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# Acute pancreatitis due to severe hypertriglyceridemia in the COVID-19 era: The role of therapeutic plasma exchange

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ABSTRACT

The psychosocial consequences of the COVID-19 pandemic caused multifaceted challenges in clinical and therapeutic practices. This was the case at the Therapeutic Apheresis Unit of the Padua University Hospital too.

Several published reports describe the increase in alcohol and food addiction diseases. In this context, during the last months, the Padua Therapeutic Apheresis Unit treated many more patients with acute pancreatitis due to severe hypertriglyceridemia with therapeutic plasma exchange than in the previous ten years. Furthermore, retrospective cohort studies have been recently published describing the onset of acute pancreatitis during the COVID-19 infection even if, to date, there is still insufficient evidence to establish a direct causality.

Anyway, the COVID-19 pandemic translated into changes of the overall disease prevalence scenario and therefore the Padua Therapeutic Apheresis Unit will need to reorganise its Therapeutic Apheresis activity.

During the Coronavirus Disease 2019 (COVID-19) pandemic clinical and therapeutic practices have faced multifaceted challenges in all areas of medicine.

In this regard, the quick reorganization of treatments' schedule from March to April 2020 at the Padua Therapeutic Apheresis Unit (TA Unit) resulted in a reduction of the overall procedures, as compared to the same time period in 2018 and 2019 [1].

Unfortunately, after one year, the COVID-19 pandemic is still ongoing, and as part of its massive impact on clinical ground its consequences at psychosocial level need also to be taken into account [2]. In fact, as suggested by several reports, it seems that COVID-19 related distress could be associated with alcohol and food addiction problems [3], resulting in changes in the overall disease prevalence scenario.

In this context, a particular attention should be given to acute pancreatitis (AP) due to severe hypertriglyceridemia (HTG-AP), a rare and complex disorder with a pathophysiological mechanism determined by genetic, metabolic, environmental and patient-specific factors [4]. In the latest American Society of Therapeutic Apheresis (ASFA) Guidelines [5], therapeutic plasma exchange (TPE) for the treatment of HTG-AP is indicated in category III (optimum role of apheresis therapy is not established; decision making should be individualized), because of the current lack of randomized controlled clinical trials. Therefore, TPE efficacy in the treatment of HTG-AP is still unclear and controversial [6]. Nevertheless, an adjuvant role of TPE in this disease seems dependent on the rapid reduction of triglycerides (TG) levels and on the potential addition of deficient endothelial lipoprotein-lipase [7], when fresh frozen plasma (FFP) is added as a replacement fluid.

Several case reports and retrospective cohort studies have been published describing the onset of AP during the COVID-19 infection even if, to date, there is still insufficient evidence to establish causality. Only few patients (0,07 %) with COVID-19 developed AP [8], while most presented only high lipasemia without typical signs of AP [9].

Furthermore, the AP temporality, symptoms and severity are very heterogeneous in relationship to the COVID-19 infection. Pathogenesis of AP in COVID-19 positive patients seems dependent on inflammation, impaired microcirculation and destruction of pancreatic acinar cells. The COVID-19 virus targets the angiotensin-converting enzyme 2 (ACE2) receptor, that is most remarkably expressed on lung alveolar epithelial cells and enterocytes, but also in pancreatic tissue [10].

Moreover, tocilizumab (TCZ) is a treatment option for severe COVID-19 patients: since chronic use of TCZ in rheumatoid arthritis has been shown to increase lipid parameters, in particular TG, it is advisable to monitor hyper-TG levels in COVID-19 patients treated with TCZ [11]. To the best of our knowledge, so far only a case of HTG-AP in association

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**Table 1**
Characteristics of HTG-AP patients treated with TPE at the Padua Hospital in the past decade.

| PATIENT | AGE SEX | YEAR | TG VALUES PRE AND POST(mmol/l) – reduction % | COMORBIDITIES |
|---|---|---|---|---|
| 1 | 30 M | 2014 | 613<br>119<br>80% | alcohol abuse |
| 2* | 34 F | 2015 | 252<br>111<br>56 % | hyperglycemia<br>obesity |
| 3 | 34 M | 2019 | 585<br>3,8<br>93 % | alcohol abuse<br>hypercholesterolemia |
| 4 | 53 M | 2019 | 495<br>4,1<br>92 % | alcohol abuse<br>hypercholesterolemia |
| 5 | 47 F | 2020 | 368<br>9,4<br>75% | diabetes mellitus |
| 6 | 47 M | 2020 | 677<br>3,9<br>94 % | alcohol abuse<br>obesity |
| 7 (1st episode) | 43 F | 2020 | 469<br>4,5<br>90 % | obesity<br>diabetes mellitus<br>hypercholesterolemia |
| 7 (2nd episode) | 44 F | 2021 | 476<br>8,2<br>83 % | obesity<br>diabetes mellitus<br>hypercholesterolemia |
| 8 | 53 M | 2021 | 311<br>6,8<br>78 % | alcohol abuse<br>hypercholesterolemia<br>COVID-19 |
| 9 | 40 M | 2021 | 620<br>5,5<br>91 % | alcohol abuse<br>diabetes mellitus |
| 10 | 44 M | 2021 | 610<br>4,8<br>92 % | alcohol abuse |

* TPE by using only albumin solution as a replacement fluid.

with the COVID-19 infection has been described [12].

Our TA Unit, has been traditionally involved in the first-line therapy of HTG-AP in urgent cases (within 24 h), also because its associated mortality can exceed 30 % [13]. The general incidence of HTG-AP throughout the years has been gradually increasing [4], but in our experience it increased more rapidly during these last months of the COVID-19 pandemic.

In fact, between January 2020 and February 2021 we treated 6 patients with HTG-AP (in total we performed 7 procedures because one patient suffered from relapsing HTG-AP). Four of these six patients were treated during the last 2 months. These data seem meaningful, considering that from 2011 to 2019 we treated only 4 patients for HTG-AP. Furthermore, between 2011 and 2019 the number of annual TPE sessions performed by the TA Unit has been about 1100 procedures per year, instead in 2020, due to the COVID-19 pandemic, the TPE sessions performed were only 822 [1].

The 10 HTG-AP patients treated with TPE at the Padua Hospital from 2011 to 2021 were 7 males and 3 females (one patient was hospitalized twice in 2020 and 2021). They were treated with a single session of TPE, by exchanging one total plasma volume with 2/3 albumin solution and 1/3 FFP (in one patient only albumin solution was used). In all cases TG values before TPE were higher than 226 mmol/L (2.000 mg/dL), with an observed median reduction in TG levels of 90 % (range 56–94 %) within 48 h after apheresis treatment. Common comorbidities were alcohol abuse, hyperlipemia, obesity and diabetes mellitus. One patient was also found positive to COVID-19 after a molecular and antigenic nasopharyngeal swab performed before the hospitalization. He had a paucisymptomatic course with mild cough, needing low flow Oxygen therapy for few days (Table 1). All patients recovered from HTG-AP and were discharged from the hospital after a mean of 12 days (range 7–21).

The importance of adding FFP as a partial replacement fluid has to be highlighted as it enhances TG removal beyond the expected results (≥90 % in 6 out of 11 HTG-AP episodes), while keeping with the putative addition of plasma lipoprotein-lipase activity [14].

In the last year, the pandemic and the restrictions that followed have significantly affected the lifestyles of the general population. The limitation of commercial activities and sports facilities, as well as limits imposed on travelling, especially during lockdown, determined a proportional decrease in the population carrying out physical activity and reshaped alcohol abuse and massive food intake [15]. Obviously, these factors have probably influenced the frequency of some clinical disorders, including HTG-AP, as we recently observed.

In this regard, the 2020 Report on Fair and Sustainable Wellbeing (BES), presented by ISTAT (the Italian National Institute of Statistics) on 10th March 2021, highlights a worsening of mental health indices. Obese patients have particularly increased (455% of peoples over the age of 18 are overweight). Moreover, alcohol abuse, that concerned the 168% of the population over the age of 14, is slightly increasing with respect to 2019.

Consequently, the current efforts of the Padua TA Unit are focused on re-organizing the TA activity and on providing efficient therapeutic responses, especially in the urgency setting, while waiting for a desirable resolution of the current pandemic.

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