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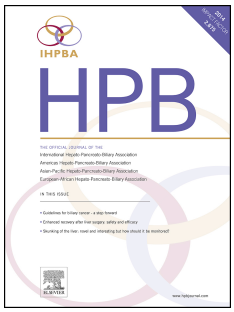

Systematic review of peritoneal lavage and dialysis for patients with severe acute pancreatitis

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PII: S1365-182X(25)00030-9

DOI: https://doi.org/10.1016/j.hpb.2025.01.011

Reference: HPB 2063

To appear in: *HPB*

Received Date: 9 December 2024

Revised Date: 22 January 2025

Accepted Date: 28 January 2025

Please cite this article as: Kowal MR, Bhatnagar V, Pine J, Pathak S, Smith A, Shapey I, Systematic review of peritoneal lavage and dialysis for patients with severe acute pancreatitis, *HPB*, https://doi.org/10.1016/j.hpb.2025.01.011.

Systematic review of peritoneal lavage and dialysis for patients with severe acute pancreatitis

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Funding sources/sponsors
The systematic review described in this study received no funding.

Conflicts of interest
None declared.

Word count (excluding abstract)
3181

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Abstract

Aims**:** Severe acute pancreatitis (SAP) remains a lethal condition with a rising incidence worldwide. Recent randomised trials suggest that peritoneal lavage and/or dialysis (PLD), when administered early in SAP, may be beneficial to improve patient outcomes. This study aimed to review this data systematically.

Methods**:** Studies featuring PLD for the treatment of SAP were searched systematically (2012 Atlanta classification to 2023). A traditional approach to reporting data was augmented by a narrative synthesis.

Results**:** 210 articles were reviewed, of which six studies featuring 499 patients were included. The technical approach, duration and type of lavage varied in each study and no safety concerns were reported. In patients undergoing PLD, improvements in inflammatory markers and length of stay were seen in all studies. Where reported, fewer invasive procedures for peri-pancreatic fluid collections were required after PLD. Lower mortality was seen in cohorts receiving laparoscopic lavage alone and combined lavage and dialysis when compared with standard treatment. All studies were rated at moderate or high risk of bias.

Conclusions**:** PLD demonstrates potential as an early therapy to improve outcomes for patients with SAP. Further research is required to define intervention delivery, explore acceptability and investigate efficacy through a powered randomised controlled trial.

Introduction

Acute pancreatitis is a common condition with significant morbidity, mortality and financial consequences for healthcare systems(1, 2). Despite better understanding of pathophysiology and optimised treatment pathways in recent years, approximately 20% of patients with acute pancreatitis will develop severe disease. Severe acute pancreatitis (SAP) is a lethal condition with a reported overall mortality of 15-20%, which increases to 35% in the presence of infected necrosis(3-5). Damage to the pancreatic parenchyma induces the activation of trypsinogen into trypsin and initiates a cascade effect of inflammatory cytokine release(6). Locally, this can lead to necrosis of the pancreas and peri-pancreatic fat which may become infected and cause sepsis. Systemically, cytokine release causes multi-organ dysfunction syndrome, with respiratory failure occurring in 40-60% of patients, cardiovascular failure in 20-40% and hepatic failure in 20% of patients (7-9). Organ failure is the most important predictor in acute pancreatitis, accounting for nearly all observed in-hospital mortality(10), and consequently shapes the internationally accepted Atlanta 2012 definition of SAP(11). Taking into account a rising incidence worldwide, improving outcomes in acute pancreatitis is an urgent unmet clinical need(12).

The pathophysiological formation of biologically active agents, such as cytokines, are likely contributors towards the high morbidity and mortality observed in SAP, and therefore represent a potential target for therapeutic interventions(13, 14). There are two mechanisms whereby the production of biologically active agents could be targeted with potential therapies. One involves the loco-regional direct release of biologically active agents into the peripancreatic tissues and peritoneal cavity. The second relates to the systemic impact of inflammatory and toxic factors as described by the gut-lymph model of critical illness(15). In the gut-lymph hypothesis, splanchnic vasoconstriction and subsequent gut ischaemia in severe acute illness leads to the release of inflammatory and toxic factors. These factors are absorbed by mesenteric lymphatics, which bypass the portal system and associated hepatic detoxification, and enter the systemic circulation directly via the thoracic duct. The two hypothesised routes of inflammatory and toxic

factors have several potential treatment strategies. Animal models in the context of acute pancreatitis have shown that mesenteric lymph causes significant cardiac dysfunction, which can be reduced upon thoracic duct ligation and external drainage of mesenteric lymph(16). A variation of the procedure, thoracic duct drainage, is well documented in human studies(17) but the effect of the treatment for SAP is not yet fully understood.

Intraperitoneal installation of medicines, with preferential uptake into the mesenteric lymphatics, offers an alternative route to deliver therapies.(18) This could be combined with reducing the ascitic burden of inflammatory and toxic factors, which may further improve outcomes for patients with SAP. Peritoneal lavage and dialysis (PLD) is a potential therapeutic intervention that was first trialled in the 1970s(19, 20). Initial randomised-control trial (RCT) evidence did not report a clinical benefit in heterogenous populations, although this is conflicted by data from more contemporary studies. This systematic review aims to collate the most recent evidence for the role of PLD in SAP, in the context of the Atlanta 2012 classification, in order to inform clinical management and further research.

Methods

Study design

The study protocol was developed in accordance with the PRISMA and AMSTAR 2 guidelines and was prospectively registered with PROSPERO (registration number CRD42023465284) (21, 22). PLD was defined as the intra-peritoneal instillation and removal of solutions to treat SAP and included continuous and intermittent processes, lavage or dialysis techniques, crystalloid and colloid solutions, and open, percutaneous and laparoscopically placed catheters. The Atlanta 2012 classification for SAP was used, defined as acute pancreatitis with persistent single or multi organ failure (lasting over 48 hours)(11).

Selection criteria

In order to describe the current use of PLD in SAP and its associated clinical outcomes, all study types apart from case reports were included. Studies published since the Atlanta 2012 classification up until September 2023 were considered for inclusion. Restricting inclusion to studies published since 2012 was intended to reduce heterogeneity in SAP cohorts and enable a more accurate analysis. Exclusion criteria included: case reports; mild pancreatitis (acute pancreatitis with no organ failure or local or systematic complications; moderately-severe pancreatitis (acute pancreatitis with transient organ failure under 48 hours or local or systemic complications without persistent organ failure). Data for patients undergoing PLD was compared with those who did not undergo PLD.

Systematic literature search

Embase (Ovid), MEDLINE (Ovid), PsycInfo (Ovid) and Cochrane Library databases were systematically searched in September 2023. All identified studies were reviewed against the inclusion and exclusion criteria to assess eligibility. Referenced studies within identified literature were accessed and considered for inclusion. Screening was performed by two independent

investigators (MK and VB) and studies identified were analysed for relevance to the systematic review prior to full inspection. Any discrepancies between the independent investigators were addressed by a third senior investigator (IS) until consensus was achieved. The search strategies used are displayed in full in Appendix S1.

Primary and secondary outcomes

The primary outcomes of interest were: the inflammatory state (infection and inflammation); morbidity (incidence and resolution of organ failure); length of stay (critical care and total hospital); mortality; intervention delivery (timing, placement, technique, duration) and procedural complications. The secondary outcomes included the need for additional interventions following PLD and the development of peri-pancreatic collections.

Data extraction

Two independent investigators (MK & VB) extracted data using a standardised data collection proforma, which included the following data fields:

1. Demographics: age, country of origin, study sample, sex, BMI, comorbidities and pancreatitis aetiology;
2. Study Characteristics: Type of study design;
3. Interventions:
    a. timing of treatment, in relation to presentation - early (<72 hours), clinically guided (72hrs-6 weeks), late (> 6 weeks);
    b. anatomical placement of catheters (intra- vs retro-peritoneal), number of catheters (if >1, were both infusion AND drainage, or infusion OR drainage), type of catheter (e.g., Tenckhoff catheter, Robinson drain etc.);
    c. insertion technique (open, percutaneous, laparoscopic), mobilisation of anatomical structures and final placement of catheters;

d. duration of lavage - days, and indication to stop treatment;

e. type of lavage - continuous (gravity), intermittent (gravity) automated (machine);

f. Solution type;

4. Outcomes: As per primary and secondary outcomes.

Data synthesis

Included studies were tabulated and grouped according to dialysis or lavage interventions. Data relating to the outcomes of interest were recorded, but due to the anticipated heterogeneity amongst study types, a meta-analysis of effect estimates was not planned. Alongside the traditional approach to reporting data, a structured narrative synthesis was conducted in line with the Guidance on the Conduct of Narrative Synthesis in Systematic Reviews from the Economic and Social Research Council(23).

Risk of bias

Risk of bias assessment was conducted by MK and VB independently. The Cochrane's tool for assessing risk of bias in randomised trials was used (24). Where applicable, the RoB-2 score was be used for randomised controlled trials and the Robins-1 for non-randomised trials. Using the tools described, the reviewers judged the risk of bias criteria as "low risk, "high risk" or "unclear risk" for each study.

Results

Included and excluded studies

The search strategy returned 210 articles after removing duplicate studies. Following abstract screening, 206 articles were excluded. The main reasons for exclusion were studies not involving dialysis or lavage as an intervention for SAP. A further two studies meeting inclusion criteria were identified through reference searches within identified systematic reviews. The six included studies subsequently underwent full review. This selection process is outlined in the PRISMA flowchart in Figure 1.

Study characteristics

The six included studies featured a total of 499 patients within three randomised controlled trials and three non-randomised retrospective cohort studies. Five involved the use of peritoneal dialysis and one study featured the use of lavage for management of SAP. The comparators included standard of care, continuous renal replacement therapy (CRRT) and percutaneous drainage (PD). The study characteristics are displayed in Table 1.

PLD technique

Considerable variation was observed in the PLD technique between the five studies (Table 2). Timing of PLD administration varied between immediate at admission to three days from admission, with one study not reporting on timing(25). Four out of the five dialysis studies reported on catheter type and insertion technique, which involved 8-12Fr catheters inserted using Seldinger or open techniques under local anaesthetic and placed in the paracolic gutter or pelvis(25-28). All PLD interventions involved dialysis solution with three studies reporting on dialysis duration, which extended in some instances until the output was deemed to be clear fluid or until day five or seven from commencing the intervention. (25-27)

Wang *et al.* reported their technique of Laparoscopic Lavage (LL)(29). This involved a general anaesthetic procedure within three days of admission, with laparoscopy used to open the lesser sac through a retroperitoneal approach via peri-renal fascia. Debridement and washout were then performed using sterile saline and two to three drains placed within the lesser sac. Dialysis was performed using continuous veno-venous haemo-filtration (CVVHF) via intra-vascular access.

Outcomes

In comparisons between inflammatory markers, several studies showed statistically significant decreases in PLD intervention groups (Table 3). Jiang and colleagues demonstrated decreased c-reactive protein (CRP) levels in the PLD group at day three and seven(25). Similar results were obtained by Zhang *et al.* and Matsumoto *et al.* with reduced CRP, white blood cell count, procalcitonin (PCT), interleukin six (IL-6) and eight (IL-8) and tumour necrosis factor (TNF) on day seven in the PLD groups(28, 30). The LL intervention study also demonstrated reduced IL-6, IL-8 and TNF levels on day three.

When examining complications associated with PLD, He and colleagues found that patients in the PLD group had a reduced incidence of pancreatic encephalopathy and deep venous thrombosis (DVT) (26). The authors also demonstrated a decreased need for further interventions (endoscopic or open drainage) in patients undergoing PLD. Wang *et al.* demonstrated reduced complication rates in their LL cohort, although the exact morbidities were not defined(29).

The length of stay (LOS) for intervention groups was also significantly different in PLD and LL studies. Jiang and colleagues showed a reduction in LOS by an average of five days in their PLD cohort(25). This was also demonstrated in the LL study, with an average LOS reduction of 30 days when compared to the standard treatment(29). Zhang *et al.* reported a statistically significant

reduction in LOS for their PLD cohort, however the exact reduction was not demonstrated in the results(30). In the LL trial, a significant reduction in mortality was seen in both the cohorts receiving laparoscopic lavage alone (9% absolute; 45% relative) and combined lavage and dialysis (13% absolute, 65% relative) when compared with standard treatment(29). All studies reported no significant complications directly related to percutaneous or laparoscopic interventions.

Quality assessment

The Robins-1 tool was employed to assess the quality of non-randomised studies. All three retrospective cohort studies were deemed at “critical risk of bias”. For RCTs, the Rob-2 tool was used. Two studies were assessed as “some concerns” for risk of bias, with the remaining RCT being deemed at “high risk of bias”.

Discussion

This systematic review reports findings from six studies on early intervention for SAP following publication of the Atlanta 2012 classification, featuring a total of 499 patients. The included studies provide a signal towards PLD curtailing the severity of the systemic inflammatory response as observed by a reduction in inflammatory markers. This supports the hypothesis that PLD can reduce the burden of inflammatory and toxic factors that occur in the abdomen as a consequence of SAP. Beneficial effects of PLD on clinical outcomes are suggested through lower mortality, shorter hospital length of stay, and fewer secondary complications arising from SAP including treatment for peri-pancreatic collections and thrombosis. However, these conclusions need to be tempered as the quality of the current evidence is low, with most studies being rated at high risk of bias.

Operative peritoneal lavage (open surgery) for acute pancreatitis was advocated in the early twentieth century (31) but was abandoned following increased mortality in this patient cohort. The treatment then returned through the advent of minimally invasive techniques, with insertion of catheters under local anaesthetic, first proposed by Wall in 1965, who described two survivors from amongst three cases of SAP with refractory shock and oliguria(32). Ranson (New York) further developed this concept and reported data from a series of 24 patients and suggested that both early mortality from organ failure and late death from sepsis were reduced in the PLD cohort (33). Two insufficiently powered randomised trials followed(34, 35), as well as a multi-centre randomised clinical trial in the UK (Leeds/Glasgow/Bristol)(36), where 91 patients with predicted severe pancreatitis were randomised to PLD *versus* standard care with no difference in the reported outcomes. Here, severe pancreatitis was predicted according by findings at diagnostic peritoneal lavage (Leeds scoring criteria) or by multiple laboratory criteria (Glasgow scoring criteria) (37, 38). The trial was powered at 90% to detect a large (r=50%) reduction in mortality and major morbidity. Although no improvement was reported with PLD, closer interrogation of

the data shows that no distinction between early and later mortality was made, and slightly lower mortality from fulminant pancreatitis and sepsis were seen, in keeping with the findings reported by Ranson(33). The UK trial was not powered to detect a medium-sized change (r=30%) thus the 'signal' from both the UK (McMahon/Imrie) and US (Ranson) data suggests ought not be dismissed outright. Over-interpretation of small numbers is dangerous but were a 25% reduction of death from fulminant pancreatitis and 40% reduction of death from sepsis to be likewise demonstrated in a large cohort it would be considered clinically important today. Therefore, PLD as an early technique to attenuate SAP requires re-evaluation in an appropriately powered RCT.

Strong evidence in support of a step-up approach, endoscopic internal drainage of peri-pancreatic collections, and the advancement of critical care as a medical specialty, has led to a significant change in the role of surgical therapy in the management of patients with SAP in recent years(39, 40). Whilst these shifts in clinical care have contributed to a reduction in medium term morbidity and mortality, early in-hospital mortality and post-discharge mortality at 1 year remain unchanged(41). Medical therapies to attenuate the inflammatory response continue to be widely investigated but few, if any, have a current role to play in routine clinical practice(42). One reason for the failure of medical therapies may be that blockage of a single inflammatory molecule is insufficient to counter the pro-inflammatory drive of multiple parallel pathways(42). Thus, the need for a safe, reproducible, minimally invasive and effective therapy to limit localised and systemic complications of SAP remains and PLD is worthy of consideration. This is important because PLD may reduce respiratory, cardio-vascular and renal failure that drive early in-hospital mortality and reduce the incidence infected peri-pancreatic collections driving later in-hospital mortality.

A meta-analysis from 2016, including data from the early trials in 1985 onwards to 2014, reported a 53% reduction of mortality in patients undergoing PLD for SAP(43). A major limitation of this meta-analysis, however, were the various diagnostic criteria for severe acute pancreatitis, non-uniformity of the definitions of local and systemic complications and various differences of procedural technique. An earlier meta-analysis from 2010, including 10 RCTs from 1982 to 2007,

reported no significant differences between PLD and control groups (44). Heterogeneity and various definitions of SAP, similar to the 2016 meta-analysis, are likely to be sources of considerable bias. The Atlanta 2012 classification of Acute Pancreatitis and its accompanying definitions of the associated complications addresses these issues, and hence a post-2012 systematic analysis of the published data is required. An expanded inclusion criteria is also required to account for advances in minimally invasive procedures in recent decades such as laparoscopic and ultrasound guided placement of lavage catheters. In this review, most of the smaller studies (n<80) featured a 12Fr catheter placed in the pelvis or paracolic gutter using the Seldinger technique under local anaesthesia and dialysis continued until the effluent was clear or the 7th day of intervention(25, 26). However, in the largest RCT (n~250), and the only study to confer a reduction in mortality, a laparoscopic approach under general anaesthesia was pursued, and dialysis was performed via haemo-dia-filtration(29). This study by Wang is useful because it shows that both the lavage and dialysis components are important with each conferring a 45% and additional 20% relative reduction in mortality respectively.

To our knowledge, this is the first systematic review of PLD for SAP including studies since the Atlanta 2012 classification. The analysis will facilitate the standardisation of the PLD technique when used in the context of future research. Our approach of incorporating a narrative synthesis alongside the traditional presentation of data offers both objective reporting and a meaningful interpretation of heterogenous studies and populations. Whilst this heterogeneity may represent a limitation of our study, it does provide a “real-world” representation of the published literature. Synthesis and analysis of the pooled data would have been misleading and was not performed on this occasion. However, the systematic reporting of this data is helpful in identifying the need for, and nature of, a definitive randomised trial of PLD in SAP.

This systematic review provides a greater understanding of the PLD protocols performed to date and lays an important foundation on which to expand our knowledge of this possible therapeutic intervention. The use of PLD for SAP is currently limited by a lack of appropriately

powered and well performed RCTs. This is shown by the statistical limitations of historic studies and the quality assessments of contemporary studies included as part of this review. This study has also observed a large variation in PLD protocols, which should be standardised in future studies. The evidence presented as part of this review calls for an iteration of studies in line with the IDEAL framework for surgical innovation(45). A phase 2a prospective study, involving different PLD delivery methods, would build on the data already obtained from animal and human studies, enabling the standardisation and quality assurance of an agreed protocol(46). This would facilitate the development of a safe, minimally invasive and reproducible method for PLD delivery that is acceptable for patients and healthcare professionals. Once established, the PLD protocol could be evaluated in a feasibility trial, providing important feasibility metrics before proceeding to a definitive study. With these findings, a multi-centre RCT comparing PLD to standard care could be designed and powered to detect, if present, a clinically significant change in mortality. The envisaged research would provide definitive evidence to guide PLD therapy for patients with SAP, with a substantial potential to improve clinical outcomes and cost-effectiveness. The role of adjunctive intra-peritoneal therapies could be evaluated thereafter.

Conclusions

PLD is a minimally invasive and safe intervention for SAP that can be performed both laparoscopically and percutaneously. The current literature suggests that the severity of inflammatory response, extent of peri-pancreatic local complications, incidence of multi-organ dysfunction and morbidity, mortality and length of stay in hospital may be curtailed by PLD in SAP. The current evidence base is of low quality and at substantial risk of bias. The findings of this review demonstrate the need for an iteration of studies in line with the IDEAL framework, to develop a standardised and acceptable method for PLD delivery and to investigate its efficacy for patients with SAP in future research.

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Table 1 Study and patient characteristics.

Ref.	Origin	Study type	n	Patient characteristics				
				Age	BMI	Sex (M/F%)	Aetiology n (%)	Severity scores
(25)	China	NRS	52	43	NA	40/60	Gallstones 27 (52) Alcohol 8 (15) Hypertriglyceridemia 11 (21) Other 6 (12)	APACHE-II: CRRT + PLD =9.3 CRRT =9.5
(26)	China	RCT	80	77	NA	25/75	Gallstones 9 (26) Alcohol 9 (11) Hypertriglyceridemia 22 (28) Other 4 (5)	APACHE-II: PCD =17 PLD =20
(30)	China	RCT	64	35	NA	53/47	Gallstones 39 (61) Alcohol 3 (5) Hypertriglyceridemia 13 (20) Other 9 (14)	APACHE-II: PLD: 14.2 Control: 14.1
(27)	China	NRS	35	49	24.8	69/31	Gallstones 18 (51) Alcohol 9 (26) Hypertriglyceridemia 8 (23)	NA
(28)	Japan	NRS	23	NA	NA	70/30	Gallstones 6 (26) Alcohol 7 (30) Other 10 (44)	APACHE-II =7
(29)	China	RCT	245	45	NA	50/50	Gallstones 92 (38) Alcohol 50 (20) Hypertriglyceridemia 51 (21) Other 52 (21)	APACHE-II: Basic treatment=16.5 PLD=16.5 CRRT=16 PLD+CRRT=17

APACHE-II: Acute Physiology and Chronic Health Evaluation II; BMI: Body Mass Index; CRRT: Continuous renal replacement therapy; PLD: Peritoneal lavage & dialysis; RCT: Randomised Controlled Trial; NA: Not available; NRS: Non-randomised study.

Table 2 Intervention protocols.

Ref.	Technique	Timing	Insertion (anaesthetic)	Catheter location (size)	Solution	Duration
(25)	Dialysis	NA	Percutaneous (LA)	Pelvis (12 Fr)	Peritoneal dialysate, exchanged every 2-4 hours	7 days
(26)	Dialysis	<3 days of symptom onset	Percutaneous (LA)	Intra-peritoneal - location not described (8Fr)	0.5L dialysis solution (Baxter Healthcare) exchange every hour	Until solution clear or day 5
(30)	Dialysis	<24 hours of admission	NA	NA	1.5% dextrose dialysis solution 1.5L exchanged every 3-4 hours	NA
(27)	Dialysis	82 hours of admission average	Open cutdown (LA)	Paracolic gutters (NA)	Repeated 2-4 times per day, solution N/A	Until fluid clear
(28)	Dialysis	<72 hour of symptom onset	Open cutdown (LA)	Pelvis (NA)	1.5% dextrose dialysis solution 2L exchanged every 3-4 hours	NA
(29)	Lavage	<72 hour of admission	Laparoscopic (GA)	Lesser sac (NA)	Sterile water until clear	NA

LA: Local anaesthetic, GA: General Anaesthetic, NA: Not available

Table 3 Study outcomes.

Ref.	n	Intervention / Comparator	Primary outcomes	Power	Inflammation/Infection	Morbidity	Mortality	Length of stay (days)	Safety	Significant findings	Risk of bias
(25)	52	CRRT + PLD vs CRRT alone (CRRT commenced if SIRS score >2, AKI 3, persistent organ failure or fluid overload	Biochemical parameters (PCT, IL-6, CRP) and clinical parameters (duration of SIRS, APACHE-II, abdominal pain/distension relief time, hospital cost, complications, mortality, ICU and total LOS)	NA	CRP Day 3 (mg/L) CRRT + PLD = 152.8 CRRT = 223.4 P<0.01 CRP Day 7 (ng/L) CRRT + PLD = 82.2 CRRT = 124.6 P<0.01 PCT Day 3 (ng/L) CRRT + PLD = 12.3 CRRT = 18.3 P<0.01 PCT Day 7 (ng/L) CRRT + PLD = 2.1 CRRT = 12.5 P<0.01 IL-6 Day 3 (pg/L) CRRT + PLD = 627.3 CRRT = 863.4 P<0.01 IL-6 Day 7 (pg/L) CRRT + PLD = 153.8 CRRT = 527.4 P<0.01	Incidence of Clavien-Dindo(47) grade IIIA or above CRRT + PLD = 5 CRRT = 6 P=0.734	CRRT + PLD = 1 CRRT = 3 P=0.610	ICU CRRT + PLD = 15.3 CRRT = 20.6 P<0.01 Total CRRT + PLD = 35.2 CRRT = 40.7 P<0.01	NA	Decreased LOS and inflammatory markers with PLD	Critical risk

(26)	80	PLD vs PCD (continuous external drainage, no lavage/dialysis)	Mortality and major complications, which included new-onset multiple-organ failure and IPN	80%	IPN PLD = 12 PCD = 13 P = 0.47 Persistent SIRS PLD = 30 PCD = 27 P = 0.14 Septicaemia PLD = 5 PCD = P = 0.22	Single-organ failure PLD = 13 PCD = 7 P = 0.052 Multi-organ failure PLD = 8 PCD = 5 P = 0.17 ACS PLD = 6 PCD = 5 P = 0.35 Acute cerebral infarction PLD = 0 PCD = 1 P = 0.26 DIC PLD = 1 PCD = 1 P = 0.49 DVT PLD = 0 PCD = 4 P = 0.03 Pancreatic encephalopathy PLD = 0 PCD = 5 P = 0.02	PLD = 6 PCD = 6 P = 0.35	ICU PLD = 9 PCD = 10 P=0.47 Total PLD = 20 PCD = 24 P=0.33	Need for further interventions (endoscopic or open drainage) PLD = 8 PCD = 19 P = 0.008	Decreased morbidity and need for further interventions with PLD	Some concerns

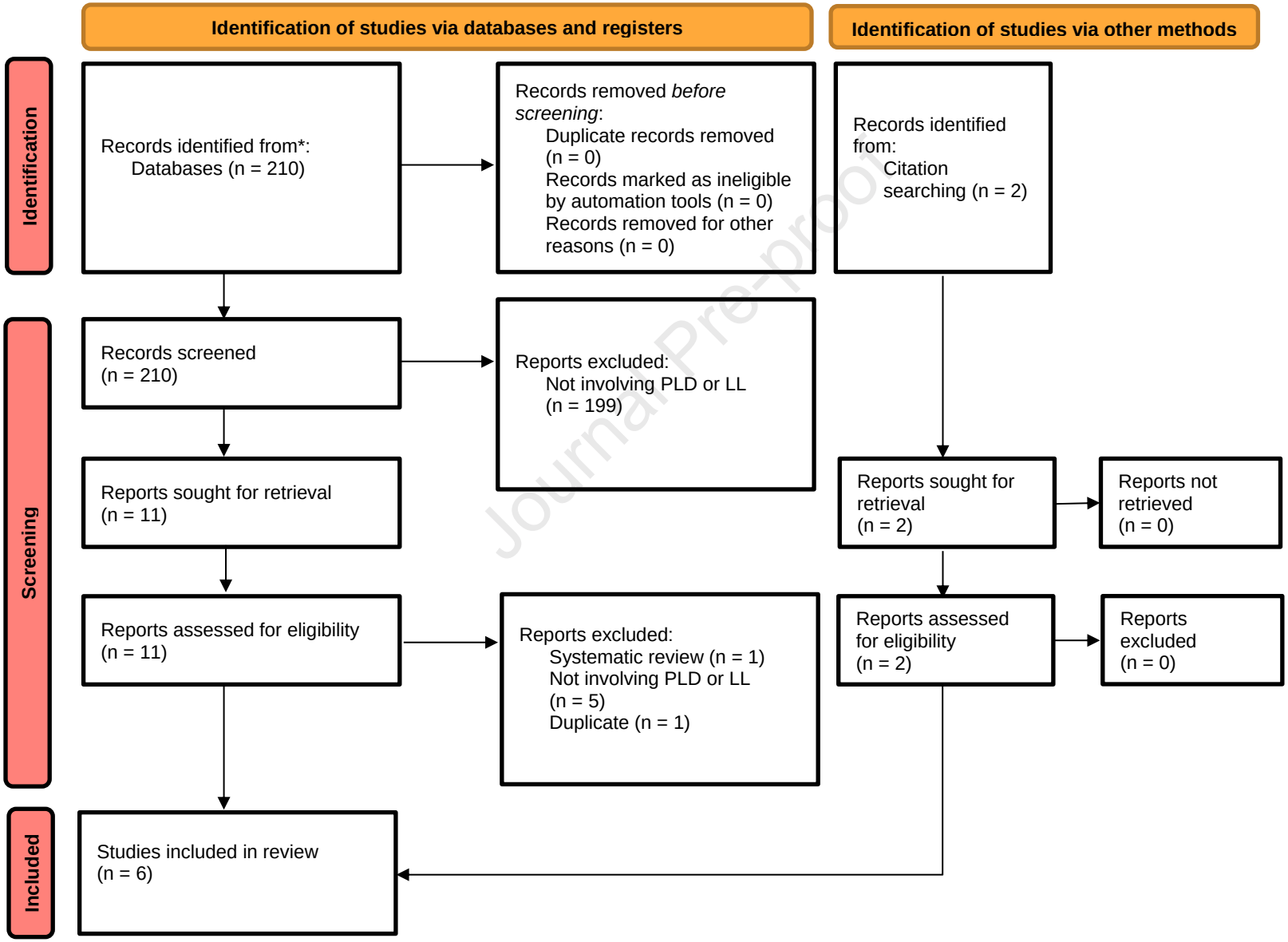
(30)	64	PLD vs standard of care control	NA	NA	No raw values available, authors state PLD reduced CRP, PCT, IL-6/8 and TNF on day 7 (P<0.05)	ARDS PLD = 26 Control = 28 P = 0.491 AKI PLD = 9 Control = 10 P = 0.784 Pancreatic encephalopathy PLD = 3 Control = 6 P = 0.281 Pancreatic abscess PLD = 1 Control = 3 P = 0.302 Pancreatic pseudocyst PLD = 6 Control = 9 P = 0.375	PLD = 2 Control = 3 P = 0.641	No raw values available, authors state decreased in PLD (P<0.05)	NA	Decreased LOS and inflammatory markers with PLD	High risk
(27)	35	PLD vs PCD	NA	NA	NA	All complications (not defined) PLD = 1 PCD = 3 P = 0.261	PLD = 3 PCD = 1 P = 0.316	Total PLD = 31 PCD = 42.8 P = 0.211	Bleeding PLD = 1 PCD 0 Site infection PLD = 0 PCD = 1 Catheter blockage PLD = 0 PCD = 2	PLD is safe when used for SAP	Critical risk

(28)	23	PLD (no control)	NA	NA	SIRS score Day 0 = 3 Day 5 = 1 P = 0.0001 WBC (/mm^3) Day 0 = 14,050 Day 5 = 7,100 P = <0.0001 CRP (mg/dL) Day 0 = 16 Day 5 = 7.8 P = 0.0028 Lactate dehydrogenase (IU/L) Day 0 = 288 Day 5 = 261 P = 0.0074 Amylase (mg/dL) Day 0 = 592 Day 5 = 99 P = <0.0001	Bacteraemia = 2 Pseudocyst = 3 IPN = 1 Pseudoaneurysm = 1 Pancreatic fistula = 1	1	50	N/A	Speculative reduction in mortality with PLD	Critical risk
(29)	245	LL vs LL+CRRT vs CRRT vs standard of care control	NA	NA	No raw values available, authors state IL-6, IL8, TNF-alpha reduced in LL and LL + CRRT by day 3, 1 and 2 respectively (P<0.05) compared with basic treatment	All complications (not defined) Control = 18 LL = 5 CRRT = 6 LL + CRRT = 6 Compared to control P<0.05	Control = 12 (20%) LL = 7 (11%) CRRT = 8 (12%) LL + CRRT = 4 (7%) Compared to control P<0.05	ICU Control = 21.3 LL = 10.4 CRRT = 12.5 LL + CRRT = 7.8 Compared to control P<0.05 Total Control = 61.4	No difference in complication rates	LL and LL in combination with CRRT decreased inflammatory cytokines, morbidity, LOS and mortality	Some concerns

											LL = 31.3 CRRT = 35 LL + CRRT = 25.6 Compared to control P<0.05

ACS: Acute Coronary Syndrome; AKI: Acute Kidney Injury; APACHE-II: Acute Physiology and Chronic Health Evaluation II; ARDS: Acute respiratory distress syndrome; CRP: C-reactive protein; CRRT: Continuous renal replacement therapy; DIC: Disseminated intravascular coagulation; DVT: Deep venous thrombosis; IL-6: Interleukin-6; IPN: Infected pancreatic necrosis; LL: Laparoscopic Lavage; NA: Not available; PCD: Percutaneous drainage; PCT: Procalcitonin; PLD: Peritoneal lavage & dialysis; SIRS: Systemic Inflammatory Response Syndrome; TNF: Tumour necrosis factor.

Figure 1: PRISMA Flow Diagram for study selection. Adapted from (21)



Appendix

S1: Systematic Review Search Strategy for OVID and Cochrane Library

Search number	Keyword Search Strategy
1	pancreatitis.mp
2	acute pancreatitis.mp
3	severe acute pancreatitis.mp
4	pancreatitis, acute h?emorrhagic.mp
5	pancreatitis, acute necroti?ing.mp
6	pancreatitis, alcoholic.mp
7	peritoneal lavage.mp
8	peritoneal dialysis.mp
9	peritoneal lavage and dialysis.mp
10	1 OR 2 OR 3 OR 4 OR 5 OR
11	7 OR 8 OR 9
12	10 AND 11

Cochrane Library Search Strategy

(pancreatitis OR acute pancreatitis OR severe acute pancreatitis OR pancreatitis, acute h?emorrhagic OR pancreatitis, acute necrotic?ing OR pancreatitis, alcoholic) AND (peritoneal lavage OR peritoneal dialysis OR peritoneal lavage and dialysis)

Systematic review of peritoneal lavage and dialysis for patients with severe acute pancreatitis

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Conflicts of interest / sources of funding
The authors declare no conflicts of interest in relation to this work. The systematic review did not receive any funding for its production.