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Prophylactic antibiotics to reduce morbidity and mortality in neonates with umbilical artery catheters (Review)

Inglis GDT, Jardine LA, Davies MW

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[Intervention Review]

Prophylactic antibiotics to reduce morbidity and mortality in neonates with umbilical artery catheters

Garry DT Inglis[1], Luke A Jardine[2], Mark W Davies[1]

[1]Grantley Stable Neonatal Unit, Royal Brisbane and Women's Hospital, Department of Paediatrics & Child Health, The University of Queensland, Brisbane, Australia. [2]Department of Neonatology, Mater Mother's Hospital, Mater Medical Research Institute, The University of Queensland, South Brisbane, Australia

Contact: Garry DT Inglis, Grantley Stable Neonatal Unit, Royal Brisbane and Women's Hospital, Department of Paediatrics & Child Health, The University of Queensland, Butterfield Street, Herston, Brisbane, Queensland, 4029, Australia. garry_inglis@health.qld.gov.au.

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ABSTRACT

Background

Umbilical artery catheters are often used in unwell neonates. Infection related to the use of these catheters may cause significant morbidity and mortality. The use of prophylactic antibiotics has been advocated for all newborns with umbilical artery catheters in order to reduce the risk of colonisation and acquired infection. Countering this is the possibility that harm, such as the emergence of antibiotic resistant organisms, may outweigh benefit.

Objectives

The primary objective was to assess whether prophylactic antibiotics reduce mortality and morbidity in neonates with umbilical artery catheters. Two different policies regarding the prophylactic use of antibiotics in neonates with umbilical artery catheters were reviewed: 1) a policy of prophylactic antibiotics for the duration of catheterization (or other fixed duration of antibiotic treatment) versus placebo or no treatment among neonates with umbilical artery catheters; 2) a policy of continuing versus discontinuing prophylactic antibiotics among neonates with umbilical artery catheters who had been started on antibiotics at the time of catheterization but whose initial cultures to rule out sepsis are negative.

Search methods

MEDLINE (January 1950 to May 2007), CINAHL (1982 to May 2007), the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2007), the Cochrane Neonatal Group Specialised Register and reference lists of articles were searched. This search was updated in November 2010.

Selection criteria

Randomised and some non-randomised (i.e., quasi-randomised trials) controlled trials of adequate quality in which newborn infants with umbilical artery catheters are randomised to receive prophylactic antibiotics versus placebo or no treatment.

Data collection and analysis

Two reviewer authors independently assessed trial quality.

Main results

Two quasi-randomised trials have been included. However, given their poor quality, we have not pooled the results. There were no statistically significant differences in important outcomes in either study.

Authors' conclusions

There is insufficient evidence from randomised trials to support or refute the use of prophylactic antibiotics when umbilical artery catheters are inserted in newborn infants, and no evidence to support or refute continuing antibiotics once initial cultures rule out infection in newborn infants with umbilical artery catheters.

PLAIN LANGUAGE SUMMARY

Prophylactic antibiotics to reduce morbidity and mortality in neonates with umbilical artery catheters

There is not enough evidence from randomised trials to either support or refute the routine use of preventive antibiotics in newborn babies with umbilical artery catheters. Sick newborn babies occasionally require the insertion of an umbilical artery catheter [a special drip that goes into the artery in the umbilicus (belly button)]. This allows fluid and medicines to be given and blood tests to be taken. Some people believe that antibiotics should be given to all babies with umbilical artery catheters in order to reduce the chance of infection occurring. However, antibiotics can have unwanted effects. The reviewers found inadequate evidence from randomised trials to either support or refute the routine use of antibiotics for all babies with umbilical artery catheters.

BACKGROUND

Description of the condition

Umbilical artery catheters are commonly used in the management of newborn infants with respiratory distress and other potentially life-threatening disorders. Infection related to the use of these catheters may cause significant morbidity and mortality. Morbidity may include increased duration of respiratory illness (including chronic lung disease and need for respiratory support), increased length of hospital stay and impaired neurodevelopmental outcome. The extent of the problem of infection related to umbilical artery catheters is largely unknown due to the widespread use of antibiotics in the population of infants who have umbilical artery catheters.

By virtue of their underlying illness, patients requiring umbilical artery catheters may, have impaired defence mechanisms - both local and systemic. Prematurity is recognised as a risk factor for late onset sepsis (Dear 1999). Preterm neonates are at high risk of infection because of impaired immunity and umbilical artery catheters may further increase this risk because they are foreign bodies.

Description of the intervention

It is common practice in neonatal units to start antibiotics in infants with respiratory distress and suspected infection. Many of these infants will have an umbilical artery catheter inserted. It is not clear whether antibiotics should be discontinued if no infection is proven. It has been common practice in some units that if the infant has an umbilical artery catheter then antibiotics be continued in order to reduce the rate of colonisation of the umbilicus and likewise reduce the risk of acquired infection (van Vliet 1973).

How the intervention might work

Prophylactic antibiotics may prevent colonisation of the umbilicus or umbilical artery catheters (Adam 1982) but may not decrease infection and infection-related morbidity and mortality. In an observational study, Krauss et al (Krauss 1970) found no reduction in catheter contamination with antibiotic use. In another observational study, Landers et al (Landers 1991) found that a longer duration of antibiotic therapy was significantly associated with increased risk for umbilical arterial catheter-related sepsis, but found no link between duration of catheter placement and sepsis. A policy of prophylactic antibiotic use should take into account the possibility of encouraging increased resistance among pathogenic bacteria (Dear 1999), which may vary between different antibiotics.

Why it is important to do this review

This review updates the existing review of 'Prophylactic antibiotics to reduce morbidity and mortality in neonates with umbilical artery catheters' which was originally published in the Cochrane Library Issue 3, 2004 (Inglis 2005). In the 2007 update, no new studies were identified. However, two studies (Bard 1973; Cowett 1977) that were previously excluded because they were quasi-randomised were included.

OBJECTIVES

The primary objective was to assess whether prophylactic antibiotics reduce mortality and morbidity in neonates with umbilical artery catheters.

Two different policies regarding the prophylactic use of antibiotics in neonates with umbilical artery catheters were reviewed:

1) a policy of prophylactic antibiotics for the duration of catheterization (or other fixed duration of antibiotic treatment) versus placebo or no treatment among neonates with umbilical artery catheters. This addresses the question of whether or not neonates with umbilical artery catheters, who do not have clinical or laboratory evidence of infection at that time, should be routinely started on antibiotics at the time of catheterization.

2) a policy of continuing versus discontinuing prophylactic antibiotics among neonates with umbilical artery catheters who had been started on antibiotics at the time of catheterization, but whose initial cultures to rule out sepsis are negative. This addresses the question of whether or not antibiotics should routinely be stopped at the time rule out sepsis cultures are reported as negative.

Subgroup analyses were planned to determine whether results differ by:
1. gestational age (e.g., preterm versus term, < 28 weeks gestational age (GA) or not, < 32 weeks GA or not);
2. type of antibiotic (e.g., penicillins, macrolides, aminoglycosides, cephalosporins, or combinations).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials and quasi-randomised controlled trials, of adequate quality, in which either individual newborn infants or clusters of infants are randomised to receive prophylactic antibiotics versus placebo or no treatment. Trials where the cluster unit is time were not included (as this would not allow the assessment of antibiotic resistance).

Types of participants

Neonates with umbilical artery catheters.

Types of interventions

Any antibiotic, or combination of antibiotics, versus placebo or no treatment. This could include:
1) a policy of all neonates with umbilical artery catheters having antibiotics compared with placebo or no treatment; or
2) a policy of neonates with umbilical artery catheters continuing on antibiotics, once initial cultures to rule out sepsis are negative, compared with ceasing antibiotics and continuing on placebo and/or no treatment

Types of outcome measures

Primary outcomes

- Mortality (neonatal, at hospital discharge, or at one year, eighteen months, two years, or five years).

- Proven septicaemia (blood culture positive) or either suspected septicaemia or clinical septicaemia (however defined in individual studies).

Secondary outcomes

- Chronic lung disease (oxygen requirement at 36 weeks postmenstrual age).
- Duration of ventilation (hours or days).
- Duration of respiratory support (hours or days).
- Duration of oxygen therapy (hours or days).
- Duration of hospital stay (days).
- Number of resistant organisms (i.e., species) identified per time period per infant or per cluster unit.
- Neurodevelopmental outcome (cerebral palsy, sensorineural hearing loss, visual impairment and/or developmental delay - at one year, eighteen months, two years, or five years).

Search methods for identification of studies

The standard search strategy for the Cochrane Neonatal Review Group was used. Searches were done of MEDLINE from 1950 to May 2007, CINAHL from 1982 to May 2007, and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2007 using the following strategy:

MeSH search terms ("Umbilicus" AND "Catheterization") OR the textwords ("umb$" AND ("cathet$" OR "cannul$")) OR "UAC" OR "umbilical artery catheter"
AND
MeSH search term "Infant, newborn" OR the textwords "neonat$" OR "infant"'
AND
MeSH search term "Anti-Bacterial Agents" OR the textword "antibiotic"
AND
MeSH search terms "Chemoprevention" OR "Antibiotic Prophylaxis" OR the textword "prophyl$".

Previous reviews (including cross references) were also searched. Searches were not restricted to publications in the English language or published data.

In November 2010, we updated the search as follows: MEDLINE (search via PubMed), CINAHL, EMBASE and CENTRAL (*The Cochrane Library*) were searched from 2007 to 2010. Search terms: umbilical artery catheter AND ((infant, newborn[MeSH] OR newborn OR neon* OR neonate OR neonatal OR premature OR low birth weight OR vlbw OR LBW) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans[mh]))

In November 2010 clinicaltrials.gov and controlled-trials.com were also searched for relevant studies.

Data collection and analysis

Standard methods of the Cochrane Collaboration and the Cochrane Neonatal Review Group were used.

Selection of studies

All randomised and quasi-randomised controlled trials fulfilling the selection criteria described in the previous section were included.Two of the review authors worked independently to search for and assess trials for inclusion and methodological quality. The review authors resolved any disagreement by discussion.

Data extraction and management

The review authors extracted data independently. Differences were resolved by discussion.

Assessment of risk of bias in included studies

Two review authors independently searched for and assessed trials for inclusion and methodological quality. Studies were assessed for methodological quality using the following key criteria: allocation concealment (blinding of randomisation), blinding of intervention, completeness of follow up and blinding of outcome measurement. For each criterion, assessment was yes, no, can't tell. Two review authors separately assessed each study. Any disagreement was resolved by discussion. This information was added to the Characteristics of Included Studies table.

In addition, for the update in 2010, the following issues were evaluated and entered 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 categorized the method used to generate the allocation sequence as:

- adequate (any truly random process e.g. random number table; computer random number generator);

- inadequate (any non random process e.g. odd or even date of birth; hospital or clinic record number);

- unclear.

(2) Allocation concealment (checking for possible selection bias). Was allocation adequately concealed? For each included study, we categorized the method used to conceal the allocation sequence as:

- adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);

- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);

- unclear.

(3) Blinding (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study? At study entry? At the time of outcome assessment? For each included study, we categorized the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or classes of outcomes. We categorized the methods as:

- adequate, inadequate or unclear for participants;

- adequate, inadequate or unclear for personnel;

- adequate, inadequate or unclear for outcome assessors.

(4) 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 described the completeness of data including attrition and exclusions from the analysis. We noted 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 was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorized the methods as:

- adequate (< 20% missing data);

- inadequate (≥ 20% missing data):

- unclear.

(5) Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting? For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);

- inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest 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);

- unclear.

(6) 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 described any important concerns we had about other possible sources of bias (for example, 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 assessed whether each study was free of other problems that could put it at risk of bias as:

- yes; no; or unclear.

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

Measures of treatment effect

We planned to report categorical outcomes as the relative risk (RR), risk difference (RD and number needed to treat (NNT). Continuous data was to be reported as a weighted mean difference (WMD).

Assessment of heterogeneity

We planned to estimate the treatment effects of individual trials and examine heterogeneity between trials by inspecting the forest plots and quantifying the impact of heterogeneity using the I-squared statistic. If we detected statistical heterogeneity, we planned to explore the possible causes (for example, differences in study quality, participants, intervention regimens, or outcome assessments) using *post hoc* sub group analyses. We planned to use a fixed effects model for meta-analysis.

Data synthesis

For continuous variables, weighted mean differences (WMD) and 95% confidence intervals were to be reported. For categorical outcomes, the relative risks (RR) and 95% confidence intervals were to be reported. For significant findings, the risk difference (RD) and number needed to treat (NNT) were also to be reported. Each treatment effect was to be tested for heterogeneity to help determine suitability for pooling of results in a meta-analysis. The fixed effects model was used for meta-analysis.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were planned to determine whether results differ by:
1. gestational age (e.g., preterm versus term, < 28 weeks gestational age (GA) or not, < 32 weeks GA or not);
2. type of antibiotic (e.g., penicillins, macrolides, aminoglycosides, cephalosporins, or combinations).

RESULTS

Description of studies

Using the above search strategy, four potentially eligible reports were found. Wesstrom and Finnstrom (Wesstrom 1979) reported on a case series of infants with umbilical artery catheters and Pulido et al (Pulido 1985) studied umbilical venous catheters. Both of these studies were excluded from this review. Two quasi-randomised controlled trials (Bard 1973; Cowett 1977) were included in this review (see Table, Characteristics of Included Studies). Both included studies were conducted in the 1970s and studied infants with umbilical arterial catheters inserted as management for respiratory distress. In both, treated infants were given kanamycin and either penicillin or ampicillin. The protocols of both studies included blood cultures (taken from a peripheral site and from the catheter) at catheter removal and culture of the catheter tip. Mortality and rates of positive cultures were reported.

Risk of bias in included studies

Neither of the included studies was randomised - both were quasi-randomised. Bard et al (Bard 1973) used alternate group assignment; Cowett et al (Cowett 1977) allocated infants according to date of birth (i.e., odd versus even days). Allocation concealment was not used in either study. There appeared to be no blinding of intervention or outcome assessment. Both reported at least one important outcome for > 80% of enrolled infants. The overall methodological quality of both studies was poor.

Effects of interventions

See also Table, Characteristics of included studies. Two poor-quality studies (Bard 1973; Cowett 1977), with a total of 212 infants,

met the criteria for inclusion in this review. Given their significant methodological shortcomings, the results have not been presented as a pooled analysis.

Bard et al (Bard 1973) alternately placed 75 infants with umbilical artery catheters inserted for respiratory distress syndrome into a treatment group (n = 37) receiving ampicillin and kanamycin, and a control group (n = 38) receiving no antibiotics. Blood cultures were obtained from the umbilical artery catheters at insertion and daily thereafter, and from a peripheral site just prior to catheter removal (if removal was elective) or by cardiac puncture in the event of death of the infant. The umbilical artery catheter tip was sent for culture after removal. Of the "peripheral" blood cultures taken at or after catheter removal, three were positive (all in the control group). This was not a statistically significant result. One (Corynebacterium) was considered a contaminant, one (*Pseudomonas aeruginosa*) was from a post-mortem cardiac puncture specimen and the other (*Staphylococcus aureus*) was actually collected two days after catheter removal, for clinical reasons. The infant with Pseudomonas septicaemia had the same organism identified in a catheter blood culture collected prior to death, but not in the catheter tip culture. Peripheral and catheter blood cultures taken about 24 hours prior to death were negative. The infant with Staphylococcus septicaemia had no positive blood cultures during the period of catheterization. There were significantly fewer positive catheter blood cultures in the treated group (8 of 37 vs. 19 of 38) but most organisms were considered contaminants. "Pathogens" were identified in the catheter blood cultures of three infants, all of whom were in the control group. This was not a statistically significant result. There was a statistically significant decrease in positive catheter tip cultures (all organisms) in the treated group, but not in "pathogenic" organisms in tip cultures. Two infants (one from each group) had localised umbilical infection. There was no statistically significant difference in overall mortality during the study period. All deaths were ascribed to hyaline membrane disease. No mention is made of length of follow up.

Cowett et al (Cowett 1977) allocated 137 infants requiring umbilical artery catheterization to different policies of antibiotic use according to even or odd birth dates: if born on even dates (n = 58; Group one), routine penicillin and kanamycin; if born on odd birth dates (n = 79), selective antibiotics, i.e. no routine antibiotics unless their physician requested antibiotics because of suspected infection. Those who received no antibiotics (n = 54) were called Group two, and those who received antibiotics at physician request (n = 25) were called Group three. The mean birth weight was significantly lower in Group three than in Group two. Blood cultures were drawn from a peripheral vein and the catheter at the time of catheter insertion, and again at removal. At removal, none of the 36 peripheral blood cultures or 37 catheter blood cultures were positive in Group one. Likewise, there were no positive peripheral (n = 18) or catheter (n = 16) blood cultures at catheter removal in Group three; whereas three of 35 peripheral blood cultures and 14 of 34 catheter blood cultures were positive in Group two. Of these, one of the positive peripheral blood cultures and 10 of the positive catheter blood cultures were considered contaminants. Two infants had matching positive peripheral and catheter blood cultures, but negative or non-matching catheter tip cultures and were therefore deemed not to reflect catheter sepsis. One of these infants was clinically unwell, whereas the other was well. The two remaining infants with positive catheter blood cultures did not have matching peripheral blood cultures, and were clinically well. The difference in rates of positive catheter blood cultures between Groups one and two was found to be statistically significant. No other differences in positive blood culture (either peripheral or catheter) rates between individual groups were reported to be statistically significant. Death occurred in nine of 58 infants in Group one (15.5%) , six of 54 in Group two (11.1%) and two of 25 in Group three (8.0%). This was not a statistically significant difference. No mention is made of length of follow-up.

DISCUSSION

This review has attempted to determine whether prophylactic antibiotics are warranted in either of two circumstances:
1. should infants with umbilical artery catheters be commenced on routine prophylactic antibiotics at the time of catheter insertion?
2. should infants with umbilical artery catheters, who are commenced on antibiotics pending investigation results, be continued on antibiotics once initial infection is ruled out?

A major limiting factor in trying to determine the place of prophylactic antibiotics in infants with umbilical artery catheters is that catheter placement is quite often undertaken, for ease of blood sampling, in the context of clinical signs (e.g., respiratory distress) that may reflect infection. Newborn infants with such illnesses are usually started on antibiotics because those problems may indicate infection at the same time that they may lead to the decision to insert an umbilical artery catheter. Because the majority of newborns in whom umbilical artery catheters are placed would be treated in this way, the first scenario described above would be relevant to relatively few newborns. While the second scenario described above would be the more common one encountered, no such studies were found for inclusion in this review.

Both of the included studies were conducted in the 1970s. Much has changed in neonatal practice since that time including the recognition that organisms previously thought to be non-pathogenic (particularly coagulase-negative staphylococci) can in fact cause septicaemia in newborn infants. This will influence interpretation of positive blood culture results and, potentially, management of infants at risk of infection, including umbilical catheter care. Also, the overall mortality rates (28% in the study by Bard 1973; 12% in the study by Cowett 1977) are much higher than would be expected in similar populations today.

Bard et al (Bard 1973) suggest that all of the deaths in their study population were "related to hyaline membrane disease" despite isolating *Psuedomonas aeruginosa* in blood culture specimens from one of the infants that died. This infant was 920 g at birth and died at three days of age. Approximately 24 hours before death, the infant had blood cultures drawn peripherally and from the catheter - both were negative. Another catheter-drawn blood culture before death, as well as a post-mortem cardiac puncture blood culture, grew pseudomonas, although the catheter tip did not. This infant was in the control group but it is noted that the prophylaxis used in the study may not have been effective in preventing this infection. Another control infant in the same study had *Staphyloccos aureus* septicaemia and survived. In this instance the positive blood culture was collected two days after catheter removal. This casts doubt on the inclusion of this as an episode of septicaemia in assessing the outcomes.

Cowett et al (Cowett 1977) placed all infants with umbilical artery catheters, born on even dates, on antibiotics. By their own admission, such antibiotic use in some of these infants may not have been prophylactic as no attempt was made to distinguish between those who received antibiotics for the presence of the catheter and those who would have been given antibiotics for other clinical indications. Of those born on odd dates, there were important differences between those not given antibiotics and those given antibiotics for clinical reasons. The latter group had lower mean birth weight and gestational age. Caution must therefore be used when comparing the outcomes between the three groups of study infants. Also, the only important outcome for which there was adequate (i.e., > 80%) follow-up was mortality. This was not achieved for any of the microbiology outcomes.

The overall methodological quality of the included studies was poor. Both trials were non-randomised (quasi-randomised). They had no apparent allocation concealment, did not blind intervention or outcome assessment, and reported few important outcomes. This weakens the conclusions drawn in the individual studies and makes drawing definitive conclusions from a meta-analysis impossible. The authors of both of these studies conclude that there is no evidence to support the use of prophylactic antibiotics in infants with umbilical artery catheters. However, the results should be treated with caution, as they are prone to significant bias. Specifically, with alternate group assignment, if two equally eligible infants present at the same time with different risks for infection a clinician might (consciously or not) enter them into the study in the order that would allow the infant that they believed should receive antibiotics to get antibiotics. If a large number of infants were enrolled in this way serious imbalance in the treatment groups with respect to factors affecting the outcome would result (Hennekens 1987). Similarly, with alternate day assignment, clinicians may or may not enrol infants into the study if they believe that the infant should be or not be in the group allocated for that day.

In order to justify the use of prophylactic antibiotics (rather than treatment of infection as it arises) in infants with umbilical artery catheters there should be evidence that the benefit outweighs the harm. This should include an adequate assessment not only of short-term outcomes such as infection rate and duration of hospital admission, but also of long-term outcomes such as mortality, long-term respiratory morbidity and neurodevelopmental outcome.

Theoretical concerns about the potential harm of prophylactic antibiotic use include antibiotic resistance, superinfection and drug toxicity. Altered antibiotic resistance patterns may be of consequence not only to the individual in whom prophylactic antibiotics are used but also to other patients within the hospital setting and to the wider community.

AUTHORS' CONCLUSIONS

Implications for practice

- There is insufficient evidence from randomised trials to support or refute the use of prophylactic antibiotics when inserting umbilical artery catheters in newborn infants.
- There is no evidence from randomised trials to support or refute continuing antibiotics once initial cultures rule out infection in newborn infants with umbilical artery catheters.

Implications for research

- If prophylactic antibiotics are to be considered when inserting umbilical artery catheters then good quality randomised controlled trials are required to show that their benefits outweigh the harms. Unfortunately, most newborn infants who have umbilical artery catheters inserted are likely to receive antibiotics to cover possible infection and a randomised controlled trial may not be practicable or ethical.
- A more pressing question is whether infants who initially receive antibiotics for presumed infection should be continued on antibiotics once initial cultures rule out infection. Good quality randomised controlled trials are required to address this issue.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bard 1973

Methods	Quasi-randomised controlled trial using alternate group assignment. Placebo was not used. Allocation concealment: no Blinding of intervention: no Completeness of follow up: yes Blinding of outcome measurement: no
Participants	Single unit study in Montreal, Canada. Subjects recruited from 1 April 1971 to 31 March 1972. Infants with respiratory distress syndrome and having umbilical arterial catheters inserted were considered eligible for inclusion. Catheters were inserted under sterile conditions, within 24 hours of birth. There were 37 infants in the treatment group and 38 in the control group. Birth weight range was 720 - 3500 grams and gestational age at birth ranged from 25 to 40 weeks.
Interventions	Ampicillin 25 mg/kg intravenously every 6 hours plus kanamycin 7.5 mg/kg intramuscularly every 12 hours versus no treatment. At catheter insertion and daily thereafter 1.5-3 mL of blood for culture

Bard 1973 *(Continued)*

	was collected from the catheter. Just prior to catheter removal, blood for culture was collected from a cleansed peripheral site on an upper limb (or in the event of death, via a cardiac puncture) and from the catheter. The distal 1-2 cm of catheter was collected for culture in 33 treated infants and 35 control infants. The following organisms were considered contaminants: coagulase-negative Staphylococci, Micrococcus species, alpha-haemolytic Streptococcus, and diphtheroids.
Outcomes	Mortality: 11 of 37 treated infants and 10 of 38 control infants died. All deaths were judged to be due to hyaline membrane disease. Catheter-drawn blood cultures just prior to catheter removal: positive in 8 of 37 treated infants (all considered contaminants) and 19 of 38 control infants (16 considered contaminants). Peripherally-drawn blood cultures: positive in no treated infants and 3 of 38 control infants (one considered a contaminant). Of the two considered pathogens, one was Pseudomonas aeruginosa and the other was Staphylococcus aureus. The Pseudomonas was isolated from a post-mortem cardiac puncture specimen, and also from a catheter-drawn specimen collected prior to the infant's death. It was not isolated from the catheter tip, and blood cultures (both catheter-drawn and peripherally-drawn) 24 hours prior to death were negative. The Staphylococcus aureus was isolated in a blood culture specimen drawn 2 days after catheter removal. Catheter-tip colonisation: organisms were isolated from the tips of catheters of 8 of 33 treated infants (6 were considered contaminants) and 19 of 35 control infants (13 were considered contaminants). Two infants (one from each group) had localised umbilical infection.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	Quasi-randomised controlled trial using alternate group assignment. Placebo was not used.
Allocation concealment?	High risk	Allocation concealment: no
Blinding? All outcomes	High risk	Blinding of intervention: no Blinding of outcome measurement: no
Incomplete outcome data addressed? All outcomes	Unclear risk	Completeness of follow up: yes

Cowett 1977

Methods	Quasi-randomised controlled trial using group assignment based on date of birth (odd dates vs even dates). Placebo was not used. Allocation concealment: no Blinding of intervention: no Completeness of follow up: yes Blinding of outcome measurement: no
Participants	Single unit study in Rhode Island, United States. Subjects recruited from 15 January 1974 to 15 April 1975. Infants requiring insertion of an umbilical arterial catheter in the first 24 hours of life as part of their management were considered eligible for inclusion. All infants were catheterised for respiratory distress. Catheters were inserted using an aseptic technique. One hundred and thirty-seven infants were enrolled. Eighty-three were given antibiotics (58 as prophylaxis; 25 at treating physician request) and 54 were not.
Interventions	Infants born on even days were allocated to Group 1: penicillin 25,000 U/kg intravenously every 12 hours and kanamycin 5 mg/kg intramuscularly every 8 hours. Infants born on odd days were allocated to Group 2 or Group 3, at treating physician discretion. Those who were given antibiotics at the request

Cowett 1977 *(Continued)*

	of the treating physician were in Group 3. The remainder (Group 2) were given no antibiotics. Enrolled infants had blood for culture collected from a peripheral vein just prior to catheter insertion and at the time of catheter removal, and from the catheter at insertion and just prior to removal. The volume of blood collected for culture was 0.5 to 1 mL. At catheter removal, the tip was sent for culture.
Outcomes	Mean (standard deviation) birth weight was 1835 (644) grams in Group 1, 2036 (696) grams in Group 2, and 1686 (819) grams in Group 3. Mean (standard deviation) gestational age was 33 (3) weeks in Group 1, 33 (7) weeks in Group 2, and 32 (4) weeks in Group 3. Mean (standard deviation) duration of catheterisation was 76 (53) hours in Group 1, 76 (48) hours in Group 2, and 94 (63) hours in Group 3. Mortality was 9 of 58 in Group 1 (15.5%), 6 of 54 in Group 2 (11.1%) and 2 of 25 in Group 3 (8.0%). No death was attributed to infection. Peripherally-collected blood cultures, taken at catheter removal, were obtained from 89 infants (65%); catheter blood cultures, taken just prior to catheter removal, were obtained from 87 infants (64%); catheter tip cultures were obtained from 98 catheters (72%). Rates of positive peripheral blood cultures were 0 of 36 in Group 1, 3 of 35 in Group 2 (two were considered pathogens), and 0 of 18 in Group 3. Catheter blood cultures were positive in 0 of 37 Group 1 infants, 14 of 34 Group 2 infants (four were considered pathogens), and 0 of 16 Group 3 infants. Catheter tip cultures were positive in 8 of 37 in Group 1 (none were considered pathogens), 12 of 36 in Group 2 (one was considered a pathogen), and 1 of 25 in Group 3 (not considered a pathogen). The two pathogens isolated in peripheral blood cultures were Proteus mirabilis and Escherichia coli. In both cases the same organism was isolated from catheter blood cultures but not from the catheter tip. Of the two infants concerned, one (positive for Proteus mirabilis) was clinically unwell, whereas the other was not. Two other infants, also in Group 2, had Escherichia coli isolated in catheter blood cultures but peripheral blood culture was either negative or not taken - both infants were clinically well.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	Quasi-randomised controlled trial using group assignment based on date of birth (odd dates vs even dates). Placebo was not used.
Allocation concealment?	High risk	Allocation concealment: no
Blinding? All outcomes	High risk	Blinding of intervention: no Blinding of outcome measurement: no
Incomplete outcome data addressed? All outcomes	Low risk	Completeness of follow up: yes

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Pulido 1985	Wrong population - only studied umbilical venous catheters.
Wesstrom 1979	Not a controlled trial - reported on a case series of infants with umbilical artery catheters.

WHAT'S NEW

Date	Event	Description
7 December 2010	New search has been performed	This review updates the existing review "Prophylactic antibiotics to reduce morbidity and mortality in neonates with umbilical artery catheters" published in the Cochrane Database of Systematic Reviews (Inglis 2007). Updated search in 2010 found no new trials. No changes to conclusions.

HISTORY

Protocol first published: Issue 2, 2004
Review first published: Issue 3, 2004

Date	Event	Description
10 September 2008	Amended	Converted to new review format.
12 June 2007	New search has been performed	This review updates the existing review of "Prophylactic antibiotics to reduce morbidity and mortality in neonates with umbilical artery catheters", published in The Cochrane Library, Issue 3, 2004 (Inglis 2004). No new trials were identified as a result of our most recent search. Two quasi-randomised trials previously excluded have now been included.
12 June 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Original review:
GDI & MWD searched for studies and assessed studies for inclusion
GDI wrote the review
MWD co-wrote the review

Review Update:
GDI and LAJ searched for studies and assessed studies for inclusion
GDI updated the text
LAJ & MWD reviewed the text

The December 2010 update was conducted centrally by the Cochrane Neonatal Review Group staff (Yolanda Montagne, Diane Haughton, and Roger Soll). This update was reviewed and approved by GDI.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Grantley Stable Neonatal Unit, Royal Women's Hospital, Brisbane, Australia.
- Dept of Paediatrics and Child Health, University of Queensland, Brisbane, Australia.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibiotic Prophylaxis [mortality]; *Umbilical Arteries; Catheterization [*adverse effects] [mortality]

MeSH check words

Humans; Infant, Newborn