

Differential diagnosis in inflammatory bowel disease colitis: State of the art and future perspectives

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Received: July 16, 2014

Peer-review started: July 16, 2014

First decision: August 15, 2014

Revised: October 3, 2014

Accepted: November 7, 2014

Article in press: November 11, 2014

Published online: January 7, 2015

Abstract

Distinction between Crohn's disease of the colon-rectum and ulcerative colitis or inflammatory bowel disease (IBD) type unclassified can be of pivotal importance for a tailored clinical management, as each entity often involves specific therapeutic strategies and prognosis. Nonetheless, no gold standard is available and the uncertainty of diagnosis may frequently lead to misclassification or repeated examinations. Hence, we have performed a literature search to address the problem of differential diagnosis in IBD colitis, revised current and emerging diagnostic tools and refined disease classification strategies. Nowadays, the differential diagnosis is an untangled issue, and the proper diagnosis cannot be reached in up to 10% of patients presenting with IBD colitis. This topic is receiving emerging attention, as medical therapies, surgical approaches and leading prognostic outcomes require more and more disease-specific strategies in IBD patients. The optimization of standard diagnostic approaches based on clinical features, biomarkers, radiology, endoscopy and histopathology appears to provide only marginal benefits. Conversely, emerging diagnostic techniques in the field of gastrointestinal endoscopy, molecular pathology, genetics, epigenetics, metabolomics and proteomics have already shown promising results. Novel advanced endoscopic imaging techniques and biomarkers can shed new light for the differential diagnosis of IBD, better reflecting diverse disease behaviors based on specific pathogenic pathways.

Key words: Crohn's disease; Ulcerative colitis; Inflammatory bowel disease unclassified; Advanced endoscopic imaging; Biomarkers; Histopathology

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Core tip: Distinction between Crohn's disease and ulcerative colitis or inflammatory bowel disease (IBD) type unclassified can be of pivotal importance for a tailored clinical management, as each entity often involves specific therapeutic strategies and prognosis. Nonetheless, the differential diagnosis is an untangled issue, and the proper diagnosis cannot be reached in up to 10% of patients presenting with colitis. Hence, we address the problem of differential diagnosis in IBD colitis, thereby revising current and emerging diagnostic tools to refine disease classification.

Tontini GE, Vecchi M, Pastorelli L, Neurath MF, Neumann H. Differential diagnosis in inflammatory bowel disease colitis: State of the art and future perspectives. *World J Gastroenterol* 2015; 21(1): 21-46 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i1/21.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i1.21>

INTRODUCTION

Inflammatory bowel diseases (IBDs) are chronic inflammatory disorders of the gastrointestinal system affecting more than 1 million people in the United States and several million worldwide^[1-4]. Large-bowel involvement is common, and this may ensue from either ulcerative colitis (UC) or IBD type unclassified (IBDU), as well as from the subset of non-complicated Crohn's disease (CD) with an isolated colonic localization^[5,6]. Conversely, the disease spread in other gastrointestinal segments definitively leads to the diagnosis of CD. Differential diagnosis in patients presenting with IBD colitis is nowadays of pivotal importance for a tailored clinical management, as each entity involves specific therapeutic and coping strategies^[7-10]. Nevertheless, non-classical forms of either UC or Crohn's colitis still represent a remarkable clinical matter, as no single diagnostic gold standard is available yet^[6-11]. Therefore, 5% to 15% of cases do not meet strict criteria for either UC or CD^[12-15] and in up to 14% of patients classified as UC and CD the diagnosis changes over time^[16-21].

In the last years, basic science data have outlined a more panoramic knowledge of these disorders, suggesting novel ways to achieve the diagnosis. Recent innovations in the field of bio-medical technology have led to new serologic biomarkers and endoscopic techniques focused on polishing our traditional approach to identify and characterize patients with IBD.

This review aims to update the problem of the differential diagnosis in patients with IBD colitis, providing an overview of current and emerging diagnostic tools that might improve clinical practice within the near future.

SIZE OF THE PROBLEM

The prevalence of IBD varies according to geographic

region, showing a sharp gradient between Western industrialized and developing countries, as well as when comparing urban vs rural areas^[1,2]. Studies exploring temporal trends have shown that the incidence of IBD continues to increase in many areas of the world, reporting higher growth rates in those regions that have become more industrialized^[1-4,22]. Accordingly, IBDs are advisedly considered as emerging global diseases^[23].

In prevalence studies, UC estimates ranged greatly from 4.9 to 505 per 100000 in Europe, 4.9 to 168.3 per 100000 in Asia and the Middle East, and 37.5 to 248.6 per 100000 in North America. CD estimates ranged from 0.6 to 322 per 100000 in Europe, 0.88 to 67.9 per 100000 in Asia and the Middle East, and 16.7 to 318.5 per 100000 in North America^[1-4,22,23]. The differential diagnosis is relatively easy when CD involves different gastrointestinal tract areas or shows extraluminal complications such as strictures, abscesses or fistula. However, one-third of CD patients have a pure colonic location ("L 2") and at least two-thirds a non-stricturing, non-penetrating behaviour at the time of diagnosis, thereby sharing many behaviors with UC^[15,24-30]. Disease localization appears to be quite stable a trait of CD over time, showing spreading of the disease into the small bowel in only a few cases^[24,25]. By contrast, in up to one-third of cases disease behaviour is expected to change during the next 20 years, consistent with the development of strictures and/or penetrating lesions^[24-26,31-33]. Within ulcerative and Crohn's colitis with long-term follow up, disease reclassification is close to 5%-14% and mainly driven by an increased proportion of CD in adults^[16-21].

IBD restricted to the colon that cannot be allocated to the CD or UC category is best termed "inflammatory bowel disease unclassified", while the term "indeterminate colitis" is now confined to operative specimens, as originally described by Price in 1978^[5,34-36]. This condition has been associated with worse prognosis than UC because of the higher frequency of relapses^[37], the increased risk of colon cancer^[38] and less favorable outcomes after ileal pouch-anal anastomosis, especially among those who were positive or not sorted by serological status^[39-42]. To date, very few data are available on the prevalence of IBDU. In adults, studies from European countries show that the prevalence varies between 3 and 7 per 100000 inhabitants^[43]. Diagnosis of IBDU accounts for 5%-15% of new cases of IBD^[12-15,43] with remarkable differences between pediatric and adult cohorts (5%-30% and 5%-12%, respectively)^[11,12,44-46]. A recent meta-analysis of 32 studies investigating both pediatric ($n = 14$) and adult ($n = 18$) patients showed that 13% of children and 6% of adults with IBD are classified as IBDU; this difference was statistically relevant ($P < 0.0001$), thereby confirming that IBDU is significantly associated with earlier onset of IBD^[44]. It is not clear whether the high frequency of IBDU observed in children represents an IBD phenotype associated with childhood disease onset or reflects the difficulties in establishing a defined diagnosis^[26,44,45]. Actually, for most patients, IBDU represents a provisional diagnosis, as it

has been estimated that 80% of them will be reclassified to either CD or UC within 8 years^[11,12,42,46]. However, in a subset of cases, IBDU remains the most accurate diagnosis as a true separate clinical entity^[36,41,43-45,47].

Consistent with the above-mentioned epidemiological data, we can roughly estimate that the differential diagnosis within IBD colitis involves over 1.5 million IBD subjects in Europe (1.4 million UC plus 200000 CD-L2-B1), and almost one million in North America (830000 UC plus 140000 CD-L2-B1). In approximately 10% of them, the assessment of a distinct diagnosis is an open issue variably leading to either the diagnosis of IBDU or further reclassification of the disease, as well as to unspecific and incorrect therapeutic management.

Accordingly, the next section focuses on the potential clinical relevance of the differential diagnosis, in an attempt to show “why” patients presenting with a non-distinct entity of IBD colitis may represent an untangled matter capable of remarkable impact on both the physician’s approach and the patient’s coping strategy.

CLINICAL RELEVANCE: WHEN THE DIFFERENTIAL DIAGNOSIS AFFECTS CLINICAL MANAGEMENT

During the last fifteen years, the development of biological therapies and a widespread use of immunomodulators have radically changed treatment strategy in IBD. Consistently, prognostic indexes focusing on the assessment of mucosal inflammation have become an important treatment goal predicting long-term outcomes in terms of disease progression, complications and steroid sparing^[48-54]. In this context, the issue of differential diagnosis has received renewed attention, because both medical and surgical treatments imply more and more disease-specific strategies^[7-10,34,54].

Medical therapies

Since the causes of IBD are complex and only partially understood, the current medical approaches for the treatment are based on drugs exerting a direct (*e.g.*, corticosteroids and immunomodulators) or indirect (*e.g.*, antibiotics) effect on the inflammatory cascade of either disease^[55-57]. Accordingly, most drugs are approved for both UC and CD. However, medical treatments such as certolizumab pegol and natalizumab have been approved for CD only (FDA exclusively), while golimumab and calcineurin inhibitors (cyclosporine and tacrolimus) for UC only. Furthermore, disease-specific advantages and response rates have been shown using several medical treatments. For example, aminosalicylates are recommended as a first-line option for treating and maintaining remission in UC but, besides their possible chemopreventive properties, play a much more marginal role in the management of CD^[7,8,58,59]. In contrast, methotrexate has shown a higher rate of response in CD than in UC^[60-64]. As a matter of fact, the results of two

separate phase 3, randomized, double-blind, placebo-controlled studies of the new monoclonal antibody vedolizumab, targeting the $\alpha 4\beta 7$ integrin, have shown a substantially diverse efficacy in patients with UC *vs* CD^[65].

In recent years, growing efforts have been made to characterize and dissect the pathogenic mechanisms within the inflammatory cascade of either diseases in order to identify new targets for disease-specific therapies^[51,66-71]. Besides the possible effect of a better disease control, the use of such disease-specific and targeted therapies should reduce the rate of side effects related to the use of unspecific immunomodulating treatments (*i.e.*, malignancies, infections and life-threatening allergic reactions), therewith supporting cost-saving policies^[57,72-77]. Therefore, the importance of the distinction between CD and UC will remarkably grow, as new therapies with disease-specific targets will be available in clinical practice.

Finally, yet importantly, a firm diagnostic definition is usually mandatory to fit the inclusion criteria of clinical therapeutic trials, which often represent a possible alternative to surgery in patients with refractory IBD colitis.

Surgery treatments

The differential diagnosis between UC and CD is particularly relevant for surgical therapies, especially in the case of procto-colectomy. Restorative procto-colectomy with ileal-pouch-anal-anastomosis (IPAA) is the procedure of choice in fulminant or chronic, treatment-refractory UC and UC-associated colonic neoplasia^[7,78]. The vast majority of UC patients undergoing IPAA do well^[79-81] and patients with a long history of severe disease recurrences may even report an ameliorated health-related quality of life^[82-88]. Previous conflicting studies have reported comparable^[79,89] rather than worse^[90-93] long-term outcome in IBDU and indeterminate colitis. On the contrary, up to 90% of CD patients with IPAA develop complications including perianal abscess/fistula, pouchitis or anal stricture and approximately 50% require pouch revision or diversion^[79-81,88,94-97]. Accordingly, patients with UC and IBDU can benefit from the option of a restorative procto-colectomy with IPAA, thereby mitigating the impact of such a radical approach on coping strategy and health-related quality of life. By contrast, a restorative surgery is not recommended in all CD patients and total procto-colectomy frequently results in a permanent ileostomy. Nevertheless, the postsurgical reclassification of UC into CD is not rare, occurring in 3.5%-12% of prospective and retrospective series of procto-colectomized patients, even in referral IBD centres^[19,79,81,90, 98-101].

Secondly, the differential diagnosis is crucial for the treatment of non-fistulizing perianal diseases such as hemorrhoids, skin tags, anal fissures and ulcers. Data focused on the long-term outcomes of different treatment strategies in non-fistulizing perianal disorders

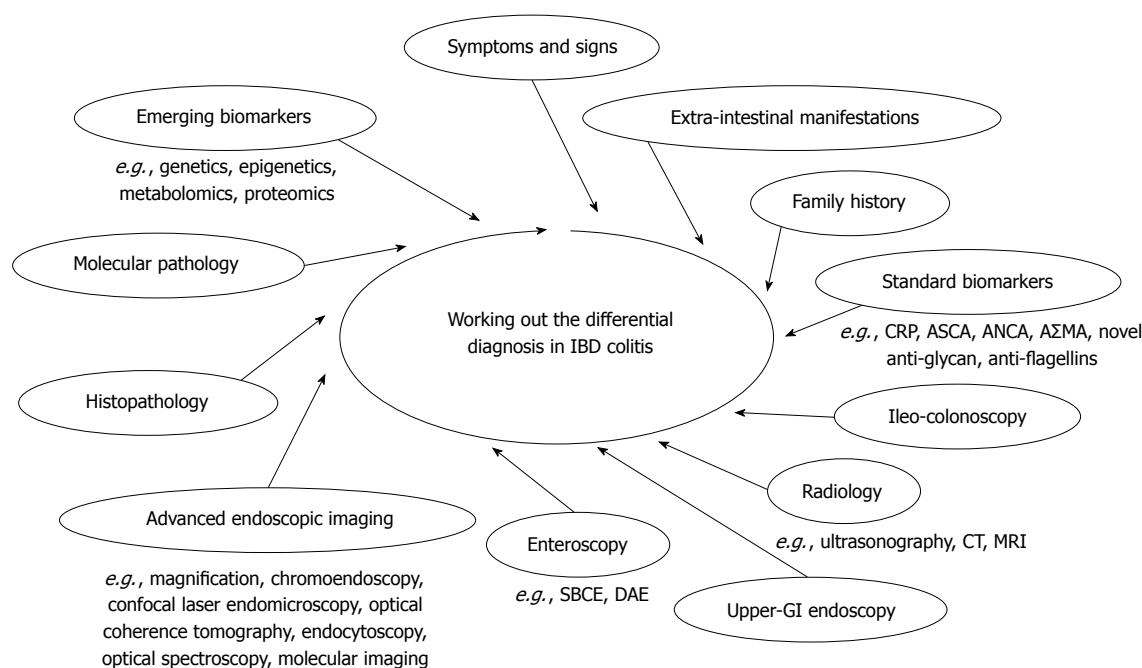


Figure 1 Differential diagnosis in inflammatory bowel disease colitis.

are still lacking in IBD, and particularly in UC and IBDU patients. A study published in 1993 designed to define the outcome of surgery for symptomatic hemorrhoids and anal fissures in patients with known CD reported a substantial incidence of complications (2/17 and 3/22, respectively)^[102]. Another study by Jeffery *et al*^[103] showed that both surgical and conservative approaches for hemorrhoids are associated with low complication rates in UC, whereas in patients with CD the complication rate is high. Consistently, when non-fistulizing perianal diseases occur in CD patients, a conservative approach is recommended and efforts should be directed to achieve healing by means of both medical and less invasive surgical therapies^[104-107].

Mucosal healing

Mucosal healing is nowadays a pivotal treatment goal beyond mere symptom control. Endoscopic remission is recognized as a primary end-point in clinical trials and an important prognostic factor^[6,48-54]. For UC patients, mucosal healing represents a leading clinical outcome to assess response to therapy and to drive all decision-making processes before dose escalation, drug switching and withdrawal; on the contrary, the clinical relevance of mucosal healing in CD should be weighed against signs of transmural inflammation and extraluminal complications^[48,51,54,108]. In addition, there are substantial differences between CD and UC in the effect of different drugs on mucosal healing^[54,109-111]. Based on all above considerations, the differential diagnosis in IBD colitis has acquired growing interest, thereby endorsing the emerging attention for all diagnostic steps capable of reducing the number of unclassified diseases.

DIFFERENTIAL DIAGNOSIS: CURRENT APPROACH

IBD colitis may present with a variety of unspecific features turning the differential diagnosis among UC, CD and IBDU into one of the greatest diagnostic challenges in gastroenterology. As stated above, no single gold standard is available for the diagnosis and the distinction of IBD. The diagnosis rests on a multidisciplinary work-up, based on clinical evaluation integrated with a combination of endoscopic, histological, radiological, and/or biochemical investigations (Figure 1)^[6-11].

Symptoms and signs

IBD colitis-associated symptoms depend on several factors, including extent and severity of disease, as well as localization of the colonic involvement. Furthermore, superinfection with enteric pathogens and/or ongoing therapies may also alter the clinical presentation.

The main symptom of UC is visible blood in the stools, which is reported in more than 95% of active disease^[112]. Rectal urgency, tenesmus and, occasionally, severe constipation represent the classical complaints of rectal involvement, while chronic diarrhea with nocturnal defecation and crampy abdominal pain are typical of left-sided or extensive UC^[112].

Patients affected by Crohn's colitis often present a UC-like clinical phenotype. Blood or muco-purulent exudates with the stool can be seen in up to 40% to 50% of patients with Crohn's colitis, but less frequently than in UC subjects^[113]. By contrast, chronic diarrhea is the most common presenting symptom in classical ileo-colonic CD, followed by abdominal pain and weight loss^[34,114].

Consistent with the above clinical features, a nested, case-controlled study by Melmed *et al.*^[21] showed that UC patients with either non-bloody diarrhea or weight loss as onset symptoms have an increased likelihood of subsequent change in diagnosis to CD (100%) compared to those with none of these risk factors (16%, $P < 0.001$), and might thus warrant further diagnostic work-up.

Systemic symptoms such as fever, tachycardia and weight loss are usually restricted to severe and extensive disease in UC, but occur more frequently in CD, particularly in the case of severe relapse or transmural complication^[34,112].

IBD colitis with persistent perianal and rectal complaints should raise the suspect of a perianal disease, which could occur in up to 10% of new onset and much more frequently during the clinical course of CD^[34,105,106,115]. However, non-fistulizing, non-stricturing perianal disorders such as hemorrhoids, skin tags or anal fissures are also common in UC and IBDU, because of severe and prolonged diarrhea or as sporadic, unrelated disorders^[112]. Bonheur *et al.*^[116] have recently characterized the anal skin tags of 169 consecutive IBD patients (62% CD) looking for distinctive morphological features of UC and CD. They found that 75% of anal skin tags “type 1”, previously called “elephant ears” and referred to as IBD, had CD ($P = 0.005$). Interestingly, this anal finding was also associated with the colonic involvement of CD ($P = 0.067$). By contrast, anal skin tags “type 2” showed no preference for any IBD type. This finding typically results from healed anal fissures, ulcers or hemorrhoids, and equally occurs in IBD and in non-IBD subjects^[116].

Extra-intestinal manifestations

Patients with IBD may present a number of extra-intestinal manifestations (EIMs) involving most organ systems^[117-121]. The probability of having EIMs increases with the duration of the intestinal disease and is generally higher in CD (24%-40%), especially Crohn's colitis (47%), than in UC (26%-31%)^[121,122]. Notably, many EIMs show disease-specific prevalence rates, thereby providing some aid in the differential diagnosis^[30].

The most common EIM is represented by enteropathic arthritis. These peripheral and axial arthropathies have a lifetime prevalence of 11% in UC and 20% in CD, showing a peculiar tropism for the colonic location^[28,120-122]. Peripheral arthropathies typically arise during intestinal relapses, sometimes accompanied by other EIMs such as erythema nodosum, which is similarly characterized by a higher prevalence in CD (8%-15% *vs* 3%-10% in UC), especially if the colon is involved^[28,122-125].

Conversely, primary sclerosing cholangitis (PSC) occurs more frequently in UC (2%-4%) than in CD (1%-2%)^[28,120,122,124]. This rare precancerous condition is more common in men than in women (2:1) and is unusual in non-IBD subjects (30% of cases). Most PSC patients have an associated IBD, particularly UC (77%). Notably, those with CD have colitis in 94% of cases^[126].

Previous studies have also shown a slight predominance

of uveitis and episcleritis in UC and Crohn's colitis; these ocular disorders affect 3%-6% of subjects with IBD, mainly women (2:1), usually during the course of an intestinal relapse^[120,122,125,127].

Other disorders positively correlated with the diagnosis of IBD such as metabolic osteopathy (22%-67%)^[128-131], aphthous stomatitis (4%-30%)^[28,132], asthma (7%-8%)^[117], venous thromboembolism (1%-7%)^[133-136], neurological disorders (3%)^[137], pyoderma gangrenosum (1%-2%)^[28,121,122,124], psoriasis (1%-2%)^[117,138] and pulmonary disorders ($< 0.5\%-1\%$)^[139] show variable or no disease-specific prevalence and cannot provide any reliable aid in the attempt to refine the differential diagnosis of IBD colitis.

Familial history

Several studies have firmly established that a family history positive for IBD is the strongest risk factor for the onset of these disorders, showing that disease pattern of relatives with a previous diagnosis of IBD may provide valuable information to predict both phenotype and course of new cases^[140-145]. The lifetime risk of developing IBD has been estimated to be 5% for first-degree relatives of a CD subject and 1.6% for first-degree relatives with a UC proband, suggesting that genetic/environmental influences are stronger in CD than in UC^[144].

The clinical pattern within familial cases of IBD presents high rates of concordance for both disease diagnosis (75%-83%) and localization (64%-33%), particularly in families with CD^[144-146]. Consistently, a longitudinal study based on UC patients after IPAA has shown that a family history positive for CD has a significant influence on the development of CD after surgery, thereby recommending a deeper initial diagnostic work-up^[101]. Thus, a familial history positive for UC, and particularly for CD, might serve as a clue for the final diagnosis in patients presenting with IBD colitis and no specific features.

Biomarkers

The main roles of biomarkers in IBD include support in making the diagnosis, prediction of further development of CD and UC in IBDU patients, determination of disease activity, risk stratification and prediction of response to therapy^[52,147,148].

C-reactive protein (CRP) is a serum marker of acute phase (half-life about 19 h) produced by the liver in response to a variety of inflammatory conditions^[148]. During active IBD, levels can range from 5-200 mg/L depending on disease severity, extent, and several variables affecting an individual's capacity to produce CRP such as nutritional status, body mass index, liver function and gene polymorphisms^[148,149]. CRP is used to distinguish organic from functional disorders, active from quiescent IBD, and response to therapy, but is poorly capable of differentiating CD from UC^[110,150,151]. In fact, elevations in CRP are much more common (approximately 80% *vs* 50%) and sensitive in active CD than in UC, probably because of the deeper bowel inflammation and higher

serum IL-6 levels^[147,152-154]. Despite this relatively low sensitivity in UC, previous studies have shown that CRP level corresponds with both disease extent and severity, thereby showing that most UC patient with increased CRP have a moderate to severe flare exceeding the left flexure^[154-156]. Rodgers *et al.*^[156] have prospectively evaluated the correlation between CRP and clinical/endoscopic activity in patients with IBD. CRP was elevated in 14%, 42%, 64%, and 83% of UC and in 54%, 70%, 75%, and 100% of CD subjects with quiescent, mild, moderate, and severe disease, respectively. A linear correlation of log(CRP) with clinical score was found for all UC extents except for proctitis, thereby confirming that CRP can broadly correlate with clinical activity and disease extent in UC^[156].

Fecal biomarkers consist of proteins, leukocyte products, and leukocytes leaking from a permeable mucosa, thereby reflecting mucosal acute cellular infiltration^[148]. Indium-labeled leukocytes, calprotectin, lactoferrin, PMN-elastase, neopterin and S100A12 proteins have been implemented in IBD to exclude functional disorders, assess the presence, the extent and the degree of gut mucosal inflammation, monitor the response to therapy and drive the timing of endoscopic controls^[147,148,157-160]. Previous studies have shown that both calprotectin and lactoferrin perform better than CRP in predicting active disease at endoscopy, showing 70% to 100% sensitivity and 44% to 100% specificity depending on the cut-off value^[147,157,158]. Fecal biomarker sensitivity is higher in colonic disease compared to ileal involvement^[161,162] and is more influenced by endoscopic severity than by disease extent^[163]. Recent data suggest that fecal calprotectin correlates more closely with endoscopic and symptom scores in UC than in CD, even excluding patients with pure ileal CD^[157,158]. However, none of the available fecal biomarkers can be considered useful to refine the differential diagnosis in subjects with IBD colitis.

Various immunologic biomarkers have been used individually and as panels in attempts to improve the diagnosis of IBD, to identify homogeneous phenotypes, and to distinguish CD from UC^[39,147]. Current serologic tests mainly include antibodies recognizing self-antigens or cross-reacting with several bacterial and fungal antigens. The existence of these antibodies in IBD patients often precedes the disease onset^[164,165] and highlights the abnormal immune response to commensal enteric microorganisms, possibly reflecting diverse genetic predispositions and pathogenic mechanisms^[40,166-170].

Perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) and anti-*Saccharomyces cerevisiae* antibodies (ASCA) were the first available and utilized in the setting of IBD. It is noteworthy that the performance of conventional ASCA IgG/IgA and the more recently studied gASCA IgG/IgA (antibodies against covalently immobilized mannan) tests^[171] are comparable for CD diagnosis^[39,170,172]. Therefore, in this review the term "ASCA" will refer to the conventional test, as well

as to gASCA. Increased titers of ASCA identify CD patients with high specificity (85%-100%) and moderate sensitivity (approximately 39%-76%), characterizing definite disease phenotypes, such as those with ileal involvement (L1, L3), young age at onset, stricturing or penetrating behaviour and multiple bowel surgery^[39,173-175]. In contrast, pANCA are more common in patients with UC (20%-85%) than in CD (2%-28%), but not nearly as sporadic in Crohn's pancolitis^[39,173,176] as in other forms of colitis, such as eosinophilic and collagenous colitis^[177,178]. According to a meta-analysis of 60 studies based on 7860 IBD subjects and 3748 controls published in 2006, the ASCA+/pANCA- tests distinguished adults affected by CD from those diagnosed as UC with 55% sensitivity and 93% specificity, while the combination pANCA+/ASCA- performed particularly well only in pediatric UC patients (70% sensitivity and 93% specificity)^[179]. However, when the evaluation has been restricted to patients with colonic disease, ASCA sensitivity for CD and pANCA specificity for UC decrease, resulting in a pANCA/ASCA test that discriminates less well between CD and UC^[173,175,179,180]. This figure, together with a suboptimal sensitivity, hampers the contribution of such serological markers in clinical practice^[39,41,181].

Addition of other serological markers to ASCA and pANCA, such as antibody to *Escherichia coli* outer membrane porin (anti-OmpC), bacterial flagellin (anti-CBir1) and *Pseudomonas fluorescens* (anti-I2), has been shown to provide only a marginal benefit^[182-184]. As a matter of fact, the above-mentioned nested, case-control study by Melmed *et al.*^[21] clearly demonstrated that weight loss and non-bloody diarrhea at diagnosis but not ASCA, pANCA, anti-OmpC, anti-CBir1 and anti-I2 were predictive of a change in diagnosis from UC to CD. Accordingly, new serologic tests have been recently evaluated in the attempt to better assess the differential diagnosis in IBD^[39,176]. Novel antiglycan antibodies such as anti-chitobioside carbohydrate antibodies, anti-laminaribioside carbohydrate antibodies, anti-mannobioside carbohydrate antibodies, anti-chitin IgA (Anti-C) and anti-laminarin IgA (Anti-L) have been found positive in at least one third of CD patients negative for ASCA, but their overall sensitivity in CD was low (respectively, 9%-27%, 20%-26%, 12%-27%, 10%-25% and 17%-26%), especially among those with colonic disease^[170,171,176,185-187]. Similarly, anti-synthetic mannoside antibodies (ASMA) showed lower sensitivity in CD compared to ASCA (38% *vs* 55%). Nonetheless, ASMA were seen in 24% of CD patients who were negative for ASCA and were closely associated with colonic involvement (OR = 1.61, 95%CI: 1.03-2.51, *P* = 0.03)^[175]. In a recent study by Schoepfer *et al.*^[188], serum reactivity towards two new anti-flagellins, anti-A4-Fla2 and anti-Fla-X, was found in 59% and 57% of CD patients as compared to only 6% of UC patients, thereby suggesting a possible role in distinguishing CD from UC.

The need for such serologic tests would be maximal

in patients with IBDU and indeterminate colitis. One European, multicenter, follow-up study found that nearly half (48.5%) of the patients with IBD type unclassified had negative ASCA and pANCA assays and that most of them continued to have clinical characteristics precluding a final diagnosis of CD or UC over a mean disease duration of 10.7 years^[41]. Positive results from ASCA or pANCA were predictive of the later development of CD and UC in 44% of patients after a mean follow-up period of 6 years. Among 26 IBDU patients with ASCA+/pANCA- result at baseline, 31% were later diagnosed as CD and 8% as UC, while ASCA-/pANCA+ corresponded to the diagnosis of CD and UC in 20% and 35% of cases out of 20 positive patients at baseline. Comparable results were also found in other studies^[173,189]. Addition of tests for I2 and anti-OmpC beyond ASCA and pANCA does not appreciably increase the ability to categorize the type of IBD within unclassified colitis, with only a marginal increase in the predictive capacity and a substantial decrease in the specificity^[190]. In an historical cohort of 20 patients with a well-established diagnosis of IBD type unclassified, AEMA were found to predict development of CD with higher sensitivity (45% *vs* 27%) and specificity (100% *vs* 71%) than ASCA, thereby confirming their peculiar linkage with CD “L2” location^[175].

Among IBDU and UC patients undergoing proctocolectomy with restorative IPAA, ASCA, anti-L, anti-OmpC and anti-CBir1 positivity before surgery was associated with an increased risk of CD of the pouch and post-operative fistula^[39,40,101]. Conversely, high rates of chronic pouchitis have been often reported in IBDU and UC with positive serologic profile (ASCA, high pANCA titer, anti-OmpC/anti-I2), but in this case, serological positivity could reflect a more aggressive phenotype in lieu of a different diagnosis^[39,190-192]. To the best of our knowledge, solid pieces of evidence on novel antiglycan antibodies and new anti-flagellin performance in IBDU/IC subjects are still lacking.

In summary, serological tests provide additional clues in differentiating CD from UC; although there is substantial heterogeneity of antibody reactivity in both diseases, this often represents a double-edged sword. A positive predictive value $\geq 85\%$ has been suggested to be clinically relevant to differentiate between CD and UC^[193]. However, the above-mentioned data show that this criterion is not always achieved using the available serologic markers and that the negative predictive value is lower. The use of large serologic panels including ASCA, pANCA and the above-mentioned novel serologic tests (*e.g.*, AEMA, anti-A4-Fla2 or anti-Fla-X) might enhance testing accuracy, especially among patients with UC-like phenotype, for whom the diagnostic question is most relevant and either sensitivity or specificity based on ASCA/pANCA test is lower. At the end of the day, beyond histopathological evaluation based on large surgical colorectal specimens, the serological studies are probably the most useful tool to determine the diagnosis

of UC or CD from those with IBDU and indeterminate colitis, as well as to predict surgical outcome after IPAA.

Cross-sectional imaging

Cross-sectional imaging can detect and stage inflammatory, obstructive and fistulizing CD and is fundamental at first diagnosis to stage disease and to monitor follow-up^[194]. Several complementary tools such as ultrasonography, computed tomography, magnetic resonance imaging and barium contrast radiology are helpful to detect small-bowel inflammation and lesions indicating the diagnosis of CD^[195]. Furthermore, cross-sectional imaging generally precedes endoscopic examination in the small bowel^[196]. The decision on which radiological technique should be performed depends on several factors such as patient features, nature and location of the small-bowel lesion, as well as local availability and expertise of the examiners^[194]. Apart from detection of pathognomonic lesion of the small bowel, cross-sectional imaging techniques have the potential to assess the thickness of the colonic wall and its different layers to allow differentiation of CD from UC. Trans-abdominal ultrasonography is able to image inflamed and non-inflamed colonic wall with high accuracy using a total wall thickness threshold > 3 mm^[197]. In addition, emerging evidence suggests that magnetic resonance colonography has a high accuracy for diagnosis of disease activity, location, and severity in IBD, as well as for penetrating and stricturing lesions, characteristic of CD^[198,199]. However, no published studies based on trans-abdominal ultrasonography or magnetic resonance imaging have shown different wall layers capable of making the diagnosis between CD and UC. Very recently, a prospective endoscopic-ultrasonography study was able to distinguish between active UC and active CD using a forward-viewing radial echoendoscope in the sigmoid colon, hereby assessing the amount of thickening of each single wall layer in combination with absence/presence of paracolon lymph nodes^[200]. Even if this study could not differentiate IBD in remission from healthy controls, endoscopic-ultrasonography appears as a promising and safe technique, ready for a wider distribution in IBD clinical practice.

Ileo-colonoscopy

It has been known for a long time that ileo-colonoscopy is the exam of choice to achieve the diagnosis in patients with suspected IBD^[6,11,34,45,112,201,202]. Typical forms of CD and UC have several endoscopic disease-specific features, which orient towards the proper diagnosis with high confidence in at least three quarters of cases^[6,11,34,45,112]. Inspection of the terminal ileum is sufficient to confirm the diagnosis of CD in most cases. In addition, Crohn's colitis shows a discontinuous pattern of inflammation, anal lesions and cobblestoning. Uninvolved areas frequently separate diseased segments and transition is usually abrupt (“skip lesions”). Deep linear ulcers, “absolute” rectal sparing and strictures are also typical, but not specific for CD^[6,11,34,45]. By contrast, classical UC has a diffuse and continuous

inflammation extending proximally from the rectum sometimes up to the ileo-cecal valve; UC endoscopic findings include granularity (sandpaper appearance to the mucosa), friability (bleeding of the mucosa to light touch), erosions and small superficial ulcers overlapped on a background of diffuse inflammation^[6,45,112]. Based on these features, the accuracy of ileo-colonoscopy was found to be very high in expert hands (89%), the rate of unclassified disease low (7%) and the misdiagnosis very rare (4%) and mainly related to severe inflammatory activity (9%)^[203]. Pera *et al.*^[203] noticed that the most useful endoscopic features for the differential diagnosis in IBD colitis are discontinuous involvement, anal lesions, and cobblestoning of mucosa in CD, and erosions or microulcers and granularity for UC.

However, other studies have described various degrees of heterogeneous endoscopic findings associated with both CD and UC, pointing out remarkable rates of atypical features compared to the established literature^[6]. For instance, a mild and localized involvement of terminal ileum, known as “backwash ileitis” has been seen in up to 20% of extensive UC^[204,205]. Similarly, slight signs of discontinuous peri-appendiceal inflammation (“cecal patch”) were reported in up to 75% of distal UC^[206-209]. In the peculiar setting of primary sclerosing cholangitis, UC has been depicted without the classical distal gradient of inflammation or even with a more severe involvement of the right colon^[210]. In addition, “relative” rectal sparing and “patchy colitis” have been reported in up to 20%-40% of untreated UC children^[211-214], as well as in up to 10%-30% of adults receiving topical or systemic treatment^[215-217]. Finally, tissue repairing can induce fibrotic changes within the mucosal and submucosal layers, which increase wall stiffness and mould benign luminal narrowing detectable in approximately 10% of longstanding UC^[218]. Consistent with these atypical findings, 10%-20% of ileo-colonoscopy reveals an unspecific IBD pattern of colitis, thereby depicting an incomplete frame to correctly address both further histopathological analysis and clinical work-up.

Histopathology of terminal ileum and colorectal specimens

Histology based on at least two specimens separately collected from at least five sites along the colon, including the rectum, and the terminal ileum during ileo-colonoscopy and stored in separate jars is recognized as the gold standard to confirm both diagnosis and disease subclassification^[6,11,34,112,219]. Colorectal mucosal histological abnormalities concerning architectural, epithelial and inflammatory changes characterized by discontinuity or variable degree in different ileo-colonic segments, focal or patchy cryptitis and lamina propria chronic inflammation with relative mucin preservation are in favor of CD. By contrast, Paneth cell metaplasia in distal colon, severe mucin depletion, heavy and widespread cell infiltration, distorted and atrophic crypts or surface erosions are more suggestive of UC^[220,221].

Epithelioid well-formed, isolated, non-caseating granuloma unrelated to crypt injury (*i.e.*, basally oriented in the mucosa and distant from crypts) is the most reliable discriminant for distinguishing CD from UC^[11,219-222]. Out of the above-mentioned detailed statements, granuloma specificity decrease and other granulomatous conditions such as tuberculosis^[223,224], *Yersinia*^[225,226] acute bacterial enterocolitis^[227-231], complicated diverticular disease^[232-235], diversion colitis^[235,236], sarcoidosis^[223] and even UC^[235,237-239] should be ruled out before confirming the diagnosis. We know from previous studies that colorectal granuloma is present in approximately 30% of adults and in 40% of children affected by CD^[240,241] with a great variability in the literature ranging from 7% to 100% for surgical specimens^[232,240]. However, in ileo-colonic biopsies, granuloma detection is quite unusual, being reported in only 13%-30% of CD^[240,242]. Therefore, even when a diagnosis of IBD is made confidently, histopathological classification as UC or CD can be an ordeal because of the absence of specific microscopic features (*i.e.*, non-cryptolytic granulomas), as well as for the presence of some exceptions occurring in UC such as discontinuous changes (*i.e.*, cecal patch, skip lesion in appendiceal UC, uneven distribution in children and longstanding and treated UC, refractory and fulminant colitis), focal ileal inflammation (with or without macroscopic evidence of backwash ileitis) and relative rectal sparing (*e.g.*, in children or treated UC)^[11,36,219-221,230,239,243]. Additional histopathological features of CD useful for the differential diagnosis lie in the submucosal or in the transmural layer (*e.g.*, transmural lymphoid aggregates, granulomas in the subserosa, and submucosal nerve fiber hyperplasia with ganglionitis)^[11,34,220]. However, all these lesions mainly reside in the deeper layers of the bowel wall and are not reachable by endoscopic biopsies. Nevertheless, even when large colectomy specimens are available, indeterminate colitis still represents the most reliable diagnosis in between 5% and 20% of cases^[36]. Therefore, one may envision that beyond conventional H&E-stained slides and additional immunohistochemistry, new molecular techniques should be used in order to refine histopathology accuracy^[244]. In a recent study, Yantiss *et al.*^[245] assessed the expression of two monoclonal antibodies directed against an unknown colonic epithelial protein (Das-1) and human tropomyosin isoform-5 (CG-3) in colonic biopsy specimens from patients with colitis (25 UC, 15 CD, 15 lymphocytic, 15 collagenous, 15 ischemic) and in 10 normal controls. The results showed that suppression of Das-1 staining occurs more frequently in UC (96%) compared with CD (20%), lymphocytic (20%), collagenous (13%), and ischemic colitis (0%) cases, as well as controls (10%, $P < 0.001$ for all comparisons). In addition, CG-3 positivity in crypt epithelium was significantly more common in UC (52%) compared with all other groups ($P \leq 0.02$ for all comparisons)^[245]. These data suggest that DAS-1/CG-3 molecular staining might be useful in distinguishing UC from CD and from other colitides. This innovation

represents a possible step towards the extension of IBD histopathology into the molecular realm adding to, although not replacing, current gold standards.

Upper endoscopy

Esophagogastroduodenoscopy (EGD) is aimed at integrating the diagnostic work-up of IBD patients with suspected CD, upper gastrointestinal symptoms, anemia and signs of malabsorption^[6,34,45,112,246]. The involvement of the upper gastrointestinal tract has been traditionally considered as a hallmark for CD^[6,11,45,219,246-248]. Accordingly, classical lesions suggesting CD involvement such as stenosis, fistula, ulcers, erosions and aphthous lesions have been reported with pertinent microscopic features (*e.g.*, focal chronic inflammation, focal crypt irregularity, irregular villous architecture, and epithelioid granulomas) in 1%-16% of symptomatic adult CD^[247-252] and in 22%-53% of children^[26,214,241,253,254]. Similarly, the chance to detect non-caseating, epithelioid granulomas in esophagus, stomach and proximal duodenum is quite low in adult series (0, 2%-20%)^[255-258], while substantial in children (11%-43%)^[26,45,259-267]. In 2%-21% of children with new onset CD, the diagnosis relies on the detection of granulomas at EGD^[259-264], while no study addresses this issue in adults, in whom this percentage is expected to be much lower. Notably, even if granuloma is touted to represent the most reliable hallmark of upper CD, it is not diagnostic *per se*, since many other gastrointestinal disorders such as *Helicobacter pylori* infection, tuberculosis, gastric adenocarcinoma and sarcoidosis can lead to granulomatous lesions^[219,231,257,268,269]. Random biopsies upon apparently normal mucosa should be collected from each site (*e.g.*, duodenum, antrum, corpus, fundus, esophagus) using separate jars with the foresight to sample esophageal mucosa at least 2 cm above the Z-line to exclude inflammatory changes caused by gastro-esophageal reflux disease. Recent studies have shown that absence of specific symptoms does not preclude proximal lesions in CD populations, especially in young patients and in ileo-colonic diseases^[26,34,253,258-260,262]. Conversely, "L2" locations are less likely to have an upper involvement or a stricturing disease^[241].

In contrast with common beliefs, several studies have shown that in UC and also IBDU, upper gastrointestinal lesions are common and EGD findings more frequent than in healthy controls^[265,270-278]. Studies based mostly on asymptomatic subjects and pediatric cohorts report a considerable prevalence of mild macroscopic gastroduodenal lesions^[214,247,254,271,277] and microscopic features pertinent with IBD (*i.e.*, crypt distortion, focal cryptitides, crypt abscess, patchy distribution of inflammatory changes)^[45,246,248,255,259,260,262,265,267,270,277,279,280] in *Helicobacter pylori*-negative subjects with either UC (4%-50% and 38%-70%, respectively) or CD (20%-75% and 60%-90%, respectively). However, there is no consensus concerning the definitions of what qualifies as significant involvement of IBD in the upper gastrointestinal tract and evidence of clinical correlates is lacking^[246-248].

Many recent trials have directed attention to focally enhanced gastritis (FEG), a perifoveolar/periglandular mononuclear (typically CD3+ lymphocytes and CD68R+ histiocytes) and neutrophilic infiltrate around gastric crypts of the antrum and angulus in *Helicobacter pylori*-negative subjects, which corresponds to no or mild signs of mucosal inflammation at standard white-light endoscopy^[255,270,281]. These histological features are common in both adults and child patients with CD and in those with limited colonic location (43%-76%)^[219,255,258,265,270,275,282]. Further data have shown that FEG may affect also IBDU (18%-33%) and UC (8%-24%) subjects^[45,258,265,273-275,282], whereby indicating that FEG may serve as a marker of IBD compared to the general population (2%-19%)^[265,273-275] rather than reliably distinguishing between patients with CD and UC^[274,275].

Two retrospective studies based on CD and UC subjects and negative controls have recently suggested that duodenal focal cryptitis and lymphocytic esophagitis are also common in children with IBD, and particularly in CD^[265,272]. Data assessing the prevalence of duodenal focal cryptitis and lymphocytic esophagitis in adults are still lacking. Indeed, most of the macroscopic and microscopic findings observed in the upper gastrointestinal tract of asymptomatic IBD subjects are nonspecific and not helpful in discriminating CD from UC^[246]. We believe that at present it is more convenient to consider every significant upper gastrointestinal involvement relating to IBD as a clue to the underlying diagnosis of CD, rather than as an atypical manifestation of UC and IBDU.

In conclusion, the value of upper endoscopy and related findings is still a topic of debate. Currently, EGD is recognized as part of the initial evaluation of children with suspected IBD and a valuable additional tool among adults presenting with either suspected CD or upper gastrointestinal symptoms^[6,34,45,112,246,266]. Nevertheless, endoscopic and histopathological assessment of the upper gastrointestinal tract seems to have a limited impact for the differential diagnosis in asymptomatic adults with IBD colitis^[6].

Small-bowel endoscopy

IBD patients who present symptoms and endoscopic features consistent with colitis may show small-bowel and upper GI lesions as proof of an underlying CD^[196,283]. Therefore, cross-sectional imaging and small-bowel endoscopy are as useful to confirm the diagnosis in suspected CD as to exclude it in patients diagnosed with UC and IBDU. Consistent with an international consensus, cross-sectional imaging should generally precede enteroscopic examination^[194,196]. Conversely, agreement on whether small-bowel capsule endoscopy (SBCE), rather than device-assisted enteroscopy, should be performed has not been completely achieved and the best choice is subject to the nature and location of the lesion, as well as to the availability of the technique

and to local expertise^[194-196,200]. A consensus group met in 2008 and concluded that in patients with suspected small-bowel CD with no obstructive symptoms, capsule endoscopy is an effective and smart strategy^[196] given the high rate of complete small-bowel evaluations and the high negative predictive value^[195,283-289]. The use of SBCE has been better defined in established CD patients with inconclusive results after conventional endoscopy and radiology^[195,196,289-292].

However, SBCE has several practical limitations among subjects with either suspected or definite diagnosis of IBD. Firstly, trials focused on SBCE are mostly based on a non-validated, arbitrary score setting the finding of at least three ulcers as diagnostic of CD^[6,293]. Secondly, small-bowel CD, NSAID-induced enteropathy, mycophenolate mofetil-induced enteropathy, tuberculosis, Behçet's disease, vasculitis, ischemia and lesions of unknown clinical significance, which are reported in up to 20% of healthy subjects, may share a nonspecific appearance at capsule endoscopy, thereby requiring further enteroscopy for biopsy sampling^[195,196,289,294-299]. Thirdly, emerging evidence suggests that a negative SBCE does not exclude a future diagnosis of CD^[196,300,301]. In addition, a recent study based on SBCE and CD patients variably affected by abdominal pain and/or diarrhea (45%), increased number of soft stools (39%), anemia (7%), or asymptomatic (9%) has shown that jejunal involvement is less common in Crohn's colitis (12%) compared to ileo-colonic diseases (38%)^[283]. This evidence seems to lead to reconsideration of the impact of SBCE assessment in the subset of CD patients with isolated colitis, thereby shrinking the value of deep enteroscopy for those IBD patients with an unclear diagnosis.

In UC and IBDU, evidence assessing the diagnostic value of small-bowel endoscopy is still limited and mostly based on SBCE. Recent trials have revealed that minute superficial lesions ("reddish lesions and erosions") are common among UC subjects (20%-57%). However, the findings revealed by capsule endoscopy were consistent with the diagnosis of CD only in a small group of UC (0%-16%)^[302-305]. By contrast, the amount of small-bowel CD appeared substantial in IBDU (16%-43%), with the highest rates in pediatric subjects, symptomatic CD or refractory IBD colitis^[300,303,306,307].

Taken together, these initial data reveal that small-bowel endoscopic assessment has a limited impact in IBD subjects with colonic involvement. Both SBCE and device-assisted enteroscopy are useful in patients with known or suspected CD but can also aid in the diagnosis of IBDU or UC in the case of crucial choices^[6,195]. Currently, there is no clear evidence to recommend the use of deep enteroscopy as a standard diagnostic tool for the differential diagnosis in IBD colitis.

EMERGING AND FUTURE PERSPECTIVES

Advanced endoscopic imaging

Recent innovations in gastrointestinal endoscopy have changed our traditional approach to diagnosis in

patients with IBD^[195,308-310]. Emerging endoscopic imaging techniques such as high-definition^[311-313], magnification^[314-316] and dye-less chromoendoscopy^[317,318] enable a detailed visualization of mucosal surface architecture and vascular pattern. Despite their potential in refining the differential diagnosis in subjects with suspected or established IBD, there is no evidence of clear advantages beyond standard white-light endoscopy or dye-based chromoendoscopy with either indigo carmine or methylene blue^[318]. Conversely, the newly developed confocal laser endomicroscopy (CLE)^[319-327] and endocytoscopy^[328,329] allow for the characterization in "real time" of microscopic structures at a cellular and subcellular level, where disease specific features of both UC and CD are so far revealed only by histopathological analysis *ex vivo*.

Looking for confocal-aided signs of epithelial cell shedding in the terminal ileum, Liu *et al.*^[323] have shown that "gap density" is of value in distinguishing patients with IBD and healthy controls (61 *vs* 18 gaps/1000 cells, $P < 0.001$) but cannot easily differentiate patients with CD from those with UC (67 *vs* 61 gaps/1000 cells, $P > 0.05$). Recently, a study based on 79 consecutive IBD patients with a well-established diagnosis of CD ($n = 40$) and UC ($n = 39$) has shown that CLE with *in vivo* fluoresceine can clearly discriminate the presence of several disease-specific microscopic changes, which are conventionally used by standard histopathology to differentiate UC from CD. Based on such findings, the proposed CLE scoring system assessed with excellent accuracy (94%) the differential diagnosis blind to both clinical history and histopathological results, used as golden standards^[330].

Compared with the single photon excitation performed by CLE, the newly introduced multiphoton microscopy has a superior effective resolution in thick tissue samples and an increased penetration depth without requiring exogenous fluorophores^[331]. This resolution corresponds to images perfectly suited for 3D acquisition capable of reproducing the architecture of mucosal and superficial submucosal structures in detail. To the best of our knowledge, multiphoton microscopy has so far been tested in IBD tissue specimens only *ex vivo*^[332].

Another novel advanced endoscopic technique, named "molecular imaging", combines confocal imaging with exogenous fluorescently labeled probes to highlight *in vivo* specific microscopic changes on the basis of their molecular signature, thereby overcoming the limits of traditional morphological analysis to characterize either biochemical processes or molecular epitopes^[333,334]. This technique has already shown "promising and immediate potential for translational science and prompt effects into clinical practice" in several fields of gastrointestinal endoscopy including IBD^[333]. The possible applications of such a technique to improve the differential diagnosis in IBD colitis lies in identifying and developing proper molecular biomarkers. In the above-mentioned study by Yantiss *et al.*^[245], DAS-1/CG-3 molecular staining

was found to be useful in distinguishing UC from CD and from other colitides in histopathological colonic specimens *ex vivo*. Consistently, endoscopic molecular imaging has the potential to achieve comparable results *in vivo* combining the topical application of fluorescein-labeled DAS-1/CG-3 antibodies with CLE. Nonetheless, there is no published trial based on endoscopic molecular imaging techniques to address the matter of differential diagnosis in IBD.

Finally, several studies have recently shown the makings of another new advanced endoscopic technique based on the principle of contact light microscopy and known as endocytoscopy, for *in vivo* gastrointestinal microscopic imaging at a magnification up to 1390-fold^[328,329,335-337]. In a pilot study, endocytoscopy was found to characterize and discriminate different inflammatory cells in the colonic mucosa of IBD patients with high accuracy, but its potential in the clinical setting is not yet established^[329].

Optical coherence tomography (OCT or VLE: volumetric laser endomicroscopy) is a probe-based imaging technique, which allows for a resolution of 7-10 μm with an imaging depth of 2-3 mm^[338-340]. The ability of OCT to scan multiple gastrointestinal wall layers can find utility in diagnosing the transmural inflammation of CD. In a prospective, blinded study based on 40 patients with CD and 30 with UC, Shen *et al.*^[341] described disrupted layered structure of the colonic wall, as a hallmark of transmural inflammation, with 90% sensitivity and 83% specificity for the diagnosis of CD. This study suggests that OCT may represent a valuable tool to distinguish CD from UC, especially when the differential hallmarks lie into the deepest mucosal layers and endoscopic biopsies are insufficient to assess transmural inflammation.

Optical spectroscopy is another intriguing advanced endoscopic imaging technique that includes fluorescence, reflectance and light-scattering spectroscopy and optical coherence tomography. Spectroscopy depends on the wavelength of the light source and on tissue characteristics^[339]. Different light spectra backscattered between cells are specific for various diseases such as ischemia, inflammation, and malignancy. Accordingly, Raman spectroscopy has been recently proposed for distinguishing CD from UC *in vitro* in *ex vivo* tissue samples from IBD patients^[342].

Taken together, current advanced endoscopic imaging techniques could offer an *in vivo* additional method to conventional histopathologic diagnosis. Nevertheless, further efforts are still required both in the clinical setting and in technological advancements before expanding their clinical application in differentiating UC from CD patients. There is great promise that molecular imaging will aid as a complementary tool to identify disease-specific features accurate for UC or CD at a molecular level; until then, the endoscopic diagnosis of IBD will have to rest exclusively on the morphological assessment of inflammatory changes.

Genetics

Over the last ten years, with the advent of genome-wide association studies (GWAS), a wealth of susceptibility loci have been discovered shedding some light into the knowledge of UC- and CD-specific genomic profiles^[343,344]. In this respect, the recent imputation-based association analysis by Jostins and colleagues represents a milestone in the development of GWAS in IBD^[345]. They have performed a meta-analysis based on 15 GWAS and ImmunoChip (Illumina, Inc, San Diego, CA) data of CD and/or UC, followed by extensive validation of significant findings, with a combined total of more than 75000 cases and controls. Seventy-one new associations were identified, expanding the number of confirmed IBD susceptibility loci to 163. These data have confirmed the existence of an important overlap in genetic risk factors between IBD and other immune-mediated disorders (70%) and that most loci contribute to both IBD phenotypes (67%)^[345]. IBD genetics has highlighted a common Th17/IL23 pathway for CD and UC^[345-347], in line with evidence concerning gene expression in inflamed mucosa^[348], and revealed relatively fewer disease-specific involved mechanisms, such as barrier integrity for UC^[349-352] and autophagy for CD^[350-353]. This degree of sharing of genetic risk suggests that nearly all of the so far known susceptibility loci involved in one disease may have some role in the other^[345] and tightens the implementation of genetic panels to address discrimination of UC from CD^[354].

To date, efforts made to find genetic diagnostic markers in IBD have mostly focused on colonic tissue samples retrieved by endoscopic biopsy^[355,356]. In the research by von Stein^[357], seven candidate cDNAs differentially expressed in the colonic inflamed tissues of UC and CD patients were initially identified using the molecular subtraction process termed “subtractive suppression hybridization”. In quantitative polymerase chain reaction experiments, the differential expressions of identified genes were analyzed using a classification algorithm and the possible clinical value of these markers was overall evaluated in 301 patients in 3 stepwise studies. Accordingly, the multigene analysis based on these seven markers was able to discriminate between patients suffering from UC, CD, or IBS with an area under the receiver-operating characteristic curves ranging from 0.915 to 0.999 ($P < 0.0001$) using the clinical diagnosis as gold standard. Furthermore, in a subset of 20 IBDU patients, the genetic panel predicted correctly 9 out of 10 changes in clinical diagnosis made 4-12 mo later by a blinded physician^[356]. More recently, this genetic panel was tested in 78 active patients with a complicated course diagnosed as most probably UC in 38, CD in 18 and IBDU in 22^[358]. The tests led to the proper diagnosis in a substantial number of cases initially named as UC (11/13) or CD (3/4) and suggested the correct diagnosis in most IBDU patients (9/10) clinically reclassified as UC or CD one year later^[358]. Further confirmations in larger

and more heterogeneous populations are required before implementing this approach in clinical practice; yet, the era of genetic differential diagnosis in IBD colitis has begun^[359].

Epigenetics

Genetics accounts for only a portion of overall disease variance, indicating that gene-environment interactions affecting gene expression with no changes in the DNA sequence, namely epigenetics, play a central role in the pathogenesis of IBD and other diseases^[351,360]. Among epigenetic modifications, DNA methylation is probably the most widely studied; this process occurs when a methyl group is covalently added to cytosines that are part of cytosine-guanine dinucleotides (CpG)^[351]. Methylation of “CpG islands” in promoter gene areas may lead to transcriptionally repressive activity and is associated with gene silencing^[351]. DNA methylation in colonic epithelial cells normally occurs with aging but is accelerated in IBD, where it is touted to favor genetic instability and development of colorectal cancer^[361]. DNA methylation change is a quantitative trait and therefore an attractive biomarker that can be found in a range of body fluids. A panel of relevant hypomethylated or hypermethylated CpGs measured in fecal and blood samples might someday be capable of distinguishing between UC and CD, enabling disease stratification, predicting treatment response, identifying patients with cancer or those who are prone to cancer development^[351].

Several genome-wide expression studies are so far attracting more attention to RNA interference, providing new interesting tools to assess and characterize IBD diagnosis and phenotype^[351]. MicroRNAs (miRNAs) are short (typically 22 nucleotides in length), endogenous, non-coding single-stranded RNAs that have been highly conserved throughout evolution and act in concert as master drivers of post-transcription by regulating expression of their target messenger RNAs^[351]. Analysing hundreds of miRNAs present in colonic biopsy specimens, distinct profiles were identified in IBD *vs* controls, as well as between quiescent or active UC *vs* CD, and in UC patients with active or inactive disease, thereby confirming the putative role of miRNAs as contributors to IBD pathogenesis^[351,362-364]. Likewise, distinctive miRNA profiles have been described in the peripheral blood of UC, CD and nonIBD subjects, suggesting their use as minimally invasive circulating biomarkers^[365-367].

However, when interpreting results from epigenetic studies, a potential pitfall lingers in determining causality, that is, whether a particular epigenetic profile is the cause or consequence of disease. The above-mentioned epigenetic studies in IBD patients were mostly performed with whole tissues, such as blood or colon biopsy samples, where epigenetic features of each cell can be masked by those of heterogeneous cell groups, making the results difficult to compare and interpret^[351]. Accordingly, the development of miRNA profile-based diagnostic tools for IBD needs further studies to

confirm the ability of circulating and colonic miRNAs in distinguishing IBD subtypes and their specificity in less selected populations.

Metabolomics and proteomics

The first full genome sequences were established in the mid-1990s. Shortly thereafter, genome-scale metabolic network reconstructions appeared to provide a repository of all human metabolites^[368]. Metabolomics performs an analytical description of complex biological samples and aims to characterize and quantify all the small molecules involved, thereby revealing the unique chemical fingerprints that specific cellular processes leave behind^[369]. Because the global cellular function depends upon the protein network environment as a whole, multivariate analysis of metabolic profiling of biofluids dovetails beautifully with IBD to screen for new molecular players involved in disease pathogenesis, measure and characterize disease activity and differentiate between disease biophenotypes. Several recent studies have highlighted how metabolic profiling of biofluids from IBD patients may represent a powerful approach to collect a huge amount of information on amino acids and related metabolites, on Krebs cycle intermediates, and on molecules involved in fatty acid and purine metabolism^[370,371].

Similarly, proteomic and subproteomic (*i.e.*, cellular compartments, organelles and biological fluids) array profiles have shown promise with regard to identifying active disease, providing insight into disease pathogenesis and differentiating between CD and UC^[147,370]. Metabolic and proteomic profiles of serum and plasma have provided a distinctive characterization between IBD and healthy controls, as well as between UC and CD patients irrespective of the analytical technique used^[370-372]. Encouraging data have been also described by protein profile analysis on peripheral blood mononuclear cells^[373] and colonic tissue specimens^[373-377]. By contrast, metabolomic patterns from urinary and fecal samples have often led to more conflicting results in differentiating UC from CD, likely due to the possible influence of environmental variation in urinary metabolomics, disturbances from gut microbiota, and other confounding factors such as ongoing anti-TNF α therapy or bowel resections^[371].

Undeniably, current technology supporting metabolomics and proteomics analysis is sophisticated, complex and expensive^[378]. Nonetheless, considering the potential breakthroughs in understanding inflammation processes, identifying new molecular targets for therapy, mapping individual gut microbiota and helping in differential diagnosis, metabolomic and proteomic techniques appear like an expanding constellation into the IBD universe.

CONCLUSION

Current classification of large-bowel involvement in IBD relies on clinical grounds and acknowledges three distinct

phenotypes, UC, CD and IBDU^[5]. Such a distinction is of paramount value for optimized clinical management, since surgery, modern therapies and emerging prognostic indices nearly always work on disease-specific strategies. Established clinical diagnostic methods usually prove successful in pointing at proper and defined diagnoses. However, the substantial group of IBD patients with ambiguous colonic diseases still represents an unresolved problem bearing the names of “misdiagnosis”, “disease reclassification over time” and “IBD unclassified (*pro tempore*)”. This implies less successful treatment strategies and can lead to repeated diagnostic tests, thereby producing a considerable overexploitation of resources, time and patients’ compliance.

The use of serologic panels including ASCA and pANCA with the addition of more recent antibodies featuring complementary profiles could partially enhance testing accuracy in IBD colitis, refine the classification of patients diagnosed as IBDU and predict surgical outcomes after IPAA.

Relatively recent innovations in gastrointestinal endoscopy have made the small bowel more accessible and have clearly improved the quality in endoscopic imaging. However, benefits in terms of differential diagnosis seem to be marginal and both specificity and clinical correlates are poor.

In the attempt to make a forecast, hereby distinguishing between emerging and future perspectives to improve the differential diagnosis in IBD, molecular pathology, optical spectroscopy and confocal laser endomicroscopy appear as the most promising tools ready for distribution in the next years (Figure 1). On the other hand, the encouraging results coming from genetics, epigenetics, metabolomics and proteomics are simultaneously shedding light on IBD biologic systems and generating non-invasive tests, which may both aid the diagnosis and contribute to further reclassifying IBD into new and more homogeneous subgroups^[167]. The success of this strategy relies on the development of multiple, complimentary biomarkers relating to a molecular classification of IBD colitis, which can better reflect diverse disease behaviors from the pathogenic standpoint.

To date, the differential diagnosis in IBD colitis still relies on a multidisciplinary approach based on clinical evaluation, standard biomarkers, lower and upper endoscopy, histopathology and radiology^[6,11,45,112]. Additional investigations such as deep enteroscopy, novel serologic tests and advanced endoscopic imaging techniques can help in specific situations but should not routinely be advocated. Clinical trials are now warranted to confirm the potential role of experimental laboratory tools assessing the genetic and/or metabolomic fingerprints of IBD in daily clinical practice.

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