Minimally Invasive and Novel Therapeutics (M.I.N.T.)
September 13th- 15th 2023

Managing severe pancreatitis… Where is the evidence?

Enrique de-Madaria MD PhD Dr. Balmis General Univ. Hospital. Alicante, Spain

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American people

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Spanish people

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Dictionary Thesaurus stereotype

Yes, all the time

Stereotype

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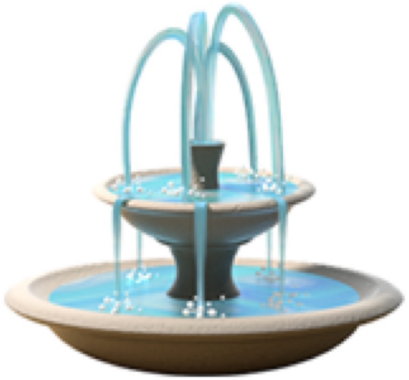
Aim: to review stereotypes in the treatment of acute pancreatitis



Fluid therapy

Nutrition

Infections

ERCP

Pain

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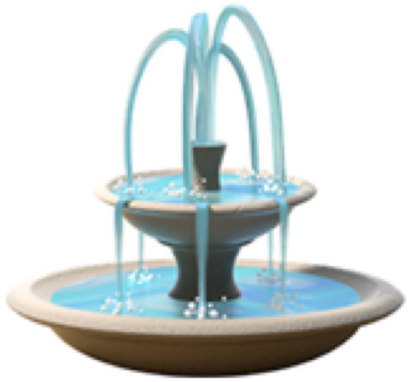

Fluid therapy

Aggressive fluid resuscitation saves lives

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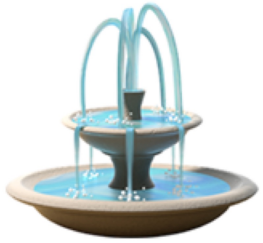
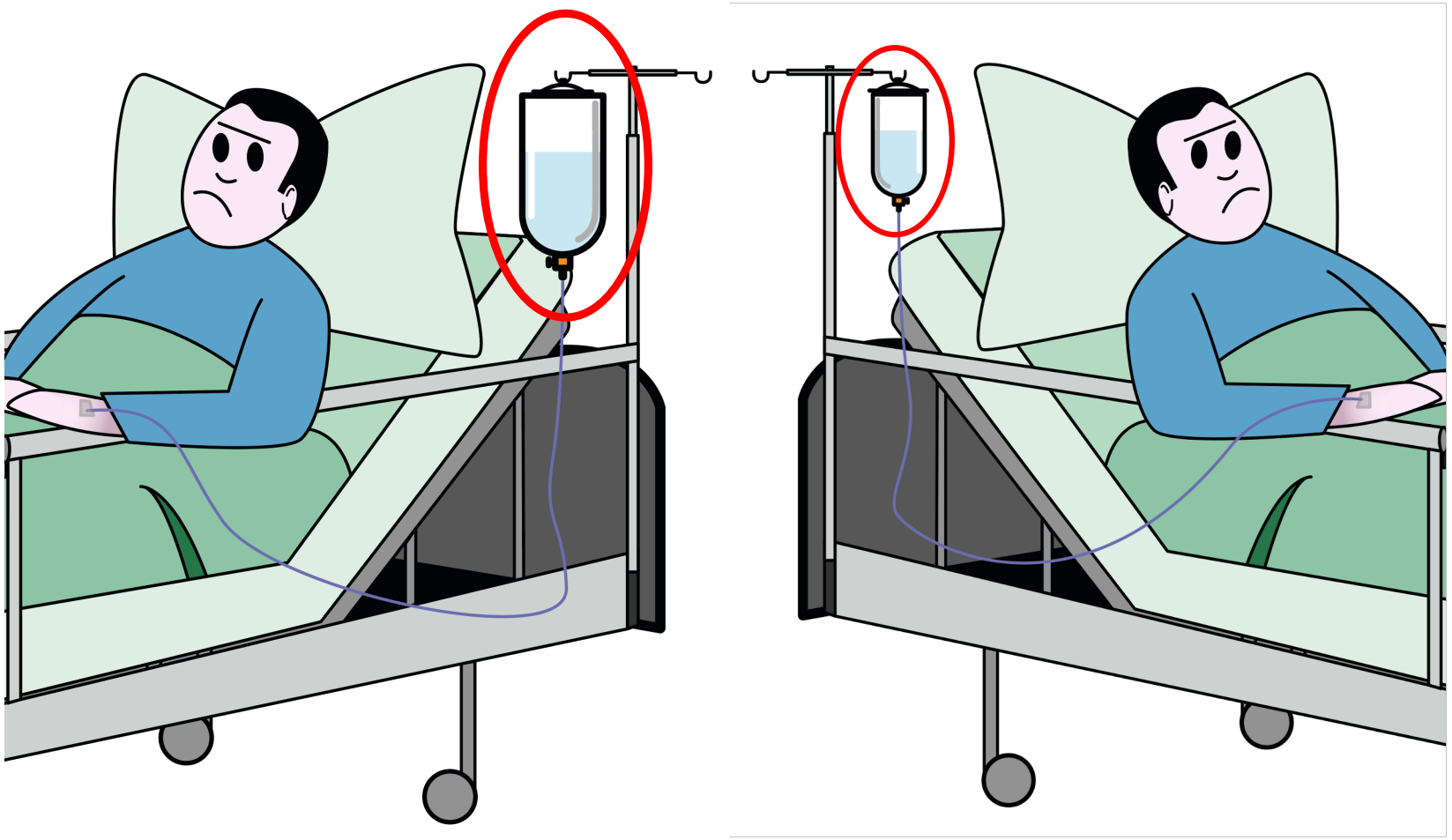


Volume



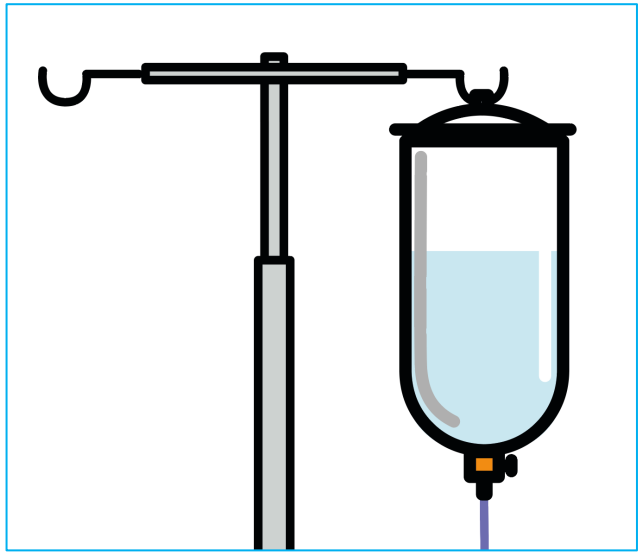
WATERFALL trial

International open-label goal-directed randomized clinical trial

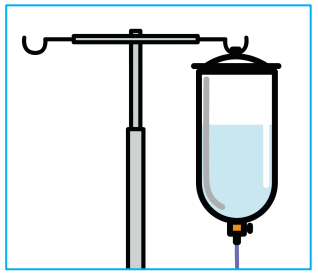
Aggressive vs. moderate fluid resuscitation

LACTATED RINGER

	Aggressive	Moderate
0h	20 ml/kg in 2h 3 ml/kg/h	Hypovolemia: 10 ml/kg in 2h 1.5 ml/kg/h
12h 24h 48h 72h	**Hypovolemia** 20 ml/kg in 2h 3 ml/kg/h	**Hypovolemia** 10 ml/kg in 2h 1.5 ml/kg/h
	Normovolemia 1.5 ml/kg/h	**Normovolemia** 1.5 ml/kg/h
	Hypervolemia Decrease/stop infusion	**Hypervolemia** Decrease/stop infusion



VS



Main efficacy endpoint

Moderate to severe AP

At least 1:

Local complications

Exacerbation of comorbidity

Organ failure

Main safety endpoint

Fluid overload

At least 2:

Dyspnea

Signs of fluid overload

Radiology/hemodynamics of fluid overload

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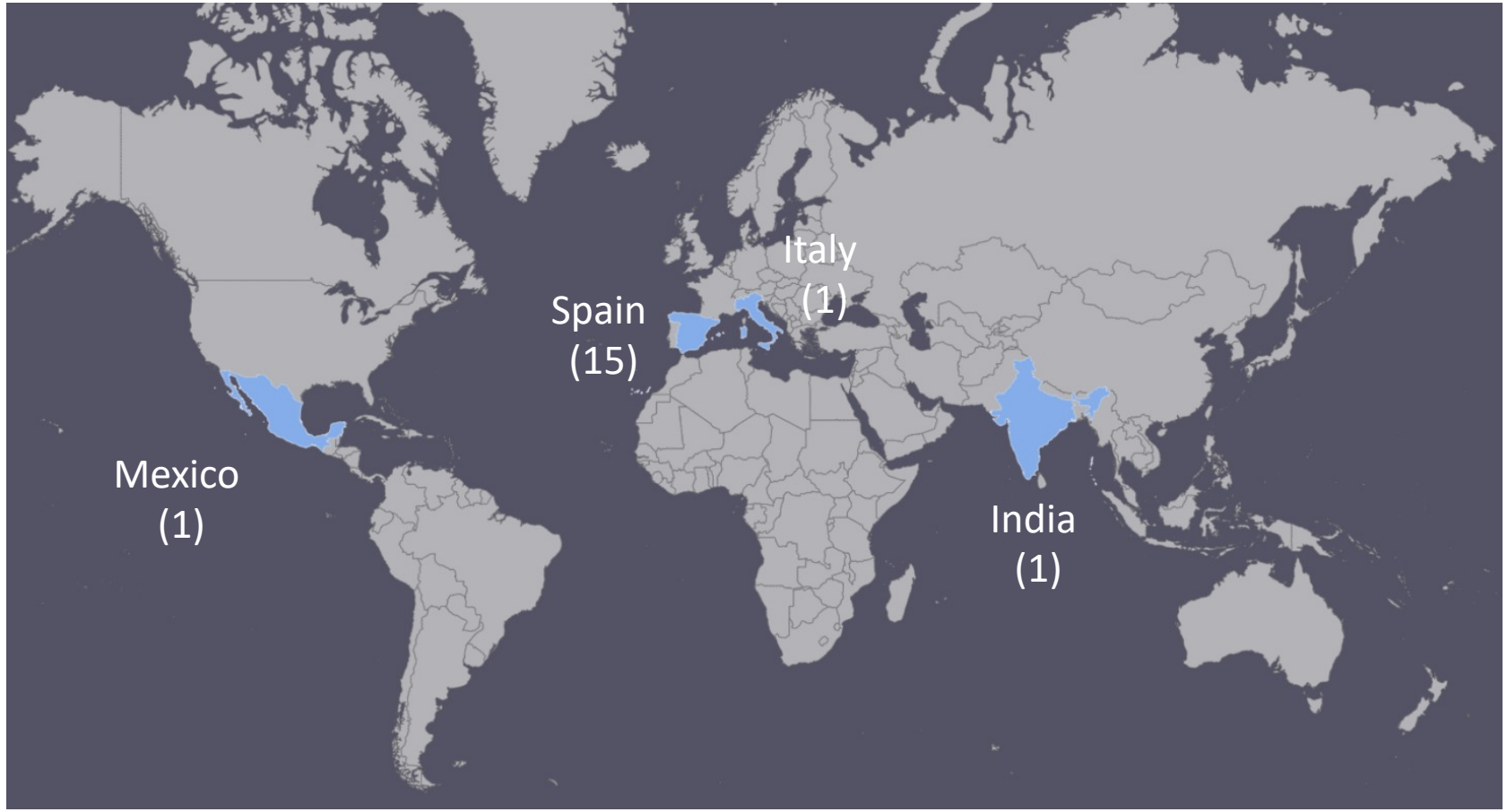
INTERNATIONAL LEAGUE AGAINST BILIARY-PANCREATIC DISEASES



ericaresearch.com

18 centers

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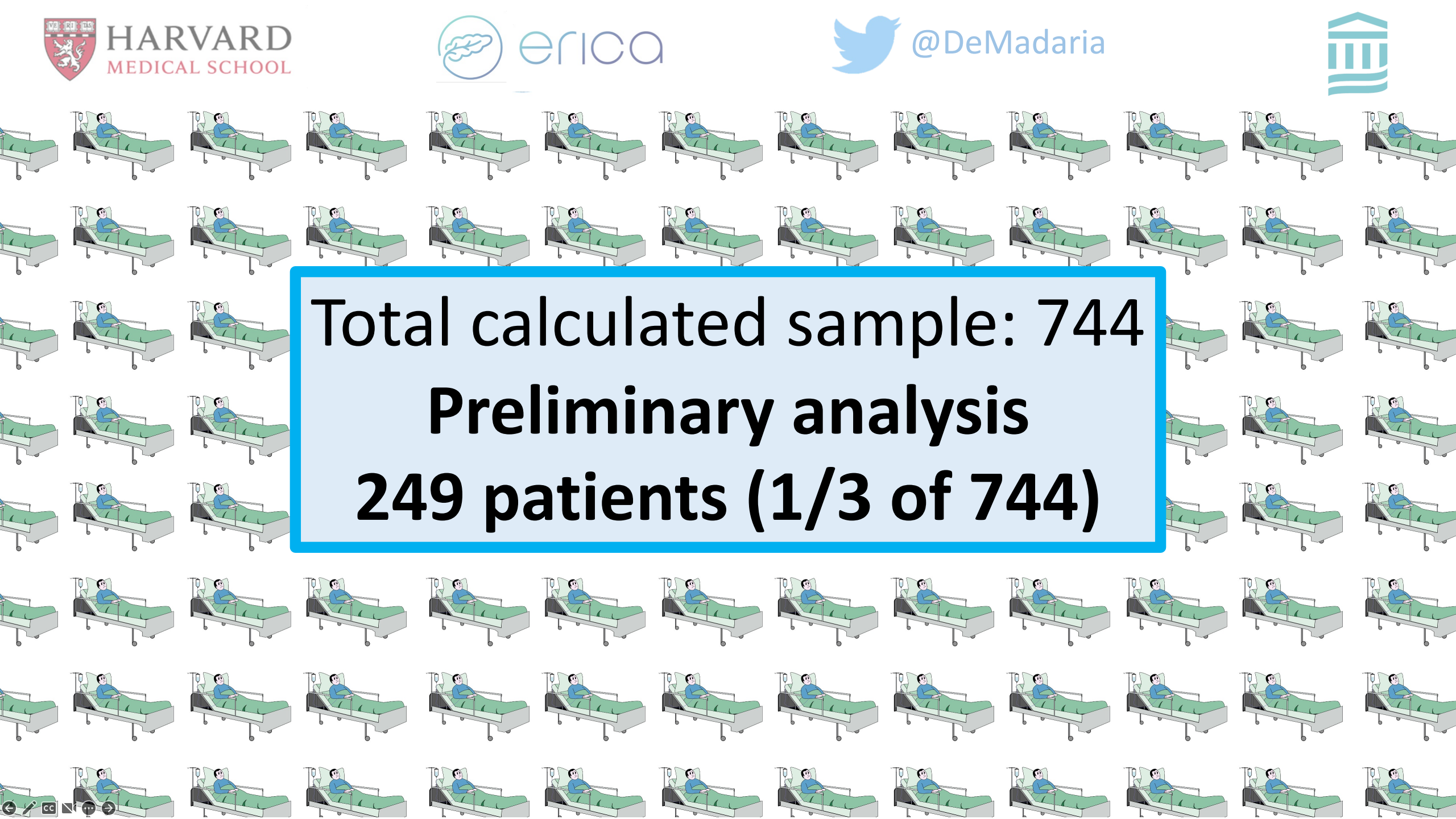

Total calculated sample: 744

Preliminary analysis

249 patients (1/3 of 744)

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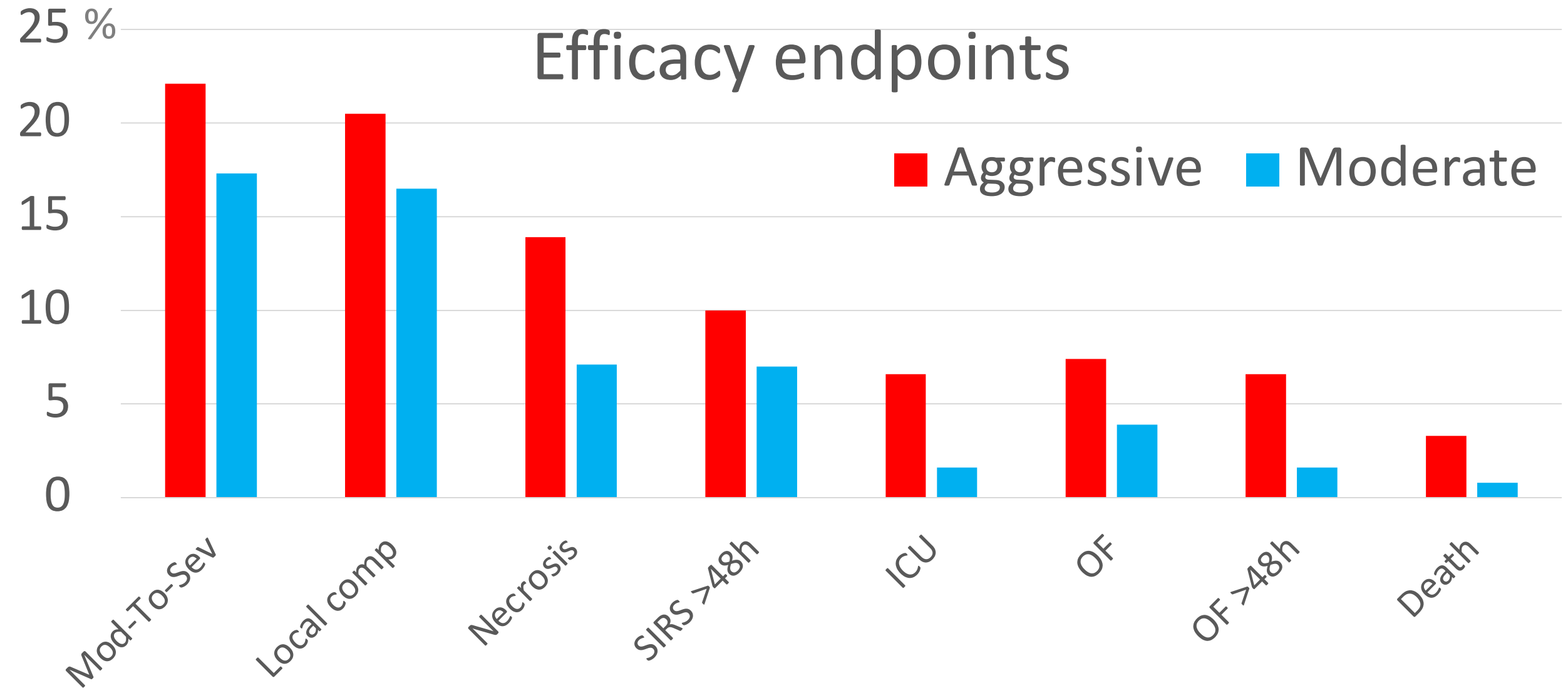

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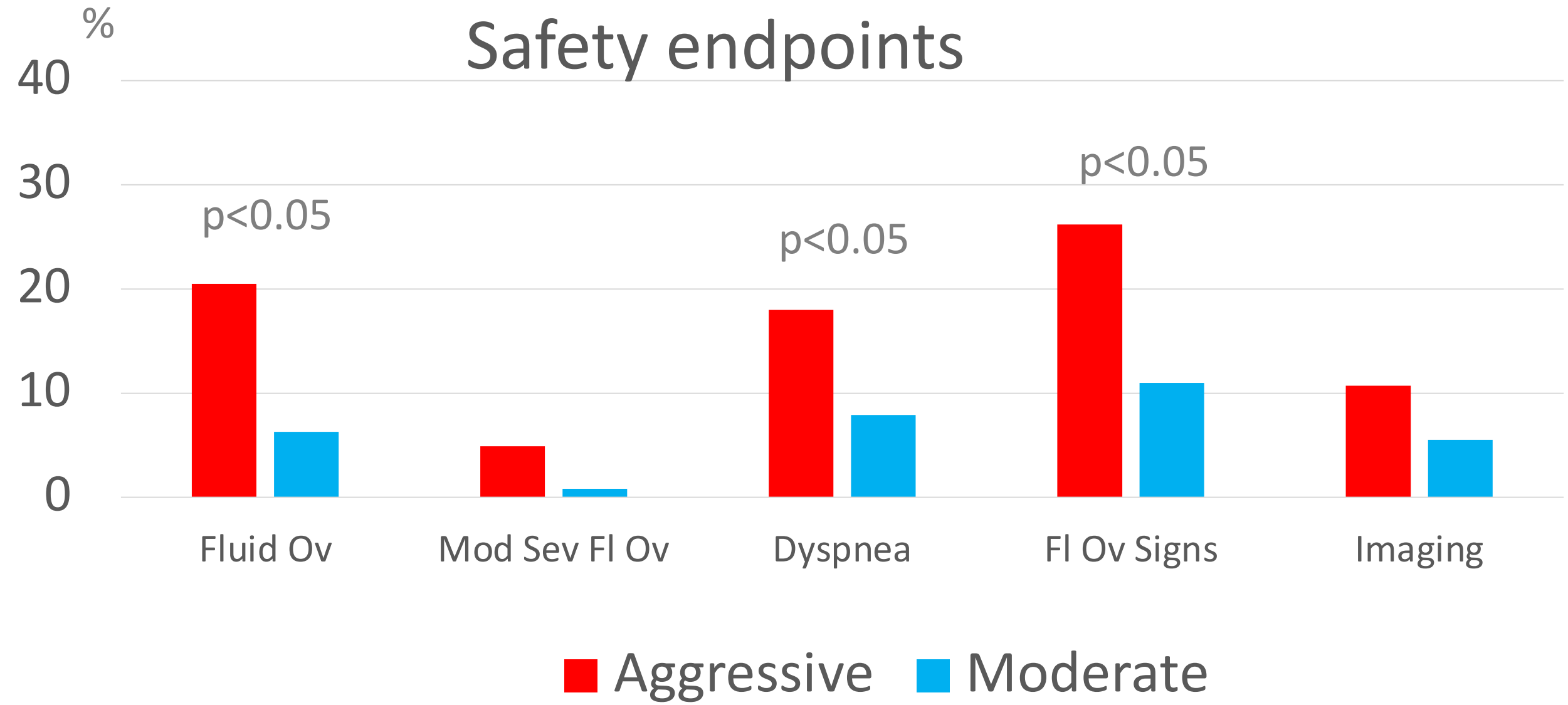
The study was stopped for safety reasons



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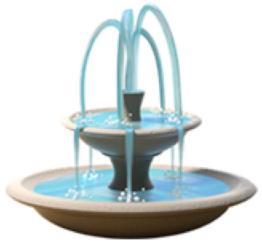

Volume

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Aggressive or Moderate Fluid Resuscitation in Acute Pancreatitis

E. de-Madaria, J.L. Buxbaum, P. Maisonneuve, A. García García de Paredes, P. Zapater, L. Guilabert, A. Vaillo-Rocamora, M.Á. Rodríguez-Gandía, J. Donate-Ortega, E.E. Lozada-Hernández, A.J.R. Collazo Moreno, A. Lira-Aguilar, L.P. Llovet, R. Mehta, R. Tandel, P. Navarro, A.M. Sánchez-Pardo, C. Sánchez-Marin, M. Cobreros, I. Fernández-Cabrera, F. Casals-Seoane, D. Casas Deza, E. Lauret-Braña, E. Martí-Marqués, L.M. Camacho-Montaño, V. Ubieto, M. Ganuza, and F. Bolado, for the ERICA Consortium*

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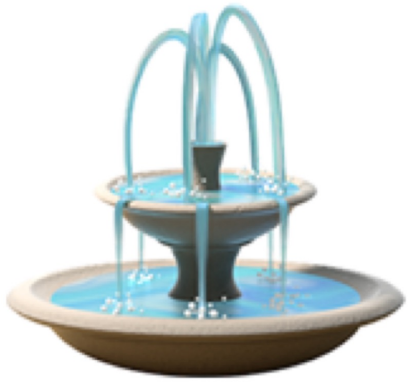
INTERNATIONAL LEAGUE AGAINST BILIARY-PANCREATIC DISEASES

de-Madaria et al, NEJM 2022



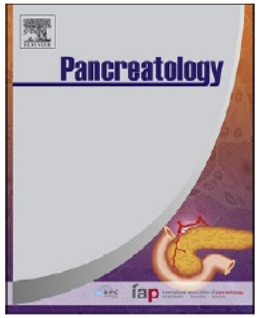
Fluid therapy

Normal saline is the standard fluid in acute disease

Contents lists available at ScienceDirect

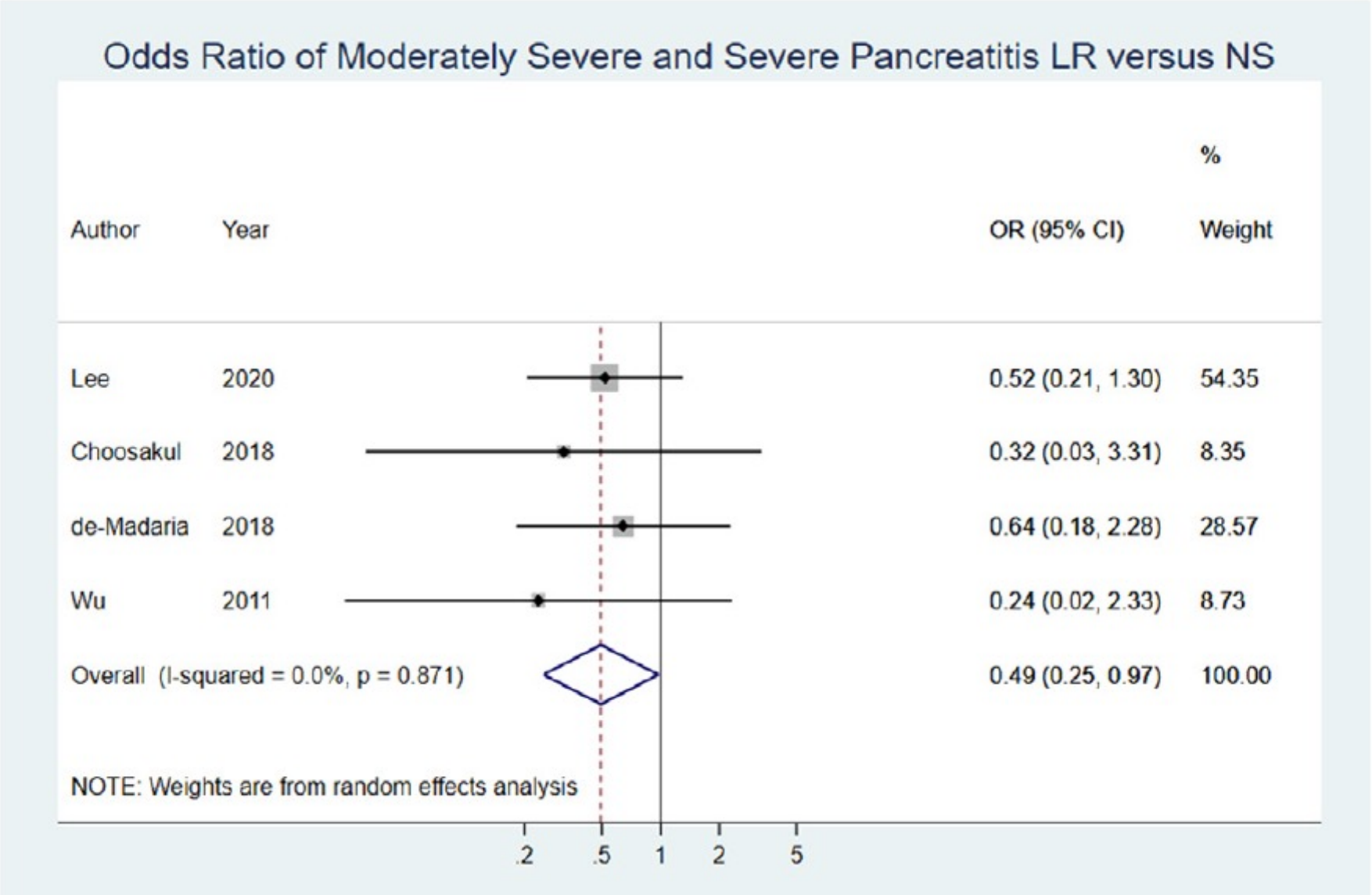
Pancreatology

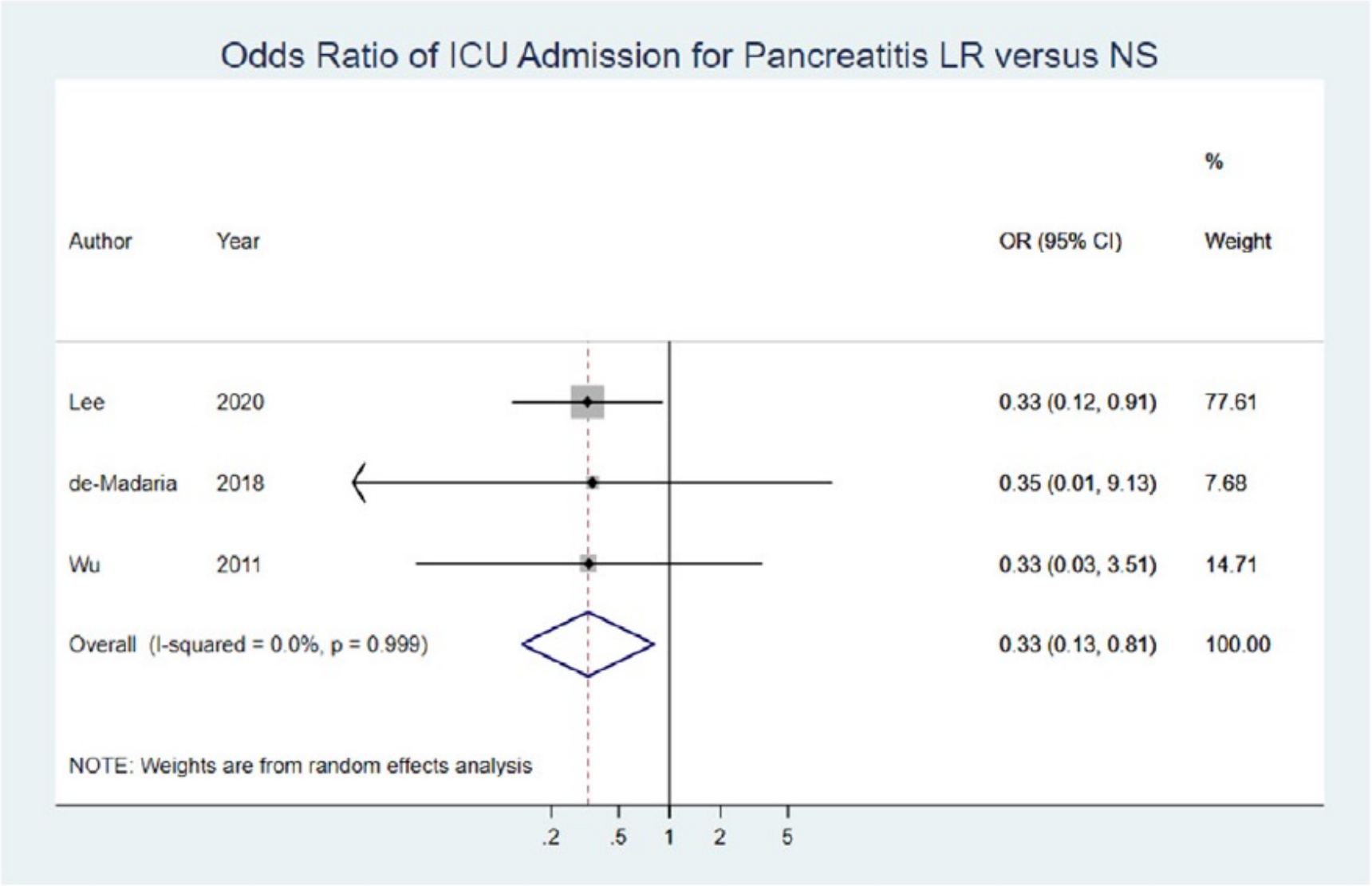
journal homepage: www.elsevier.com/locate/pan

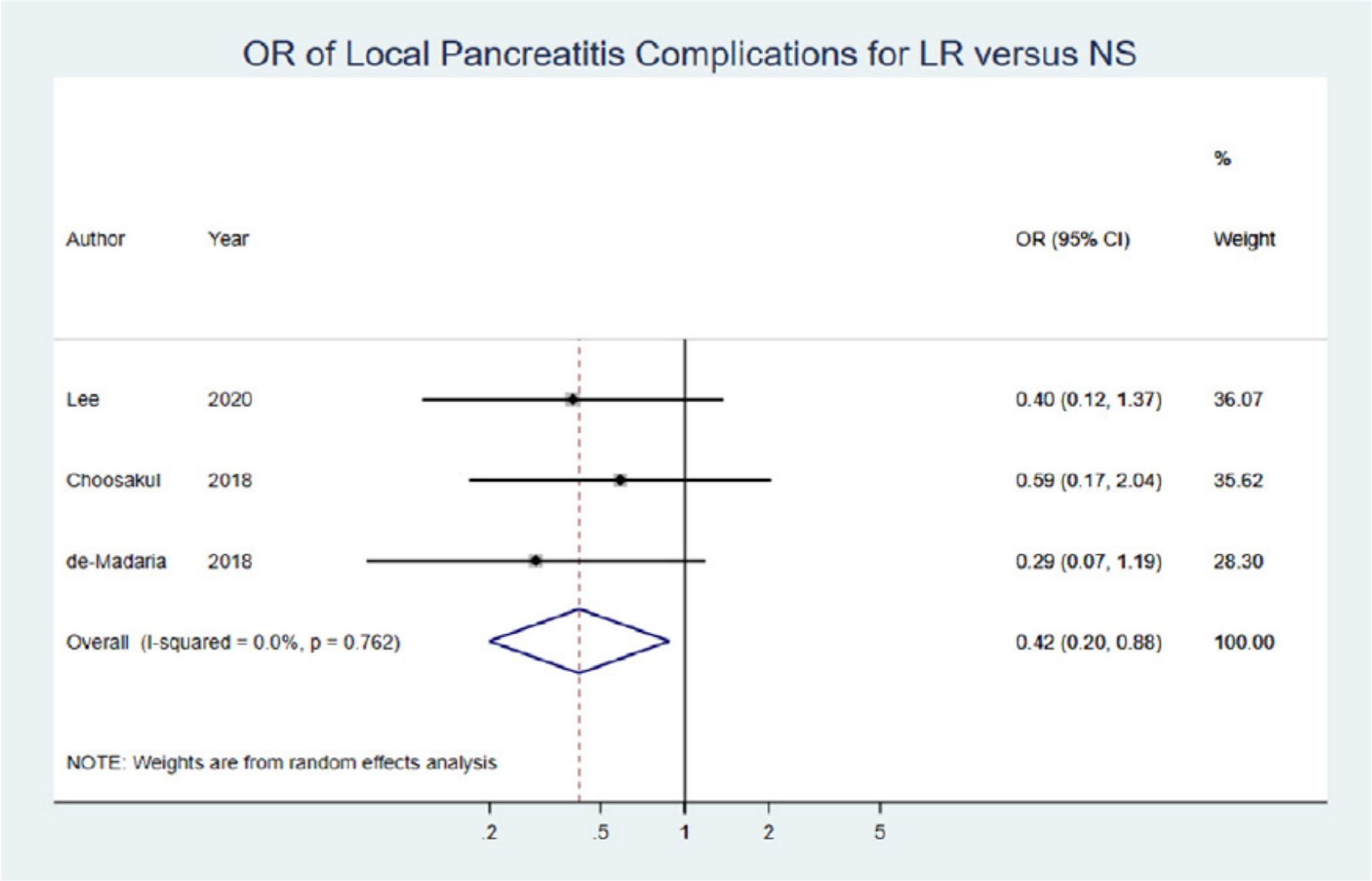


Comprehensive meta-analysis of randomized controlled trials of Lactated Ringer's versus Normal Saline for acute pancreatitis

Selena Zhou [a], Carlos Buitrago [a], Andrew Foong [a], Vivian Lee [a], Lillian Dawit [a], Brent Hiramoto [a], Patrick Chang [a], Hannah Schilperoort [b], Alice Lee [c], Enrique de-Madaria [d], James Buxbaum [a, *]


Odds Ratio of Moderately Severe and Severe Pancreatitis LR versus NS
Author
Year
OR (95% CI)
%
Weight
Lee 2020 0.52 (0.21, 1.30) 54.35
Choosakul 2018 0.32 (0.03, 3.31) 8.35
de-Madaria 2018 0.64 (0.18, 2.28) 28.57
Wu 2011 0.24 (0.02, 2.33) 8.73
Overall (I-squared = 0.0%, p = 0.871) 0.49 (0.25, 0.97) 100.00
NOTE: Weights are from random effects analysis
.2
.5
1
2
5


Odds Ratio of ICU Admission for Pancreatitis LR versus NS
Author
Year
OR (95% CI)
%
Weight
Lee
2020
0.33 (0.12, 0.91)
77.61
de-Madaria
2018
0.35 (0.01, 9.13)
7.68
Wu
2011
0.33 (0.03, 3.51)
14.71
Overall (I-squared = 0.0%, p = 0.999)
0.33 (0.13, 0.81)
100.00
NOTE: Weights are from random effects analysis
.2
.5
1
2
5


OR of Local Pancreatitis Complications for LR versus NS
Author
Year
OR (95% CI)
%
Weight
Lee
2020
0.40 (0.12, 1.37)
36.07
Choosakul
2018
0.59 (0.17, 2.04)
35.62
de-Madaria
2018
0.29 (0.07, 1.19)
28.30
Overall (I-squared = 0.0%, p = 0.762)
0.42 (0.20, 0.88)
100.00
NOTE: Weights are from random effects analysis
.2
.5
1
2
5

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INTERNATIONAL LEAGUE AGAINST BILIARY-PANCREATIC DISEASES

The WATERLAND trial

Normal saline vs. Ringer

Open-label multicenter randomized controlled trial

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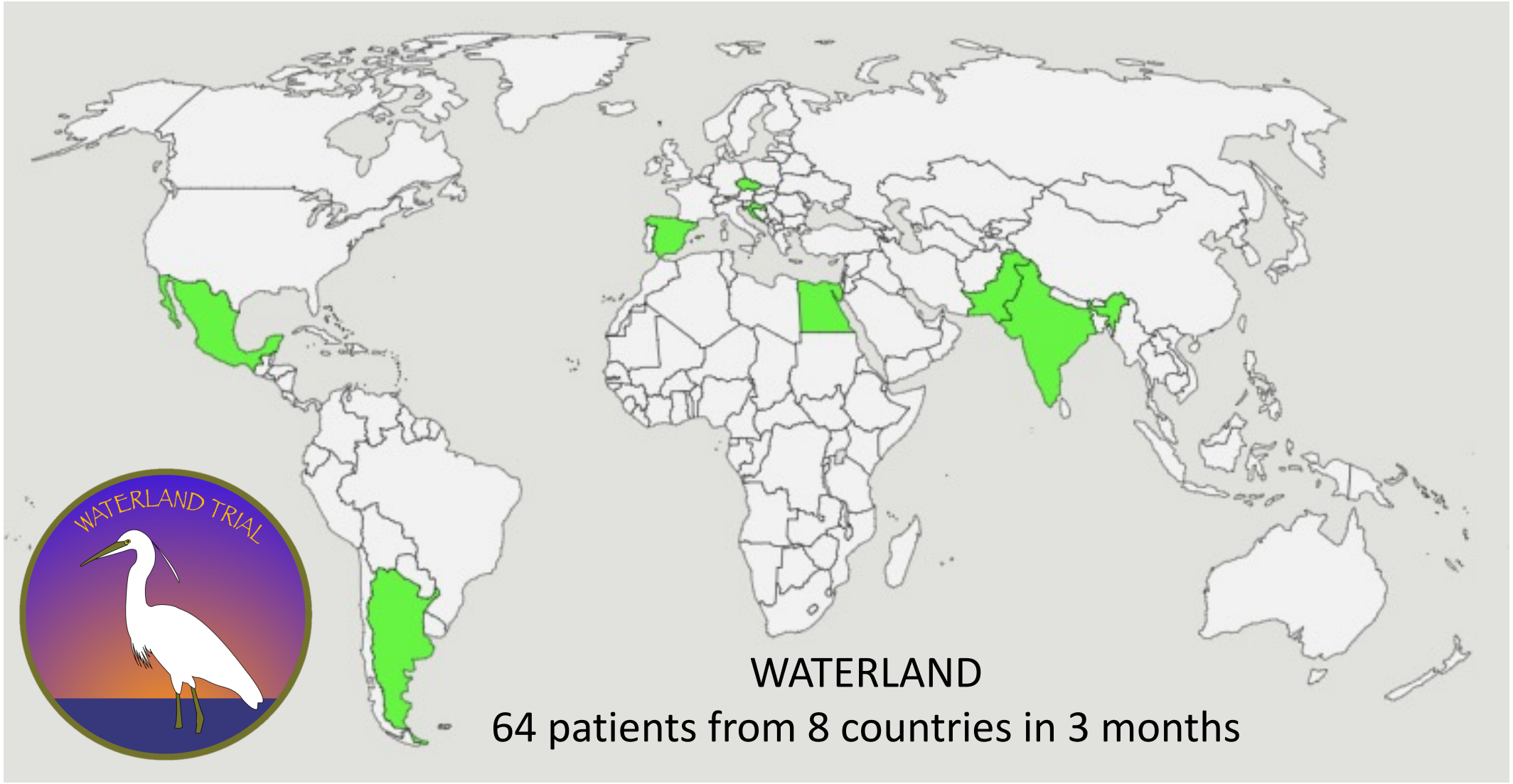

WATERLAND

64 patients from 8 countries in 3 months

Nutrition

Gradually begin to reintroduce oral feeding

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RCTs on when and how to reintroduce the oral feeding in **predicted mild** AP

Early vs delayed

Clear liquid vs soft/solid

- *Eckerwall* 2009: based on pain, shorter stay if early refeeding
- *Teich* 2010: based on blood lipase, no differences
- *Ramírez-Maldonado* 2021: early & solid vs progressive and delayed (mild or moderate AP)
- *Sathiaraj* 2009: soft vs clear liquids
- *Rajkumar* 2013: soft vs clear liquids
- *Moraes* 2010: solid vs soft vs clear liquids
- *Jacobson* 2007: low-fat solid vs clear liquids
- *Lariño* 2014: Early vs delayed/stepwise vs full

EARLY AND SOFT/SOLID

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Nutrition

Nutritional support saves lives in predicted severe or severe acute pancreatitis

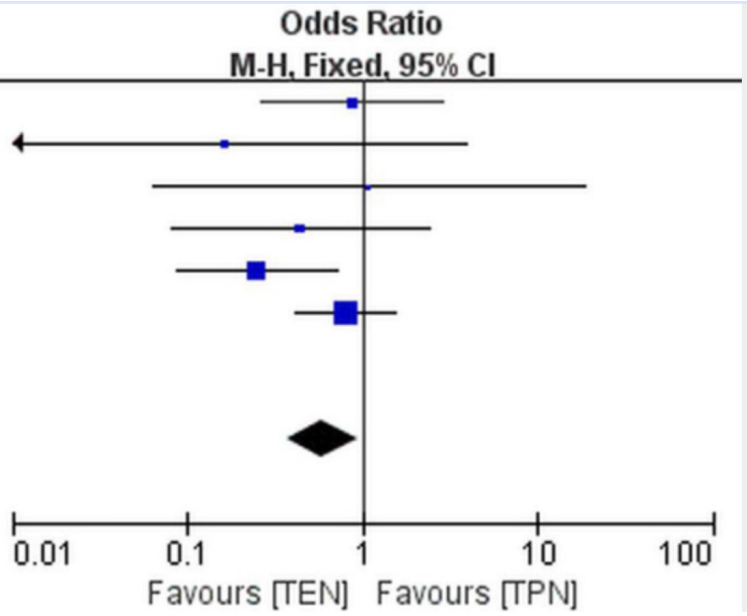
Predicted severe AP

Enteral vs. parenteral nutritional support

Study or Subgroup	TEN Events	TEN Total	TPN Events	TPN Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Abou-Assi S et al 2002	7	26	8	27	12.1%	0.88 [0.26, 2.90]
Casas M et al 2007	0	11	2	11	5.1%	0.17 [0.01, 3.88]
Eckerwall GE et al 2006	1	24	1	26	1.9%	1.09 [0.06, 18.40]
Oláh A et al 2003	2	41	5	48	9.3%	0.44 [0.08, 2.40]
Petrov MS et al 2006	7	35	17	34	29.2%	0.25 [0.09, 0.73]
Stimac D et al 2016	21	107	25	107	42.5%	0.80 [0.42, 1.54]
Wu XM et al 2010	11	53	44	0		Not estimable
Total (95% CI)		**297**		**253**	**100.0%**	**0.59 [0.37, 0.94]**
Total events	49		102			

Heterogeneity: Chi² = 4.66, df = 5 (P = 0.46); I² = 0%

Test for overall effect: Z = 2.24 (P = 0.03)



Mortality in predicted severe AP

Liu et al, APM, 2021

Great heterogeneity

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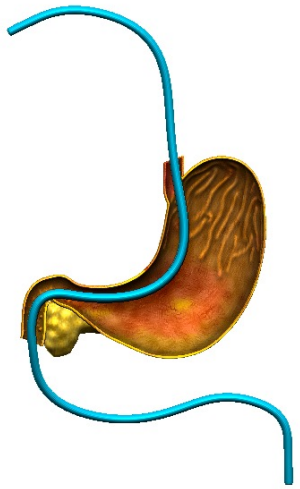
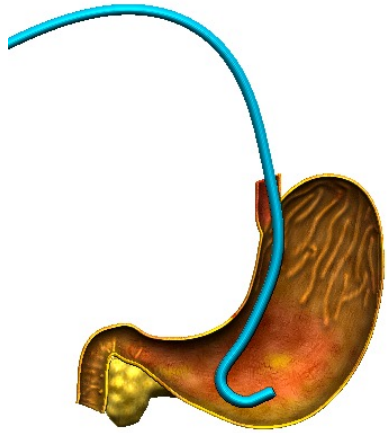
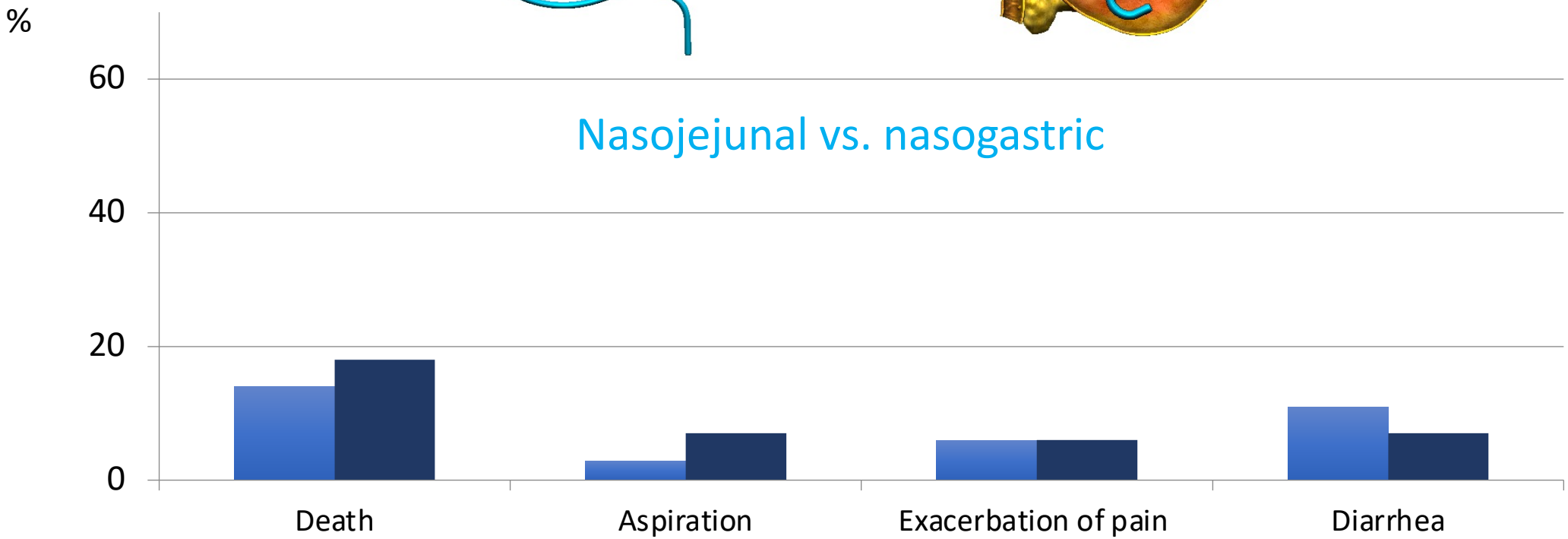




3 clinical trials
157 patients



Great heterogeneity

Chang et al, Crit Care 2013

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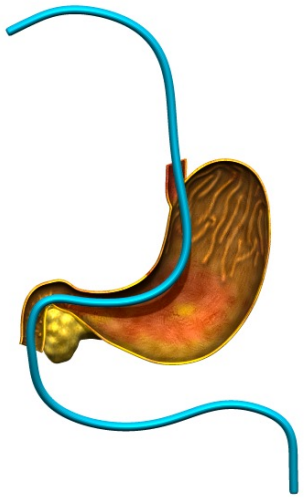
Predicted severe acute pancreatitis
n=208

Enteral

Nasojejunal tube
in 1st 24h

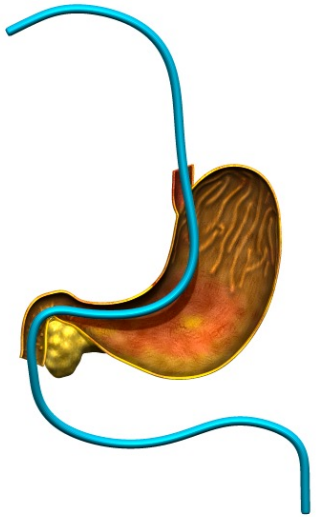


On demand

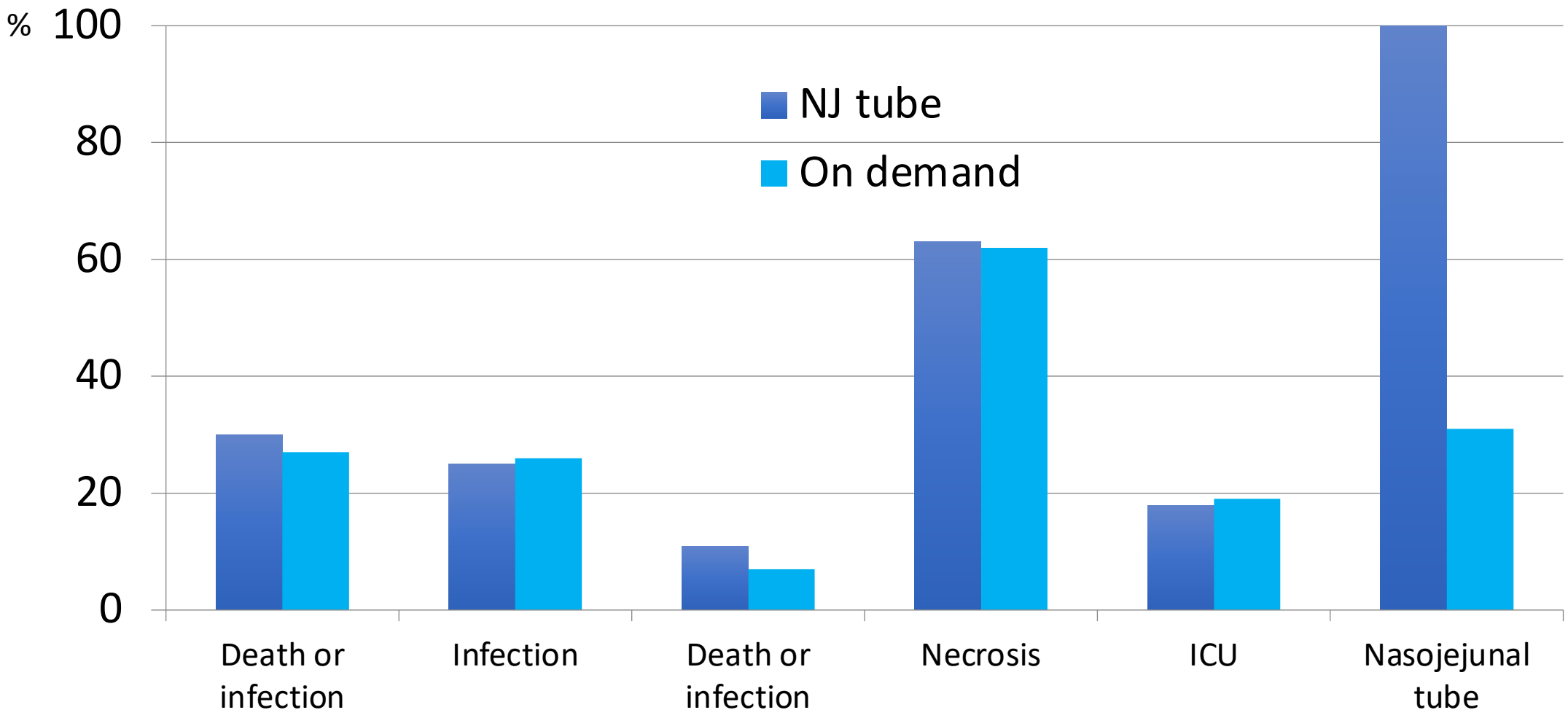
Oral diet at day 3

Not tolerated on the 4th day

Nasojejunal tube



Bakker et al, NEJM 2014


%
100
80
60
40
20
0
NJ tube
On demand
Death or infection
Infection
Death or infection
Necrosis
ICU
Nasojejunal tube

Infections

Antibiotics are helpful to prevent infection of necrosis

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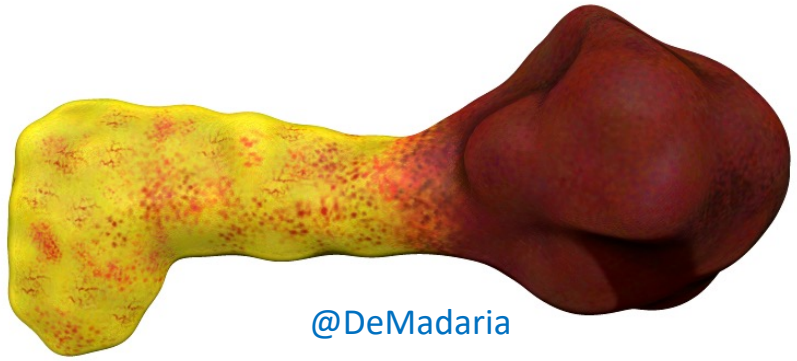
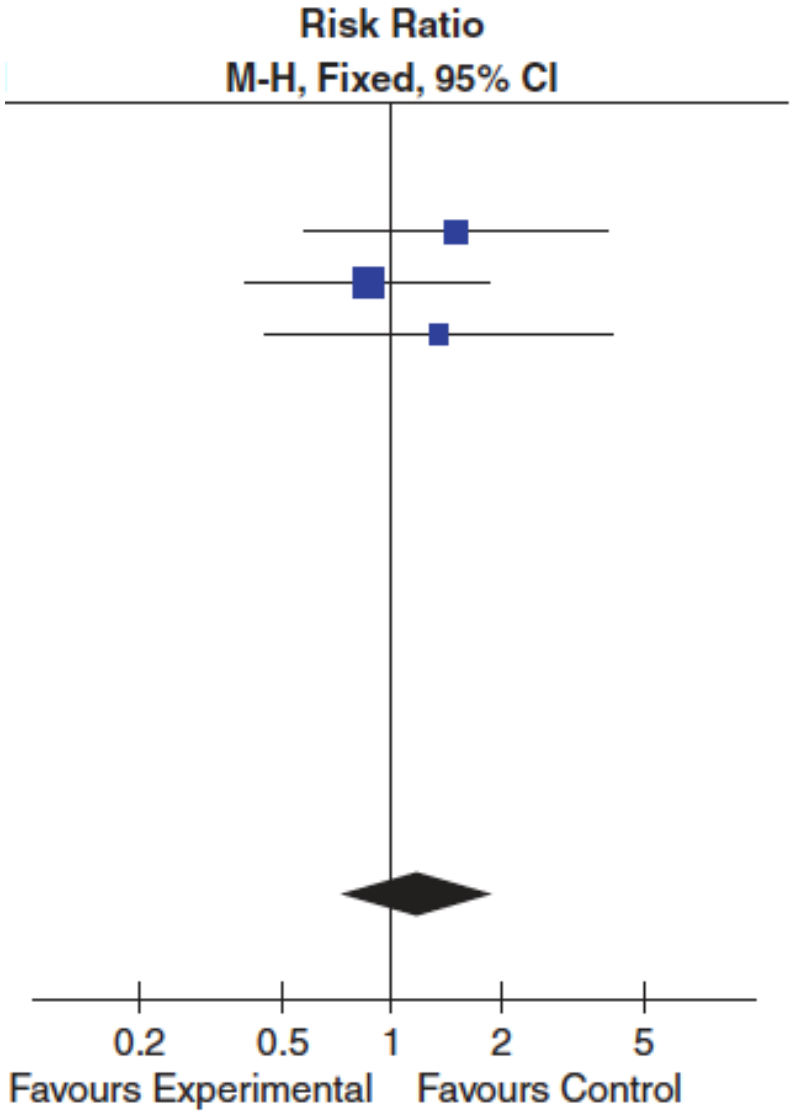
Prophylactic antibiotics and infection of pancreatic necrosis





Clinical trials at low risk of bias: ATB prophylaxis vs. placebo

Wittau, Scand J Gastro 2011

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Infections

Our experience as clinicians is very useful in deciding when to give empirical antibiotics

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THE LANCET
Gastroenterology & Hepatology

NHS
Manchester University
NHS Foundation Trust

A procalcitonin-based algorithm to guide antibiotic use in patients with acute pancreatitis (PROCAP): a single-centre, patient-blinded, randomised controlled trial

Ajith K Siriwardena, Santhalingam Jegatheeswaran, James M Mason, on behalf of the PROCAP investigators

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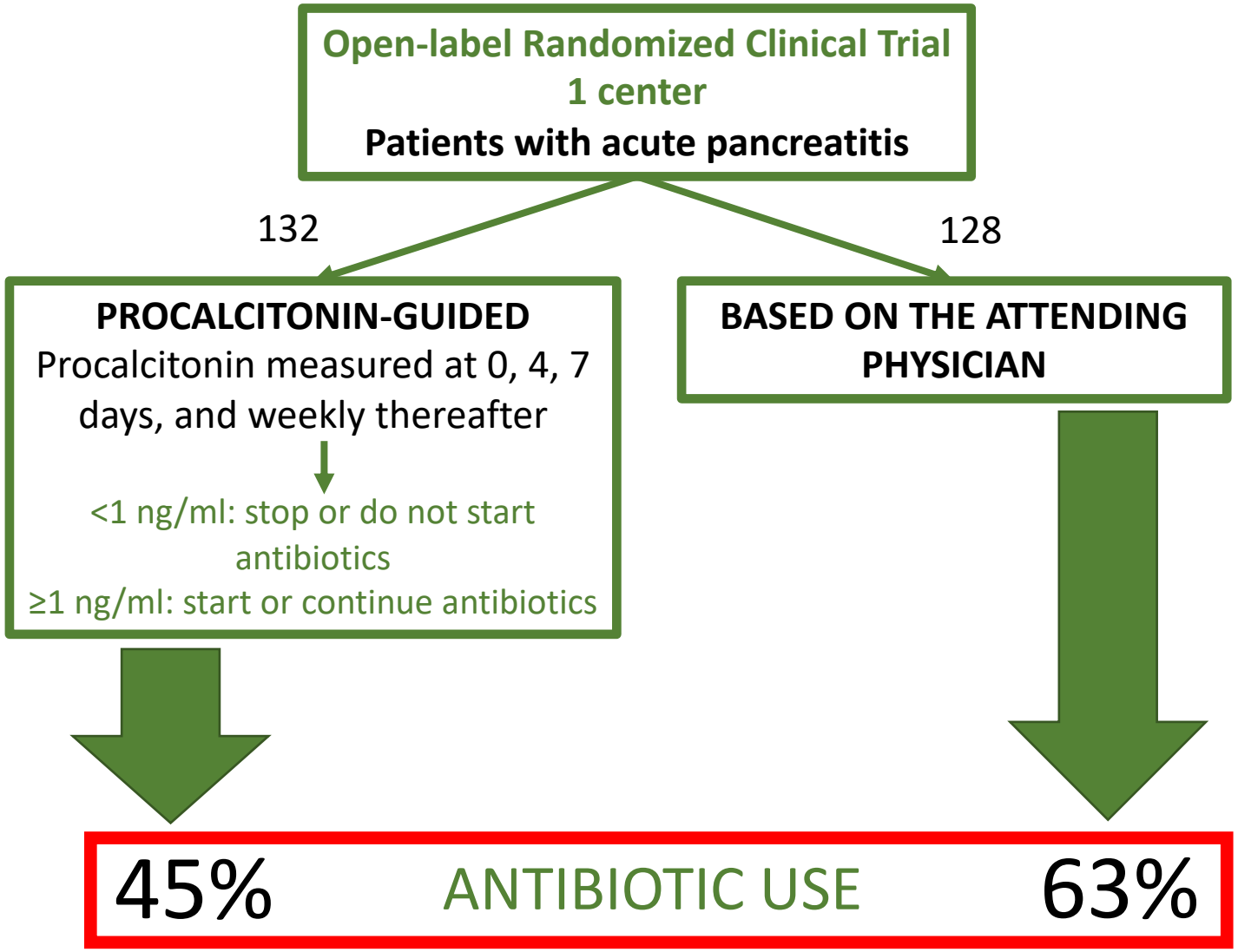

Procalcitonin-based protocol: less patients, same outcomes

Infections

Pancreatic infection should be drained ASAP and surgery is necessary if there is no improvement

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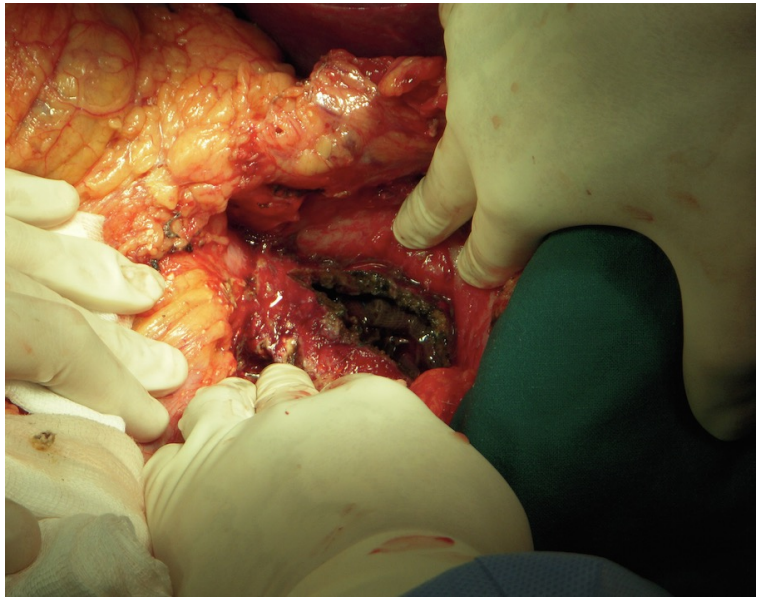
Antibiotics/support

Open surgery



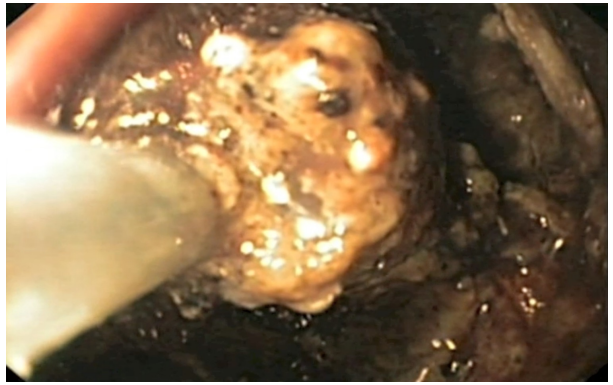
Minimally invasive treatments

Drainage

Percutaneous

Endoscopic

Necrosectomy



Endoscopic

VARD: video-assisted retroperitoneal debridement

STEP-UP APPROACH

Patients with AP and infected necrosis

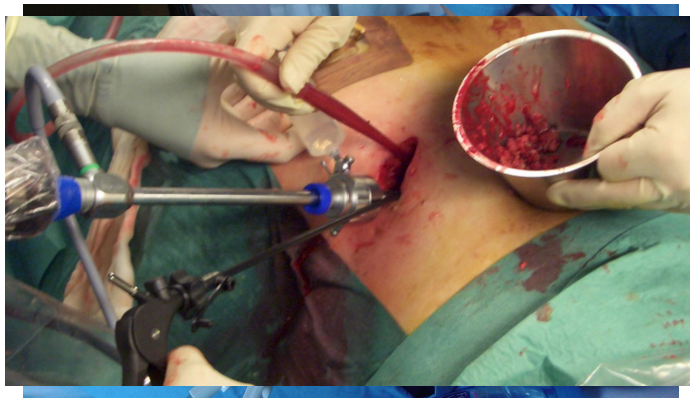
n=88

Step-up approach

Percutaneous or endoscopic drainage

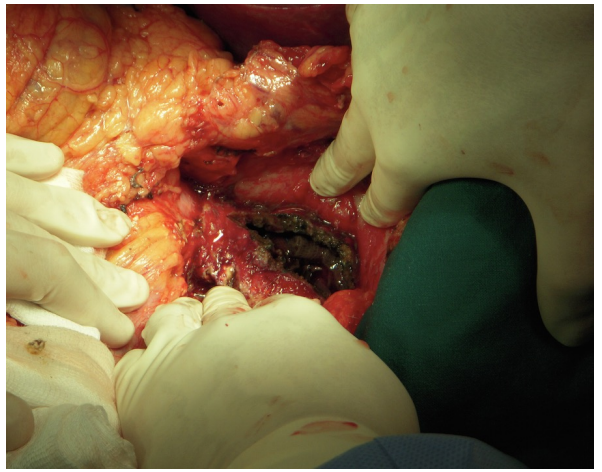
↓ No improvement

VARD



Classic management

Open surgery



Van Santvoor, NEJM 2010

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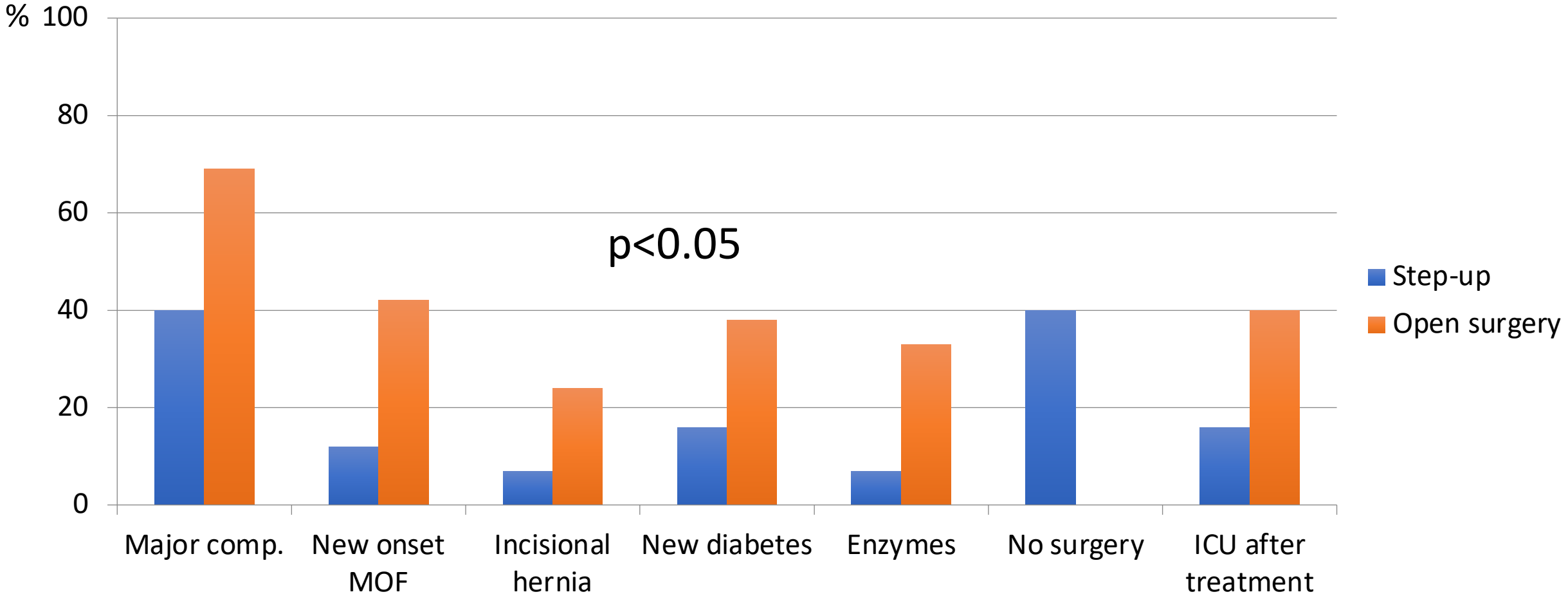

Step-up approach (drain and minimally invasive surgery if it goes wrong) less sequelae than open surgery

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TENSION TRIAL

Patients with AP and infected necrosis

n=98

Endoscopic step-up approach

Surgical step-up approach

Endoscopic drainage

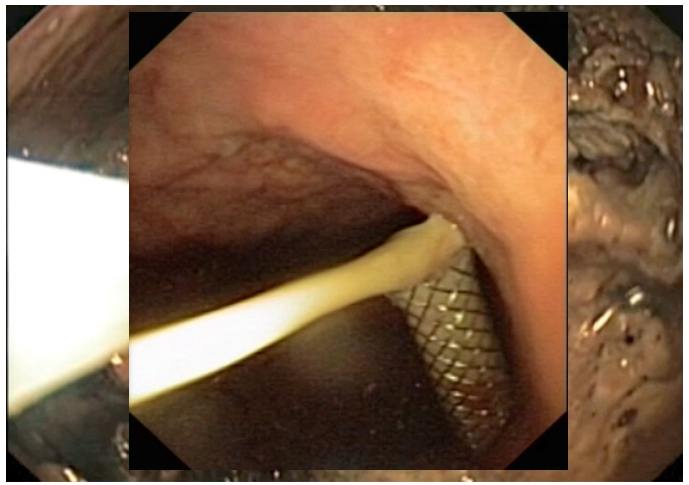
↓ No improvement

Endoscopic necrosectomy

Percutaneous drainage

↓ No improvement

VARD



Van Brunschot, Lancet 2018

No differences in:

Primary endpoint (major complication or death)

New organ failure

Bleeding

Incisional hernia

Pancreatic endocrine/exocrine insufficiency

Wound infection

Mortality

Differences in:

Pancreatic fistula (5% vs 32%)

Days of hospitalization (median 35 vs 65 days)

POINTER TRIAL

Patients with AP and infected necrosis n=104

Early drainage: Percutaneous and/or endoscopic drainage within 24h of suspected infection

Median: 24 days

Late drainage: Percutaneous and/or endoscopic drainage only if no adequate response to antibiotics.

Median: 34 days

Boxhoorn, NEJM 2021

Late drainage:

Fewer invasive procedures (mean 2.6 vs. 4.4)

39% were resolved with antibiotics

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Early ERCP

Patients with pancreatitis with predicted severity and jaundice benefit from early ERCP

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THE LANCET

Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy versus conservative treatment in predicted severe acute gallstone pancreatitis (APEC): a multicentre randomised controlled trial

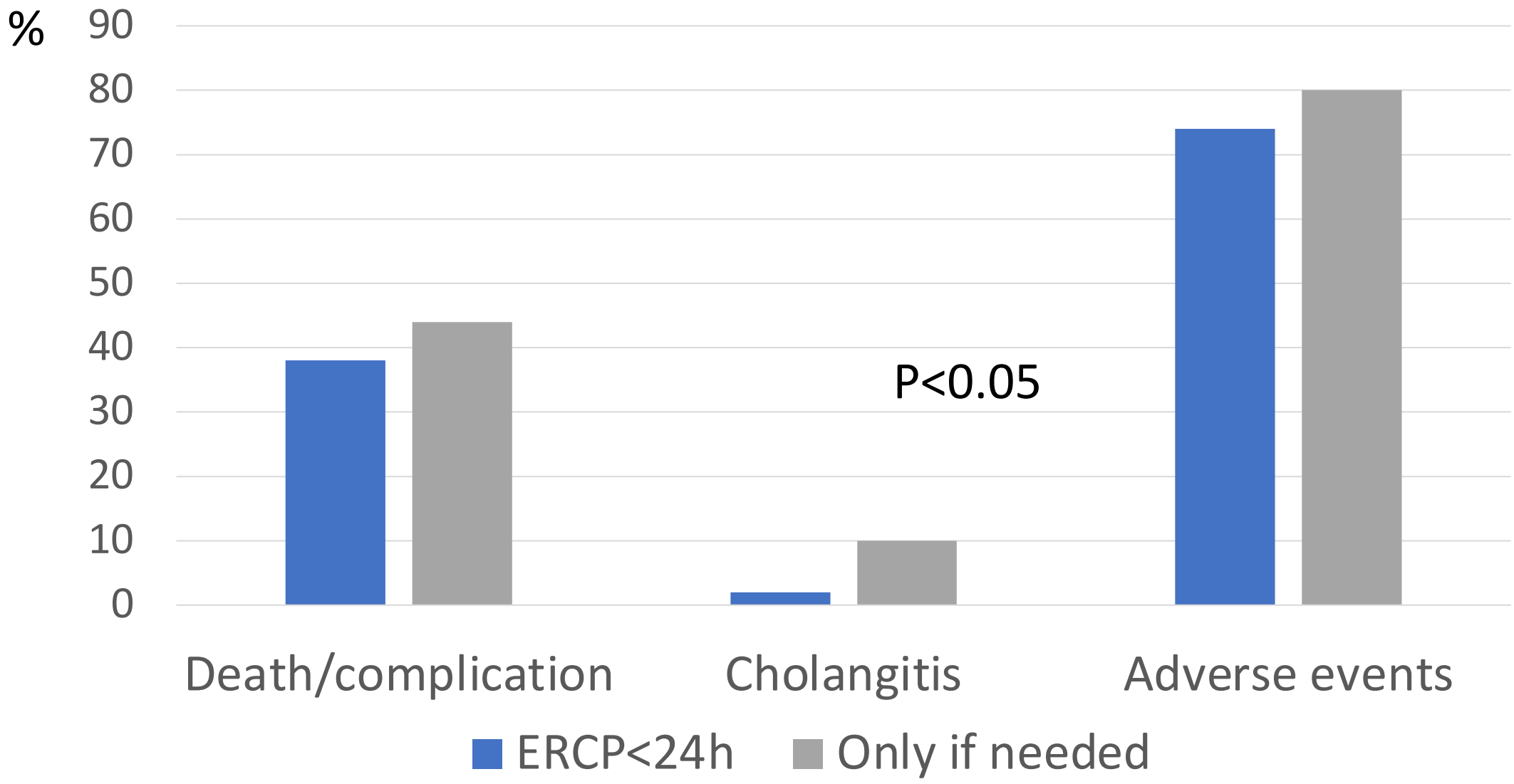
Nicolien J Schepers, Nora D L Hallensleben, Marc G Besselink, Marie-Paule G F Anten, Thomas L Bollen, David W da Costa, Foke van Delft, Sven M van Dijk, Hendrik M van Dullemen, Marcel G W Dijkgraaf, Casper H J van Eijck, G Willemien Erkelens, Nicole S Erler, Paul Fockens, Erwin J M van Geenen, Janneke van Grinsven, Robbert A Hollemans, Jeanin E van Hooft, Rene W M van der Hulst, Jeroen M Jansen, Frank J G M Kubben, Sjoerd D Kuiken, Robert J F Laheij, Rutger Quispel, Rogier J J de Ridder, Marno C M Rijk, Tessa E H Römkens, Carola H M Ruigrok, Erik J Schoon, Matthijs P Schwartz, Xavier J N M Smeets, B W Marcel Spanier, Adriaan C I T L Tan, Willem J Thijs, Robin Timmer, Niels G Venneman, Robert C Verdonk, Frank P Vleggaar, Wim van de Vrie, Ben J Witteman, Hjalmar C van Santvoort, Olaf J Bakker, Marco J Bruno, on behalf of the Dutch Pancreatitis Study Group

Schepers
2020

Open-label, randomized, multicenter study, predicted severe gallstone AP, no cholangitis

232 patients

<24h


%
90
80
70
60
50
40
30
20
10
0
P<0.05
Death/complication
Cholangitis
Adverse events
ERCP<24h
Only if needed

Pain

The most important thing in the early treatment of acute pancreatitis is to avoid local and systemic complications.

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Gut

2020

Design and validation of a patient-reported outcome measure scale in acute pancreatitis: the PAN-PROMISE study

Enrique de-Madaria ,[1] Claudia Sánchez-Marin,[1,2] Irene Carrillo,[3] Santhi Swaroop Vege,[4] Serge Chooklin ,[5] Andriy Bilyak,[5] Rafael Mejuto,[6] Violeta Mauriz,[6] Peter Hegyi ,[7,8] Katalin Márta,[7,8] Ayesha Kamal ,[9] Eugenia Lauret-Braña,[10] Sorin T Barbu,[11] Vitor Nunes,[12] M Lourdes Ruiz-Rebollo,[13] Guillermo García-Rayado,[14] Edgard E Lozada-Hernandez,[15] Jorge Pereira,[16] Ionut Negoi,[17] Silvia Espina,[18] Marcus Hollenbach ,[19] Andrey Litvin,[20] Federico Bolado-Concejo,[21] Rómulo D Vargas,[22] Isabel Pascual-Moreno,[23] Vikesh K Singh,[9] José J Mira[3,24]

Each item is scored from 0 to 10. Ask for the worst score in the last 24h (0 none, 10: the highest possible intensity)

English

1. Pain, especially in the abdomen, chest or back
2. Abdominal distention (bloating, sensation of excess gas)
3. Difficulty eating, sensation of food being stuck in the stomach
4. Difficulty with bowel movements (constipation or straining on bowel movements)
5. Nausea and/or vomiting
6. Thirst
7. Weakness, lack of energy, fatigue, difficulty moving

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Pain

Paracetamol
Mild pain Combination with NSAIDs
Excellent safety profile
Paracetamol 1g/6 to 8h IV

Pandanaboyana et al, Current Op Gastroenterol 2022

190 patients

Predicted severe AP

Conventional treatment		**IV parecoxib 3 days + oral celecoxib 7 days**	
40%	Severe AP	20%	p<0.01
34%	Local complications	19%	p<0.05

Parecoxib required less meperidine

Huang, Am J Gastro 2020

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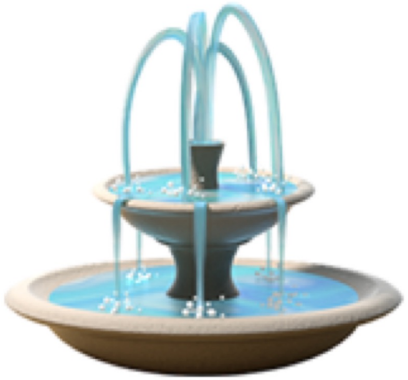
Aggressive fluid therapy does not improve efficacy outcomes and is associated with fluid overload

Lactated Ringer may have some advantages



Conclusions

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Acute pancreatitis

Patient feels able to eat

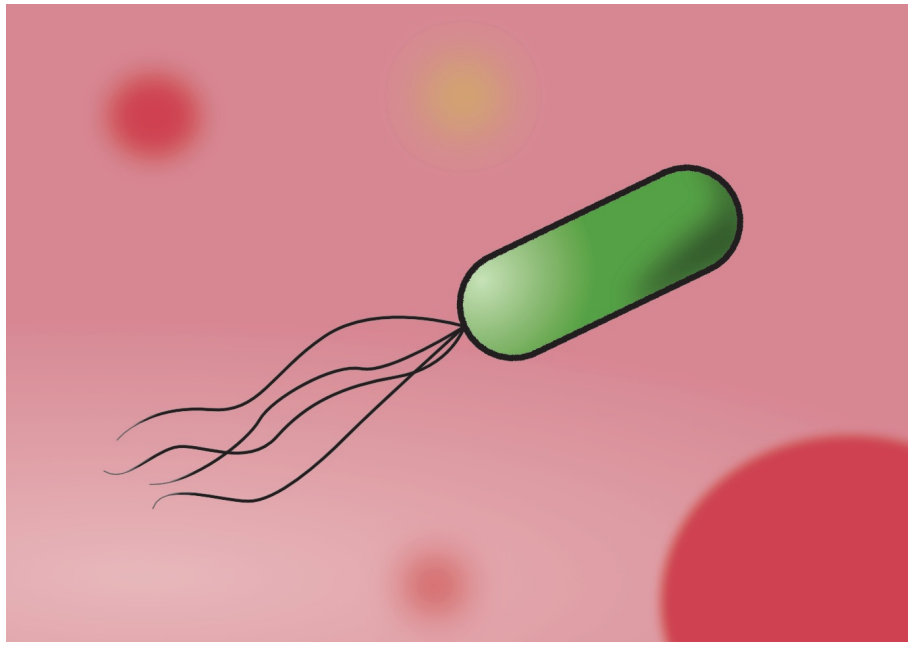
Sedation

Nasogastric or nasojejunal tube feeding

Oral feeding

Not tolerated on day 4th

Conclusions



Prophylactic antibiotics are useless
Procalcitonin seems useful to start and stop antibiotics

Conclusions

Infected pancreatic necrosis

Conservative management 1st 4 weeks (if unstable: percutaneous drainage, otherwise wait)

>4 weeks: if infection persists, proceed to endoscopic or percutaneous drainage
If not controlled, endoscopic necrosectomy or VARD
Endoscopic approach is slightly better

Conclusions

No benefit for early ERCP in absence of cholangitis

Conclusions

PAN-PROMISE scale

More studies needed to know the best guidelines for pain management

Conclusions

Massachusetts General Hospital
Founding Member, Mass General Brigham

Minimally Invasive and Novel Therapeutics (MINT) in Foregut Disease