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[Intervention Protocol]

Antibiotic regimens for late-onset neonatal sepsis

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To compare the beneficial and harmful effects of different antibiotic regimens for neonates with late-onset sepsis.

BACKGROUND

Description of the condition

Definition

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection (Singer 2016). There is currently no international consensus on specific criteria for neonatal sepsis (Wynn 2014; Wynn 2016). The most commonly used neonatal sepsis criteria in clinical trials are based on a combination of clinical and laboratory parameters (see Table 1) (Morris 2016; Wynn 2014).

Sepsis that occurs before 28 days after birth is termed neonatal sepsis (Bakhuizen 2014; Camacho-Gonzalez 2013). Depending on the time of onset, neonatal sepsis is termed either early-onset sepsis or late-onset sepsis. The most commonly accepted distinction between these two subgroups is cases occurring before 72 hours after birth and after 72 hours after birth, but other definitions exist, e.g. 48 hours and 7 days after birth (Bakhuizen 2014; Bizzarro 2008; Camacho-Gonzalez 2013; Manan 2016; Metsvaht 2010; Shah 2014; Shane 2013; Shane 2014; Tripathi 2012; Zaidi 2009; Zea-Vera 2015). This distinction is based on the different etiologies and pathophysiology of pathogens typically seen before and after 72 hours (Camacho-Gonzalez 2013; Metsvaht 2010; Shah 2014; Shane 2013).

Late-onset sepsis frequently presents with clinical deterioration including apnoea, tachypnoea, increased ventilatory requirement, hypotension, abnormal heart rate, hyperglycaemia, abnormal temperature (hypo- or hyperthermia), cyanosis, acidosis, feeding intolerance, abdominal distension, lethargy, and skin mottling (Craft 2000; Tsai 2014). As some of these clinical manifestations can be non-specific, it can be difficult to clinically distinguish between sepsis and deep-seated infections, such as meningitis, osteomyelitis, and necrotising enterocolitis (Camacho-Gonzalez 2013; Zea-Vera 2015).

Epidemiology

Studies from the USA and Australia suggest that late-onset sepsis constitutes 3 to 6 per 1000 live births, while early-onset sepsis ranges from 0.9 to 3.5 per 1000 live births (Isaacs 1999; Schuchat 2000; Vergnano 2005; Vergnano 2011). However, since there is neither consensus on criteria for neonatal sepsis nor agreement on the cut-off between early-onset and late-onset sepsis (48 hours, 72 hours, or 7 days) (see 'Definition' section above), it is difficult to estimate the exact incidence of neonatal sepsis (Bakhuizen 2014).

Late-onset sepsis is most common in premature (< 37 weeks) and low birthweight (< 2500 g) neonates (Stoll 2011; Tsai 2014).

Neonatal sepsis is a major cause of morbidity and mortality. It is the third leading cause of neonatal mortality globally, constituting 13% of overall neonatal mortality (Lawn 2005; Liu 2012). In high-income countries, the mortality rate due to neonatal sepsis ranges from 5% to 20%, and neonatal sepsis results in major disability or death in 39% of all cases despite initiation of conventional treatment. Mortality rates higher than 70% can be observed in some low- and middle-income countries (LMICs) (Bakhuizen 2014; Kabwe 2016; Weston 2011; Wynn 2014).

Sepsis during the neonatal period can result in several complications, such as multiple organ failure, cerebral haemorrhage, periventricular leukomalacia, meningitis, and respiratory distress syndrome (Sharma 2007; Stoll 2010). In survivors, sepsis is associated with serious long-term morbidity, such as cerebral palsy, cognitive and psychomotor delay, auditory and visual impairment, and bronchopulmonary dysplasia (Bakhuizen 2014; Benjamin 2006; Klinger 2010; Schlapbach 2011). Most of these associations are based on observational cohort studies and therefore do not distinguish between causality and association. It remains uncertain whether it is possible to prevent these subsequent sequela by treating neonatal sepsis with an appropriate empirical antibiotic regimen (Bakhuizen 2014).

Etiology

The pathogens that cause late-onset sepsis include gram-positive and gram-negative bacteria, as well as fungal infections (Boghossian 2013). The mortality and the distribution pattern of pathogens that cause late-onset infection differ between LMICs and high-income countries. Important variations can sometimes even be seen between individual neonatal intensive care units (NICUs) in a given country. The predominant organisms responsible for neonatal sepsis within regions have also changed over time (Dong 2015; Stoll 1996).

The most common etiological pathogen responsible for late-onset sepsis is coagulase-negative staphylococci, constituting 53% to 78% of all cases of late-onset sepsis in high-income countries (Bizzarro 2005; Bizzarro 2008; Dong 2015; Isaacs 1996; Rubin 2002; Stoll 2011; Weston 2011). However, since coagulase-negative staphylococci are skin commensals, these organisms are also common blood culture contaminants and there is a lack of consensus regarding how to interpret blood cultures that are positive for coagulase-negative staphylococci (Rubin 2002). Other agents prevalent in late-onset sepsis are *Escherichia coli*, group B *Streptococcus*, *Klebsiella pneumoniae*, *Enterococcus*, *Candida*, and *Pseudomonas* (Isaacs 1996; Rubin 2002; Stoll 2011; Vergnano 2011).

In LMICs coagulase-negative staphylococci are still very common, constituting 36% to 47% of all cases of late-onset sepsis (Dong 2015; Hammoud 2012). The second most common gram-positive pathogen is *Staphylococcus aureus* (Dong 2015; Zaidi 2005). Gram-negative pathogens are relatively more common in LMICs (Dong 2015; Zaidi 2005). The most frequent gram-negative pathogens are *Klebsiella* spp., *E. coli*, *Pseudomonas*, and *Salmonella* spp (Breurec 2016; Hammoud 2012; Vergnano 2005; WHO 1999; Zaidi 2005). The pathogen with the highest case fatality ratio is considered to be *Pseudomonas aeruginosa* (Hammoud 2012; Tsai 2014).

Late-onset sepsis has several risk factors. Major risk factors are immaturity, mechanical ventilation, intravascular catheterisation, the failure of early enteral feeding with breast milk, a prolonged duration of parenteral nutrition, surgery, underlying respiratory and cardiovascular diseases, and hospitalisation (Boghossian 2013; Leal 2012; Stoll 2002; Tröger 2014; Tsai 2014). Furthermore, neonates are theoretically immunocompromised as several components of the immune system are not fully developed at birth (Camacho-Gonzalez 2013; Kumar 2016). Preterm neonates are especially immunocompromised due to even more immature innate and adaptive immune systems (Kan 2016; Rogosch 2012; Walker 2011; Ygberg 2012; Zemlin 2007).

Description of the intervention

Antibiotics are antimicrobial drugs that treat and prevent bacterial infections by either killing or inhibiting the growth of the bacteria (Waksman 1947). Early initiation of antibiotic therapy on neonates with suspected sepsis reduces both mortality and morbidity (Bakhuizen 2014). The choice of antibiotic used is often empirical and based on several factors, such as age at onset, likely pathogens, and antibiotic susceptibility patterns (Dong 2015; Manan 2016; Rubin 2002).

A recent study from the USA showed that the antibiotics were discontinued in the majority (63%) of patients that received empirical antibiotics for suspected sepsis, as sepsis was ruled out by a negative blood culture (Cantey 2015). The most commonly used first-line treatment is a beta-lactam antibiotic (most commonly ampicillin, flucloxacillin, or penicillin) combined with an aminoglycoside (most commonly gentamicin) (Dong 2015; Vergnano 2011). However, there has been an increased use of alternatives, such as vancomycin and cephalosporins, due to increased drug resistance among the most common pathogen e.g. coagulase-negative staphylococci (Dong 2015; Rubin 2002).

Most guidelines recommend a penicillin together with an aminoglycoside for all cases of neonatal sepsis (Cortese 2016; Manan 2016; Muller-Pebody 2011; Vergnano 2005; Vergnano 2011; WHO 2013). However, other protocols exist where a cephalosporin or a glycopeptide is used as a first-line option to treat late-onset sepsis (Fernando 2008; Marchant 2013; Stockmann 2014). Guidelines may differ due to local antibiotic resistance of the most common pathogens or whether the empirical regimen is supposed to cover the common but low virulence coagulase-negative staphylococci (Bizzarro 2015; Marchant 2013). Vancomycin is to be considered if staphylococcal infection is suspected (Stockmann 2014).

Antibiotic susceptibility

Antibiotic resistance is a growing problem that increases the morbidity, mortality, and costs associated with infections globally (Cohen 1992; Foster 2006; Huynh 2016; Vergnano 2005). Studies indicate that bacterial resistance to antibiotics results primarily from the selective pressure exerted by the use and overuse of antibiotics (Foster 2006; Kunin 1990; McGowan 1994; Murray 1994; Sáez-Llorens 2000). The spread of drug-resistant organisms in hospitals is a recognised problem, although neonates admitted from the community may also carry drug-resistant pathogens (Bhutta 1996). Studies that compare antibiotic susceptibility over time in the same unit show increased resistance to the most used antibiotics (Vergnano 2005).

The pathogens that cause neonatal infections and their antibiotic susceptibility patterns change over time and may differ between countries (Breurec 2016; Isaacs 2003; May 2005; Stoll 2003; Stoll 2005; Vergnano 2011). Furthermore, the definition and epidemiology of neonatal sepsis differs between countries (Vergnano 2005). This makes the comparison of antibiotic susceptibility between countries difficult. When comparing the epidemiology of neonatal sepsis in LMICs with high-income countries, some important differences emerge in the pattern of etiological pathogens and their antibiotic resistance (Khatua 1986; Tallur 2000; Tessin 1990; Vesikari 1985).

In high-income countries, most pathogens that cause late-onset sepsis (84%) were susceptible to the commonly used empiric antibiotics (penicillin/gentamicin and flucloxacillin/gentamicin) (Vergnano 2011).

In LMICs, estimations suggest that up to 70% of pathogens isolated from neonatal sepsis may not be covered by the recommended empirical regimen of ampicillin and gentamicin (Zaidi 2005). Some studies in LMICs have shown almost universal resistance (92% to 100% resistance) among some of the most common pathogens to first- and second-line antibiotics (Dagnew 2013; Kabwe 2016; Zaidi 2005).

In addition to antibiotic coverage, supportive care aiming to reverse the life-threatening organ dysfunction caused by a dysregulated host response to infection is also part of the care for neonates with sepsis. This includes respiratory support, maintenance of peripheral perfusion (intravenous fluids and inotropics), phototherapy, temperature, and glucose regulation (Seale 2015; WHO 2013).

Adverse effects

Use of ampicillin has been associated in some studies with adverse effects, such as rashes, diarrhoea, nausea, and nephrotoxicity (Golan 2011; Katzung 2009; Mrvos 2013). Contrary to these findings, a recent systematic review of randomised clinical trials showed that ampicillin only increased the incidence of candidiasis with no significant increase in the above-mentioned adverse effects (Gillies 2015).

Aminoglycosides (e.g. gentamicin) have been shown to be toxic (nephrotoxicity and ototoxicity) in adults. However, their toxicity in neonates remains unclear (Huth 2011; Jackson 1971; Mattie 1989; McGlone 2008; Mingeot-Leclercq 1999; Musiime 2015; Schultze 1971; Selimoglu 2007; Wargo 2014).

The most common adverse effects caused by vancomycin are fever, phlebitis, and, in rare cases, nephrotoxicity and ototoxicity (Rybak 2009). However, in addition to the development of resistance towards vancomycin, one must also consider that observational studies suggest a 3- to 4-fold increase in nephrotoxicity when aminoglycosides are combined with vancomycin (Farber 1983; Hailemeskel 1999; Rybak 2009; Sorrell 1985).

Cefotaxime, which is considered an alternative first-line agent, might have a broad spectrum of activity. However, cefotaxime is also associated with increased risk of death and invasive candidiasis in non-randomised studies (Clark 2006a; Cotten 2006; Stockmann 2014).

In addition to the specific adverse effects of each antibiotic, extended use of antibiotics is also associated with higher risk of neonatal candidaemia (Filioti 2007; Spiliopoulou 2012).

How the intervention might work

Antibiotics are antimicrobial drugs that treat and prevent bacterial infections by either killing or inhibiting the growth of the bacteria (Waksman 1947). They can be classified based on: 1) their mechanism of action (bactericidal or bacteriostatic); 2) bacterial spectrum (broad or narrow); and 3) chemical structure (e.g. penicillins, macrolides, quinolones, tetracyclines, or aminoglycosides) (Bérdy 2005).

A combination of different antibiotics might have several advantages. Firstly, it is thought to provide an enhanced effect beyond the additive effects of the individual therapies (Allan 1985). Secondly, it can be used to broaden the spectrum of antibiotic coverage when used empirically to increase the chances of covering the alleged causative bacteria. Thirdly, a combination therapy is thought to suppress the development of subpopulations of microorganisms resistant to antibiotics (Allan 1985; Milatovic 1987; Tamma 2012).

Why it is important to do this review

Despite the high burden of neonatal sepsis, high-quality evidence in diagnosis and treatment is scarce (Zea-Vera 2015). Yet, in adults, appropriate empirical antibiotic treatment halves the fatality associated with sepsis (Ibrahim 2000; Leibovici 1998; Paul 2010). Due to the diagnostic challenges of sepsis, and the relative immunosuppression of the newborn, many neonates receive antibiotics for suspected sepsis. In fact, antibiotics have become the most commonly used therapeutics in NICUs (Clark 2006b). Studies suggest that up to 95% of newborns treated with antibiotics for suspected sepsis prove to have no evidence of infection (Bedford Russell 2015; Cantey 2015; Luck 2003). This presumed inappropriate use of antibiotics seems to contribute to the development and spread of resistant pathogens in the NICUs, and seems to be associated with adverse events (e.g. invasive candidiasis, and increased antimicrobial resistance) (Clark 2006a; Cordero 2003; Cotten 2006; Cotten 2009; Foster 2006; Kuppala 2011).

The Cochrane Review published in 2005 concluded that there is inadequate evidence from randomised trials in favour of any particular antibiotic regimen for the treatment of suspected late-onset neonatal sepsis (Gordon 2005). No other systematic review has been conducted to date to assess the effects of different antibiotic regimens for suspected late-onset sepsis. There is therefore an urgent need for an updated systematic review that assesses the effects of different antibiotic regimens for late-onset sepsis, taking into account both risks of systematic errors and random errors (Jakobsen 2014).

OBJECTIVES

To compare the beneficial and harmful effects of different antibiotic regimens for neonates with late-onset sepsis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised, quasi-randomised, and cluster-randomised clinical trials. We will include trials regardless of publication type, publication status, publication date, and language. We will exclude crossover trials.

Types of participants

Participants suspected of or diagnosed with late-onset sepsis (as defined by the trial authors).

We will include participants if described as newborns or 72 hours of life or more (at randomisation), suspected or diagnosed with neonatal sepsis, meningitis, osteomyelitis, endocarditis, or necrotising enterocolitis.

We will exclude trials that assess treatment of fungal infections.

Types of interventions

We will accept any type of antibiotic or combination of antibiotics, such as the following.

- Broad-spectrum beta-lactam antibiotics, defined as broad-spectrum penicillins (e.g. ampicillin, amoxicillin, piperacillin, ticarcillin, carbenicillin, and mezlocillin), cephalosporins (e.g. cefazolin, cephalexin, cefuroxime, cefotetan, cefoxitin, ceftriaxone, cefotaxime, ceftazidime, cefepime, cefazolin, ceftobiprole, ceftolozane, and cefoperazone), carbapenems (e.g. imipenem, meropenem, doripenem, and ertapenem), and monobactams (e.g. aztreonam). Narrow-spectrum antibiotics will include narrow-spectrum penicillins (e.g. oxacillin, cloxacillin, dicloxacillin, nafcillin, methicillin, and penicillin G).
- Beta-lactam antibiotics with beta-lactamase inhibitors such as avibactam, clavulanic acid, sulbactam, and tazobactam.
- Combination of beta-lactam with aminoglycoside (e.g. gentamycin).
- Combination of beta-lactam with glycopeptide (e.g. vancomycin and teicoplanin).
- Combination of glycopeptide with aminoglycoside.

We plan to assess the following comparisons.

- Aminoglycoside added to any type of antibiotic versus any type of antibiotic (same antibiotic as in the experimental group).
- Broad-spectrum beta-lactam antibiotic and aminoglycoside versus narrow-spectrum beta-lactam antibiotic (as defined in the above) and aminoglycoside (same aminoglycoside as in the experimental group).
- Beta-lactam antibiotic (as defined in the above) and aminoglycoside versus beta-lactam antibiotic and glycopeptide.
- Any other used antibiotic regimen (not included in the above-mentioned comparisons) versus any other used antibiotic regimen (not included in the above-mentioned comparisons).

Types of outcome measures

Primary outcomes

- All cause mortality.

Secondary outcomes

- Proportion of participants with one or more serious adverse event. We will define a serious adverse event as any untoward medical occurrence that resulted in death, was life-threatening, jeopardised the participant, was persistent, led to significant disability, hospitalisation, or prolonged hospitalisation (Hubbard 1997). As we expect the reporting of serious adverse events in many trials to be very heterogeneous and not strictly according to the recommendations regarding good clinical practice from The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH-GCP) (Hubbard 1997), we will include the event as a serious adverse event if the trial authors either: 1) use the term ‘serious adverse event' but not refer to ICH-GCP, or 2) report the proportion of participants with an event we

consider fulfil the ICH-GCP definition. If several of such events are reported, we will choose the highest proportion reported in each trial to avoid double-counting.

- Respiratory support, defined as the proportion of participants who received respiratory support, such as non-invasive ventilation (e.g. continuous positive airway pressure (CPAP)) or invasive ventilation (e.g. respirator).
- Circulatory support, defined as the proportion of participants who received circulatory support such as fluid bolus or vasoactive medication (e.g. inotropes or vasopressors).
- Nephrotoxicity (as defined by the trial author).
- Presence of moderate-to-severe neurological developmental and sensory impairment (defined as a functional abnormality in the function of the brain, spinal cord, muscles, nerves, eyes or ears, or as any significant lag in a child's physical or motor, cognitive, behavioural, emotional or social development, in comparison with other children of the same age and sex within similar environments. If formal evaluation tools were used to assess neurodevelopmental impairment, we will use a threshold of – 2 standard deviations (SDs) of the normal. Furthermore, severe brain injury *per se* is included, such as intraventricular haemorrhage grade 3 and 4 (Papile 1978; Volpe 2008) and periventricular leukomalacia.
- Necrotising enterocolitis during or after treatment, defined by Bells criteria 2 (Bell 1978).
- Ototoxicity as defined by the trial authors.

We will assess all the dichotomised outcomes as proportions.

We will use the trial results reported at maximum follow-up. However, if the trial authors report results at multiple time points, we will primarily use the results reported at the time point closest to 1 year.

Search methods for identification of studies

We will use the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal search strategy for Specialized Register). We will search for errata or retractions from included studies published in full-text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and report the date this was done within the review.

Electronic searches

We will conduct a comprehensive search including: Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library; Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® (1946 to current); and CINAHL (1981 to current). We will not apply language restrictions. The draft search strategy is in Appendix 1.

Further searches will be performed in Embase for pharmaceutical publications and ZETOC for abstracts of scientific conferences/symposia. We will crosscheck references from identified studies for possible additional studies.

We will search the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en/) and the US National Library of Medicine's ClinicalTrials.gov (clinicaltrials.gov) via Cochrane CENTRAL. Additionally, we will search the ISRCTN Registry (www.isrctn.com/) for any unique trials not found through the Cochrane CENTRAL search.

We will search all databases from their inception to the present and we will impose no restriction on language of publication. If we identify any papers in a language not known by the review author group, we will seek help. This will be acknowledged in the Acknowledgements section of the review.

Searching other resources

We will check the reference lists of all relevant primary trials and reviews for additional references.

To identify unpublished trials we will also search clinical trial registers of Europe and the USA, websites of pharmaceutical companies, and websites of the US Food and Drug Administration (FDA) and the European Medicines Agency.

Data collection and analysis

Selection of studies

Two review authors (SKK and SS) will independently screen titles and abstracts. We will retrieve all relevant full-text study reports/publication and two review authors (SKK and SS) will independently screen the full texts and identify trials for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, by consulting a third review author (JCJ). We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009), and a 'Characteristics of excluded studies' table.

Data extraction and management

We will use data collection forms for trial characteristics and outcome data that we pilot on at least one trial included in the review. Two review authors (SKK and SS) will extract trial characteristics from included trials. We will extract the following trials characteristics.

- Methods: trial design, total duration of the trial, number of trial centres and location, trial setting, withdrawals, and date of the trial.
- Participants: number of participants in each intervention group, mean age, age range, gender, diagnostic criteria, inclusion criteria, and exclusion criteria.
- Interventions: intervention and comparison.
- Outcomes: primary and secondary outcomes specified and collected, and time points reported.
- Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (SKK and SS) will independently extract outcome data from included trials. We will note in the 'Characteristics of included studies' table if the trial authors did not report outcome data in a usable way. We will resolve disagreements by consensus or by involving a third review author (JCJ). One review author (SKK) will transfer data into the Review Manager 5 (RevMan 5) file (Review Manager 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author

(SS) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (SKK and SS) will independently assess the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool for the following domains (Higgins 2019).

- Sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Any other bias.

We will resolve any disagreements by discussion or by consulting a third review author (JCJ). See Appendix 2 for a more detailed description of risk of bias for each domain.

Assesment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the published review.

Measures of treatment effect

We will calculate risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes.

Unit of analysis issues

The unit of analysis will be the participating infant in individually randomised trials and the neonatal unit (or sub-unit) for cluster-randomised trials. For cluster-randomised trials, we will undertake analyses at the level of the individual while accounting for the clustering in the data using the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

Dealing with missing data

We will not impute missing values for any outcomes in our primary analysis. In two of our sensitivity analyses, we will impute data (see 'Sensitivity analysis').

We will contact investigators and trial sponsors in order to verify key trial characteristics and obtain missing numerical outcome data when possible (e.g. when we identify a study as an abstract only).

Assessment of heterogeneity

We visually inspect forest plots to assess signs of heterogeneity and we will explore possible heterogeneity in our prespecified subgroup analyses. We will also inspect trial characteristics across trials to identify clinical heterogeneity. We will assess the presence of statistical heterogeneity by the Chi^2 test (threshold $P < 0.10$) and measure the quantities of heterogeneity by the I^2 statistic (Higgins 2002; Higgins 2003). If we detect moderate or high heterogeneity ($I^2 \geq 50\%$), we plan to explore the possible causes (e.g. differences in study design, participants, interventions, or completeness of outcome assessments). Ultimately, we may decide that a meta-analysis should be avoided (Higgins 2019).

Assessment of reporting biases

We will use a funnel plot to assess publication bias if 10 or more trials meet the inclusion criteria. We will visually inspect funnel plots to assess the risk of bias. As we plan to report results when we analyse dichotomous outcomes using RRs, we will not use any test to assess funnel plot asymmetry when analysing dichotomous outcomes (Higgins 2019).

Data synthesis

Meta-analysis

We will undertake this meta-analysis according to the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). We will use RevMan 5 to analyse data (Review Manager 2014).

We will assess our intervention effects using fixed-effect meta-analyses (Demets 1987), in accordance with the policies of the Cochrane Neonatal review group. We will use one primary outcome and, therefore, we will consider a P value of 0.05 or less as the threshold for statistical significance (Jakobsen 2014). We will use the 8-step procedure to assess if the threshold for significance are crossed (Jakobsen 2014). Our primary conclusion will be based on results with low risk of bias (Jakobsen 2014). Where data are only available from one trial, we will use Fisher's exact test for dichotomous data (Fisher 1922).

Where multiple trial arms are reported in a single trial, we will include only the relevant trial arms. If two comparisons are combined in the same meta-analysis, we will halve the control group to avoid double-counting.

Trial sequential analysis (TSA)

Traditional meta-analysis runs the risk of random errors due to sparse data and repetitive testing of accumulating data when updating reviews. We will therefore perform TSA on the outcomes, in order to calculate the required information size and the cumulative Z-curve's breach of relevant trial sequential monitoring boundaries (Brok 2008; Brok 2009; Thorlund 2009; Thorlund 2011; TSA 2011; Wetterslev 2008; Wetterslev 2009; Wetterslev 2017). We wish to control the risks of type I errors and type II errors. A more detailed description of TSA can be found at www.ctu.dk/tsa/. We will assess our TSA intervention effects with both a random-effects model (DerSimonian 1986), and a fixed-effect model (Demets 1987). We will use the more conservative point estimate of the two (Jakobsen 2014). The more conservative point estimate will be the estimate closest to zero effect. If the two estimates are similar, we will use the estimate with the widest CI.

For dichotomous outcomes we will estimate the required information size based on the observed, unweighted proportion of patients with an outcome in the control group (the cumulative proportion of patients with an event in the control groups relative to all patients in the control groups), a relative risk reduction of 20%, an alpha of 5%, a beta of 20%, and diversity as suggested by the trials in the meta-analysis.

Subgroup analysis and investigation of heterogeneity

We plan to perform the following subgroup analyses for our primary outcome.

- High risk of bias trials versus low risk of bias trials.
- Gestational age: term (≥ 37 weeks) compared to preterm.
- Trials from high-income countries compared to trials from LMICs, as defined by the World Bank (World Bank 2017).
- Late-onset sepsis defined by: onset after 48 hours, after 72 hours, after a week, or defined by the trial authors.

We will use the formal test for subgroup interactions in RevMan 5 (Review Manager 2014).

Sensitivity analysis

To assess the potential impact of the missing data, we will perform the two following sensitivity analyses on the primary outcome and the secondary outcome, serious adverse events.

- 'Best-worst-case' scenario: we will assume that all participants lost to follow-up in the experimental group have survived and have had no serious adverse event; and all those participants with missing outcomes in the control group have not survived and have had a serious adverse event.
- 'Worst-best-case' scenario: we will assume that all participants lost to follow-up in the experimental group have not survived and have had a serious adverse event; and that all those participants lost to follow-up in the control group had survived and had no serious adverse event.

We will present results of both scenarios in our review.

Other post-hoc sensitivity analyses may be warranted if we identify unexpected clinical or statistical heterogeneity during our analysis of the review results (Jakobsen 2014).

Summary of findings and assessment of the certainty of the evidence

We will create a 'Summary of findings' table using the prespecified primary outcome (all-cause mortality) and five secondary outcomes (serious adverse events, respiratory support, circulatory support, nephrotoxicity, and neurological developmental impairment) at maximum follow-up. We will use the GRADE approach, as outlined in the GRADE Handbook, to assess the certainty of evidence for our primary outcomes and five secondary outcomes (serious adverse events, respiratory support, circulatory support, nephrotoxicity, and neurological developmental impairment) (Schünemann 2013).

Two review authors will independently assess the certainty of the evidence for each of the outcomes above. We will consider evidence from randomised controlled trials as high quality, but will downgrade the quality of the evidence by one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We will use the GRADEpro Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence (GRADEpro GDT).

The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades, as follows.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

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We have based the Methods section of this protocol on a standard template used by Cochrane Neonatal.

REFERENCES

Additional references

Allan 1985

Allan JD, Moellering RC Jr. Management of infections caused by gram-negative bacilli: the role of antimicrobial combinations. *Review of Infectious Diseases* 1985;**7**(Suppl 4):S559-71. [PMID: 3909313]

Bakhuizen 2014

Bakhuizen SE, de Haan TR, Teune MJ, van Wassenaer-Leemhuis AG, van der Heyden JL, van der Ham DP, et al. Meta-analysis shows that infants who have suffered neonatal sepsis face an increased risk of mortality and severe complications. *Acta Paediatrica* 2014;**103**(12):1211-8. [DOI: 10.1111/apa.12764] [PMID: 25073543]

Bedford Russell 2015

Bedford Russell AR, Kumar R. Early onset neonatal sepsis: diagnostic dilemmas and practical management. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2015;**100**(4):F350-4. [DOI: 10.1136/archdischild-2014-306193] [PMID: 25425652]

Bell 1978

Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Annals of Surgery* 1978;**187**(1):1-7. [PMID: 413500]

Benjamin 2006

Benjamin DK Jr, Stoll BJ, Fanaroff AA, McDonald SA, Oh W, Higgins RD, et al, National Institute of Child Health and Human Development Neonatal Research Network. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. *Pediatrics* 2006;**117**(1):84-92. [DOI: 10.1542/peds.2004-2292] [PMID: 16396864]

Bérdy 2005

Bérdy J. Bioactive microbial metabolites. *Journal of Antibiotics* 2005;**58**(1):1-26. [DOI: 10.1038/ja.2005.1] [PMID: 15813176]

Bhutta 1996

Bhutta ZA. Enterobacter sepsis in the newborn--a growing problem in Karachi. *Journal of Hospital Infection* 1996;**34**(3):211-6. [PMID: 8923276]

Bizzarro 2005

Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-five years of neonatal sepsis at Yale: 1928-2003. *Pediatrics* 2005;**116**(3):595-602. [DOI: 10.1542/peds.2005-0552] [PMID: 16140698]

Bizzarro 2008

Bizzarro MJ, Dembry LM, Baltimore RS, Gallagher PG. Changing patterns in neonatal Escherichia coli sepsis and ampicillin resistance in the era of intrapartum antibiotic prophylaxis. *Pediatrics* 2008;**121**(4):689-96. [DOI: 10.1542/peds.2007-2171] [PMID: 18381532]

Bizzarro 2015

Bizzarro MJ, Shabanova V, Baltimore RS, Dembry LM, Ehrenkranz RA, Gallagher PG. Neonatal sepsis 2004-2013: the rise and fall of coagulase-negative staphylococci. *Journal of Pediatrics* 2015;**166**(5):1193-9. [PMID: 25919728]

Boghossian 2013

Boghossian NS, Page GP, Bell EF, Stoll BJ, Murray JC, Cotten CM, et al, Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Late-onset sepsis in very low birth weight infants from singleton and multiple-gestation births. *Journal of Pediatrics* 2013;**162**(6):1120-4, 1124.e1. [DOI: 10.1016/j.jpeds.2012.11.089] [PMID: 23324523]

Breurec 2016

Breurec S, Bouchiat C, Sire JM, Moquet O, Bercion R, Cisse MF, et al. High third-generation cephalosporin resistant Enterobacteriaceae prevalence rate among neonatal infections in Dakar, Senegal. *BMC Infectious Diseases* 2016;**16**(1):587. [DOI: 10.1186/s12879-016-1935-y] [PMID: 27765017]

Brok 2008

Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *Journal of Clinical Epidemiology* 2008;**61**(8):763-9. [DOI: 10.1016/j.jclinepi.2007.10.007] [PMID: 18411040]

Brok 2009

Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive--Trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *International Journal of Epidemiology* 2009;**38**(1):287-98. [DOI: 10.1093/ije/dyn188] [PMID: 18824466]

Camacho-Gonzalez 2013

Camacho-Gonzalez A, Spearman PW, Stoll BJ. Neonatal infectious diseases: evaluation of neonatal sepsis. *Pediatric Clinics of North America* 2013;**60**(2):367-89. [DOI: 10.1016/j.pcl.2012.12.003] [PMID: 23481106]

Cantey 2015

Cantey J, Wozniak PS, Sánchez PJ. Prospective surveillance of antibiotic use in the neonatal intensive care unit: results from the SCOUT study. *Pediatric Infectious Disease Journal* 2015;**34**(3):267-72. [DOI: 10.1097/INF.0000000000000542] [PMID: 25191849]

Clark 2006a

Clark RH, Bloom BT, Spitzer AR, Gerstmann DR. Empiric use of ampicillin and cefotaxime, compared with ampicillin and gentamicin, for neonates at risk for sepsis is associated with an increased risk of neonatal death. *Pediatrics* 2006;**117**(1):67-74. [DOI: 10.1542/peds.2005-0179] [PMID: 16396862]

Clark 2006b

Clark RH, Bloom BT, Spitzer AR, Gerstmann DR. Reported medication use in the neonatal intensive care unit: data from a large national data set. *Pediatrics* 2006;**117**(6):1979-87. [DOI: 10.1542/peds.2005-1707] [PMID: 16740839]

Cohen 1992

Cohen ML. Epidemiology of drug resistance: implications for a post-antimicrobial era. *Science (New York, N.Y.)* 1992;**257**(5073):1050-5. [PMID: 1509255]

Cordero 2003

Cordero L, Ayers LW. Duration of empiric antibiotics for suspected early-onset sepsis in extremely low birth weight infants. *Infection Control and Hospital Epidemiology* 2003;**24**(9):662-6. [DOI: 10.1086/502270] [PMID: 14510248]

Cortese 2016

Cortese F, Scicchitano P, Gesualdo M, Filaninno A, De Giorgi E, Schettini F, et al. Early and late infections in newborns: where do we stand? A review. *Pediatrics and Neonatology* 2016;**57**(4):265-73. [DOI: 10.1016/j.pedneo.2015.09.007] [PMID: 26750406]

Cotten 2006

Cotten CM, McDonald S, Stoll B, Goldberg RN, Poole K, Benjamin DK Jr, National Institute for Child Health and Human Development Neonatal Research Network. The association of third-generation cephalosporin use and invasive candidiasis in extremely low birth-weight infants. *Pediatrics* 2006;**118**(2):717-22. [PMID: 16882828]

Cotten 2009

Cotten CM, Taylor S, Stoll B, Goldberg RN, Hansen NI, Sánchez PJ, et al, NICHD Neonatal Research Network. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. *Pediatrics* 2009;**123**(1):58-66. [DOI: 10.1542/peds.2007-3423] [PMID: 19117861]

Craft 2000

Craft AP, Finer NN, Barrington KJ. Vancomycin for prophylaxis against sepsis in preterm neonates. *Cochrane Database of Systematic Reviews* 2000, Issue 2. Art. No: CD001971. [DOI: 10.1002/14651858.CD001971]

Dagnew 2013

Dagnew M, Yismaw G, Gizachew M, Gadisa A, Abebe T, Tadesse T, et al. Bacterial profile and antimicrobial susceptibility pattern in septicemia suspected patients attending Gondar University Hospital, Northwest Ethiopia. *BMC Research Notes* 2013;**6**:283. [DOI: 10.1186/1756-0500-6-283] [PMID: 23875886] [PMID: 23875886]

Demets 1987

Demets DL. Methods of combining randomized clinical trials: strengths and limitations. *Statistics in Medicine* 1987;**6**(3):341-50. [PMID: 3616287]

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**(3):177-88. [PMID: 3802833]

Dong 2015

Dong Y, Speer CP. Late-onset neonatal sepsis: recent developments. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2015;**100**(3):F257-63. [DOI: 10.1136/archdischild-2014-306213] [PMID: 25425653]

Farber 1983

Farber BF, Moellering RC Jr. Retrospective study of the toxicity of preparations of vancomycin from 1974 to 1981. *Antimicrobial Agents and Chemotherapy* 1983;**23**(1):138-41.

Fernando 2008

Fernando AM, Heath PT, Menson EN. Antimicrobial policies in the neonatal units of the United Kingdom and Republic of Ireland. *Journal of Antimicrobial Chemotherapy* 2008;**61**(3):743-5. [DOI: 10.1093/jac/dkm543] [PMID: 18238883]

Filioti 2007

Filioti J, Spiroglou K, Roilides E. Invasive candidiasis in pediatric intensive care patients: epidemiology, risk factors, management, and outcome. *Intensive Care Medicine* 2007;**33**(7):1272-83. [PMID: 17503015]

Fisher 1922

Fisher RA. On the interpretation of χ2 from contingency tables, and the calculation of P. *Journal of the Royal Statistical Society* 1922;**85**(1):87-94.

Foster 2006

Foster KR, Grundmann H. Do we need to put society first? The potential for tragedy in antimicrobial resistance. *PLOS Medicine* 2006;**3**(2):e29. [PMID: 16398572]

Gillies 2015

Gillies M, Ranakusuma A, Hoffmann T, Thorning S, McGuire T, Glasziou P, et al. Common harms from amoxicillin: a systematic review and meta-analysis of randomized placebo-controlled trials for any indication. *CMAJ: Canadian Medical Association Journal* 2015;**187**(1):E21-31. [DOI: 10.1503/cmaj.140848] [PMID: 25404399]

Golan 2011

Golan DE, Tashlian AH, Amstrong EJ, Armstrong AW. Principles of Pharmacology. 3rd edition. Philadelphia: Lippincott Williams & Wilkins, 2011.

Gordon 2005

Gordon A, Jeffery HE. Antibiotic regimens for suspected late onset sepsis in newborn infants. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No: CD004501. [DOI: 10.1002/14651858.CD004501.pub2]

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Version accessed 13 December 2017. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015. Available at gradepro.org.

Hailemeskel 1999

Hailemeskel B, Namanny M, Wutoh A. Frequency of nephrotoxicity with vancomycin and aminoglycoside antibiotic therapy. *Hospital Pharmacy* 1999;**34**(12):1417-20.

Hammoud 2012

Hammoud MS, Al-Taiar A, Thalib L, Al-Sweih N, Pathan S, Isaacs D. Incidence, aetiology and resistance of late-onset neonatal sepsis: a five-year prospective study. *Journal of Paediatrics and Child Health* 2012;**48**(7):604-9. [DOI: 10.1111/j.1440-1754.2012.02432.x] [PMID: 22404730]

Higgins 2002

Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**(11):1539-58. [DOI: 10.1002/sim.1186] [PMID: 12111919]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ (Clinical Research Ed.)* 2003;**327**(7414):557-60. [PMID: 12958120]

Higgins 2019

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from training.cochrane.org/handbook.

Hubbard 1997

Hubbard WK. International Conference on Harmonisation; Good Clinical Practice: Consolidated Guideline; Availability. In: Federal Register. Vol. 62. Pennsylvania: Barnett International/ PAREXEL, 1997:25691-709. [PMID: 11656783]

Huth 2011

Huth ME, Ricci AJ, Cheng AG. Mechanisms of aminoglycoside ototoxicity and targets of hair cell protection. *International Journal of Otolaryngology* 2011;**2011**:937861. [DOI: 10.1155/2011/937861] [PMID: 22121370]

Huynh 2016

Huynh BT, Padget M, Garin B, Delarocque-Astagneau E, Guillemot D, BIRDY study group. Bacterial neonatal sepsis and antibiotic resistance in low-income countries. *Lancet* 2016;**387**(10018):533-4. [DOI: 10.1016/S0140-6736(16)00220-8] [PMID: 26867442]

Ibrahim 2000

Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest* 2000;**118**(1):146-55. [PMID: 10893372]

Isaacs 1996

Isaacs D, Barfield C, Clothier T, Darlow B, Diplock R, Ehrlich J, et al. Late-onset infections of infants in neonatal units. *Journal of Paediatrics and Child Health* 1996;**32**(2):158-61. [PMID: 9156527]

Isaacs 1999

Isaacs D, Royle JA. Intrapartum antibiotics and early onset neonatal sepsis caused by group B Streptococcus and by other organisms in Australia. Australasian Study Group for Neonatal Infections. *Pediatric Infectious Disease Journal* 1999;**18**(6):524-8. [PMID: 10391182]

Isaacs 2003

Isaacs D, Australasian Study Group For Neonatal Infections. A ten year, multicentre study of coagulase negative staphylococcal infections in Australasian neonatal units. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2003;**88**(2):F89-93. [PMID: 12598493]

Jackson 1971

Jackson GG, Arcieri G. Ototoxicity of gentamicin in man: a survey and controlled analysis of clinical experience in the United States. *Journal of Infectious Diseases* 1971;**124**(Suppl):S130-7. [PMID: 5126239]

Jakobsen 2014

Jakobsen JC, Wetterslev J, Winkel P, Lange T, Gluud C. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. *BMC Medical Research Methodology* 2014;**14**:120. [DOI: 10.1186/1471-2288-14-120] [PMID: 25416419]

Kabwe 2016

Kabwe M, Tembo J, Chilukutu L, Chilufya M, Ngulube F, Lukwesa C, et al. Etiology, antibiotic resistance and risk factors for neonatal sepsis in a large referral center in Zambia. *Pediatric Infectious Disease Journal* 2016;**35**(7):e191-8. [DOI: 10.1097/INF.0000000000001154] [PMID: 27031259]

Kan 2016

Kan B, Razzaghian HR, Lavoie PM. An immunological perspective on neonatal sepsis. *Trends in Molecular Medicine* 2016;**22**(4):290-302. [DOI: 10.1016/j.molmed.2016.02.001] [PMID: 26993220]

Katzung 2009

Katzung BG, Masters SB, Trevor AJ. Basic and Clinical Pharmacology. 11th edition. New York (NY): McGraw-Hill Medical Publishing Division, 2009.

Khatua 1986

Khatua SP, Das AK, Chatterjee BD, Khatua S, Ghose B, Saha A. Neonatal septicemia. *Indian Journal of Pediatrics* 1986;**53**(4):509-14. [PMID: 3542818]

Klinger 2010

Klinger G, Levy I, Sirota L, Boyko V, Lerner-Geva L, Reichman B, Israel Neonatal Network. Outcome of early-onset sepsis in a national cohort of very low birth weight infants. *Pediatrics* 2010;**125**(4):e736-40. [DOI: 10.1542/peds.2009-2017] [PMID: 20231184]

Kumar 2016

Kumar SKM, Bhat BV. Distinct mechanisms of the newborn innate immunity. *Immunology Letters* 2016;**173**:42-54. [DOI: 10.1016/j.imlet.2016.03.009] [PMID: 26994839]

Kunin 1990

Kunin CM, Johansen KS, Worning AM, Daschner FD. Report of a symposium on use and abuse of antibiotics worldwide. *Reviews of Infectious Diseases* 1990;**12**(1):12-9. [PMID: 2405465]

Kuppala 2011

Kuppala VS, Meinzen-Derr J, Morrow AL, Schibler KR. Prolonged initial empirical antibiotic treatment is associated with adverse outcomes in premature infants. *Journal of Pediatrics* 2011;**159**(5):720-5. [DOI: 10.1016/j.jpeds.2011.05.033] [PMID: 21784435]

Lawn 2005

Lawn JE, Cousens S, Zupan J, Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: when? Where? Why? *Lancet* 2005;**365**(9462):891-900. [DOI: 10.1016/S0140-6736(05)71048-5] [PMID: 15752534]

Leal 2012

Leal YA, Álvarez-Nemegyei J, Velázquez JR, Rosado-Quiab U, Diego-Rodríguez N, Paz-Baeza E, et al. Risk factors and prognosis for neonatal sepsis in southeastern Mexico: analysis of a four-year historic cohort follow-up. *BMC Pregnancy and Childbirth* 2012;**12**:48. [DOI: 10.1186/1471-2393-12-48] [PMID: 22691696]

Leibovici 1998

Leibovici L, Shraga I, Drucker M, Konigsberger H, Samra Z, Pitlik SD. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. *Journal of Internal Medicine* 1998;**244**(5):379-86. [PMID: 9845853]

Liu 2012

Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, et al, Child Health Epidemiology Reference Group of WHO and UNICEF . Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet (London, England)* 2012;**379**(9832):2151-61; Erratum in: Lancet 2012; 380(9850):1308. [DOI: 10.1016/S0140-6736(12)60560-1] [PMID: 22579125]

Luck 2003

Luck S, Torny M, d'Agapeyeff K, Pitt A, Heath P, Breathnach A, et al. Estimated early-onset group B streptococcal neonatal disease. *Lancet (London, England)* 2003;**361**(9373):1953-4.

Manan 2016

Manan MM, Ibrahim NA, Aziz NA, Zulkifly HH, Al-Worafi YM, Long CM. Empirical use of antibiotic therapy in the prevention of early onset sepsis in neonates: a pilot study. *Archives of Medical Science* 2016;**12**(3):603-13. [DOI: 10.5114/aoms.2015.51208] [PMID: 27279855]

Marchant 2013

Marchant EA, Boyce GK, Sadarangani M, Lavoie PM. Neonatal sepsis due to coagulase-negative staphylococci. *Clinical & Developmental Immunology* 2013;**2013**:586076. [PMID: 23762094]

Mattie 1989

Mattie H, Craig WA, Pechère JC. Determinants of efficacy and toxicity of aminoglycosides. *Journal of Antimicrobial Chemotherapy* 1989;**24**(3):281-93. [PMID: 2681115]

May 2005

May M, Daley AJ, Donath S, Isaacs D, Australasian Study Group for Neonatal Infections. Early onset neonatal meningitis in Australia and New Zealand, 1992-2002. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2005;**90**(4):F324-7. [DOI: 10.1136/adc.2004.066134] [PMID: 15878934]

McGlone 2008

McGlone A, Cranswick N. Evidence behind the WHO guidelines: hospital care for children: what is the evidence of safety of gentamicin use in children? *Journal of Tropical Pediatrics* 2008;**54**(5):291-3. [DOI: 10.1093/tropej/fmn059] [PMID: 18710895]

McGowan 1994

McGowan JE Jr. Do intensive hospital antibiotic control programs prevent the spread of antibiotic resistance? *Infection Control and Hospital Epidemiology* 1994;**15**(7):478-83. [PMID: 7963440]

Metsvaht 2010

Metsvaht T, Ilmoja M-L, Parm Ü, Maipuu L, Merila M, Lutsar I. Comparison of ampicillin plus gentamicin vs. penicillin plus gentamicin in empiric treatment of neonates at risk of early onset sepsis. *Acta Paediatrica* 2010;**99**(5):665-72. [DOI: 10.1111/j.1651-2227.2010.01687.x] [PMID: 20096030]

Milatovic 1987

Milatovic D, Braveny I. Development of resistance during antibiotic therapy. *European Journal of Clinical Microbiology* 1987;**6**(3):234-44. [PMID: 3305004]

Mingeot-Leclercq 1999

Mingeot-Leclercq MP, Tulkens PM. Aminoglycosides: nephrotoxicity. *Antimicrobial Agents and Chemotherapy* 1999;**43**(5):1003-12. [PMID: 10223907]

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology* 2009;**62**(10):1006–12. [PMID: 19631508]

Morris 2016

Morris JM, Roberts CL, Bowen JR, Patterson JA, Bond DM, Algert CS, et al, PPROMT Collaboration. Immediate delivery compared with expectant management after preterm pre-labour rupture of the membranes close to term (PPROMT trial): a randomised controlled trial. *Lancet* 2016;**387**(10017):444-52. [DOI: 10.1016/S0140-6736(15)00724-2] [PMID: 26564381]

Mrvos 2013

Mrvos R, Pummer TL, Krenzelok EP. Amoxicillin renal toxicity: how often does it occur? *Pediatric Emergency Care* 2013;**29**(5):641-3. [DOI: 10.1097/PEC.0b013e31828e9e78] [PMID: 23603656]

Muller-Pebody 2011

Muller-Pebody B, Johnson AP, Heath PT, Gilbert RE, Henderson KL, Sharland M, iCAP Group. Empirical treatment of neonatal sepsis: are the current guidelines adequate? *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2011;**96**(1):F4-8. [DOI: 10.1136/adc.2009.178483] [PMID: 20584804]

Murray 1994

Murray BE. Can antibiotic resistance be controlled? *New England Journal of Medicine* 1994;**330**(17):1229-30. [DOI: 10.1056/NEJM199404283301710] [PMID: 8139634]

Musiime 2015

Musiime GM, Seale AC, Moxon SG, Lawn JE. Risk of gentamicin toxicity in neonates treated for possible severe bacterial infection in low- and middle-income countries: systematic review. *Tropical Medicine & International Health* 2015;**20**(12):1593-606. [DOI: 10.1111/tmi.12608] [PMID: 26426298]

Papile 1978

Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *Journal of Pediatrics* 1978;**92**(4):529-34. [PMID: 305471]

Paul 2010

Paul M, Shani V, Muchtar E, Kariv G, Robenshtok E, Leibovici L. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. *Antimicrobial Agents and Chemotherapy* 2010;**54**(11):4851-63. [DOI: 10.1128/AAC.00627-10] [PMID: 20733044]

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rogosch 2012

Rogosch T, Kerzel S, Hoss K, Hoersch G, Zemlin C, Heckmann M, et al. IgA response in preterm neonates shows little evidence of antigen-driven selection. *Journal of Immunology (Baltimore, Md. : 1950)* 2012;**189**(11):5449-56. [DOI: 10.4049/jimmunol.1103347] [PMID: 23105134]

Rubin 2002

Rubin LG, Sánchez PJ, Siegel J, Levine G, Saiman L, Jarvis WR, Pediatric Prevention Network. Evaluation and treatment of neonates with suspected late onset sepsis: a survey of neonatologists' practices. *Pediatrics* 2002;**110**(4):e42. [MEDLINE: 22247548] [PMID: 12359815]

Rybak 2009

Rybak MJ, Lomaestro BM, Rotschafer JC, Moellering RC Jr, Craig WA, Billeter M, et al. Therapeutic monitoring of vancomycin in adults summary of consensus recommendations from the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Pharmacotherapy* 2009;**29**(11):1275-9. [PMID: 19873687]

Sáez-Llorens 2000

Sáez-Llorens X, Castrejón de Wong MM, Castaño E, De Suman O, De Morös D, De Atencio I. Impact of an antibiotic restriction policy on hospital expenditures and bacterial susceptibilities: a lesson from a pediatric institution in a developing country. *Pediatric Infectious Disease Journal* 2000;**19**(3):200-6. [PMID: 10749459]

Schlapbach 2011

Schlapbach LJ, Aebischer M, Adams M, Natalucci G, Bonhoeffer J, Latzin P, et al, Swiss Neonatal Network and Follow-Up Group. Impact of sepsis on neurodevelopmental outcome in a Swiss National Cohort of extremely premature infants. *Pediatrics* 2011;**128**(2):e348-57. [DOI: 10.1542/peds.2010-3338] [PMID: 21768312]

Schuchat 2000

Schuchat A, Zywicki SS, Dinsmoor MJ, Mercer B, Romaguera J, O'Sullivan MJ, et al. Risk factors and opportunities for prevention of early-onset neonatal sepsis: a multicenter case-control study. *Pediatrics* 2000;**105**(1 Pt 1):21-6. [PMID: 10617699]

Schultze 1971

Schultze RG, Winters RE, Kauffman H. Possible nephrotoxicity of gentamicin. *Journal of Infectious Diseases* 1971;**124**(Suppl):S145-7. [PMID: 5126240]

Schünemann 2013

Schünemann H, Brożek J, Guyatt G, Oxman A, editor(s). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from gdt.guidelinedevelopment.org/app/handbook/handbook.html.

Seale 2015

Seale AC, Obiero CW, Berkley JA. Rational development of guidelines for management of neonatal sepsis in developing countries. *Current Opinion in Infectious Diseases* 2015;**28**(3):225-30. [DOI: 10.1097/QCO.0000000000000163] [PMID: 25887615]

Selimoglu 2007

Selimoglu E. Aminoglycoside-induced ototoxicity. *Current Pharmaceutical Design* 2007;**13**(1):119-26. [PMID: 17266591]

Shah 2014

Shah BA, Padbury JF. Neonatal sepsis: an old problem with new insights. *Virulence* 2014;**5**(1):170-8. [DOI: 10.4161/viru.26906] [PMID: 24185532]

Shane 2013

Shane AL, Stoll BJ. Recent developments and current issues in the epidemiology, diagnosis, and management of bacterial and fungal neonatal sepsis. *American Journal of Perinatology* 2013;**30**(2):131-41. [DOI: 10.1055/s-0032-1333413] [PMID: 23297182]

Shane 2014

Shane AL, Stoll BJ. Neonatal sepsis: progress towards improved outcomes. *Journal of Infection* 2014;**68 Suppl 1**:S24-32. [DOI: 10.1016/j.jinf.2013.09.011] [PMID: 24140138]

Sharma 2007

Sharma R, Tepas JJ 3rd, Hudak ML, Mollitt DL, Wludyka PS, Teng RJ, et al. Neonatal gut barrier and multiple organ failure: role of endotoxin and proinflammatory cytokines in sepsis and necrotizing enterocolitis. *Journal of Pediatric Surgery* 2007;**42**(3):454-61. [DOI: 10.1016/j.jpedsurg.2006.10.038] [PMID: 17336180]

Singer 2016

Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016;**315**(8):801-10. [DOI: 10.1001/jama.2016.0287] [PMID: 26903338]

Sorrell 1985

Sorrell TC, Collignon PJ. A prospective study of adverse reactions associated with vancomycin therapy. *Journal of Antimicrobial Chemotherapy* 1985;**16**(2):235-41. [PMID: 3934126]

Spiliopoulou 2012

Spiliopoulou A, Dimitriou G, Jelastopulu E, Giannakopoulos I, Anastassiou ED, Christofidou M. Neonatal intensive care unit candidemia: epidemiology, risk factors, outcome, and critical review of published case series. *Mycopathologia* 2012;**173**(4):219-28. [PMID: 22076411]

Stockmann 2014

Stockmann C, Spigarelli MG, Campbell SC, Constance JE, Courter JD, Thorell EA, et al. Considerations in the pharmacologic treatment and prevention of neonatal sepsis. *Paediatric Drugs* 2014;**16**(1):67-81. [PMID: 24218112]

Stoll 1996

Stoll BJ, Gordon T, Korones SB, Shankaran S, Tyson JE, Bauer CR, et al. Late-onset sepsis in very low birth weight neonates: a report from the National Institute of Child Health and Human Development Neonatal Research Network. *Journal of Pediatrics* 1996;**129**(1):63-71. [PMID: 8757564]

Stoll 2002

Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics* 2002;**110**(2 Pt 1):285-91. [MEDLINE: 22155756] [PMID: 12165580]

Stoll 2003

Stoll BJ, Hansen N. Infections in VLBW infants: studies from the NICHD Neonatal Research Network. *Seminars in Perinatology* 2003;**27**(4):293-301. [PMID: 14510320]

Stoll 2005

Stoll BJ, Hansen NI, Higgins RD, Fanaroff AA, Duara S, Goldberg R, et al, National Institute of Child Health and HumanDevelopment. Very low birth weight preterm infants with early onset neonatal sepsis: the predominance of gram-negative infections continues in the National Institute of Child Health and Human Development Neonatal Research Network, 2002-2003. *Pediatric Infectious Disease Journal* 2005;**24**(7):635-9. [PMID: 15999007]

Stoll 2010

Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, et al, Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics* 2010;**126**(3):443-56. [DOI: 10.1542/peds.2009-2959] [PMID: 20732945]

Stoll 2011

Stoll BJ, Hansen NI, Sánchez PJ, Faix RG, Poindexter BB, Van Meurs KP, et al, Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. *Pediatrics* 2011;**127**(5):817-26. [DOI: 10.1542/peds.2010-2217] [PMID: 21518717]

Tallur 2000

Tallur SS, Kasturi AV, Nadgir SD, Krishna BV. Clinico-bacteriological study of neonatal septicemia in Hubli. *Indian Journal of Pediatrics* 2000;**67**(3):169-74. [PMID: 10838717]

Tamma 2012

Tamma PD, Cosgrove SE, Maragakis LL. Combination therapy for treatment of infections with gram-negative bacteria. *Clinical Microbiology Reviews* 2012;**25**(3):450-70. [DOI: 10.1128/CMR.05041-11] [PMID: 22763634]

Tessin 1990

Tessin I, Trollfors B, Thiringer K. Incidence and etiology of neonatal septicaemia and meningitis in western Sweden 1975-1986. *Acta Paediatrica Scandinavica* 1990;**79**(11):1023-30. [PMID: 2267918]

Thorlund 2009

Thorlund K, Devereaux PJ, Wetterslev J, Guyatt G, Ioannidis JP, Thabane L, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? *International Journal of Epidemiology* 2009;**38**(1):276-86. [DOI: 10.1093/ije/dyn179] [PMID: 18824467]

Thorlund 2011

Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for Trial Sequential Analysis (TSA), 2011. ctu.dk/tsa/files/tsa_manual.pdf (accessed 7 January 2015).

Tripathi 2012

Tripathi N, Cotten CM, Smith PB. Antibiotic use and misuse in the neonatal intensive care unit. *Clinics in Perinatology* 2012;**39**(1):61-8. [DOI: 10.1016/j.clp.2011.12.003] [PMID: 22341537]

Tröger 2014

Tröger B, Göpel W, Faust K, Müller T, Jorch G, Felderhoff-Müser U, et al, German Neonatal Network. Risk for late-onset blood-culture proven sepsis in very-low-birth weight infants born small for gestational age: a large multicenter study from the German Neonatal Network. *Pediatric Infectious Disease Journal* 2014;**33**(3):238-43. [DOI: 10.1097/INF.0000000000000031] [PMID: 24030351]

TSA 2011

Copenhagen TU. TSA - Trial Sequential Analysis, 2011. ctu.dk/tsa/ (accessed 7 January 2015).

Tsai 2014

Tsai MH, Hsu JF, Chu SM, Lien R, Huang HR, Chiang MC, et al. Incidence, clinical characteristics and risk factors for adverse outcome in neonates with late-onset sepsis. *Pediatric Infectious Disease Journal* 2014;**33**(1):e7-13. [DOI: 10.1097/INF.0b013e3182a72ee0] [PMID: 23899966]

Vergnano 2005

Vergnano S, Sharland M, Kazembe P, Mwansambo C, Heath PT. Neonatal sepsis: an international perspective. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2005;**90**(3):F220-4. [DOI: 10.1136/adc.2002.022863] [PMID: 15846011]

Vergnano 2011

Vergnano S, Menson E, Kennea N, Embleton N, Russell AB, Watts T, et al. Neonatal infections in England: the NeonIN surveillance network. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2011;**96**(1):F9-14. [DOI: 10.1136/adc.2009.178798] [PMID: 20876594]

Vesikari 1985

Vesikari T, Janas M, Grönroos P, Tuppurainen N, Renlund M, Kero P, et al. Neonatal septicaemia. *Archives of Disease in Childhood* 1985;**60**(6):542-6. [PMID: 3925895]

Volpe 2008

Volpe JJ. Intracranial hemorrhage: germinal matrix intraventricular hemorrhage. In: Neurology of the Newborn. 5 edition. Philadelphia (PA): Saunders Elsevier, 2008:517-88.

Waksman 1947

Waksman SA. What is an antibiotic or an antibiotic substance? *Mycologia* 1947;**39**(5):565-9. [PMID: 20264541]

Walker 2011

Walker JC, Smolders MA, Gemen EF, Antonius TA, Leuvenink J, de Vries E. Development of lymphocyte subpopulations in preterm infants. *Scandinavian Journal of Immunology* 2011;**73**(1):53-8. [DOI: 10.1111/j.1365-3083.2010.02473.x] [PMID: 21129003]

Wargo 2014

Wargo KA, Edwards JD. Aminoglycoside-induced nephrotoxicity. *Journal of Pharmacy Practice* 2014;**27**(6):573-7. [DOI: 10.1177/0897190014546836] [PMID: 25199523]

Weston 2011

Weston EJ, Pondo T, Lewis MM, Martell-Cleary P, Morin C, Jewell B, et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005-2008. *Pediatric Infectious Disease Journal* 2011;**30**(11):937-41. [DOI: 10.1097/INF.0b013e318223bad2] [PMID: 21654548]

Wetterslev 2008

Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *Journal of Clinical Epidemiology* 2008;**61**(1):64-75. [DOI: 10.1016/j.jclinepi.2007.03.013] [PMID: 18083463]

Wetterslev 2009

Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Medical Research Methodology* 2009;**9**:86. [DOI: 10.1186/1471-2288-9-86] [PMID: 20042080]

Wetterslev 2017

Wetterslev J, Jakobsen JC, Gluud C. Trial Sequential Analysis in systematic reviews with meta-analysis. *BMC Medical Research Methodology* 2017;**17**(1):39. [DOI: 10.1186/s12874-017-0315-7] [PMID: 28264661]

WHO 1999

World Health Organization Young Infants Study Group. Bacterial etiology of serious infections in young infants in developing countries: results of a multicenter study. *Pediatric Infectious Disease Journal* 1999;**18**(10 Suppl):S17-22. [PMID: 10530569]

WHO 2013

World Health Organization. Pocket book of hospital care for children: Second edition. Guidelines for the management of common childhood illnesses. apps.who.int/iris/bitstream/10665/81170/1/9789241548373_eng.pdf?ua=1 (accessed 16 February 2018).

World Bank 2017

World Bank. World Bank country and lending groups. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups accessed 9 December 2019.

Wynn 2014

Wynn JL, Wong HR, Shanley TP, Bizzarro MJ, Saiman L, Polin RA. Time for a neonatal-specific consensus definition for sepsis. *Pediatric Critical Care Medicine* 2014;**15**(6):523-8. [DOI: 10.1097/PCC.0000000000000157] [PMID: 24751791]

Wynn 2016

Wynn JL. Defining neonatal sepsis. *Current Opinion in Pediatrics* 2016;**28**(2):135-40. [DOI: 10.1097/MOP.0000000000000315] [PMID: 26766602]

Ygberg 2012

Ygberg S, Nilsson A. The developing immune system - from foetus to toddler. *Acta Paediatrica* 2012;**101**(2):120-7. [DOI: 10.1111/j.1651-2227.2011.02494.x] [PMID: 22003882]

Zaidi 2005

Zaidi AKM, Huskins WC, Thaver D, Bhutta ZA, Abbas Z, Goldmann DA. Hospital-acquired neonatal infections in developing countries. *Lancet* 2005;**365**(9465):1175-88. [DOI: 10.1016/S0140-6736(05)71881-X] [PMID: 15794973]

Zaidi 2009

Zaidi AKM, Thaver D, Ali SA, Khan TA. Pathogens associated with sepsis in newborns and young infants in developing countries.

Pediatric Infectious Disease Journal 2009;**28**(1 Suppl):S10-8. [DOI: 10.1097/INF.0b013e3181958769] [PMID: 19106757]

Zea-Vera 2015

Zea-Vera A, Ochoa TJ. Challenges in the diagnosis and management of neonatal sepsis. *Journal of Tropical Pediatrics* 2015;**61**(1):1-13. [DOI: 10.1093/tropej/fmu079] [PMID: 25604489]

Zemlin 2007

Zemlin M, Hoersch G, Zemlin C, Pohl-Schickinger A, Hummel M, Berek C, et al. The postnatal maturation of the immunoglobulin heavy chain IgG repertoire in human preterm neonates is slower than in term neonates. *Journal of Immunology* 2007;**178**(2):1180-8. [PMID: 17202383]

ADDITIONAL TABLES

Table 1. Commonly used clinical and laboratory criteria of sepsis

Clinical criteria	Laboratory criteria
• Abdominal distension • Skin and subcutaneous lesions such as petechial rash, abscesses, sclerema • Cardiovascular signs (tachycardia/bradycardia, hypotension, poor perfusion) • Respiratory signs (apnoea, cyanosis, tachypnoea, need for ventilator, increased oxygen requirement) • Abnormal temperature (fever or hypothermia) • Central nervous system signs (lethargy, hypotonia, seizure) • Feeding problems	• White blood cell (WBC) • Immature to total WBC ratio • Platelet count • C-reactive protein • Metabolic acidosis • Neutropenia • Abnormal fibrinogen • Hyperglycaemia and hypoglycaemia

Abbreviations: WBC: white blood cell.

APPENDICES

Appendix 1. Search strategies

MEDLINE via Ovid

1	exp Neonatal Sepsis/
2	(sepsis adj3 (neonat$ or neo nat$)).ti,ab
3	(sepsis adj3 (newborn$ or new born$ or newly born$)).ti,ab.
4	(septic$ adj3 (neonat$ or neo nat$)).ti,ab.
5	(septic$ adj3 (newborn$ or new born$ or newly born$)).ti,ab.
6	(infect$ adj3 (neonat$ or neo nat$)).ti,ab.
7	(infect$ adj3 (newborn$ or new born$ or newly born$)).ti,ab.
8	(bacter$ adj3 (neonat$ or neo nat$)).ti,ab.
9	(bacter$ adj3 (newborn$ or new born$ or newly born$)).ti,ab.
10	(gram adj2 negative).ti,ab.
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp Anti-Bacterial Agents/

(Continued)

13	antibiot$.ti,ab.
14	antimicrob$.ti,ab.
15	lactam$.ti,ab.
16	aminoglycoside$.ti,ab.
17	glycoprotein.ti,ab.
18	(penicillin or oxacillin or cloxacillin or dicloxacillin or nafcillin or methicillin).ti,ab.
19	(ampicillin or amoxicillin or piperacillin or ticarcillin or carbenicillin or mezlocillin).ti,ab.
20	(cephalosporins or cefazolin or cephalexin or cefuroxime or cefotetan or cefoxitin or ceftriaxone or cefotaxime or ceftazidime or cefepime or cefazolin or ceftobiprole or cefoperazone).ti,ab.
21	(carbapenems or imipenem or meropenem or doripenem or ertapenem).ti,ab.
22	(monobactams or aztreonam).ti,ab.
23	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24	11 and 23
25	exp Infant/
26	(infan$ or newborn or neonat$ or premature or very low birth weight or low birth weight or VLBW or LBW).mp.
27	25 or 26
28	24 and 27
29	randomised controlled trial.pt.
30	controlled clinical trial.pt.
31	randomized.ab.
32	placebo.ab.
33	clinical trials as topic.sh.
34	randomly.ab.
35	trial.ti.
36	29 or 30 or 31 or 32 or 33 or 34 or 35
37	exp animals/ not humans.sh.
38	36 not 37
39	28 and 38

PubMed

(((pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb])))) AND ((((((neonatal sepsis[MeSH Terms]) OR ((sepsis[Title/Abstract] OR septic*[Title/Abstract] OR Infect*[Title/Abstract] OR bacter*[Title/Abstract] OR gram negative[Title/Abstract])))) AND ((AntiBacterial Agents[MeSH Terms]) OR ((antibiot*[Title/Abstract] OR antimicrob*[Title/Abstract] OR lactam*[Title/Abstract] OR aminoglycoside* [Title/Abstract] OR glycoprotein[Title/Abstract] OR penicillin[Title/Abstract] OR oxacillin[Title/Abstract] OR cloxacillin[Title/Abstract] OR dicloxacillin[Title/Abstract] OR nafcillin[Title/Abstract] OR methicillin[Title/Abstract] OR ampicillin[Title/Abstract] OR amoxicillin[Title/Abstract] OR piperacillin[Title/Abstract] OR ticarcillin[Title/Abstract] OR carbenicillin[Title/Abstract] OR mezlocillin[Title/Abstract] OR cephalosporins[Title/Abstract] OR cefazolin[Title/Abstract] OR cephalexin[Title/Abstract] OR cefuroxime[Title/Abstract] OR cefotetan[Title/Abstract] OR cefoxitin[Title/Abstract] OR ceftriaxone[Title/Abstract] OR cefotaxime[Title/Abstract] OR ceftazidime[Title/Abstract] OR cefepime[Title/Abstract] OR cefazolin[Title/Abstract] OR ceftobiprole[Title/Abstract] OR cefoperazone[Title/Abstract] OR carbapenems[Title/Abstract] OR imipenem[Title/Abstract] OR meropenem[Title/Abstract] OR doripenem[Title/Abstract] OR ertapenem[Title/Abstract] OR monobactams[Title/Abstract] OR aztreonam[Title/Abstract])))))) AND (((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomised [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])))))

Embase via Ovid

1	exp Neonatal Sepsis/
2	(sepsis adj3 (neonat* or neo nat*)).ti,ab.
3	(sepsis adj3 (newborn* or new born* or newly born*)).ti,ab.
4	(septic* adj3 (neonat* or neo nat*)).ti,ab.
5	(septic* adj3 (newborn* or new born* or newly born*)).ti,ab.
6	(infect* adj3 (neonat* or neo nat*)).ti,ab.
7	(infect* adj3 (newborn* or new born* or newly born*)).ti,ab.
8	(bacter* adj3 (neonat* or neo nat*)).ti,ab.
9	(bacter* adj3 (newborn* or new born* or newly born*)).ti,ab.
10	(gram adj2 negative).ti,ab.
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp Anti-Bacterial Agents/
13	antibiot*.ti,ab.
14	antimicrob*.ti,ab.
15	lactam*.ti,ab.
16	aminoglycoside*.ti,ab.
17	glycoprotein.ti,ab.
18	(penicillin or oxacillin or cloxacillin or dicloxacillin or nafcillin or methicillin).ti,ab.
19	(ampicillin or amoxicillin or piperacillin or ticarcillin or carbenicillin or mezlocillin).ti,ab.

(Continued)

20	(cephalosporins or cefazolin or cephalexin or cefuroxime or cefotetan or cefoxitin or ceftriaxone or cefotaxime or ceftazidime or cefepime or cefazolin or ceftobiprole or cefoperazone).ti,ab.
21	(carbapenems or imipenem or meropenem or doripenem or ertapenem).ti,ab.
22	(monobactams or aztreonam).ti,ab.
23	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24	11 and 23
25	(infan* or newborn or neonat* or premature or very low birth weight or low birth weight or VLBW or LBW).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
26	exp infant/
27	25 or 26
28	(human not animal).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
29	(randomised controlled trial or controlled clinical trial or randomised or placebo or clinical trials as topic or randomly or trial or clinical trial).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
30	27 and 28 and 29
31	24 and 30

CINAHL

S1	(antibiot* OR antimicrob* OR lactam* OR aminoglycoside* OR glycoprotein OR penicillin OR oxacillin OR cloxacillin OR dicloxacillin OR nafcillin OR methicillin OR ampicillin OR amoxicillin OR piperacillin OR ticarcillin OR carbenicillin OR mezlocillin OR cephalosporins OR cefazolin OR cephalexin OR cefuroxime OR cefotetan OR cefoxitin OR ceftriaxone OR cefotaxime OR ceftazidime OR cefepime OR cefazolin OR ceftobiprole OR cefoperazone OR carbapenems OR imipenem OR meropenem OR doripenem OR ertapenem OR monobactams OR aztreonam)
S2	(infan* OR newborn OR neonat* OR premature OR low birth weight OR VLBW OR LBW) AND (randomised controlled trial OR controlled clinical trial OR randomised OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)
S3	(sepsis N3 (neonat* or neo nat*))
S4	(sepsis N3 (newborn* or new born* or newly born*))
S5	(septic* N3 (neonat* or neo nat*))
S6	(septic* N3 (newborn* or new born* or newly born*))
S7	(infect* N3 (neonat* or neo nat*))

(Continued)

S8	(infect* N3 (newborn* or new born* or newly born*))
S9	(bacter* N3 (neonat* or neo nat*))
S10	(bacter* N3 (newborn* or new born* or newly born*)
S11	(gram N2 negative)
S12	S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
S13	S1 AND S2 AND S12

CRS Web

1	(infan* or newborn or neonat* or premature or preterm or very low birth weight or low birth weight or VLBW or LBW) AND CENTRAL:TARGET
2	MESH DESCRIPTOR Neonatal Sepsis EXPLODE ALL AND CENTRAL:TARGET
3	(sepsis NEAR3 (neonat* or neo nat*)) AND CENTRAL:TARGET
4	(sepsis NEAR3 (newborn* or new born* or newly born*)) AND CENTRAL:TARGET
5	(septic* NEAR3 (neonat* or neo nat*)) AND CENTRAL:TARGET
6	(septic* NEAR3 (newborn* or new born* or newly born*)) AND CENTRAL:TARGET
7	(infect* NEAR3 (neonat* or neo nat*)) AND CENTRAL:TARGET
8	(infect* NEAR3 (newborn* or new born* or newly born*)) AND CENTRAL:TARGET
9	(bacter* NEAR3 (neonat* or neo nat*)) AND CENTRAL:TARGET
10	(bacter* NEAR3 (newborn* or new born* or newly born*)) AND CENTRAL:TARGET
11	(gram NEAR2 negative) AND CENTRAL:TARGET
12	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13	MESH DESCRIPTOR Anti-Bacterial Agents EXPLODE ALL AND CENTRAL:TARGET
14	(antibiot* OR antimicrob* OR lactam* OR aminoglycoside* OR glycoprotein OR penicillin OR oxacillin OR cloxacillin OR dicloxacillin OR nafcillin OR methicillin OR ampicillin OR amoxicillin OR piperacillin OR ticarcillin OR carbenicillin OR mezlocillin OR cephalosporins OR cefazolin OR cephalexin OR cefuroxime OR cefotetan OR cefoxitin OR ceftriaxone OR cefotaxime OR ceftazidime OR cefepime OR cefazolin OR ceftobiprole OR cefoperazone OR carbapenems OR imipenem OR meropenem OR doripenem OR ertapenem OR monobactams OR aztreonam) AND CENTRAL:TARGET
15	#13 OR #14
16	#1 AND #12 AND #15

Appendix 2. Risk of bias tool

We will use the standard methods of Cochrane and Cochrane Neonatal to assess the methodological quality of the included trials. For each included trial, we will seek information regarding the method of randomisation, blinding, and reporting of all outcomes of all infants enrolled in the trial. We will assess each criterion as being at either low, high, or unclear risk of bias. Two review authors will separately assess each study. We will resolve any disagreement by discussion. We will add this information to the 'Characteristics of included studies' table. We will evaluate the following issues and enter the findings into the 'Risk of bias' table.

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we will categorise the method used to generate the allocation sequence as:

- low risk (any truly random process e.g. random number table; computer random number generator);
- high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we will categorise the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we will categorise the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding will be assessed separately for different outcomes or class of outcomes. We will categorise the methods as:

- low risk, high risk, or unclear risk for participants; and
- low risk, high risk, or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we will categorise the methods used to blind outcome assessment. Blinding will be assessed separately for different outcomes or class of outcomes. We will categorise the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we will describe the completeness of data including attrition and exclusions from the analysis. We will note whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported or supplied by the trial authors, we will re-include missing data in the analyses. We will categorise the methods as:

- low risk (< 20% missing data);
- high risk (≥ 20% missing data); or
- unclear risk.

6. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we will describe how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we will compare prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we will contact study authors to gain access to the study protocol. We will assess the methods as:

- low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); or
- unclear risk.

7. Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we will describe any important concerns we had about other possible sources of bias (e.g. whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We will assess whether each study was free of other problems that could put it at risk of bias as:

- low risk;
- high risk;
- unclear risk.

If needed, we plan to explore the impact of the level of bias through undertaking sensitivity analyses.

WHAT'S NEW

Date	Event	Description
9 December 2019	Amended	Authors have revised the protocol prior to conducting the updated review. This protocol and subsequent review will replace the review of "Antibiotic regimens for suspected late onset sepsis in newborn infants" (Gordon 2005).

HISTORY

Protocol first published: Issue 12, 2020

Date	Event	Description
7 July 2016	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Steven Kwasi Korang (SKK) and Sanam Safi (SS) conceived, designed, and drafted the protocol. Ulrik Lausten-Thomsen (ULT), Munish Gupta (MG), Gorm Greisen (AG), and Janus C Jakobsen (JCJ) provided general advice and revised the protocol.

All protocol authors agreed on the final protocol version.

DECLARATIONS OF INTEREST

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