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Review Article

Review Article

Inflammatory Bowel Disease and Pancreatitis: A Review

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Abstract

Background and aims: Pancreatic abnormalities are common in inflammatory bowel disease (IBD) patients and represent a heterogeneous group of conditions that include acute pancreatitis, chronic pancreatitis, autoimmune pancreatitis and asymptomatic abnormalities. We sought to review the available evidence concerning the aetiology, clinical presentation, diagnosis and treatment of pancreatic conditions in IBD patients.

Methods: A PubMed/Medline query was conducted addressing pancreatic disorders in IBD. Reference lists from studies selected were manually searched to identify further relevant reports. Relevant manuscripts about pancreatic disorders in patients with IBD were selected and reviewed.

Results: Thiopurines and gallstones are the most frequent causes of acute pancreatitis in IBD patients. Thiopurine-induced acute pancreatitis is usually uncomplicated and self-limited. Some evidence suggests that chronic pancreatitis may be more common in IBD. Most cases are idiopathic, affecting young males and patients with ulcerative colitis. Autoimmune pancreatitis is a relatively newly recognized disease and is increasingly diagnosed in IBD, particularly for type 2 autoimmune pancreatitis in ulcerative colitis patients. Asymptomatic exocrine insufficiency, pancreatic duct abnormalities and hyperamylasaemia have been identified in up to 18% of IBD patients, although their clinical significance and relationship with IBD remain undefined.

Conclusions: The wide spectrum of pancreatic manifestations in IBD is growing and may represent a challenge to the clinician. A collaborative approach with a pancreas specialist may be the most productive route to determine aetiology, guide additional diagnostic workup, illuminate the aetiology and define the treatment and follow-up of these patients.

Key Words: Inflammatory bowel disease; ulcerative colitis; Crohn's disease; acute pancreatitis; chronic pancreatitis; autoimmune pancreatitis; exocrine insufficiency; hyperamylasaemia; hyperlipasaemia

1. Introduction

Inflammatory bowel disease (IBD) is an idiopathic chronic and recurrent condition that comprises Crohn's disease (CD) and ulcerative colitis (UC). Its pathogenesis involves a complex interaction between genetic susceptibility traits, environmental factors and intestinal microflora, which leads to an abnormal and excessive immune response, compromised epithelial barrier function and, ultimately, gastrointestinal tract inflammation and tissue damage.[1] Being a multisystemic disease, it may affect many organs. Extraintestinal manifestations, defined as complications occurring distant from the bowel, are reported in 21–47% of IBD patients,[2] and will be extensively reviewed in the upcoming First European Evidence-Based Consensus on Extra-Intestinal Manifestations in Inflammatory Bowel Disease, to be published in this journal.

Pancreatic abnormalities in IBD patients are common and represent a heterogeneous group of conditions,[3,4] including acute pancreatitis (AP), chronic pancreatitis (CP), autoimmune pancreatitis (AIP), asymptomatic exocrine insufficiency, enzyme elevations and imaging abnormalities.[5–7] Since the last review on IBD and pancreatitis was published in 2010,[6] new information has emerged, particularly regarding thiopurine-associated pancreatitis and AIP. Hence, we sought to prepare an updated review of the spectrum of pancreatic disorders in patients with IBD.

2. Methods

We performed a broad literature search to identify relevant studies addressing pancreatic disorders in IBD. PubMed and Medline were searched up to May 2015, using the keywords 'IBD', 'UC' and 'CD' combined with 'AIP', 'AP', 'CP', 'idiopathic pancreatitis', 'drug-induced pancreatitis', 'exocrine pancreas insufficiency' or 'pancreatic autoantibodies'. Articles in English, French, Portuguese and Spanish were reviewed. Articles reporting on the clinical presentation, diagnosis, treatment and outcome of pancreatic diseases and silent pancreatic abnormalities in IBD were selected and reviewed. Moreover, a manual search of the reference list of initially selected articles was conducted. Articles published only as abstracts were excluded.

3. Acute pancreatitis

3.1. Definition and epidemiology

Acute pancreatitis is a pancreatic acute inflammatory process that can extend to regional tissues and/or distant organs[8] and is usually followed by full resolution of clinical and histological abnormalities.[9] Worldwide, the annual incidence of AP ranges from 13 to 45/100 000 people,[10–12] equally affecting men and women. Some have argued that its incidence may be increased among patients with IBD.[3] In a retrospective multicentre Spanish study, the 14-year risk of AP was 1.6% among 5073 IBD patients.[13] Similarly, Weber et al.[14] observed that 1.4% of 852 CD patients developed AP over a 10-year period. The 15-year hospitalization risk for a first episode of AP was 0.6% in a national Danish cohort of 15 526 IBD patients. Furthermore, the authors demonstrated a 4-fold increased risk of AP in CD and a 2-fold increased risk of AP in UC, in relation to the expected AP incidence rate in the general population.[15]

3.2. Aetiology

The most common causes of AP in IBD patients are gallstones and drugs (Table 1). The incidence of alcohol-induced AP in IBD patients seems to be much lower than in the general population.[13,14,16,17] Less common causes include post-endoscopic retrograde cholangiopancreatography (ERCP), balloon enteroscopy, hypercalcaemia and

Table 1. Summary of series of acute pancreatitis in inflammatory bowel disease (IBD) patients.

Study	Bermejo *et al.*, 2008[13]	Moolsintong *et al.*, 2005[16]	Inoue *et al.*, 2005[17]	Weber *et al.*, 1993[14]
Country of origin	Spain	USA	Japan	Germany
Study design and period	Multicentre, retrospective 14 years	Single centre, retrospective 1976–2001 (25 years)	Single centre, retrospective 1989–2001 (12 years)	Single centre, retrospective 1981–91 (10 years)
IBD population	Total IBD population 5073. AP: 53 patients CD (64 episodes); 14 UC (18 episodes)	48 CD patients with AP	Of 22 UC patients 3 had AP	852 CD patients, AP in 12 patients
AP criteria	Serum amylase/lipase ≥3 times upper limit of normal and/or characteristic CT findings	Serum amylase/lipase ≥2 times upper limit of normal and/or imaging (CT or US)	Serum amylase/lipase ≥3 times upper limit of normal and/or characteristic CT findings	All but one case had pancreatic enzymes elevation and characteristic imaging
% (*n*) males	CD 38% (13) UC 61% (11)	50% (24)	100% (3)	33% (4)
Age at AP diagnosis (years)	CD mean 39 ± 12.3 UC mean 42 ± 12.4	Median 47 (14–91)	23, 29 and 40 years	Median 23 (10–50)
AP aetiology, % (*n*)	Thiopurines 69% (46) Unknown 15% (10)[1] Gallstones 15% (10) Oral mesalamine 9% (6) Duodenal CD 1.5% (1) Hypertriglyceridaemia 1.5% (1) Post-ERCP 1.5% (1)	Gallstones 21% (10) Unknown 21% (10) Alcohol 15% (7) Thiopurines 15% (7) Duodenal CD 15% (7) Postoperative 12,5% (6) Post-ERCP 10% (5) 5-aminosalicylate 2% (1) Pancreatic cancer 2% (1)	Thiopurines 33% (1) Mesalamine 33% (1) Unknown 33% (1)	Unknown 83% (10)[a] Drug-induced 17% (2)
Severity of AP	Mild 98%, *n* = 81	Hospitalization 85% ICU stay 12.5%	Mild 100%	Mild 100%
Mortality	None			
Recurrence, % (*n*)	13% (9) (4 cases unknown, 3 biliary, 1 mesalamine, 1 thiopurine rechallenge)	21% (10) (6 patients unknown, 1 patient each for medication, alcohol, postoperative and duodenal CD)	N/A	17% (2)

[a]Bile duct stones, alcohol, viral infections, trauma, drug history and hyperparathyroidism ruled out.

AP, acute pancreatitis; CD, Crohn's disease; UC, ulcerative colitis; CT, computed tomography; US, ultrasound; ERCP, endoscopic retrograde cholangiopancreatography; ICU, intensive care unit; N/A, not available.

hypertriglyceridaemia.[13,14,16–18] Extremely rare causes, mostly described as case reports, are primary sclerosing cholangitis (PSC) [19] and CD-associated granulomatous inflammation of the pancreas[20] or of the common bile duct and ampulla.[21] Duodenal CD has also been suggested as a risk factor for AP, the hypothesis being that relative duodenal stenosis could lead to increased intraduodenal pressure and reflux of duodenal contents to the pancreatic duct[16] (Supplementary Table 1). Nonetheless, there are only a few retrospective series studying AP in IBD patients and the relative frequencies of different aetiologies vary (Table 1), with 10–33% of cases having an unknown aetiology.

3.2.1. Gallstones

An association between cholelithiasis and IBD, particularly with CD, has been recognized since 1970.[22] While most studies do not show an increased risk of cholelithiasis in UC,[23–26] there is an increased risk in CD, ranging from 11 to 34%, as compared with the general population (7–15%).[26] In a large case–control prospective study, Parente et al.[25] showed a 2-fold relative risk (odds ratio (OR) 2.09; 95% confidence interval (CI) 1.20–3.64) for gallstones after adjusting for age, sex and body mass index. Risk factors for gallstones in CD include previous intestinal resection (>30 cm and number of resections), age (≥50 years), involvement of ileum and colon, disease duration (>10 years), number of hospitalizations (≥3), number of relapses (≥3), total parental nutrition and hospitalization duration.[25,26] In contrast to cholelithiasis in the general population,[27] female gender appeared as a risk factor in only one of the nine studies included in the systematic review.[26] Both cholesterol and pigment stones are noted at increased frequency in CD patients.[28] Proposed

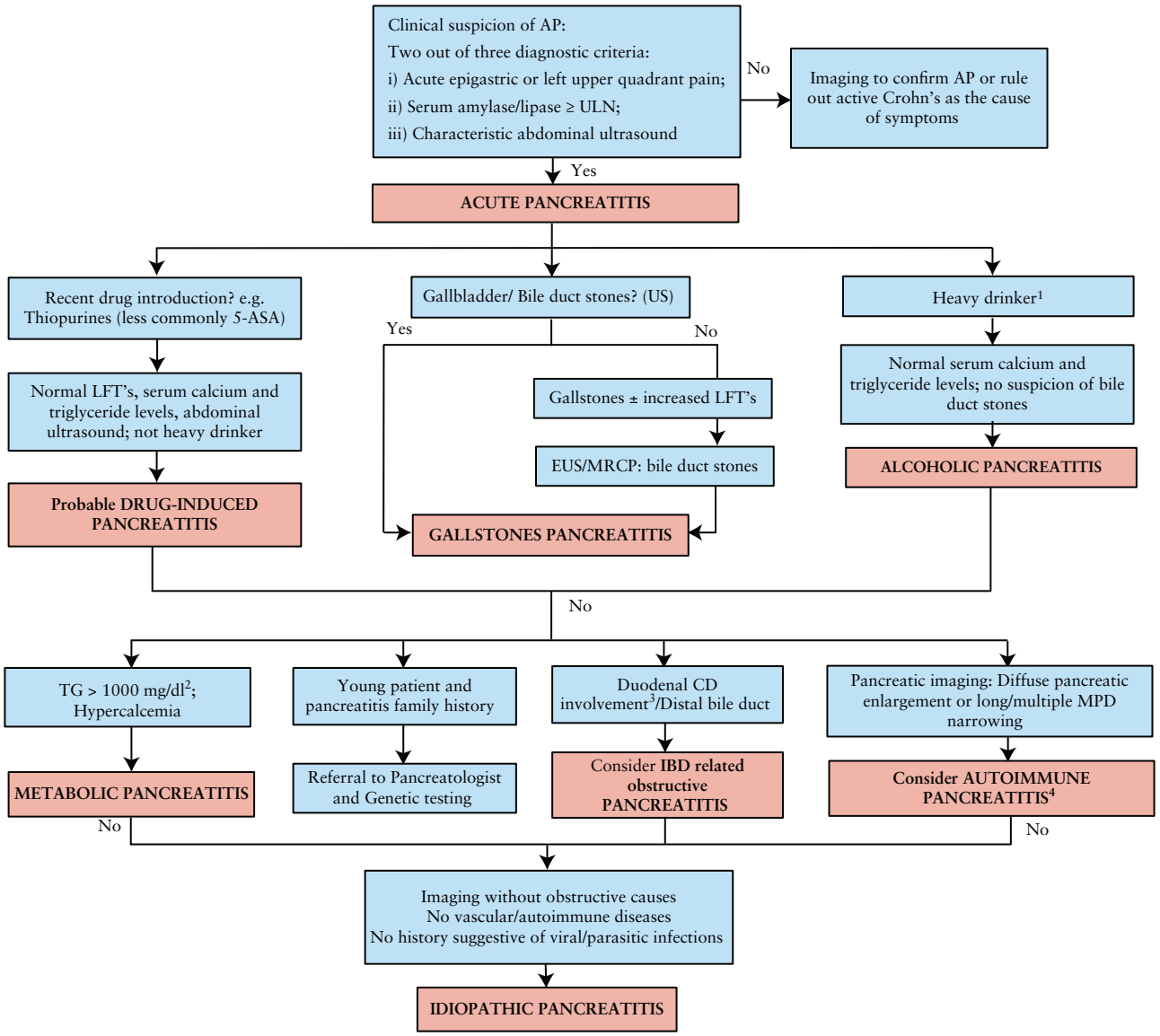

Figure 1. Diagnostic work-up of acute pancreatitis aetiology in inflammatory bowel disease. [1]Alcoholic pancreatitis should be considered in a heavy drinker and after excluding gallstones and drugs, given that only 2–3% of heavy drinkers develop acute pancreatitis. [2]Triglyceride values should be above 1000 mg/dl. When the initial diagnostic workup raises the possibility of hypertriglyceridemia the fasting triglyceride level should be re-assessed 1 month after discharge. [3]In severe cases pancreatic head inflammation may cause duodenal stenosis, so findings should interpreted with caution and the timing of endoscopy should be selected on a case-by-case basis. [4]Determine serum IgG4 levels and review CT/MRI/physical examination for other organ involvement. AP, acute pancreatitis; BUN, blood urea nitrogen; CT, computed tomography; EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; MPD, main pancreatic duct; ULN, upper limit of normal; US, abdominal ultrasound.

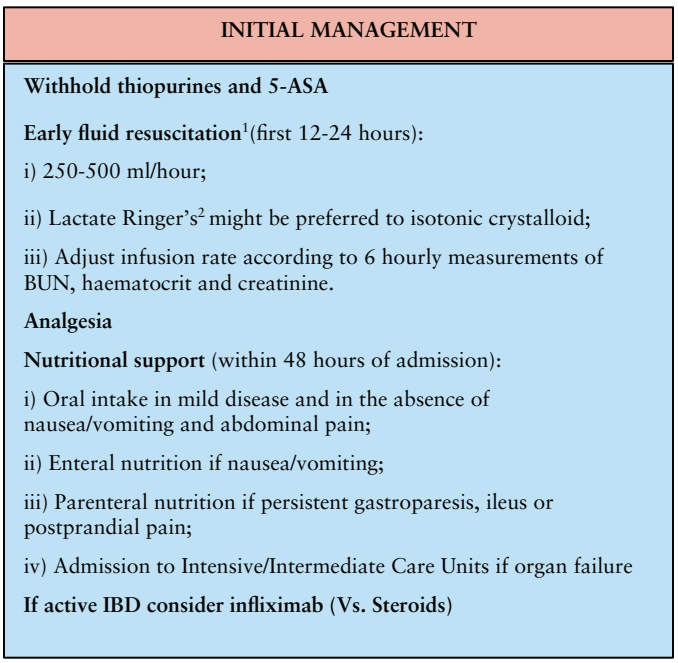

Figure 2. Initial management of acute pancreatitis in inflammatory bowel disease (IBD). [1]Caution in elderly and patients with cardiac and/or renal disease. [2]Contraindicated in hypercalcaemic patients. 5-ASA, aminosalicylates.

explanations include decreased intestinal reabsorption of bile salts, resulting in supersaturated bile with cholesterol; impaired enterohepatic cycling of bilirubin with increased biliary bilirubin levels; reduced gallbladder motility; and decreased gallbladder emptying associated with total parental nutrition and fasting.[25–27]

3.2.2. Medications

As noted earlier, drugs are a frequent cause of AP in IBD. The first requirement for a diagnosis of drug-induced pancreatitis is to rule out other common causes.[29,30] A definite diagnosis of drug-induced pancreatitis, however, requires three additional criteria: temporal sequence between medication introduction and appearance of AP; symptom cessation after drug discontinuation; and AP recurrence after re-exposure. In clinical practice rechallenge is usually not performed.[29] Clinically, drug-induced AP is generally uncomplicated and resolves rapidly after drug withdrawal.[13,29,30] Thiopurines, 5-aminosalycilates (5-ASA), metronidazole and steroids are common drugs used in IBD treatment, and all of these drug classes have been shown by rechallenge to be definite causes of drug-induced pancreatitis.[29,30]

Thiopurines are the drugs most frequently implicated as a cause of AP in IBD patients,[13,14,16,17] with a reported incidence of 3–4% in patients on this therapy.[31,32] AP is a dose-independent idiosyncratic reaction that usually develops within the first month of treatment.[13,31,33] Female patients are at increased risk of developing thiopurine-induced AP (TIAP). Curiously, some studies have reported an increased incidence in CD as compared with other immune diseases for which these drugs are also used, although this observation is not universal.[13,31,33] While *TPMT* (thiopurine S-methyltransferase) polymorphisms have not been associated with the risk of TIAP,[34] there may be other genetic predispositions to this complication. A European genome wide association study of 172 patients with definite or probable TIAP found a significant association between TIAP and the single nucleotide polymorphism rs2647087, located within the class II HLA region. Additionally, the alleles HLA-DQA1*02:01 and HLA-DRB1*07:01 were also significantly associated with the development of TIAP.[35] These findings have been further replicated in an independent IBD case–control cohort with 78 cases and 472 controls. An estimated pancreatitis risk of 9% was calculated for heterozygotes at rs2647087 and 17% for homozygotes.[35] In the future, this polymorphism might be used to identify populations at high risk of TIAP.

Thiopurine-induced AP is usually an absolute contraindication to thiopurine reintroduction since recurrence is expected on re-exposure. To be sure, some authors have reported successful introduction of 6-mercaptopurine after azathioprine-induced pancreatitis in both paediatric[36] and adult[37,38] populations. However, these sporadic cases are confined to individual reports or small series, so this strategy should best be avoided on account of the high risk involved. It is also worth noting that treatment with 6-thioguanine has not been associated with a higher risk of AP and may therefore be a reasonable alternative, bearing in mind the risk of nodular regenerative hyperplasia at higher doses.[39,40]

Less frequently, 5-ASA (oral formulations, enemas and suppositories) have been implicated in drug-induced AP.[41–43] This observation was questioned, however, in a large case–control study from Denmark, where 5-ASAs were not associated with an increased risk of AP, including IBD patients.[44] Pancreatitis associated with metronidazole or steroids is exceedingly rare.[6]

3.2.3. Alcohol

Alcohol seems to be a less frequent cause of pancreatitis in IBD, as compared with gallstones and medications (Table 1). In fact, alcohol was reported as a cause of AP in only one study, following gallstone pancreatitis.[16] In the remaining three series, medications were the most frequent cause.[13,14,17] Noteworthy is the fact that research focusing on alcohol consumption in IBD patients is very scarce. Swanson et al.[45] recently reported the pattern and quantity of alcohol consumption in 90 patients with inactive IBD. Current drinkers constituted 62% of IBD patients (similar rates for CD and UC), most of them light (39%) or moderate (48%) drinkers. Although the percentage of moderate drinkers in the IBD group was slightly higher than that in the general US population, the authors found no

Table 2. Summary of case-series of chronic pancreatitis in inflammatory bowel disease (IBD).

	Authors and country		
	Axon *et al*., 1979[53] UK	Barthet *et al*., 1999[52] France	Gómez *et al*., 2008[54] Spain
Design and period	Retrospective, single centre	Retrospective, multicentre 1981–96	Retrospective, 2 centres
Population	In 59 patients with abnormal pancreatograms (ERCP) 5 also had IBD (1 UC, 4 CD)	8 cases CP and IBD (6 UC; 2 CD)	4 cases of idiopathic pancreatitis identified in 1057 IBD patients (3 UC; 1 CD)
Demographics	Males 40% (2) Median age CP diagnosis 45 years (16 min, 70 max)	Males 63% (5) Median age CP diagnosis 31 years (16 min, 43 max)	Males 75% (4) Median age CP diagnosis 39 years (27 min, 49 max)
CP diagnostic criteria	ERCP pancreatogram	Pancreatic symptoms and pancreatogram or histology	Symptoms and/or EUS and/or ERCP
Time of CP diagnosis	80% (4) after IBD 20% (1) simultaneously with IBD	63% (5) after IBD 37% (3) before IBD	75% (3) after UC 25% (1) after CD
Probable aetiology, % (*n*)	Idiopathic 60% (3) Gallstones 20% (1) PSC 20% (1)	Idiopathic (100%) 4 cases had bile duct involvement (1 PSC).	Idiopathic (100%)
Clinical presentation, % (*n*)	Incidental 40% (2) AP 20% (1) Jaundice 20% (1) Abdominal pain 20% (1)	AP 50% (4) Jaundice 25% (2) Severe abdominal pain and weight loss 12.5% (1) Anicteric cholestasis 12,5% (1)	Recurrent AP 100% (4)
Pancreatic insufficiency and calcifications, % (*n*)	N/A	Exocrine 25% (2) Pancreatic calcification 12.5% (1)	Exocrine 100% (1 case tested)
Imaging findings, % (*n*)	Diffuse/focal MPD irregular narrowing 60% (3) Dilated MPD 20% (1) Isolated side branch duct abnormalities 20% (1)	Long stenosis MPD[a] 37.5% (3) (one with choledocus short stenosis) Slight dilatation MPD[a] 37.5% (3) (one with PSC related short juxta-ampullary stenosis) Pancreatic head nodular formation 25% (2) Pancreatic calcification 12.5% (1)	Diffuse narrowing MPD 25% (1) [a] Lobulated pancreatic parenchyma with hyperechoic foci/tracts and fibrous tracts 50% (2)[b]
Surgery, % (*n*)	No	Pancreatic nodules 25% (2)	No

[a]Detected in ERCP.

[b]Observed in EUS.

AP, acute pancreatitis; CD, Crohn's disease; UC, ulcerative colitis; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; PSC, primary sclerosing pancreatitis; N/A, not available.

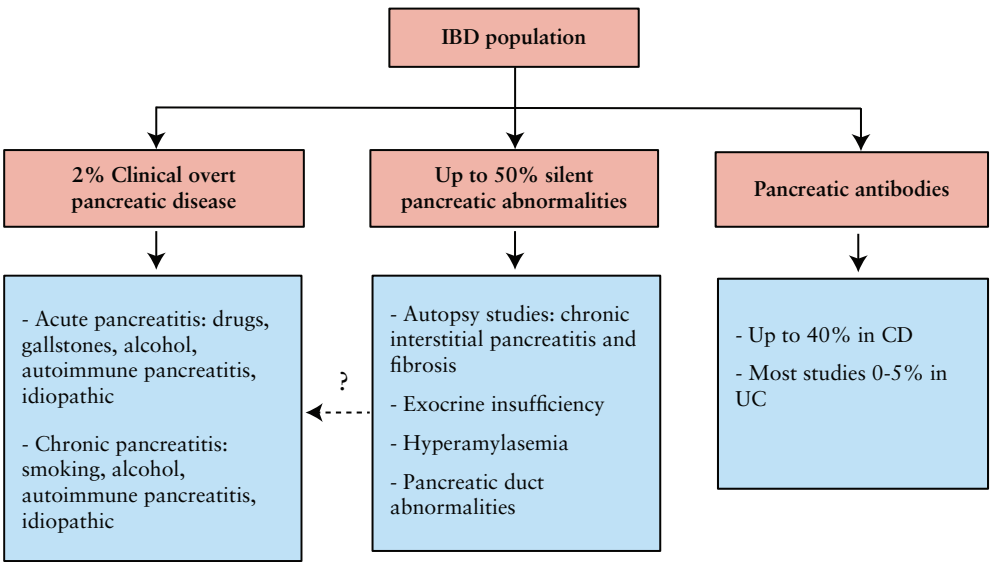

Figure 3. Spectrum of pancreatic abnormalities in inflammatory bowel disease (IBD). CD, Crohn's disease; UC, ulcerative colitis.

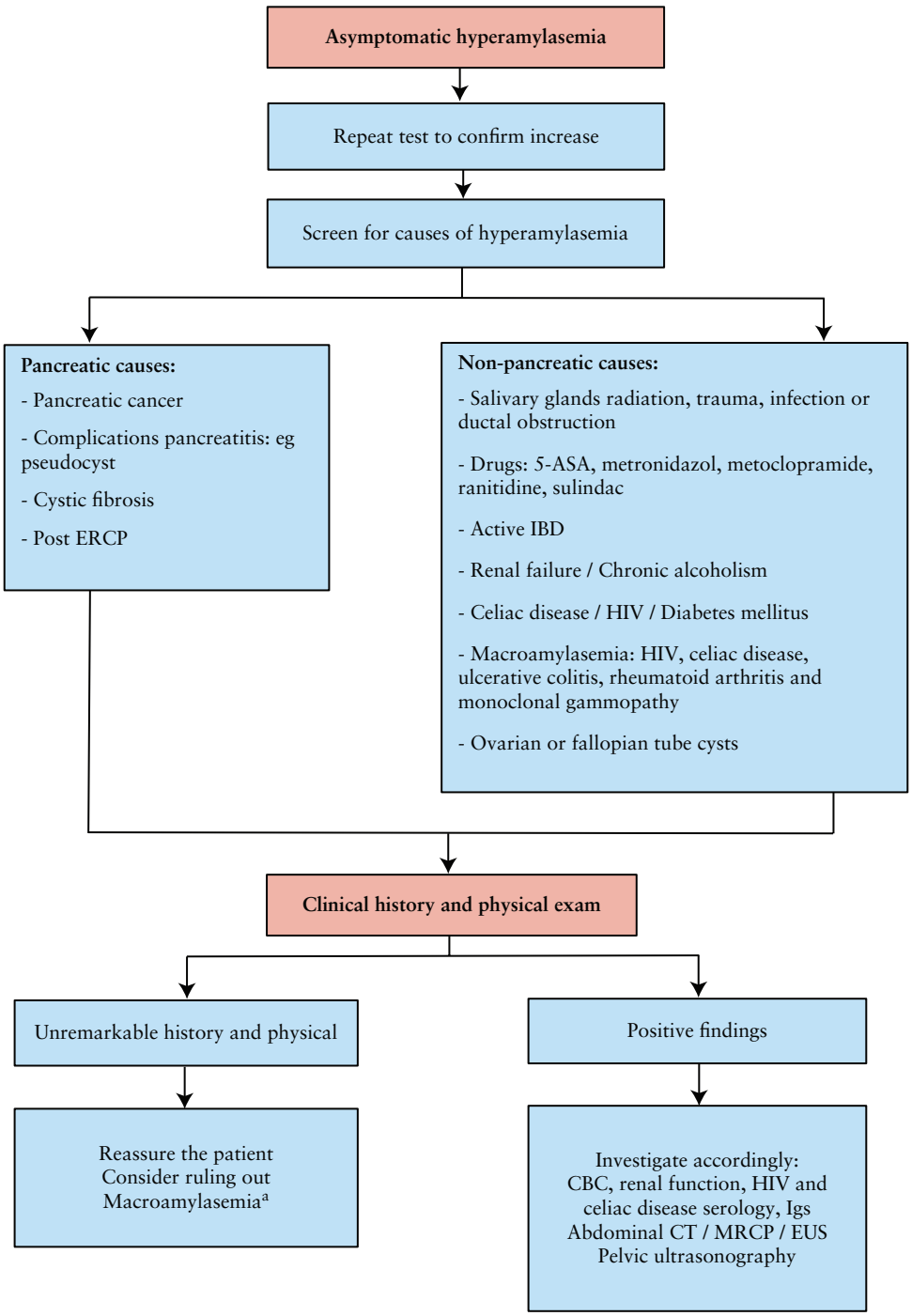

Figure 4. Approach strategy to asymptomatic hyperamylasemia in inflammatory bowel disease (IBD). [a]Molecular weight of serum amylase will be increased in macroamylasaemia. Amylase-to-creatinine ratio (24-h urine): in macroamylasaemia the ratio will be reduced since there is decreased glomerular filtration of the macroamylase complexes. 5-ASA, aminosalicylates; CBC, complete blood count; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; HIV, human immunodeficiency virus; Igs, serum immunoglobulin; MRCP, magnetic resonance cholangiopancreatography.

differences in the rate of current drinkers and the number of binge or heavy drinkers.[45]

3.3. Diagnosis

The diagnosis of AP follows the same criteria as in the general population and is established when at least two of the following three criteria are present: (i) acute and sudden pain, of variable intensity (although usually severe), located in the epigastric or left upper quadrant, that can irradiate to the back, chest or flank and is usually accompanied with nausea and/or vomiting; (ii) increase in serum amylase or lipase greater than three times the upper limit the of normal; and (iii) characteristic AP imaging findings[46] (Figure 1). It is important to mention that, in the asymptomatic patient, elevated pancreatic enzymes are not sufficient to make the diagnosis of AP and therefore tests for these

enzymes should not be routinely ordered. Amylase and lipase serum concentrations may be elevated in intra-abdominal non-pancreatic inflammatory disease processes[47] and in up to 14% of asymptomatic IBD patients.[48] In IBD patients, particularly those with CD, AP may require some degree of clinical suspicion. In patients with risk factors for AP (gallstone disease, newly starting thiopurines), the onset of pain with typical features of AP should trigger suspicion of this complication. The hasty attribution of symptoms to active IBD, without pancreatic enzyme measurement and/or imaging, should be avoided as it may underestimate the diagnosis of AP. On the other way around, TIAP should be properly documented and diagnosed, to avoid unnecessary withdrawal of the drug.

3.4. Management

The management of AP in IBD patients should follow the same approach as in the general population, and involves fluid therapy, electrolyte replacement and symptom management (including analgesia)[46,49] (Figure 2). Most cases of AP in IBD tend to be mild and easy to manage. However, it may be clinically challenging to treat active IBD in a patient with AP. In the setting of moderate to severe AP, corticosteroid may increase the risk of necrosis and fluid collection infection. Triantafillidis et al.[50] reported the case of a young male with moderately severe acute idiopathic pancreatitis, in whom infliximab was started for severe recurrent CD. Clinical and biological remission was achieved and AP resolved without organ failure or development of local complications.

4. Chronic pancreatitis

Chronic pancreatitis is an inflammatory disease that progresses to fibrosis and destruction of pancreatic parenchyma, followed by exocrine and/or endocrine insufficiency.[9] The incidence of CP in the general population ranges from 5 to 12 per 100 000 and the risk seems to be increased in immune-mediated diseases, such as IBD.[3]

Chronic pancreatitis is associated with several risk factors, with alcohol and smoking being the major contributors. Other conditions associated with CP include autoimmune pancreatitis, hypercalcaemia, hyperlipidaemia, chronic renal failure, genetic mutations (*PRSS1*, *CFTR*, *SPINK1*), vascular disease, pancreas divisum, sphincter of Oddi disorders, tumour duct obstruction and post-traumatic duct scars.[9,51] In IBD patients most cases of CP are idiopathic.[52–57] Less commonly reported causes are PSC,[53] autoimmune pancreatitis [58] and primary biliary cirrhosis.[59] Little research exists on pancreatic changes in patients with PSC, especially in PSC-IBD patients. Said et al.[60] studied 103 PSC patients, 76% with concomitant IBD, and found that 24% of PSC patients had pancreatic ductal changes (side branch or main pancreatic duct (MPD) dilatation) diagnosed by magnetic resonance cholangiopancreatography. None of the patients had typical imaging features of AIP and only one patient had clinical and laboratory findings diagnostic of CP. Importantly, when the authors compared PSC patients with and without pancreatic duct changes, they found no differences in smoking, alcohol consumption >40 g/day, ever performed ERCP, history of acute pancreatitis and gallstone frequency. Moreover, there was no association between pancreatic duct abnormalities and immunoglobulin (Ig) G4 levels or the frequency of signs of CP on magnetic resonance imaging (MRI). Pancreatic duct changes were more frequent in patients with both extra- and intrahepatic PSC involvement (92%) compared with intrahepatic involvement alone (71%), and the mean duration of PSC was longer in patients with pancreatic duct changes (11 years) than in those without such changes (6 years). These findings suggest that pancreatic changes in PSC may represent a 'pancreatic manifestation' of PSC, which over time can evolve to CP-like pancreatic parenchymal abnormalities. On the other hand, other studies indicate that there may be no differences in pancreatic abnormalities detected on MRI between patients with PSC and other chronic liver diseases. However, no information is provided regarding alcohol habits, a common cause of chronic liver disease and a potential confounding factor while interpreting MPD changes.[61]

Some authors have proposed that CP may be an extraintestinal manifestation of IBD based on case series and case reports of CP in IBD patients without a defined aetiology, most of which were published before 2000.[52,54,57] Moreover, three small retrospective series have assessed CP in IBD patients (Table 2).[52–54] Most cases of CP were diagnosed in males (65%), at a young age (median 36 years) and more commonly in UC patients (76%). In 24% of cases the diagnosis of CP preceded the diagnosis of IBD while in the remaining patients CP was diagnosed simultaneously (12%) or after IBD (64%). The main diagnostic modality used was ERCP in the two studies published up to 1999.[52,53] In the most recent study, endoscopic ultrasound (EUS) findings were used to support the diagnosis of CP.[54] It should be noted, however, that some of these cases had imaging abnormalities consistent with the now well-defined entity of AIP.[52]

5. Autoimmune pancreatitis

Autoimmune pancreatitis is a rare but increasingly recognized chronic benign pancreatic disease thought to be immune-mediated and unrelated to alcohol.[62] It is subclassified into two separate entities. Type 1 AIP or lymphoplasmocytic sclerosing pancreatitis (LPSP), first reported in 1961 and designated of autoimmune pancreatitis in 1995, is now considered the pancreatic manifestation of IgG4-related disease. Type 2 AIP or idiopathic duct centric pancreatitis (IDCP)[63,64] was first recognized in Europe and North America in patients with CP and presumed pancreatic cancer who underwent pancreatic resection.[65]

The most recent criteria for AIP, the international consensus diagnostic criteria (ICDC), include five types of abnormalities: histology, imaging, serology (IgG4), other organ involvement and response to steroids.[63] The practical application of these criteria is relatively complex and referral to a pancreas specialist is preferable. Nevertheless, one should consider the diagnosis of AIP in patients with diffuse pancreatic enlargement and/or long/multiple MPD strictures and increased IgG4 levels. Importantly, when patients present with atypical features of AIP, such as focal pancreatic enlargement, pancreatic mass, MPD dilatation or distal atrophy, a thorough work-up for cancer is mandatory.[63] Also, AIP is very responsive to steroids and radiological improvement can be seen after only 2 weeks of prednisolone. Therefore, a course of steroids for IBD can potentially mask the radiological manifestations of AIP. It is noteworthy that histology is not mandatory for a definitive diagnosis of type 1 AIP, which can be made in the presence of typical imaging findings, other organ involvement and increased IgG4 (≥2 times the upper limit). On the contrary, definitive diagnosis of type 2 AIP implies compatible histological features.[66]

The prevalence of IBD in patients with AIP seems to be increased compared to the general population, with 6 to 27% of AIP patients having concomitant IBD, predominantly UC.[7,77–83] Additionally, type 2 AIP has a much higher IBD prevalence rate (17%) compared with type 1 (1%).[62] However, the only study assessing the prevalence of AIP in IBD patients found a 0.4% prevalence of AIP type 2 (n = 7) in an IBD cohort of 1751 patients.[4]

Three small series specifically evaluated AIP features in IBD patients.[4,58,73] Most patients had UC (14 out of 17) and type 2 AIP. In two studies there was a male predominance[4,58] and in the study by Park et al.[73] most patients were women. In the general population there is a male predominance in type 1 AIP[62,69–71] and no gender predilection in type 2 AIP.[62,69–71] In patients with IBD, AIP presents at a younger age (26–54 years) [4,58,73] compared with the general population (seventh decade in type 1 and fourth or fifth decade in type 2).[62,69–71] Obstructive jaundice and abdominal pain are the most common presentations. One patient presented with clinical features of CP (steatorrhoea and new-onset diabetes), denoting previous asymptomatic pancreatic inflammation.[58] On the other hand, in the series of Ueki et al.,[4] in which all (n = 7) patients had type 2 AIP, AP was the most common presentation. Hence, the presentation of AIP in IBD patients does not seem to differ from that in patients without IBD[67,69–72] and atypical complaints like cachexia, anorexia and pain requiring narcotics should raise the suspicion of cancer.[63,65] Autoimmune pancreatitis was diagnosed simultaneously (n = 7) or after (n = 10) IBD. On the other hand, the impact of AIP in the natural history of IBD is not clear. In two series, UC seemed to be more severe, with 4 out of 10 patients requiring colectomy.[58,73] On the contrary, Ueki et al.[4] found no differences in disease extent or activity in UC patients with or without AIP.

6. Silent pancreatic abnormalities

Histological changes, pancreatic duct abnormalities and exocrine insufficiency have been described in IBD patients without clinical symptoms[74–78] (Figure 3). Autopsy studies showed that 38% of CD patients had pancreatic fibrosis[74] and 53% of UC patients presented chronic interstitial pancreatitis.[75] Pancreatic duct abnormalities identified by magnetic resonance cholangiopancreatography were reported in 16.4% of asymptomatic UC patients without alcohol intake or previous episodes of AP.[76] Exocrine pancreatic insufficiency was observed in 4–18% of IBD patients independently of imaging abnormalities or elevation of serum pancreatic enzymes.[77,78] Of note, two-thirds of patients had normal faecal elastase levels after 4–6 months,[78] suggesting that, at least in some patients, this insufficiency is transient. Elevation of serum pancreatic enzymes is present in 11% (> 3 times the upper limit of the normal for amylase) to 14% of asymptomatic IBD patients (> 2 times the upper limit of the normal for amylase and lipase),[48,79,80] and not related to other causes, such as salivary gland disease, macroamylasaemia, renal impairment and familiar pancreatic hyperenzymaemia. The diagnostic approach of an IBD patient with persistent asymptomatic amylase elevation is similar to that of the general population and includes a detailed history and physical examination and a thorough screening for pancreatic and non-pancreatic conditions (Figure 4). Abdominal imaging should be reserved for patients with positive findings in clinical evaluation, particularly in older patients to rule out a malignant neoplasm that secretes amylase.[81,82]

In most studies, pancreatic autoantibodies (PABs) occur in up to 39% of CD patients compared with 4–23% of UC patients and 3% of healthy controls.[83] These autoantibodies are directed against exocrine pancreas and thus far two antigens have been identified: glycoprotein 2 (GP2) and CUB/zona pellucida-like domain-containing protein (CUZD1).[84] Although the target of PABs is the pancreas, Barthet et al.[85] failed to show an association between PABs and AP, exocrine insufficiency or pancreatic duct changes. Seibold and colleagues[86] found that PABs were more frequent in IBD patients with exocrine insufficiency (27 versus 8%). A relationship between IBD phenotype and PABs has also been sought. Some studies showed an association with more severe disease (penetrating behaviour, perianal disease), extraintestinal manifestations and small bowel surgery,[87,88] while others failed to demonstrate a negative clinical impact.[89–91]

The pathogenic and clinical roles of PABs in both IBD and its pancreatic manifestations needs further research, and therefore its current use for diagnostic or prognostic purposes is not recommended.

7. Conclusions

Acute and chronic pancreatitis may complicate the course of IBD. The most common causes of AP are thiopurines and gallstones. The course of thiopurine-induced AP is usually uncomplicated and self-limited. New genetic markers for thiopurine-induced pancreatitis are being identified and in the future may prove to be a useful tool in selecting patients for this therapy. Most cases of CP are idiopathic and some authors have suggested that this condition may be an extraintestinal manifestation of IBD. However, the evidence is scarce and restricted to case reports and case series. In addition, exocrine dysfunction and pancreatic duct abnormalities have been identified in up to 18% of asymptomatic IBD patients. Although exocrine pancreatic insufficiency seems to be the most common pancreatic manifestation in IBD, its clinical significance remains undefined. Autoimmune pancreatitis is a relatively recently recognized entity that should be considered in the differential diagnosis of pancreatitis, especially among IBD patients, since up to 27% of AIP patients also have IBD, mostly UC. The wide spectrum of pancreatic manifestations and severity in patients with IBD may represent a challenge to the clinician, particularly in the setting of asymptomatic abnormalities and CP, idiopathic or recurrent pancreatitis. In these situations a collaborative approach with a pancreas specialist may be the most productive way to decide additional diagnostic workup, illuminate the aetiology and define the follow-up of these patients.

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Conflict of Interest

None of the authors has any conflicts of interest to declare related to the publication of this manuscript.

Author Contributions

LRR designed the review, performed the literature search and drafted the manuscript. JT designed the review and critically reviewed the manuscript for important intellectual content. DBS, CD and JFC revised and critically reviewed the manuscript for important intellectual content. All authors approved the submitted version.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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