Acute Pancreatitis: current management strategies

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Since 1456

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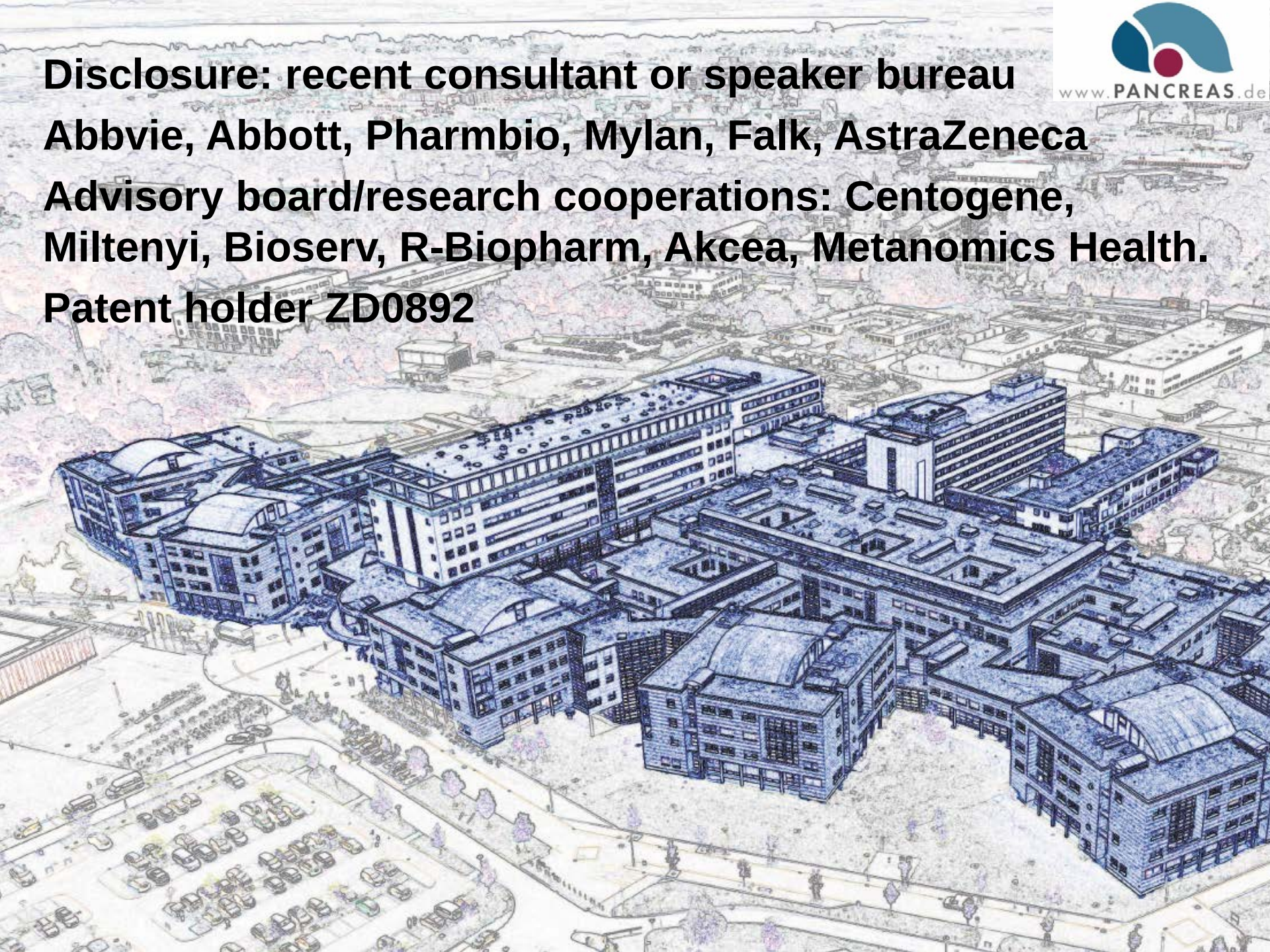
Disclosure: recent consultant or speaker bureau

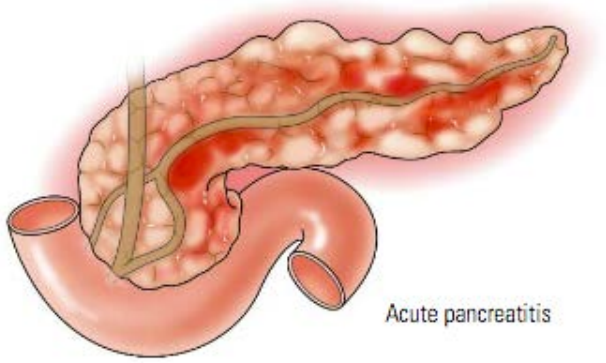
Abbvie, Abbott, Pharmbio, Mylan, Falk, AstraZeneca

Advisory board/research cooperations: Centogene, Miltenyi, Bioserv, R-Biopharm, Akcea, Metanomics Health.

Patent holder ZD0892



Acute pancreatitis – background



Inflammation of the pancreas – onset not usually caused by infectious agents.

The most frequent reason for hospital admission among all non-malignant GI diseases in the US.

Acute pancreatitis is in 20% severe and associated with complications.

With a complicated course it is fatal in 5-20% (1.500 deaths in Germany, 13.500 in Europe)

Peery AF Gastroenterology 2012; 143: 1179-1187
Lerch MM, Lammert F. Weissbuch Gastroenterologie 2017

Current Treatment Principles

- Stabilization of vital signs:
  - Pain treatment
  - Oxygen via mask or nasal tube
  - Volume replacement
- Antibiotics
- Nutrition
- Interventions for infected necrosis

Aghdassi A. et al. Expert Rev Gastroenterol Hepatol. 2018;12:1207-1218

Fluid replacement therapy - Risks

Inadequate or excessive fluid replacement

Early or late fluid resuscitation ?

Retrospective study, 45 patients. Impact of initial i.v. fluid resuscitation in first 24 hrs on mortality, persistent organ failure, median length of hospital stay.

	Early Resus.	late Resus.	p-value
0-24h [l]	4,895	1,714	< 0.001
24-48h [l]	4,144	3,139	0.420
48-72h [l]	3,165	2,908	0.710
Total [l]	12,190	7,664	0.074

Clinical outcome	Early Resus.	late Resus.	p-value
Mortality	0	5 (18%)	< 0.033
Persistent OF	6 (35%)	12 (43%)	0.309
Mean DOS [days]	40±66	37±70	0.880
Median DOS [days]	12	11	

Gardner TB et al. Pancreatology 2009; 9: 770-776

Rapid or slow fluid resuscitation ?

Prospective single center study, 247 patients.
2500 ml/24h after admission / more than 2500 ml/24h / more than 4000 ml

Variables	< 2500ml **n=25**	> 2500ml **n=184**	> 4000 ml **n=151**	p-value
Necrosis	12.5%	14.1%	22.4%	n.s.
OF	24%	8.2%	17.2%	<0.05
Respiratory failure	12%	5.4%	12.1	n.s.
Renal failure	16%	6%	13.8%	n.s.
ICU admission	8%	3.8%	12.1%	n.s.
Mortality	16%	1.6%	5.2%	0.01

- Administration of less than 2500 ml/24h is associated with organ failure and higher mortality.
- Excessive fluid volume within the first 24h (> 4000 ml) is associated with local complications, respiratory failure and mechanical ventilation.

De-Madaria E et al. Am J Gastroenterology 2011; 106: 1843-1850

Abdominal Compartment Syndrome in Acute Pancreatitis - systematic review

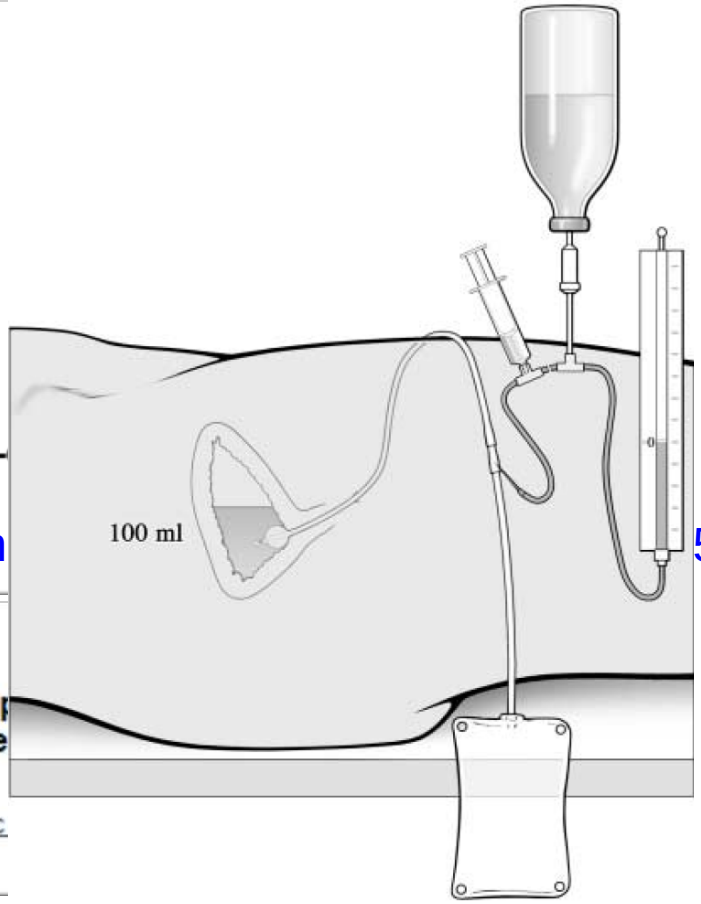
271 patients, 103 (38%) with ACS. Mortality in AP with ACS was 49%.
Decompressive laparotomy was performed in 74% of patients with ACS.

Study name	Statistics for each study				
	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Bezmarevic et al	0,833	0,369	0,977	1,469	0,142
Chen et al	0,750	0,522	0,892	2,127	0,033
Davis et al	0,250	0,097	0,508	-1,903	0,057
De Waele et al	0,750	0,238	0,966	0,951	0,341
Leppaniemi et al	0,400	0,158	0,703	-0,628	0,530
Mentula et al	0,462	0,284	0,650	-0,392	0,695
Tao et al	0,333	0,168	0,553	-1,497	0,134
	0,475	0,373	0,579	-0,474	0,636

-1,00

$I^2 = 57\%$, $p = 0.03$

Brunsch 5



BMC Surg. 2010 Jul 12;10:22. doi: 10.1186/1471-2482-10-22.

Decompressive laparotomy with temporary abdominal closure versus p abdominal catheter in patients with abdominal compartment syndrome and design of multicenter, randomised, controlled study.

Radenkovic DV[1], Bajec D, Ivancevic N, Bumbasirevic V, Milic N, Jeremic V, Gregoric P, Karamarkovic V.

Results of trial still pending

Rapid or Controlled fluid Resuscitation ?

Randomised controlled trial, 76 patients, severe acute pancreatitis

Group 1: Rapid fluid expansion (10-15 ml/kg/h > 10.000 ml/12h)
Group 2: Controlled fluid expansion (5-10 ml/kg/h > 5.000 ml/12h)

Treatment goal: 2 or more criteria: HR<120 beats/min, MAP 65-85 mmHg, urine output > 1ml/kg/h and Hct < 35. Crystalloids and colloids were infused simultaneously at a 2:1 ratio.

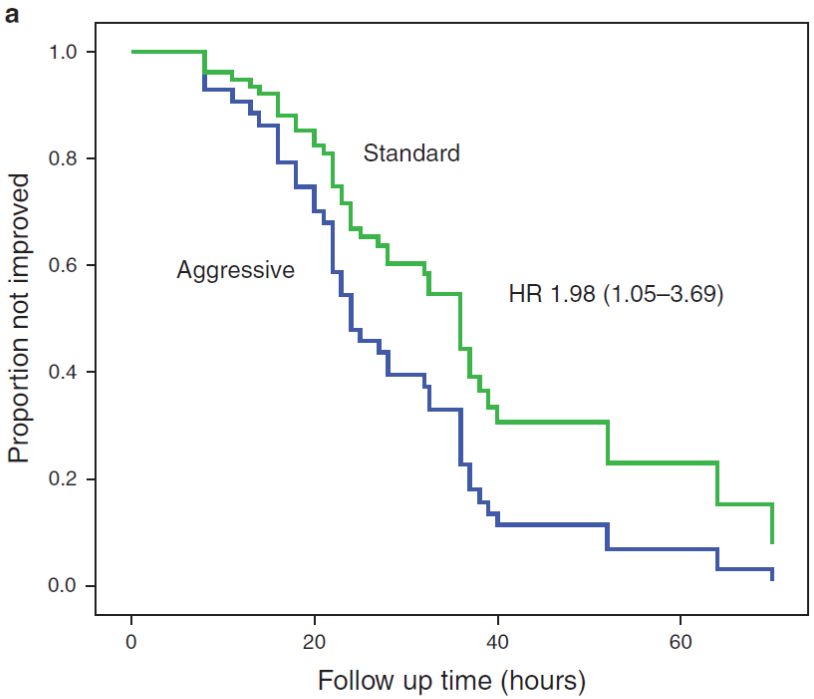
Variables	Group 1 n=36	Group 2 n=40	p-value
Time interval until fluid expansion [h]	13±6.6	24±5.4	0.00
APACHE II Score	13.6±5.3	14.8±5.6	0.34
Mechanical Ventilation	94.4%	65%	0.00
Incidence ACS	72.2%	32.5%	0.00
Incidence of sepsis	63.9%	37.5%	0.02
Mortality	30.6%	10%	0.03

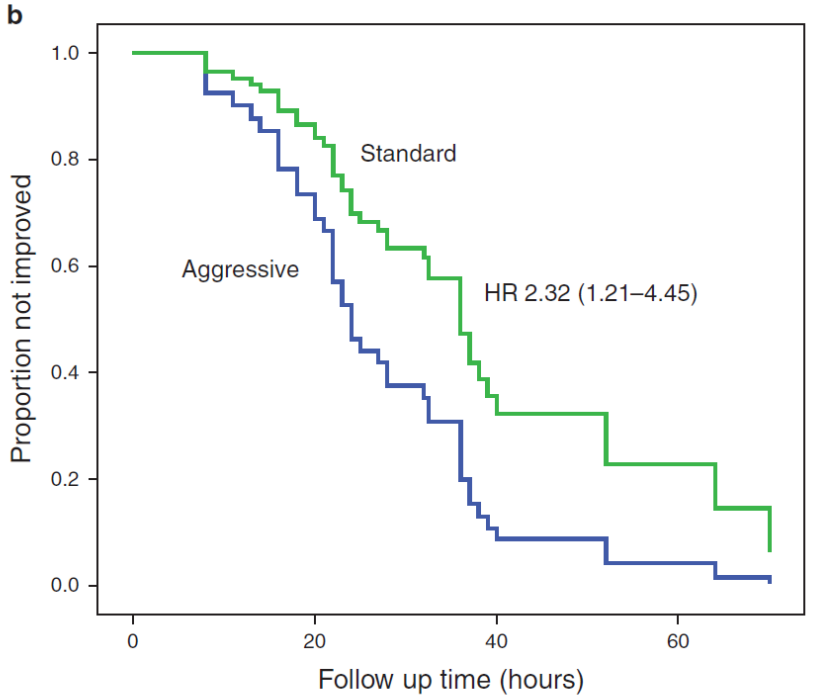
Mao E, Chin Med J 2009; 122: 169-173

Too much or too little fluid replacement ?

Mild acute pancreatitis. Exclusion of SIRS and NYHA ≥II ‚stopping rule' for fluid overload

Randomized to 20 ml/kg Bolus (1600ml) thereafter 3 ml/kg/h (Ø5,6ltr. in 24h)
vs. standard (10 ml/kg Bolus (800ml) thereafter 1.5 mg/kg/h (Ø3.9ltr. in 24h)

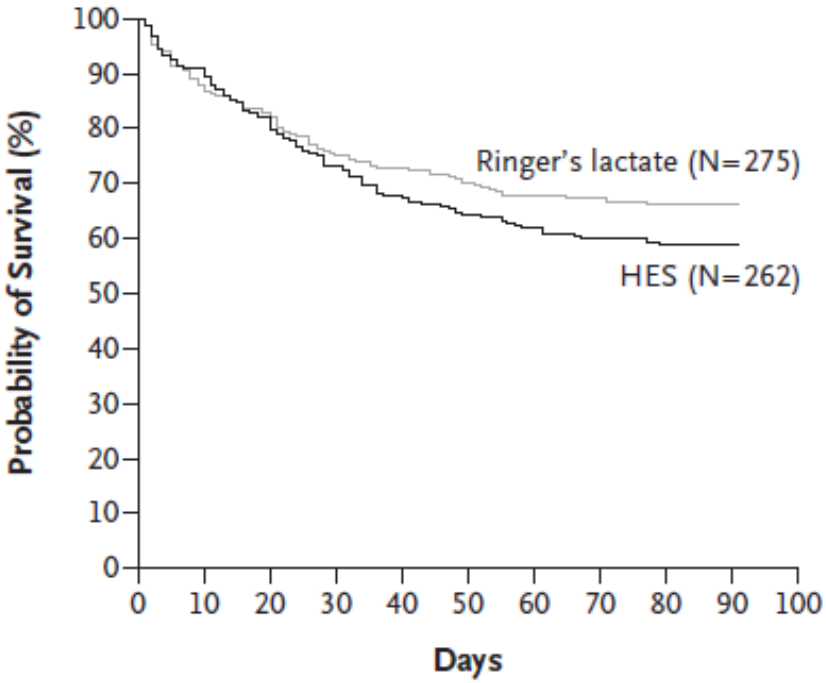


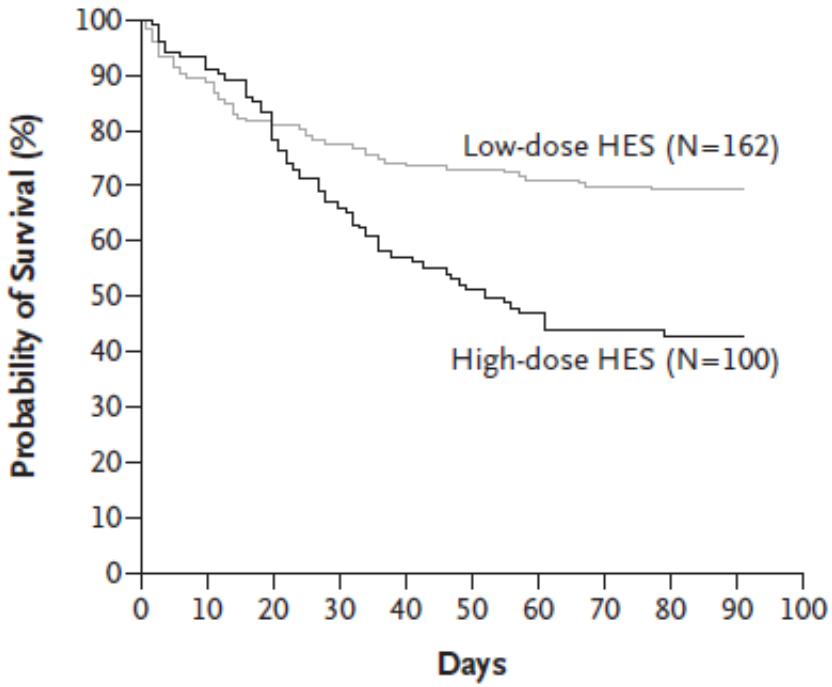


Non-responder to therapy a) non-adjusted b) adjusted to Leukocytes >12

Buxbaum JL, et al. Am J Gastroenterol 2017;112:797-803

Colloids or crystalloids? VISEP Study





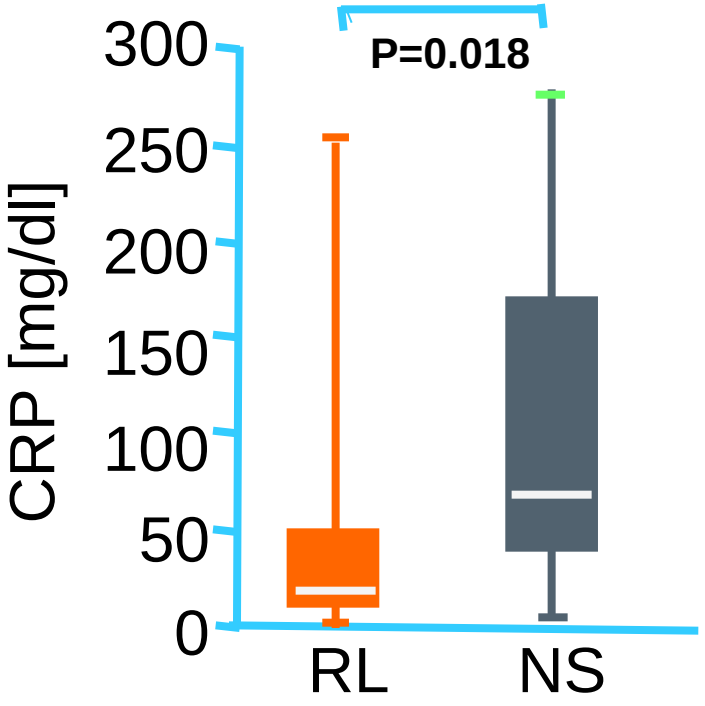
- The trial was stopped early by data safety monitoring committee.
- Patients who received HES were more likely to have renal failure (30.9% vs. 21.7%, p=0.04) and higher mortality
- The need for renal replacement therapy was significantly correlated with the cumulative dose of HES (p<0.001).

Brunkhorst FM New Engl J Med 2008; 358: 125-139
Perner A, New Engl J Med 2012; 367:124-134.

Ringer's Lactate or Saline

Randomized, multicenter trial with a two-by-two factorial design investigating the role of **Ringer's lactate** versus **saline** in resuscitation. n=40, median APACHE score: 3 (= mild pancreatitis). Primary endpoint CRP at 24hrs.

Significant reduction in SIRS after 24 hours among subjects resuscitated with **lactated Ringer's solution**, compared with **normal saline** (84% reduction vs. 0%, p=.035)



administration of **lactated Ringer's** solution reduced levels of CRP, compared with **normal saline** (51.5 vs 104 mg/dL, *P* .02).

Lactated Ringer's solution reduced systemic inflammation in comparison with saline.

Wu Clin Gastroenterol Hepatol 2011; 9: 710-717

Treatment with Antibiotics - Risks

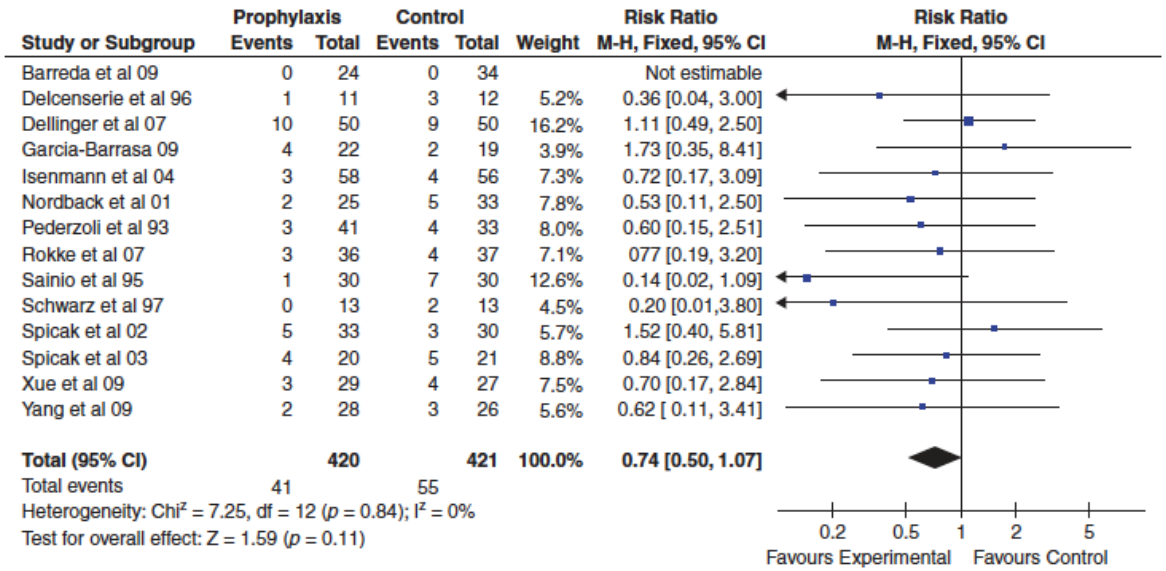
Inappropriate use of broad spectrum antibiotics

Prophylactic Antibiotics Metaanalysis – Mortality

No recommendation for an antibiotic prophylaxis in severe acute pancreatitis

Meta-analysis of 14 RCTs (841 pts.):
no statistically significant reduction in:

- mortality (RR 0.74, 95% CI 0.50-1.07)
- infected necrosis (RR 0.78, 95% CI 0.60-1.02)
- non-pancreatic infections (RR 0.70, 95% CI 0.46-1.06)
- surgical interventions (RR 0.93, 95% CI 0.72-1.20)



Study or Subgroup	Prophylaxis Events	Prophylaxis Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barreda et al 09	0	24	0	34		Not estimable
Delcenserie et al 96	1	11	3	12	5.2%	0.36 [0.04, 3.00]
Dellinger et al 07	10	50	9	50	16.2%	1.11 [0.49, 2.50]
Garcia-Barrasa 09	4	22	2	19	3.9%	1.73 [0.35, 8.41]
Isenmann et al 04	3	58	4	56	7.3%	0.72 [0.17, 3.09]
Nordback et al 01	2	25	5	33	7.8%	0.53 [0.11, 2.50]
Pederzoli et al 93	3	41	4	33	8.0%	0.60 [0.15, 2.51]
Rokke et al 07	3	36	4	37	7.1%	077 [0.19, 3.20]
Sainio et al 95	1	30	7	30	12.6%	0.14 [0.02, 1.09]
Schwarz et al 97	0	13	2	13	4.5%	0.20 [0.01,3.80]
Spicak et al 02	5	33	3	30	5.7%	1.52 [0.40, 5.81]
Spicak et al 03	4	20	5	21	8.8%	0.84 [0.26, 2.69]
Xue et al 09	3	29	4	27	7.5%	0.70 [0.17, 2.84]
Yang et al 09	2	28	3	26	5.6%	0.62 [0.11, 3.41]
Total (95% CI)		**420**		**421**	**100.0%**	**0.74 [0.50, 1.07]**
Total events	41		55			

Heterogeneity: Chi² = 7.25, df = 12 (p = 0.84); I² = 0%
Test for overall effect: Z = 1.59 (p = 0.11)

Wittau M. Scand J Gastroenterol. 2011; 46: 261-70

Antibiotics should be given for infected pancreatic necrosis or for concomitant extrapancreatic infection (i.e. cholangitis, pneumonia, urinary tract infection)

Working Group IAP/APA Acute Pancreatitis Guidelines, Pancreatology 2013; 13:e1-e15; American College of Gastroenterology Guideline, Am J Gastroenterol 2013; 1-16)

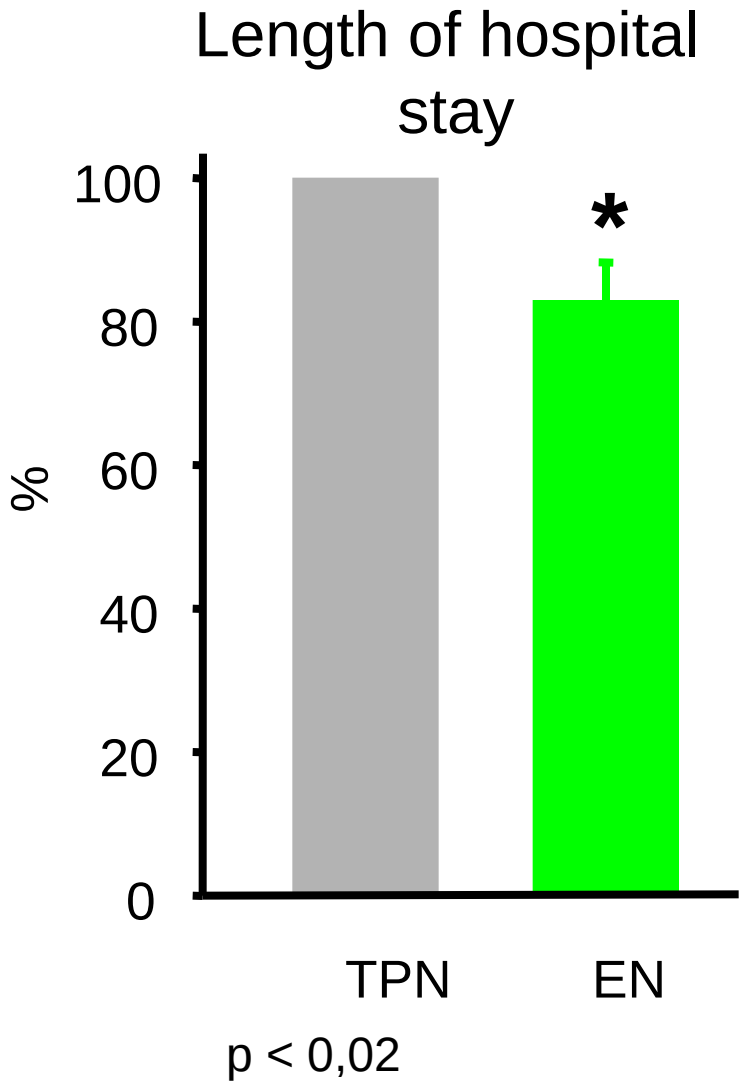
Indication for antibiotics

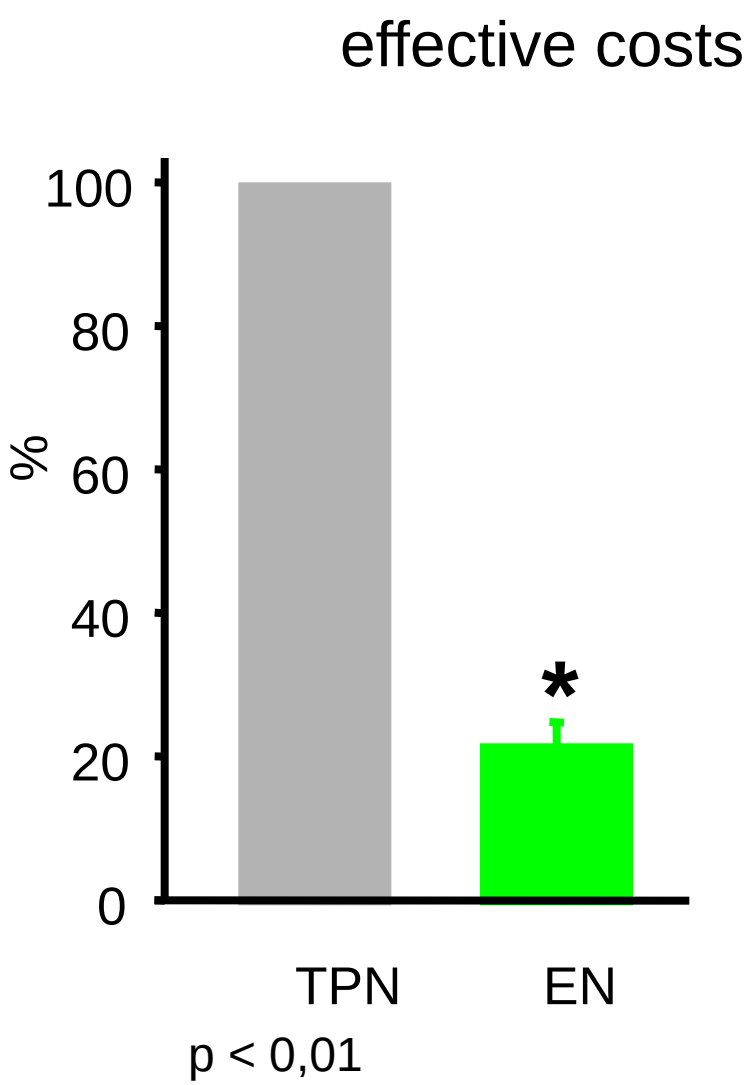
Infected pancreatic necrosis usually develops late in the disease course and is signalled by clinical deterioration (SIRS, SEPSIS) and on CT imaging (air). Broad spectrum antibiotics should not be given prophylactically, nor when SIRS is the consequence of pancreatitis (rather than of infection), but immediately when sings of infected pancreatic necrosis arise. Discussion to be continued.

Nutrition in Pancreatitis - Risks

Untimely and unsuitable nutrition

Enteral versus parenteral nutrition in acute pancreatitis – metaanalysis





Mayerle Nat Clin Pract Gastroenterol Hepatol 2005;2:473-83

Enteral nutrition is superior to total parenteral nutrition

Meta-Analyse from 8 randomized studies, 348 patients:

TEN vs. TPN	Odds Ratio	95% CI
All patients with acute pancreatitis	0.50	0.28-0.91
Severe acute pancreatitis	0.18	0.006-0.58

Al-Omran M. Cochrane Database Syst Rev 2010

Meta-analysis from 8 studies with severe acute pancreatitis, 184 patients:

TEN vs. TPN	P value	RR (95% CI)
Mortality	0.001	0.37 (0.21-0.68)
Infectious complications	0.004	0.46 (0.27-0.48)
Organ failure	0.02	0.44 (0.22-0.88)
Surgical intervention	0.003	0.41 (0.23-0.74)
Length of hospital stay	0.22	14.10 (-36.48-8.26)
Duration of nutrition	0.72	-1.50 (-9.56-6.56)

Yi F. Intern Med 2012; 51:523-530

Early (<48h) or 'On-Demand' (>48h-72h) Enteral Nutrition in Acute Pancreatitis ?

Primary Endpoint

867 patient s assessed for eligibilty

Outcome	Early Enteral Nutrition (N = 101)	Nutrition On Demand (N = 104)	Risk Ratio (95% CI)	P value
Primary composite end point: Infection or death – no. (%)	30 (30)	28 (27)	1.07 (0.79 – 1.45)	0.76
Individual components				
Infections – no. (%)	25 (25)	27 (26)	0.97 (0.70 – 1.34)	0.87
Infected pancreatic necrosis	9 (9)	15 (14)	0.74 (0.43 – 1.26)	0.28
Bacteraemia	17 (17)	18 (17)	0.98 (0.68 – 1.43)	1.00
Pneumonia	12 (12)	13 (13)	0.97 (0.63 – 1.50)	0.84
Death – no. (%)	11 (11)	7 (7)	1.27 (0.85 – 1.89)	0.33

In patients with (predicted) severe acute pancreatitis a very early start of enteral tube feeding did NOT improve outcome (composite endpoint of infection and mortality)

Bakker OJ et al. N Engl J Med. 2014 Nov 20;371(21):1983-93.

Current Treatment Principles

- Stabilization of vital signs:
  - Pain treatment
  - Oxygen via mask or nasal tube
  - Volume replacement: Ringer‘s Lactate) 2,5 to 4(5) ltr/24h, 5-10 ml/kg/h.

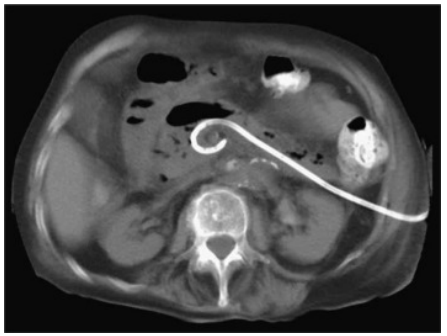
- Antibiotics: only for suspected or proven infection (to be continued).
- Nutrition: oral before enteral before parenteral. Enough time to contemplate options.
- Interventions for infected necrosis: as late and minimally invasive as possible

Aghdassi A. et al. Expert Rev Gastroenterol Hepatol. 2018;12:1207-1218

A Step-Up Approach or Open Necrosectomy for Necrotizing Pancreatitis

Pancreatitis Werkgroep Nederland

van Santvoort HC, et al N Engl J Med. 2010; 362: 1491-502.



Multicenter study including 88 patients with severe necrotizing pancreatitis, randomized to open necrosectomy versus „step-up-approach“ (first, percutaneous intervention, followed, if needed, by VARD).

Primary Endpoint: Severe complications (MOF, Perforation Bleeding) and/or death.

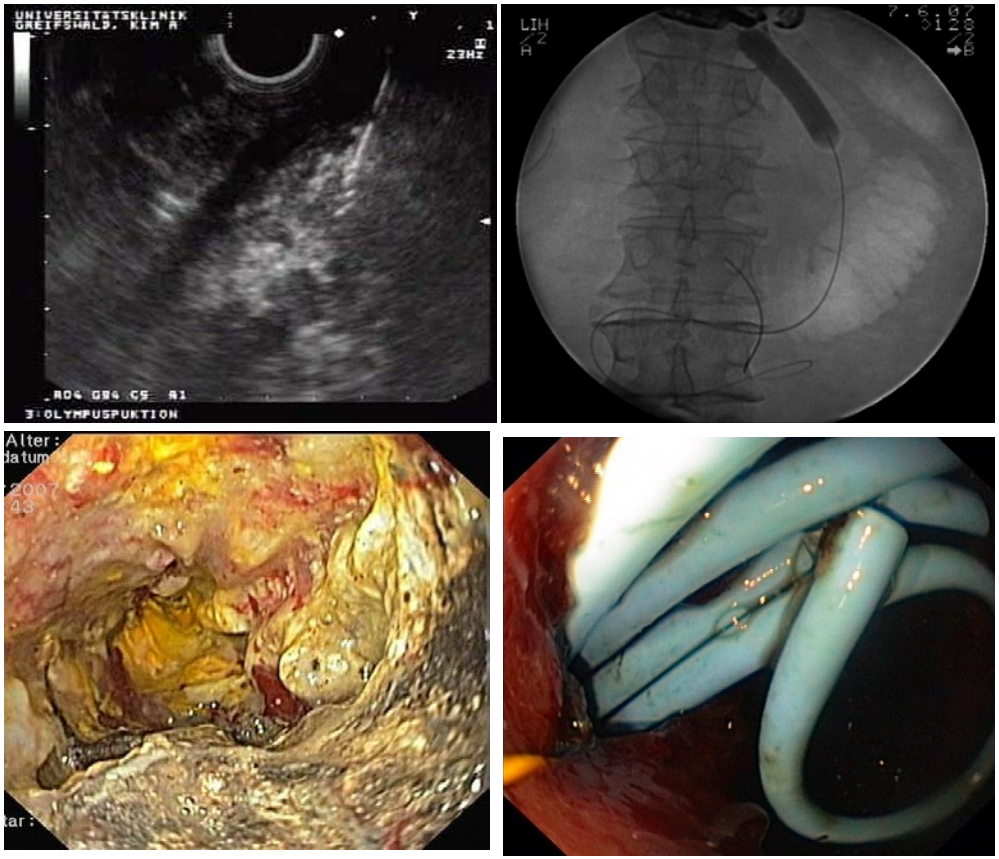
Result: Primary endpoint in 69% for open surgery group versus 40% for step-up-approach (p=0.006)

35% needed only percutaneous drainage and did not require VARD

Conclusion: minimal invasive necrosectomy is superior to open necrosectomy (and often not even needed)

Question: is it better than endoscopic necrosectomy?

Endoscopic versus minimally invasive necrosectomy



Bakker OJ et al. JAMA 2012;307:1053-61.

randomized trial including 22 patients: endoscopic versus minimally invasive necrosectomy (VARD): primary endpoint: IL-6, secondary endpoint severe complications or death

Summary: Endoscopic transgastric drainage caused less postoperative SIRS. Secondary endpoint in endoscopy group 20% vs. 80% VARD group (p=0.03).

Endoscopic versus minimally invasive necrosectomy

TENSION trial: 98 patient, 19 Dutch centers, randomized towards surgical step up approach versus endoscopic necrosectomy.

NO difference in primary endpoint (severe complications or death)

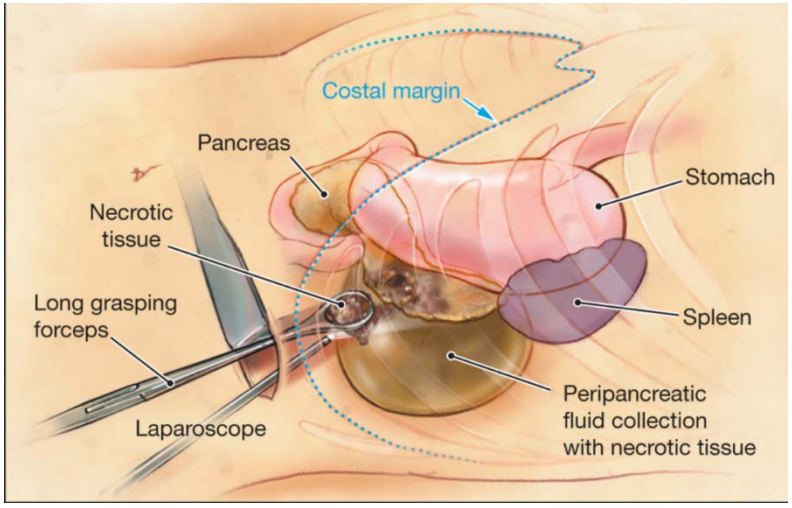
20% vs. 28%; p=.35; 41% vs 49% required no debridement after drainage

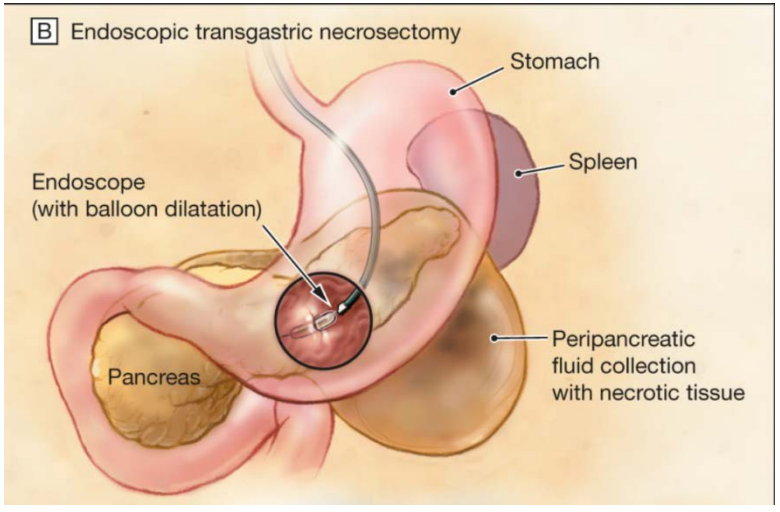
Endoscopy burdened with less fistulas (p=.001)

and less hospital days (36 vs. 69d); Endoscopy lower cost of treatment p=.03

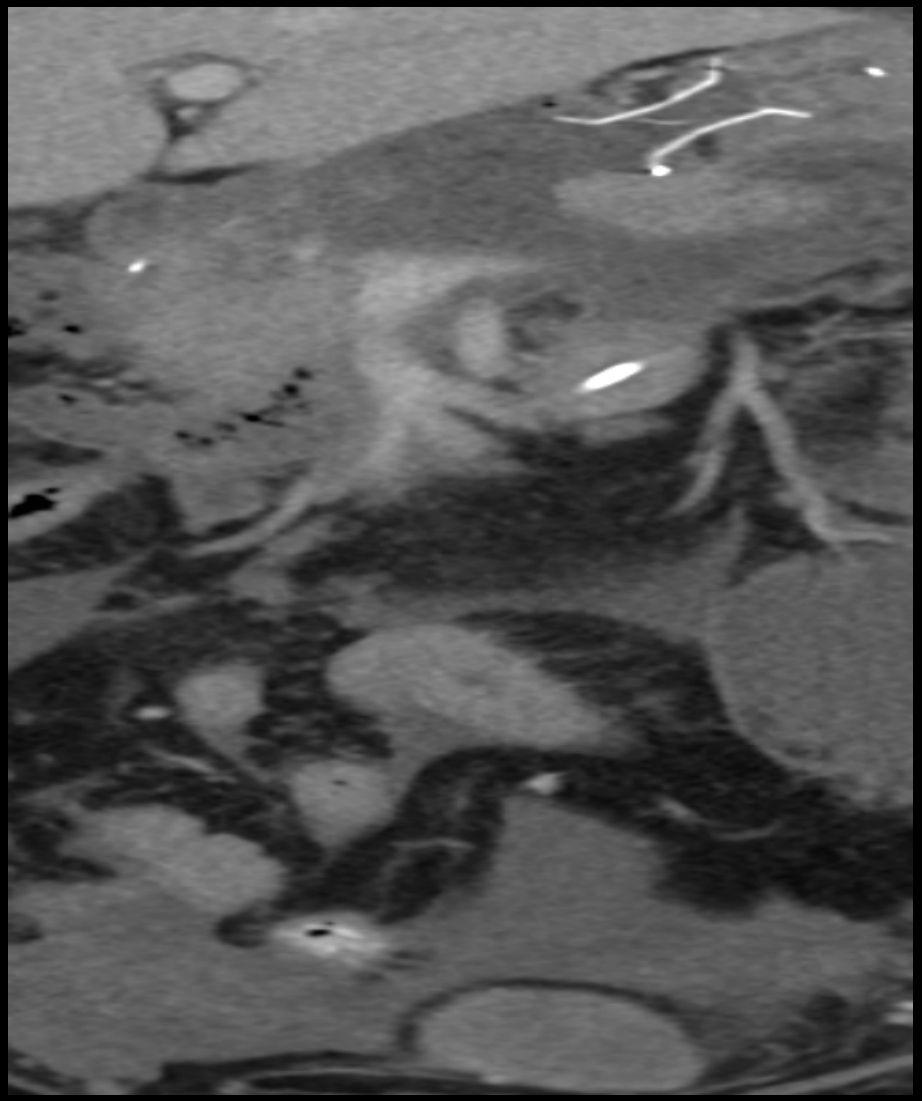
Van Brunschot et al. Lancet. 2017 Nov 3. pii: S0140-6736(17)32404-2

Conclusion: you need both options available for adequate patient management; ~ half the patients don't need aggressive necrosectomy

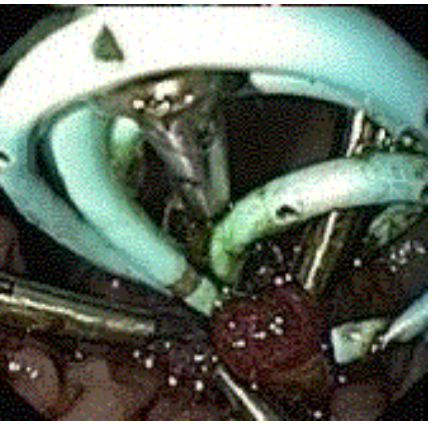


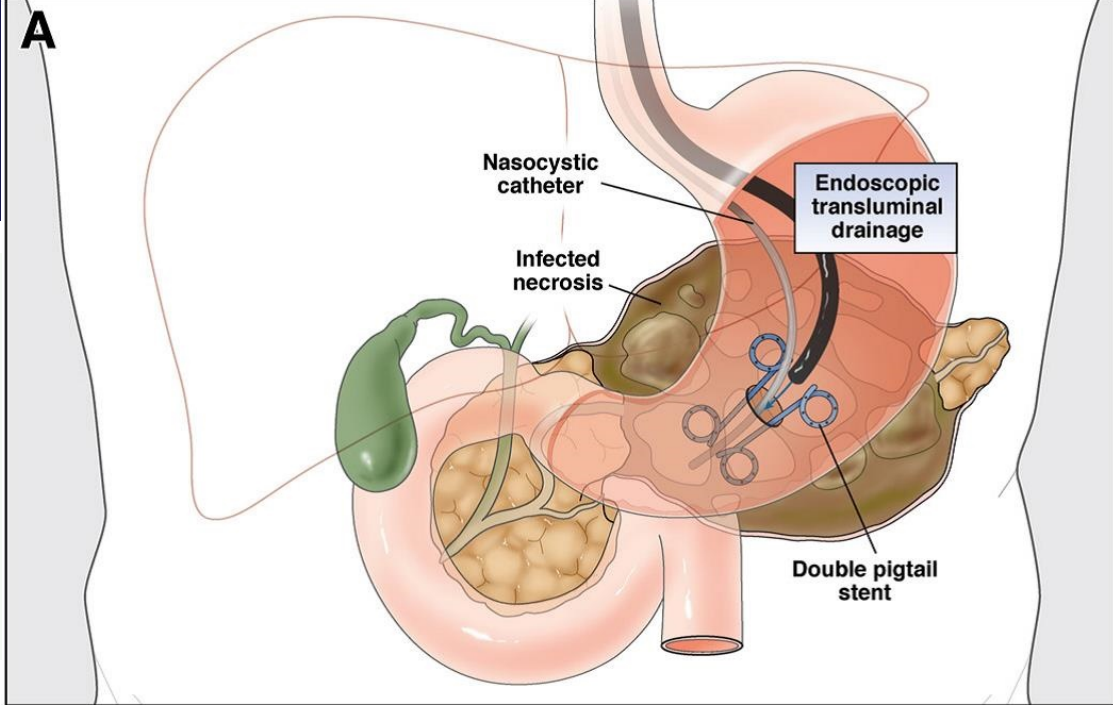


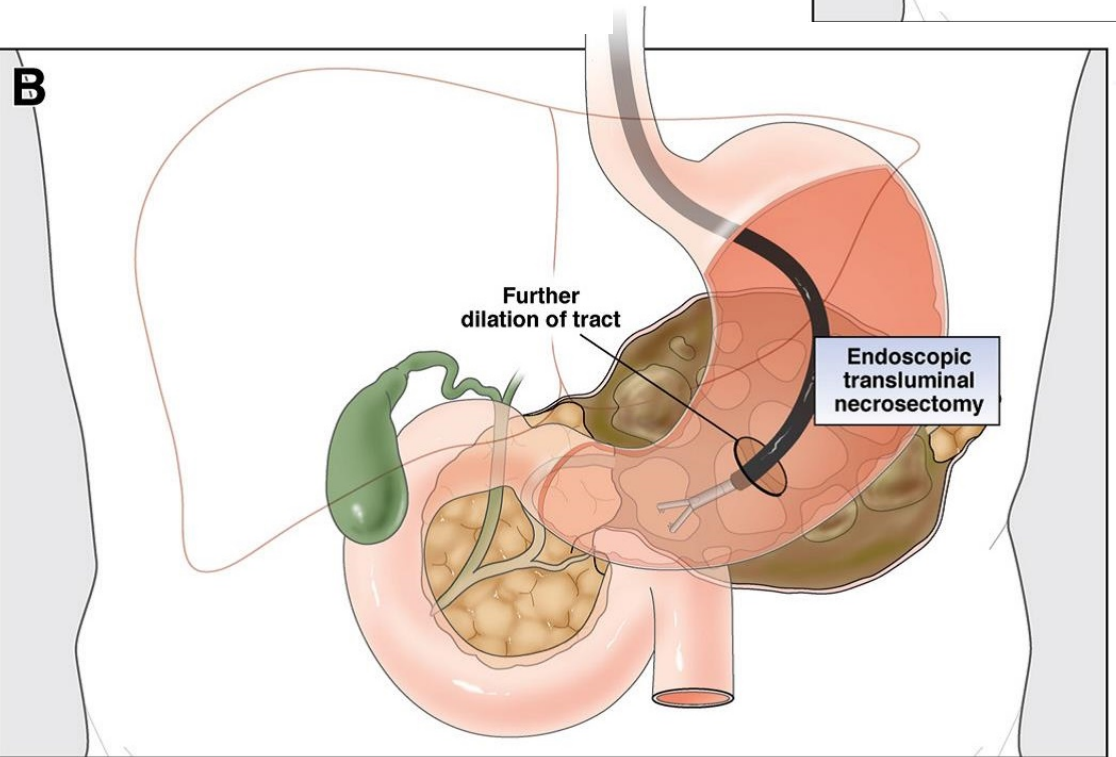
Transgastric endoscopic necrosectomy - limits

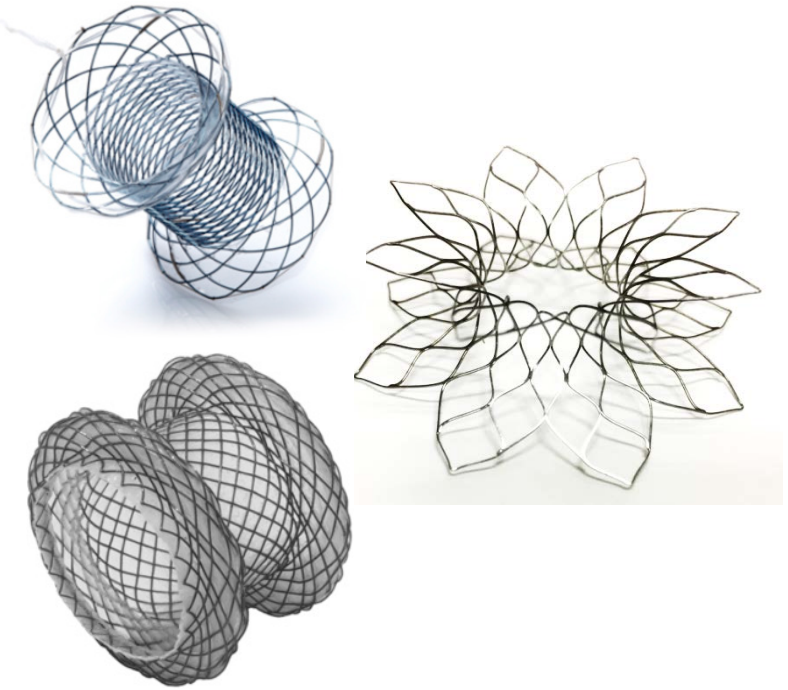


LAMS versus Pig Tail Stents



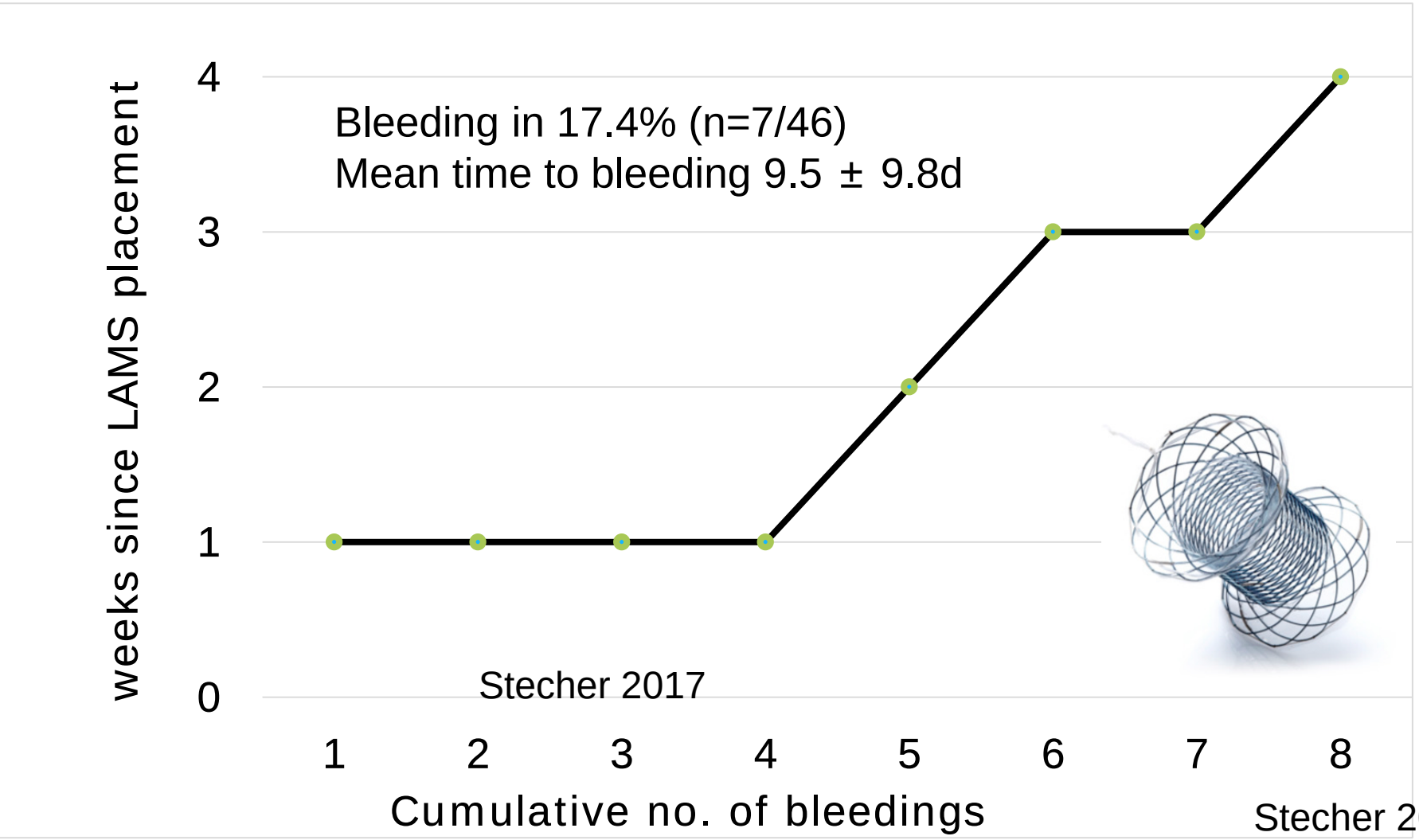






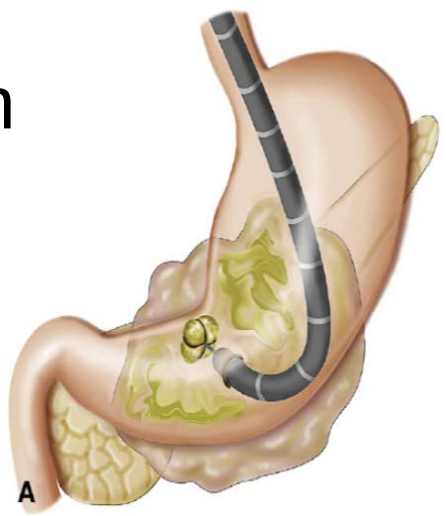
Bleeding complications of LAMS

Delayed severe bleeding complications after treatment of pancreatic fluid collections with lumen-apposing metal stents.
Stecher S, et al Gut 2017; Jan 12. pii: gutjnl-2016-313562



Interventional Treatment

- Drain pancreatic fluid collections and walled-off pancreatic necrosis only when infected and a wall is established (trials Under way for earlier time points and percutaneous drainage.



- Avoid open surgery
- Transgastric endoscopic drainage has advantages over minimally invasive surgery but both have the same mortality.
- At a pancreas center you need all three options, radiology, surgery and endoscopy.
- Endoscopists love LAMS but they cause problem after a time and need to be replaced by pigtails.

Aghdassi A. et al. Expert Rev Gastroenterol Hepatol. 2018;12:1207-1218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