REVIEW ARTICLE

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Evidence of negative pressure therapy for anastomotic leak: a systematic review

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Abstract

Background: Anastomotic leak (AL) is a devastating complication. Several new treatment options are available, endoluminal negative pressure therapy is one. The aims of this systematic review are; to report success rates and stoma closure rates following endoluminal negative pressure therapy in colorectal AL patients.

Methods: A systematic review of MEDLINE, PubMed, Cochrane and Embase databases from inception to June 2018. Search limits were; English language, humans, sample >5 and >18 years. Search terms were Endospong* OR Endo-spong* OR Endo spong* OR Endoluminal negative pressure OR Endoluninal vac* OR Vacuum assisted OR negative pressure. Combined with colon OR rectum OR colorect* AND anastomotic leak OR leak*.

Results: Twenty articles met inclusion criteria. There were 334 patients. Reported success rates ranged from 60% to 100%. However, success definition varied considerably. The most widely used definition was endoscopic assessment of residual cavity size, but this also varied from 0.5 cm to 3 cm. Stoma closure rates were only reported in 11 studies and ranged from 31% to 100%. Complication rates were reported in 13 studies (65%). The most common was on-going sepsis.

Conclusions: Included studies suggest that 60–100% of ALs heal with endoluminal negative pressure therapy. However, results from this review need to be interpreted with caution because of the variable definition of success. A more objective assessment of success may be stoma closure but this is only reported in 60% of studies. Further studies are needed to assess the benefit of negative pressure therapy in anastomotic leaks.

Introduction

Anastomotic leak (AL) is a devastating complication following colorectal surgery[1,2] due to its associated morbidity and mortality.[3,4] AL has also been shown to be a costly complication not only from a societal fiscal perspective but also at a personal level in that defunctioning stomas may now be irreversible.[5] Furthermore, AL has been shown to increase the risk of subsequent recurrence in patients undergoing resection for a colorectal cancer.[1,3,4,6]

Because of the significance attached to AL numerous studies have looked at risk factors of AL and methods to allow early detection and treatment.[7] Well established risk factors for AL include the height of the rectal anastomoses, use of neoadjuvant radiotherapy as well as other patient factors such as preoperative nutritional status and smoking.[8–10] There is also evidence to suggest that those who suffer an AL have a high chance of ending up with a permanent stoma[11] and higher mortality especially if reintervention is required.[12] To mitigate the impact of an AL, a defunctioning ileostomy is commonly used for extraperitoneal rectal anastomoses. The use of near infrared technology has shown promise in reducing anastomotic failures from issues of vascularization.[5] More recently, it has also been demonstrated that the gut microbiome may have a role to play in AL which could explain the reason why AL classically occurs about a week after formation.[10,13] Notwithstanding this once the AL has occurred, management is variable. Newer methods of management include minimally invasive alternatives such as endoscopically placed endoluminal negative pressure therapy. These systems followed the successes of negative pressure wound management and apply the same pathophysiological principles in the pre-sacral space. Negative pressure therapy is thought to improve

the microcellular milieu and promote cell division thereby accelerating anastomotic healing and negating the adverse effects of AL.[14]

While the literature on endoluminal negative pressure therapy for AL has demonstrated some promising preliminary results most of these studies comprise of small numbers of heterogenous patients with variable definitions of success. Furthermore, the use of negative pressure therapy has not been adapted widely by local or international institutions, although this may reflect the labour intensive nature and cost associated with treatment rather than treatment failures. Endosponge is one such endoluminal negative pressure therapy device and seems to be the most commonly used. The primary aim of this systematic review is to report the documented success rate of endoluminal negative pressure therapy regarding AL in the colorectal population within the current literature. The second aim is to report on stoma closure rates following endoluminal negative pressure therapy in colorectal AL patients.

Methods

Protocol

The protocol of this systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines.[15] This manuscript also followed the PRISMA Statement.[16] Approval by the human research ethics committee was not required.

Search strategy

A sensitive literature search was conducted on MEDLINE, PubMed, Cochrane and Embase databases from inception to June 2018. The search was limited to English language, humans and participants over the age of 18 years. The search terms used were Endospong* OR Endo-spong* OR Endo spong* OR Endoluminal negative pressure OR Endoluninal vac* OR Vacuum assisted OR negative pressure. This was combined with search terms colon OR rectum OR colorect* AND anastomotic leak OR leak* using Boolean connectors. References of included articles and review articles were hand searched to ensure the search was comprehensive.

Study selection

Peer-reviewed articles of any design investigating the use of endoluminal negative pressure therapy for a colorectal AL were included. Eligible studies should include the investigation on at least one of the following outcomes in the colorectal population: (i) documented success rate of endoluminal negative pressure therapy; and (ii) stoma closure rates following endoluminal negative pressure therapy. We excluded studies that reported ≤5 patients, commentaries/editorials and abstracts published in conference proceedings. Studies reporting on other minimally invasive AL management systems (e.g. clips, stents) were excluded unless data on endoluminal negative pressure therapy could be

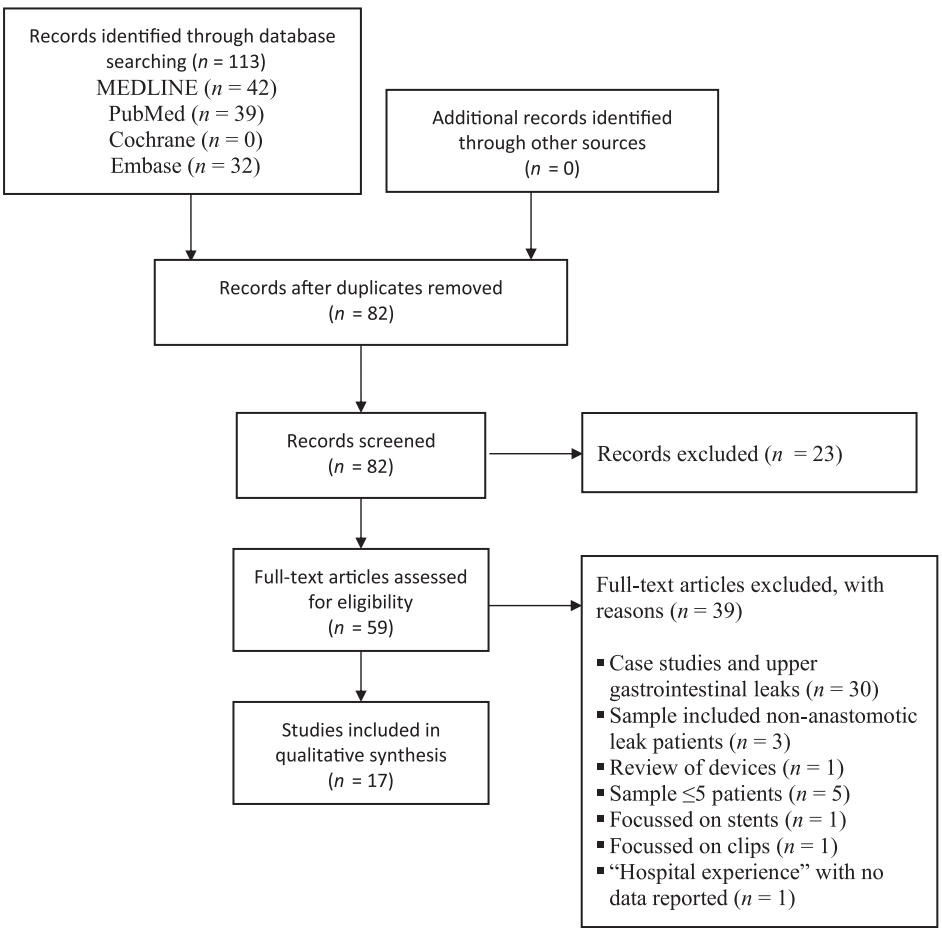

Fig 1. Flow diagram of literature search and inclusion criteria.

extracted independently. Studies where endoluminal negative pressure was utilized for pelvic sepsis from causes other than an AL were excluded unless data for AL patients could be extracted independently.

Data extraction and critical appraisal

Two reviewers independently extracted data from studies in a piloted data extraction sheet. The following data were extracted from the included studies: demographic details, definition of success, success rate, complications, defunctioning stoma rate, stoma reversal rate and reasons for not reversing. Additional data was also collated: tumour type, neoadjuvant radiotherapy, type of anastomoses, type of negative pressure therapy device used, leak identification from index surgery, time until initiation of endoluminal negative pressure therapy, amount of days per sponge change, number of sponge changes, days of therapy, additional therapy used and follow-up. Disagreements within the data extraction were resolved between the review authors.

Statistical analysis

The intention of this systematic review was to pool data particular to our aims. These aims were to investigate the documented success rate of endoluminal negative pressure therapy regarding AL in the colorectal population and to highlight the reported stoma closure rates following endoluminal negative pressure therapy in colorectal AL patients. However, due to the heterogeneity encountered between the included studies, it was not possible or appropriate to pool the findings. Therefore the results are presented descriptively.

Results

Study selection

Search of Medline (n = 42), PubMed (n = 39), Cochrane (n = 0) and Embase (n = 2) databases yielded 113 articles; no additional material was found. Of these, 17 articles met the inclusion and exclusion criteria and were included in the review (Fig. 1).

Study characteristics

There were no randomized controlled trials identified. Of the 17 articles included, 10 were prospective cohort studies and seven were retrospective cohort studies (Table 1). The majority of the studies were undertaken in European institutions (n = 15), with the remaining two studies undertaken in England (n = 1) and USA (n = 1).

Patient characteristics

A total of 264 patients from the 17 studies were treated with endoluminal negative pressure therapy. Gender was reported in

Table 1 Study characteristics

Author, year	Sample, *n*	Study type	Sex, *n* (%)	Age range (median)	Country	Tumour type (%)	Received neoadjuvant radiotherapy, *n* (%)	Type of rectal anastomoses/operation (%)
Areezo, 2015	14	R	F 9 (64)	55–85 (68)	Italy	12 M (86); 2 B (14)	7 (58)	AR 12 (86%); transanal resection 2 (14%)
Borstlap, 2017	30	P	F 11 (37)	40–79 (66)	Netherlands	30 M (100)	22 (73)	AR 30 (100%)
Gardenbroek, 2014	15	P	F 3 (20)	25–56 (37)	Netherlands	15 B (100)	0 (0%)	IPAA 15 (100%)
Glitsch, 2008	17	P	F 3 (18)	42–84 (62)	Germany	17 M (100)	9 (53)	AR 13 (76%); STC 3 (18%); right hemicolectomy 1 (6%)
Keskin, 2015	15	R	F 8 (53)	24–72 (NR)	Turkey	12 M (80); 3 B (20)	6 (50)	AR 12 (80%); IPAA 2 (13%); ileorectal anastomoses (IRA) 1 (7%)
Manta, 2016	7	R	NR	23–28 (NR)	Italy	NR	NR	AR 4 (57%); left hemicolectomy 2 (29%); ileorectal anastomoses 1 (14%)
Mencio, 2018	10	R	F 5 (50)	NR	USA	NR	NR	AR 10 (100%)
Milito, 2017	14	P	F 4 (29)	45–48 (65)	Italy	14 M (100)	14 (100)	AR 14 (100%)
Mussetto, 2017	11	R	F 5 (45)	55–82 (NR)	Italy	11 M (100)	5 (45)	AR 11 (100%)
Nerup, 2013	13	R	F 2 (15)	36–71 (64)	Denmark	13 M (100)	6 (46)	AR 13 (100%)
Rottoli, 2018	8	P	NR	18–59 (37)	Italy	8 B (100)	0 (0)	IPAA 8 (100%)
Srinivasamurthy, 2013	8	R	F 1 (12.5)	45–79 (66)	England	7 M (88); 1 B (12)	7 (100)	AR 7 (86%); IPAA 1 (14%)
Strangio, 2015	25	P	F 7 (28)	37–89 (NR)	Italy	22 M (88); 3 B (12)	18 (82)	AR 19 (76%); left hemicolectomy 5 (20%); IPAA 1 (4%)
van Koperen, 2009	16	P	F 7 (44)	19–78 (64)	Netherlands	13 M (81); 3 B (19)	11 (85)	AR or IPAA (no numbers for each given)
Verlaan, 2011	6	P	F 1 (17)	29–68 (52)	Netherlands	1 M (17); 5 B (84)	1 (100)	IPAA 5 (84%); AR 1 (6%)
von Bernstorff, 2009	26	P	F 5 (21)	42–84 (64)	Germany	26 M (100)	14 (54)	AR 24 (92%); ileorectal anastomoses 2 (8%)
Weidenhagen, 2008	29	P	F 5 (17)	42–79 (NR)	Germany	28 M (97); 1 B (3)	9 (32)	AR 29 (100%)

AL, anastomotic leak; APR, abdominoperineal resection; AR, anterior resection; B, benign; F, female; IPAA, ileal pouch anal anastomoses; LAR, low anterior resection; M, malignant; NR, not reported; P, prospective; R, retrospective; STARR, stapled transanal resection of the rectum; STC, subtotal colectomy; TC, total colectomy; TEM, transanal endoscopic microsurgery; TME, total mesorectal excision; TPC, total proctocolectomy.

Table 2 Sponge therapy and additional therapies

Author, year	Sponge device	Leak identified (days) post index surgery (range)	Time from index operation to sponge placement (days)	Amount of days to change sponge	Number of sponge changes	Days of sponge therapy	Additional therapy used
Arezzo, 2015	ES	10/14 < 60 days; 4/14 > 60 days	Mean (range): NR (5–485)	2–3 days	Median (range): 12.5 (4–40)	NR	OTSC 2/14; fibrin glue 1/14
Borstlap, 2017	ES	Median (range): 14 (3–75)	Median (range): 23 (3–158)	3–4 days	Median (range): 4 (2–15)	Median (range): 13 (5–51)	Suture closure
Gardenbroek, 2014	ES	NR	Median (range): 2 (NR)	NR	Median (range): 3 (3–4)	Median (range): 12 (7–15)	Suture closure
Keskin, 2015	ES	Early group: 8/15 < 30 days; late group: 7/15 > 30 days	Early group: mean (range): 15 (6–27); late group: mean (range): 173 (43–343)	NR	Mean (range): 2 (1–5)	NR	Drain placed in the remaining cavity
Manta, 2016	ES	1/7 < 7 days; 6/7 > 7 days	NR	NR	NR	NR	NR
Milito, 2017	ES	Median range): 14 (7–21)	NR	NR	Median (range): NR (3–14)	Median (range): 35 (16–51)	NR
Mussetto, 2017	ES	NR	NR	2–3 days	Mean (range): 16 (9–23)	Mean (range): 37 (18–65)	NR
Nerup, 2013	ES	NR	NR	2–3 days	Mean (range): 8 (1–18)	Median (range): 18 (3–40)	NR
Rottoli, 2018	ES	Median (range): 14 (6–35)	Median (range): 6.5 (1–15)	2–3 days	Median (range): 3 (1–10)	Median (range): 12 (3–32)	Abscess drained via CT prior to ES
Srinivasamurthy, 2013	ES	Median (range): 29 (10–115)	Mean (range): 87 (10–398)	NR	Median (range): 4 (1–7)	Median (range): 26 (7–49)	NR
Strangio, 2015	ES	Median (range): 17 (0–102)	Median (range): 16 (0–53)	2–3 days	Median (range): 9 (1–39)	Median (range): 28 (7–224)	NR
van Koperen, 2009	ES	Median (range): 11 (3–150)	Median (range): 41 (13–1602)	3–4 days	Median (range): 13 (8–17)	Median (range): 40 (28–90)	NR
Verlaan, 2011	ES	Mean (range): 12 (5–21)	Mean (range): 13 (8–23)	NR	Median (range): 3 (1–6)	Median (range): 14 (5–28).	Suture closure 4/6; OTSC 2/6
von Bernstorff, 2009	ETVARD	Mean (range): 11 (1–34)	Mean (range): 15 (3–39)	2–4 days	Mean (range): 6 (1–24)	Mean (range): 22 (4–88)	NR
Glitsch, 2008	ETVARD	NR	Mean (range): 15 (3–39)	NR	Median (range): 5 (1–24)	Median (range): 21 (4–88)	Fibrin glue 15/17
Mencio, 2018	'Granulo-foam'	NR	Mean (range): 171 (6–534)	4 days	Mean (range): 6 (NR)	Mean (range): 23 (NR)	NR
Weidenhagen, 2008	'Open cell polyurethane ether sponge'	Mean (range): 8 (3–17)	NR	2–3 days	Median (range): 11 (1–27)	Median (range): 34 (4–79)	Fibrin glue 9/29

ES, endo-sponge; ETVARD, endoscopic transanal vacuum-assisted rectal drainage; NR, not reported.

15 (88%) studies and female patients accounted for 29% of the total study cohort. Age ranged from 18 to 89 years. Resection reason was recorded in 15 of the 17 studies, 78% were undertaken for malignancy with 62% of these receiving neoadjuvant radiotherapy (Table 1).

Procedural and leak characteristics

The majority of recorded resection type was anterior resection (75%). Endosponge was the most frequently used device (76%). Leak identification following index surgery occurred within 0 to 150 days, while the actual placement of negative pressure

Table 3 Definition of success, stoma reversal and follow-up

Author, year	Definition of success	Success rate (%)	Complications (%)	Defunctioning stoma	Stoma reversal rate (%)	Reason for failure to reverse stoma	Follow-up (months)
Arezzo, 2015	'…healed when direct endoscopic examination with the aid of direct water soluble contrast injection during endoscopy showed a complete restoration of the wall epithelium.'	79%	Peritonitis 1/14 (7%); poor compliance 2/14 (14%)	8/14 primary; secondary NR	NR	NR	NR
Borstlap, 2017	'…no signs of contrast extravasation during abdominal CT or contrast enema and there was intact anastomosis during endoscopy'	70%	Nil	23/30 primary; 7/30 secondary	67%	Chronic sinus 7/30 (23%); patient choice 2/30 (7%)	Median (range): 14 (7–29)
Gardenbroek, 2014	'no sign of leakage of contrast during a contrast enema or abdominal CT scan with intravenous, oral and rectal contrast and an intact anastomosis during endoscopic inspection'	100%	Nil	4/15 primary; secondary NR	93%	High stoma output 1 (7%)	Median (range): 25 (12–39)
Glitsch, 2008	'once the cavity was <1.5 × 1.5 cm treatment ceased'	94%	Ongoing sepsis 1 (6%)	13/17 primary; secondary NR	NR	Patient morbidity 1 (6%)	Median (range): 2 (2)
Keskin, 2015	'Treatment was discontinued as soon as sufficient granulation tissue had developed in the cavity…'	80%	Pelvic sepsis 2/15 (14%); bleeding 1/15 (7%)	14/15 (does not specify if primary or secondary)	71%	Mortality 3 (20%)	NR
Manta, 2016	'A complete leakage closure was verified at endoscopic and/or radiological assessment'. '…until fistula closure was achieved…'	100%	Nil	NR	NR	NR	NR
Mencio, 2018	'…resolution of the leak or perforation with restoration of GI continuity…'	60%	Nil	7/10 primary; 3/10 secondary	NR	NR	Median (range): 1 (1)
Milito, 2017	'Complete healing was defined as endoscopically proven closure of the insufficiency cavity with achievement of the normal mucosa level'	93%	Pain 5/14 (36%)	14/14 primary	NR	NR	NR
Mussetto, 2017	'Closure was defined as a decreased cavity covered with granulation tissue that did not allow the insertion of a new sponge'	91%	Anastomotic stricture 2/11 (18%)	11/11 primary	91%	Treatment failure 1/11 (9%)	Mean (range): 29 (6–64)
Nerup, 2013	'We ceased treatment when the cavity was about 3 cm wide and covered with granulation tissue'	100%	Colonic stenosis 1/13 (8%)	13/13 primary	92%	Colonic stenosis 1/13 (8%)	NR

Table 3 Continued

Author, year	Definition of success	Success rate (%)	Complications (%)	Defunctioning stoma	Stoma reversal rate (%)	Reason for failure to reverse stoma	Follow-up (months)
Rottoli, 2018	'Healing was defined as the closure of the defect after a progressive reduction in size of the cavity with-out signs of infection or complications, not requiring any intervention than the follow-up pouchoscopy'	100%	Nil	8/8 primary	88%	Patient choice 1/8 (12%)	Median (range): 1 (NR)
Srinivasamurthy, 2013	'complete closure, or a reduction in the size of the abscess cavity'	75%	Iatrogenic intra-abdominal injury during sponge placement 1/8 (12%)	8/8 primary	64%	Colovesical fistula 1/8 (12%); perianal sepsis 1/8 (12%); iatrogenic injury 1/8 (12%)	Median (range): 41 (10–45)
Strangio, 2015	'when the cavity was less than 1 cm in diameter'	88%	Ileal fistula 1/25 (4%); ureteric fistula 1/25 (4%); pararectal abscess 1/25 (4%)	13/25 (does not specify if primary or secondary)	85%	NR	Median (range) 9 (5–12)
van Koperen, 2009	'Definitive resolution'	65%	Bleeding 1/16 (6%); pain 1/16 (6%); failure 1/16 (6%)	9/16 primary; 7/16 secondary	31%	Awaiting reversal 2/16 (12%); permanent stomas due to malignancy 2/16 (12%)	Median (range) 4 (2–16)
Verlaan, 2011	'…cavity considered clean'	83%	Nil	0/6 primary; 5/6 secondary	100%	Not applicable	NR
von Bernstorff, 2009	'Once the size of the cavity had decreased to less than 1.5 cm × 1.5 cm in depth and width. Endpoint of the study was complete closure of the cavity'	88%	Intra-abdominal fistulas 2/26 (8%); poor compliance 1/26 (4%)	18/26 primary; 3/26 secondary	NR	NR	Median (range): 2 (2)
Weidenhagen, 2008	'Endovac therapy was stopped when the size of the cavity was less than 0.5 cm × 1.0 cm'.	97%	Bleeding 1/29 (3%)	21/29 primary; 4/29 secondary	88%	Mortality 2/29 (7%); Hartmann's 1/29 (3%)	NR

CT, computed tomography; NR, not reported.

therapy following index surgery ranged from 0 to 534 days. Most devices were changed every 2 to 3 days and therapy lasted between 3 and 224 days. Additional cavity closure techniques used in conjunction with negative pressure therapy took place in 48% of the included studies (Tables 1,2).

Success definition

The definition of success, one of our main outcomes, varied greatly between studies (Table 3). The majority used endoscopy alone (76%) or endoscopy and computed tomography (24%) to define success. The most commonly used endoscopic definition of success was cavity size. Nine of the 17 studies referred specifically to cavity size as their marker of success. There was no consensus on cavity size relating to success, ranging from 0.5 cm to 3.0 cm (Table 3). Success rates within the studies sample ranged from 60% to 100%. Four studies reported 100%.[17–20] Fifty-eight percent of the studies had >84% success rate.[17–25] The four studies that reported 100% success each had varying definitions which included; 'no sign of leakage of contrast during a contrast enema or abdominal CT scan with intravenous, oral and rectal contrast and an intact anastomosis during endoscopic inspection',[17] 'A complete leakage closure was verified at endoscopic and/or radiological assessment'. '…until fistula closure was achieved…',[18] 'We ceased treatment when the cavity was about 3 cm wide and covered with granulation tissue',[19] 'Healing was defined as the closure of the defect after a progressive reduction in size of the cavity without signs of infection or complications, not requiring any intervention than the follow-up pouchoscopy'.[20] Interestingly, follow-up in these four studies was not reported for two,[18,19] one followed up patients at 1 month[20] and one had a median follow-up of 25 months.[17]

Stoma closure

Sixteen of the 17 studies recorded stoma formation rates. Five studies had 100% primary stoma formation.[19–22,26] Six studies reported

both primary and secondary stoma formation rates[25,27–30] and eight reported only primary stoma formation rates.[17,19–23,26,31] Two studies gave a stoma formation rate but did not specify whether these were primary or secondary.[24,32] The total number of stomas formed was $n = 213$ (81% of *total* systemic review sample $n = 264$), of which $n = 157$ (74%) were reported as primary and $n = 29$ (14%) reported as secondary following leak detection. The two studies that did not differentiate between stoma type amounted to $n = 27$ (13%) stoma formations. Rates of stoma reversal were described in 65% of the studies and ranged from 31% to 100% (median 79%). Only four of these had reversal rates >90% (range of 91–100%).

Complications

Complications were reported in 11 studies (65%). The total sample included in these 11 studies amounts to $n = 188$, of these there were 26 (14%) reported complications. The most common being pain ($n = 6$), on-going sepsis ($n = 5$), fistulae ($n = 4$), anastomostic stenosis ($n = 3$), bleeding ($n = 3$), 'compliance' issues ($n = 3$), 'failure' ($n = 1$) and one iatrogenic intra-abdominal injury.[26] No mortalities. However, described follow-up was only reported in 10 studies (59%) and ranged from 1 to 64 months with a median of 13 months.

Discussion

The primary aim of this systematic review is to report the documented success rate of endoluminal negative pressure therapy regarding AL in the colorectal population within the current literature. The findings of our systematic review included 264 patients from 17 studies eligible for inclusion in the review demonstrated that endoluminal negative pressure therapy was successful in the majority of patients (median 86%, range 60 to 100%). However, the results of this review should be interpreted with caution because of the heterogeneity in definition of success and the small sample sizes across all studies with limited follow-up. All included studies were also cohort studies with no comparison arm. Inclusion criteria were also highly variable including AL within the pelvis and extrapelvic AL even if they were of colorectal origin.

The highly varied definition of success is interesting and ranged from contrast extravasation on radiology to endoscopic assessment of residual cavity size to stoma closure. A standardized definition should be developed to allow meaningful comparison across modalities. Intuitively, one could argue that stoma closure is an important endpoint particularly for the patient and could be a better surrogate measure for success. However, as seen in this review, not all patients with AL had a stoma (median of 81%) which is arguably also one of the advantages of negative pressure therapy as it may negate the need for a defunctioning stoma to promote healing. Considering the importance of restoring gastrointestinal function, it is surprising that stoma closure rates were only reported in 65% of studies (11/17 studies). The median stoma closure rate was 79% (range 31–100%). The total number of reported reversed stomas was 136 (64%), this number represents 52% of the original total patient sample ($n = 264$). Clearly not all failures to close a defunctioning stomas are related to failure of endoluminal negative pressure therapy. Other patient or disease factors, such as patient preference for stoma, fitness for further surgery or concerns regarding continence will affect stoma closure rates. Nonetheless, considering the associated quality of life issues and patients' perception of 'success', future studies should ensure that stoma closure is included as an end point alongside another objective and validated measure of success as stoma closure alone will be inadequate as an endpoint for almost one in five patients (19%) who did not require a defunctioning stoma.

It is also noteworthy that while the authors attributed successful treatment of the AL to negative pressure therapy, nine of the 17 studies reported the use of an adjunct to aid with anastomotic healing.[17,20,23,25,29,31–33] All of these studies reported success >70%, with two studies reporting 100% success.[17,20] One therefore has to question if the success rates reported in these studies in fact confirm any additive benefit with negative pressure therapy or indeed, as suggested by these studies, a treatment benefit from negative pressure therapy alone.

No consensus regarding a single objective marker was used between studies, instead each produced its own unique 'success' definition or indeed did not give a definition at all. Success included arbitrary fistula cavity sizes that remained patent with a range from 0.5 to 3 cm.[19,23–25,30] The studies that refer to success but give a residual cavity size reported success rates of 88% to 100%. Nerup *et al*. (2013) who ceased treatment when the cavity was 'about 3 cm' wide reported a 100% success rate but interestingly did not report any follow-up data. Only one of these studies had a follow-up greater than 2 months;[24] whilst two had no follow-up recorded.[19,25] Other non-objective definitions included such comments as 'definitive resolution'[28] and 'cavity considered clean'.[29] These measures of success are subjective and non-validated, and in the authors' opinion, need to be interpreted with caution.

Following on from the success of negative pressure therapy for chronic lower limb wounds, it is rational and intuitive to adopt the same principles for ALs where healing is usually challenged by the same factors that contribute to a persisting wound. As demonstrated by Argenta *et al*. (1997) chronic non-healing wounds usually have an unfavourable microcellular milieu including tissue hypoxia, tissue oedema and increased bacterial load. The negative pressure exerts two positive influences. Firstly, by reducing tissue oedema, it improves the extra cellular milieu by reducing bacterial load, improving tissue oxygenation. Secondly, the negative pressure exerts a force on the cells promoting cell division and hence tissue healing.[34] However, unlike negative pressure therapy on a surface wound on a lower limb, endoluminal negative pressure therapy application can be challenging. Placement of the device into the cavity is often uncomfortable enough to require sedation or a general anaesthetic, thereby reducing its utility because patients commonly remain an in-patient for the duration of treatment. This necessarily compounds on the cost of managing these expensive complications. It is also interesting that in an era where there is ever-increasing competition for resources that the cost–benefit of endoluminal negative pressure therapy has never been reported. This is an important end point that warrants assessment in future studies.

Although the current review suggests that endoluminal negative pressure therapy is a useful treatment options in patients with colorectal related AL, there are a number of relevant clinical questions that remain unanswered. These include the most effective device, the optimal intervals for device change and also the ideal level of negative pressure to optimize healing. The heterogeneity of the included studies precluded further conclusions to be drawn about its clinical application. Similarly, while it would seem that studies suggest higher success rates with early use of negative pressure therapy, it is unclear what the optimal timing for commencement of therapy is. Throughout the literature there is a clear consensus that endoluminal negative pressure therapy is to be utilized only in the stable, non-peritonitic patient. Septic, peritonitic patients must proceed to operative management for a washout, appropriate drainage, stoma formation and possibly even anastomotic take down. There also appears agreement to support the use of endoluminal negative pressure therapy when the AL is detected earlier.[17,19,21,26–28,31–33] Arezzo *et al*. (2015) reported their success rate fell from 89% in acute leaks (<60 days) to 50% in 'chronic leaks' (>60 days). While van Koperen (2009) reported better abscess closure rates in those who commenced endoluminal negative pressure therapy prior to 6 weeks post operatively (75%) when compared to those who started therapy >6 weeks (56%). In another study by Borstlap *et al*. (2017) commencing endoluminal negative pressure therapy before 3 weeks was found to be associated with a better success rate. Based on these studies, it would seem that early commencement of endoluminal negative pressure therapy is recommended although one should be cognisant of the small numbers in all these studies.

A number of limitations need to be acknowledged. Firstly, inclusion criteria for negative pressure therapy were heterogeneous. Some included studies reported both malignant and benign pathologies, some purely benign or purely malignant disease. The inclusion of AL from both benign and malignant resections and combining both these results together is probably somewhat misleading. Patients with inflammatory bowel disease are usually younger and fitter patients, although the use of steroids or other immunosuppressive agents including that of biologics in this population may affect wound healing. Patients with cancer face unique obstacles, tend to be older and may have undergone neoadjuvant chemoradiation. This was the case in the large majority of patients within the studied population, culminating in poorer wound healing.[17,26,27,30,31,33] There were no commonly used standardized protocols and as such almost all parameters differed, including but not limited to; study type, type of anastomoses, sponge device, time from leak to sponge placement, number of changes, period between changes, additional therapies used, use of defunctioning stomas and definition of success. Included studies also tended to have very short follow-up with some studies not reporting any follow-up at all.

Conclusion

AL is a challenging problem to manage. Overall, the results of this systematic review suggests that endoluminal negative pressure therapy is a useful treatment option for patients with AL of colorectal origin although these results should also be interpreted with caution because of the quality of available evidence in existing literature and the high level of heterogeneity of the present studies outlined above. Results of individual studies may suggest that negative pressure therapy is useful; however, a number of important questions remain unanswered including stoma closure rates, long-term outcome and cost-effectiveness of the intervention compared to current management strategies. Furthermore, a number of clinical questions remain unanswered with respect to negative pressure therapy, which include the ideal level of suction to facilitate healing without increasing complications, the ideal dressing change interval and duration of therapy. Future studies are needed before definitive conclusions about negative pressure therapy can be drawn.

Author contributions

GARY SHARP: Conceptualization; data curation; formal analysis; investigation; methodology; writing-review and editing. **Daniel Steffens:** Formal analysis. **Cherry Koh:** Conceptualization; supervision; writing-review and editing.

Conflicts of interest

None declared.

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