

A Decade of Progress in Acute Pancreatitis: Key Developments and Implications for Patient Care

Virtual CME Saturday
Mercy Hospital of Buffalo
Buffalo, NY
September 25, 2021

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DEDICATED
TO THE
MEMORY
OF DR.
NOSRAT
ALIDOOST
(1944-2019)
AND HIS
LIFELONG
FRIENDSHIP
WITH DR.
REZA SAMIE

Conflicts of Interest

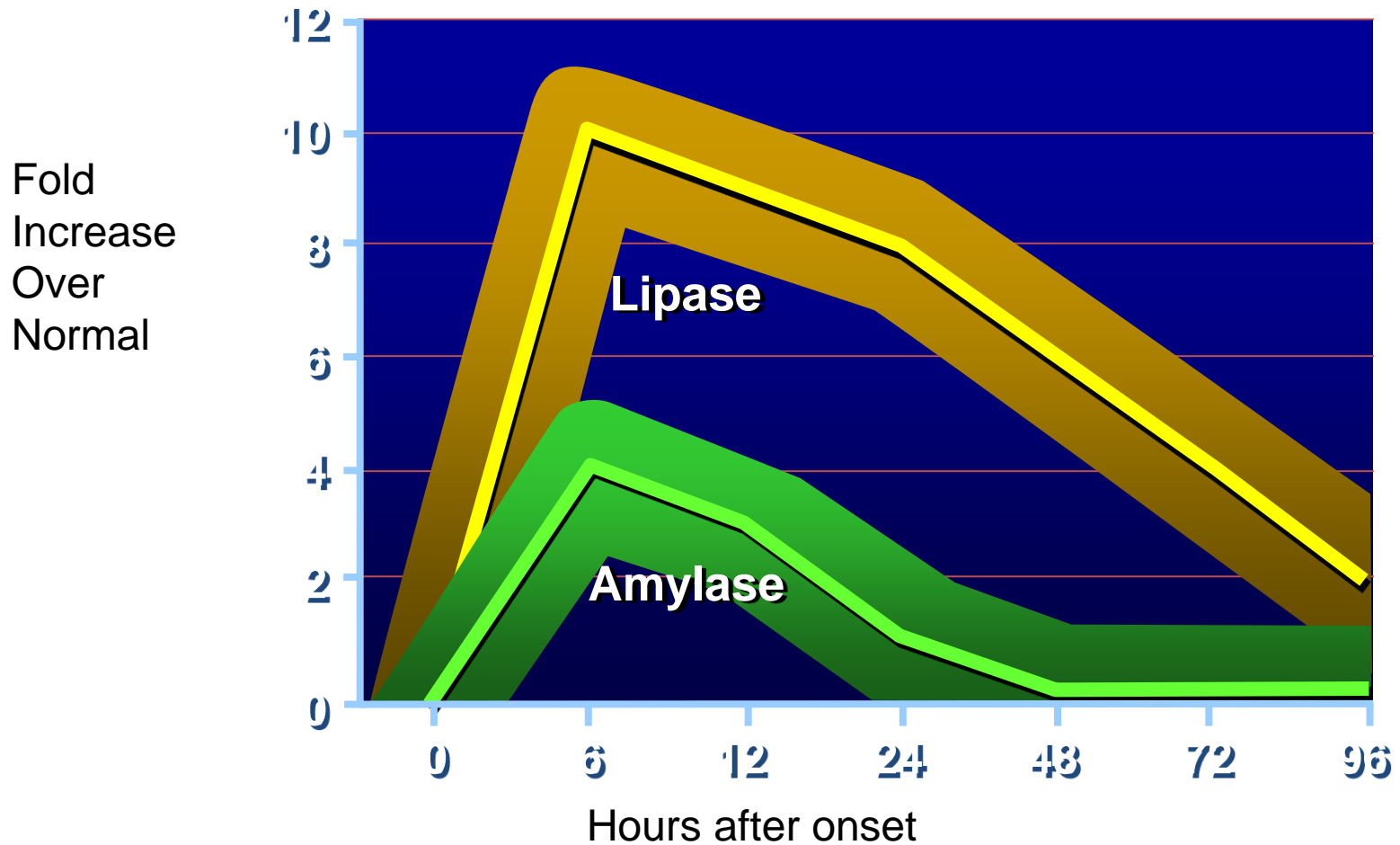
- Consultant to Abbvie
- Speaker for Nestle Health Science
- Advisory board participant for Envara
- Scientific advisory board for Kyttaro
- Grant funding from Abbvie, Orgenesis and Theraly

How do you diagnose acute
pancreatitis?

Diagnosis

- 2 out of the following 3:
 - Characteristic abdominal pain
 - Amylase and/or lipase levels 3 times the upper limit of normal
 - Reference range can vary by institution:
 - Upper limit of normal lipase is 63 (JHH) and 393 (JHBMC)
 - Imaging demonstrating changes of acute pancreatitis
 - Early presentation CT may show normal pancreas

Serum Levels of Pancreatic Lipase and Amylase Peak at 6 Hours After Onset of Symptoms



There are many nonpancreatic causes of amylase and lipase elevations

Chart 1 - Causes of elevation of amylase and lipase serum levels

Amylase	Lipase
Acute pancreatitis	Acute pancreatitis
Pseudopancreatic cyst	Pseudopancreatic cyst
Chronic pancreatitis	Chronic pancreatitis
Pancreatic carcinoma	Pancreatic carcinoma
Biliary tract disease (cholecystitis, cholangitis, choledocholithiasis)	Biliary tract disease (cholecystitis, cholangitis, choledocholithiasis)
Intestinal occlusion/subocclusion	Intestinal occlusion/subocclusion
Intestinal ischemia	Intestinal ischemia
Intestinal perforation	Intestinal inflammatory disease
Acute appendicitis	
Ectopic pregnancy	Renal insufficiency
Renal insufficiency (<50 ml/min)	Alcohol abuse
Parathyroiditis	Nervous bulimia/anorexia
Macroamylasemia	Malignant neoplasia
Ovarian cyst/ovarian neoplasia	Hepatitis C
Lung carcinoma	
Diabetic ketoacidosis	
HIV infection	
Intracranial trauma	

Adapted from: Forsmark CE, Baillie J; AGA Institute Clinical Practice and Economics Committee; AGA Institute Governing Board. AGA Institute technical review on acute pancreatitis. *Gastroenterology*. 2007;132(5):2022-44. Review.

HIV – Human immunodeficiency virus

REVIEW ARTICLE

Significant elevations of serum lipase not caused by pancreatitis: a systematic review

Ahmer M. Hameed¹, Vincent W. T. Lam^{1,2} & Henry C. Pleass^{1,2}

¹Department of Surgery, Westmead Hospital, Westmead, NSW, Australia and ²Discipline of Surgery, University of Sydney, Sydney, NSW, Australia

HPB (Oxford) 2015; 17: 99-112

Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Gianluca Rompianesi¹, Angus Hann², Oluyemi Komolafe³, Stephen P Pereira⁴, Brian R Davidson⁵, Kurinchi Selvan Gurusamy⁵

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Cochrane Database Syst Rev 2017: 4: CD012010

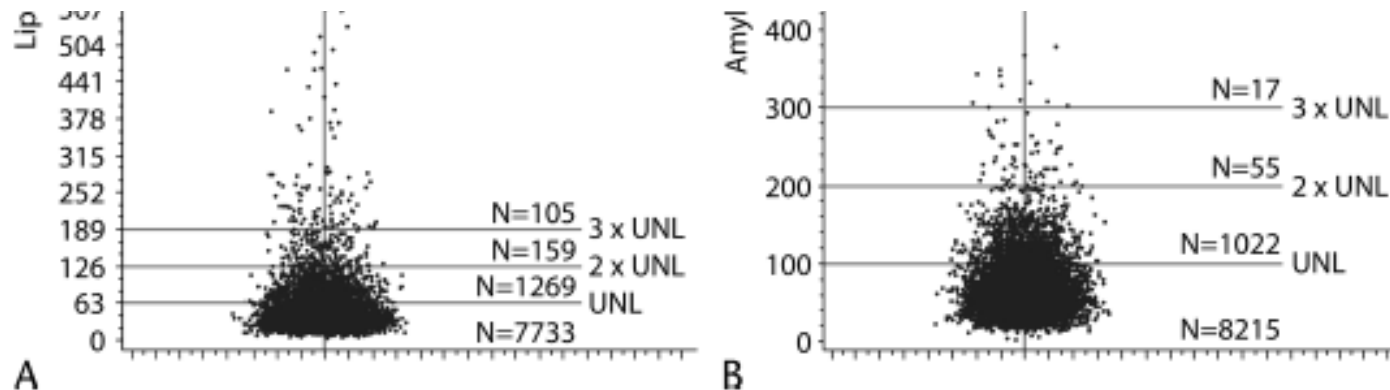
LEADER 3—Lipase and Amylase Activity in Subjects With Type 2 Diabetes

Baseline Data From Over 9000 Subjects in the LEADER Trial

William M. Steinberg, MD, Michael A. Nauck, MD,† Bernard Zinman, MD,‡ Gilbert H. Daniels, MD,§ Richard M. Bergenstal, MD,|| Johannes F.E. Mann, MD,¶ Lasse Steen Ravn, MD, PhD,# Alan C. Moses, MD,# Mette Stockner, MD,# Florian M.M. Baeres, MD,# Steven P. Marso, MD,** and John B. Buse, MD, PhD†† on behalf of the LEADER Trial investigators*



~25% of type 2 diabetics have amylase and/or lipase elevations in the absence of symptoms of acute pancreatitis



Amylase and Lipase Levels

- Only useful for DIAGNOSING acute pancreatitis
- Not useful for
 - Predicting severity of acute pancreatitis
 - Following response to treatment
 - Determining risk of complications

J Clin Gastroenterol 2002; 34: 459-62
Am J Gastroenterol 2002; 97: 1309-18

Lipase is Preferred over Amylase

Laboratory diagnosis of acute pancreatitis: in search of the Holy Grail

Giuseppe Lippi¹, Massimo Valentino², and Gianfranco Cervellin³

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Organization/s	Preferred biomarker	Diagnostic threshold	Reference
Société Nationale Française de Gastro-Entérologie	Lipase	≥ 3 times the URL	[56]
Japanese Society of Emergency Abdominal Medicine	Lipase	Not set	[57]
British Society of Gastroenterology; Association of Surgeons of Great Britain and Ireland, Pancreatic Society of Great Britain and Ireland, Association of Upper GI Surgeons of Great Britain and Ireland	Lipase	Value interpreted according to the time since the onset of symptoms	[59]
American of Gastroenterology	Lipase	≥ 2 to ≥ 4 times the URL	[10]
American Gastroenterological Association	Lipase	≥ 3 times the URL	[60]
American of Family Physicians	Lipase	Not set	[61]
Japanese Ministry of Health, Labour, and Welfare	Lipase	Not set	[62]
Working Group of the Italian Association for the Study of the Pancreas	Lipase	Not set	[63]

URL, upper limit of the reference interval.

Twenty Things Physicians and Patients Should Question

Do not test for amylase in cases of suspected acute pancreatitis. Instead, test for lipase.

Amylase and lipase are digestive enzymes normally released from the acinar cells of the exocrine pancreas into the duodenum. Following injury to the pancreas, these enzymes are released into the circulation. While amylase is cleared in the urine, lipase is reabsorbed back into the circulation. In cases of acute pancreatitis, serum activity for both enzymes is greatly increased.

Serum lipase is now the preferred test due to its improved sensitivity, particularly in alcohol-induced pancreatitis. Its prolonged elevation creates a wider diagnostic window than amylase. In acute pancreatitis, amylase can rise rapidly within 3–6 hours of the onset of symptoms and may remain elevated for up to five days. Lipase, however, usually peaks at 24 hours with serum concentrations remaining elevated for 8–14 days. This means it is far more useful than amylase when the clinical presentation or testing has been delayed for more than 24 hours.

Current guidelines and recommendations indicate that lipase should be preferred over total and pancreatic amylase for the initial diagnosis of acute pancreatitis and that the assessment should not be repeated over time to monitor disease prognosis. Repeat testing should be considered only when the patient has signs and symptoms of persisting pancreatic or peripancreatic inflammation, blockage of the pancreatic duct or development of a pseudocyst. Testing both amylase and lipase is generally discouraged because it increases costs while only marginally improving diagnostic efficiency compared to either marker alone.

Basnayake C, Ratnam D. Blood test for acute pancreatitis. *Aust Prescr.* Aug 2015;38:128-30.

Lankisch PG, Burchard-Reckert S, Lehnick D. Underestimation of acute pancreatitis: patients with only a small increase in amylase/lipase levels can also have or develop severe acute pancreatitis. *Gut.* Apr 1999;44(4):542-4.

Lippi, G, Valentino, M, Cervellini G. Laboratory diagnosis of acute pancreatitis: In search of the Holy Grail. *Crit Rev Clin Lab Sci.* Jan – Feb 2012; 49(1):18-21.

Shafiqet MA, Brown TV, Sharma R. Normal lipase drug-induced pancreatitis: a novel finding. *Am J Emerg Med.* Mar 2015; 33(3):476.e5-6.

Smith RC, Southwell-Keely J, Chesher D. Should serum pancreatic lipase replace serum amylase as a biomarker of acute pancreatitis? *ANZ J Surg.* Jun 2005;75(6):399-404.

Yadav D, Agarwal N, Pitchumoni CS. A critical evaluation of laboratory tests in acute pancreatitis. *Am J Gastroenterol.* Jun 2002;97(6):1309-18.

Viel JF, Foucault P, Bureau F, Albert A, Drosowsky MA. Combined diagnostic value of biochemical markers in acute pancreatitis. *ClinChimActa.* 1990;189(2):191-198.

Teachable Moment | LESS IS MORE

Unnecessary Repeat Enzyme Testing in Acute Pancreatitis

A Teachable Moment

Adam Reisman, BS; Hyung J. Cho, MD; Horatio Holzer, MD

In summary, lipase levels are unhelpful in monitoring patients with acute pancreatitis, do not correlate with disease severity, and should not be routinely repeated after a diagnosis is confirmed. Standardized scores such as the SIRS score can aid in prognosis and can also be used to monitor patients with acute pancreatitis.

Avoid early and excessive cross-sectional abdominal imaging

Imaging

- Increased utilization not associated with improved outcomes
- Early scan limitations
 - Don't pick up pancreatic necrosis
 - Infection uncommon in first week
- Reasons to obtain imaging
 - Clinical deterioration in first 72 hours
 - Unsure of diagnosis
 - Exclude alternative intraabdominal pathology

ORIGINAL ARTICLE

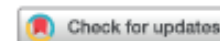
Early Abdominal Imaging Remains Over-Utilized in Acute Pancreatitis

David X. Jin¹ · Julia Y. McNabb-Baltar¹ · Shadeah L. Suleiman¹ · Bechien U. Wu² · Ramin Khorasani³ · Thomas L. Bollen⁴ · Peter A. Banks¹ · Vikesh K. Singh⁵

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ORIGINAL ARTICLE



Persistent SIRS and acute fluid collections are associated with increased CT scanning in acute interstitial pancreatitis

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What is Severe Acute Pancreatitis?

What has a Greater Impact on Mortality?: Persistent Organ Failure or Infected Pancreatic Necrosis

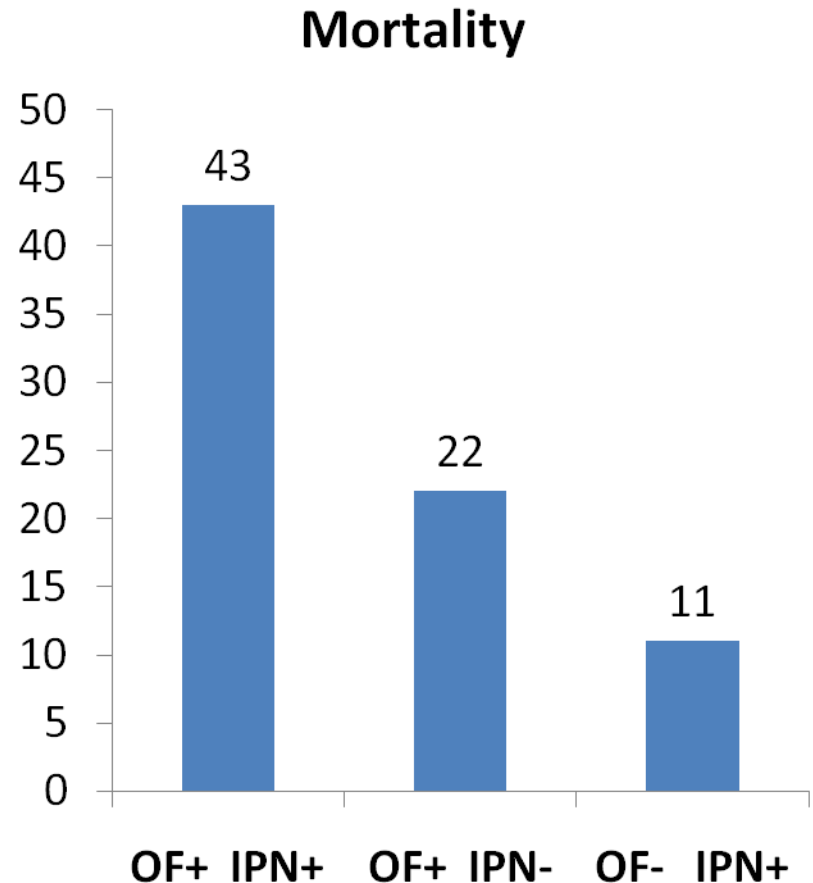


Organ Failure and Infection of Pancreatic Necrosis as Determinants of Mortality in Patients With Acute Pancreatitis

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- Systematic review
- 14 studies between 1993-2009 with 1,478 patients with NP
- 179 out of 600 OF (\pm IPN) patients died (mortality 30%)
- 102 out of 314 IPN (\pm OF) patients died (mortality 32%)



Conclusion

‘In patients with acute pancreatitis, the absolute influence of OF and IPN on mortality is comparable and thus the presence of either indicates severe disease. The relative risk of mortality doubles when OF and IPN are both present and indicates extremely severe disease or critical acute pancreatitis’

Persistent Organ Failure and/or Infected Necrosis Define Severe Acute Pancreatitis

Classification	Criteria
Atlanta Classification 1992	
Mild	No organ failure and no local complications
Severe	Organ failure and/or local complications
Revised Atlanta Classification 2007 (published 2013)	
Mild	No organ failure and no local or systemic complications
Moderate	Transient organ failure and/or local complications
Severe	Persistent organ failure
Determinant-Based Classification 2012	
Mild	No (peri)pancreatic necrosis and no organ failure
Moderate	Sterile necrosis and/or transient organ failure
Severe	Infected necrosis or persistent organ failure
Critical	Infected necrosis and persistent organ failure

Persistent Organ Failure Greater
Impact on Mortality than Infected
Necrosis

High Mortality Associated with Persistent Organ Failure in Multivariable Analyses of Large Prospective Studies

- 447 patients with NP between 2009-2012
- Mortality was 13% overall, 15% sterile necrosis and 18% infected necrosis
- Adjusted OR for mortality:
 - POF 16.7
 - ASA class 3.56,
 - Bacteremia 2.76
 - Age 1.07
- 731 patients with AP, 154 NP, 98 IPN between 2004-2007
- Overall mortality 8.3%
- Adjusted OR for mortality:
 - POF 18
 - Bacteremia 3.42
 - Age 1.05

Infected Pancreatic Necrosis is
Associated with No to Low Mortality in
the Absence of Persistent Organ
Failure

The Atlanta Classification, Revised Atlanta Classification, and Determinant-Based Classification of Acute Pancreatitis

Which Is Best at Stratifying Outcomes?

Vivek Kadiyala, MD,* Shadeah L. Suleiman, BS,* Julia McNabb-Baltar, MD,* Bechien U. Wu, MD, MPH,†
Peter A. Banks, MD,* and Vikesh K. Singh, MD, MSc‡

	n	Mortality, n (%)
All patients, N	338	14 (4.1)
No OF*	255	0 (0)
Interstitial pancreatitis	242	0 (0)
Sterile necrosis	10	0 (0)
Infected necrosis	3	0 (0)
Transient OF*	40	3 (7.5) [†]
Interstitial pancreatitis	33	3 (9.1) [†]
Sterile necrosis	5	0 (0)
Infected necrosis	2	0 (0)
Persistent OF*	43	11 (25.6)
Interstitial pancreatitis	27	4 (14.8)
Sterile necrosis	14	6 (42.9)
Infected necrosis	2	1 (50.0)
Single system	27	2 (7.4) [†]
Multisystem	16	9 (56.3) [‡]

Primary and Secondary Organ Failures Cause Mortality Differentially in Acute Pancreatitis and Should be Distinguished

Rajesh Kumar Padhan, MD, DM, Saransh Jain, MD, DM,* Samagra Agarwal, MBBS,* Suresh Harikrishnan, MD, DM,* Padmaprakash Vadiraja, MD, DM,* Sanatan Behera, MD, DM,* Sushil Kumar Jain, MD, DM,* Rajan Dhingra, MD, DM,* Nihar Ranjan Dash, MS,† Peush Sahni, MS, PhD,‡ and Pramod Kumar Garg, MD, DM**

	All Patients (n = 614)		Patients With IPN (n = 283)		
	OF Present n = 274	OF Absent n = 340	OF Present n = 208		OF Absent n = 75
			Primary OF n = 111	Secondary OF n = 97	
Mortality	39.4%*	0.08%*	49.5% ^{†‡}	36% ^{†‡}	4% [‡]

* $P < 0.001$ (OF vs no OF).

[†] $P = 0.06$ (primary OF vs secondary OF).

[‡] $P < 0.001$ (primary or secondary OF vs no OF).

Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis

Nicolien J Schepers,¹ Olaf J Bakker,² Marc G Besselink,³ Usama Ahmed Ali,⁴ Thomas L Bollen,⁵ Hein G Gooszen,⁶ Hjalmar C van Santvoort,² Marco J Bruno,¹ for the Dutch Pancreatitis Study Group

- 639 patients with NP, 240 with OF (38%), 202 with IPN (32%)
- Mortality did not change based on time of onset and duration of persistent organ failure
- Mortality of OF alone was 44% (47/108), OF + IPN was 29% (38/132) and IPN without OF was 4% (3/70)
- Adjusting for age, sex, ASA class and CTSI:
 - HR for mortality was 1.9 (1.0, 3.5) for OF alone versus OF +IPN
 - HR for mortality was 17.9 (3.8,38.7) for OF + IPN versus IPN alone

What is Predicted Severe Acute
Pancreatitis?

Clinical Prognostic Scoring Systems

Clinical Score	First Validation Study, Year (Reference)	Country	Outcomes Predicted in the First Validation Study
Ranson score/criteria	Ranson et al, 1974 (5); Ranson and Pasternack, 1977 (6)	United States	Severity (death, ≥ 7 d in the intensive care unit)
Glasgow score/criteria	Blamey et al, 1984 (7)	United Kingdom	Severity (mortality, surgery, complications)
Simplified prognostic criteria	Agarwal and Pitchumoni, 1986 (8)	United States	Severity (complications)
APACHE II	Wilson et al, 1990 (9) Larvin and McMahon, 1989 (10)	United Kingdom	Severity, mortality
Japanese Severity Score (original)	Ogawa et al, 2002 (11)	Japan	Mortality
Logistic Organ Dysfunction Score	Halonen et al, 2002 (12)	Finland	Mortality
Multiple Organ Dysfunction Score	Halonen et al, 2002 (12)	Finland	Mortality
SOFA	Halonen et al, 2002 (12)	Finland	Mortality
SIRS score	Ogawa et al, 2002 (11)	Japan	Mortality, severity (Multiple Organ Dysfunction Score)
	Buter et al, 2002 (13)	United Kingdom	Mortality, severity (Multiple Organ Dysfunction Score)
APACHE III	Liu et al, 2003 (14)	United States	Mortality
BALI score	Spizer et al, 2006 (15)	United States	Mortality
Early Warning Score	Garcea et al, 2006 (16)	United Kingdom	Mortality, severity (Atlanta criteria)
Mortality Probability Model	Göçmen et al, 2007 (17)	Turkey	Mortality, severity (Atlanta criteria)
Panc 3 score	Brown et al, 2007 (18)	United States	Severity (Atlanta criteria)
Pancreatitis Outcome Prediction Score	Harrison et al, 2007 (19)	United Kingdom	Mortality
Simple Prognostic Score	Ueda et al, 2007 (20)	Japan	Mortality, severity (infection, organ failure)
SAPS	Göçmen et al, 2007 (17)	Turkey	Mortality, severity (Atlanta criteria)
BISAP	Wu et al, 2008 (4)	United States	Mortality
Harmless Acute Pancreatitis Score	Lankisch et al, 2009 (21)	Germany	Severity (necrosis, need for ventilation or dialysis, death)
Japanese Severity Score (revised)	Ueda et al, 2009 (22)	Japan	Mortality

APACHE = Acute Physiology and Chronic Health Evaluation; BISAP = Bedside Index of Severity in Acute Pancreatitis; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment; SIRS = Systemic Inflammatory Response Syndrome.

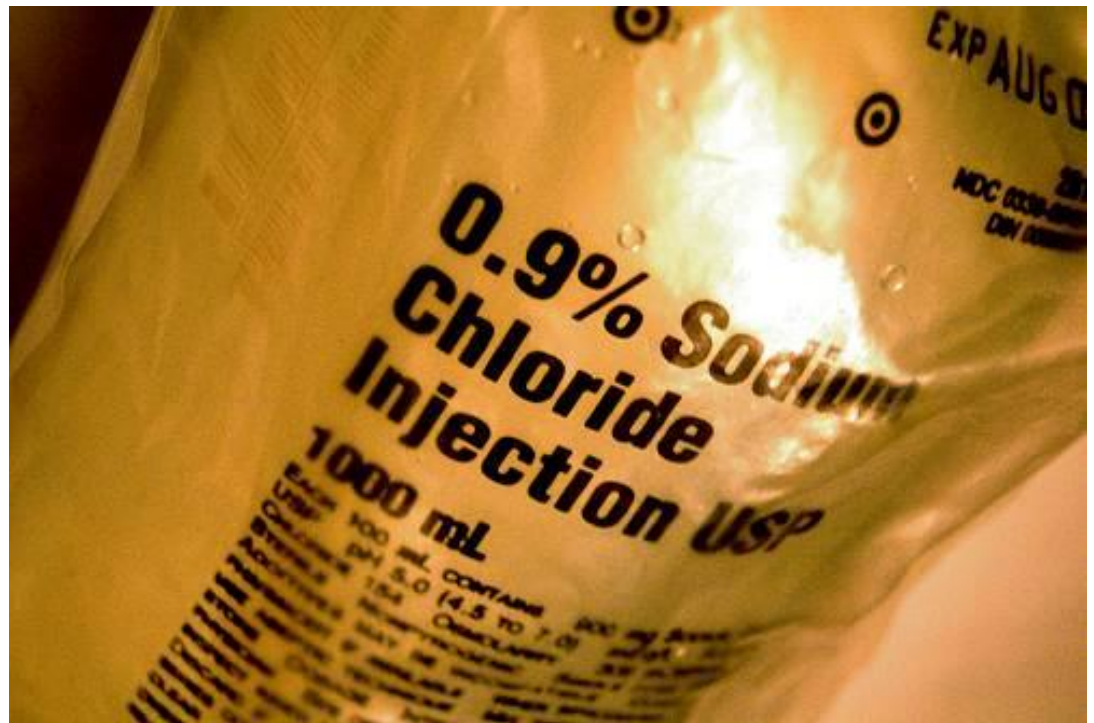
Predicted Severe Acute Pancreatitis Usually Ends up not being Severe Acute Pancreatitis!

Comparison of Existing Clinical Scoring Systems to Predict Persistent Organ Failure in Patients With Acute Pancreatitis

RAWAD MOUNZER,* CHRISTOPHER J. LANGMEAD,[‡] BECHIEN U. WU,[§] ANNA C. EVANS,* FARAZ BISHEHSARI,* VENKATA MUDDANA,* VIKESH K. SINGH,[§] ADAM SLIVKA,* DAVID C. WHITCOMB,* DHIRAJ YADAV,* PETER A. BANKS,[§] and GEORGIOS I. PAPACHRISTOU*[¶]

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	NPV	PPV
TRAINING COHORT (N=256)	85-95%	32-70%
VALIDATION COHORT (N=397)	94-99%	11-23%



Fluid Resuscitation

Aggressive Fluid Resuscitation Universally Recommended

Author	Journal	Initial fluid recommendation
IAP/APA	Pancreatology 2013	5-10 cc/kg/hr
Pandol S et al	Gastroenterology 2007	Severe: 500-1000cc/hr Moderate: 300-500 cc/hr Mild: 250-350 cc/hr
Forsmark C and Baillie J	Gastroenterology 2007	Vigorous fluid resuscitation Urine output >0.5ml/kg/hr
Whitcomb DC	N Engl J Med 2006	Fluid bolus to achieve hemodynamic stability + 250-500 ml/hr crystalloid
Banks PA and Freeman ML	Am J Gastroenterol 2006	Aggressive IV fluid
Vege SS et al	JAMA 2004	Aggressive fluid resuscitation
Tenner S	Am J Gastroenterol, 2004	At least 250-300 cc/h for 48 hr

Fluid Resuscitation

- **Current evidence: effects on outcome of aggressive fluid resuscitation (first 24-72 hours)**

Improved outcome

Brown 2002
Gardner 2009
Wall 2011
Warndorf 2011



Detrimental outcome

Eckerwall 2006
Mao 2007
Mao 2009
Mao 2010
de-Madaria 2011

What are the Problems with
Studies evaluating Fluid Therapy?

Fluid Study Flaw: Cause and Effect

Studies evaluating fluid resuscitation in the first 24-72 hours after admission, impossible to distinguish between:

**Retrospective Studies
Assume**

**Patients receiving aggressive
fluid resuscitation due to
worsening clinical status**

Patient with AP



Aggressive fluid resuscitation



SIRS, Necrosis, Oliguria, Hypotension,
Renal failure

Patient with AP

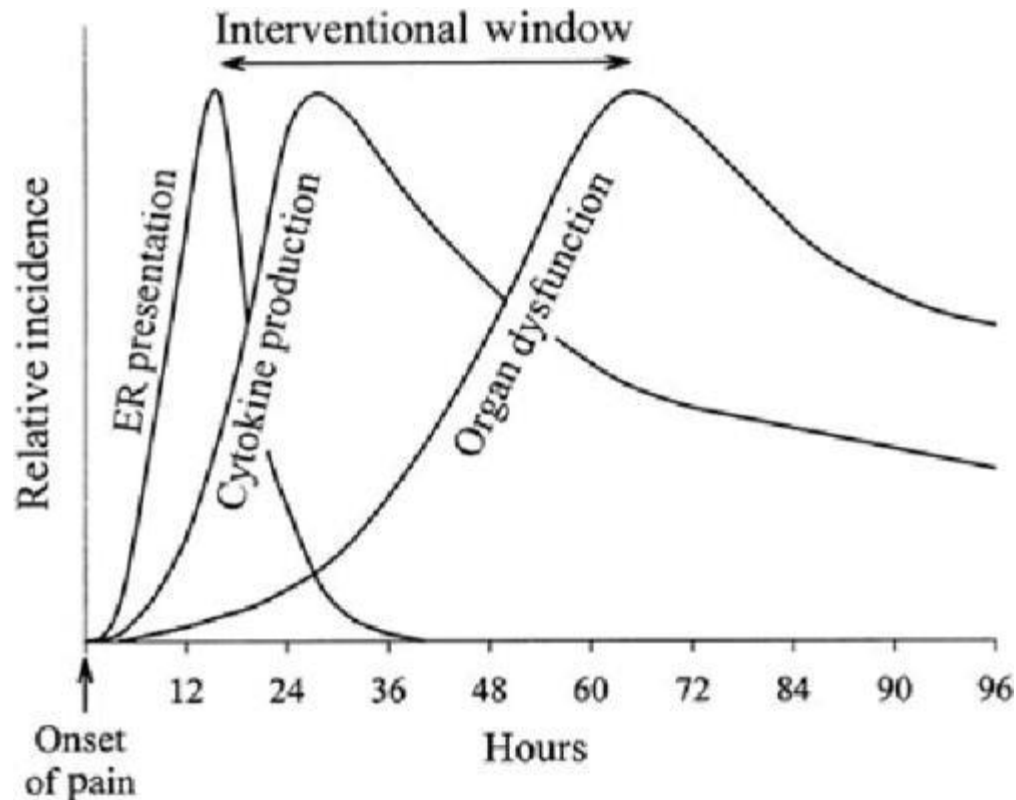


SIRS, Necrosis, Oliguria, Hypotension,
Renal failure

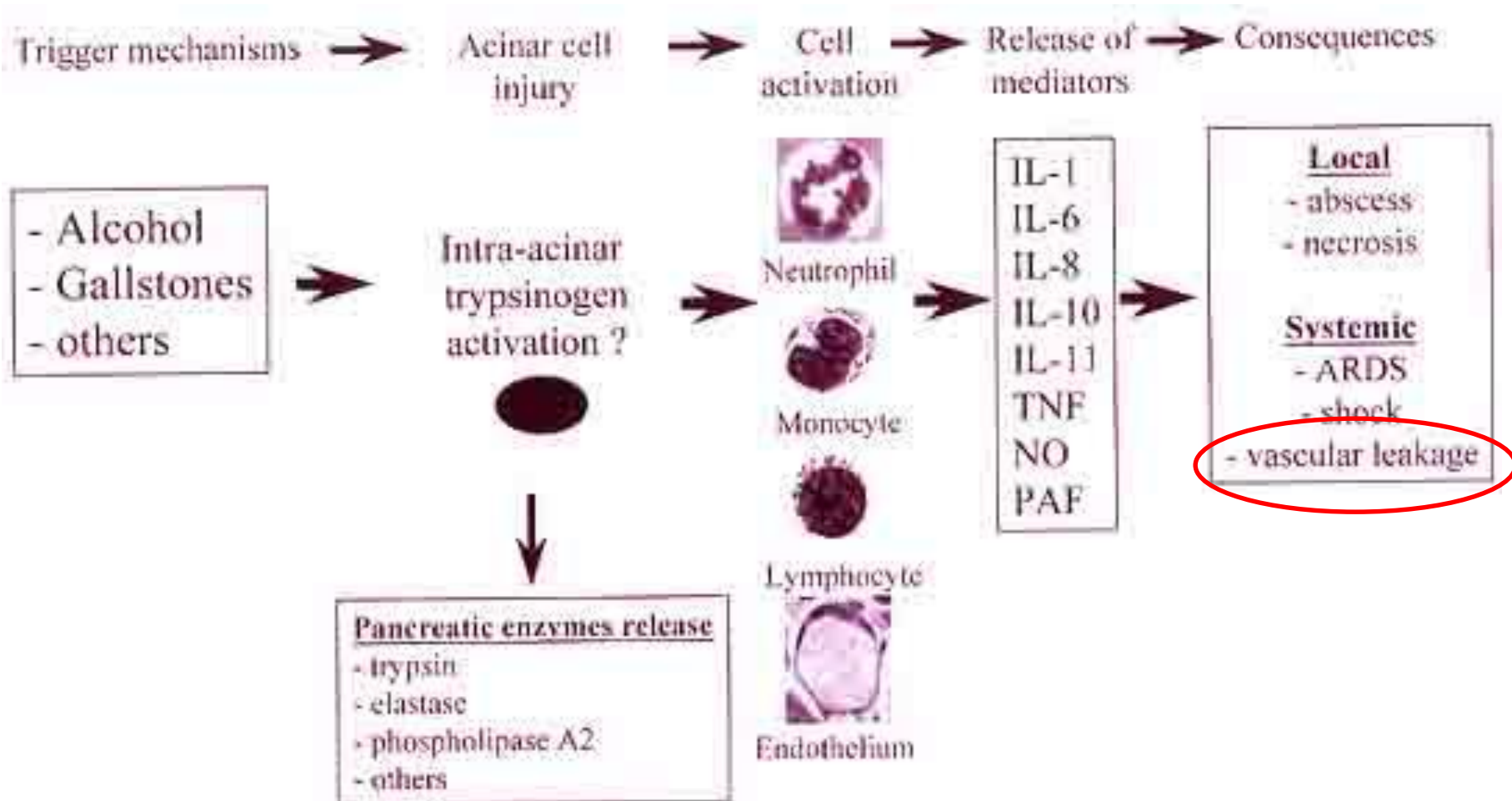


Aggressive fluid resuscitation

Fluid Therapy in AP: Are we Missing the Therapeutic Window?



Fluid Therapy Does not Fix Capillary Leak



What is the best evidence for fluid therapy in 2021?

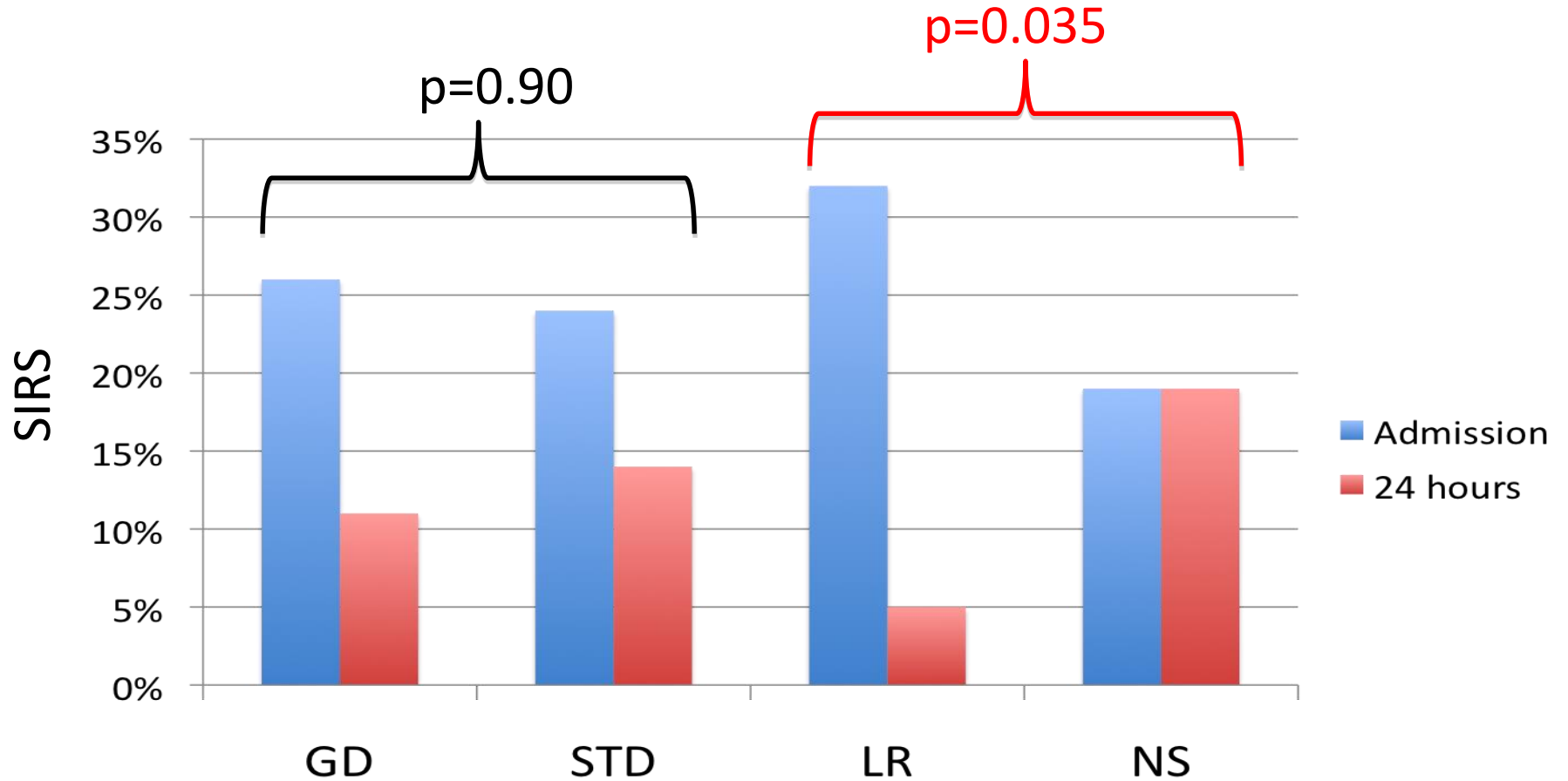
Lactated Ringer's Solution Reduces Systemic Inflammation Compared With Saline in Patients With Acute Pancreatitis

BECHIEN U. WU,* JAMES Q. HWANG,[‡] TIMOTHY H. GARDNER,[§] KATHRYN REPAS,* RYAN DELEE,[§] SONG YU,* BENJAMIN SMITH,^{||} PETER A. BANKS,* and DARWIN L. CONWELL*

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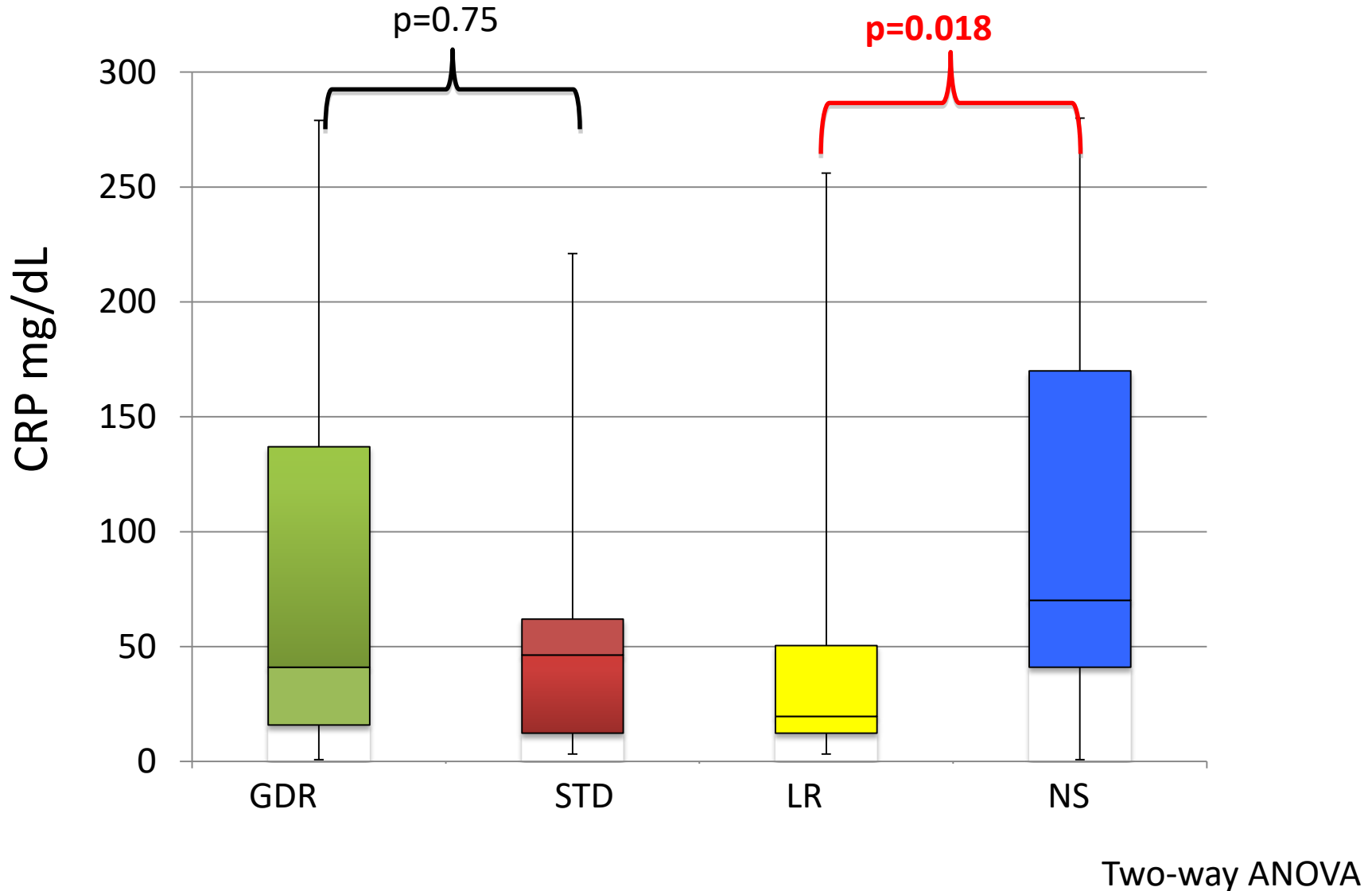
Primary Endpoint: n=40

LR reduced SIRS at 24 hours



Two-way anova

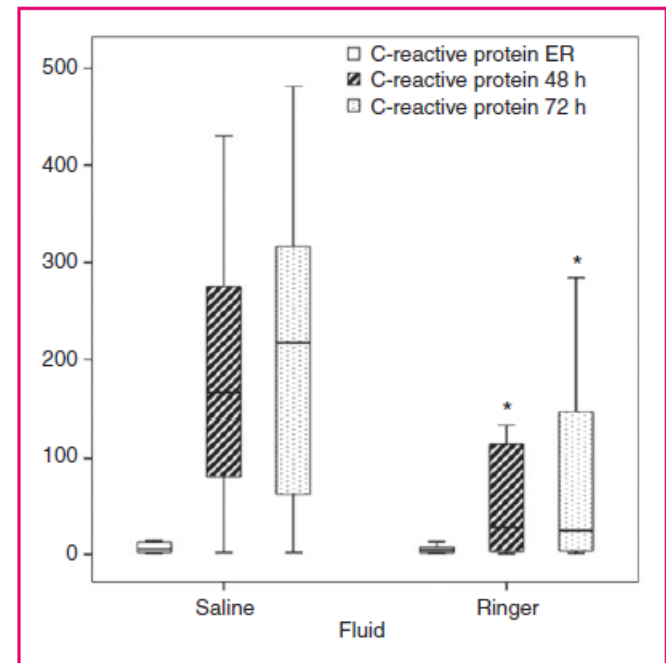
Secondary Endpoint: LR had lower CRP at 24 hours



Fluid resuscitation with lactated Ringer's solution vs normal saline in acute pancreatitis: A triple-blind, randomized, controlled trial

Enrique de-Madaria¹, Iván Herrera-Marante¹, Verónica González-Camacho², Laia Bonjoch³, Noé Quesada-Vázquez¹, Isabel Almenta-Saavedra¹, Cayetano Miralles-Maciá¹, Nelly G Acevedo-Piedra¹, Manuela Roger-Ibáñez¹, Claudia Sánchez-Marin¹, Rosa Osuna-Ligero¹, Ángel Gracia⁴, Pere Llorens², Pedro Zapater⁵, Vikesh K Singh⁶, Rocío Moreu-Martín⁵ and Daniel Closa³

Time from randomization	Variable	Normal Saline	Lactated Ringer's solution	<i>p</i>
Basal	SIRSc	14 (66.7%)	9 (47.4%)	0.218
	SIRSn	2 (1-2)	1 (1-2)	0.181
24 hours	SIRSc	4 (19%)	4 (21.1%)	0.874
	SIRSn	1 (1-1)	0 (0-1)	0.147
48 hours	SIRSc	9 (42.9%)	3 (15.8%)	0.062
	SIRSn	1 (1-2)	1 (0-1)	0.060
72 hours	SIRSc	7 (33.3%)	3 (15.8%)	0.281
	SIRSn	1 (1-2)	0 (0-1)	0.064



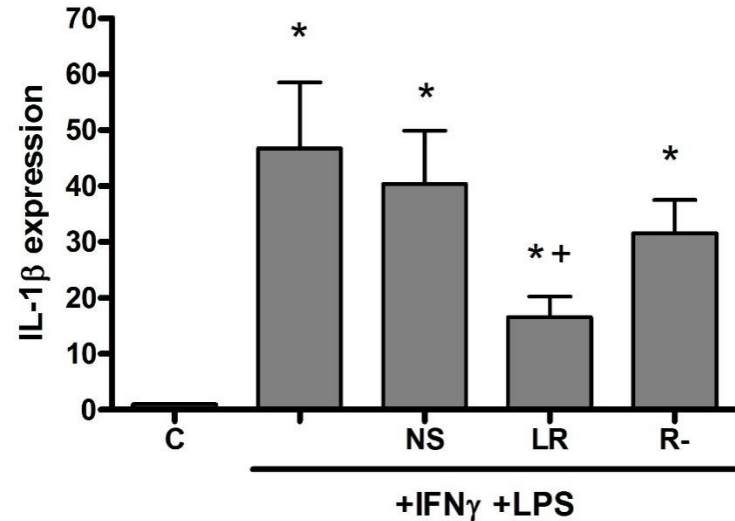
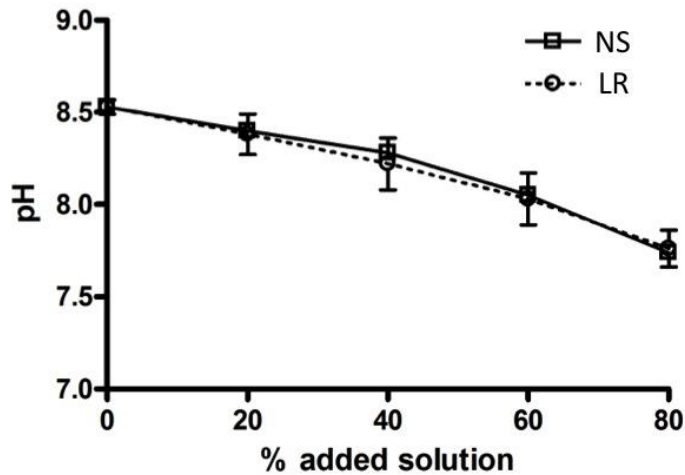
Normal Saline

- pH 5.5
- 154 mEq Na
- 154 mEq Cl

Lactated Ringer's

- pH 6.5
- 130 mEq Na
- 109 mEq Cl
- 28 mEq lactate
- 4 mEq K
- 3 mEq Ca

Lactated Ringer's does not Change pH but Inhibits Macrophages



Early Aggressive Hydration Hastens Clinical Improvement in Mild Acute Pancreatitis

James L. Buxbaum, MD¹, Michael Quezada, MD¹, Ben Da, MD¹, Niraj Jani, MD¹, Christianne Lane, PhD², Didi Mwendela, MD¹, Thomas Kelley, MD¹, Paul Jhun, MD³, Kiran Dhanireddy, MD⁴ and Loren Laine, MD^{5,6}

	20 cc/kg bolus then 3 cc/kg/hr Aggressive hydration (N=27)	10 cc/kg bolus then 1.5 c/kg/hr Standard hydration (N=33)	Adjusted odds ratio (95% CI)
Clinical Improvement within 36 h	19 (70%)	14 (42%)	7.0 (1.8–27.8)
Development of SIRS	4 (14.8%)	9 (27.3%)	0.14 (0.02–0.92)
Persistent SIRS	2 (7.4%)	7(21.2%)	0.12 (0.02–0.94)
Development of hemoconcentration	3 (11.1%)	12 (36.4%)	0.08 (0.01–0.49)

CI, confidence interval; SIRS, systemic inflammatory response syndrome.

Total Volume Administered in a Hypothetical 70 Kg Patient

FLUID STRATEGY	WEIGHT	FLUID TOTAL OVER 24 HOURS
AGGRESSIVE	70 KG	6.4 L
STANDARD	70 KG	3.2 L
MAINTENANCE	70 KG	2.5 L

Lactated Ringers vs Normal Saline Resuscitation for Mild Acute Pancreatitis: A Randomized Trial



Alice Lee,^{1,2} Christopher Ko,¹ Carlos Buitrago,¹ Brent Hiramoto,¹ Liam Hilson,¹ and James Buxbaum,¹ on behalf of the NS-LR Study Group

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10 cc/kg bolus followed by 3 cc/hr

	NS (n = 60) n (%)	LR (n = 61) n (%)	RR	Adjusted RR ^a
ICU admission	15 (25)	6 (9.8)	0.4 (0.2–0.9)	0.3 (0.1–0.9)
Moderate-severe pancreatitis	15 (25.0)	9 (14.8)	0.8 (0.4–1.4)	0.5 (0.2–1.1)
Local complications	9 (15)	4 (6.6)	0.4 (0.1–1.3)	0.3 (0.1–1.5)
Organ failure	9 (15)	7 (11.5)	0.8 (0.3–1.9)	1 (0.4–2.7)
Adverse events	0	1	—	—
Recurrent AP post-discharge	8 (13.1)	6 (10.0)	1.3 (0.5–3.6)	0.9 (0.4–2.0)
Hyperchloremia (Serum Cl > 108 mm/L) at 24 h	15 (25.4)	3 (5.6)	0.2 (0–0.6)	0.2 (0.1–0.6)

	NS (n = 60) n (%)	LR (n = 61) n (%)	RR	Adjusted RR ^b
SIRS 24 h	19 (32.2%)	21 (37.5%)	1.2 (0.7–1.9)	1.1 (0.7–1.6)
SIRS 48 h	18 (38.3%)	18 (41.9%)	1.1 (0.7–1.8)	1.0 (0.6–1.5)
SIRS 72 h	14 (32.6%)	11 (32.4%)	1.0 (0.5–1.9)	1.0 (0.5–1.8)

	NS Median (IQR)	LR Median (IQR)	P value
Length of hospitalization (d)	4.6 (3–7.4)	3.5 (2–5.9)	.049
Fluid administered in first 24 h following randomization (L)	5.8 (4.8–6.8)	6.0 (5.2–6.9)	.194

Response and outcome from fluid resuscitation in acute pancreatitis A Prospective Cohort Study

Tao Jin^{1,2,1}, Kun Jiang^{1,1}, Lihui Deng¹, Jia Guo¹, Yuwan Wu¹, Zhengyan Wang¹, Na Shi¹, Xiaoxin Zhang¹, Ziqi Lin¹, Varsha Asrani³, Peter Jones⁴, Anubhav Mittal⁵, Anthony Phillips⁶, Robert Sutton², Wei Huang^{1,2}, Xiaonan Yang¹, Qing Xia¹ & John A. Windsor⁷

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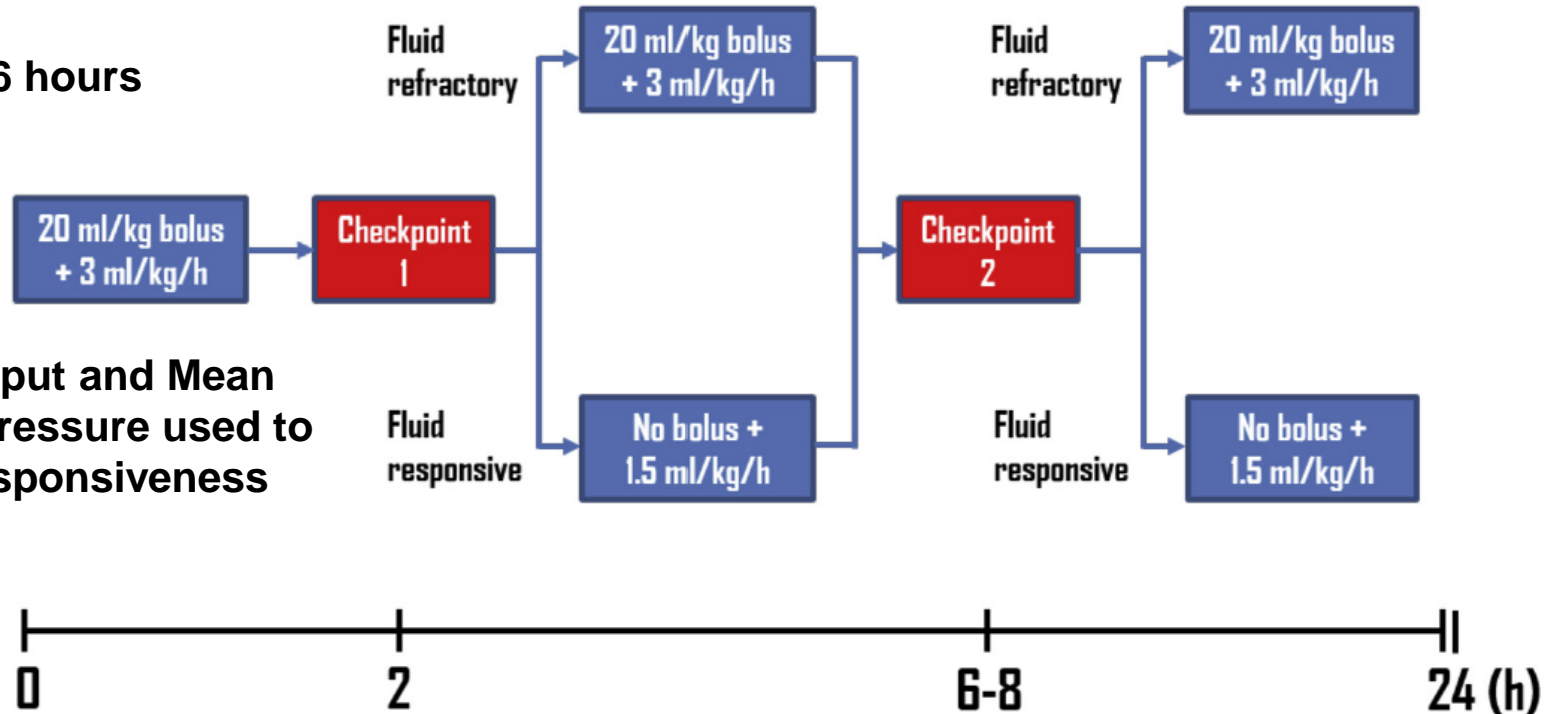
Inclusion

Criteria:

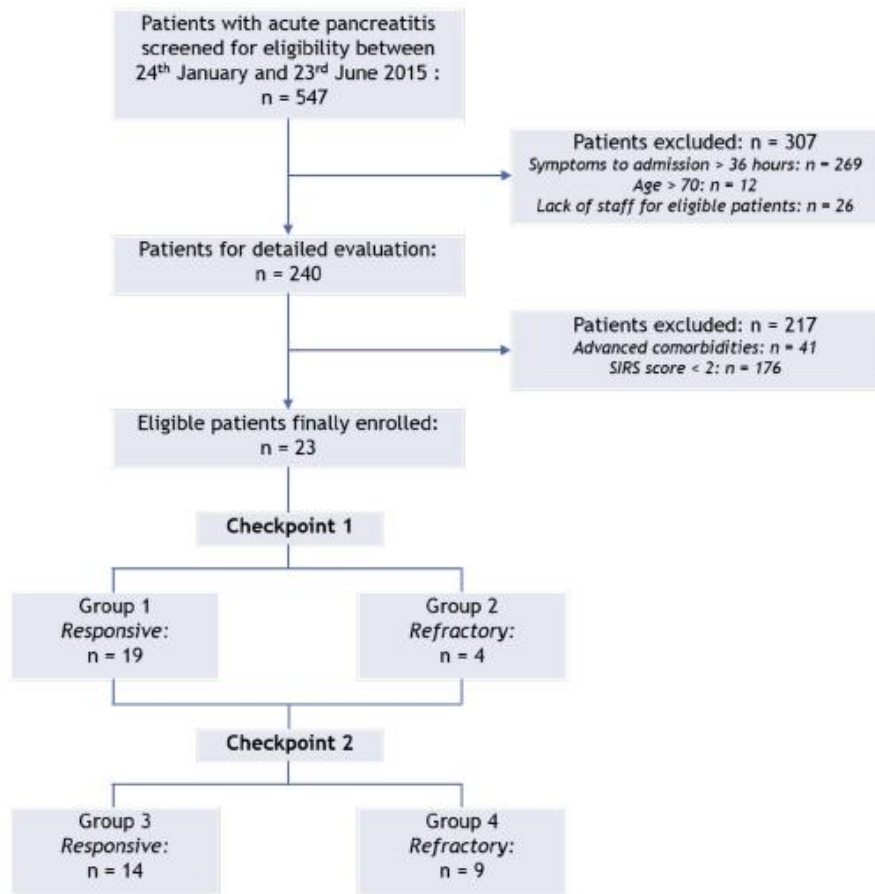
Pain <36 hours

SIRS \geq 2

Urine Output and Mean Arterial Pressure used to assess responsiveness



Urine output and mean arterial pressure were inadequate to assess which patients need more fluid



- Group 4 (compared to group 3) had higher rates of persistent OF, necrosis and infected necrosis, extrapancreatic infections, need for surgery, need for ICU and mortality
- Additional fluid therapy did not change outcome

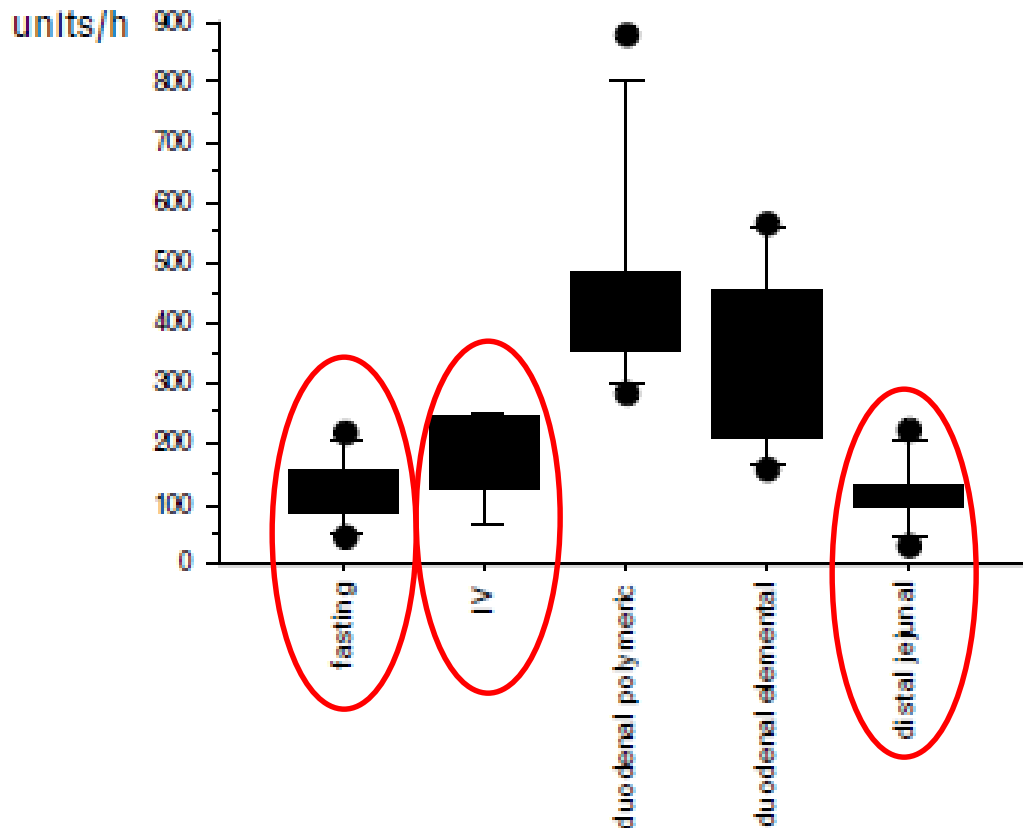


NUTRITION

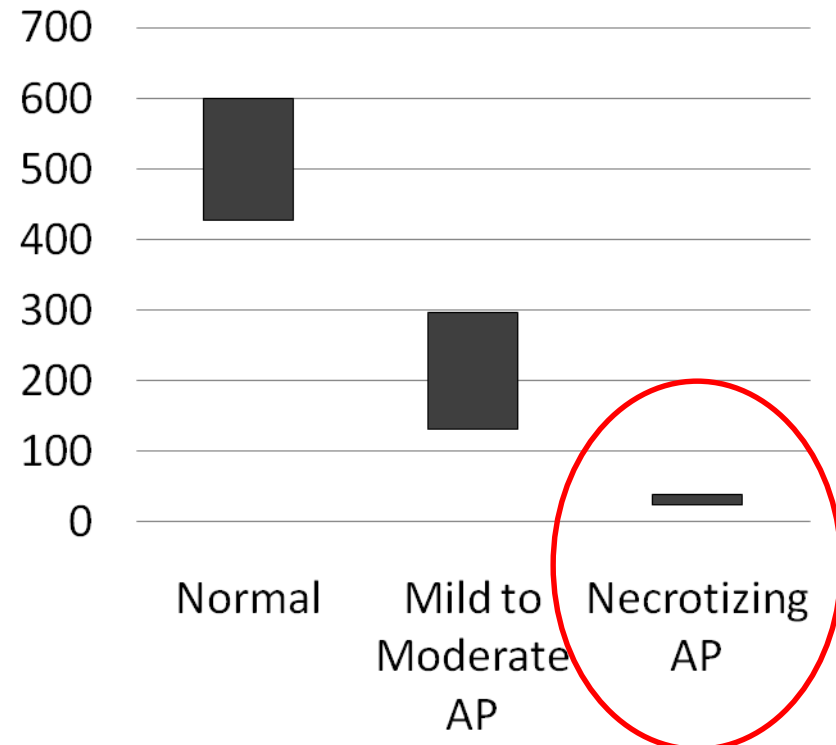
Try oral, if possible, first and this can be solid low fat, low residue. If patient does not tolerate, NG or NJ. Start as soon as possible but preferably within the first few days of hospitalization.

Distal Enteral Feeding and Acute Necrotizing Pancreatitis are Associated with Lowest Trypsin Secretion Rates

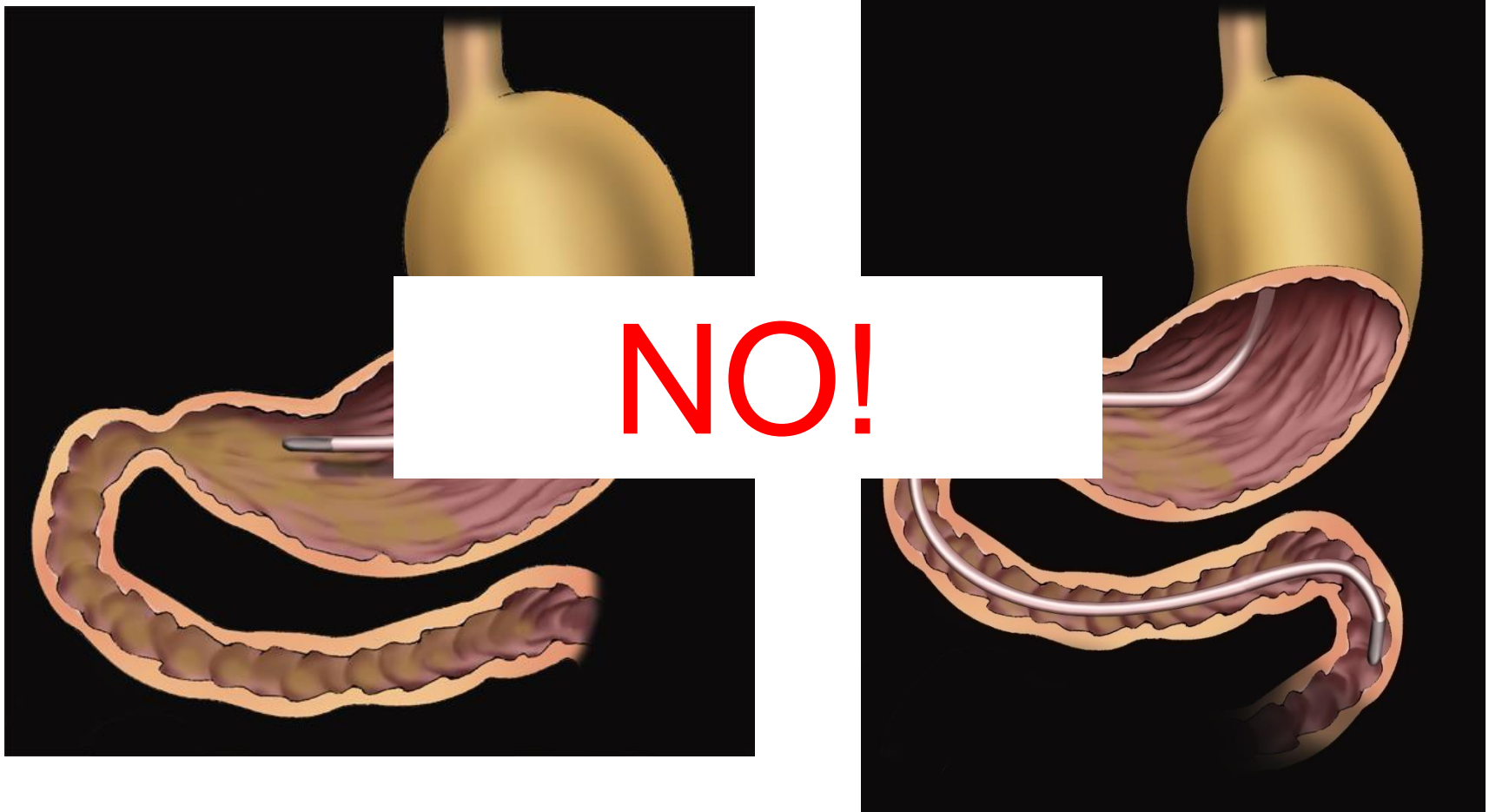
Normal Individuals



Duodenal Trypsin Secretion Rates (units/h)



Does Route of Enteral Feeding in Severe Acute Pancreatitis Matter?



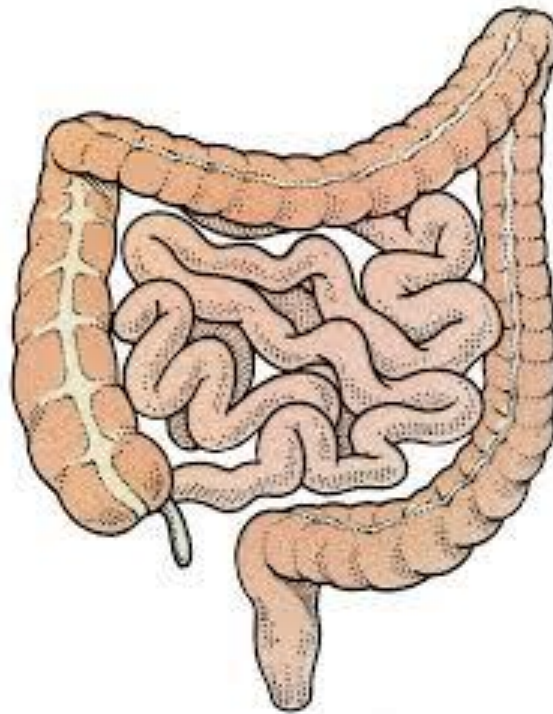
Eatock FC et al. Am J Gastroenterol 2005; 100: 432-9.

Kumar A et al. J Clin Gastroenterol 2006; 40: 431-34.

Singh N et al. Pancreas 2012; 41: 153-59

Gut Barrier Dysfunction in Severe Acute Pancreatitis

Decreased
Microcirculation
(Ischemic/Reperfusion
Injury)

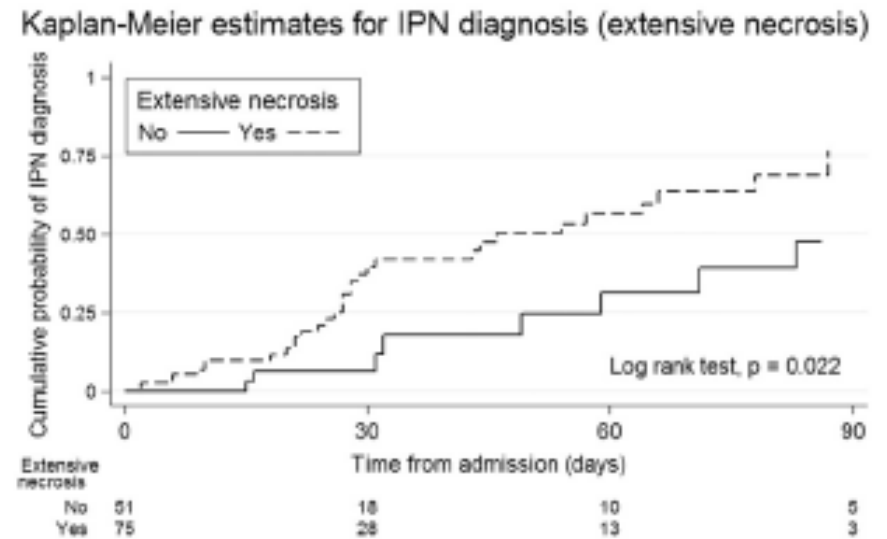
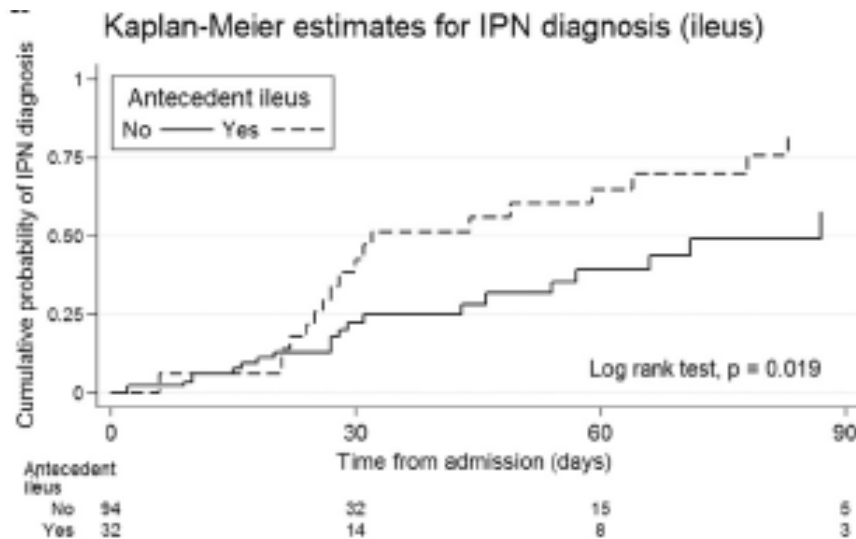


Increased Intestinal
Permeability

Impaired Intestinal
Motility
(Enteric Bacterial
Colonization and
Overgrowth)

Ileus is a predictor of local infection in patients with acute necrotizing pancreatitis

Robert A. Moran ^{a, b}, Niloofar Y. Jalaly ^b, Ayesha Kamal ^b, Sandesh Rao ^c, Robert Klapheke ^c, Theodore W. James ^c, Swetha Kambhampati ^c, Martin A. Makary ^d, Kenzo Hirose ^d, Vivek Kumbhari ^b, Ellen M. Stein ^{a, b}, Mouen A. Khashab ^b, Anne Marie Lennon ^b, Anthony N. Kalloo ^{a, b}, Atif Zaheer ^{a, e}, Ruben Hernaez ^b, Vikesh K. Singh ^{a, b, *}



Nutrition in Severe Acute Pancreatitis

- Enteral nutrition is superior to parenteral nutrition
 - Preserves gut barrier which prevents bacterial translocation
 - Associated with less mortality, organ failure, and infection

Al-Omran M, et. al. Cochrane Database Syst Rev 2010; 1: CD002837

Wu P, et. al. Bioscience Reports 2018; 1-9

Timing of Enteral Nutrition in Severe Acute Pancreatitis – the Earlier the Better!

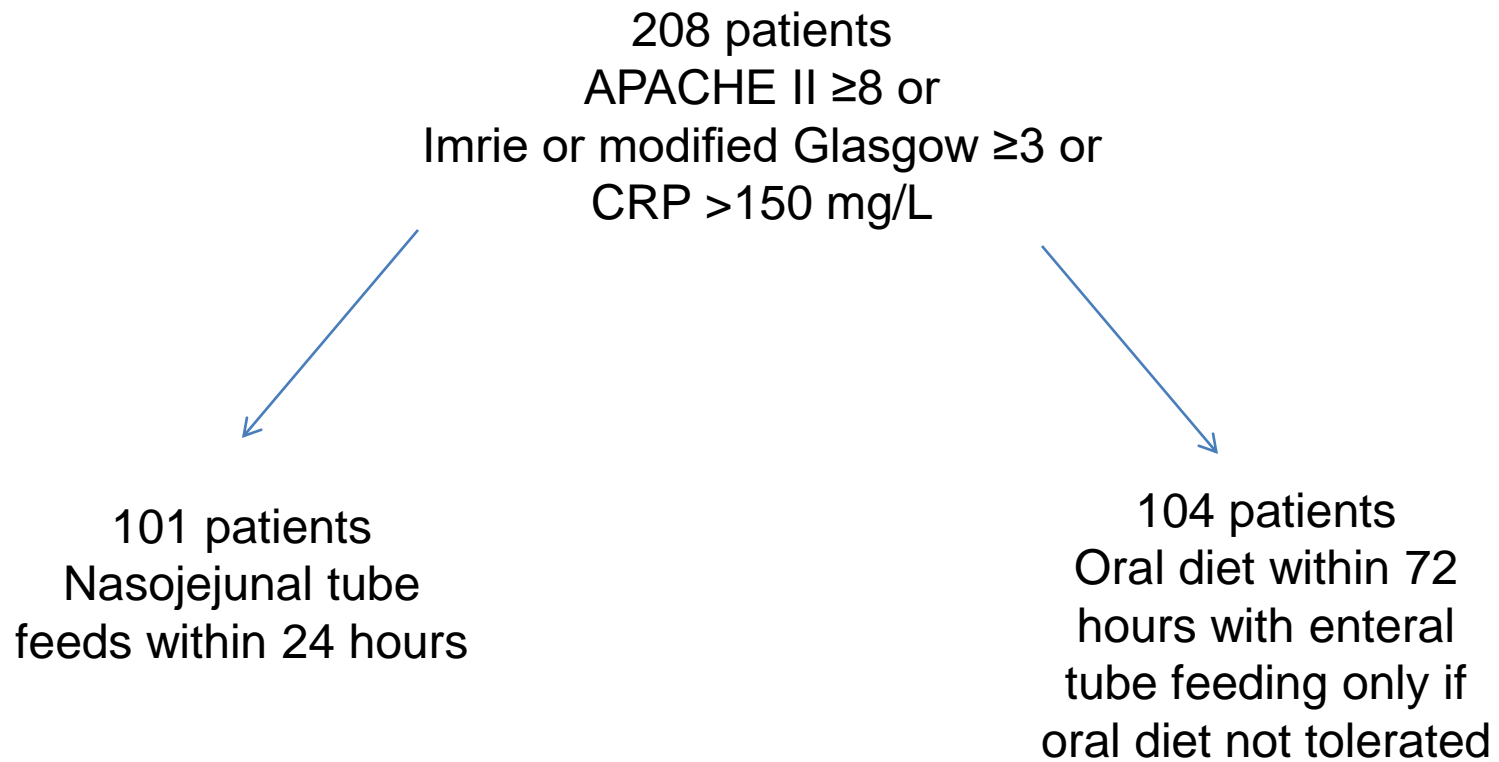
- Meta-analysis of 10 studies, 1051 patients with predicted or actual severe acute pancreatitis
 - Initiation of enteral nutrition <48 hours associated with less systemic and local infection, mortality, multiple OF, and operative intervention
- RCT of 197 patients with predicted severe acute pancreatitis
 - Initiation of nasojejunal tube feeding <48 hours associated with less mortality, infected necrosis, respiratory failure, and ICU

Song J et al. *Medicine* 2018; 97: 34(e11871)

Wereszczynska-Siemiatkowska U et al. *Pancreas* 2013; 42: 640-6.

Early versus On-Demand Nasoenteric Tube Feeding in Acute Pancreatitis

O.J. Bakker, S. van Brunschot, H.C. van Santvoort, M.G. Besselink, T.L. Bollen, M.A. Boermeester, C.H. Dejong, H. van Goor, K. Bosscha, U. Ahmed Ali, S. Bouwense, W.M. van Grevenstein, J. Heisterkamp, A.P. Houdijk, J.M. Jansen, T.M. Karsten, E.R. Manusama, V.B. Nieuwenhuijs, A.F. Schaapherder, G.P. van der Schelling, M.P. Schwartz, B.W.M. Spanier, A. Tan, J. Vecht, B.L. Weusten, B.J. Witteman, L.M. Akkermans, M.J. Bruno, M.G. Dijkgraaf, B. van Ramshorst, and H.G. Gooszen, for the Dutch Pancreatitis Study Group




Results

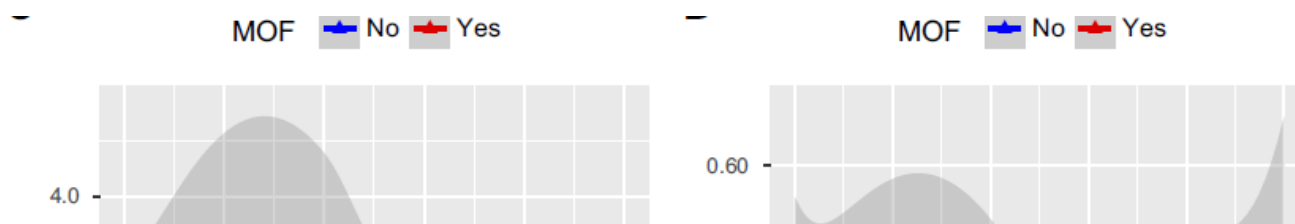
Table 2. Primary and Secondary End Points, According to the Intention-to-Treat Analysis.*

Outcome	Early Tube Feeding (N= 101)	On-Demand Tube Feeding (N= 104)	Risk Ratio (95% CI)	P Value
Primary composite end point: infection or death — no. (%)	30 (30)	28 (27)	1.07 (0.79–1.44)	0.76
Secondary end points				
Infection — 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
Bacteremia	17 (17)	18 (17)	0.98 (0.68–1.43)	1.00
Pneumonia	12 (12)	13 (12)	0.97 (0.63–1.50)	1.00
Death — no. (%)	11 (11)	7 (7)	1.27 (0.85–1.89)	0.33
Necrotizing pancreatitis — no. (%)‡	64 (63)	65 (62)	1.06 (0.77–1.47)	0.76
CT severity index§	4±2	4±3	—	0.29
ICU admission after randomization — no. (%)	18 (18)	20 (19)	0.95 (0.66–1.38)	0.86
Mechanical ventilation — no. (%)	12 (12)	14 (13)	0.93 (0.60–1.44)	0.84
New-onset organ failure — no./total no. at risk (%)¶				
Single organ failure	26/67 (39)	31/73 (42)	0.92 (0.65–1.32)	0.73
Persistent single organ failure	10/67 (15)	10/73 (14)	1.05 (0.65–1.70)	1.00
Multiple organ failure	7/67 (10)	6/73 (8)	1.14 (0.67–1.95)	0.77
Persistent multiple organ failure	4/67 (6)	4/73 (5)	1.05 (0.51–2.14)	1.00

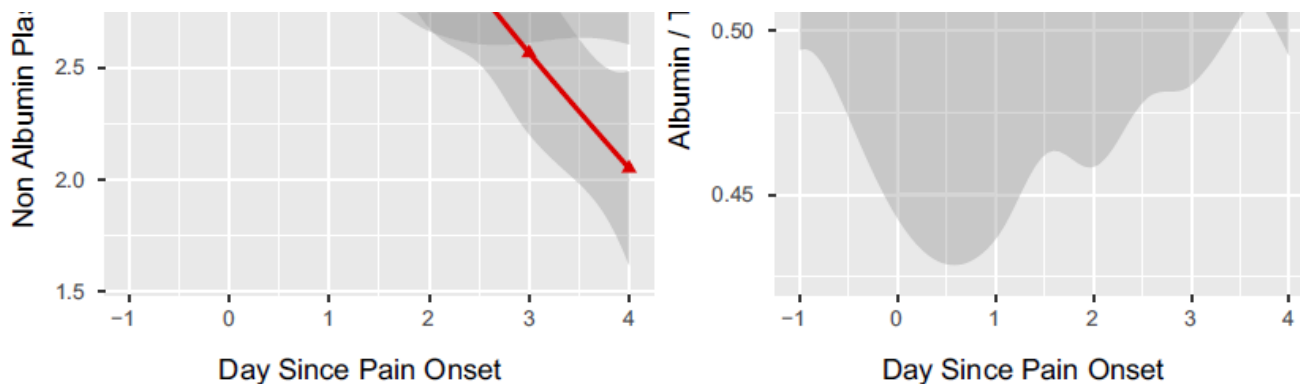
Severe acute pancreatitis: capillary permeability model linking systemic inflammation to multiorgan failure

Nicole L. Komara,^{1*} Pedram Paragomi,^{1*} Phil J. Greer,¹ Anette S. Wilson,¹ Cameron Breze,² Georgios I. Papachristou,¹ and  David C. Whitcomb^{1,3,4}

¹Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; ²Ariel Precision Medicine, Pittsburgh, Pennsylvania; ³Departments of Cell Biology and Molecular Physiology, University of Pittsburgh, Pittsburgh, Pennsylvania; and ⁴Department of Human Genetics, University of Pittsburgh, Pittsburgh, Pennsylvania

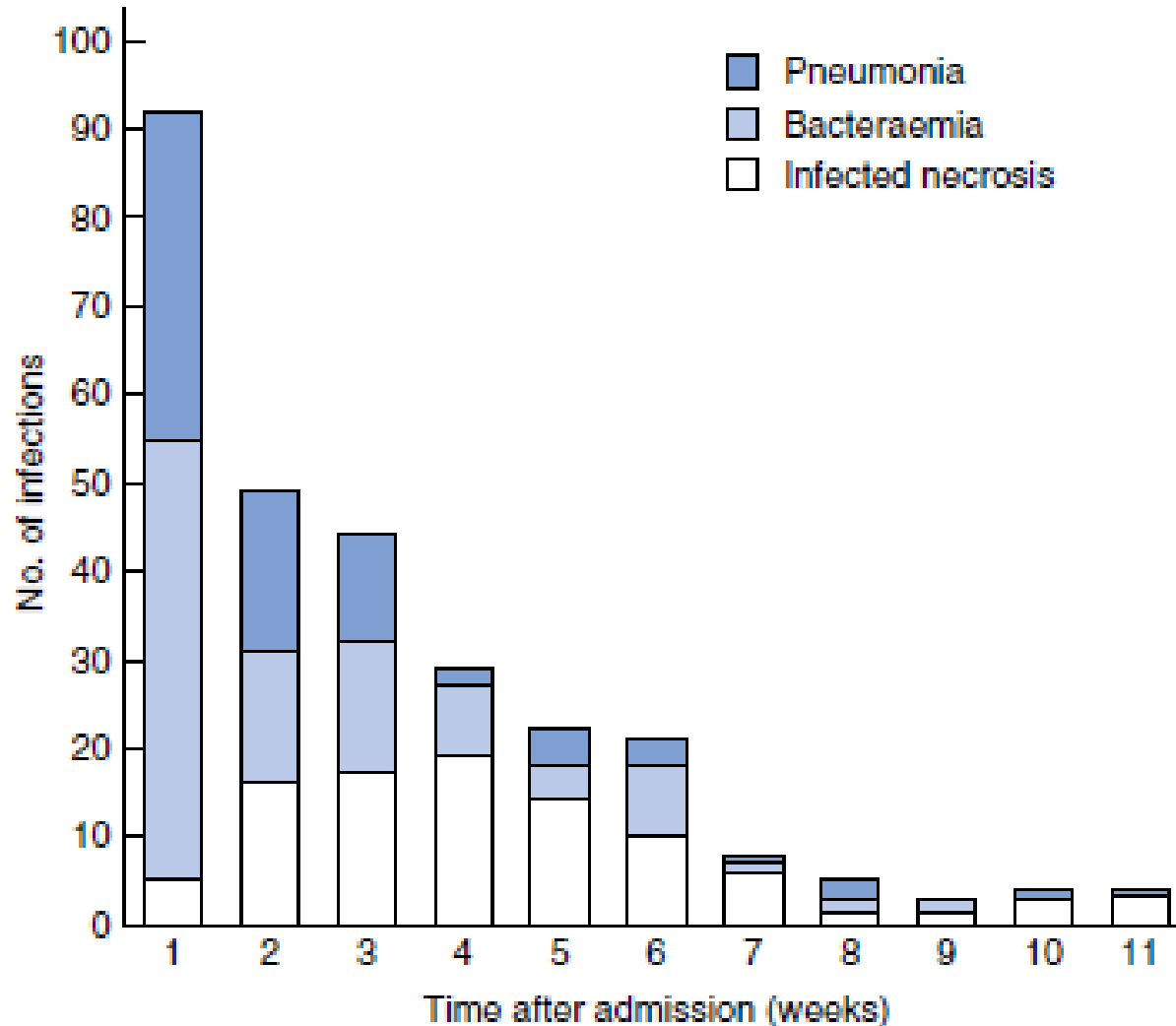


Enteral nutrition may maintain plasma oncotic pressure by preventing loss of albumin and non-albumin plasma protein and thereby prevent organ failure



No role for prophylactic antibiotics

Extrapancreatic Infections are seen in 25% of Patients with Acute Pancreatitis

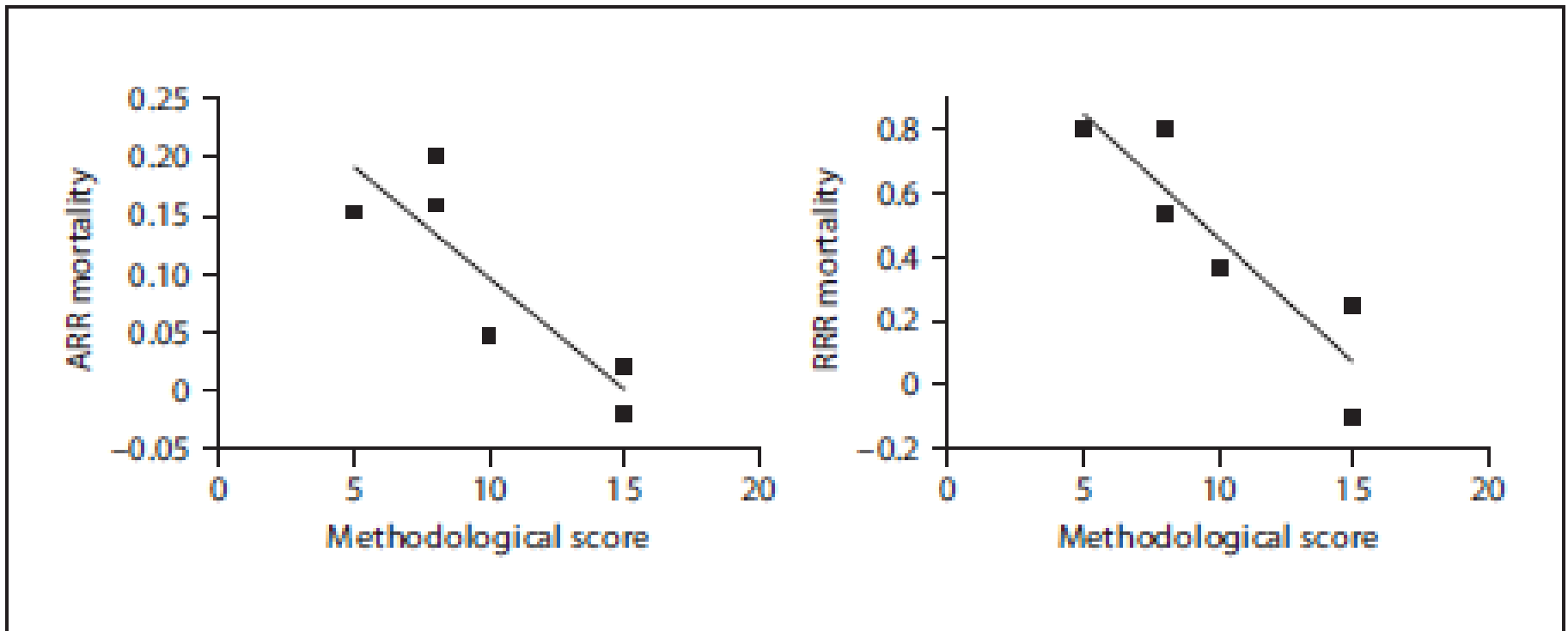


Systemic Inflammatory Response Syndrome (SIRS)

- SIRS is very common
 - 20-60% of AP patients have SIRS on presentation
 - 18-30% of AP patients develop persistent (>48 hours) SIRS
- SIRS due to infection cannot be differentiated from SIRS due to acute pancreatitis

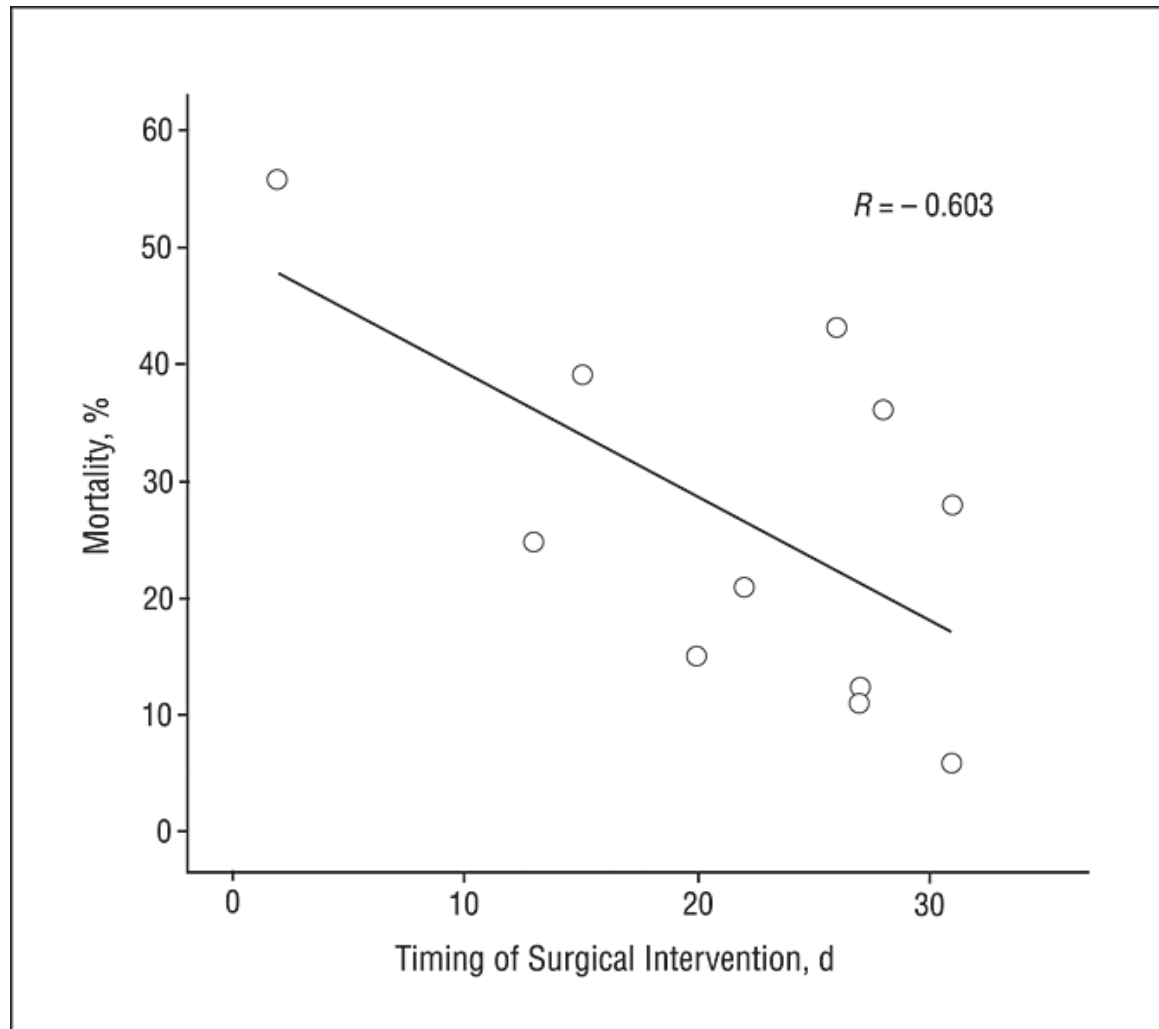
Jin T et al. HPB (Oxford) 2018; 20: 1082-91
Wu BU et al. Clin Gastroenterol Hepatol 2011; 9: 710-17
Sharma D et al. Dig Dis Sci 2017; 62: 3468-478
Grover AS et al. Pancreas 2017; 46: 106-9
Singh VK et al. Clin Gastroenterol Hepatol 2009; 7: 1247-51

Prophylactic Antibiotics for Pancreatic Necrosis: Findings Related to Study Quality



Early (<4 weeks) open surgical and endoscopic necrosectomy is associated with increased mortality. Try to delay intervention as long as possible to allow for the development of walled off necrosis at which time endoscopy or minimally invasive surgery can be used for treatment. If early (<4 weeks) intervention is required, only percutaneous drain should be used.

Association between Time of Surgical Intervention (from initial admission) for Necrotizing Pancreatitis and Mortality



Besselink MG et al. Arch Surg 2007;142:1194-1201.

Early (<4 Weeks) Versus Standard (\geq 4 Weeks) Endoscopically Centered Step-Up Interventions for Necrotizing Pancreatitis

Guru Trikudanathan, MD¹, Pierre Tawfik, MD², Stuart K. Amateau, MD, PhD¹, Satish Munigala, MBBS, MPH³, Mustafa Arain, MD¹, Rajeev Attam, MD¹, Gregory Beilman, MD⁴, Siobhan Flanagan, MD⁵, Martin L. Freeman, MD¹ and Shawn Mallory, MD¹

Outcomes	NP patients with interventions < 4 weeks (usually ANC collections) (n= 76)	NP patients with interventions \geq 4 weeks (usually WON collections) (n= 117)	p value
Mortality (%)	10 (13.2%)	5 (4.3%)	0.024
Morbidity (%)			
^a Median length of stay in days (IQR)	37 (27–61)	26 (0–207)	<0.001
^b Median length of ICU stay in days (IQR)	2.5 (0–22)	0 (0–3)	<0.001
<i>Complications (procedure and disease related)</i>			
Stent occlusion and infection	30(40%)	39(33%)	0.36
Bleeding	8 (10.5%)	12 (10.3%)	0.95
Perforation	0	7 (6.0%)	0.044
Fistulae (including pancreatic-, cyst-, or entero-cutaneous)	25 (32.9%)	24 (20.5%)	0.054
New-onset diabetes	15 (19.7%)	25 (21.4%)	0.785

Mortality was significantly higher in patients undergoing early endoscopy (<4 weeks) for an acute necrotic collection

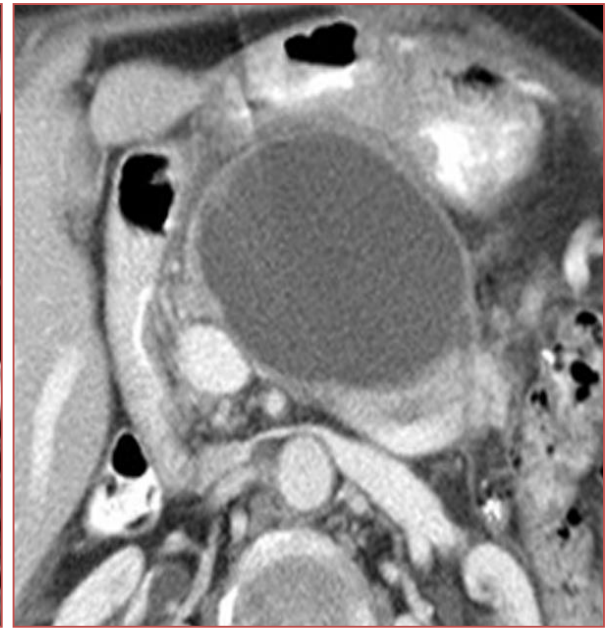
Evolution of Acute Necrotic Collection into Walled-Off Necrosis



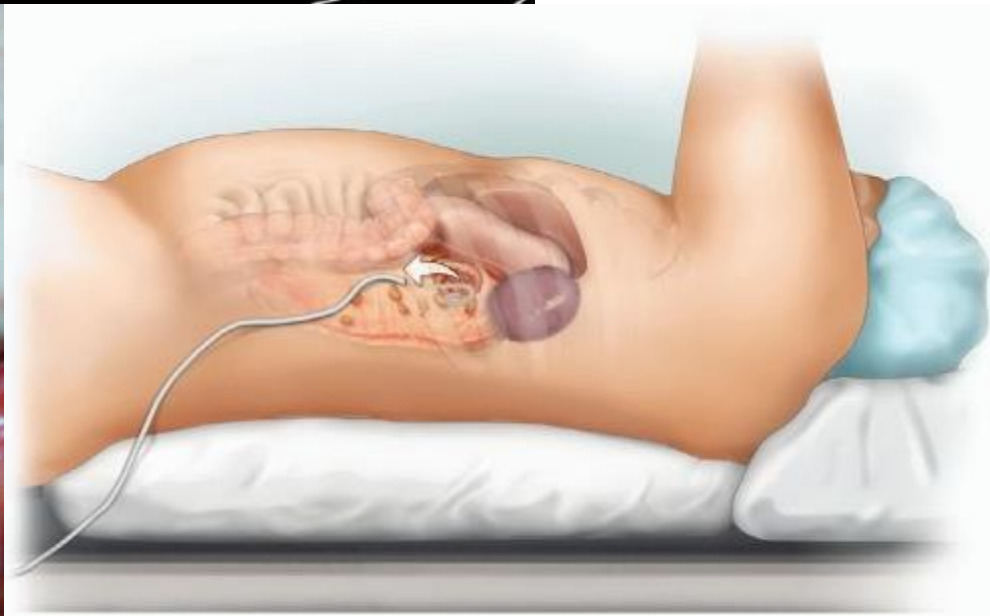
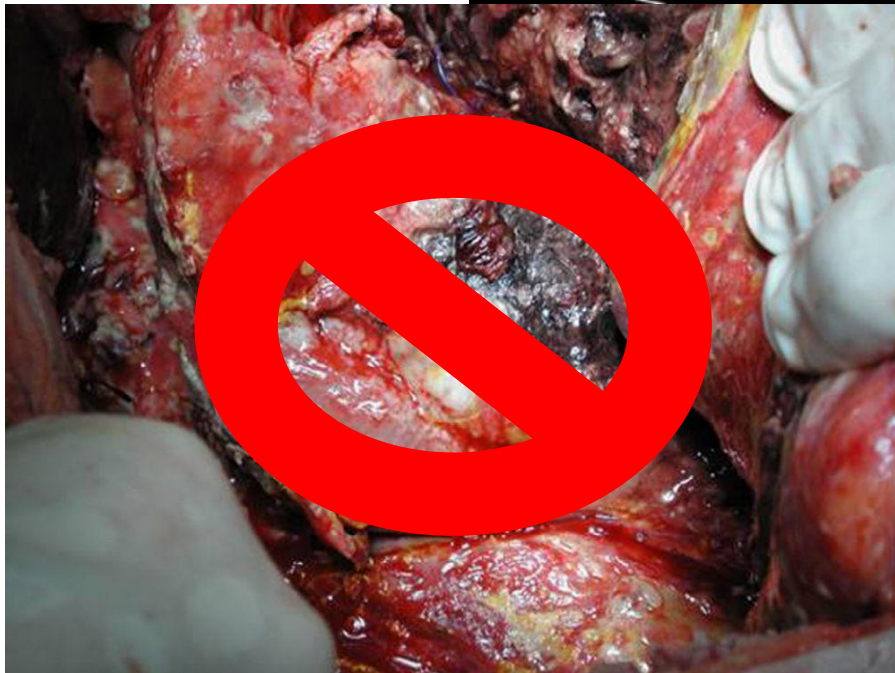
Day 1



Day 7



Day 28

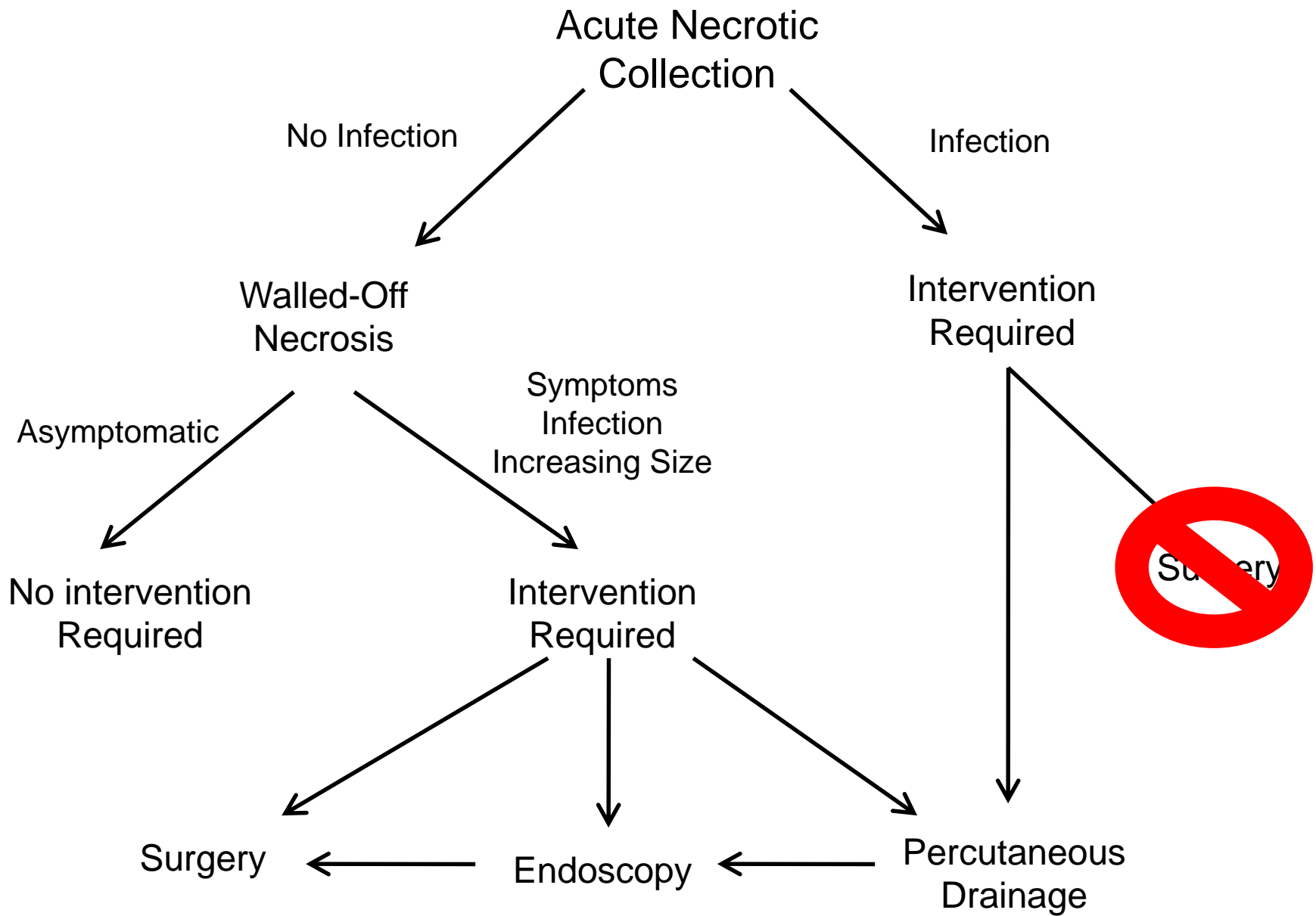


Efficacy of Conservative Treatment, Without Necrosectomy, for Infected Pancreatic Necrosis: A Systematic Review and Meta-analysis

VENIGALLA PRATAP MOULI,¹ VISHNUBHATLA SREENIVAS,² and PRAMOD KUMAR GARG¹

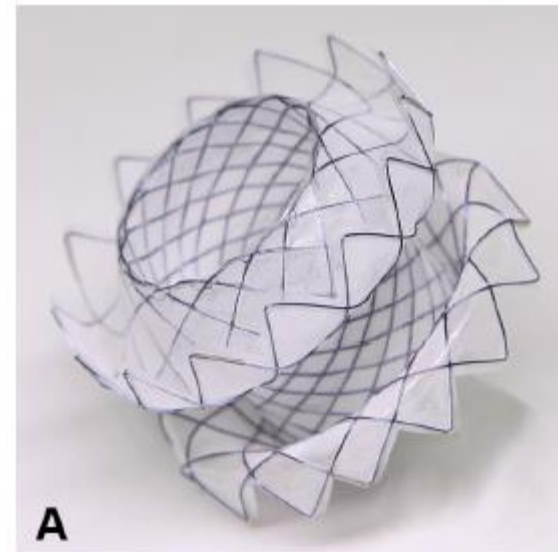
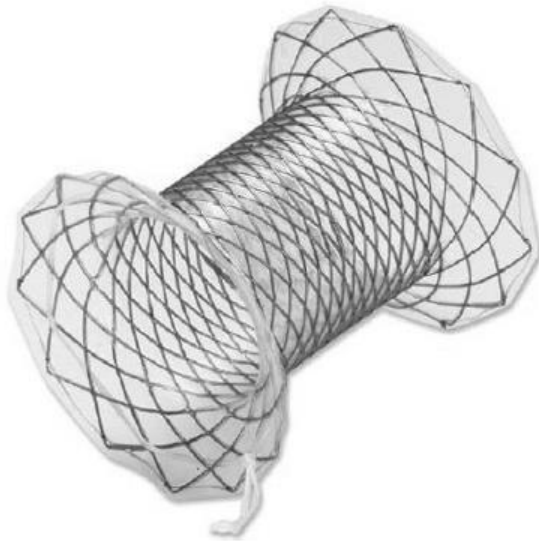
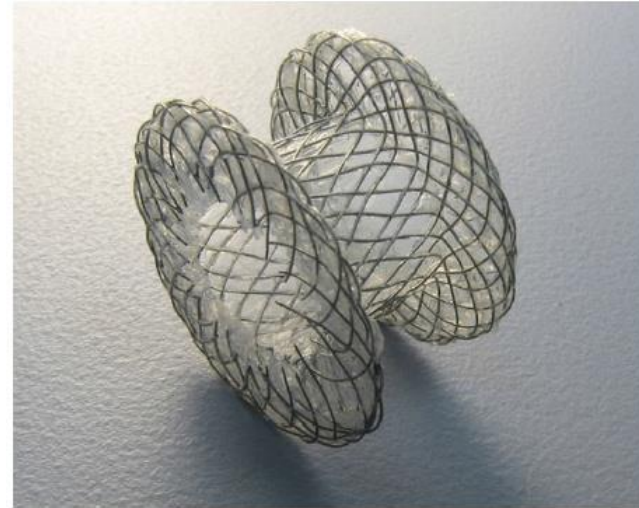
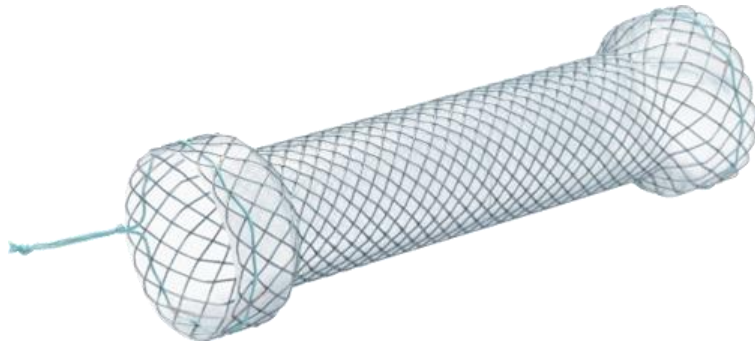
¹Department of Gastroenterology and ²Biostatistics, All India Institute of Medical Sciences, New Delhi, India

Gr	No. of patients with IPN on primary conservative	Patients undergoing percutaneous	Successful	Need for	Hospital stay (median/mean \pm SD ^b).	
64% of patients can be managed using conservative therapy (antibiotics +/- percutaneous drain)						
Gluck et al ³⁶	20	100 (20/20)	70 (14/20)	15 (3/20)	54	15 (3/20)
Alsfasser et al ³⁷	20	50 (10/20)	65 (13/20)	30 (6/20)	NR	5 (1/20)
Group B						
Freeny et al ³⁸	34	100	47.1 (16/34)	52.9 (18/34)	45	11.8 (4/34)
Navalho et al ³⁹	30	100	63.3 (19/30)	33.3 (10/30)	24	16.6 (5/30)
Bruennler et al ⁴⁰	80	100	47.5 (38/80)	20 (16/80)	51	33.8 (27/80)
Mortelé et al ⁴¹	13	100	46.2 (6/13)	53.8 (7/13)	33	7.7 (1/13)



“STEP-UP THERAPY”

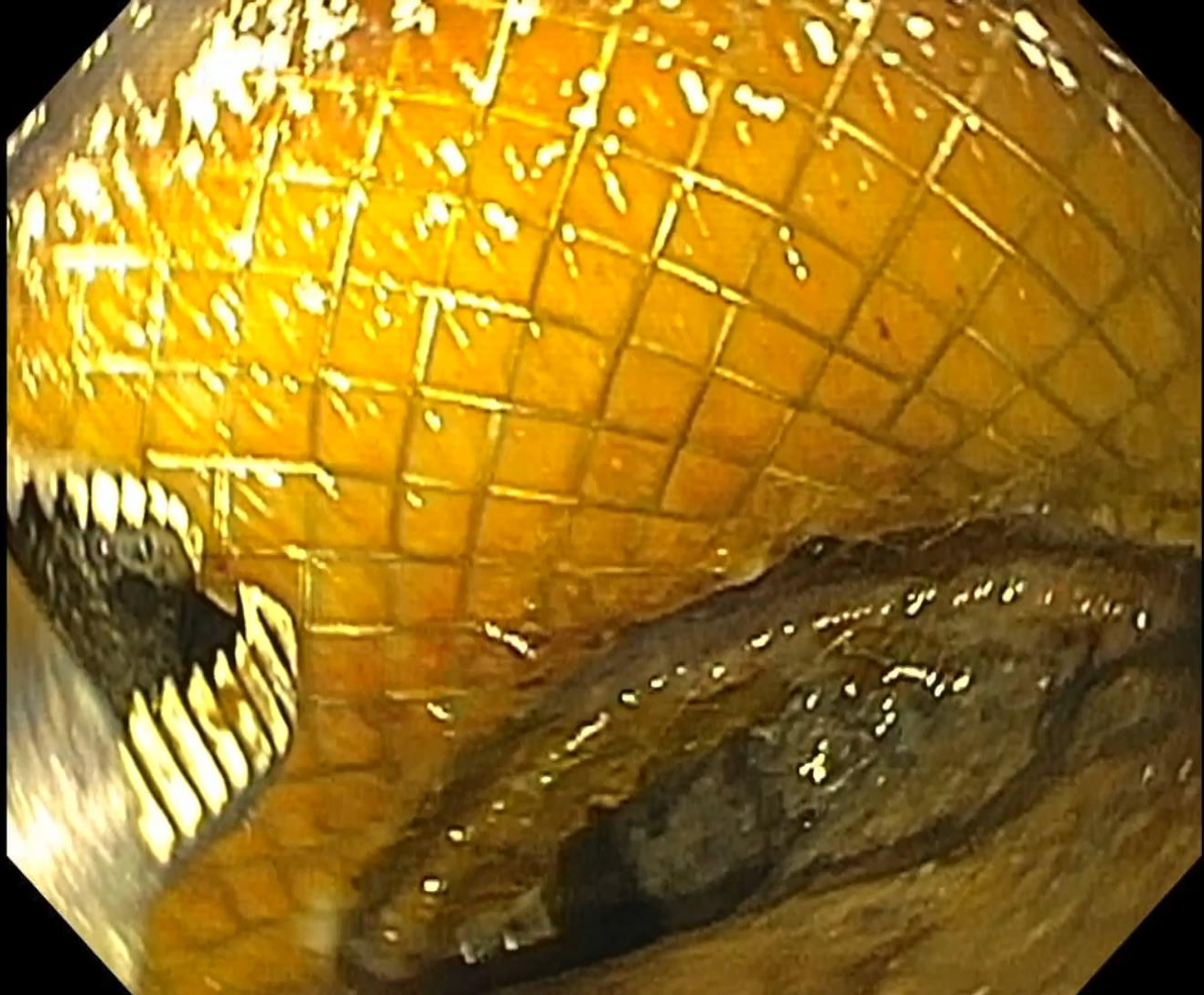
Transmural Fully-Covered Metal Stents for Walled-Off Necrosis



Direct Endoscopic Necrosectomy through Lumen-Apposing Stent for Walled-Off Necrosis



Endoscopic Morcellator Device



Endoscopy and Minimally Invasive Surgery have Similar Outcomes for WON Drainage but Complications Including Pancreatic Fistula more Common in Surgery

	PENGUIN trial ⁷⁷		TENSION trial ⁹⁶		MISER trial ⁷⁸	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Modality	Endoscopic	Surgical	Endoscopic	Surgical	Endoscopic	Surgical
No. of patients	10	10	51	47	34	32
Infected necrosis, n (%)	10 (100)	9 (90)	23 (45)	27 (57)	31 (91)	30 (94)
New-onset organ failure, n (%)						
Single	NR	NR	7 (14)	13 (28)	NR	NR
Multiple	0 (0)	5 (50)	2 (4)	6 (13)	2 (6)	3 (9)
Death, n (%)	1 (10)	4 (40)	9 (18)	6 (13)	3 (9)	2 (6)
Composite endpoint, n (%)	2 (20)	8 (80)	22 (43)	21 (45)	4 (12)	13 (41)
Complications, n (%)						
Bleeding	0 (0)	0 (0)	11 (22)	10 (21)	0	3 (9)
Perforation	0 (0)	2 (20)	4 (8)	8 (17)	0	0
Fistula (pancreatic)	1 (10)	7 (70)	2/42 (5)	13/41 (32)	0	9 (28)

Trikudanathan G et al. Gastroenterology 2019; 156: 1994-2007, Bakker OJ et al. JAMA 2012; 307: 1053-1061, van Brunschot S et al. Lancet 2018; 391: 51-58, Bang JY et al. Gastroenterology 2019; 156: 1027-1040

Key Points

- Abdominal pain and pancreatic enzyme elevation are not specific for acute pancreatitis as there are many other disease that present this way, only use lipase for diagnosing acute pancreatitis
- Avoid early and excessive cross-sectional imaging in acute pancreatitis
- Persistent /multisystem OF are the primary determinant of mortality in NP and therefore define severe AP
- IPN alone in the absence of OF is associated with no to low mortality
- Predicted severe AP infrequently ‘predicts’ the development of actual severe AP
- Use lactated Ringer’s, more aggressive volume appears to reduce inflammation/length of stay in mild AP but no biomarker predicts who needs more fluid in severe AP
- Try oral route if possible with low fat/low residue diet, if this is not tolerated NG or NJ. Start within the first few days of hospitalization
- No role for prophylactic antibiotics but antibiotics are often given for SIRS and extrapancreatic infections
- Early open surgical or endoscopic necrosectomy is associated with increased mortality so try to delay to enable development of walled off necrosis when endoscopy or minimally invasive surgical techniques can be successfully employed for treatment. Only percutaneous drain should be used early if required with “step-up” as needed.

Thank You
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