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Oral immunoglobulin for the treatment of rotavirus diarrhea in low birth weight infants (Review)

Pammi M, Haque KN

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TABLE OF CONTENTS

[Intervention Review]

Oral immunoglobulin for the treatment of rotavirus diarrhea in low birth weight infants

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ABSTRACT

Background

Rotavirus infection is the most common neonatal nosocomial viral infection. It is a major health problem worldwide. Epidemics with the newer P(6)G9 strains have been reported in neonatal units globally. These strains can cause severe symptoms in most infected infants. Infection control measures become necessary and the utilization of hospital resources increase. Local mucosal immunity in the intestine to rotavirus is important in the resolution of infection and protection against subsequent infections. Boosting local immunity by oral administration of anti-rotaviral immunoglobulin preparations might be a useful strategy in treating rotaviral infections, especially in low birth weight babies.

Objectives

To determine the effectiveness and safety of oral immunoglobulin preparations for the treatment of rotavirus diarrhea in hospitalized low birth weight infants (birth weight less than 2500 g)

Search methods

Electronic databases including The Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 3, 2004), MEDLINE, EMBASE and CINAHL, Biological Abstracts (BIOSIS) were searched by the strategy outlined in the protocol. Science Citation Index search for all articles that referenced Barnes 1982 were searched. The proceedings of the Pediatric Academic Societies published online at 'Abstracts Online' were searched. Ongoing registered trials at www.clinicaltrials.gov and www.controlled-trials.com were searched. Authors prominent in the field were contacted for any unpublished articles and more information on published articles was sought. Reference lists of identified clinical trials and personal files were also reviewed. The above search was updated in July 2011.

Selection criteria

The criteria used to select studies for inclusion were:
1) Design: randomized or quasi-randomized controlled trials
2) Hospitalized low birth weight infants with rotavirus diarrhea
3) Intervention: Oral immunoglobulin preparations compared to placebo or no intervention
4) At least one of the following outcomes were reported: All cause mortality during hospital stay, mortality due to rotavirus infection during hospital stay, duration of diarrhea, need for rehydration, duration of viral excretion, duration of infection control measures, length of hospital stay in days, recurrent diarrhea or chronic diarrhea

Data collection and analysis

The two reviewers were to independently abstract data from eligible trials. No data were available for analysis.

Main results

No eligible randomized controlled trials were found.

Authors' conclusions

No randomized controlled trials that assessed the effectiveness or safety of oral immunoglobulin preparations for the treatment of rotavirus diarrhea in hospitalized low birth weight infants were found. Clinical trials that address the issue of oral immunoglobulin treatment of rotavirus infection are needed.

PLAIN LANGUAGE SUMMARY

Oral immunoglobulin for the treatment of rotavirus diarrhea in low birth weight infants

Rotavirus infection can cause significant problems including diarrhea in the newborn. This is particularly true in babies weighing less than 2500 g (low birth weight infants). Rotavirus infection is becoming more common in newborn babies and can spread from one baby to another in the neonatal unit. Administration of antibodies against rotavirus to babies may be one of the methods to treat this infection and to prevent the spread of infection in the neonatal unit. In this review, we did not identify any trial that used antibodies to treat rotavirus infection. More research is needed to address these issues.

BACKGROUND

Description of the condition

Group A rotavirus infection is a major cause of diarrheal morbidity in children. Globally, it is estimated that in children < 5 years of age, rotavirus causes 111 million episodes of gastroenteritis requiring only home care, 25 million clinic visits, two million hospitalizations and 440,000 deaths. 82% of deaths occurred in the poorest countries (Parashar 2003). It has been recognized as the most common neonatal nosocomial viral infection (Strodtbeck 1986). Several outbreaks of rotaviral infection in neonatal nurseries in different countries have been reported (Bryden 1982; Shif 1983; Omoigberale 1995; Akinci 1991).

Rotavirus infection epidemics appear to be seasonal, being more common in the colder winter months. Infection rates range from 13% to 78% of neonates in the neonatal unit during epidemics (Widdowson 2000; Tufvesson 1986; Kilgore 1996; Cicirello 1994). The main reservoir of rotavirus infection in neonatal nurseries seems to be the infected neonate (Grillner 1985) and most infection occurs in the first few days of life (Kilgore 1996; Cicirello 1994). Cohorting healthy newborns in nurseries is no longer standard practice and hence this is not a problem in term newborns. However, survival rates have improved over the last decade for very low birth weight and extremely premature infants who stay longer in neonatal units. Premature and low birth weight infants and infants staying in the neonatal unit longer have shown to have a greater risk of acquiring rotavirus infection (Dennehy 1985; Walther 1984; Dearlove 1983). Rotavirus, especially the newer strains, can cause severe diarrhea and dehydration in already sick neonates. Rotavirus infection has been shown to be associated with necrotizing enterocolitis (NEC) in premature infants during an outbreak in a neonatal unit (Mogilner 1983). In another study, 29% of neonates with NEC were stool rotavirus positive. Although these infants had lower Bell's Staging of NEC, the outcome of these infants regarding mortality or complication rates did not differ from rotavirus negative infants who had NEC (Sharma 2004). A significantly higher incidence of bradycardia-apnoea episodes (BAE) has been noticed two days before and two days after the diagnosis of rotavirus infection in infants. These episodes were followed by cyanosis and required intervention more often than did BAE episodes in rotavirus negative infants (Riedel 1996). Rotavirus infected neonates stay in the hospital longer than non-infected neonates, causing increased stress to the family and increased cost to the neonatal unit (Strodtbeck 1986). Strict infection control measures have been advocated including hand protection, hand disinfection, individual nursing sets, and cohorting infected babies (Grehn 1990). Closure of neonatal units (Valmari 1984) has been recommended to control and eradicate outbreaks of nosocomial rotavirus infections, placing considerable stress on busy neonatal units.

Newer strains of rotavirus P(6)G9 genotypes that previously have not been known to cause outbreaks of diarrhea have been identified to cause epidemics in the UK (Cubitt 2000), US (Ramachandran 1999), Bangladesh (Unicomb 1999) and Europe (Widdowson 2000; Widdowson 2002). Unlike previous strains, the new P(6)G9 strains can cause serious outbreaks of diarrhea in neonatal units and cause severe symptoms in most infected neonates. Most mothers have not been exposed to these new strains and thus a high proportion of neonates lack protective antibodies, which could explain high attack rates in the neonatal unit and the severity of symptoms. Predominance of neonatal cases compared to few cases in older children may indicate that neonates have an increased risk of infection by P(6)G9 strains.

Description of the intervention

Determinants of protective immunity against rotavirus are unclear but it has been suggested (Molyneaux 1995) that local mucosal immunity in the intestine may protect against rotavirus illness. While local antibodies may be important in the resolution of infection and protection from subsequent infections, there is no specific antibody that could be used reliably as a marker of protection (Ward 1996). Breast-fed infants are less susceptible to rotavirus infection, probably due to the presence of anti-rotaviral secretory IgA and trypsin inhibitors in the breast milk (McLean 1981; Jayashree 1988). The protective efficacy of breast milk correlates positively with the concentrations of anti-rotaviral secretory IgA in the breast milk (Jayashree 1988). Breast-fed infants tend to excrete fewer viruses than bottle-fed infants after infection with rotavirus (Chrystie 1978).

Oral administration of immunoglobulin containing preparations of bovine colostrum from immunized cows, egg yolk immunoglobulin from immunized hens (Mine 2002) or pooled plasma derived immunoglobulins can provide passive immunity. The highest titers of neutralizing anti-rotaviral antibodies are in bovine colostrum, then in egg yolk followed by human pooled plasma derived immunoglobulin (Bogstedt 1996). These preparations may inhibit intestinal viral adherence or viral replication and may have a role in the treatment of rotavirus infections. Oral immunoglobulin preparations are resistant to proteolytic digestion and retain significant neutralizing activity in the stools of treated infants .The newborn infant's immaturity of proteolytic enzymes or rapid gastro-intestinal transit time permits intact or nearly intact IgG to pass throughout the gastrointestinal system (Hilpert 1987; Blum 1981). In a prospective randomised placebo controlled study of oral human serum immunoglobulin in children (but not neonates) with acute rotaviral gastroenteritis, there was a reduction in total duration of viral diarrhea, and viral excretion, and a faster clinical improvement compared to controls (Guarino 1994). Bovine colostrum from hyperimmunized pregnant cows has been shown to reduce viral excretion, stool output and the need for rehydration when used in the treatment of acute rotaviral gastroenteritis in children other than neonates (Hilpert 1987; Sarker 1998; Mitra 1995). It has also been shown to prevent diarrhea from rotavirus infection when used as prophylaxis (Ebina 1996; Turner 1993). Antibodies derived from the yolk of rotavirus immunized hens have been tested in acute rotaviral gastroenteritis in children beyond the neonatal period in a randomized placebo controlled trial, and found to cause earlier clearance of virus from the stools and an improvement of diarrhea (Sarker 1998, Sarker 2001).

How the intervention might work

Advantages of administering oral immunoglobulin-containing preparations in neonates, especially low birth weight infants, would be a reduction in morbidity, reduction in the need for rehydration, earlier clearance of the virus thereby reducing the duration of infection control measures, and a reduction in hospital stay. Infection control measures are expensive and sometimes involve closure of infected units; oral immunoglobulins could be a cheaper and an easier alternative.

Why it is important to do this review

Rotavirus diarrhea has the potential to resurface as a major problem in low birth weight infants especially with the newer strains. A systematic review of the efficacy and safety of oral immunoglobulin therapy in low birth weight infants for the treatment of rotavirus diarrhea, according to Cochrane methodology is appropriate.

OBJECTIVES

To determine the effectiveness and safety of oral immunoglobulin preparations for the treatment of rotavirus diarrhea in hospitalized low birth weight (birth weight < 2500 g) infants.

METHODS

Criteria for considering studies for this review

Types of studies

Studies in which hospitalized low birth weight infants with rotavirus diarrhea were randomized or quasi-randomized to receive oral immunoglobulin preparations OR either a placebo or no intervention.

Types of participants

Hospitalized low birth weight infants (birth weight < 2500 g) with rotavirus diarrhea.

Types of interventions

Oral immunoglobulin preparations, namely a) pooled plasma, b) colostrum from rotavirus immunized cows or c) egg yolk immunoglobulin from rotavirus immunized hens, used for treatment of rotavirus diarrhea at any dose or duration.

Types of outcome measures

Primary outcomes

- All cause mortality during hospital stay.
- Mortality due to rotavirus infection during hospital stay.
- Duration of diarrhea.
- Need for rehydration

Secondary outcomes

- Duration of viral excretion.
- Duration of infection control measures.
- Length of hospital stay in days.
- Recurrent diarrhea.
- Chronic diarrhea.

Definitions

- Rotavirus infection - detection of rotavirus or antigen in the stools.
- Diarrhoea - loose watery stools.
- Rotavirus diarrhea - rotavirus infection with diarrhea.
- Recurrent diarrhea - recurrence of diarrhea after 48 hrs of normal stools.
- Chronic diarrhea - persistence of diarrhea beyond 14 days.
- Rehydration for rotavirus diarrhea - fluid needed above maintenance requirements to maintain normal hydration by any route.
- Duration of diarrhea - time till the last loose watery stools from the onset of diarrhea measured in days.
- Duration of viral excretion - time till two rotavirus negative stools from the time of positive diagnosis measured in days.
- Mortality due to rotavirus infection during hospital stay - deaths directly attributable to rotavirus infection.
- Duration of infection control measures - days per infant of extra infection control measures as a result of rotavirus infection above what is normally practised in that hospital for that infant infected with rotavirus.

Search methods for identification of studies

See: Collaborative Review Group search strategy
The search strategy used to identify studies was devised according to the guidelines of the Cochrane Neonatal Review Group. The following search strategy was updated in July 2011.

Relevant trials in any language were identified through:
1. The Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, Issue 2, 2011).

2. Electronic journal reference databases-
MEDLINE (1966 to present) and PREMEDLINE;
EMBASE (1980 to present);
CINAHL (1982 to present);
Biological Abstracts (BIOSIS)(1980 to present).

3. Science citation index search for all articles, which quoted Barnes 1982 was performed.

4. Abstracts of conferences - proceedings of the Pediatric Academic Societies (American Pediatric Society, Society for Pediatric Research and the European Society for Paediatric Research). The reference lists of identified trials and abstracts published in Pediatric Research (1991 to 1999) and 'Abstracts Online' (2000 to 2011) were searched in MEDLINE and EMBASE for full published articles.

5. Ongoing registered trials at www.clinicaltrials.gov and www.controlled-trials.com were searched.
6. Communication was made with published authors for more information if necessary and other prominent authors in the field for possible unpublished studies whether or not they were presented as abstracts.
7. Additional searches were made in reference lists of identified clinical trials and in the reviewer's personal files.

MEDLINE, PREMEDLINE, EMBASE, CINAHL, Biological Abstracts search strategy
#1 Search Rotavirus
#2 Search Infant, newborn
#3 Search Infant, newborn, diseases
#4 Search neonat*
#5 Search Infant, low birth weight
#6 Search Infant, Very Low birth weight
#7 #2 OR #3 OR #4 OR #5 OR #6
#8 Search Immunoglobulin AND Oral
#9 Search Antibodies AND Oral

#10 Search Gammaglobulin AND Oral
#11 #8 OR #9 OR #10
#12 #1 AND #7 AND #11
#13 Limit #12 to (TG = Human) and (PG = Clinical trial)

No language restriction was applied. The reviewers erred on the side of over inclusion and later the articles that did not meet the eligibility criteria were excluded.

Data collection and analysis

The current methods of the Cochrane Neonatal Review Group were employed in creating this update.

Selection of studies

The titles and the abstracts of studies identified by the search strategy were assessed by the two authors independently. We planned to include all randomized and quasi-randomized controlled trials fulfilling the selection criteria described in the previous section. Both authors reviewed the results of the search and separately selected the studies for inclusion. The review authors resolved any disagreement by discussion.

Data extraction and management

Data extraction was to be done independently by the authors using paper proforma, and compared for differences, which were to be resolved by discussion.

Assessment of risk of bias in included studies

The standard methods of the Cochrane Neonatal Review Group were employed.

If eligible studies were found, we planned to independently assess risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

We planned on using the following methodological criteria:

1. Sequence generation: Was the allocation sequence adequately generated? For each included study, we planned to describe the method used to generate the allocation sequence. We planned to assess the methods 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); unclear risk.

2. Allocation concealment: Was allocation adequately concealed? For each included study, we planned to describe the method used to conceal the allocation sequence and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, of changed after assignment. We planned to assess the methods as:

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

3. Blinding of participants, personnel and outcome assessors: Was knowledge of the allocated intervention adequately prevented during the study? For each included study, we planned to assess the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We judged studies to be at low risk of bias if they were blinded, or if we judged that the lack of blinding could not have affected the results. We assessed blinding separately for different outcomes or classes of outcomes. We planned to assess the methods as:

a. low risk, high risk or unclear risk of bias for participants;

b. low risk, high risk or unclear risk of bias for personnel;

c. low risk, high risk or unclear risk of bias for outcome assessors.

4. Incomplete outcome data: Were incomplete outcome data adequately addressed? For each included study and for each outcome, we planned to describe the completeness of data including attrition and exclusions from the analysis. We planned to address whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. We planned to assess the methods as: low risk; high risk; unclear risk.

5. Selective outcome reporting: Are reports of the study free of suggestion of selective outcome reporting? For each included study we planned to describe how we examined the possibility of selective outcome reporting bias and what we found. We planned to assess the methods as:

low risk (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);high risk (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 risk.

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 planned to describe any important concerns regarding other possible sources of bias. We planned to assess whether each study was free of other problems that could put it at risk of bias: low risk; high risk; unclear risk.

Measures of treatment effect

We planned to use the standard methods of the Neonatal Review Group. If eligible studies were located, we planned to perform statistical analyses using Review Manager software. We planned to analyze data using relative risk (RR), risk difference (RD) and the number needed to treat (NNT). We planned to analyze continuous data using weighted mean difference (WMD). We planned to report the 95% Confidence interval (CI) on all estimates.

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

If multiple eligible studies were found, we planned on performing the meta-analysis using Review Manager software (RevMan 5), supplied by the Cochrane Collaboration. For estimates of typical relative risk and risk difference, we planned to use the Mantel-Haenszel method. For measured quantities, we planned to use the inverse variance method. We planned to perform all meta-analyses using the fixed effect model.

Subgroup analysis and investigation of heterogeneity

We did not have data to perform the intended subgroup analyses. However as more research is done we believe that subgroup analyses listed below could be performed in the updates of this review:

1) birth weight:
birth weight < 1500 grams;
birth weight from 1500 to 2500 grams.

2) Type of oral immunoglobulin preparations:
oral immunoglobulin derived from pooled plasma;
oral immunoglobulin from the colostrum of rotavirus immunized cows;
oral immunoglobulins from egg yolk of rotavirus immunized hens.

3) Type of rotavirus strains:
newer G(9) strains;
non G(9) strains.

RESULTS

Description of studies

Three studies were identified by our search strategy that could potentially be eligible to be included in the review: Lodinova 1984; Ventura 1993; Barnes 1982.
All three studies were excluded.

Lodinova 1984
The first author confirmed that this study appeared as three reports (see References to studies, excluded studies). Fifty-six infants (preterm and term) admitted with diarrhea were administered colostrum from cows immunised against 6 serotypes of E.Coli. They were compared with 29 infants (preterm and term) admitted with diarrhea who were administered the standard treatment (no intervention). Outcomes reported were i) cure of diarrhea (not defined) ii) need for oral antibiotics iii) need for parenteral rehydration iv) weight gain v) number of stools vi) quality of stools vii) bacterial pathogens before and after treatment viii) need for parenteral antibiotics ix) additional illnesses. This study was excluded because it was not a randomized study and rotavirus diarrhea was not an eligibility criterion for this study.

Barnes 1982
The participants in this study were 75 infants with birth weights ranging from 2000 to 2500 g, who were admitted to the special care baby unit, where rotavirus infection was known to be endemic. Rotavirus infection was not an eligibility criterion nor was diarrhea. Seventy-five infants were randomized to receive either oral gammaglobulin or placebo within 12 hours of birth. A subset of 25 infants who excreted rotavirus sometime in the first two weeks of life were analyzed in the study report for the following outcomes: timing of excretion of rotavirus, grading of severity of rotavirus excretion, duration of excretion of rotavirus and the incidence of clinically important diarrhea requiring low lactose feeds. Fifty out of 75 infants who did not excrete rotavirus were excluded from the analysis in the study report. This study was excluded because rotavirus diarrhea in the participants was not an entry criterion.

Ventura 1993
Fifty-four infants (aged 1 to 36 months) admitted with acute diarrhea were randomized to oral gammaglobulin (24 infants) or placebo (30 infants). Outcomes reported were duration of diarrhea and duration of excretion of rotavirus in the two groups. Age and birth weight details are not available and, therefore, the study was excluded.

No studies were found eligible for inclusion in this review at this point.

Risk of bias in included studies

No trials were eligible.

Effects of interventions

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

DISCUSSION

Rotavirus infection is a major global problem and affects infants in both the developing and the developed countries (Bern 1992). It accounts for a significant amount of diarrheal morbidity and mortality in children less than five years of age (Parashar 2003). Newer strains of rotavirus [P(6)G9] cause significant morbidity in infected neonates especially low birth weight and or premature neonates. It has the potential to resurface as a major problem in low birth infants admitted to the neonatal units who are at risk of significant morbidity. Infection control measures become imperative in affected neonatal units and place a considerable burden on health resources. This could mean closure or restriction of available neonatal cots or services and more health costs. Therefore, effective treatment of rotavirus infected neonates with diarrhea assumes great clinical importance, more so in developing countries.

Active immunization with rotavirus vaccines can be an effective strategy to prevent rotavirus infections. The initial vaccine licensed was a tetravalent rhesus-human reassortment vaccine (Rotashield). Vaccination with this vaccine was discontinued because of safety concerns, as there was an association with intussuception. Currently available vaccines RotaTeq and RIX4414 (Rotarix) have not been shown to be associated with intussuception and have shown about 70% efficacy against any rotavirus disease and 90-100% efficacy in preventing severe rotavirus disease (Vesikari 2006). The American Academy of Pediatrics recommends routine vaccination against rotavirus with either the pentavalent human-bovine reassortment rotavirus vaccine (RV5) or the live attenuated human rotavirus vaccine (RV1) to be given orally for three or two doses respectively starting from 6 weeks of age (AAP 2009). However, current rotavirus vaccines do not include the newer P(6)G9 rotavirus strains,and hence vaccination would not be

expected to prevent neonatal rotavirus infection in hospitalized low birth weight infants.

Newer preparations of oral anti-rotaviral immunoglobulins namely cow's colostrum and egg yolk immunoglobulins (Mine 2002), which have a high titer of anti-rotaviral immunoglobulins have become available and have already shown to be beneficial in older children. Further evaluation of these oral immunoglobulin preparations in the treatment of rotavirus diarrhea in low birth weight and or premature infants is therefore indicated.

AUTHORS' CONCLUSIONS

Implications for practice

No randomized controlled trials, which assessed the effectiveness or safety of oral immunoglobulin preparations for the treatment of rotavirus diarrhea in hospitalized low birth weight infants were found.

Implications for research

Rotavirus diarrhea remains a major problem in the developing world and could resurface as a significant problem in the developed world. There has been an emergence of newer strains of rotavirus, which cause a more severe clinical disease in infected neonates. Availability of high titre anti-rotaviral immunoglobulin preparations should encourage researchers to undertake well designed, large RCTs to evaluate the effectiveness and safety of these preparations in rotavirus infected infants, especially in low birth weight or premature infants. Low birth weight and/or premature infants are likely to have a higher mortality and morbidity after infections with newer strains of rotavirus and it will be prudent to test in this category of infants. Trialists should also be encouraged to address the treatment of rotavirus diarrhea in low birth weight infants cared for at home in the developing world, who are at significant risk of morbidity and even death. Randomized controlled trials for treatment of rotavirus infection should use rapid diagnosis (Lipson 2001) to ascertain rotavirus infection as an eligibility criterion, in order to avoid confusion with other gastro-intestinal infections in low birth weight infants. Such randomized controlled trials should assess effects on a combination of outcomes, which include mortality, morbidity and health resource utilisation. Key outcomes would be a reduction in morbidity in this high risk group of infants, as well as duration of viral excretion, which will determine the duration of expensive infection control measures. The design of these RCTs should also include cost-effectiveness evaluations.

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Mohan 2003

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Barnes 1982	Rotavirus diarrhea was not an eligibility criterion for participant inclusion
Lodinova 1984	Not a randomised study.
Ventura 1993	Age and birth weight details of the randomised infants are not available and hence the study was excluded.

3 reports of the same study.

WHAT'S NEW

Date	Event	Description
7 July 2011	New citation required but conclusions have not changed	No change to conclusions.
7 July 2011	New search has been performed	This updates the review 'Oral immunoglobulin for the treatment of rotavirus diarrhea in low birth weight infants' published in the Cochrane Database of Systematic Reviews. Updated search in July 2011 did not identify any new trials for inclusion.

HISTORY

Protocol first published: Issue 3, 2002

Review first published: Issue 1, 2003

Date	Event	Description
7 December 2010	Amended	Contact details updated.
10 June 2008	Amended	Converted to new review format.
30 April 2007	New search has been performed	This review is an update of the existing review "Oral immunoglobulin for the treatment of rotavirus diarrhea in low birth weight infants", published in The Cochrane Library, Issue 1, 2003 (Mohan 2003). There were no new trials identified by our updated search in April 2007. One study (Ventura 1993) awaiting assessment has been excluded. Abstract, background and Discussion sections have been updated. Five new references have been added to the additional references section.
17 April 2002	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Pammi Mohan
Literature search and identification of trails for inclusion
Contacting prominent authors in the field for more data and unpublished trials
Abstraction of data from eligible studies
Evaluation of methodological quality of included trials
Verifying and entering data in RevMan
Writing the text of the review

Khalid Haque
Abstraction of data from eligible studies
Evaluation of methodological quality of included trials
Writing the text of the review

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- National Perinatal Epidemiology Unit, Headington, Oxford, UK.
- Epsom & St Helier NHS Trust, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Infant, Low Birth Weight; Administration, Oral; Cross Infection [*therapy] [virology]; Diarrhea [*therapy] [virology]; Immunoglobulins [*administration & dosage]; Rotavirus Infections [*therapy]

MeSH check words

Humans; Infant; Infant, Newborn