

## SUPPLEMENTARY TABLES

**Supplementary table 1.** Level of evidence based on the Grading quality of evidence and strength of recommendations (adapted from Atkins et al. BMJ 2004 and Cornberg et al. J Hep 2019).

<b>Level</b>	<b>Criteria</b>	<b>Simple model for grade of evidence: high, low and very low*</b>
1	Randomized controlled trials (RCT)	High: Further research is unlikely to change our confidence in the estimate of effect
2	Randomized controlled trials (RCT) or observational studies with dramatic effects; Systematic Reviews (SR) of lower quality studies (i.e. non-randomized, retrospective)	
3	Non-randomized controlled cohort/follow-up Study/control arm of randomized trial (systematic review is generally better than an individual study)	Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
4	Case-series or case-control	
5	Expert opinion (Mechanism-based Any estimate of effect is uncertain Reasoning)	Very Low: Any estimate of effect is very uncertain

\*Decrease grade if: • Serious ( – 1) or very serious ( – 2) limitation to study quality • Important inconsistency ( – 1) • Some ( – 1) or major ( – 2) uncertainty about directness • Imprecise or sparse data ( – 1) • High probability of reporting bias ( – 1)

**Supplementary table 2.** Grades of recommendation (adapted from Cornberg M, et al. J Hepatol 2019)

<b>Grade</b>	<b>Wording</b>	<b>Criteria</b>
Strong	Shall, should, is recommended shall not, should not, is not recommended	Evidence, consistency of studies, risk-benefit ratio, patient preferences, ethical obligations, feasibility
Weak/open	Can, may, is suggested may not, is not suggested	

## Group 1

**Supplementary table 3.** Studies evaluating antibiotics administered when treating patients with direct endoscopic necrosectomy (DEN) for WON (statement 1.1).

Authors	Type	N° pts	Conclusions
<b>Negm AA. et al. 2013 (1)</b>	Prospective, observational, multicenter study	44	Colonization of PPFCs was found in 59% of PPFC cultures, whereas all but 2 (13%) concomitant blood cultures showed no microbial growth. In 23 patients with fluid colonization despite empiric antibiotic therapy, the treatment had to be adjusted in 18 patients (78%) according to the observed antibiotic susceptibility profile
<b>Moka P. et al 2018 (2)</b>	Ambispective	556	34% developed bacterial infection; however, bacteremia was present in 34%. Nearly 50% of patients (n = 94) acquired extremely drug-resistant bacterial infection at some time and emerged as key reason for prolonged hospital and intensive care unit stay
<b>Sahar N. et al. 2018 (3)</b>	Retrospective	182	41% were infected. <i>Candida</i> spp. accounted for 27%; 85% had symptomatic sterile WON. Empiric antibiotic use successfully predicted infection 70% of the time. Multidrug-resistant organisms were found.
<b>Garret C. et al 2020 (4)</b>	Retrospective cohort study	56	Infected pancreatic necrosis confirmed in 48 (86%) patients. Multidrug- or extensively drug-resistant bacteria were identified at some point in half the patients.

**Supplementary table 4.** Studies using specific antibiotics for infected pancreatic necrosis undergoing DEN (statement 1.2)

STUDY	DESIGN	NUMBER OF PTS	ANTIBIOTIC	OUTCOMES
<b>Thompson CC et al., 2016 (5)</b>	Prospective	60	1-2L warmed <u>Bacitracin-saline solution</u> (25,000 units/L)	-
<b>Kumar N et al., 2014 (6)</b>	Prospective	12	1 to 2 L warmed <u>Bacitracin-saline solution</u> (25,000 units/L)	-
<b>Ge R. et al., 2020 (7)</b>	Retrospective	112	<u>bacitracin 25,000 units</u> in 1 litre of warmed saline	-
<b>Lariño-Noia J et al., 2021 (8)</b>	Retrospective	20	<u>imipenem/cilastatin</u>	less than half of the patients with infected WON, who did not respond to systemic antibiotics, required necrosectomy.

**Supplementary table 5.** Studies about the insertion of a naso-cystic tube (statement 1.4)

STUDY	DESIGN	NUMBER OF PTS	Naso-cystic tube insertion	OUTCOMES
<i>Maharshi S et al., 2021 (9)</i>	RCT	50	Nasocystic irrigation with H <sub>2</sub> O <sub>2</sub> (Group A) versus biflanged metal stent placement (Group B)	No differences in technical success, clinical success, requirement for additional procedures, and adverse events
<i>Bang JY et al., 2013 (10)</i>	Retrospective	76	Nasocystic catheter to facilitate irrigation of the necrotic cavity with 200 mL of normal saline every four hours (in both the groups examined)	Endoscopic treatment was successful in 53 of 76 (69.7%) patients. Treatment success was higher in patients undergoing Multi-Gateway technique than in those in whom conventional drainage was used
<i>Tamura T et al., 2019 (11)</i>	Retrospective	19	10 pts received transmural nasocyst continuous irrigation vs 9 pts did not	Time taken to reduce WON, implementation rate of endoscopic necrosectomy and number of endoscopic necrosectomy sessions were significantly lower in the Nasocystic group

**Supplementary table 6.** Studies reporting technical success, clinical success and adverse events (AEs) after H<sub>2</sub>O<sub>2</sub> assisted direct endoscopic necrosectomy (DEN) (statement 1.5).

Author, year	Study details	No. pts in H <sub>2</sub> O <sub>2</sub> group	Stent used	Details of H <sub>2</sub> O <sub>2</sub> intervention	Mean no. of sessions	Definition: clinical success	Technical success	Clinical success	AEs
<b>Gunay et al., 2021 (12)</b>	Retrospective, open-label observational study	11	Pancreatic SEMS	50% diluted H <sub>2</sub> O <sub>2</sub> , 250 mL	4.2 ± 1.4	Absence of recurrence	91%	100%	18%
<b>Messallam et al., 2020 (13)</b>	Retrospective, multicenter	122	LAMS	3% H <sub>2</sub> O <sub>2</sub> diluted 1:2 to 1:10, 10-1000 mL	2.4	Resolution of WON	100%	94%	5%

<b>Othman et al., 2017 (14)</b>	Retrospective case series, single center	19	Viabil or two 10F plastic stents	H2O2, 30 mL mixed with 30 mL water	2	Resolution of WON	100%	95%	16%
<b>Coe et al., 2016 (15)</b>	Retrospective single-center case series	6	LAMS (Axios)	.3% H2O2, 100 mL	3	Resolution of symptoms attributed to WON	100%	83%	0%
<b>Galasso et al., 2015 (16)</b>	Case series	4	LAMS (Axios)	3% H2O2, 40-60 mL	5	Absence of recurrence	100%	100%	25%
<b>Siddiqui et al., 2014 (17)</b>	Retrospective case series, dual-center.	14	Biliary FC-SEMS or two 10F plastic stents	3% H2O2 at 1:5-1:10 dilutions, 100-500 mL	3	Resolution of WON	100%	79%	29%
<b>Abdelhefez et al., 2013 (18)</b>	Retrospective case series.	10	Two 10F plastic stents	.1-.3% H2O2, 100-300 mL	1.4	Resolution of WON	100%	100%	60%

**Supplementary table 7.** Studies considering on/off Proton-Pump Inhibitors (PPI) for infected pancreatic necrosis undergoing DEN (statement 1.6)

<b>STUDY</b>	<b>Design</b>	<b>No. Of pts</b>	<b>PPI</b>	<b>Outcomes</b>
<b>Thompson CC et al., 2016 (5)</b>	Prospective	60	OFF (to encourage auto-digestion of the necrosis and to further address potential infectious complications)	-
<b>Powers PC et al., 2019 (19)</b>	Retrospective	272	136 on PPI and 136 off PPI during the interval of DEN	PPI group required a median of 4.6 procedures, compared to 3.2 in the non-PPI group (p<0.01)
<b>Ge PS et al., 2020 (7)</b>	Retrospective	112	All PPI were discontinued until WON resolution	-

**Group 2**

**Supplementary Table 8.** Characteristics of studies including the evaluation of feeding route among patients with *patients with pancreatic fluid collection* (statement 2.1).

Study	Country	Study period/ design	Intervention	Population	Number of patients	Main result	Complications	Notes
<b>Rai et al., 2021 (20)</b>	India	2017-2019/ RCT	Hunger-Based Versus Conventional Oral Feeding	Moderate and severe acute pancreatitis	56 vs 54	Reduced Length of hospitalization and fasting duration in hunger based regimen	No differences in infective or septic complications	
<b>Maldonado et al., 2021 (21)</b>	Spain	2017-2019/ RCT	Immediate versus conventional oral refeeding	Mild and Moderate acute pancreatitis	71 vs 60	Reduced Length of hospitalization (LOH) and fasting duration in immediate refeeding (3.4 vs 8.8 mean days; SD 1.7 vs 7.9 LOH)	Reduced complications and progression of acute pancreatitis	
<b>Zhao et al., 2015 (22)</b>	China	2011-2012/ RCT	Early hunger based oral refeeding (EORF) vs conventional oral refeeding (CORF)	Moderate and severe acute pancreatitis	67 vs 71	The total length of hospitalization (13.7 +/- 5.4 days versus 15.7 +/- 6.2 days [mean +/- SD] p=0,039) and duration of fasting were shorter in the EORF group than in the CORF group	No difference in the number of adverse events and/or complications	
<b>Stimac et al., 2016 (23)</b>	Croatia	2007-2012/ RCT	Early nasojejunal refeeding vs nihil-by-mouth	Acute pancreatitis	107 vs 107	Similar occurrence of SIRS between two groups, 45 % vs 48 %;	No differences in occurrence of local complications of acute pancreatitis	Same results also according to severity score.

						No reduction of persistent organ failure and mortality		
<b>Bakker OJ et al., 2014 (24)</b>	Netherlands	2008-2012/ RCT	Early (<24 h) nasoenteric tube refeeding vs on demand (72 h) oral or nasoenteric refeeding	Acute pancreatitis	101 vs 104	No differences in early composite primary end-point (infection or death) within 6 months, 30 % vs 27 %	No differences in occurrence of necrotizing pancreatitis or ICU admission	

RCT: Randomized controlled trial; h: hours; SD standard deviation; ICU: intensive care unit.

**Supplementary table 9.** Studies evaluating the timing to start enteral nutrition in patients with pancreatic fluid collection and inability to be fed orally (statement 2.3).

Author (year)	Study type	N° studies	N° pts tot	Conclusion
<b>Qi D et al., 2018 (25)</b>	Meta-analysis	8	727 (281 eEN vs 281 vs 165 PN)	eEN within 24 hours of admission is safe and provides benefits (reduced organ failure and infections) for SAP, but not for mild to moderate PA
<b>Bakker OJ et al., 2014 (26)</b>	Meta-analysis	8	165 (100 eEN vs 65 dEN)	eEN (within 24 h of admission) reduced the composite endpoint of mortality, infected pancreatic necrosis and organ failure
<b>Li X et al., 2014 (27)</b>	Meta-analysis	12	625 (301 eEN vs 324 dEN or PN)	eEN (within 24h) is associated with reduced risk of pancreatic infection, mortality, organ failure, hyperglycemia, and catheter-related septic complications
<b>Song J et al., 2018 (28)</b>	Meta-analysis	10	1051	eEN (within 48hours) significantly reduced the mortality, organ failure, operative intervention, systemic infections, local septic complications and gastrointestinal symptoms compared with late EN or PN in patients with SAP
<b>Petrov MS et al., 2009 (29)</b>	Systematic review	11	451	When started within 48 h of admission, EN vs PN showed statistically significant reduction in the risks of MOF, pancreatic infectious complications and mortality.  After 48 h of admission, EN vs PN did not result in a statistically significant reduction in the risks of MOF, pancreatic infectious complications and mortality

<b>Feng P et al., 2017 (30)</b>	Meta-analysis	4	1007	eEN (<48h) was related to a reduced risk of multiple organ failure, but not for necrotizing pancreatitis. There was a tendency for decreased systemic inflammatory response syndrome in the eEN group, but the trend was not significant.
<b>Jin M et al., 2017 (31)</b>	Prospective	-	104	The third day after hospital admission was the best cut-off time of early EN. After PS matching, the proportion of secondary infection in the early EN group was significantly lower than the late EN group.

eEN: early Enteral Nutrition; dEN: delayed Enteral Nutrition; PN: Parenteral Nutrition; AP: Acute Pancreatitis; SAP: Severe acute Pancreatitis

**Supplementary table 10.** Studies evaluating NG or NJ route in patients with pancreatic collections starting enteral nutrition (statement 2.4).

<b>Author (year)</b>	<b>Study type</b>	<b>N° studies</b>	<b>N° pts tot</b>	<b>Conclusion</b>
<b>Eatock FC et al., 2005 (32)</b>	RCT	-	<b>49</b> (27 NG vs 22 NJ)	NG feeding is as good as NJ in patients with SAP (in terms of complication exacerbation of PA, hospital stay, toleration)
<b>Kumar A et al., 2006 (33)</b>	RCT	-	<b>31</b> (15 NG vs 16 NJ)	No difference in outcome measures (discharge, surgery, death) nor toleration, recurrence or worsening of pain in SAP
<b>Singh N et al., 2012 (34)</b>	RCT	-	<b>78</b> (39 NG vs 39 NJ)	Early enteral feeding through NG was not inferior to NJ in pts with SAP (Infections, pain in refeeding, intestinal permeability, endotoxemia were comparable)
<b>Nally DM et al., 2014 (35)</b>	Meta-analysis	6>4	<b>258</b> (97 NG vs 85 NJ)	No significant differences in reaching nutritional targets nor risk of change to TPN, diarrhoea, exacerbation of pain or tube displacement
<b>Chang Y et al., 2013 (36)</b>	Meta-analysis	3	<b>157</b> (82 NG vs 75 NJ)	No significant differences in the incidence of mortality, tracheal aspiration, diarrhea, exacerbation of pain and meeting energy balance between the two groups of SAP
<b>Zhu Y et al., 2016 (37)</b>	Meta-analysis	4	<b>237</b> (122 NG vs 115 NJ)	No significant differences in the incidence of mortality, infectious and digestive complications, achievement of energy balance and length of hospital stay
<b>Piciocchi M. et al., 2010 (38)</b>	Prospective	-	<b>116&gt;25</b> (60% NG vs 40% NJ)	No significant difference in clinical outcome (mortality, infected pancreatic necrosis, bleeding)

**Supplementary table 11.** *Studies including evaluation of semi-elemental or polymeric Enteral Nutrition (EN) for patients with PFCs (statement 2.5).*

<b>Study</b>	<b>Country</b>	<b>Study period/ Design</b>	<b>Intervention</b>	<b>Population</b>	<b>Number of patients</b>	<b>Main results</b>	<b>Complications</b>
<b>Tiengou LE et al., 2006 (39)</b>	Caen, France	1-year period Randomized pilot study	Semi-elemental VS polymeric enteral nutrition	Pts with severe AP	15 VS 15	Evaluation at 7 days of: - Tolerance (VAS, stool frequency, steatorrhea): NO differences - Weight loss: less marked in semi-elemental group - Length of hospital stay: shorter in semi-elemental group - Infections rate: NO differences  Both EN are well tolerated. Semi-elemental formula supports the hypothesis of a more favorable clinical course than nutrition with a polymeric formula	none
<b>Petrov MS et al., 2009 (40)</b>	New Zeland	1997-2008 Systematic Review and Meta-analysis	Polymeric VS semi-elemental nutrition	20 RCT (12 RCT on severe AP only)	1070 pts with AP  (825 with severe and 245 with mild acute pancreatitis )	The use of polymeric, compared with semi-elemental, formulation does not lead to a significantly higher risk of feeding intolerance, infectious complications or death in patients with PA.	
<b>Poropat G. et al., 2015 (41)</b>	Croatia	1989-2013 Systematic Review	Enteral nutrition formulations for acute pancreatitis	15 RCT  2 RCT (126 pts): Semi-elemental EN vs control (No	1376 pts with AP	PRIMARY ENDPOINT: SEMI-ELEMENTAL - All-cause mortality: NO differences - Length of hospital stay: NO differences  FIBER-ENRICHED - All-cause mortality (2): NO differences - SIRS(1): NO differences	



				<p>intervention or polymeric)</p> <p>2 RCT (103 pts): Fiber-enriched EN vs control (no intervention or polymeric formulation)</p>	<p>- Organ failure(1): decreased risk in fiber enriched BUT difference not reach statistical significance</p> <p>- Adverse events: not reported</p> <p>SECONDARY ENDPOINT:</p> <p>- Local septic complication(1): NO differences</p> <p>- Other infections (1): Lower rate fiber enriched group</p> <p>- Length of hospital stay: shorter in fiber-enriched</p> <p>Both trials included patients with SAP according to the specified criteria; therefore analysis based on severe forms of disease corresponds to the main analysis.</p>	
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**Supplementary table 12.** Studies evaluating the timing of starting nutrition (enteral and/or parenteral nutrition) among patients with PFCs (statement 2.8a).

Author (year)	Study type	N° studies	N° pts tot	Conclusion
<b>Qi D et al., 2018 (25)</b>	Meta-analysis	8	<b>727</b> (281 eEN vs 281 vs 165 PN)	Early EN within 24 hours of admission is safe and provides benefits (reduction in MOF and pancreatic-related infections) for SAP, but not for mild to moderate PA
<b>Bakker OJ et al., 2014 (26)</b>	Meta-analysis	8	<b>165</b> (100 eEN vs 65 dEN)	eEN (within 24 h of admission) reduced the composite endpoint of mortality, infected pancreatic necrosis and organ failure
<b>Li X et al., 2014 (27)</b>	Meta-analysis	12	<b>625</b> (301 eEN vs 324 dEN or PN)	Early EN (within 24h) is associated with reduced risk of pancreatic infection, mortality, organ failure, hyperglycemia, and catheter-related septic complications.

<b>Song J et al., 2018 (28)</b>	Meta-analysis	10	<b>1051</b>	Early EN (within 48hours) significantly reduced the mortality, MOF, operative intervention, systemic infections, local septic complications and gastrointestinal symptoms compared with late EN or PN in patients with SAP or pSAP
<b>Petrov MS et al., 2009 (29)</b>	Systematic review	11 (7 early vs 4 delayed)	<b>451</b>	When started within 48 h of admission, EN vs PN showed statistically significant reduction in the risks of MOF, pancreatic infectious complications and mortality.  After 48 h of admission, EN vs PN did not result in a statistically significant reduction in the risks of MOF, pancreatic infectious complications and mortality
<b>Feng P et al., 2017 (30)</b>	Meta-analysis	4	<b>1007</b>	eEN (<48h) was related to a reduced risk of multiple organ failure, but not for necrotizing pancreatitis. There was a tendency for decreased systemic inflammatory response syndrome in the eEN group, but the trend was not significant.
<b>Jin M et al., 2017 (31)</b>	Prospective	-	<b>104</b>	The third day after hospital admission was the best cut-off time of early EN. After PS matching, the proportion of secondary infection in the early EN group was significantly lower than the late EN group.  EN was a protective factor against secondary infection

**Supplementary table 13.** Studies evaluating the type of nutrition (enteral and/or parenteral nutrition) among patients with PFCs (statement 2.8b-2.2a).

<b>Author (year)</b>	<b>Study type</b>	<b>N° studies</b>	<b>N° pts tot</b>	<b>Conclusion</b>
<b>Marik PE et al., 2004 (42)</b>	Meta-analysis	6	<b>263</b>	EN was associated with a significantly lower incidence of infections, reduced surgical interventions to control pancreatitis and a reduced length of hospital stay VS PN
<b>Petrov MS et al., 2008 (43)</b>	Meta-analysis	5	<b>202</b> (95 EN vs 107 PN)	EN reduced the risk of infectious complications, pancreatic infections and mortality
<b>Petrov MS et al., 2008 (44)</b>	Systematic review	15	<b>617</b> (266 EN vs 280 PN vs 71 none)	EN is associated with a lower risk of infectious complications compared with PN
<b>Cao Y et al., 2008 (45)</b>	Meta-analysis	6	<b>224</b> (106 EN vs 118 PN)	EN was associated with a significantly lower risk of infections, pancreatitis-related complications, organ failure, MOF and mortality.

<b>Al-Omran M et al., 2010 (46)</b>	Meta-analysis	8	<b>348</b>	EN vs PN significantly decreases mortality by 50%, rate of infection, MOF, surgery, hosp stay.  If only patients with SAP were included, mortality further decreased by >80%.
<b>Petrov MS et al., 2010 (47)</b>	Meta-analysis	5	<b>174</b> (82 EN vs 92 PN)	Reduction in infectious complications and mortality associated with the use of EN over PN.
<b>Quan H et al., 2011 (48)</b>	Meta-analysis	6	<b>326</b> (158 EN vs 168 PN)	EN was associated with a significantly lower incidence of pancreatic infection complications, MOF, surgical interventions and mortality.
<b>Yi F et al., 2012 (49)</b>	Meta-analysis	8	<b>381</b> (184 EN vs 197 PN)	EN was significantly superior to PN when considering mortality, infectious complications, organ failure and surgical intervention

**Supplementary table 14.** Studies evaluating nutrition (enteral and/or parenteral nutrition) among patients with PFCs (statement 2.8c-2.2b)

<b>Author (year)</b>	<b>Study type</b>	<b>N° studies</b>	<b>N° pts tot</b>	<b>Conclusion</b>
<b>Yao H et al., 2017 (50)</b>	Meta-analysis	5	348	Compared with PN, EN was associated with a significant reduction in overall mortality and the rate of MOF
<b>Li W et al., 2018 (51)</b>	Meta-analysis	9	500 (244 EN vs 256 PN)	EN group had significantly lower mortality rate, duration of hospitalization, a lower risk of pancreatic infection and related complications, MOF and surgical intervention than PN group
<b>Wu P et al., 2018 (52)</b>	Meta-analysis	11	562 (281 EN vs 281 PN)	EN can significantly decrease the mortality rate, the risk of infection and complications and the mean hospitalization time compared to PN
<b>Wu P et al., 2010 (53)</b>	RCT	-	107 (53 EN vs 54 PN)	EN n is better than PN in the prevention of pancreatic necrotic infection in SAP
<b>Yi F et al., 2012 (49)</b>	Meta-analysis	8	381	EN better than PN in terms of mortality, infectious complications, organ failure, surgical intervention.

<b>Eckerwall GE et al., 2006 (54)</b>	RCT	-	50 (24 EN vs 26 PN)	In predicted SAP, nasogastric early EN was feasible and resulted in better control of blood glucose levels, although the overall early complication rate was higher in the EN group. No differences in GI symptoms or abdominal pain
<b>Stimac D et al., 2016 (23)</b>	RCT	-	214 (107 EN vs 107 none)	No significant differences between the 2 groups in terms of SIRS, mortality, organ failure, local complications, infected pancreatic necrosis, surgical interventions, length of hospital stay, adverse events and inflammatory response
<b>Bevan MG et al., 2017 (55)</b>	Meta-analysis	17	2024	patients with PFC are 3.5 times more likely to develop Oral feeding intolerance than patients without them

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