EBM討論報告

2013.01.14

EBM月會**<**婦產部**>**

報告者**: R1** 林士文

臨床情境

- **This 33 y/o female patient was pregnant for 30 weeks with G2P1A0. Sudden watery discharge at 5:30AM this morning**
- **IMP: pregnancy 30 weeks with PPROM**
- **Plan: cefazolin 1gm Q8H, $MgSO_4$ was given**
  Steroid treatment to promote fetal pulmonary maturation
- 用哪一種抗生素比較好呢?

臨床問題

- 對於**Preterm premature rupture of membranes** 的病人，用哪一種抗生素的效果比較好呢**?**
- 對媽媽及小孩的預後又有甚麼差別呢**?**

Background question

Preterm premature rupture of membranes

- Premature rupture of membranes (PROM) refers to membrane rupture before the onset of uterine contractions;
- preterm PROM (PPROM) is the term used when the pregnancy is less than 37 completed weeks of gestation.
- PPROM occurs in 3 percent of pregnancies and is responsible for, or associated with, approximately one-third of preterm births

Etiology and risk factors

- A history of PPROM in a previous pregnancy
- Genital tract infection
- Antepartum bleeding
- Cigarette smoking have a particularly strong association with PPROM

Outcome

- **Approximately one-third of women with PPROM develop potentially serious infections, such as intraamniotic infection (chorioamnionitis and funisitis), endometritis, or septicemia.**

- **Endometritis is more common after cesarean than vaginal delivery.**

Antibiotics Prophylaxis

- **The rationale for antibiotic prophylaxis is that infection appears to be both a cause and consequence of PPROM and is related to preterm delivery.**

- **The goal of antibiotic therapy is to reduce the frequency of maternal and fetal infection and delay the onset of preterm labor (ie, prolong latency).**

- **The importance of reducing infection is underscored by studies suggesting a relationship between chorioamnionitis, and development of cerebral palsy or neurodevelopmental impairment.**

Foreground question

- What’s the best choice for antibiotics of PPROM?

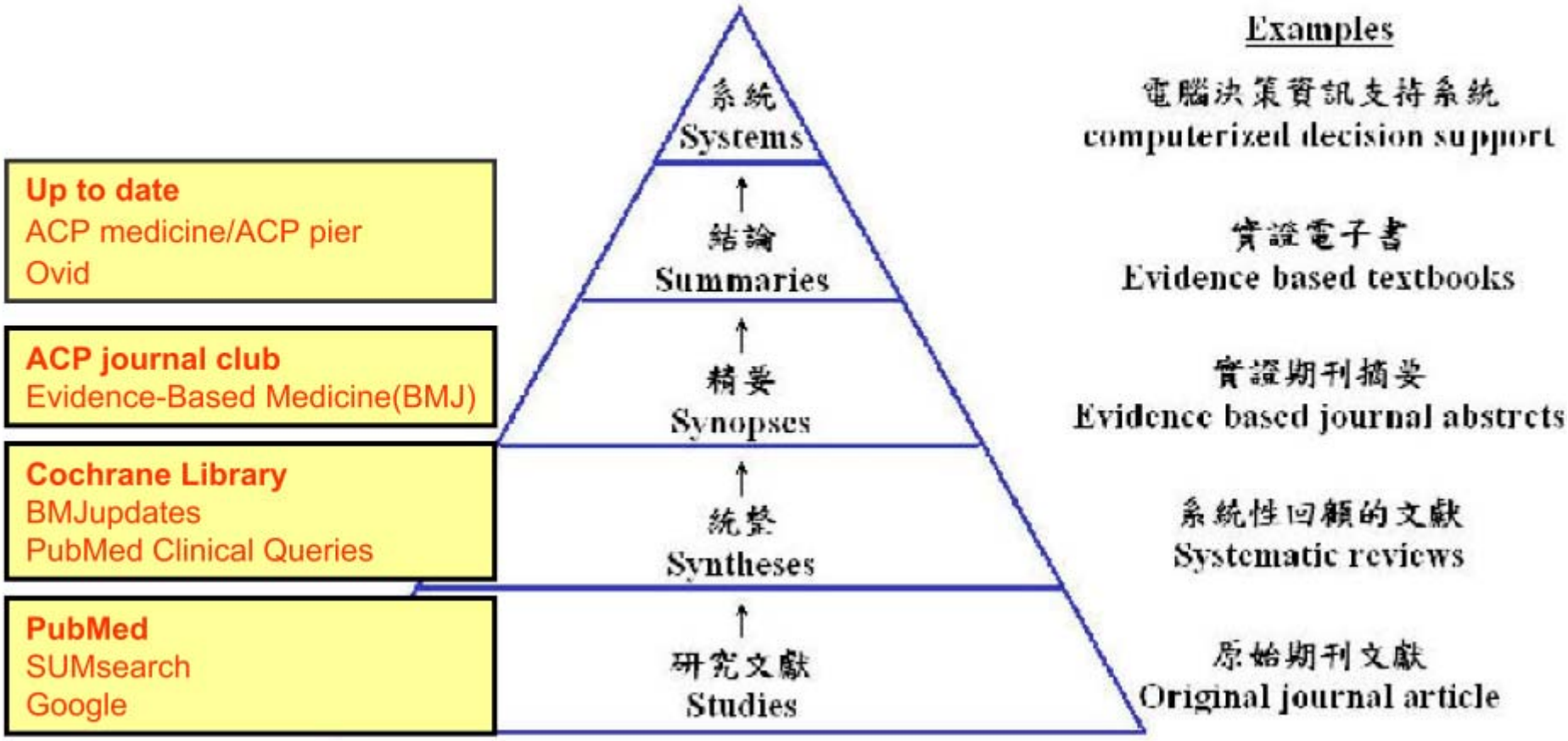
PICO

Patient / Problem	Pregnancy 30 wks with preterm labor
Intervention	Cefazolin
Comparison	Other antibiotics
Outcome	**•Improved latency** **•Without increasing the rate of postpartum endometritis** **•Less frequent newborn sepsis**
Time	Days to weeks

Key words

- Antibiotics
- Preterm premature rupture of membranes
- Fetal surveillance

5S Model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Systematic reviews
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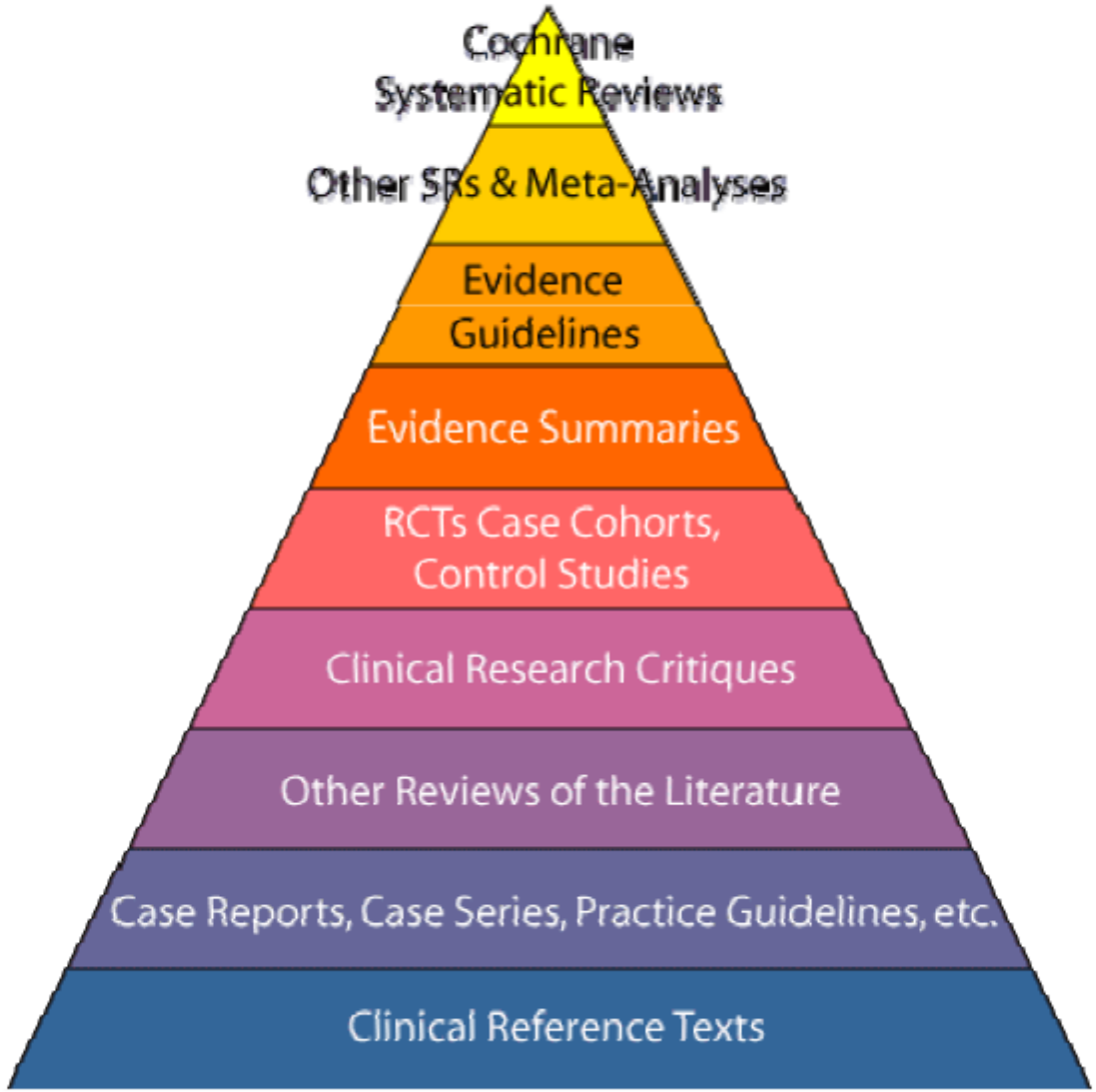
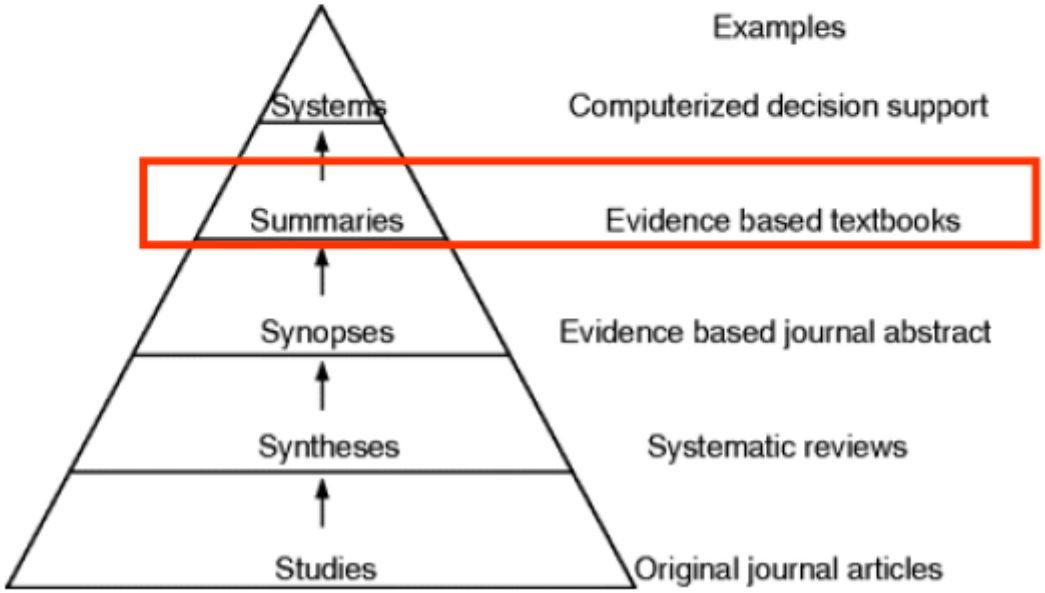
Original journal article

Evidence-Based Practice Tools Summary

http://healthlinks.washington.edu/ebp/ebptools.html#cochrane

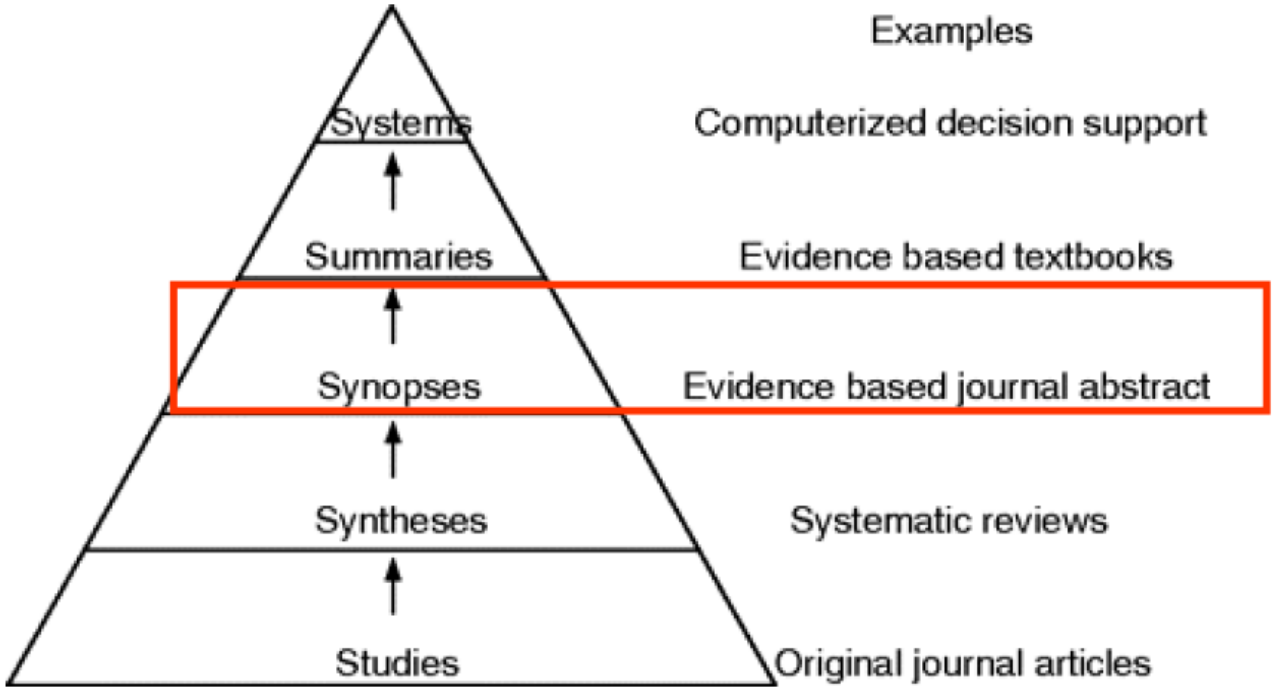


System- uptodate



Synopses- ACP journal club

- 搜尋結果：none



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preterm labor, antibiotics Search

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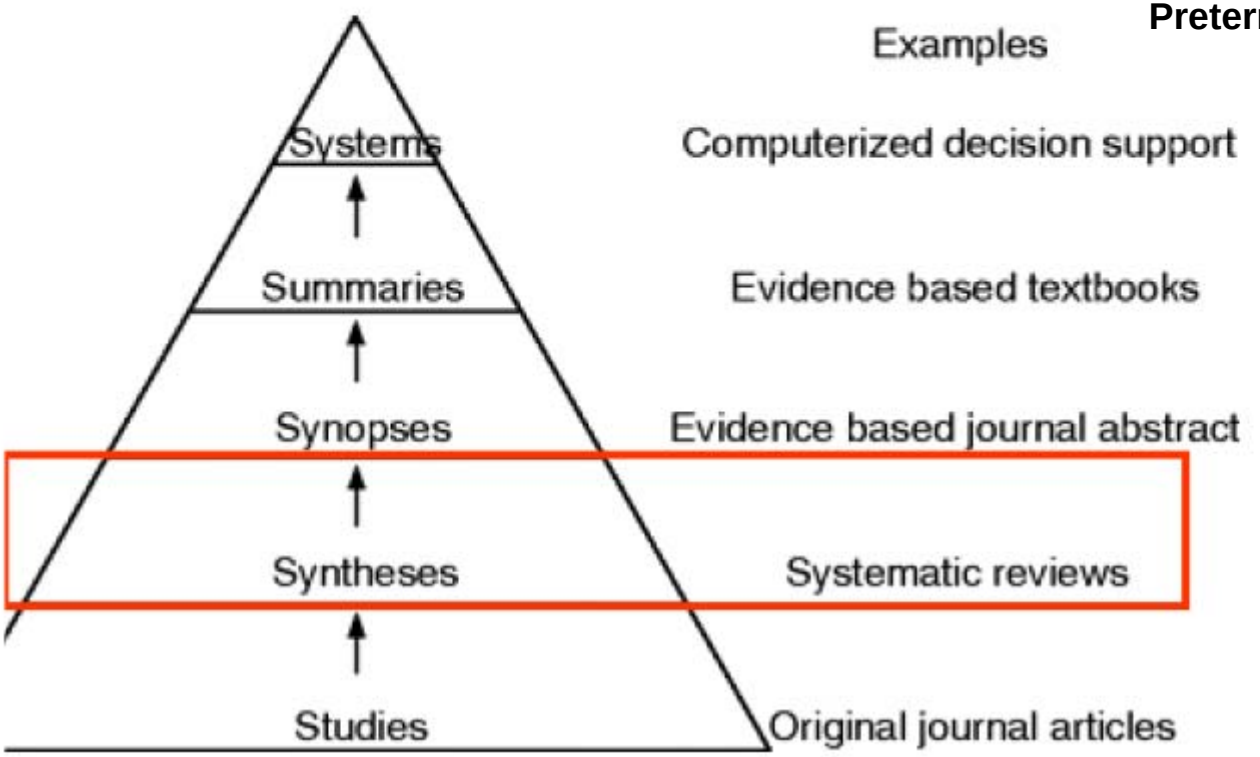
Suggestions:

- Make sure all words are spelled correctly.
- Try different keywords.
- Try more general keywords.

Syntheses- Cochrane Library



- 搜尋結果:

Preterm labor & antibiotics: 7 →

無用

Cochrane library

Key words: preterm labor & antibiotics

Intrapartum **antibiotics** for known maternal Group B streptococcal colonization
Arne Ohlsson and Vibhuti S Shah
July 2009

Review

Antibiotics for **preterm** rupture of membranes
Sara Kenyon , Michel Boulvain and James P Neilson
August 2010

Ns Cc Review

Vaginal chlorhexidine during **labour** to prevent early-onset neonatal group B streptococcal infection
Brenda C Stade , Vibhuti S Shah and Arne Ohlsson
April 2008

Review

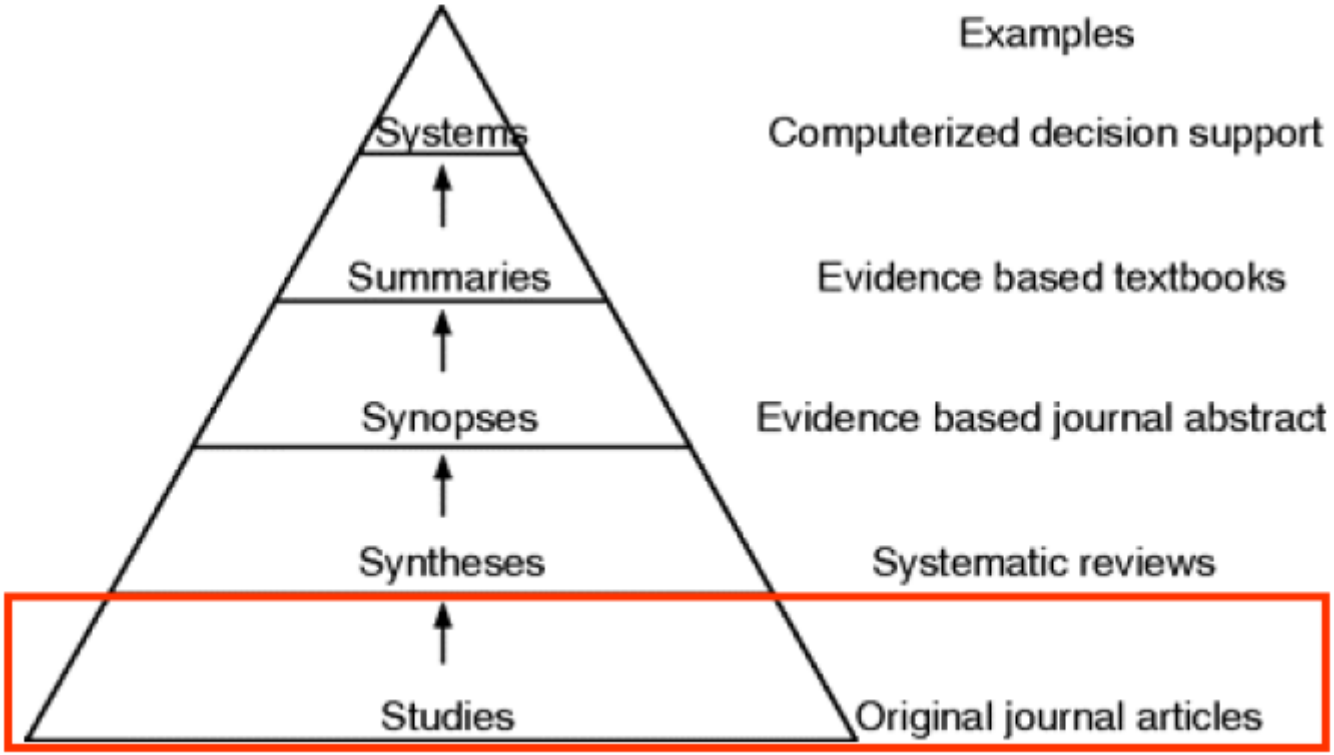
Tocolytics for **preterm** premature rupture of membranes
A Dhanya Mackeen , Jolene Seibel-Seamon , Jacqueline Grimes-Dennis , Jason K Baxter and Vincenzo Berghella
October 2011

Review

Antenatal lower genital tract infection screening and treatment programs for preventing **preterm** delivery
Ussanee S Sangkomkamhang , Pisake Lumbiganon , Witoon Prasertcharoensook and Malinee Laopaiboon
October 2009

Ns Review

Studies- NCBI



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National Institutes of Health

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1. Assessment of fetal inflammatory syndrome by "classical" markers in the management of **preterm labor**: a possible lesson from metabolomics and system biology.
Ferrazzi E, Muggiasca ML, Fabbri E, Fontana P, Castoldi F, Lista G, Primerano L, Livio S, Di Francesco S.
J Matern Fetal Neonatal Med. 2012 Oct;25(Suppl 5):54-61. doi: 10.3109/14767058.2012.716984.
PMID: 23025770 [PubMed - in process]
Related citations

2. Mycoplasma genitalium, an emerging sexually transmitted pathogen.
Cazanave C, Manhart LE, Bébéar C.
Med Mal Infect. 2012 Sep;42(9):381-92. doi: 10.1016/j.medmal.2012.05.006. Epub 2012 Sep 10.
PMID: 22975074 [PubMed - in process]
Related citations

3. Prevention of perinatal group B streptococcal disease: updated CDC guideline.
Cagno CK, Pettit JM, Weiss BD.
Am Fam Physician. 2012 Jul 1;86(1):59-65. Erratum in: Am Fam Physician. 2012 Aug 15;86(4):318.

17. Management of **preterm** birth: best practices in prediction, prevention, and treatment.

Rayburn WF.

Obstet Gynecol Clin North Am. 2012 Mar;39(1):xi-xii. doi: 10.1016/j.ogc.2012.02.002. No abstract available.

PMID: 22370111 [PubMed - indexed for MEDLINE]

Related citations

18. **Antibiotics** in the management of PROM and **preterm labor**.

Mercer B.

Obstet Gynecol Clin North Am. 2012 Mar;39(1):65-76. doi: 10.1016/j.ogc.2011.12.007. Epub 2012 Jan 28. Review.

PMID: 22370108 [PubMed - indexed for MEDLINE]

Related citations

19. Intrapartum evidence of early-onset group B streptococcus.

Tudela CM, Stewart RD, Roberts SW, Wendel GD Jr, Stafford IA, McIntire DD, Sheffield JS.

Obstet Gynecol. 2012 Mar;119(3):626-9. doi: 10.1097/AOG.0b013e31824532f6.

PMID: 22353962 [PubMed - indexed for MEDLINE]

Related citations

20. Stump appendicitis and chorioamnionitis due to incomplete appendectomy: a case report.

Bellı S, Yalçinkaya C, Ezer A, Bolat F, Çolakoğlu T, Şimşek E.

Turk J Gastroenterol. 2011 Oct;22(5):540-3.

PMID: 22234765 [PubMed - indexed for MEDLINE] **Free Article**

Related citations

Antibiotics in the Management of PROM and Preterm Labor

Obstet Gynecol Clin N Am **39** (2012) 65–76

Antibiotics for PROM (premature rupture the membranes)

- Fetal membrane rupture before the onset of contractions is associated with brief latency from membrane ruptured to delivery, umbilical cord compression, and an increased risk of chorioamnionitis.

- Bacterial colonization results in local release of proinflammatory cytokines or hydrolytic enzymes that weaken the fetal membranes some cases.

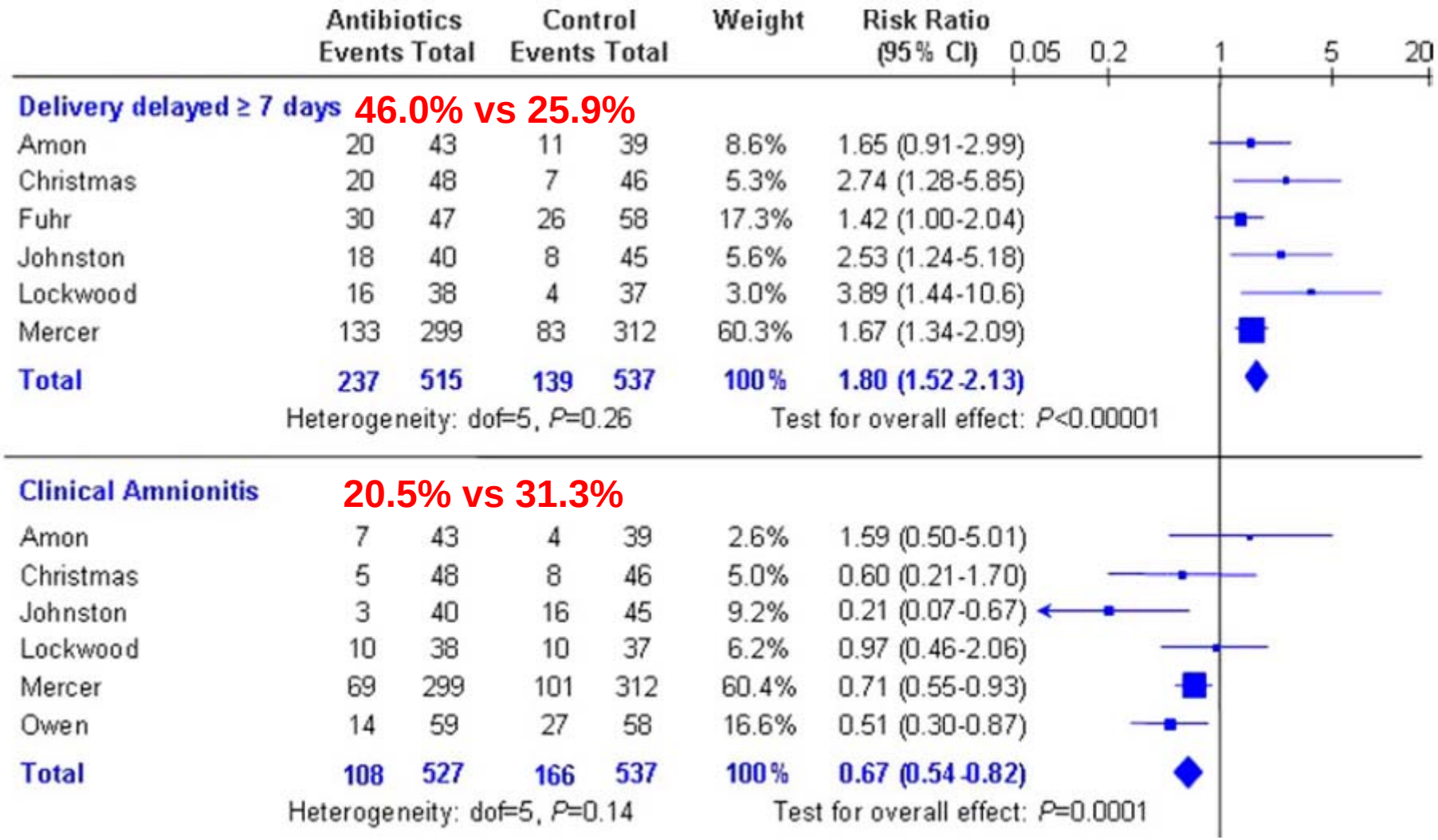
- Secondary ascending bacterial colonization of the decidua and amniotic fluid after membrane rupture is also plausible.

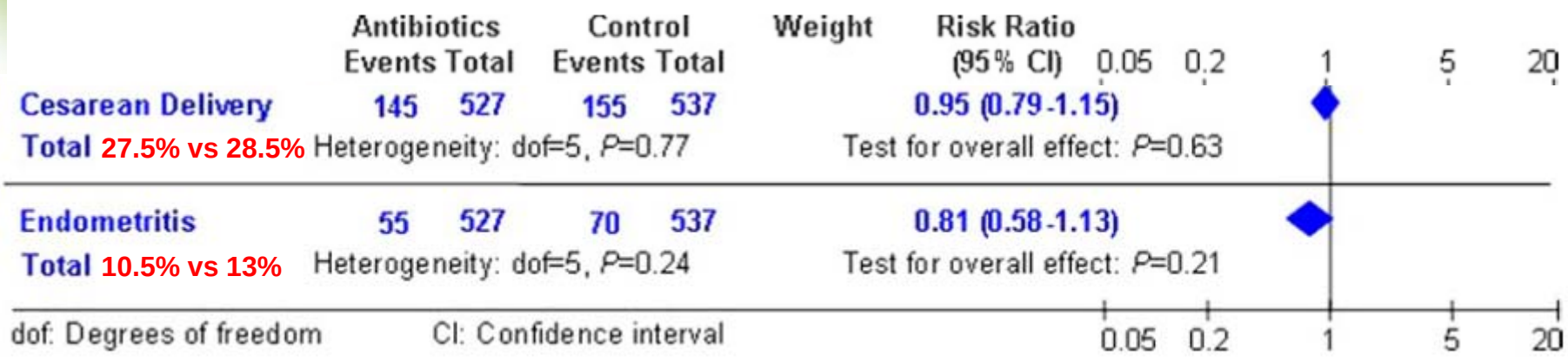
Antibiotics for PROM

- Antibiotic treatment reduces the risk of chorioamnionitis without significantly increasing other maternal morbidities.

- Such antibiotic treatment reduces neonatal infections, major cerebral abnormalities and neonatal ICU days without decreasing or increasing the risk of necrotizing enterocolitis or respiratory distress syndrome.

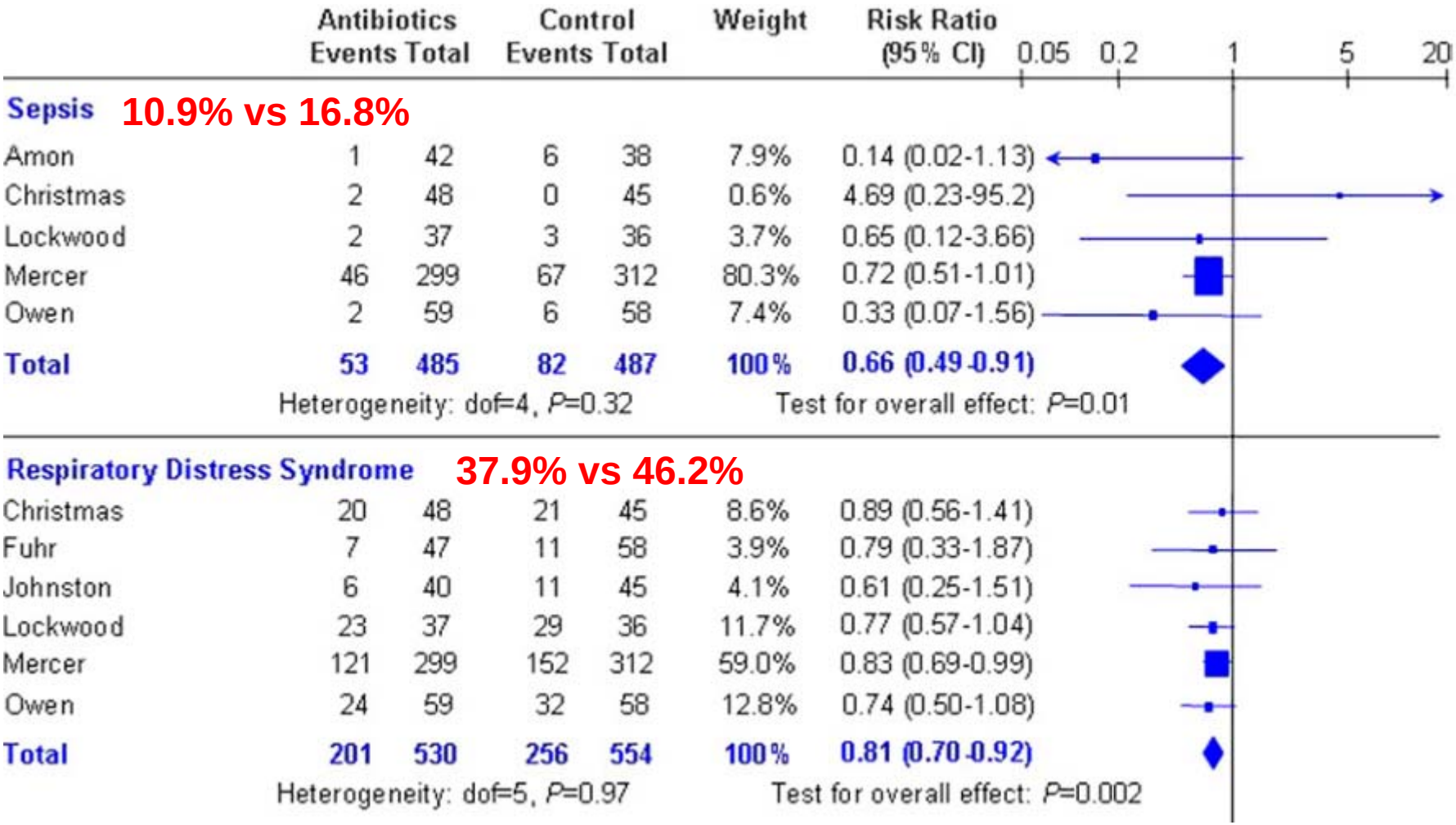
Meta-analysis of pregnancy outcomes associated with adjunctive antibiotic treatment versus control or placebo during conservative management of preterm premature rupture of the membranes at or before 34 weeks' gestation.

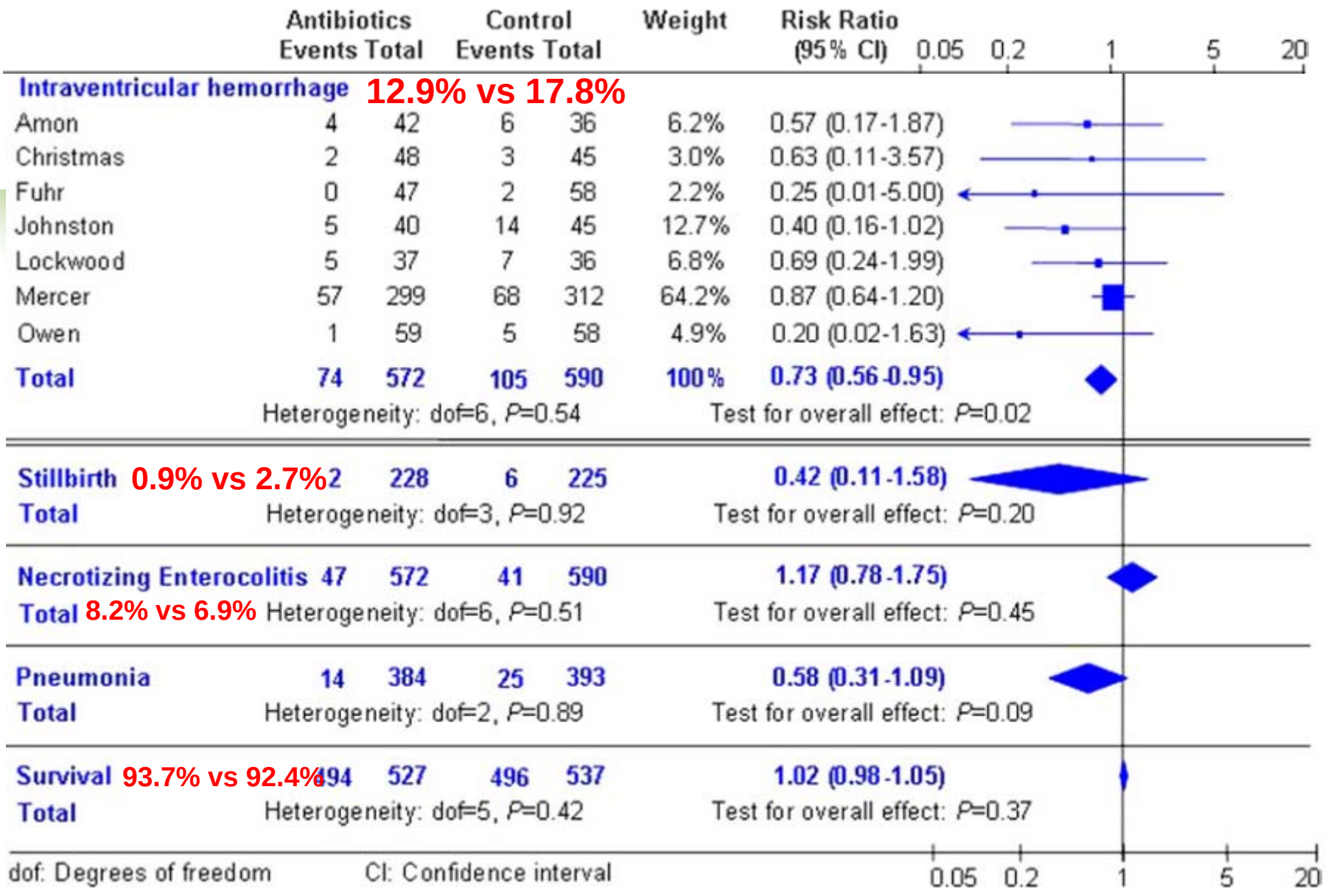




Broad-spectrum adjunctive antibiotic treatment with initial parenteral therapy during conservative management of PROM at or before 34 weeks gestation results in improved latency and less frequent amnionitis without increasing the risks of cesarean delivery or the rate of postpartum endometritis.

Meta-analysis of newborn outcomes associated with adjunctive antibiotic treatment versus control or placebo during conservative management of preterm PROM at or before 34 weeks' gestation.




Antibiotics
Events Total
Control
Events Total
Weight
Risk Ratio
(95% CI)
0.05 0.2 1 5 20
Intraventricular hemorrhage
12.9% vs 17.8%
Amon 4 42 6 36 6.2% 0.57 (0.17-1.87)
Christmas 2 48 3 45 3.0% 0.63 (0.11-3.57)
Fuhr 0 47 2 58 2.2% 0.25 (0.01-5.00)
Johnston 5 40 14 45 12.7% 0.40 (0.16-1.02)
Lockwood 5 37 7 36 6.8% 0.69 (0.24-1.99)
Mercer 57 299 68 312 64.2% 0.87 (0.64-1.20)
Owen 1 59 5 58 4.9% 0.20 (0.02-1.63)
Total 74 572 105 590 100% 0.73 (0.56-0.95)
Heterogeneity: dof=6, P=0.54
Test for overall effect: P=0.02
Stillbirth 0.9% vs 2.7% 2 228 6 225 0.42 (0.11-1.58)
Total
Heterogeneity: dof=3, P=0.92
Test for overall effect: P=0.20
Necrotizing Enterocolitis 47 572 41 590 1.17 (0.78-1.75)
Total 8.2% vs 6.9%
Heterogeneity: dof=6, P=0.51
Test for overall effect: P=0.45
Pneumonia 14 384 25 393 0.58 (0.31-1.09)
Total
Heterogeneity: dof=2, P=0.89
Test for overall effect: P=0.09
Survival 93.7% vs 92.4% 494 527 496 537 1.02 (0.98-1.05)
Total
Heterogeneity: dof=5, P=0.42
Test for overall effect: P=0.37
dof: Degrees of freedom
CI: Confidence interval
0.05 0.2 1 5 20

- Such treatment results in less frequent newborn sepsis as well as less frequent gestational age-dependent morbidities, including respiratory distress syndrome and intraventricular hemorrhage.

- Aggressive, broad-spectrum, adjunctive antibiotic treatment is not associated with altered rates of necrotizing enterocolitis, stillbirth, or survival to discharge.

Antibiotics for PROM

- A study of oral erythromycin therapy for preterm PROM, found reductions in newborn need for surfactant with erythromycin treatment alone, but no reductions in other morbidities, and no improvement in latency beyond 48 hours.

- This suggests that broad-spectrum treatment not only suppressed subclinical infection during treatment, but actually successfully treated it.

A trial by NICHD-MFMU Network

- Participants with preterm PROM between 24^0 and 32^0 weeks gestation were assigned to receive intravenous ampicillin and erythromycin for 48 hours, followed by oral amoxicillin and erythromycin for up to 5 days or matching placebo if undelivered.

- Those with a positive GBS culture received ampicillin for 7 days, and were treated again in labor.

- Overall, subjects assigned to antibiotic treatment had less frequent newborn composite morbidity, respiratory distress, and stage 2 or 3 necrotizing enterocolitis, and chronic lung disease (bronchopulmonary dysplasia) in addition to less frequent amnionitis.

A trial by NICHD-MFMU Network

- broad-spectrum antibiotic treatment reduced the frequencies of neonatal sepsis and pneumonia among those who were not GBS carriers.

- initiating broad-spectrum treatment, and giving intrapartum prophylaxis to identified GBS carriers of preterm PROM at 32^0 weeks gestation or less, resulted in pregnancy prolongation, and reduced infectious and gestational age-dependent morbidities without increasing perinatal complications.

The ORACLE I trial

- This group found that oral erythromycin treatment alone was associated with only brief pregnancy prolongation.
- Oral erythromycin treatment reduced the need for supplemental oxygen and resulted in less frequent positive blood cultures.
- Oral amoxicillin-clavulanic acid treatment alone prolonged pregnancy and reduced the need for supplemental oxygen.
- However, this study found oral amoxicillin-clavulanic acid treatment alone to increase the risk of necrotizing enterocolitis.

The ORACLE I trial

- Regardless, based on this study and the availability of other treatments, it would be prudent to avoid oral amoxicillin clavulanic acid in this setting.

- Seven-year follow-up of these infants using a structured parental questionnaire revealed no evident differences between antibiotic and control groups regarding medical conditions, behavioral difficulties, or functional impairment.

Antibiotics for preterm labor

- Women with preterm labor with intact membranes before 36 weeks gestation were randomly assigned to oral amoxicillin-clavulanic acid, erythromycin, both, or placebo.

- No improvements in latency or newborn infectious or gestational age-dependent morbidities were identified with antibiotic treatment given either individually or in combination.

Antibiotics for preterm labor

- Aggressive intravenous and oral adjunctive antibiotic therapy during acute management of idiopathic preterm labor is not associated with consistent improvement in latency or improvements in newborn outcomes.

- Given this, and the potential for risks from intrauterine antibiotic exposure in this setting, antibiotic treatment for pregnancy prolongation and reduction of infant morbidity is not recommended.

- Antibiotic treatment of preterm labor should be reserved for women with clear indications, such as known acute infections amenable to antibiotic therapy, intrapartum GBS prophylaxis, and chorioamnionitis.

對找到的文章進行
critical appraisal

證據等級

Level	與[治療/預防/病因/危害]有關的文獻
1a	用多篇RCT所做成的綜合性分析(SR of RCTs)
1b	單篇RCT(有較窄的信賴區間)
1c	All or none
2a	用多篇世代研究所做成的綜合性分析
2b	單篇cohort及低品質的RCT
2c	Outcome research / ecological studies
3a	SR of case-control studies
3b	Individual case-control studies
4	Case-series(poor quality :cohort / case-control studies)
5	沒有經過完整評讀醫學文獻的專家意見

Grades of Recommendation

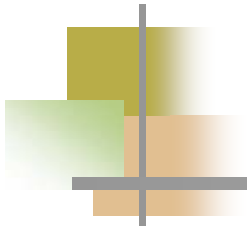
A	consistent level 1 studies
B	consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies
C	level 4 studies ***or*** extrapolations from level 2 or 3 studies
D	level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level

Did one course of action lead to clinically important gains in life-expectancy or other utility measure? Yes

- Meta-analysis
- 7 RCT

Was the same course of action preferred despite clinically sensible changes in probabilities and utilities? No

- 24~32 weeks
- Antibiotics
  - intravenous ampicillin and erythromycin for 48 hours, followed by oral amoxicillin and erythromycin for up to 5 days
  - resulted in pregnancy prolongation, and reduced infectious and gestational age-dependent morbidities



Thanks for your attention !