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New perspectives in the management of acute pancreatitis – focus on antibiotic prophylaxis, management of necrosis and COVID-19 implications.

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Abstract

This review highlights the recent development in the management of acute pancreatitis in the area of antibiotic prophylaxis, management of necrosis and correlation with SARS-CoV-2 infection. The evidence from recent studies has not shown a significant benefit of administration of antibiotic prophylaxis in acute pancreatitis. Additionally, a few trials draw attention to the disadvantages of prophylactic use of antibiotics. However, in this area more trials have to be conducted. When it comes to management of necrosis, the recent data recommends a postponed drainage. Delayed procedure is considered now as preferential treatment. Furthermore, delayed drainage is associated with fewer interventions and necrosectomies compared to immediate drainage. There is still insufficient data to confirm the influence of SARS-CoV-2 infection on the development and course of pancreatitis. Special attention should be brought to all COVID-19 patients presenting with gastrointestinal symptoms. Measurement of amylase and/or lipase levels in the serum is recommended for preliminary diagnosis. If suspicion arises, full diagnosis of acute pancreatitis should be conducted for early implementation of supportive treatment.

Keywords: Acute pancreatitis; antibiotic prophylaxis; management of necrosis; COVID-19

Introduction

Acute pancreatitis (AP) is frequently diagnosed gastrointestinal disease with diverse clinical presentation and variety of etiological factors. Cholelithiasis and alcohol consumption, being the most common ones, constitute 62% of cases (40% and 22%, respectively). Other causative agents include metabolic abnormalities, such as hypertriglyceridemia and hypercalcemia, viral and parasite infections, genetic and autoimmune predispositions, or, in some cases, iatrogenic damage. Endoscopic retrograde cholangiopancreatography (ERCP) is said to be responsible for nearly 4% of AP cases. Despite an abundance of possible triggers, in 25,6% of diagnosed patients, etiology remains unidentified [1].

In the vast majority of cases patients develop a mild AP without local and systemic complications. Nevertheless, it can rapidly progress to severe AP with persistent organ failure and mortality up to 35% [2]. Therefore, it is vital to properly assess and diagnose patients presenting with symptoms typical for AP, as well as conduct appropriate treatment.

Aim of study

The aim of the study is to discuss a new insight into acute pancreatitis in the subject of antibiotic prophylaxis, management of the necrosis and COVID-19 correlation.

Materials and methods

The literature available in PubMed database was reviewed using following keywords: “Acute pancreatitis”, “Antibiotic prophylaxis”, “Management of Necrosis”, “Covid-19”.

Use of antibiotics

According to the Atlanta classification created in 2012, acute pancreatitis (AP) can be divided into three types, based on its severity: mild, moderate and severe. Mild acute pancreatitis (MAP) is the most common type of the AP and it proceeds without organ failure and local complications. Moderately severe acute pancreatitis is related with temporary organ failure, local and systemic complications. Whereas severe acute pancreatitis (SAP) is associated with persistent organ failure, that lasts more than 48 hours, local and systemic complications. Local complications are peripancreatic fluid collections, pancreatic and peripancreatic necrosis,

while systemic complications include exacerbation of pre-existing co-morbidity [3]. Mortality rate for MAP is <1-3%, while for moderately severe acute pancreatitis and SAP it is estimated around 13-35% [2]. The summarization of types of AP is shown in Table 1.

Table 1. Types of acute pancreatitis, according to Atlanta classification 2012

Feature	Mild acute pancreatitis (MAP)	Moderately severe acute pancreatitis	Severe acute pancreatitis (SAP)
Organ failure	Absent	Present, temporal <48 h	Present, persistent >48 h
Local or systemic complications	Absent	Present	Present

The type of AP and clinical course of illness indicates the type of treatment that should be applied [3]. MAP's treatment is mostly limited to supportive care, that includes fluid resuscitation and pain control, due to its self-limiting course [4]. Patients with moderately severe acute pancreatitis and SAP are at increased risk of developing infective complications [4,5,6]. Infected pancreatic necrosis is the main factor that contributes to a higher mortality in patients with AP. Wherefore there is still ongoing discussion whether the patients with AP require additional treatment with antibiotic prophylaxis to prevent infective complications [4].

Antibiotic prophylaxis consists in administration of antibiotics in patients with AP, who have no clinical signs of the current pancreatic infection. The main objective of that procedure is prevention of possible infection before it occurs [2]. Early trials and meta-analyses indicated that prophylactic use of antibiotics in patients with SAP may reduce the incidence of pancreatic necrosis, infective complications and has beneficial effects on outcome of the illness and mortality [7-12]. However, subsequent studies did not confirm such benefits [13-15]. Japanese guidelines published in 2015 suggested that antibiotic prophylaxis may be beneficial in SAP if it is initiated in the early phase (within 72 hours of onset) [16]. However, most recent studies started to become a more one-sided opting against the benefit of antibiotic prophylaxis, indicating that prophylactic use of antibiotics in AP patients does not reduce the incidence of pancreatic necrosis and mortality [2, 5, 17-22]. In the meta-analysis from 2020 findings suggested that antibiotic prophylaxis may reduce the incidence of non-pancreatic infection and

urinary tract infection. Aside from that there were no statistically significant benefits if it comes to infected pancreatic necrosis, mortality, surgical intervention, pneumonia and fungal infection [4]. Few studies drew attention to the negative effect of prophylactic use of antibiotics in patients with AP. The concerns pertained to increasing antibiotic resistance, including multi-drug-resistant bacteria, increased risk of fungal infections and *Clostridium difficile*-associated diarrhea [4, 21-23].

The subject of antibiotic prophylaxis in SAP is still unclear [4]. There is still not enough evidence to support the prophylactic use of antibiotics in patients with SAP [4, 21, 24]. In recent years many studies assessing the impact of antibiotic treatment in patients with AP have been conducted, however recommendations remain uncertain.

In patients suffering from infected pancreatitis available data suggest treatment with antibiotics. Proper diagnostic process seems to be crucial and may reveal the infection, which determines further management. Several guidelines and studies recommend antibiotics for the treatment [2, 5, 24]. It is crucial to recognize the sights of infection efficiently. The examination of choice is CT-guided fine-needle aspiration (FNA) which allows to confirm infected pancreatic necrosis (IPN) and helps to choose an individualized antibiotic treatment [2]. Aside from IPN another condition that can appear during AP is infected peripancreatic fluid collections (IPFCs). In this case diagnostic tools are also CT or MRI scans [24].

A helpful biomarker that can also be used in the diagnosis of bacterial infection is procalcitonin (PCT), which allows to select the patients that might need and benefit from antibiotic administration [25, 26]. Antibiotics that are usually used and recommended in infected pancreatitis are carbapenems, quinolones and metronidazole, due to their effective penetration to pancreatic tissue. The spectrum of empiric antibiotic therapy should comprise both aerobic and anaerobic, Gram-negative and Gram-positive bacteria. [2, 24].

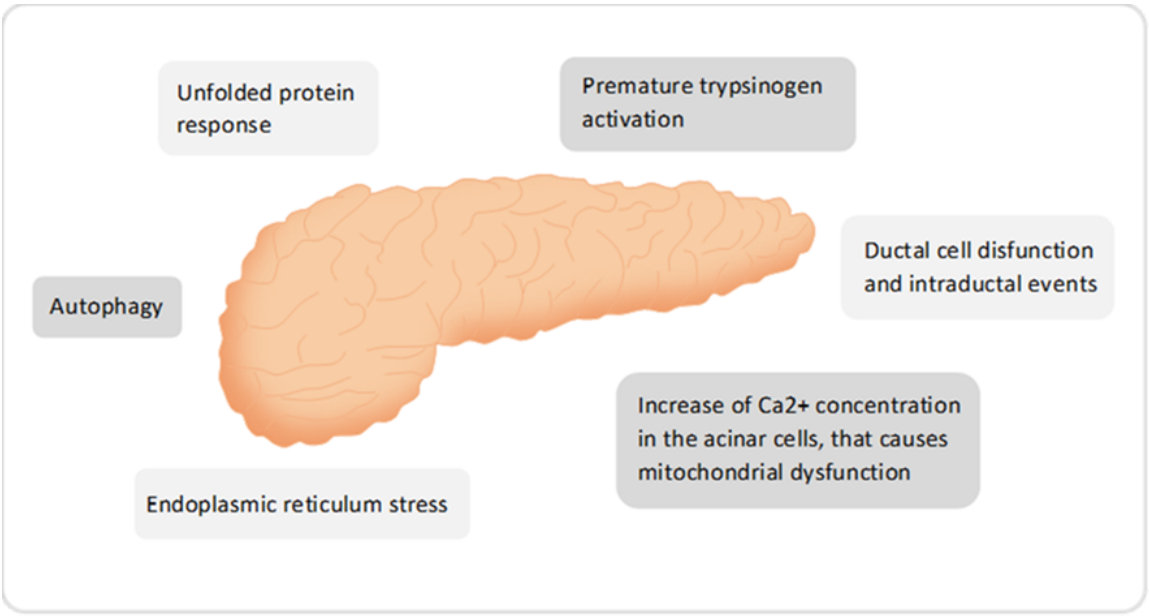
Management of necrosis

Necrotizing pancreatitis affects around 5-10% of patients with AP. It usually manifests as necrosis that involves both the pancreas and peripancreatic tissues. Necrosis that is limited only to the pancreas or only to the peripancreatic tissues occurs less often [3].

A pathogenesis of pancreatic necrosis consists of a few cellular mechanisms [5]. The first one is pathological elevation of Ca2+ concentration in the acinar cells, that indicates

mitochondrial dysfunction, loss of ATP and necrosis [5, 27, 28]. The second mechanism that can lead to pancreatic necrosis is premature trypsinogen activation, where trypsinogen is activated to trypsin. Thus, activated trypsin causes autodigestion of the acinar cells. Other events that can provoke pancreatic necrosis are autophagy, endoplasmic reticulum stress and unfolded protein response, ductal cell dysfunction and intraductal events [5, 28]. All mechanisms are shown in Figure 1.

Figure 1. Cellular mechanisms of pancreatic necrosis.



Pancreatic and peripancreatic necrosis can be sterile or become infected [3]. Infected necrosis constitutes about 10-20% of cases in patients with SAP [26]. The presence of sterile and non-obstructive necrosis is not an indication for intervention and can be managed with watch-and-wait strategy, as spontaneous resolution is possible [29-31]. If there are signs of infection, sepsis or necrosis causes compression on the surrounding organs, the intervention should be implemented [29]. Primal preferential treatment for infected necrotizing pancreatitis is a minimally invasive step-up approach, with endoscopic or percutaneous drainage [31].

Local complications such as infected necrosis foci are usually diffused in the early stages of AP, whereby recommendations suggest delaying the intervention preferably 4 weeks after the onset of the disease [2, 5, 28-32]. The mentioned delay is optimal for the development of infected walled-off-necrosis (WON), which is more suitable for drainage and lowers the risk of complications during invasive intervention [5].

The POINTER trial investigated the results and differences between the immediate and postponed drainage. The trial involved 104 patients with infected necrotizing pancreatitis. The patients were randomly assigned to immediate drainage and postponed drainage. The results did not show superiority of immediate drainage over delayed drainage. Complications and mortality also did not differ between the groups. However, among those who received postponed drainage, 35% of patients were successfully treated with antibiotics alone. Additionally, delayed drainage was associated with fewer interventions and necrosectomy was required only in 22% of patients with postponed drainage, compared to 51% in the group with immediate drainage [32]. The procedure of endoscopic transduodenal or transgastric drainage involves the placement of plastic or a lumen-apposing metal stent (LAMS) [30]. The randomized controlled trial from 2019 compared efficacy and clinical outcome of both types of stents, but the results did not show relevant differences [33].

In some cases when non-invasive drainage fails, an invasive intervention such as necrosectomy should be performed [28, 29]. However, open necrosectomy is associated with a higher mortality rate in comparison to less invasive endoscopic methods [29].

COVID-19 and AP

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for global pandemic of COVID-19, declared by World Health Organization on 11th of March 2020 and which by definition lasts to this day. Even though it is no longer considered as a public health emergency of international concern (PHEIC), it still poses a tremendous challenge for public health with over 772 millions of documented cumulative cases and nearly 7 million deaths attributed to the disease. With numerous cases emerging over time, it became clear that SARS-CoV-2 infection is not limited to respiratory tract and should be rather considered as systemic disease presenting with a variety of symptoms, including gastrointestinal manifestations. According to performed meta-analysis, up to 9,8% of COVID-19 patients may manifest one or more GI symptoms, including the most observed: nausea, vomiting, diarrhea and abdominal pain [34]. However, SARS-CoV-2 infection is said to be affecting not only digestive tract, but also accessory organs, including pancreas. While available data are insufficient to unequivocally confirm causality of COVID-19 and AP [35], there are numerous case reports and reviews on hand linking the two diseases; Liu *et al* discovered that angiotensin-

converting enzyme 2 (ACE2) - the receptor for SARS-CoV-2 - has higher expression in the pancreas than in the lung tissue, making it a potential target for infection [36]. Moreover, several studies showed that there is clinical evidence of pancreatic injury, defined as amylase and/or lipase above normal, that can be found in COVID-19 patients [36, 37].

Potential mechanisms of pancreatic injury in patients with SARS-CoV-2 infection.

Among the possible explanations for pancreatic injury concomitant with COVID-19, direct viral cytotoxic effect is one of the most commonly discussed. As mentioned earlier, SARS-CoV-2 receptor is highly expressed in the pancreas, nevertheless essential for successful infection is co-expression of ACE2 and transmembrane serine protease 2 (TMPRSS2), which was argued in one of the studies. According to Coate *et al*, both proteins are co-expressed only in less than 1% of non-endocrine cells. In addition, no such phenomenon was observed in islet-beta-cells [38]. This puts in question whether a direct virus-mediated injury can be the cause of elevated pancreatic enzymes and glycemia fluctuations observed in COVID-19 patients.

In severe cases of SARS-CoV-2 infection pancreatic damage might be attributed to the systemic release of proinflammatory immune mediators - so called 'cytokine storm'. Hegyi *et al* discovered that both in COVID-19 and AP the pattern of produced cytokines is surprisingly similar, with high levels of interleukin-6, interleukin-8 and interleukin-10 being produced. These molecules drive further inflammatory response and, in extreme cases, can lead to multi-organ failure, including acute respiratory distress syndrome (ARDS) and pancreatitis.

'Cytokine storm' can also be triggered by circulating unsaturated fatty acids (UFAs) released as a result of lipolysis [39]. It has been observed that UFAs cause pancreatic necrosis by release of intracellular calcium [40]. Therefore, elevated lipase activity in the course of COVID-19 might resemble lipotoxicity presented in SAP. It is also possible that SARS-CoV-2 can cause direct lipolysis by targeting adipocytes. However, more studies need to be performed in order to explore this topic.

Subsequent explanation for development of AP is related to COVID-19 tendency for thrombotic events. There are numerous reports on elevated D-dimer observed in the course of the disease [41]. Therefore, it is also conceivable that thrombosis can occur in pancreatic vasculature, leading to impaired blood supply and ischemic changes in the pancreas. As hypoperfusion is an established etiology of AP [42], this theory seems plausible but is not yet properly investigated.

Another hypothesis for pancreatic injury in coronaviral infection is based on the role that neutrophil extracellular traps (NETs) play in virus-induced inflammatory response. It is known that various pathogens, including SARS-CoV-2, can trigger a process called NETosis in which the neutrophil disintegration is accompanied by release of modified chromatin targeting pathogenic microbes. However, it often acts as a double-edged sword. A significant NET increase was observed in patients on mechanical ventilation and those presenting with acute respiratory distress syndrome (ARDS) [43, 44]. Moreover, Murthy *et al* discovered that the level of NET formation biomarkers marked in a serum correlates with severity of AP [45]. It may suggest a cause-and-effect relationship between virus-induced immune response and AP.

Finally, acute pancreatitis developing in COVID-19 patients might be caused by iatrogenic injury. There are few reports suggesting that treatment for SARS-CoV-2 infection might instigate pancreatic damage and lead to drug-induced acute pancreatitis (DIAP). The drugs in question include common anti-inflammatory drugs, antipyretics and antihypertensives, as well as antibiotics, antiviral agents, biological drugs and propofol [46]. Khadka *et al* reported a case of AP that developed in a course of remdesivir therapy administered for treatment of COVID-19 [47]. Another case report suggests that especially patients previously demonstrating hypertriglyceridemia are prone to developing acute necrotizing pancreatitis while on remdesivir [48]. Elkhouly *et al* found that it is an increased triglyceride level that is a secondary mechanism of pancreatic injury in DIAP [49]. Therefore, it is vital to pay close attention to side effects of pharmacological therapy implemented in coronaviral infections, especially in those presenting with GI symptoms.

Potential mechanisms for pancreatic injury in SARS-CoV-2 infection are depicted in Figure 2.

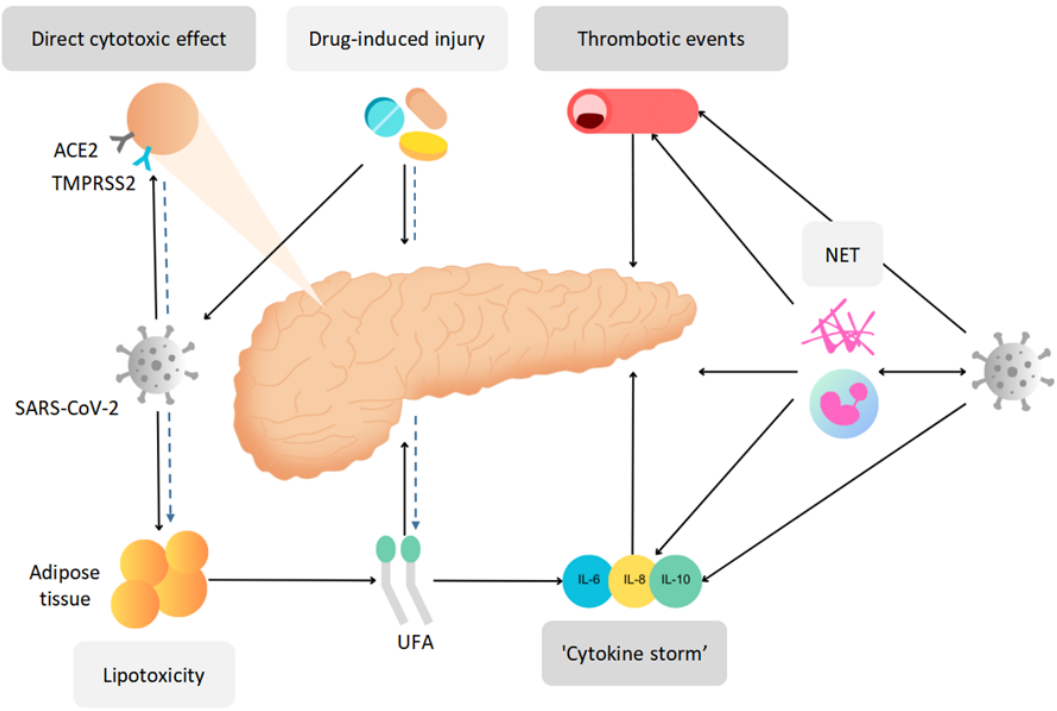


Figure 2. Potential mechanisms of pancreatic injury in SARS-CoV-2 infection. Coronavirus might damage pancreatic tissue through direct cytotoxic effect, using ACE2 and TMPRSS2 as receptors for cell-entry. Leakage of intracellular enzymes, including lipase, results in disintegration of adipocytes present in proximity. It is also plausible, though unconfirmed, that SARS-CoV-2 can directly cause lipolysis. Released UFAs exacerbate local inflammatory response, as well as propel 'cytokine storm'. Systemic inflammation can be additionally aggravated by extracellular traps released from neutrophils as a response to infection. Prothrombotic tendencies observed in COVID-19 might affect pancreatic vasculature and be responsible for ischemic damage of the tissue. Finally, treatment implemented in the course of the disease can affect pancreas, often in relation to hypertriglyceridemia.

Causality assessment.

Even though there are many plausible hypotheses on SARS-CoV-2 inducing pancreatic injury, the question whether COVID-19 can be a new-found etiology of AP remains unanswered. In order to systematize this issue, we applied Bradford Hill's criteria for causation as follows: strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy [50].

If the association of COVID-19 and AP was a strong one, we could expect an adequate increase in acute pancreatitis labeled as idiopathic in patients with SARS-CoV-2 infection. There are numerous reports at hand describing cases of patients presenting with the two concomitant diseases [51-55], in which the majority of key risk factors for acute pancreatitis have been ruled out in the diagnostic process (Table 2.). One of the studies conducted in New York shows, that among patients presenting with AP who tested positive for SARS-CoV-2 infection, the most commonly diagnosed pancreatitis was idiopathic, with 69% of cases, compared to 21% in COVID-19 negative group (P <0.0001) [56]. Pandanaboyana *et al* also observed a higher proportion of AP of unknown etiology in SARS-CoV-2 positive patients, however they proved it to be statistically insignificant (p=0.08). Moreover, among 1777 patients with AP that were a subject of this study, gallstones were the most common etiology in both COVID-19 negative and positive group [57]. Another study conducted in Spain, showed that incidence of pancreatitis among SARS-CoV-2 infected patients admitted to ED was lower (0,71‰) than in general ED population [58]. This puts in question the strength of the association.

As for consistency, numerous case reports and cohort studies concerning AP and COVID-19 have been regularly published since the early stages of the pandemic. Unfortunately, there is no established methodology in which this research has been carried out, which results in significant limitation as to reproducibility. The heterogeneity of presented data, including differences in applied diagnostic criteria, makes it more difficult to interpret.

Concerning specificity, acute pancreatitis is a disease known for its diverse etiology, starting from alcohol abuse and cholelithiasis, and ending with autoimmune and genetic factors. Infection-induced AP accounts for only 10% of the cases [59], whereas in over 25% a cause of the disease remains unidentified [1]. According to Hill's criteria, this variety of potential triggers for AP weakens probability of causal relationship.

There are several studies at hand reporting evident temporary connection between SARS-CoV-2 infection and onset of symptoms typical for AP, including most cases summarized in Table 1. Nonetheless, there is also contradictory evidence available, with clinical manifestations of pancreatitis developing on the 2nd week of hospitalization [53]. That dissociation raises doubts as to direct cytopathic damage caused by coronavirus. However, it doesn't exclude other possible mechanisms of pancreatic injury, as presented in Figure 2.

Considering biological gradient, there are no indicators that SARS-CoV-2 viral load has an impact on prevalence of AP. Pandanaboyana *et al* observed that patients with two concomitant diseases were at greater risk of developing moderate-to-severe and severe AP as

well as local and systemic complications [57]. However, this correlation applies only to SARS-CoV-2 positive group in comparison to SARS-CoV-2 negative group. No differentiation between mild and severe cases of COVID-19 has been featured. In fact, severity of infection varies between the cases described, from significant respiratory failure requiring mechanical ventilation [51], to mild upper respiratory tract symptoms with no need for treatment [54]. Therefore, biological gradient seems to be irrelevant.

Causality of COVID-19 and AP certainly seems plausible, as there are numerous mechanisms, in which infection could trigger pancreatic injury and lead to inflammation (Figure 1.).

As for coherence, other viral infections have already been identified as etiological factors of AP, including *Coxsackie* and mumps virus, cytomegalovirus (CMV) and human immunodeficiency virus (HIV). In addition, Shepis *et al* detected SARS-CoV-2 RNA in a pseudocyst fluid sample collected from COVID-19 patient who developed AP [60]. Although this finding might speak for coronaviral tropism for pancreas, we cannot rule out other routes of entry, including retrograde contamination from duodenum and infection through immune cells.

Experimental evidence on animal models is lacking, however there are interesting reports on pancreatitis caused by coronaviral disease in ferrets [61]. A similar association was observed in a study on coronaviruslike virus isolated from pigeons, in which inoculated specific pathogen-free (SPF) chickens developed pancreatitis [62].

At present, there is still insufficient evidence on the topic to draw unambiguous conclusions as to causality of COVID-19 and AP. Further large studies with unified methodology of collecting and presenting data need to be performed.

Clinical implications.

A retrospective analysis of patients presenting with AP in a course of COVID-19 showed statistically significant increase in incidence of multi-organ failure (MOF) and persistent organ failure (POF), as well as tendency for higher BISAP score. Despite that, it did not reveal remarkable differences in mortality between SARS-CoV-2 positive and negative cohort [63]. In contrary, Pandanaboyana *et al* found 30-day mortality of 14,7% markedly higher in COVID-19 positive group than in patients not infected with coronavirus [57]. In addition, a rise in incidence of local complications, ARDS, POF and prolongation of hospital stay was noticed. More severe courses of the disease might result from overactivation of immune system

and self-perpetuating inflammatory response. As to pattern of AP, there were no significant changes observed, including prevalence of splanchnic venous thrombosis, endocrine insufficiency of infected necrosis [63].

At present, no guidelines for managing AP concomitant with COVID-19 have been established. Nevertheless, it is vital for clinicians to pay close attention to gastrointestinal symptoms in SARS-CoV-2 patients and to routinely mark amylase and/or lipase in such cases. If suspicion arises, full diagnosis of acute pancreatitis should be conducted for early implementation of supportive treatment.

Table 2. Summary of reviewed case reports describing AP developing in the course of SARS-CoV-2 infection. On account of insufficient data, severity of AP as well as local and systemic complications were omitted.

Reference	**Sex and age**	**Symptoms on admission**	**Initial diagnosis**	**Onset of AP symptoms**	**Need for mechanical ventilation**	**Other risk factors for AP excluded during the diagnostic process**	**Comorbidities**
[51]	F 47	fever, headache, neck pain, anorexia, sore throat, dyspnea	COVID-19	<12 hours after admission	yes	cholelithiasis, alcohol overconsumption, hypertriglyceridemia, hypercalcemia	none
[51]	F 68	fever, epigastric pain, vomiting, diarrhea, fatigue, polydipsia	COVID-19	prior to admission	yes	hypertriglyceridemia, hypercalcemia	hypertension, hypothyroidism, osteoporosis

[52]	F 36	fever, dry cough, dyspnea, nausea, vomiting, diarrhea, epigastric pain	AP with ARDS	2 days prior to admission	no	cholelithiasis, alcohol overconsumption, hypertriglyceridemia	obesity (BMI = 35), chronic anxiety
[53]	F 36	dry cough, breathlessness, fever	COVID-19	on the 7th day of admission	no	cholelithiasis, alcohol overconsumption, hypertriglyceridemia, hypercalcemia, autoimmunity, ischemic changes, other infectious causes, drug abuse	post-HELLP syndrome, chronic kidney disease (stage V), hypertension
[54]	M 24	epigastric pain, nausea, vomiting, mild upper respiratory tract symptoms	COVID-19	2 days prior to admission	no	cholelithiasis, alcohol overconsumption	none
[55]	F 49	fever, dry cough, lethargy, shortness of breath	COVID-19	on the 2nd day of admission	no	cholelithiasis, alcohol overconsumption, hypertriglyceridemia,	none

						hypercalcemia, drug abuse	

Conclusions

In conclusion, there is still not enough evidence to support the prophylactic use of antibiotics in patients with SAP. When it comes to the management of necrosis recommendations suggest delaying the intervention, preferably 4 weeks after the onset of the disease. The mentioned delay is optimal for the development of infected walled-off-necrosis (WON), which is more suitable for drainage and lowers the risk of complications during invasive intervention. There is still insufficient data to unequivocally identify SARS-CoV-2 as an etiological factor of AP. At present, no guidelines for managing AP concomitant with COVID-19 have been established. Nevertheless, it is vital for clinicians to pay close attention to gastrointestinal symptoms in SARS-CoV-2 patients.

Authors contributions

Conceptualization, Aleksandra Woźniak, Michał Jakub Cioch; methodology, Julia Nowak and Michał Jakub Cioch; software, Katarzyna Doman and Marcin Mycyk; check, Agnieszka Najdek and Daria Oleksy; formal analysis, Dawid Komada and Kamil Hermanowicz; investigation, Dawid Komada and Aleksandra Woźniak; resources, Julia Nowak and Katarzyna Doman; data curation, Urszula Kaczmarska and Daria Oleksy; writing - rough preparation, Aleksandra Woźniak; writing - review and editing, Aleksandra Woźniak; visualization, Kamil Hermanowicz, Agnieszka Najdek; supervision, Urszula Kaczmarska, Marcin Mycyk; project administration, Aleksandra Woźniak

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Data Availability Statement

The data presented in this study is available upon request from the corresponding author.

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Conflict of Interest Statement

All authors declare that they have no conflicts of interest.

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