Acute Pancreatitis: What Research is Needed?

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Disclosures

- Calcimedica: Investigator for CM 4620 (Auxora) acute pancreatitis (Phase 2b) trial

What Research is Needed?

- Challenges of acute pancreatitis trials
  - Infrastructure
- Resuscitation
- Nutrition
- Analgesia
- Pharmacotherapy

Lexipafant

- Platelet activating factor (PAR) inhibitor
  - Attenuates inflammatory response
- Large British study (N=37) of acute pancreatitis patients with APACHE>6
- Within **72 hours** of diagnosis
- Late enrollment
  - "Within 72-96 hours" is "industry standard"
  - Damage likely done after first 24 hours
  - Salvage trials

	Lexipafant	Placebo
Organ Failure	**57%**	**58%**
Local complications	**20%**	**30%**

Johnson, Gut 2001; 48: 62-69, Gardner, Pancreatology 2009; 9: 770-776, Warndorf, Clin Gastroenterol Hepatol 2011; 9: 705-9, Vege Gastroenterology 2015; 149: 318-320

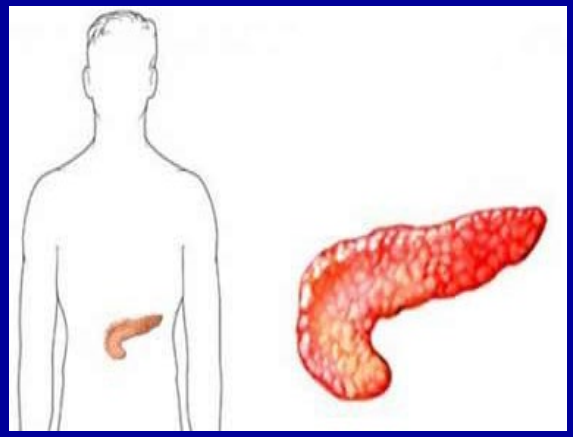
Timing-What is Needed?

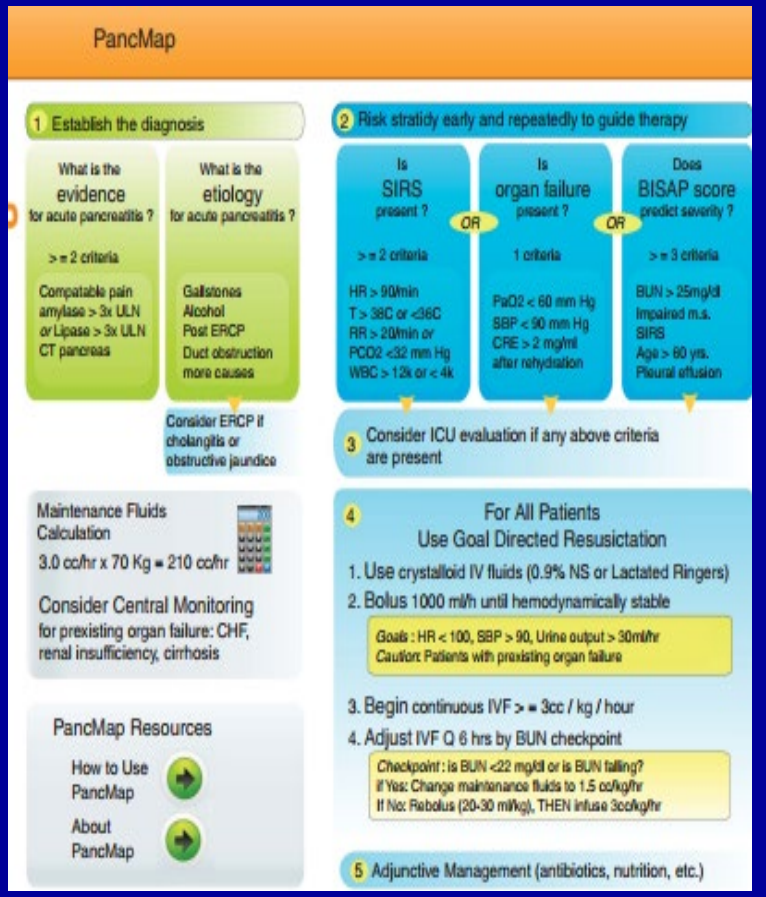
- Early enrollment
  - Informs clinical decision making
  - Need collaborative team at each site
    - Emergency room, laboratory medicine, radiology physicians
    - Intensivists, gastroenterologists, surgeons

Have a PANCREATITIS patient?

CALL **(213) 919-PANC** 24/7 LAC+USC pancreas study team

Or in numbers: (213) 919-7262



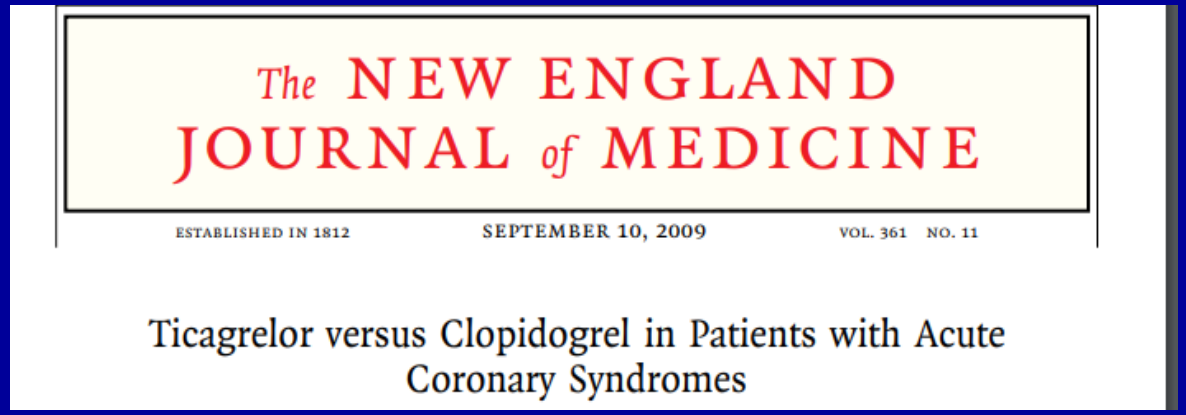


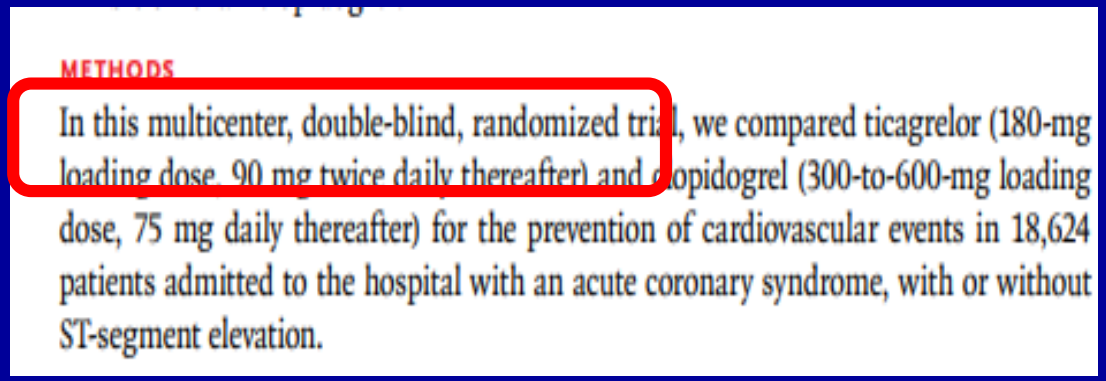
DiMagno, Am J Gastroenterol 2014

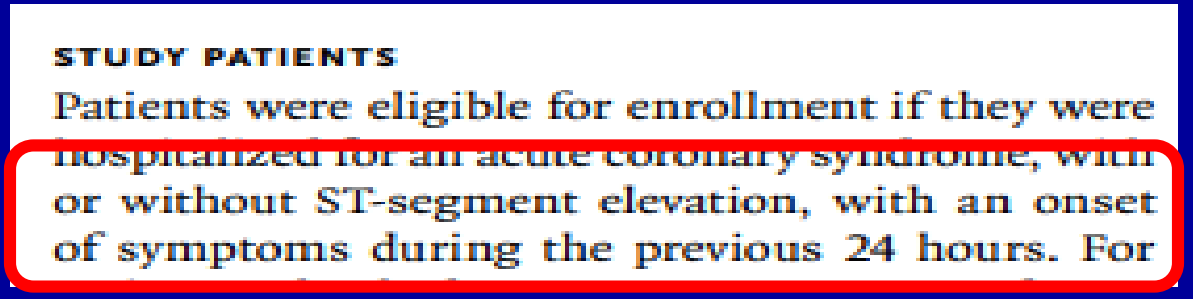
Challenge: Population and Outcome

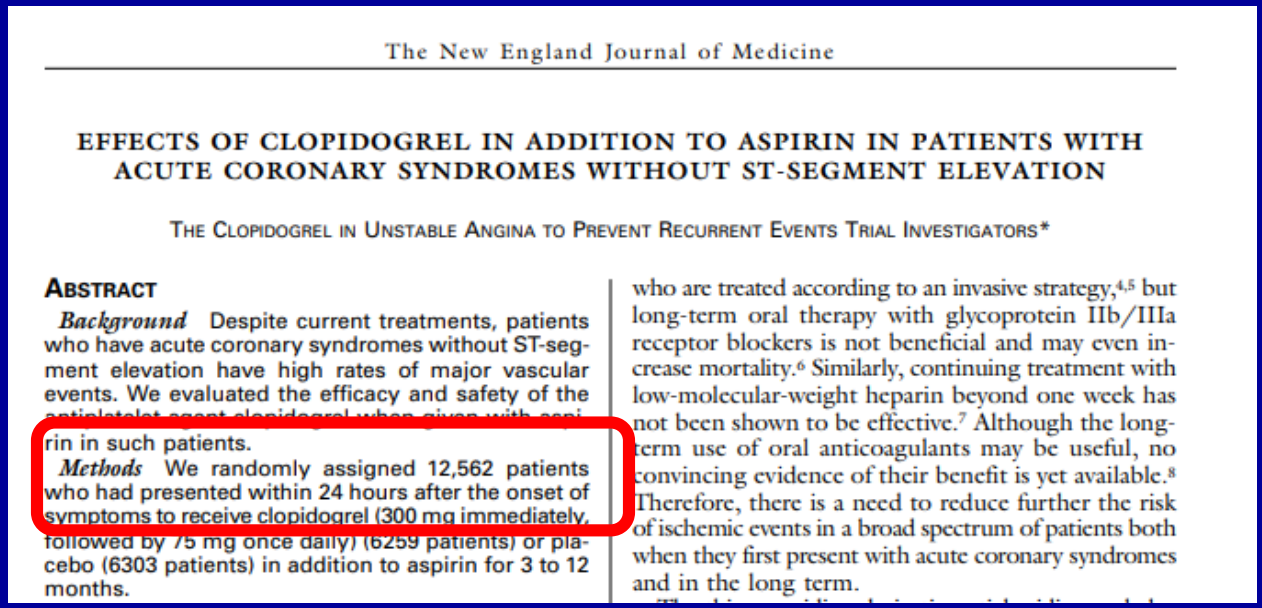
- Mild pancreatitis (80%) typically resolves 3-5 days without therapy
  - Overall low organ failure and mortality
- Recent high quality single center RCT's of pentoxifylline and rectal NSAID for acute pancreatitis
  - Limited by predominance of mild disease
    - Bias to the null
  - Challenge to reliably predict severe disease

Vege, Pancreatology 2020; 20: 1592-1597, Machicado, Clin Trans Gastroenterol 2021; 12: e00415









- Early Enrollment
  - Multi-specialty team site
- Detect significant (rare) outcomes
- Large multicenter study

Wallenson, NEJM 2009; 361(11): 1045-57, Yusuf, NEJM 2001; 345(7):494-502

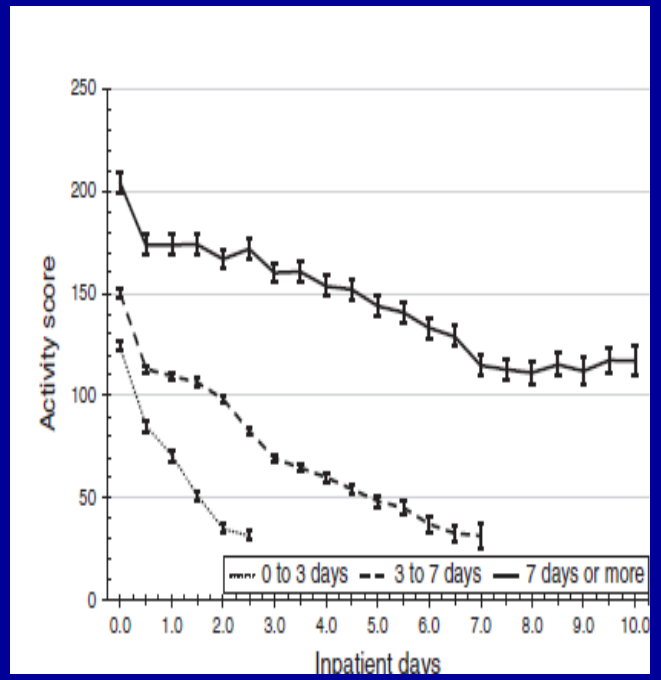
Population and Outcome-what is needed?

- Develop consortia of high volume acute pancreatitis sites for large high quality randomized controlled trials
  - Dutch Pancreatitis Study Group: FLUYT
  - Chinese Acute Pancreatitis Clinical Trials Group: TRACE (Thymosin alpha)
  - Hungarian Pancreatic Study Group: GOULASH
  - Spain (Mexico, Italy) ER**I**CA (int**ER**national league aga**I**nst biliary-pancreati**C** dise**A**ses: Galadrial
- Needed United States and multi-national groups
  - Type 1 Diabetes in Acute Pancreatitis Consortium might help with foundation (T1DAPC): DREAM

Ke, Intensive Care Med; 2022 in press, Marta, BMJ Open 2017; 7, e015874

Population and Outcome-what is needed?

- Additional Consensus metrics to enroll patients and measure endponts
- Refer to *Predictive Tools and Biomarkers for Severe Acute Pancreatitis* by Dr. Papachristou
- Validated activity score may be used for both roles
  - PASS pancreatitis activity scoring system
- Ariel Dynamic Acute Pancreatitis (ADAPT) tool
  - Predict severe pancreatitis
  - Highly personalized



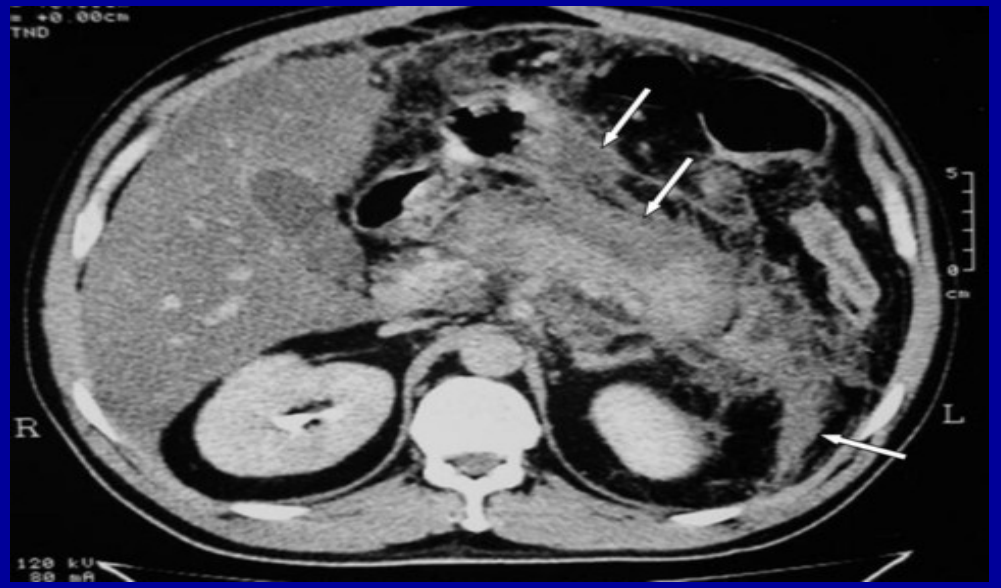
ADAPT Name	Percent Mortality	Baseline fluid needs (L)	Predicted severity?
USC_Project7	1.95	2.515	6
USC_Project9	3.17	2.845	-
USC_Project19	12.65	2.609	-
USC_Project27	2.49	2.8	-
USC_Project28	39.08	1.83	6
USC_Project32	1.95	1.603	-

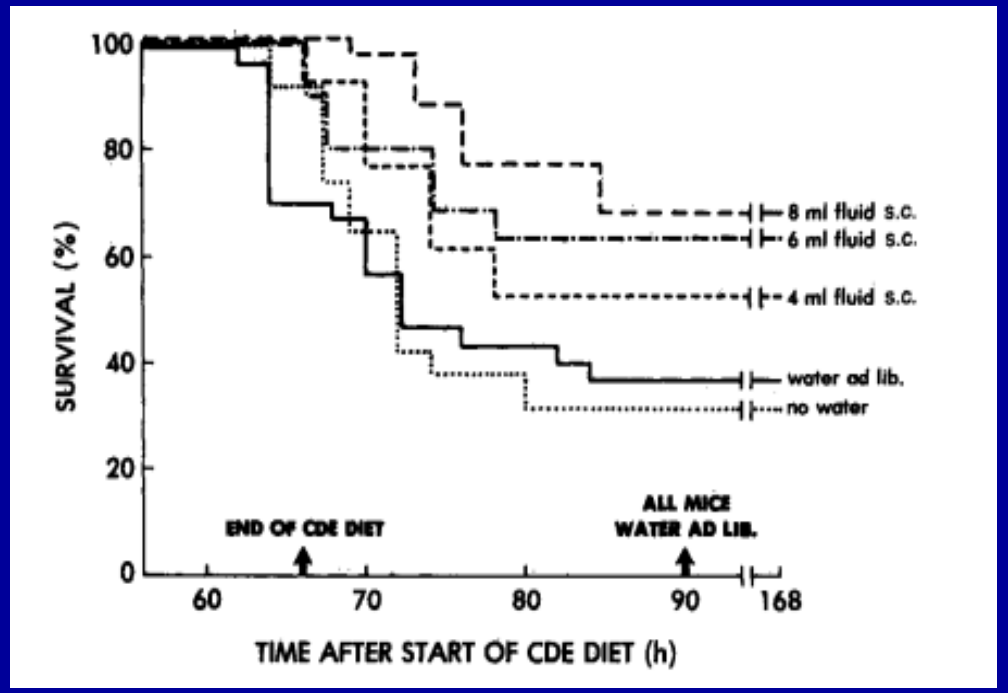
Courtesy of David Whitcomb MD PhD, Patrick Chang MD https://adapt-demo.arielmedicine.com/, Wu, Am J Gastroenterol 2017;112:1144–1152, Buxbaum, Am J Gastroenterol 2018; 113(5):755-764, Paragomi, Clin Gastroenterol Hepatol 2021; 20(6):1334-1342, Paragomi, Pancreas 2020; 49(10): 1276-1282,

What Research is Needed for the Future: Resuscitation

Fluid Resuscitation- Volume

- Animal models
  - Increase in survival with increasing parenteral fluid resuscitation
    - Dose response
- In-vivo microscopy and oxygen tension
  - Regions of hypo-perfusion correlate with regions of ischemia and **<u>hemorrhagic necrosis</u>**





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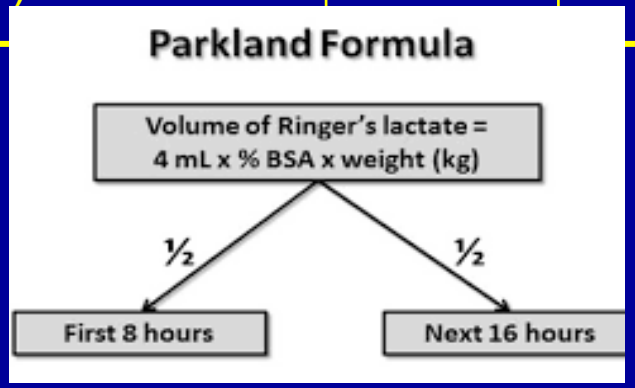
Cohort Studies on Volume of Resuscitation

Warndorf et al	Early N=340	Late (94)	P
Fraction of total fluid in first 24 hours	>1/3	<1/3	
SIRS at 48 hours	14%	33%	<0.01
Organ failure at 72 hours	5%	10%	<0.05
Hospital stay (days)	8	11	0.01

De Madaria et al	1st quintile	2-3 quintiles	4th quintile
Fluids in initial 24 hours	< 3.0 L	3.1-4.1L	> 4.1L
Organ Failure (%)	6.3	1.6	13.1
Initial hematocrit >44	19%	39%	57.4%



Warndorf, Clin Gastroenterol Hepatol 2011;9:705-9, de-Madaria, Am J Gastroenterol 2011;106:1843-50, Baxter, Burn Care Rehab 1995;16:218, msu.edu

Randomized Trials Fluid Rate

- Mao et al
  - Severe pancreatitis (n=76)
  - Randomized: rapid versus controlled expansion
    - Less ventilator support (65% versus 94%) and lower mortality (90% versus 69.4%) for **controlled** expansion
- Buxbaum et al
  - Mild pancreatitis (n=60)
  - Randomized: Aggressive versus moderate hydration
    - Greater clinical improvement at 36 hours (70% versus 42%) and less persistent SIRS 7.4% versus 21%) with **aggressive** hydration

Mao et al	Rapid Expansion	Controlled Expansion
Rate	*10-15 cc/kg/hr i.e. 1000cc/hr*	*5-10 cc/kg/hr i.e. 400cc/hr*
Buxbaum et al	Aggressive Hydration	Standard Hydration
Rate	*3cc/kg/hr i.e. 240cc/hr*	*1.5 cc/kg/hr i.e. 120cc/hr*

Mao EQ, Chin Med J (Engl) 2009;122:169-73 Buxbaum, Am J Gastroenterol 2017; 112: 797-803

Early **W**eight-Based **A**ggressive vs. Modera**TE** Goal-Di**R**ected **F**luid Resuscit**A**tion (WATERFALL)

- 18 center randomized trial of aggressive versus moderate fluid resuscitation
  - Aggressive: **20 mL/kg bolus followed by 3 mL/kg/hour** x 12 hours, then 1.5ml/kg/hour until **48 hours**
  - Moderate: 10 mL/kg bolus if hypovolemic or no bolus if normovolemic, followed by 1.5 mL/kg/hour x **20 hours**
  - Checkpoint 12, 24, 36 hours with bolus (20cc/kg aggressive, 10cc/kg moderate) if hypovolemic, diet started at 12 hours if pain free
- Main Endpoint: Moderately severe/severe pancreatitis by Revised Atlanta Classification
- Secondary Endpoint: Adverse events
- Study halted at planned interim analysis (N=249)

de-Madaria, Buxbaum, DDW 2022

WATERFALL

Endpoint	Aggressive fluid resuscitation (N=122)	Moderate fluid resuscitation (N=127)	Relative risk (95% CI)
Moderate or Severe Pancreatitis	22.1%	17.3%	1.28 (0.77-2.12)
Severe Pancreatitis	6.6%	1.6%	4.16 (0.90-19.2)
Local Complication	20.5%	16.5%	1.24 (0.73-2.09)
Necrosis	**13.9%**	**7.1%**	**1.97 (0.91-4.24)**
ICU Admission	**6.6%**	**1.6%**	**4.16 (0.90-19.20)**
Organ Failure	7.4%	3.9%	1.87(0.65-5.43)
Shock	4.1%	0.8%	5.21 (0.62-43.9)
Respiratory Failure	7.4%	2.4%	3.12 (0.87-11.30)
Kidney Failure	3.3%	2.4%	1.39 (0.32-6.07)
Death	3.3%	0.8%	4.16 (0.47-36.70)
Fluid Overload	**20.5%**	**6.3%**	**3.25 (1.53-6.93)**
Moderate/Severe Fluid Overload	**4.9%**	**0.8%**	**6.25 (0.76-51.10)**

Median length of hospitalization 6 (IQR 4-8) aggressive versus 5 days (IQR 3-7) moderate p=0.17

Waterfall

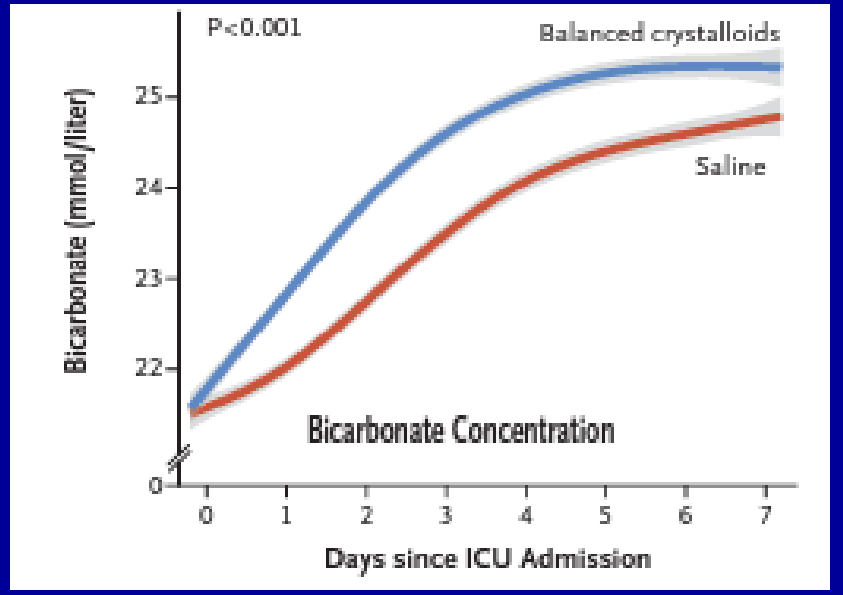
- Aggressive hydration first 48 hours regardless of severity associated increased fluid overload (20.5% versus 6.5%)
  - 2.0% vs. 0.0 were controlled by decreased hydration alone; 88.0% vs. 100% with diuretics, 8.0% vs. 0.0 required inotropes, and no patient required hemofiltration
- Aggressive hydration in unselected patientsdid not reduce moderate/severe pancreatitis, trend more ICU admission and organ failure (respiratory)

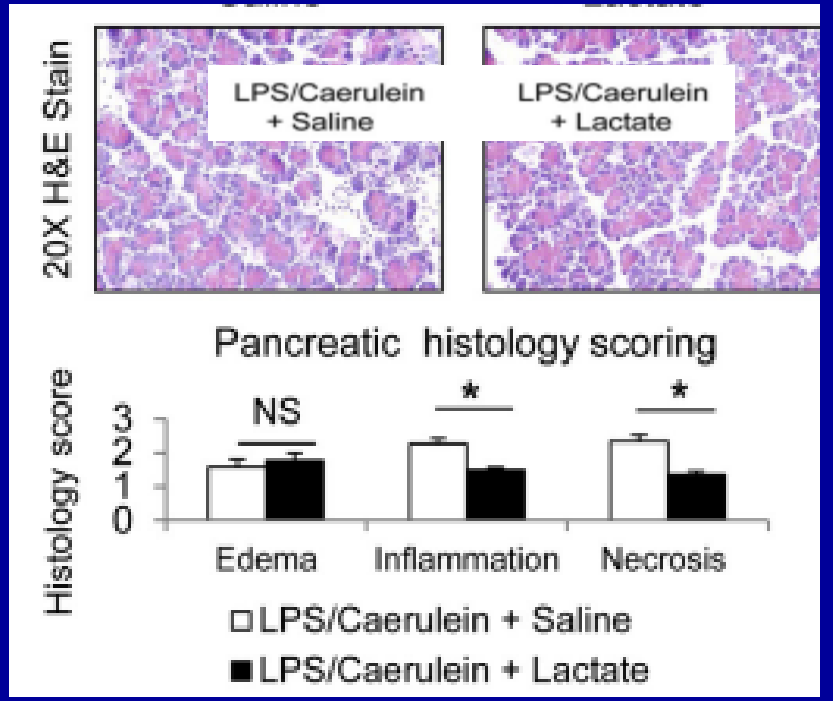
What research is needed future-volume fluid resuscitation

- Nuanced approach to resuscitation based on volume status
- Initial assignments only to 12 hours with modulation based on clinical assessment
- Underscores need to develop better non-invasive ways of assessing status, i.e. quantitative bedside technology

Fluid Type

- Normal saline (NS) vs Lactated Ringer's (LR)
  - Balanced fluids more similar plasma and less likely to cause acidosis
  - Major adverse renal events reduced LR vs NS (SALT and SMART trials)
- Animal models
  - LR associated less inflammatory changes, edema, and trypsin activation
    - Higher pH reduces zymogen activation
      - Lactate anti-inflammatory





Young, JAMA 2015; 314(16): 1701-10, Self, N Eng J Med 2018; 378(9): 819-828, Semler, N Eng J Med 2018; 378(9): 829-839 , Bhoomagoud, Gastroenterology 2009; 137: 1083-1092, Reed, J Biol Chem 2011;286(3):1919-26, Niederau, J Clin Invest 1988; 81(1):229-36, Kellum JA et al. Am J Physiol Regul Integr Comp Physiol 2004;286: 686-92, Hoque Gastroenterology 2014; 146: 1763-1774

Fluid Type: NS versus LR

- SIRS prevalence surrogate outcome
  - Persistent SIRS (>48) hours associated necrosis
- Major clinical outcomes rare

	Wu et al		de-Madaria et al		Choosakul et al	
	LR (%)	NS (%)	LR (%)	NS (%)	LR (%)	NS (%)
N						
SIRS baseline	31	19	47	67	35	42
SIRS 24 hours	5	19	21	19	9	38

Wu BU, Clin Gastroenterol Hepatol 2011;9:710-7 e1, de-Madaria, United European Gastroenteorl J; 2018; 6: 63-72, Choosakul, Pancreatology 2018; 18: 507-512, Singh, Clin Gastroenterol Hepatol 2011; 9: 1098-1103, Kumar Pancreas 2014; 43(7): 1101-1105

Table 1. Outcomes in Patients With AP Treated With NS vs LR Solution

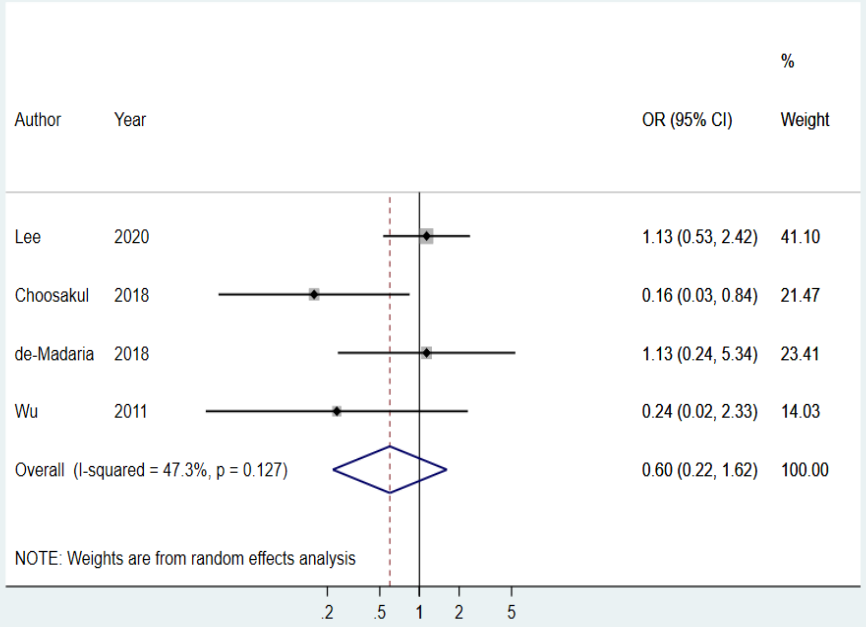
	NS (n = 60) n (%)	LR (n = 61) n (%)	RR	Adjusted RR[a]
ICU admission	15 (25)	6 (9.8)	0.4 (0.2–0.9)	0.3 (0.1–0.9)
Moderate-severe pancreatitis	15 (25.0)	9 (14.8)	0.8 (0.4–1.4)	0.5 (0.2–1.1)
Local complications	9 (15)	4 (6.6)	0.4 (0.1–1.3)	0.3 (0.1–1.5)
Organ failure	9 (15)	7 (11.5)	0.8 (0.3–1.9)	1 (0.4–2.7)
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)

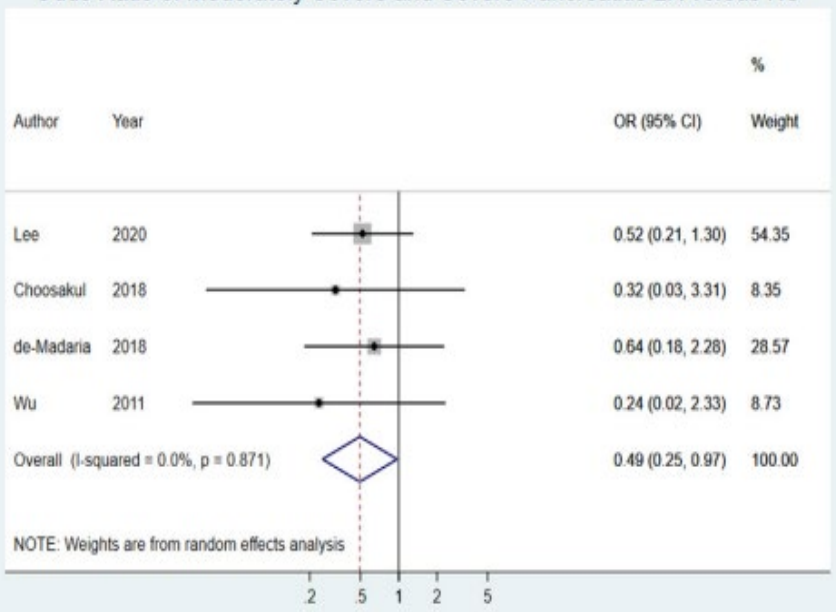
	NS Median (IQR)	LR Median (IQR)	*P* value
Length of hospitalization (*d*)	4.6 (3–7.4)	3.5 (2–5.9)	.049
Fluid administered in first 24 h following randomization (*L*)	5.8 (4.8–6.8)	6.0 (5.2–6.9)	.194

Lee, Gastroenterology 2021; 160: 955-957

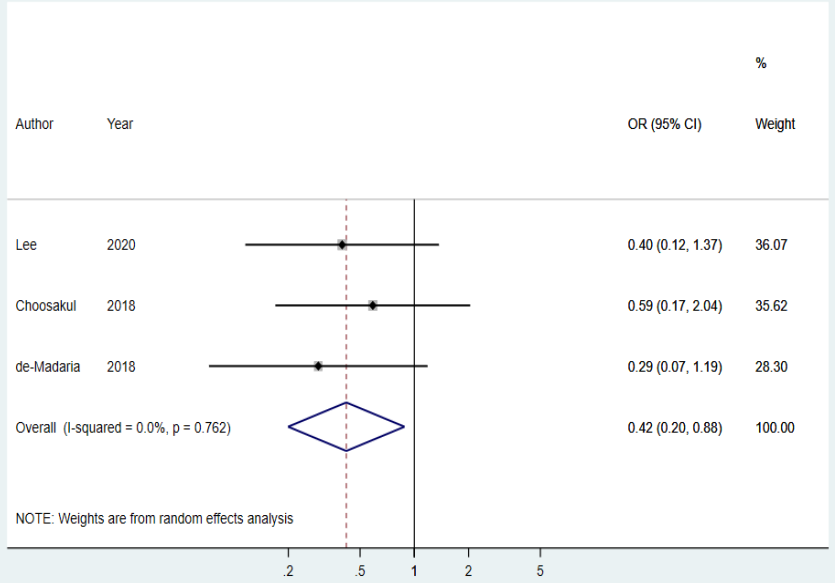
OR of SIRS at 24 Hours LR versus NS in Acute Pancreatitis



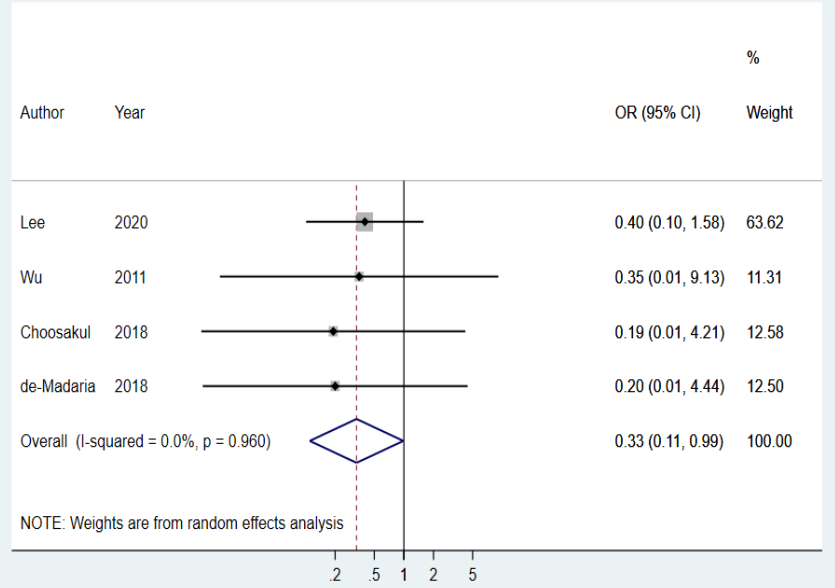
Odds Ratio of Moderately Severe and Severe Pancreatitis LR versus NS



OR of Local Pancreatitis Complications for LR versus NS



OR of Pancreatic Necrosis LR Vs NS

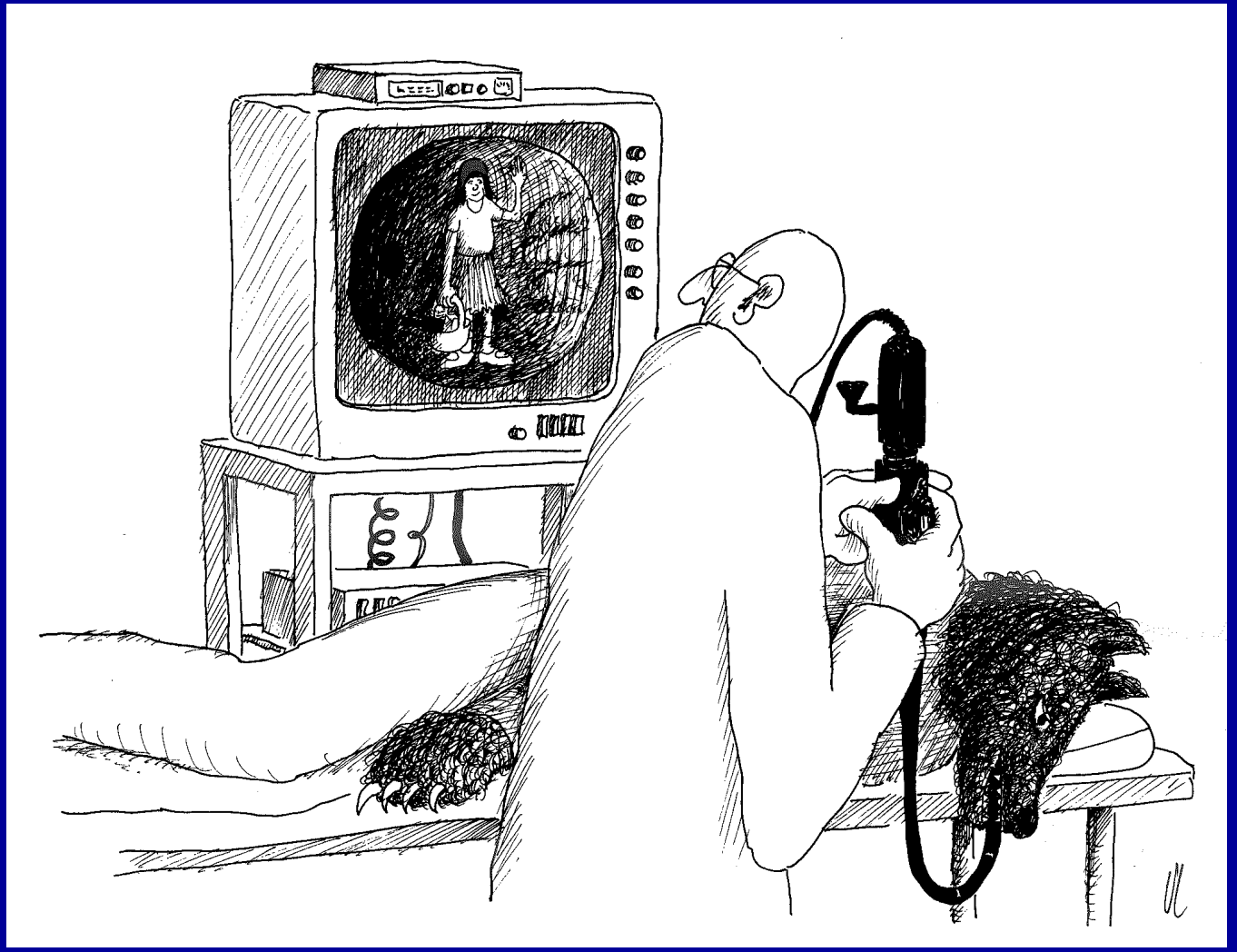


Zhou, Pancreatology 2021; 21(8):1405-1410.

Fluid Type: What Research is Needed for the Future

- Trend in favor of Lactated Ringer's (balanced fluids)
  - Indeterminate regarding systemic inflammatory response syndrome
  - Limited evidence may reduce moderately severe/severe pancreatitis by decreasing local complications→necrosis
- Large fully powered doube-blind (highly feasible) randomized trial LR versus NS
- Development of fluids with more specific calcium and phosphate balance for shifts seen in acute pancreatitis

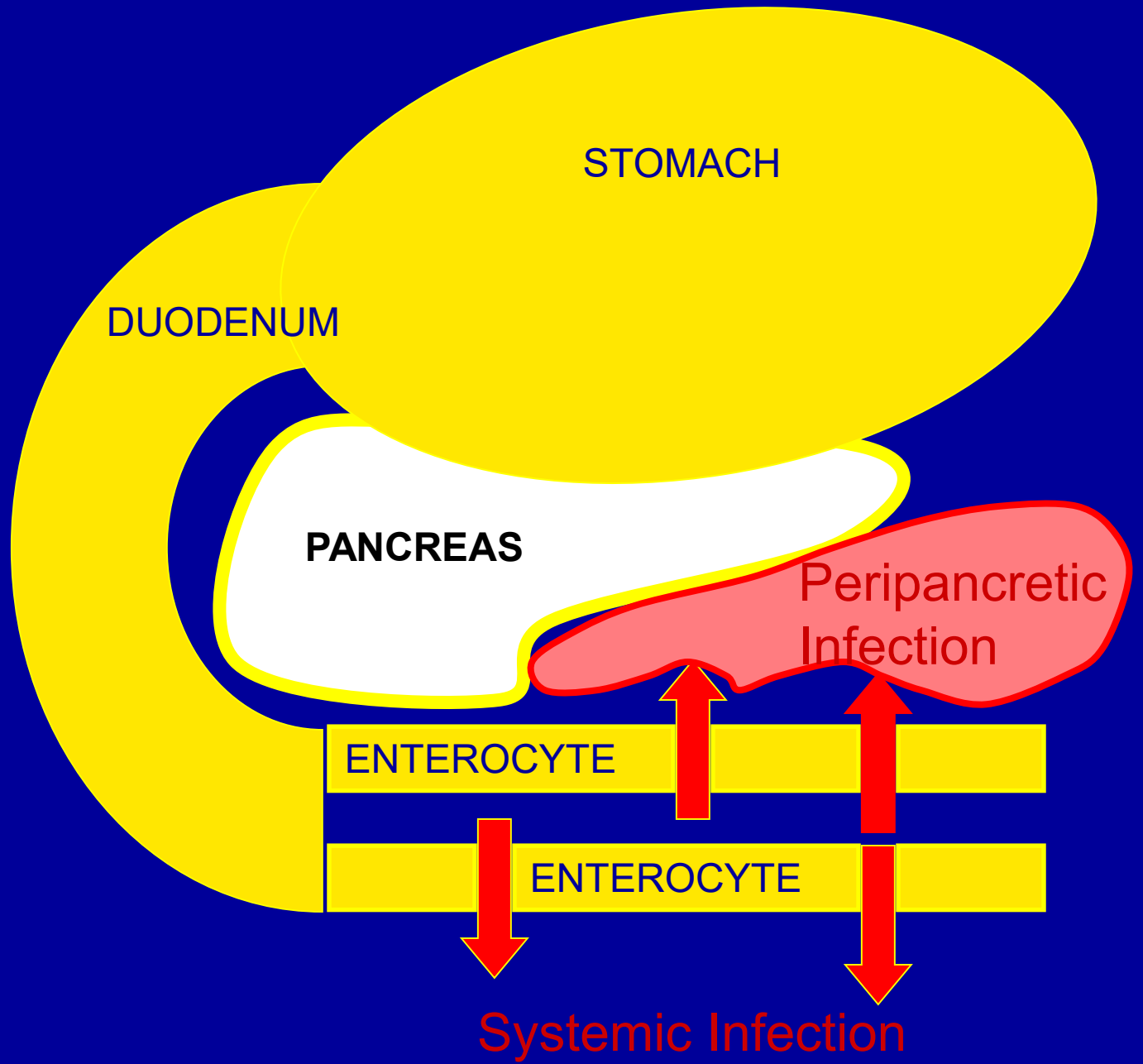
What Research is Needed for the Future: Nutrition



Lange, WC Calender of Endoscopy, 1990

Leaky Gut

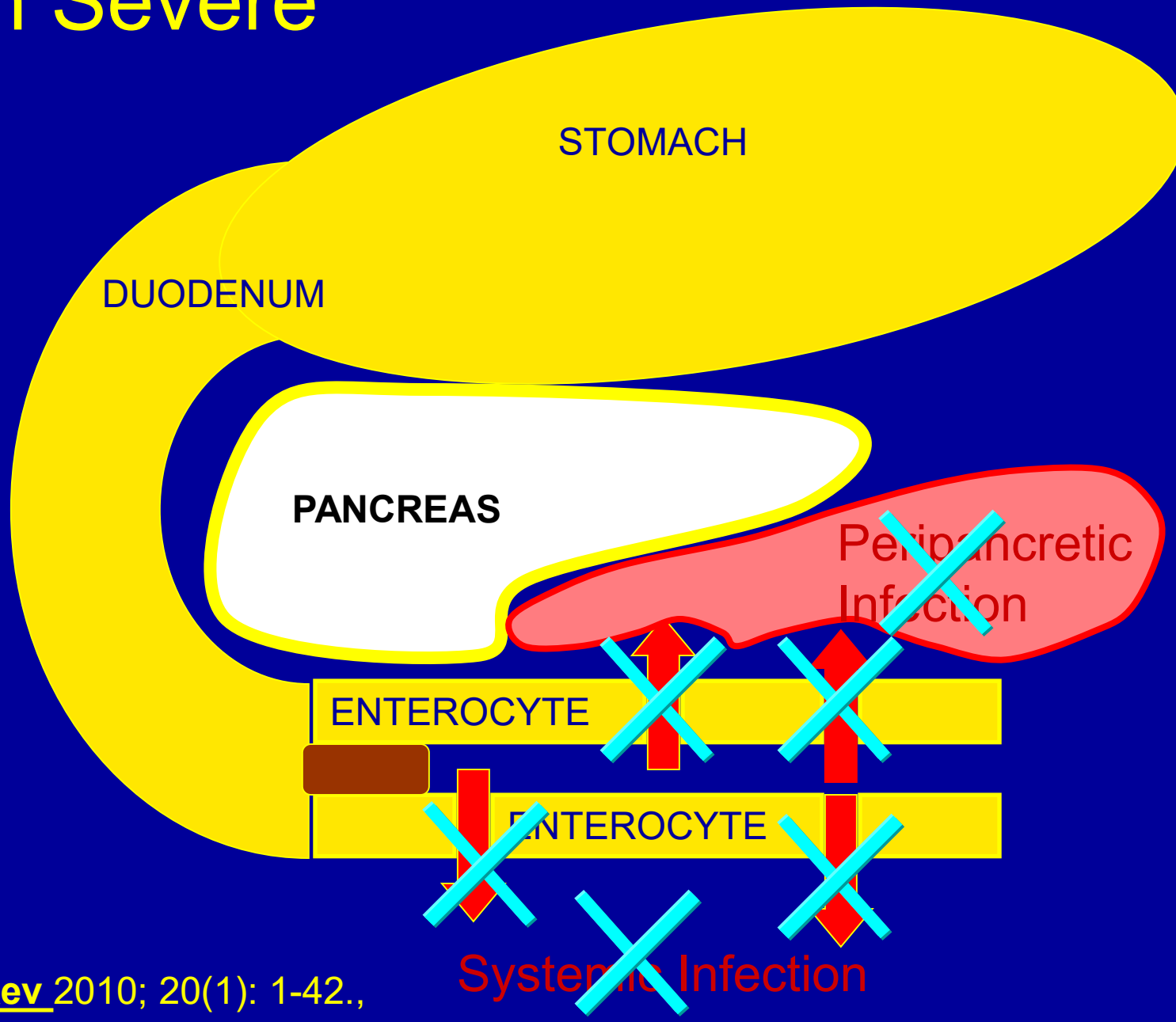
- Critical illness
  - Ischemia and reperfusion injury to the bowel
    - Leakage of “tight” junctions
- Pancreatitis
  - Bacterial culture of peri-pancreatic collections indicates barrier dysfunction in >50%



Wu, LM et al. BJS 2014; 101: 1644-56, Petrov MS, Dig Surg 2006; 23: 336-345

Enteral Nutrition in Severe Pancreatitis

- Enteral feeding reduces septic complications in high risk burn and trauma patients
- Reduces mortality and persistent organ failure severe pancreatitis
- ? Mild moderate pancreatitis



Al Omran, **Cochrane Database Syst Rev** 2010; 20(1): 1-42.,

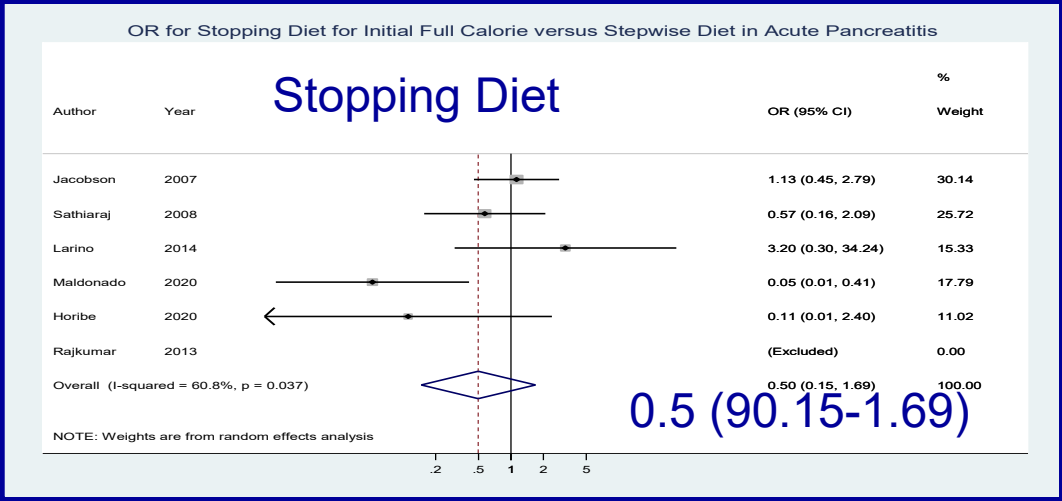
Type and Timing of Enteral Nutrition in Non-severe Pancreatitis

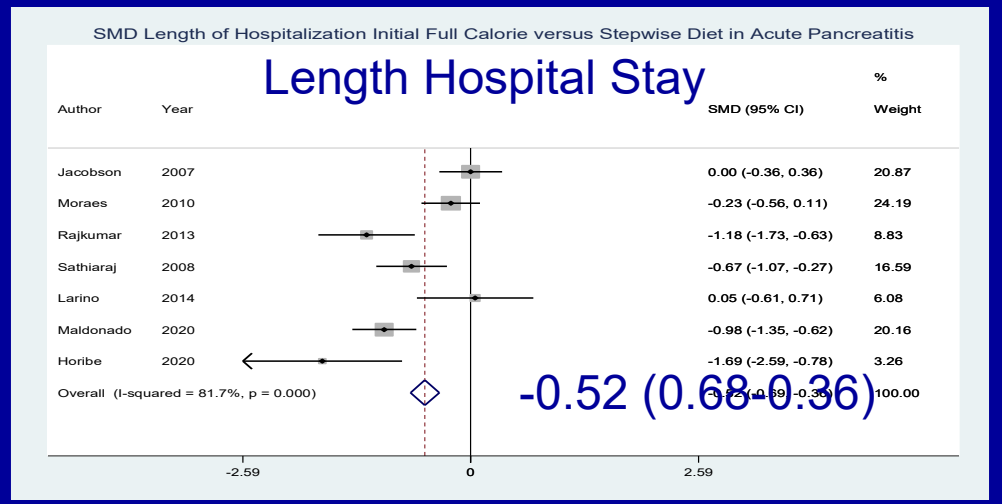
Study	N	Intervention Group		Comparator Group	
		Type of Diet	Timing of Diet Initiation	Type of Diet	Timing of Diet Initiation
Jacobson et al, 2007	121	Solid: low fat	Per the discretion of medical team	Stepwise: liquid to solid	Per the discretion of medical team
Sathiaraj et al, 2008	101	Solid: soft	Standard	Stepwise: liquid to solid	Standard
Moraes et al, 2010	140	Solid: diet C in study	Standard	Stepwise: liquid to solid (diet A)	Standard
Rajkumar et al, 2013	60	Solid: soft	Standard	Stepwise: liquid to solid	Standard
Larino-Noia et al, 2014	72	Solid: full calorie, group IV in study	Early: as soon as bowel sounds present	Stepwise: increase in calories	Standard
Horibe et al, 2020 N=26	26	Solid: low fat	Early: within 24 hours of diagnosis	Stepwise: liquid to solid	Standard
Ramirez-Maldonado et al, 2021	121	Solid: low fat	Early: immediately upon hospital admission	Stepwise: liquid to solid	Standard

Type and Timing of Diet in Non-Severe Pancreatitis

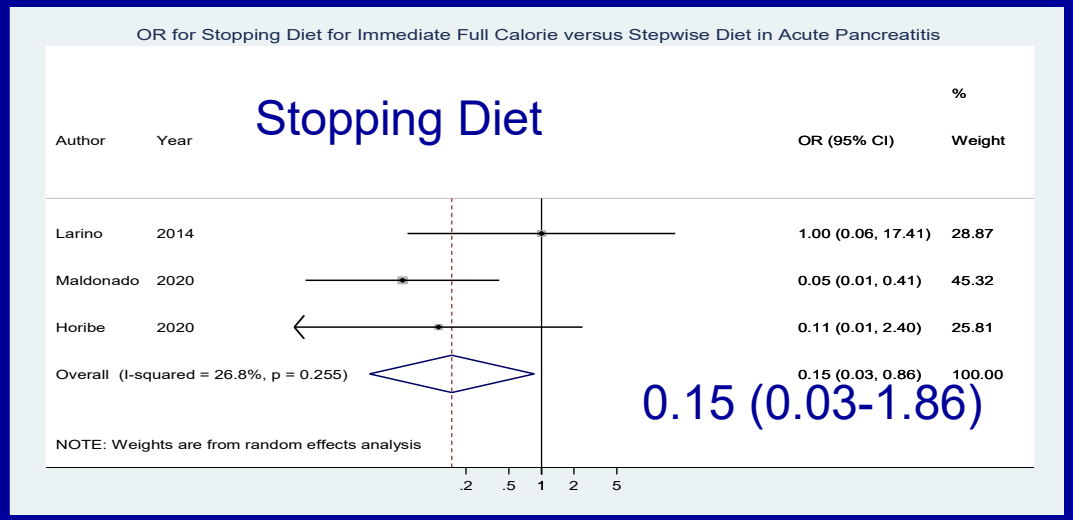
INITIAL SOLID VERSUS STEP-WISE

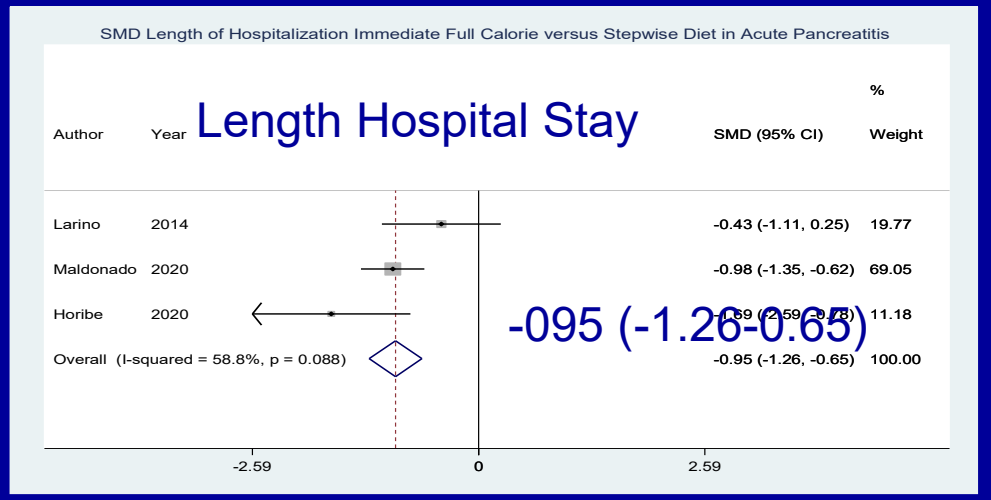
STANDARD (SYMPTOMS RESOLUTION)





VERY EARLY





Chowdhury, DDW 2022

Timing of Nutrition Severe Pancreatitis (PYTHON)

Multicenter (N=19) Dutch study in 208 patients predicted severe APACHE >8, Imrie/Glasgow >3, CRP >150mg/L)

Very Early: Nasoenteric tube feeding within 24 hours after randomization

Selective Delayed: Oral diet at 72 hours after presentation (on demand) with tube feeding if not tolerated

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

Bakker, N Eng J Med 371: 21: 1983-1993

Audit of Practices In U of Toronto Hospitals

- 8 affiliated hospitals
  - Audit patients non-severe pancreatitis
- Guideline: regular diet on admission, if fail to tolerate advance slowly from NPO
- In practice:
  - 81% maintained NPO for first 24 hours
  - 19% clear liquids
  - 0% solid diet used as initial nutrition strategy

Greenberg, J Gastrointest Surg 2016; 20 : 392-400

What Research is Needed for the Future: Nutrition

- Large multi-center trial very early oral (substantial calories) for acute pancreatitis versus NPO/clear liquid diet to reflect and potentially change actual clinical practice
- Stratified by severity post-hoc
  - Critically ill cross-over to enteral feeding
- Caloric blends aimed to match very specific nutritional needs pancreatitis

What Research is Needed for the Future: Pain Management

Randomized Trials Acute Pain Management

Trial	N	Agent 1	Agent 2	Outcome Metric
Blamey 1984	32	IM Suboxone	IM Demerol	Linear analogue scale
Ebbehoj 1985	30	Indomethacin	Placebo	Visual Analogue Scale (VAS)
Jakobs 2000	39	Suboxone	Novocaine	VAS, rescue demand
Stevens 2002	32	Fentanyl, Demerol	Demerol	0-5 relief scale and satisfaction
Kahl	101	Novocaine	Talwin	Rescue demand, VAS
Peiro	16	Metamizole	Morphine	Proportion pain relief, time to pain relief
Wilms 2009	42	Novocaine	Placebo	Rescue analgesia (Demerol) dose
Layer 2011	44	Novocaine	Placebo	Rescue demand VAS
Sadowski 2015	35	Bupividaine + Fentanyl epidural	Fentanyl PCA	Safety, pancreatic persusion CT
Gulen 2016	90	Tramadol vs Tyelonol vs Dexketoprofen		VAS
Mahapatra 2019	50	Talwin	Diclofenac	Rescue dose (Fentanyl)
Kumar 2020	41	Diclofenac	Ultram	VAS

Thavanesan, World J Surg 2022; 46: 878-90 , Ona, Cochrane Library 2013

Randomized Trials: Pain Management

- Local anesthetics not as effective
- Small trials
- Non-opiate question unclear
- Highly heterogenous designs and outcomes
  - Some test impact of an additional medication on fentanyl dilaudid dose

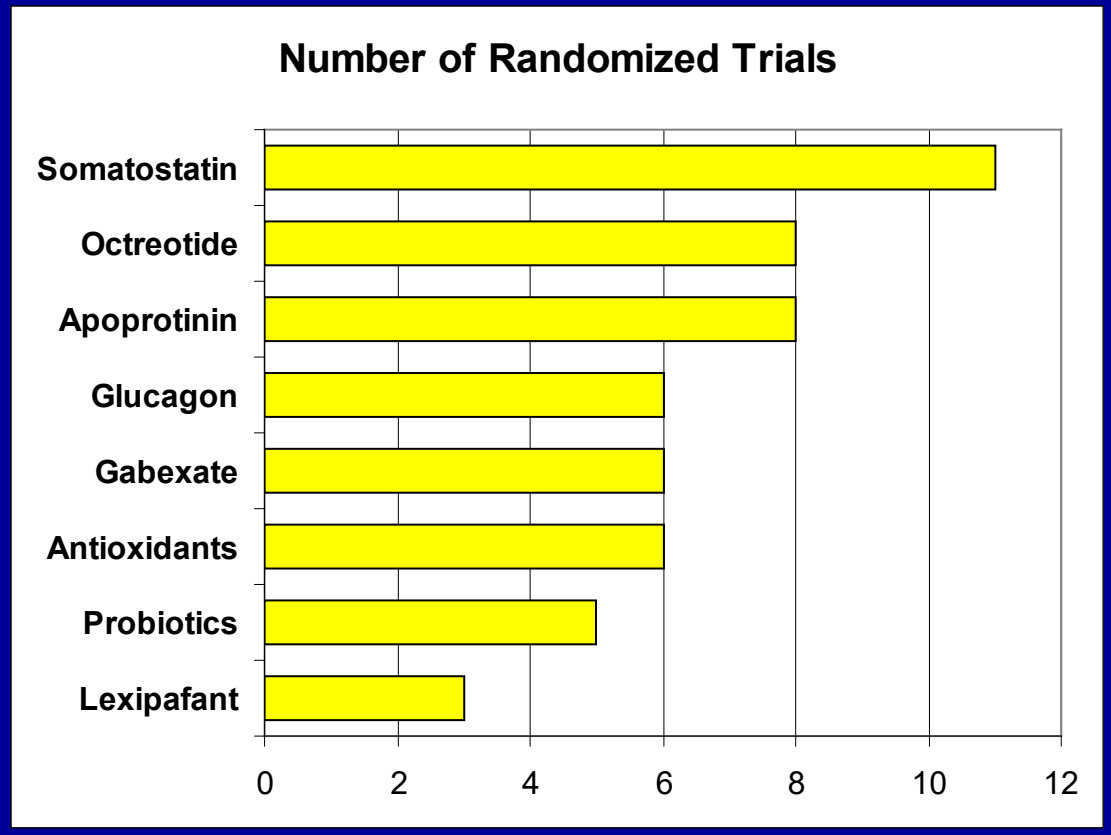
What Research is Needed for the Future: Pain Management

- Address divergent practice patterns and concern that opiates may delay recovery
  - Compare opiates with acetaminophen/NSAIDs (opiates for breakthrough)
  - Outcome: symptoms such as pain, nausea, oral tolerance also length of hospital stay and inpatient complications
- Enhanced recovery bundle akin to surgery in small trial (N=46)
  - Increasing doses of IV dilaudid diet per team versus
  - Early solid diet, around-the-clock Tylenol, with ketorolac moderate pain
  - Shortened time successful refeeding 142.8 to 13.8 hours
  - Need larger trial with standardized diets or a factorial design

Dong, Pancreas 2019; 48(2): 176-181

What Research is Needed for the Future: Pharmaceutical Treatment

- Cochrane Review
  - "Very Low Quality Evidence"
  - NO "consistent clinical benefits with any interventions"
- Low quality studies suggest benefit
- Refuted by higher quality double blind trials



Additional Trials: NSAIDs (n=2), calcitonin (n=2), cimetidine (n=2), ulnistatin (n=2), thymosin (n=1) activated protein C (n=1), iniprol (n=1)

Moggia, Cochrane Library, 2017

Pharmacologic Targets

INJURY: Alcohol toxin, bile, mechanical force

Pathologic Calcium Signalling

--Calcium release-activated channel (CRAC)

-CRAC protein (ORAI1)

-High levels of cytosolic calcium pathologic

Abnormal Cell Processes

-Premature trypsinogen activation-

colocalization l lysosome (cathepsin B) + zymogen

-Mitochondrial dysfunction

High calcium opens permeability transition pores, lose membrane potential->damages calcium clearance mechanisms

-Impaired autophagy and unfolded protein response (high ER stress) needed proper acinar cell function

Lipolysis (i.e. lipase) of pancreatic and peri-pancreatic triglycerides

Free fatty acid injury

-unsaturated fatty acids (linoleic acid) inhibit mitochondria and increase inflammatory response

Pathologic Inflammatory Cascade

-Injured cell release cytokines, chemokines, damage associated molecular patterns

-Activates monocytes, NF-kB pathway/inflammasome pathway, TNF, IL-6, prostaglandins

Lee, Papachristou, Nat Rev Gastro Hepatol 2019; 16: 479-496, Saluja Gastroenterology 2019; 159: 1979-1993

Pharmacologic Agents-Recently Published or Underway

Pathologic Calcium Signalling

--CM4620: Calcium release-activated channel (CRAC) inhibitors

Abnormal Cell Processes

--HMG-CoA inhibitors (statins): promote unfolded protein response

Free fatty acid injury

Pathologic Inflammatory Cascade

-Pentoxifylline-downregulates NF-kB, TNF synthesis

Lactated Ringer's: + GP81 negative regulator for TLR mediated inflammation

NSAIDs: inhibit prostaglandins

Goodman, Pancreas 2022; 51(1): e10-11, Machicado, Cl inTr Gastroenterol 2021; 12: e00415, Huang, Am J Gastroenterol 2020; 115: 473-480, Vege, Pancreatology 2020; 20: 1592-1597,

Pharmacologic Agents-Potential Targets

Pathologic Calcium Signalling

--- GSK-7975A: ORAI1 inhibitor

Abnormal Cell Processes

-TR040303: prevents loss membrane potential

Free fatty acid injury

-Orlistat-inhibit breakdown of triglycerides to free fatty acids

Pathologic Inflammatory Cascade

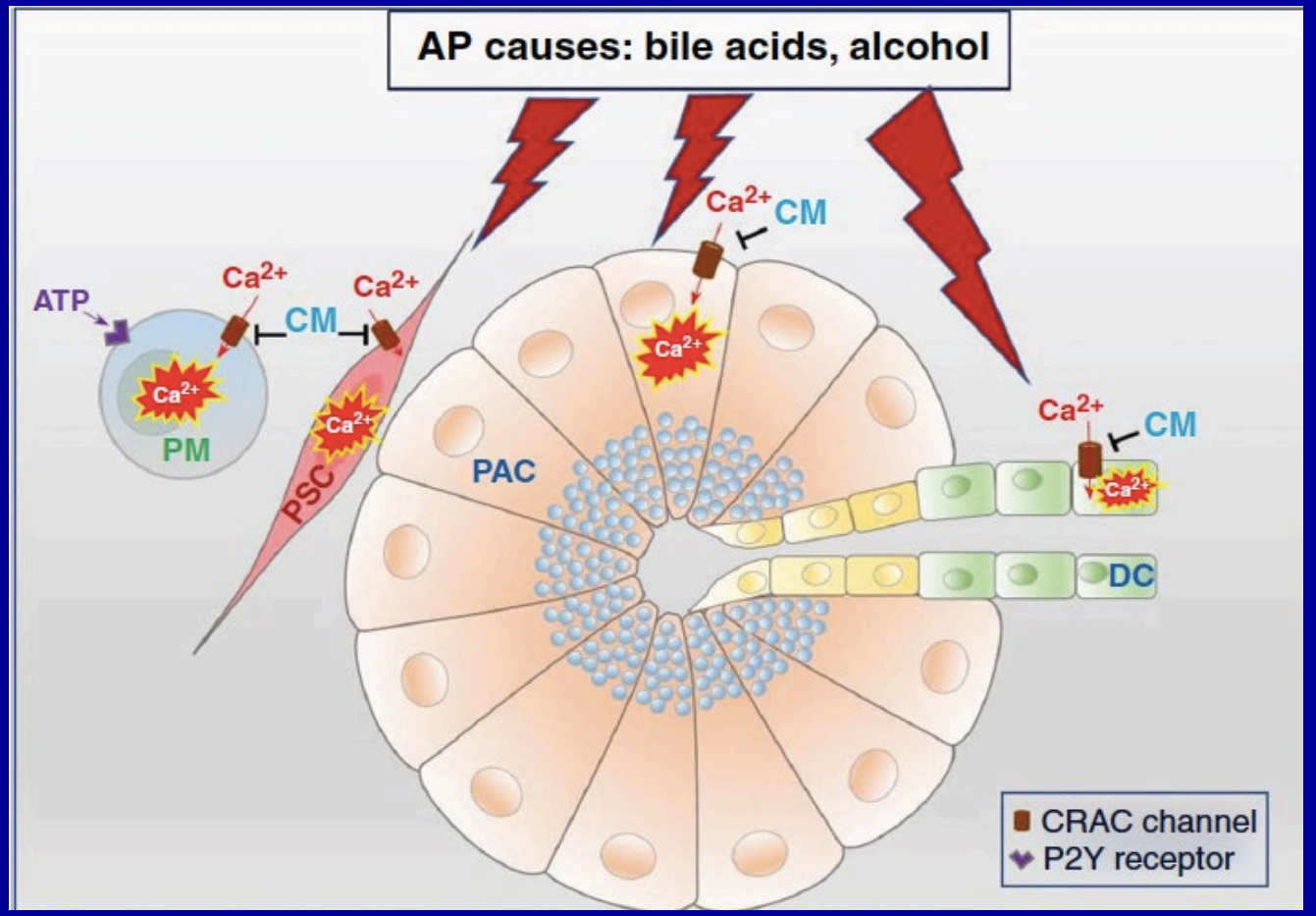
-MCC950 inflammasome pathway inhibitor

-Tocilizumab (IL-6 antiagonist)

Gerasimenko, Proc Nat Acad Sci USA 110: 13186-13191, Stone, NEJM 2017; 377: 317-328, Javed, Pancreas 2018; 47: 18-24, Lee, Papachristou, Nat Rev Gastroenterol Hepatol 2019; 16: 479-496

CM 4620

- Pancreatitis excessive Ca2+ release and depletion intracellular stores
  - Activates calcium release activated (CRAC) channels
    - Destructive feed forward cycle
  - Toxic overload acinar, stellate, and ductal cells of pancreas
    - Damaged cells release ATP, protease, pro-inflammatory cytokines
- CRAC channel inhibitor CM4620 evaluated 2a study to treat acute pancreatitis with hypoxemia and SARS COV2 pneumonia
  - Favorable initial results and safety profile



Bruen, Pancreas 2021;50: 537–543, Gerasimenko, J Phys 2022; 600(7): 1597-1598, Seely, J Clin Inv

CARPO Trial

- Multicenter randomized, double-blind placebo controlled trial CM 4620 (Auxora) Acute Pancreatitis (Phase 2b) (NCT 04681066)
- **Cohort sick enough to benefit**
  - *SIRS*
  - *Requires peripancreatic fluid collection or abdominal guarding/rebound or Hematocrit ≥44 men ≥40 women*
- **Treatment at early, potentially treatable stage**
  - CT scan <12 hours before randomization to confirm ABSENCE of necrosis
  - Enrollment within 6 hours SIRS development
- **Large enough cohort to find significant outcomes and overcome deficiencies in identifying a moderate-high risk cohort**
- Ongoing enrollment at 19 US centers

What Research is Needed in Future-Pharmaceutical Agents

- First-High quality studies (early timing, at risk population, meaningful) of agents to address major targets
  - Abnormal calcium signalling and cell processes, fatty acid injury, inflammatory cascade
- Next-combination of different classes
- Holy Grail- optimal combination of drugs with correct resuscitation, nutrition, pain control!!!

What Research is Needed in Future

- Infrastructure
  - Individual centers with multi-speciality teams
  - Coordinated groups of centers to conduct multi-center trials
  - Enroll at-risk patients early and in large numbers to address meaningful outcomes (utilize quantitative scoring/predictive systems)
- Resuscitation
  - Flooding unselected patients with aggressive hydration is suboptimal
    - Need to study resuscitation more closely targeted to patients volume status
  - Definitive study comparing NS versus LR

What Research is Needed in Future

- Nutrition: Convincing study of early substantial oral diet in non-severe pancreatitis
  - Clarify timing of nutrition for all severity levels
- Pain Management: Define role of non-opiate analgesia
- Drugs: Address aberrant calcium signaling, cellular processes, and subsequent inflammatory and free fatty acid injury
- Ultimate goal is a cocktail of pharmaceuticals and evidence based clinical pathway