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Un Nuevo Concepto en Medicina Perinatal

Neo Red

Randomised trial of azithromycin to eradicate *Ureaplasma* in preterm infants

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- Ureaplasma es un factor independiente para desarrollar DBP
  - Proinflamatorio + profibrótico
  - Tratamiento con azitromicina erradicaría la DBP y disminuiría el riesgo

- Estudio randomizado, controlado, doble ciego, multicéntrico
- PT 24+ 0/7 a 28+ 6/7 sem
- Desde noviembre 2013 a Enero 2016
- Menores de 72 h que recibieron al menos 1 h de ventilación a presión positiva
- Criterios de exclusión:
  - No viable o definido tratamiento paliativo
  - Malformaciones congénitas
  - Múltiples >2
  - QT largo
  - Falla hepática
  - Exposición a otros macrólidos
  - Compromiso de sistema nervioso central probado o sospecha

- Los participantes fueron estratificados por EG
  - 24 + 0/7 a 26 + 6/7
  - 27 + 0/7 a 28 + 6/7
- Randomizados a azitromicina v/s placebo
- El grupo tratado recibió eritromicina 20 mg/Kg en una concentración de 2 mg/mL en SG 5% e.v en 60 minutos, cada 24 h por 3 dosis
- Toma de muestra de Ureaplasma:
  - En pacientes intubados: 2 aspirados traqueales separados de al menos 2 horas (cultivo) + 1 muestra por tórula nasal (PCR)
  - En pacientes no intubados: 2 muestras nasofaringeas (cultivo y PCR)
  - Tomadas antes de la primera dosis de azitromicina
  - Luego se controlaban las muestras a los 2-4-5 dias posterior a la última dosis y a los 21 días de edad postnatal

- kjlkj

Table 1 Baseline characteristics of the study participants for the total cohort and stratified by *Ureaplasma* status

	No. of participants (%)					
	Total cohort		*Ureaplasma* positive		*Ureaplasma* negative	
	(n=121)		(n=44)		(n=77)	
Characteristic	AZM (n=60)	Placebo (n=61)	AZM (n=19)	Placebo (n=25)	AZM (n=41)	Placebo (n=36)
Male, n (%)	26 (43)	32 (52)	11 (58)	10 (40)	15 (37)	22 (61)
Race, n (%)						
White	36 (60)	15 (25)	13 (68)	5 (20)	23 (56)	10 (28)
African-American	21 (35)	43 (70)	6 (32)	19 (76)	15 (37)	24 (67)
Asian	0 (0)	1 (2)	0	1 (4)	0	0
Multiple/biracial	3 (5)	2 (3)	0	0 (0)	3 (7)	2 (6)
Hispanic ethnicity, n (%)	2 (3)	0 (0)	0 (0%)	0 (0)	2 (5)	0 (0)
Birth weight, mean (SD), g	895 (215)	903 (245)	897 (195)	851 (282)	895 (226)	939 (213)
Gestational age, mean (SD), weeks	26.2 (1.4)	26.2 (1.4)	25.8 (1.1)	25.8 (1.4)	26.4 (1.5)	26.5 (1.4)
Gestational age strata, n (%)						
24^0–26^6 weeks	40 (67)	43 (70)	16 (84)	20 (80)	24 (59)	23 (64)
27^0–28^6 weeks	20 (33)	18 (30)	3 (16)	5 (20)	17 (41)	13 (36)
SGA, n (%)	2 (3)	1 (2)	0 (0)	1 (4)	2 (5)	0 (0)
Preterm labour, n (%)	47 (78)	49 (80)	17 (89)	18 (72)	30 (73)	31 (86)
PPROM, n (%)	23 (38)	29 (48)	9 (47)	17 (68)	14 (34)	12 (33)
Duration rupture of membranes, n (%)						
<1 hour	36 (60)	29 (48)	9 (47)	7 (28)	27 (66)	22 (61)
≥1 hour	22 (37)	29 (48)	9 (47)	16 (64)	13 (32)	13 (36)
Unknown	2 (3)	3 (5)	1 (5)	2 (8)	1 (2)	1 (3)
Maternal Pe-eclampsia, n (%)	0 (0)	2 (3)	0 (0)	1 (4)	0 (0)	1 (3)
Antenatal steroids, n (%)	51 (85)	48 (79)	16 (84)	19 (76)	35 (85)	29 (81)
Maternal macrolide, n (%)						
Erythromycin	10 (17)	11 (18)	4 (21)	8 (32)	6 (15)	3 (8)
Azithromycin	9 (15)	9 (15)	2 (11)	1 (4)	7 (17)	8 (22)
Both	1 (2)	0	0 (0)	0	1 (2)	0 (0)
Neither	40 (67)	41 (67)	13 (68)	16 (64)	27 (66)	25 (69)
Route of delivery, n (%)						
SVD	27 (45)	27 (44)	9 (47)	13 (52)	18 (44)	14 (39)
C/S	33 (55)	34 (56)	10 (53)	12 (48)	23 (56)	22 (61)
Apgar 1 min, median (IQR)	5 (3,7)	4 (2,6)	4 (2,8)	4 (2,5)	5 (3,7)	5 (2.5 to 6.5)
Apgar 5 min, median (IQR)	7 (6,8)	7 (6,8)	6.5 (5,8)	6 (6,8)	7 (6,8)	7 (5.5 to 8)
Respiratory support at enrolment, n (%)						
None	2 (3)	1 (2)	1 (5)	0 (0)	1 (2)	1 (3)
Non-invasive*	28 (47)	34 (56)	10 (53)	15 (60)	18 (44)	19 (53)
Invasive†	30 (50)	26 (43)	8 (42)	10 (40)	22 (54)	16 (44)
Duration IMV at enrolment, median (IQR), hours	24.9 (10.3,52.3)	29 (15.0,46.8)	20.5 (0.3,53.0)	30.9 (21.1,49.3)	26.5 (12,49.2)	22.2 (10.5,46.4)
Effective FIO_2 at enrolment, median (IQR)	0.24 (0.21,0.28)	0.25 (0.21,0.33)	0.26 (0.21,0.30)	0.27 (0.21,0.30)	0.22 (0.21,0.27)	0.25 (0.21,0.36)
Postnatal age at time of first dose, mean (SD), hours	58.5 (23.1)	56.2 (19.4)	58.3 (24.1)	50.4 (18.7)	58.5 (22.9)	60.3 (19.0)
Ureaplasma spp. respiratory colonisation, n (%)	19 (32)	25 (41)	19 (100)	25 (100)		
U. parvum	14 (23)	19 (31)	14 (74)	19 (76)	N/A	N/A
U. urealyticum	3 (5)	4 (7)	3 (16)	4 (16)		
Both species	1 (2)	2 (3)	1 (5)	2 (8)		
Untyped	1 (2)	0 (0)	1 (5)	0 (0)		

*Non-invasive ventilation included oxyhood, low flow nasal cannula, high flow nasal cannula, nasal continuous positive pressure and nasal intermittent positive pressure ventilation.
†Invasive ventilation included synchronised intermittent mechanical ventilation, high frequency oscillatory ventilation and high frequency jet ventilation.
AZM, azithromycin; C/S, caesarean section; FIO_2, fractional inspired oxygen; IMV, intermittent mandatory ventilation; PPROM, preterm premature rupture of membranes; SGA, small for gestational age; SVD, spontaneous vaginal delivery.

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Table 2 Primary and secondary outcomes of total cohort and stratified by *Ureaplasma* respiratory colonisation status

	No. of participants (%)								
	Total cohort (n=121)			*Ureaplasma* positive (n=44)			*Ureaplasma* negative (n=77)		
Outcome	AZM (n=60)	Placebo (n=61)	P value*	AZM (n=19)	Placebo (n=25)	P value*	AZM (n=41)	Placebo (n=36)	P value*
Ureaplasma-free survival, n (%)	55 (92)	37 (61)	<0.001	16 (84)	3 (12)	<0.001	39 (95)	34 (94)	>0.99
Survival, n (%)	55 (92)	55 (90)	0.78	16 (84)	21 (84)	>0.99	39 (95)	34 (94)	>0.99
Ureaplasma clearance post-treatment, n (%)	19/19 (100)	4/25 (16)	<0.001	19/19 (100)	4/25 (16)	<0.001	N/A	N/A	
Discharged to home, n (%)	39 (65)	30 (49)	0.10	13 (68)	8 (32)	0.03	26 (63)	22 (61)	0.86
Survival free of physiological BPD, n (%)†	31/59 (53)	36/59 (61)	0.42	9 (47)	13/24 (54)	0.54	22 (55)	23 (66)	0.33
Physiological BPD, n (%)†‡	25/56 (45)	18/54 (33)	0.28	8/17 (47)	8/21 (38)	0.49	17/39 (44)	10/33 (30)	0.25
Modified Shennan BPD, n (%)‡	28/57 (49)	23/56 (41)	0.45	8/17 (47)	11/22 (50)	0.99	20/40 (50)	12/34 (35)	0.21
Moderate-severe BPD, n (%)‡	31/57 (54)	23/56 (39)	0.20	9/17 (53)	10/22 (45%)	0.51	22/40 (55)	13/34 (38)	0.15
Postnatal steroids exposure, n (%)	15 (25)	14 (23)	0.86	7 (37)	6 (24)	0.33	8 (20)	8 (22)	0.74
Passed hearing screen, n (%)§	50/54 (93)	52/54 (96)	0.68	13/16 (81)	19/21 (90)	0.63	37/38 (97)	33/33 (100)	>0.99
Duration IMV, median (IQR), days¶	12 (3–31)	4 (1–44)	0.36	15 (5–66)	3 (1–44)	0.25	11 (2–20)	4 (1–47)	0.51
Duration supplemental oxygen, median (IQR), days¶	73 (39–114.5)	68 (33–118)	0.94	87 (30–140)	75 (55–135)	0.98	70 (40–91)	60 (26–94)	0.81
Duration hospitalisation, median (IQR), days¶	87 (62.5–138.5)	87 (67–111)	0.91	109 (54–147)	87 (59–111)	0.62	83 (66–136)	87 (72–112)	0.53

*P values for binary outcomes are based on a score test from generalised estimating equations to account for correlations between twins, or Fisher's exact test when one of the cell sizes has an expectation of less than 5. P values for quantitative outcomes are based on non-parametric tests using multiple outputation to account for correlations between twins.
†Three participants could not be classified with respect to physiological BPD and are excluded from these percentages.
‡Excludes eight participants (three azithromycin and five placebo) who died prior to BPD assessment.
§Based on only those who survived until discharge but excludes two survivors who did not have a hearing screen.
¶In computing the median and IQR, those who died are included as having the worst outcomes.
AZM, azithromycin; BPD, bronchopulmonary dysplasia; IMV, intermittent mandatory ventilation.

Table 4 Primary and secondary outcomes among tracheal aspirate *Ureaplasma*-positive participants by treatment assignment

Outcome	No. of participants (%)		P value*
	Azithromycin (n=10)	Placebo (n=11)	
Ureaplasma-free survival, n (%)	8 (80)	0 (0)	<0.001
Survival, n (%)	8 (80)	7 (64)	0.64
Ureaplasma clearance post-treatment, n (%)	10 (100)	1 (9)	<0.001
Survival free of physiological BPD, n (%)†	5 (50)	2 (18)	0.18
Physiological BPD, n (%)†	3/8 (38)	6/8 (75)	0.31
Modified Shennan BPD, n (%)†	3/8 (38)	6/8 (75)	0.31
Moderate/severe BPD, n (%)†	3/8 (38)	6/8 (75)	0.31
Discharge home, n (%)	5 (50)	2 (18)	0.18
Postnatal steroids, n (%)	4 (40)	6 (55)	0.67
Passed hearing screen, n (%)‡	6/8 (75)	6/7 (86)	>0.99
Total duration IMV, median (IQR)§	24.5 (8–72)	53 (31 to –)	0.11
Total duration supplemental oxygen, median (IQR)§	95.5 (39–174)	142 (114 to –)	0.13
Duration of hospitalisation, median (IQR)§	80.5 (27–173)	134 (91 to –)	0.08

*P values for categorical outcomes are based on Fisher's exact tests. P values for quantitative analysis are based on two-sample Wilcoxon tests.
†Excludes five participants (two azithromycin, three placebo) who died prior to 36 weeks PMA.
‡Excludes six (two azithromycin, four placebo) participants who died before hearing screen was obtained.
§In computing the median and IQR, those who died are included as having the worst outcomes. For the tracheal aspirate *Ureaplasma*-positive participants, more than 25% died, so it was not possible to specify the actual 75th percentile.
BPD, bronchopulmonary dysplasia; IMV, intermittent mandatory ventilation; PMA, postmenstrual age.

Table 5 Morbidities of prematurity by treatment group

Morbidity	Azithromycin (n=60) N (%) acquired prior to discharge	Placebo (n=61) N (%) acquired prior to discharge	P value*
Pneumothorax	**7/55 (13)**	**4/57 (7)**	**0.49**
PDA	25/55 (45)	21/56 (38)	0.33
Feeding intolerance	20/51 (39)	34/58 (59)	0.04
Gastro-oesophageal reflux	14/60 (23)	11/61 (18)	0.54
Intestinal perforation	2/60 (3)	4/61 (7)	0.68
NEC ≥stage 2	4/60 (7)	5/61 (8)	>0.99
Culture-confirmed sepsis	8/60 (13)	14/61 (23)	0.18
IVH†			0.33
None	31/53 (58)	40/54 (74)	
Grade 1	10/53 (19)	7/54 (13)	
Grade 2	5/53 (9)	5/54 (9)	
Grade 3	5/53 (9)	1/54 (2)	
Grade 4	2/53 (4)	1/54 (2)	
Shunted PHH	6/60 (10)‡	0/61 (0)	0.01
PVL	4/60 (7)	5/61 (8)	>0.99
ROP (highest stage)§			0.28
None	18/56 (32)	25/56 (45)	
Stage 1	17/56 (30)	17/56 (30)	
Stage 2	10/56 (18)	10/56 (18)	
Stage 3	11/56 (20)	3/56 (5)	
Stage 4	0/56 (0)	1/56 (2)	

- La colonización por *Ureaplasma* continua en pacientes no tratados hasta por 3 semanas luego del nacimiento
- AZT 20 mg/Kg por 3 días es efectiva para erradicarlo
- Demuestra la eficacia del tratamiento con AZT pero ninguna diferencia respecto a mortalidad, soporte respiratorio prolongado y DBP en PT EBPN

Review

OPEN ACCESS

Implementation of bowel ultrasound practice for the diagnosis and management of necrotising enterocolitis

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- La mortalidad aumenta luego de una perforación intestinal, motivo por el cual la detección precoz de isquemia o áreas de necrosis podría mejorar el manejo y la sobrevida
- Signos patognomónicos radiológicos (gas portal y neumatosis) son poco sensibles, especialmente en los casos menos severos
- Signos radiológicos más sensibles, son inespecíficos (edema de pared, distensión abdominal, ascitis)

Box 1 List of appropriate indications for bowel ultrasound (BUS)

Appropriate indications for BUS

- Earlier diagnosis of necrotising enterocolitis (NEC).
- Establishing the diagnosis of NEC when abdominal radiograph (AXR) is equivocal.
- AXR demonstrating a gasless abdomen.
- Evaluating for complications in known NEC.
- Evaluation for features suggestive of need for surgical intervention in the setting of clinical deterioration.

Box 2 Representative protocol for sonographer with key components of the exam

Necrotising enterocolitis bowel ultrasound technique/ protocol

Scan all four quadrants

- RLQ→ RUQ→LUQ→LLQ.
- Images in sagittal and transverse.

Greyscale

Bowel wall

- Thickness.
  Normal between 1 mm and 2–2.7 mm.
- Echogenicity.
- Dilation.
- Peristalsis.
  Obtain cine clips.
  May have to watch for >1 min.

Pneumatosis

- If air is seen in bowel in supine position, change to decubitus to see if air shifts or remains in the wall.

Ascites

- Simple or complex.

Pneumoperitoneum

Colour Doppler

- Decreased pulse repetition frequency to see subtle hyperaemia or lack of flow.
- Portal vein: assess for portal venous gas.
- Superior mesentric artery and vein only if easily identifiable.

Spectral Doppler

- PVG=typical artefact sharp bidirectional spikes of Doppler shift superimposed on portal venous waveform.

Tips

- Ensure adequate pain control prior to exam, providing a dose of medication if needed.
- Patient does not need to be NPO.
- Greyscale.
- High frequency transducer for detail of wall.
- Low frequency transducer to look for free fluid/abscess and so on.
- Harmonics=decreased artefacts and better resolution.
- Panoramic images can be obtained for long segment.
- Can do without compression, graded compression or graded anterior and posterior compression as patient condition permits.

Table 1 A summary of statistical analysis of key BUS and AXR findings derived from previous meta-analyses, obtaining a range of data without further statistical analysis

Statistical significance of key bowel ultrasound findings*

	For the diagnosis of NEC					Eventual need for surgery or death
BUS finding	**Sens (%)[28]**	**Spec (%)[28]**	**AXR correlate**	**AXR Sens (%)[10]**	**AXR Spec (%)[10]**	**OR[15 16]**
Early findings						
Increased bowel perfusion	–	–	None.	–	–	NSS
Simple (anechoic) ascites	45	92	Bowel loops displaced centrally if large volume.	–	–	NSS
Dilated bowel	–	–	Dilated bowel.	–	–	3.50–3.59
Intermediate findings						
Portal venous gas	27	94	PVG.	13	100	NSS
Pneumatosis intestinalis	48	91	Pneumatosis.	44	100	2.01–2.23
Bowel wall thickening	31	67	Enlarged mucosal folds.	–	–	3.7–4.74
Increased bowel echogenicity	–	–	None.	–	–	8.58
Late findings						
Bowel wall thinning	22	96	None.	–	–	7.11–7.97
Absent peristalsis	3	95	Stationary patulous bowel loops on serial exams.	–	–	8.19–10.68
Absent bowel perfusion	–	–	None.	–	–	6.08–6.99
Focal fluid collections	19	98	None.	–	–	15.37–17.92
Complex (echogenic) ascites	–	–	None.	–	–	11.28
Pneumoperitoneum	27	94	Pneumoperitoneum.	52	92	8.25–9.63

*Data reported are a compilation of the currently known sensitivity and specificity as reported in the referenced meta-analyses. It should be noted that not all studies included reported data on all categories. Further research is needed in this area to elucidate the most accurate data.
AXR, abdominal radiograph; BUS, bowel ultrasound; NEC, necrotising enterocolitis; NSS, not statistically significant; PVG, portal venous gas.

- Eco de abdomen puede servir para diagnóstico y seguimiento de NEC
- Una ecografía sin hallazgos no descarta NEC. Estudios muestran que entre un 20 – 40 % de recién nacidos con NEC pueden tener ecografías normales
- Eco v/s Rx tiene alta especificidad y VPP
- Signos de alerta ecográficos en pacientes con NEC confirmada:
  - Adelgazamiento de la pared intestinal
  - Ausencia de perfusión o peristalsis
  - Aire libre o colecciones