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CENTRO DE MEDICINA MATERNOFETAL Y NEONATAL BARCELONA

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HOSPITAL MATERNOINFANTIL - UNIVERSITAT DE BARCELONA

Prevención y diagnóstico precoz de la enterocolitis necrotizante

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CURSO INTERNACIONAL DE NEONATOLOGIA Y MATRONERIA NEONATAL
PUERTO MONTT 10 Y 11 DE NOVIEMBRE 2017
AUDITORIO UNIVERSIDAD SAN SEBASTIAN - SEDE PATAGONIA

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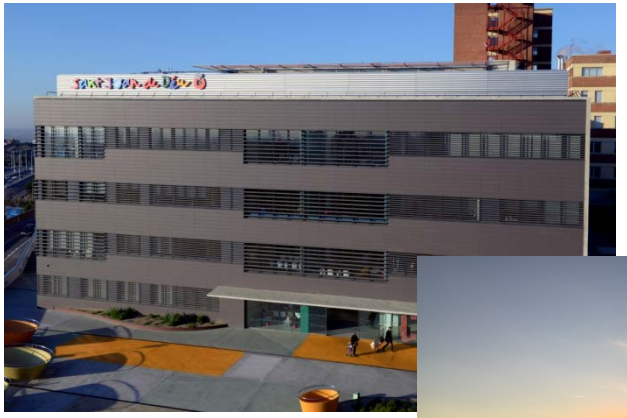
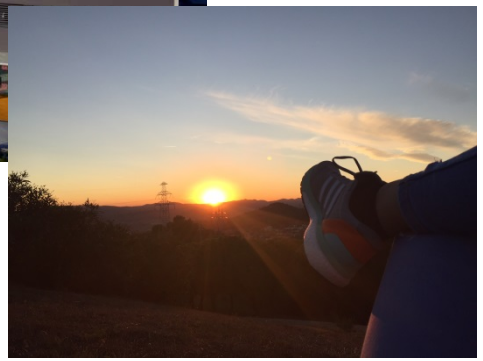




-Hospital pediátrico
-Unidad de obstetricia de alta complejidad, 3000 partos/año
-Unidad neonatal nivel IV (cirugía, ECMO)
-Unidad abierta
-600 ingresos/año en Unidad neonatal

Esquema de la charla

1. INTRODUCCIÓN: LA NEC
2. PATOGENIA Y DATOS PROPIOS
3. CONSIDERACIONES DIAGNÓSTICAS
4. NUEVOS BIOMARCADORES
5. ESTRATEGIAS PREVENTIVAS
6. DATOS PROPIOS Y CONCLUSIONES

Soy Neonatóloga del HSJD

En la Unidad Neonatal ingresan 70-80 RNPT <32s/<1500g cada año.

No conflictos de interés

1. La Enterocolitis necrotizante

-**Enfermedad GI letal más frecuente en prematuros**

-85% de casos en RNPT <32s, <1500g (pero **no es exclusiva del prematuro**-DIFERENTES TIPOS DE NEC) Mortalidad elevada: 30%

-Diferente incidencia entre centros y entre países (1-10% de prematuros)

-**Secuelas en supervivientes**: intestino corto

-Enfermedad cara (Ingreso hospitalario, cirugía)

-**Relación con alimentación enteral causa demora en progresión de alimentación enteral en las UCIN** (más días de vía central)

2. NEC, patogenia

"Alteración en la barrera intestinal que conlleva necrosis intestinal y puede desembocar en fallo multiorgánico y muerte"

Good et al, Expert Rev Clin Immunol 2014; 10:875-884

Necrotizing Enterocolitis: The Mystery Goes On

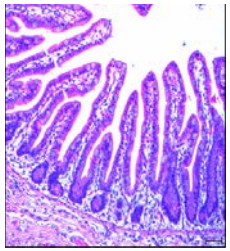
Josef Neu

Pathogenesis of Necrotizing Enterocolitis

Modeling the Innate Immune Response

Scott M. Tanner,*† Taylor F. Berryhill,* James L. Ellenburg,* Tamas Jilling,‡ Dava S. Cleveland,§ Robin G. Lorenz,† and Colin A. Martin*

merican Journal of Pathology, Vol. 185, No. 1, January 2015

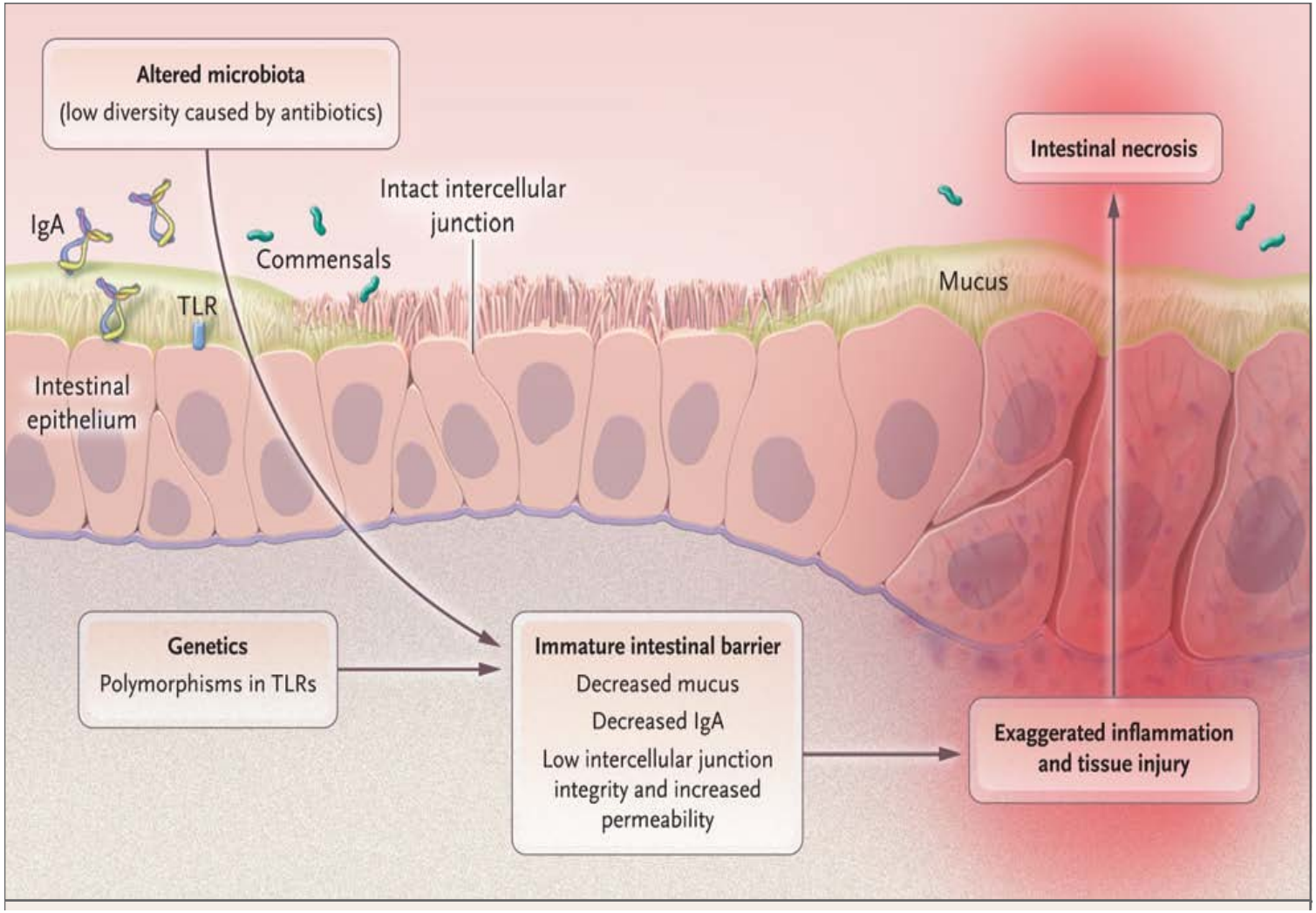


CORIOAMNIONITIS

Hipoxia-isquemia

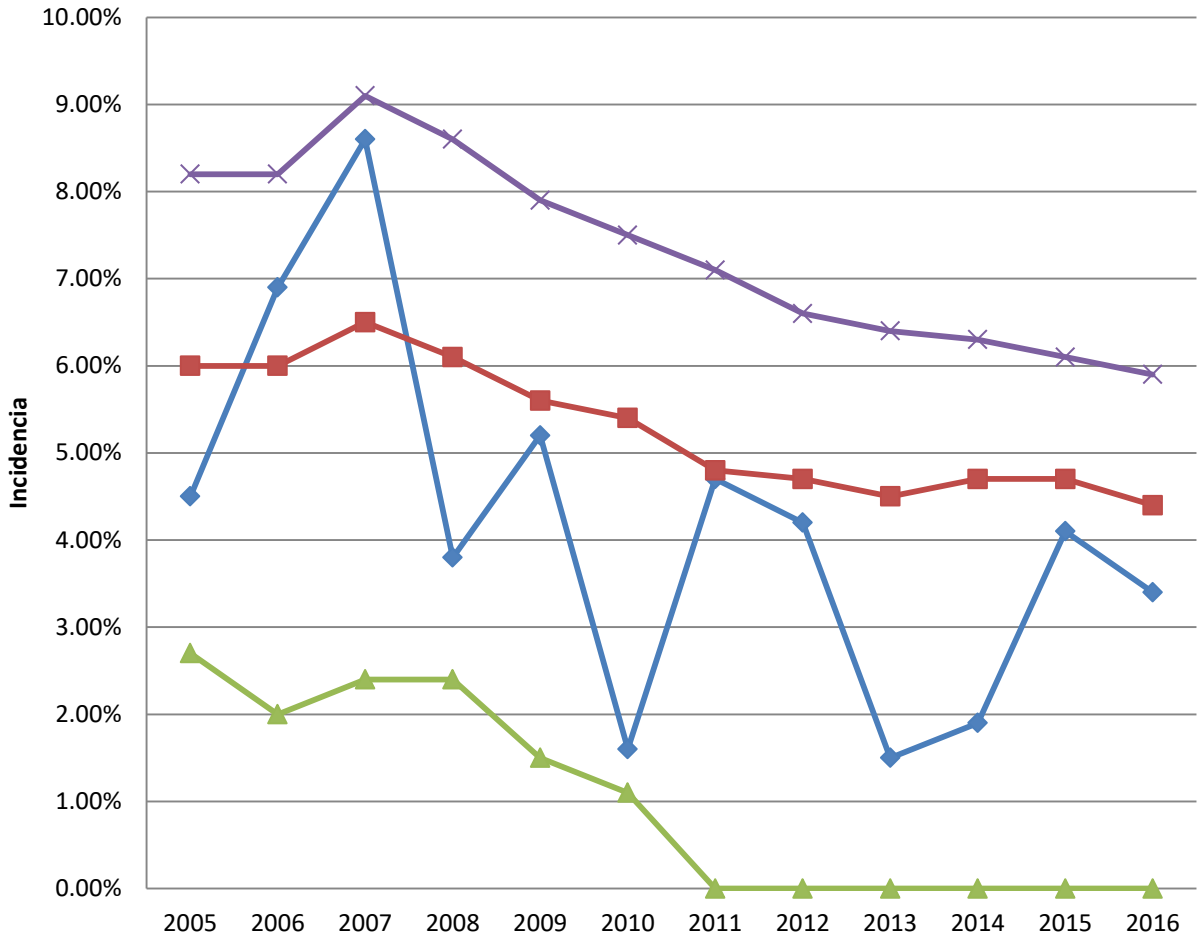
-Prematuridad + alimentación + tratamientos en UCIN: REACCIÓN INFLAMATORIA ANORMAL…

TRIADA madre-niño-sistema-inmunitario



Josef Neu, M.D., and W. Allan Walker, M.D.

NEC. RNPT ≤30 SEG y/o Peso ≤1500g INBORN HSJD



-En HSJD Ingresan 4-6 RN/año con NEC

-1-2 pacientes/año internos

Vermont Oxford NETWORK

3. Diagnóstico: La Enterocolitis necrotizante y sus "imitadores"

Table 1. Bell staging criteria for necrotizing enterocolitis, modified from Walsh and Kliegman[6,47].

Stage	I	IIA	IIB	IIIA	IIIB
Description	Suspected NEC	Mild NEC	Moderate NEC	Severe NEC	Severe NEC
Systemic signs	Temperature instability, apnea, bradycardia	Similar to stage I	Mild acidosis, thrombocytopenia	Respiratory and metabolic acidosis, mechanical ventilation, hypotension, oliguria, DIC	Further deterioration and shock
Intestinal signs	Increased gastric residuals, mild abdominal distension, occult blood in the stool	Marked abdominal distension ± tenderness, absent bowel sounds, grossly bloody stools	Abdominal wall edema and tenderness ± palpable mass	Worsening wall edema with erythema and induration	Evidence of perforation
Radiographic signs	Normal or mild ileus	Ileus, dilated bowel loops, focal pneumatosis	Extensive pneumatosis, early ascites ± PVG	Prominent ascites, fixed bowel loop, no free air	Pneumoperitoneum

DIC, disseminated intravascular coagulopathy; NEC, necrotizing enterocolitis; PVG, portal venous gas.

DIFERENCIAR DE PIF

NEC GRADO I? MUY INESPECÍFICA: ileo 2ª a sepsis

¿Por qué es difícil el diagnóstico?

Necrotizing Enterocolitis

Answer **"Yes"** if the infant had Necrotizing Enterocolitis (NEC) diagnosed at surgery, at postmortem examination or clinically and radiographically using the following criteria:

At least one of the following clinical signs present:

- Bilious gastric aspirate or emesis
- Abdominal distension
- Occult or gross blood in stool (no fissure)

And

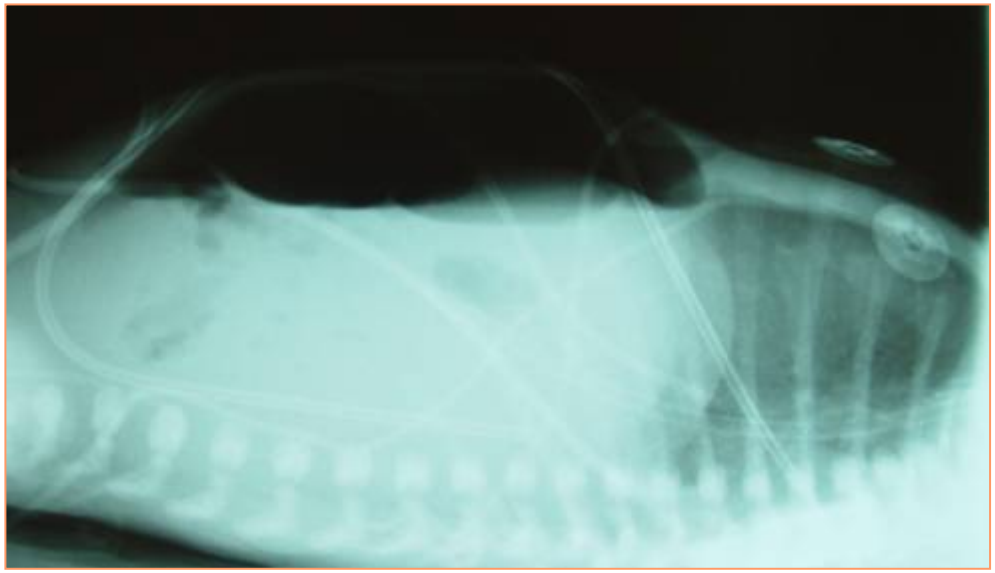
At least one of the following radiographic findings present:

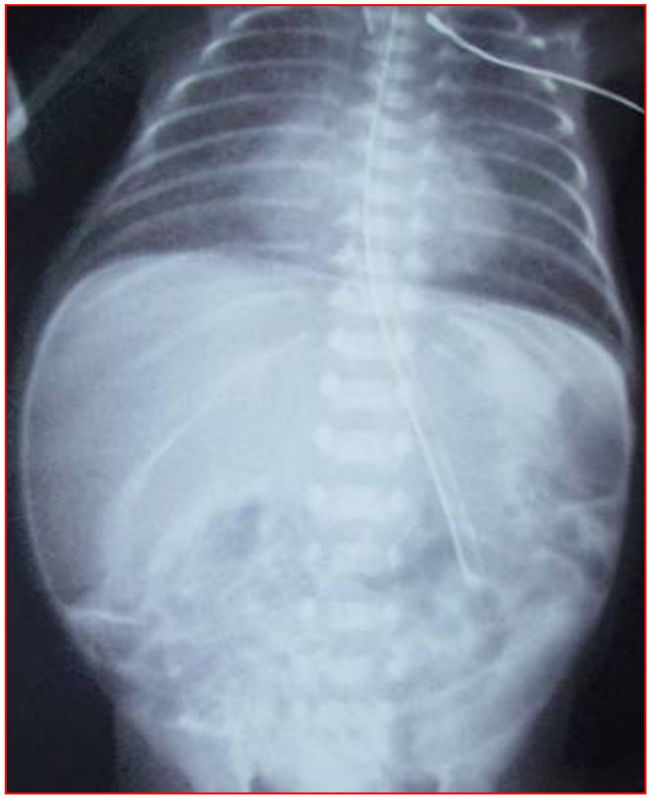
- Pneumatosis intestinalis
- Hepato-biliary gas
- Pneumoperitoneum

Answer **"No"** if the infant did not satisfy the above definition of NEC.

CRITERIOS VON

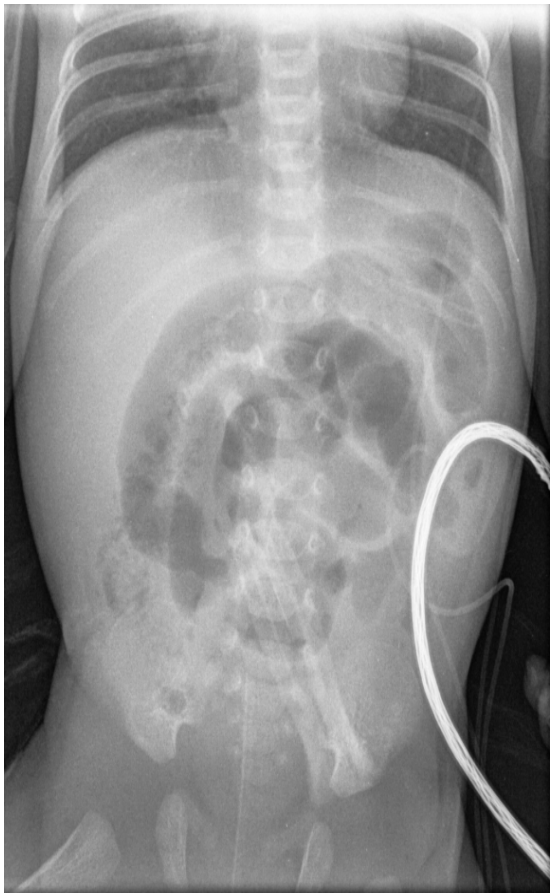
Algunas situaciones son de diagnóstico “sencillo” …

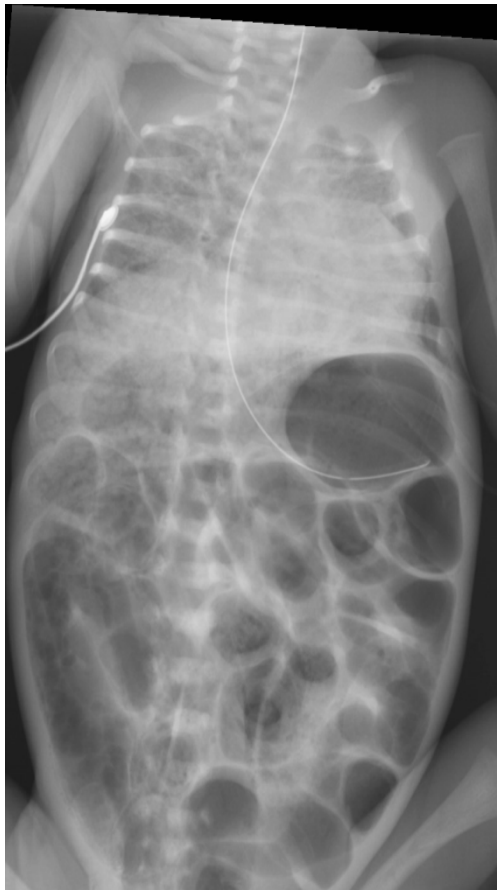


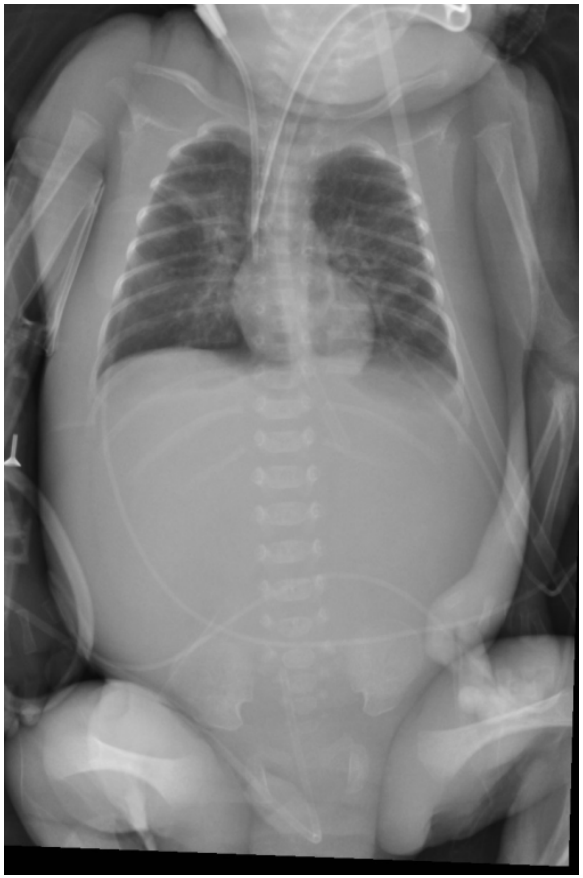


Neumoperitoneo

…Pero a veces la situación se complica

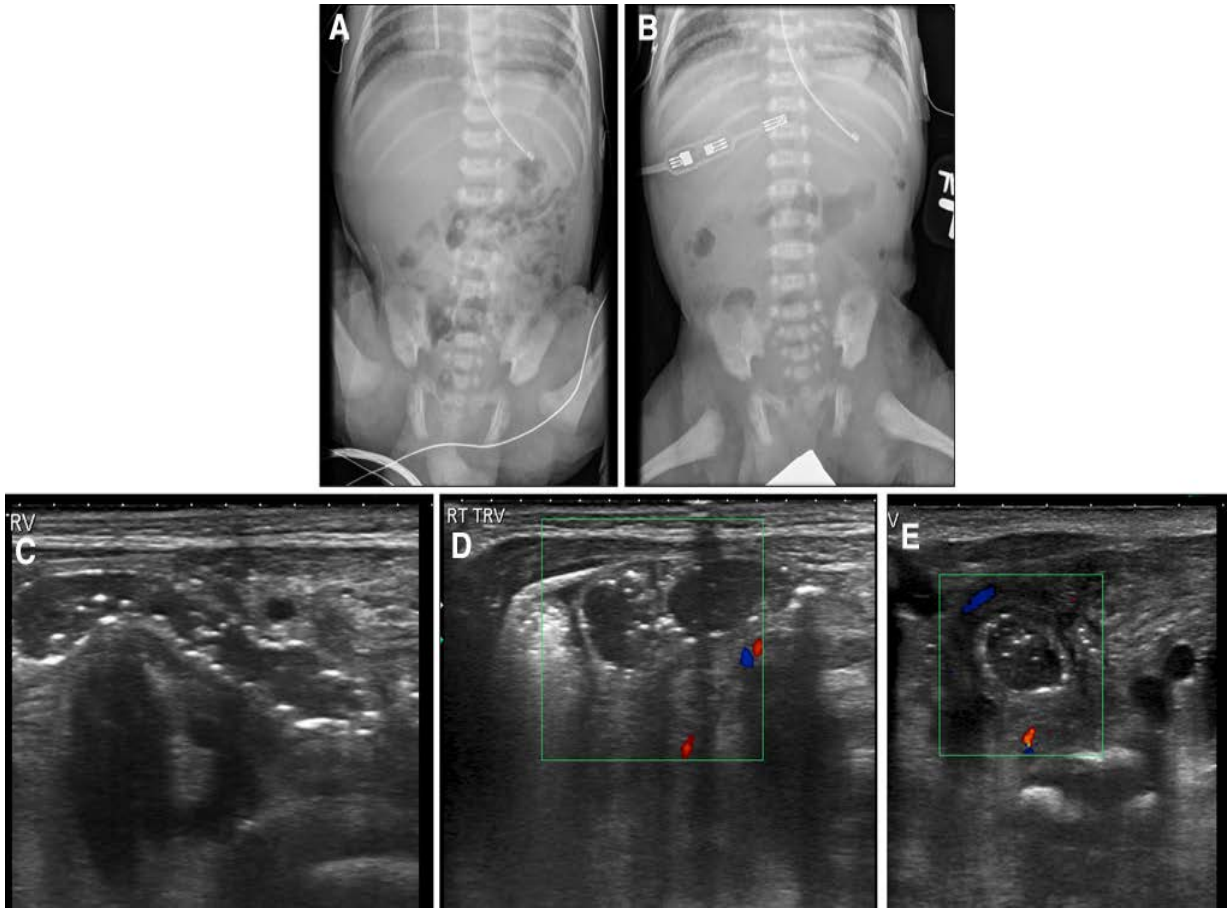






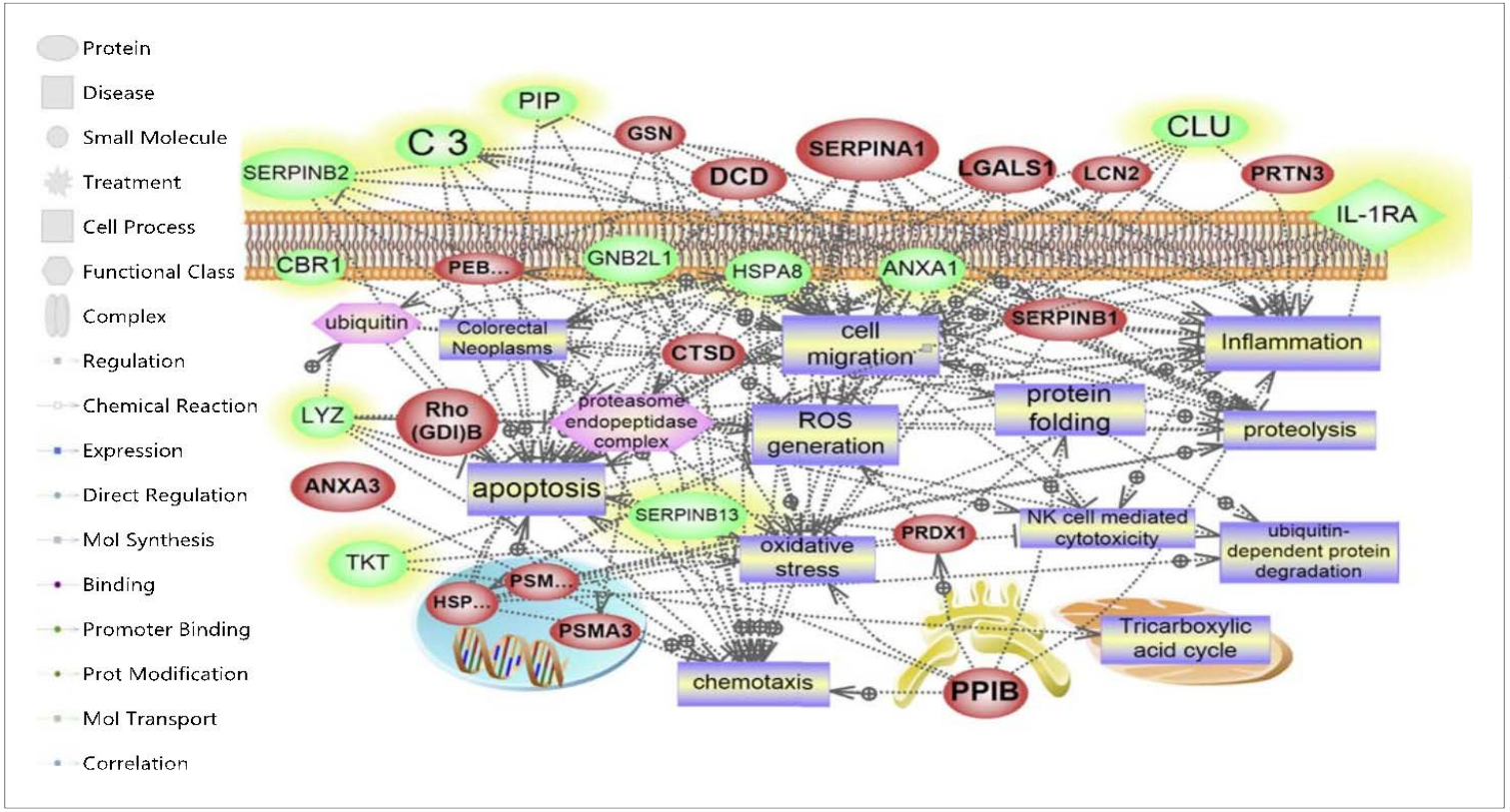
Existe discordancia alta entre radiólogos/neonatólogos/residentes de pediatría en diagnóstico de neumatosis intestinal - Rehan VK, Seshia MM, Johnston B, Reed M, Wilmot D, Cook V: Observer variability in interpretation of abdominal radiographs of infants with suspected necrotizing enterocolitis. Clin Pediatr 1999;38:637–643.

NEC y Ecografía abdominal



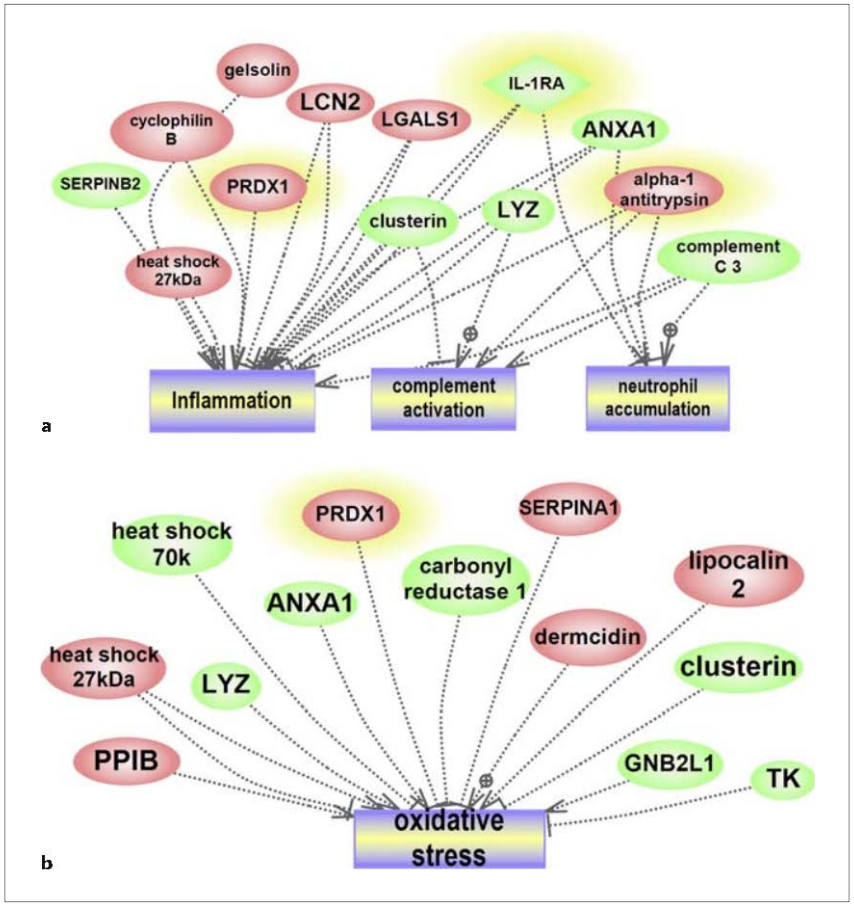
Pediatr Surg Int (2014) 30:1231–1240

4. NUEVAS ESTRATEGIAS DIAGNÓSTICAS: BIOMARCADORES



Torrazza et al. Pilot study using proteomics to identify predictive biomarkers of necrotizing enterocolitis form buccal swabs in very low birth weight infants. Neonatology 2013;104:234-242

4. BIOMARCADORES



-Biomarcadores en estudio: I-FABP (liberado por entrocitos dañados, en orina), claudina 3, calprotectina e IL-8

Torrazza et al. Pilot study using proteomics to identify predictive biomarkers of necrotizing enterocolitis form buccal swabs in very low birth weight infants. Neonatology 2013;104:234-242

OTROS POSIBLES MARCADORES

-NIRS

-ANÁLISIS DE VARIABILIDAD DE FC Y/O DECELERACIONES

Review

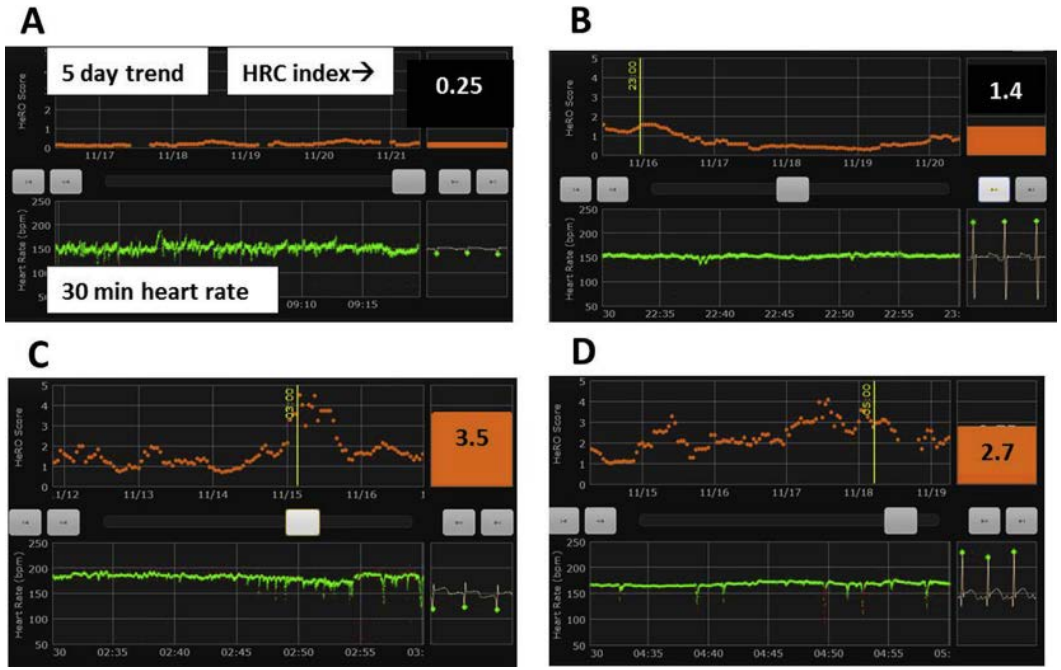
Predictive monitoring for sepsis and necrotizing enterocolitis to prevent shock

Brynne A. Sullivan [a,*], Karen D. Fairchild [b]

atal Medicine 20 (2015) 255–261

OTROS POSIBLES MARCADORES

-ANÁLISIS DE VARIABILIDAD DE FC Y/O ACELERACIONES/DECELACIONES



-Poca experiencia aún

-Casos aislados

Fig. 2. Four screen shots from the heart rate characteristics (HRC) index (HeRO) monitor. See text for clinical scenarios. (A) Normal heart rate characteristics and a low HRC index. The individual patient view on the monitor shows the five-day trend in the HRC index (orange, top), the last 30 min of heart rate (green, bottom), and the current HRC index (right, 0.25). (B) At the yellow vertical line, there was a small increase in the HRC index to 1.4. The 30 min HR tracing at that time shows decreased beat-to-beat variability (green). (C) At the yellow line, the HRC index had increased from a baseline of 1–2 to 3.5 and continued to increase for about 12 h before declining. The corresponding HR tracing shows multiple small decelerations and relatively few accelerations. (D) The five-day trend shows the HRC index ranging from 2 to 5 in an infant with severe chronic lung disease.

5. ESTRATEGIAS PREVENTIVAS

A -LACTANCIA MATERNA

-Es la estrategia protectora más eficaz para prevenir la NEC

Los recién nacidos prematuros alimentados con fórmula tienen una incidencia de NEC 6-10 veces mayor que los recién nacidos que reciben LM de manera exclusiva (en RNPT más de 30 semanas esta incidencia era 20 veces mayor)

Lucas A, Cole TJ. Breast milk and neonatal necrotising enterocolitis. Lancet. 1990;336(8730):1519–1523

-NNT de 6 niños tratados con LM exclusiva para prevenir un caso de NEC

Cristofalo EA, Schanler RJ, Blanco CL, et al. Randomized Trial of Exclusive Human Milk versus Preterm Formula Diets in Extremely Premature Infants. The Journal of pediatrics. 2013;163(6):1592–1595

A-LACTANCIA MATERNA

-El efecto beneficioso de la LM es “dosis dependiente”

-1272 RN, por cada incremento de 100ml/kg de LM disminuía riesgo de NEC un 13%

Meinzen-Derr J, Poindexter B, Wrage L, Morrow AL, Stoll B, Donovan EF. Role of human milk in extremely low birth weight infants’ risk of necrotizing enterocolitis or death. Journal of perinatology: official journal of the California Perinatal Association. 2009;29(1):57–62

¿Por qué estos efectos beneficiosos?

- Nitratos/Nitritos: precursores de NO, facilitan flujo sanguíneo intestinal
- L-Arginina: para facilitar flujo sanguíneo intestinal (aumenta síntesis de NO)
- L-Glutamina: estimula crecimiento celular intestinal. Cocharane 2013, su suplementación no tiene no efectos sobre NEC
- Oligosacáridos: actúan sobre flora intestinal modulando su respuesta infmunológica (PREBIÓTICOS)
- Lactoferrina
- Factores de Crecimiento: EGF, HB-EGF
- MICROORGANISMOS (Buenos)

Polycarpou E, Zachaki S, Tsolia M, et al. Enteral L-arginine Supplementation for Prevention of Necrotizing Enterocolitis in Very Low Birth Weight Neonates: A Double-Blind Randomized Pilot Study of Efficacy and Safety. JPEN. Journal of parenteral and enteral nutrition. 2013

Good M, Sodhi CP, Hackam DJ.
Evidence-based feeding strategies before and after the development of necrotizing enterocolitis.
Expert Rev Clin Immunol. 2014 Jul;10(7):875-84

Efectos beneficiosos de LM

FORTIFICACIÓN INDIVIDUALIZADA

OBTENCIÓN DEL CALOSTRO

CIRCUITO DE LA LECHE

" Esfuerzo (económico y de recursos) se debe dirigir a promover y apoyar la lactancia materna"

APOYO A LAS MADRES

CONSULTOR DE LACTANCIA (24 HORAS)

HOMOGENEIDAD EN EL EQUIPO— FORMACIÓN CONTINUADA

B- Leche de donante

- Al estar pasteurizada, no microorganismos..
- Mantienen los oligosacáridos su efecto prebiótico en este contexto?

Formula versus donor breast milk for feeding preterm or low birth weight infants (Review)

Quigley M, McGuire W

Cochrane Database of Systematic Reviews 2014

Cochrane Library

Cochrane Database of Systematic Reviews

Polycarpou E, Zachaki S, Tsolia M, et al. Enteral L-arginine Supplementation for Prevention of Necrotizing Enterocolitis in Very Low Birth Weight Neonates: A Double-Blind Randomized Pilot Study of Efficacy and Safety. JPEN. Journal of parenteral and enteral nutrition. 2013

Expert Rev Clin Immunol. 2014 Jul;10(7):875-84. doi: 10.1586/1744666X.2014.913481. Epub 2014 Jun 5.
Evidence-based feeding strategies before and after the development of necrotizing enterocolitis.
Good M1, Sodhi CP, Hackam DJ.

www.medicinafetalbarcelona.org/

Leche de donante

Formula versus donor breast milk for feeding preterm or low birth weight infants (Review)

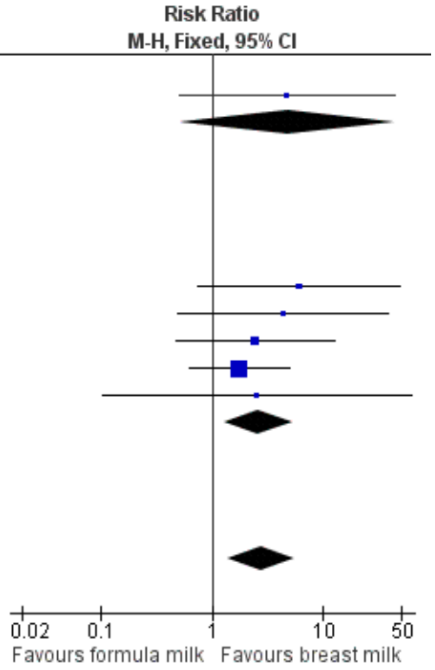
Cochrane Library

Cochrane Database of Systematic Review

Quigley M, McGuire W

Figure 6. Forest plot of comparison: 1 Formula (term or preterm) versus donor breast milk, outcome: 1.20 Necrotising enterocolitis.

Study or Subgroup	Formula milk Events	Total	Donor breast milk Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.20.1 Term formula						
Gross 1983	3	26	1	41	7.4%	4.73 [0.52, 43.09]
Subtotal (95% CI)		**26**		**41**	**7.4%**	**4.73 [0.52, 43.09]**
Total events	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.38 (P = 0.17)						
1.20.2 Preterm formula						
Cristofalo 2013	5	24	1	29	8.6%	6.04 [0.76, 48.25]
Lucas 1984a	4	76	1	83	9.1%	4.37 [0.50, 38.23]
Lucas 1984b	5	173	2	170	19.2%	2.46 [0.48, 12.49]
Schanler 2005	10	88	5	78	50.5%	1.77 [0.63, 4.96]
Tyson 1983	1	44	0	37	5.2%	2.53 [0.11, 60.39]
Subtotal (95% CI)		**405**		**397**	**92.6%**	**2.61 [1.27, 5.35]**
Total events	25		9			
Heterogeneity: Chi² = 1.39, df = 4 (P = 0.85); I² = 0%						
Test for overall effect: Z = 2.62 (P = 0.009)						
Total (95% CI)		**431**		**438**	**100.0%**	**2.77 [1.40, 5.46]**
Total events	28		10			
Heterogeneity: Chi² = 1.68, df = 5 (P = 0.89); I² = 0%						
Test for overall effect: Z = 2.94 (P = 0.003)						
Test for subgroup differences: Chi² = 0.25, df = 1 (P = 0.62), I² = 0%						



¿Comparación fórmula vs LB fortificada?

www.medicinafetalbarcelona.org/

Controversias N enteral en RNPT y NEC

- **Nutrición enteral mínima (**<20ml/kg/día) … Cuánto tiempo??

- A qué **ritmo progresar** nutrición enteral? 15-20 vs 30-35ml/kg/día

- **Efecto de suplementos en LM sobre NEC**?

Expert Rev Clin Immunol. 2014 Jul;10(7):875-84. doi: 10.1586/1744666X.2014.913481. Epub 2014 Jun 5.
Evidence-based feeding strategies before and after the development of necrotizing enterocolitis.
Good M1, Sodhi CP, Hackam DJ.

CERTEZAS N enteral en RNPT y NEC

- **No hay ningúna evidencia que relacione volumen de restos gástricos y NEC (independientemente de toooooodos los matices de verde)**

- **Catéter arterial umbilical no se relaciona con NEC**

Expert Rev Clin Immunol. 2014 Jul;10(7):875-84. doi: 10.1586/1744666X.2014.913481. Epub 2014 Jun 5.
Evidence-based feeding strategies before and after the development of necrotizing enterocolitis.
Good M1, Sodhi CP, Hackam DJ.

Razones para parar alimentación enteral en RNPT

N Hay, ESPR Copenhague 2010

1.**Distensión adominal**-Miedo a NEC
2. **Restos orogástricos biliosos**-miedo a NEC
3**. Portador de CVU o CAU**- miedo a isquemia intestinal/NEC
4**. Apnea**-miedo a RGE
5. **Taquipnea** – Miedo a aspiración
6**. DAP**-Miedo a isquemia intestinal/NEC
7. **Indometacina**-Miedo a isquemia intestinal/NEC
8**. PCR elevada**-miedo a metabolismo disminuido, proteolisis
9**. Exantema**-miedo a alergias
10. **Hiperglucemias**-miedo a metabolismo alterado
11. **Hipotermia**-miedo a sepsis
12. **Hipertermia**-miedo a sepsis
13. **Policitemia**-riesgo de NEC
14**. Puede necesitar cirugía**- ?
15- **SpO2 baja**-no puede metabolizar nutrientes
16. **Tto con catecolaminas**: miedo a isquemia intestinal, NEC

17. **“No le veo bien”**

C. PROBIÓTICOS Y NEC

A FAVOR

"There seems to be no further reason to delay the introduction of this evidence-based therapy"

"The efficacy of probiotics is no longer questionable"

EN CONTRA

"We suggest that the effect of probiotics on the incidence on NEC is stil controversiall"

"There is no evidence of benefit of this intervention in this population"

EMBLETON. BUDAPEST ESPR 2015

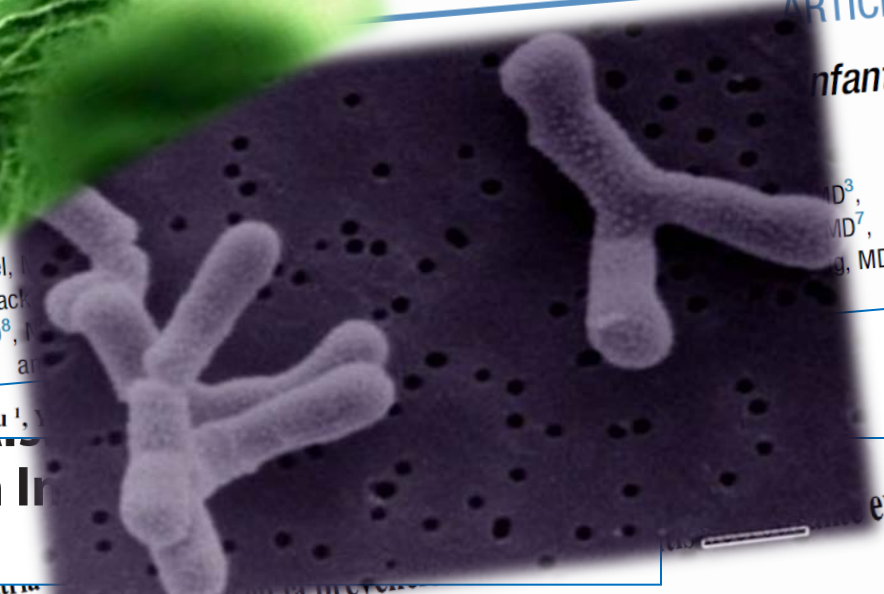
PROBIÓTICOS Y NEC

-PROBIÓTICO: “Organismo vivo que administrado en cantidades adecuadas proporciona beneficios en la salud del huésped” OMS 2001

-Tipos de probióticos: **Lactobacillus** (L. acidophilus, L. casei, L. reuteri, L. brevis, L. cellobiosus, L. fermentum, L. plantarum) Saccharomyces boulardii, Estreptococcis salivaris therm, **Bifidobacteria** (B. bifidum, B. adolescentis, B. animalis, B. infantis, B. longum, B. Thermophilum) **Enterococcis faecium, Estreptococcus diacetyllactis, Estreptococcus intermedius**

De Dra A Herranz. GEN 2015.

Probiotics Reduce the Risk of Necrotizing Enterocolitis in Preterm Infants: A Meta-Analysis



Vrinda Nair[1] and Amuchou S. Soraisham[1,2,3]

[1] Section of Neonatology, Department of Pediatrics, University of Calgary, Calgary, AB, Canada T1N 1N4
[2] Alberta Children's Hospital Research Institute for Child and Maternal Health, University of Calgary, Calgary, AB, Canada
[3] Department of Pediatrics, Foothills Medical Centre, Rm C211-1403-29th Street NW, Calgary, AB, Canada

Ping Zhou [1], ...

Empleo de probióticos en la prevención de enterocolitis necrosante en recién nacidos prematuros

Marta Suárez Rodríguez y G. Solís Sánchez

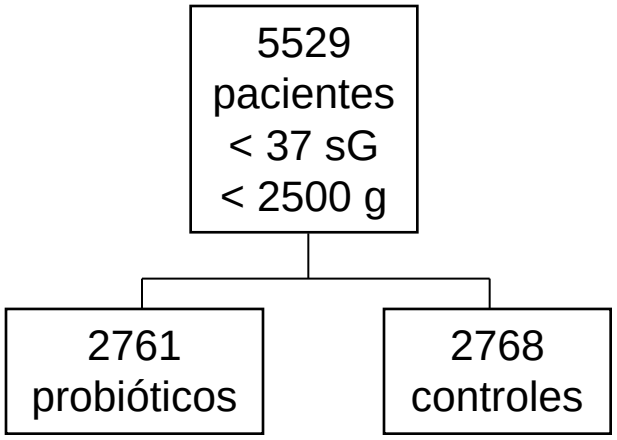
Servicio de Neonatología. AGC Pediatría. Hospital Universitario Central de Asturias. España.

Probiotics for prevention of necrotizing enterocolitis in preterm infants (Review) AlFaleh K, Anabrees J

THE COCHRANE COLLABORATION®

2014

24 estudios



Types of outcome measures

Primary outcomes

- Severe NEC (stage II or more) as per Bell's criteria (Bell 1978; Walsh 1986), diagnosed prior to discharge
- Nosocomial sepsis, defined as positive blood or cerebrospinal fluid cultures taken beyond five days of age
- All cause mortality

Secondary outcomes

- Any NEC (according Bell's criteria)
- The composite of nosocomial sepsis or NEC or death
- Systemic infection with the supplemented organism
- Duration of total parenteral nutrition (days)
- Time to establish full enteral feeds (days)
- Duration of hospitalization (days)
- Weight gain (any measurement scale)
- Neurodevelopmental impairment i.e. rates of cerebral palsy, cognitive delay, deafness, blindness, or their composite, reported at 18 months corrected age or later.

De Dra A Herranz. GEN 2015.

THE COCHRANE COLLABORATION®

Analysis 1.1. Comparison 1 Probiotics versus control (all infants), Outcome 1 Severe necrotising enterocolitis (stage II-III).

Study or subgroup	Probiotics n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Al-Hosni 2012	2/50	2/51		1.2 %	1.02 [0.15, 6.96]
Bin-Nun 2005	1/72	10/73		6.2 %	0.10 [0.01, 0.77]
Braga 2011	0/119	4/112		2.9 %	0.10 [0.01, 1.92]
Costalos 2003					
Dani 2002					
Demirel 2013					
Fern ndez-Carrocera 2013					
Kitajima 1997					
Lin 2005					
Lin 2008	4/217	14/217		8.7 %	0.29 [0.10, 0.85]
Manzoni 2006	1/39	3/41		1.8 %	0.35 [0.04, 3.23]
Manzoni 2009					
Mihatsch 2010					
Mohan 2006					
ProPrems 2013					
Rojas 2012	9/372	15/378		9.3 %	0.61 [0.27, 1.38]
Roug`x00e9` 2009	2/45	1/49		0.6 %	2.18 [0.20, 23.21]
Samanta 2009	5/91	15/95		9.1 %	0.35 [0.13, 0.92]
Sari 2010	6/110	10/111		6.2 %	0.61 [0.23, 1.61]
Stratiki 2007	0/38	3/31		2.4 %	0.12 [0.01, 2.19]
Total (95% CI)	**2761**	**2768**		**100.0 %**	**0.43 [0.33, 0.56]**
Total events: 68 (Probiotics), 159 (Control)					

0.005 0.1 1 10 200

Favours probiotics Favours control

Comparison 2. Probiotics versus control (infants < 1500 g)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severe necrotising enterocolitis (stage II-III)	17	4914	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.31, 0.56]

CONCLUSIÓN: "LOS PROBIÓTICOS PREVIENEN LA MORTALIDAD Y LA NEC EN RNPT. ESTA REVISIÓN ACTUALIZADA RESPALDA DE MANERA FIRME UN CAMBIO EN LA PRÁCTICA CLÍNICA HABITUAL"

De Dra A Herranz. GEN 2015.

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Probiotic Effects on Late-onset Sepsis in Very Preterm Infants: A Randomized Controlled Trial

Susan E. Jacobs, Jacinta M. Tobin, Gillian F. Opie, Susan Donath, Sepehr N. Tabrizi, Marie Pirotta, Colin J. Morley and Suzanne M. Garland

Pediatrics; originally published online November 18, 2013; DOI: 10.1542/peds.2013-1339

The ProPrem trial

TABLE 3 Other Secondary Outcomes

	Probiotic Group, *n* = 548	Control Group, *n* = 551	RR (95% CI)	*P* Value
NEC				
NEC (Bell stage 2 or more), *n* (%)	11 (2.0)	24 (4.4)	0.46 (0.23 to 0.93)	.03
Subgroup analyses:				
Gestational age				[a]
<28 wk, *n* (%)	11 (5.0)	17 (7.2)	0.69	
≥28 wk, *n* (%)	0	7 (2.2)		
Birth weight				.08[b]
<1000 g, *n* (%)	10 (4.3)	14 (5.9)	0.73	
≥1000 g, *n* (%)	1 (0.3)	10 (3.2)	0.10	
Age at NEC (Bell stage 2 or more), d, median (IQR)	20.5 (15.5–34.5)	21 (17.0–30.5)		.99
Mortality				
Death, *n* (%)	27 (4.9)	28 (5.1)	0.97 (0.58 to 1.62)	.91
Age at death, d, mean (SD)	21.7 (18.5)	23.3 (16.7)		.75
Death during primary hospitalization, *n* (%)	30 (5.5)	31 (5.6)	0.97 (0.60 to 1.58)	.91
Age at death during primary hospitalization, d, median (IQR)	21 (7–40)	24.5 (10–42·5)		.49
Causes of death, *n* (%)				
Late-onset sepsis			.55 (0.43 to 5.32)	.52
NEC			.37 (0.12 to 1.14)	.07
Composite of death or NEC (Bell stage 2 or more), *n* (%)			.81 (0.52 to 1.26)	.35

Son seguros, baratos y fácil de aplicar.

-1100 RN
-Baja tasa de NEC

Variables dependientes 2[arias]:

-NEC

Reducción absoluta de riesgo 2.4% (NO EFECTO EN <28 SEMANAS)

- Mortalidad n.s.

PROBIÓTICOS VERSUS OTRAS INTERVENCIONES EMPLEADAS EN UCIN

Table 1 Recent interventions in neonatology, outcome and number of enrolled patients

Intervention	Outcome	Size of effect	Number of babies
Inhaled nitric oxide for hypoxic respiratory failure in term infants	Mortality	NS	1469
	Need for ECMO	RR 0.61 (0.51, 0.72)	
Hypothermia for HIE	Mortality	RR 0.75 (0.63, 0.88)	638
	Mortality or NDI	RR 0.76 (0.69, 0.84)	506
Antenatal steroids for preterm	Mortality	RR 0.77 (0.67, 0.89) NNT=23	4269
Probiotics in preterm infants	Mortality	RR 0.55 (0.40, 0.75)	2495
	NEC	RR 0.40 (0.29, 0.55)	4089

Janvier A et al. Acta Paediatr 2013

PROBIÓTICOS Y NEC: CUÁLES SON LAS “DUDAS”

-Qué cepa? (Mejor varias que una sola)

-Cuando? A Quién?

-Siempre la misma dosis independientemente de edad gestacional?

Cuánto tiempo?

PROBIÓTICOS Y NEC: ÚLTIMO ECA

Bifidobacterium breve BBG-001 in very preterm infants: a randomised controlled phase 3 trial

*Kate Costeloe, Pollyanna Hardy, Edmund Juszczak, Mark Wilks, Michael R Millar, on behalf of The Probiotics in Preterm Infants Study Collaborative Group**

Vol 387 February 13, 2016

	Bifidobacterium breve BBG-001 probiotic (n=650)	Placebo (n=660)	Adjusted* risk ratio (95% CI)
Necrotising enterocolitis†	61 (9%)	66 (10%)	0·93 (0·68–1·27)
Sepsis‡	73 (11%)	77 (12%)	0·97 (0·73–1·29)
Death before discharge home§	54 (8%)	56 (9%)	0·93 (0·67–1·30)

Data are n (%), unless otherwise indicated. *Adjusted for sex, gestational age at birth, and randomisation within 24 h of birth. Adjustment by centre was excluded because the model did not converge. Allowances for correlations between multiple births are accounted for. †Necrotising enterocolitis (Bell stage 2 or 3).[9,10] ‡Sepsis is defined as bloodstream infection with non-skin commensals after 72 h postnatal age and before 46 weeks' postmenstrual age. §Includes three infants who remained on paediatric wards at the time of analysis and are included as survivors; all were later discharged home.

Table 2: **Primary outcomes**

NO DIFERENCIAS!

PROBIÓTICOS Y NEC: ÚLTIMO ECA

Bifidobacterium breve BBG-001 in very preterm infants: a randomised controlled phase 3 trial

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	Bifidobacterium breve BBG-001 probiotic (n=650)	Placebo (n=660)	Adjusted* risk ratio
Stool culture at 2 weeks' postnatal age†			
B breve	436 (74%)	122 (21%)	3·51 (2·83–4·34)
MRSA	1 (<1%)	2 (<1%)	Too few data
VRE	0	1 (<1%)	Too few data
ESβL	18 (3%)	20 (3%)	0·76 (0·36–1·61)
Stool PCR at 2 weeks' postnatal age			
PCR positive§	416 (84%)	177 (35%)	2·42 (2·06–2·85)
B breve positive by culture or PCR	505 (85%)	219 (37%)	2·30 (1·99–2·66)
Stool culture at 36 weeks' postmenstrual age‡			
B breve	438 (84%)	253 (49%)	1·69 (1·50–1·91)
MRSA	1 (<1%)	0	Too few data
VRE	3 (1%)	1 (<1%)	2·97 (0·15–57·67)
ESβL	19 (4%)	18 (4%)	0·98 (0·44–2·18)

Data are n (% of received). MRSA=meticillin-resistant *Staphlococcus aureus*. VRE=vancomycin-resistant enterococcus. ESβL=extended spectrum β lactamase- producing Gram-negative bacteria. *Adjusted for sex, gestational age at birth, and randomisation within 24 h of birth. Adjustment by centre was excluded because the model did not converge. Allowances for correlations between multiple births are accounted for. †Includes 1266 infants alive, 1186 (94%) stools received. ‡Includes 1245 infants alive, 1043 (84%) stools received. §Of 1186 stools received at 2 weeks' postnatal age, there was sufficient material available to do PCR to detect *B breve* BBG-001 in addition to culture on 1007.

Table 4: Analysis of stool culture and PCR results on stools collected at 2 weeks' postnatal and 36 weeks'

-**PROBLEMA:**
Colonización cruzada en grupo placebo (49% de grupo placebo tenían cultivo de heces positivo para Bifidobacterium breve a las 36 semanas de EPM) …
PUEDE HABER MITIGADO EL EFECTO DEL TTO?

www.medicinafetalbarcelona.org/

Bifidobacterium breve BBG-001 in very preterm infants: a randomised controlled phase 3 trial

*Kate Costeloe, Pollyanna Hardy, Edmund Juszczak, Mark Wilks, Michael R Millar, on behalf of The Probiotics in Preterm Infants Study Collaborative Group**

Research in context

Evidence before this study

Extensive and regular searches of the literature written in English were conducted and we identified a small number of trials of probiotic in preterm infants, none with sepsis, and only one with necrotising enterocolitis as a primary outcome in a trial with multiple exclusions and very low incidence. The first Cochrane review of the topic was published in 2008, including a total of 11 trials with a meta-analysis suggesting reduced necrotising enterocolitis and death, but with no effect on sepsis. The authors commented on the heterogeneity of the trial participants and interventions, the difficulty of extracting outcome data for the high risk group below 1000 g birthweight, and the need for large trials.

Added value of this study

To the best of our knowledge, this study is the largest and the first statistically powerful published trial of the efficacy of a probiotic to reduce necrotising enterocolitis and sepsis in the preterm population. The population is likely to be more representative than the total population in recent meta-analyses. Furthermore, this is the first trial systematically to study stool colonisation in both groups of the trial and to emphasise both the incomplete colonisation in the active and the high cross colonisation in the placebo group. This trial reinforces the message from others that, in the short term, probiotic interventions are safe.

Implications of all the available evidence

The current results support the view that strains should be assessed separately and challenge the validity of combining trials of different interventions in meta-analyses. It is not plausible that cross colonisation with administered probiotic is confined to this trial; routine use of probiotic is likely to modify the gut microbiota of infants other than those for whom it is prescribed. We conclude that at the present time the evidence from clinical trials does not support the routine use of probiotics to prevent necrotising enterocolitis and sepsis in the preterm infant.

PROBIÓTICOS Y NEC: DUDAS

-Sepsis por Bifidobacterias descritas en RN

-Contaminación por hongos de productos empleados como probióticos:

Estos no están sujetos a controles farmacológicos

-Es adecuado combinar estudios con diferentes cepas en un metanálisis?

Bertelli C, Pillonel T, Torregrossa A, et al. *Bifidobacterium longum* bacteraemia in preterm infants receiving probiotics. *Clin Infect Dis* 2015; **60**: 924–27.

Zbinden A, Zbinden R, Berger C, Arlettaz. Case series of *Bifidobacterium longum* bacteraemia in three preterm infants on probiotic therapy. *Neonatology* 2015; **107**: 56–59.

US Centers for Disease Control and Prevention. Fatal gastrointestinal mucormycosis in an infant following ingestion of contaminated dietary supplement—Connecticut, 2014. http://emergency.cdc.gov/han/han00373.asp (accessed Nov 19, 2015).

D. ANTIBIÓTICOS Y NEC

The impact of postnatal antibiotics on the preterm intestinal microbiome

Majd Dardas[1], Steven R. Gill[2,3], Alex Grier[3], Gloria S. Pryhuber[1], Ann L. Gill[2], Yi-Horng Lee[4] and Ronnie Guillet[1]

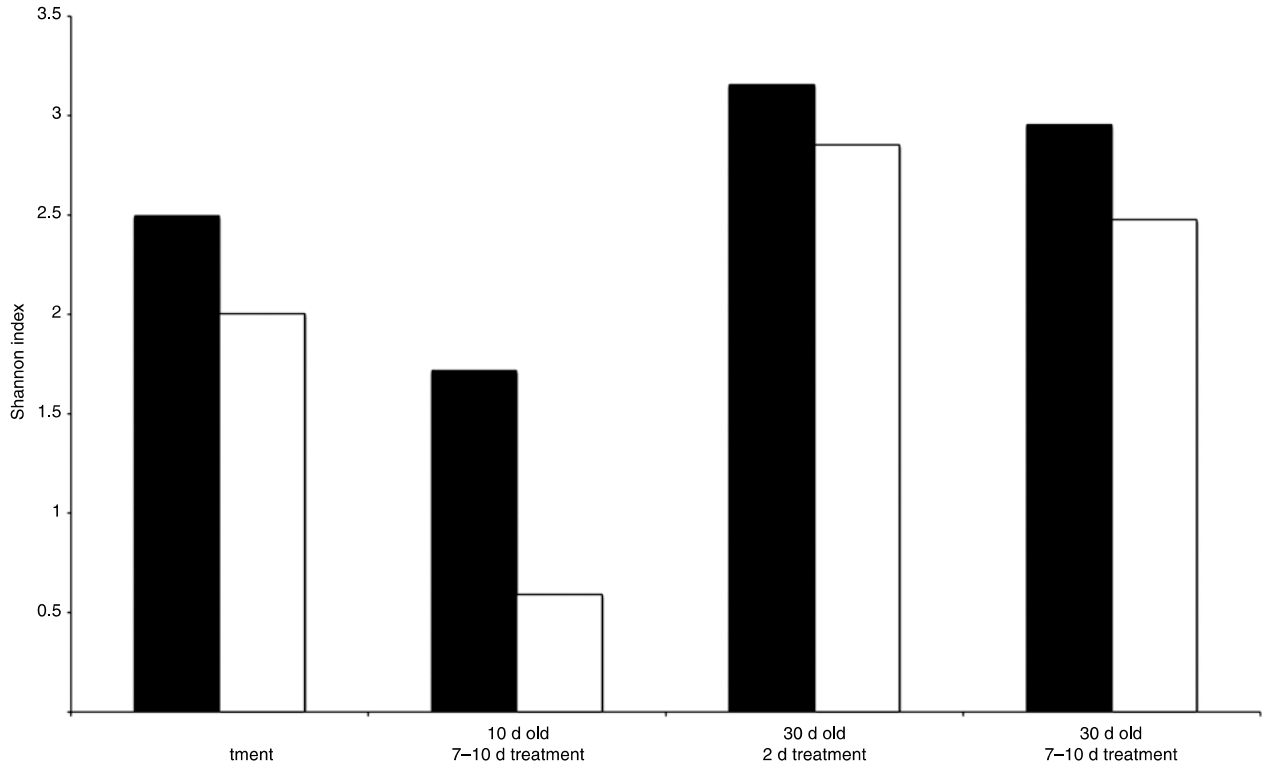


Figure 4. Shannon diversity index (α-diversity) based on age and antibiotic treatment. Diversity within each of the four groups separated by age, antibiotic treatment, and typical vs. atypical composition was determined using Shannon's diversity index. Samples with typical composition are shown in black bars. Samples with atypical composition are shown in white bars.

Pediatric RESEARCH Volume 76 | Number 2 | August 2014

-27 RNPT de <32 semanas alimentados con LM

-Comparan expuestos a dos días de AB vs 7 días de AB

-Diferencias en microbioma dependiendo de duración de antibióticos!

E. Empleo de anti H2

-Por qué se usan en RNPT?

-"Para tratamiento del RGE" --- todos tienen RGE
-"Como profilaxis de úlceras de estrés" … A quiénes
-"En postoperatios" … ¿Cúanto tiempo?
-"Puede mejorar apneas asociadas a RGE" … ?¿?
-"no sabía que llevara Ranitidina" …

Empleo de anti H2 y NEC

Table 1 Studies, which explored the association of use of ranitidine/H2 antagonists with NEC

Study	Study group	Study type	Outcome	Timing of intervention and treatment duration	Key results	Comments
Guillet *et al* (2006)[1]	787 preterm infants with NEC were studied with 2361 matched controls (BW 401–1500 g) Three controls were matched to each NEC case on the basis of birth weight category, race, and cei	Retrospective case control study (3b)	H2 antagonists treatment	H2-blocker use the day before diagnosis of NEC or later was not included. H2 antagonists started a mean of 18.9±15.5 days before NEC. Total duration of treatment collected but not presented	Treatment with H2 antagonists was associated with a higher incidence of NEC in VLBW infants(OR: 1.71; 95% CI 1.34 to 2.19; p<0.0001)	Lack of information on breast milk or formula feeding, feeding protocol
Terrin *et al* (2012)[2]	91 ex we pre we ranitidine Mean GA and birth weight of exposed infants: 29 (28.7–29.5) weeks; 1091 (1057–1124) grams. Mean GA and birth weight of control infants: 29 (28.7–29.8) weeks; 1083 (1031–1036) grams		duration of hospital stay	collected but not presented	(9.8%) than in those not exposed to ranitidine (1.6%). In newborns treated with ranitidine, more infections (OR 5.5, 95% CI 2.9 to 10.4, p<0.001), higher mortality rate (9.9% vs 1.6%, p=0.003), and longer hospitalisation (median 52 days vs 36 days, p<0.001) was noted.	nformation about in prevalence of e use, use of ilk and outcomes entres. Indication for ranitidine treatment was not specified. Differences in antibiotic usage were also not mentioned
Bilali *et al* (2013)[3]	116 preterm infants with NEC were studied with 116 controls (matched on the basis of gestational age, birth weight and year of birth). Any infant born <37 weeks was included.	Retrospective case control study (3b)	H2 antagonists treatment	Exposure to H2 antagonists was defined as any infant who received treatment 1 day prior to NEC diagnosis or in controls 1 day prior to the matched chronological age at which NEC developed. Total duration of treatment not presented	H2 blocker treatment was significantly associated with an increased incidence of NEC in preterm infants (adjusted OR: 3.71; 95% CI 0.98 to 14.03; p=0.05)	Small sample size (infants with NEC). Full demographic data not given

BW, birth weight; GA, gestational age; NEC, necrotising enterocolitis; VLBW, very low birth weight.

OR NEC en tratados con Ranitidina entre 1,7 y 5,5 (con 95% IC siempre mayores de 1)

Empleo de anti H2 y NEC

Bovine Lactoferrin Supplementation for Prevention of Late-Onset Sepsis in Very Low-Birth-Weight Neonates

A Randomized Trial

-Días promedio de exposición a Ranitidina eran 3 días

-Cada día de ranitidina aumentaba riesgo de sepsis un 3,7%

Table 3. Multivariable Logistic Regression Analysis Controlling for the Most Important Risk Factors Possibly Associated With Late-Onset Sepsis[a]

Factor	OR (95% CI)[b]	*P* Value
Treatment[c]		
BLF	0.32 (0.14-0.77)	.01
BLF + LGG	0.21 (0.08-0.55)	.002
Sex[c]	1.91 (0.89-4.09)	.10
Gestational age, per week	0.71 (0.57-0.89)[d]	.002
Birth weight, per gram	1.00 (1.00-1.00)[d]	.35
Milk type[c]		
Mix	2.43 (0.50-11.75)	.48
Maternal	2.69 (0.50-14.63)	
Human (nonmaternal)	4.78 (0.64-35.94)	
Use of H_2 blockers, total days	1.04 (0.99-1.08)[d]	.09
Use of postnatal steroids, total days	1.10 (0.54-2.25)[d]	.79
Daily mean human fresh milk intake, mL/kg	0.99 (0.98-1.01)[d]	.29

Abbreviations: BLF, bovine lactoferrin; CI, confidence interval; LGG, *Lactobacillus rhamnosus* GG; OR, odds ratio.

[a] Within-center correlation = 3.4% (*P* = .28). Log likelihood of full model = −109.41775; Wald test (11 *df*) = 52.73 (*P* < .001).

[b] Adjusted for all other terms listed in the table.

[c] Referents were placebo for treatment, male for sex, and formula milk for milk type.

[d] OR for a 1-unit increase.

Prevention of Neonatal Necrotizing Enterocolitis

Vivien Carrion and Edmund A. Egan

Journal of Pediatric Gastroenterology and Nutrition
11:317–323 © 1990 Raven Press, Ltd., New York

TABLE 2. *Demographic characteristics of HCl-supplemented and control group*

	Feeding supplement	
	Sterile water	HCl
No. enrolled	34	34
Birth weight (g)	840 ± 87	870 ± 77
Gestational age (weeks)	26 ± 2	27 ± 2
Sex (F/M)	15/19	22/12
Race (B/W)	10/24	12/22
Age at first feed (days)	10.5 ± 6	9.5 ± 8
Weight at first feed (g)	740 ± 93	772 ± 99
Age at total alimentary nutrition (days)	26 ± 11	23 ± 13

Values represent mean ± SD.

-68 RNPT <1250g
-Reclutamiento 1986-1987, CI
-Tasa NEC en centro 18%
-Suplementación 0,01-0,02ml de HCL a LM/Fórmula

TABLE 4. *Cases of necrotizing enterocolitis by degree of severity*

		Severity of necrotizing enterocolitis					
	N	Clinical diagnosis	Pneumatosis intestinalis	Bowel perforation	Short bowel	Death	Total NEC
Sterile water supplement	34	3	2	2	0	1	8*
1 *N* HCl supplement	34	0	0	1	0	0	1

* $p = 0.016$ by Fisher's exact test.

Empleo de anti H2

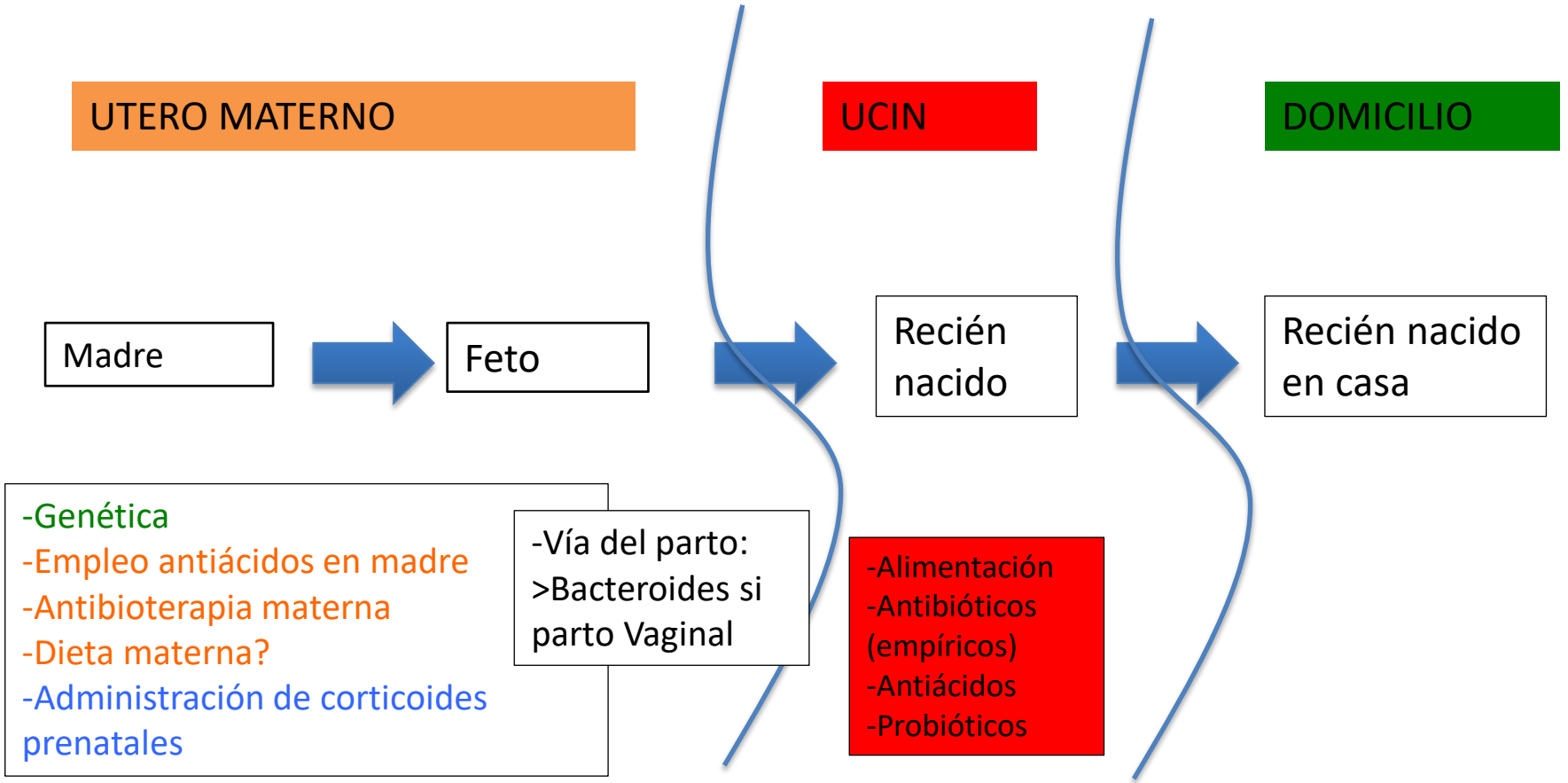
Clinical bottom line

- Ranitidine use should be avoided in preterm infants.
- Ranitidine/H2 antagonists administration is associated with increased incidence of NEC (level 2b).

B Philips Does the use of Ranitidine increase the risk of NEC in preterm infants?

Arch Dis Child April 2014 Vol 99 No 4

Prevención de la NEC



Preterm infant nutrition, gut bacteria, and necrotizing enterocolitis
Josef Neu. Curr Opin Clin Nutr Metab Care. 2015 May;18(3):285-8

6.CONCLUSIÓN: DIAGNÓSTICO Y PREVENCIÓN DE NEC

1. Hay margen de mejora

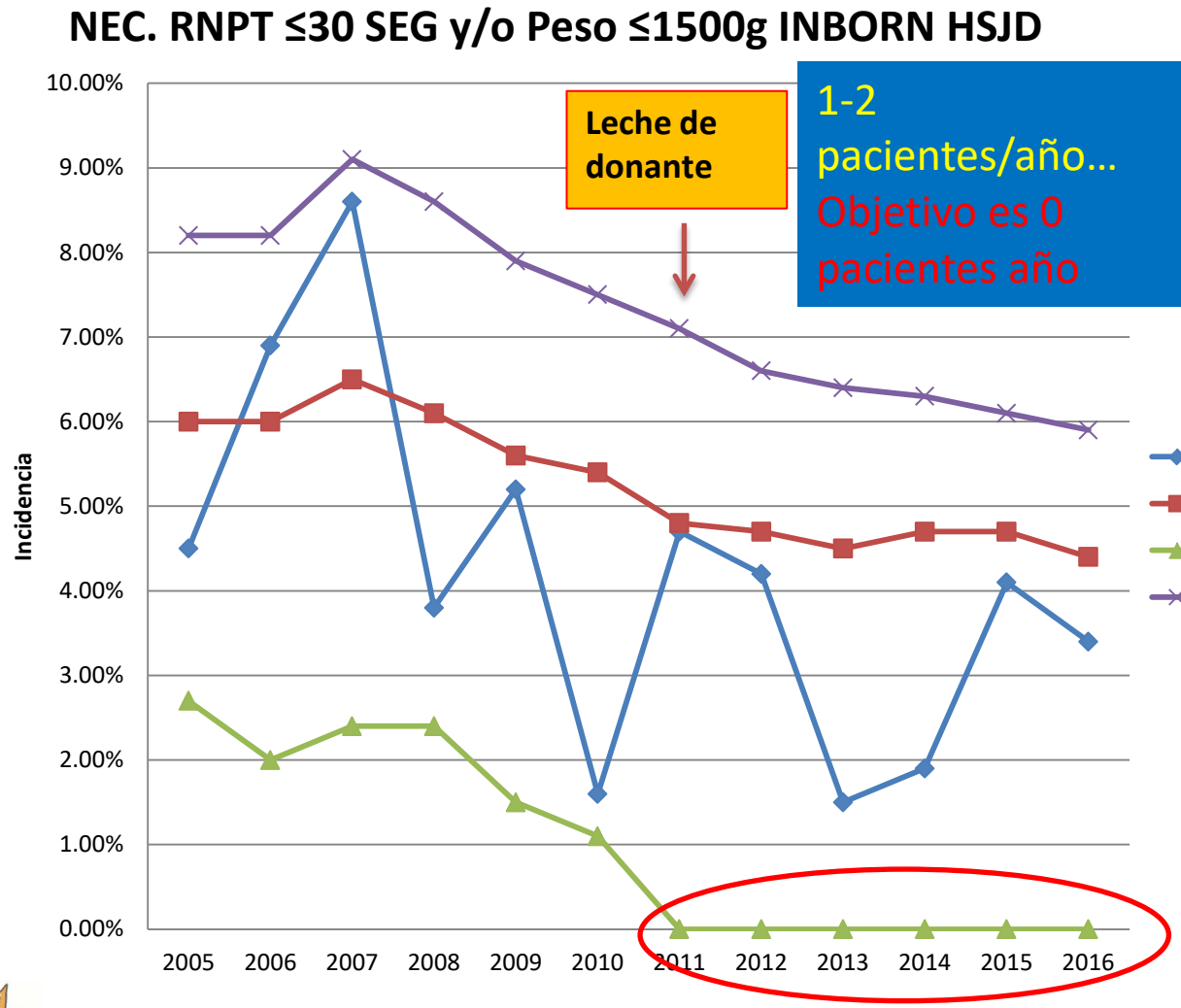
2. Más investigación para disponer de mejores criterios diagnósticos y pronósticos

- **mejorar modelos animales existentes: diferentes "tipos" de NEC**
- **Biomarcadores de gravedad a pie de cama +/- Otras pruebas dx**

3. Estrategias preventivas actuales

-Favorecer y potenciar LM
-Acortar duración de antibioterapia empírica inicial 48 horas si cultivos negativos
-Evitar antiácidos de rutina en grupo de pacientes
-Probióticos?

CONCLUSIÓN: DIAGNÓSTICO Y PREVENCIÓN DE NEC



Leche de donante

1-2 pacientes/año…
Objetivo es 0 pacientes año

-No usamos probióticos

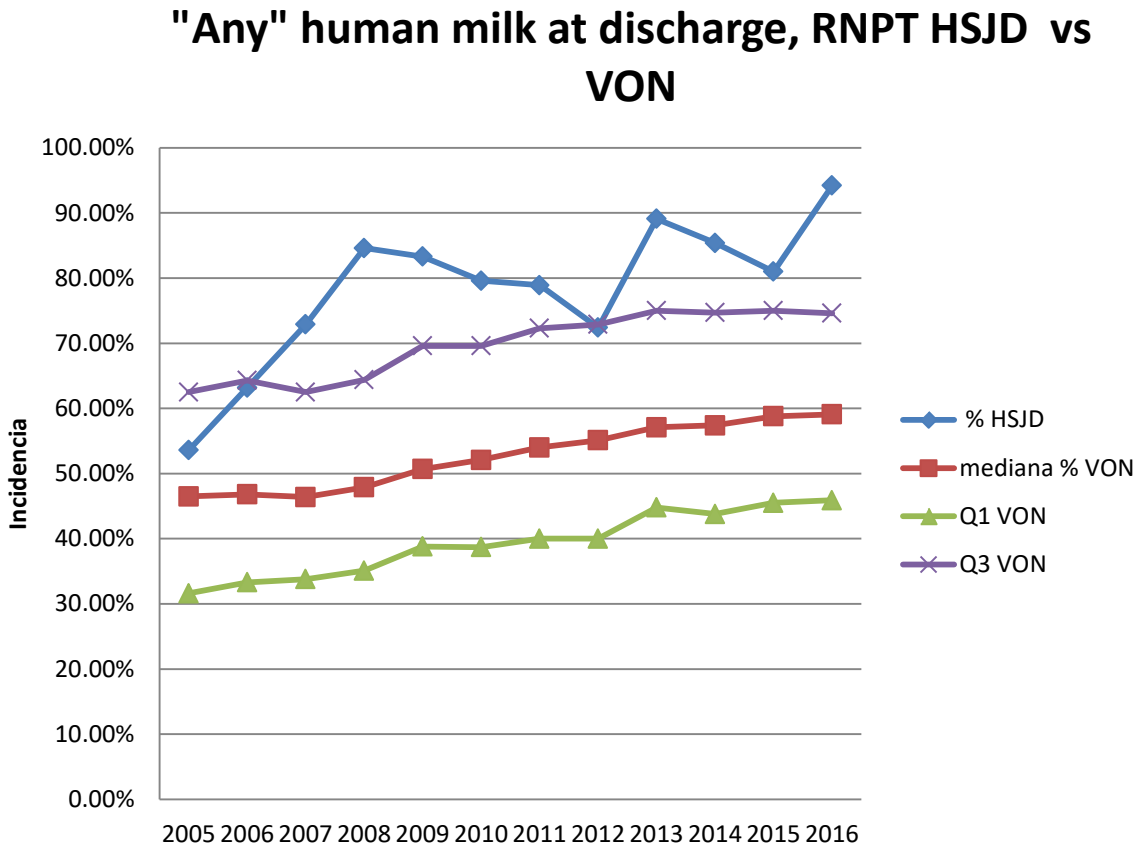
-No datos de empleo de antiH2

-Esfuerzo por acortar AB empírica

-Objetivo 2018: " grupo calostro"

Comisión GI: 2012

CONCLUSIÓN: DIAGNÓSTICO Y PREVENCIÓN DE NEC



CONCLUSIÓN-Impacto en las familias…

Perspectives from parents of infants impacted by NEC: NEC communication in the NICU

NEC Society, Ann Arbor, MI

Jennifer Canvasser, M.S.W.; Samir Gadepalli, M.D., M.B.A.; Sheila Gephart, Ph.D., R.N.; Jae Kim, M.D., Ph.D. **Contact**: Jennifer Canvasser, jmcanvasser@gmail.com, 408-515-3455

Objetivo es 0 pacientes/año


Gracias!