Current Diagnostic Approach of Inflammmatory Bowel Disease

Anggilia Stephanie, Dadang Makmun***
* Department of Internal Medicine, Faculty of Medicine, University of Indonesia
Dr. Cipto Mangunkusumo General National Hospital, Jakarta
** Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine
University of Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta

ABSTRACT

Inflammatory bowel disease (IBD) has begun to emerge in Indonesia. The disease is further classified into two types, ulcerative colitis (UC) and Crohn's disease (CD). Diagnosis of IBD is initiated from symptom findings such as diarrhea, abdominal pain, bleeding diarrhea, and weight loss, and supported by physical examination and additional tests. The options for additional examinations of IBD are mainly endoscopy (esophagogastroduodenoscopy, colonoscopy, and also intestinal endoscopy), imaging techniques, and laboratory examinations either from blood or feces. The application of these modalities should be prompted by sufficient clinical suspicion to promote their efficiency as well as prevent underdiagnosis or overdiagnosis. In primary health care settings, patients with IBD are expected to be recognized for therapy or to use appropriate referral system to warrant a proper treatment.

Keywords: *inflammatory bowel disease, diagnosis terkini, kolitis ulseratif, penyakit Crohn*

ABSTRAK

Inflammatory bowel disease (IBD) mulai banyak ditemukan di Indonesia. Penyakit ini terbagi atas dua jenis yaitu kolitis ulseratif (KU) dan penyakit Crohn (PC). Diagnosis IBD dimulai dari gejala yang ditemukan seperti diare, nyeri perut, buang air besar berdarah dan penurunan berat badan, serta didukung oleh pemeriksaan fisik dan pemeriksaan penunjang. Pilihan pemeriksaan penunjang untuk IBD secara garis besar adalah endoskopi (esofagogastroduodenoskopi, kolonoskopi maupun endoskopi usus halus), pencitraan, dan pemeriksaan laboratorium, baik dari darah atau feses. Penggunaan berbagai modalitas ini harus didahului adanya kecurigaan yang cukup secara klinis agar tepat guna, mencegah under- atau overdiagnosed. Pada tingkat layanan primer, pasien IBD juga diharapkan dapat ditemukan untuk diterapi atau menggunakan sistem rujukan yang tepat agar ditatalaksana dengan baik.

Kata kunci: *inflammatory bowel disease, diagnosis terkini, kolitis ulseratif, penyakit Crohn*

INTRODUCTION

A digestive tract abnormality, inflammatory bowel disease (IBD), is categorized as inflammatory disease with still unknown cause. IBD is divided into 2 main disease entities, such as ulcerative colitis (UC) and Crohn's disease (CD). If it is still undetermined between the two, it can be called undetermined colitis.[1] The peak age of patients with IBD is quite young (25-30 years old) and there is no significant difference between male and female.[2] Most IBD patients are 15-30 years old, although it may happen in all ages. UC is slightly fewer in male, while CD is more frequent in female.[3] Initially, incidence tends to increase in developed countries with tendency in white race, high social economy, non-smoker, oral contraception recipient and low fiber diet. But the incidence in this century

tends to persist in developed countries and increases in developing countries.[1] From Centers for Disease Control and Prevention (CDC) data, it is known that the incidence rate of UC varies from 0.5–24.5/100,000 persons, while CD from 0.1–16/100,000 persons. It is predicted that currently as much as 1.4 million people in United States suffer from this disease.[3]

Data in Cipto Mangunkusumo Hospital from total colonoscopies in 2002, as much as 5.2% were UC cases, while 5.2% were CD.[1] Meanwhile from colonoscopy results in 2001-2006, it was found that total colonoscopies were 1541 times and IBD was diagnosed as much as 8.3%, with 5.4% UC and 2.9% CD.[1] In several other hospitals, it was also reported that more UC was found as compared to CD.[1,2] Currently, there has been no quite satisfactory epidemiology data, only endoscopy database from each hospital. Based on symptoms complained by IBD patients, the most common was bleeding chronic diarrhea and stomachache, followed by chronic diarrhea, and the least was hematoschezia.[1]

Diagnosis of IBD supposedly can be confirmed from primary health care, however without suffient directed suspicion, even in tertiary health care centre this disease may be missed. In contrast, not all chronic diarrhea or bleeding diarrhea is caused by intestinal inflammation, therefore over diagnosing also needs to be hindered.[4]

CONFIRMING DIAGNOSIS

There is no definite diagnostic test for IBD. Diagnosis is expected to be made clinically, particularly in health care centre which is not tertiary. Diagnosis is made based on the symptoms and physical examination, strengthened by endoscopy, radiology, laboratory and histopathology findings. In both types of IBD, clinical presentation varies. The differential diagnosis is gastrointestinal tuberculosis. Through radiology and endoscopy, they are difficult to be differed from each other and may have similar predilection anatomy. Meanwhile, the degree of disease activity may be evaluated using disease activity index which is different for CD and UC.[1,2]

Ulcerative colitis according to the definition is an inflammation condition which is limited to the colon, therefore it is mainly divided anatomically, particularly proxitis (limited to the rectum), left side colitis (sigmoid colon with or without descending colon involvement), or pancolitis. Some patients also experience inflammation of the ileum, known as 'backwash ileitis' condition. This last condition frequently causes difficulty to differentiate UC and ileocolitis in CD.[5]

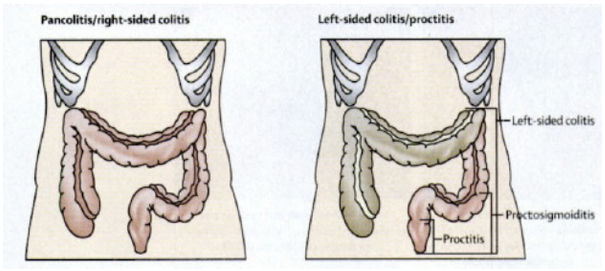

Figure 1. Illustration of anatomical involvement in ulcerative colitis[5]

Clinical Manifestations

There are four main symptoms frequently complained by IBD patients, which are diarrhea, stomachache, bloody stool and decreased body weight. Meanwhile a review by Jellema et al found that these four symptoms were neither sensitive nor specific to confirm the diagnosis of IBD.[6] Several diagnostic criteria based on symptoms (symptom-based criteria) have been developed, such as Manning and Kruis criteria. If group of one's complaints is inserted to this criteria, the sensitivity and specificity to diagnose is better, with the number of more than 65% for both in several studies.[6]

Confirming Diagnosis in Primary Health Care Centre

In Indonesia primary health care centre plays very important role, considering the spread of population in variable geographical terrain, while the access to reach tertiary health care centre or type A hospital may be difficult. IBD complaints are quite varied, ranging from mild symptom, such as localized stomachache, up to quite a lot of digestive tract bleeding, which makes it necessary to perform simple diagnostic method that could be performed as soon as possible in primary health care centre. In a review by Jellema et al, three groups of main diagnostic steps which has been studied in primary health care centre or similar were reviewed, particularly those based on symptoms and signs, blood and fecal test, and abdominal ultrasonography (USG).[6] Jellema et al in their systematic review found that between those three diagnostic modalities, only faecal calprotectin test and USG had quite good results, but both were still rare to be performed in primary health care centre level.[6] In Indonesia, a national consensus has been arranged, including algorithm of diagnostic work-up and management in variable health care level, starting from primary to tertiary.[1]

Endoscopy

To diagnose IBD, one of the most frequently used procedures is endoscopy. Either colonoscopy or even esophagogastroduodenoscopy (EGD) is needed to visualize digestive tract mucosa as much as possible. Normal colon mucosa has clear vascular pattern and pale glossy colour. The occurrence of inflammation in IBD changes the appearance partially or even entire colon mucosa.[1,2]

Table 1. Endoscopic appearances in inflammatory bowel disease[1,2]

Endoscopic appearance	Ulcerative collitis	Chron's disease
Continuous characteristic	+++	+
Presence of skip area	0	+++
Rectum involvement	+++	+
Easily bleeding lesion	+++	+
Cobblestone appearance/pseudopolyps	+	+++
Ulcer characteristics		
Found in inflamed mucosa	+++	+
Ileal involvement	0	++++
Discrete ulcer lesion	+	++++
Ulcer shape		+++
Diameter > 1 cm	+	+++
Depth, linear shape	+	+++
Aphtoid	0	++++

0: not found; +: mild/less found; ++ : much found; +++: abundantly found

Several abnormalities which may be found in UC: 1) Vascular pattern disappears, due to mucosal edema and erythema. Petechiae, exudate, and contact bleeding may appear; 2) In more severe cases, macroulceration, significant bleeding or exudation may occur; 3) Continuous involvement of colon; pseudopolyp may be present due to past inflammatory process. Meanwhile in CD, abnormalities which may be found: 1) Focal ulcer appearance, beside mucosa which looks to be normal; 2) Partial mucosa showed polypoid appearance which forms the cobblestone appearance; 3) Involvement of partial mucosa (with skip areas) is typical appearance, which differs it with UC; 4) Pseudopolyp is mucosal membrane mass which is hypertrophic, may appear in CD, as well as UC.[2]

Definitely, UC showed signature involvement, which is from distal, rectum, and continuously involve the proximal area, broad or limited. While in CD involved mucosa may be only one area. Both cause the need of small intestine mucosa visualization which is generally difficult to reach through endoscopy.[2]

SMALL INTESTINE ENDOSCOPY AS DIAGNOSTIC TOOL OF INFLAMMATORY BOWEL DISEASE

Guidelines from European Crohn's and Colitis Organisation (ECCO) and Organisation Mondiale d'Endoscopie Digestive (OMED) are specifically about the use of small intestine endoscopy for diagnosis of IBD. There are several types of small intestine endoscopy, which are: small-bowel capsule endoscopy (SBCE), push enteroscopy, double-balloon enteroscopy (DBE), single-balloon enteroscopy (SBE), intraoperative enteroscopy (IOE), and the latest technique is spiral enteroscopy.[7]

Small-bowel Capsule Endoscopy

Small-bowel capsule endoscopy (SBCE) uses a capsule containing camera which directly transmits pictures to computer which has been installed with specific software as long as the battery life, which is 8-10 hours, without manual probe. The weaknesses are that particular manuever cannot be performed if an area need to be examined more detailed and inability to perform biopsy at the same time. The contraindication occurs when it is suspected that an obstruction might be present although partial, because camera impaction inside the body might occur.[7]

Push Enteroscopy

This enteroscopy uses a long flexible endoscopic tool (paediatric colonoscope, or enteroscope), which end is continued until it passes Traits ligament. However, this technique can only visualize until proximal jejunum.[7]

Double-balloon Enteroscopy

Double-balloon enteroscopy (DBE) technique is included as device assisted endoscopy (DAE), which is endoscopy using additional auxiliary tool in the form of balloon and overtube. In DBE, overtube and two balloons at both ends are being used. So that, endoscope with overtube may go further to distal/proximal of intestine, inflation and deflation of the balloon is performed alternately in those two baloons, simultaneously with endoscope insertion and retraction.[7]

Manes et al in their study regarding the use of DBE in CD in high prevalence of CD in tertiary health care centre, found that the ability of DBE to diagnose PC was only in 50% patients.[8] Although, this examination is still more sensitive compared to radiological examination. Radiology can only detect larger lesion or there has been complication, such as stricture. The advantage of DBE in this case is that if found, visualization can be more focused and biopsy can be performed. The success of DBE with oral or anal insertion route, needs good technical ability, and needs

information from previous examinations, particularly about location and possibility of a lesion to be present.[8]

Single-balloon Enteroscopy

Using similar principle to DBE, in single-balloon enteroscopy (SBE) only endoscope, overtube and without balloon at the distal end are being used. This technique is considered more simple compared to DBE.[7]

Intraoperative Enteroscopy

In intraoperative enteroscopy (IOE), enteroscopy is performed intraoperative by using scope inserted through mouth or even through enterotomy. Progression of enteroscope is assisted manually from outer part of small intestine during surgery.[7]

Spiral Enteroscopy

This technique uses enteroscope with overtube with spiral end and can rotate by itself. Further studies are still needed about its usage in the diagnosis of IBD.[7]

HISTOPATHOLOGY

Pathological appearance in UC is important to differentiate it with infective colitis. Pathological findings include crypt abcess, gland atrophy, loss of mucin in goblet cells, crypt distortion, mononuclear and polymorphonuclear (PMN) cells infiltration in lamina propria. This findings differentiate UC with other diseases.[9] While in CD, there will be tuberculoid granuloma, macrophage and lymphocytes infiltration to lamina propria, also deep ulcer.[1,2]

LABORATORY EXAMINATION

Some of IBD markers which are evaluated are in the form of antibodies, while the others are in the form of acute phase protein, or other molecule protein found in the serum or faeces of IBD patients. The presence of antibody which is used as an IBD marker is thought to be due to the lost of immune system tolerance to antigen which is normally found in the intestinal lumen. Probably it is also caused by the increase of intestinal wall permeability.[10] Some autoantibodies are expected to be used in differentiating between CD and UC, but longitudinal studies are still needed to know their predictive values.[10]

ASCA and pANCA

Two antibodies which have been quite widely studied are anti *Saccharomyces cerevisiae* antibody (ASCA) and atypical perinuclear anti-neutrophil cytoplasmic antibody (pANCA). Although individually the sensitivity or specificity is quite small, but the combination use of both is beneficial to confirm the diagnosis of IBD, even to differentiate between UC and CD.[10]

From a study followed by 582 IBD patients, it was reported that the sensitivity was 40-60% if used alone or in combination, and specificity was > 90% to detect IBD compared to control. Meanwhile from the serology used to categorize undetermined colitis into UC or CD, it was found that 32% (31/97) patients which succeed to be categorized further, with the outcome of ASCA-positive and pANCA-negative in association with CD, as much as 80% confirmed. While ASCA-negative and pANCA-positive associated UC, as much as 63% matched. ASCA is also found positive in celiac disease, therefore ASCA is possibly a non-specific immune response in small intestine abnormality. Additionally, it is also reported that ASCA has ever increased in cystic fibrosis, and intestinal tuberculosis (TB).[4]

Larger number was found in a study performed by Nisihara et al.[10]. Sensitivity and specificity of pANCA to diagnose UC were 51% and 100% respectively, while the sensitivity and specificity of ASCA for CD were 62% and 93%, respectively. If the use of both was combined to differentiate between UC and CD, the specificity rate found was larger, compared to only one of the tests. Combination of pANCA positive and ASCA negative (pANCA+/ASCA -) had specificity rate to diagnose as much as 95% for UC. In contrast, combination of pANCA negative and ASCA positive (pANCA-/ASCA+) had diagnostic specificity of 90% for CD. Nisihara et al found the high association of ASCA IgG compared to the tendency of CD in the ileal location, and younger age onsite. In analysis of pANCA, positive value was closely associated with the presence of UC in the form of left-sided colitis or pancolitis.[10]

Anti-OmpC Antibody

OmpC is porin in the outer membrane of *Eschericia coli* which is immunoreactive to pANCA monoclonal antibody. It is reported to be found positive in 46% from 303 adults with CD, studies on other antibodies are still ongoing.[11]

C-reactive Protein

Acute phase protein increases in IBD, and is generally higher in CD compared to UC. The C-reactive protein (CRP) level is reported to be associated with the activity of CD, and may predict CD, but is still controversial.[9]

Bacterial Profile

The role of intestinal microbes in the etiology of IBD is thought to be based on the principle of presence of intestinal mucosa immune activation which is inappropriate to the intestinal microbe.[12] Microbes profile in different types of IBD phenotypes is also found to be different. Microbes composition in patients with CD is different compared to healthy individuals or even those with UC. While in UC patients, there is not much difference with healthy individuals. Specific changes which have been found in ileal type CD are decrease of specific types of bacteria, such as: *Faecalibacterium* and *Roseburia*, also the increase of *Enterobacteriaceae* and *Ruminococcus gnavus*.[12] This is proved by Willing et al through their study, microbes profile using pyrotag, towards 40 twin pairs who suffered IBD, either concordant or discordant.[12]

Procalcitonin

Procalcitonin (PCT) has been widely studied as a good infection marker, particularly in post surgery and sepsis. Joo et al evaluated the role of PCT in bacterial gastroenteritis and IBD, two intestinal inflammation conditions which are frequently found and difficult to differentiate. The study proved PCT with the cut off of 0,5 ng/mL has 40% sensitivity and 92% specificity for bacterial gastroenteritis (GE). While in IBD patients, PCT was not increased either in active or inactive phase of the disease. This study also found that other inflammatory markers, such as erythrocyte sedimentation rate (ESR) and CRP were found to be increased in active IBD, while PCT was still below the cut off value.[13]

MANNAN-BINDING LECTIN

Mannan-binding lectin (MBL) is a binding molecule which may activate complement through lectin pathway. This is an activated non-specific immune response to microorganisms. Therefore, it is predicted that the level is increased in IBD. A study by Hoffman et al, in 98 CD patients, 83 UC, 189 healthy controls, and 82 rheumatic patients as controls, there was no difference found in the MBL level and MBL genotype difference in those groups. Thus, MBS until recently is proved to be not beneficial in diagnosing IBD.[14]

S100 Protein Group

S100 protein group has been widely known to play role in many diseases, either inflammation or malignancy. It is named S100 because all these proteins dissolve in 100% ammonium sulphate. Those associated with digestive tract inflammation, include calprotein, and calgranulin. Sample was collected from blood, intestinal biopsy, or faeces. The level of calprotein and calgranulin increased in IBD, and can differentiate between IBD, healthy subjects, or IBS. Unfortunately the level also increased in bacterial gastroenteritis. In a meta-analysis cited by Manolakis et al with 5.983 patients, it was reported that the sensitivity and specificity of calprotectin faeces for IBD diagnosis was 95 and 91%, respectively.[15]

Fecal Calprotectin

Fecal calprotectin is the most protein found in the cytosol of inflammed cell. The calprotectin level in faeces is predicted to be able to detect the possibility of someone to suffer from IBD. Hence, calprotectin is expected to be a screening tool for IBD, and prevent unnecessary endoscopy procedure in patients with slight possibility of IBD. From a meta-analysis by van Rheenen et al, which included 13 studies in adults and children, found that the sensitivity rate of 93% and specificity rate of 96% in adults. In this study, faecal calprotein screening in patients suspected with IBD, could decrease the number of endoscopy need as much as 67%.[16]

Fecal Lactoferin

Marker from feces is predicted to have higher specificity for IBD because the level is not increased in process occuring outside the digestive tract. Lactoferin is a glicoprotein found in secondary granule in polymorphonuclear (PMN). If there is an inflammation process in the intestinal mucosa, PMN will infiltrate mucosa and this secondary granule is released, therefore the level of lactoferin in the faeces will increase. The level increases before the increase of CRP and ESR, and examination through faeces decreases the possibility to be influenced by other factors, such as other systemic markers.[17]

The level of fecal lactoferin increases in IBD, compared to healthy controls and IBS patients. But the level is also increased in other gastroenteritis infection, although not as much as IBD. From many studies, it was concluded that the sensitivity and specificity was as much as 80% and 82%, as a combination of UC and CD. With subanalysis, it was found that the sensitivity and specificity of UC were 74% and 82%, and for CD the sensitivity and specificity were 75% and 77%. The association of faecal lactoferin with disease activity either clinically (using activity index*)* or even histopathology and endoscopy were quite strong. Hence, it is expected that detecting the increase may visualize the activity and prognosis of IBD.[17]

Chromogranin A

Chromogranin A (CgA) is an acid glicoprotein, and has been proved to be a sensitive marker for neuroendocrine tumor, including gastrointestinal carcinoid. However, the level is also found to be increased in kidney failure, atrophy gastritis, PPI therapy, or in the presence of neuroendocrine involvement in a condition, such as: rheumatoid arthritis, other malignancy, and chronic obstructive pulmonary disease (COPD). Based on several new studies, increase of CgA level was found in IBD, simultaneous with the presence of finding of increased risk of carcinoid tumor in IBD. Although this does not made CgA as one of the IBD diagnostic modalities, CgA may be examined as a marker if there is suspicion of carcinoid or neuroendocrine tumor in patients diagnosed with IBD.[18]

A study performed by Sciola et al evaluated the level of plasma CgA in IBD patients and control. It was found that CgA level was significantly higher in IBD, with significant cut-off value of 100 U/L, for carcinoid tumor, with or without the presence of IBD.[18]

IMAGING

Abdominal Ultrasonography

Ultrasonography (USG) has been widely studied as a diagnostic tool for IBD which is noninvasive and quite easy to perform, the availability of the device has reached primary health care level. Several studies included the cut-off value of the involved colon wall thickness, with the combination of symptoms and other signs from IBD. The sensitivity reaches 73% (95% CI = 65–80%) and specificity reaches 95% (95% CI = 91–97%).[6]

Magnetic Resonance Imaging

Application of imaging techniques in diagnosis of IBD was initially targeted to invent a more comfortable and non-invasive diagnistic tool. A study was conducted to design a scoring system based on magnetic resonance imaging (MRI) which consisted of intestinal wall thickness, contrast enhancement in intestinal wall, and the presence of regional lymph nodes. Using this system, more than 90% of patients with any intestinal changes were diagnosed appropriately and have been categorized into mild, moderate, or severe inflammation.[19]

Nevertheless, some studies also found the limitation of MRI in IBD detection, which was its inaccuracy in detecting mild intestinal inflammation, as compared to endoscopic capsule. On the other hand, endoscopic examinations would not be able to determine the depth of intestinal wall inflammation or the presence of transmural abnormalities such as fistula. Hence, endoscopic capsule and MRI are considered to be complemental to each other. By performing MRI in advance, in case of an intestinal stricture, the use of endoscopic capsule would not be necessary.[19, 20]

Magnetic Resonance Imaging: Oral Contrast

Magnetic resonance imaging using orally ingested contrast medium was supposed to detect lesions on intestinal mucosal walls. This sort of imaging used an orally ingested contrast medium, followed by serial MRI examinations, in given sections, in accordance to the appropriate time the contrast needed to reach certain parts of intestines. Examination is complete once contrast-filled colon distension is sufficient and the images have been taken until the contrast reached cecum.[21]

Cronin et al reported their study and found 16 of 53 patients undergoing oral contrast MRI had some abnormalities. All of them had thickened intestinal walls, and the second most common finding was lumen constriction. The best imaging and intestinal distensions were acquired from the sections of cecum and ascending colon. The most common lesions were found in cecum and transverse colon. Compared to endoscopy, oral contrast MRI had 80% sensitivity and 100% specificity.[21]

Double Contrast Magnetic Resonance Imaging (DC-MRI)

The term 'double contrast' in double contrast magnetic resonance imaging (DC-MRI) procedure refers to the use of two contrast media simultaneously, negative superparamagnetic oral contrast and positive paramagnetic intravenous contrast. This technique will eventually result in black-white image, or two contrast effect which defines a solid difference between intestinal and luminal walls, especially in an inflammed area in T1-T2 weighted image. Specifically, this method will enhance the contrast on the intrinsic intestinal wall on T2 weighted image; hence, any signs of intestinal wall edema will be visualized clearly. In an active Crohn's disease, image of intestinal wall edema will be enhanced simultaneously with intravenous gadolinium contrast and on mural signal of T2 image, as compared to the dark luminal effect. Another name of this DC-MRI is negative MR-enterography due to the dark luminal image on both T1 and T2 produced by oral superparamagnetic contrast medium. T2 signal enhancement may also be found in

adjacent mesenteric tissues, which suggests serositis and/or inflammation and edema of the mesenterium. These three findings have been associated as the marker of CD activity in other studies.[22]

UC images may also be identified using DC-MRI. Thickened wall was continuously found at the level of rectum, sigmoid colon, and sometimes along the colon to cecum in T1 and T2 images. Wall enhancement and local hypervascularities could be visible in active colitis, although it might not be as clear as in colitis caused by PC. Besides, pathological findings may reveal the loss of haustrae and luminal stricture in coronal T2 images.[22]

Optimization of tissue lesion imaging depends on proper sequences, negative intestinal contrast medium, adipose suppression, and type of intravenous contrast medium being used. These are vital in identification of IBD lesions in colon and intestines. Besides, primary markers of mural and transmural inflammation in CD may be found in T1-T2 weighted image to assess the disease activity.[22]

CONCLUSION

IBD is found quite often in tertiary health services. Based on the symptoms suffered by patients with IBD, the most common ones are chronic and bleeding diarrhea, abdominal pain, and chronic diarrhea. Many diagnostic modalities are available, while the most common and mainly used is endoscopy. Endoscopy followed by histopathologic examination is expected to help distinguish it from other differential diagnosis such as bacterial infective colitis or intestinal tuberculosis

Several examinations as being discussed in this review are not yet available in Indonesia, but they may expand the knowledge on novel diagnostic modalities in IBD. Further studies are needed to determine their specificities and sensitivities in Asian population, especially Indonesians. These numerous modalities are anticipated to be diagnostic options for IBD in every level of healthcare services, from primary to tertiary. Financial and geographic limitations make primary health services essential in first recognition of IBD. A thorough literature review focusing on the effectiveness of diagnostic modalities for IBD in primary health services is needed.

REFERENCES

1. Kelompok Studi *Inflammatory Bowel Disease* (IBD) Indonesia. Djojoningrat D, Simadibrata M, Makmun D, Abdullah M, Syam AF, Lelosutan SAR, eds. Konsensus Nasional Penatalaksanaan IBD di Indonesia. Jakarta: Interna Pub 2011.
2. Dharmika Djojoningrat. *Inflammatory bowel disease* alur diagnosis dan pengobatannya di Indonesia. Dalam: Sudoyo AW, Setyohadi B, Alwi I, Simadibrata S, Setiati S, eds. Buku Ajar Ilmu Penyakit Dalam Jilid III. 4th ed. Jakarta: Pusat Penerbitan Departemen Ilmu Penyakit Dalam FKUI 2006.p.386-90.
3. Inflammatory bowel disease (IBD) [cited 2013 Jan 8]. Available from: URL: www.cdc.gov /ibd/.
4. Friedman S, Blumberg RS. Inflammatory bowel disease. In: Longo DL, Kasper DL, Jameson JL, Fauci AS, Hauser SL, Loscalzo J, et al, eds. Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw-Hill 2011.p.2403-5.
5. Baumgart, Daniel C. Sandborn, William J. Gastroenterology 2: Inflammatory bowel disease: clinical aspects and established and evolving therapies. Lancet 2007;369:1641-57.
6. Jellema P, van Tulder MW, van der Horst HE, Florie J, Mulder CJ, van der Windt DAWM. Inflammatory bowel disease: a systematic review on the value of diagnostic testing in primary care. The Association of Coloproctology of Great Britain and Ireland. Colorectal Dis 2011;13:239–54.
7. Bourreille A, Ignjatovic A, Aabakken L, Loftus Jr EV, Eliakim R, Pennazio M, et al. Role of small-bowel endoscopy in the management of patients with inflammatory bowel disease: an International OMED–ECCO consensus. Endoscopy 2009;4:618–37.
8. Manes G, Imbesi V, Ardizzone S. Cassinotti A, Pallotta S. Porro GB. Use of double-balloon enteroscopy in the management of patients with Crohn's disease: feasibility and diagnostic yield in a high-volume centre for inflammatory bowel disease. Surg Endosc 2009;23:2790–95.
9. Yantiss RK, Odze RD. Diagnostic difficulties in inflammatory bowel disease pathology. Histopathology 2006;48:116.
10. Nisihara RM, Carvalho WB, Utiyama SR, Amarante H, Baptista ML. Diagnostic role and clinical association of ASCA and ANCA in Brazilian patients with inflammatory bowel disease. Dig Dis Sci 2010;55:2309–15.
11. Cohavy O, Bruckner D, Gordon LK, Misra R, Wei B, Eggena ME, et al. Colonic bacteria express an ulcerative colitis pANCA-related protein epitope. Infect Immun 2000;68:1542.
12. Willing BP, Dicksved J, Halfvarson J, Andersson AF, Lucio M, Zheng Z, et al. A pyrosequencing study in twins shows that gastrointestinal microbial profiles vary with inflammatory bowel disease phenotypes. Gastroenterology 2010;139:1844–54.
13. Joo Thia KT, Yen Chan ES, Ling KL, Yoong Ng W, Jacob E, Ooi CJ. Role of procalcitonin in infectious gastroenteritis and inflammatory bowel disease. Dig Dis Sci 2008;53:2960–8.
14. Hoffmann C, Hoffmann P, Lun A, Büning C, Hiepe F, Scherer HU, et al. Is there a role for mannan-binding lectin in the diagnosis of inflammatory bowel disease?. Immunogenetics 2010;62:231–5.
15. Manolakis AC, Kapsoritakis AN, Tiaka EK, Potamianos SP. Calprotectin, calgranulin C, and other members of the S100 protein family in inflammatory bowel disease. Dig Dis Sci 2011;56:1601–11.
16. van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. BMJ 2010;341:c3369.

17. Gisbert JP, McNicholl AG, Gomollon F. Questions and answers on the role of fecal lactoferrin as a biological marker in inflammatory bowel disease. Inflamm Bowel Dis 2009;5:1746-54.
18. Sciola V, Massironi S, Conte D, Caprioli F, Ferrero S, Ciafardini C, et al. Plasma chromogranin A in patients with inflammatory bowel disease. Inflamm Bowel Dis 2009;15:867– 71.
19. Thomas CL. MRI of inflammatory bowel disease. 2008 Jul [cited 2013 Jan 22]. Available from: URL: http://www.appliedradiology.com.
20. Albert JG, Martiny F, Krummenerl A, Stock K, Lesske J, Gobel CM, et al. Diagnosis of small bowel Crohn's disease: A prospective comparison of capsule endoscopy with magnetic resonance imaging and fluoroscopic enteroclysis. Gut 2005;54:1721-7.
21. Cronin CG, Lohan DG, Browne AM, Roche C, Murphy JM. Does MRI with oral contrast medium allow single-study depiction of inflammatory bowel disease enteritis and colitis?. Eur Radiol 2010;20:1667–74.
22. Francesca M. Double-contrast magnetic resonance imaging of the small and large bowel: effectiveness in the evaluation of inflammatory bowel disease. Abdom Imaging 2010;35:31–40.

Correspondence:
Dadang Makmun
Division of Gastroenterology
Department of Internal Medicine
Dr. Cipto Mangunkusumo General National Hospital
Jl. Diponegoro No. 71 Jakarta Indonesia
Phone: +62-21-3153957 Facsimile: +62-21-3142454
E-mail: hdmakmun@yahoo.com