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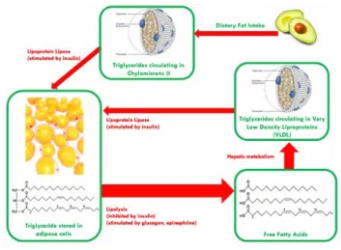
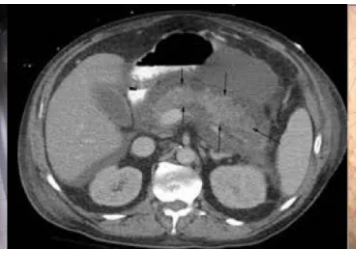
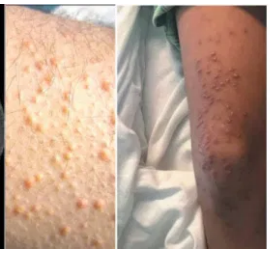
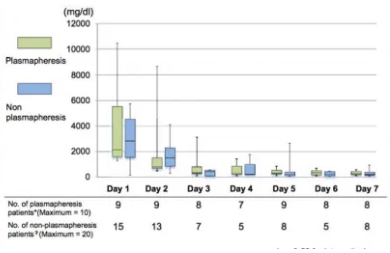
Hypertriglyceridemic Pancreatitis

August 28, 2020 by **Josh Farkas**



(https://emcrit.org/ibcc/hypertag/attachment/panctop/) **CONTENTS**

evidentiary basis for hypertriglyceridemic pancreatitis

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Hypertriglyceridemic pancreatitis occupies an uncomfortable position in the medical literature, which is typical for many critical illnesses. Hypertriglyceridemic pancreatitis is *uncommon* but not *rare*, accounting for perhaps ~8% of patients with acute pancreatitis. In the United States,

with trends towards increasing obesity, hypertriglyceridemic pancreatitis is likely to become more common over time. Thus, any sizable ICU will encounter this disorder regularly and must have expertise in dealing with it.

However, hypertriglyceridemic pancreatitis is *uncommon* enough that almost no high-quality evidence exists regarding it. Case reports and recommendations in the literature abound, but contradict one another. Practice varies widely from being extremely aggressive (e.g., immediate plasmapheresis) to being very conservative (e.g., using only subcutaneous insulin). *Most patients will improve with supportive care*, so it's easy for different authors to obtain case series of patients who appear to respond to their preferred therapy. To date, only a single prospective RCT has been performed to rigorously test *any* of these therapies (and – spoiler alert – the more conservative treatment arm had superior outcomes). (27574886 (https://pubmed.ncbi.nlm.nih.gov/27574886/))

The treatment strategy described below attempts to cut a middle ground through this literature, with a strategy which is reasonably aggressive yet fairly noninvasive. In the absence of definitive evidence, this is only *one* of *many* reasonable therapeutic approaches.

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pathophysiological model

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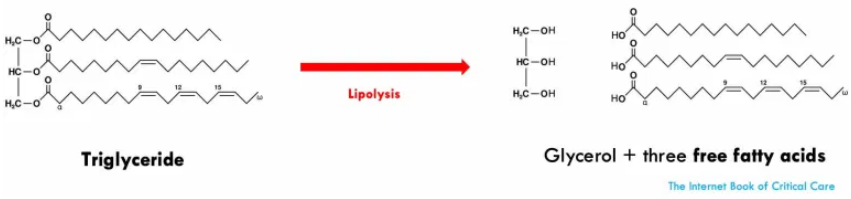
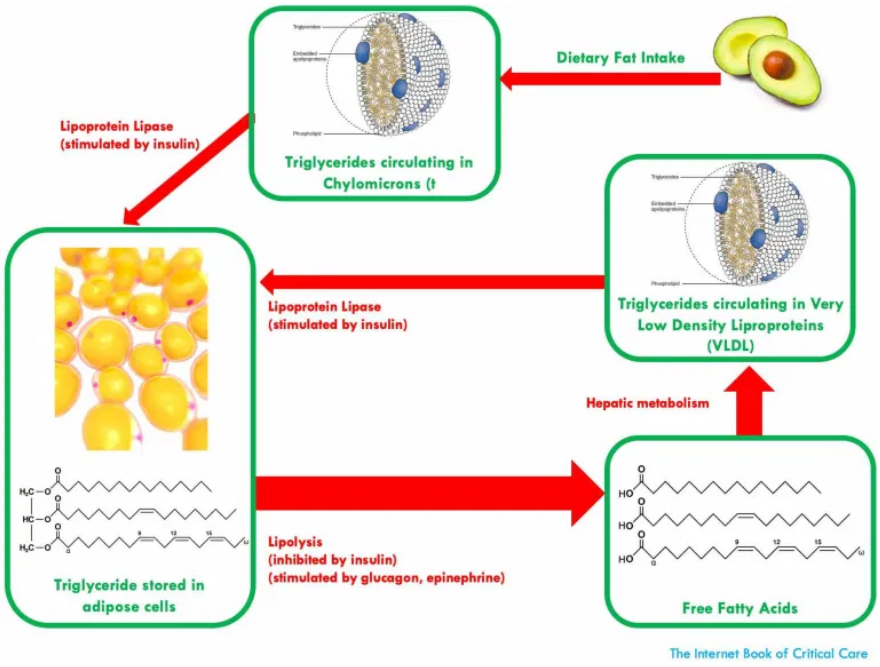


(https://emcrit.org/?attachment_id=478090) **biochemistry**

- *Triglycerides* consist of three fatty acids fused to a glycerol backbone (above figure, left). Triglycerides are a form of fat which is trafficked around the body stuffed together within small particles (e.g., chylomicrons or Very Low Density Lipoproteins, VLDL). Triglycerides are also the main form of fat stored within adipose tissue.
  - Triglycerides within chylomicrons or VLDL particles seem to be relatively *inert*.
- Triglycerides may be metabolized into glycerol plus *free fatty acids*.
  - Free fatty acids are more water-soluble, so they can dissolve in the blood directly.
  - Free fatty acids appear to be more toxic than triglycerides (more on this below).

accumulation of triglycerides and free fatty acids in patients with insulin resistance



(https://emcrit.org/ibcc/hypertag/attachment/tagphys/)

- Insulin resistance (e.g., type II diabetes) can increase levels of free fatty acids and circulating triglycerides, as shown above.(30723557 (https://pubmed.ncbi.nlm.nih.gov/30723557/))
  - (1) Insulin normally promotes the storage of triglycerides in adipose tissue. Inadequate insulin activity leads to lipolysis of triglycerides in adipose cells, releasing free fatty acids into circulation. Some of these free fatty acids are converted by the liver back into triglycerides which circulate in the bloodstream in the form of Very Low Density Lipoproteins (VLDL).
  - (2) Insulin normally promotes absorption of triglycerides into the fat tissue (via stimulation of lipoprotein lipase, which helps disassemble triglycerides and traffic the fatty acids into adipose tissue). Inadequate insulin activity leads to an accumulation of triglycerides in circulation (e.g., chylomicrons formed from dietary fat absorption and Very Low Density Lipoproteins formed in the liver).
- When insulin's effects are severely deficient, this physiology may also lead to ketoacid production (as free fatty acids are metabolized into ketoacids). This explains the following clinical phenomena:
  - Patients presenting with diabetic ketoacidosis may have elevated levels of triglycerides. In some cases, insulin deficiency may simultaneously trigger diabetic ketoacidosis *and* hypertriglyceridemic pancreatitis.

how does dysregulated lipid metabolism cause pancreatitis?

- The exact mechanism causing pancreatitis isn't entirely clear. Two possible mechanisms are as follows:
- (1) Toxicity due to elevated triglyceride levels ?? – Very high levels of triglycerides may theoretically occlude capillaries.
  - However, many patients live for *years* with extremely high triglyceride levels and do not develop pancreatitis, so hypertriglyceridemia alone doesn't seem to be particularly toxic.
  - It's *debatable* whether triglycerides are toxic at all, with some authors stating that they lack inherent toxicity.(32571534 (https://pubmed.ncbi.nlm.nih.gov/32571534/))
- (2) Toxicity due to free fatty acids – this seems more likely to be the primary cause of pancreatitis. Free fatty acids can stimulate inflammation and form conglomerates that act as a detergent to damage cell membranes.

"hypertriglyceridemic pancreatitis" is probably a misnomer

- "Hypertriglyceridemic pancreatitis" is misleading, because this implies that the triglycerides cause the pancreatitis. As discussed above, this doesn't appear to be true.
  - Rather than hypertriglyceridemia, it's probably the elevation of *free fatty acid levels* which causes pancreatitis. Thus, a more accurate term might be "free fatty acid pancreatitis."
- Unfortunately, it's impossible to measure free fatty acid levels in clinical practice, whereas it is easy to measure triglyceride levels. Thus, we remain fixated on the triglyceride level – although this level probably serves as a *surrogate* measurement of free fatty acid levels (which may be the true culprit).
  - Hypocalcemia might be an indirect measurement of elevated fatty acid levels, because the fatty acids can bind to calcium.

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natural history of triglyceride levels in hypertriglyceridemic pancreatitis

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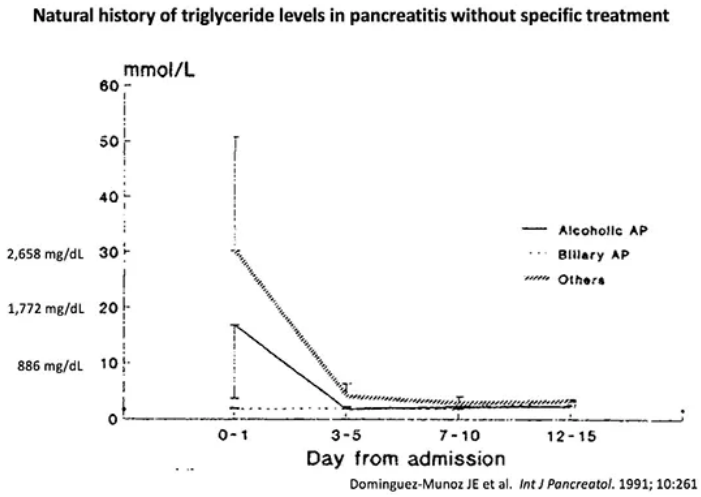
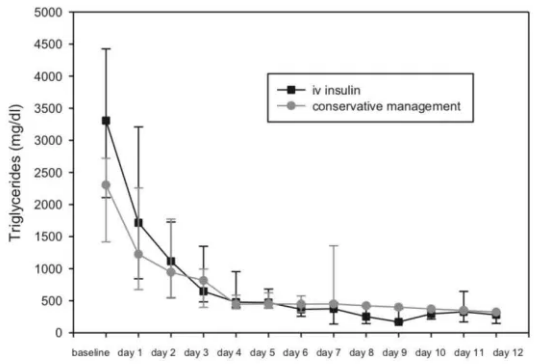
Without any specific therapy, triglyceride levels tend to fall over time. This natural fall has been well documented over decades; for example, in this study from 1991:(1787337 (https://pubmed.ncbi.nlm.nih.gov/1787337/))



(https://emcrit.org/pulmcrit/hypertriglyceridemic-pancreatitis/attachment/nat/)

Insulin infusion would be expected to accelerate the fall in triglyceride levels (e.g., due to stimulation of lipoprotein lipase, which encourages triglyceride absorption by adipose tissue). However, a recent retrospective study compared the rate of triglyceride clearance among patients treated with insulin versus patients who didn't receive insulin. No difference was detected, as shown below.(31993551 (https://pubmed.ncbi.nlm.nih.gov/31993551/)) Once again, a natural drop in triglyceride levels is observed over time, precisely in line with Dominguez-Munoz et al.'s study from 1991 above.



Number of subjects	baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12
iv insulin	51	30	39	30	20	15	11	6	6	7	5	4	5
conservative management	55	22	26	18	12	7	5	3	1	1	2	1	2

Figure 1. Median [25th, 75th percentile] TG concentrations in the iv insulin and conservative management groups over 12 days. TG concentrations were not checked daily in every patient. The number of subjects whose TG concentrations were available at each day is shown beneath the X-axis.
*$P < 0.001$ for comparison between groups Dhindsa S et al. 2019 PMID 31993551

(https://emcrit.org/ibcc/hypertag/attachment/tagdrop/) Why didn't insulin accelerate triglyceride clearance to any measurable extent? It seems that the primary driver of the drop in triglyceride levels over time may be reduced oral fat intake and gentle fluid resuscitation. Insulin administration may not add much in addition to these treatments. This drop in triglyceride levels with *conservative therapy only* has been replicated by another recent study as well.(31077464 (https://pubmed.ncbi.nlm.nih.gov/31077464/))

It's *extremely important* to realize that triglyceride levels will fall on their own, without any fancy intervention. Many case reports have demonstrated that triglyceride levels fall with various interventions (e.g., plasmapheresis). However, these reductions in triglyceride level may just reflect the natural history of the disease.

treatment implications of this model

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The above model of hypertriglyceridemic pancreatitis hasn't been rigorously proven, but seems consistent with observed evidence. This model has implications for the treatment of hypertriglyceridemic pancreatitis – specifically, that treatments should focus largely on reducing the *free fatty acid levels* (not necessarily reducing the triglyceride level). When viewed through this lens, treatment implications include the following:

insulin therapy

- A biochemical understanding of fatty acid metabolism suggests that insulin should be the front-line therapy for hypertriglyceridemic pancreatitis. Insulin administration is the fastest way to shut off fatty acid production and reduce free fatty acid levels (analogous to diabetic ketoacidosis, insulin administration has the ability to drop free fatty acid levels *within hours*).(21593106 (https://pubmed.ncbi.nlm.nih.gov/21593106/))
- Historically, insulin infusions have often been continued until the patient reached a certain triglyceride level (often <1,000 mg/dL or <11.2 mM). However, this doesn't make sense, given that insulin doesn't appear to substantially affect triglyceride levels (see above). A more sensible approach may be to simply continue an insulin infusion until the patient is making a sustained clinical recovery.

lack of utility of plasmapheresis

- Plasma exchange can be used to reduce triglyceride levels. However, the entire concept behind this may be fundamentally flawed:
  - If the pathophysiological problem is predominantly free fatty acids (rather than triglycerides), then *plasmapheresis is a fundamentally misguided therapy.* Unlike insulin, plasmapheresis won't shut off the synthesis of free fatty acids, so plasmapheresis might actually have little effect on free fatty acid levels.
- Plasmapheresis has numerous additional drawbacks, including the following:
  - It is invasive (requiring placement of a large bore hemodialysis catheter).
  - Plasmapheresis is expensive and not widely available. Adopting a strategy of plasmapheresis will require greater levels of interhospital transfer (with attendant risks and costs).
  - Plasmapheresis incurs delays to treatment initiation (many hours elapse between the decision to perform plasmapheresis and any reduction in the patient's triglyceride level).
  - Citrate involved in plasmapheresis may decrease calcium levels (which are often already low). Alternatively, if heparin is used for anticoagulation of the dialysis circuit, this may increase the risk of hemorrhagic pancreatitis and perhaps the risk of mortality. (25047332 (https://pubmed.ncbi.nlm.nih.gov/25047332/))
  - If plasma is used as replacement fluid, this carries risks of allergic reaction or disease transmission. Alternatively, if albumin is used as replacement fluid, this may exacerbate coagulopathy.
- Plasmapheresis is not supported by any clinical evidence.
  - Available clinical series show that clinical outcomes from plasmapheresis are equivalent to treatment with insulin infusion or simply conservative management.(15259080 (https://pubmed.ncbi.nlm.nih.gov/15259080/) , 25047332 (https://pubmed.ncbi.nlm.nih.gov/25047332/) , 28233051 (https://pubmed.ncbi.nlm.nih.gov/28233051/))
  - There is no clear evidence that plasmapheresis reduces triglyceride levels any faster than simply eliminating oral fat intake and providing fluid resuscitation. One retrospective series suggested equivalent reductions in triglyceride levels over time, regardless of whether plasmapheresis was used! (figure below)(28233051 (https://pubmed.ncbi.nlm.nih.gov/28233051/))
  - One RCT involving 66 patients with hypertriglyceridemic pancreatitis compared insulin infusion versus high-volume hemofiltration (an extracorporal technique used to remove triglycerides which is even more effective than plasmapheresis). High-volume hemofiltration was *dramatically effective* at reducing the triglyceride level. Hemofiltration achieved triglyceride levels <500 mg/dL within nine hours, which was much more effective than the insulin infusion. However, patients treated with insulin infusion did better clinically (with lower rates of severe pancreatitis and lower rates of persistent organ failure). This study arguably represents the highest quality evidence comparing filtration techniques to remove triglyceride versus an insulin infusion. Insulin was less expensive, less invasive, and clinically superior.(27574886 (https://pubmed.ncbi.nlm.nih.gov/27574886/))
- Overall, there is a notable lack of any compelling theoretical or clinical evidence to support plasmapheresis. In particular, it seems likely that insulin infusion is more effective (while simultaneously being less invasive and safer). Plasmapheresis for hypertriglyceridemic pancreatitis is analogous to using hemodialysis to treat diabetic ketoacidosis – hemodialysis *will* clear the ketones, but it's a fundamentally flawed approach.

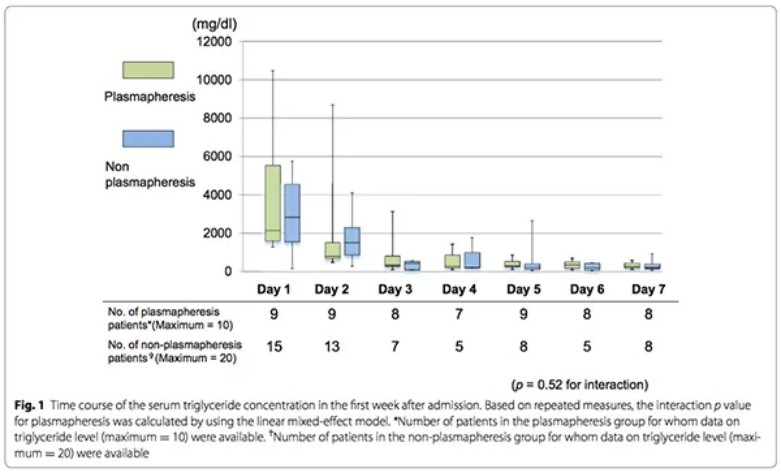

Fig. 1 Time course of the serum triglyceride concentration in the first week after admission. Based on repeated measures, the interaction *p* value for plasmapheresis was calculated by using the linear mixed-effect model. *Number of patients in the plasmapheresis group for whom data on triglyceride level (maximum = 10) were available. †Number of patients in the non-plasmapheresis group for whom data on triglyceride level (maximum = 20) were available

Miyamoto K et al. *Intensive Care Med*. 2017

(https://emcrit.org/pulmcrit/hypertriglyceridemic-pancreatitis/attachment/trig3/)

lack of utility of heparin

- Historically there was some interest in using heparin as a therapy, given that heparin may up-regulate the activity of endothelial lipoprotein lipase. Unfortunately, heparin also causes endothelial lipoprotein lipase to diffuse into the bloodstream (rather than staying stuck on the capillary wall). Free lipoprotein lipase may actually tend to *increase the level of free fatty acid* (as opposed to endothelial-bound enzyme, which promotes the uptake of fatty acids intracellularly).
- Heparin could also promote bleeding, specifically retroperitoneal hemorrhage.
- *Thus, heparin could make matter worse*. In one large series of patients with hypertriglyceridemic pancreatitis undergoing plasmapheresis, anticoagulation with heparin was associated with a 10-fold higher mortality compared with patients treated with citrate anticoagulation (11% vs. 1%)(25047332 (https://pubmed.ncbi.nlm.nih.gov/25047332/))

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diagnosis of hypertriglyceridemic pancreatitis

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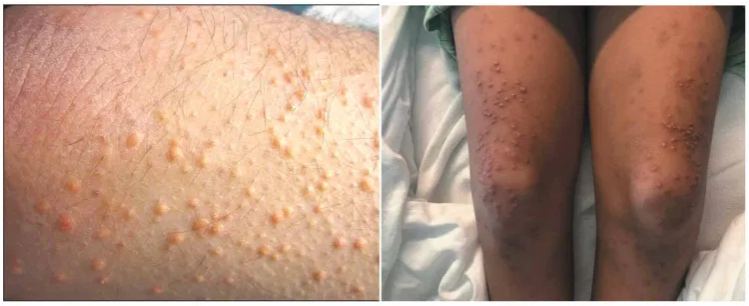
Diagnosing hypertriglyceridemic pancreatitis isn't quite as simple as merely measuring a triglyceride level. For example, there are many people in the community with hereditary hypertriglyceridemia who are happily living their lives with triglyceride levels >1,000 mg/dL. If such a person were to develop a gallstone obstructing their pancreatic duct, they would have pancreatitis *and* hypertriglyceridemia – but the hypertriglyceridemia wouldn't really be the cause of their pancreatitis.



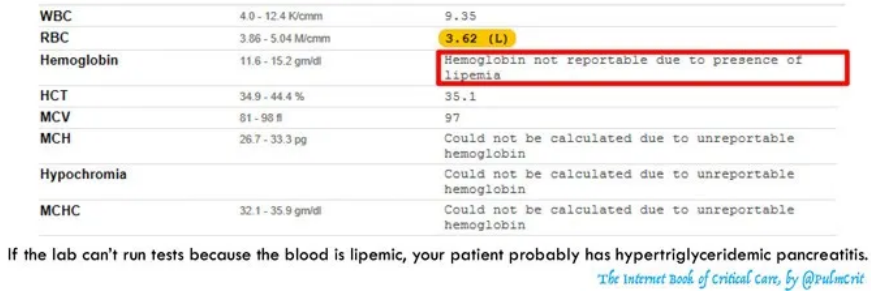
Eruptive xanthomas may be seen in some patients with extreme hypertriglyceridemia. These are grouped, firm, yellow-red papules seen over the trunk, extremities, and buttocks. Treatment of the hyperlipidemia will cause regression of these lesions within weeks to months.
Ladizinski B and Lee KC PMID 23754108; Lee SY and Sheth C PMID 31528286

(https://emcrit.org/ibcc/hypertag/attachment/eruptivexan/)

Requirements for diagnosing hypertriglyceridemic pancreatitis are therefore roughly threefold:

- (1) A clinical diagnosis of pancreatitis. This requires at least two of the following (more on this here (https://emcrit.org/ibcc/pancreatitis/#diagnosis)).
  - (a) Clinical history and examination suggestive of pancreatitis (e.g., epigastric abdominal pain, nausea/vomiting).
  - (b) Imaging (typically a CT scan) demonstrating pancreatic inflammation.

- (c) Lipase >3 times the upper limit of normal.
- (2) Triglyceride level is >1,000 mg/dL (>11.2 mM)
  - This cutoff is somewhat arbitrary. For example, one study involving 95 patients with hypertriglyceridemic pancreatitis suggested using a cutoff of >1,772 mg/dL (>20 mM).(21906399 (https://pubmed.ncbi.nlm.nih.gov/21906399/))
  - The higher the triglyceride level is, the more likely it is to be causing pancreatitis.
  - *Timing* of measuring the triglyceride level is also relevant, since levels will drop rapidly over time.
- (3) There is no other obvious cause of pancreatitis
  - This includes the absence of gallstone obstruction or medications which are likely to cause pancreatitis
  - More on the causes and investigation of pancreatitis *here* (https://emcrit.org/ibcc/pancreatitis/#evaluating_the_cause_of_pancreatitis) .



WBC	4.0 - 12.4 K/cmm	9.35
RBC	3.86 - 5.04 M/cmm	3.62 (L)
Hemoglobin	11.6 - 15.2 gm/dl	Hemoglobin not reportable due to presence of lipemia
HCT	34.9 - 44.4 %	35.1
MCV	81 - 98 fl	97
MCH	26.7 - 33.3 pg	Could not be calculated due to unreportable hemoglobin
Hypochromia		Could not be calculated due to unreportable hemoglobin
MCHC	32.1 - 35.9 gm/dl	Could not be calculated due to unreportable hemoglobin

(https://emcrit.org/ibcc/pancreatitis/attachment/hypertag/)

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causes of hypertriglyceridemia

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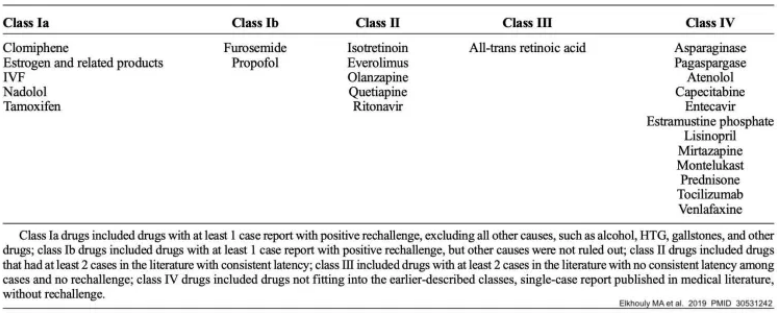
the most common causes:

- Diabetes (predominantly type II), obesity, and metabolic syndrome
- Alcoholism (it is often unclear whether pancreatitis is due to alcoholism, hypertriglyceridemia, or both)
- Hereditary hyperlipoproteinemia (usually types IV and V)
- Pregnancy
- Hypothyroidism
- Medications – see table below (30531242 (https://pubmed.ncbi.nlm.nih.gov/30531242/))



Class Ia	Class Ib	Class II	Class III	Class IV
Clomiphene	Furosemide	Isotretinoin	All-trans retinoic acid	Asparaginase
Estrogen and related products	Propofol	Everolimus		Pagaspargase
IVF		Olanzapine		Atenolol
Nadolol		Quetiapine		Capecitabine
Tamoxifen		Ritonavir		Entecavir
				Estramustine phosphate
				Lisinopril
				Mirtazapine
				Montelukast
				Prednisone
				Tocilizumab
				Venlafaxine

Class Ia drugs included drugs with at least 1 case report with positive rechallenge, excluding all other causes, such as alcohol, HTG, gallstones, and other drugs; class Ib drugs included drugs with at least 1 case report with positive rechallenge, but other causes were not ruled out; class II drugs included drugs that had at least 2 cases in the literature with consistent latency; class III included drugs with at least 2 cases in the literature with no consistent latency among cases and no rechallenge; class IV drugs included drugs not fitting into the earlier-described classes, single-case report published in medical literature, without rechallenge.

(https://emcrit.org/ibcc/hypertag/attachment/medspanc/)

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resuscitation

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traditional dogma: large volume fluid resuscitation

- Traditionally patients have been treated with massive fluid resuscitation (e.g. 250-500 ml/hr, resulting in ~8-14 liters fluid administration over the first day). This is insanity.
- There is *no evidence* to support massive volume administration. Available prospective studies show that more aggressive fluid administration increases rates of infection, abdominal compartment syndrome, ARDS, and death.[10] [11]

reasonable approach?

- Nobody knows the best approach, there is little high-quality prospective data to guide this.
- A reasonable approach to resuscitation is probably similar to a septic shock resuscitation:
  - Give fluid based on hemodynamic assessment (e.g. with ultrasonography). Most patients may benefit from a *moderate* amount of fluid initially (e.g. 2-4 liters total over the first day).
  - Don't give much fluid after the initial resuscitation (e.g. beyond 12-24 hours). Following stabilization, it's generally wise to target an *even* fluid balance (inputs = outputs).
  - Use vasopressors (e.g. norepinephrine) early, as needed to maintain an adequate MAP. This may reduce the amount of fluid given, thereby reducing the risk of abdominal compartment syndrome (more on this below).
- Be careful about the use of *fluid-responsiveness* in these patients. Even if the patient is fluid-responsive, administered fluid will rapidly leak out of the vascular space. Pancreatitis patients will often be fluid-responsive regardless of how much fluid they are given.
- Patients will often develop renal failure due to acute tubular necrosis. This doesn't respond to additional fluid administration.

lactated ringers (LR) is preferred

- Lactated Ringers appears to be the fluid of choice, given one RCT in pancreatitis that found reduced inflammation when using LR compared to normal saline.[12]
- LR is an excellent (https://emcrit.org/pulmcrit/smart/) resuscitative fluid anyway, so it shouldn't take a lot of evidence to convince us to use it here.

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nutrition

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the concept of "pancreatic rest" is dangerously misleading dogma

- Traditionally there was a concept that nutrition would stimulate pancreatic secretions and thereby worsen pancreatitis.
- Not only is this wrong, it's probably backwards.[13] Early enteral nutritional support (ideally within 24 hours) may improve outcomes, for example
  - Improved intestinal function (reduced rate of ileus, decreased bacterial translocation into the bloodstream)
  - Reduced risk of infected pancreatic necrosis.
  - Reduced hospital length of stay.
  - Decreased gastrointestinal symptoms.[1]

fat-free enteral nutrition is probably ideal for hypertriglyceridemic pancreatitis

- Oral diet may be started immediately if tolerated clinically (e.g., in the absence of nausea and vomiting).
- Cessation of oral fat intake may be important to help triglyceride levels fall. Thus, a truly **non-fat diet** might be beneficial initially.
  - For nonintubated patients, this could include foods such as fruit and pasta which are extremely low in fat.
  - For intubated patients, modular protein supplementation could be provided in addition to intravenous dextrose.
- Once triglyceride levels have fallen (typically after ~3-4 days), this might be advanced to a low-fat diet.

nutritional support for the non-intubated patient

- Some patients are unable to tolerate food (e.g. due to pain or emesis). This may be observed for a couple days. If the patient still isn't eating after 3-5 days, a small-bore nasal feeding tube may be placed to provide nutrition.[14] It's ideal to place this in a post-pyloric location, but gastric feeding is also fine.

nutritional support for the intubated patient

- Enteral tube feeding should be started immediately after the initial resuscitation. Start feeds at a trickle level (10-20 ml/hr) and advance as tolerated.
- It is controversial whether to feed the stomach (e.g. via nasogastric/orogastric tube) or to use a post-pyloric tube.
  - RCTs show no differences in outcome: either route is fine.
  - Among intubated patients it's usually easier to place an orogastric tube, so this route is often used initially.
  - If the patient has problems with gastroparesis or vomiting, then switching to a post-pyloric tube may be helpful.

total parenteral nutrition should be avoided

- RCTs in pancreatitis have shown harm from parenteral nutrition. This has been shown to increase the risk of infected pancreatic necrosis and multi-organ failure.[13]
- Parenteral nutrition should be used only as a last resort, when enteral nutrition is impossible.

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analgesia

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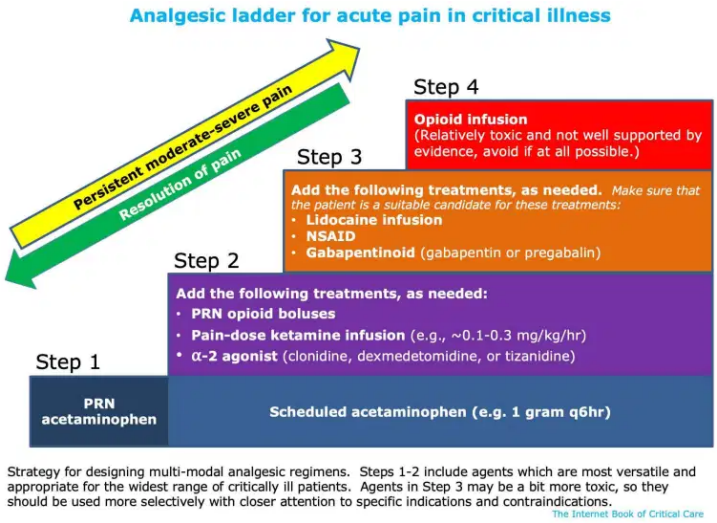

(https://emcrit.org/ibcc/pain/attachment/opioidladder/)

- Opioids may promote ileus, interfering with nutrition and potentially increasing the risk of abdominal compartment syndrome. Most patients will need some amount of opioid, but this should be kept to a minimum.
- Pain-dose ketamine infusions (e.g. 0.1-0.3 mg/kg/hr) may be helpful to control pain while avoiding opioids.[15] [16] [17]
- Scheduled acetaminophen shouldn't be forgotten, as this may also be opioid-sparing (e.g. acetaminophen 1 gram every six hours). Among patients with cirrhosis or severe alcoholism, this should probably be reduced to a dose of two grams daily (e.g. 650 mg every eight hours).[18]
- Non-steroidal anti-inflammatory agents should be avoided in critically ill patients (and especially among patients with pancreatitis), because these patients are at a higher risk of acute kidney injury.
- Epidural analgesia may be considered if available.
- For more on analgesia in critical care, see the chapter *here* (https://emcrit.org/ibcc/pain/) .

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antibiotics & infected pancreatic necrosis

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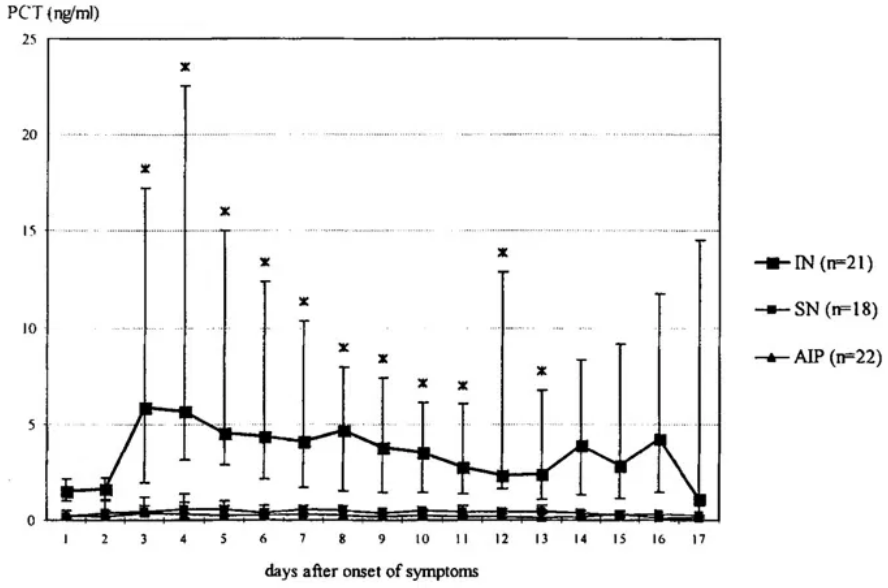
avoid antibiotics in the first week

- As discussed above, there are many parallels between sepsis and pancreatitis. These will cause the pancreatitis patient to *look* infected upon arrival (e.g. pancreatitis commonly causes fever, leukocytosis, hypotension, and vasodilatory shock). However, this is generally a reflection of sterile inflammation rather than true infection.
- Historically there was a concept that *prophylactic antibiotics* could prevent the development of infected pancreatic necrosis. This has been debunked and should not be used. Up-front antibiotics will select out resistant organisms, which cause problems later on (when true infection actually does occur).
- Antibiotics should generally be avoided during the first week, with the following exceptions:
  - (a) The diagnosis of pancreatitis is unclear and there is concern for septic shock with a focus of infection elsewhere.
  - (b) The patient has coexisting ascending cholangitis (which is a true bacterial infection and requires decompression & antibiotics).
- Infectious complications of pancreatitis (e.g. infected necrosis) are rare during the first week. During this time frame, inflammatory symptoms (e.g. fever, leukocytosis) likely reflect sterile pancreatic inflammation.

infected pancreatic necrosis

- This peaks about 10-14 days after the onset of pancreatitis. The classic presentation would be a patient who initially improves, but subsequently deteriorates with worsening sepsis.
- Investigation typically begins with repeat CT scan. Occasionally, radiologic features may be diagnostic (e.g. air within pancreatic tissue implies infection).
- Fine-needle aspiration to determine whether infection is present is routinely used at some centers and recommended in the Canadian guidelines for acute pancreatitis.[19] However, empiric antibiotics are favored at some centers due to fear of introducing infection into the pancreas during fine-needle aspiration.[20]
- Traditionally a carbapenem (e.g. meropenem) as used for improved penetration of the pancreas. However, other antibiotics also penetrate the pancreas well (e.g. cefepime/metronidazole, piperacillin-tazobactam).[21] [22] Given that these patients often remain in the ICU for some weeks, using piperacillin-tazobactam initially (instead of a carbapenem) could limit the selection of resistant pathogens.
- A team approach is required for these stubborn problems, including pancreatic surgeons, interventional radiologists, and invasive gastroenterologists. Ideally this should be managed at a large center which offers a range of minimally invasive debridement techniques.[2]



Procalcitonin trends among patients who develop infected necrosis (**IN**), sterile necrosis (**SN**), or acute interstitial edematous pancreatitis (**AIP**). Infected necrosis is associated with an early elevation in procalcitonin values (e.g. on day 3-4) as well as re-elevation of procalcitonin (e.g. on days 14-16). Rao et al. 2000 (PMID 18470712).

(https://i1.wp.com/emcrit.org/wp-content/uploads/2016/11/pcttrends.jpg)**procalcitonin use in pancreatitis?**

- Although procalcitonin is often conceptualized as a test for bacterial sepsis, it can be elevated in pancreatitis as well (as might be expected based on similarities between these two conditions). Procalcitonin may potentially be used for two purposes:
- (1) Risk stratification
  - Greater procalcitonin elevation reflects more severe inflammation, which may predict a more severe disease course.
  - Elevation of procalcitonin >0.5 ng/mL predicts severe pancreatitis with moderate reliability (sensitivity 73%, specificity 87%).[23]
- (2) Diagnosis of infected pancreatic necrosis
  - Pancreatitis alone generally doesn't cause profound elevation in procalcitonin. Therefore, a markedly elevated procalcitonin level (e.g. >3.5 ng/ml) is suggestive of infected pancreatic necrosis.[24] [25]
  - Other causes of procalcitonin elevation include renal failure and other foci of nosocomial infection (e.g. line infection, pneumonia).
  - The value of procalcitonin for infected pancreatic necrosis is likely as a *rule-out* test (e.g. a low procalcitonin argues against infected necrosis, whereas an elevated value is nonspecific). This might be useful in avoiding unnecessary antibiotic courses or invasive procedures in patients at low risk for true infection. Further prospective evidence is needed to validate this.

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abdominal compartment syndrome

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- Compartment syndrome can cause deterioration and multi-organ failure.

- This is largely an iatrogenic complication, due to the use of excessive volumes of crystalloid. As we are moving away from large-volume resuscitation of pancreatitis, this seems to be less of a problem.

oral antilipemic therapy

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- Gemfibrozil 600 mg BID should be started once patients can take oral medication (or another similar fibrate).

insulin & dextrose infusion

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general concept of insulin use

- The goal of the insulin infusion is to shut off the production of free fatty acids in adipose tissue (more detail on this above (#pathophysiological_model)). This ought to drop the serum level of free fatty acids within a few hours (although direct proof of this is lacking in hypertriglyceridemic pancreatitis).
- The goal of the insulin infusion is *not* necessarily to reduce the triglyceride level (since the best available evidence suggests that insulin is *ineffective* for this, as explored above (#natural_history_of_triglyceride_levels_in_hypertriglyceridemic_pancreatitis)).
- The dose of insulin required to shut off fatty acid production isn't known. However, this is probably similar to the dose required to treat diabetic ketoacidosis (since, in both cases, we are aiming to shut down the metabolic conversion of fats into fatty acids).

what is the appropriate insulin dose?

- This is unknown. Most studies have reported use of an insulin infusion at 0.1 U/kg/hr, but the range of published doses extends roughly between 0.1-0.3 U/kg/hr.
- Perhaps most importantly, *there probably is no single appropriate dose of insulin for all patients*. Rather, the amount of insulin required will vary widely depending on how insulin-resistant any individual patient is.
  - Patients with greater insulin resistance (e.g., patients with type II diabetes and large home insulin requirements) will require more insulin.
  - Patients who are insulin naive will require less insulin.
- The goal of the insulin infusion is to establish an *anabolic state* (i.e., a state where metabolic substrates are being stored in the form of glycogen and fat, rather than being broken down). Clinically, *we can tell that the patient is in an anabolic state if we are giving them dextrose and they aren't becoming hyperglycemic*. This implies that the appropriate dose of insulin may be *whatever dose is required to prevent hyperglycemia in the face of a significant dextrose administration*.
  - Below is a simple protocol for achieving this. There is no prospective evidence supporting this protocol.

one protocol for insulin infusion in hypertriglyceridemic pancreatitis

- **Before starting**: Replete potassium (targeting ~5-5.3 mEq/L) and phosphate (if hypophosphatemia is present).
- **Initiation**:
  - Start peripheral D10W at ~100-125 ml/hour. Continue D10W infusion at a fixed rate. (If the patient has central access, then D20W or D50W may be used at a lower volume, but establishing central access solely for this purpose shouldn't generally be needed.)
  - Titrate the insulin infusion as necessary to achieve a serum glucose of ~140-220 mg/dL. Typically, the insulin infusion will run at rates around 0.1-0.3 units/kg/hour, but this may vary depending on how insulin-sensitive the patient is.
- **Maintenance**
  - (1) Follow electrolytes (including magnesium and phosphate) q6hr. Replete aggressively.
  - (2) Follow glucose q1hr.
  - (3) Follow volume status. Administer a loop diuretic (e.g., IV furosemide or bumetanide) as necessary to avoid volume overload.
  - (4) Follow the triglyceride level daily.
- **When to stop the insulin infusion**
  - If the triglyceride level falls below 1,000 mg/dL (<11.2 mM), then the insulin infusion can likely be stopped.
  - If the patient is making solid clinical improvement, the insulin infusion may probably be stopped after >48-72 hours (even if the triglyceride level remains elevated; more discussion of this above (#treatment_implications_of_this_model)). This is an evidence-free zone.

- **How to stop the insulin infusion**
  - If the patient is on chronic insulin (e.g., for diabetes), then their basal chronic insulin should be initiated. Some patients with newly diagnosed Type-II diabetes will require initiation of long-acting insulin (sometimes at very high doses).
  - The insulin and dextrose infusions may be simultaneously weaned off, with careful attention to the glucose level.

summary

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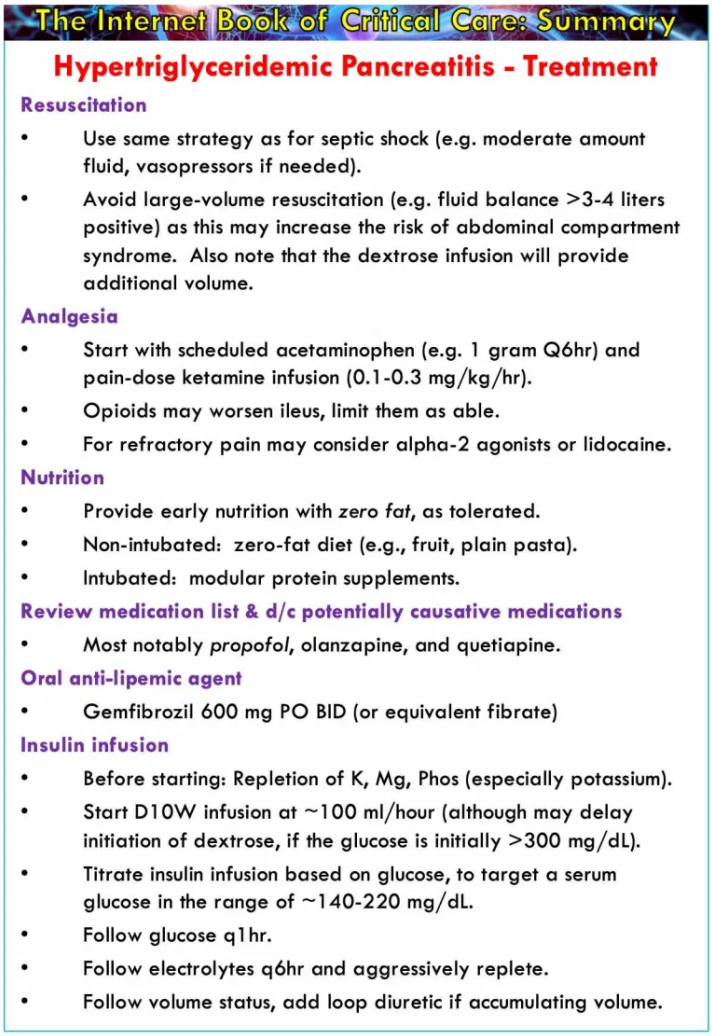

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questions & discussion

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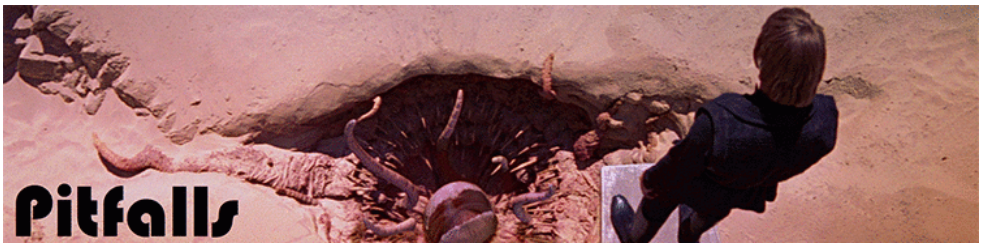
To keep this page small and fast, questions & discussion about this post can be found on another page ***here*** (https://emcrit.org/pulmcrit/hyperthermia/) .



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- Failure to diagnose hypertriglyceridemic pancreatitis due to not checking triglyceride levels.
- Plasmapheresis for hypertriglyceridemic pancreatitis is expensive, invasive, and lacks any evidentiary basis. Plasmapheresis is recommended by many sources, but this is very hard to justify from an evidence-based medicine standpoint.
- Administering an insulin infusion with inadequate attention to electrolyte levels (e.g., potassium) may be dangerous. The approach to insulin in these patients should be similar to its use in diabetic ketoacidosis, with careful monitoring of electrolytes and glucose levels.
- Providing a full diet for patients with hypertriglyceridemic pancreatitis may make it impossible to reduce the triglyceride level. Thus, a truly *fat-free* diet is probably preferable here.
- Excessive fluid administration may lead to volume overload and intra-abdominal compartment syndrome. Follow volume status carefully for patients undergoing ongoing infusions of dextrose and insulin. Consider judicious use loop diuretics to avoid volume overload.

Related

- Hypertriglyceridemic pancreatitis (https://emcrit.org/pulmcrit/hypertriglyceridemic-pancreatitis/) (PulmCrit)

Going further:

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