Surg Endosc (2014) 28:1425–1438
DOI 10.1007/s00464-013-3382-9

Endoscopic transluminal necrosectomy in necrotising pancreatitis: a systematic review

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Received: 27 August 2013 / Accepted: 4 December 2013 / Published online: 8 January 2014

Abstract
Objective We performed a systematic review to assess the outcome of endoscopic transluminal necrosectomy in necrotising pancreatitis with additional focus on indication, disease severity, and methodological quality of studies.
Design We searched the literature published between January 2005 and June 2013. Cohorts, including patients with (infected) necrotising pancreatitis, undergoing endoscopic necrosectomy were included. Indication, disease severity, and methodological quality were described. The main outcomes were mortality, major complications, number of endoscopic sessions, and definitive successful treatment with endoscopic necrosectomy alone.
Results After screening 581 papers, 14 studies, including 455 patients, fulfilled the eligibility criteria. All included studies were retrospective analyses except for one randomized, controlled trial. Overall methodological quality was moderate to low (mean 5, range 2–9). Less than 50 % of studies reported on pre-procedural severity of disease: mean APACHE-II score before intervention was 8; organ failure was present in 23 % of patients; and infected necrosis in 57 % of patients. On average, four (range 1–23) endoscopic interventions were performed per patient. With endoscopic necrosectomy alone, definitive successful treatment was achieved in 81 % of patients. Mortality was 6 % (28/460 patients) and complications occurred in 36 % of patients. Bleeding was the most common complication.
Conclusions Endoscopic transluminal necrosectomy is an effective treatment for the majority of patients with necrotising pancreatitis with acceptable mortality and complication rates. It should be noted that methodological quality of the available studies is limited and that the combined patient population of endoscopically treated patients is only moderately ill.

Keywords Necrotising pancreatitis · Endoscopy · Intervention · Necrosectomy · Systematic

Acute pancreatitis is a common and potentially lethal disease. In approximately 80 % of patients, the clinical course is mild and the disease resolves spontaneously within several days. Approximately 20 % of patients develop necrotising pancreatitis, which is associated with a mortality rate of 15 % [1]. The major cause of death, next to early organ failure, is infection of extrapancreatic or pancreatic necrosis,

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leading to sepsis and multiple organ failure. Secondary infection of pancreatic necrosis develops in approximately 30 % of patients with necrosis and increases mortality to approximately 39 % [1–6]. Infected necrosis is virtually always an indication for intervention. In recent years, minimally invasive interventions are gradually replacing traditional open necrosectomy in an attempt to reduce the high rate of mortality (11–39 %) and complications (34–95 %) associated with open necrosectomy [4, 5, 7–13].

Currently, a widely used treatment for infected necrosis is a minimally invasive surgical step-up approach, consisting of percutaneous catheter drainage, followed by minimally invasive surgical necrosectomy, when needed [6]. A recent, randomized, controlled trial demonstrated that this approach reduces major complications from 69 to 40 % compared with primary open necrosectomy [6]. However, a complication rate of 40 % remains high and could potentially be further reduced by expanding the indication for endoscopic necrosectomy. Endoscopic necrosectomy can be performed under sedation without the need for general anesthesia and has been shown to reduce the inflammatory response and complications, such as new onset organ failure, in these often already critically ill patients [14]. Furthermore, endoscopic necrosectomy avoids a laparotomy or lumbotomy with its related surgical stress and complications, such as wound infection, intestinal or pancreatic fistula, and incisional hernia. Endoscopic necrosectomy was first described by Seifert et al. [15] in 2000. Since then, various observational cohort-studies on endoscopic necrosectomy have been published.

We performed a systematic review of the literature on endoscopic necrosectomy in (infected) necrotising pancreatitis. The objective was threefold: (1) to evaluate success of endoscopic necrosectomy in terms of definitive treatment and relevant clinical outcomes, such as mortality, and complications in individual studies and the pooled data; (2) to explore differences in indication and disease severity among studies to allow comparison of data between series, and comparison of outcome after endoscopic necrosectomy and surgical necrosectomy as reported in the literature; and (3) to perform an in depth-analysis of methodological quality of the available studies to systematically investigate areas of improvement for further research.

Methods

Study selection

The PRISMA guidelines for reporting on meta-analyses and systematic reviews of observational studies were applied [16]. A systematic literature search from January 2005 to June 2013 was performed in PubMed, Embase, and the Cochrane Library according to a prespecified protocol. Only articles written in English were included. The search terms are provided in Appendix 1. All titles and abstracts of studies identified by the initial search were screened to select those reporting on patients undergoing endoscopic necrosectomy of (extra-) pancreatic collections associated with acute pancreatitis. Duplicate references were excluded. Full-text papers of the selected studies were screened independently by two authors to assess eligibility. All cross-references were screened for potentially relevant studies not identified by the initial literature search. The final decision on eligibility was reached by consensus between the two screening authors.

Inclusion criteria were: (1) consecutive series of patients with necrotising pancreatitis undergoing endoscopic necrosectomy for (suspected) infected necrosis or symptomatic sterile pancreatic necrosis (i.e., clinical deterioration or significant mechanical obstruction); (2) the following outcomes were reported: percentage of infected peripancreatic collections, number of interventions, endoscopic necrosectomy success rate (i.e., needing no additional percutaneous or surgical intervention), mortality, and complications.

Exclusion criteria were: (1) studies with less than 5 patients; (2) studies also including patients with chronic pancreatitis with results for acute pancreatitis not reported separately; (3) studies on a selected subgroup of patients with acute pancreatitis, classified as "pseudocysts" or "pancreatic abscesses" as defined by the 1992 Atlanta classification [17] with results of these subgroups not reported separately; (4) studies including sterile pancreatic necrosis with results of infected pancreatic necrosis not reported separately or, otherwise uncomplicated sterile pancreatic necrosis.

Methodological quality assessment

Studies included in this systematic review were assessed for quality using two validated checklists [18, 19]. Downs et al. [18] described a checklist with 27 items (1 point for each item) which can be used for quality assessment for both randomized and nonrandomized studies. The MINORS checklist, proposed by Slim et al., contains 8 items for noncomparative studies and 12 items for comparative studies (maximum of 2 points for each item) [19]. In both scoring systems, a low methodological quality score reflects a high risk of bias, whereas a high score reflects a low risk of bias. To facilitate comparison of both lists, each score was converted to a value on a 0–10 scale. In order to signify the overall methodological quality of each study, a final score was determined by calculating the mean of the Downs and MINORS scores. We defined high methodological quality as a final score $\geq$8, moderate quality as a

score of 6–8, moderate/low quality as a score of 4–6, and low quality as a score ≤3.

Data extraction

The following variables were extracted, where available: number of patients undergoing endoscopic necrosectomy, etiology, predictive severity scores before intervention (e.g., Imrie/Modified Glasgow score and Acute Physiology And Chronic Health Evaluation [APACHE]-II score), organ failure before endoscopic necrosectomy, ICU admission before endoscopic necrosectomy, computed tomography (CT) severity scores (CT severity Index (CTSI) [20], modified CTSI [21], Balthazar grade [22]), indication for intervention, percentage of patients with infected necrosis confirmed by first culture, time between hospital admission and endoscopic necrosectomy, total number of interventions, total length of ICU and hospital stay, definitive successful treatment with endoscopic necrosectomy alone (defined as no need for additional percutaneous or surgical intervention), number of patients requiring an additional percutaneous or surgical intervention, complications, and death.

Primary outcome measures were death and complication rate. The nominator for calculation was represented by the number of patients who died or suffered from reported complications (e.g., bleeding, perforation of a hollow organ, pancreatic fistula). The denominator was the total number of patients with infected necrotising pancreatitis. Patients lost to follow-up were excluded.

Statistical analysis

The data were analysed and reported to describe methodological quality, characteristics of included studies, patient characteristics, and outcome. Descriptive statistics were used to describe baseline characteristics and outcome variables for all studies separately and for the pooled data. In order to pool data of continuous outcomes in systematic reviews average values are needed. However, continuous outcomes are often reported with different summary statistics, such as means, medians, range, and size of the trial, etc. Hozo et al. [23] described a method to calculate or estimate (depending on the sample size) the mean using the values of the median, low and high end of the range, and sample size. We used this method to calculate weighted means for all outcomes. To this end, we received additional data through personal communication with the author of one study [14].

A forest plots for mortality was generated using Comprehensive Meta-analysis Version 2 (Borenstein M, Hedges L, Higgins J et al., Biostat, Englewood, NJ, 2005). I^2 was calculated to assess heterogeneity. The I^2 statistic indicates the proportion of total variation among the effect estimates attributed to heterogeneity rather than sampling error and has the advantage of being intrinsically independent of the number of studies. Heterogeneity was ruled out when the test of heterogeneity was not significant ($p > 0.05$) and I^2 was less than 30 % [24, 25].

Results

Literature search

The systematic literature search identified 581 potentially relevant papers after removing duplicates. The study selection flowchart is shown in Fig. 1. Of the 581 papers, 567 papers were excluded after reviewing title, abstract, and full-text for the following reasons: cohorts of less than 5 patients ($n = 18$), cohorts of patients with carcinoma ($n = 50$), non-English papers ($n = 6$), cohorts including only sterile necrosis ($n = 15$), cohorts including only endoscopic drainage and no endoscopic necrosectomy ($n = 16$), cohorts also including chronic pancreatitis, "pseudocysts," "pancreatic abscesses," and results of these subgroups were not reported separately ($n = 222$), cohorts that did not report one or more predescribed essential outcomes (i.e., number of endoscopic necrosectomy sessions, definitive successful treatment, complications, and death) ($n = 9$) separately, and cohorts excluded because of other reasons (e.g., percentage of infected necrosis was not reported, cohorts of patients receiving nonendoscopic treatment, cohorts of patients receiving treatment for nonpancreatitis diseases, cohorts that did not show original patient data, such as reviews or solely descriptive publications) ($n = 231$).

Study characteristics

A total of 14 studies were included in this systematic review [14, 26–38]. Study characteristics are summarized in Table 1.

Seven studies were retrospective, noncontrolled cohort studies; four were retrospective, noncontrolled cohort studies with prospective databases; one was a retrospective, noncontrolled cohort study with a prospective follow-up; one was a retrospective, noncontrolled cohort study in a partially prospective database; and one was a randomized, controlled trial. From four studies, we included a selection of the reported cohort, because only a subgroup fulfilled the selection criteria and data were reported separately [14, 31, 34, 36].

Methodological quality

Table 2 shows the converted quality scores of the Downs et al. and MINORS checklist on a 0–10 scale and the mean of

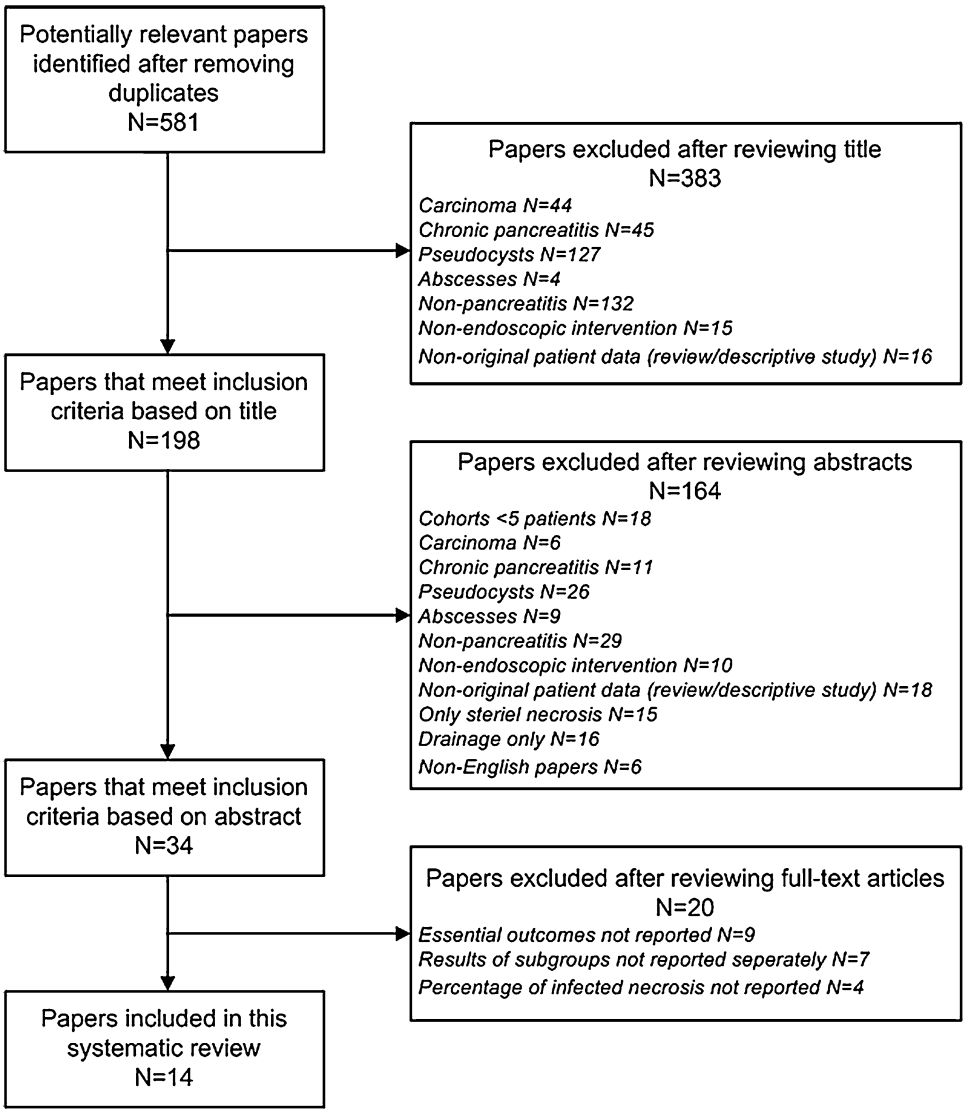

Fig. 1 Study selection flow chart

both checklists. Overall methodological quality was moderate to low (mean 5, range 2–9). The randomized trial scored high, 1 study scored moderate, 11 studies scored moderate to low, and 1 study scored low. Studies scored good on reporting design (e.g., stating a clear purpose, patient characteristics, type of intervention, and outcome), main findings, and adverse events. However, the majority of studies were retrospective and, therefore, scored lower, because they, for example, had no power calculation, no randomized allocation of treatment, no blinding, and did not correct for differences in length of follow-up. Furthermore, no actual probability values with accompanying estimates of the random variability were reported in most studies.

Patient characteristics

The pooled data comprised of 455 patients undergoing endoscopic necrosectomy. The number of patients per study ranged from 5 to 104. Patient characteristics of the individual studies are shown in Table 3. The weighted means of baseline characteristics in the pooled data are given in Table 4. Sixty-three percent of all patients were male, and the mean age was 56 (SD 10) years. Twelve studies (432/455 patients) reported on etiology, which was biliary in 52 % of patients, alcoholic in 19 %, and of other origin in 29 %. On average, follow-up was 23 months (Table 1).

Six of the 14 (43 %) studies reported predictive severity scores, CTSI, and/or clinical details before intervention. Mean APACHE-II score was 8 (SD 5), CTSI 7 (SD 2), organ failure before intervention was present in 23 % of patients (14/62 patients), and 32 % of patients (62/195 patients) were admitted to the ICU before intervention. The average number of days between diagnosis and first intervention was 57 (range 6–510). Fifty-seven percent of patients (261/455 patients) had infected necrosis proven by

Table 1 Characteristics of the included studies

Study	Country	Year	Study design	Inclusion criteria	Technique used	Number of patients	Study period (mo)	Follow-up (mo)
Seewald et al. [36]	Germany	2005	Retrospective cohort	Pancreatic necrosis, endoscopic necrosectomy	EUS, drainage, dilatation, daily necrosectomy + lavage	5[d]	1997–2004 (88)	26[f]
Charnley et al. [28]	UK	2006	Retrospective cohort[a]	Infected pancreatic necrosis, endoscopic necrosectomy	EUS, drainage, dilatation, necrosectomy	13	2002–2004 (30)	19
Voermans et al. [38]	The Netherlands	2007	Retrospective cohort[b]	Symptomatic organized pancreatic necrosis, endoscopic necrosectomy	EUS, drainage, dilatation, necrosectomy	25	2003–2006 (42)	13
Papachristou et al. [33]	USA	2007	Retrospective cohort[b]	Symptomatic or infected WOPN, endoscopic therapy	EUS/non-EUS, drainage, dilatation, necrosectomy	53	1998–2006 (101)	6
Escourrou et al. [30]	France	2008	Retrospective cohort[b]	Infected pancreatic necrosis, endoscopic necrosectomy	EUS, drainage, dilatation, necrosectomy	13	2004–2007 (42)	20
Schrover et al. [35]	The Netherlands	2008	Retrospective cohort	Infected pancreatic necrosis, endoscopic necrosectomy	EUS, drainage, dilatation, necrosectomy	8	2001–2006 (61)	23
Coelho et al. [29]	Brazil	2008	Retrospective cohort	Pancreatic necrosis, endoscopic necrosectomy	Drainage, dilatation, necrosectomy	56	2002–2007 (72)	23
Seifert et al. [37]	Germany	2009	Retrospective cohort	Infected pancreatic necrosis, endoscopic necrosectomy	EUS, drainage, dilatation, necrosectomy	93	1999–2005 (84)	44
Gardner et al. [31]	USA	2009	Retrospective cohort[c]	Symptomatic WOPN, endoscopic necrosectomy	EUS/non-EUS, drainage, dilatation, necrosectomy	25[d]	1998–2007 (115)	14
Gardner et al. [32]	USA	2011	Retrospective cohort	WOPN, endoscopic necrosectomy	EUS/non-EUS, drainage, dilatation, necrosectomy	104[e]	2003–2010 (88)	20
Bakker et al. [14]	The Netherlands	2012	Randomized controlled trial	Infected necrotising pancreatitis	EUS, drainage, dilatation, necrosectomy	10[d]	2008–2010 (20)	6
Bausch et al. [27]	Germany	2012	Retrospective cohort	WOPN, endoscopic necrosectomy	EUS, drainage, dilatation, necrosectomy	18	1998–2010 (144)	nr
Abdelhafez et al. [26]	Egypt	2013	Retrospective cohort[b]	WOPN, endoscopic necrosectomy	Drainage, dilatation, necrosectomy	10	2011–2012 (17)	10

Table 1 continued

Study	Country	Year	Study design	Inclusion criteria	Technique used	Number of patients	Study period (mo)	Follow-up (mo)
Risch et al. [34]	Germany	2013	Retrospective cohort	WOPN, endoscopic necrosectomy	EUS, drainage, dilatation, necrosectomy	22[d]	2006–2011 (69)	28

WOPN walled-off pancreatic necrosis

[a] Retrospective study in a partially prospective database

[b] Retrospective study in a prospective database

[c] Retrospective study with prospective follow-up

[d] A selection of the cohort reported in the original article

[e] Including 25 patients from Gardner 2009 and 14 patients from Papachristou 2007

[f] Given for the whole cohort

Table 2 Methodological quality of the included studies

Study	MINORS checklist[a] [19]	Checklist for (non-) randomized trials[a] [18]	Mean MINORS and Downs checklist	Methodological quality
Seewald et al. [36]	2,5	1	1,8	Low
Charnley et al. [28]	6,3	3	4,7	Moderate/low
Voermans et al. [38]	6,3	3,3	4,8	Moderate/low
Papachristou et al. [33]	6,3	3,3	4,8	Moderate/low
Escourrou et al. [30]	7,5	3,3	5,4	Moderate/low
Schrover et al. [35]	6,3	3,3	4,8	Moderate/low
Coelho et al. [29]	6,3	3,3	4,8	Moderate/low
Seifert et al. [37]	6,3	3,7	5	Moderate/low
Gardner et al. [31]	5	3,3	4,2	Moderate/low
Gardner et al. [32]	5	3,3	4,2	Moderate/low
Bakker et al. [14]	9,2	9,6	9,4	High
Bausch et al. [27]	6,3	4,1	5,2	Moderate/low
Abdelhafez et al. [26]	7,5	5,6	6,6	Moderate
Risch et al. [34]	6,3	3,7	5	Moderate/low

[a] All scores are 0–10, with 10 reflecting the highest methodological score

a positive bacteriological culture of pancreatic or peripancreatic necrosis before or at first necrosectomy. In 11 of the 14 studies, endoscopic transluminal necrosectomy was performed under sedation. One study used moderate sedation or general anesthesia, one study used conscious sedation with oral intubation, and one study did not report which per procedural sedation was used.

Outcome

The clinical outcomes after endoscopic necrosectomy in the individual studies are given in Table 5 and the calculated weighted means in Table 4. The overall mortality rate was 6 % (28/455 patients) with a range of 0–15 % per study. Two studies reported the in hospital mortality rate, whereas 12 studies described the mortality rate within the follow-up period. Mortality is shown in a forest plot (Fig. 2). There was no substantial heterogeneity for mortality ($I^2 < 30$ %, $p = 0.93$). There was no correlation between mortality and the percentage of patients with infected necrosis. Mortality seems higher in patients with organ failure before intervention. Because only six studies reported APACHE-II scores and CTSI before intervention, we were unable to draw conclusions about their correlation with mortality. Complications occurred in 36 % of patients (163/455 patients). The most common complication was bleeding, which occurred in 18 % (76/420 patients) of patients. Bleeding was treated endoscopically by

Table 3 Patient characteristics of included studies

Study	Number of patients	M/F (%)	Age (mean)	Etiology	APACHE-II score (mean)	CT severity index (mean)	Organ failure (%)	ICU admission (%)	Infected necrosis (%)	Collection size in cm (mean)	Diagnosis to first intervention in days (mean)	Drainage as first intervention (%)	Drainage to necrosectomy in days (mean)
Seewald et al. [36]	5[a]	5/0 (100/0)	62	B: 3, A:1, O: 1	nr	nr	nr	5 (100)	5 (100)	14.5	nr	5 (100)	nr
Charnley et al. [28]	13	9/4 (69/31)	50	nr	9	7	4 (31)	5 (38)	11 (85)	nr	nr	0	0
Voermans et al. [38]	25	12/13 (48/52)	56	B: 10, A:5, O: 10	nr	nr	nr	nr	19 (76)	11	144	25 (100)	4
Papachristou et al. [33]	53	28/25 (53/47)	61	B: 37, A: 1, Ia: 5, O: 10	6	nr	nr	18 (34)	20 (38)	16	49	53 (100)	18
Escourrou et al. [30]	13	12/1 (92/8)	55	B 7, A: 3, O: 3	13	8	4 (31)	13 (100)	13 (100)	14	28	0	0
Schrover et al. [35]	8	2/6 (25/75)	53	nr	7	6	2 (25)	0	8 (100)	nr	36	8 (100)	nr
Coelho et al. [29]	56	30/26 (54/46)	44	B: 35, A: 12, O: 9	nr	nr	nr	nr	25 (45)	18	35	56 (100)	nr
Seifert et al. [37]	93	63/30 (68/32)	57	B: 43, A: 28, Ia: 5, O: 17	nr	nr	nr	19 (20)	50 (54)	11.4	41	54 (58)	nr
Gardner et al. [31]	25[a]	17/8 (68/32)	61	B: 15, A: 1, O: 9	nr	7 (± 1.6)	nr	nr	19 (76)	14.8 (± 5)	74	0	0
Gardner et al. [32]	104[b]	67/37 (64/36)	58	B: 48, A:18, O: 38	nr	7	nr	nr	40 (38)	15	46	104 (100)	nr
Bakker et al. [14]	10[a]	6/4 (60/40)	62	B: 6, A: 2, O: 2	10	8	4 (40)	2 (20)	10 (100)	nr	48	9 (90)	nr
Bausch et al. [27]	18	10/8 (56/44)	54	B: 5, A: 4, O: 9	nr	nr	0	nr	13 (72)	nr	78	0	0
Abdelhafez et al. [26]	10	6/4 (60/40)	44	B: 4, A: 2, Ia: 1, O: 3	9	nr	nr	nr	7 (70)	13	65	10 (100)	8
Risch et al. [34]	22[a]	22/5 (82/18)[c]	63[c]	B: 13, A: 8, O: 6[c]	nr	nr	nr	nr	21 (78)[c]	nr	nr	22 (100)	nr

nr not reported; *A* alcoholic; *B* biliary; *Ia* iatrogeny; *O* other

[a] A selection of the cohort reported in the original article

[b] Including 25 patients from Gardner 2009 and 14 patients from Papachristou 2007

[c] Given for the whole cohort

Table 4 Weighted means for baseline and outcome

	Number of studies	Number of patients	Mean
Follow-up (mo)	13	437	23
Methodological quality	14	455	5
Sex (M/F) (%)	14	455	63/37
Age (ys	14	455	56
Etiology (B; A; Ia; O) (%)	12	432	52; 19; 3; 26
APACHE-II score	6	107	8
CTSI	6	173	7
Organ failure (%)	5	62	23
ICU admission (%)	7	195	32
Infected necrosis (%)	14	455	57
Collection size (cm)	9	384	14
Diagnosis to first intervention (days)	10	377	57
Drainage as first intervention (%)	14	455	92
Drainage to necrosectomy (days)	7	157	7
Number of endoscopic sessions	13	437	4
Endoscopy alone (%)	14	455	84
Additional procedures (%)	14	455	16
Definitive resolution (%)	14	455	81
Mortality (%)	14	455	6
Complications (%)	14	455	36
Bleeding (%)	12	420	18
Perforation (%)	6	249	4
Air embolism (%)	3	207	1
Pancreatic fistula (%)	5	187	5

endoscopic coagulation, epinephrine injections, or clips in 93 % of patients; 7 % of patients required angiography with coiling or surgery. Pancreatic fistula occurred in 5 % (9/187), spontaneous perforation of a hollow organ (apart from the stomach or duodenum due to the intervention) in 4 % (9/249), and air embolism in 1 % (2/207) of patients.

On average, 4 (range 1–23) endoscopic sessions were performed per patient; 382 of 455 patients (84 %) were treated with endoscopy alone. The remaining subgroup of patients underwent one or more additional percutaneous or surgical interventions. Of this subgroup, additional intervention was percutaneous in 18 patients, surgical in 46 patients, percutaneous and surgical in 7 patients, and other in 2 patients. Main indications for intervention were persistent collections, recurrent collections, extended necrosis, perforation of a hollow organ, and bleeding. Primary endoscopic necrosectomy was successful as definitive treatment in 81 % (372/455) of patients.

Discussion

This systematic review shows that endoscopic transluminal necrosectomy is a safe and effective minimally invasive treatment in infected necrotising pancreatitis. More than 80 % of patients were treated successfully with endoscopic necrosectomy alone. This was associated with a mortality rate of 6 % and complication rate of 36 %.

Of note, the methodological quality of the vast majority of included studies was moderate to low. Furthermore, the vast majority of included studies did not report on the most relevant parameters of disease severity (e.g., APACHE-II score, preoperative organ failure, and infected necrosis) or outcome measures. Only two studies reported clear definitions for organ failure and only one study reported definitions for pancreatic fistula and perforation of a visceral organ. Just little more than half of the patients had proven infected necrosis. This is low, because the main indication for intervention in necrotising pancreatitis is nowadays considered to be infected necrosis [9, 39, 40]. In accordance with international guidelines, patients with sterile necrosis often can be successfully managed conservatively (i.e., without any form of radiologic, endoscopic, or surgical intervention) [41, 42]. The only exception for intervention in patients with sterile necrosis are patients with gastrointestinal or hepatobiliary obstruction persisting for several months and perhaps in very few patients with progressive organ failure despite maximal supportive therapy in the intensive care unit [39, 40, 43]. Iatrogenic infection of sterile necrosis by percutaneous or transluminal drainage is a well-recognized risk that needs to be avoided [44, 45]. Thus, intervention in the case of sterile necrosis is, in our opinion, obsolete and potentially harmful. Of the included studies, intervention could probably been avoided in a considerable number of patients. Patients with infected necrosis are generally thought to be more severely ill compared with patients with sterile necrosis. This study however showed no correlation between the percentage of patients with infected necrosis and mortality. Five studies had a high percentage of patients with infected necrosis and low mortality. This could be a result of the fact that these studies were relatively small, had lower quality scores, and the majority did not report disease severity before intervention. Several studies were excluded for this review, because they did not report data on the percentage of patients with infected necrosis.

The historical treatment of infected necrotising pancreatitis has always been surgical necrosectomy. Many cohort studies on surgical necrosectomy have been published over the past decade. These series can be compared to the literature on endoscopic necrosectomy in many ways. First, sample sizes of endoscopic necrosectomy series are comparable to open and minimally invasive surgical

Table 5 Outcome of included studies

Study	Number of patients	Number of endoscopic sessions (mean)	Endoscopy alone (%)	Additional procedures	Definitive resolution (%)[c]	Mortality (%)	Complications (%)	Bleeding (%)	Perforation of a hollow organ (%)	Air embolism (%)	Pancreatic fistula (%)	Other
Seewald et al. [36]	5[a]	15	3 (60)	2: surgery	3 (60)	0	3 (60)	2 (40)	nr	nr	nr	1: recurrent pseudocyst
Charnley et al. [28]	13	5	9 (69)	2: surgery, 2: percutaneous	9 (69)	2 (15)	2 (15)	nr	nr	nr	nr	2: DM type 1
Voermans et al. [38]	25	2	23 (92)	2: surgery	24 (96)	0	12 (48)	9 (36)	nr	nr	nr	1: perforation of cystic wall, 2: recurrent pseudocyst
Papachristou et al. [33]	53	3	28 (53)	5: surgery, 13: percutaneous, 7: surgery and percutaneous	28 (53)	3 (6)	34 (64)	9 (17)	1 (2)	nr	2 (4)	1: gallbladder puncture, 1: loss of access to collection, 5: DVT, 3: ischaemia/perforation/peritonitis, 3: clostridium difficille colitis, 2: ileus, 1: bowel obstruction, 5: recurrent/persisting pseudocyst, 1: flank abscess
Escourrou et al. [30]	13	2	11 (85)	2: percutaneous	11 (85)	0	10 (77)	3 (23)	nr	nr	4 (31)	3: sepsis
Schrover et al. [35]	8	4	6 (75)	2: surgery	6 (75)	1 (13)	3 (38)	1 (13)	1 (13)	nr	nr	1: relapse of AP
Coelho et al. [29]	56	5	49 (88)	6: surgery	49 (88)	2 (4)	6 (11)	2 (4)	0	nr	nr	3: secondary infected collection, 1: stent clogging
Seifert et al. [37]	93	6	80 (86)	12: surgery, 1: transesophageal fenestration	75 (81)	7 (8)	27 (29)	13 (14)	nr	2 (2)	2 (2)	1: oesophageal variceal haemorrhage, 5: perforation of the necrosis into the abdominal cavity, 1: seizure, 1: intracerebral hemorrhage, 1: pneumoperitoneum, 1: colonic fistula
Gardner et al. [31]	25[a]	4	24 (96)	1: surgery	22 (88)	0	8 (32)	8 (32)	nr	nr	nr	8: recurrent collection
Gardner et al. [32]	104[b]	4	102 (98)	2: surgery	95 (91)	7 (7)	38 (37)	21 (20)	2 (2)	1 (1)	nr	1: bacteremia, 6: recurrent collection, 1: secondary infected collection, 3: pneumoperitoneum, 3: recurrent pancreatitis, 1: clostridium colitis
Bakker et al. [14]	10	4	8 (80)	2: surgery	8 (80)	1 (10)	5 (50)	0	0	0	1 (10)	2: DM, 2: persisting collections
Bausch et al. [27]	18	nr	10 (56)	7: surgery 1: percutaneous	9 (50)	1 (6)	8 (44)	3 (17)	5 (28)	nr	0	nr
Abdelhafez et al. [26]	10	1	10 (100)	0	9 (90)	1 (10)	4 (40)	4 (40)	nr	nr	nr	1: aspiration

Table 5 continued

Study	Number of patients	Number of endoscopic sessions (mean)	Endoscopy alone (%)	Additional procedures	Definitive resolution (%)[c]	Mortality (%)	Complications (%)	Bleeding (%)	Perforation of a hollow organ (%)	Air embolism (%)	Pancreatic fistula (%)	Other
Risch et al. [34]	22[a]	4	19 (86)	3: surgery	19 (86)	3 (14)	3 (13)[d]	1 (5)	nr	nr	nr	1: myocardial infarction

nr not reported

[a] A selection of the cohort reported in the original article

[b] Including 25 patients from Gardner 2009 and 14 patients from Papachristou 2007

[c] Definitive resolution with only endoscopic necrosectomy

[d] Given for the whole cohort

necrosectomy series. However, surgical necrosectomy series more often are prospective cohort studies and therefore score better on methodological quality. Second, patients in endoscopic necrosectomy series seam less ill with a lower rate of infected necrosis compared with surgical series. If we compare the patients from the recent randomized PANTER study who underwent a minimally invasive surgical step-up approach [6] with the patients from the current pooled dataset, there are obvious differences in baseline characteristics: APACHE-II scores (15 vs. 8), organ failure rate (49 vs. 23 %), ICU admission rate (54 vs. 32 %), and the percentage of patients with proven infected necrosis (91 vs. 57 %) were all higher in the surgical group. This is confirmed by the results of a recent systematic review on videoscopic-assisted retroperitoneal debridement (VARD) [46]. In the pooled data of 128 patients undergoing VARD mean APACHE-II score was 14, organ failure was present in 40 % of patients, 60 % of patients were admitted to the ICU before intervention, and 91 % of patients had infected necrosis. Third, the number of procedures performed with endoscopic necrosectomy seems higher than for surgical necrosectomy. In this review, there was a wide range regarding the number of procedures needed, ranging from 1 to 23 sessions with a mean of 4 sessions per patient. In minimally invasive surgical series, an average of three (range 1–5) procedures were needed per patient [46]. This may lead to a difference in costs. Unfortunately, the included studies did not report total hospital stay and costs. We therefore cannot draw firm conclusions on this matter. Although more procedures may be needed, endoscopic necrosectomy seems less invasive than surgical necrosectomy and potentially induces less surgical stress, which could reduce complications and improves outcome. Fourth, successful definitive treatment with endoscopy seems higher (i.e., 81 % in the current study) compared with minimally invasive surgical necrosectomy (i.e., 61 % in a recent review) [46]. Mortality in the endoscopic necrosectomy series was lower compared with minimally invasive surgery (6 vs. 13 %) [46]. This could, however, reflect the difference in baseline characteristics or be due to the fact that both the surgical and endoscopy studies are not powered to show a difference in solely mortality. Overall, the percentage of complications between endoscopic and surgical series seems comparable (36 vs. 35 %) [46]. The pancreatic fistula rate, however, is apparently much lower after endoscopic necrosectomy than after surgical necrosectomy (5 vs. 17 %) [46]. This is an obvious difference because endoscopic necrosectomy avoids any abdominal wall incision. However, pancreatic fistula is associated with severe morbidity and therefore is an important outcome measure. The incidence of bleeding, mostly controlled by direct endoscopic coagulation, epinephrine injection or clips, does not seem different

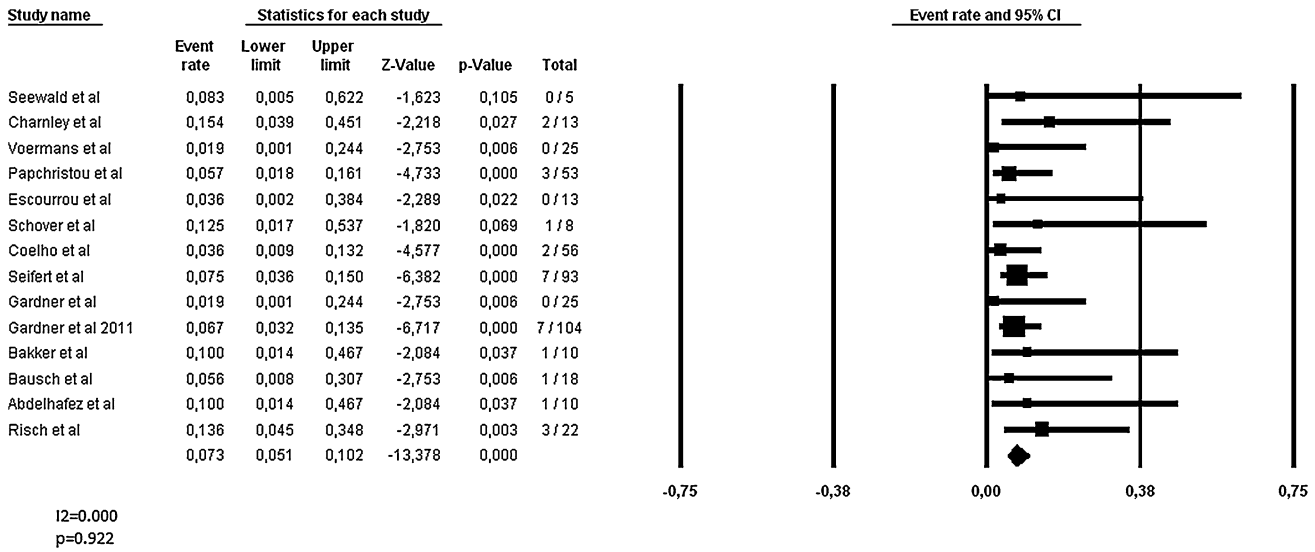

Fig. 2 Forest plot of included studies analyzing mortality

between endoscopic and surgical necrosectomy (18 vs. 13 %) [46]. The percentage of perforations also is the same (4 vs. 4 %) [46].

Theoretically, by avoiding a laparotomy or lumbotomy and general anesthesia, endoscopic necrosectomy induces less inflammatory stress and can reduce the number of early and late complications as new onset organ failure, intestinal and/or pancreatic fistula, and incisional hernia [14]. Furthermore, general anesthesia is known to induce or prolong systemic inflammation in critically ill patients [47]. A potential limitation of endoscopic necrosectomy is that acute complications, such as perforations and to a lesser extend bleedings, are more difficult to manage endoscopically. Importantly, endoscopic necrosectomy is an advanced type of intervention that not only requires the expertise from an interventional endoscopist, but also the dedicated involvement of interventional radiologists and pancreatic surgeons to manage potential complications. For this reason, endoscopic necrosectomy procedures should only be performed in expert centers with multidisciplinary expertise.

There are some limitations to this systematic review. First, most included studies were relatively small and retrospective analyses were performed. A formal assessment of the methodological quality of selected studies showed that most studies scored only "moderate to low." Furthermore, baseline data on disease severity before intervention and clear definitions for organ failure and complications were poorly reported. When reported, scores were relatively low compared with most surgical series, suggesting a less ill patient category [6]. The lack of uniform patient selection criteria has undoubtedly led to selection bias. Lastly, the primary endpoint in most studies was radiologic findings (e.g., complete resolution of collections op CT), which does not necessarily correlate with current disease stage and outcome in every patient.

What are the implications of this study for clinical practice? In case of infected necrosis, "drainage first" avoids surgery in approximately 35 % of patients [6]. Knowing that, it may be advisable to perform endoscopic treatment in a step-up fashion: i.e., endoscopic transluminal drainage first, if necessary followed by endoscopic transluminal necrosectomy. Endoscopic necrosectomy is being used with increasing frequency worldwide. However, as with the introduction of any new technical procedure, for example laparoscopic cholecystectomy, rapid, widespread, clinical implementation often precedes firm scientific proof and also is associated with increased complication rates [48–50]. Large prospective or preferably randomized trials are required to confirm the favourable results of this systematic review and reliably compare endoscopic necrosectomy to surgical necrosectomy. We strongly recommend that these studies only include patients with (suspected) infected necrotising pancreatitis and well-describe baseline criteria (e.g., etiology, APACHE-II, CTSI, organ failure, percentage of infected necrosis, days from initial admission to necrosectomy) and clinically relevant outcome measures (e.g., number of endoscopic procedures, mortality, complications such as bleeding, perforation, fistula). Such a study is currently enrolling patients (controlled trials ISRCTN09186711).

Endoscopic transluminal necrosectomy is a good treatment option for patients with infected necrotising pancreatitis. However, the favourable results of this systematic

review should be regarded in the light that the pooled data comprises of moderately ill patients and the methodological quality of the included studies is limited.

Disclosures No potential conflict of interest relevant to this article was reported.

Funding Sandra van Brunschot is sponsored by the Dutch Maag Lever Darm Stichting (MLDS) and Fonds Nuts Ohra to perform a randomized, controlled clinical trial on necrotising pancreatitis. The sponsors had no involvement in any stage of the study design, data collection, data-analysis, and interpretation of the study results.

Appendix 1

Extensive search terms used within the PubMed, Embase, and Cochrane Library

The PubMed search terms were '((endoscopic transluminal necrosectomy*) OR (endoscopic necrosectomy*) OR (endoscopic debridement*) OR (endoscopic drainage*) OR (transluminal drainage*) OR (transgastric necrosectomy*) OR (transgastric debridement*)) AND ((pancreatitis[Mesh]) OR (Pancreatitis [Text Word]) OR (pancreatic*) OR (pancreas*) OR (infected necrosis*) OR (OPN*))'.

The following strategy was used to search Embase: (pancreatitis/or pancreatic/or pancreas/or infected necrosis/or OPN.tw)) AND (endoscopic transluminal necrosectomy/or endoscopic necrosectomy/or endoscopic debridement/or endoscopic drainage/or transluminal drainage/or transgastric necrosectomy/or transgastric debridement.tw).

Search terms for the Cochrane Library were: '((pancreatitis*) OR (pancreatic*) OR (pancreas*) OR (infected necrosis*) OR (OPN*)) AND ((endoscopic transluminal necrosectomy*) OR (endoscopic necrosectomy*) OR (endoscopic debridement*) OR (endoscopic drainage*) OR (transluminal drainage*) OR (transgastric necrosectomy*) OR (transgastric debridement*)), restricted to title, abstract, keywords and the English language.

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