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## Be or Not to Be a Crohn's Disease: CD and Its Numerous Differential Diagnosis

Amandine Gagneux-Brunon<sup>1</sup>, Bernard Faulques<sup>2</sup> and Xavier Roblin<sup>2\*</sup>

<sup>1</sup>*Infectious and Tropical Diseases Department, CHU de Saint-Etienne,*

<sup>2</sup>*Gastroenterology Department, CHU de Saint-Etienne*

*France*

### 1. Introduction

Nowadays, there is still no gold standard test for Inflammatory Bowel Disease (IBD). Many etiologies are responsible of an inflammation of the gut. When a patient presents with signs suggestive of IBD (abdominal pain, diarrhea, and sometimes fever), the clinician had to establish whether the patient suffers from an IBD or from one of the numerous alternative diseases. The use of immunosuppressive agents and biotherapies in IBD treatment enforces the necessity to distinguish them from infectious diseases, particularly from tuberculosis. Clinical signs of IBD are not specific. This review will focus on the differential diagnosis of Crohn's Disease (CD) and on the helpful tests for the diagnosis. Histopathological findings are sometimes insufficient to establish the diagnosis, granuloma is not specific and inconstant in CD (only in 15 to 60 % of cases). Serological assays (perinuclear antineutrophil antibodies pANCA and anti-*Saccharomyces cerevisiae* antibodies ASCA) are contributing to the diagnosis, but their sensitivity and specificity are too weak for a gold standard. This review will be divided in 2 parts: first, a review of etiologies inducing granulomas in the gut (infections, systemic diseases, drug related disorder...), second, a review of controversies in the distinction between ulcerative colitis (UC) and CD. This review will contribute to provide to clinicians a strategy for differential diagnosis of CD (infection, systemic disease, neoplasm, drug related disorders, non specific inflammation...). Therefore, sensible and specific biomarkers are needed to facilitate the diagnosis of IBD in the future.

Crohn's disease is an Inflammatory Bowel Disease (IBD), able to affect all the gut mucosa. Crohn disease may induce lesion of epithelioid granuloma. However, this type of lesion may be associated with others affections, certain of these affections are infectious diseases, and contra-indicate formally the immunotherapy. Nowadays, there is no gold standard assay to make the etiological diagnosis of granuloma of the gastrointestinal (GI) tract.

### 2. How differentiate CD from tuberculosis?

The differential diagnosis of CD and tuberculosis of the digestive tract is challenging, as the incidence of CD is dramatically increasing in countries where TB is too prevalent, and as TB epidemic restarts in the developed countries. Since the presence of a caseation necrosis in

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\* Corresponding Author

endoscopic biopsies confirms TB, this histological findings stay uncommon in the most cases of digestive TB. Surgical biopsies are more efficient to establish the diagnosis of TB (1). A confusion between TB and CD is not Exceptional. In a saoudian study, 21% of the patients treated for a digestive TB, were really affected by CD (2). Clinically, the differential diagnosis is uneasy. Digestive TB is induced by hematogenous spread after the inhalation of the bacillus or by ingestion of *mycobacterium bovis*. In case of an infection by *mycobacterium tuberculosis*, the association with a pulmonary TB is inconsistent. Certain localizations for lesion are more frequent in TB than in CD. Preponderant localizations are presented in table 1. After a comparison between 53 patients with CD and 53 others with digestive TB, *Makharia et al.* establish a clinical, endoscopic et histological score to differentiate TB (3). In this study, chronic diarrhea, blood in the stools, perianal disease and extraintestinal manifestations were significantly more frequent in CD than in TB. On the other side, abdominal pain, constipation, intestinal obstruction, loss of appetite, and weight loss were associated with TB. Sites of CD involvement were more often rectum, sigmoid, ascending and descending colon. The type of lesions in endoscopy was also different in the two groups: skip lesions, friability, aphtous, linear and superficial ulcers, and cobblestoning were more often observed in the CD group. Nodular lesions were more frequent in the TB group. Histological examination found more and larger granulomas per section in TB, and more often lesion of focally enhanced colitis in CD. The developed score is: -2,5\*Involvement of sigmoid colon-2,1\* blood in stool+2,3\*weight loss-2,1\*focally enhanced colitis+7 where each characteristics were given 1 if present and 0 if absent. With a cutt-off of 5,1, this score demonstrated a good sensibility, a good specificity and a good ability to correctly classify the two diseases. The area under the receiver operating curve (AUC-ROC) was 89,2. Endoscopic examination is really helpful to differentiate TB from CD. Considering that anorectal lesions, longitudinal ulcers, aphtous ulcers cobblestone appearance were typical in CD, and that involvement of fewer than four segments, a patulous ileocecal valve, transverse ulcers, and scars of pseudopolypes were typical of intestinal TB, *Lee et al.* hypothesized that CD diagnostic could be made when the number of parameters characteristic of CD was greater than parameters associated with TB (4). With these assumptions, diagnosis was correctly made in 87,5 % of the patients. Histological examination is also useful. However, characteristic lesions of TB as confluent granulomas, more than 10 granulomas per biopsy sites, and caseous necrosis are present in only a limited number of TB cases (50%, 33%, 22% respectively)(5). *Mycobacterium* is found by direct examination of biopsy in only 20 to 50% of intestinal TB cases.

Crohn's Disease	Tuberculosis
Rectum	Ileocecal region
Sigmoid colon	Ascending colon
Descending colon	Rectum
Jejunum	

Table 1. Principal localisations of granuloma in CD and TB

Serological test to differentiate CD and ulcerative colitis (UC) as detection of perinuclear anti-neutrophil antibodies (p-ANCA), and anti-saccharomyces cerevisiae antibodies (ASCA) are not useful to differentiate CD from TB. Several studies had shown that IgA and/or IgG level of ASCA was not different between patients with CD and intestinal tuberculosis. P-ANCA was also similar in patients with CD than in patients with intestinal TB. Nowadays,

serological test with p-ANCA & ASCA are not helpful to differentiate TB from CD. Intradermoreaction with tuberculin is not enough sensible or enough specific to make the diagnosis of intestinal TB, as it can be positive in the case of infections due to others *Mycobacteriae* and after vaccination and negative in immunocompromised patients. Quantiferon is a blood test of reactivity of lymphocytes T to TB antigens with production of interferon gamma which is not influenced by vaccination. Up today, no study is published on the diagnosis value of quantiferon TB for differentiating between TB and CD. There are only cases reports about positive quantiferon in case of intestinal TB. However, quantiferon is often negative in cases of extrapulmonary TB as osteitis due to *Mycobacteria*.

Cultures of *Mycobacteria* are difficult and long (3 to 8 weeks). Polymerase Chain Reaction (PCR) in intestinal biopsy, or in stools might be a good tool. Yet, the sensibility of the PCR *Mycobacterium tuberculosis* varies from 31 to 60% in biopsies (6). A positive PCR was less frequent than caseation necrosis, and presence of bacillus after Ziehl and Neelsen staining. A PCR positive in stools might help to make the diagnosis of intestinal TB, with a sensibility of 79% and a good specificity, however, this PCR may be positive in case of pulmonary TB without intestinal involvement (7).

### **3. Non tuberculous *mycobacteria*: Another cause of intestinal granuloma or an agent for CD?**

In immuno-compromised patients (particularly HIV-positive subjects and transplanted patients), *Mycobacterium avium paratuberculosis* (MAP) is often incriminated in intestinal granulomatous disorders. However, several authors hypothesized that it might be a causal agent of CD. Long term blood culture from a great number of CD patients are positive for MAP, yet a great proportion of healthy controls exhibit positive blood culture. The frequency of MAP positive blood culture is greater in the groups of CD patients (8). However, these results are insufficient to conclude that MAP is a causal agent for CD. It might be a consequence of a modified commensal microbiota. A defective sensing and killing of bacteria (due to mutation in pattern-recognition receptors) might contribute to the onset of the disease (9). The only temporary efficacy of anti-tuberculous therapy in patients with CD is not in favor of a causal role of MAP in CD (10).

### **4. *Helicobacter pylori* (HP): An under-estimated agent of granulomatous gastritis**

HP is a potential agent for granulomatous gastritis. Its frequency might be under-estimated. In 18 patients with granulomatous gastritis, HP was found in 14 cases, diagnosis of CD was made in only 1 case (11). For others, infection with HP is only concomitant of CD (12).

### **5. Gastro-intestinal histoplasmosis: A difficult but urgent diagnosis**

*Histoplasma capsulatum* (HC) is a mold which is common in mid-western USA, and south America. The most of patients with a disseminated histoplasmosis exhibits HC in gastrointestinal tract. First, HC is inhaled and disseminated in the all organism. Risk factors for HC are immunodepression: AIDS, CD4 lymphopenia, immunosuppressive agents. Gastrointestinal involvement may occur as a result of the adjacent mediastinal adenitis or fibrosing mediastinitis. Clinical manifestations are dysphagia, upper gastrointestinal

bleeding, broncho-oesophageal fistula, abdominal pain, weight loss, lower GI bleeding, intestinal occlusion in the case of an intestinal involvement. However, GI involvement of HC may be asymptomatic. Diagnosis can be made after periodic acid Schiff (PAS) stain, antigen detection in blood and urine, serology and cultures are useful to establish the diagnosis as they are often positive in patients with histoplasmosis (13). This pathology is uncommon, but in the most of cases, no travel in endemic zone is identified. Other manifestations can be seen as hyperferritinemia, macrophagic activation syndrome, pancytopenia. The presence of these extradigestive manifestations in immunocompromised patients may encourage physicians to look for histoplasmosis.

### **6. *Tropheryma whipplei* (TW): A “real” pathogen with frequent asymptomatic carriers**

Whipple's disease is unfrequent. Nine percent of the patients with manifestations of Whipple's disease had duodenal biopsies with granulomatous gastritis without caseation necrosis. Clinical manifestations are malabsorption, chronic diarrhea associated with arthritis, arthralgia, neurological disorders: supranuclear ophthalmoplegia, cognitive disorders. PCR for *T. Whipplei* is helpful to make the diagnosis. However, as this PCR is positive in 1 on 174 healthy patients, the diagnosis is definitive when the PAS staining and the PCR are positive, in association with evocating clinical manifestations. Furthermore, this PCR is positive in duodenal biopsies in stools of respectively 5 % and 11% of the patients with gastric disorders. There are many subjects who are asymptomatic carriers of TW (14).

### **7. GI granuloma: Do not forget Syphilis?**

At the secondary and tertiary stage of *Treponema Pallidum* infection, GI involvement is possible with granulomatous lesions (15). Gastric ulcers and upper GI bleeding may be seen. Diagnosis is made with serologies TPHA, VDRL, PCR, and immunofluorescence staining in biopsies. Differential diagnosis are gastric lymphoma and linitis.

### **8. *Yersinia*: A frequent agent for granulomatous appendicitis**

*Yersinia enterocolitica* and *pseudotuberculosis* may cause granulomatous appendicitis, ileitis, mesenteric adenitis and colitis. The cultures are positive in around 25% of granulomatous appendicitis(16). The contamination is due to the ingestion of the bacteria. Some authors hypothesized that the defects in mucosal barrier induced by CD favors infection by *Yersinia* (17).

### **9. Sarcoidosis: Rare but not impossible granulomatous involvement of digestive tract**

Sarcoidosis is a systemic granulomatosis, which rarely involves in the gastrointestinal tract (almost 3% of the patients). This is a disease, affecting people from 20 to 40 years old; the incidence is more frequent in blacks and north Europeans. Gastric lesions and extrinsic compression by mediastinal lymphadenopathy are the most frequent (18). Furthermore, any cases were reported of, small bowel polyps and colonic obstruction(19,20). Small bowel involvement may cause a real enteropathy. To confirm the diagnostic, physicians needs to obtain two biopsies from two different sites positive for giant granuloma without caseum,

and after having excluded all the other potential diagnosis. Skin biopsies, lymphadenectomy, bronchoscopy with biopsy, 18-fluoro-desoxy-glucose scintigraphy may be useful to confirm the diagnosis. The dosage of the angiotensin converting enzyme (ACE) is not really helpful as every granuloma are secreting (21), as there is a polymorphism for its gene (22), with individuals with low level of ACE, even with sarcoidosis.

### **10. Other systemic granulomatous disorders: a more frequent GI involvement**

Wegener's granulomatosis and Churg-Strauss syndrome affects in 80 % of the cases the GI tract. Clinically, patients exhibit abdominal pains, nausea, diarrhea and digestive hemorrhage (23). Gastroduodenal ulcers may be found. Granuloma is not always found in biopsy. Clinically, asthma is always found in Churg-Strauss syndrome and associated with hypereosinophilia. The dosage of antineutrophil cytoplasmic antibodies is interesting for the diagnosis as the sensibility is almost 70 to 80 % and a similar specificity (23). Anti-PR3 are associated with Wegener's granulomatosis.

### **11. Other anecdotic etiologies**

Gastric lymphoma may represent an alternative diagnosis for a gastric granulomatous lesion (12). It is often T cells lymphoma or, lymphoma of the gut associated lymphoid tissue. Necrosis could be seen in this situation. In Shapiro's study, 2 patients on 42- with a gastric granuloma- were affected by a lymphoma. They also described in this retrospective study, cases of adenocarcinoma of the distal oesophagea. Some toxic agents may cause granuloma; yet, digestive involvement is rare. These agents are beryllium,  $\alpha$ -interferon, BCG therapies for bladder cancer, and allopurinol. *Taeniasis* may be associated with granuloma of GI tract. There is a genetic disease, which causes immunodeficiency and systemic granulomatosis. Chronic septic granulomatosis is often linked to X-chromosome. Patients are susceptible to bacterian and fungal infections; it's the consequence of a modified NADPH-oxydase in macrophages. Granulomatous lesions of GI tract are frequent, particularly in colon(24).

### **12. Which strategy adopting when histopathological examination is not sufficient to make the diagnosis?**

First line, second and third line, laboratory assays helpful to make a diagnosis are presented in table 2, 3 and 4. In many cases, the etiological diagnosis is made with all clinical and biological arguments. Finally, when the diagnosis stays difficult, an anti-TB treatment might be started and its efficacy might lead physicians to conclude for a diagnosis of TB.

### **13. Clinical diagnosis with Crohn's disease among various forms of intestinal inflammation**

**These diagnosis depend about the anatomic localization of the process**

#### **Ileitis:**

A variety of conditions may mimic Crohn's ileitis. Table 5 report differential diagnosis of ileitis. Some others rare aetiologies can be explain ileitis. Infiltrative diseases (amyloidosis and eosinophilic gastroenteritis), lymphoid nodular hyperplasia and radiation enteritis must be researched also.

Laboratory assays	Diagnostic orientation	Diagnostic value
Hemogram	Lymphopenia : HIV infection, immunodespression Hypereosinophilia : Churg-Strauss syndrome Inflammatory syndrome in all cause of digestive granuloma	No sensibility, No specificity
C-reactive protein	Confirms inflammation	No sensibility, no specificity
Lactate deshydrogenase	May orientate to lymphoma if increase	No sensibility, no specificity
Creatinine, albumine in urine/creatinine ratio	An associated nephropathy may be observed in Wegener's granulomatosis and Churg-Strauss syndrome	No specificity
Tuberculin test	Tuberculosis, sarcoidosis if asynergy	No specificity (past immunization by BCG), no sensibility in immunocompromised patients
Chest radiography	Tuberculosis	Only 30% patients with TB of GI tract have a pulmonary TB
Testing for HIV by serological assay	Orientate to opportunistic infection : <i>histoplasmosis</i> or <i>non tuberculosis mycobacteria</i>	Sensible and specific for HIV testing but only give an orientation
Stools cultures Parasitological examination of the stools	<i>Yersinia</i> , parasites	Sensible
<i>Helicobacter pylori</i> culture in biopsies, or <i>Hp</i> serology	<i>Hp</i> infection	Culture may be negative if proton pump inhibitor therapy

Table 2. First line biological examination in patients with evidence of a GI tract granuloma

Laboratory assays	Diagnostic orientation	Diagnostic value
Quantiferon TB gold	Tuberculosis	Not evaluated in digestive tuberculosis
<i>Mycobacterium tuberculosis</i> PCR in stools and biopsies	Tuberculosis	Not enough sensible in biopsies, lack of specificity in stools as it may be positive in pulmonary TB
ANCA detection	Wegener's granulomatosis and Churg-Strauss syndrome Ulcerative colitis	Good sensibility, good specificity for these three etiologies
ASCA detection	Crohn disease	Not specific, may be positive in TB
Angiotensin Converting enzyme	sarcoidosis	Not sensible, not specific and genetic polymorphism
18-FDG scintigraphy	May guide some deep biopsies	Sensible but not specific
Chest and abdominal tomodensitometry	Search other sites of involvement to orientate the diagnosis as infiltrative pneumopathy	Not specific

Table 3. Second line biological or radiological tests

Laboratory assays	Diagnostic orientation	Diagnostic value
<i>Tropheryma Whipplei</i> PCR	Whipple's disease	Good sensibility, but often positive in asymptomatic patients
Urine and blood antigen detection of <i>histoplasmosis</i> , serology	Think to histoplasmosis if the patients stayed in endemic area, or in immunocompromised ones	
Angiotensin converting enzyme genotyping	Sarcoidosis to interpret ACE levels	
<i>Yersinia</i> PCR	Yersiniosis	Sensible

Table 4. Third line biological tests

<b>Infection</b>	<b>Inflammation</b>	<b>gynecologic</b>
Yersinia enterocolitica Yersinia pseudotuberculosis Mycobacterium tuberculosis Mycobacterium avium-intracellulare Typhlitis Histoplasma capsulatum Salmonella Cryptococcosis Anisakiasis Actinomyces israelii	Appendicitis Appendiceal abscess Cecal diverticulitis	Pelvic inflammatory disease Tuboovarian abscess Ovarian cyst or tumor Endometriosis Ovarian torsion Ectopic pregnancy
<b>Neoplasm</b>	<b>Drug related</b>	<b>Vascular</b>
Cecal or small bowel (ileal) adenocarcinoma Lymphoma Lymphosarcoma Carcinoid tumor Metastatic cancer	Nonsteroidal antiinflammatory drug-related ulcer or stricture Ischemic: oral contraceptives, ergotamine, digoxin, diuretics, antihypertensives	Ischemia Vasculitides: polyarteritis nodosa, Churg-Strauss syndrome, Takayasu's arteritis, Wegener's granulomatosis, lymphomatoid granulomatosis, giant cell arteritis, rheumatoid arthritis vasculitis, thromboangiitis obliterans Henoch-Schoenlein purpura Systemic lupus erythematosus Behçet's syndrome

Table 5. Differential diagnosis of ileitis

**Proctitis:**

In addition to ulcerative proctitis, proctitis may also occasionally be the presentation of Crohn's disease. The other differential diagnosis are brief (Table 6).

**Colitis:**

**The causes of colitis are legion.**

Numerous infectious agents may cause a transient colitis, but the clinical course of most enteric infections is usually complete within 2 weeks of onset. The most important infections are: Cytomegalovirus, Shigella, Campylobacter, Clostridium difficile, Salmonella, Aeromonas pleisioides, Amebiasis, Enterohemorrhagic E. coli (EHEC), Mycobacterium tuberculosis, Yersinia enterocolitica, Schistosomiasis and strongyloidosis. Nevertheless, others aetiologies must be evoked in function of associated symptoms and patient: Ischemic colitis, diverticulitis, microscopic colitis, diversion colitis or radiation, Behçet disease and sarcoidosis.

Infection	Others
Herpes simplex type II <i>Neisseria gonorrhoeae</i> Syphilis ( <i>Treponema pallidum</i> ) Lymphogranuloma venereum <i>Chlamydia trachomatis</i> Whipworm infestation	Prolapse Solitary rectal ulcer Trauma Chemical injury

Table 6. Differential diagnosis of Crohn's disease or ulcerative proctitis

Drug related colitis must be researched: NSAIDs, gold, penicillamine) or toxic like cannabis; Some aetiologies are rare and must be evocated after these hypothesis: Chronic granulomatous disease, graft-vs-host disease.

	Ulcerative colitis	Crohn's disease
Distribution	Continuous, symmetric, and diffuse, with granularity or ulceration found in entire involved segments;	Often discontinuous and asymmetric with skipped segments, normal intervening mucosa,
Rectum	Typically involving rectum and distributed proximally	Complete or, more often, relative rectal sparing may be present
Mucosal lesions	Microulcers more common, larger ulcers possible, pseudopolyps more common	Aphthous ulcers common in early disease; late disease notable for ulcers with stellate, "rake," "bear-claw," linear or serpiginous ulcers; cobblestonin
Depth of inflammation	Mucosal, not transmural except in fulminant disease	Submucosal, mucosal, and transmural
Histology	Crypt abscesses and ulcers are the defining lesion Crypt abscesses may be present Ulceration on a background of inflamed mucosa	Crypt abscesses may be present Ulceration on a background of inflamed mucosa Hallmark is focally enhanced inflammation, often on a normal background
Complications	Parianal findings not prominent	Parianal lesions (40%), strictures, fistulas

Table 7. Clinical distinctions between ulcerative colitis and Crohn's disease.

When a causative agent is not identified, the issue of sorting out a first presentation of IBD from an acute self-limited colitis arises. Such a distinction relies strongly on histologic rather than endoscopic findings. Once a diagnosis of IBD has been established, Crohn's disease should be distinguished from ulcerative colitis.

#### **14. Controversies in the distinction between ulcerative colitis and Crohn's disease**

Many distinctions—clinical, anatomic, histologic—have been drawn between the 2 major forms of IBD (Table 7). A gold standard of diagnosis has yet to be attained, however.

Some clinical distinctions challenged by careful observation. Theoretically, ileum is not involved, except as “backwash” ileitis in panulcerative colitis. Conversely, ileum is often involved in Crohn's disease. Backwash ileitis has long been recognized as a feature of panulcerative colitis but may yet throw even the experienced diagnostician off the trail if more than a few centimeters of ileal inflammation are present. When ileitis in the setting of pancolitis is more extensive than this, careful appraisal of the ileocecal valve may be helpful. A patulous valve with extensive backwash is more convincing as a feature of ulcerative colitis than lengthy ileitis behind a constricted, stenotic valve, more suggestive of Crohn's disease.

Complications are very frequent in the natural history of Crohn's disease. The 20-year cumulative rate of all complications is more than a population-based cohort (25); CD evolution relates to disease location. Small bowel involvement might be complicated at diagnosis or during the first years after diagnosis by an abscess or fistula, or by a stricture followed by formation of a fistula, whereas colonic disease can remain uncomplicated or inflammatory for many years. Strictureing and penetrating lesions can coexist in the same individual or even within the same intestinal segment. Conversely, in UC perianal findings are not prominent. If fissure or fistula have been present, they should be uncomplicated. Strictures are rarely present and are suggestive of adenocarcinoma. Moreover, fistulas are not present, except for rare occurrence of rectovaginal fistula. In CD, about 20%-30% of patients present with perianal lesions and 15%-20% have or had a fistula (26). Another diagnostic criterion challenged by careful observation is the classic observation of continuous involvement of colonic mucosa without skip areas in ulcerative colitis. Although this distinction is generally true, care must be taken in interpreting the finding of skip areas. Topical therapies may lead to a false impression of “rectal sparing,” whereas oral or systemic therapies may result in patchy healing, depending on the timing of endoscopy or completeness of response (27). Accordingly, the most accurate diagnosis may be made at the earliest evaluation, before anatomy and histology have been confounded by treatment.

Given this limitation, it is not surprising that, in some cases, it will be impossible to distinguish between ulcerative colitis and Crohn's disease, with potential implications for prognosis and treatment. Prospective, population-based studies suggest that approximately 1 in 20 patients with IBD will have a diagnosis of indeterminate colitis (28). Subsequent follow-up leads to a firmly established diagnosis of ulcerative colitis in one third of these cases, whereas 17% are assigned a diagnosis of Crohn's disease (29). The clinical value of pANCA or ASCA testing in patients presenting with non-specific gastrointestinal symptoms is limited because of inadequate sensitivity. Thus tests are infrequently positive in

individuals who do not have IBD. With the addition the latest panel of 7 antibodies has improved the positive and negative values of serologies. Using all of the serologic markers reported for CD, the sensitivity for diagnosing CD is greater than 80% and the positive predictive value is over 90% but only when the prevalence of CD is high, 38% (30). ANCA positivity has been observed in other colitides, such as eosinophilic and collagenous colitis. The specificity of ASCA seems to be higher, but ASCA positivity has been observed in patients with Behçet's disease, primary biliary cirrhosis, autoimmune hepatitis, and celiac disease. The cost effectiveness of serologic tests in the sequential diagnostic testing of IBD in children has been shown to avoid unnecessary and costly evaluations (31), but it has not been confirmed by other studies (32).

Serologic evaluation of ANCA and ASCA could be of help in patients with indeterminate colitis (33). In these patients, early knowledge of the exact diagnosis could be of clinical importance with regard to therapeutic decisions and prognosis (34). Patients who are pANCA positive and ASCA negative are 19 times more likely to have UC, whereas patients who are ASCA positive and pANCA negative are 16 times more likely to have CD (35). A remarkable finding is that patients who do not have antibodies, to either ASCAs or ANCA, are remaining indeterminate colitis after a mean duration of 9.9 years (33). Further refinement of serologic tests and/or the combination of serologic testing with routine laboratory and fecal tests testing and noninvasive imaging may offer efficient cost-effective screening in the future.

## 15. Conclusion

The increases in incidence and prevalence of IBD over the last 15 years and its emergence in developing countries indicate a role of the environment in pathogenesis. Their diagnosis may be difficult and are clinical, endoscopic and histologic assessment. The issue remains that no gold standard test exists for the diagnosis of IBD. For these reasons, diagnosing crohn's disease and ulcerative colitis continues to be a more than occasional challenge to the practicing gastroenterologists. In the time of biotherapies, a casual diagnosis of IBD may result in critical errors in management in that incorrect diagnosis may result in inappropriate or even contraindicated treatment.

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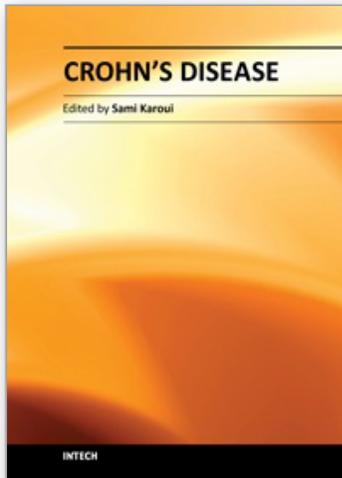
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In this book, several important points regarding Crohn's disease are discussed. In the first section, we focus on etiopathogeny of Crohn's disease and the recent advances in our overall understanding of the disease - specifically, the role of the gut epithelium, alterations of the epithelial crypts, and the roles of the different cytokines in the pathophysiology of Crohn's disease. In the second section, a diagnosis of Crohn's disease is discussed. Another particular area of focus is in the diagnosis of intestinal tuberculosis, and the role of mycobacterium avium in Crohn's disease. In the third and final section, the management of Crohn's disease is discussed, with a focus on recent evidence-based medicine recommendations.

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Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

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