28 M with ALL presenting with pancreatitis

Rajesh Jain

Endorama June 1, 2017

HPI

28 M with B-ALL with CNS involvement who presented with abdominal pain. He presented to clinic with abdominal pain 5/10 and several episodes of diarrhea. He was febrile in clinic to 38.5 with tachycardia to 120s.

He was given tylenol, IV fluids, dilaudid, ceftriaxone empirically, and admitted from clinic.

Labs showed elevated lipase of 510 and TG > 4425.

Endocrinology consulted for further management.

Extended History

PMH: B-ALL, denies that his cholesterol had ever been checked before

- Diagnosed 4 months prior when he presented with fatigue and back pain
- Found to be pancytopenic (Hgb 6.1, WBC 3.2, Plt 61) with multiple enhancing foci within multiple vertebral bodies
- Found to have CNS involvement
- Started on CALGB chemotherapy that includes cyclophosphamide, cytarabine, intrathecal and IV methotrexate, pegasparargase, vincristine

Extended History

Home medications: Acetaminopen-caffeine butalbital, Acyclovir, Famotidine, lorazepam PRN for nausea/vomiting, scopolamine patch, ondansetron, polyethylene glycol, sennosides-docusate, bactrim, ursodial

PSH: None

Allergies: NKDA

Social history: Coast guard mechanic, previously used to drink 6-12 beers per week but has stopped since diagnosis. Non-smoker. Married with a 3 year old child.

Family history: No one with early CVD or high cholesterol. DM in mother.

Exam

T 37.6, P 126, BP 121/71, R 23, SpO2 94%, Ht 5’11, Wt 76.8 kg, BMI 23.4

Gen: No acute distress

HEENT: EOMI, oropharynx clear

Neck: supple, no thyromegaly

Lung: Normal respiratory effort, course breath sounds

Chest wall: no tenderness or deformity

CV: tachycardic, regular, no murmurs

Abdomen: Soft, diffusely tender, bowel sounds present

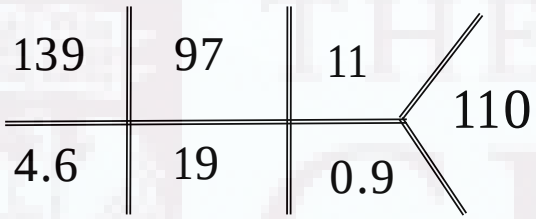
Extremities: Normal, atraumatic

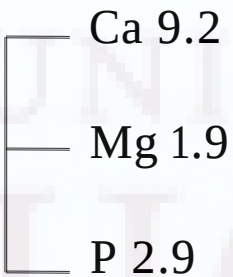
Skin: No xanthomas

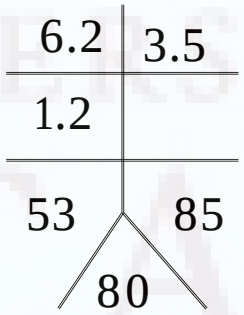
Neuro: Alert, cooperative

Psych: Normal mood and affect

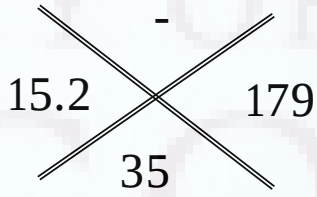
Initial Labs







Couldn't run due to lipemia



Amylase 145
Lipase 510
TG > 4425

Recommendations overnight?

- Conservative measures

  (IV fluids, NPO, pain control)

- Recheck lipase and TG to trend

Asparaginase

- Derived from E. coli
- Depletes external sources of asparagine
  - Most malignant lymphocytes have limited asparagine synthetase activity
  - Lack of asparagine leads to apoptosis
- Known toxicities: Hypersensitivity, pancreatitis, severe hyperlipidemia, altered liver function, allergic reactions, thrombosis

Asparaginase induced pancreatitis

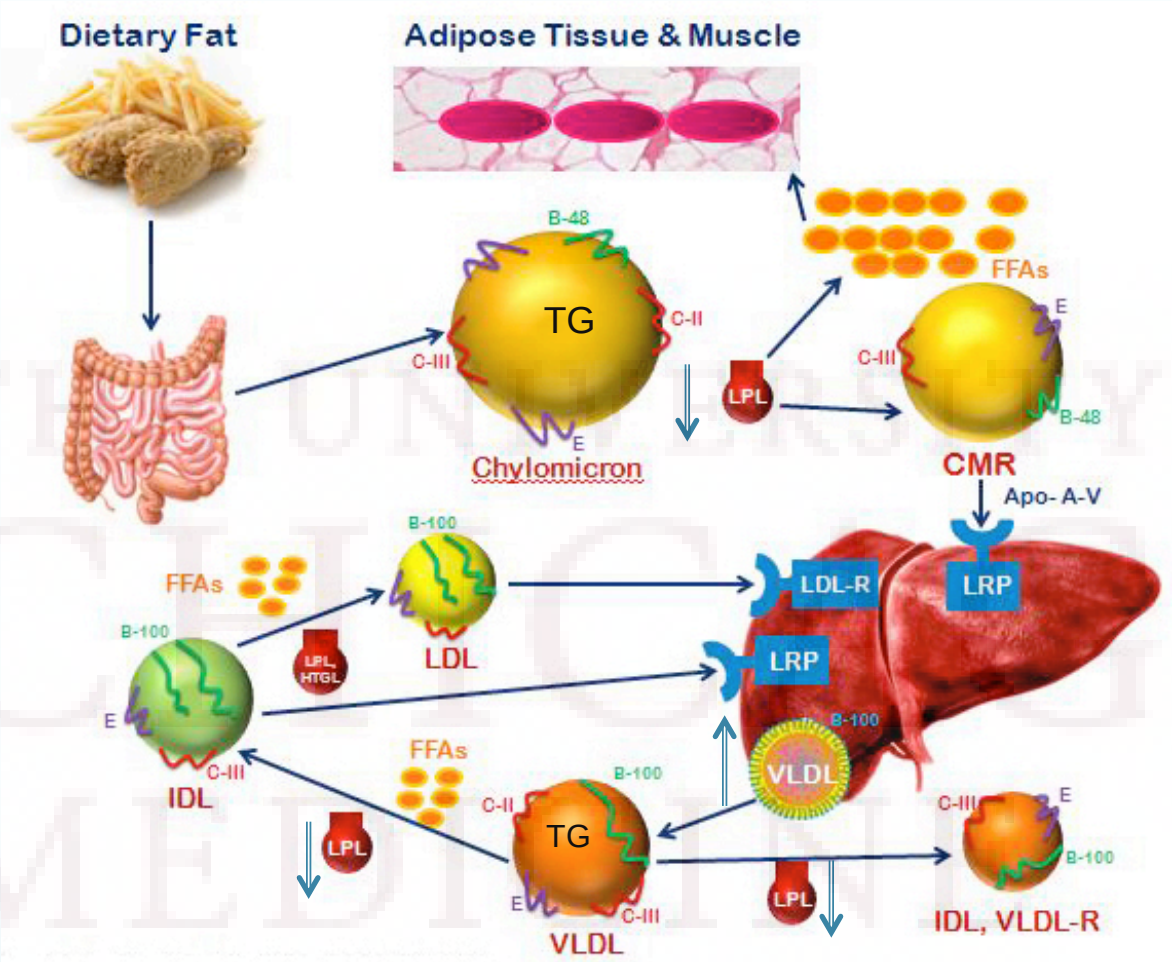
- Unknown mechanism and usually **not** associated with hyperTG
- Usually occurs relatively early in the course of therapy, suggesting it is related to a genetic predisposition rather than cumulative dose
  - Our patient had received 3 doses
  - Recent GWAS study identified variants in a pancreatic carboxypeptidase seemed to predispose individuals to pancreatitis but the mechanism is not clear
- Greater risk with older age with adults having 5% risk

Liu et al. Clinical and genetic risk factors for acute pancreatitis in patients with acute lymphoblastic leukemia. J Clin Oncol 2016.

Asparaginase-induced Hypertriglyceredemia

- Related to increases in endogeneous synthesis of vLDL and decreased lipoprotein lipase activity

  → leads to decreased removal of TG from plasma



Adapted from Miller M. et al. *Circulation.* 2011;123:2297.

B-48, B-100, C-II, C-III, E indicate apolipoproteins B-48, B-100, C-II, C-III, and E

LPL = lipoprotein lipase

FFAs = free fatty acids

CMR = chylomicron remnant

Apo-A-V = apolipoprotein A-V

LDL = low density lipoprotein

LRP = LDL receptor-related protein

LDL-R = LDL receptor

VLDL = very low density lipoprotein

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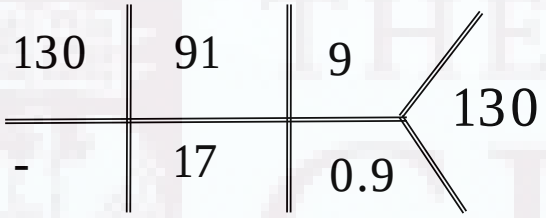
Next set of labs



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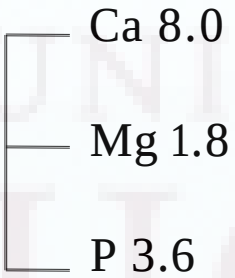
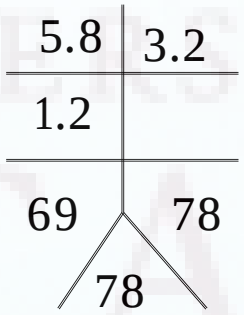
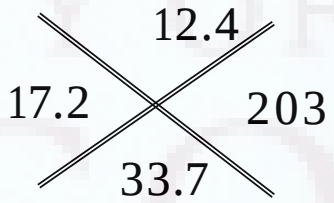






Amylase 145 → 205
Lipase 510 → 1155
TG > 4425 → >4425 (No change)
Lactic Acid 5.0

Now what?

Hypertriglyceridemia-induced pancreatitis

- There is a paucity of data or guidance
- No large studies of plasmapheresis or insulin
- No studies comparing plasmapheresis vs insulin
- Four lines in Endocrine Society guidelines for hyperTG: “We do not recommend the use of heparin infusion or plasmapheresis in the treatment of very severe hypertriglyceridemia with pancreatitis. The treatment of underlying causes including dietary fat restriction and use of long-term fibrate therapy should suffice”

Plasmapheresis

- Quickly removes TG
- Also thought to remove circulating activated enzymes, proteases, and inflammatory mediators
- HyperTG is a Category III indication (“optimum role of apheresis is not established, decision making should be individualized”) for plasmapheresis per the American Society of Apheresis

Study	Size	Design	TG Drop	Outcomes
Chen	20	Retrospective review Compared to 40 patients who did not receive TPE and/or 34 treated before TPE was available	2019± 780 → 691± 333	"No difference in morbidity or mortality" **but small & not a RTC**. Patients who rec'd TPE seemed to have worse pancreatitis.
Yeh	18	Retrospective review of patients refractory to previous therapy. No comparator group.	1971± 761 → 693± NR	Effective and well tolerated
Gubensek	50	Retrospective review. No comparator group.	5212±3610 → 956±956	Two cases of hypotension, one with GI bleeding (heparin) 15% mortality in subset of 40

Table 1. Clinical characteristics and critical scores of the patients

Patient No.	Age years	Ranson score	Glasgow pancreatitis score	APACHE II score	CRP level (normal <0.8 mg/dl) mg/dl	Baltazar CT stage score	Type of hyper-lipidemia (Frederickson classification)	APACHE II score after plasmapheresis
1	45	6	4	12	14	4	V	9
2	55	6	5	16	17	5	V	12
3	50	4	3	11	10	4	IV	8
4	37	7	5	16	12	10	V	13
5	26	6	5	17	17	7	IV	13

CRP = C-reactive protein.

11.3 mmol/L = 1000 mg/dL

Table 2. Results of the patients treated with plasmapheresis

Patient	Triglycerides (normal 0.34–1.7 mmol/l)								Improvement	
	admission	1st plasmapheresis		2nd plasmapheresis		3rd plasmapheresis		discharge	pain	clinical
		before	after	before	after	before	after			
1	26	24	18	18	9	8.4	4.5	2.83	yes	yes
2	20	17	10.9	7.4	0.93	–	–	1.07	yes	yes
3	12	19	2.6	–	–	–	–	2.1	yes	yes
4	23	20	2.1	–	–	–	–	2.0	yes	no
5	13	13	2.4	–	–	–	–	2.1	yes	yes

Kyriakidis et al. Plasmapheresis in the management of acute severe hyperlipidemic pancreatitis: Report of 5 cases. Pancreatology 2005.

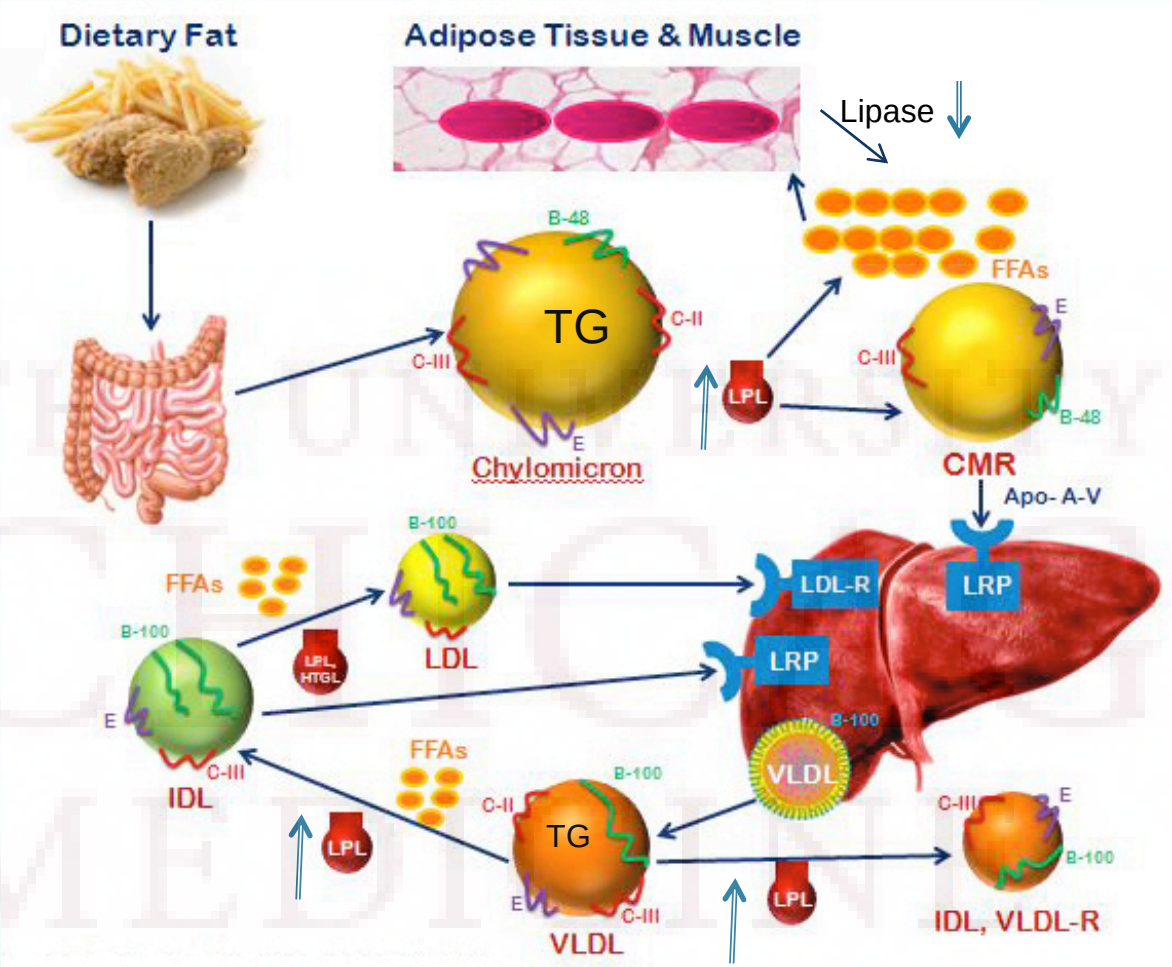
Insulin

- Potent activator of lipoprotein lipase
- Also inhibits hormone-sensitive lipase in adipocytes, which breaks down adipocyte TG and releases free fatty acids into the circulation
- Often requires aggressive dosing, e.g. 0.1-0.3 units/kg/hr
  - Will require dextrose containing IV fluids if patient does not have diabetes
- Effective but generally slower

Case series of 12 patients treated with insulin gtt

Patients	1	2	3	4	5	6	7	8	9	10	11	12	Mean	SD
Age [years]/gender	41/Male	48/Female	54/Male	35/Male	43/Female	30/Female	59/Male	46/Male	40/Female	45/Male	65/Male	46/Male	46	9.75
Serum amylase (25–125 U/l)	155	128	84	635	497	259	780	368	424	490	530	330	390.00	211.72
Serum lipase (10–60 U/l)	350	286	196	376	138	86	420	115	146	198	245	166	226.83	109.05
Serum calcium (9–11 mg/dl)	8.5	8.4	9.6	8.3	6.8	7.4	7.8	9.2	8.4	7.6	8.5	8.8	8.27	0.77
Serum triglycerides (50–250 mg/dl):														
d1	1118	1176	1228	1027	1004	1086	1130	1156	1124	1235	1190	1215	1140.75	74.74
d2	540	635	712	760	684	756	710	654	785	796	810	774	718.00	79.37
d3	355	464	489	496	476	481	528	498	494	524	590	520	492.92	54.51
d4	272	248	385	415	346	390	425	432	384	434	445	370	378.83	62.93
d5	243	232	358	366	252	324	373	290	296	276	356	298	305.33	49.81

Coskun et al. Treatment of hypertriglyceridemia-induced acute pancreatitis with insulin. Prz Gastroenterol 2015.



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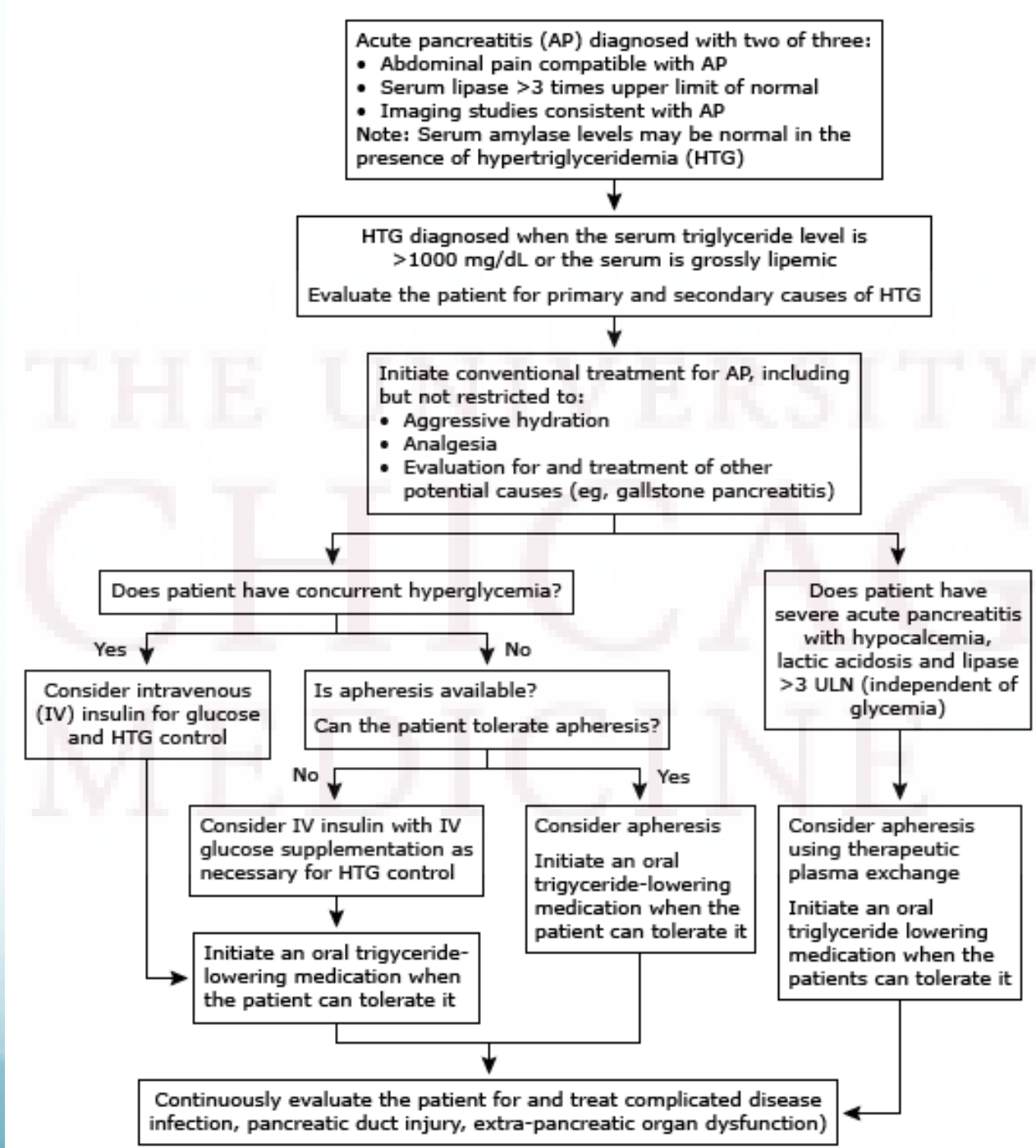
Heparin

- Temporarily increases lipoprotein lipase
- But there is an increase in lipoprotein lipase metabolism by the liver, thus making the effect temporary
- Generally has fallen out of favor


Acute pancreatitis (AP) diagnosed with two of three:
• Abdominal pain compatible with AP
• Serum lipase >3 times upper limit of normal
• Imaging studies consistent with AP
Note: Serum amylase levels may be normal in the presence of hypertriglyceridemia (HTG)
HTG diagnosed when the serum triglyceride level is >1000 mg/dL or the serum is grossly lipemic
Evaluate the patient for primary and secondary causes of HTG
Initiate conventional treatment for AP, including but not restricted to:
• Aggressive hydration
• Analgesia
• Evaluation for and treatment of other potential causes (eg, gallstone pancreatitis)
Does patient have concurrent hyperglycemia?
Yes
No
Consider intravenous (IV) insulin for glucose and HTG control
Is apheresis available?
Can the patient tolerate apheresis?
No
Yes
Consider IV insulin with IV glucose supplementation as necessary for HTG control
Consider apheresis
Initiate an oral trigyceride-lowering medication when the patient can tolerate it
Initiate an oral trigyceride-lowering medication when the patient can tolerate it
Does patient have severe acute pancreatitis with hypocalcemia, lactic acidosis and lipase >3 ULN (independent of glycemia)
Consider apheresis using therapeutic plasma exchange
Initiate an oral triglyceride lowering medication when the patients can tolerate it
Continuously evaluate the patient for and treat complicated disease infection, pancreatic duct injury, extra-pancreatic organ dysfunction)

Clinical Course

- We recommended plasmapheresis x 2
- Start Fenofibrate 145 mg daily when able
- Check lipid panel in the future
- Primary team also started octreotide 100 mcg q8h

Octreotide

- Theoretically is beneficial in pancreatitis to reduce pancreatic enzymes that can cause glandular destruction
- Has been trialed for pancreatitis in general with mild effects seen
- There are specific case reports in asparaginase associated pancreatitis
  - Particularly appealing in children given its relative safety

Wu et al. Ocreotide therapy in aspraginase-associated pancreatitis in childhood ALL. Pediatr Blood Cancer 2008.
Choi et al. Somatostatin in the treatment of acute pancreatitis: a prospective randomised controlled trial. Gut 1989.

TG and Lipase Trend

	12/6	12/7	12/9 4 AM	12/9 11 AM	12/10	12/11
TG	>4425	5910	659	757	294	402
Lipase	518	1155	194		68	

Plasmapheresis

Plasmapheresis

	12/12	12/14	12/16	12/21	12/23	12/30
TG	478	381	308	202	198	138
Lipase	42	68	83	101		

Is asparaginase now contraindicated?

- Asparaginase has proven mortality benefit in ALL
- Expert panel on asparaginase toxicities recommends permanently discontinuing asparaginase for clinical pancreatitis with amylase or lipase > 3 x ULN for >3 days
  - OK to continue if no clinical symptoms
  - OK to continue for hyperTG > 1000 if no pancreatitis, once TG returns to the normal range

Stock et al. Prevention and management of asparaginase/pegasparaginase-associated toxicities in adults and older adolescents: recommendations of an expert panel. Leukemia and lymphoma 2011.

Follow-up

- Has done well since discharge, only 1 hospitalization for chemo
- Remained on fibrate until recently when repeat TG was found to be 119
- Patient tolerated a modified regimen without asparaginase, currently on maintenance therapy

References

Liu et al. Clinical and genetic risk factors for acute pancreatitis in patients with acute lymphoblastic leukemia. J Clin Oncol 2016.

Coskun et al. Treatment of hypertriglyceridemia-induced acute pancreatitis with insulin. Prz Gastroenterol 2015.

Chen et al. Therapeutic plasma exchange in patients with hyperlipidemic pancreatitis. World J Gastroenterol 2004;10(15):2272-2274.

Yeh et al. Plasmapheresis for severe lipemia: comparison of serum-lipid clearance rates for the plasma-exchange and double-filtration variants. Journal of Clinical apheresis 2003.

Gubensek et al. Treatment of hyperlipidemic acute pancreatitis with plasma exchange: A single-center experience. Therapeutic apheresis and dialysis 2009.

Kyriakidis et al. Plasmapheresis in the management of acute severe hyperlipidemic pancreatitis: Report of 5 cases. Pancreatology 2005.

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