

## Therapeutic Alternatives for the Treatment of Infected Pancreatic Necrosis. An Overview

Alternativas Terapéuticas para el Tratamiento de la Necrosis Pancreática Infecciosa. Una Visión General

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MANTEROLA, C.; URRUTIA, S. & APODACA, F. Therapeutic alternatives for the treatment of infected pancreatic necrosis. An overview. *Int. J. Morphol.*, 32(4):1357-1364, 2014.

**SUMMARY:** Despite diagnostic and therapeutic advances, the treatment of infected pancreatic necrosis (IPN) continues to be a complex problem to solve. The aim of this study is to evaluate the effectiveness of different surgical alternatives for the treatment of IPN. Articles published between 2000 to 2013, and related to effectiveness of open surgery (OS) and minimally invasive treatment (MIT) in patients with IPN were evaluated. PubMed, MEDLINE, The Cochrane Database of Systematic Reviews, Cochrane Central Register RCT, DARE, IBECS, SciELO, LILACS, PAHO, WHOLIS, ASERNIP-S, NIHR, HTA, Clinical Excellence, York Health Economic Consortium and Tripdatabase were reviewed, searching systematic reviews (SR), randomized clinical trials (RCT) and observational studies (OST), in which the effectiveness of OS and MIT was evaluated in relation to the variables mortality, intra-abdominal bleeding, development of enterocutaneous fistula or hollow viscera perforation, development of pancreatic fistula, reoperations for complications, reoperations for new necrosectomy, development of diabetes mellitus and pancreatic enzyme requirements. Three hundred eighty-nine articles were retrieved, 10 of which met the selection criteria (2 SR, 1 RCT and 7 OST). The studies have a level of evidence of 2a, 2b, 3a and 4. MIT are associated with better results than OS in all variables analyzed, but significantly only in the development of diabetes mellitus and pancreatic enzyme requirement. Articles found are few and heterogeneous, making meaningful conclusions difficult. Studies with a better level of evidence, methodological quality and population size are needed to make conclusions and recommendations.

**KEY WORDS:** "Pancreatitis, Acute Necrotizing/complications"; "Pancreatitis, Acute Necrotizing/therapy"; Infected pancreatic necrosis; Necrosectomy; Evidence-based medicine; Overview.

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### INTRODUCTION

Acute pancreatitis is an inflammatory process of varying severity, from slight and self-limiting forms with interstitial edema, to severe forms with pancreatic necrosis and extensive bleeding (Al Mofleh, 2008). Pancreatic necrosis, associated with septic conditions, determines the production of so-called infected pancreatic necrosis (IPN), a leading cause of death (Khanna *et al.*, 2013) which can yield figures of 45% (Alsfasser *et al.*, 2012).

Despite aggressive multiple organ support in the initial stages of the disease, patients continue to die from necrosis and septic complications, culminating in multiple organ failure, which is associated with high mortality rates (Buter *et al.*, 2002).

Conventional treatment of IPN usually occurs in intensive care units, with nutritional support, antimicrobials,

vasoactive drugs and surgery (Donald *et al.*, 2012) based on sessions of necrosectomy by laparotomy or lumbotomy, associated with irrigation and continuous washing of the retroperitoneum, and possibly with contained laparostomy or open abdomen. However, to date there is no consensus regarding the most appropriate surgical strategy for IPN (Hart & Baron, 2013).

Evidence suggests that the treatment for IPN is surgical debridement, and that the alternative minimally invasive accesses can be used in select circumstances (Banks *et al.*, 2006; Wysocki *et al.*, 2010; Navaneethan *et al.*, 2009). Contrasting evidence maintains that the laparoscopic, endoscopic and retroperitoneal accesses can reduce morbidity and mortality in these patients (Navaneethan *et al.*; Heinrich *et al.*, 2006; Stem & Matthews, 2011).

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In recent years, a significant number of minimally invasive techniques (MIT) have been described. In 2007 Windsor classified these procedures according to the type of technique (endoscopic, laparoscopic and nephroscopic), the access (transperitoneal, transgastric and retroperitoneal) and the synchronization of the surgery: “step-down approach” (open surgery and MIT of the complications) and “step-up approach” (minimally invasive draining technique followed by open necrosectomy) (Windsor, 2007). Furthermore, there is a guide developed by the National Institute for Clinical Evidence that merely describes the situation and notes the lack of consensus regarding the issue (Dillon, 2011).

The aim of this study is to assess the effectiveness of the different surgical alternatives for the treatment of IPN.

## MATERIAL AND METHOD

**Design:** Overview of the available evidence.

**Population:** Articles that evaluated surgical techniques to treat IPN in the population over 18 years of age, published between 2000 and 2013 in English, Spanish, French, Italian, Portuguese and German.

**Inclusion criteria:** Systematic reviews (SR), randomized clinical trials (RCT) and observational studies (OST: cohort studies, cases and controls, and other types of comparative studies).

**Exclusion criteria:** Articles with no information in terms of the type of necrosis that affected the patients in the study were excluded. Also excluded were those studies included in SR selected for analysis.

**Search strategy:** The search was conducted according to PICO components: population of interest (p), intervention to be evaluated (i), the comparator for the intervention being studied (Co), and the variable result measured from the intervention (R). Using this strategy, studies were sought regarding subjects with IPN (p), those where conventional surgery was performed (I), that were compared with MIT (Co), and whose response variables would be: mortality, systemic complications, local, etc. (R). To do this, the following databases were reviewed: PubMed, MEDLINE, The Cochrane Database of Systematic Reviews, Cochrane Central Register RCT, DARE, IBECS, SciELO, LILACS, PAHO, WHOLIS, ASERNIP-S, NIHR, HTA, Clinical Excellence, York Health Economic Consortium and TRIPdatabase. Sensitive searches were conducted using

MeSH terms, free words and the Boolean connectors AND and OR, using strategies adapted for each database.

Thus, the following commands were generated: For PubMed "Pancreatitis, Acute Necrotizing" OR "Pancreatitis, Acute Necrotizing/surgery"[Mesh] OR "Pancreatitis, Acute Necrotizing/therapy"[Mesh] OR “infected pancreatic necrosis” with the limits: Clinical Trial, Controlled Clinical Trial, Review, Meta-Analysis, Systematic Reviews, Randomized Controlled Trial, Publication date from 2000/01/01 to 2013/12/31, Humans, Adult: 19+ years. For MEDLINE, The Cochrane Database of Systematic Reviews, Cochrane Central Register RCT, DARE, IBECS, SciELO, LILACS, PAHO, WHOLIS searches were done through the BVS using the strategy (tw:(Pancreatitis Aguda Necrotizante)) “(tw:(necrosis pancreatica)) OR (tw:(pancreatic necrosis)) AND (tw:(infected)) OR (tw:(infectada))” with the filters: Collection: International databases, Cochrane Library, national databases. Databank: MEDLINE, LILACS, IBECS (España), CENTRAL-Register of controlled clinical trials, DARE-Evaluated systematic reviews, NHS-EED Economic evaluations. Type of study: Controlled Clinical Trial, Cohort Study, Evaluated Systematic Reviews, Case and Control Studies, Overview. Clinical aspect: Therapy. Limit: Humans, Adult. Type of document: Article. And the databases ASERNIP-S, NIHR, HTA, Clinical Excellence, York Health Economic Consortium, through TRIPdatabase using the strategy “(Infected pancreatic necrosis) (Surgery) (minimally invasive treatment) (morbidity)”.

**Synthesis and evaluation of the evidence:** This began with an evaluation of the internal validity of the studies, for which summary tables were created using the CEBM format. The Jadad Scale for RCT (Jadad *et al.*, 1996; Roa, 2008) and validity tables were constructed (using the design proposed by SIGN) (Scottish Intercollegiate Guidelines Network, 2014). Then, a classification was made of levels of evidence, using the system proposed by CEBM (Centre for Evidence-based Medicine at the University of Oxford, 2009). Finally, an overall classification of the evidence was made for each intervention, grouped into high, moderate and low, applying a modified approach of the GRADE system, which includes the study design, the internal validity, the coherence, the accuracy of the results, the publication bias and whether the evaluation of the evidence is direct or indirect (Guyatt *et al.*, 2006).

**Measurement variables:** Effectiveness of open surgery (OS) vs. MIT with respect to the variables mortality, intra-abdominal bleeding, development of enterocutaneous fistula or hollow viscera perforation, development of pancreatic fistula, reoperation due to complications, reoperation for new necrosectomy, development of diabetes mellitus and pancreatic enzyme requirements.

**Plan of analysis:** The selected data were collected in a Windows Excel spreadsheet. Then, the information from each article was analyzed, extracting the data of interest.

**Ethical Aspects:** During the analysis of the selected articles, the authors and centers where the studies originated were masked to further reduce selection and analysis bias.

**Funding:** Medical Sciences Ph.D. program. Universidad de La Frontera, Chile.

**RESULTS**

Three hundred eighty-nine records were recovered, 10 of which fulfilled the selection criteria: 2 SR, 1 RCT

and 7 OS (Bakker *et al.*, 2012; Bausch *et al.*, 2012; Boland *et al.*, 2010; Cirocchi *et al.*, 2013; Connor *et al.*, 2005; Guo *et al.*, 2013; Horvath *et al.*, 2010; Senthil Kumar *et al.*, 2012; Tan *et al.*, 2012; van Baal *et al.*, 2011). The flow chart of the selected articles is detailed in Figure 1.

The results reported below are based on data from a total population of 25 studies (10 articles already defined and 15 included in the two SR (van Baal *et al.*; Freeny *et al.*, 1998; Gambiez *et al.*, 1998; Fotoohi *et al.*, 1999; Baril *et al.*, 2000; Cheung *et al.*, 2005; Navalho *et al.*, 2006; Lee *et al.*, 2007; Bruennler *et al.*, 2008; Mortelé *et al.*, 2009; Rocha *et al.*, 2009; van Santvoort *et al.*, 2010; Raraty *et al.*, 2010) [two of which are repeated in the two SR (Gambiez *et al.*; van Santvoort *et al.*)], and 1461 subjects operated on for IPN: 896 with MIT and 565 with OS.

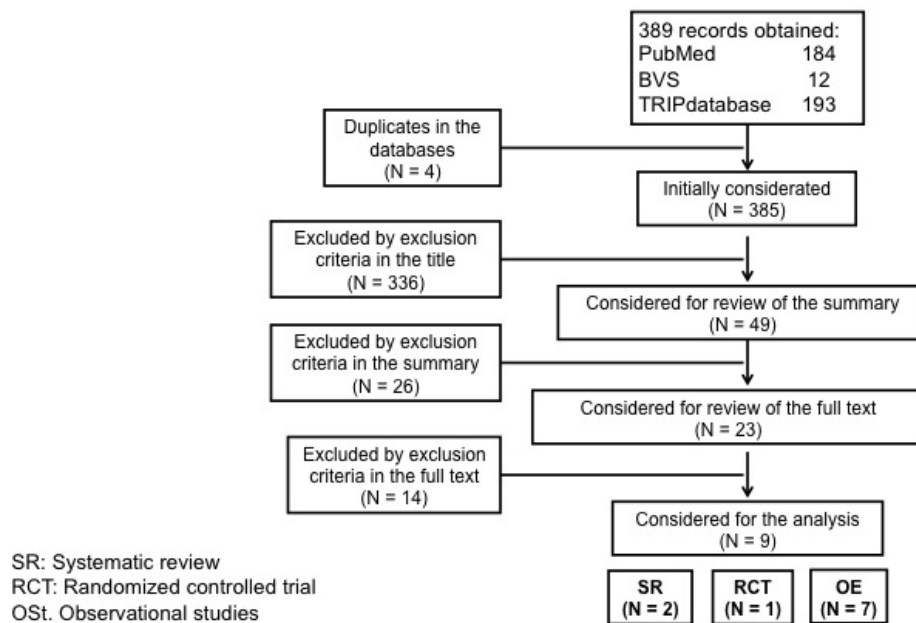


Fig. 1. Flow chart of the search results according to the strategies described.

Table I. Summary of studies included.

Authors	Year of publication	Type of study	n of cases included	Level of evidence
Bakker <i>et al.</i>	2012	RCT	20	2b
Bausch <i>et al.</i>	2012	OST	50	4
Boland <i>et al.</i>	2010	OST	21	4
Cirocchi <i>et al.</i>	2013	SR	346	2a
Connor <i>et al.</i>	2005	OST	88	4
Guo <i>et al.</i>	2013	OST	412	4
Horvath <i>et al.</i>	2010	OST	34	4
Senthil Kumar <i>et al.</i>	2012	OST	30	4
Tan <i>et al.</i>	2012	OST	76	4
Van Baal <i>et al.</i>	2011	SR	384	3a

SR: Systematic review; RCT: Randomized clinical trial; OST: Observational study

The techniques evaluated for MIT were retroperitoneal necrosectomy (RN), endoscopic transgastric necrosectomy (EGN), percutaneous drainage (guided by US or CT), video-assisted surgical necrosectomy (VASN) and laparoscopic necrosectomy (LN). The following details the synthesis of the findings, a summary of which can be found in Table I.

In relation to the variable “perioperative mortality”, 2 SR, 1 RCT and 5 OST (treatment studies 2a, 2b, 3a and 4) were found that reported the variable. For this variable, figures ranged from 4.0% to 63.0%, with the lower numbers being for the MIT. In one SR, 17.2% and 29.8% were reported for MIT and OS respectively ( $p=0.06$ ); and OR of 0.43 (CI 95% of 0.18–1.05) (Boland *et al.*); in a RCT where VASN was compared to EGN, lower mortality was reported for VASN (40.0% vs. 10.0%;  $p=0.30$ ; RR=0.3 (CI 95% from -0.08–0.60) (Bakker *et al.*). Finally, in 5 OS, 63.0%, 21.0%, 6.0% were described for OS, RN and EGN respectively (Bausch *et al.*); 39.0% and 19.0% for OS and MIT ( $p=0.06$ ) (Connor *et al.*); 20.4% and 8.3% for OS and RN respectively ( $p=0.004$ ) (Guo *et al.*); 11.0% y 4.0% for percutaneous and retroperitoneal drainage (Horvath *et al.*); and 4.0% and 5.9% for LN and OS respectively ( $p=0.791$ ) (Tan *et al.*) (High, moderate and low quality).

For the variable “intra-abdominal bleeding”, 1 RS and 5 OST (treatment studies 2a and 4) were found that reported the variable. For this, numbers ranged from 1.9% to 26.0%, with the lower numbers being for the MIT. One SR reported 13.0% and 16.5% for MIT and OS respectively ( $p=0.46$ ); and OR of 0.79 (CI 95% of 0.45–1.50) (Cirocchi *et al.*); and in 5 OS the following figures were described: 26.0%, 21.0% and 17.0% OS, RN and EGN respectively (Bausch *et al.*); 10.0% and 13% for OS and MIT respectively (Connor *et al.*); 6.3% and 1.9% for OS and RN respectively ( $p=0.08$ ) (Guo *et al.*); 11.0% and 8.0% for percutaneous and retroperitoneal drainage (Horvath *et al.*); and 4.0% and 5.9% for MIT and OS respectively ( $p=0.672$ ) (Tan *et al.*) (High and low quality).

For the variable “development of enterocutaneous fistula or hollow viscera perforation”, 1 SR, 1 RCT and 5 OST (treatment studies 2a, 2b and 4) were found that reported the variable. For this variable, numbers ranged from 1.9% to 21.4%, with the lower numbers being for the MIT. In a SR, 11.7% and 21.4% were reported for MIT and OS respectively ( $p=0.06$ ); and OR of 0.43 (CI 95% of 0.30 – 1.46) (Cirocchi *et al.*); in a RCT where VASN was compared to EGN, lower development of fistulae was reported for EGN (20.0% vs. 0.0%;  $p = 0.47$ ; RR = 0.2 (IC 95% of -0.11 – 0.51) (Bakker *et al.*); and 5 OS in which the following figures were reported: 0.0 and 28.0% for OS and EGN (Bausch

*et al.*); 5.0% and 4.0% for OS and MIT ( $p<0.05$ ) (Connor *et al.*); 9.5% and 1.9% for OS and RN ( $p=0.009$ ) (Guo *et al.*); 44.0% and 8.0% for percutaneous and retroperitoneal drainage (Cirocchi *et al.*); and 5.9% and 4.0% for MIT and OS respectively ( $p=0.672$ ) (Tan *et al.*) (High, moderate and low quality).

For the variable “development of pancreatic fistula”, 1 SR, 1 RCT and 2 OST (treatment studies 2a, 2b and 4) were found that reported the variable. For this variable, numbers ranged from 9.7% to 70.0% with the lower numbers being for the MIT. In a SR, 9.7% and 18.7% are reported for MIT and OS respectively ( $p=0.30$ ); and OR of 0.66 (CI 95% of 0.30–1.46) (Cirocchi *et al.*); in a RCT where VASN was compared to EGN, lower development of pancreatic fistulae were reported with EGN (70.0% vs. 10.0%;  $p=0.02$ ; RR = 0.6 (CI 95% of -0.17–0.81) (Bakker *et al.*); in 2 OS, the following figures were described: 29.6% and 47.0% for MIT and OS respectively ( $p=0.002$ ) (Connor *et al.*); 32.0% and 54.9% for MIT and OS ( $p=0.001$ ) (Tan *et al.*) (High, moderate and low quality).

For the variable “reoperation due to postoperative complications”, 1 SR and 4 OST (treatment studies 2a and 4) were found that reported the variable. For this variable, numbers ranged from 4.0% to 43.3%, with the lower numbers being for the MIT. In the SR, 27.6% and 43.3% for MIT and OS were reported respectively ( $p=0.08$ ); and OR of 0.50 (CI 95% of 0.23–1.08) (Cirocchi *et al.*). In one OS, 5.9% and 4.0% were described for MIT and OS respectively, with a value of  $p = 0.63$  (Tan *et al.*) (High and low quality).

For the variable “reoperation for necrosectomy”, 1 SR, 1 RCT and 2 OST (treatment studies 2a, 2b, 3a and 4) were found that reported the variable. For this variable, numbers ranged from 21.0% to 96.7%, with the lower numbers being for the MIT. In one SR, 63.7% and 96.7% were reported for MIT and OS respectively ( $p=0.19$ ); and OR of 0.16 (CI 95% of 0.00–3.07) (Cirocchi *et al.*); in a RCT where VASN was compared to EGN, a lower number of reoperations for necrosectomy was reported with EGN (3 vs. 1;  $p=0.007$ ) (Bakker *et al.*). In 2 OS the following figures were described: 21.0% and 28.0% for RN and EGN respectively ( $p=0.002$ ) (Bausch *et al.*); 26.6% and 46.6% for RN and OS ( $p=0.366$ ) (Senthil Kumar *et al.*) (High, moderate and low quality).

For the variable “development of diabetes mellitus”, 1 RS and 1 RCT (treatment studies 2a and 2b) were found that reported the variable. For this variable, numbers ranged from 16.0% to 38.0% with the lower numbers being for the MIT. In the SR, 16.0% and 38.0% were reported for MIT and OS respectively ( $p=0.03$ ); and OR of 0.32 (CI 95% of

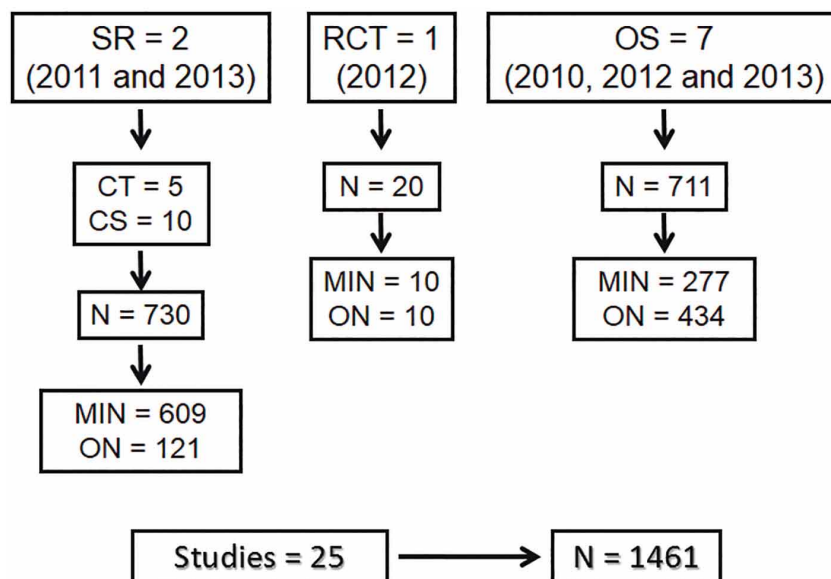


Fig. 2. Diagram of the distribution of studies, patients and surgical techniques used for the treatment of IPN.

Table II. Summary of evidence.

Study variables	n of studies	Quality of evidence	Summary of findings
<b>Perioperative mortality</b>	2 SR	High and low	Lower mortality with MIT
	5 OST		
<b>Intra-abdominal bleeding</b>	1 RCT	Moderate	Lower mortality with VASN than with EGN
	1 SR		
<b>Enterocutaneous fistula or hollow viscera perforation</b>	5 OST	High and Low	Lower mortality with MIT
	1 RCT		
<b>Pancreatic fistula</b>	1 SR	High and low	Lower frequency with MIT
	5 OST		
<b>Reoperation due to postoperative complications</b>	1 RCT	Moderate	Lower frequency of occurrence with EGN vs. VASN
	1 SR		
<b>Reoperation due to necrosectomy</b>	2 OST	High and low	Lower frequency with MIT
	1 RCT		
<b>Development of diabetes mellitus</b>	1 SR	Moderate	Lower frequency of occurrence with EGN vs. VASN
	4 OST		
<b>Pancreatic enzyme requirement</b>	1 SR	High and low	Lower frequency with MIT
	2 OST		
<b>Development of diabetes mellitus</b>	1 RCT	Moderate	Lower frequency with EGN vs. VASN
	1 SR		
<b>Pancreatic enzyme requirement</b>	1 RCT	High	Significantly lower with MIT
	1 SR		
<b>Pancreatic enzyme requirement</b>	1 RCT	Moderate	Lower frequency with EGN vs. VASN
	1 SR		
<b>Pancreatic enzyme requirement</b>	1 RCT	Moderate	Lower frequency with EGN vs. VASN
	1 SR		
<b>Pancreatic enzyme requirement</b>	1 RCT	High	Significantly lower with MIT
	1 SR		

High quality: it is highly unlikely that future studies will change the confidence in the estimation of the effect and therefore the confidence is high.

Moderate quality: is likely that future studies will change the confidence in the estimation of the effect.

Low quality: it is highly unlikely that future studies will change the confidence in the estimation of the effect.

0.12–0.88) (Cirocchi *et al.*); and in the RCT that compared VASN vs. EGN, lower development of diabetes mellitus was reported with EGN (30% vs. 22% (p=0.33); RR = 0.28 (CI 95% of -0.17–0.63) (Bakker *et al.*) (High and moderate quality).

Finally, for the variable “pancreatic enzyme requirement”, only 1 SR (treatment studies 2a) was found that reported the variable. 7.0% and 33.0% for MIT and OS respectively (p=0.005); and OR of 0.005 (CI 95% of 0.04–0.57) (Cirocchi *et al.*) (High quality).

## DISCUSSION

The surgical treatment of IPN remains controversial, not only in relation to the therapeutic option, but also at the moment surgery must be performed. To date numerous articles that provide information regarding the results of various more or less invasive techniques have been published unfortunately mainly as review articles and retrospective case series with less than rigorous criteria in patient selection, a situation that makes their reproduction unfeasible. Moreover, low productivity of comparative studies, the low level of evidence of what does exist and the very small population that these studies employ are all worthy of note.

As a result of the search, we only managed to obtain two SR related directly to the objective, no 1a level of evidence (in one RCT and OST are combined; and the other uses only OST as a study population); only one RCT with a study population of only 20 patients (10 for each branch [2b level of evidence]); and 7 OST, all of which are retrospective (in total representing 711 patients treated with different techniques [4 level of evidence]). Therefore, the articles are also of intermediate and low methodological quality.

From the little evidence available, it can be concluded that in general terms, the MIT are associated with better results than OS in most of the analyzed variables, significantly only in the development of DM and pancreatic enzyme requirement.

The ideal form of treatment of the patient with IPN is yet to be determined. The need for studies with a better level of evidence, good methodological quality and larger populations is clear. Hopefully these can lead to establishing a cost-benefit ratio, cost effectiveness or cost utility among the different IPN treatment options, as well as to assessing the health-related quality of life associated with these procedures.

A summary of the available evidence respect to the objective of this study is shown in Table II.

## AGRADECIMIENTOS

Agradecemos la colaboración de Covidien Surgical Solutions quienes nos han dado soporte para el desarrollo de esta iniciativa.

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MANTEROLA, C.; URRUTIA, S. & APODACA, F. Alternativas terapéuticas para el tratamiento de la necrosis pancreática infecciosa. Una visión general. *Int. J. Morphol.*, 32(4):1357-1364, 2014.

**RESUMEN:** A pesar de los avances diagnósticos y terapéuticos, el tratamiento de la necrosis pancreática infecciosa (NPI) sigue siendo un problema complejo de resolver. El objetivo de este estudio es evaluar la eficacia de las diferentes alternativas quirúrgicas para el tratamiento del NPI. Fueron evaluados artículos publicados entre 2000 y 2013, relacionados con la efectividad de la cirugía abierta (CA) y el tratamiento mínimamente invasivo (TMI) en pacientes diagnosticados con NPI. Se PubMed, MEDLINE, The Cochrane Database of Systematic Reviews, Cochrane Central Register RCT, DARE, IBECs, SciELO, LILACS, PAHO, WHOLIS, ASERNIP-S, NIHR, HTA, Clinical Excellence, York Health Economic Consortium y Tripdatabase, en búsqueda de revisiones sistemáticas (RS), ensayos clínicos aleatorios (ECA) y estudios observacionales (EO). En estos estudios se evaluó la eficacia de la cirugía y el TMI en relación con diferentes variables, como la mortalidad, el sangrado intra-abdominal, el desarrollo de fístula enterocutánea o la perforación de víscera hueca, el desarrollo de fístula pancreática, reintervenciones por complicaciones, reintervenciones por necrosectomía, el desarrollo de diabetes mellitus y la necesidad de enzimas pancreáticas. Se consiguieron 389 artículos, de los cuales 10 cumplieron con los criterios de selección (2 RS, 1 ECA y 7 EO). Los estudios presentaron un nivel de evidencia de 2a, 2b, 3a y 4. El TMI se asocia con mejores resultados que la CA en todas las variables analizadas, pero en forma significativa sólo en el desarrollo de la diabetes mellitus y la necesidad de enzimas pancreáticas. Los artículos encontrados son pocos y heterogéneos, lo que hace difícil poder alcanzar conclusiones significativas. Se necesitan estudios con un mejor nivel de evidencia, calidad metodológica y tamaño de población estudiada para poder establecer conclusiones y recomendaciones.

**PALABRAS CLAVE:** "Pancreatitis, necrosante aguda/complicaciones"; "Pancreatitis, aguda necrotizante/terapia"; Necrosis pancreática infecciosa; Necrosectomía; Medicina Basada en la Evidencia; Visión general.

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Received: 11-07-2014  
Accepted: 04-10-2014