CLINICAL—PANCREAS

Efficacy of Conservative Treatment, Without Necrosectomy, for Infected Pancreatic Necrosis: A Systematic Review and Meta-analysis

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BACKGROUND & AIMS: Conservative treatment (intensive care, a combination of antimicrobial agents, and nutritional support, with or without drainage of the infected fluid) has recently been shown to be effective for patients with infected pancreatic necrosis (IPN), but the data from individual studies are not robust enough to recommend it as the standard of care. We performed a systematic review and meta-analysis of studies related to primary conservative management for IPN. **METHODS:** We performed a literature search of MEDLINE/PubMed from January 1990 to March 2012 for studies of a priori protocols for primary conservative treatment, without necrosectomy, for consecutive patients with IPN. We analyzed data from 8 studies, comprising 324 patients with IPN who received primary conservative management. We then analyzed an additional 4 studies (comprising 157 patients) that reported the efficacy of percutaneous drainage in nonconsecutive patients with IPN. Outcome measures were the success of conservative management strategy, need for necrosectomy, and mortality. **RESULTS:** There was significant heterogeneity in results among the studies. Based on a random effects model, conservative management was successful for 64% of patients (95% confidence interval [CI], 51%–78%); mortality was 12% (95% CI, 6%–18%), and 26% of patients required necrosectomy or additional surgery for complications (95% CI, 15%–37%). A separate analysis of 4 studies that reported outcomes of nonconsecutive patients with IPN following percutaneous drainage had comparable results; 50% had successful outcomes (95% CI, 43%–58%), mortality was 18% (95% CI, 6%–30%), and 38% of patients required surgery (95% CI, 20%–56%). **CONCLUSIONS: Conservative management without necrosectomy is a successful approach for 64% of patients with IPN. This approach has low mortality and prevents surgical necrosectomy.**

Keywords: Acute Pancreatitis; Necrosis; Therapy; Infection.

Acute pancreatitis is a potentially lethal disease with considerable morbidity and 10% to 40% mortality.[1] There are 2 major forms of acute pancreatitis: interstitial and necrotizing. Acute necrotizing pancreatitis usually runs a severe course and is the cause of most of the morbidity and mortality.[2] Although patients with sterile pancreatic necrosis may have a severe course and die, infection of the nonviable necrotic pancreatic tissue is an ominous development during the course of acute pancreatitis. We and others have shown that the extent and infection of pancreatic necrosis correlate with the development of organ failure and mortality in acute pancreatitis.[3,4] Infected pancreatic necrosis (IPN) is the cause of most of the late mortality during the course of acute pancreatitis. Although conservative treatment is recommended for sterile necrosis, surgical necrosectomy has generally been considered the standard of care for IPN according to various practice guidelines.[5–7] Conservative treatment has not been considered a viable option in patients with IPN. However, in addition to a few anecdotal case reports, 2 case series have shown that conservative treatment might be successful in a substantial percentage of patients with infected necrosis.[8–12] We showed in a comparative study that conservative treatment is effective and comparable to surgical necrosectomy.[13] However, the data from individual studies are not robust enough to change the practice recommendations for patients with infected necrosis from surgical necrosectomy to conservative treatment. To derive a meaningful conclusion from these studies, we performed a systematic review and meta-analysis of all published studies that have reported management of patients with IPN primarily with conservative treatment without necrosectomy. Conservative therapy for IPN included intensive care, combination antimicrobials, and nutritional support, with or without drainage of the infected fluid collections in the reported studies. Although percutaneous drainage is a form of intervention and not truly conservative, it has been considered a part of medical conservative treatment because it does not involve surgery or formal necrosectomy. Our objective was to determine the effectiveness of therapy for IPN without necrosectomy; thus, for the purpose of this systematic review and meta-analysis, we included studies that used a conservative management protocol for consecutive patients with IPN that allowed for percutaneous drainage but not any form of necrosectomy: percutaneous, endoscopic laparoscopic, or open surgical.

Abbreviations used in this paper: APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; CTSI, computed tomography severity index; IPN, infected pancreatic necrosis.

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Subjects and Methods

Study Selection

A systematic literature search was conducted to locate the relevant published articles on treatment of IPN through MEDLINE/PubMed from January 1990 to March 2012. The keywords used for the search included a combination of "infected pancreatic necrosis," "organized pancreatic necrosis," "walled off pancreatic necrosis," or "acute pancreatitis" AND "conservative treatment," "necrosectomy," or "nonsurgical treatment." Studies published as full articles in any language were eligible, but those published only as abstracts were not included. Cross-references were also searched manually. The authors of the selected articles were contacted to provide any missing relevant information and data. Attempts were made to contact the authors of respective studies that were published in languages other than English. The authors of a Korean study published in the Korean language provided data in English.[14]

Inclusion Criteria

Studies in which conservative treatment was reported as the primary management modality for consecutive patients with IPN were included in this meta-analysis. Conservative treatment was defined as supportive treatment, including care in an intensive care unit and antimicrobial therapy with or without percutaneous drainage but without any form of necrosectomy (ie, surgical, endoscopic, laparoscopic, retroperitoneal, or nephroscopic). Nonresponse (ie, failure of conservative treatment) was defined as the need for any form of necrosectomy and/or mortality. A few studies reported endoscopic drainage alone without necrosectomy in some patients, and that has been mentioned separately.

Exclusion Criteria

Studies with a small sample size (≤5 in number), studies in which any form of necrosectomy or endoscopic drainage was performed as the primary treatment modality, and studies that included patients with chronic pancreatitis were excluded.

There have been a few published studies with a sizeable number of patients with IPN that reported the efficacy of the percutaneous drainage procedure but did not include consecutive patients with IPN. Although these studies did not exactly fulfill our inclusion criteria, we have summarized and analyzed them separately because these studies also highlighted the principle of conservative management for IPN.

Data Extraction

Data regarding the following variables were extracted from the final selected studies: total number of patients with acute necrotizing pancreatitis during the study period, age, sex, etiology of pancreatitis, severity of pancreatitis, organ failure, computed tomography severity index (CTSI), severity scores (Acute Physiology and Chronic Health Evaluation II [APACHE II], Ranson), number of patients with IPN, criteria for diagnosing IPN, type of treatment, reason for offering a particular type of treatment (particularly conservative treatment) for infected necrosis, need for additional treatment (ie, necrosectomy in any form or surgery) for complications pertaining to percutaneous drainage/conservative management, type of necrosectomy (open surgical, minimally invasive surgical, endoscopic, or percutaneous), and mortality. The data were extracted, collated, and analyzed by 2 of the authors independently. Any difference was resolved by consensus.

Outcome Measures

The outcomes measures were (1) successful outcome of patients with IPN with conservative treatment (antibiotics and/or percutaneous drainage) without necrosectomy, (2) need for any form of necrosectomy or surgical intervention for complications related to percutaneous drainage/conservative management, and (3) mortality.

Statistical Analysis

The relevant extracted data were entered into an Excel sheet (Microsoft Corp, Redmond, WA). Stata version 11.1 (Stata Corp, College Station, TX) was used for statistical analysis. Analysis was performed using the command metan. I^2 test was used to assess heterogeneity of results among the studies. The random effects model was used for the meta-analysis when there was significant heterogeneity among the included studies. Random effects weights were estimated based on the DerSimonian and Laird method. Publication bias was assessed by Egger test.

Results

Characteristics of the Included Studies

The literature search revealed 965 articles, of which 932 were excluded after reviewing the title and abstract. A complete review of the full text was conducted for the remaining 33 articles, and 21 were excluded (Figure 1). The reasons for exclusion were as follows: conservative management not being the primary treatment (6 studies),[15–20] studies without characterization of patients into sterile or infected pancreatic necrosis (4 studies),[21–24] studies including ≤5 patients (3 studies),[8,9,25] percutaneous debridement (2 studies),[26,27] duplication of part of data (2 studies),[28,29] short reviews of other relevant studies (2 papers),[30,31] combined percutaneous and endoscopic drainage with high-volume lavage (1 study),[32] and inability to procure the results of a Chinese study in the English language (1 study).[33] Eight studies fulfilled completely the criteria for inclusion in the current meta-analysis, and these are presented as the group A studies.[11–14,34–37] In addition, 4 studies that reported the results of only those patients who underwent percutaneous drainage for the management of IPN are summarized in group B because they reflected the principle of conservative management for IPN.[38–41] The patients included in the group B studies were not consecutive, but rather were se-

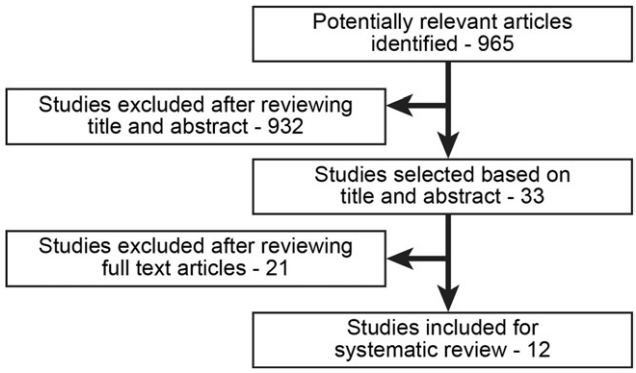

Figure 1. Flow-chart regarding selection of relevant studies.

CLINICAL PANCREAS

Table 1. Study Characteristics

Reference	Year	Country	Study design	Study period
Group A				
Rünzi et al[11]	2005	Germany	Retrospective observational study	1987–1999
Song et al[14]	2006	Korea	Retrospective observational study	1989–2005
Lee et al[12]	2007	Korea	Prospective observational study	2000–2004
Garg et al[13]	2010	India	Retrospective-prospective comparative study	2000–2008
Van Santvoort et al[34]	2010	The Netherlands	Randomized controlled trial	2005–2008
Zerem et al[35]	2011	Bosnia and Herzegovina	Retrospective observational study	1989–2009
Gluck et al[36]	2012	United States	Retrospective comparative study	2006–2011
Alsfasser et al[37]	2012	Germany	Retrospective-prospective comparative study	2000–2007
Group B				
Freeny et al[38]	1998	United States	Retrospective observational study	1991–1995
Navalho et al[39]	2006	Portugal	Retrospective observational study	1993–2003
Bruennler et al[40]	2008	Germany	Retrospective observational study	1992–2004
Mortelé et al[41]	2009	United States	Retrospective observational study	Not reported

lected patients with IPN. The details regarding the included studies are summarized in Table 1.

All 8 studies in group A included consecutive patients with IPN. Of these 8 studies, 4 were observational,[11,12,14,35] 3 were comparative,[13,37,36] and one was a randomized controlled trial.[34] In 6 of these 8 studies, patients underwent primary conservative management for IPN.[11–14,35,37] In one study, standard percutaneous drainage was the main treatment strategy during the initial half of the study period and dual-modality drainage with an endoscopic and percutaneous approach was the main treatment strategy during the latter half of the study period; the patients who underwent only standard percutaneous drainage were included in this meta-analysis.[36] In one study, randomization was performed for either primary surgical management or a step-up treatment approach in which patients first underwent conservative treatment.[34] Patients in the step-up arm were included in this meta-analysis.

Patient Characteristics (Group A Studies)

In the 8 studies in group A, 409 patients had IPN; of these, 324 patients underwent primary conservative management. Forty-five patients in one study underwent primary surgical treatment as part of a randomization protocol,[34] 34 patients in one study underwent dual-modality drainage,[36] and 6 patients in 2 studies underwent surgery due to acute surgical indications.[14,37] The number of patients with IPN in these studies ranged from 21 to 88. The etiology of acute pancreatitis was reported in 5 studies, and gallstone disease was the most common cause in 4 of them.[12,13,34–36] Sex distribution was reported in 6 studies, which showed a male predominance in 5 of them.[12,13,34–37] The patient characteristics are provided in Supplementary Table 1. The data regarding disease severity, as indicated by the presence of organ failure, clinical severity scores, or CTSI, are given in Table 2.

Treatment in Patients With IPN (Group A Studies)

All patients received antibiotics. In 4 studies, prophylactic antibiotics were started.[11–13,34] The choice of antibiotics was variable, but the most common antibiotics used were third-generation cephalosporins, carbapenems, ureidopenicillin, and metronidazole. The percentage of patients who

Table 2. Severity of Illness

	Severity scores (mean)				
Reference	APACHE II	Ranson	CTSI (mean)	>50% necrosis (%)	Organ failure (%)
Group A					
Rünzi et al[11]	16.9	5.9	8	68.8	62.5
Song et al[14]	9 (median)	4 (median)	8 (median)	NR	NR
Lee et al[12]	NR	3.8	7.5	NR	NR
Garg et al[13]	9.4	NR	7	52	52.6
Van Santvoort et al[34]	14.6	NR	8 (median)	27.9	84
Zerem et al[35]	15.5	3.4	8 (median)	NR	68.6
Gluck et al[36]	NR	NR	7.4	NR	65
Alsfasser et al[37]	16.1	3.9	7.9	92	58.5
Group B					
Freeny et al[38]	NR	NR	8.2	41	38 respiratory failure, 35 shock, 26 renal failure, 15 gastrointestinal bleed
Navalho et al[39]	NR	5.4	NR	NR	NR
Bruennler et al[40]	18 (median)	2 (median)	6 (median)	NR	65 respiratory failure, 29 renal failure
Mortelé et al[41]	NR	NR	9.6	NR	23

NR, not reported.

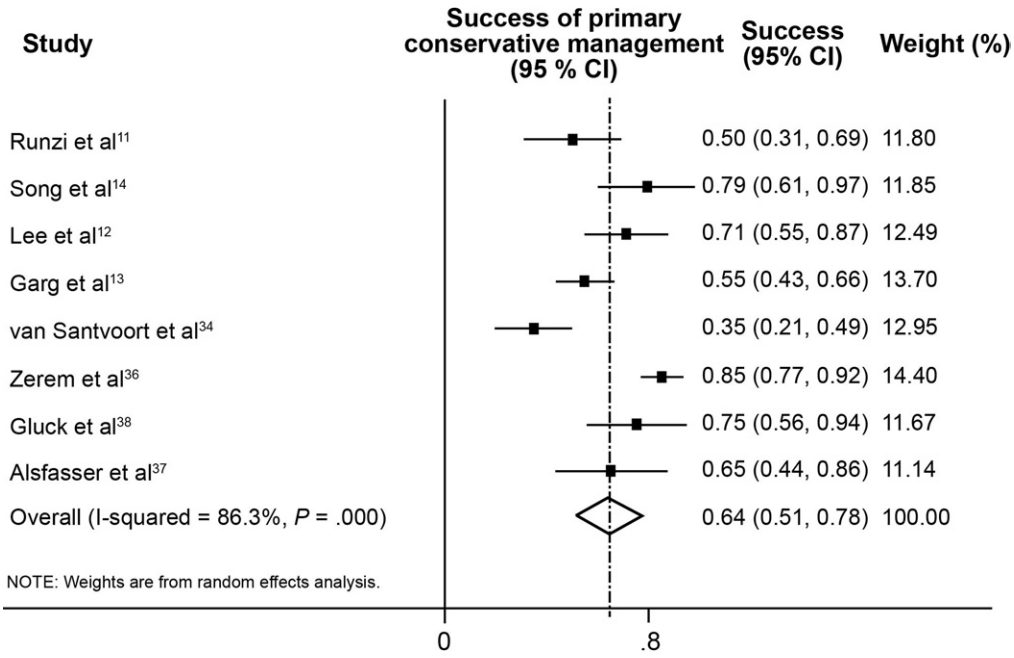

Figure 2. Forrest plot of group A studies analyzing the success of primary conservative management for the treatment of IPN.

underwent percutaneous drainage varied from 18.75% to 100%. Only one study reported the size of the catheter used, but only 11.8% of patients had catheters greater than 12F in size and 11% had more than 2 catheters.[35] The duration of percutaneous drainage was reported in 2 studies as 136 and 15 days (median), respectively.[35,36]

Endoscopic instead of percutaneous drainage was performed in 2 to 5 patients in 3 studies.[12,14,34] Gluck et al[36] used dual-modality drainage by means of percutaneous plus endoscopic drainage in the latter half of their study in 34 patients with 97.1% success and 2.9% mortality, and none of the patients required surgery in this group.

The length of hospital stay varied from 13 to 54 days. The cost of treatment was reported in only one study as $88,664 per patient.[34]

Outcomes (Group A Studies)

In view of the significant heterogeneity among the various studies with regard to the outcomes analyzed, the random effects model was used for analysis. The success of primary conservative management strategy was 64% (95% confidence interval [CI], 51%–78%) (Figure 2). Additional surgery for necrosectomy or for complications related to percutaneous drainage was required in 26% (95% CI, 15%–37%) (Figure 3). The mortality in patients who were managed with primary conservative treatment was 12% (95% CI, 6%–18%) (Figure 4). There was no significant publication bias as assessed by Egger test ($P > .26$). Data from the individual studies regarding the outcomes are summarized in Table 3.

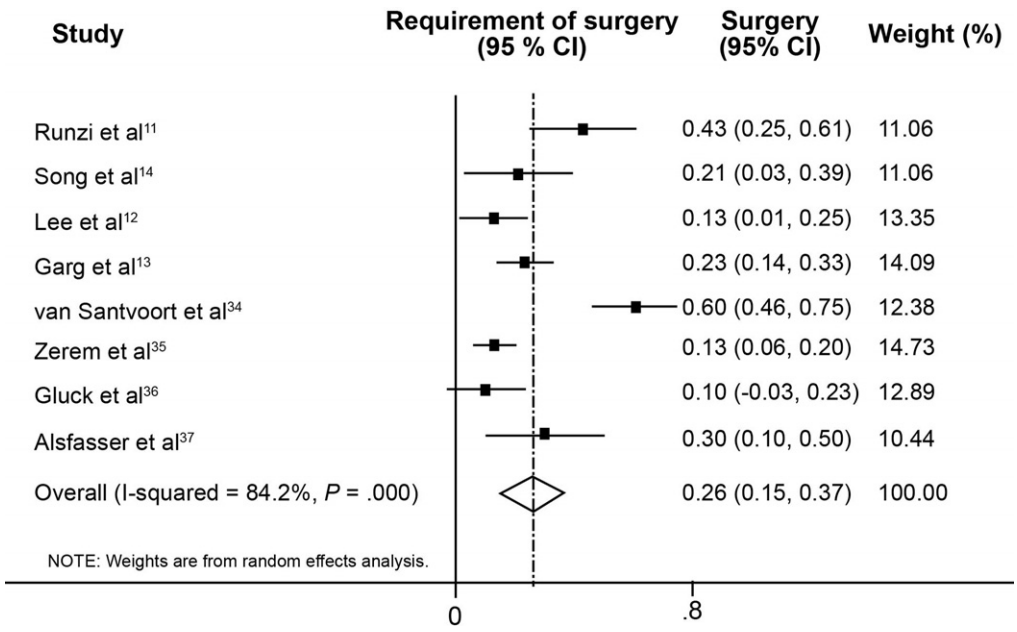

Figure 3. Forrest plot of group A studies analyzing the requirement of surgery for necrosectomy or for complications pertaining to percutaneous drainage in patients with IPN.

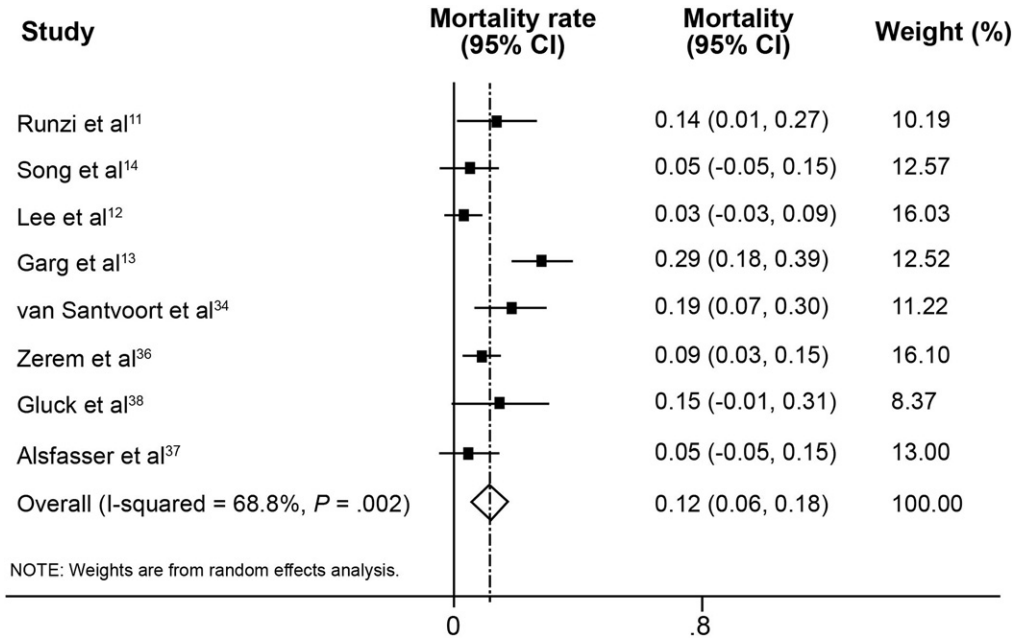

Figure 4. Forrest plot of group A studies analyzing mortality with primary conservative management in patients with IPN.

Outcomes in Patients With Percutaneous Drainage Versus No Drainage

Of the 8 studies, 3 reported drainage in all patients whereas 5 reported a total of 66 patients treated with antibiotics alone and 137 patients requiring additional drainage of infected collections. The mortality in those treated with antibiotics alone was nil in 4 studies and 15% in one study.[11–13,35,37] Almost all of the deaths occurred in patients who required additional drainage and subsequently surgery, suggesting that these patients had severe sepsis and large infected collections. It should not be construed that the better outcome in those treated with antibiotics alone was due to the type of treatment given.

Complications pertaining to the percutaneous drainage procedure were reported in 5 studies. The most common complication was fistula, which developed in 6.4% to 14.6%. Other complications included perforation, colonic injury, and pericatheter leak in a minority of patients.[12,13,34–36]

Results of the Studies Included in Group B

There were 4 retrospective observational studies that reported the success of percutaneous drainage for IPN.[38–41] A total of 157 patients with IPN in these 4 studies underwent percutaneous drainage procedures. However, the denominator (ie, the total number of patients with IPN) was not reported in any of the 4 studies, and thus the overall proportion of patients undergoing percutaneous drainage could not be ascertained. The data regarding the disease severity of the included patients and the outcomes in these studies are summarized in Tables 2 and 3, respectively.

Table 3. Outcomes With Patients With IPN Following Primary Conservative Management

Reference	No. of patients with IPN on primary conservative treatment	Patients undergoing percutaneous drainage (%)	Successful outcome (%)	Need for surgery (%)	Hospital stay (median/ mean ± SD[b], days)	Mortality (%)
Group A						
Rünzi et al[11]	28	18.75 (3/16)[a]	50 (14/28)	42.9 (12/28)	54 ± 10[b]	14.3 (4/28)
Song et al[14]	19	86.36 (38/44)	78.9 (15/19)	21.1 (4/19)	70	5.3 (1/19)
Lee et al[12]	31	67.7 (21/31)	71 (22/31)	12.9 (4/31)	37.7 ± 28.5[b]	3.2 (1/31)
Garg et al[13]	77	45.45 (35/77)	54.5 (42/77)	23.4 (18/77)	26.5	28.6 (22/77)
Van Santvoort et al[34]	43	95.3 (41/43)	34.9 (15/43)	60.4 (26/43)	50	18.6 (8/43)
Zerem et al[35]	86	80.2 (69/86)	84.9 (73/86)	12.8 (11/86)	13	9.3 (8/86)
Gluck et al[36]	20	100 (20/20)	70 (14/20)	15 (3/20)	54	15 (3/20)
Alsfasser et al[37]	20	50 (10/20)	65 (13/20)	30 (6/20)	NR	5 (1/20)
Group B						
Freeny et al[38]	34	100	47.1 (16/34)	52.9 (18/34)	45	11.8 (4/34)
Navalho et al[39]	30	100	63.3 (19/30)	33.3 (10/30)	24	16.6 (5/30)
Bruennler et al[40]	80	100	47.5 (38/80)	20 (16/80)	51	33.8 (27/80)
Mortelé et al[41]	13	100	46.2 (6/13)	53.8 (7/13)	33	7.7 (1/13)

[a]These 16 patients underwent conservative management.
[b]Values expressed as mean ± SD.

One study reported the use of a very large-bore catheter (up to 32F) to allow for drainage of necrotic material.[38] Another study showed no effect of catheter size on the outcome of percutaneous drainage.[40] The duration of percutaneous drainage was 36.5 and 85 days (median) as reported in 2 studies.[38,40] The length of hospital stay varied from 24 to 51 days.

The success of primary conservative management with percutaneous drainage was 50% (95% CI, 43%–58%) (Supplementary Figure 1). Necrosectomy or surgery for complications pertaining to percutaneous drainage was required in 38% (95% CI, 20%–56%) (Supplementary Figure 2). The mortality in these patients was 18% (95% CI, 6%–30%) (Supplementary Figure 3). There was no significant publication bias as assessed by Egger test ($P > .26$).

Predictive Factors for Early Surgery

Because many patients who failed to respond to conservative treatment required surgery, we attempted to identify the factors that could have predicted the need for early surgery. Two studies sought to determine such factors. Zerem et al[35] showed that Ranson, Glasgow, and APACHE II scores; CTSI; and C-reactive protein could predict the need for surgery in their patients, but the 95% CI showed that none of the factors were found to be a significant predictor. Another study analyzed the predictors of mortality and showed that high APACHE II score and serum creatinine level were predictive of mortality.[13] All other studies have shown that nonresponse to conservative treatment and development of local complications such as bleeding and colonic perforation were indications for surgery.[11,12,14,34,36,37] However, none of the studies could identify a particular variable that could be clinically useful to offer an alternate intervention to patients.

Discussion

IPN is a potentially life-threatening complication of acute pancreatitis. The standard treatment of pancreatic necrosis has been surgical necrosectomy, based on the surgical dogma of removing the dead necrotic tissue that is susceptible to infection and further escalates the inflammatory response. In 1991, Bradley and Allen showed that conservative treatment was associated with a better outcome in patients with sterile pancreatic necrosis.[42] Many studies subsequently confirmed these observations, and conservative treatment without necrosectomy became the standard recommendation for treating patients with sterile necrosis over the next 2 decades.[43] IPN has, however, been considered an absolute indication for necrosectomy for many reasons: (1) surgical principles dictate removal of the solid infected material, (2) antibiotics do not penetrate well into pancreatic necrotic tissue, and (3) such patients are quite sick, requiring early intervention to control sepsis. Thus, the various practice guidelines have advocated surgical necrosectomy for patients with IPN.[5,7] A few case reports showed successful outcomes of selected patients with IPN following conservative treatment more by serendipity than by design but presented at least a proof of concept.[8–10] Over the past 5 years or so, a number of case series and comparative trials have shown that primary conservative treatment could be successful for IPN.[11–14,35–37] However, the data from individual studies are not sufficient to recommend a change in practice guidelines. Moreover, there could be a patient selection bias and/or publication bias in case series that have shown a successful outcome following conservative treatment for IPN. If, however, the a priori protocol is conservative treatment for all consecutive patients with IPN, then the chances of such a bias are minimized. We found 8 studies that have reported conservative treatment as the initial and primary treatment for all comers with infected necrosis, and these studies were included in the present meta-analysis. The results of the meta-analysis show that indeed a strategy of primary conservative treatment is not only feasible but also successful in treating patients with IPN.

Of the 8 studies, Rünzi et al[11] reported reasonable success with the conservative approach and additional necrosectomy was required in 42.9% of patients with a mortality of 14.3%, which was lower than that reported following surgical necrosectomy. Lee et al[12] showed excellent results with a very low mortality of 3.2%, which could be due to relatively stable patients in their series. Another Korean study showed a high success rate of 78.9% with conservative treatment.[14] In a randomized controlled trial by the Dutch pancreatitis group, which was included in the present meta-analysis because patients were treated with a conservative first approach in one arm of the study, one-third of patients improved with conservative treatment alone and the remainder underwent minimally invasive necrosectomy.[34] The requirement of necrosectomy was high in that study because the trial was designed to compare open surgery with a minimally invasive approach and thus the threshold for necrosectomy was low. Zerem et al[35] also showed a high success rate of 84.9% and a mortality of only 9.3%. A study from our center compared conservative treatment with surgical necrosectomy.[13] Although it was not a randomized trial, it did show that the mortality in patients treated conservatively was lower although not statistically significant compared with surgical necrosectomy. Similarly, another study from Germany compared conservative management with surgical necrosectomy and reported significantly lower mortality with conservative management.[37] Gluck et al[36] showed that the success rate of standard percutaneous drainage was 70% with a mortality of 15%. They subsequently changed their management strategy from standard percutaneous drainage to a dual-modality percutaneous and endoscopic drainage. We have included only those patients who underwent standard percutaneous drainage but not dual-modality drainage in this meta-analysis to maintain as much homogeneity as possible.

There was significant heterogeneity in the included studies. This was due to the variable severity of illness of the patients treated at different centers, variable time of referral of patients to these hospitals, and variability in the treatment

protocols. Overall, nearly two-thirds of the patients with IPN improved with conservative management alone, about one-fourth required additional surgical procedures for necrosectomy or for complications related to the percutaneous drainage, and the mortality was approximately 12%.

An important argument is that percutaneous drainage is an intervention and thus may not be considered as part of conservative treatment. However, we included percutaneous drainage in conservative treatment because (1) most studies included percutaneous drainage in their conservative treatment protocol and (2) the primary goal of this analysis was to assess the effectiveness of nonsurgical versus surgical management of IPN. Although a few studies have mentioned that large-bore percutaneous catheters could achieve better drainage of necrotic material, that did not amount to formal necrosectomy. Large-bore catheters up to 32F were used to drain necrotic material in only one study,[38] but another study showed that the size of the catheter did not influence the outcome.[40] We have not included studies using endoscopic drainage because almost all studies have combined endoscopic necrosectomy with drainage, which is another form of necrosectomy, albeit less invasive than surgery. Inclusion of such studies would have required a different analysis that compared (1) surgical necrosectomy, (2) endoscopic necrosectomy, and (3) no necrosectomy.

The analysis of the studies that only reported the outcomes of percutaneous drainage, albeit in nonconsecutive patients with IPN, also yielded similar results. There is a possibility of selection bias in this group of studies (included in group B), and thus these studies were analyzed separately. However, the results were quite similar and reinforced the view that conservative treatment has a substantial role in the management of patients with IPN.

There has been an overwhelming surgical bias in treating patients with IPN to remove the nonviable infected tissue. However, surgery is marred by many problems, such as intraoperative collateral tissue damage, bleeding, worsening organ failure due to surgical trauma, multiple operations, stormy postoperative course, lengthy stay in the intensive care unit, and a high mortality of up to 75%, particularly if performed early.[44,45] In a randomized controlled trial, complications developed in 69% of patients who underwent open surgical necrosectomy.[34] In another study, 144 operations were required in 20 patients with IPN who underwent open surgery with a mortality of 45%.[37]

The issue of medical versus surgical treatment for IPN has been intensely debated.[46] Management of patients with sterile pancreatic necrosis has turned around from a primary surgical to a conservative approach. It is quite possible that many patients with presumed sterile necrosis might have had IPN because infection was not ruled out in most cases by fine needle aspiration. Current evidence suggests that conservative treatment might be successful for IPN as well. Multiple factors possibly contribute to the success of conservative management of patients with IPN. These include full organ support, the use of effective new-generation antibiotics, aggressive nutritional support, and timely percutaneous drainage.

Notwithstanding the success of conservative treatment, there could be a subset of patients with IPN who would benefit from early surgical intervention. Most studies have shown that nonresponse to conservative treatment and development of local complications such as bleeding and colonic perforation are indications for surgery. The reasons for failure of conservative therapy could be a large amount of thick necrotic debris at difficult-to-drain locations and resistant organisms, although these have not been categorically stated in the included studies. The group of sickest patients, as defined by the presence of organ failure, emerged as the one requiring surgery and at high risk for mortality in most studies. Specifically, however, no predictive factor was identified in any of the studies that could guide a clinician to move toward early surgical intervention. This is an important lacuna in our understanding and merits further study.

It seems logical now to suggest a randomized controlled trial to compare conservative treatment with the accepted standard of care (ie, surgical necrosectomy) for patients with IPN.

This systematic review has shown that a conservative-first approach is feasible and successful in patients with IPN. Necrosectomy may either be completely avoided or delayed in the majority of patients. While following the conservative-first approach, it is important to recognize that some patients might require necrosectomy later as a step-up therapy at an appropriate time. The logical indications for necrosectomy—poorly localized and solid necrotic debris, as well as a relatively good surgical risk patient not yet improving—require evidence from studies designed specifically to address this particular question.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2012.10.004.

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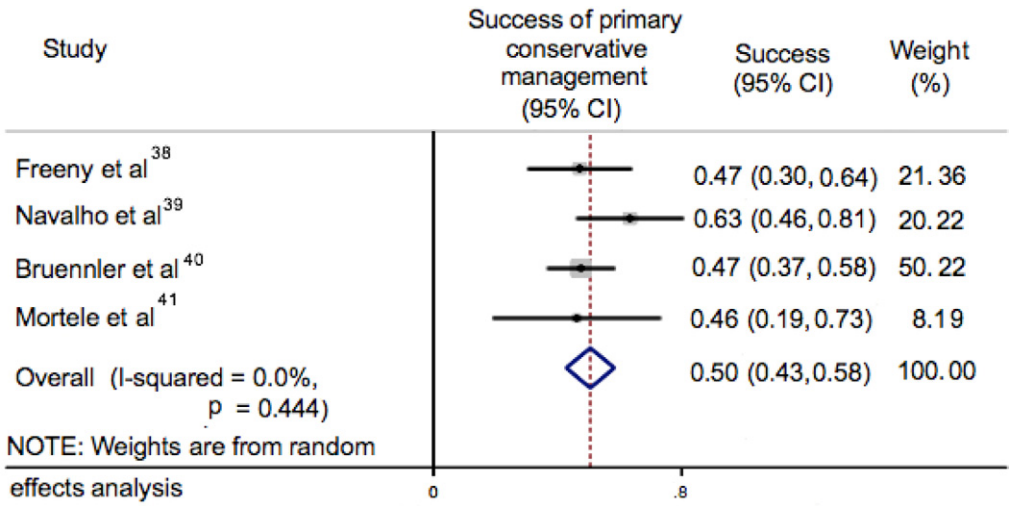
Conflicts of interest

The authors disclose no conflicts.

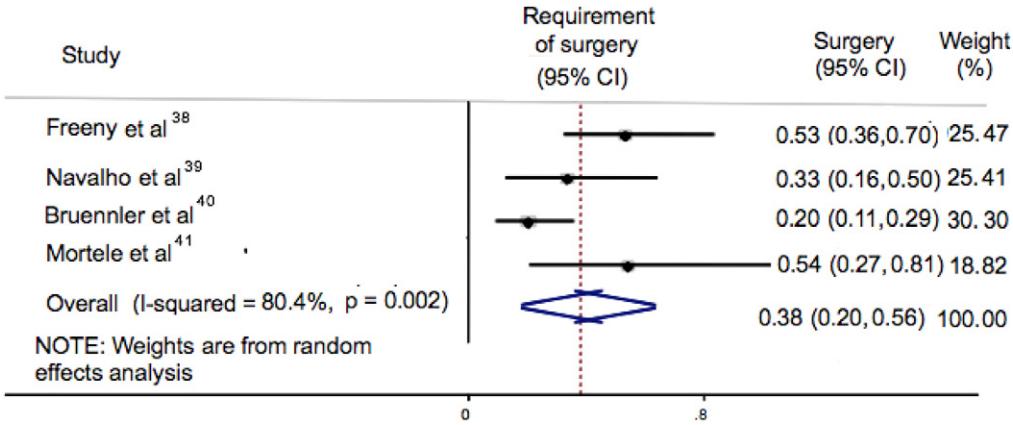
Supplementary Table 1. Patient Characteristics

Reference	No. of patients with acute necrotizing pancreatitis	No. of patients with IPN (%)	Mean age (*y*)	Male sex (%)	Etiology (%)
Group A					
Runzi et al[11]	88	28 (31.8)	46.9	NR	NR
Song et al[14]	71	21 (29.6)	NR	NR	NR
Lee et al[12]	77	31 (40.3)	49.1	71	G 38.7, A 25.8, I 19.4
Garg et al[13]	172	77 (44.8)	41.7	66.2	G 58.4, A 16.9
Van Santvoort et al[34]	378	88 (23.3)	57.6	72	G 60, A 7
Zerem et al[35]	155	86 (55.48)	48.6	65	G 30.2, A 45.4
Gluck et al[36]	NR	54	54	55	G 55
Alsfasser et al[37]	NR	24	55	25	NR
Group B					
Freeny et al[38]	NR	34	56	76.50	G 35, A 21, I 9
Navalho et al[39]	NR	30	58	63	G 57, A 30, I 10
Bruennler et al[40]	NR	80	57 (median)	67.50	G 32.5, A 40, I 18.8
Mortele et al[41]	35	13 (37.1)	48.5	77	G 34, A 23, I 11

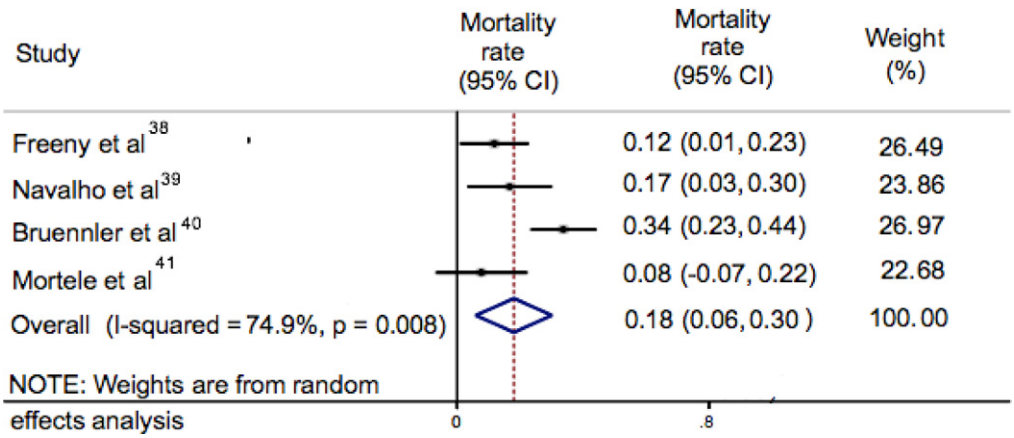
NR, not reported; G, gallstone disease; A, alcohol; I, idiopathic.



Supplementary Figure 1. Forrest plot of group B studies analyzing the success of primary conservative management for the treatment of patients with IPN.



Supplementary Figure 2. Forrest plot of group B studies analyzing the requirement of surgery for necrosectomy or for complications pertaining to percutaneous drainage in patients with IPN.



Supplementary Figure 3. Forrest plot of group B studies analyzing the mortality rate with primary conservative management in patients with IPN.