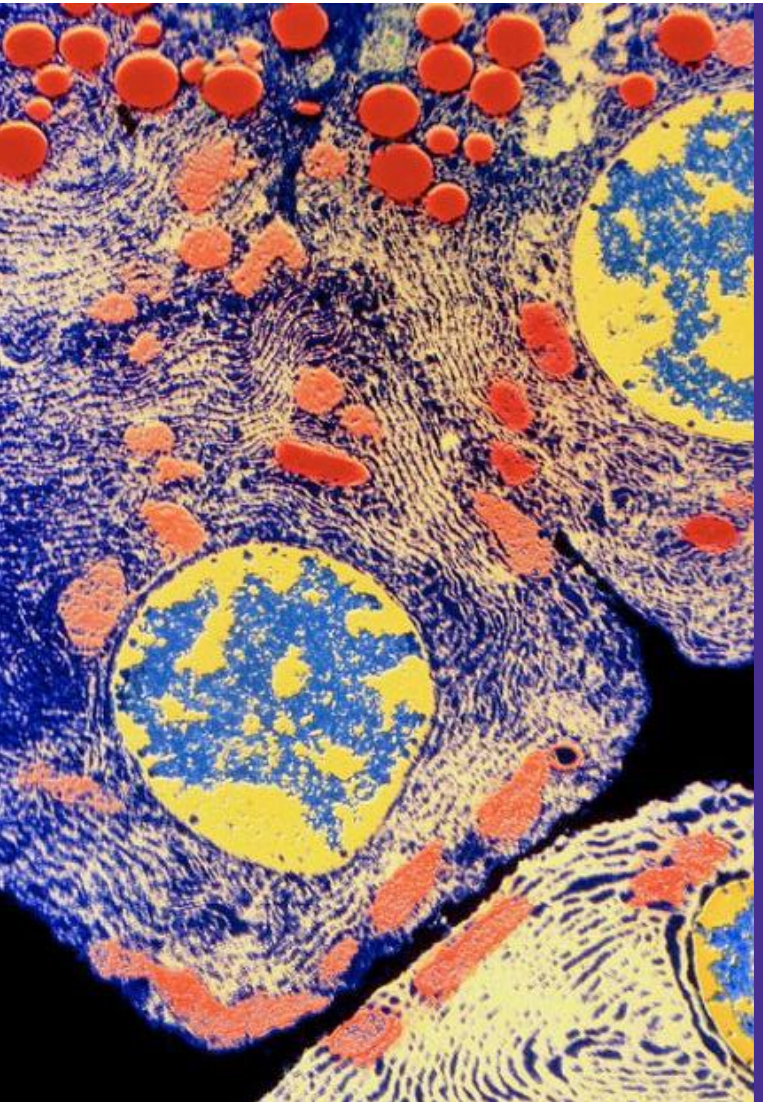
CalciMedica

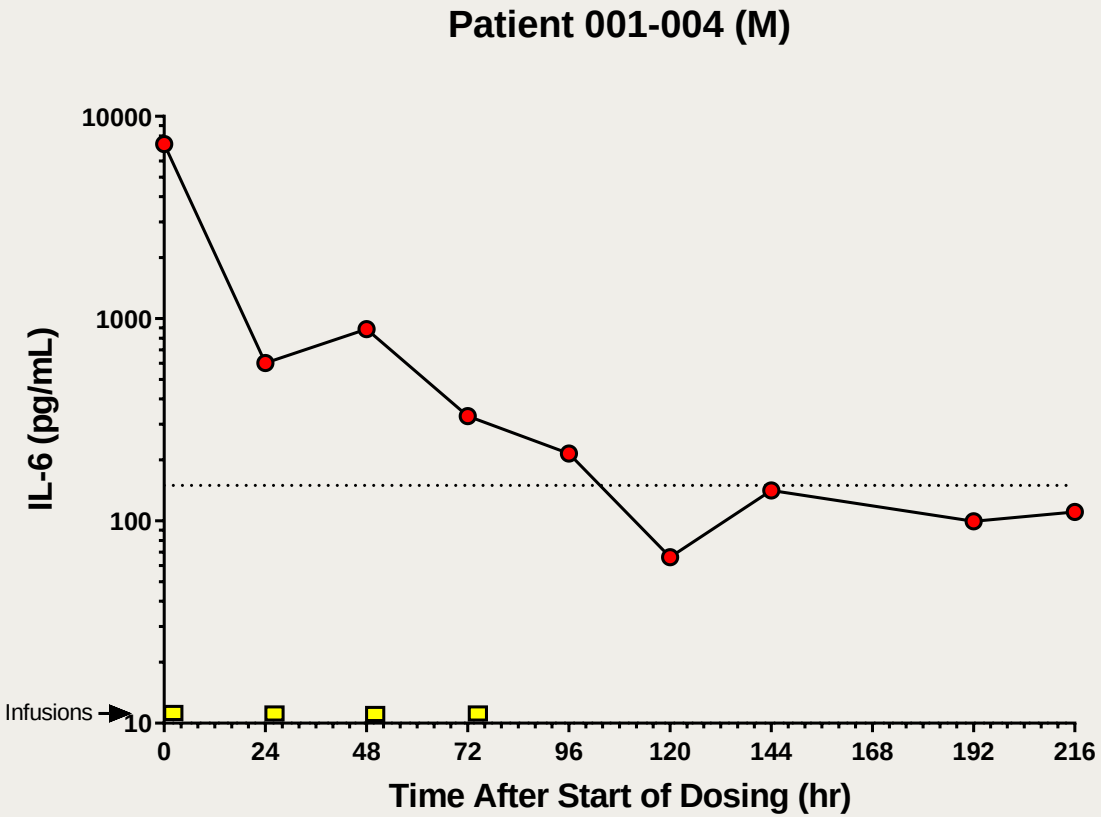


Developing Novel Therapies for Acute Inflammatory and Immunologic Diseases

Acute Pancreatitis Clinical Expert Event

September 21, 2023

Individual Case of a Critically Ill Patient with AP



- Critically ill patient presented with respiratory failure and acute pancreatitis in the ED.
- Randomized to receive high dose of Auxora
- IL-6 >7296 pg/mL at study entry, 66 at 120 hrs
- Managed with high flow oxygen and intermittent bi-pap; no invasive mechanical ventilation
- Discharged home on room air day 8 eating a solid food diet

Forward-Looking Statements

This presentation contains forward-looking statements which include, but are not limited to, statements regarding CalciMedica's business strategy and clinical development plans; the design and potential benefits of CalciMedica's product candidates; CalciMedica's ongoing and planned clinical trials; and the timing for CalciMedica's receipt and announcement of data from its clinical trials. These forward-looking statements are subject to the safe harbor provisions under the Private Securities Litigation Reform Act of 1995. CalciMedica's expectations and beliefs regarding these matters may not materialize. Actual outcomes and results may differ materially from those contemplated by these forward-looking statements as a result of uncertainties, risks, and changes in circumstances, including but not limited to risks and uncertainties related to: the impact of fluctuations in global financial markets on CalciMedica's business and the actions it may take in response thereto; CalciMedica's ability to execute its plans and strategies; the ability to obtain and maintain regulatory approval for CalciMedica's product candidates; results from clinical trials may not be indicative of results that may be observed in the future; potential safety and other complications from CalciMedica's product candidates; economic, business, competitive, and/or regulatory factors affecting the business of CalciMedica generally; CalciMedica's ability to protect its intellectual property position; and the impact of government laws and regulations. Additional risks and uncertainties that could cause actual outcomes and results to differ materially from those contemplated by the forward-looking statements are included under the caption "Risk Factors" in CalciMedica's most recently filed periodic report, and subsequent periodic reports filed by CalciMedica, under the Securities Exchange Act of 1934, as amended, from time to time and available at www.sec.gov. These documents can be accessed on CalciMedica's web page at calcimedica.com.

These forward-looking statements are based on information available to, and expectations of, CalciMedica of the date of this presentation. CalciMedica disclaims any obligation to update these forward-looking statements, except as may be required by law.

Investment Highlights

Differentiated Technology	Proprietary technology targeting CRAC[1] channel inhibition to develop novel therapies for life-threatening inflammatory diseases with high unmet need
Compelling Proof-of-Concept Data	AuxoraTM has been studied in multiple Phase 2 trials, demonstrating positive and consistent clinical results and favorable safety profile
Substantial Market Opportunity	~100K target patient population in acute pancreatitis represents a potential $1B+ U.S. market opportunity with no approved therapies
Next Clinical Milestones	**Acute Pancreatitis[2]** Phase 2b Data 1H24 / **Asparaginase-Induced Pancreatic Toxicity[3]** Phase 1/2 Data 2H23 / **Acute Kidney Injury[4]** Phase 2 1H24 (pending funding)
Strong IP	Composition of matter (2036), formulation (2038), and methods of use (2036-2041+) worldwide patent protection

1) **CRAC:** Calcium release-activated calcium; 2) **AP:** Acute Pancreatitis; 3) **AIPT:** Asparaginase-Induced Pancreatic Toxicity; 4) **AKI:** Acute Kidney Injury

Differentiated Pipeline

Program[1,2]	Indication	Phase of Development				Anticipated Milestones
		Preclinical	Phase 1	Phase 2	Phase 3	
Pancreas						
Auxora	Acute Pancreatitis					CARPO Phase 2b trial ongoing; Data in 1H24
Auxora	Aparaginase-Induced Pancreatic Toxicity					CRSPA Phase 1/2 trial ongoing; Trial expansion underway
CM6336	Chronic Pancreatitis (Oral)					Submit IND in 2024 (pending funding)
Kidney						
Auxora	Acute Kidney Injury					Submit IND 2H23 Phase 2 trial in 1H24 (pending funding)
Lung						
Auxora	ARDS - Ventilated COVID-19 Patients					Data expected 2H23 Will inform the development plan for ARDS

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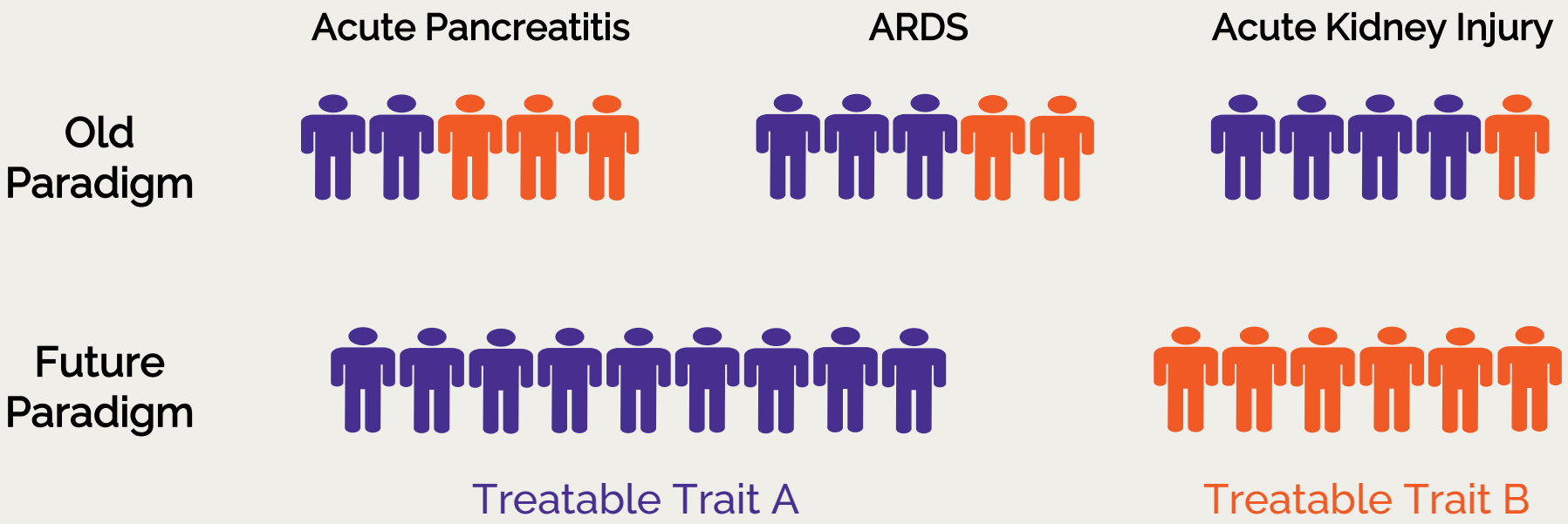
1) Programs in pancreatitis except chronic pancreatitis are funded through steps indicated. Other studies and programs are subject to further funding.
2) All programs are IV for rapid onset in the acute care stetting. CM6018 is intended for chronic oral dosing.

Acute Inflammation: Underlying Cause Across Many Diseases



Auxora has demonstrated positive clinical results in all 3 of these large, underserved patient populations

1) Sources: Reddy, Kiran, Carolyn S. Calfee, and Danny F. McAuley. "Acute respiratory distress syndrome subphenotypes beyond the syndrome: a step toward treatable traits?." American Journal of Respiratory and Critical Care Medicine 203.12 (2021): 1449-1451.

Large U.S. Market Opportunity in Acute Inflammatory Diseases

AP with SIRS[1]	AKI Stages 2 & 3	AIPT
		
• <u>No approved therapies</u> • SOC[2] primarily supportive care • Disease progression: ➢ Severe AP ➢ Pancreatic necrosis ➢ Mortality	• <u>No approved therapies</u> • SOC primarily supportive care • Disease progression: ➢ Chronic kidney disease ➢ End stage renal disease ➢ Mortality	• <u>No approved therapies</u> • Ultra-orphan pediatric indication • Potentially PRV[3] eligible • Accelerated approval opportunity • Disease progression: ➢ Pancreatic necrosis in 50%

Patient figures represent estimated numbers of annual U.S. cases

1) **SIRS**: Systemic Inflammatory Response Syndrome; 2) **SOC**: Standard of Care; 3) **PRV**: Priority Review Voucher;
4) Sources: Primary Market Research, KOLs, Healthcare Cost and Utilization Project, Pancreatitis Foundation

Anticipated Milestones

AP	Phase 2b Data Expected in 1H24 Phase 3 Initiation Expected in 2025
AIPT	Initial First Cohort Data Release Expected in 4Q23 Trial Expansion Underway
AKI	IND filing Expected in 2H23 Phase 2 Clinical Trial Initiation 1H24 (pending funding)
ARDS	Phase 2 Data in Ventilated COVID Patients Publication Expected in 2H23 Will inform the development plan for ARDS
Cash Runway	Current Cash Runway into 2H24

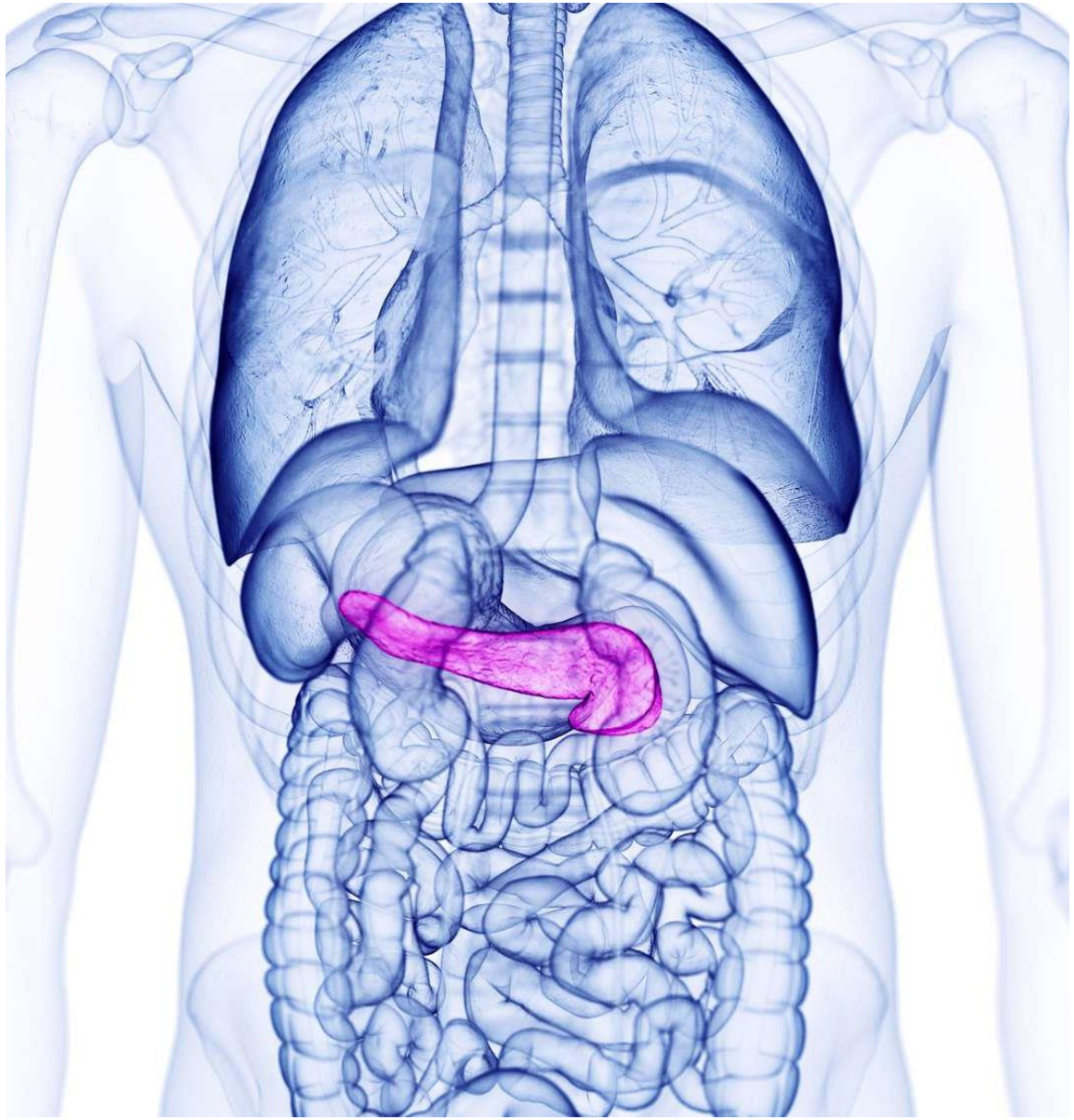
HENRY FORD HEALTH®

Acute Pancreatitis

Joseph Miller, MD, MS
Clinical Associate Professor
Henry Ford Health | Michigan State University
Department of Emergency Medicine

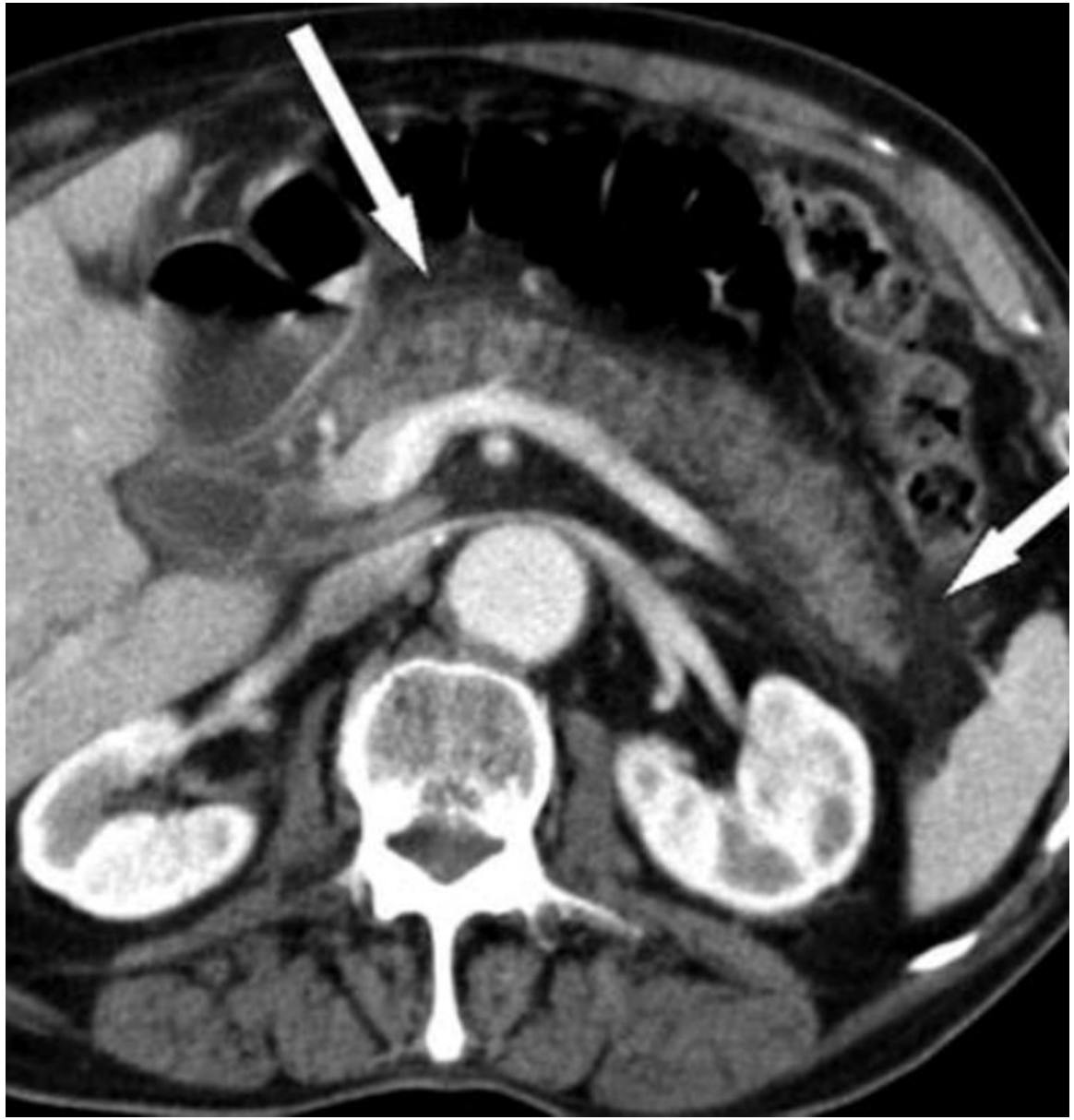
Acute Pancreatitis

- Definition:
  - Acute inflammation of the pancreas
- Clinical Presentation:
  - Patients have constant abdominal pain
  - Pain may radiate to back
  - Pain aggravated by eating, drinking, lying down
  - Associated symptoms may include nausea, vomiting, low to moderate grade fever



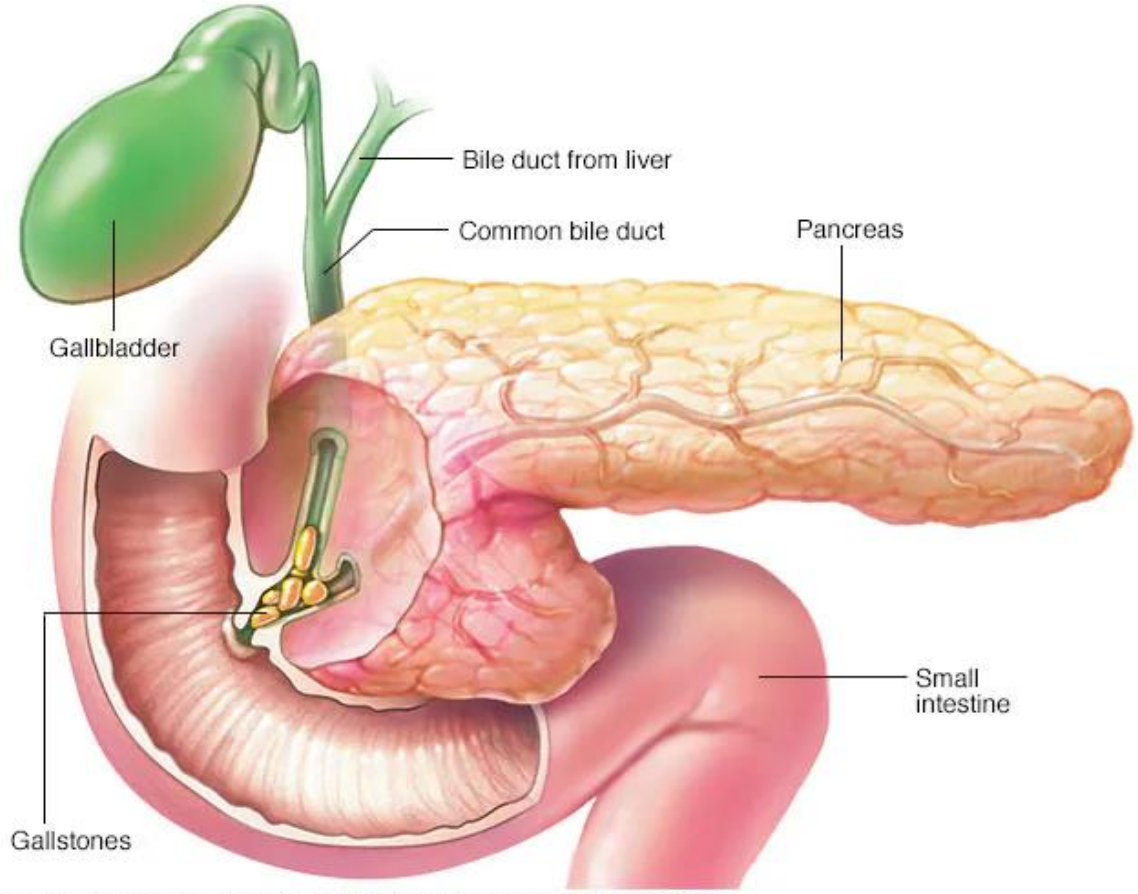
Diagnosis

- Presence of at least 2 of the 3 following criteria:
  - Abdominal pain suggestive of acute pancreatitis
  - Serum amylase or lipase >3x upper limit of normal
  - CT or MRI findings consistent with acute pancreatitis



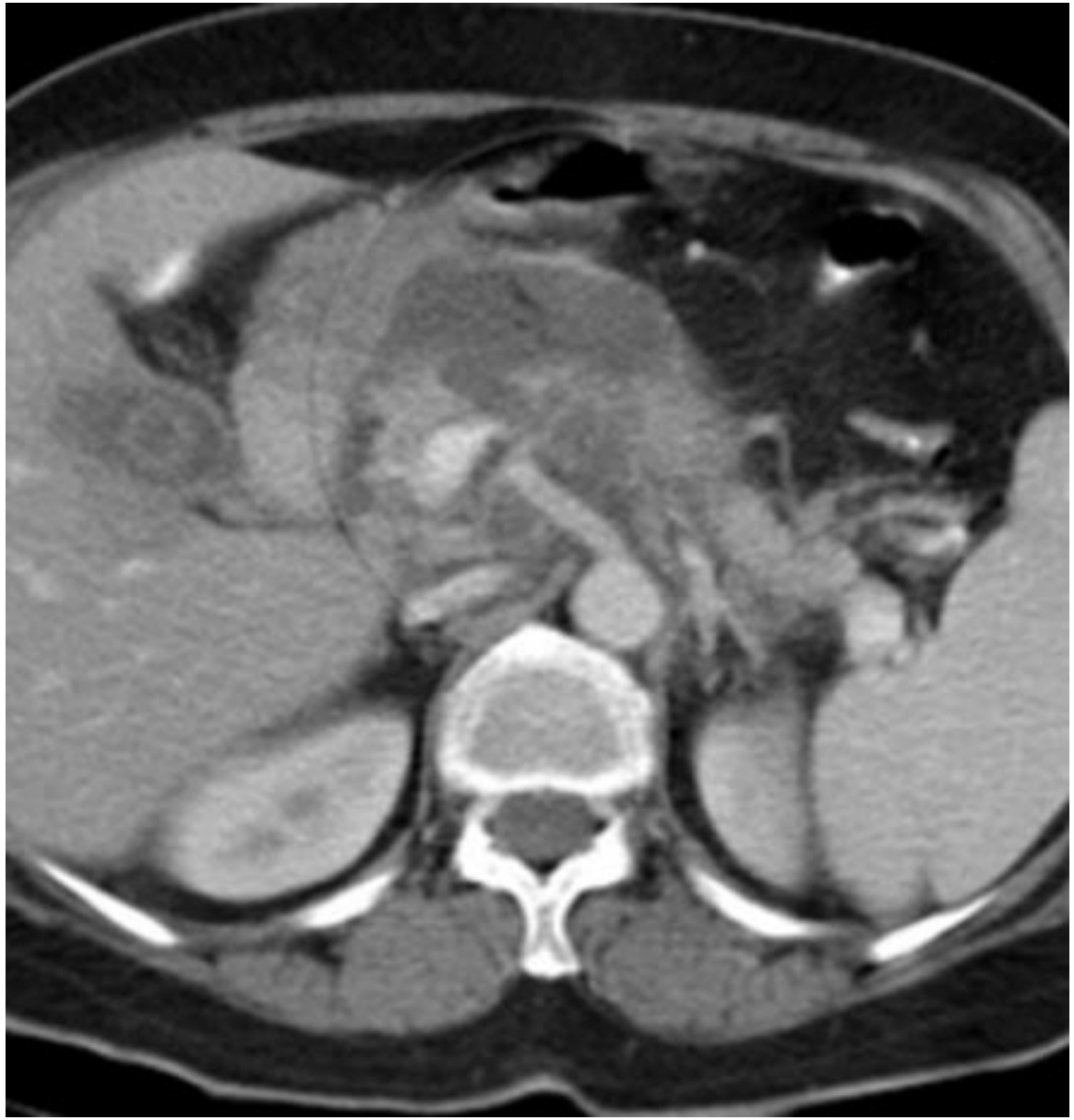
Etiology

- Etiology
  - Gallstones 40%
  - Alcohol 30%
  - Hypertriglyceridemia 5%
  - Others include: hypercalcemia, trauma, iatrogenic, medications



Prognosis

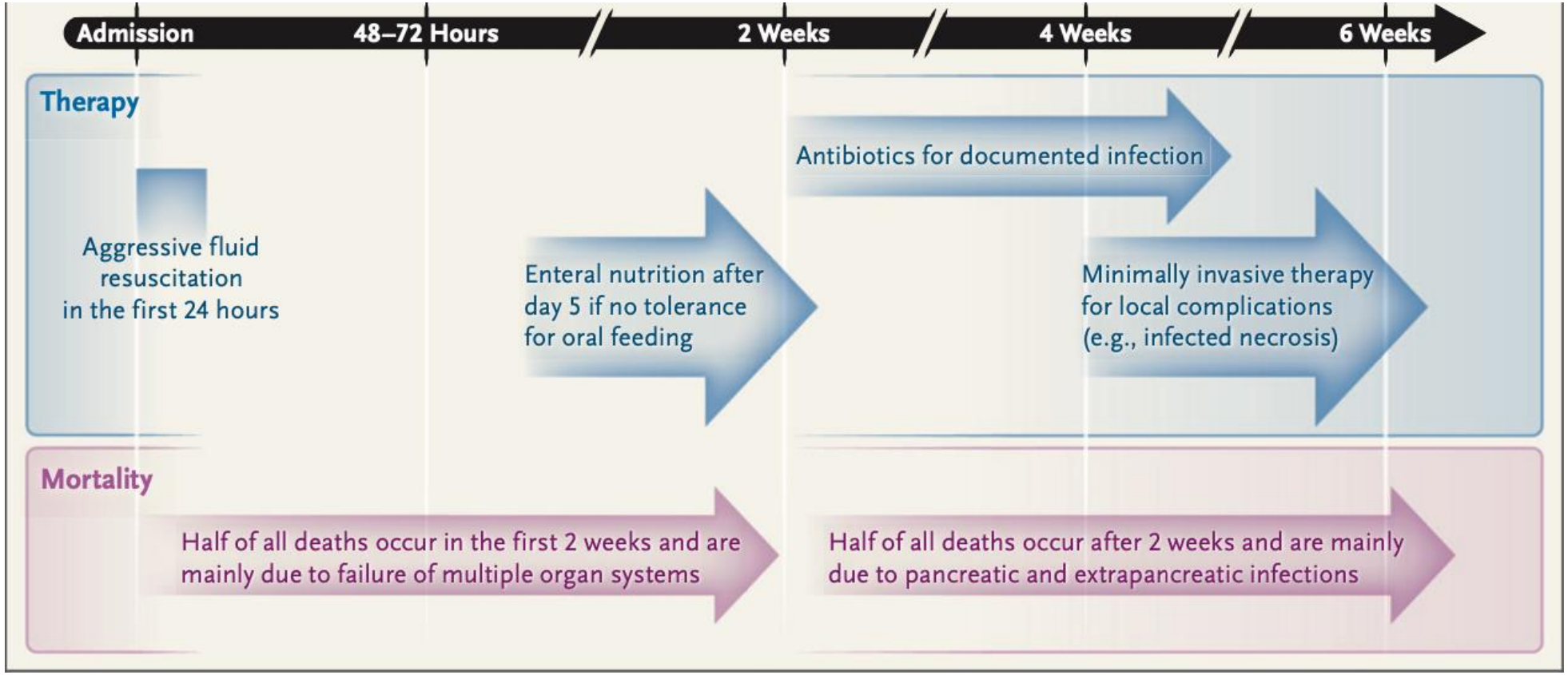
- 80% develop mild disease (no complications) or moderately severe disease (develop a local complication such as a fluid collection around the pancreas or necrosis of the pancreas)
- 20% develop severe disease- development of organ failure, usually the lung
- Mortality 20% in patients who develop severe disease!



Goals in the ED

- Rapid Diagnosis of Acute Pancreatitis
  - Straightforward with current diagnostic criteria
- Identification of Patients at Risk of Developing Severe Disease
  - Presence of Systemic Inflammatory Syndrome
  - Presence of Hypoxemia
  - Age >60 years + SpO2 <96% + SIRS had almost 42 times the odds of death
- Triage to Appropriate Hospital Unit
  - Hospitalist
  - Surgeon
  - Intensivist

Current Management: Limited



***Those at Risk for Severe Disease Treated No Differently Than Those at Risk for Mild Disease**

HENRY FORD HEALTH®

N Engl J Med 2016;375:1972-81

Economic Burden

- 288,220 annual number of hospitalizations in 2018 in US with AP as principal diagnosis
- 15.4% readmission rate within 30 days
- Aggregate cost 3 billion dollars

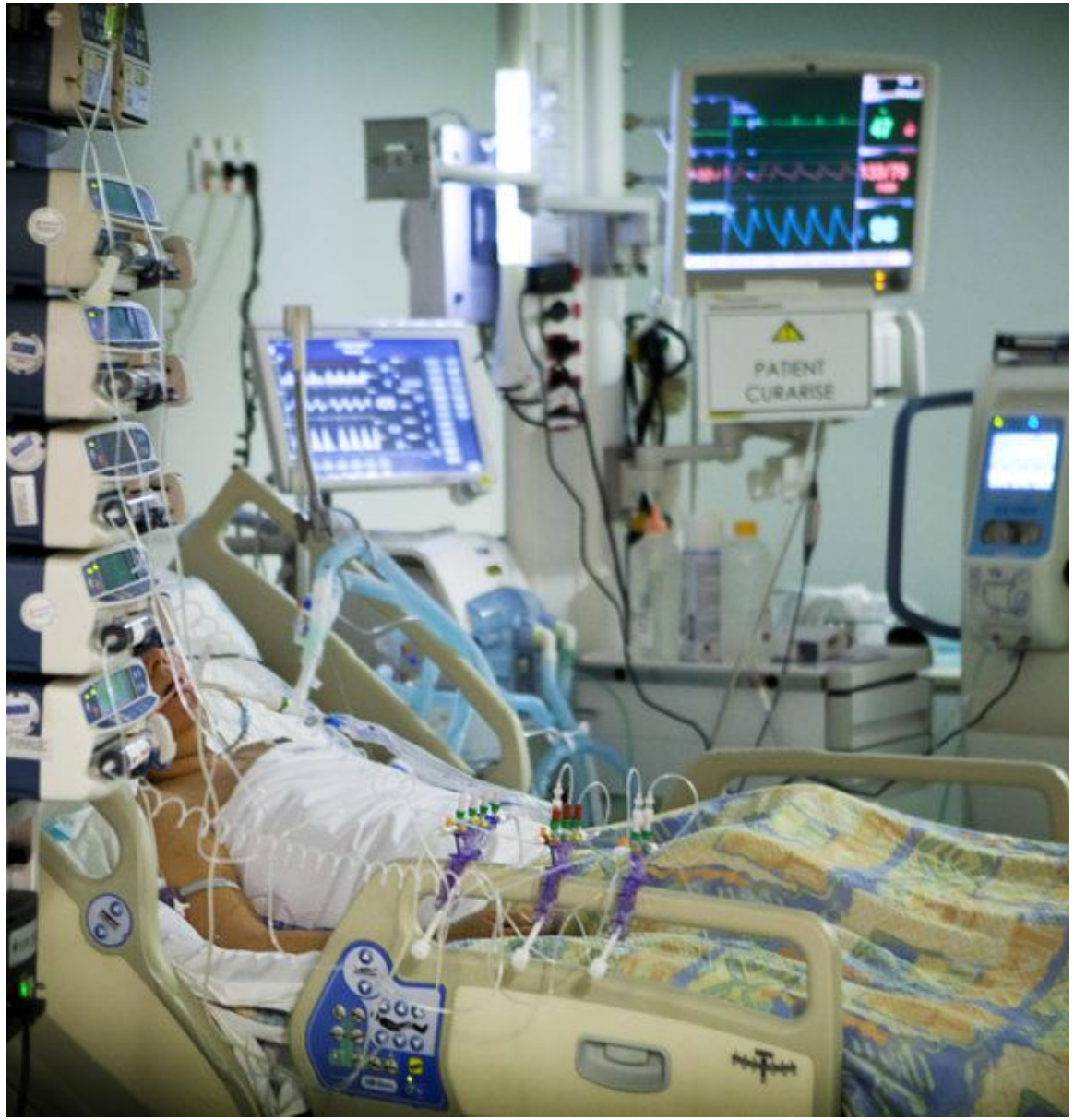
Peery, Anne F., et al. "Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2021." Gastroenterology 162.2 (2022): 621-644.

Patient Story

HENRY FORD HEALTH®

AP Patient

- 68 year-old female with gallstone pancreatitis
- Admitted to hospital and soon sent to ICU
- Placed on ventilator for lung injury
- Delirium
- Pneumonia
- Infected pancreatic pseudocysts
- Gastrointestinal bleeding
- Became dialysis dependent
- Hospital stay = 90 days



HENRY FORD HEALTH®

Advances in Acute Pancreatitis

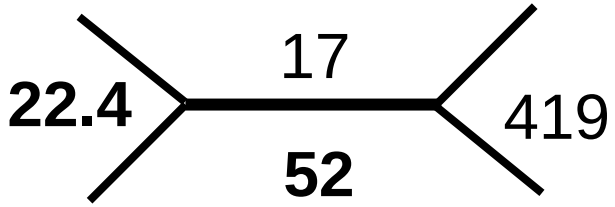
Georgios Papachristou, MD PhD
Professor and Chief
Division of Gastroenterology, Hepatology, and Nutrition

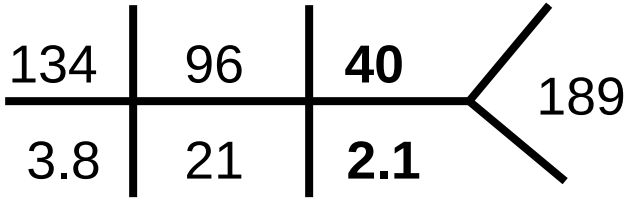
Case presentation

- **HPI**
  - 58 yo M with acute onset of severe upper abdominal pain radiating to back x 3 hours
  - Nausea and vomiting
- **Exam**
  - VS: T 38.5, HR 117, RR 24, BP 84/43, BMI 43
  - Moderate distress
  - Abdomen: obese, +BS, soft, tender with no guarding

Case presentation

- **Labs**





What is the Diagnosis?

Acute Pancreatitis

T

ALT 790

Triglycerides 153

AST 624

LDH 755

AP 167

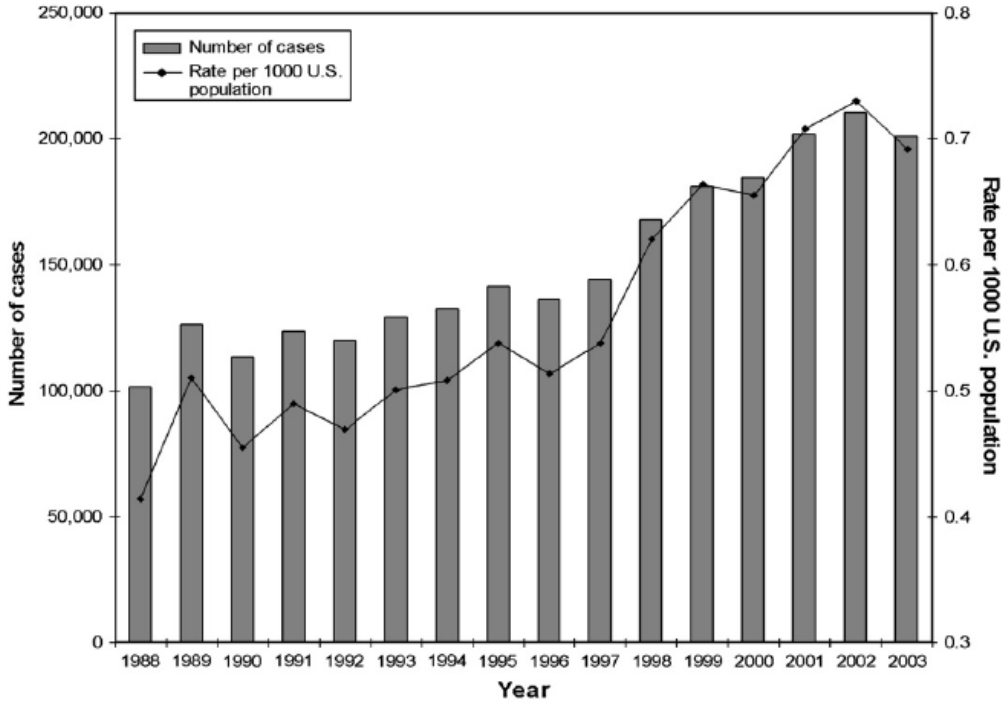
Ca 8.8 with nl Alb

Epidemiology & Burden of AP

Common and costly disease

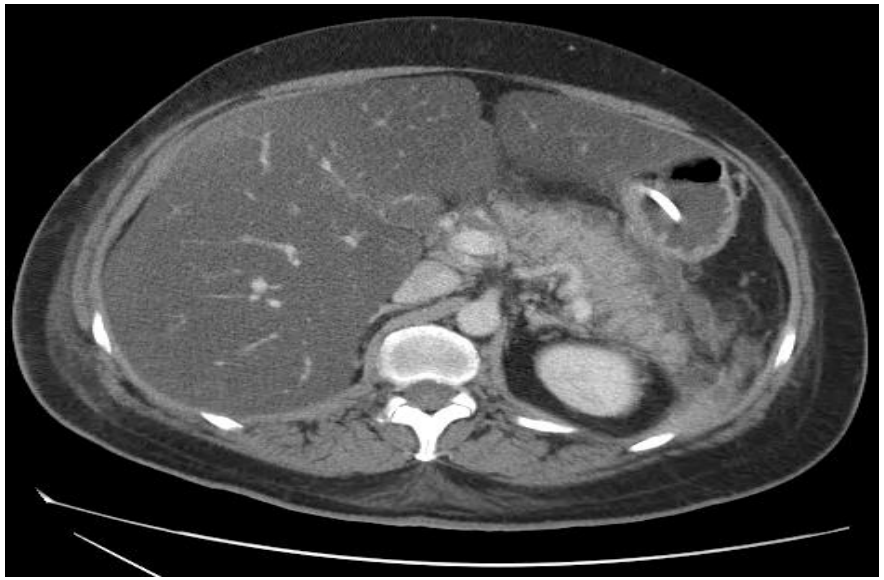
- ~300k hospitalizations/year
- Annual cost ~3 billion dollars in US

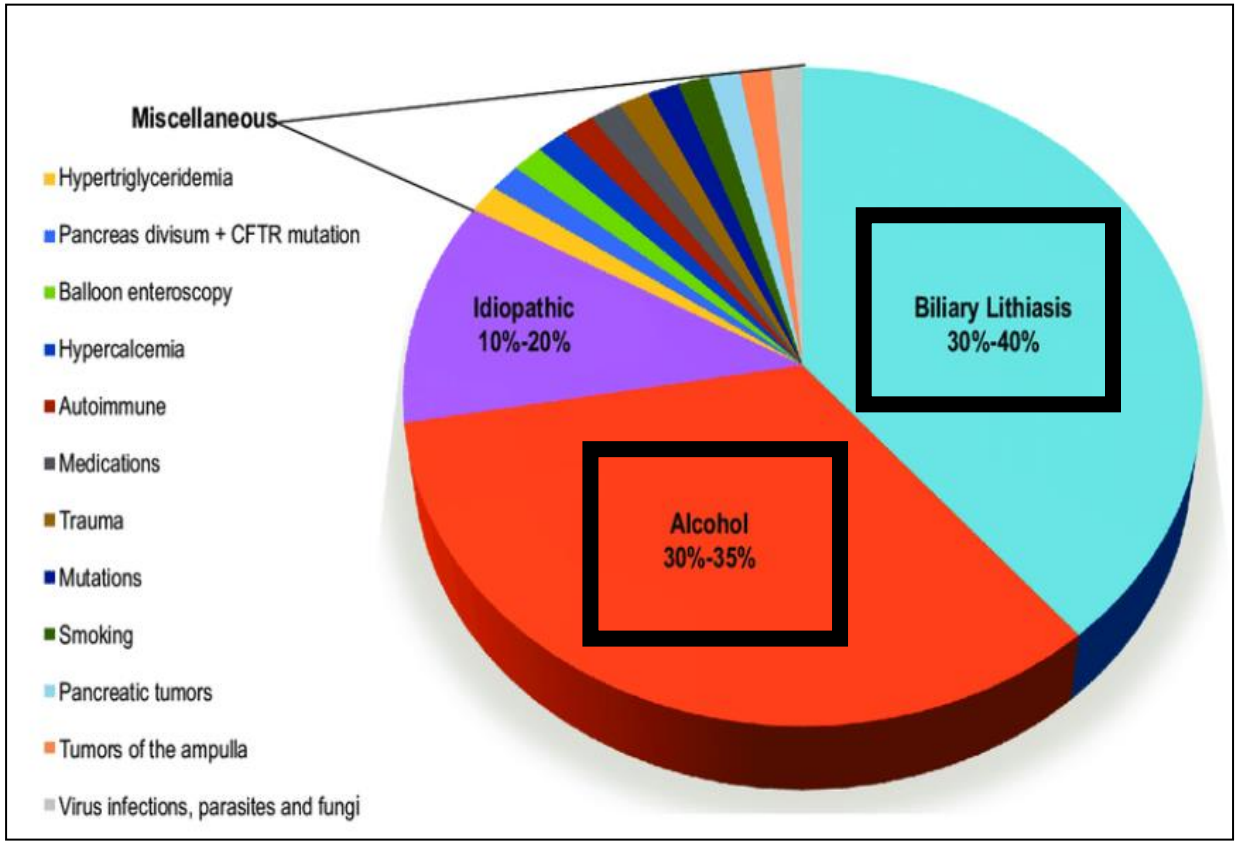
- **Incidence increasing worldwide**
  - Awareness
  - Overdiagnosis
  - Obesity epidemic: gallstones



AP: Diagnosis and Etiology

- **≥ 2 of 3 Criteria**
  - Typical upper abdominal pain
  - Amylase/lipase >3x ULN
  - Imaging findings





Diaz et al, Rev Col Gastroenterol, 2015
Otero, Edit Panam Form e Impresos, 2016

Dynamic Process

- Rapid progression
- Early assessment is key
- Important to assess which patients will progress to severe disease
- Start supportive therapy immediately

Definition of Severity

1. **Severe (5-10%)**

   Persistent Organ failure (>48 hrs) of ≥1 of the following:

   a. Shock - Systolic BP <90 mm Hg

   b. Pulmonary - PaO_2 < 60 mm Hg

   c. Renal – Creatinine >2 mg/dL, after rehydration

2. **Moderately Severe (5-10%)**

   Local Complications: pancreatic necrosis, fluid collections

   Exacerbation of chronic comorbidities

   Transient organ failure (<48 hrs)

3. **Mild (80-85%)**

Revised Atlanta Classification (2013)

Morbidity & Mortality of AP

Short-term complications (within 2 weeks)

- Driven by systemic inflammatory response to pancreatic injury
- Majority of deaths occur due to multi-system organ failure

Long-term complications (>2 weeks)

- Mostly driven by infected necrotic pancreatic collections
- Thought to occur from seeding via bloodstream or translocation of gut microorganisms

Risk Stratification

Back to our patient

Prediction of SAP: Ranson's Criteria

- **On admission**
  - Age over 55 — **Yes**
  - WBC > 16K — **Yes**
  - Glucose > 200 mg/dl — **No**
  - LDH over 350 IU/DL — **Yes**
  - ALT over 250 IU/dl — **Yes**
- **First 48 hours**
  - Hct decreases over 10% — **?**
  - BUN rise over 5 mg/dl — **?**
  - Serum calcium below 8 mg/dl — **?**
  - Arterial PO2 below 60 mmHg — **?**
  - Base deficit over 4 mEq/L — **?**
  - Fluid sequestration > 6 liters — **?**

Signs:	0-2	3-4	5-6	7-8
% Died	0.9	16	40	100
% ICU	3.7	40	93	100

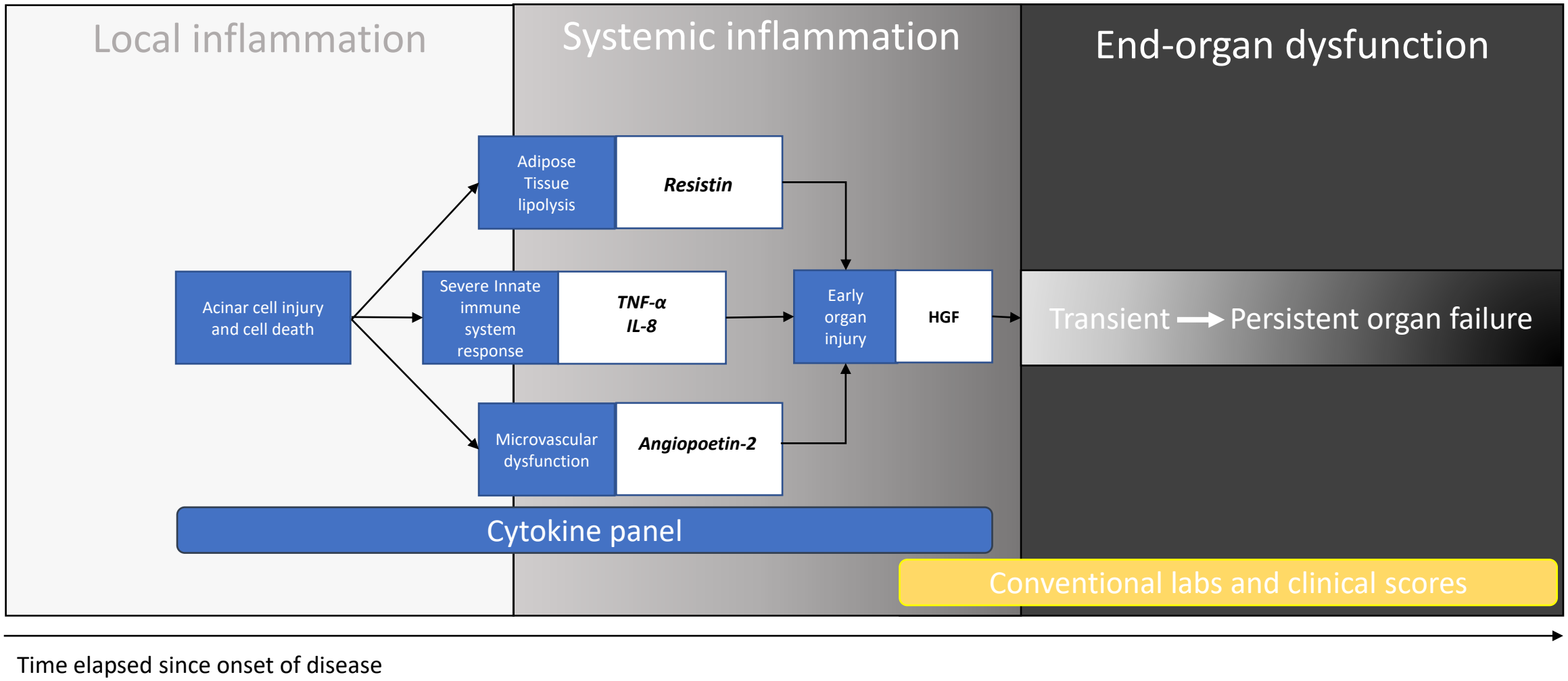
Plethora of Prognostic Scores

Score	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC	Complete data[a]
APACHE-II	7	0.84 (±0.11)	0.71 (±0.06)	0.49 (±0.11)	0.93 (±0.08)	0.77 (±0.07)	96%
BISAP	2	0.61 (±0.20)	0.84 (±0.04)	0.54 (±0.10)	0.87 (±0.10)	0.72 (±0.10)	100%
Glasgow	2	0.85 (±0.08)	0.83 (±0.07)	0.61 (±0.06)	0.95 (±0.05)	**0.84** (±0.06)	98%
HAPS	1	0.70 (±0.11)	0.53 (±0.21)	0.32 (±0.11)	0.85 (±0.13)	0.62 (±0.06)	99%
JSS	2	0.59 (±0.13)	0.92 (±0.05)	0.70 (±0.16)	0.88 (±0.07)	0.76 (±0.07)	95%
Panc 3	1	0.76 (±0.15)	0.52 (±0.05)	0.34 (±0.11)	0.87 (±0.11)	0.64 (±0.06)	99%
POP	9	0.57 (±0.15)	0.76 (±0.06)	0.43 (±0.16)	0.85 (±0.08)	0.67 (±0.09)	99%
Ranson	2	0.66 (±0.09)	0.78 (±0.10)	0.49 (±0.17)	0.88 (±0.08)	0.72 (±0.06)	98%
SIRS	2	0.70 (±0.18)	0.71 (±0.04)	0.43 (±0.10)	0.88 (±0.11)	0.70 (±0.10)	98%
BUN	23	0.56 (±0.10)	0.86 (±0.05)	0.57 (±0.14)	0.86 (±0.05)	0.71 (±0.03)	98%
Creatinine	1	0.77 (±0.09)	0.59 (±0.04)	0.38 (±0.08)	0.89 (±0.04)	0.68 (±0.06)	98%
Validation cohort							
APACHE-II	7	0.97 (±0.08)	0.44 (±0.06)	0.14 (±0.04)	0.99 (±0.02)	0.71 (±0.05)	100%
BISAP	2	0.62 (±0.20)	0.76 (±0.04)	0.20 (±0.06)	0.96 (±0.04)	0.69 (±0.11)	100%
Glasgow	2	0.65 (±0.24)	0.82 (±0.05)	0.22 (±0.08)	0.97 (±0.02)	**0.74** (±0.10)	91%
HAPS	1	0.73 (±0.26)	0.58 (±0.09)	0.12 (±0.06)	0.97 (±0.02)	0.66 (±0.09)	92%
JSS	2	0.42 (±0.19)	0.89 (±0.05)	0.23 (±0.18)	0.95 (±0.01)	0.66 (±0.11)	91%
Panc 3	1	0.62 (±0.31)	0.52 (±0.05)	0.11 (±0.05)	0.94 (±0.04)	0.57 (±0.16)	100%
POP	9	0.46 (±0.31)	0.81 (±0.04)	0.16 (±0.12)	0.95 (±0.02)	0.64 (±0.16)	90%
Ranson	2	0.46 (±0.28)	0.80 (±0.03)	0.16 (±0.11)	0.95 (±0.02)	0.63 (±0.15)	91%
SIRS	2	0.69 (±0.16)	0.58 (±0.04)	0.11 (±0.03)	0.96 (±0.03)	0.64 (±0.01)	93%
BUN	23	0.65 (±0.26)	0.81 (±0.04)	0.21 (±0.09)	0.97 (±0.03)	0.73 (±0.13)	96%
Creatinine	1	0.77 (±0.20)	0.63 (±0.07)	0.14 (±0.12)	0.97 (±0.02)	0.70 (±0.11)	98%

Existing scores have only modest predictive accuracy of ≤ 0.75

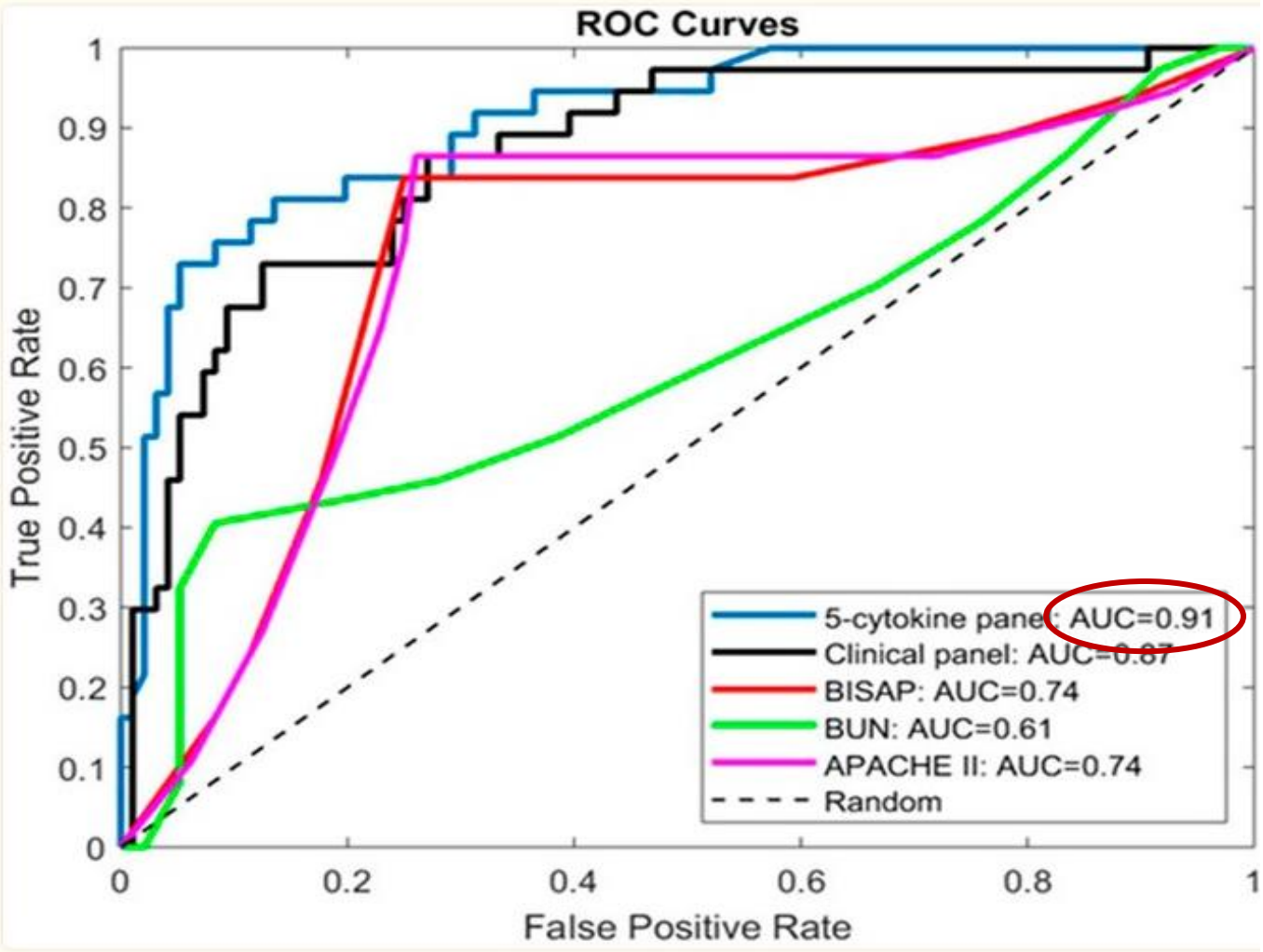
Mounzer R, Papachristou GI et al, Gastroentrol 2012

Conceptual Model for Prediction of Severe AP



Lee PJ, et al. CTG 2021

Multi-cytokine panel's AUC



Lee PJ, …, Papachristou GI. Clin Transl Gastroenterol 2020

MoSAIC Study

- NIH-funded, observational, multi-center study focusing on early events in AP
- Collaboration between Immunologists & Pancreatologists
- Aim 1: Validate the novel multi-cytokine panel for early prediction of SAP
- Aim 2: Identify circulating immune cells that correspond with early cytokine signatures & characterize the immune pathways driving SAP development

MoSAIC Study

CLINICAL

- ~200 AP subjects within 36 hrs
- 4 enrolling sites
  - OSU, UPMC, UIC & USC
- A well-phenotyped data registry and a robust biorepository

IMMUNOLOGIC

- Early & Serial Blood Samples (enrollment, D2 and D7)
- Cytokine measurement (OLINK)
- Mass Cytometry for Immune Cell Shifts (CyTOF)
- Whole blood RNAseq for Transcriptional Signatures

Back to AP Management: Supportive Care

- No AP-specific Pharmacologic Therapy available
- Early Fluid Resuscitation
- Pain Control

- Nutritional Support
- Correction of Primary Insult
  - Consider early ERCP
  - Cease Alcohol use
  - Correct Triglyceride or Calcium levels
- Prevention of Future Attacks

Fluid Resuscitation
WATERFAL trial

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. Carruza, and F. Bolado, for the ERICA Consortium*

Table 3. Safety Outcomes.*

Outcome	Aggressive Fluid Resuscitation (N=122)	Moderate Fluid Resuscitation (N=127)	Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)	P Value
Fluid overload†					
Moderate-to-severe fluid					
Symptoms of fluid overl					
Signs of fluid overload					
Peripheral edema					
Pulmonary rales					
Increased jugular venous pressure, hepatojugular reflux, or both	5 (4.1)	3 (2.4)	1.74 (0.42–7.16)	1.55 (0.33–7.11)	0.58
Evidence of fluid overload on hemodynamic testing or imaging	13 (10.7)	7 (5.5)	1.93 (0.80–4.68)	1.34 (0.54–3.36)	0.53
Evidence of heart failure on echocardiogram	0	1 (0.8)	0.35 (0.01–8.43)§	NA	0.32
Radiographic evidence of pulmonary congestion	13 (10.7)	7 (5.5)	1.93 (0.80–4.68)	1.34 (0.54–3.36)	0.53
Invasive cardiac catheterization	1 (0.8)	2 (1.6)	0.52 (0.05–5.67)	0.50 (0.05–5.51)	0.56

Aggressive Fluid Resuscitation does not prevent Moderately Severe/Severe AP (22% vs. 17%), but results in significant Fluid Overload (21% vs. 6%, p=0.004)

De Madaria et al, NEJM, 2022

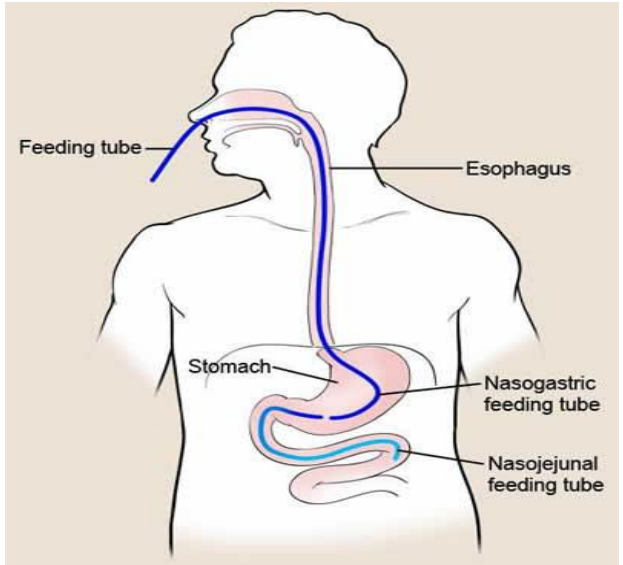
Fluid Resuscitation

- Inadequate Hydration → Hypotension, Renal Dysfunction, Damage to Pancreatic Microcirculation
- Cornerstone of Therapy
  - 1 L bolus, followed by 150 cc/hr of IVF for 48hr
  - **Lactated Ringers** preferred: decreases Pancreatic Acidosis, Trypsin Activity, & the Inflammatory Response (**WATERLAND** trial underway)
- Adequacy assessed by improvement in vitals, urine output, correction of hemoconcentration (BUN, Cr, Hct)

Wu et al. Clin Gastro Hep, 2010
Vege et al, Gastro, 2018

Nutritional Support (NS)

- In mild AP, attempt oral feeding within 24h
- NS required in AP pts predicted to remain fasting for >72h (Severe AP, large PNec)
- ~30% of pts in tertiary centers receive NS
- Enteral feeding (NG or NJ) preferred to TPN



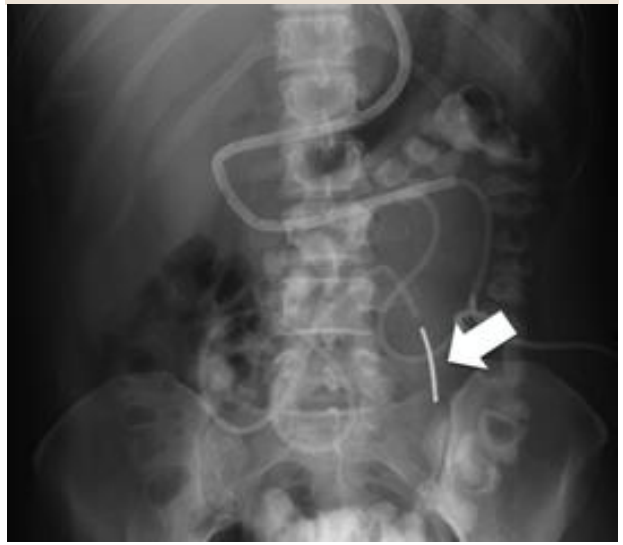


Table 3
Effect of enteral nutrition compared with parenteral nutrition on clinical outcomes

	Infection	Organ Failure	LOS	SIRS	Mortality
McClave et al,[15] 2006	++	++	+	NR	None
Al-Omran et al,[13] 2010	NR	NR	+	None	++
Blaser et al,[3] 2017	++	NR	NR	None	NR
Petrov et al,[4] 2008	++	None	NR	NR	++

McClave et al, JPEN 2006
Crockett et al, 2018
Machicado et al, Pancreas, 2018
Roberts et al, Gastro Clin N Am, 2019

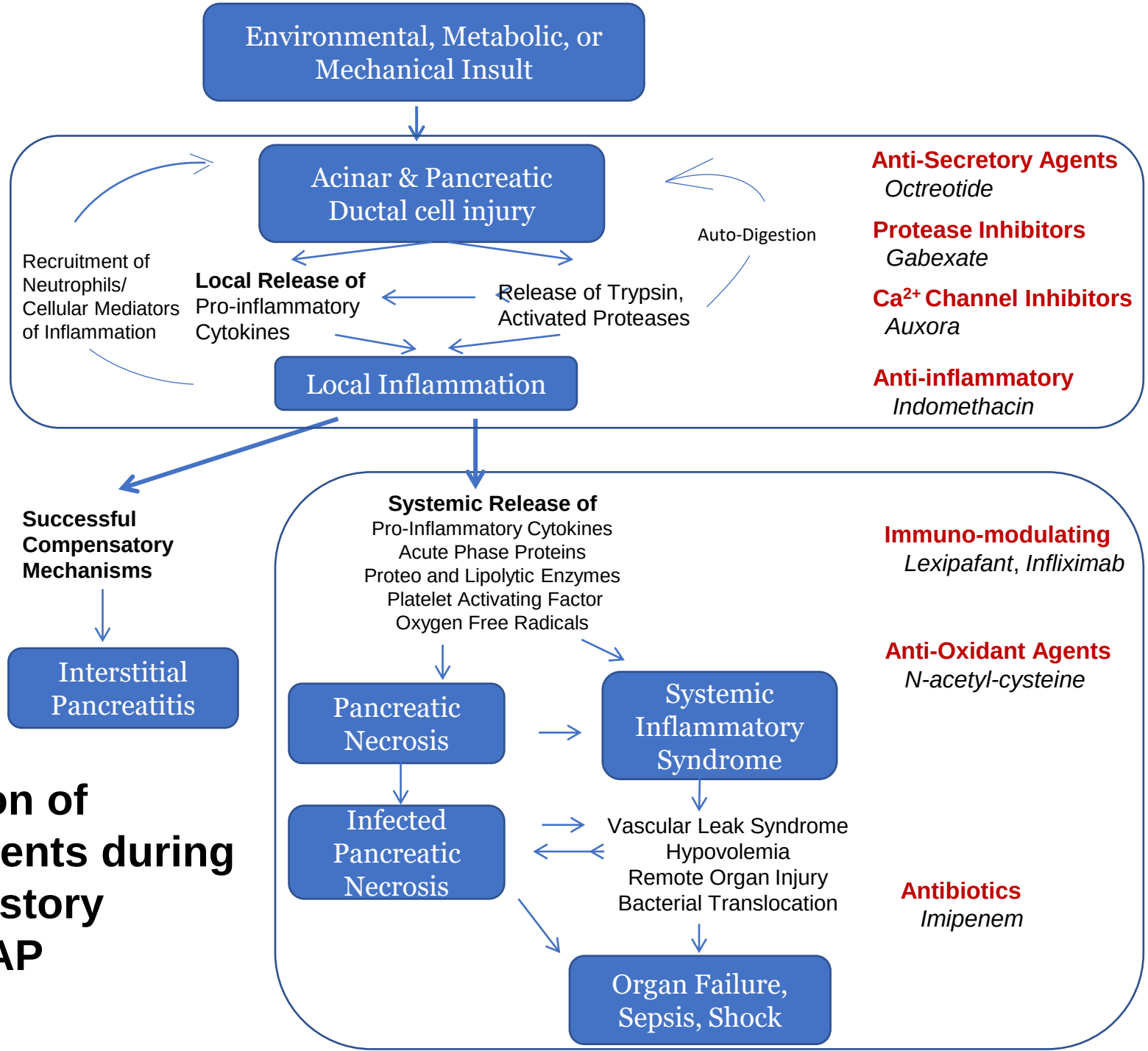
Specific AP-Modifying Therapies

- Molecular targets

- Historical perspectives
  - Clinical trial successes and failures

There is great interest in developing therapeutics for AP, currently no specific disease-modifying therapies

Sites of Action of Pharmacological Agents during the Natural History of Severe AP



Historical Randomized Trials

TABLE 2. Randomized Trials on Medical Treatment for Severe AP

Reference	n	Level of Evidence	Design	Treatment	Dosage	Application	Need for surgery	Sepsis	MOF	Mortality
Buchler et al[19]	115	I	db	Gabexate	53 mg/kg per day	Cont inf	25/115[§] (22%)	—	—	18/115 (16%)
	108			Placebo			23/108[§] (21%)	—	—	16/108 (15%)
Chen et al[22]	26	II	rand	Gabexate	100 mg/hr	Cont inf	7/27 (25,9%)*	—	—	2/26 (7.7%)*
	26			Control			13/26 (50%)	—	—	8/26 (30, 8%)
Johnson et al[27]	148	I	db	Lexipafant	100 mg/day	Cont inf	—	4/148 (3%)*	85/148 (57%)	14/148 (10%)
	138			Placebo			—	13/138 (9%)	80/138 (58%)	21/136 (15%)
McKay et al[28]	26	I	rand	Lexipafant	100 mg/day	Cont inf	—	—	2/11[†] (18.2%)	3/26 (11.5%)
	24			Placebo			—	—	5/15[†] (33.3%)	6/24 (25%)
Uhl et al[31]	98	I	db	Octreotide	100 μg	3 × 1 sc	13/98 (13%)	4/98 (4.1%)	—	15/98 (15%)
	101			Octreotide	200 μg	3 × 1 sc	14/101 (14%)	5/101 (5%)	—	12/101 (12%)
	103			Placebo			19/103 (18%)	4/103 (3.9%)	—	16/103 (16%)
Paran et al[35]	25	II	rand	Octreotide	100 μg	3 × 1 sc	—	6/25 (24%)*	2/25 (8%)[‡]	2/25 (8%)*
	25			Control			—	19/25 (76%)	3/25 (12%)[‡]	8/25 (32%)
Planas et al[34]	24	II	rand	Octreotide	3.5 μg/kg per hour	Cont inf	9/24 (37.5%)	21/24 (87.5%)	—	9/24 (38%)
	22			Control			14/22 (63.3%)	20/22 (90.9%)	—	7/22 (32%)
McKay et al[32]	28	II	db	Octreotide	40 μg/hr	Cont inf	—	—	3/28 (10.7%)	5/28 (17.9%)
	30			Placebo			—	—	4/30 (13.3%)	6/30 (20%)

*Significant in original publication.
[†]New MOF after treatment start (total: 17/26 (65.4%) vs. 14/24 (58.3%); improvement of MOF: 9/15 (69%) vs. 5/9 (55.5%).
[‡]Only renal failure reported.
[§]Indication for surgery not defined.
MOF indicates multiorgan failure; db, randomized double-blind trial; rand, randomized trial; cont inf, continuous infusion; sc, subcutaneous injection.

GASTROENTEROLOGY 1993;104:1165–1170

Gabexate Mesilate in Human Acute Pancreatitis

MARKUS BÜCHLER,* PETER MALFERTHEINER,‡ WALDEMAR UHL,* JÜRGEN SCHÖLMERICH,§ FRITZ STÖCKMANN,‖ GUIDO ADLER,¶ WILHELM GAUS,# KLAUS ROLLE,** HANS G. BEGER,* and the GERMAN PANCREATITIS STUDY GROUP‡‡

- 293 pts from 29 hospitals randomly assigned ***Gabexate mesilate*** *i.v.* 4 g/day for 7 days vs. placebo

Table 1. Inclusion Criteria

Obligatory criteria
First symptoms of acute pancreatitis ≤168 hours until enrollment of patients
Threefold enzyme elevations of total amylase or lipase within 96 hours after onset of acute pancreatitis
Upper abdominal pain
Written informed consent of the patient
Facultative criteria (4 had to be fulfilled)
Upper abdominal guarding
Subileus/ileus
Arterial pO_2 <65 mm Hg
Shock: pulse rate ≥100/min; systolic RR ≤80 mm Hg for longer >10 minutes
Anuria
Leukocyte count ≥12 G/L
Blood glucose (fasting) ≥8.4 mmol/L (this criterion was excluded in case of pre-existing diabetes mellitus)
Characteristic findings of moderate to severe acute pancreatitis by ultrasound and/or CT scan
Hypocalcemia ≤2.0 mmol/L
Serum creatinine >240 μmol/L

Table 8. Number and Type of Newly Developed Complications

	Placebo (n = 108)	GM (n = 115)
Shock	9	7
Sepsis	18	17
Pulmonary failure	15	18
Renal failure	10	11
Peritonitis	6	5
Hemorrhage	2	2
Ileus/subileus	6	3
Hypocalcemia	24	26
Clotting disorders	4	7
Jaundice[a]	10	19
Hyperglycemia	10	15
Encephalopathy	2	2
Metabolic acidosis	23	28
Death	16 (15%)	18 (16%)
Pancreatitis-related operations	23 (21%)	25 (22%)

- No statistical difference in either mortality or AP complications between placebo and gabexate groups

Gut 1999;45:97–104

A randomised, double blind, multicentre trial of octreotide in moderate to severe acute pancreatitis

W Uhl, M W Büchler, P Malfertheiner, H G Beger, G Adler, W Gaus, and the German Pancreatitis Study Group

- 302 patients from 32 hospitals randomly assigned to:
  - group P (n=103) received placebo
  - O1(n=98) & O2(n=101) received 100 & 200mcg ***Octreotide*** *sc* TID for 7 d.

Table 1 Inclusion criteria

Necessary criteria
First symptoms of acute pancreatitis not more than 96 hours before enrolment
Serum amylase or lipase increased at least threefold during this period
Spontaneous upper abdominal pain during this period
Written informed consent to participate in the study*
Supporting criteria (fulfilment of at least four required)
Local abdominal resistance
Subileus/ileus
Shock: pulse ⩾100/min and systolic blood pressure ⩽80 mm Hg for more than 10 minutes
Arterial Po_2 <60 mm Hg
Leucocyte count >12 g/l
C-reactive protein >120 mg/l
Fasting blood glucose >8.4 mmol/l†
Hypocalcaemia ⩽2.0 mmol/l
Serum creatinine >240 µmol/l
Characteristic findings of moderate or severe acute pancreatitis on ultrasound or contrast enhanced CT

Table 11 Primary and secondary outcome variables in the valid for efficacy analysis

		Treatment groups		
Outcome variables	*Total (n=251)*	*Placebo (n=90)*	*O1 (n=78)*	*O2 (n=83)*
Death	27 (11%)	13 (14%)	7 (9%)	7 (8%)
Death ⩽14 days	4	1	2	1
Death >14/⩽30 days	8	3	2	3
Death >30 days	15	9	3	3
Patients with newly developed complications	180 (73%)	61 (68%)	59 (76%)	60 (72%)
Duration of pain (days)*	6 (0–209)	6 (0–209)	6 (0–105)	7 (1–89)
Hospital stay (days)*	21 (5–210)	22 (7–210)	21 (5–105)	20 (7–163)

- An intent to treat analysis revealed no significant differences in
  - mortality (P:16%; O1:15%; O2:12%),
  - rate of newly developed complications, duration of pain, surgical interventions, or LOS

Gut 2001;48:62–69

Double blind, randomised, placebo controlled study of a platelet activating factor antagonist, lexipafant, in the treatment and prevention of organ failure in predicted severe acute pancreatitis

C D Johnson, A N Kingsnorth, C W Imrie, M J McMahon, J P Neoptolemos, C McKay, S K C Toh, P Skaife, P C Leeder, P Wilson, M Larvin, L D Curtis, for the UK Acute Pancreatitis Study Group

- 290 AP ps randomly assigned placebo vs. ***Lexipafant*** *i.v.* 100 mg/24 hrs for 7 days

Inclusion and exclusion criteria

All of the following were required for inclusion: severe abdominal pain of <72 hours duration at initiation of study treatment; serum amylase level >3 times the upper limit of the normal range in the 72 hours before study entry; a clinical picture consistent with acute pancreatitis; and an APACHE II score[27] >6 in the 24 hours

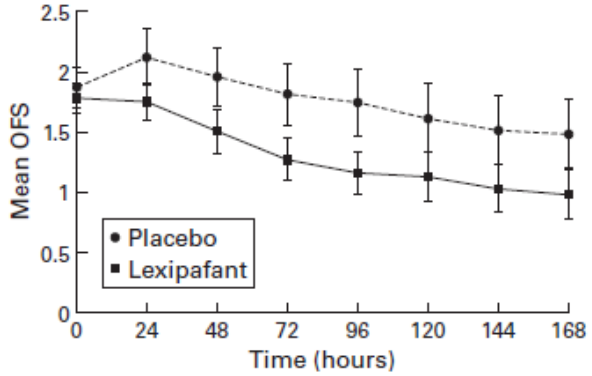


Table 3 Incidence of organ failure, local complications, and deaths in the two groups

Complications	*Placebo group*	*Lexipafant group*
Organ failure		
On admission	59 (43%)	67 (45%)
Day 3	46 (33%)	40 (27%)
Day 7	36 (26%)	29 (20%)
Overall	80/138 (58%)	85/148 (57%)
Local complications		
Pseudocyst	19 (14%)	8 (5%)[a]
Necrosis	29 (21%)	23 (16%)
Abscess	6 (4%)	5 (3%)
Overall	41/138 (30%)	30/148 (20%)[b]
Systemic sepsis	13/138 (9%)	4/148 (3%)[c]
Deaths		
All attributable deaths	21/136 (15%)	14/147 (10%)
Attributable deaths in patients treated ≤48 h	17/95 (18%)	8/104 (8%)[d]

- Organ failure scores reduced in Lexipafant group only on D3.
- Lexipafant had no effect on new OF during treatment.
- The high incidence of OF within 72 hrs of symptom onset undermined 1ry hypothesis

Oral Pentoxifylline RCT

- Design: single-center, double-blind, randomized placebo-controlled trial conducted at Mayo (2015-2017)
- Population: 83 adults with AP within 72h of admission
  - 233 met eligibility criteria, 176 approached, 91 declined: **36% enrolled**
- Intervention: Oral pentoxifylline 400 mg, three times daily, total 9 doses
- Primary Endpoint: Composite Outcome including
  - Death, pancreatic necrosis, persistent organ failure, persistent SIRS, hospital stay >4 days, need for intensive care
- Findings: Pentoxifylline use not associated with any benefit
  - but with longer stay & higher readmission rates

Vege SS et al. Pancreatology 2020

Rectal Indomethacin RCT

- Design: single-center, parallel-group, double-blind, randomized placebo-controlled trial conducted at UPMC (2015-2019)
- Population: 42 adults with AP +SIRS within 72h of admission
- Intervention: Rectal Indomethacin q8h, total 6 doses
- Primary Endpoint: SIRS score change from baseline to 48h
- Results: Safe when administered over 48 hours
  - however, not superior to placebo in reducing SIRS or clinical progression in a high-risk AP population

Machicado JD, Papachristou GI. Clin Transl Gastroenterol 2021

Why did previous RCTs fail?

- **Sample Size**
  - Single center, small trials: Pentoxifylline, Indomethacin
- **Time between Presentation & Enrollment**
  - Gabexate 7d; Octreotide 4d
- **Inaccurate Predictive Tools**
  - 4 supporting criteria, APACHE-II >6, SIRS >1, all comers
- **Primary Endpoints**
  - Composite Outcome, Death, Organ Failure, SIRS change, CRP levels

Novel Drugs

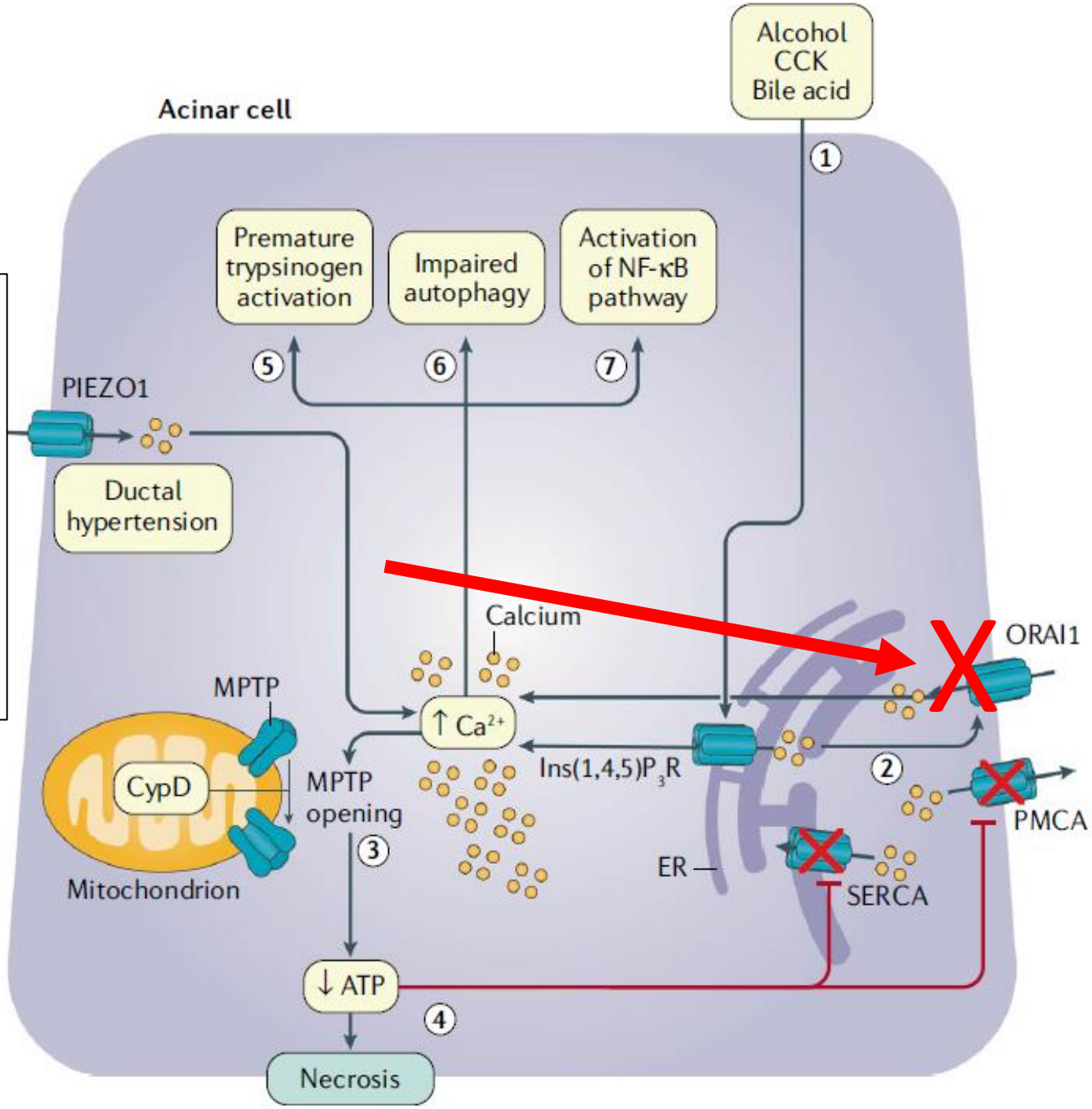
ORIGINAL ARTICLE

OPEN

Auxora for the Treatment of Patients With Acute Pancreatitis and Accompanying Systemic Inflammatory Response Syndrome

Clinical Development of a Calcium Release-Activated Calcium Channel Inhibitor

Charles Bruen, MD,† Joseph Miller, MD,‡§ John Wilburn, MD,|| Caleb Mackey, MD,¶# Thomas L. Bollen, MD,** Kenneth Stauderman, PhD,†† and Sudarshan Hebbar, MD††*

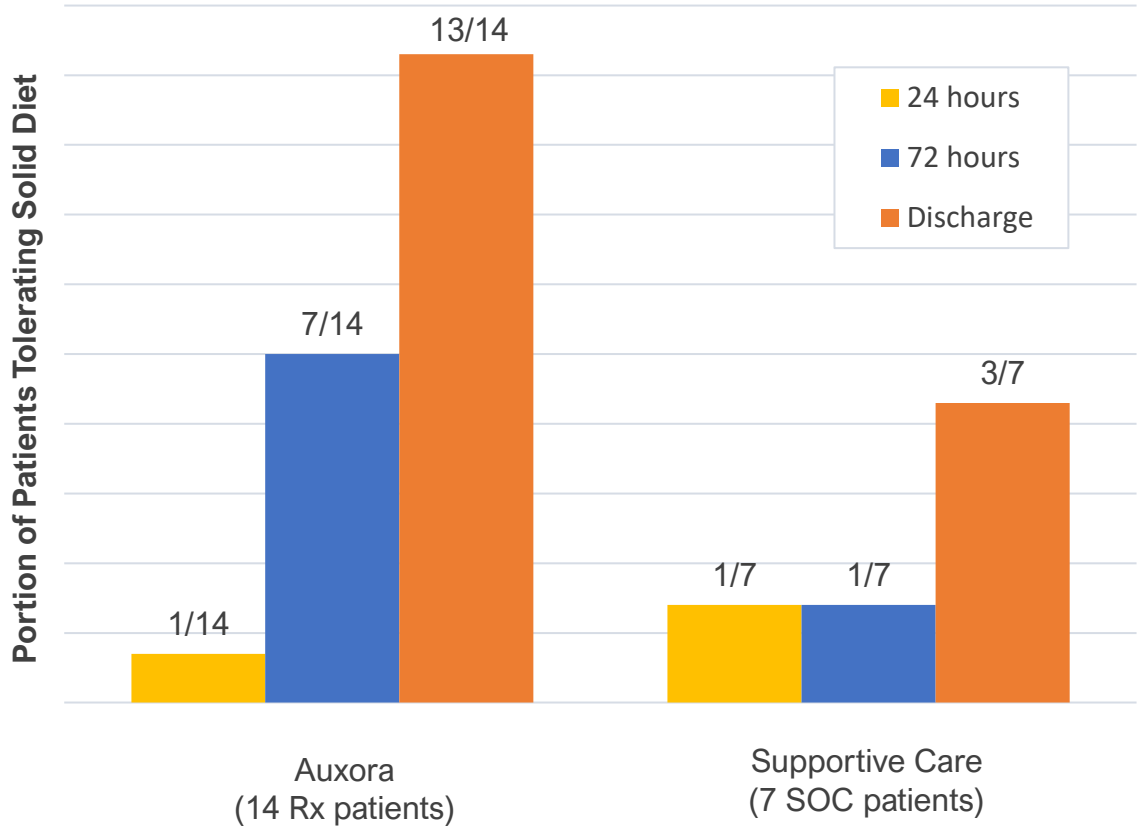


Auxora Pilot Study

- Phase 2a, open-label, dose-response, multi-center
- 21 subjects with 2:1 randomization
- Inclusion: SIRS + Hypoxemia
- Endpoint: **Solid Food Tolerance***

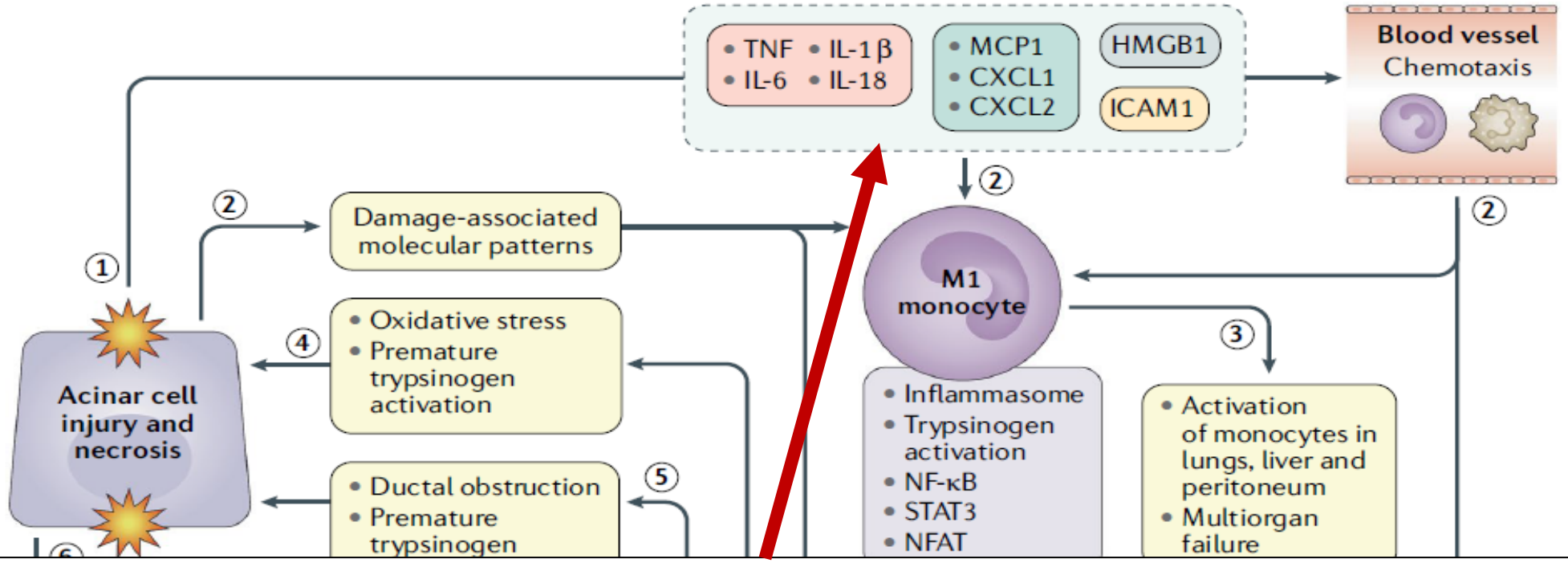
- Auxora-treated pts tolerating solid food
  - Admission: 1/14
  - At 72 hours: 7/14
  - At Discharge: 13/14

- SOC pts tolerating solid food
  - Admission: 1/7
  - At 72 hours: 1/7
  - At Discharge: 3/7



**eating ≥ 50% of solid meal without vomiting or increase in pain*

Bruen C et al. Pancreas 2021



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ClinicalTrials.gov

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Randomised Treatment of Acute Pancreatitis With Infliximab: Double-blind Multi-centre Trial (RAPID-I) (RAPID-I)

ClinicalTrials.gov Identifier: NCT03684278

⚠ The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

Recruitment Status ⓘ : Suspended (COVID-19 Pandemic)
First Posted ⓘ : September 25, 2018
Last Update Posted ⓘ : November 4, 2020

Sponsor:
Professor Robert Sutton

Table 2 | **Potential therapeutic targets and target pathways in acute pancreatitis**

Agent	Target	Target pathway	Status
GSK-7975A	ORAI1	Store-operated calcium entry channel; calcium signalling pathway	Preclinical[20,31]
CM4620	Calcium release-activated calcium channel	Store-operated calcium entry channel; calcium signalling pathway	Phase II[274]
TRO40303	Mitochondrial permeability transition pore	Mitochondrial dysfunction	Preclinical[19]
Disaccharide trehalose	Unknown	Autophagy	Preclinical[33]
HMG-CoA inhibitors	HMG-CoA	Unfolded protein response	Commercially available; clinical trial in progress[97]
Lactated Ringer's solution	G_i protein-coupled receptor 81	NLRP3 inflammasome pathway; binds free fatty acid	Pilot clinical trial completed[133,138,195]
Pentoxifylline	Synthesis of TNF	Phosphodiesterase; inflammatory response	Pilot clinical trial in progress[144]
Orlistat	Unsaturated free fatty acids	Hydrolysis of triglycerides to free fatty acids; lipotoxicity	Commercially available; no trials conducted
Tocilizumab	IL-6	Inhibition of IL-6 receptor; inflammatory response	Preclinical in acute pancreatitis in progress; successful clinical trials in other diseases[145,147,275]

HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; NLRP3, LRR- and pyrin domain-containing 3; ORAI1, calcium release-activated calcium channel protein 1.

Lee, PJ, Papachristou, GI. Nat Rev Gastroenterol Hepatol 2019

CARPO Study

- Phase 2b, Double-Blind, Dose-Ranging, RCT of Auxora (*CRAC Inhibitor*) in AP pts & accompanying SIRS

- **Inclusion Criteria**
  - AP Dx based on RAC
  - SIRS diagnosis based on ≥2 of 4 criteria
    - Temperature; Heart rate; Respiratory rate; WBC
  - Additionally, ≥1of following criteria:
    - Peripancreatic fluid collection or pleural effusion on CECT within 12h
    - Abdominal guarding or rebound tenderness on exam
    - Hematocrit ≥44% for men or ≥40% for women

- All pts receive Screening CECT scan before randomization & at Day 30

CARPO Study

- 216 pts to be randomized at ~30 sites

- Pts randomized to Auxora receive 1:1:1 dose levels
  - 2 mg/kg, 1 mg/kg, or 0.5 mg/kg (IV infusion over 4 hrs) every 24 hrs for 3 days

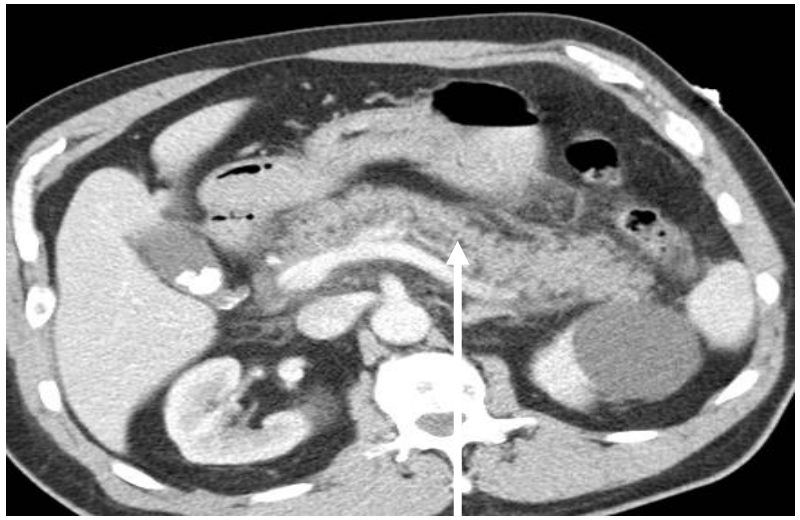
- **Primary Outcome**
  - Time to solid food tolerance

- **Secondary Outcomes**
  - Solid food tolerance at 48, 72, & 96 hrs, and at discharge
  - Time to medically indicated discharge, LOS, & ICU LOS
  - Re-hospitalization for AP by Day 30
  - Change in CTSI score from screening to Day 30 CECT, Development of necrosis
  - Persistence of SIRS ≥48 hours; Development & duration of OF
  - Mortality by Day 30
  - Change in pain score and opioid use (*patient centered outcome*)

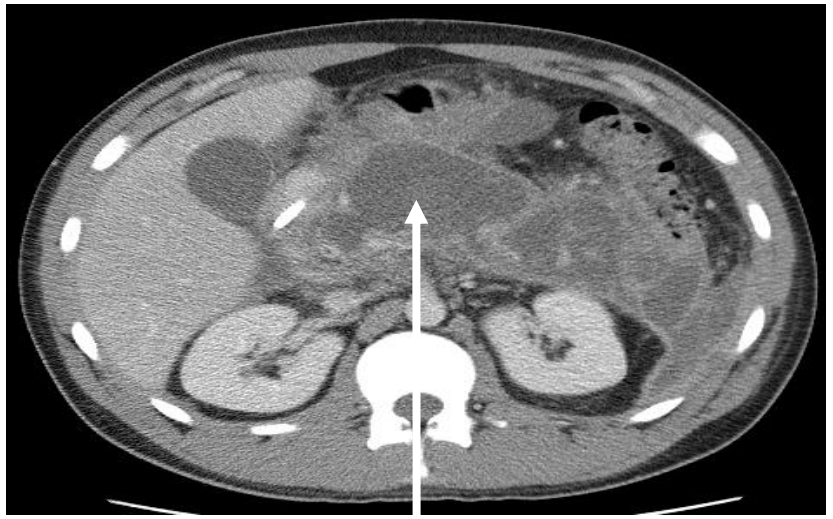
CARPO Design

- Adequate Sample Size, Double-Blinded
- Unclear Time between presentation & study enrollment
- Predictive tools for Inclusion
  - **Composite Tool**: SIRS + one of: CECT findings, Abdominal exam, or ↑ Hct
  - High-risk population; more difficult to enroll; less generalizable results
- Primary Outcome
  - Meaningful to patients & health care providers; Indirectly associated with LOS
- Intense Protocol
  - Several assessments & blood draws (team fatigue; incomplete data/samples)
- 30 Day f/u with CECT scan
  - Concerns for subject compliance & drop out rates

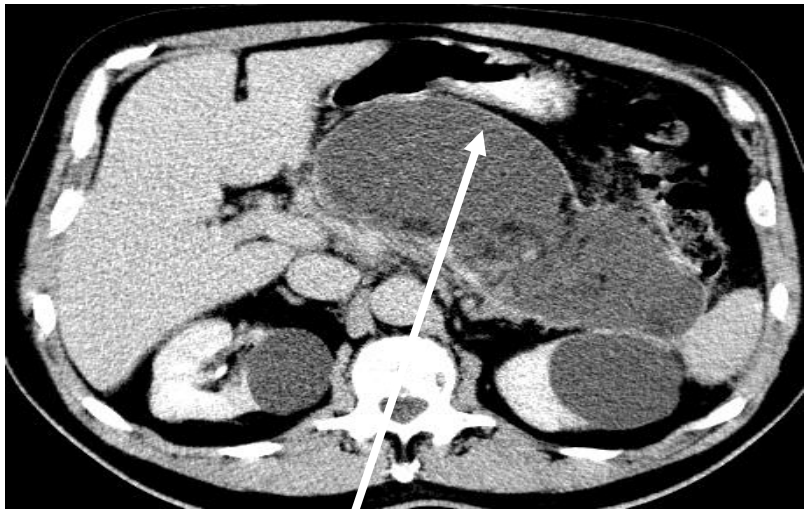
Pancreatic Necrosis (PNec)



Normally enhancing pancreas



Non-enhancing necrosed pancreas



Capsule

- Approx 10-20% of AP patients at tertiary medical centers develop PNec
  - Infectious complications occur in ~20-30%
  - 2-5 weeks from occurrence of PNec
  - New fevers, worsening abdominal pain, nausea, vomiting, growth of collection
  - Septic complications from infected PNec account for most of late AP deaths

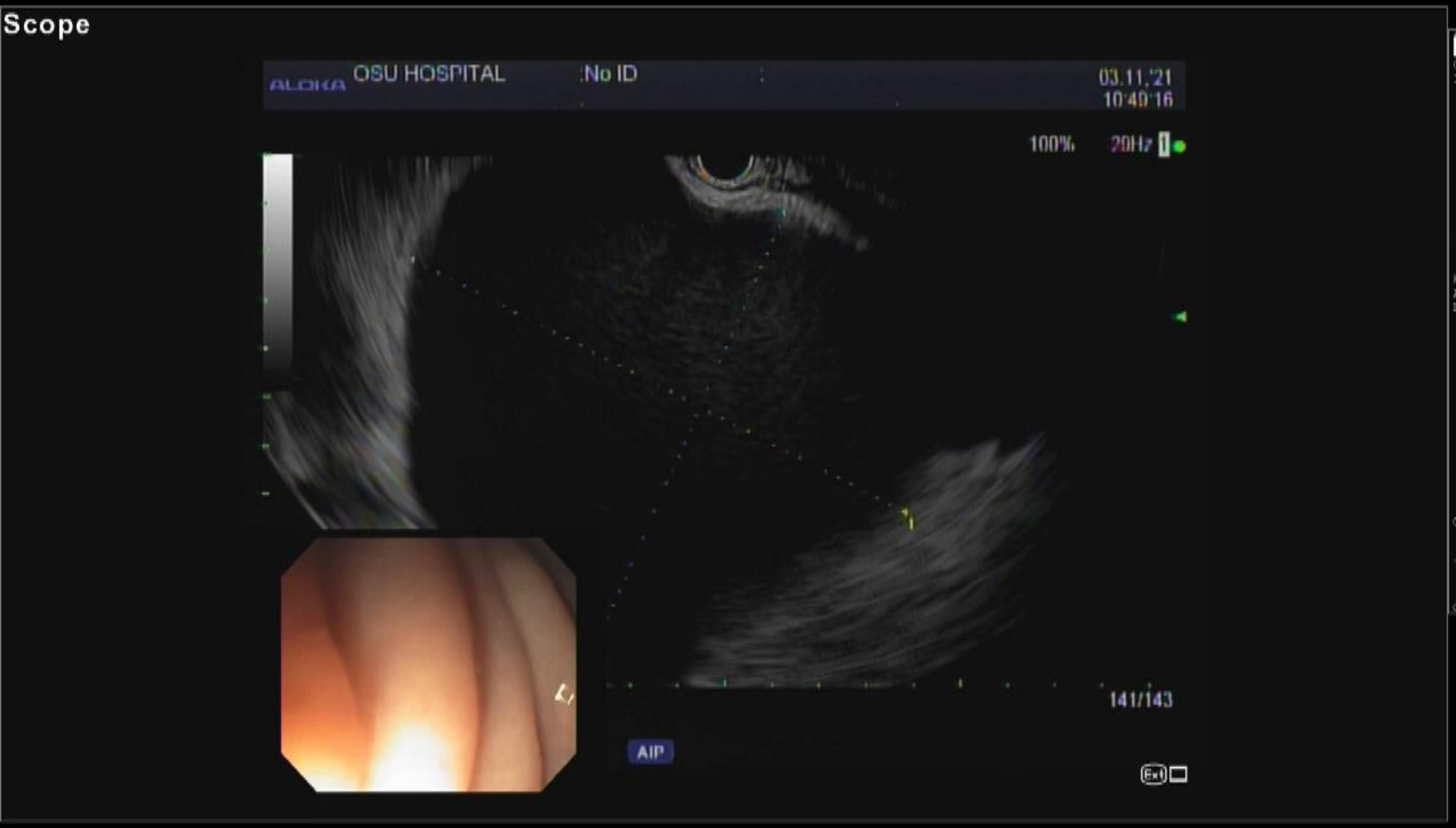
2020 AGA Clinical Practice Update

An endoscopic step-up paradigm as the evolving first-line approach to treating patients with Infected Pancreatic Necrosis

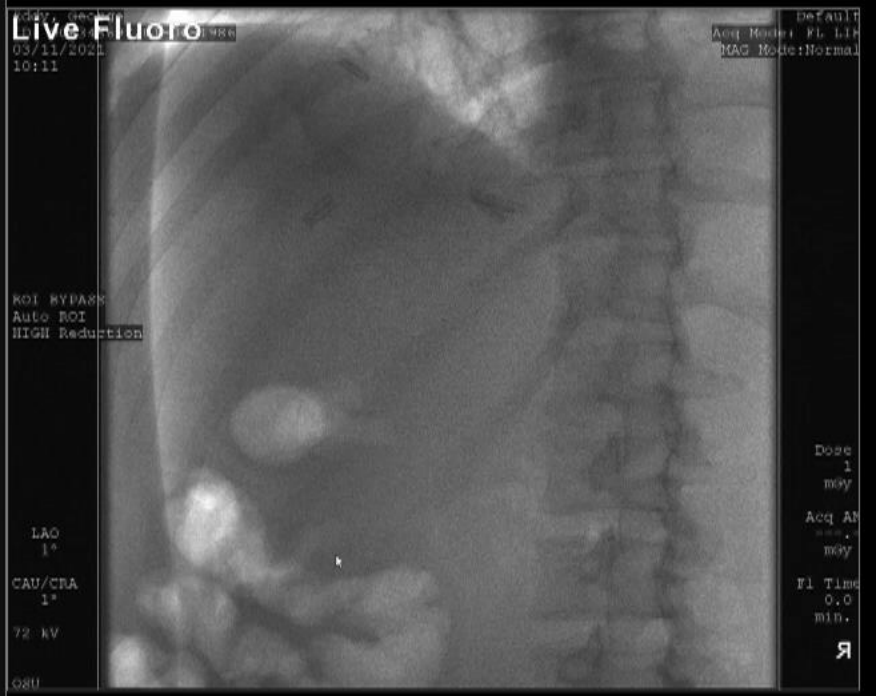
Back to our patient

- Transferred to the ICU
- Developed Respiratory and Renal Failure
- Follow up CT scan showed extensive pancreatic necrosis
- Six weeks later…

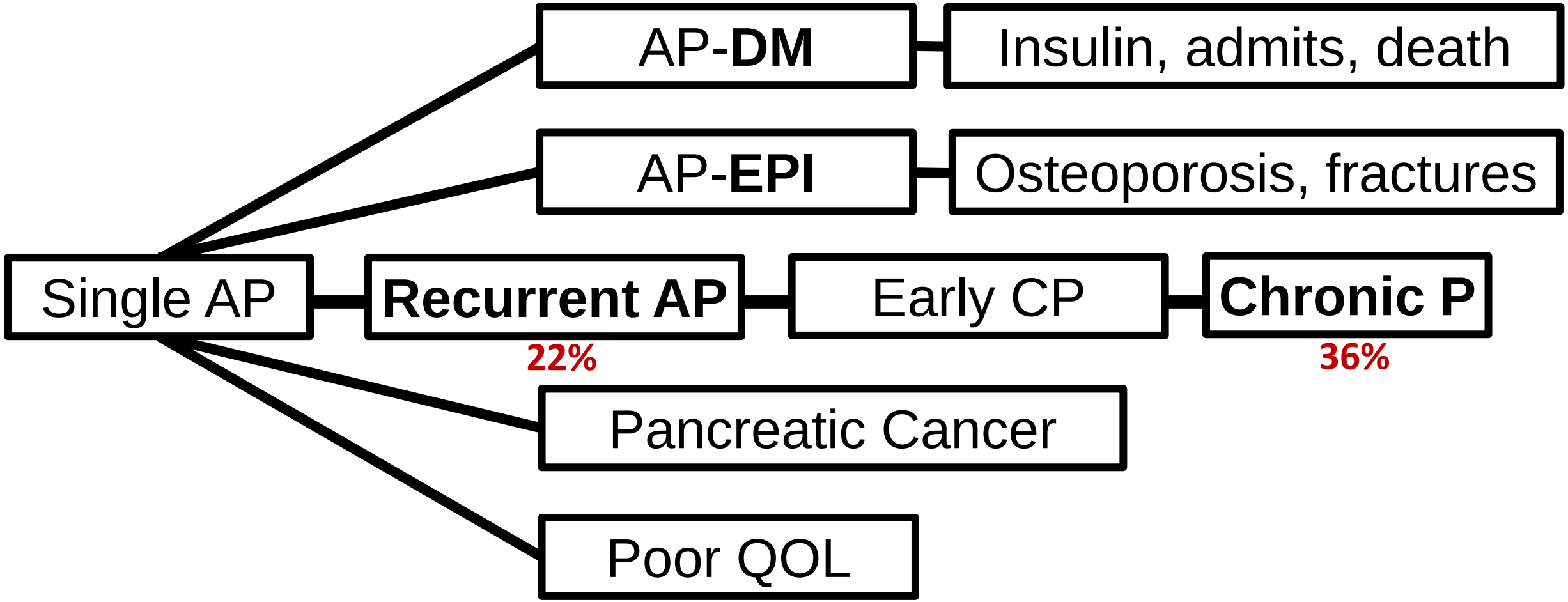
Scope



Live Fluoro

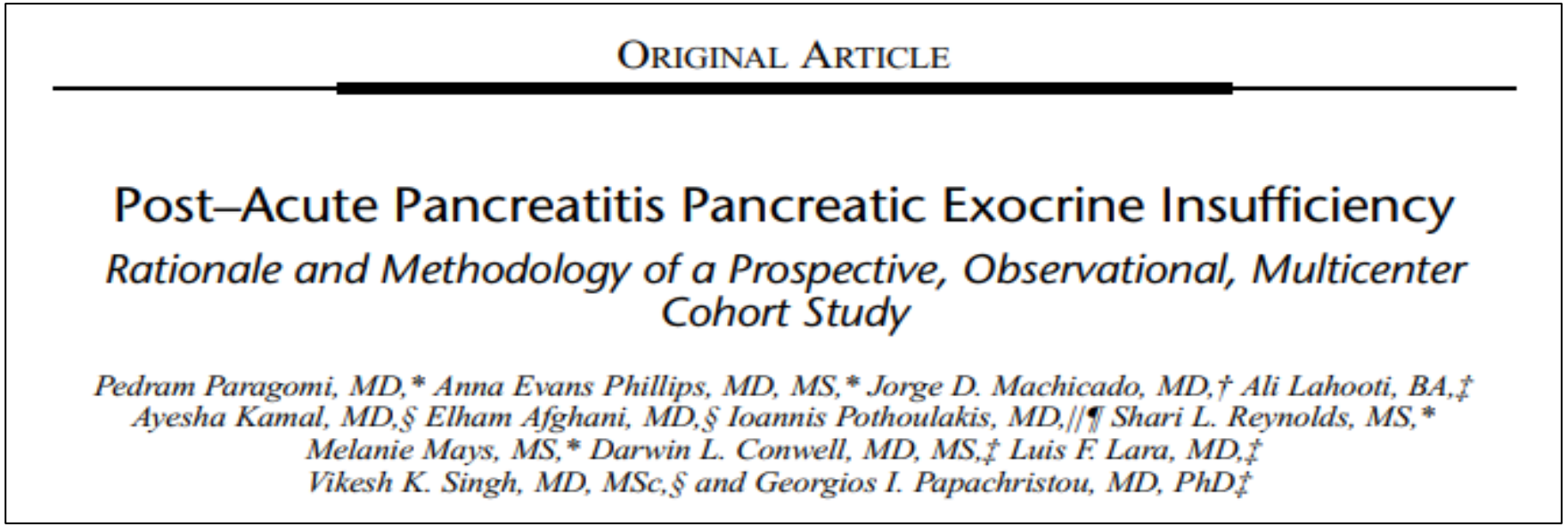


Progression & Long-term Sequelae of AP



Whitcomb DC, et al. Pancreatology 2016
Petrov MS, Yadav D. Nature Gastroenterology 2019

PAPPEI Study



ORIGINAL ARTICLE

Post–Acute Pancreatitis Pancreatic Exocrine Insufficiency

Rationale and Methodology of a Prospective, Observational, Multicenter Cohort Study

Pedram Paragomi, MD, Anna Evans Phillips, MD, MS,* Jorge D. Machicado, MD,† Ali Lahooti, BA,‡ Ayesha Kamal, MD,§ Elham Afghani, MD,§ Ioannis Pothoulakis, MD,||¶ Shari L. Reynolds, MS,* Melanie Mays, MS,* Darwin L. Conwell, MD, MS,‡ Luis F. Lara, MD,‡ Vikesh K. Singh, MD, MSc,§ and Georgios I. Papachristou, MD, PhD‡*

A prospective, observational, & longitudinal AP cohort at OSU, UPMC & JHU

- To estimate the 3- & 12-mo incidence rate of AP-EPI & AP-DM
- To define risk factors; evaluate impact of EPI on Nutritional Status & QoL
- ~90 pts completed 12-mo f/u
- Incidence of AP-DM **10%** & AP-EPI **34%** at 12 months

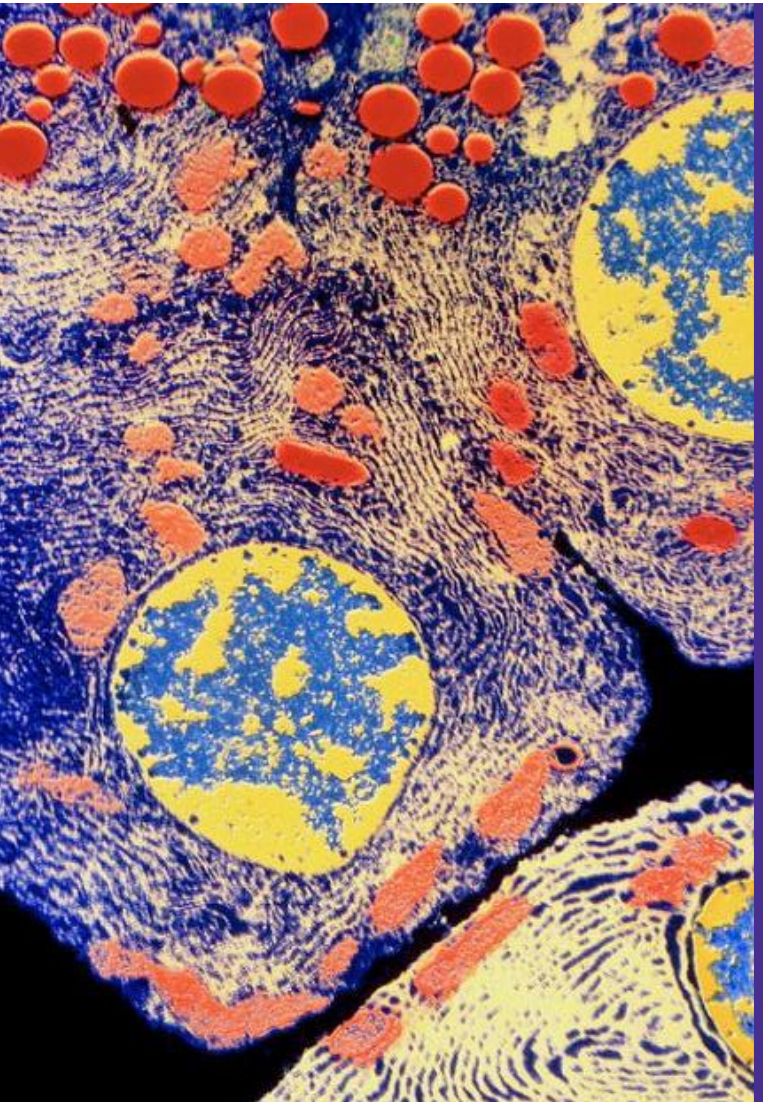
Paragomi et al, Pancreas, 2021

DREAM Study

- NIH-U01 funded consortium of 10 sites in the US in 2020
  - Study the Prevalence & Mechanisms of AP-DM

T1DAPC
Type 1 Diabetes in Acute Pancreatitis Consortium

CalciMedica

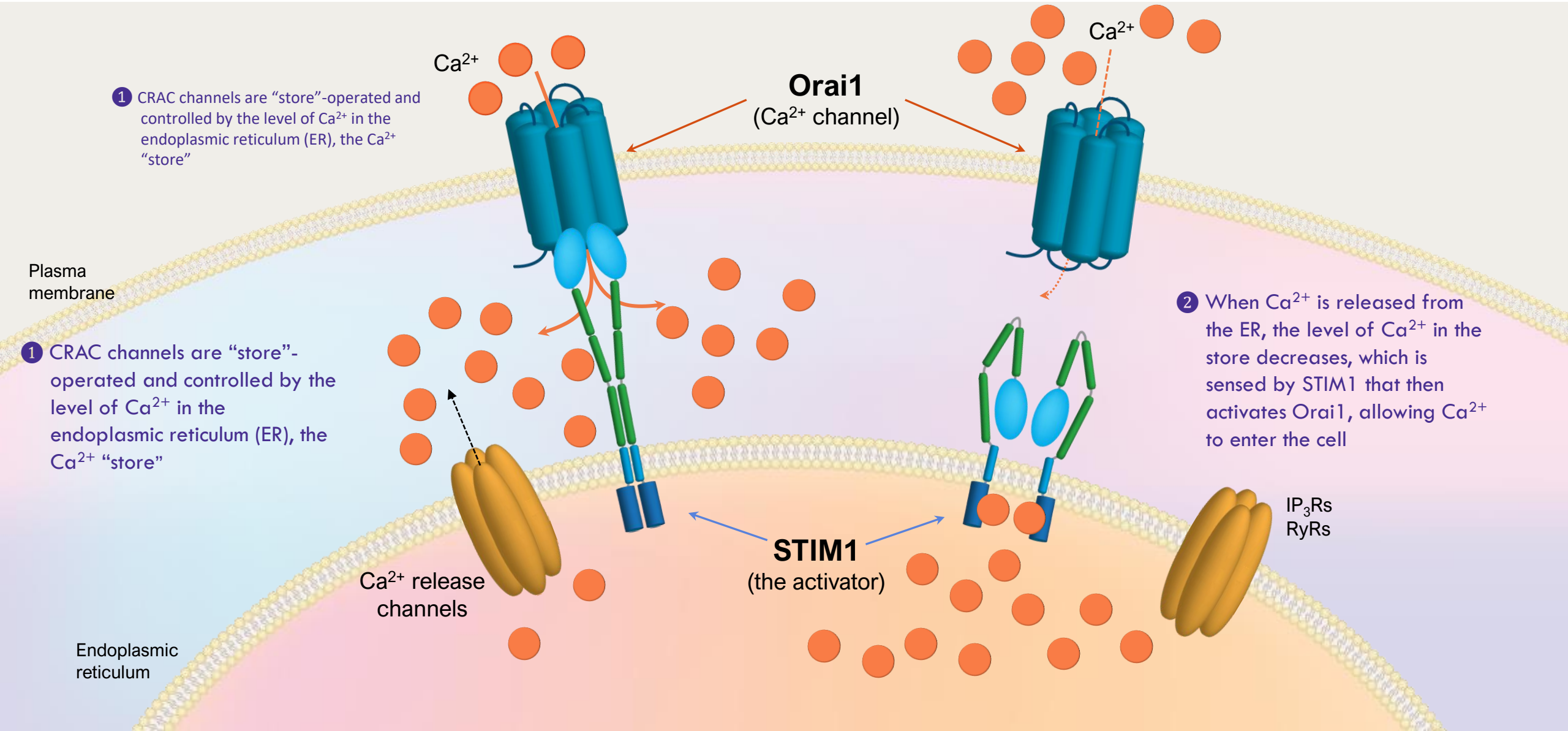


CRAC Channels, Auxora™ and Clinical Program Overview

Sudarshan Hebbar, M.D.

CMO, CalciMedica

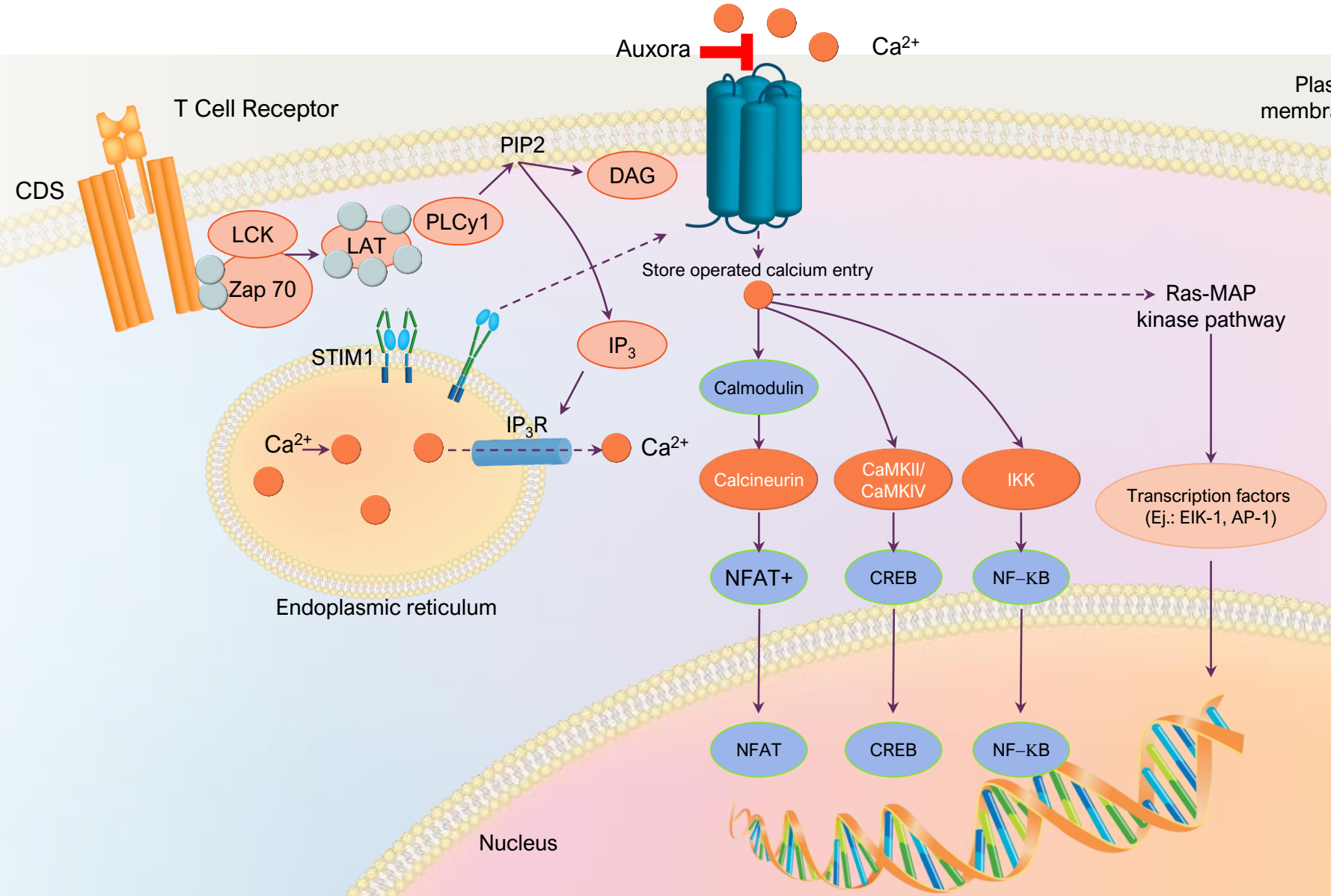
CRAC Channels Play Essential Role in Store Operated Calcium Release



CRAC Channels Play an Essential Role in Activating T cells

- Antigen binding to the T cell receptor causes Ca2+ release from the ER through IP3R, activating STIM1 and opening CRAC channels
- Ca2+ entering the cell through open CRAC channels activates the calcineurin/NFAT pathway, and other pathways, resulting in cytokine expression and release
- CRAC channel inhibitors modulate the downstream calcium-dependent pathways, most notably the calcineurin/NFAT pathway

NFAT: Nuclear Factor of Activated T cells



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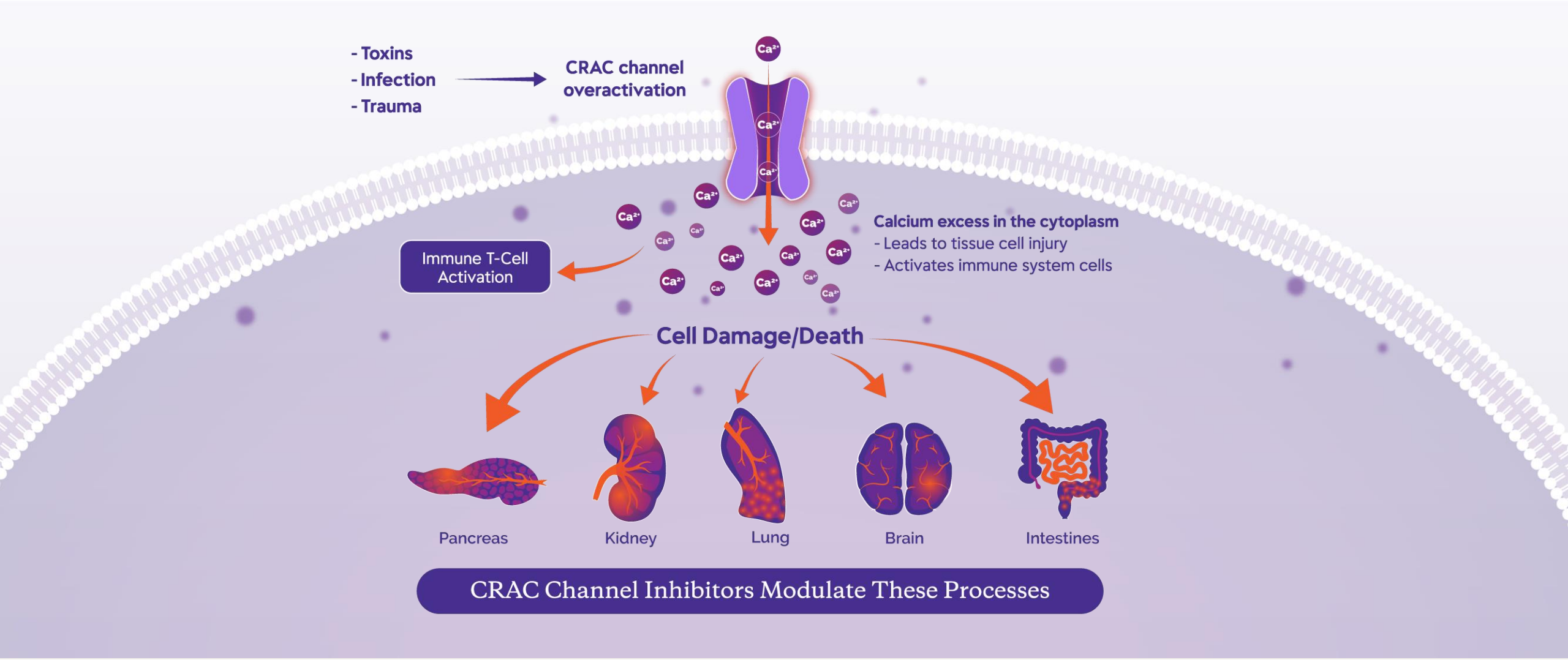
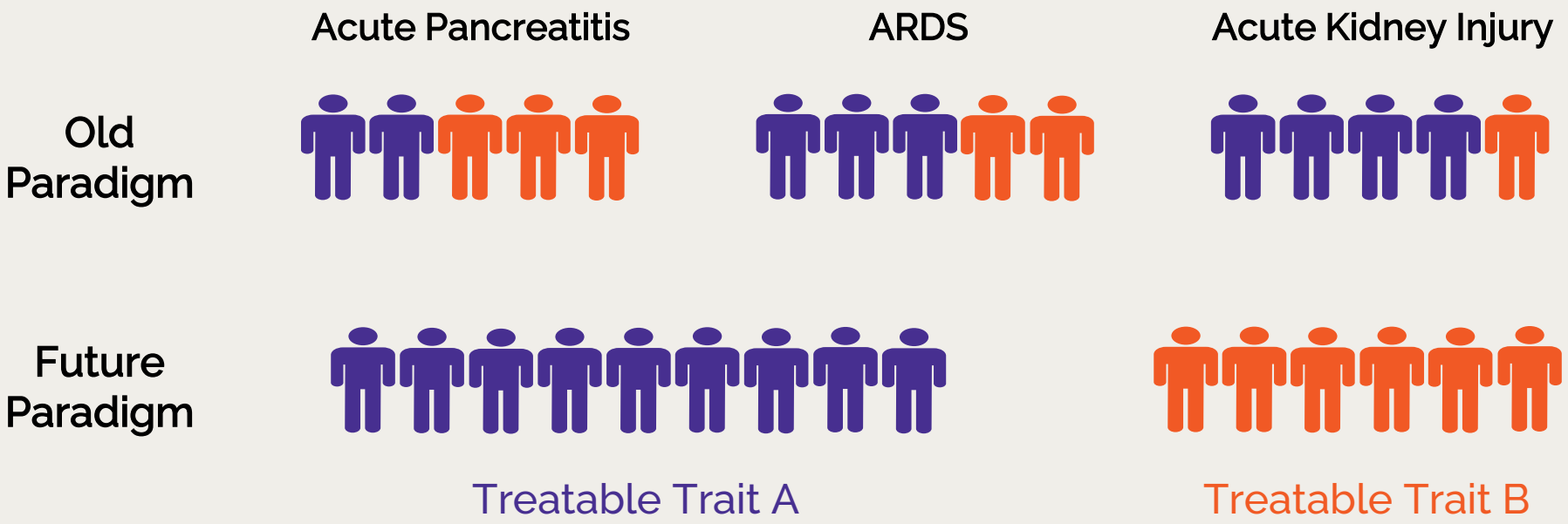
Adapted from Feske, Nat Rev Immunol, 2007

Overactivation of CRAC Channels:
Immune System Activation and Tissue Cell Injury



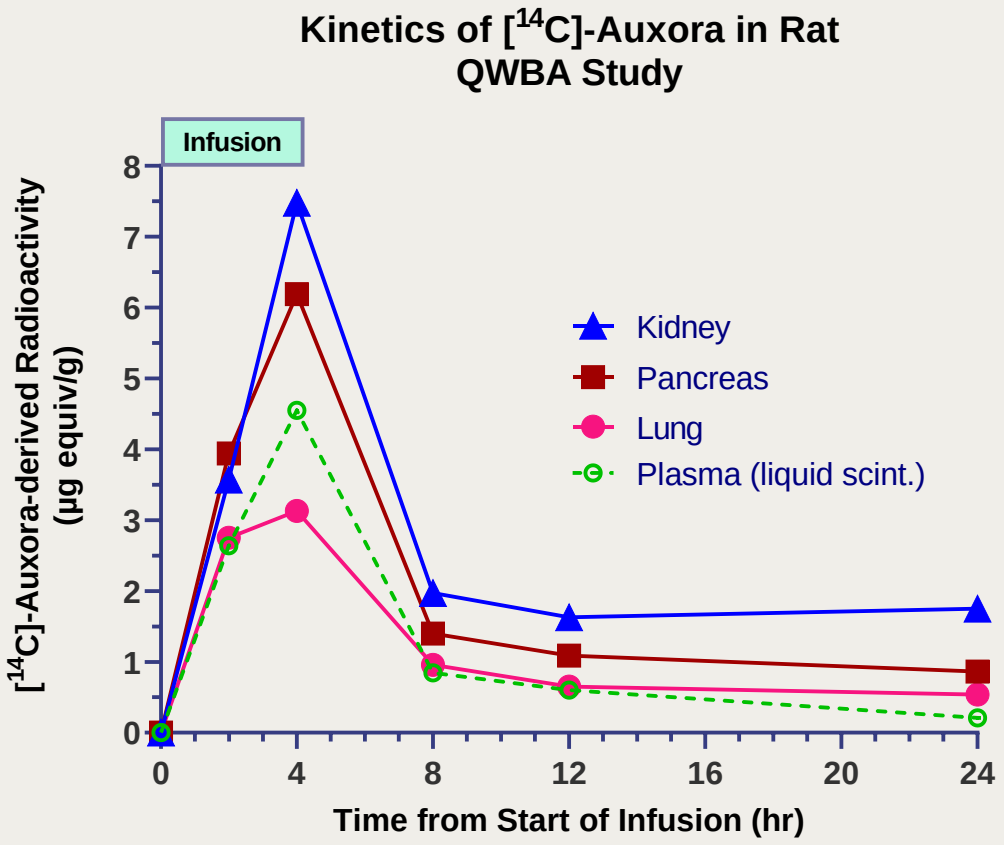
Acute Inflammation: Underlying Cause Across Many Diseases



Auxora has demonstrated positive clinical results in all 3 of these large, underserved patient populations

1) Sources: Reddy, Kiran, Carolyn S. Calfee, and Danny F. McAuley. "Acute respiratory distress syndrome subphenotypes beyond the syndrome: a step toward treatable traits?." American Journal of Respiratory and Critical Care Medicine 203.12 (2021): 1449-1451.

Auxora: IV Lipid Nanoemulsion of Zegocractin
Rapid Targeting of Inflamed Tissues

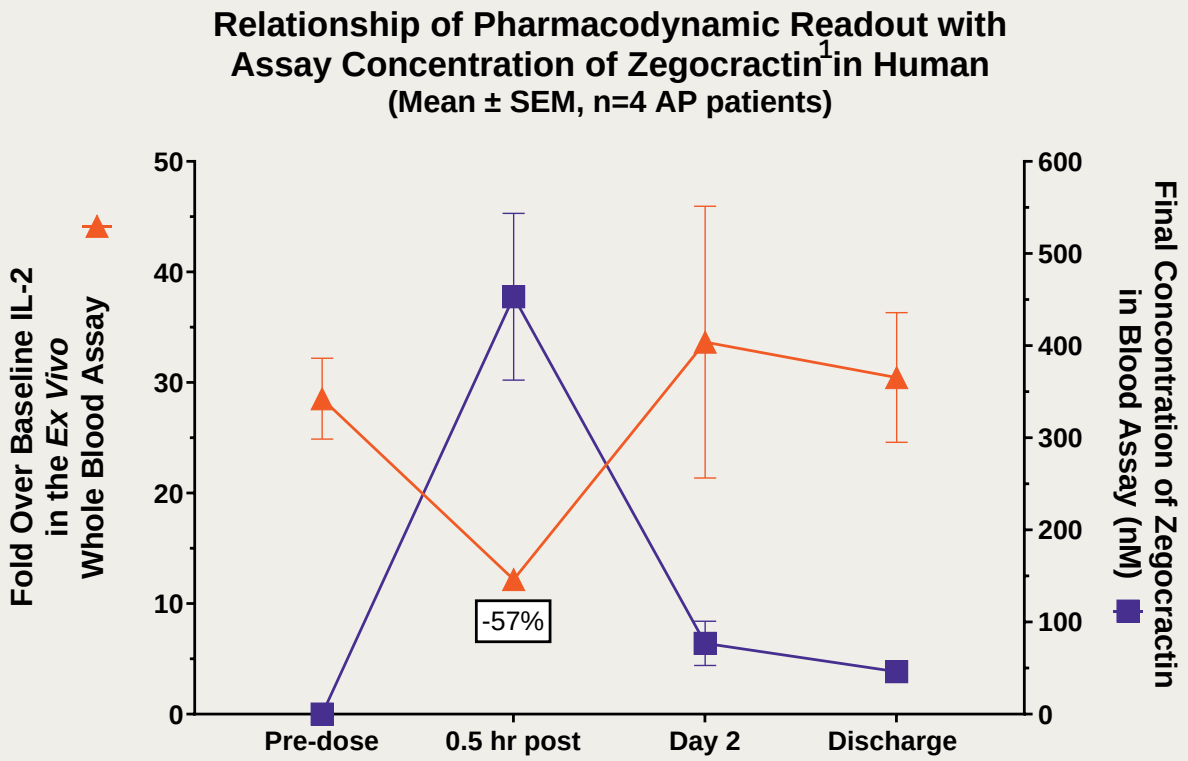


- Clearance predominantly via the liver
- No metabolites identified in human plasma
- No inhibitory effect on P450 system

- QWBA = Quantitative whole-body autoradiography

IV Formulation Provides Ideal Benefits for Acute Inflammation

Rapid onset of immunomodulatory action reaches peak by the end of 4-hour infusion



Recovery within 24-48 hours of dosing may limit the potential for immunosuppression

1) Zegogractin is the active pharmaceutical ingredient in Auxora

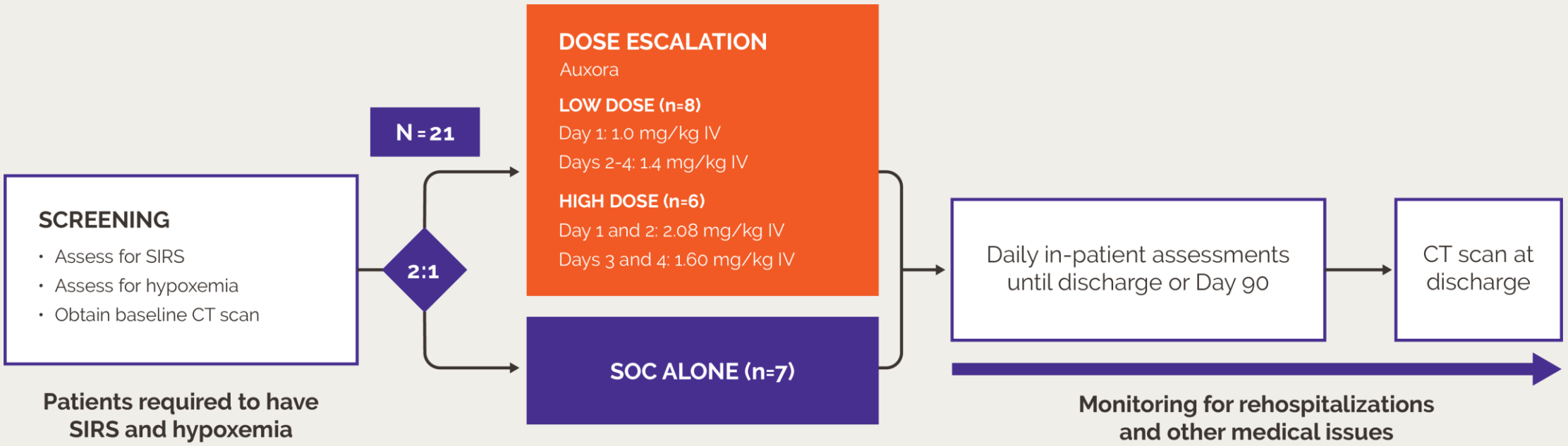
Auxora: Demonstrated Biological Activity and Favorable Safety Profile in Multiple Phase 2 Trials

Population	Results
Pancreas	
Asparaginase- Inducted Pancreatic Toxicity	• Trial ongoing, preliminary results show rapid resolution of pain and food tolerance
Acute Pancreatitis	• Trial ongoing
Acute Pancreatitis[1]	• Target engagement of CRAC channels in peripheral lymphocytes
Acute Pancreatitis[1] Accompanied by SIRS and Hypoxemia	• Rapid increase in patients tolerating solid diet (potential trial pivotal endpoint) • >2-day reduction in hospital stay and 50% reduction SIRS
Lung	
COVID-19 with Respiratory Failure on LFO_2[2] and HFNC[3]	• 56% statistically significant decrease in mortality at Day 30 • 33% reduction in ventilation • >2-day shorter hospital stay • ~40% reduction in reported acute kidney injury
COVID-19 with Respiratory Failure on IMV[4]	• Open-label trial with varying doses showing pharmacodynamic response

1) Completed Phase 1 trials in healthy volunteers showed no evidence of dose-dependent safety or tolerability findings through 365 days
2) **LFO_2**: Low Flow Oxygen; 3) **HFNC:** High-Flow Nasal Cannula; 4) **IMV**: Invasive Mechanical Ventilation

AP Phase 2a Clinical Trial

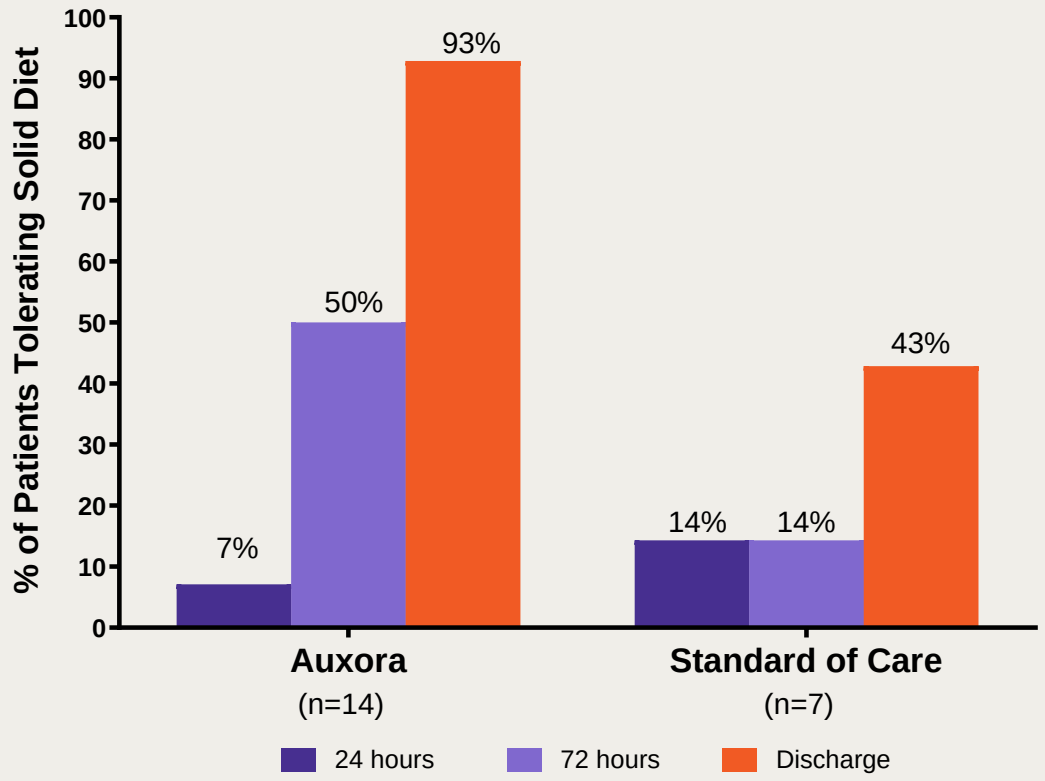
Safety, tolerability, and efficacy trial for various doses of Auxora compared to standard of care



Positive Phase 2a Results on Potential Pivotal Trial Primary Endpoints

Rapid Increase in Patients Tolerating Solid Diet

Potential Pivotal Trial Primary Endpoint



>2 Fewer Days Spent in Hospital

Median Hospital Stay

SOC patients (n=7)	6.0 days
Auxora-treated patients (n=14)	**3.7 days**

Only Auxora Patients Improved on CTSI[1] Scores

Moderate to Severe CTSI[1] Scores

SOC patients (n=4)	0/4
Auxora-treated patients (n=8)	**3/8**

50% Reduction in Persistent SIRS

Patients with Persistent SIRS

SOC patients (n=7)	5/7
Auxora-treated patients (n=14)	**5/14**

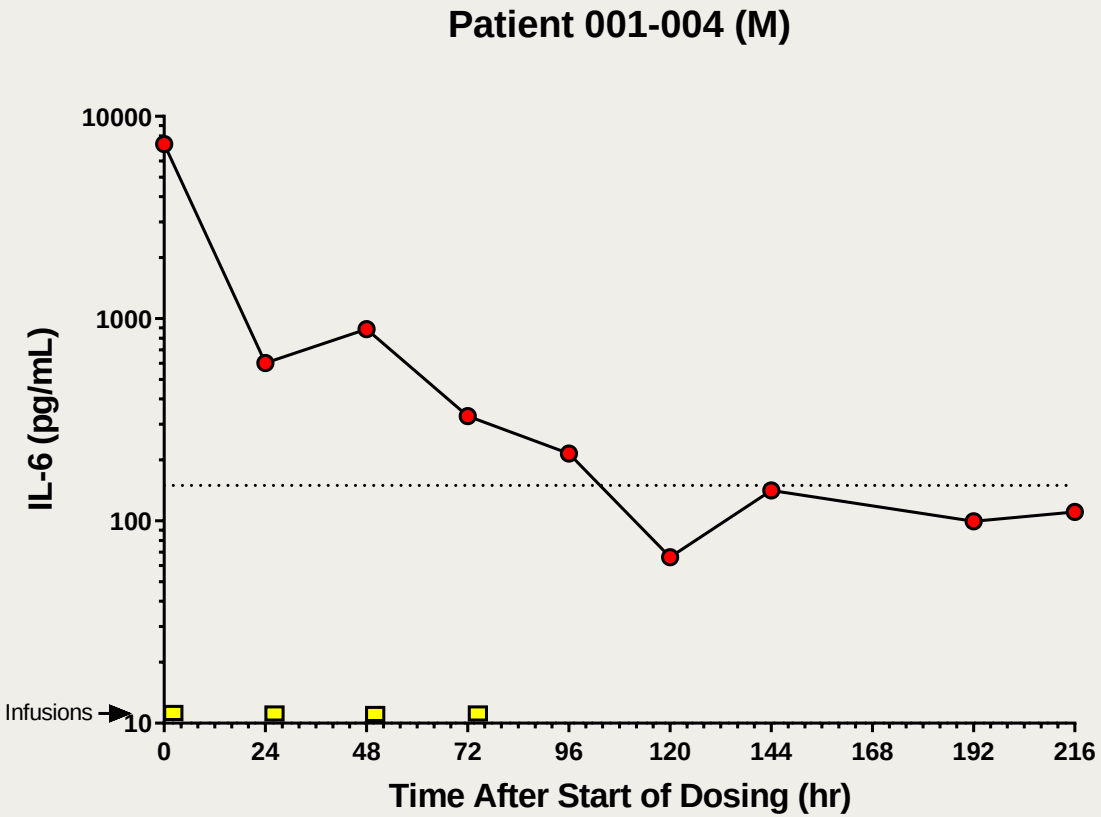
1) CTSI: CT Severity Index

IL-6 Reduction with Auxora

	Admission IL-6 levels		Discharge IL-6 levels	
	IL-6 ≥ 1000 pg/mL	150 pg/mL ≤ IL-6 <1000 pg/mL	IL-6 ≥ 1000 pg/mL	150 pg/mL ≤ IL-6 <1000 pg/mL
201 Standard of Care Alone	0	3	0	2
201 Low Dose Auxora	0	4	0	0
201 High Dose Auxora	2	1	0	1
202 Single Dose Auxora	0	1	0	0

2/3 of patients treated with standard of care continued to have elevated IL-6 levels
Only 1/8 patients treated with Auxora continued to have elevated IL-6 levels

Individual Case of a Critically Ill Patient with AP



- Critically ill patient presented with respiratory failure and acute pancreatitis in the ED.
- Randomized to receive high dose of Auxora
- IL-6 >7296 pg/mL at study entry, 66 at 120 hrs
- Managed with high flow oxygen and intermittent bi-pap; no invasive mechanical ventilation
- Discharged home on room air day 8 eating a solid food diet

Potential Clinical Benefits of Auxora for Patients with Predicted Severe AP

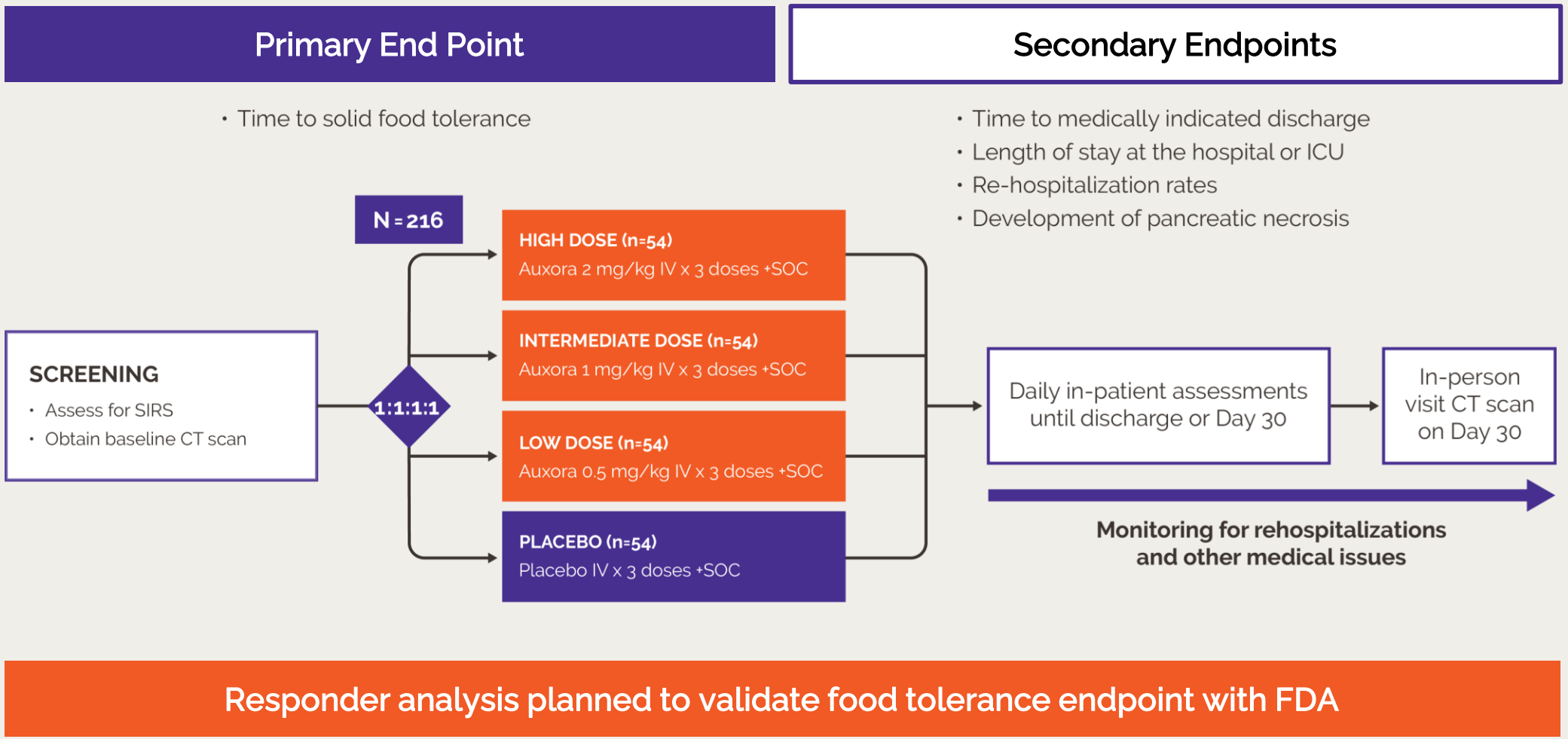
Current standard of care is limited to supportive therapy

- Fluid resuscitation
- Enteral nutrition for food tolerance
- Antibiotics for infection
- Minimally invasive therapy for local complications

Auxora benefits are expected to drive adoption

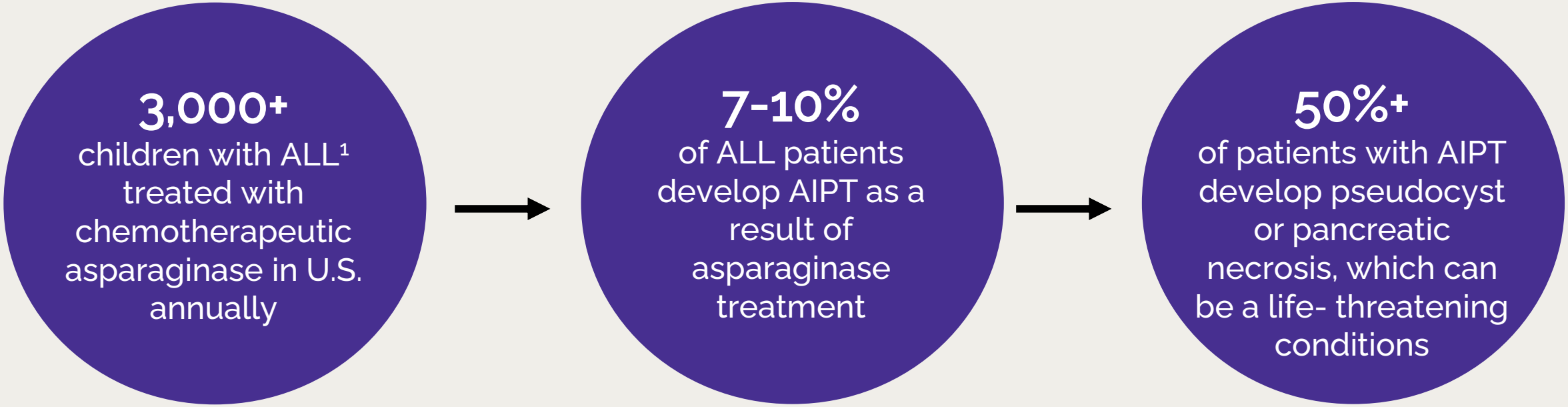
- Reduction in organ failure
- Reduction in pancreatic necrosis
- Earlier food tolerance
- Fewer days in hospital or ICU

CARPO Phase 2b Clinical Trial in AP
Ongoing with Data Expected 1H 2024



Responder analysis planned to validate food tolerance endpoint with FDA

Potential Clinical Benefits in Asparaginase-Induced Pancreatic Toxicity (AIPT)



Auxora has potential to rapidly resolve AIPT with improvement in food tolerance and pain while preventing development of further complications such as pancreatic necrosis

1) **ALL:** Acute Lymphoblastic Leukemia
2) Sources: Liu C, Yang W, Devidas M, et al. Clinical and Genetic Risk Factors for Acute Pancreatitis in Patients With Acute Lymphoblastic Leukemia. J Clin Oncol. 2016. Abaji R, Gagne V, Xu CJ, et al. Whole-exome sequencing identified genetic risk factors for asparaginase-related complications in childhood ALL patients. Oncotarget. 2017;8: 43752-43767. Rank C, Wolthers B, Grell K, et al. Asparaginase-associated pancreatitis in acute lymphoblastic leukemia: results from the NOPHO ALL 2008 treatment of patients 1-45 years of age. J Clin Oncol. 2019 38:145-154.

Proof-of-Concept Ongoing in AIPT
Pediatric Patients Had Rapid Resolution of Pain and Food Intolerance

CRSPA Phase 1/2 Trial in Pediatric AIPT

- Investigator-initiated open-label trial being conducted at St. Jude Children's Research Hospital
- Assess the safety in pediatric patients with ALL who have developed AIPT
- Estimate the efficacy of Auxora to prevent pseudocyst or necrotizing pancreatis in pediatric patients with AIPT

Trial Status

- Cohort 1 complete, expanding to additional sites
- Blinded matched historical control comparison underway

Trial Status

- 8 patients received four daily infusions of Auxora and had rapid resolution of pain and food intolerance
- 1 patient received less than a single infusion of Auxora and developed pancreatic necrosis

Data release planned for 4Q23

St. Jude historical database