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

Inglis GDT, Davies MW

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ABSTRACT

Background
Umbilical venous 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 newborns with umbilical venous catheters in order to reduce the risk of colonisation and acquired infection. Countering this is the possibility that harm may outweigh benefit. Prophylactic antibiotics may be effective in preventing catheter-related blood stream infection, but may have the undesirable effect of promoting the emergence of resistant strains of micro-organisms. A policy of prophylactic antibiotic use should take into account this possibility, and has been used as a basis for arguing against its implementation.

Objectives
The primary objective was to assess whether prophylactic antibiotics, in neonates with umbilical venous 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 venous catheters: 1) Among neonates with umbilical venous 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 venous 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 April 2005), CINAHL (1982 to April 2005), the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2005).

Selection criteria
Randomised controlled trials or quasi-randomised trials in which newborn infants with umbilical venous catheters are randomised to receive prophylactic antibiotics versus placebo or no treatment.

Data collection and analysis
Two reviewers independently assessed trial quality.

Main results
One study, of poor quality, met the criteria for inclusion in this review. Twenty-nine term infants, who had umbilical venous catheters inserted specifically for transfusion procedures for hyperbilirubinaemia or polycythaemia, allocated non-randomly (quasi-randomised - alternate allocation) to treatment (n = 15) or control (n = 14) groups. Those in the treatment group received penicillin and gentamicin for three days. 5/15 infants given antibiotics and 5/14 control infants having positive blood cultures three days after catheter insertion. All positive blood cultures were considered contaminated, due to lack of corroborating clinical and haematological evidence of infection. Therefore, no infants were identified with evidence of sepsicaemia.
Authors’ conclusions
There is insufficient evidence from randomised trials to support or refute the use of prophylactic antibiotics when umbilical venous catheters are inserted in newborn infants. There is no evidence to support or refute continuing antibiotics once initial cultures rule out infection in newborn infants with umbilical venous catheters.

Plain Language Summary
There is insufficient evidence from randomised trials to either support or refute the routine use of preventive antibiotics in newborn babies with umbilical vein catheters.

Sick newborn babies occasionally require the insertion of an umbilical vein catheter (a special tube) that goes into the vein in the umbilicus (belly button). This allows fluid and medicines to be given. Some people believe that antibiotics should be given to all babies with umbilical vein catheters in order to reduce the chance of infection occurring. However, antibiotics can have unwanted effects. The reviewers found insufficient evidence to either support or refute the routine use of antibiotics for all babies with umbilical vein catheters.

Background
Umbilical venous catheters are commonly used in the management of newborn infants who are preterm or have other potentially life-threatening illness. The use of central venous catheters is recognised as a risk factor for nosocomial infection (Adams-Chapman 2002; Chien 2002; Nagata 2002; Stoll 2002). It is unclear whether umbilical venous catheters are an independent risk factor for late-onset sepsis. Stoll (Stoll 2002) analysed numerous factors in a multivariate model and did not find umbilical venous catheters to be an independent significant risk. However, Chien (Chien 2002), on behalf of the Canadian Neonatal Network, concluded that umbilical venous catheters are a significant risk factor. Hyperalimentation with parenteral nutrition is an indication for the use of umbilical venous catheters, and is also a risk factor for nosocomial infection (Adams-Chapman 2002). Nosocomial infection may cause significant morbidity and mortality (Stoll 2002). Morbidity may include increased duration of respiratory illness, including chronic lung disease, and need for respiratory support (Stoll 2002; Ogawa 1999); increased length of hospital stay (Stoll 2002; Isaacs 2003); and impaired neurodevelopmental outcome (Stoll 2004). The extent of the problem of infection related to umbilical venous catheters is largely unknown due to the widespread use of antibiotics in the population of infants who have umbilical venous catheters.

Patients requiring umbilical venous 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 venous 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, or in those delivered following pre-term labour. Many of these infants will have an umbilical venous catheter inserted. It is not clear whether antibiotics should be discontinued if no infection is proven. It has been common practice in some neonatal units that if the infant has an umbilical venous catheter then antibiotics be continued in order to reduce the rate of colonisation of the umbilicus and likewise reduce the risk of acquired infection. Prophylactic antibiotics may be effective in preventing catheter-related blood stream infection (CRBSI), but may have the undesirable effect of promoting the emergence of resistant strains of micro-organisms (Freij 1999). A policy of prophylactic antibiotic use should take into account this possibility, and has been used as a basis for arguing against its implementation (Isaacs 2000; Isaacs 2003). Promotion of the emergence of resistant strains of organisms may vary between different antibiotics.

A recent Cochrane systematic review on the use of prophylactic antibiotics for neonates with umbilical artery catheters showed that there is no evidence from randomised trials to support or refute the use of prophylactic antibiotics when using umbilical artery catheters in newborn infants (Inglis 2004).

Objectives
The primary objective was to assess whether prophylactic antibiotics, in neonates with umbilical venous catheters, reduce mortality and morbidity. Morbidity included proven sepsis, clinical septicaemia, and suspected sepsis. Septicaemia was as defined in individual studies.

In separate comparisons, we planned to review two different policies regarding the prophylactic use of antibiotics in neonates with umbilical venous catheters:
1) Among neonates with umbilical venous 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 venous 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 venous 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);
- type of antibiotic (e.g. penicillins, macrolides, aminoglycosides, cephalosporins, or combinations).

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

We planned to include the following:
- randomised controlled trials in which either individual newborn infants or clusters of infants are randomised to receive prophylactic antibiotics versus placebo or no treatment;
- some types of non-randomised trials, i.e. quasi-randomised trials, in which either individual newborn infants or clusters of infants are allocated to receive prophylactic antibiotics versus placebo or no treatment.

Trials where the unit of allocation is the catheter (in which case different catheters within the same patient might be managed differently) were not included.

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 venous catheters. The standard definition of “neonate” was used i.e. up to 28 days of age.

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 venous catheters having antibiotics compared with placebo or no treatment; or 2) a policy of neonates with umbilical venous 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 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)

Septicaemia might occur more than once in the same patient and may be reported in several different ways. We planned to tabulate this as a categorical outcome (e.g. proportion of patients having one or more episodes)

Secondary:
- Chronic lung disease (oxygen requirement at 36 weeks post-menstrual 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 will be considered as separate components - at one year, eighteen months, two years, or five years)

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Neonatal Group methods used in reviews.

See: Cochrane Neonatal Review Group search strategy

The standard search strategy for the Cochrane Neonatal Review Group was used. We searched MEDLINE from 1966 to April 2005, CINAHL from 1982 to April 2005, and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2005) using the following strategy:

MeSH search terms (“Umbilicus” AND “Catheterization”) OR the textwords (“umb$” AND (“cathet$” OR “cannul$”)) OR “UVC” OR “umbilical vein catheter” OR “umbilical venous catheter” AND MeSH search term “Infant, newborn” OR the textwords “neonat$” OR “infant” AND MeSH search term “Antibiotics” OR the textword “antibiotic”
Methods 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 authors worked independently to search for and assess trials for inclusion and methodological quality. Studies were assessed using the following key criteria: allocation concealment (blinding of randomisation), blinding of intervention, completeness of follow up and blinding of outcome measurement assigning a rating of 'Yes', 'No' or 'Can't tell' for each. The authors extracted data independently. Differences were resolved by discussion. We contacted the second author of the study by Bhatt et al (Bhatt 1970) for additional information or data.

For pooled results: 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 to be used for meta-analysis. If there were sufficient included studies, heterogeneity was to be assessed using the I squared test. If statistical heterogeneity was found the authors planned to look for an explanation. If studies with heterogenous results were thought to be comparable, a random effects model was to be used to combine the data.

Data permitting, a sensitivity analysis was planned to see if results differed by quality of included studies i.e. adequacy of randomisation - quasi randomised versus randomised.

Methodological quality

There were significant methodological flaws in the only study identified (Pulido 1985) for inclusion in this review:

- the study was non-randomised (quasi-randomised, using alternate group allocation);
- the intervention appears to have been non-blinded, but the report is not explicit on this matter;
- it is unknown whether outcome assessment was blind;
- completeness of follow up is unclear;
- allocation concealment was not blinded.

Results

One study (Pulido 1985) was included in this review.

For primary outcomes:

- Proven septicaemia - 5/15 intervention and 5/14 control infants had positive blood cultures three days after UVC insertion. All positive blood cultures were considered contaminated, due to lack of corroborating clinical and haematological evidence of infection. Therefore, no infants were identified with evidence of septicaemia.
- Mortality - not assessed/reported

For secondary outcomes:
Chronic lung disease (oxygen requirement at 36 weeks post-menstrual age) - not assessed/reported

Duration of ventilation (hours or days) - not assessed/reported

Duration of respiratory support (hours or days) - not assessed/reported

Duration of oxygen therapy (hours or days) - not assessed/reported

Duration of hospital stay (days) - not assessed/reported

Number of resistant organisms - not assessed/reported

Neurodevelopmental outcome - not assessed/reported

**DISCUSSION**

This review has attempted to determine whether prophylactic antibiotics are warranted in either of two circumstances:

1. Should infants with umbilical venous catheters be commenced on routine prophylactic antibiotics at the time of catheter insertion?

2. Should infants with umbilical venous 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 venous catheters is that catheter placement is quite often undertaken, for ease of fluid and drug administration, in the context of clinical circumstances (e.g. respiratory distress, preterm delivery) which may reflect infection. Newborn infants in such circumstances are usually commenced on antibiotics because their clinical circumstances may indicate infection at the same time that they may lead to the decision to insert an umbilical venous catheter. Because the majority of newborns in whom umbilical venous 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.

One non-randomised (quasi-randomised) trial was found for inclusion in this review. Pulido et al (Pulido 1985) performed a small study on the use of antibiotic prophylaxis in infants undergoing transfusion procedures for hyperbilirubinaemia or polycythaemia via an umbilical venous catheter. The authors conclude that no infant in the study developed sepsicaemia following the procedure, and that the use of antibiotic prophylaxis is not indicated. A study of this size would have been underpowered to detect anything other than a very large effect. The study covered a period of only two months. It has been noted previously that nosocomial infections can occur in clusters (Adams-Chapman 2002). If the study under consideration here coincided with a nadir in nosocomial infection, then the resultant underestimation of sepsicaemia rates in one or both arms of the study could have affected the conclusions.

It is difficult to generalise the findings of this study for a number of reasons. Since its publication there have been significant changes in the practice of neonatal medicine, including use and maintenance of vascular access devices. The use of umbilical venous catheters in this study was for specific indications and the background risk of infection in the study subjects may have been low. The average age at catheter insertion in this study was probably significantly greater than would be seen in most units today. Given the poor methodological quality of the study, we cannot rely on the results provided with regard to effects on infection rates.

Quasi-randomised trials are inherently prone to bias, and their results should be interpreted with caution. The alternate group assignment makes the upcoming treatment group allocation predictable, and that is a problem in the case of every eligible infant. Also, 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).

In order to justify the use of prophylactic antibiotics (rather than treatment of infection as it arises) in infants with umbilical venous 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 emergence of resistant strains of bacteria, 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 broader community.

**AUTHORS’ CONCLUSIONS**

**Implications for practice**

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

**Implications for research**

- If prophylactic antibiotics are to be considered when inserting umbilical venous catheters, then good quality randomised controlled trials are required to show that their benefits outweigh...
the harms. Unfortunately, most newborn infants who have um-
bilical venous 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 re-
 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

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- No sources of support supplied

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- Dept of Paediatrics and Child Health, University of Queens-
  land, Brisbane AUSTRALIA
- Neonatal Unit, Department of Pediatrics, McMaster University,
  Hamilton CANADA

REFERENCES

References to studies included in this review

Pulido 1985 (published data only)
Pulido N, Montesinos A, Arriaza M, Esparza P. Prophylactic use of
antibiotics in umbilical catheterization in newborn infants [Uso pro-
filactico de antibacterianos en cateterismo umbilical en recien nacidos].

References to studies excluded from this review

Bhatt 1973
Bhatt H, Albert G, Teasdale F, Doray B, Martineau B. Prophylactic
antibiotics in chronic umbilical artery catheterization in respiratory

Bhatt 1970
Bhatt DR, Hodgman JE, Tatter D. Evaluation of prophylactic antibi-
otics during umbilical catheterization in newborns. Clinical Research

Cowett 1977
Cowett RM, Peter G, Hakanson DO, Stern L, Oh W. Prophylactic
antibiotics in neonates with umbilical artery catheter placement: a
prospective study of 137 patients. The Yale Journal of Biology and

Additional references

Adams-Chapman 2002
Adams-Chapman I, Stoll BJ. Prevention of nosocomial infections in

Chien 2002

Dear 1999

Freij 1999

Hennekens 1987

Inglis 2004

Isaacs 2000

Isaacs 2003

Nagata 2002

Ogawa 1999

Stoll 2002

Stoll 2004

* Indicates the major publication for the study

TABLES

Characteristics of included studies

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<thead>
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<th>Study</th>
<th>Pulido 1985</th>
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<td>Methods</td>
<td>This non-randomised (quasi-randomised - alternate allocation) study took place between July and August 1984 at a regional neonatal intensive care unit in Chile. Enrolled infants were allocated alternately into intervention and control groups. All subjects had 2 peripheral blood cultures and a full blood count (FBC) drawn three days following the procedure. At this stage antibiotics were discontinued if there was deemed to be no clinical or laboratory (i.e. FBC) evidence of infection. Blood cultures were read at 7 days. Septicaemia was defined as positive blood culture combined with clinical and laboratory evidence of infection. Intervention was probably not blinded. Completeness of follow up is not addressed. It is unclear whether outcome assessment was blinded.</td>
</tr>
<tr>
<td>Participants</td>
<td>Twenty-nine infants were studied. All were term. Twenty-three underwent exchange transfusion for hyperbilirubinaemia, and 6 underwent globuloforesis (partial exchange transfusion) for haematocrit greater than 0.70. All infants had their procedures performed via umbilical venous catheter. Infants requiring repeat procedures were excluded from the study (the number of such infants, if any, is not specified). There were 15 infants in the intervention group and 14 in the control group.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Infants in the intervention group (n = 15) received penicillin and gentamicin for 3 days following the procedure. Control infants (n = 14) received no antibiotics. No placebo was used. Other care was similar.</td>
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</table>
Characteristics of included studies (Continued)

Outcomes
Septicaemia: based on positive blood culture (3 days after UVC insertion) in conjunction with clinical and haematological evidence of infection.

Notes
Allocation concealment D
FBC = full blood count and examination
UVC = umbilical venous catheter

Characteristics of excluded studies

Bhatt 1970 Published in Abstract form only. The second author was contacted and could offer no further data, except that the study involved infants with arterial, rather than venous, catheters.
Cowett 1977 Study of umbilical artery catheters.

ANALYSES

Comparison 01. Prophylactic antibiotics versus no antibiotics

<table>
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<th>Outcome title</th>
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<th>No. of participants</th>
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<td>Relative Risk (Fixed) 95% CI</td>
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COVER SHEET

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

Authors
Inglis GDT, Davies MW

Contribution of author(s)
Preparation of protocol - GDI
Revision of protocol - MWD
Searches for published and unpublished studies - GDI and MWD
Inclusion assessments - GDI and MWD
Validity assessments - GDI and MWD
Data collection - GDI and MWD
Data entry - GDI and MWD
Data Analysis - GDI and MWD
Preparation of review - GDI
Revision of review - MWD

Issue protocol first published
2005/2

Review first published
2005/4

Date of most recent amendment
23 August 2005

Date of most recent SUBSTANTIVE amendment
12 July 2005

What's New
Information not supplied by author

Date new studies sought but none found
Information not supplied by author
## Analysis 01.01. Comparison 01 Prophylactic antibiotics versus no antibiotics, Outcome 01 Septicaemia

Review: Prophylactic antibiotics to reduce morbidity and mortality in neonates with umbilical venous catheters
Comparison: 01 Prophylactic antibiotics versus no antibiotics
Outcome: 01 Septicaemia

<table>
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Test for heterogeneity: not applicable
Test for overall effect: not applicable

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