ClinicalEvidence

Neonatal infections: group B streptococcus

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Paul T. Heath and Luke Jardine

ABSTRACT

INTRODUCTION: One in four women carry group B streptococci vaginally, which can infect the amniotic fluid before delivery or can infect the baby during delivery, causing sepsis, pneumonia, or meningitis. Very low-birthweight infants are at much higher risk of infection or mortality, with up to 3% infected and mortality rates of up to 30%, even with immediate antibiotic treatment. Late-onset group B streptococcal infection begins from 7 days of age, and usually causes fever or meningitis, but is less often fatal compared with early infection. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: what are the effects of prophylactic treatment of asymptomatic neonates less than 7 days old with known risk factors for early-onset group B streptococcal infection? We searched: Medline, Embase, The Cochrane Library, and other important databases up to November 2013 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 5 studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: different antibiotics, monitoring and selective treatment, and routine antibiotic prophylaxis.

QUESTIONS

INTERVENTIONS

Key points

- Early-onset neonatal sepsis, typically caused by group B streptococcal infection, usually begins within 24 hours of birth, affects up to 2 infants per 1000 live births, and leads to death if untreated.

  One in four women carry group B streptococci vaginally, which can infect the amniotic fluid before delivery or infect the baby during delivery, causing sepsis, pneumonia, or meningitis.

  Very low-birthweight infants are at much higher risk of infection or mortality, with up to 3% infected, and mortality rates of up to 30%, even with immediate antibiotic treatment.

  Late-onset group B streptococcal infection begins from 7 days of age and usually causes fever or meningitis, but is less often fatal compared with early-onset infection.

- Routine antibiotic prophylaxis, either given to asymptomatic infants born to mothers with risk factors for neonatal infection or given to low-birthweight babies after birth, does not seem to be beneficial in reducing neonatal infection or mortality compared with close monitoring and selective antibiotics.

  We don't know which antibiotic regimen is most effective at preventing group B streptococcal infection in high-risk neonates.

- Increasing peripartum antibiotic prophylaxis may be associated with a shift in the pathogens causing sepsis in preterm and very low-birthweight infants, with *Escherichia coli* becoming a more prevalent cause.

DEFINITION

Early-onset neonatal sepsis usually occurs within the first 7 days of life, and is typically caused by infection with group B streptococcus. About 90% of cases present within 24 hours of birth. [1] Group B streptococcus exists as part of the normal bacterial flora in the vagina and gastrointestinal tract. Infection can be transmitted by aspiration of group B streptococcus-infected amniotic fluid by the fetus. [2] Symptoms of early-onset group B streptococcal infection may be non-specific, including temperature instability, poor feeding, excessive crying or irritability, and respiratory distress. Early-onset group B streptococcal infection typically presents with sepsis (69% of cases), pneumonia (26% of cases), respiratory distress (13% of cases), and, rarely, meningitis (11% of cases). [3] [4] [5] Late-onset group B streptococcus infection occurs from 7 to 90 days of age, and differs from early-onset group B streptococcal infection in terms of group B streptococcus serotype, clinical manifestations, and outcome. Late-onset infection typically presents with fever or meningitis. [3] [4] This review deals with full-term and premature asymptomatic babies born with a known risk factor for group B streptococcal infection, but in whom a specific diagnosis of group B streptococcus (either by blood, urine, or cerebrospinal fluid) has not yet been made. The antenatal or intrapartum treatment of women with known group B streptococcal colonisation or infection is outside the scope of this review.

INCIDENCE/ PREVALENCE

The overall incidence of neonatal bacterial infections is between one and eight infants per 1000 live births, and between 160 and 300 per 1000 very low-birthweight infants. [6] Group B streptococcal infection accounts for nearly 50% of serious early-onset neonatal bacterial infections. [7] Surveillance conducted between 2000 and 2001 estimated that there were 0.72 cases of group B streptococcal infection per 1000 live births in the UK and Ireland and that, of these, 0.48 cases per 1000 live births were early onset, and 0.24 cases per 1000 live births were late-onset infection. [5] Although the estimated incidence of early-onset group B streptococcal infection is 0.5 per 1000 births in the UK overall, incidence varies geographically from 0.21 per 1000 live births in Scotland to 0.73 per 1000 live births in Northern Ireland. [8] Overall, the US and the UK currently have relatively similar incidences. [8] Data from the US indicate that the rate of early-onset infection has decreased from 1.7 cases per 1000 live births in 1993 to 0.28 cases per 1000 live births in 2008. [9] This is thought to be a result of the increasing use of maternal intrapartum antibiotic prophylaxis.

AETIOLOGY/ RISK FACTORS

The main risk factor for group B streptococcal infection in the baby is maternal group B streptococcal colonisation. [10] Bacteria originating in the maternal genital tract can infect the amniotic fluid via intact or ruptured membranes. Neonatal infection can result from fetal aspiration or ingestion of the infected amniotic fluid. [1] Infection of the neonate can also occur during birth, when the neonate moves through the vagina, with systemic infection then occurring via the umbilical cord, respiratory or gastrointestinal tract, or skin abrasions. [1] Other risk factors for group B streptococcal infection include prematurity, low birthweight, prolonged rupture of membranes, intrapartum fever, chorioamnionitis, maternal ethnicity (black and Hispanic mothers are at increased risk compared with white mothers), endometritis, heavy maternal colonisation, and frequent vaginal examinations during labour and delivery. [1] [11] [12] [13] [8] Lower maternal age (<20 years) and cigarette smoking may be associated with an increased risk of early-onset group B streptococcal infection, but these associations have not been shown consistently. [12] Other factors that may increase the risk of group B streptococcal infection include lower socio-economic status, and maternal urinary tract infection during the third trimester. The role of group B streptococcal colonisation of fathers, siblings, and close household contacts in the development of late-onset group B streptococcal infection is unclear. [14] Late-onset group B streptococcus infection is predominantly associated with serotype III. [8]

PROGNOSIS

Group B streptococcal infection is a frequent cause of neonatal morbidity and mortality. In the UK, one study has estimated that early-onset group B streptococcus infection causes more than 40 neonatal deaths and around 25 cases of long-term disability every year, whereas late-onset group B streptococcus infection causes around 16 deaths and 40 cases of long-term disability every year. [1] In the US, the case fatality ratio of early-onset group B streptococcal disease declined from approximately 50% in the 1970s to 4% to 6% in recent years, primarily because of improved medical neonatal care. [15] [16] [17] Mortality is higher among pre-term infants; one prospective surveillance study (396,586 live births between February 2006 and December 2009) reported a mortality rate of 30% for pre-term infants with early-onset group B streptococcus infection. [18] Late-onset group B streptococcus infection typically presents as bacteraemia or meningitis. Less frequently, late-onset group B streptococcus infection may cause septic arthritis, cellulitis, or focal infections such as osteomyelitis. [8] Late-onset group B streptococcal infection tends to have a less fulminant onset and is less often fatal than early-onset infection. [19] One observational study reported a mortality rate of 14% with early-onset group B streptococcal infection compared with 4% with late-onset infection. [3] Little information is available concerning long-term sequelae for survivors of neonatal group B streptococcal infection, except in the case of group B streptococcus meningitis, where nearly 50% of survivors may have long-term neurodevelopmental sequelae. [20] [21]

AIMS OF INTERVENTION

To prevent morbidity, mortality, and complications associated with group B streptococcal infection, with minimal adverse effects of treatment.

OUTCOMES

Primary outcomes for this review are mortality, development of infection or sepsis, hospital length of stay or hospital readmission rates, and adverse effects of treatments, including ototoxicity, renal toxicity, and antimicrobial-resistant organism colonisation of individual infants or clusters within a neonatal unit. Secondary outcomes are sequelae of infection, such as developmental delay or neurological abnormality (blindness, deafness, cerebral palsy, as assessed by motor or psychomotor indices), seizures, renal dysfunction, pulmonary disorders, immune dysfunction, necrotising enterocolitis, and malabsorption.

METHODS

Clinical Evidence search and appraisal November 2013. The following databases were used to identify studies for this systematic review: Medline 1966 to November 2013, Embase 1980 to November 2013, and The Cochrane Database of Systematic Reviews 2013, issue 10 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of

Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against predefined criteria by an evidence scanner. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: RCTs and published systematic reviews of RCTs in the English language, containing at least 20 individuals (at least 10 per arm). There was no minimum length of follow-up or level of blinding required to include studies. There was no maximum loss to follow up. We included RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 9). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of prophylactic treatment of asymptomatic neonates less than 7 days old with known risk factors for early-onset group B streptococcal infection?**

OPTION **ROUTINE ANTIBIOTIC PROPHYLAXIS VERSUS MONITORING AND SELECTIVE TREATMENT FOR EARLY-ONSET GROUP B STREPTOCOCCAL INFECTION**

- For GRADE evaluation of interventions for Neonatal infections: group B streptococcus, see table, p 9 .
- Routine antibiotic prophylaxis, either given to asymptomatic infants born to mothers with risk factors for neonatal infection or given to low-birthweight babies after birth, does not seem to be beneficial in reducing neonatal infection or mortality compared with close monitoring and selective antibiotics.

Benefits and harms

Early antibiotic prophylaxis versus monitoring and selective antibiotic treatment in asymptomatic infants born to mothers with risk factors for neonatal infection:

We found one systematic review (search date 2004 [22]), which identified two RCTs, [23] [24] which compared the effects of prophylactic antibiotics versus selective antibiotics in asymptomatic infants born to mothers with one or more risk factors for neonatal infection, and who had not received intrapartum antibiotics. Maternal risk factors for neonatal infection included confirmed maternal group B streptococcal infection, fever (greater-than or equal to38°C during labour), pre-labour or intrapartum rupture of membranes >18 hours previously, and chorioamnionitis or amnionitis. [22]

Rate of infection or sepsis

Early antibiotic prophylaxis compared with monitoring and selective antibiotic treatment in asymptomatic infants born to mothers with high risk for neonatal infection We don't know whether routine early prophylaxis with penicillin is more effective than monitoring and selective antibiotic treatment at reducing the incidence of early-onset group B streptococcal infections (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rate of infection					
[22] Systematic review	67 asymptomatic infants In review [23] Data from 1 RCT	**Group B streptococcal infection** 0/29 (0%) with routine early penicillin prophylaxis immediately after birth 0/38 (0%) with delayed penicillin treatment	No events, effect size not estimable		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		See Further information on studies for treatment group details			
[22] Systematic review	49 asymptomatic term and preterm infants In review [24] Data from 1 RCT	**Neonatal infection** 0/24 (0%) with prophylactic antibiotics for 7 days 4/25 (16%) with monitoring, selective antibiotics if clinical evidence of sepsis See Further information on studies for treatment group details	RR 0.12 95% CI 0.01 to 2.04	⟷	Not significant

Mortality

Early antibiotic prophylaxis compared with monitoring and selective antibiotics treatment in asymptomatic infants born to mothers with risk factors for neonatal infection We don't know whether routine early prophylaxis with penicillin is more effective at reducing mortality than monitoring and selective antibiotic treatment (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[22] Systematic review	67 asymptomatic infants In review [23] Data from 1 RCT	**Neonatal deaths** 0/29 (0%) with routine early penicillin prophylaxis immediately after birth 0/38 (0%) with delayed penicillin treatment See Further information on studies for treatment group details	No events, effect size not estimable		
[22] Systematic review	49 asymptomatic term and preterm infants In review [24] Data from 1 RCT	**Reported outcome** 0/24 (0%) with prophylactic antibiotics for 7 days 0/25 (0%) with monitoring, selective antibiotics if clinical evidence of sepsis See Further information on studies for treatment group details	No events, effect size not estimable		

Adverse effects

No data from the following reference on this outcome. [22] [23] [24]

Early antibiotic prophylaxis versus monitoring and selective antibiotic treatment in low-birthweight, preterm infants:

We found one systematic review (search date 2003) [25] that assessed the effect of prophylatic intramuscular penicillin (administered within 4 hours of birth) versus placebo or no treatment in low-birthweight (between 501 and 2000 g), preterm infants. [25] The review identified one unblinded RCT, which compared routine early penicillin prophylaxis versus monitoring for temperature stability, respiratory status, and other markers of sepsis in low-birthweight, preterm infants. [26]

Rate of infection or sepsis

Early antibiotic prophylaxis compared with monitoring and selective antibiotic treatment in low-birthweight, preterm infants Routine early prophylaxis with penicillin seems no more effective than monitoring and selective antibiotic treatment at reducing the incidence of early-onset group B streptococcal infections (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rate of infection					
[25] Systematic review	1187 low-birthweight, preterm infants In review [26] Data from 1 RCT	**Incidence of early-onset group B streptococcal infection** 10/589 (1.7%) with routine early penicillin prophylaxis 14/598 (2.3%) with monitoring See Further information on studies for treatment group details Infants who showed signs of sepsis were given antibiotics (gentamicin plus penicillin or ampicillin)	RR 0.73 95% CI 0.32 to 1.62	⟷	Not significant

Mortality

Early antibiotic prophylaxis compared with monitoring and selective antibiotic treatment in low-birthweight, preterm infants Routine early prophylaxis with penicillin seems no more effective than monitoring and selective antibiotic treatment at reducing mortality (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[25] Systematic review	1187 low-birthweight, preterm infants In review [26] Data from 1 RCT	**Overall neonatal mortality** 49/589 (8.3%) with routine early penicillin prophylaxis 63/598 (10.7%) with monitoring See Further information on studies for treatment group details Infants who showed signs of sepsis were given antibiotics (gentamicin plus penicillin or ampicillin)	RR 0.78 95% CI 0.55 to 1.11	⟷	Not significant
[25] Systematic review	1187 low-birthweight, preterm infants In review [26] Data from 1 RCT	**Neonatal mortality in infants with early group B streptococcus infection** 6/10 (60.0%) with routine early penicillin prophylaxis 8/14 (57.1%) with monitoring See Further information on studies for treatment group details Infants who showed signs of sepsis were given antibiotics (gentamicin plus penicillin or ampicillin)	P = 0.39	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [25] [26]

Further information on studies

[23] Quasi-randomised RCT. Penicillin was administered prophylactically or delayed. Penicillin was initiated in the delayed treatment group if bacterial culture revealed group B streptococcus in the external auditory canal, gastric aspirate, or fetal side of the placenta, usually starting 24 to 48 hours after birth.

[24] Infants were born to mothers with prolonged rupture of membranes (>24 hours). Infants in the treatment group received penicillin and kanamycin for 7 days. Infants in the control group received no prophylactic antibiotics, but received selective antibiotics if there was clinical evidence of sepsis.

[26] Unblinded RCT. Low birth-weight infants received early penicillin prophylaxis. Infants in the control group did not receive prophylactic penicillin. Infants with suspected sepsis received gentamicin and either penicillin or ampicillin, regardless of initial group assignment.

Comment:

The two small RCTs identified by the first systematic review had weak methods, and may have been underpowered to detect clinically important differences in outcomes. [22] The first RCT identified by the first review found that most neonates became symptomatic during the first hour of life, suggesting that the group B streptococcal infection was transmitted in utero. [23] Infections transmitted in utero may be less susceptible to single-dose prophylaxis at birth. Three neonates in the RCT identified by the second review (1 in the prophylaxis group and 2 in the monitoring group) [26] tested negative for group B streptococcus on initial blood culture (taken within 1 hour of birth), but developed symptoms of sepsis within 4 hours of birth and had group B streptococcal infection confirmed on repeat culture (taken within 3 and 70 hours of birth).

Penicillin may cause allergic reactions, although the risk in neonates is low. [7] [27] [28] [29] [30] The estimated incidence of penicillin-triggered anaphylaxis is 1 in 10,000 people treated, and may be fatal in as many as 10% of occurrences. [8]

Clinical guide:

One overview of the antenatal prevention of neonatal group B streptococcal infection, reviewing two studies published in 1990 and 1999, reported that some strains had developed resistance to macrolide and lincosamide antibiotics (erythromycin and clindamycin), and one of these studies reported an increased resistance to clindamycin associated with an increased use of intrapartum antibiotics. [8] Although we found no evidence of ampicillin resistance among group B streptococcus, resistance to macrolides and clindamycin appears to be emerging. Intrapartum antibiotic prophylaxis aims to prevent early-onset neonatal infection, by passage of the antibiotic to the neonate via the placenta and by reducing the bacterial density in the birth canal. [2] This review, however, does not currently examine intrapartum antibiotic prophylaxis given to the mother to prevent group B streptococcal infection in the neonate. The alternative is to administer antibiotics directly to the infant after birth. However, this approach is not commonly used because of the disadvantages of postnatal administration in the infant, including the fact that infection may already be established before birth, causing an added delay in reaching effective serum and tissue antibiotic concentrations in the infant. [1] Routine prophylaxis may encourage the evolution of penicillin-resistant group B streptococcus organisms. However, studies have not yet shown this to be a significant risk. [28] [29] [31] Judicious and selective use of antibiotics, based on clinical findings and the presence of specific risk factors, may reduce this risk. [29] Avoiding the use of unnecessarily broad-spectrum antibiotics solely for prophylaxis will also help reduce the risk of antibiotic resistance. [32] Prophylaxis may lead to falsely negative body fluid culture results, which may delay the recognition and prompt treatment of group B streptococcus bacteraemia. However, findings from one large non-randomised controlled trial (18,738 neonates) suggested that neonatal penicillin prophylaxis did not result in under-diagnosis of group B streptococcal infection. [27] Co-incident with increasing perinatal prophylaxis against group B streptococcus in colonised/at-risk mothers, a shift in pathogens causing sepsis in pre-term and very low-birthweight infants has been described, with *Escherichia coli* becoming an increasingly prevalent cause of neonatal sepsis. [33] [34] [35] [36]

OPTION COMPARISON OF DIFFERENT ANTIBIOTICS FOR ROUTINE ANTIBIOTIC PROPHYLAXIS FOR GROUP B STREPTOCOCCAL INFECTION

- For GRADE evaluation of interventions for Neonatal infections: group B streptococcus, see table, p 9 .
- We don't know which antibiotic regimen is most effective at preventing group B streptococcal infection in high-risk neonates.

Benefits and harms

Different antibiotic regimens versus each other:

We found no systematic reviews or RCTs.

Comment: **Antibiotic resistance:**
See comment on Routine antibiotic prophylaxis versus monitoring and selective treatment for group B streptococcal infection, p 3 .

GLOSSARY

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

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Paul T. Heath
Professor/Consultant in Paediatric Infectious Diseases
St. George's University of London
London
UK

Neonatal infections: group B streptococcus

Luke Anthony Jardine
Neonatologist
Department of Neonatology
Mater Mothers' Hospital
Brisbane
Australia

Competing interests: PTH is an author of publications that are referenced in this review; LAJ declares he has no competing interests.

Disclaimer

GRADE **Evaluation of interventions for Neonatal infections: group B streptococcus.**

Important outcomes			Mortality, Rate of infection or sepsis						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of prophylactic treatment of asymptomatic neonates less than 7 days old with known risk factors for early-onset group B streptococcal infection?									
2 (116) [22] [23] [24]	Rate of infection or sepsis	Early antibiotic prophylaxis versus monitoring and selective antibiotic treatment in asymptomatic infants born to mothers with risk factors for neonatal infection	4	–3	0	0	0	Very low	Quality points deducted for sparse data, methodological weaknesses, and inclusion of quasi-randomised RCT
2 (116) [22] [23] [24]	Mortality	Early antibiotic prophylaxis versus monitoring and selective antibiotic treatment in asymptomatic infants born to mothers with risk factors for neonatal infection	4	–3	0	0	0	Very low	Quality points deducted for sparse data, methodological weaknesses, and inclusion of quasi-randomised RCT
1 (1187) [25] [26]	Rate of infection or sepsis	Early antibiotic prophylaxis versus monitoring and selective antibiotic treatment in low-birthweight, preterm infants	4	–1	0	0	0	Moderate	Quality point deducted for lack of blinding
1 (1187) [25] [26]	Mortality	Early antibiotic prophylaxis versus monitoring and selective antibiotic treatment in low-birthweight, preterm infants	4	–1	0	0	0	Moderate	Quality point deducted for lack of binding

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.