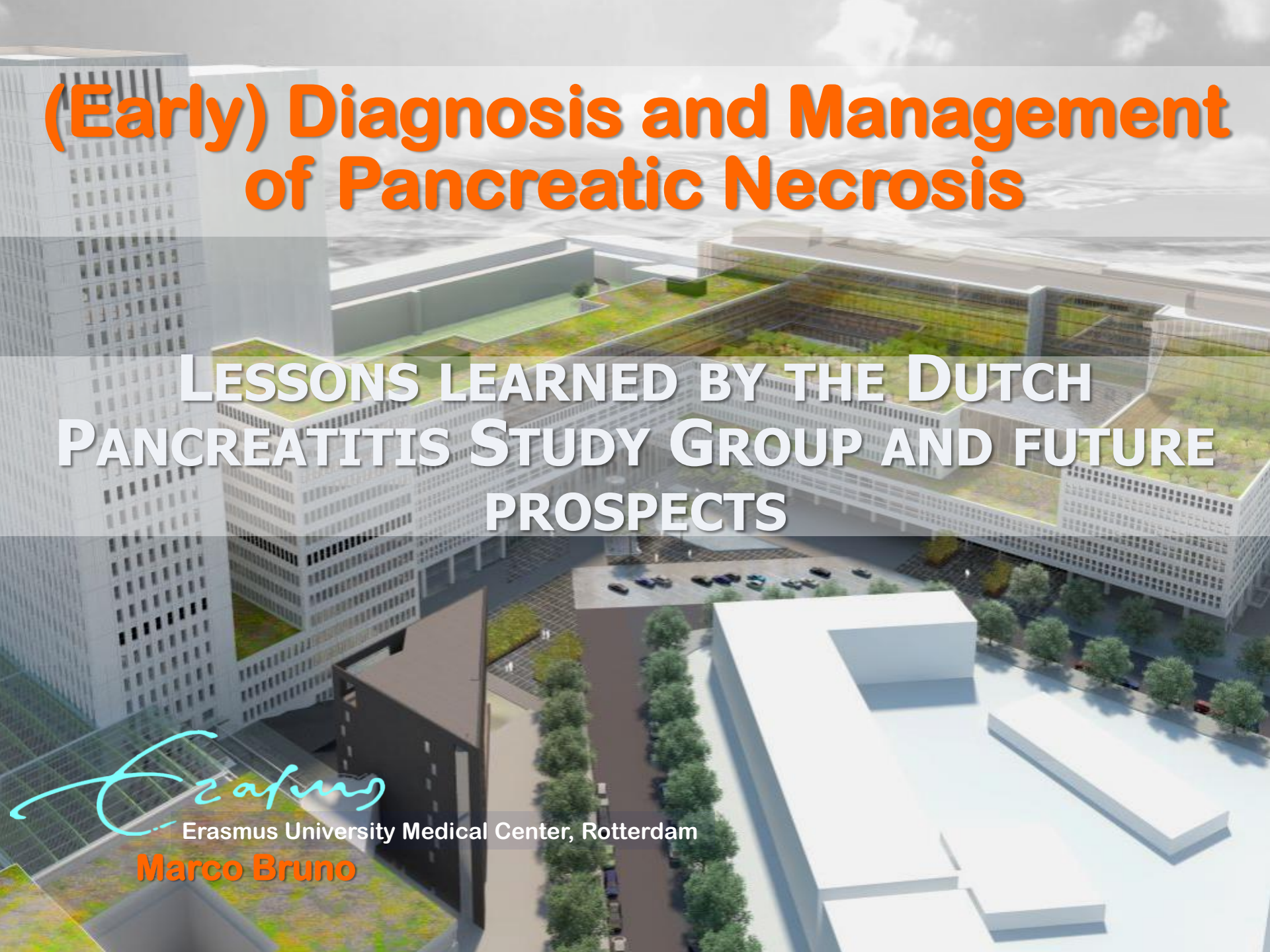
(Early) Diagnosis and Management of Pancreatic Necrosis

Lessons learned by the Dutch Pancreatitis Study Group and future prospects



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Disclosures

Compagnies:

- Boston Scientific: Consultant, lecturer & study support
- Cook Medical: Consultant, lecturer & study support
- Pentax Medical: Consultant, lecturer & study support
- InterScope: study support
- Mylan**:** study support

Societies & (governmental) institutions:

- Dutch National Health Care Institute: Advisor & Care & Cure committee member
- Dutch Digestive Disease Foundation: Advisor & Member scientific board
- Dutch Pancreatitis Study Group: Member & former chair
- Dutch Association for Pancreas Research: Board member & treasurer
- Dutch Pancreatic Cancer Research Group: Board member
- European Association of Gastroenterology, Endoscopy & Nutrition (EAGEN): Board member and treasurer
- United European Gastroenterology (UEG): former chair Education committee and former Scientific committee member

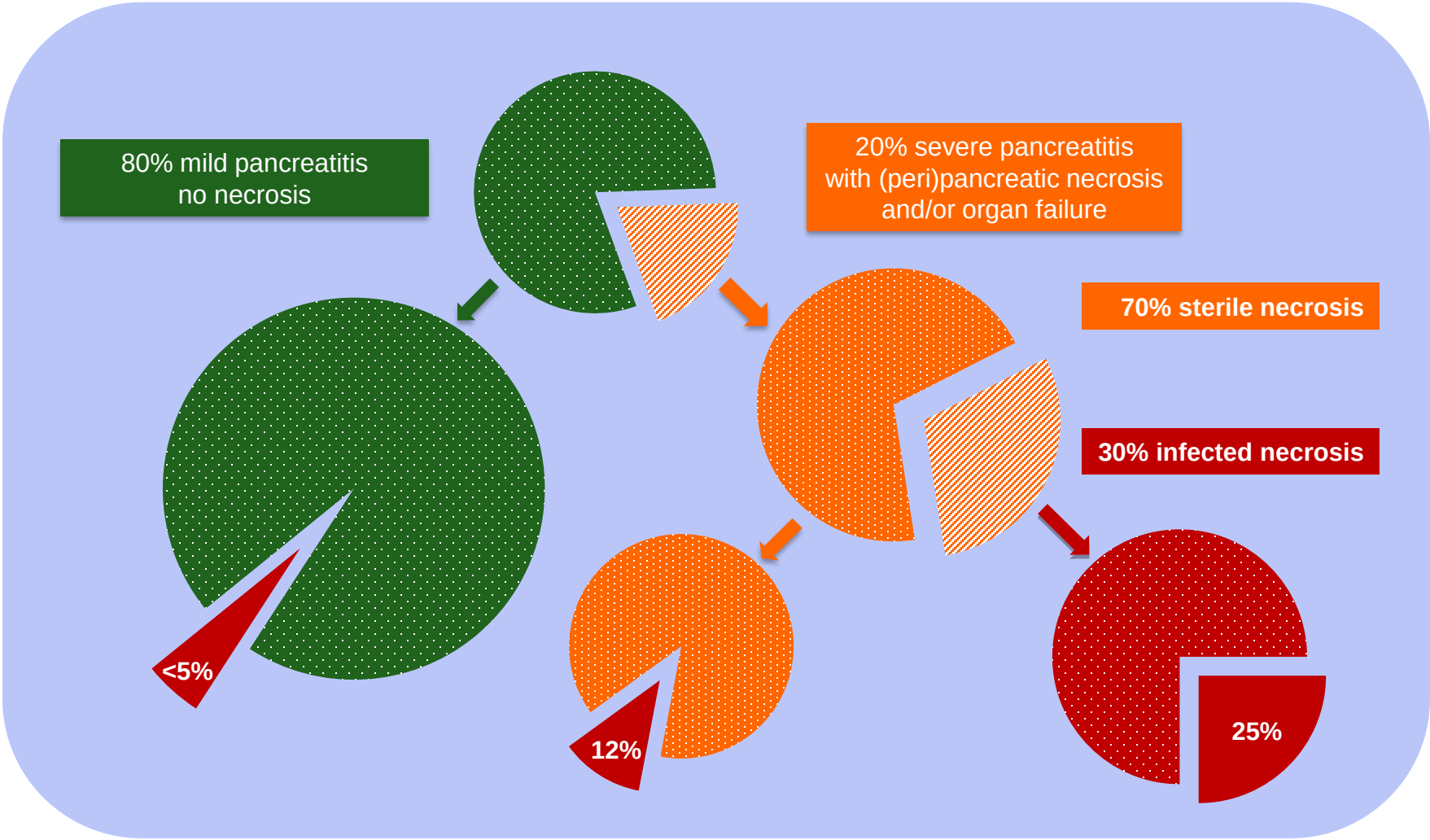
Acute Pancreatitis
Background

- In USA the most common GI reason for hospitalization [1]
  - ✓$ 2.6 billion per year

- In the Netherlands, AP incidence has been reported to rise steadily since the 90-ties by 5% annually [2]

[1] Peery et al. Gastroenterology 2012
[2] KiwaPrismant NL 2020

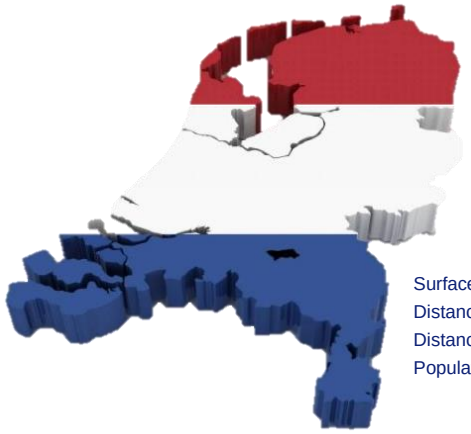
Acute Pancreatitis
Severity & mortality



Dutch Pancreatitis Study Group

History & goal

- Founded in 2002
- The goal is to improve prognosis of patients with acute and/or chronic pancreatitis through a combination of:
    1. consultation
    2. centralization
    3. multicenter research



Surface area: 41,526 km2
Distance north – south : 300 km
Distance east – west: 200 km
Population: 16,800,000

Dutch Pancreatitis Study Group

Multicenter collaboration

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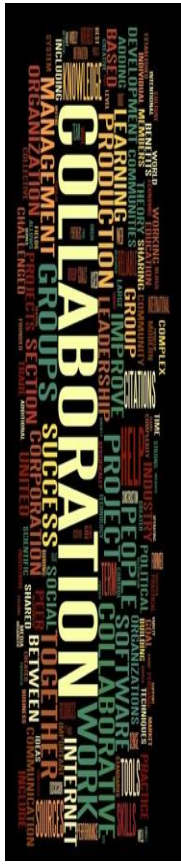
- Low incidence of complex disease manifestations
- Improve patient accrual for studies
- Higher likelihood for funding
- Alternating principal investigators
- Data center and pool of PhD fellows + research nurses who run the studies on a day-to-day basis



Pancreatitis Werkgroep Nederland

Dutch Pancreatitis Study Group

Published & ongoing studies

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Improve outcome in the early phase of pancreatitis

PROPATRIA, PYTHON, APEC 1 & 2, FLUYT

Improve interventions in (severe) infected necrotizing pancreatitis

PANTER, PENGUIN, TENSION, POINTER, EXTENSION, RESOLVE

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Acute Necrotising Pancreatitis
IAP/APA guidelines for intervention

Q28. What are the indications for intervention in necrotizing pancreatitis?

Common indications for intervention (either radiological, endoscopical or surgical) in necrotizing pancreatitis are:

- Clinical suspicion of, or documented, infected necrotizing pancreatitis with clinical deterioration, preferably when the necrosis has become walled-off.
- In the absence of documented infected necrotizing pancreatitis, ongoing organ failure for several weeks after the onset of acute pancreatitis, preferably when the necrosis has become walled-off.

Less common indications for intervention are:

- Abdominal compartment syndrome
- Ongoing acute bleeding
- Bowel ischemia
- Ongoing gastric outlet, intestinal, or biliary obstruction due to mass effect from large walled-off necrosis (arbitrarily >4–8 weeks after onset of pancreatitis)

(GRADE 1C, strong agreement).

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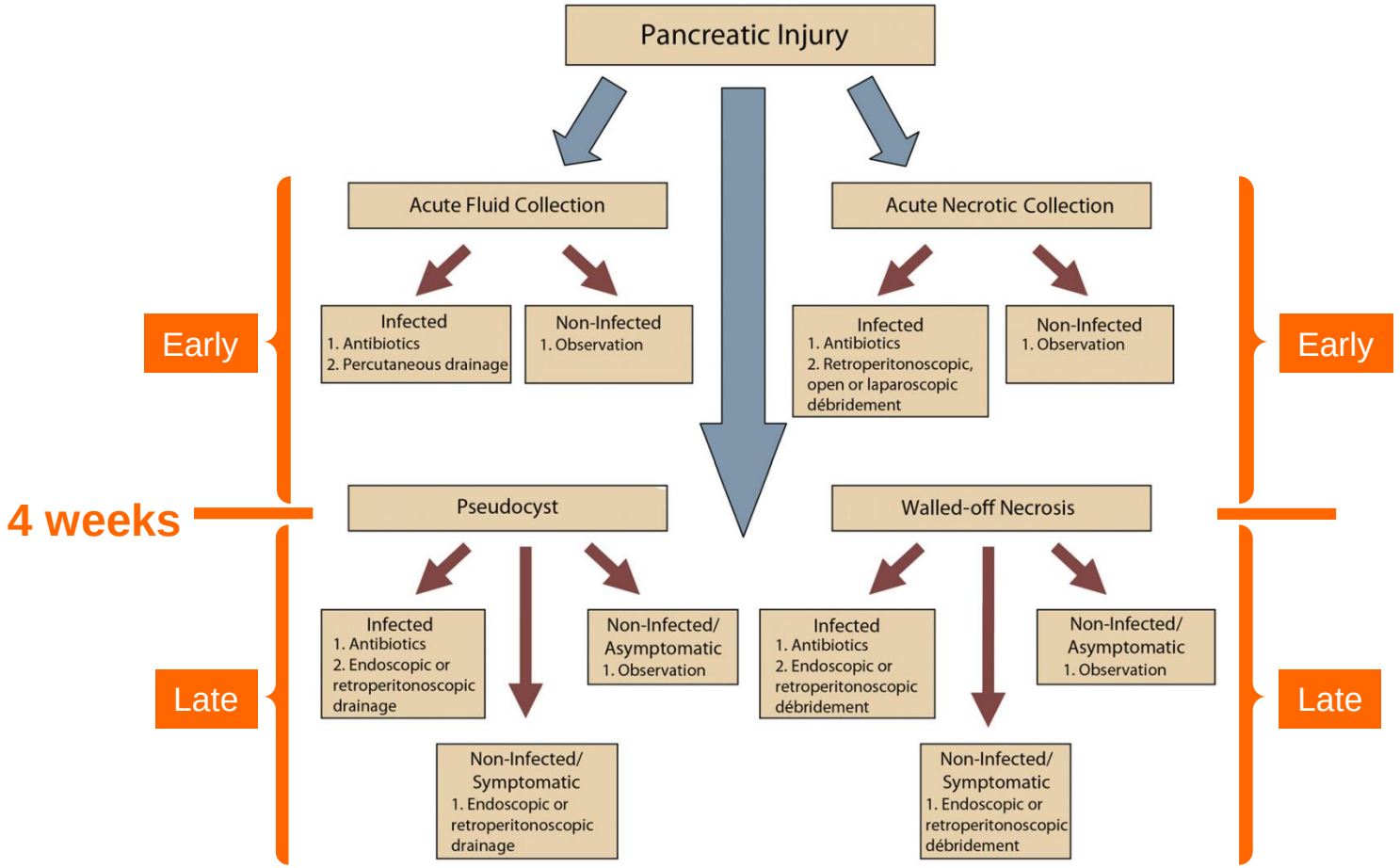
Working Group IAP/APA Acute Pancreatitis Guidelines Pancreatology 2013: e1-e15

Acute Necrotising Pancreatitis
Revised Atlanta criteria



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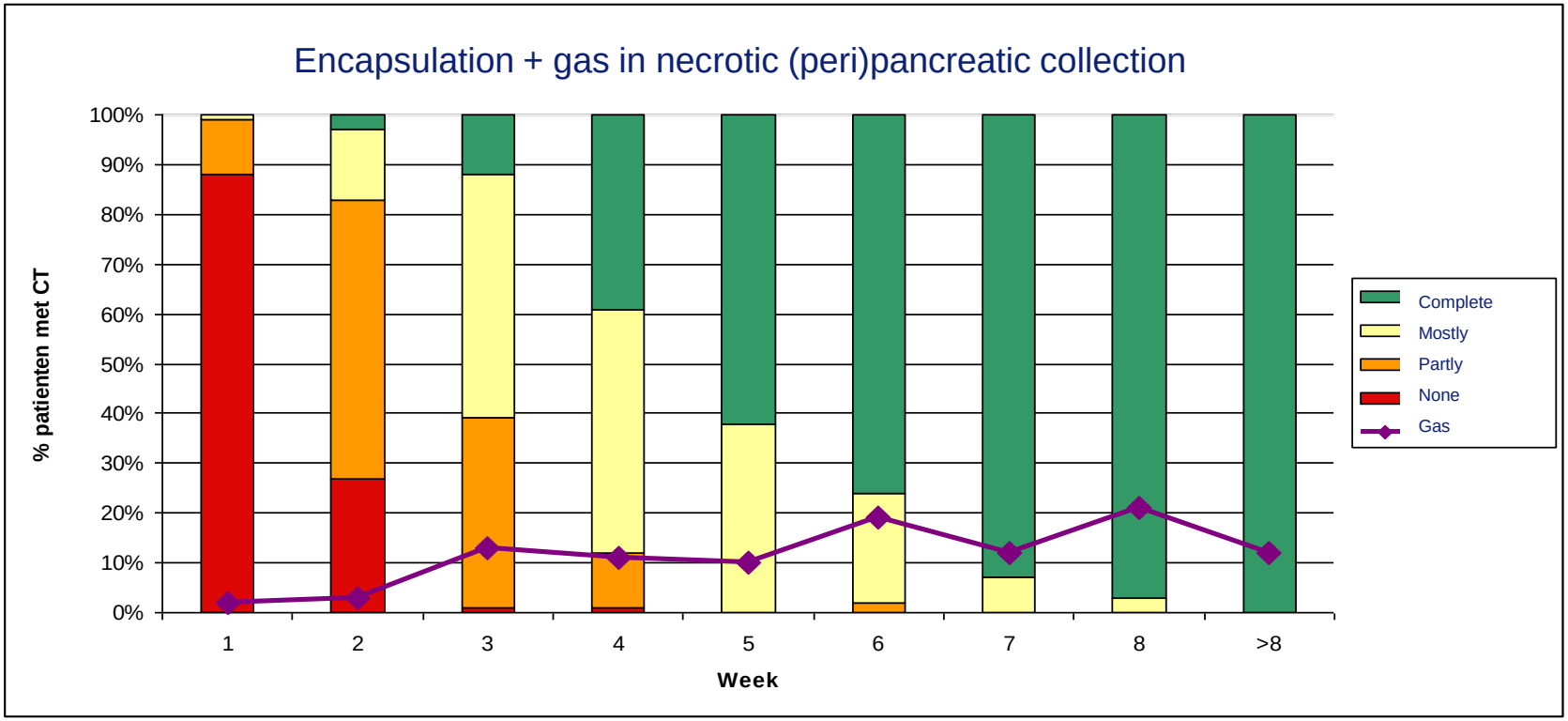
Necrotic Pancreatic Fluid Collections

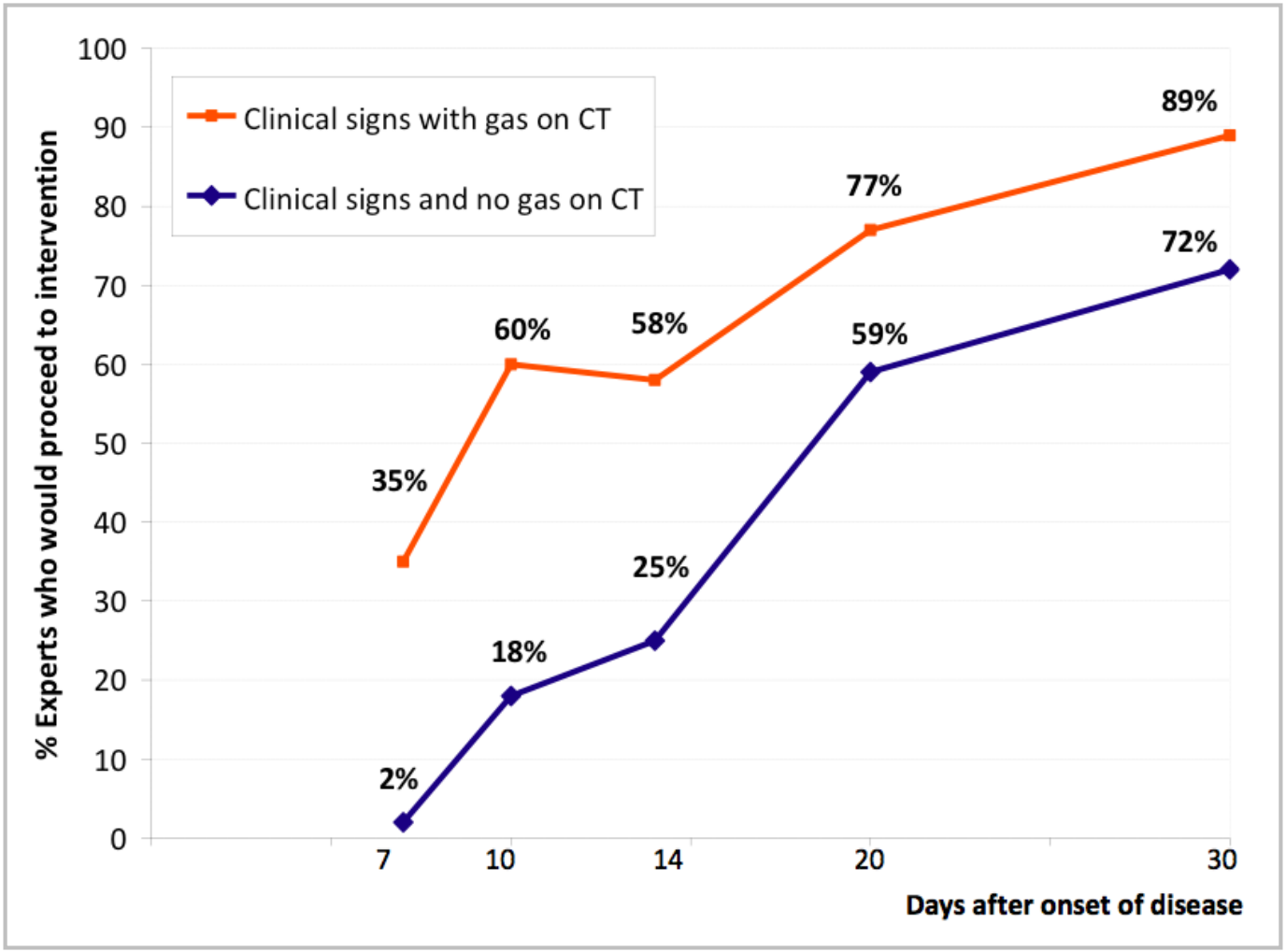
When does encapsulation occur?



van Grinsven et al,. for the DPSG, unpublished data

Infected Pancreatic Necrosis

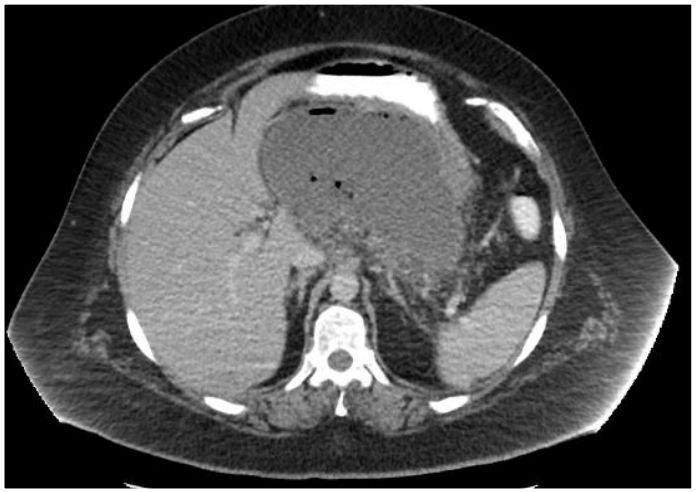
International survey; signs of infection & when to intervene



van Grinsven et al. for the DPSG, HPB 2016

Acute Necrotising Pancreatitis
Diagnosing infected necrosis

- Imaging ‘gas on CT’
  - ✓ in 24-42% [1,2]
- Fine needle aspiration (FNA)
  - ✓ false negative (10-29%) [2,3]
  - ✓ false positive (4%) [2]
- Clinical symptoms
  - ✓ 90% accuracy ‘in a postponed strategy’



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[1] Baril .Ann Surg 2000
[2] Baal et al. for the DPSG. Surgery 2014

Acute Infected Necrotising Pancreatitis

Questions related to improving clinical outcome

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1. Is a step-up approach superior to open necrosectomy
2. Is endoscopic treatment superior to open necrosectomy (step-up approach?
3. What is the ideal timing for intervention?
4. What is the long-term clinical outcome
5. What is are optimal tools to facilitate endoscopic debridement

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Infected Pancreatic Necrosis
Open necrosectomy

Traditionally an open necrosectomy was performed [1-5]

- ✓ complete removal of infected necrosis
- ✓ high morbidity (34-95%)
- ✓ high mortality (11-39%)
- ✓ pancreatic fistula
- ✓ pancreatic insufficiency

[1] Buchler et al. Ann Surg 2000
[2] Ashleyet al. Ann Surg 2001
[3] Rau et al. Surgery 2005
[4] Rodriguez et al. Ann Surg 2008
[5] Tsiotos et al. Br J Surg 1998

Infected Pancreatic Necrosis
Surgical "step-up" approach

Less surgical stress in already critically ill patients?

1. percutaneous (retroperitoneal) catheter drainage
2. videoscopic assisted retroperitoneal debridement (VARD)

Infected Pancreatic Necrosis

PANTER study: "Step-up" approach or open necrosectomy

N ENGL J MED 362;16 The NEW ENGLAND JOURNAL of MEDICINE APRIL 22, 2010

A Step-up Approach or Open Necrosectomy for Necrotizing Pancreatitis

Hjalmar C. van Santvoort, M.D., Marc G. Besselink, M.D., Ph.D., Olaf J. Bakker, M.D., H. Sijbrand Hofker, M.D., Marja A. Boermeester, M.D., Ph.D., Cornelis H. Dejong, M.D., Ph.D., Harry van Goor, M.D., Ph.D., Alexander F. Schaapherder, M.D., Ph.D., Casper H. van Eijck, M.D., Ph.D., Thomas L. Bollen, M.D., Bert van Ramshorst, M.D., Ph.D., Vincent B. Nieuwenhuijs, M.D., Ph.D., Robin Timmer, M.D., Ph.D., Johan S. Laméris, M.D., Ph.D., Philip M. Kruyt, M.D., Eric R. Manusama, M.D., Ph.D., Erwin van der Harst, M.D., Ph.D., George P. van der Schelling, M.D., Ph.D., Tom Karsten, M.D., Ph.D., Eric J. Hesselink, M.D., Ph.D., Cornelis J. van Laarhoven, M.D., Ph.D., Camiel Rosman, M.D., Ph.D., Koop Bosscha, M.D., Ph.D., Ralph J. de Wit, M.D., Ph.D., Alexander P. Houdijk, M.D., Ph.D., Maarten S. van Leeuwen, M.D., Ph.D., Erik Buskens, M.D., Ph.D., and Hein G. Gooszen, M.D., Ph.D., for the Dutch Pancreatitis Study Group*

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Van Santvoort et al., for the DPSG. New Engl J Med 2010; 16: 1491-502

Infected Pancreatic Necrosis

PANTER study: "Step-up" approach or open necrosectomy

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Endpoint	Open necrosectomy (N= 45)	Minimally invasive step-up approach (N= 43)	Risk Ratio (95%-CI)	P
Death or major morbidity	31 (69%)	17 (40%)	0.57 (0.38-0.87)	0.006
New onset multiple organ failure	19 (42%)	5 (12%)	0.28 (0.11-0.67)	0.001
Intra-abdominal bleeding	10 (22%)	7 (16%)	0.73 (0.31-1.75)	0.48
Enterocutaneous fistula/ Perforation of a visceral organ	10 (22%)	6 (14%)	0.63 (0.25-1.58)	0.32
Death	7 (16%)	8 (19%)	1.20 (0.48-3.01)	0.70

!!! In 35% of cases no additional necrosectomy was needed !!!

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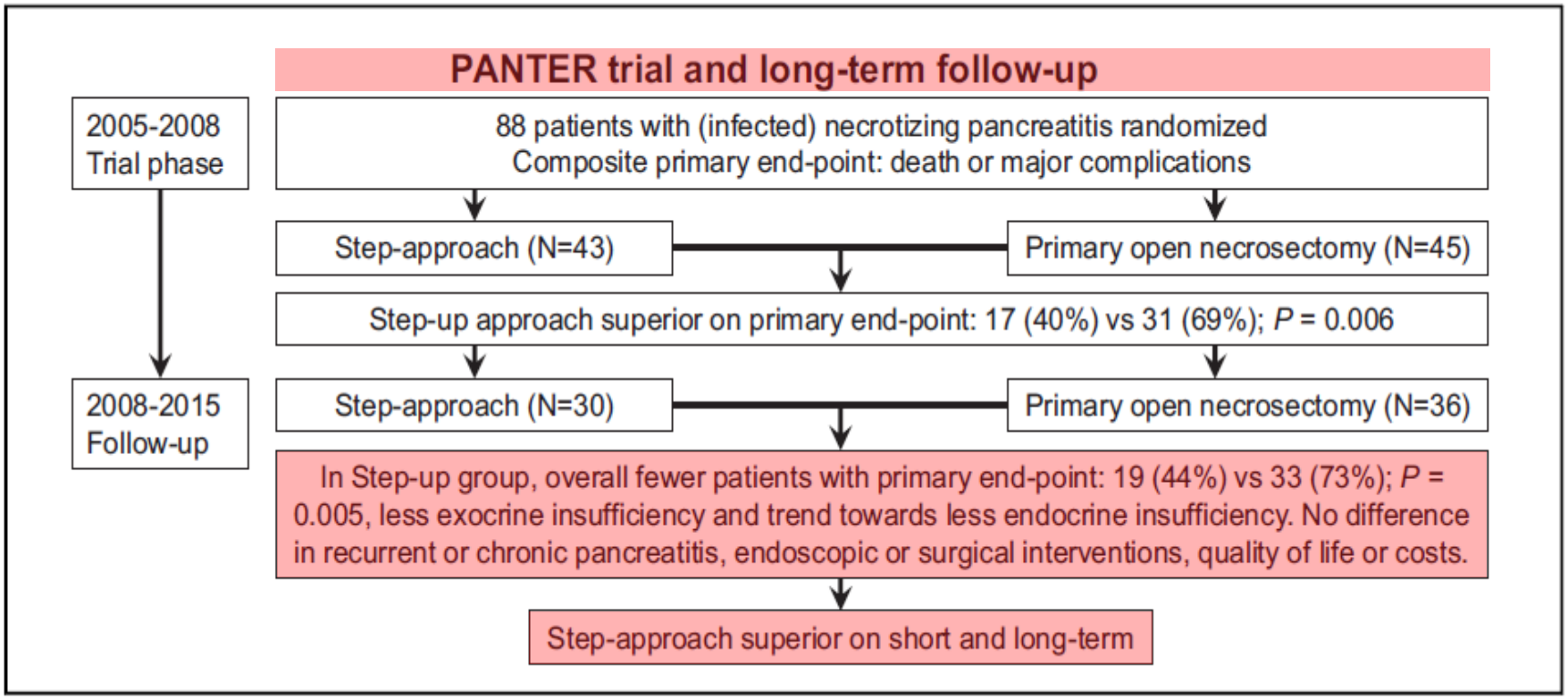
Van Santvoort et al., for the DPSG. New Engl J Med 2010; 16

Infected Pancreatic Necrosis

PANTER study: "Step-up" approach or open necrosectomy

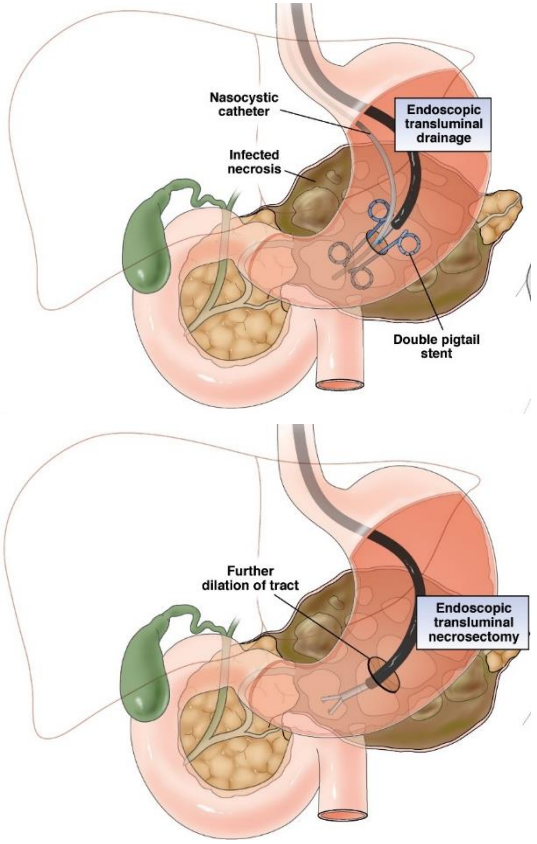


Hollemans et al., for the DPSG. Gastroenterology 2019; 158: 1016-1026

Infected Pancreatic Necrosis

Step-up approach; delay, drain, debride

- Percutaneous drainage followed by surgical debridement
  - ✓ treatment of choice in patients with infected necrotizing pancreatitis [1,2]
  - ✓ mortality and major morbidity 40% [1]
- Alternative: endoscopic treatment
  - ✓ transluminal drainage
  - ✓ followed by endoscopic necrosectomy
  - ✓ increasing experience



Pancreatitis Werkgroep Nederland

[1] Van Santvoort & DPSG. NEJM 2010
[2] IAP/APA guidelines
Van Brunschot & DPSG Clin Gastroenterol Hepatol 2012

Infected Pancreatic Necrosis

PENGUIN trail; endoscopic transgastric necrosectomy

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Endoscopic Transgastric vs Surgical Necrosectomy for Infected Necrotizing Pancreatitis

A Randomized Trial

Trial Registration isrctn.org Identifier: ISRCTN07091918

JAMA. 2012;307(10):1053-1061

Context Most patients with infected necrotizing pancreatitis require necrosectomy. Surgical necrosectomy induces a proinflammatory response and is associated with a high complication rate. Endoscopic transgastric necrosectomy, a form of natural orifice transluminal endoscopic surgery, may reduce the proinflammatory response and reduce complications.

Objective To compare the proinflammatory response and clinical outcome of endoscopic transgastric and surgical necrosectomy.

Design, Setting, and Patients Randomized controlled assessor-blinded clinical trial in 3 academic hospitals and 1 regional teaching hospital in the Netherlands between August 20, 2008, and March 3, 2010. Patients had signs of infected necrotizing pancreatitis and an indication for intervention.

Interventions Random allocation to endoscopic transgastric or surgical necrosectomy. Endoscopic necrosectomy consisted of transgastric puncture, balloon dilatation, retroperitoneal drainage, and necrosectomy. Surgical necrosectomy consisted of video-assisted retroperitoneal debridement or, if not feasible, laparotomy

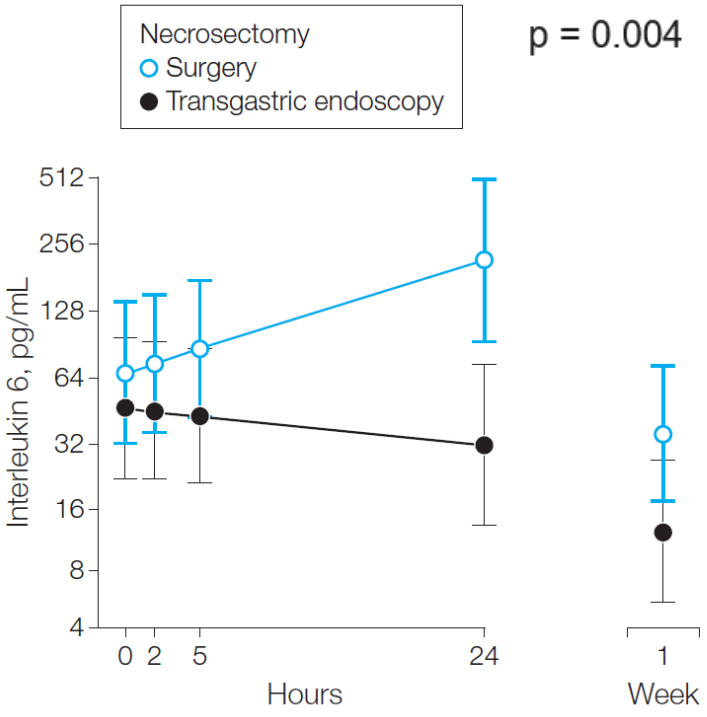
Pancreatitis Werkgroep Nederland

Bakker et al., for the DPSG. JAMA 2012; 307; 1053-61

Infected Pancreatic Necrosis

PENGUIN trail; endoscopic transgastric necrosectomy

- 22 patients with infected necrotizing pancreatitis
- 4 hospitals (2008-2010)
- Intervention: endoscopic transgastric necrosectomy
- Control: surgical necrosectomy
- Outcome: pro-inflammatory response



Bakker et al., for the DPSG. JAMA 2012; 307; 1053-61

Infected Pancreatic Necrosis

PENGUIN trail; endoscopic transgastric necrosectomy

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Endpoint	Endoscopic Transgastric Necrosectomy (N= 10)	Surgical necrosectomy (N= 10)	Risk Difference (95%-CI)	P
Major complications or death	2 (20%)	8 (80%)	0.60 (0.16-0.80)	0.03
New-onset multiple-organ failure	0 (0%)	50 (50%)	0.50 (0.12-0.76)	0.03
Intra-abdominal bleeding	0 (0%)	0 (0%)	-	-
Enterocutaneous fistula	0 (0%)	2 (20%)	0.20 (-0.11-0.51)	0.47
Pancreatic fistula	1 (10%)	7 (70%)	0.60 (0.17-0.81)	0.02
Death	1 (10%)	4 (40%)	0.30 (-0.08-0.60)	0.30

Pancreatitis Werkgroep Nederland

Bakker et al., for the DPSG. JAMA 2012; 307; 1053-61

Infected Pancreatic Necrosis

TENSION trial; Endoscopic or surgical step-up approach

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Lancet 2018; 391: 51–58

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Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial

*Sandra van Brunschot, Janneke van Grinsven, Hjalmar C van Santvoort, Olaf J Bakker, Marc G Besselink, Marja A Boermeester, Thomas L Bollen, Koop Bosscha, Stefan A Bouwense, Marco J Bruno, Vincent C Cappendijk, Esther C Consten, Cornelis H Dejong, Casper H van Eijck, Willemien G Erkelens, Harry van Goor, Wilhelmina M U van Grevenstein, Jan-Willem Haveman, Sijbrand H Hofker, Jeroen M Jansen, Johan S Laméris, Krijn P van Lienden, Maarten A Meijssen, Chris J Mulder, Vincent B Nieuwenhuijs, Jan-Werner Poley, Rutger Quispel, Rogier J de Ridder, Tessa E Römkens, Joris J Scheepers, Nicolien J Schepers, Matthijs P Schwartz, Tom Seerden, B W Marcel Spanier, Jan Willem A Straathof, Marin Strijker, Robin Timmer, Niels G Venneman, Frank P Vleggaar, Rogier P Voermans, Ben J Witteman, Hein G Gooszen, Marcel G Dijkgraaf, Paul Fockens, for the Dutch Pancreatitis Study Group**

Summary

Background Infected necrotising pancreatitis is a potentially lethal disease and an indication for invasive intervention. The surgical step-up approach is the standard treatment. A promising alternative is the endoscopic step-up approach. We compared both approaches to see whether the endoscopic step-up approach was superior to the surgical step-up

Pancreatitis Werkgroep Nederland

van Brunschot et al., for the DPSG. Lancet 2018; 391: 51-8

Infected Pancreatic Necrosis

TENSION trial; Endoscopic or surgical step-up approach

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	Endoscopic step-up approach (n=51)	Surgical step-up approach (n=47)	Relative risk (95% CI)	p value
Primary endpoint				
Major complications or death*	22 (43%)	21 (45%)	0·97 (0·62–1·51)	0·88
Secondary endpoints				
New-onset organ failure†				
Single organ failure	7 (14%)	13 (28%)	0·50 (0·20–1·14)	0·09
Persistent single organ failure	6 (12%)	11 (23%)	0·50 (0·20–1·28)	0·13
Multiple organ failure	2 (4%)	6 (13%)	0·33 (0·07–1·45)	0·11
Persistent multiple organ failure	2 (4%)	5 (11%)	0·37 (0·08–1·81)	0·20
Death	9 (18%)	6 (13%)	1·38 (0·53–3·59)	0·50
Other endpoints‡				
Pancreatic [illegible]	2/42 (5%)	13/41 (32%)	0·15 (0·04–0·62)	0·0011
[illegible] insufficiency				
Use of enzymes	16/42 (38%)	13/41 (32%)	1·20 (0·66–2·17)	0·54
Fecal elastase <200 mg/g	22/42 (52%)	19/41 (46%)	1·13 (0·73–1·75)	0·58
Steatorrhoea	6/42 (14%)	7/41 (17%)	0·84 (0·31–2·28)	0·73
Endocrine insufficiency	10/42 (24%)	9/41 (22%)	1·08 (0·49–2·39)	0·84
Biliary strictures	3 (6%)	3 (6%)	0·92 (0·20–4·34)	0·92
Days in hospital within 6 months of randomisation				
Median (IQR)	35 (19–85)	65 (40–90)	..	..
Mean (SD)	53 (47)	69 (38)	..	0·014

Difference in total mean costs of €13655 (19%) in favour of the endoscopic step-up approach

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van Brunschot et al., for the DPSG. Lancet 2018; 391: 51-8

Infected Necrotising Pancreatitis

EXTENSION; long-term follow-up endo vs. surgical step-up approach

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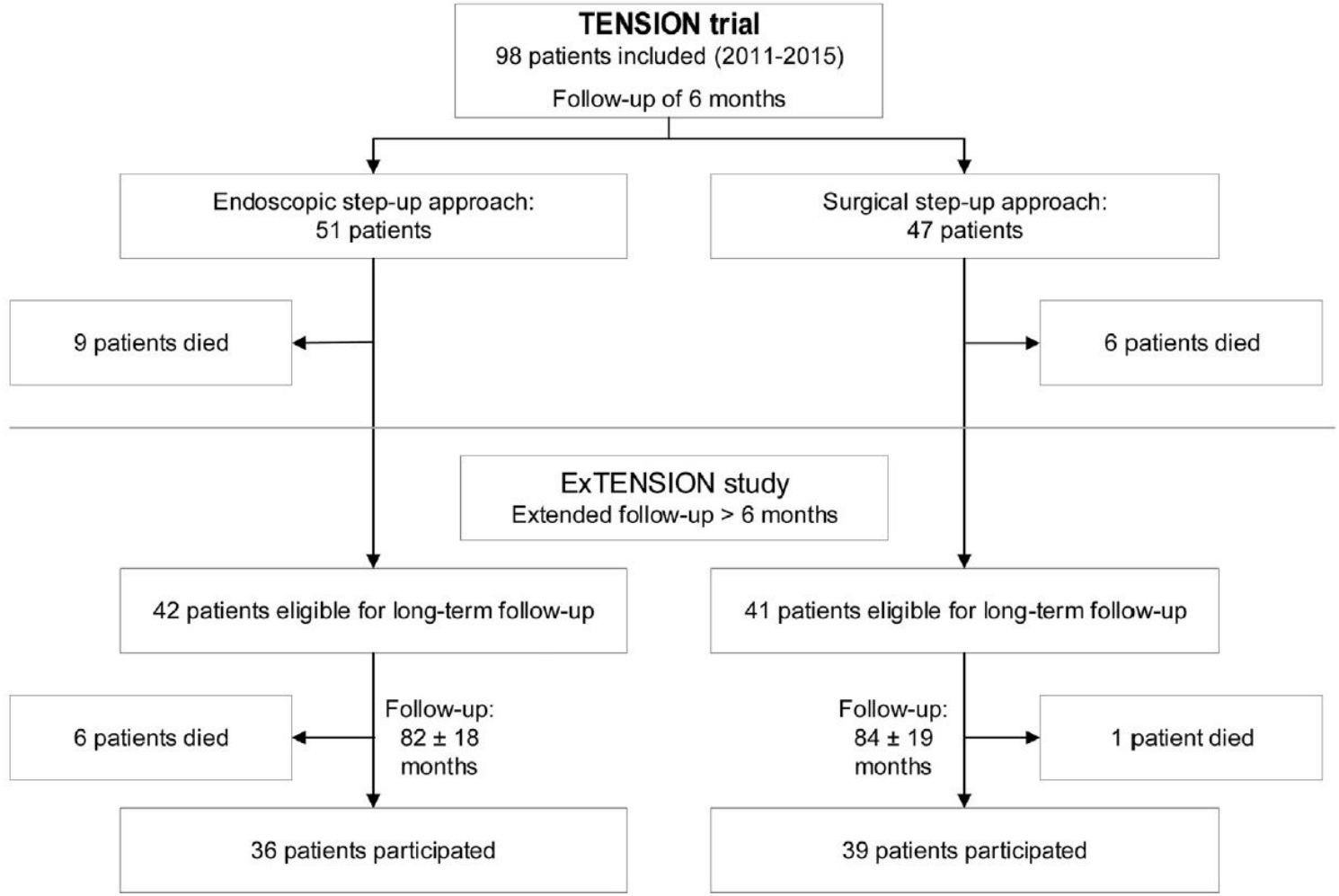

Pancreatitis Werkgroep Nederland

Onnekink et al. Gastroenterology 2022; online ahead of print

Infected Necrotising Pancreatitis

EXTENSION; long-term follow-up endo vs. surgical step-up approach

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Outcome	Overall follow-up (Between randomization and the end of long-term follow-up)				New events after the initial 6-month follow-up (Excluding events as reported in the TENSION trial)			
	Endoscopic step-up approach (n = 51)	Surgical step-up approach (n = 47)	RR (95% CI)	*P* value	Endoscopic step-up approach (n = 42)	Surgical step-up approach (n = 41)	RR (95% CI)	*P* value
Primary end point[a]								
Major complications or death[a]	27 (53)	27 (57)	0.92 (0.65–1.32)	.688	11 (26)	8 (20)	1.34 (0.60–3.00)	.603
Secondary end points[b]								
Death	15 (29)	7 (15)	1.98 (0.88–4.42)	.096	6 (14)	1 (2)	5.86 (0.74–46.55)	.109
New-onset organ failure[c]	11 (22)	15 (32)	0.68 (0.35–1.32)	.263	4 (10)	2 (5)	1.95 (0.38–10.08)	.676
Multiple new-onset organ failure[c]	4 (8)	6 (13)	0.61 (0.19–2.04)	.513	2 (5)	0 (0)	-	.494
Bleeding requiring intervention	13 (26)	11 (23)	1.09 (0.54–2.19)	1	2 (5)	1 (2)	1.95 (0.18–20.71)	1
Perforation or enterocutaneous fistula requiring intervention	6 (12)	11 (23)	0.5 (0.20–1.25)	.182	2 (5)	3 (7)	0.65 (0.12–3.70)	.676
Incisional hernia	4 (8)	4 (9)	0.92 (0.24–3.48)	1	4 (10)	3 (7)	1.3 (0.31–5.46)	1
Other end points								
Biliary stricture	3 (6)	4 (9)	0.69 (0.16–2.93)	.707	0 (0)	1 (2)	…	.494
Wound infection	3 (6)	4 (9)	0.69 (0.16–2.93)	.707	1 (2)	1 (2)	0.98 (0.06–15.09)	1
Pancreatic fistula	4 (8)	16 (34)	0.23 (0.08–0.64)	.002	2 (5)	2 (5)	0.98 (0.14–6.61)	1
Endocrine pancreatic insufficiency	19 (37)[d]	17 (36%)[d]	1.03 (0.61–1.73)	1	9/24 (38)[e]	9/27 (33)[e]	1.13 (0.54–2.36)	.778
Exocrine pancreatic insufficiency[b]								
FE-1 <200 μg/g	31 (61)	31 (66)	0.92 (0.68–1.25)	.677	8/20 (40)[e]	9/22 (41)[e]	0.98 (0.47–2.04)	1
Use of pancreatic enzymes	19 (37)	19 (40)	0.92 (0.56–1.52)	.836	2/20 (10)[e]	2/22 (9)[e]	1.1 (0.17–7.10)	1

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Onnekink et al. Gastroenterology 2022; online ahead of print

Acute Necrotising Pancreatitis
IAP/APA guidelines for intervention

3.10. Timing of intervention in necrotizing pancreatitis

Q31. What is the optimal timing of intervention for suspected or confirmed infected necrosis?

For patients with proven or suspected infected necrotizing pancreatitis, invasive intervention (i.e. percutaneous catheter drainage, endoscopic transluminal drainage/necrosectomy, minimally invasive or open necrosectomy) should be delayed where possible until at least 4 weeks after initial presentation to allow the collection to become 'walled-off'.
(GRADE 1C, strong agreement).

Working Group IAP/APA Acute Pancreatitis Guidelines Pancreatology 2013: e1-e15

Infected Pancreatic Necrosis

POINTER study; when to intervene and drain?

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Immediate versus Postponed Intervention for Infected Necrotizing Pancreatitis

L. Boxhoorn, S.M. van Dijk, J. van Grinsven, R.C. Verdonk, M.A. Boermeester, T.L. Bollen, S.A.W. Bouwense, M.J. Bruno, V.C. Cappendijk, C.H.C. Dejong, P. van Duijvendijk, C.H.J. van Eijck, P. Fockens, M.F.G. Francken, H. van Goor, M. Hadithi, N.D.L. Hallensleben, J.W. Haveman, M.A.J.M. Jacobs, J.M. Jansen, M.P.M. Kop, K.P. van Lienden, E.R. Manusama, J.S.D. Mieog, I.Q. Molenaar, V.B. Nieuwenhuijs, A.C. Poen, J.-W. Poley, M. van de Poll, R. Quispel, T.E.H. Römkens, M.P. Schwartz, T.C. Seerden, M.W.J. Stommel, J.W.A. Straathof, H.C. Timmerhuis, N.G. Venneman, R.P. Voermans, W. van de Vrie, B.J. Witteman, M.G.W. Dijkgraaf, H.C. van Santvoort, and M.G. Besselink, for the Dutch Pancreatitis Study Group*

ABSTRACT

BACKGROUND

Infected necrotizing pancreatitis is a potentially lethal disease that is treated with the use of a step-up approach, with catheter drainage often delayed until the infected necrosis is encapsulated. Whether outcomes could be improved by earlier catheter drainage is unknown.

Pancreatitis Werkgroep Nederland

Boxhoorn et al. New Engl J Med 2021; 385: 1372-81

Infected Pancreatic Necrosis

POINTER study; when to intervene and drain?

- Mean number of drainage procedures was 4,4 in the immediate drainage and 2,6 in the postponed drainage group (mean difference, 1.8; 95% CI, 0.6 to 3.0)

- Median hospital stay was 48 days and 35 days (P=0.07)

- In the postponed drainage group, 19 patients (39%) were successfully treated with antibiotics alone

Boxhoorn et al. New Engl J Med 2021; 385: 1372-81

Infected Pancreatic Necrosis

POINTER study; when to intervene and drain?

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End Point	Immediate Catheter Drainage (N = 55)	Postponed Catheter Drainage (N = 49)	Relative Risk or Mean Difference (95% CI)
Primary end point			
Comprehensive Complication Index score — mean (95% CI)*	57 (50 to 65)	58 (50 to 67)	−1 (−12 to 10)†
Secondary end points — no. (%)‡			
Death within 6 months	7 (13)	5 (10)	1.25 (0.42 to 3.68)
New-onset organ failure§	14 (25)	11 (22)	1.13 (0.57 to 2.26)
Pulmonary	5 (9)	8 (16)	0.56 (0.20 to 1.59)
Cardiovascular	11 (20)	9 (18)	1.09 (0.49 to 2.40)
Renal	3 (5)	4 (8)	0.67 (0.16 to 2.84)
New-onset multiple organ failure	4 (7)	8 (16)	0.45 (0.14 to 1.39)
Bleeding	8 (15)	10 (20)	0.71 (0.31 to 1.66)
Perforation of a visceral organ or enterocutaneous fistula	5 (9)	4 (8)	1.11 (0.32 to 3.91)
Pancreaticocutaneous fistula	6 (11)	4 (8)	1.34 (0.40 to 4.46)
Incisional hernia	0	0	—
Wound infection	0	1 (2)	—
Exocrine insufficiency			
Use of enzymes	20 (36)	19 (39)	0.94 (0.57 to 1.54)
Fecal elastase <200 mg/g¶	25 (48)	14 (32)	1.51 (0.90 to 2.53)
Endocrine insufficiency	11 (20)	10 (20)	0.98 (0.46 to 2.11)
Clavien–Dindo ≥III complication‖	42 (76)	40 (82)	0.94 (0.77 to 1.14)

Pancreatitis Werkgroep Nederland

Boxhoorn et al. New Engl J Med 2021; 385: 1372-81

Debridement of Infected Pancreatic Necrosis

RESOLVE study; conventional tools vs. Endorotor

van der Wiel et al. Endoscopy 2018; 50: E240-ER241
van der Wiel et al. Endosc Int Open 2020; 8: E274-E280

Infected Pancreatic Necrosis

Lessons learned: summary & conclusion

Erasmus MC

- A step-up approach for infected pancreatic necrosis is superior to open necrosectomy
- Up to 39% of patients managed according to a postponed drainage strategy are successfully treated with antibiotics alone
- Up to 35% of patients after percutaneous or endoscopic drainage do not require debridement
- An endoscopic step-up approach is superior to a surgical step-up approach for the occurrence of pancreatic fistula, length of hospital stay, and overall costs, but not for organ failure or death
- Immediate catheter drainage is clinically not superior to postponed catheter drainage while being associated with more interventions

Pancreatitis Werkgroep Nederland