Systematic review

Distal feeding–bowel stimulation to treat short-term or long-term pathology: a systematic review

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ABSTRACT

Background Distal feeding (DF) describes the insertion of a feeding tube into a fistula or stoma to administer a liquid feed into the distal bowel. It is currently used clinically in patients who are unable to absorb enough nutrition orally. This systematic review investigates DF as a therapeutic measure across a spectrum of patients with stomas and fistulae.

Methods A total of 2825 abstracts and 44 full-text articles were screened via OVID. Fifteen papers were included for analysis. Randomised controlled trials, cohort and observational studies investigating DF as a therapeutic measure were included.

Results Three feeds were used across the studies—reinfusion of effluent, infusion of prebiotic or a mixture. The studies varied the length of feeding between 24 hours and 61 days, and the mode of feeding, bolus or continuous varied.

DF was demonstrated to effectively wean patients from parenteral nutrition in two papers. Two papers demonstrated a significant reduction in stoma output. Three papers demonstrated improved postoperative complication rates with distal feeding regimens, including ileus (2.85% vs 20% in unfed population, p=0.024). One paper demonstrated a reduction in postoperative stool frequency.

Conclusions This review was limited by study heterogeneity and the lack of trial data, and in the patient groups involved, the variability in diet and length of regimen. These studies suggest that DF can significantly reduce stoma output and improve renal and liver function; however, the mechanism is not clear. Further mechanistic work on the immunological and microbiological action of DF would be important.

Summary box

Distal feeding is a treatment modality used in patients with intestinal failure internationally that is demonstrated to

- Reduce stoma output, especially in proximal enterocutaneous fistulae.
- Reduce reliance on parenteral nutrition, or allow patients to be entirely weaned from its use.
- Improve renal and liver function in the acute setting.

What are the new findings?

- Distal feeding reduces postoperative complications (ileus) in patients following rectal cancer resection.
- It has a direct impact on the local immune response in the gut and increases gut enterocyte cell proliferation markers, suggesting that it improves gut absorptive capacity.
- It reduces stool frequency in patients who have undergone reversal of stoma following formation of ileoanal pouch.

How might it impact on clinical practice in the foreseeable future?

- The implications of this treatment are wide ranging. First, in any group of patients who are undergoing reversal of stoma, this simple intervention performed by patients themselves could have a significant clinical impact on their postoperative complication rates, long-term bowel function and directly on the normal function of the gut. This review demonstrates that this therapy could help a wide variety of patients with ostomies, and not just those with insufficient lengths of bowel to absorb nutrition normally.

INTRODUCTION

Distal feeding (DF) describes the insertion of a feeding tube into a fistula or stoma to administer a liquid feed into the distal bowel. It is currently used clinically in patients who are unable to absorb enough nutrition orally.[1] It is most widely used

in intestinal failure (IF) for patients with short bowel syndrome (SBS) but has recently been investigated in patients following low anterior resection for rectal cancer.[2]

Distal feeding is usually used in one of two ways: either as a chyme reinfusion—where small bowel effluent is either manually or mechanically recycled through the defunctioned limb of the distal bowel[3]; or as bolus feeding with a prebiotic solution, usually elemental, polymeric or semi-polymeric.[4] Advantages are clinically seen with both methods in patients who do not have sufficient length of bowel in continuity to adequately absorb nutrients. Large retrospective studies have demonstrated a reduction in intestinal output,[5] improved nitrogen coefficients,[6] normalised citrulline (a marker of bowel mass and therefore bowel health), improved nutritional status and reduction in liver function test (LFT) abnormalities.[7] Microbiological, hormonal and immunological factors are likely to be involved in the therapeutic action of distal feeding.

Distal feeding is used in several disease states: in patients with longstanding intestinal failure on parenteral nutrition to reduce stoma output, in patients prior to re-establishment of continuity and in patients with immediate iatrogenic injuries following emergency surgery. These patients encompass a variety of both pathologies including inflammatory bowel disease, ischaemic bowel disease and rectal cancer.

The interest in this area is due to its potential range of applications, from bowel prehabilitation to improving postoperative function. This systematic review investigates both the clinical impact, practical application and the mechanisms of action that are currently known.

METHODS

Medline (1948 to present) and EMBASE (1974 to present) were searched via OVID, including non-English language publications. Web of Science and grey literature were also searched, along with a hand search of the paper references included. The study was registered on PROSPERO (CRD42019130818) prior to data extraction and analysis of results.

The terms used were

ENTEROCLYSIS; FISTULOCLYSIS; DISTAL or EFFERENT or enteral or Limb or intracolonic or intra-colonic or intraileal or intra-ileal adj5 (FEEDING or nutrition or infusion*; chyme reinfusion; bowel or stoma*; STOMA, ILEOSTOM*, COLOSTOM*; MUCUS FISTULA*; ENTEROCUTANEOUS FISTULA*; INTESTINAL FISTULA*; colon* absorption; enteric fistula*; ileum, enterostom*;

SEARCH

All databases were searched aiming to capture a large number of papers but with high sensitivity. Due to the complexity of this search, and the varied nature of the terms concerning the therapeutic measure, this search was assisted by Imperial College medical library. Careful consideration was given to the fact that multiple different terms are used for distal feeding including efferent limb feeding, distal feeding and bowel stimulation. Exploded search terms and Boolean operators were used to maximise discovery of papers, alongside the suffix .mp (to map terms together).

INCLUSION CRITERIA

All interventional and observational studies were included if they used distal feeding as a therapeutic measure for patients and described intubating the distal limb and feeding with any liquid diet.

EXCLUSION CRITERIA

Case series with fewer than 10 participants, any studies concerning paediatric patients, any basic physiology studies examining normal enteral reflexes in a normal population of patients, all systematic reviews, letters, case reports and conference proceedings were excluded. Where results of the intervention were reported, unless clinical or mechanistic, the study was excluded.

STUDY SELECTION

Papers were manually selected and individually reviewed by SMD and LG. Discrepancies were resolved with discussion and mutual agreement. Studies were selected depending on whether they described the process of distal feeding as being different to tube feeding as the main source of enteral nutrition—that is, papers on PEG or jejunostomy feeding as an oral alternative were not included, but papers discussing distal feeding as a contemporaneous treatment or either oral or parenteral nutrition (PN) were.

We were unable to acquire one paper of key interest, despite attempts to contact the author and request via specialist library services, otherwise all relevant papers were obtained, translated as necessary and included. Aside from this, biases related to language and availability were eradicated.

All studies except two were observational studies in very specific groups of patients, and both trials did not detail their randomisation process, so the impact of selection bias was difficult to determine.

SYNTHESIS OF EVIDENCE

Of 2825 studies screened, 14 reached the selection criteria for analysis. One further paper was identified in a reference search that was not identified in our initial search. Therefore, 15 studies are included (figure 1).

Summary measures were heterogeneous and difficult to compare, with these papers representing both rare groups of patients and largely new experimental outcomes; therefore, a meta-analysis was impossible to accomplish.

Type, length and method of distal feeding

Three distal feeding diets were discussed across this cohort of studies—the first is an elemental diet, of which

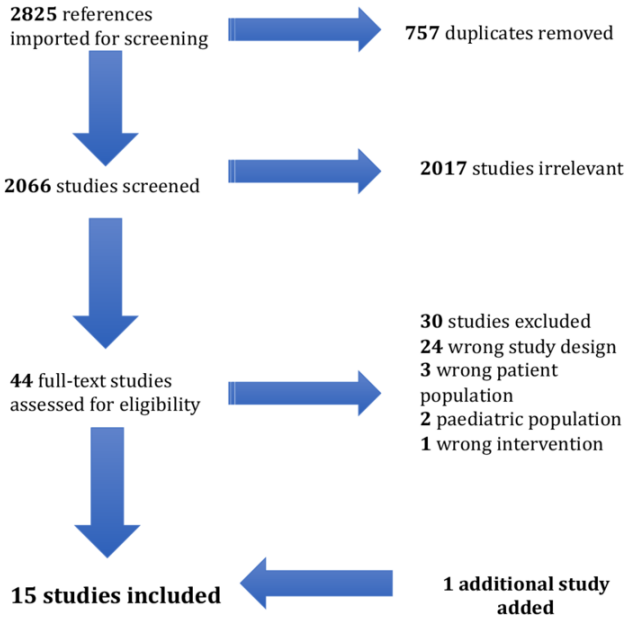

Figure 1 PRISMA schematic.

several varieties are used depending on the geographical location of the study.[8] Second, small bowel effluent is reinfused either manually by sieving for larger pieces of matter and then infusing via a feed bottle, or using a specialised infusion pump into the distal limb.[9] The third feeding regimen, which is prevalent across several studies, is a mixture of chyme and elemental feed. Finally, patients have been distally fed with thickened saline (Abrisqueta *et al*)[2] or with a glucose solution as a control (Lévy *et al*).[10] Abrisqueta *et al* used saline thickened with a Nestle product which is a complex carbohydrate, therefore can be considered a prebiotic feed. Infusions of feed were continuous, interrupted or given as bolus once or twice a day.

Feed choices between these centres appear to be divided in rationale between trophic feeding–baseline maintenance of bowel mucosa with a small amount of a prebiotic feed, or as a full substitute for the absent faecal stream, and this is reflected in table 1, which describes the diets used.

Length of feeding

Length of feeding varied between 24 hours and 61 days between studies, and it also varied between patients in the same study; for example, Berta *et al*[9] fed patients up until restoration of continuity surgery and Lévy *et al*[10] fed patients for a single day and observed the impact on stoma output. The different feeding regimen lengths are likely based on different study aims—stoma output versus impact on physiology versus length of hospitalisation.

Impact of distal feeding on clinical outcomes

Distal feeding has several documented outcomes which are similar across studies. First, improved nutritional state is measured in several ways, such as patient weight, reduction in PN requirement, reduction in stoma output or improvement in electrolytes, or length of time to restoration of continuity.

Second, resolution of postoperative complications is broadly divided into immediate complications such as postoperative ileus, wound infection and re-admission, and general markers of outcome such as length of hospital stay or the cost of PN per admission.

Reduction in PN use

Several papers discuss a reduction in PN as a significant end point, particularly in patients with SBS. Markers to discern whether clinicians were happy to reduce PN included increase in citrulline, which is a marker of small bowel mass, and increase in patient weight following distal feeding.

One paper (Coetzee *et al*[11]) examined 20 patients with proximal enterocutaneous fistulae. These patients were fed with chyme which started at day 14 of admission, given continuously at 20 mL/h via a feed bottle and were compared with patients managed without chyme refeeding in the same period. Re-continuity surgery was attempted when the patients had stable electrolytes and weight. The unfed group required PN for mean 48 days compared with the fed group which was weaned from PN at a mean of 20 days.

Farrer *et al*[12] examined 12 patients with intestinal failure and jejunocutaneous and ileocutaneous fistulae, with outputs of greater than 500 mL a day. Distal feed was a standard polymeric mix, containing 15% medium-chain fatty acids, and if successful, the rate was increased to 20 mL/h/day. The main outcome measure was cost compared with PN and the end point was operative closure of fistula. Distal feeding replaced PN in 11 out of 12 patients. There was no difference in fistula output between groups.

Reduction in stoma output

Lévy *et al*[10] administered a single day of chyme reinfusion, on a background of a PN only with no oral intake, in 30 patients with peritonitis and either an enterocutaneous fistula or temporary double-barrelled stoma. This led to a significant reduction in mean proximal output of 30% ($p<0.001$). After a further 24 hours, a subsequent distal feed of dialysate solution was given to 13 of these patients. This also resulted in a reduction in mean proximal output by 20% ($p<0.01$).

Picot *et al*[7] examined 232 patients from 2000 to 2014 referred for chyme reinfusion, of whom 212 had intestinal failure. They used a novel reinfusion device, and data were collected before and after reinfusion. They demonstrated a reduction in intestinal output, improved nitrogen coefficients, normalised citrulline, improved nutritional status and a reduction in LFT abnormalities (88%–51%). The main problem the team identified with this form of feeding were the dietary restrictions for the patients involved since only pureed food could be eaten, otherwise the reinfusion device was blocked.

Table 1 Type and length of distal feeding regimen

	Study type	Country	Study size	Patient inclusion criteria	Feed type	Feed regimen
Abrisqueta 2014	Single blinded randomised control trial	Spain	n=70 35 controls, 35 intervention	Low anterior resection patients with ileostomy	Thickened saline	Bolus feed 500 mL, 2 weeks
Berta 1980	Case series	France	n=16	Enterocutaneous fistulae, all aetiologies	Reinfusion of chyme	Continuous infusion—collecting chyme and reinfusion/15–90 days prior to continuity surgery
Calicis 2002	Prospective cohort study	France	n=21	Prospective cohort study on patients with postoperative peritonitis	Reinfusion of chyme, some cases mixed with elemental feed	Continuous infusion for 62 days
Coetzee 2014	Case–control study	South Africa	n=20	Enterocutaneous fistulae	Reinfusion of chyme—manually sieved 12 patients had additional feed mixed with effluent	Reinfusion of chyme manually filtered, infused 20 mL/h, stepped up on day 2/41±16 days
Cosnes 1990	Prospective observational study	France	n=10	Short bowel syndrome and long-term enterocutaneous fistula	Chyme vs Vivonex/Entéronutril with saline	Continuous infusion 20 mL/h with three 1 h interruptions a day/32±12 days
Kuster 1993	Non-randomised study	USA	n=34 10 control, 24 intervention	Patients with ulcerative colitis following total colectomy+ileoanal J pouch reconstruction with temporary ileostomy+mucous fistula	Ensure mixed 50% with warm water	50 mL twice a day increasing to 250 mL 4 weeks postoperatively
Lévy 1983	Prospective observational study	France	n=30	Patients with small bowel peritonitis	Reinfusion of chyme vs infusion of lactic acid/glucose solution	Continuous feed with stylised machine, variable times
Lévy 1988	Prospective observational study	France	n=20	Patients with high output enterocutaneous fistulae and short bowel syndrome	Reinfusion of chyme	24 h only continuous feed, day 3 of observation period
Nagar 2018	Prospective observational study	India	n=35	Patients with short bowel syndrome and high enterocutaneous fistulae (<120 cm from duodenojejunal flexure)	Glucose solution then reinfusion of chyme	Sieved manual reinfusion for 4–6 weeks prior to restoration of continuity
Picot 2017	Prospective observational study	France	n=212	Patients with intestinal failure and temporary double enterostomy	Reinfusion of chyme	Enteromate2 system—continuous reinfusion of chyme
Meng 2014	RCT (randomised method not detailed)			Patients with enterocutaneous fistulae	Nutrison/Nutrison fibre mixed with chyme reinfusion vs Nutrison/Nutrison	8 days of treatment assessed—slow continuous infusion initially, then increased
Teubner 2004	Prospective observational study	UK	n=12	Patients with ileocutaneous or jejunocutanous fistulae	Polymeric feed	Continuous feed
Wu 2014	Retrospective observational study	China	n=95 60 controls, 35 intervention	High output high enterocutaneous fistulae with intact small bowel length >100 cm	Reinfusion of chyme and enteral feeding vs enteral feeding	Continuous feed—at least 24 days of reinfusion
Zhu 2011	Prospective observational study	China	n=16	Patients with enterocutaneous fistulae	Reinfusion of chyme and enteral feeding	10-day NG feed only, 10-day reinfusion of chyme—collected 2–4 hourly and continuously reinfused
Zhu 2015	Prospective observational study	China	n=10	Patients with high intestinal perforation	Reinfusion of chyme	10 day NG feed only, 10 days reinfusion of chyme—collected 2–4 hourly and continuously reinfused

Reduction in postoperative complications

Abrisqueta *et al*[2] discussed the reduction of postoperative ileus in their paper looking at a patient cohort following low anterior resection with protective ileostomy.

They defined postoperative ileus as an 'intolerance to oral food' in the absence of mechanical bowel obstruction. This study showed that the stimulated group had a reduced rate and duration of postoperative ileus (2.85% vs 20%, p=0.024), time to tolerating food (1.06 days[1–3] vs 2.57 days,[1–14] p=0.007) and reduced time to initial flatus (1.14 days[1 2] vs 2.85 days,[1–17] p≤0.001).

Meng *et al*[13] identified a 11% reduction in postoperative complications which were ill defined.

This paper compared hospital length of stay and cost of treatment which were statistically reduced (p<0.05) in patients who were distally fed. Clinical outcomes related to weaning of PN and improvement in electrolyte balance or 'complications' which the author did not fully define. The recruited group had a clinical success rate of 96.63% when compared with control 79.63% (p<0.05). The incidence of complications from the observation group is 7.27% (4/55), compared with 18.52% (10/54) in the control group (p<0.05).

Kuster and Andree[14] examined the use of distal feeding to reduce stool frequency in patients with ileoanal pouch reconstruction. Thirty-four patients with ulcerative colitis who had undergone total colectomy, ileoanal J pouch reconstruction and formation of a mucous fistula

and ileostomy were included. Distal feeding was initiated via mucous fistula 4 weeks following surgery in 24 patients with 10 unfed controls as a comparator. Feed containing *Ensure* was mixed with 50% water starting at 50 mL twice daily and increasing to 250 mL as tolerated. A significant reduction in mean daytime stool frequency following ileostomy reversal, performed at 3 months, was noted at 10 days and 1 month post-surgery in the patients who received distal feeding (6.7 and 4.3 vs 14.2 and 11.3).

Improvement in liver function

Wu *et al*[15] distally fed 95 patients with high output fistulae (defined as a stoma output of greater than 500 mL a day). Thirty-five patients received fistuloclysis with total enteral nutrition (TEN). This cohort was divided into three subgroups: biliary fistula, jejunal-ileal fistula and duodenal fistula. Sixty patients were treated with TEN alone, and their fistula effluent was discarded and fluid inbalance corrected with intravenous fluid.

All of the patients improved their LFTs over the course of treatment, but in the DF group, a more profound, statistically significant reduction in LFTs was demonstrated. Wu *et al* also looked at efficacy of DF in different locations with patients with biliary fistula having the greatest response to DF and small bowel fistulae the least in terms of reducing LFTs. They also demonstrated a reduction in fistula output when distally fed. Finally, a statistically significant difference in 1-year survival was demonstrated between the distally fed group and the control group.

Economic impact of distal feeding

In the developed world, the price of PN is high, and therefore several papers from the UK, South Africa and India speculate on the impact of distal feeding reducing the overall cost of patient stay, either by reducing the length of time on PN or on hospital stay. These were not statistically analysed but are an important focus for future research.

MECHANISTIC OUTCOMES

Two papers investigated the mechanistic basis of distal feeding.

Improvement in immune response

Zhu *et al*[16] looked at intestinal intraepithelial T lymphocytes (IIELS) at three time points, taken 20 cm, 25 cm and 30 cm from the patients' fistula opening, during distal feeding alongside the expression of proliferating cell nuclear antigen (PCNA) in intestinal epithelial cells. PCNA is a marker reflecting cell division and proliferation.

They demonstrated an increase in IIELS after 14 days of intestinal fluid reinfusion ($p>0.05$), but not after 7 days ($p=0.544$). The percentage of IIELS and PCNA all increased following this feeding regimen ($p=0.000$).

Absorption of nutrition in the defunctioned gut

Zhu *et al*[17] undertook a longitudinal study comparing carbohydrate absorption from patient stool before and after distal feeding, by measuring volumes of proximal effluent and faecal mass.

The distally fed patients increased their absorption rate of carbohydrate when compared with pre-infusion levels ($90.9\pm7.8\%$ vs $82.7\pm15.2\%$), nitrogen ($82.4\pm49.8\%$ vs $67.2\pm15.4\%$) ($p<0.05$), serum protein and fibronectin: 285 ± 643.6 mg/L versus $157.0+22.6$ mg/L ($p<0.01$).

Discussion

These heterogeneous papers represent the scientific and clinical basis of a treatment modality that until 2015 was limited to patients following abdominal disaster or with long-standing IF and SBS. It is clear from the literature described that distal feeding reduces stoma output and PN requirements, and improves weight, electrolyte balance and enterocyte health. It is also suggested that distal feeding significantly reduces hospital stay and postoperative complications.

Several methods have been discussed to explain the mechanism for distal feeding. The first, proposed by Lévy *et al*, speculated that an inhibitory response was responsible for the reduction in stoma output demonstrated: the 'ileal brake'. The mechanistic papers from China suggest that a change in immune response is significant in restoring enterocyte health and function. These findings are significant, as they demonstrate the impact of feeding on adaptive immunity, which may start to explain the reduction in postoperative complications shown in the studies with clinical outcomes, and, by demonstrating an increase in carbohydrate, protein and fibronectin absorption, Zhu *et al* demonstrate a clear clinical benefit initiated at the bowel mucosa. However, despite these hypotheses, the mechanism of distal feeding remains unclear.

Although distal feeding has until now been used only in the setting of IF and SBS, the implications of it are widespread. This has the potential to impact all elective surgeries involving stomas or fistulae, and may, if the outcomes are similar to intestinal failure, reduce hospital stay, postoperative ileus and speed up a return to normal gut function. It may be the case that all relevant patients benefit from distal feeding as a form of bowel prehabilitation prior to surgery.

It is not clear what the optimal feed and feeding regimen are. This may be partly due to the heterogeneity of anatomy and aetiology, even within the small community of patients with SBS, or it may be due to practical elements of the feeding regimen. Specifically, unanswered questions regarding the practicalities of distal feeding include the timing and duration of feeding (in relation to restoration of continuity), the nature and volume of the feed (supplements vs chyme, for example) and the frequency of feed (are once and twice daily feeds equivalent?), and the views of patients

on distal feeding, both in general and in its specifics, all remain and will be crucial in determining a final and optimised regimen. Many of these questions may be best answered with an improved understanding of the mechanism of action, and may differ according to aetiology and anatomy, for example, the presence of the TI, the height and length of the distally fed segment, and the length of the residual colon. These studies were so heterogeneous that any form of formal systematic analysis was both implausible and impossible and represent the most significant limitation of this paper.

Whether distal feeding simply shortens the period of improvement in symptoms following restoration of continuity surgery, or has a more profound effect, either through reduction of complications following surgery or by facilitating an improved final level of function and quality of life, remains a crucial question, although this cheap and easy intervention may well be worthwhile even in the absence of the latter.

Currently, most patients being offered distal feeding in the UK are either those who have suffered abdominal catastrophe and have IF, or those with IF awaiting continuity surgery. Studies from South Africa, where distal feeding has been performed in the community, suggest that it may be of benefit as a form of bowel prehabilitation.

Two papers, Kuster *et al* and Abrisqueta *et al*, investigate alternative groups (patients with defunctioning ileostomies above ileoanal pouches and following anterior resection, respectively), but a key question, as to whether distal feeding is an acute intervention—that is, one to rapidly improve patient health when critically unwell or to slow down stoma output or a prehabilitative treatment, prior to planned surgery is not answered with this review.

St Mark's has been distally feeding patients with IF for the last 10 years, to similar clinical effect to that illustrated in this review. We also offer distal feeding for patients undergoing TME surgery with defunctioning loop ileostomy. Uptake among these patients is around 50%. Several of the questions requiring further investigation discussed earlier, including evaluation of the systemic immunological changes brought on by feeding, the qualitative impact of feeding and the optimal length and type of feed, are the subject of active research in our institution.

Contributors SMD and LG selected and analysed the papers. SMD wrote the paper with LG with editing input from MS, PT, AI-W and CJV. MY interpreted the Chinese papers. Clara Blanchard interpreted the French papers.

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