Ureaplasma: Biclar-y-be happy?

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Wintervergadering VVK

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Overview

1. Introduction
2. Journey of BPD and ureaplasma
3. Ureaplasma and BPD: the evidence
4. Role of macrolides in prevention of BPD
5. Ureaplasma: challenges and experience
6. Conclusion

Ureaplasma

- Mycoplasma species
  - Smallest free-living organisms
  - Lacking cell-wall: resistent to many commonly used antimicrobial agents (e.g. beta-lactam)
- 2 serotypes:
  - *Ureaplasma parvum*
  - *Ureaplasma urealyticum*
- Colonisation of urogenital tract in 70% of men and women

Ureaplasma

- ‘Opportunistic pathogen’

- Associated with:
  - adverse pregnancy outcomes
  - neonatal morbidities of prematurity including bronchopulmonary dysplasia (BPD), necrotizing enterocolitis, ROP and severe intraventricular hemorrhage
- Transmitted in one of three ways:
  1. In utero by ascending route secondary to maternal urogenital colonization
  2. Hematogenous route through placental infection
  3. At delivery through the infected birth canal
- Vertical transmission rate
  - inversely related to gestational age
  - increases with the duration of rupture of membranes.

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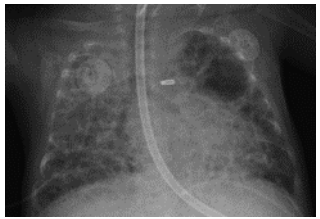
Bronchopulmonary dysplasia

- Still a major health problem in preterm infants
- Challenge for neonatologists worldwide
- Incidence up to 44-70% in ELBW infants
- Definition
  - Based on treatment (rather than symptoms/pathophysiology)
  - Large variation
  - ‘Observer-dependent’?



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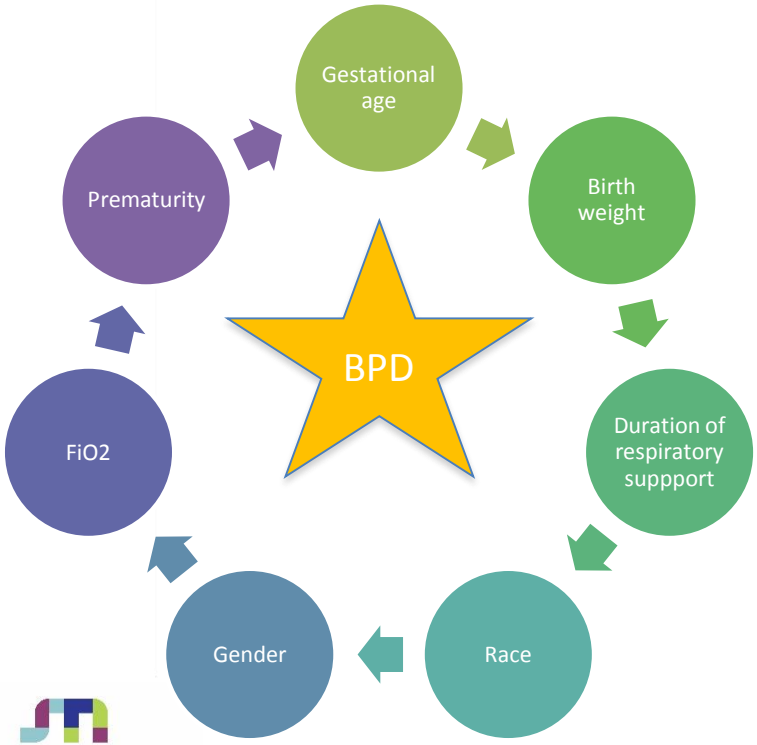
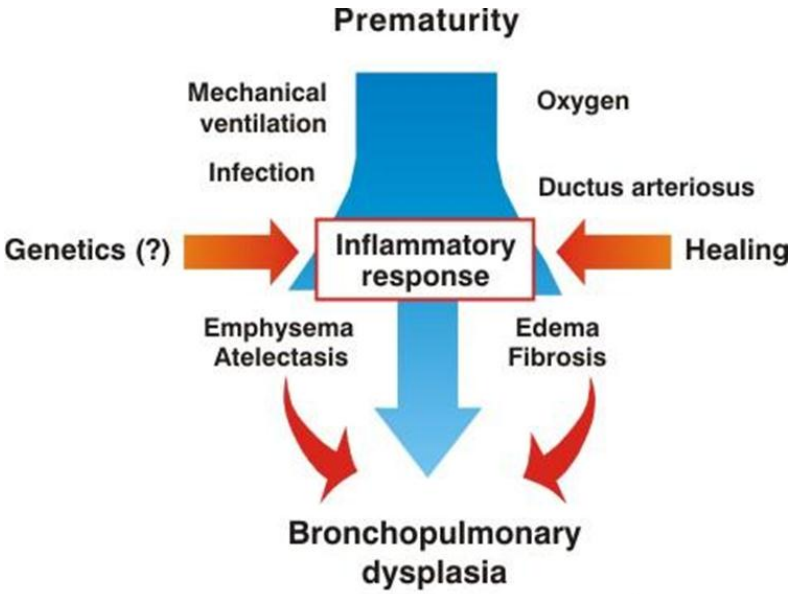
Bronchopulmonary dysplasia

- Multiple risk factors



- Multifactorial pathogenesis



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Journey of Ureaplasma and BPD

'OLD BPD'

First description of

1967 •Staged evolution of n
toxicity and dama
ventilation

Beginning of su

•Larger number of

1988 •Requirement of c
→better predictor
of age

New era

•Widespread use

Late '90s - 21st century •Optimizing respir
– 'Gentle' ventilation
– Avoiding ventilation

•Minimal invasive approach – new management strategies
– E.g. HFNC
– Less invasive surfactant administration
– ....

'NEW BPD'

VOLUME 82 • OCTOBER 1988 • NUMBER 4

Pediatrics

Abnormal Pulmonary Outcomes in Premature Infants: Prediction From Oxygen Requirement in the Neonatal Period

Andrew T. Shennan, MB, MRCP(UK), FRCP(C), Michael S. Dunn, MD, FRCP(C), Arne Ohlsson, MD, FRCP(C), Kathryn Lennox, RN, and Elizabeth M. Hoskins, MD, FRCP(C)

definition

dency at 28d

ment at 36w

f BPD severity[8]

	Gestational age at birth	
	< 32 weeks	≥ 32 weeks
Time point of reassessment *	36 weeks PMA or discharge to home †	56 days postnatal age or discharge to home †
Mild BPD	Breathing room air	Breathing room air
Moderate BPD	Need for FiO_2 < 0.30 ‡ §	Need for FiO_2 < 0.30 ‡ §
Severe BPD	Need for FiO_2 ≥ 0.30 and/or CPAP or MV ‡ §	Need for FiO_2 ≥ 0.30 and/or CPAP or MV ‡ §

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Journey of Ureaplasma and BPD

‘OLD BPD’

Oxygen toxicity and barotrauma from prolonged mechanical ventilation

↓

Lung Injury

Ureaplasma

- First description — 1950’s
- Role of ureaplasma in neonatal lung disease — 1970’s

INFLAMMATION ←

- Animal studies

Interruption of normal development by preterm birth -> aberrations in both alveolar and pulmonary vascular development

↓

‘Growth Arrest’

- First meta-analysis: association with BPD at 28d — 1995
- Second meta-analysis: association with BPD at 36w — 2005

‘NEW BPD’

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Journey of Ureaplasma and BPD

‘OLD BPD’

Oxygen toxicity and barotrauma from prolonged mechanical ventilation

↓

Lung Injury

Interruption of normal development by preterm birth -> aberrations in both alveolar and pulmonary vascular development

↓

‘Growth Arrest’

‘NEW BPD’

Ureaplasma

No changes in association of Ureaplasma and BPD since first reports, despite major changes in BPD pathophysiology, prevention and treatment

1950’s

1970’s

1995

2005

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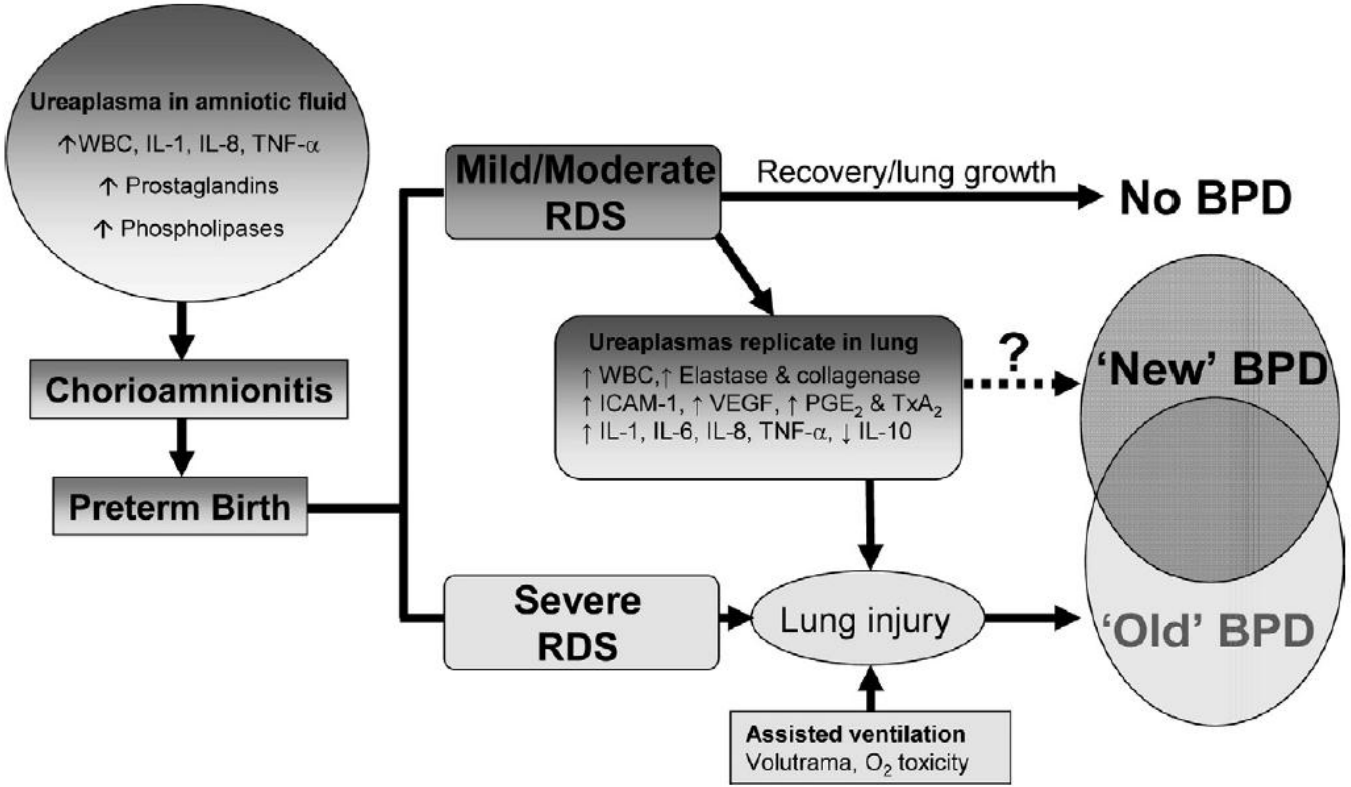
Ureaplasma and BPD: pathogenesis



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** Schelonka R and Waites K. Ureaplasma Infection and Neonatal Lung Disease. Seminars Perinatology 2013*

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Ureaplasma and BPD: the evidence

- Numerous studies since 1970's debating a possible association:
  - Small sample sizes
  - Different inclusion criteria
  - Varying BPD-definitions – evolution of BPD over time
  - Various sampling techniques
  - Different ventilation strategies
- Pre- versus post-surfactant era
- 2 large meta-analysis

Ureaplasma and BPD: the evidence

1. **Association of *Ureaplasma urealyticum* colonization with chronic lung disease of prematurity: results of a metaanalysis**
   - Journal of Pediatrics; 1995
   - **RR** for the development of CLD in colonized neonates was **1.72** (95% confidence interval, 1.5 to 1.96) times that for uncolonized neonates

CLD defined as oxygen dependency at 28d

Ureaplasma and BPD: the evidence

2. Critical appraisal of the role of Ureaplasma in the development of bronchopulmonary dysplasia with metaanalytic techniques.

- The pediatric infectious disease journal; 2005
- RR in ureaplasma positive group for developing BPD
  - At 28d: 2,8 (CI 2,3-3,5)
  - At 36w: 1,6 (CI 1,1-2,3)

Substantial heterogeneity between studies

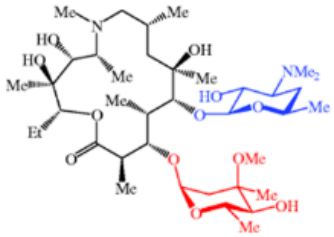
Most studies contributing to strong association: small sample size

Ureaplasma and BPD: the evidence

- Evidence for the role of ureaplasma species in BPD development continues through the past decades
- Inflammatory effect of ureaplasma on:
  - Lung inflammation
    - ‘old BPD’ pathogenesis
    - Synergistic effect with mechanical ventilation and oxygen toxicity
  - Alveolar growth and development
    - ‘new BPD’
    - Effect independent of mechanical ventilation and other influencing factors
- Next question arises: role of ureaplasma therapy/eradication in BPD prevention?

Macrolides and BPD prevention

- Macrolides:
  - Anti-microbial agents
  - Anti-inflammatory properties



Azithromycin

Clarithromycin (R = Me)
Erythromycin (R = H)

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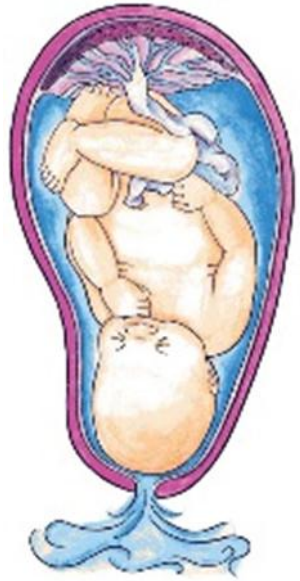
Macrolides and BPD prevention

- Macrolide treatment in PPROM:
  - Prolongation of pregnancy
  - Significant decrease in short-term neonatal morbidities
    - Need for surfactant and oxygen therapy
    - IVH/PVL
    - Neonatal infection
  - No effect on BPD
  - No evidence of longer-term benefit in childhood



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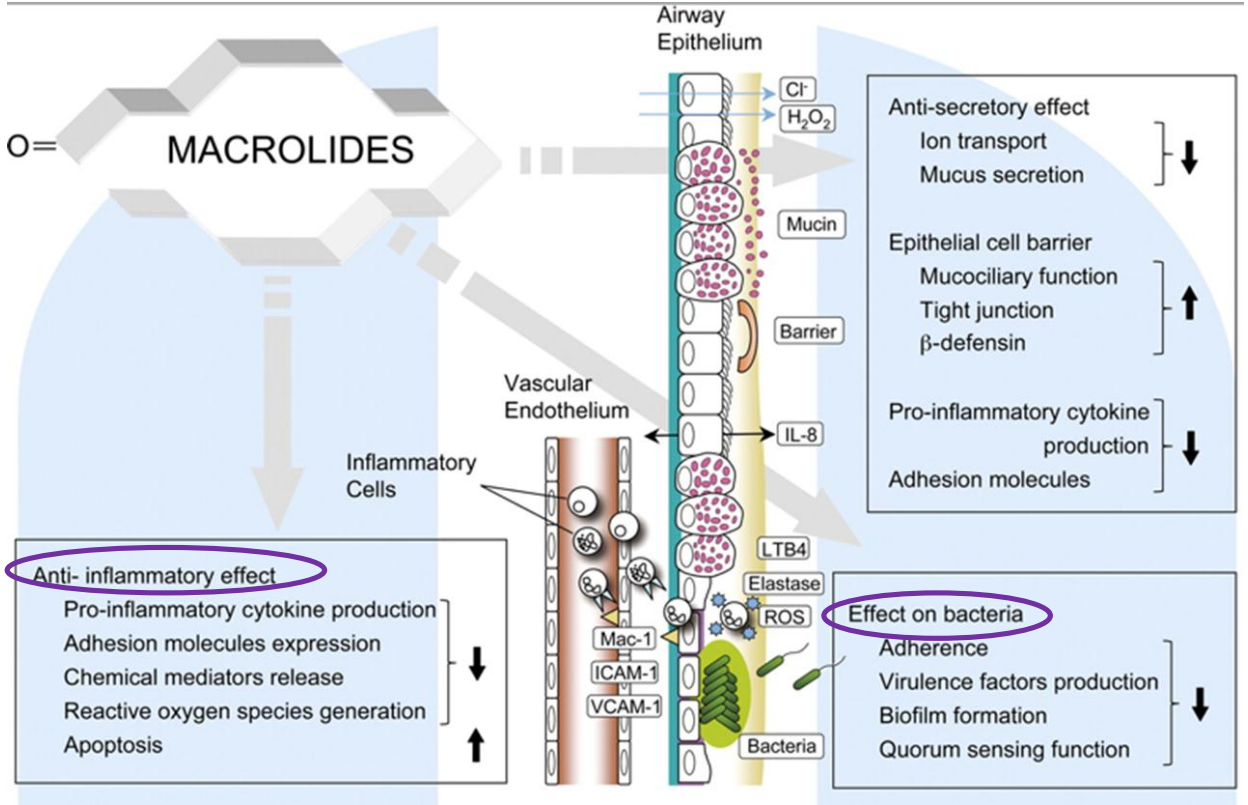
Macrolides and BPD prevention



* *Kanoh S1, Rubin BK. Mechanisms of action and clinical application of macrolides as immunomodulatory medications. Clin Microbiol Rev. 2010 Jul;23(3):590-615*

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Macrolides and BPD prevention

- Limited evidence regarding use of marcolides in:
  - Treatment of Ureaplasma colonization
  - Prevention of BPD
  - Studies of small sample size
  - Variation in incidence of BPD between centres

Macrolides and BPD prevention

Studies

1998 *First 2 small studies:*

- Erythromycin versus placebo
- Ventilated babies < 30w GA
- 1 ureaplasma +, 1 all infants

2003 *First meta-analysis: Cochrane review*

2011 *2 Largest RCT's*:

- *Ballard et al:*
  - Prophylactic azithromycin vs placebo
  - Ventilated babies < 1250g
- *Ozdemir et al:*
  - Clarithromycin versus placebo
  - All ureaplasma pos infants 750-1250g

Results

No effect on prevention of death or BPD

Reduction of BPD in ureaplasma positive babies

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Macrolides and BPD prevention

Recent meta-analysis

- Neonatology; 2014
- Inclusion of 6 RCT's
- Significant reduction in BPD and composite outcome of death or BPD:
    - In subgroup of ureaplasma positive infants
    - Treated with prophylactic azithromycin
    - NNT = 10
- No significant effect of:
    - Prophylactic azithromycin in overall population
    - Treatment with macrolides in ureaplasma positive infants

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Macrolides and BPD prevention

Table 1. Characteristics of the trials included in the analysis

Source	Inclusion criteria	*Ureaplasma* colonization rate and detection technique	Macrolides used	Dosage and duration	Macrolide initiation	Primary outcome
Jonsson et al. [21], Sweden	<30 weeks, ventilated and *Ureaplasma* positive	19%; tracheal and nasopharyngeal aspirate cultures	erythromycin	40 mg/kg/day × 10 days	as soon as cultures were available (mean: 7 days)	BPD, clearance of colonization with *Ureaplasma*
Lyon et al. [20], Edinburgh	<30 weeks and ventilated	15%; tracheal aspirate cultures and PCR	erythromycin	45 mg/kg/day × 7 days	at birth	BPD, cytokine levels in tracheal aspirates
Ballard et al., USA [22]	BW <1,000 g and ventilated	19%; tracheal aspirate cultures	azithromycin	10 mg/kg/day × 7 days[1]	0–72 h of age	BPD
Ballard et al. [23], USA	BW <1,250 g and ventilated	35%; tracheal aspirate PCR	azithromycin	10 mg/kg/day × 7 days[1]	0–72 h of age	BPD
Ozdemir et al. [25], Turkey	BW 750–1,250 g and *Ureaplasma* culture positive	33%; nasopharyngeal swab cultures	clarithromycin	20 mg/kg/day × 10 days	0–72 h of age	BPD
Gharehbaghi et al. [24], Iran	<32 weeks and <1,500 g	sampling not done	azithromycin	10 mg/kg/day × 7 days followed by 5 mg/kg/day × 7 days	day 7 of life	BPD

IMV = Intermittent mandatory ventilation; BW = body weight. [1] Followed by 5 mg/kg/day until the infant no longer required IMV or supplemental O_2, to a maximum of 6 weeks.

Macrolides and BPD prevention: considerations

- In vitro superior antibacterial activity of clarithromycin compared to erythromycin and azithromycin
- BPD definition…?
- Almost 1/3 of entire study population < Ballard study
  - Azithromycin dose used: inferior to higher-dose schedule of shorter duration (based on more recent PK studies)
  - High incidence of BPD in study population/control group (94-84%!)
- Tracheal versus nasopharyngeal aspirates; culture versus PCR
- Cave possible side effects: NEC, sepsis, prolongation of QT-interval

Ureaplasma: experience and challenges

- Retrospective cohort study
  - Preterm babies < 32w
  - Ventilated at admission
  - 2012-2016; N= 199
- 9% ET-culture ureaplasma positive
  - <-> 15-35 % ureaplasma positive infants in literature

➢ *<u>Challenge 1</u>: low sensitivity of available sampling and detection methods*

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Ureaplasma: experience and challenges

- Prevalence of combined outcome of death or BPD at 36 weeks

	No death or BPD at 36w	Death or BPD at 36w	Total
Ureaplasma -	71 (70,3%)	30 (29,7%) (*)	N= 101
Ureaplasma +	5 (50%)	5 (50%) (*)	N= 10

(*) p= 0,28

- 88 missing data

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Ureaplasma: experience and challenges

- Multivariate analysis:
  - Significant correlation between death or BPD at 36w and:
    - birthweight (p=0,03)
    - ventilation days (p=0,00)
  - No significant correlation between ureaplasma status and death or BPD at 36w (p=0,20)

➢ *Challenge 2: BPD definition, confounding factors; Ureaplasma as causative factor vs bystander phenomenon?*

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Ureaplasma: experience and challenges

- No experience so far with use of macrolides in BPD prevention

➢ *<u>Challenge 3</u>: defining possible role of macrolides as part of BPD prevention:*

  – Ureaplasma eradication versus anti-inflammatory effect?

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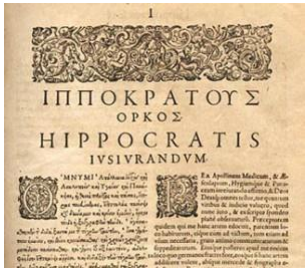
Ureaplasma and BPD: conclusion

- Evidence supporting association of ureaplasma colonisation and BPD development
- Limited evidence for use of macrolides in BPD prevention
- Cave possible side-effects:
  - NEC, sepsis, prolongation of QT-interval
- First do not harm!


ΙΠΠΟΚΡΑΤΟΥΣ
ΟΡΚΟΣ
HIPPOCRATIS
IVSIVRANDVM

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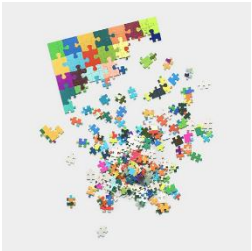
Ureaplasma and BPD: the future?

- Targeted treatment?
  - Prophylactic vs therapeutic
  - Role of maternal (genital) cultures
  - Dosing, duration, IV vs oral, …?
- Need for multicenter, PK/PD, efficacy and safety studies

- Ureaplasma = just a small part of the BPD-puzzle!



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Questions?

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