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Acid suppression therapy, gastrointestinal bleeding and infection in acute pancreatitis – An international cohort study

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Abbreviations: AP, acute pancreatitis; ASD, acid suppressing drug; CI, confidence interval; ERCP, endoscopic retrograde cholangio-pancreatography; GI, gastrointestinal; H2-RA, histamine-2-receptor antagonist; OR, odds ratio; PPI, proton pump inhibitor; SCT, stool culture test.

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ABSTRACT

Background: Acid suppressing drugs (ASD) are generally used in acute pancreatitis (AP); however, large cohorts are not available to understand their efficiency and safety. Therefore, our aims were to evaluate the association between the administration of ASDs, the outcome of AP, the frequency of gastrointestinal (GI) bleeding and GI infection in patients with AP.
Methods: We initiated an international survey and performed retrospective data analysis on AP patients hospitalized between January 2013 and December 2018.
Results: Data of 17,422 adult patients with AP were collected from 59 centers of 23 countries. We found that 23.3% of patients received ASDs before and 86.6% during the course of AP. ASDs were prescribed to 57.6% of patients at discharge. ASD administration was associated with more severe AP and higher mortality. GI bleeding was reported in 4.7% of patients, and it was associated with pancreatitis severity, mortality and ASD therapy. Stool culture test was performed in 6.3% of the patients with 28.4% positive results. *Clostridium difficile* was the cause of GI infection in 60.5% of cases. Among the patients with GI infections, 28.9% received ASDs, whereas 24.1% were without any acid suppression treatment. GI infection was associated with more severe pancreatitis and higher mortality.
Conclusions: Although ASD therapy is widely used, it is unlikely to have beneficial effects either on the outcome of AP or on the prevention of GI bleeding during AP. Therefore, ASD therapy should be substantially decreased in the therapeutic management of AP.

Introduction

Acute pancreatitis (AP) is an acute inflammatory condition of the pancreas that can involve peripancreatic tissue or remote organ systems. The global incidence of AP is 30–100 cases per 100,000 general population per year, and it is one of the most frequent gastrointestinal (GI) causes of hospital admission [1]. Unfortunately, research activity in the field is more underrepresented than it should be [2]. Not surprisingly, there is no specific therapy available for AP, symptomatic and curative treatments are based on guidelines and the prior experience of the medical staff. Strikingly, current AP guidelines do not include any information regarding the administration of acid suppressing drugs (ASDs) such as proton pump inhibitors (PPIs) and histamine-2-receptor antagonists (H2-RAs) in AP [3–6], despite the fact that ASDs are routinely administered in clinical practice in the majority of AP cases.

Conventionally, the management of AP patients included nothing by mouth from the time of hospital admission. It was believed that by doing so the inflamed pancreas can rest, because fluid intake or solid nutrients would stimulate exocrine pancreatic functions and promote the release of proteolytic enzymes. However, prior studies failed to support this idea and showed no benefit from fasting or nasogastric suction [7,8]. In experimentally induced pancreatitis, results showed that pantoprazole treatment reduced tissue infiltration of inflammatory cells and acinar cell necrosis in severe AP. They concluded that pantoprazole possesses anti-inflammatory *in vivo* properties and attenuates the course of AP [9]. During fasting for the protection of the upper GI mucosa and to rest the inflamed pancreas, ASD administration could be a potentially good therapeutic option. Patients with severe AP, especially those who require intensive care treatment or mechanical ventilation are carrying a higher risk for stress-related acute gastric mucosal lesions [10], which can lead to ulceration and GI hemorrhage. Protection of the gastric mucosa is a critical therapeutic goal in a wide spectrum of gastric-acid-related diseases. H2-RAs and PPIs are the cornerstones in the therapy of diseases in which gastric acid has a causative primary or contributory role to prevent the damage or propagate the healing of gastric mucosa. Nowadays, PPIs are among the most commonly prescribed drugs with constantly increasing usage, while several studies raising concerns regarding their overprescription. Possible reasons for the continuous increase in ASD use can be the empirical treatment of various GI symptoms and prescriptions for inappropriate conditions [11–13].

There are contradictory results in the literature on the beneficial and harmful effects of ASD administration in patients with AP [14–17]. Such therapy might be beneficial if it decreases severity or mortality; however, acid suppression can be harmful as it might increase the risk for GI infections. Although many international cohort studies were published in AP [18–20], few data are available on the use of ASDs, GI bleeding, and infection. Therefore, our aims were to understand the current global practice of ASD administration in AP patients and to investigate the safety and efficacy of these drugs in this patient population.

Materials and methods

Patients and data collection

To assess the worldwide trend of ASD administration in AP patients, an invitation letter was sent out to the members of the International Association of Pancreatology in January 2019 to participate in the present study. The time period of data collection was from January 2013 to December 2018. The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council in Hungary (TUKEB-22254-1/2012/EKU).

Centers had to provide data on the gender and age of the patient, severity of pancreatitis and mortality. In addition to the general demographic data, they had to indicate whether the patients received ASDs (PPI or H2-RA) upon admission, during hospitalization and at discharge irrespectively to its indication, timing, dosing and form of administration. Centers had to include data on the signs and cause of GI bleeding. It had to be recorded if a stool culture test (SCT) was performed along with its result. In the case of positive testing, the name of the pathogen had to be included.

Based on the data above, patients were assigned to two groups depending on their ASD administration status during hospitalization, one which received ASD treatment (group 'ASD') and the other which did not (group 'NoASD'). In the case of GI bleeding and GI infection, the ASD treatment in the hospital was the indicator to assign a patient to 'ASD' or 'NoASD' groups.

Data quality

Data were complete on age, gender, severity of AP and mortality, in hospital ASD administration, registering the signs of GI bleeding, and whether SCT was performed or not and its result. ASD administration was unknown on admission in 1046 of the cases, and in 10 patients at discharge. The cause of GI bleeding was unknown in 5 patients.

Diagnostic criteria

The diagnosis of AP was based on the IAP/APA evidence-based guidelines for the management of AP A1 recommendation [3]. At least two from the following three criteria should be confirmed in patients: clinical (upper abdominal pain), laboratory (serum amylase or lipase >3x upper limit of normal) and/or imaging (CT, MRI, ultrasonography). Severity of pancreatitis was determined based on the revised Atlanta classification [21]. This classification defines three degrees of severity: mild, moderately severe (moderate) and severe AP.

Signs of GI bleeding were provided by each center. These included positive rectal digital examination, macroscopically observed bleeding in the stool, vomit or gastric juice, positive stool blood test, and bleeding verified by an imaging technique. We excluded the bleeding cases that occurred in association with endoscopic retrograde cholangio-pancreatography (ERCP) since administration of ASDs does not have an effect on this type of bleeding. If the cause of the GI bleeding could not be determined, patients were not included in the analyses regarding GI bleeding.

The presence of pathogens in the stool verified by laboratory testing was considered GI infections. Non-specific signs such as fever, diarrhea and vomiting without testing were not accepted. The pathogens were identified for each patient.

Statistical analysis

To identify differences between categorical variables the Chi-square with Fisher's exact test was used. The significance level was set at 0.05. Binary logistic regression with stepwise forward elimination was used to observe independent prognostic factors (age, gender, severity, ASD treatment, GI bleeding and infection) for the main outcomes (ASD administration, GI bleeding and infection).

Results

Characteristics of the cohort

Data of 17,422 adult patients with AP were collected retrospectively from 59 centers (Fig. 1, Supplementary Table 1). 9803 of patients were male (56.3%) and 7619 were female (43.7%) (Supplementary Figure A), the average age was 56.4 years (Supplementary Figure B) in the cohort. In the studied population 10,490 (60.2%) of patients had mild, 4508 (25.9%) had moderate and 2424 (13.9%) had severe AP (Supplementary Figure C). In total 4.6% (800 patients) of patients died; the mortality rate was 0.4% (n = 44/10,490) in mild, 1.5% (n = 68/4508) in moderate and 28.4% (n = 688/2424) in severe AP (Supplementary Figure D). Upon admission, 23.3% of patients (n = 3817/16,376) took some kind of ASD (Supplementary Figure E). From these patients, 88.3% (n = 3369/3817) was admitted with a PPI, 11.3% (n = 432/3817) with a H2-RA, and 0.4% (n = 16/3817) received both kind of ASD. During hospitalization, 86.6% of patients (n = 15,096/17,422) received ASD treatment (Supplementary Figure E), 81.8% (n = 12,354/15,096) of these patients had only PPIs, 15.4% (n = 2331/15,096) had solely H2-RAs and 2.7% (n = 411/15,096) had both PPIs and H2-RAs. At the time of discharge from the hospital, 57.6% of patients (n = 10,034/17,412) were prescribed an ASD (Supplementary Figure E), 92.6% (n = 9293/10,034) of them received prescription for PPIs, 7.3% (n = 734/10,034) for H2-RAs and 0.1% (n = 7/10,034) for both ASDs. For the following parameters in the result section, only data during hospitalization were analyzed.

Acid suppression therapy is associated with more severe AP and higher mortality

Patients were assigned to 'ASD' or 'NoASD' groups based on their ASD administration status in the hospital. Among 'ASD' patients mild AP (n = 8649/15,096, 57.3%) was significantly less frequent compared to those in the 'NoASD' group (n = 1841/2326, 79.1%, p < 0.001). However, in case of moderate and severe pancreatitis, there were significantly more patients in the 'ASD' group (moderate: n = 4139/15,096, 27.4%; severe: n = 2308/15,096, 15.3%) than in the 'NoASD' group (moderate: n = 369/2326, 15.9%, p < 0.001; severe: n = 116/2326, 5.0%, p < 0.001) (Fig. 2A). Mortality was significantly higher in patients with acid suppressing therapy (n = 744/15,096, 4.9%) compared to those without acid suppression (n = 56/2326, 2.4%, p < 0.001) (Fig. 2B). Based on the results of logistic regression, the patient's gender did not influence the administration of ASD treatment (OR = 1.015, 95% CI = 0.927–1.110, p = 0.748); however, older age (OR = 1.006, 95% CI = 1.003–1.008, p < 0.001) and worse than mild AP severity (OR = 2.202, 95% CI = 2.031–2.387, p < 0.001) increased the patients' chance for receiving ASDs during hospitalization.

Acid suppressing drug therapy is associated with higher risk for GI bleeding in AP

Data for 17,282 patients were evaluated after excluding ERCP-associated bleedings and bleedings of unknown origin. From these patients, 817 (4.7%) had GI bleeding (Fig. 3A). The number of patients having mild pancreatitis without GI bleeding was significantly higher compared to those with GI bleeding (n = 10,193/16,465, 61.9% vs. n = 221/817, 27.1%, p < 0.001, respectively). However, among patients with GI bleeding there were significantly more moderate (No bleeding: 4181/16,465, 25.4% vs. Bleeding: n = 283/817, 34.6%, p < 0.001) and severe AP (No bleeding: 2091/16,465, 12.7% vs. Bleeding: n = 313/817, 38.3%, p < 0.001) cases (Fig. 3B). In case of GI bleeding, the rate of mortality was significantly higher compared to patients without bleeding (No bleeding: n = 650/16,465, 3.9% vs. Bleeding: n = 138/817, 16.9%, p < 0.001) (Fig. 3B). There were significantly more patients suffering from GI bleeding while receiving acid suppressing treatment compared to those who did not ('ASD': n = 766/14,975, 5.1% vs. 'NoASD': n = 51/2307, 2.2%, p < 0.001, respectively) (Fig. 3A).

The age (OR = 0.998, 95% CI = 0.992–1.005, p = 0.585) and the gender (OR = 0.915, 95% CI = 0.732–1.143, p = 0.432) of patients did not influence the chance of GI bleeding; however, worse AP severity carried an almost 3 times higher probability of GI bleeding (OR = 2.994, 95% CI = 2.623–3.418, p < 0.001). Furthermore, ASD treatment during hospitalization increased the chance of GI bleeding by 1.5-fold (OR = 1.543, 95% CI = 1.040–2.291, p = 0.031), and in case of verified GI infection the chance of GI bleeding was almost 2.8 times higher (OR = 2.789, 95% CI = 1.997–3.894, p <

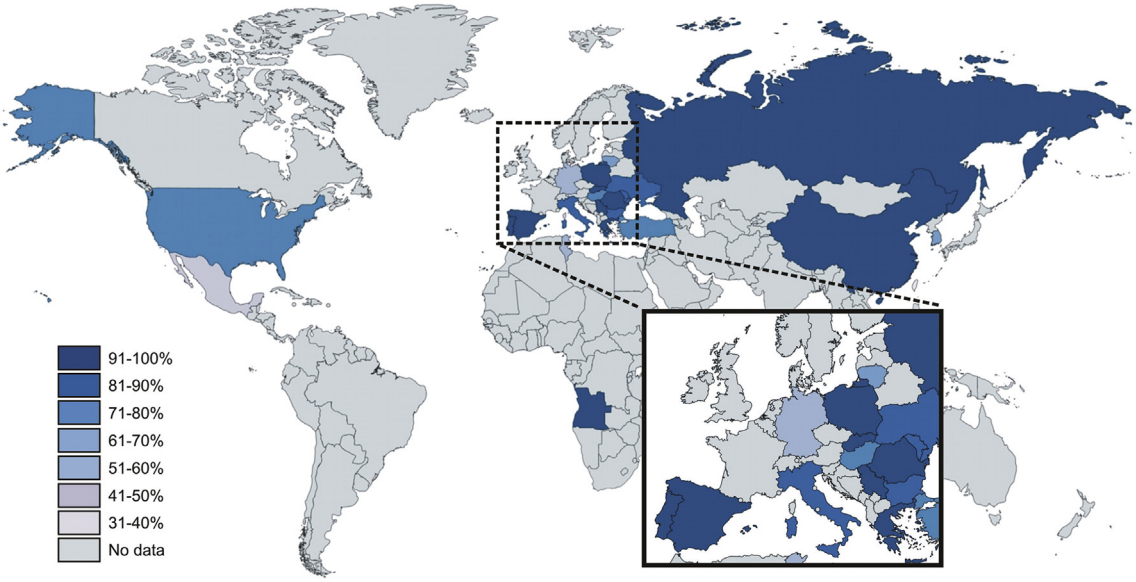
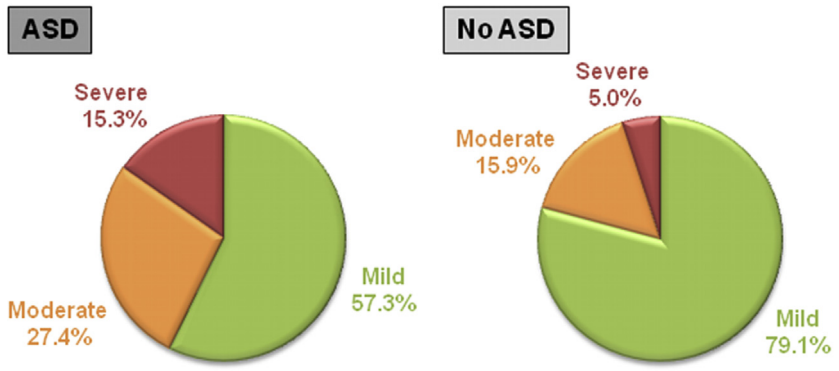


Fig. 1. Map of worldwide acid suppressing drug usage. Map shows the use of acid suppressing drugs in patients with acute pancreatitis during hospitalization.

A



B

			MILD		MODERATE		SEVERE		MORTALITY	
GROUPS	n	%	n	%	n	%	n	%	n	%
ASD	15,096	86.6	8,649	82.4	4,139	91.8	2,308	95.2	744	4.9
No ASD	2,326	13.4	1,841	17.6	369	8.2	116	4.8	56	2.4
	17,422		10,490	100.0	4,508	100.0	2,424	100	800	

Fig. 2. Disease severity and mortality rate in patients with or without acid suppressing drug (ASD) treatment. A) Disease severity in patients with (ASD) or without ASD (No ASD) therapy. **B)** Number (n) and percentage of patients who received ASDs in the different severity groups, and mortality rates in ASD and No ASD groups.

0.001).

Characterization of patients undergone SCT

From the 17,422 patients, an SCT was performed in 1102 cases (6.3%) (Fig. 4A). There were significantly more patients with mild AP who did not undergo stool culture testing (NoSCT: n = 9961/16,320, 61% vs. SCT: n = 529/1102, 48%, p < 0.001). In case of moderate and severe AP, the number of patients that underwent testing during hospitalization was significantly higher (NoSCT: n = 4214/16,320, 25.8% vs. SCT: n = 294/1102, 26.7%, p < 0.001 and NoSCT: n = 2145/16,320, 13.2% vs. SCT: n = 279/1102, 25.3%, p < 0.001, respectively) (Fig. 4B). Mortality was significantly higher in patients with stool culture testing (NoSCT: n = 698/16,320, 4.3% vs. SCT: n = 102/1102, 9.3%, p < 0.001) (Fig. 4C). The frequency of SCT orders increased with the severity of AP, mild: 5.0% (n = 529/10,490), moderate 6.5% (n = 294/4508), severe: 11.5% (n = 279/2424). From the 1102 patients who underwent stool culture testing, 313 of them (28.4% of tested patients) had positive results. The most common pathogens causing GI infections were *Clostridium difficile* (n = 210/347, 60.5%) and the *Klebsiella* species (n = 35/347, 10.1%) (Supplementary Table 2A), and there was only a single pathogen verified in 91.4% of the cases (n = 286/313) (Supplementary Table 2B).

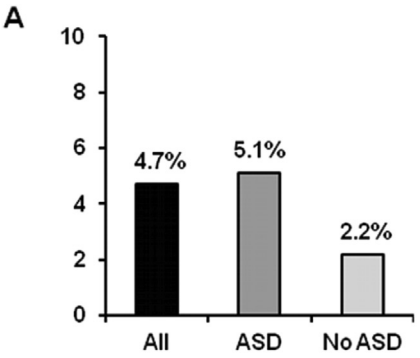
Acid suppressing treatment is not associated with higher risk for GI infection

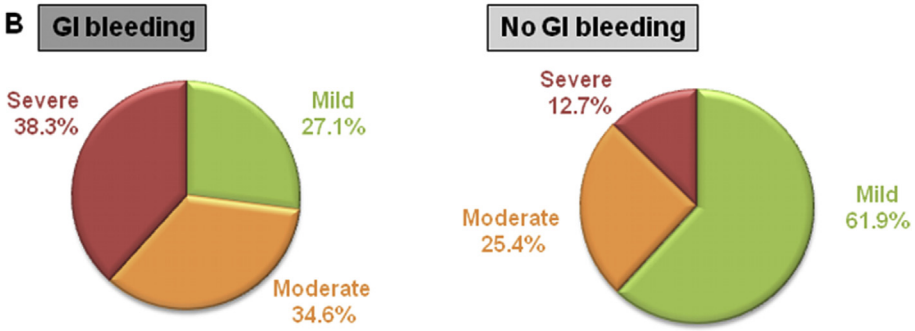
Among patients with GI infections, there was a significantly lower number of patients in the mild AP group (n = 95/313, 30.4%) compared to the number of mild cases in patients without an infection (n = 434/789, 55%, p < 0.001) (Fig. 4D). We found significantly more moderate (Positive: n = 103/313, 32.9% vs. Negative: n = 191/789, 24.2%, p < 0.001) and severe (Positive: n = 115/313, 36.7% vs. Negative: n = 164/789, 20.8%, p < 0.001) cases in patients with positive SCT (Fig. 4D). In patients with GI infection, the mortality rate was significantly higher compared to the rate in the group tested negative for GI infections (Positive: n = 42/313, 13.4% vs. Negative: n = 60/789, 7.6%, p = 0.003) (Fig. 4E). GI bleeding was significantly more frequent in patients with verified GI infection (GI bleeding and GI infection: n = 54/302, 17.9% vs. GI bleeding without GI infection: n = 81/770, 10.5%, p = 0.001) (Table 1). There was no significant difference in the occurrence of GI infection between patients with or without ASD treatment ('ASD': n = 285/986, 28.9% vs. 'NoASD': n = 28/116, 24.1%, p = 0.276) (Table 2).

Investigating the different factors that could have an effect on the above results we found that the age (OR = 0.999, 95% CI = 0.992–1.006, p = 0.781) and the gender (OR = 1.073, 95% CI = 0.847–1.359, p = 0.559) of patients, and whether they received ASDs or not (OR = 1.447, 95% CI = 0.969–2.161, p = 0.071) did not have an impact on the chance of having GI infection; however, patients with worse than mild AP severity had a 2.5 times higher odds for GI infections (OR = 2.5, 95% CI = 2.178–2.870, p < 0.001).

Discussion

ASDs, especially PPIs are among the most frequently prescribed drugs with increasing use every year. Even though there are well established indications for a wide array of diseases when and how to conduct treatment with ASDs, several studies were published regarding their overprescription, and difficulties to discontinue their application. Some suggests that possible reasons could be prescription based on empirical decision or for conditions without any indication [12,13,22,23]. Data from our cohort supports the worldwide overuse of ASDs, specifically in patients with AP. 23.3% of patients received ASD treatment before being admitted to the hospital, and their number has increased by 3.7-fold during hospitalization with almost all of the patients receiving some kind of ASD. More than 50% of patients had remained on an ASD after discharge, a more than 2-fold increase relative to the number at admission. These numbers are in accordance with literature data





C

	MILD		MODERATE		SEVERE		MORTALITY	
	n	%	n	%	n	%	n	%
GI bleeding	221	2.1	283	6.3	313	13.0	138	16.9
No GI bleeding	10,193	97.9	4,181	93.7	2,091	87.0	650	3.9

Fig. 3. Disease severity and mortality rate in patients with or without gastrointestinal (GI) bleeding. A) Percentage of patients with GI bleeding in the entire cohort, in patients with or without acid suppressing drug (ASD) treatment. **B)** Disease severity in patients with and without GI bleeding. **C)** Number (n) and percentage of patients who had GI bleeding or did not have GI bleeding in the different severity groups, and mortality rates.

whereas patients after receiving ASDs during hospitalization get usually discharged with them [23]. Unfortunately, this is another example which shows that big difference can occur between guidelines and their application [24]. Moreover, ASD treatment in AP was associated with more severe pancreatitis and higher mortality rate in our cohort.

There are contradictory results in the literature about the safety of ASD use in AP. In a Korean randomized clinical trial, the investigators separated AP patients into two groups, one receiving pantoprazole intravenously during fasting and later orally, and another without PPI treatment. In this study, treatment with pantoprazole did not influence the clinical course of AP [14]. In another randomized clinical trial from China, severe AP patients receiving conventional therapy were compared to patients on conventional therapy with esomeprazole treatment, and PPI therapy did not show benefit on alleviating systemic inflammatory response and improving clinical scores in severe AP patients, and did not prevent the development of peptic ulcer and GI hemorrhage [15]. Data from 10,400 severe AP patients were analyzed in a Japanese retrospective study, and even though the rates of upper GI bleeding and organ failure were significantly higher in patients with PPI therapy, after propensity analysis, data showed that PPIs did not have an effect on mortality [16]. On the contrary, in a Swedish population-based case-control study, they observed association between current use of H2-RAs or PPIs and increased risk of AP, besides previous literature data where they reported ASDs to cause AP [17].

Systemic inflammatory response syndrome is often a complication of severe AP, which leads to high level of inflammatory markers [26] and organ dysfunctions. Patients with severe AP, especially those who require intensive care treatment or mechanical ventilation are prone to develop stress-related acute gastric mucosal lesions [10]. Acute GI mucosal lesions can range from simple gastritis and erosions to ulceration and bleeding [25], more than half of patients with AP may develop upper GI ulcers, and the occurrence shows positive correlation with the severity of pancreatitis [8,27]. Hypersecretion of gastric acid seems to play a major role at the pathogenesis of stress-related acute gastric mucosal lesions. Therefore, in these cases it can be indicated to use prophylaxis for peptic ulcer disease [8,28]. Based on our results, not only in case of severe, but also in moderate pancreatitis cases there were significantly more patients receiving ASD treatment which supports our previous data about their frequent usage.

Protection of upper GI mucosa could be a possible indication for ASD administration in AP patients, which could decrease the rate of GI bleeding. Since ERCP- and surgery-related vascular complications cannot be prevented with ASD treatment, we did not include these types of GI bleedings in our analyses. In the studied population, 4.7% of patients suffered from GI bleeding. Although we did

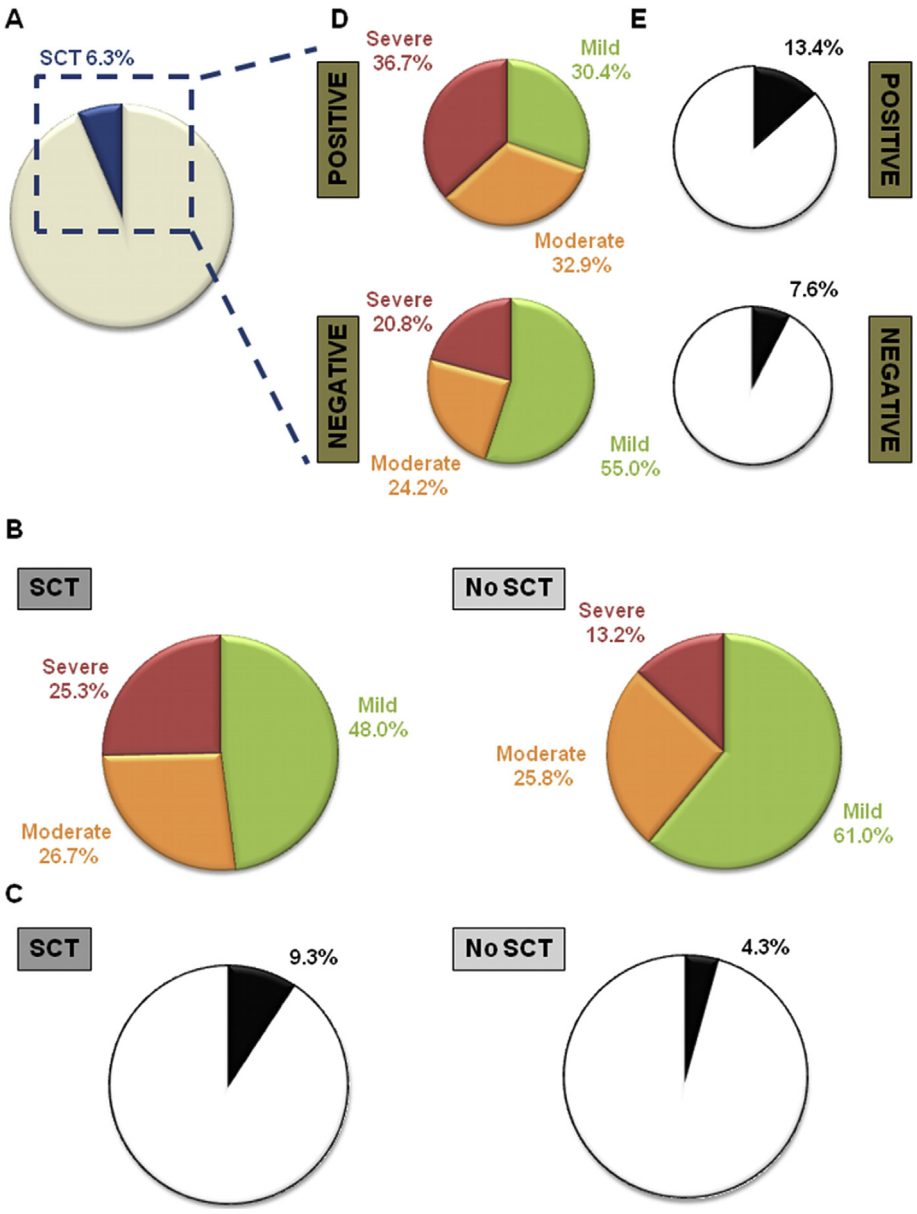


Fig. 4. Disease severity and mortality rate in patients undergone stool culture testing (SCT). A) Percentage of patients who had SCT. **B–C)** Severity of acute pancreatitis and mortality rate in tested and not tested patients. **D-E)** Severity and mortality in patients with or without gastrointestinal infection.

Table 1
Gastrointestinal (GI) infection in patients with or without GI bleeding. Results of stool culture testing (SCT) in patients with or without GI bleeding with patient number (n) and percentage.

	No bleeding		GI bleeding		
	n	%	n	%	
NEGATIVE SCT	689	89.5	81	10.5	770
POSITIVE SCT	248	82.1	54	17.9	302

Table 2
Gastrointestinal infection in patients with or without acid suppressing drug (ASD) treatment. Result of stool culture testing (SCT) in patients with or without ASD therapy with patient number (n) and percentage.

	No ASD		ASD	
	n	%	n	%
NEGATIVE SCT	88	75.9	701	71.1
POSITIVE SCT	28	24.1	285	28.9
	116		986	

not collect data on the cause of death, GI bleeding was associated with higher morbidity and mortality, which increases the length and cost of hospitalization. Investigating the association between ASD treatment and GI bleeding, we found that bleeding occurred more frequently in patients on ASD therapy which correlates with literature data [15,16]. Based on the study of Chen et al. [8] in which all the included patients received PPIs when a GI lesion was detected with endoscopy, 22% of severe pancreatitis patients had GI bleeding [8]. We did not collect data on the time of bleeding and the start of ASD therapy. A possible explanation could be that when GI bleeding was recognized then ASD therapy was started, although, that still does not give an explanation why more than 80% of patients had to receive ASDs. Especially that more than 60% of patients had mild AP, and in that group only 2.1% of patients were

suffering from GI bleeding. Therefore, these results suggest GI bleeding recognition is not the indication of starting ASD treatment in AP patients, and it also does not explain why more than 50% of patients have to receive ASDs upon discharge from the hospital.

ASDs are considered well tolerated and effective, and only rare and mild side effects have been reported in short-term use. However, nonessential long-term ASD treatment can lead to various side effects in spite of their reported good safety profile [12]. Such as elevated prevalence of small intestinal bacterial overgrowth which results in malabsorption [29], increased risk for respiratory infections [30,31] and several GI cancers (gastric, colorectal, liver or pancreatic cancers) [13,31–35]. Other long-term side effects can be micronutrient deficiencies, kidney disease, osteoporosis and dementia. Long-term administration without proper re-evaluation and guidelines will lead to polypharmacy and potential drug-drug interactions [31]. Although several studies have shown association between adverse events and complications of long-term ASD use, they have led to contradictory results [11]. Side effects are also including elevated risk for GI infections by repressing the gastric acid barrier and altering the microbiome. Notably, *Clostridium difficile* infection has shown strong association with ASD therapy [12,22,30,31,36,37]. From the wide array of possible long-term complications, we investigated the relationship between acid suppressing therapy and occurrence of GI infections in AP patients. According to our results, ASD administration did not elevate the risk for GI infections. However, ordering of SCTs has been associated with more severe AP and higher mortality rate. Even though, there was relatively low number of testing among the included patients, almost 30% of them had GI infections. In our cohort, the most common pathogen was *Clostridium difficile* (60%) in accordance with literature data in other diseases. An important factor that has to be taken into consideration is the frequent usage of unnecessary antibiotic drugs in AP patients. The most frequently used antibiotics can be effective for the most common GI infections [38]. In the studied patient population, GI infections have been associated with more severe AP, higher rate of GI bleeding and worse mortality. Therefore, length of hospitalization and the cost of treatment could be worse in patients with GI infections.

Our cohort analysis has its limitations, since it is a retrospective data analysis, we cannot draw causative conclusions from the findings above, only associations can be determined between the investigated parameters.

Our aim was to investigate the current place of ASDs in patients with AP and evaluate their safety and effectiveness that we could present in a large AP population. Based on the epidemiologic characteristics of our cohort and the numerous international centers who contributed data, our patient population substantiates a general representation of patients with AP [39,40]. Our data shows a worldwide unnecessary ASD use in AP patients, even though there is no substantial evidence that ASD treatment is beneficial for the therapy of AP. Hereby, we present their association with higher morbidity and mortality. Our cohort analysis is among the first to report data on the rate of GI bleeding not related to surgery or ERCP in patients with AP. Based on our data, ASD administration during AP did not increase the risk for GI infections. Taking into consideration the advice from the American Gastroenterological Association, the benefits of ASDs outweigh their risks if appropriately prescribed, but when there is no indication, modest risks become important because there is no potential benefit [15]. Therefore, according to our results, the routine administration of ASDs is not recommended in patients with AP if there is no other indication for their administration. Long-term complications could be avoided by re-evaluating the current clinical practices, incorporate recommendations to current guidelines, and by giving detailed plans for patients and their general practitioners how to gradually reduce or leave the ASDs, and when to follow up on them.

Author contributions

AD and PH contributed to study conception and design; AD and LK contributed to data acquisition; IC, GM, MKS, RN, DW, WH, QX, LD, MHo, ASc, MHi, OI, ÁV, JB, PS, LC, DI, FI, LG, MP, JHam, MV, PK, EB, AM, BE, RC, CR, CI, LM, EJ, VC, MVM, GB, PI, MPL, ASR, ST, ET, EMP, HZ, VNu, AGom, TCG, MF, JC, MRRMS, JP, BM, GC, VS, IN, CC, VNe, SBu, CG, SBa, ATa, MT, EDu, AIS, CT, AGh, AL, NS, YR, MB, PJH, JHan, JARO, IMS, EPC, DIG, AJC, AQC, YTC, MCC, AK, ATi, SK, VG, DD, HTK, EA, SCho, SChu, AGou and GP provided substantial patient data; SV, MFJ, KO, EDa and EM managed patient related data; ASz and AP coordinated data collection and controlled data quality; AD, PH and ASo performed data analyses; ASo performed statistical analyses; AD drafted the manuscript and prepared the figures; PH contributed critical revisions and all authors approved the final manuscript.

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Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary data

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