

## Effectiveness of Intensive Insulin Therapy in the Management of Acute Necrotizing Pancreatitis Induced by Very Severe Hypertriglyceridemia

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**Hypertriglyceridemia may be responsible for up to 4% of acute pancreatitis. Complicated pancreatitis is a serious medical condition and might be fatal. Therefore, treating the underlying cause along with supportive measures is crucial to prevent further deterioration and possible death. There have been reports where Insulin has been the mainstay of treatment for reducing triglyceride levels in patients with pancreatitis, however, there are no well-established guidelines.**

**We present a forty-year-old female patient diagnosed with acute necrotizing pancreatitis. CT abdomen revealed acute necrotic pancreatitis (Balthazar E) with extensive peri-pancreatic and peritoneal fluid collections. The patient was managed in the ICU for 28 days. She continued to receive gemfibrozil and insulin infusion, initiated according to the ICU's Protocol - Algorithm 1 targeting glucose values of 4.4 mmol/L to 10 mmol/L along with heparin infusion. She was successfully treated and recovered. She was discharged on antidiabetic and lipid lowering medications.**

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Acute pancreatitis (AP) is a common medical condition with multiple causes. Gallstones and chronic alcohol consumptions are the two most common causes responsible for AP<sup>1,2</sup>. The third most common cause is hypertriglyceridemia pancreatitis (HTG-P) accounting for 1% to 4% of all cases<sup>3</sup>.

HTG is defined as fasting serum triglyceride more than 1.7 mmol/L. It is classified as mild (1.7-2.2 mmol/L), moderate (2.3-11.2 mmol/L), severe (11.2-22.4 mmol/L) and very severe (>22.4 mmol/L)<sup>4</sup>. There is a five percent risk of developing acute pancreatitis with severe HTG and 10% to 20% risk with very severe HTG<sup>5</sup>. Although patients with HTG-P present with similar complaints to other etiologies inducing pancreatitis, studies suggest that the risk of complications are more severe with HTG-P<sup>3,6</sup>. The exact mechanism and pathophysiology of HTG inducing pancreatitis is still not clearly established; yet, several medical treatment modalities such as plasmapheresis, apolipoprotein CII infusion and intensive insulin therapy and heparin infusion were reported<sup>7-11</sup>.

The aim of this report is to present a patient diagnosed with very severe HTG-P complicated by necrosis of the pancreas, which was successfully treated with conservative management and insulin infusion therapy.

### THE CASE

A forty-year-old female presented to the emergency department complaining of a one-day history of left sided chest pain. The pain was radiating to the left side of the abdomen, graded as severe (9/10) with no aggravating or relieving symptoms. It was not associated with nausea or vomiting. The patient had a past medical history of type 2 diabetes mellitus (DM) and hypertriglyceridemia; she was on oral hypoglycemic agents (gliclazide and metformin) and fibrates (gemfibrozil 600 mg once daily). However, the patient was not compliant with her medications due to her desire to conceive and knowing that her medications must be stopped at conception. She had a history of acute complicated pancreatitis two years previously, for which, she had undergone exploratory laparotomy.

On physical examination, the patient was afebrile. Systolic blood pressure was 133 mmHg, and diastolic blood pressure was 97 mmHg. Respiratory rate was 19 breaths per minute. Heart rate was 75 beats per minute and SpO<sub>2</sub> was 99% on room air. The epigastrium and the left upper quadrant of the abdomen were tender.

The patient's laboratory investigations at admission were as follows: triglyceride level was 26.9 mmol/L; LDL, HDL and

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VLDL were 4.1, 0.96 and 5.38 mmol/L respectively; Lipase level was 3732.2 U/L (normal range 114-286 U/L); amylase level was 454.2 U/L (normal range 23-85 U/L); fasting blood glucose was 14.4 mmol/L. Complete blood count showed a white blood cell count of  $10.45 \times 10^9/L$  and hemoglobin of 16.8 g/dl. Chest X-ray was normal. Abdominal X-ray revealed dilated small bowel loops and a sentinel loop. Ultrasound of the abdomen revealed an edematous pancreas with hypoechoic surrounding tissue and evidence of epigastric and left hypochondriac fluid collection. No gallstones were seen. The image was suggestive of acute pancreatitis.

In the ward, the patient was kept NPO and was treated with IV hydration and analgesics and prescribed gemfibrozil 600 mg twice daily and insulin infusion. Two days post admission, she was tachypneic, tachycardic, hypotensive and in metabolic acidosis. She also complained of nausea and vomiting and was transferred to the Intensive Care Unit (ICU).

In the ICU, she was intubated and mechanically ventilated. Her calculated APACHE II score upon ICU admission was 32. The arterial blood gasses were pH 7.27, PaO<sub>2</sub> 67 mmHg, PaCO<sub>2</sub> 20 mmHg and HCO<sub>3</sub> 9.2 mmol/L. She was sedated with remifentanyl. Her blood pressure was maintained without vasopressor support. CT abdomen with IV contrast was performed, which showed Balthazar classification Grade E, acute necrotic pancreatitis, extensive peripancreatic and peritoneal fluid collections, hepatomegaly and fatty liver.



**Figure 1: CT Abdomen Showing Acute Necrotic Pancreatitis (Balthazar E) with Extensive Peri-Pancreatic and Peritoneal Fluid Collections (Arrow)**

The patient continued to receive gemfibrozil and insulin infusion initiated according to the ICU's Protocol - Algorithm 1 targeting glucose values of 4.4-10 mmol/L along with heparin infusion, see Appendix A.

**Appendix A:**

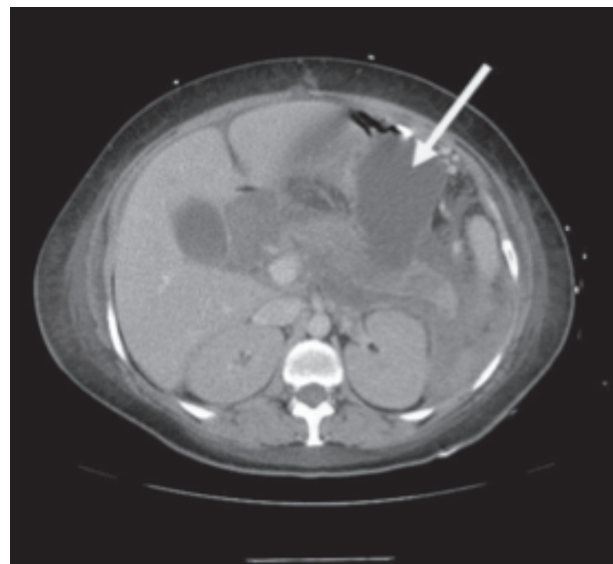
- ▶ Target Range for Glycemic Control: 7.8 mmol/L – 10 mmol/L
- 1. **Standard Drip:** 50 units human insulin (Actrapid) /50 ml 0.9% NaCl.
- 2. **Initial Infusion Rate:** Divide initial glucose level by 5.5, then round to nearest 0.5 units for initial infusion rate.

**3. Moving from Algorithm to Algorithm:**

- ▶ Moving Right: Glucose remains outside the target range after titrating insulin for more than 3 hours and falling at least 1.5 mmol/L every hour.
- ▶ Moving Left: Glucose is <7.8 mmol/L or decrease by >3 mmol/L in 1 hour.

Algorithm 1		Algorithm 2		Algorithm 3	
Glucose units/h		Glucose units/h		Glucose units/h	
< 7.8	Off	< 7.8	Off	< 7.8	Off
7.8-8.5	1	7.8-8.5	2	7.8-8.5	3
8.6-10	1.5	8.6-10	3	8.6-10	6
10.1-11.5	2	10.1-11.5	4	10.1-11.5	7
11.6-12.5	3	11.6-12.5	5	11.6-12.5	8
12.6-14	4	12.6-14	6	12.6-14	10
14.1-15.5	5	14.1-15.5	8	14.1-15.5	14
15.6-17	6	15.6-17	10	15.6-17	18
17.1-18.5	7	17.1-18.5	12	17.1-18.5	22
18.6-20	8	18.6-20	14	18.6-20	24
>20	10	>20	16	>20	28

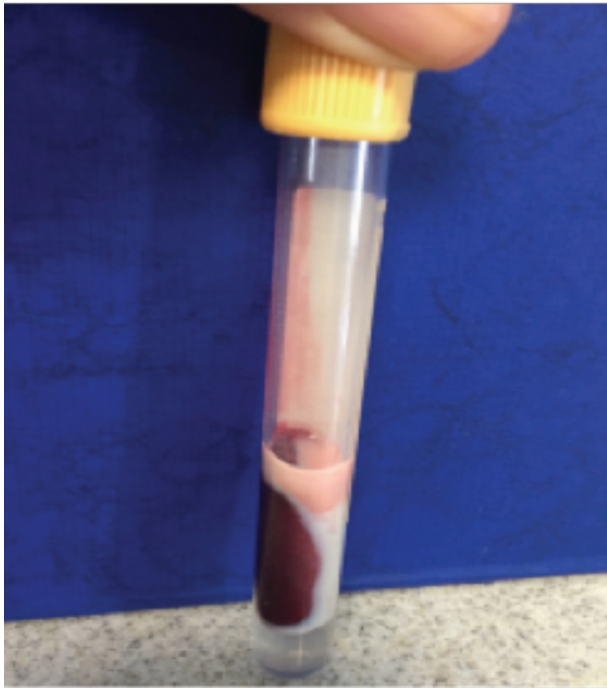
The patient was not tolerating enteral feeding from nasogastric tube and was started on partial parenteral nutrition (PPN) on day-four post-ICU admission. She developed acute kidney injury and was started on continuous renal replacement therapy (CRRT) with low inotropic support on day-seven from ICU admission. A follow-up CT revealed mild increase of the previously seen free-flowing peritoneal collection as well as the peripancreatic fluid collection, which became encysted at the infragastric region at the site of the pancreatic body-tail defect. Mild increase of the degree of derangement of pancreatic parenchyma, which became relatively hypervascularized compared to the previous CT indicating ischemic changes.



**Figure 2: Abdominal Computed-Tomography Showing Mild Increase of the Previously Seen Free-Flowing Peritoneal Collection as Well as the Peri-Pancreatic Fluid Collection, Which became Encysted at the Infragastric Region (Arrow)**

On day 12 of ICU admission, the blood glucose level was not controlled, and insulin infusion progressed to Algorithm 3, see Appendix A. During the subsequent days of ICU admission, the patient's condition improved. The patient was successfully weaned from mechanical ventilation, her renal functions recovered and triglyceride levels decreased to 2.35 mmol/L. She resumed enteral feeds and insulin infusion was tapered down to Algorithm 2, see Appendix A. After 28 days, she was discharged from the ICU, and insulin infusion was discontinued two days later. She was kept on insulin glargine and insulin aspart.

The patient remained stable. A repeat serum triglyceride was performed and had decreased to 1.64 mmol/L and lipase and amylase had decreased to 632 U/L and 223 U/L, respectively, see figure 3. She recovered with insulin therapy and gemfibrozil and did not require additional intervention. She was discharged after 44 days on insulin (insulin glargine 60 units at bedtime and insulin aspart 12 units three times daily), gemfibrozil (600 mg twice daily) and omega-3 fatty acids (2 g three times daily).



**Figure 3: Blood Sample of our Patient on Admission Showing Lipemic Sample**

## DISCUSSION

HTG is a well-known cause of acute pancreatitis. It typically could be exacerbated by secondary factors or by genetic predisposition. Suboptimally controlled diabetes, high alcohol consumption, hypothyroidism, pregnancy and medications are all examples of secondary factors. Genetic factors inducing pancreatitis include familial chylomicronemia, familial dysbetalipoproteinemia, familial hypertriglyceridemia and familial combined hyperlipidemia<sup>5,17</sup>.

The enzyme lipoprotein lipase is produced by endothelial cells. It is responsible for decreasing the level of triglyceride in the plasma. It acts by degrading triglyceride into free fatty acids and

glycerol, which further contribute to chylomicron degradation. Secondary factors lead to lipoprotein lipase deficiency resulting in elevated triglyceride level and participate in developing acute pancreatitis<sup>12</sup>. Chylomicrons are present if triglyceride levels are high in the circulation, usually large and able to occlude pancreatic capillaries, which subsequently lead to ischemia. Change in acinar structure release lipase causing lipolysis. This leads to inflammatory mediators and free radicals secretion culminating in inflammation, edema and necrosis<sup>13,14</sup>. The risk of developing HTG-P is highest if serum triglyceride level is  $> 1000\text{mg/dl}$ <sup>14-16</sup>.

Our patient had uncontrolled diabetes mellitus and HTG leading to the development of acute pancreatitis. The first aspect of management is lifestyle modification with dietary restriction of fat and carbohydrates intake, smoking cessation, decreasing alcohol consumption, weight loss and increasing physical activity. Patients with fasting triglyceride levels of  $>1000\text{ mg/dl}$  should restrict dietary fat to less than 10% of the total daily caloric intake. If the triglyceride level ranges 400 mg/dl to 1000 mg/dl, then 20% of dietary fat is allowed<sup>17</sup>.

Other treatment modalities have been described to treat acute pancreatitis induced by hypertriglyceridemia. Although dietary and lifestyle modifications are essential to prevent the accumulation of triglyceride and are the key elements in managing the condition, medications are still necessary to decrease triglyceride levels. The objective of undergoing therapy is to enhance lipoprotein lipase activity and to decrease triglyceride and chylomicron levels. This could be achieved by administering triglyceride lowering agents and insulin.

Fibrates such as gemfibrozil reduce the level of hepatic very low-density lipoprotein (VLDL) and increase the level of lipoprotein lipase<sup>18,19</sup>. It increases the high-density lipoprotein (HDL) by 20% and lowers triglyceride levels up to 50%<sup>20</sup>. Studies showed that Omega-3 fatty acids combined with triglyceride lowering agents reduces plasma triglyceride by 20%<sup>21</sup>.

Case reports showed a mean decrease in triglyceride levels by 50% within 24 hours after initiating insulin and heparin therapy<sup>12,22,23</sup>. Insulin stimulates lipoprotein lipase activity and degrades chylomicron<sup>1</sup>. Patients with diabetes mellitus diagnosed with acute pancreatitis should normalize glucose levels as soon as possible<sup>24</sup>. In our patient, serum triglyceride levels decreased within few days with insulin infusion.

## CONCLUSION

**Hypertriglyceridemia is a common condition which could precipitate acute pancreatitis when markedly elevated. Insulin infusion is a safe and effective modality to treat HT induced pancreatitis. Nevertheless, the mainstay of management is prevention through diet and compliance with medications to avoid acute and recurrent attacks.**

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