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Factors Associated With Intolerance After Refeeding in Mild Acute Pancreatitis

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Objectives: This study aimed to describe the mode of refeeding, frequency of intolerance, and related factors in mild acute pancreatitis (AP).

Methods: We included all cases of mild AP between January 2007 and December 2009 in an observational, descriptive, and retrospective study. We analyzed demographic and etiological data, admission variables, treatment, refeeding mode, intolerance frequency, and treatment. Intolerance-related variables were determined using a Cox regression.

Results: Two-hundred thirty-two patients were included (median age, 74.3 years, bedside index for severity in AP score, 1). Oral diet was reintroduced at 3 days (range, 0–11 days) in 90.9% of cases with a liquid diet. Intolerance to refeeding appeared in 28 patients (12.1%) at a median time of 1 day (range, 0–14 days). Oral diet was reduced or suspended in 71.4%; analgesic and antiemetic drugs were required in 64% and 35.7% of patients, respectively. The variables independently associated with intolerance to refeeding were choledocholithiasis (hazard ratio [HR], 12.35; 95% confidence interval [CI], 2.98–51.19; $P = 0.001$), fasting time (HR, 1.33; 95% CI, 1.09–1.63; $P = 0.005$), refeeding with complete diet (HR, 4.93; 95% CI, 1.66–14.66; $P = 0.04$), length of symptoms before admission (HR, 1.004; 95% CI, 1.001–1.006; $P = 0.012$), and metamizole dose (HR, 1.11; 95% CI, 1.02–1.21; $P = 0.014$).

Conclusions: Intolerance to refeeding is an infrequent event. We have identified several factors independently associated with intolerance.

Key Words: pancreatitis, fasting, nutrition, intolerance

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Acute pancreatitis (AP) is an acute inflammatory process of the pancreas with variable systemic and peripancreatic tissue involvement.[1,2] Pancreatitis is classified as mild, if it is associated with minimum or no organ failure and displays good disease progression without sequelae, severe, if it progresses with organ failure, local complications (necrosis, abscesses, or pseudocysts), or both.[1,2] Fortunately, 80% of all AP episodes have a mild disease progression.[3]

Refeeding and pain control are 2 key elements in the treatment of mild AP. In severe AP, early initiation of enteral nutrition by nasojejunal or nasogastric tube has been shown to reduce risk of multiorgan system failure, pancreatic infections, and mortality, as compared with parenteral nutrition.[4–7] However, the time and mode of refeeding in mild AP is not clearly defined. Despite the absence of strong evidence to support it, it is thought that bowel rest might limit pancreatic secretion.[3] Consequently, standard clinical practice consists of maintaining bowel rest until pain and nausea disappear. Then, diet is progressively reintroduced (initially liquid and subsequently low in fats).[3,8–11] In retrospective series, intolerance to refeeding is a frequent phenomenon (21%–24.6%). In these studies, intolerance was associated with an increase in the length of hospital stay but not with worse progression.[12–14]

However, a number of randomized studies and a meta-analysis have recently been published, which have assessed the mode and time of refeeding. Refeeding with complete diet after disappearance of pain has been reported to lead to no increase in intolerance or severity of mild AP when compared with progressive refeeding.[15–19] Furthermore, a small-size randomized study, which compared refeeding on admission versus refeeding after the disappearance of symptoms, detected no differences in intolerance or complications.[20] These studies have only detected a shorter duration of hospital stay among patients treated with complete or immediate refeeding.[16,17,19,20]

Accordingly, we decided to analyze the frequency of intolerance to refeeding in mild AP, treatment performed, and the variables related to intolerance in a consecutive series of patients.

MATERIALS AND METHODS

Study Design

We conducted an observational, descriptive, retrospective, cross-sectional study based on the review of the clinical documentation and clinical history databases at our hospital. We reviewed the clinical records of patients with a diagnosis of AP at discharge between January 2007 and December 2009.

Inclusion and Exclusion Criteria

Each patient's first episode of mild AP in the study period was included. Acute pancreatitis was defined as any episode that met 2 or more of the following criteria: epigastric abdominal pain suggestive of AP, elevation of serum amylase to a level greater than 3 times the upper limit of normal, and compatible diagnostic imaging technique. The following were excluded from the study: any patient who presented with criteria of severe AP (according to the Atlanta criteria) in the first 48 hours,[1] intrahospital AP, recurrent AP, death during admission, age less than 18 years, and any patient whose reason for admission did not correspond to AP.

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Dr Francisco designed the study, introduced the data, performed the statistical analysis, and wrote the article. Dr Valentín introduced the data and made comments on the article. Dr Cubiella designed the study, performed the statistical analysis, and wrote the article. Dr Alves participated in the statistical analysis and made comments on the article. Dr García designed the study, participated in the analysis, and made comments on the article. Dr Fernández designed the study and made comments on the article. Dr Fernández-Seara made comments on the article.

The authors declare no conflict of interest.

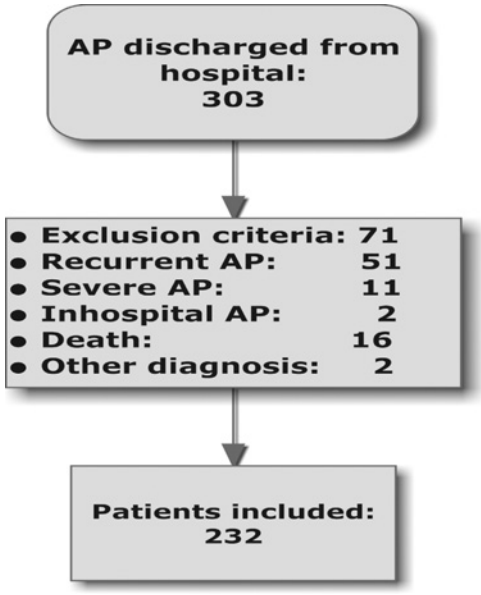

FIGURE 1. Inclusion of patients in the study.

Study Variables

Demographic variables (age and sex) and comorbidity using the Charlson comorbidity index were recorded for each patient. The following data were collected on admission: length of symptoms before admission, clinical variables (blood pressure, heart beat rate, and temperature), analytical data (levels of serum amylase, glucose, aspartate aminotransferase, creatinine, urea and total serum calcium; hematocrit; and leukocyte counts), and presence of pleural effusion. The bedside index for severity in AP was determined on admission.

We registered the treatment performed during the first 48 hours, which included volume of intravenous hydration administered, analgesia, and antiemetic drugs. The amount of opiate derivatives administered was quantified using scales of equivalence among the respective opiates in milligrams of morphine chloride (milligram pentazocine × 0.100, meperidine × 0.134). Other analgesic drugs, such as paracetamol, metamizole, and scopolamine butylbromide, were also registered.

Furthermore, we also recorded data on any complementary examinations conducted, such as abdominal ultrasound, magnetic resonance cholangiopancreatography, endoscopic ultrasonography, computed tomography (CT), and endoscopic retrograde cholangiopancreatography (ERCP), plus the most relevant findings such as, for example, lithiasis, choledocholithiasis, presence of peripancreatic collections, and Balthazar score. Acute pancreatitis etiology was determined on the basis of clinical assessment. Finally, length of hospital stay was also included in the study.

Intolerance to Refeeding

We collected fasting time (calculated from admission) and oral refeeding mode, that is, initial clear liquid or complete diet. Clear liquid diet consists of herbal teas without sweeteners and fat-free soups. Complete diet consists of a diet with the following composition: 1990 kilocalories (proteins, 24.65%; fats, 15.55%; carbohydrates, 60.10%). The clinical decision to refeed was based on improvement or disappearance of AP-related symptoms, that is, absence of pain, presence of peristalsis, and absence of vomiting. Intolerance to diet was defined as the appearance of pain, nausea, or vomiting associated with reintroduction of diet. In each case, the following were recorded: symptoms, time from reintroduction of

TABLE 1. Demographic and Baseline Variables at Date of Admission

		Intolerance		
	Total, N = 232	**No, n = 204**	**Yes, n = 28**	***P****
Age, y	74.3 (20.3–97.2)	74.1 (20.3–97.2)	73.9 (36.7–90.3)	0.166
Sex (female)	110 (47.2%)	93 (45.59%)	17 (60.71%)	0.167
Charlson comorbidity index	1 (0–7)	1 (0–7)	1 (0–5)	0.986
Length of symptoms, h	24 (0–720)	24 (1–720)	24 (0–720)	0.035
Systolic blood pressure, mm Hg	130 (80–220)	130 (80–220)	130 (100–160)	0.082
Heart beat, beats per min	74 (40–130)	74 (40–100)	74 (40–130)	0.765
Temperature, °C	36.5 (35–39)	36.45 (35–39)	36.6 (35.7–38.9)	0.423
Pleural effusion (yes)	34 (14.6%)	26 (12.7%)	8 (28.57%)	0.061
BISAP score	1 (0–4)	1 (0–4)	1.5 (0–3)	0.171
Glucose, mg/dL	131 (73–647)	130 (73–647)	141.5 (101–362)	0.516
Creatinine, mg/dL	0.9 (0.1–10.6)	0.9 (0.2–10.6)	0.9 (0.1–4.1)	0.782
Urea, mg/dL	41 (6–214)	39 (6–214)	47 (12–135)	0.508
Amylase, IU/L	1122 (35–9127)	1117 (35–9127)	1688 (47–6987)	0.836
Total calcium, mg/dL	8.5 (6.6–10)	8.6 (7.3–10)	8.2 (6.6–9.2)	0.018
Bilirubin, mg/dL	1.6 (0.3–9.2)	1.6 (0.3–9.2)	1.5 (0.6–7.2)	0.291
AST, IU/L	112 (4.5–1535)	114 (4.5–1535)	107 (13–1060)	0.783
Leukocytes, $\times 10^9$/L	10.8 (2.7–26.8)	10.8 (2.7–25.6)	11.1 (4.7–26.8)	0.481
Hematocrit, %	41.9 (21.4–66.1)	42.4 (21.4–66.1)	39.9 (33.6–44.5)	0.033

Qualitative variables are expressed in absolute numbers and as a percentage of the total; quantitative variables are expressed as median and its range. Differences with $P < 0.05$ are considered statistically significant.

*Significance of the differences in the Cox regression univariate analysis.

BISAP indicates bedside index for severity in AP; AST, aspartate aminotransferase.

TABLE 2. Treatment During the First 48 Hours

		Intolerance		
	Total, N = 232	Yes, n = 204	No, n = 28	P*
Intravenous hydration, μL	5 (0–9)	5 (0–9)	5 (4–7)	0.573
Metamizole (yes)	157 (67.24%)	134 (65.68%)	23 (82.14%)	0.137
AQ8 Metamizole dose, g	4 (0–18)	4 (0–18)	8 (0–18)	0.071
Morphine derivatives (yes)	65 (28%)	54 (26.47%)	11 (39.28%)	0.192
AQ9 Morphine dose, mg	0 (0–113.9)	0 (0–113.9)	0 (0–73.7)	0.068
Paracetamol (yes)	88 (37.93%)	79 (38.72%)	9 (32.14%)	0.454
Butylscopolamine (yes)	31 (13.4%)	29 (14.21%)	2 (7.14%)	0.258
Antiemetic drugs (yes)	156 (67%)	136 (66.67%)	20 (71.43%)	0.841

Qualitative variables are expressed in absolute numbers and as a percentage of the total; quantitative variables are expressed as median and its range. Differences with $P < 0.05$ are considered statistically significant.

*Significance of the differences in the Cox regression univariate analysis.

diet, and treatment administered, that is, analgesic drugs, antiemetic drugs, and suspension or reduction of diet.

Statistical Analysis

The data were entered into a database. Initially, a descriptive analysis of the study variables was made, with qualitative variables being expressed as absolute numbers and percentages and quantitative variables as median and its range. Intolerance-related variables were determined by a Cox regression. A univariate analysis was performed, and those variables that proved to be statistically significant or clinically relevant were then included in a Cox multivariate proportional hazards model. This association was expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). In addition, Fisher exact test was used to determine whether a relationship existed between intolerance and the number of tests performed. Finally, we performed a Kaplan-Meier survival analysis and a log-rank test to determine if there was an association between intolerance and length of hospital stay. In all cases, differences with $P < 0.05$ were considered statistically significant. All statistical calculations were performed using the SPSS statistical software, version 15.0 (SPSS, Inc, Chicago, Ill).

Ethical Aspects

The study was approved by the Galician Clinical Research Ethics Committee (code 2010/142) under decision dated April 27, 2010. Patients' clinical histories were accessed for study purposes

TABLE 3. Etiology of AP, Examinations Performed, and Duration of Hospital Stay

		Intolerance		
	Total, N = 232	No, n = 204	Yes, n = 28	P
Alcoholic etiology (yes)	25 (10.7%)	25 (12.3%)	0	0.256*
Biliary etiology (yes)	150 (64.7%)	131 (64.2%)	19 (67.9%)	0.993*
Choledocholithiasis (yes)	11 (4.7%)	7 (3.4%)	4 (14.3%)	0.021*
Balthazar score				
A	18 (27.7%)	14 (27.5%)	4 (28.6%)	0.594*
B	4 (6.2%)	3 (5.9%)	1 (7.1%)	
C	20 (30.8%)	18 (35.3%)	2 (14.3%)	
D	8 (12.3%)	6 (11.8%)	2 (14.3%)	
E	15 (23.1%)	10 (19.6%)	5 (35.7%)	
Peripancreatic collections (yes)	23 (34.8%)	16 (31.3%)	7 (46.67%)	0.638*
Abdominal ultrasound (yes)	214 (91.8%)	189 (92.6%)	25 (89.3%)	0.481†
MRCP (yes)	80 (34.3%)	69 (33.8%)	11 (34.5%)	0.637†
EUS (yes)	22 (9.4%)	19 (9.3%)	3 (10.7%)	0.872†
CT (yes)	66 (28.3%)	52 (25.5%)	14 (50%)	0.015†
ERCP (yes)	34 (14.7%)	25 (12.3%)	9 (32.1%)	0.017†
Hospital stay, d	8 (1–31)	7 (1–25)	12 (4–31)	<0.001‡

Qualitative variables are expressed in absolute numbers and as a percentage of the total; quantitative variables are expressed as median and its range. Differences with $P < 0.05$ are considered statistically significant.

*Significance of the differences in the Cox regression univariate analysis.

†Significance of the differences in the Fischer test univariate analysis.

‡Significance of the differences in the Kaplan-Meier univariate analysis.

MRCP indicates magnetic resonance cholangiopancreatography; EUS, endoscopic ultrasound study.

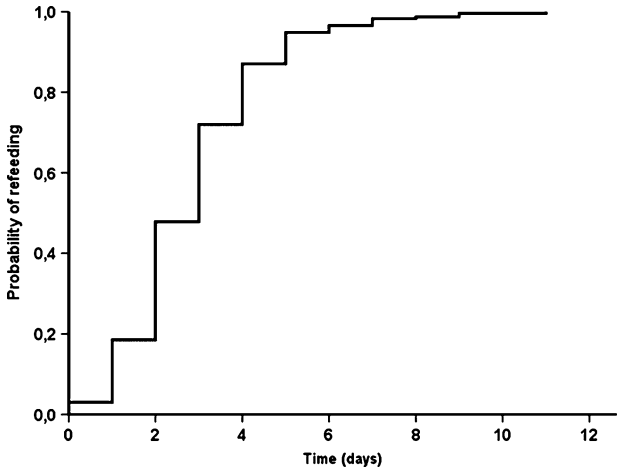

FIGURE 2. Probability of refeeding in mild AP. Survival curve of probability of refeeding.

in accordance with the research protocols available in our hospital's clinical documentation department.

RESULTS

Descriptive Analysis

During the study inclusion period, 252 patients required admission to our hospital on 303 occasions and were discharged with the diagnoses of AP. In 51 patients, 71 episodes were excluded for the reasons outlined in Figure 1. Finally, 232 patients were included in the study. The Charlson comorbidity index score was 0 point for 77 patients, 1 point for 75 patients, 2 points for 42 patients, 3 points for 22 patients, 4 points for 10 patients, and 5 or more points for 6 patients. Description of patients' hemodynamic constants and analytical determinations on admission and length of symptoms before admission are in Table 1. The bedside index for severity in AP score was 0 point for 54 patients, 1 point for 89 patients, 2 points for 66 patients, 3 points for 20 patients, and 4 points for 3 patients.

With respect to the treatment in the first 48 hours, the median amount of intravenous hydration administered was 5000 mL (range, 0–9000 mL). In 156 patients (67%), antiemetic treatment was administered (119 on demand, 37 scheduled). With respect to analgesic drugs, 157 patients (67.24%) received metamizole, 65 (28%) were given some morphine derivative, 88 (37.93%) required paracetamol, and in 31 (13.4%), the pain was treated with butylscopolamine. There were no basal differences among patients treated with metamizole and morphine derivatives. The treatments given in the first 2 days plus the dose of metamizole and opioids administered are shown in Table 2.

Median time of hospitalization was 8 days (range, 1–31 days). Acute pancreatitis was catalogued as lithiasic in 150 (64.7%), alcoholic in 25 (10.7%), related to other causes in 13 (5.6%), and idiopathic in 44 (18.9%) cases. Choledocholithiasis was determined in 11 patients and was treated by endoscopic extraction. The tests performed were abdominal ultrasound in 214 (91.8%), magnetic resonance cholangiopancreatography in 80 (34.3%), endoscopic ultrasonography in 22 (9.4%), and ERCP in 34 patients (14.7%). Balthazar scores in 66 patients (28.3%) who underwent CT scans were A (18 patients), B (4 patients), C (20 patients), D (8 patients), and E (15 patients), with peripancreatic collections being detected in 34.84% of patients evaluated with CT. Data on etiology, examinations performed, and length of hospital stay are listed in Table 3.

Refeeding and Intolerance to Diet

Diet was reintroduced at 3 days (range, 0–11 days) (Fig. 2). Feeding was initiated with a low-fat liquid diet in most patients (91%) and with a complete diet in 21 (9%). At 1 day (range, 0–14 days), 28 patients (12%) developed intolerance to diet. The symptoms were vomiting in 10 patients, nausea in 15, abdominal pain relapse in 16, fever in 2, and abdominal distension in 1. The diet was reduced in 3 patients and temporarily suspended in 17 patients. A total of 18 patients required analgesic treatment and 10 required antiemetic treatment.

In the univariate analysis, the factors associated with intolerance to refeeding were length of symptoms before admission (P= 0.035), total serum calcium (P = 0.018) and hematocrit (P = 0.033) on admission, fasting time (P = 0.011), mode of refeeding (P = 0.046), and diagnosis of choledocholithiasis (P = 0.021), as can be seen in Tables 1, 2, and 3. These variables, along with the metamizole and morphine derivative requirements, were introduced into a multivariate analysis. The variables independently associated with risk of intolerance to refeeding were choledocholithiasis (HR, 12.35; 95% CI, 2.98–51.19; P = 0.001), fasting time (HR, 1.33; 95% CI, 1.09–1.63; P = 0.005), refeeding with a complete diet (HR, 4.93; 95% CI, 1.66–14.66; P = 0.04), length of symptoms before admission (HR, 1.004; 95% CI, 1.001–1.006; P = 0.012), andmetamizole dose (HR, 1.11; 95% CI, 1.02–1.21; P = 0.014), as can be seen in Table 4.

For the examinations performed (Table 3), patients with intolerance to refeeding required significantly more CT (P = 0.015) and ERCP (P = 0.017) scans for their diagnosis and management as well as a longer hospitalization (P < 0.001).

DISCUSSION

This study describes mode of refeeding and intolerance to oral diet among a consecutive series of patients admitted to hospital, owing to an episode of mild AP. In this cohort, the probability of intolerance to oral refeeding is an infrequent

TABLE 4. Multivariate Analysis

			95% CI for HR	
	P	HR	Lower	Upper
Choledocholithiasis (yes)	0.001	12.358	2.983	51.192
Fasting time, d	0.005	1.337	1.092	1.637
Initial complete diet (yes)	0.004	4.939	1.664	14.664
Metamizole dose, g	0.014	1.112	1.022	1.211
Time of progression, h	0.012	1.004	1.001	1.006

Variables independently associated with risk of intolerance to reintroduction of oral diet in a Cox proportional hazards model. Associations are expressed as HR, their CIs, and P value.

phenomenon, controlled by reducing or temporarily suspending the diet and administering antiemetic and/or analgesic drugs. Its appearance was associated with a series of variables, namely, length of symptoms before admission, metamizole requirements in the first 48 hours, fasting time, mode of refeeding, and choledocholithiasis. Likewise, a statistically significant relationship was observed among intolerance to refeeding, longer hospitalization, and the need for additional complementary examinations.

Clinical research into nutrition and reintroduction of diet in AP has focused on severe AP, a clinical situation in which the evidence supports feeding patients by enteral rather than parenteral nutrition. Indeed, enteral nutrition is associated with a reduction in the risk of infections, multisystemic organ failure, and mortality.[4–7] Although enteral feeding was initially administered by a nasojejunal tube to maintain bowel rest, feeding by nasogastric tube has been proposed as an alternative. In this respect, a meta-analysis based on the results of 2 randomized small-size studies has reported no differences in mortality, pain, diarrhea, or intolerance to enteral diet between the 2 feeding routes.[5]

In contrast, although mild AP accounts for most of the AP episodes, there is little evidence regarding the mode and time of refeeding patients. Two prospective studies and a meta-analysis established that intolerance to refeeding is a frequent event that occurs in up to 21% to 24.6% of patients.[12–14] In these studies, such intolerance was associated with a series of factors, including Balthazar score, duration of pain, and lipase and serum C-reactive protein concentration. Similarly, they ascertained that intolerance to diet increased the duration of hospital stay in AP. We, however, observed a prevalence of intolerance lower than that described in earlier studies.

Our study displays similarities and differences from these studies. As reported in previously published studies, we found an association between risk of intolerance and duration of symptoms before and during admission. However, we were unable to evaluate pancreatic enzyme levels on the day preceding reintroduction of diet or the CT results for all patients because our study was retrospective. At our hospital, CT is performed to rule out other diagnosis or local complications in case of clinical worsening, as determined in clinical practice guidelines.[2,11] Nevertheless, no relationship was found between presence of collections and intolerance in patients with a CT study. Another limitation of our study is that we could not determine the nutritional status on admission. This variable may have a role on the prognosis of AP and the intolerance to diet refeeding.

In contrast, we assessed the effect of treatment administered in the first 2 days of admission. One of the variables related to risk of intolerance was the amount of metamizole required for pain control. This association, along with fasting time and duration of symptoms before admission, probably implies that mild AP with persistence of symptoms has a higher risk of intolerance. Finally, a statistical analysis based on a Cox proportional hazards model was performed for 2 reasons: first, the variable "intolerance to reintroduction," is associated with a time from reintroduction of the diet, which renders this type of statistical analysis ideal. Second, many of the independent variables do not have a normal distribution, which limits their analysis by parametric tests.

In recent years, 5 randomized studies and a meta-analysis have compared different modes of refeeding in mild AP.[15–20] Three of these compared refeeding with liquid, soft, or complete diets in the moment symptoms disappeared.[15–17] The fourth randomized study compared refeeding on patient's selection versus when serum lipase normalized.[18] Although it was not the primary objective of these studies, there were no differences among the study arms in intolerance to refeeding. This may be for 2 reasons. As described in our case, intolerance to reintroduction of oral diet is an infrequent event, and the studies lacked the necessary sample size to detect such differences. Furthermore, selection bias cannot be excluded, as a result of excluding patients with analgesic requirements before inclusion.[15] Moreover, patients were not stratified according to the factors associated to the risk of intolerance previously described.[12–14] Indeed, we feel that one of our study's contributions lies in the fact that we have defined criteria associated with intolerance, that is, length of symptoms before admission as well as choledocholithiasis and metamizole requirements for control of pain, which should be taken into account in future randomized studies. Finally, the study published by Eckerwallet al[20] compared immediate refeeding versus fasting and refeeding when symptoms disappear. Patients allocated to immediate refeeding had a shorter duration of hospitalization, with no differences in intolerance or reactivation of AP. In our series, diet was reintroduced in 7 patients at the date of admission. The study of Eckerwall et al proposes a mode of refeeding in mild AP completely different from standard clinical practice. These results must be validated in studies specifically designed to prevent selection biases and with an adequate sample size. In this respect, it would be desirable to have a set of criteria that are able to predict which patients have a low risk of intolerance on admission.

Finally, we have confirmed the relationship between intolerance to refeeding and a longer hospital stay already documented in previous studies.[12–14] Similarly, we detected a greater need for complementary examinations in this subgroup. Although reactivation of AP associated with refeeding cannot be excluded, we believe that the increase in health resources required is linked to a persistent evolution of mild AP or to an AP refractory to standard symptomatic treatments.

To sum up, in our series, intolerance to refeeding in mild AP was infrequent and was independently associated with length of symptoms before admission, fasting time, metamizole requirements, choledocholithiasis, and mode of refeeding. Similarly, such patients required more health resources (complementary examinations and length of hospital stay).

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