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

Inglis GDT, Davies MW

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2006, Issue 1

http://www.thecochranelibrary.com
# Table of Contents

ABSTRACT ............................................................... 1
PLAIN LANGUAGE SUMMARY ........................................... 1
BACKGROUND .......................................................... 2
OBJECTIVES ........................................................... 2
CRITERIA FOR CONSIDERATION OF STUDIES FOR THIS REVIEW ............. 2
SEARCH METHODS FOR IDENTIFICATION OF STUDIES ......................... 3
METHODS OF THE REVIEW ............................................ 3
DESCRIPTION OF STUDIES ............................................ 3
METHODOLOGICAL QUALITY ............................................ 3
RESULTS ................................................................. 3
DISCUSSION ............................................................ 3
AUTHORS' CONCLUSIONS ............................................... 4
POTENTIAL CONFLICT OF INTEREST .................................. 5
SOURCES OF SUPPORT ................................................. 5
REFERENCES ............................................................ 5
TABLES .................................................................... 6
   Characteristics of excluded studies ..................................... 6
GRAPHS AND OTHER TABLES ........................................... 6
INDEX TERMS ............................................................ 6
COVER SHEET ............................................................ 6
Prophylactic antibiotics to reduce morbidity and mortality in neonates with umbilical artery catheters (Review)

Inglis GDT, Davies MW

This record should be cited as:

This version first published online: 19 July 2004 in Issue 3, 2004.
Date of most recent substantive amendment: 26 March 2004

A B S T R A C T

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 may outweigh benefit.

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

Search strategy
We searched MEDLINE (January 1966 to February 2004), CINAHL (1982 to February 2004), the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2004), the Cochrane Neonatal Group Specialised Register and reference lists of articles.

Selection criteria
Randomised 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 reviewers independently assessed trial quality.

Main results
No study met the criteria for inclusion in this review.

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

P L A I N L A N G U A G E S U M M A R Y

There is no 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 no evidence from randomized trials to either support or refute the routine use of antibiotics for all babies with umbilical artery catheters.

**BACKGROUND**

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.

Patients requiring umbilical artery catheters may, by virtue of their underlying illness, 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.

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).

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. Landers et al (Landers 1991) found in an observational study 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.

**OBJECTIVES**

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

In separate comparisons, we planned to review two different policies regarding the prophylactic use of antibiotics in neonates with umbilical artery catheters:

1) among neonates with umbilical artery catheters, a policy of prophylactic antibiotics for the duration of catheterisation (or other fixed duration of antibiotic treatment) versus placebo or no treatment. 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 catheterisation.

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

Data permitting, subgroup analyses were planned to determine whether results differ by:

gestational age (e.g., preterm versus term, <28 weeks gestational age (GA) or not, <32 weeks GA or not);
type of antibiotic (e.g., penicillins, macrolides, aminoglycosides, cephalosporins, or combinations).

**CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW**

**Types of studies**

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 intervention
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:
- Mortality (neonatal, at hospital discharge, or at 1 year, 18 months, 2 years, or 5 years)
- Proven septicaemia (blood culture positive) or either suspected septicaemia or clinical septicaemia (however defined in individual studies)

Secondary:
- 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 1 year, 18 months, 2 years, or 5 years)

SEARCH METHODS FOR IDENTIFICATION OF STUDIES
See: Neonatal Group methods used in reviews.

The standard search strategy for the Cochrane Neonatal Review Group was used. Searches were done of MEDLINE from 1966 to February 2004, CINAHL from 1982 to February 2004, and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2004) using the following strategy:

MeSH search terms (“Umbilicus” AND “Catheterization”) OR the textwords (“umbS” AND (“cathet$” OR “cannul$”)) OR “UAC” OR “umbilical artery catheter” AND
MeSH search term “Infant, newborn” OR the textwords “neonat$” OR “infant” AND
MeSH search term “Antibiotics” OR the textword “antibiotic” AND
MeSH search terms “Chemoprevention” OR “Antibiotic Prophylaxis” OR the textword “prophyl$”.
We also searched previous reviews (including cross references). Searches were not restricted to publications in the English language or published data.

METHODS OF THE REVIEW
Criteria and methods used to assess the methodological quality of the trials: standard methods of the Cochrane Collaboration and its Neonatal Review Group were used.
The two reviewers 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.

DESCRIPTION OF STUDIES
Using the above search strategy we found four potentially eligible reports. 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. Two controlled trials (Bard 1973; Cowett 1977) were also excluded from analysis (see Table: Characteristics of Excluded Studies) because they were non-randomised (quasi-randomised) controlled trials - these trials are described below, in Discussion. We found no studies that met the criteria for inclusion in this review.

METODOLOGICAL QUALITY
No randomised controlled trials were found for inclusion in this review.

RESULTS
No randomised controlled trials were found for inclusion in this review.

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) which may reflect infection. Newborns infants with such illnesses are usually commenced 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. The second scenario described above would be the more common one encountered.

Two non-randomised (quasi-randomised) controlled trials studying the use of prophylactic antibiotics for newborn infants with umbilical artery catheters were found but excluded from analysis. Bard et al (Bard 1973) alternately placed 75 infants with umbilical artery catheters inserted for respiratory distress syndrome into a treatment group receiving ampicillin and kanamycin, and a control group receiving no antibiotics. Blood cultures were obtained from the umbilical artery catheters at insertion and just prior to removal, and from a peripheral vein and the catheter at the time of catheter insertion (3 of 75 cultures were positive, all in the control group). The umbilical artery catheter tip was sent for culture after removal. They showed a statistically significant decrease in positive cultures drawn from the umbilical artery catheters in those on antibiotics (predominantly Staph. epidermidis). There were no statistically significant differences in positive (for pathogenic bacteria) blood cultures from umbilical artery catheters or in overall mortality during the study period. No mention is made of length of follow-up.

Cowett et al (Cowett 1977) allocated 137 infants requiring umbilical artery catheterisation to different policies of antibiotic use according to even or odd birth dates: if born on even dates (n=54), routine penicillin and kanamycin; if born on odd birth dates (n=79), selective antibiotics, ie no routine antibiotics unless their physician requested antibiotics because of suspected infection. (Twenty-five of the 79 babies in the latter group did receive antibiotics because of suspected infection.) 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 which were obtained were positive in the routine antibiotics group; whereas 3 of 53 peripheral blood cultures were positive in the selective antibiotics group. Of these positive blood cultures, one was considered a contaminant, while the other two did not match umbilical artery catheter tip culture results and were therefore deemed not to reflect cannula sepsis. Death occurred in 9 of 58 infants in the routine antibiotics group (15.5%), and 8 of 79 in the selective antibiotics group (10.1%): this was not a statistically significant difference. No mention is made of length of follow-up.

The authors of both of these non-randomised (quasi-randomised) 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 2 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 no 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.

**Potential Conflict of Interest**

None

**Sources of Support**

**External sources of support**
- No sources of support supplied

**Internal sources of support**
- Grantley Stable Neonatal Unit, Royal Women’s Hospital, Brisbane AUSTRALIA
- Dept of Paediatrics and Child Health, University of Queensland, Brisbane AUSTRALIA

**References**

References to studies excluded from this review

**Bard 1973**

**Cowett 1977**

**Pulido 1985**

**Weststrom 1979**

**Additional references**

**Adam 1982**

**Dear 1999**

**Hennekens 1987**

**Krauss 1970**

**Landers 1991**

**van Vliet 1973**

*Indicates the major publication for the study*
**TABLES**

Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bard 1973</td>
<td>Not a randomised controlled trial - group allocation was determined by alternate placement into one of two groups.</td>
</tr>
<tr>
<td>Cowett 1977</td>
<td>Not a randomised controlled trial - group allocation was determined by date of birth (odd or even days of the month). Comparison of routine prophylactic antibiotics with selective antibiotics, rather than with placebo or no treatment.</td>
</tr>
<tr>
<td>Pulido 1985</td>
<td>Not a randomised controlled trial - only studied umbilical venous catheters.</td>
</tr>
<tr>
<td>Weststrom 1979</td>
<td>Not a controlled trial - reported on a case series of infants with umbilical artery catheters.</td>
</tr>
</tbody>
</table>

**GRAPHS AND OTHER TABLES**

This review has no analyses.

**INDEX TERMS**

Medical Subject Headings (MeSH)

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

MeSH check words

Humans

**COVER SHEET**

Title

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

Authors

Inglis GDT, Davies MW

Contribution of author(s)

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

Issue protocol first published

2004/2

Review first published

2004/3

Date of most recent amendment

25 May 2004

Date of most recent SUBSTANTIVE amendment

26 March 2004

What's New

Information not supplied by author

Date new studies sought but none found

Information not supplied by author

Date new studies found but not yet included/excluded

Information not supplied by author

Date new studies found and included/excluded

Information not supplied by author