

Indeterminate Colitis: A Review of the Concept — What's in a Name?

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Abstract: The precise diagnosis of colitis cannot always be established with the available diagnostic tools. The subgroup of patients with an uncertain diagnosis has been classified as “indeterminate colitis” (IC). The definition of “indeterminate,” however, has changed over the years. Originally, IC was proposed by pathologists for colectomy specimens, usually from patients operated on for severe colitis, showing overlapping features of ulcerative colitis (UC) and Crohn’s disease (CD). Later, the same terminology was used for patients showing no clear clinical, endoscopic, histologic, and other features allowing a diagnosis of either UC or CD. Therefore, it is difficult to compare different studies. An International Organization of Inflammatory Bowel Diseases (IOIBD) working party confirmed 1) the ambiguous nature of the term, and 2) proposes an updated classification for the category of patients with an unclear diagnosis. According to this, the term IBD unclassified (IBDU) is confirmed, as suggested by the Montreal Working Party 2005 for patients with clinically chronic colitis, that clearly have IBD but when definitive features of CD or UC are absent. In resected specimens the term “colitis of uncertain type or etiology” (CUTE) is preferred. It is accepted that most of the time this may have a prefix, such as severe, chronic. The classification of IBD varies when based only on biopsies rather than on a colectomy specimen. The vast majority of these have severe colitis. For those that cannot bear to abandon

the highly ambiguous term IC, if it is used at all, this is where it can be used parenthetically.

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Key Words: indeterminate colitis, updated classification, colitis of uncertain type or etiology

DIAGNOSTIC YIELD IN INFLAMMATORY BOWEL DISEASE (IBD)

Analysis of multiple biopsies allows a correct diagnosis of IBD in 66%–75% of newly diagnosed patients. Additional endoscopic and clinical data allow a final diagnosis in the large majority of patients. In 1 series of 200 consecutive patients with suspected or established colitis, the final diagnosis remained unclear in 2 patients.^{1,2} Errors are more frequent (up to 7%) in patients with severe inflammatory activity.² The terminology for cases without definite diagnosis is unclear. “Unclassified” and “uncertain” colitis have been proposed, as well as indeterminate colitis (IC).^{3,4} The latter term has become widely used but with a variety of definitions (Tables 1, 2).^{5–21} The common feature is that the type of colitis cannot be classified. Pathologists stress the severity of the disease and the need for colectomy specimens, except in 1 definition,⁸ while pediatricians, surgeons, and gastroenterologists stress the fact that some types of colitis cannot be classified irrespective of the diagnostic tools used. Most definitions indicate a need for features of chronic colitis, often without specifying.

INDETERMINATE COLITIS: THE EARLY SURGICAL PERIOD

The separation of ulcerative colitis (UC) and Crohn’s disease (CD) has been based on a variety of clinical features, symptoms, endoscopic and radiological, gross and microscopic characteristics that can be identified by clinical examination, radiologic and other scanning procedures, colonoscopy, and pathological examination of colectomy specimens and biopsies. Subsequent genetic and other studies support the concept of 2 entities. Because of the variable occurrence

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TABLE 1. Definitions

Definitions used in pathology

- Colectomy specimens showing overlapping features of Crohn's disease and ulcerative colitis or data are insufficient to make a decision.⁵
- Colectomy specimens showing overlapping features of both Crohn's disease and ulcerative colitis.⁶
- Colectomy specimens in whom a clear pathologic distinction between ulcerative colitis and Crohn's disease is impossible (because of failure to recognize or accept certain criteria as indicative of Crohn's disease or because of the absence of adequate clinical and radiographic material or because of inadequate biopsy material).⁷
- Inability to make a confident diagnosis of the pattern of colitis despite examination of an adequate surgical resectate or adequate mucosal biopsy series from the colon and rectum.⁸

Definitions used in pediatrics

- A history of chronic colitis compatible with both the diagnosis of CD or UC.⁹
- Colitis that can not definitively be declared as CD or UC based on clinical history, physical examination, endoscopic appearance, histologic findings and radiologic studies.¹⁰
- Endoscopy and histopathology are either inconclusive or divergent with regard to the diagnosis of UC or CD.¹¹
- Exclusive inflammation of the large bowel and neither endoscopic nor histologic findings typical for CD or UC.¹²
- Indeterminate colitis can only be diagnosed after a full diagnostic work-up. This must include colonoscopy with intubation of the terminal ileum, upper gastrointestinal endoscopy and small bowel follow through. Diagnosis of indeterminate colitis is suggested by histology showing acute and chronic inflammation with architectural changes confined to the colon, absence of abnormalities suggesting lymphocytic or allergic colitis, or CD, a normal small bowel follow through or enteroclysis and no definite classification of CD or UC possible with histology.¹³

Definitions of IC used by gastroenterologists, surgeons, epidemiologists

- A disease with "clear" evidence of inflammatory bowel disease but insufficient evidence to make a definite diagnosis of either UC or CD.¹⁴
- Diagnosis based on a double-contrast barium enema examination, endoscopy, and histopathology being conclusive for a diagnosis of IBD but inconclusive for a diagnosis of either definite UC or CD.¹⁵
- Patients who have the clinical and macroscopic features of either CD or UC, both pre- and per-operatively. The histology remains indeterminate both pre- and post(per)operatively (includes mucosal biopsies and colectomy specimens).¹⁶
- Inflammatory colitis containing features on macroscopic and microscopic evaluation of the colon that are consistent with both CD and UC.¹⁷
- Unequivocal diagnosis of chronic UC preoperatively but inconclusive histology on examination of the pathologic specimens intra operatively.¹⁸ (Mayo Clinic)
- Cases in which a definite diagnosis of UC or CD cannot be made. The diagnosis is typically made in the setting of fulminant colitis but can also include less severe forms of colitis in which there are overlapping histological features.¹⁹
- Colitis for which there is no identifiable cause and with clinical features of both UC and CD.
- Patients with mucosal ulcerative colitis with histologic features of CD such as skip lesions, transmural inflammation, granulomata or mucin depletion but no clinical or radiological evidence of CD.²⁰
- Colitis, for which endoscopic, histologic and radiologic criteria fail to discriminate between UC and CD of the colon.²¹

of the features, diagnostic difficulties remain and a confident diagnosis is impossible in 10%–15% of cases.^{22,23} In 1970 Kent et al⁵ performed the first retrospective study of clinical and pathological (colectomy) material from 222 patients with fulminant ($n = 12$) and chronic disease. The aim was to see whether the classical criteria could separate the 2 groups of ulcerative disease of the colon. Fourteen cases (15%) were categorized as "indeterminate" because of "overlapping features" (10%) and "data, insufficient to make a decision" (5%). One out of 12 fulminant cases was classified as indeterminate. "Overlapping features" were described as "severe mucosal and wall involvement." At that time, and in many ways as now, transmural disease was considered a feature seen primarily in CD.

In 1978 Price et al⁶ identified 30 "indeterminate cases"

(10% of all colectomies for IBD) based on the presence of overlapping features. In 27 of these 30 cases urgent surgery had been performed. Features included discontinuous ($n = 2$) or continuous disease with uneven distribution ($n = 14$), fissures ($n = 4$), nonaggregated transmural inflammation ($n = 28$), and glandular irregularities ($n = 10$). Preoperative and follow-up biopsies allowed a definite diagnosis in, respectively, 7 (3 = UC; 4 = CD) and 8 patients (3 = UC; 5 = CD). Fifteen cases remained indeterminate. A year later, in 1979, Lee et al²⁴ identified "five (16%)" cases of IC in a series of 32 colectomy specimens. All these patients underwent emergency surgery. Cardinal morphologic findings were extensive ulceration with sharp transition to normal adjacent mucosa and absence of lymphoid aggregates. Fissures reaching the muscularis propria were usually present. In

TABLE 2. Definitions of IC Used by Clinicians, Experts in IBD, from a Survey Carried Out in 2006 and Proposed Definition of IBDU

(*n*=21) IBD – but ?UC or CD (e.g., when the results of clinical, colonoscopy, biopsies, lab tests, serology are still unclear)

(*n*=6) Focal disease, segmental disease, skip lesions, rectal sparing

(*n*=6) Based on pathology, 4 on resection only, 1 not further specified, 1 when told by my pathologist

(*n*=4) IBD versus non-IBD

(*n*=1) for the following

Distribution: (severe) (pan)colitis and > 10 cm of TI inv

Fissures: anal fissure in otherwise UC

Serology: patients with continuous colitis but ASCA and ANCA and OmpC negative

Severity: severe/fulminate colitis at presentation

Outcome: bad pouch

Proposed definition of IBDU (IOIBD 2006).

Chronic colitis with features of IBD but without definitive features of ulcerative colitis or Crohn's disease.

these 3 series 33/44 cases were from fulminant disease. Reasons suggested for the occurrence of an “indeterminate pattern” with overlapping features are the healing effect of steroids, which may explain sparing of the rectum (topical treatment), the lack of evidence of disease in surviving mucosal islands with impaired healing of ulcers (systemic treatment),²⁵ and the similarity of the pathology of early acute UC and CD.⁶ The latter may explain significant variation in the histological diagnosis of colonic IBD.

So by 1980 it was clear that, primarily in the context of severe (fulminant) colitis, a subgroup of resections had been characterized that were likely to have severe colitis, often discontinuous disease with some degree of rectal sparing grossly. Histological features included areas without architectural distortion to suggest long-standing disease, deep fissuring ulcers that often went into, and sometimes through, the muscularis propria, accompanied by transmural inflammation, although usually not with the typical lymphoid hyperplasia associated with CD, and without overt granulomas. These, therefore, had many of the “buzzwords” associated with CD but did not behave like CD subsequently. It was this group of patients that were thought of as having IC, and it remained this way for the next 2 decades, during which time restorative “pouch” operations were developed using terminal ileal mucosa. The necessity for correctly diagnosing CD, including patients with severe/fulminant colitis, therefore became more important, as constructing pouches in patients with CD was recognized as frequently having a poor outcome. In 1991 Wells et al²⁹ performed a follow-up study of the original (1978) patients described by Price et al⁶ and examined the long-term outcome of 46 patients with a pathological diagnosis of IC on a colectomy specimen. In all, 19 patients were considered as probable CD, 11 as probable UC, and 16 as indeterminate based on the clinical information, pathology, and radiology. Minimum follow-up was 2.5 years. Thirteen patients remained “indeterminate.” Three were reclassified as UC and 1 as CD.

In 2003 a study from Japan included 735 patients, of whom 23 patients were identified as IC at onset (IC was defined as having features of both UC and CD). The diagnosis was based on a double-contrast barium enema examination, endoscopy, and histopathology being conclusive for a diagnosis of IBD but inconclusive for a diagnosis of either UC or CD. A diagnosis of CD was based on the presence of macroscopic features (longitudinal ulcer, cobblestone pattern, aphthous ulcerations, and granulomas). UC was based on a history of diarrhea with blood, continuous mucosal inflammation affecting the rectum in continuity with the colon, and microscopic features compatible with UC (not further defined). Thirteen patients could be identified as either CD (*n* = 8) or UC (*n* = 5) during follow-up.¹⁵

Much of the confusion may be explained by the presence of “fissuring ulcers reaching the muscularis propria” and increasingly by the fact that many of the other features considered to be those of IC were in fact those of severe colitis of any etiology. In 1998 the morphologic features of “fulminant colitis” were studied in a series of 67 cases. Macroscopic features were not helpful in differentiating UC from CD. Microscopic examination correctly diagnosed UC or CD in 58 (87%) cases. A further 3 cases (4%) were definitively classified after correlation with clinical data, leaving a residual 6 cases diagnosed as IC. Granulomas and lymphoid aggregates were the 2 most specific indicators for CD.²⁸ In 2000, in a series of 84 colectomy specimens, the diagnosis proposed by a specialist gastrointestinal pathologist differed from the initial diagnosis in 45%.²⁶ In this series, cases with ambiguous pathological features and absence of diagnostic criteria of UC or CD were classified as IC, but again many of these cases were operated on for fulminant colitis. Features required for UC included diffuse disease, involvement of the rectum, no deep fissure ulcers, no transmural lymphoid aggregates, and no granulomas. The prognostic significance of “superficial” fissuring ulceration was studied in severe chronic active colitis in 2006. It was con-

cluded that it may occur in patients with severe UC and that its presence should not be considered as an argument for a diagnosis of CD or IC, although it may be associated with subsequent pouchitis.²⁷

Based on these data, pathologists and clinicians increasingly considered IC as a temporary diagnosis, representing “diagnostic inadequacy,” to be used for cases presenting with severe (fulminant) colitis.¹⁵ A general characteristic is that many cases are seen early in the disease course.^{25,30} Overall, most cases diagnosed as IC behave as UC.

When the initial presentation is clinically severe, there is a strong need to properly classify IBD patients as either UC or CD since an ileal pouch-anal anastomosis (IPAA) is generally contraindicated in CD (and IC favoring CD, see subsequent discussion) due to a high risk of morbidity related to fistula incontinence, pouch failure, and anastomotic leaks.³¹ Furthermore, pouch salvage surgery is often unsuccessful in indeterminate colitis with Crohn’s-like features and in CD patients.³² However, the natural history of IC patients with IPAA varies considerably. In a series of 235 patients undergoing IPAA with UC only 3% had complications requiring surgery versus 50% requiring surgery with IC.¹⁷ Similar observations were made in other studies showing a failure rate for IPAA of 19% in IC versus 5%–8% for UC.^{18,33} Overall, at least 20% of IC patients develop severe pouch complications, which is intermediate in frequency between that seen in UC (10%) and CD (30%–45%). This result can be expected when the IC series represent a mixture of true UC and CD patients, or if IC itself is associated with an increased risk of pouchitis. In a series of 82 patients with IC, more episodes of pelvic sepsis, pouch fistula formation, and pouch failure were noted when compared with patients with UC. During follow-up, 15% of the patients were ultimately diagnosed as having CD. This change of diagnosis was based on the clinical course over time, the occurrence of complications at some time remote from the operation, including complex fistulas, and the histological examination of excised or biopsy specimens from the anal canal. Microgranulomas and creeping fat were not helpful for the distinction. When the rates of complications for the remaining patients with IC were compared with those with UC, the outcomes were comparable.³⁴ Similar data have been obtained in other studies.^{19,35,36} In a retrospective study of 28 patients with IC, those with 1 or more positive antibody tests preoperatively, including ANCA (antineutrophil cytoplasmic antibody), ASCA (oligomannan anti-*Saccharomyces cerevisiae*), I2 (antibody to *Pseudomonas fluorescens*), and OmpC (outer membrane porin) had a significantly higher risk of postoperative complications.³⁷ Antibody responses to ASCA, I2, and OmpC are more commonly seen in CD. These data suggest that most series of IC are heterogeneous. Most patients are or behave as UC. Pre- or peroperative features may suggest a probable diagnosis.

EPIDEMIOLOGY AND DEVELOPMENT OF IC AS A CLINICAL TERM

Retrospective incidence studies have shown repeatedly that in any cohort of patients with IBD there will be continuous change in the diagnosis over time, with up to 10% having a different final diagnosis to that originally assigned.³⁸ The most common reasons for difficulties are: sparing of the rectum; confluent mucosal involvement favoring UC but with long skip areas (including distal colitis with periappendiceal or cecal patches) that were considered to favor CD; typical UC or proctitis in the presence of anorectal skin tags favoring CD; superimposed infectious colitis; and changing pattern due to therapy.

Incidence studies with a prospective design usually have a category of “indeterminate colitis” defined as disease with “clear evidence of inflammatory bowel disease but insufficient evidence to make a definite diagnosis of either UC or CD.” Reclassified cases turn out to be UC more often than CD. In studies comparing clinical characteristics of IC, in most instances with UC, patients with IC are younger, have more extensive disease, and a more severe clinical course (severe first attack).¹⁴ In a 1990 study from Norway the diagnosis of IBD was based on “international criteria.” UC, CD, IC, and uncertain colitis were verified by endoscopy and histology, with between-specialists’ agreement, and with a scheduled follow-up at 1 and 5 years for reconfirmation of diagnosis and disease activity.^{4,39} The material consisted initially of 518 patients with UC, 221 patients with CD, 64 patients with uncertain colitis, and 40 patients with IC.⁴ Both at onset and at 1-year follow-up, the features of IC were mostly similar to UC, although a wide range was recorded for each parameter. This was true for relationship to gender, age at onset, level of C-reactive protein (CRP), concentration of hemoglobin, platelets, and albumin, blood in stools, and weight loss. At the 1-year follow-up, the initial number of IC and uncertain colitis were greatly reduced, due to changed diagnosis to UC ($n = 30$), CD ($n = 12$), and non-IBD ($n = 15$). The IC group was reduced to 6 and the uncertain colitis group to 34. Among the 40 original IC patients followed prospectively, 16 patients were treated with corticosteroids during the first year of disease. None of these patients kept their diagnosis of IC at the 1-year follow-up. The diagnosis was changed to UC in 5, to CD in 3, to uncertain in 4, and to non-IBD in 4 patients. Of the original 40 IC patients (100%), 2 were operated on. None of the 104 patients with initial diagnosis of IC or uncertain colitis kept their diagnosis at the 5-year follow-up. In IC, the diagnosis was changed to UC ($n = 18$), CD ($n = 7$), or non-IBD ($n = 8$). Seven patients were lost to follow-up. In uncertain colitis the diagnosis was changed to UC ($n = 19$), to CD ($n = 7$), or non-IBD ($n = 33$). Nine patients were lost to follow-up. For internal validation, a blind histopathological examination between 3 experienced pathologists was performed, based on prospective evaluation

of endoscopic biopsies from 9 segments of total colonoscopies. Before the examination the pathologists agreed on predefined histological definitions. The presence of the predefined characteristics was marked for each biopsy. The agreement between the pathologists varied from 50% (mononuclear infiltrate) to more than 90% (granulomas). No agreement was found for the diagnosis of IC. The lack of agreement for IC was confirmed in a subsequent study.⁴⁰ So overall, most cases turn out to be diagnosed as UC over time. Diagnostic problems occur mainly in the early phase of the disease (more cases of IC and uncertain colitis at the start, with more severe disease, steroids in 26.9% and operation in 3.8%). In this study there is a clear major trend to use IC as a holding term until a subsequent diagnosis can be better established. Some patients initially thought to have IBD were subsequently converted to non-IBD, while a few remained in a holding pattern with no positive diagnosis. The non-IBD cases are most probably due to either infections or drugs. The differential diagnosis between IBD and infectious colitis is not always possible in the early phase of the disease. A reappraisal of the lesions within weeks may allow a more precise diagnosis because the characteristic features of IBD can develop gradually.⁴¹ Similarly, a review of biopsies is also useful for patients when a change of the diagnosis is considered during follow-up, including pouch surgery. A discontinuous pattern of involvement can occur during the natural course of UC or secondary to treatment.⁴² A change in diagnosis should not be considered, therefore, unless all original diagnostic elements have been carefully reviewed, including all original biopsy material. If the original data were inconclusive, patients can be classified as IBDU.

IC AS A CLINICAL TERM IN PEDIATRICS

The trend to use IC for patients who seem to have IBD but who cannot be readily called UC or CD is even more marked in children than in adults, and further complicated by the fact that upper GI (gastric or duodenal disease or both but lacking granulomas on biopsy) can be seen in patients in whom UC seems to be the most likely diagnosis clinically. However, the upper GI pathology tends to resolve, being less common in adults (6%–12%) compared with children (20%–75%).^{43,44} So it is in some ways “sympathetic” with early disease. In 2005 a 12-year prospective population-based study included 509 cases of childhood IBD (7.2% of all IBD cases): 367 CD, 122 UC, and 20 IC (4%). The diagnosis of IC was based on a history of chronic colitis compatible with either CD or UC.⁹ In another study published the same year, including 202 patients, a diagnosis of IC was made in 45 patients (9.8% of all IBD cases). The median age was 13 years compared to 14 years for UC and CD. The diagnosis remained the same in 7 patients (3.5%).¹¹

The percentage of cases diagnosed as IC among the initial diagnosis of IBD in children varies between 4% and

23%.^{9,11,45} IC thus seems more prevalent at younger age, especially in the very young. Patients diagnosed with IBD before the age of 2 years were equally affected with UC (31%), CD (36%), and IC (33%). UC was more prevalent among those in the 3–5-year group. IC declined progressively with increasing age, being present in 9% of the 13–17-year-old patients.¹⁰ Among pediatric patients with IC, approximately 60% are ultimately reclassified as UC or CD.¹¹ Reclassified cases are more often UC.^{41,46}

As for surgical series, the definition used for the diagnosis of IC in pediatric patients is not always clear. Imprecision in diagnosis may relate to lack of or insufficient clinical imaging, or endoscopic data, or to issues regarding histological variables. In an attempt to clarify the issue a “pediatric” working party proposed that “Indeterminate colitis can only be diagnosed after a full diagnostic work-up” (Table 1).¹³ In general, the pattern of IC in children confirms data from studies in adults showing that the problem is more common soon after the onset of the disease. For many patients a definite diagnosis is reached subsequently. A small number remains unclassified.

HISTOLOGY AND THE DIFFERENTIAL DIAGNOSIS BETWEEN UC AND CD

The development of the microscopic features that are commonly used for a diagnosis of UC is a time-, disease-, and treatment-dependent process. In established disease the diagnosis is based on a combination of features. In early onset disease, few or no diagnostic features may be present. Basal plasmacytosis is observed in biopsies obtained at early onset in 38%–100% of adult patients and 58% of children with UC.^{47–49} It is especially present in (young) children. It is sometimes the first and only lesion. It may disappear during treatment.^{40,50} The diagnostic value is confirmed in established disease, being present in up to 63% of cases.⁵¹ The feature is also common in CD but rare in non-IBD colitis.⁵² Heavy, diffuse, transmucosal lamina propria cell increase favors a diagnosis of UC,⁵³ but patchy inflammation^{42,54} can also be seen in UC in adults and especially in children.⁵⁵ Patchy and focal inflammation are also reported in patients with primary sclerosing cholangitis (PSC) without clinically overt colitis, and in areas of the colon proximal to the macroscopically involved segment, in patients with distal colitis. In a review of 71 patients with PSC and IBD compared to 142 patients with UC without PSC, rectal sparing was more common in patients with PSC.^{56,57}

Glandular abnormalities can be identified with good (83%–90%) interobserver agreement. Diffuse crypt architectural irregularity is indicative of UC. It may, however, be absent in biopsies obtained at disease onset. In 1 study it was observed in biopsies obtained between 16 and 30 days after onset but not in earlier biopsies. However, in another study it was present in all biopsies obtained within days after onset. In

the latter study disease onset was defined by loss of blood.^{41,47} In established UC a villous surface is present in 17%–63% of the cases (compared to 0%–24% for CD and 0%–7% for infections). The lesion is observed in approximately one-third of the initial biopsies of children with UC. In adults this feature was present in ≈23% of the patients presenting 16–30 days after the initial symptoms but not in earlier biopsies. Paneth cell metaplasia favors UC, but can be seen wherever there has been mucosal remodeling. The predictive value is high but the sensitivity is low. It is not seen in biopsies obtained early in the disease^{4,8} and is probably related to more long-standing disease.^{52,58–60} Thus, the morphological diagnosis of UC at onset may be difficult in adults and especially in children because the histological features are not typical of those described for more established disease. The diagnosis of Crohn's colitis is also difficult because of well-known sampling problems. There are no established features for a diagnosis of IC on endoscopic biopsies.^{4,40}

IC AND SEROLOGIC MARKERS

UC and CD describe clinical entities based on definitions and criteria established over 5 decades ago and they have been revised remarkably little since. Technological advances based on genetic markers and a better knowledge of immune responses have allowed a better characterization. The latter has led to the development of serologic tests that are used for diagnostic purposes. Overall, pANCA is associated with UC, while ASCA, I2, and Ompc are more commonly positive in CD. The combinations ASCA+/pANCA– and ASCA–/pANCA+ are strongly associated with CD and UC. In a prospective study of 97 patients with clinical IC, a 48% positive predictability of ASCA–/pANCA– was found for sustained IC.⁶¹ In the population-based “IBSEN” study, however, no substantial number of IC patients with the pattern of pANCA–/ASCA– was found.⁴ Further data are needed to assess the value of serologic testing in adults and in children, where they may be less useful.⁶²

FUTURE PROSPECTS

Questions regarding predictability of IBDU and IC are difficult to answer. Wireless capsule endoscopy can identify small bowel lesions not seen with other imaging techniques. In the future it may well play a major role for the diagnostic work-up of patients with IBDU. However, whether the presence of small bowel lesions is always positive for a diagnosis of CD remains to be proven. Immunogenetic markers may increase our understanding of subgroups in IBD. At present, few data are available for patients with IBDU or IC. In 1 study *NOD2/CARD15* mutations in patients with IC were as common as in control patients (20%).⁶³ However, this is not surprising, as *NOD2* is associated with ileal disease. Studies related to HLA, new polygenic associations, or even epigenetic factors may be more rewarding in the future.

At present, only a small number of patients remain really unclassified or indeterminate. Whether this is due to therapy confusing the gross and microscopic morphology, because of concurrent disease, or for other reasons is not clear. We are still lacking controlled prospective studies with data documenting the connection between IBDU and IC and complicated disease or specific complications after surgery. With more effective medication for all subgroups of IBD patients in general, a major question will be if the subgroups of IC or uncertain colitis represent responsiveness to treatment.

CONCLUSIONS AND RECOMMENDATIONS

1. A precise diagnosis of UC or CD of the colon is not always possible either clinically or by histological examination of resected specimens.
2. Diagnostic problems are most common early in the disease in both children, especially in the very young, and adults (although in a substantial number of patients a correct diagnosis is reached during follow-up). The development of diagnostic features is time-dependent, but the precise duration has not been established. For UC, the development needs at least several days up to 4 weeks from the onset of symptoms.
3. The development of the characteristic UC lesions, however, may need more time, as shown by studies in 1) patients with PSC where the immunological response may be aberrant, 2) UC patients with limited distal UC, developing into pancolitis, and 3) de novo UC after liver transplantation.⁶⁴ Patients with PSC may be a particularly difficult subgroup, especially in those presenting with PSC in whom colitis is found incidentally.
4. The development of specific morphological features may furthermore be influenced by other concurrent diseases or treatment. Liver diseases such as hepatitis can modify the pattern in UC.⁶⁵
5. For CD there are no good data available except from postoperative follow-up studies showing new lesions already at 3 months after so-called curative surgery.⁶⁶
6. The use of the term “indeterminate colitis” (IC, IND, or IndC) has evolved from one based on colectomy specimens, to one that includes patients suspected of having IBD based on biopsy specimens without features enabling a clear diagnosis; some of these patients are ultimately considered not to have IBD. This has resulted in a hugely ambiguous terminology. Definitions of IC found in the literature are listed in Table 1, while those used by members of the IOIBD are provided in Table 2.

TABLE 3. Classification of IBD Based on the Montreal WCOG Working Party 2005 and IOIBD 2007

When the diagnosis is based on evidence including colectomy specimens	
Colitis of known type or etiology (UC, CD, etc.)	
Colitis with (some) features of CD (see text)*	
Colitis of uncertain type etiology – no features of CD (if “indeterminate colitis” is used at all this is the group it should be applied to)	
Colitis not classifiable with the available material	
When the diagnosis is based on evidence including mucosal biopsy samples	
Colitis of known type/etiology (UC, CD, etc.)	
Colitis type unclassified (IBDU)*	
Colitis of uncertain etiology (possible IBD)	
Colitis nonclassifiable with the available material	

* Implications for potential IPAA.

7. An International Working Group recommended restricting the term IC to resected specimens, and to use “IBD unclassified” (IBDU) for all other cases.⁶⁷ The reasons for this proposal were 1) the term IC was originally proposed for colectomy specimens, and 2) not all diagnostic microscopic features can be assessed on endoscopic biopsy samples. Consequently, patients who appear to have IBD colitis but who cannot be readily classified when all clinical, radiological, endoscopic, histologic, and serologic data are taken into account should be classified as IBDU. Questions regarding predictability of IBDU and IC are difficult to answer. Wireless capsule endoscopy can identify small bowel lesions not seen with other imaging techniques. It may therefore play a role for the diagnostic work-up of patients with IBDU. The majority of cases with IBDU at onset represent incipient UC. However, a substantial number may be reclassified to non-IBD because they have no relapse during follow-up.^{4,68} These were probably due to infections or drugs.⁶⁸
8. While we agree with the Working Party that, if it is used at all, the term IC should be restricted to resection specimens, we wonder if the time has not come to replace the term completely (Table 3).

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