B-TYPE NATRIURETIC PEPTIDE AS A BIOMARKER IN THE MANAGEMENT OF PATENT DUCTUS ARTERIOSUS IN PREMATURE NEONATES

PATRICK A. FLYNN, MD, RALPH L. DA GRACA, MD, PETER A. M. AULD, MD, MIRJANA NESIN, MD, AND CHARLES S. KLEINMAN, MD

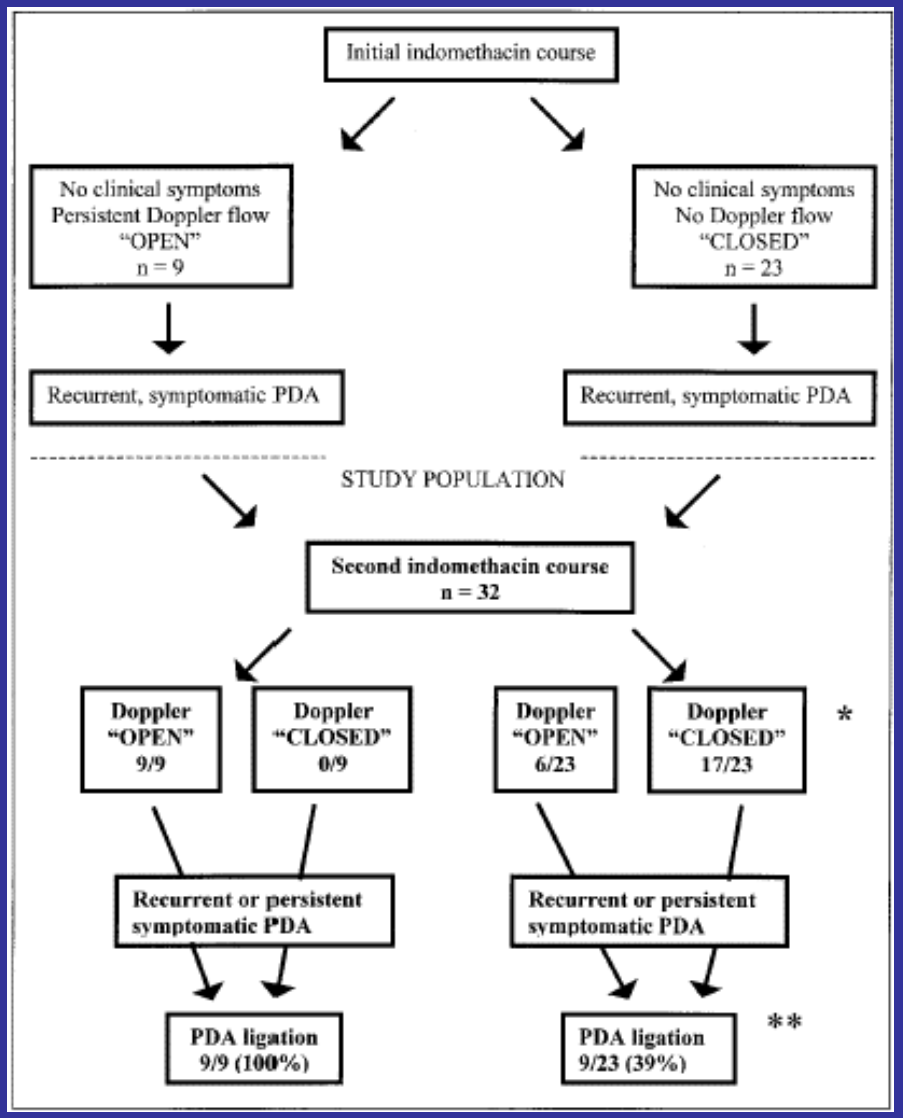
N-terminal pro-B-type natriuretic peptide: a measure of significant patent ductus arteriosus

I Farombi-Oghuvbu,[1] T Matthews,[1] P D Mayne,[2] H Guerin,[2] J D Corcoran[1]

HOSPITAL UNIVERSITARIO AUSTRAL

Persistent Doppler Flow Predicts Lack of Response to Multiple Courses of Indomethacin in Premature Infants With Recurrent Patent Ductus Arteriosus

Roberta L. Keller, MD*, and Ronald I. Clyman, MD*‡



Pediatrics, 2003

HOSPITAL UNIVERSITARIO AUSTRAL

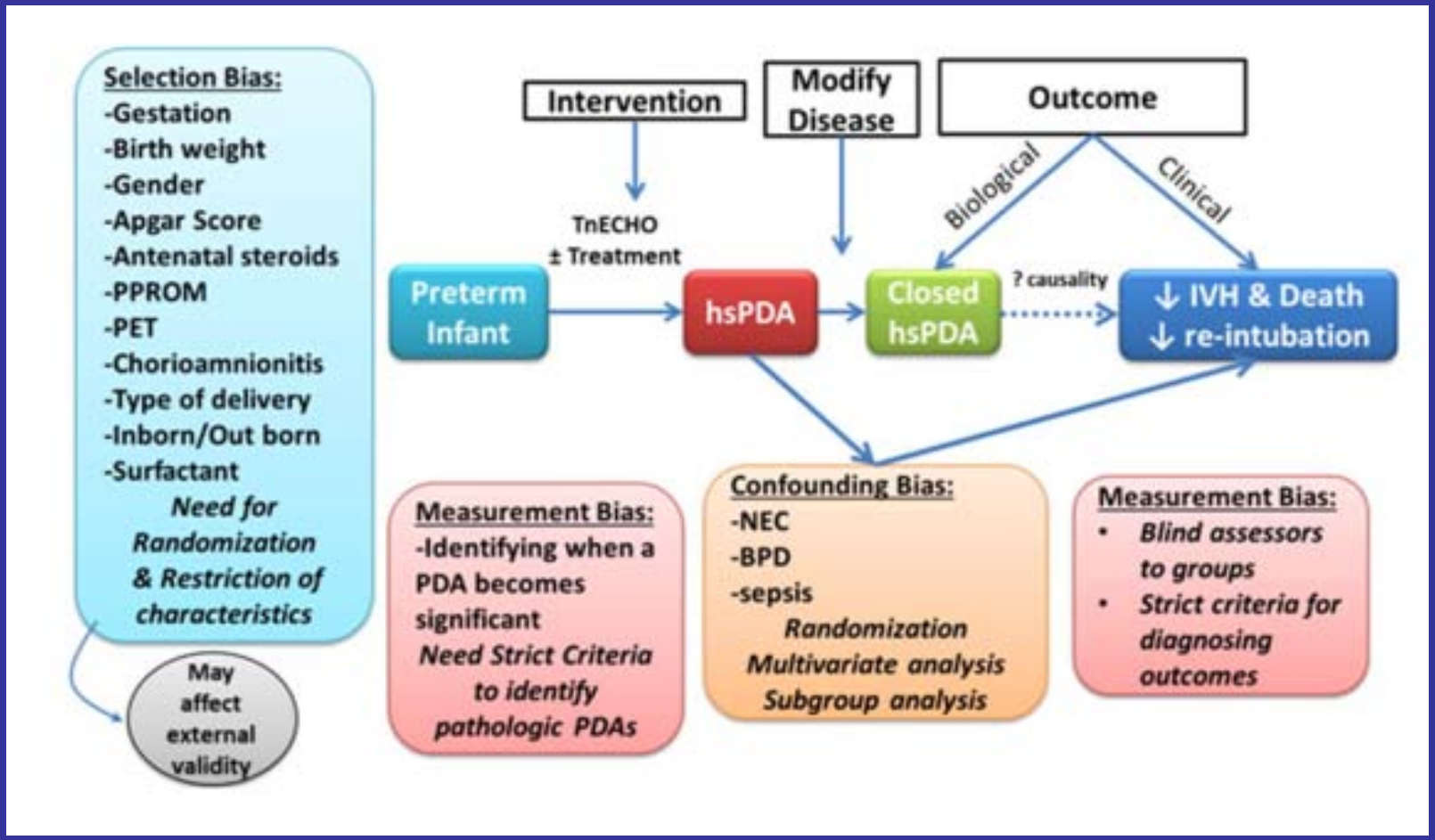
Towards rational management of the patent ductus arteriosus: the need for disease staging

Patrick J McNamara, Arvind Sehgal

- Refinar la indicación y la población a tratar
- Abandonar el esquema de pensamiento “todo o nada”
- Redefinir el Ductus hemodinámicamente significativo
- Utilizar índices de severidad
- Cuidado con los outcomes multifactoriales
- Definir el síndrome post ligadura y evaluar sus consecuencias
- Decisiones racionales e individualizadas
- Estudios clínicos en poblaciones selectas

ADC F&N, 2007

Dificultades con causalidad



Afif EL-Khuffash, Dany E Weisz and Patrick J McNamara

Arch Dis Child Fetal Neonatal Ed 2016 101: F474-F478

Resumen / Reflexión

- De tratar a todos a casi ninguno → hay evidencia?
- El tratamiento conservador impresiona razonable pero no ha sido validado por evidencia comparativa
- Sigue firme la posibilidad de resultados adversos ante la persistencia de shunts de alto volumen
- También aparece razonable el restringir racionalmente el uso de tratamiento mediante un enfoque basado en riesgo
- Dejar de ver al ductus como algo dicotómico
- Si esperamos a que estén muy enfermos puede ser tarde para que cualquier tratamiento sea efectivo
- Tener en cuenta las importantes limitaciones de la evidencia tanto a favor de tratar como en contra

Resumen Operativo

- La recomendación juiciosa de tratar el DAP debería seguir en pie aunque se debería estudiar mejor
- Indometacina profiláctica cierra el DAP y previene cirugía y HIC severa, en promedio no modifica outcomes a largo plazo y se debería reservar para poblaciones selectas (↓ mortalidad?)
- No esta claro si el tto. temprano es mejor que el del DAP sintomático (los resultados de estudios difieren pero se vienen estudios nuevos)
- No esta claro si el cierre médico es mejor que el quirúrgico pero sería mas sencillo y económico y podría tener menos efectos adversos
- Podría aún justificarse indicar cirugía en pacientes menores de 28 semanas con compromiso hemodinámico cuyo ductus no cierre con IM o Ibu contando con el equipo Qx apropiado.

Perspectivas

- Profilaxis vs sintomático, vale la pena en poblaciones selectas? La elección condicionará conducta posterior
- Definir población de riesgo
- Identificar y validar marcadores tempranos o predictivos
- Diseñar y validar scores de severidad
- Evaluar terapéuticas en ECAs con distinto diseño, incluir no intervención (en casos selectos?)
- Reconocer y manejar los sesgos
- Propuesta: hasta tener más respuestas, cautelosamente seguir tratando aquellos PT de mayor riesgo con Ductus significativo y evidencia de compromiso hemodinámico
- Atención a la evolución del cierre no quirúrgico mediante cateterismo

HOSPITAL UNIVERSITARIO AUSTRAL

Gracias!

Gabriel Musante

gmusante@cas.austral.edu.ar