

# Feed thickener for newborn infants with gastro-oesophageal reflux (Review)

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## ABSTRACT

### Background

Gastro-oesophageal reflux (GOR) is common in newborn infants. A common first line management is the use of feed thickeners.

### Objectives

In newborn infants with GOR, to evaluate the use of feed thickeners in reducing signs and symptoms of GOR, acid episodes on pH monitoring and histological evidence of oesophagitis.

### Search strategy

We searched MEDLINE from 1966 to March 2004, the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2004). CINAHL from 1982 to December 2001, and conference and symposia proceedings published in *Pediatric Research* 1990 to 1994. We also searched conference proceedings for the European Society for Paediatric Gastroenterology and Nutrition (ESPGAN) and the North American Society for Pediatric Gastroenterology and Nutrition (NASPGAN) from 1994 to December 2001. We did not restrict the searches to the English language.

### Selection criteria

All randomised controlled trials that examine the effects of thickening formulas on treating gastro-oesophageal reflux in neonates. The eligible studies were to compare thickened feeds to no intervention (unthickened feeds).

### Data collection and analysis

Two independent reviewers identified potential studies from the literature search. Quality was independently assessed by two independent reviewers.

### Main results

No studies fulfilled the requirements for inclusion in the systematic review.

### Authors' conclusions

There is no evidence from randomised controlled trials to support or refute the efficacy of feed thickeners in newborn infants with GOR. Given the absence of evidence, we cannot recommend using thickening agents for management of GOR in newborn infants.

## PLAIN LANGUAGE SUMMARY

There is no current evidence from randomised trials to show that adding feed thickeners to milk for newborn infants is effective in treating gastro-oesophageal reflux.

Many newborn babies (in the first four weeks of life) suffer from gastro-oesophageal reflux, especially if they are born premature. Thickening the milk feed is a simple manoeuvre and commonly used as first line treatment for gastro-oesophageal reflux. Thickening the feeds can be used with or without other treatments such as positioning babies on their stomach or side, and using medications that

suppress acid in the stomach or cause food to move more rapidly through the stomach. No randomised controlled studies of sufficient quality were found in this review. Therefore, there is no current evidence to support or refute the use of feed thickeners in treating newborn babies with gastro-oesophageal reflux.

## BACKGROUND

Gastro-oesophageal reflux (GOR/GERD) is a descriptive term for the reflux of stomach contents into the oesophagus and in mild form is a normal physiological process. It occurs more frequently in neonates than in older infants and children, and is found with higher rates in premature neonates. It is most commonly due to inappropriate relaxation of the lower oesophageal sphincter (Hillemeier 1996; Sutphen 1986).

The prevalence of excessive GOR in children is approximately 8%, as diagnosed on 24 hour ambulatory pH manometry studies in an unselected healthy infant population (Sacre 1989). Symptomatic regurgitation alone is more common and has been found to occur in 18% of the general infant population (Boulton 1979; Chouhou 1992). pH studies are a sensitive, objective measure indicative of acid GOR. Regurgitation alone may not always reflect pathological GOR in terms of the frequency, duration and severity of reflux of stomach contents into the oesophagus. It may be a physiological phenomenon and will not always be accompanied by sequelae such as crying, screaming, irritability and/or oesophagitis.

However, at some point GOR becomes pathological. This pathology is related to the frequency and severity of reflux episodes. Reflux becomes pathological when it leads to insufficient caloric intake and poor growth, oesophagitis and its sequelae (bleeding, anaemia, stricture), or tracheal aspiration. In the older child, long term GOR may lead to Barrett's oesophagus (and possibly carcinoma much later in life). The other aspect of the burden of this condition to consider is the parental anxiety generated by a crying, irritable child.

The clinical presentation of GOR in the neonate is variable, but classically is with regurgitation, possetting and vomiting. Other manifestations can include haematemesis, failure to thrive, irritability, disturbed sleep, respiratory symptoms, apnoeas, recurrent oxygen desaturation and bradycardias (Orenstein 1993). None of these signs or symptoms are sensitive or specific for GOR. GOR has been associated with lower respiratory tract problems in some studies (Orenstein 1993) but not others (Kahn 1992; Jolley 1986). The natural history of this condition is usually self limiting with resolution during the first two years of life, correlating with developmental maturity, more upright posture with onset of walking, and intake of more solids (Hillemeier 1981; Vanderplas 1994); hence randomised controlled trials are essential to measure the efficacy of any treatments.

Diagnosis of this condition is still fraught with difficulties. Attempts at designing symptom questionnaires have been under-

taken; however, the diagnostic validity of individual symptoms is still not proven (Orenstein 1993). The most sensitive objective measure is the pH probe test which arbitrarily distinguishes abnormal from normal amounts of reflux of acidic stomach contents into the oesophagus but will not detect alkaline reflux (Arasu 1980). The readings are based on the percentage of reflux time with pH <4 (reflux index) and the frequency and duration of reflux episodes. Normal ranges have been produced for infants (Vanderplas 1987c). Other methods of diagnosing GOR include: 1. barium swallow - which looks only at a snapshot in time and therefore its role is probably more to define associated anatomical abnormalities; 2. manometry and scintigraphy - neither method has correlated well with pH probe testing; 3. upper gastrointestinal endoscopy and oesophageal biopsy - directly looking for end points of GOR such as inflammation; 4. radionuclide milk scans to detect pulmonary aspiration (Hillemeier 1996).

Thickening of infant formulas has been recommended for almost half a century for the treatment of GOR. Agents that have been used include cereal, rice, bean gum, sodium carboxymethyl cellulose, pectin and cellulose. The rationale for this therapy has been that thickening increases the "stickiness" and weight of the feeds. Thus, it is thought that feeds tend to be retained in the stomach which will prevent reflux into the oesophagus (Orenstein 1987). This assumption may be flawed and there have been studies that show that increasing the caloric density of feeds by adding thickeners in fact delays gastric emptying (Minami 1984). Delayed gastric emptying correlates with increased GOR (Hillemeier 1981).

In a non-randomised study, babies 6-8 weeks old with abnormal initial pH monitoring parameters underwent thickening of their feeds. The use of infant food thickeners was associated with a decrease in some of the symptoms associated with GOR including regurgitation and improved sleep (Vanderplas 1987b). However, the effect of thickening on respiratory symptoms does not support a reduction in GOR. In fact, it has been shown in a crossover study using thickened and unthickened formula in random order, that thickening formulas can result in an increased number of coughing episodes (Orenstein 1992). The physiological data supporting a reduction in GOR with thickening of feeds are even less convincing. Crossover pH probe studies have shown variable effects on number of reflux episodes and oesophageal acid exposure (Ramenofsky 1981; Bailey 1987). In fact, the duration of longest acid exposure is increased (Vanderplas 1987a; Vanderplas 1987b) with thickening of feeds in non randomised controlled studies. A subsequent prospective randomised study on infants one to four months showed no difference in duration of longest period

pH<4, but an improvement of the reflux index (Vanderplas 1997). Manometry studies show an increase in rate of transient lower oesophageal sphincter relaxations (TLOSRS), indicating worsening GOR with thickening of formulae (Cucchiara 1995). The studies quoted above look at the infant, not specifically at the neonatal population.

Thickening of infant formulas is relatively free of major side effects. However, there have been anecdotal reports of acute bowel obstruction in neonates who have received feeds thickened with pectin and cellulose (Montagne 1974). The risk is even higher in infants with a premorbid predisposition to bowel obstruction, such as cystic fibrosis or Hirschsprung disease. Some gum derivatives have been associated with abdominal pain, colic and diarrhoea subsequent to fermentation in the large intestine (Vanderplas 1997). There is also a theoretical increased risk of oesophagitis and respiratory complications, based upon the finding of longer periods of acid reflux and delayed gastric emptying with thickened formulas (Vanderplas 1987b; Minami 1984).

Alternative treatment modalities also have potential drawbacks and unproven efficacy. Posturing in a prone position with head up 30 degrees has normalized pH monitoring results in only one quarter of infants and contradicts SIDS prevention guidelines (Vanderplas 1987a). Small frequent feeding is impractical. Low-fat, high-carbohydrate feeds have the hypothesized advantage of avoiding the slowing of gastric emptying associated with long chain fatty acids. However, in practice they are not effective (Tolia 1992; Vandenplas 1988; Sutphen 1989). Prokinetics have significant side effects. Cisapride is associated with prolonged QT interval on ECG (Wysowski 1996), while metoclopramide is associated with central nervous system and extrapyramidal side effects (Antonson 1988). Augood et al have completed a Cochrane review of use of cisapride treatment for GOR in children. They concluded that there was no clear evidence of reduction of symptoms of GOR with Cisapride. There was a significant publication bias for positive studies (Augood 2000). Acid suppressants do not stop reflux of gastric contents, and antacids may be associated with the potential for aluminum toxicity (Tsou 1991). Surgical procedures such as fundoplication obviously have incumbent risks.

There is an obvious need for this review given the frequency of GOR and the lack of clear evidence as to which treatments are effective based on robust scientific evidence. As a testament to the lack of consensus on treatment of this condition, there are multiple therapies used to varying degrees by different clinicians and centres around the world. As thickening of infant milk is a simple intervention without major adverse effects, it is important to determine its efficacy to establish whether or not it should be considered a first line treatment for GOR.

## OBJECTIVES

To determine if thickening of infant milk feeds reduces GOR in

newborn infants as manifested by : (a) a reduction in the signs and symptoms of reflux; or (b) a reduced number and duration of acid reflux episodes based on arbitrarily defined criteria on 24 hour ambulatory pH probe monitoring or by use of intraluminal impedance; or (c) decreased oesophagitis on biopsy. Feed thickening was compared against no treatment or placebo. A subgroup analysis was planned to see if results differed for term or preterm infants and by type of feed-thickener.

## CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

### Types of studies

All randomised controlled trials that examine the effects of thickening formulas on treating GOR in neonates. Included studies were to compare thickened feeds to no intervention (unthickened feeds). Crossover studies were excluded.

### Types of participants

Newborn infants with signs or symptoms suggestive of GOR, or newborn infants with diagnosis of GOR based on 24 hour ambulatory pH monitoring and/or oesophagitis on biopsy. Newborn infants were defined as full term infants less than 28 days. Preterm infants were included up to 44 weeks (postmenstrual) corrected age. Age criteria should be fulfilled at time of initial diagnosis.

### Types of intervention

Thickeners of all types including rice, gum, or flour based, added to all types of milk including formula and human milk, versus no treatment or placebo.

### Types of outcome measures

The outcome measures should be measured during the trial and immediately after the intervention.

#### PRIMARY

1. Symptoms or signs of GOR which include regurgitation, posetting, vomiting, haematemesis, failure to thrive, irritability, disturbed sleep, respiratory symptoms (cough, apnoeas, and recurrent oxygen desaturation) and bradycardias. Each sign or symptom shall be noted as a dichotomous and separate outcome. We note that no sign or symptom is sensitive or specific for GOR.
2. Measures of gastric and oesophageal acidity based on pH monitoring. pH probe study parameters to be included as quantitative discrete variables include : (i) a reflux index (i.e. percentage of time pH <4) , (ii) number of reflux episodes, (iii) number of episodes lasting >5 minutes and (iv) duration of longest episode.
3. Measure of intraoesophageal intraluminal electrical impedance. Parameters to be included are discrete quantitative variables including : (i) number of reflux episodes, (ii) height of refluxate in the esophagus, (iii) mean GOR duration of reflux episode.

#### SECONDARY

3. Microscopic evidence of oesophagitis on biopsy tissue. The definition was dichotomous based on the presence or absence of inflammation.

4. Significant side effects of the therapy, including (i) bowel obstruction, (ii) diarrhoea, (iii) aspiration, (iv) cough and (v) colic.

## SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

Using text word terms 'gastro-oesophageal reflux' or 'gastroesophageal reflux', or the MeSH term 'gastroesophageal reflux', and the MeSH term 'exp infant, newborn', searches were made of MEDLINE from 1966 to March 2004, the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2004, CINAHL from 1982 to December 2001, and conference and symposia proceedings published in *Pediatric Research* 1990 to 1994. We also searched conference proceedings for the European Society for Paediatric Gastroenterology and Nutrition (ESPGAN) and the North American Society for Pediatric Gastroenterology and Nutrition (NASPGAN) from 1994 to December 2001. We did not restrict the searches to the English language.

## METHODS OF THE REVIEW

Criteria and methods used to assess the methodological quality of the trials: standard method of the Cochrane Collaboration and its Neonatal Review Group were used. The two reviewers worked independently to search for and assess trials for inclusion and methodological quality. Studies were assessed using the following key criteria: blindness of randomisation, blindness of intervention, completeness of follow up and blinding of outcome measurement. Data was extracted independently by the reviewers. Differences were resolved by discussion and consensus of the reviewers. If necessary, investigators were contacted for additional information or data.

For individual trials, mean differences (and 95% confidence intervals) were reported for continuous variables. For categorical outcomes the relative risk and risk difference (and 95% confidence intervals) were reported.

For the meta-analysis, if possible, weighted mean differences (and 95% confidence intervals) were to be reported for continuous variables, and typical estimates for relative risk and risk difference (and 95% confidence intervals) were to be reported for categorical outcomes. A fixed effects model was to be used.

## DESCRIPTION OF STUDIES

No suitable studies were found for inclusion in the review. On our first search using our search strategy, 837 reports and one conference proceeding were found, and based on their abstracts we examined the full text reports of 15 promising publications. Of these 15 publications, we excluded five based on the fact that they were letters or expert opinions on the topic. We found 10 possibly eligible studies. Of these, none of them matched our inclusion criteria for study design or types of participants. On updating this review, the same criteria were implemented in March 2004 and a further 4 possibly eligible studies were unearthed.

Gouyon 1989 was still the only study that enrolled a neonatal population exclusively; however, it was not randomised and the placebo group was contaminated. All of the other thirteen excluded studies, except for Vanderhoof 2003; Iacono 2002; Wenzl 2003; Bailey 1987; Vandenplas 1994 and Miller 1999 used a study population completely outside of our defined participant age group. These six studies used some patients within our age criteria; however, it was not possible to analyse the neonatal group separately. Of these six studies only Vanderhoof 2003; Iacono 2002; Miller 1999 and Vandenplas 1994 were randomised controlled studies. Wenzl 2003 performed a randomised, placebo-controlled crossover study. Bailey 1987 was a crossover study which do not appear to have been randomised.

## METHODOLOGICAL QUALITY

No studies met the criteria for inclusion in this review.

## RESULTS

No studies met the criteria for inclusion in this review.

## DISCUSSION

Although GOR is a common condition in neonates and it is relatively common practice to thicken feeds for management of this condition, there is no evidence that it is an effective practice. Spontaneous resolution of GOR is related to developmental processes and therefore occurs more frequently in neonates (especially premature neonates) than older infants and children. The neonatal population (including premature babies) is a distinct population in which GOR has a different prevalence, and different consequences and complications compared to the older infant population. Neonates are often at higher risk than older infants of respiratory complications (including apnoeas), ventilation difficulties and failure to thrive (given their lack of body energy reserves) - therefore, it is not appropriate to simply generalise from infant studies.

Nevertheless, some lessons may be learned from infant studies. Despite the paucity of studies on the neonatal group, the infant population has been investigated with regards to the efficacy of thickened feeds as a treatment for gastroesophageal reflux. Vandenplas et al studied a small group of 20 infants aged one week to four months of age in a double-blind randomised controlled trial. The control group underwent parental reassurance, positioning and unthickened feeds. The study group received parental reassurance, positioning and thickened formula. There was no statistically significant difference in the grade of severity of regurgitation or pH probe parameters between control and treatment group (Vandenplas 1994). Miller also undertook a double blind randomised study of 25 general practice centres studying infants between 0 to 12 months. Ninety patients were randomised to receive either aluminium-free alginate or placebo. The number of vomiting or regurgitation episodes was significantly lower in patients receiving the alginate compared with placebo ( $p=0.009$ ). The severity of vomiting showed a trend towards improvement with alginate but did not achieve significance ( $p=0.061$ ). Subjective assessments made by both investigators and parent/guardian of the efficacy of alginate were favourable compared to placebo with  $p$  values of 0.008 and 0.002 respectively. On diary assessment, the improvement in mean regurgitation severity and proportion of infants with at least 10% symptom-free days achieved significance, both with  $p$  values of 0.027. Miller concludes that the use of alginate is an effective and safe treatment of GOR in paediatric patients (Miller 1999). Vanderhoof et al's study was a double blinded randomised placebo controlled trial. They undertook a study which recruited 55 babies to Enfamil AR (thickened formula) and 49 babies to a control group receiving standard commercially available cow milk based infant formulas. The Enfamil AR group showed symptomatic improvement at the end of the first week of the trial with decrease percent feedings with any regurgitation ( $p=0.045$ ), total regurgitation volume score ( $p=0.035$ ) and percent feeding with choke-gag-cough ( $p=0.004$ ) (Vanderhoof 2003). Iacona et al selected patients as they consecutively presented to six paediatric outpatient centres. They were randomised into a treatment group comprising 82 male infants of median age 1.5 months and 84 males of the same age in the control group. The treatment group received a formula thickened with carob flour (bean gum) which was designed as an anti-reflux formula. They found a significant reduction in the regurgitation score in both groups at the 4 week and 8 week follow up consistent with the natural history of GER. However, there was no difference in the regurgitation score between the treatment and control groups. 14 of the patients in the treatment group stopped the thickened formula in the first 2 weeks due to diarrhoea. (Iacono 2002)

Other studies have looked at the use of thickeners in the infant population with conflicting results, but they were not designed as randomised controlled trials (Khoshoo 2000; Orenstein 1987; Bailey 1987; Wenzl 2003). Wenzl studied 14 infants of mean age 42+/-32 days who had at least 5 small regurgitations or 1 large

regurgitation during a 3 day surveillance period. They were randomised to receive formula A-B-A-B-A-B in this order or in reverse order. A was thickened with 0.4% carob bean gum and B unthickened formula. Video surveillance, impedance and pH probe data show decreased mean regurgitation score ( $p<0.003$ ) and decrease GER episodes measured with impedance tracings ( $p<0.02$ ) with formula A. However, other measures from the impedance readings were not significantly different. (Wenzl 2003) There is currently a protocol in The Cochrane Library for a review addressing the use of thickened feedings in children under two years of age with GOR (Craig 2002) which has not progressed to a published systematic review as yet.

Only one study potentially addressed the use of a thickening agent in the neonatal population. Gouyon et al (Gouyon 1989) enrolled neonates with GOR in a trial comparing smectite, a natural clay whose rheological properties include increased viscosity with hydration, with placebo. Smectite also has an independent mucosal protectant effect. However, this study was not randomised, and there was contamination of the placebo group in that some individuals in both the intervention and placebo groups were given additional "thickeners" on the basis of undefined symptoms.

The natural history of spontaneous improvement of GOR in neonates dictates that any treatment will seem to be efficacious in treating GOR. Therefore, differentiating the natural history of the disease from effect of an intervention would require comparison with a control group, and a RCT would be essential in minimising bias and confounding. Important outcomes need to be assessed such as: symptoms or signs of GOR (including regurgitation, possetting, vomiting, haematemesis, failure to thrive, irritability, disturbed sleep, cough, apnoeas, oxygen desaturation and bradycardias); gastric and oesophageal acidity based on pH monitoring; and side effects of the therapy - bowel obstruction, diarrhoea, aspiration, cough and colic.

## AUTHORS' CONCLUSIONS

### Implications for practice

At present, there is no evidence from randomised controlled trials to support or refute the efficacy of feed thickeners in newborn infants with GOR. Although thickening feeds is a simple and cheap manoeuvre, there are some theoretical side effects of this treatment such as delayed gastric emptying with increased caloric density of feed. Therefore, given the absence of evidence, we do not recommend using thickening agents for management of GOR in the neonatal population.

### Implications for research

Given the lack of evidence from randomised controlled trials (RCT) on use of thickeners in management of GOR in neonates, we recommend that a randomised controlled study in the neonatal population be performed.

An RCT design would be vital as GOR has a strong tendency to resolution. Therefore, differentiating the natural history of the disease from effect of an intervention would require comparison with a control group. The age of the study population should be full term infants up to four weeks and preterm infants up to 44 weeks corrected age. We recommend that the intervention of thickening of infant feeds be compared to control, unthickened feeds. The outcome measures should be symptoms of reflux disease and pH probe study parameters. The size of the study should be sufficient to show differences in effect and we estimate, based on completed infant studies, that it would involve randomisation of at least 50 patients (Miller 1999).

## POTENTIAL CONFLICT OF INTEREST

nil

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\*Indicates the major publication for the study

**T A B L E S****Characteristics of excluded studies**

<b>Study</b>	<b>Reason for exclusion</b>
Bailey 1987	Patients' ages ranged from 4 days to 14 months. This was a cross over study in which each patient received both thickened and unthickened feeds, but it does not appear to be a randomised cross over trial.
Carcassonne 1975	No control group was used. The age group ranged from 40 days to five years. The patients used had anatomical abnormalities, severe burns or brain tumours.
Gouyon 1989	This study evaluated smectite in newborn infants with gastroesophageal reflux. It was rejected because of the lack of randomisation and use of further “thickeners” in some patients in both intervention and placebo group on the basis of undefined symptoms. Gouyon 1988 is an abbreviated report of the same study.
Greally 1992	The study population was aged between 2 and 18 months. Infants were randomised to receive either cisapride or gaviscon/carobel. There was no placebo group.

Iacono 2002	The study included 166 bottle fed infants under 4 months of age. Once again this included patients who were outside our definition of the neonatal group.
Khoshoo 2000	Age range was from 4 to 10 months. Not a RCT.
Le Luyer 1992	The study group ranged in age from 2 weeks to 57 months. Not a RCT (no control group). Patients were divided into two groups using different doses of a thickener (sodium alginate) without randomisation.
Miller 1999	This study was rejected on the basis of the age group encompassing 0 to 12 months. The outcome data for newborn infants could not be separated from the data of older infants.
Orenstein 1987	Ages were between 4 to 34 weeks of age. This was a cross over study, not a RCT. Each patient received both thickened and unthickened feeds.
Vandenplas 1994	Ages ranged from 1 week to 4 months old. The outcome data for newborn infants could not be separated from the data of older infants.
Vanderhoof 2003	The inclusion criteria included infants of age 14 to 120 days which was outside of the neonatal definition. The mean was 61 days which was well outside of the neonatal age definition.
Weldon 1972	Not a RCT. No control group.
Wenzl 2003	Cross over studies were excluded. The study included babies <4 months old. The mean age was 42 days which was above the definition of our neonates (<28 days post partum).
RCT = randomised controlled trial.	

## GRAPHS AND OTHER TABLES

This review has no analyses.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Food Additives [\*therapeutic use]; Gastroesophageal Reflux [\*therapy]; Infant, Newborn

### MeSH check words

Humans

## COVER SHEET

<b>Title</b>	Feed thickener for newborn infants with gastro-oesophageal reflux
<b>Authors</b>	Huang R-C, Forbes DA, Davies MW
<b>Contribution of author(s)</b>	Rae-Chi Huang - wrote protocol, undertook literature search and critical appraisal of studies, wrote review, undertook review in 2004. Mark Davies - instigated review, co-wrote protocol, undertook literature search and critical appraisal of studies, co-wrote review David Forbes - gastroenterology advice, revised review
<b>Issue protocol first published</b>	2001/3
<b>Review first published</b>	2002/3
<b>Date of most recent amendment</b>	26 May 2004
<b>Date of most recent SUBSTANTIVE amendment</b>	11 March 2002
<b>What's New</b>	This is an update of the review "Feed thickener for newborn infants with gastro-oesophageal reflux" published in The Cochrane Library, Issue 3, 2002 (Huang 2002).

Additional studies were searched for using the same criteria and four additional studies were identified. They were considered and included in “excluded studies”. No new trials were identified which fulfil our criteria. Therefore, there are no substantive changes in the review update.

<b>Date new studies sought but none found</b>	Information not supplied by author
<b>Date new studies found but not yet included/excluded</b>	Information not supplied by author
<b>Date new studies found and included/excluded</b>	17 April 2004
<b>Date authors’ conclusions section amended</b>	Information not supplied by author
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