Clinical Approach and Management of Chronic Diarrhea

Murdani Abdullah, M.Adi Firmansyah

Department of Internal Medicine, Faculty of Medicine University of Indonesia-Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Correspondence mail:
Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine University of Indonesia-Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. email: murdani.abdullah@ui.ac.id.

ABSTRAK

Diare kronik diartikan sebagai diare yang berlangsung lebih dari 4 minggu. Meskipun secara umum diperkirakan prevalensi diare kronik hanya berkisar 3–5% dari populasi namun memberikan tantangan tersendiri yang tidak kalah dibandingkan diare akut karena banyaknya diagnosis banding yang perlu dipikirkan sebagai penyebab diare kronik. Hal penting sebagai salah satu etiologi diare kronik adalah kanker kolorektal dan adanya pertumbuhan berlebih bakteri usus halus atau dikenal sebagai SIBO (small intestinal bacterial overgrowth). Secara umum, diare kronik dibagi menjadi watery, malabsorption, dan inflammatory diarrhea. Anamnesis cermat, pemeriksaan fisis teliti dan bantuan pemeriksaan penunjang menjadi modal penting seorang klinsi dalam menatalaksana diare kronik. Secara umum, penatalaksanaan diare kronik dapat dibagi menjadi dua, yakni pengobatan suportif dan farmakologik baik untuk etiologi infeksi atau non-infeksi. Pengobatan farmakologik pun dibedakan atas dua, yakni pengobatan simtomatik dan kausal yang dapat dilakukan melalui terapi empirik.

Kata kunci: *diare kronik, kanker kolon, small intestinal bacterial overgrowth, anamnesis, pemeriksaan fisis, terapi empirik.*

ABSTRACT

Chronic diarrhea is defined as the passage of loose stools that last for more than 4 weeks. Although generally it is estimated that the prevalence of chronic diarrhea only ranges 3-5% of population, but it poses some specific equally essential challenges compared to acute diarrhea because there are many differential diagnosis that should be considered as the cause of chronic diarrhea. One of them includes colorectal cancer and the small intestinal bacterial overgrowth, known as SIBO. In general, chronic diarrhea can be categorized into watery, malabsorption, and inflammatory diarrhea. A proper history taking, physical examination and laboratory investigation is therefore necessary for clinician in managing chronic diarrhea. Overall, the management of chronic diarrhea includes two types, i.e. supportive and pharmacological management both for infectious and non-infectious etiologies. Pharmacological treatment can also be classified into two kinds of treatment including symptomatic and causal treatment, which can be achieved through empirical therapy.

Key words: *chronic diarrhea, colon cancer, small intestinal bacterial overgrowth, history taking, physical examination, empirical therapy.*

INTRODUCTION

Diarrhea is one of the most common symptoms that bring a patient to a doctor, either acute or chronic diarrhea. Although generally it is estimated that the prevalence of chronic diarrhea only ranges 3-5% of population, but it poses some specific equally essential challenges compared to acute diarrhea.[1-5] There are so many differential diagnosis that should be considered as the cause of chronic diarrhea. It may also disturb the patient's quality of life, work performance and wellbeing as well as increase their expenses. It has been estimated that chronic diarrhea economical loss ranges about $ 350,000,000 annually from work-loss alone.[4]

Considering that, there are so many differential diagnoses for the cause of chronic diarrhea, the causes are then simply categorized into three groups, i.e. watery, fatty and inflammatory diarrhea.[1] However, it should be noted that not all of chronic diarrhea is solely watery, fatty or inflammatory type as overlapping or combined type may exist. A proper clinical approach to establish diagnosis is then essential considering that chronic diarrhea may indicate immunocompromised or immunodeficiency state such as colon cancer or HIV infection. It has been recently identified that chronic diarrhea can be caused by intestinal bacterial disturbance including bacterial overgrowth in gastrointestinal tract or known as small intestinal bacterial overgrowth (SIBO).[6]

On average, healthy individuals excrete stool weight approximately about 100-200 gram/day containing 100-200 ml fluid per day and their defecation ranges from once in every 2 days to 3 times over 24-hour period. Diarrhea is defined when the stool weight is more than 200 gram per 24 hours containing more than 200 ml fluid per 24 hours, or greater than 3 loose stools in 24 hours.[2,7,8] Some experts emphasize the diarrhea definition on frequency of loose stools over the stool weight.[7,8] Chronic diarrhea is defined as lasting more than 4 weeks;[1,3,4,5] however, another expert defines it as lasting more than 15 days.[8]

EPIDEMIOLOGY

In the United States, it is estimated that the incidence ranges about 1.4 episodes per person annually or approximately 211 million cases per year[1] with an estimated incidence of chronic diarrhea of 3 – 5%.[3,4,5] Results from basic health research (RISKESDAS) of Indonesian Ministry of Health in 2007 shows the prevalence of diarrhea in Indonesia of 9% and it is the 13th cause of death with 3.5% proportion based on pattern of death at all ages. Data of one study in Cipto Mangunkusumo Hospital that reviewed 207 patients with chronic diarrhea within period of 1999 – 2000 reported that the diarrhea was due to infectious cause in 100 patients (48.3%), non-infectious cause in 69 patients (33.3%) and mixed causes in 38 patients (18.4%).[8]

PATOPHYSIOLOGY

In general, it can be said that chronic diarrhea has the following mechanisms: osmotic, secretory, inflammatory, infectious diarrhea, bile acid and fat malabsorption, disturbance of anion/electrolytes active transport in enterocytes, abnormal bowel transit time, abnormal growth of intestinal bacteria and disturbed intestinal permeability.[6,7,8]

ETIOLOGY

Overall, most chronic diarrhea is caused by non-infectious disease; however, in developing countries, it is mostly due to infectious disease.[1,4,5] A 5-year study at Cipto Mangunkusumo Hospital in Jakarta reported similar data that infectious causes were greater than non-infectious causes.[8]

As mentioned before, based on the physical appearance of stools, we can divide chronic diarrhea into three groups, which are: 1). Fatty stool (fatty diarrhea); 2). Blood stool (inflammatory diarrhea); 3). No blood and no fat stool (watery diarrhea).[1,8]

Watery diarrhea can also be categorized further into osmotic (water retention due to poor absorption of certain substances), and functional (due to hypermotility) types. The use of osmotic laxatives such as sorbitol may induce osmotic diarrhea. In fact, secretory diarrhea can be distinguished from osmotic and functional diarrhea by virtue of higher stool amount/volume (more than 1 liter per day), which continue after a period of fasting and usually occurs at night. Patients with functional diarrhea usually have

lesser amount of stools (less than 350 ml per day) and no diarrhea at night.[1] The following **Table 1** summarizes differential diagnosis of chronic diarrhea.

Colorectal Cancer as an Etiology

As shown on **Table 1**, malignancy such as colorectal cancer may contribute to manifestation of chronic diarrhea. A meticulous history taking which reveals family history and the presence of prominent weight loss would assure us to get further confirmation by performing a proper abdominal examination and digital rectal examination. Further work-up of colonoscopy should be performed when there is any indication. Several studies of screening colonoscopy in asymptomatic patients have revealed the prevalence of adenoma colon ranges between 14.4% and 37.5% (7.9% with adenomas >10 mm). The prevalence is also influenced by age, male sex, and a history of family with colorectal cancer.[10] By performing detailed measurements of history taking, physical examination, and laboratory work-up, early diagnosis of colorectal

Table 1. Differential diagnosis of chronic diarrhea

Watery	Fatty (bloating and steatorrhea in many, but not all cases)	Inflammatory or exudative (elevated white blood cell count, occult or frank blood or pus)
Secretory (often nocturnal; unrelated to food intake; fecal osmotic gap <50 mOsm per kg *) Alcoholism Bacterial enterotoxins (e.g. cholera) Bile acid malabsorption Brainerd diarrhea (epidemic secretory diarrhea) Congenital syndromes Crohn disease (early ileocolitis) Endocrine disorders (e.g. hyperthyroidism [increases motility]) Medication Microscopic colitis (lymphocyte and collagenous subtypes) Microscopic colitis (lymphocyte and collagenous subtypes) Neruendocrine tumors (e.g. gastrinoma, vipoma, carcinoid tumors, mastocytosis) Nonosmotic laxatives (e.g. senna, docusate sodium [Colace]) Postsurgical (e.g., cholecystectomy, gastrectomy, vagotomy, intestinal resection) Vasculitis	**Malabsorption syndrome** (damage to or loss of absorptive ability) Amyloidosis Carbohydrate malabsorption (e.g., lactose intolerance) Celiac sprue (gluten enteropathy)-various clinical presentations Gastric bypass Lymphatic damage (e.g., congestive heart failure, some lymphomas) Medications (e.g., orlistat [Xenical; inhibits fat absorption], acarbose [Precose; inhibits carbohydrate absorption]) Mesentric ischemia Noninvasive small bowel parasite (e.g. Giardia) Postresection diarrhea Short bosel syndrome Small bowel bacterial overgrowth (>105 bacteria per mL) Tropical sprue Whipole disease (Tropheryma whippelii infection)	Inflammatory bowel disease Crohn disease (ileal or early Crohn disease may be secretory) Diverticulitis Ulcerative colitis Ulcerative jejuncileitis Invasive infectious disease *Clostridium difficile* (Pseudomembranous) colitis-antibiotic history Invasive bacterial infections (e.g., tuberculosis, yersiniosis) Invasive parasitic infections (e.g., Entamoeba)-travel history Ulcerating viral infections (e.g., cytomegalovirus, herpes simplex virus Neoplasia Colon carcinoma Lymphoma Villous adenocarcinoma Radiation colitis
Osmotic (fecal osmotic gap >125 mOsm per kg*) Carbohydrate malabsorption syndromes (e.g., lactose, fructose) Celliac disease Osmotic laxatives and antacids (e.g., magnesium, phosphate, sulfate) Sugar alcohols (e.g., mannitol, sorbitol, xylitol)	**Maldigestion** (loss of digestive function) Hepatobilliary disorders Inadequate luminal bile acid Loss of regulated gastric emptying Pancreatic exocrine insufficiency	
Functional (distinguished from secretory types by hypermotility, smaller volumes, and improvement at night and with fasting) Irritable bowel syndrome		

*Fecal osmotic gap (OG) = 290 – 2 × (Nastool + Kstool). It helps differentiate secretory from osmotic diarrhea. Normal value of fecal osmolality is 290 mOsm per kg (290 mmol per kg). Although measurement of fecal electrolytes is no longer routine, but knowing the fecal osmotic gap may confirm whether watery stools represent chronic osmotic diarrhea (OGfecal > 125 mOsm per kg) or chronic secretory diarrhea (OGfecal < 50 mOsm per kg).

cancer is supposed to be established and optimal treatment can be provided. Such measurements are essential as the sooner the diagnosis is made, the better the prognosis for patients with colon cancer. The five-year survival rates of cancer localized in intestinal wall is 90%, which may be reduced drastically to 68% if there is regional metastasis and about 10% for distant metastasis.[11]

SIBO (Small Intestinal Bacterial Overgrowth) as an Etiology

The microbiota of human gastrointestinal tract is a complex ecosystem, which consists of almost 400 bacterial species. Since the small intestine is the site of digestion and absorption of food, most of bacterial flora is excreted from the small intestines to prevent unwanted competition with the host. In addition, gas production from bacterial fermentation can be reduced. SIBO is defined when there is presence of >105 CFU/ml bacteria in the proximal small intestines.[12] SIBO is essential because other than its role as one of etiologies of chronic diarrhea, it also has important role in pathogenesis of IBD, IBS and celiac disease.[12] SIBO may occur due to disturbed defensive factors of gastrointestinal tract, including gastric acid, small intestinal motility, integrity of intestinal mucosal layers, as well as protective effect of commensal flora such as lactobacillus.

Diagnosis of SIBO is established by performing the gold standard work-up, i.e. jejuna aspiration and culture. However, since the examination is difficult to be performed, indirect examination such as CO_2 breath test, isotopes-labeled Xylosa breath test, and hydrogen breath test can be carried out.[12]

INITIAL EVALUATION

History Taking

History taking is the first important step in making diagnosis of chronic diarrhea. It is important for us to have precise understanding on what is being perceived as diarrhea by the patient who seeks treatment from us. In taking history, we should find out whether the symptom is organic or functional problem; we should also distinguish the type of diarrhea, i.e. malabsorption from inflammatory or watery diarrhea; and try to evaluate the probable specific causes of diarrhea. Symptom of diarrhea that lasts for three months with nocturnal pattern and significant weight loss may suggest to organic disease. The absence of these symptoms, but accompanied with positive symptoms such as those defined in the Manning or Rome criteria and normal physical examination suggests a functional bowel disturbance, i.e. irritable bowel syndrome, but only with a specificity of 52-74%.[10] Moreover, the criteria cannot exclude the probable inflammatory bowel disease.[10]

The presence of malabsorption is usually evident by steatorrhea and the passage of bulky malodorous pale stool. Floating stools or sticky stools to the side of the toilet bowl and may be difficult to flush away are usually reported by patients with deficiencies of nutrient or selective deficiencies of vitamin and mineral. For bloody diarrhea, symptoms depend on the cause. Moreover, symptoms of diarrhea with no bleeding and no fat also usually depend on each cause. If the diarrhea stop after 72-hour of fasting, then it is suggestive for osmotic diarrhea.

Specific risk factor may suggest to organic disorder, for example:

1. Family history. History of neoplastic, inflammatory bowel (IBD) or celiac disease.
2. Previous surgery. Extensive resections of the ileum and right colon may lead to diarrhea due to lack of absorptive surface, reduced transit time or malabsorption of bile acids. Bacterial overgrowth is also commonly associated with history of bypass surgery, such as gastric and jejunoileal bypass for obesity. Chronic diarrhea may occur in up to 10% patients after cholecystectomy through mechanisms of increased transit time, bile acid malabsorption and increased enterohepatic cycling of bile acids.[10,13]
3. History of previous pancreatic disease.
4. The presence of systemic disease. Thyrotoxicosis, diabetes mellitus, parathyroid and adrenal disease may cause chronic diarrhea through various mechanisms such as endocrine effect, autonomic dysfunction, small intestine bacterial overgrowth (SIBO), or the use of concomitant drug therapy.[14]

5. Alcohol. Chronic diarrhea commonly occurs in patients with alcohol abuse. It is assumed including mechanisms of increased bowel transit time, decreased activity of intestinal disaccharides, and reduced pancreatic function.[10,15]
6. Drugs. Approximately 4% of cases of chronic diarrhea is associated with medication (especially magnesium containing agents, antihypertensive drugs and NSAID, antibiotics, antiarrhytmics, theophyllines, and chemotherapeutic agents). **Table 2** shows drugs that may cause chronic diarrhea.
7. Recent travel. Traveler's diarrhea commonly affects people who are travelling to areas with potential sources of infectious gastrointestinal pathogens.
8. History of antibiotic therapy and Clostridium difficile infection.
9. Lactase deficiency

Physical Examination

Usually clinical manifestation of chronic diarrhea cases is more associated with vitamin and electrolytes deficiencies and nutrient malabsorption. The presence of significant weight loss or lymphadenopathy may result from chronic infection or malignancy. Episcleritis may suggest to inflammatory bowel disease and exophtalmus is suggestive for hyperthyroid causes. Abdominal examination which reveals surgical scars, increased bowel sound, tenderness (infection and inflammation) and masses should be followed by digital rectal examination (rectal touché). **Table 3** summarizes clinical physical findings that may be associated with certain condition.

Evaluation Using Laboratory Work-up

To assist physicians establishing diagnosis and the etiology of chronic diarrhea, some laboratory work-up can be performed including blood tests, stool tests, radiography and endoscopic procedures.[1,3,8,11] In accordance with the categorization mentioned above of diarrhea, the evaluations are also indicated for each category.

1. Evaluation of Secretory Chronic Diarrhea. A patient with watery diarrhea who has low fecal osmotic gap should get further examination as follows: (1) evaluation of causative microorganisms such as using fecal culture to detect bacteria and parasitology work-up for Cryptosporidium, Microsporidium, and Giardia.Giardia stool antigen test using ELISA is the most sensitive test for giardiasis. radioisotopes-labeled glucose and xylosa breath test may provide aid to detect the presence of SIBO (small-intestine bacterial overgrowth); however, the test is only available for patients with high predisposing factors for SIBO; (2) evaluation to exclude structural disorder is carried out using radiography, sigmoidoscopy or colonoscopy with multiple biopsy on colon mucosa, abdominal CT-scan and biopsy on proximal mucosa of small intestines; and (3) selective evaluation on plasma peptide levels including gastrin, calcitonin, vasoactive intestinal polypeptide and somatostatin. Examination on urine excretion of 5 HIAA (hidroxyindole acetic acid), metanephrin, or histamine levels or other endocrine function tests can be considered. Nevertheless, since the peptide-secreting tumor syndrome rarely causes chronic diarrhea, the examination of plasma

Table 2. Drugs associated with diarrhea[1,7]

Osmotic	Secretory	Motility	Malabsorption	Pseudomembranous colitis
Citrates, phosphates, antacids and laxatives containing magnesium sulfates, sugar alcohol (manitol, sorbitol, xylitol).	Antiarrhythmics (quinine), antibiotics (amoxicillin/ clavulanate), antineoplastics, biguanides, calcitonin, digitalis, colchicine, Non-steroidal anti-inflammatory drugs (may induce microscopic colitis), prostaglandins (misoprostol), Ticlopidine	Macrolides (erythromycin), metoclopramide, laxatives (Bisacodyl)	Acarbose (carbohydrate malabsorption); Aminoglycosides, Orlistat (fat malabsorption); thyroid supplements, ticlopidine	Antibiotics (e.g., amoxicillin, cephalosporin, clindamycin, fluoroquinolones), antineoplastics, immunosuppressant

peptide level will only be performed if there is strong suggestion by virtue of clinical manifestation or radiological findings.[3]

2. Evaluation of Osmotic Chronic Diarrhea. Usually, non-steatorrhea osmotic diarrhea may occur due to ingestion of slow absorbing carbohydrate intake or magnesium-containing product. Acidic stools revealed by fecal pH test are suggestive for carbohydrate malabsorption. Detailed history taking on intake and laboratory work-up such as lactose hydrogen breath test may provide aid to diagnosis. Further test also includes measurement of lactase level through mucosal biopsy specimen obtained by endoscopy. A high level of magnesium in the stools is suggestive to high intake of magnesium-containing product such as antacids or laxative abuse.
3. Evaluation of Inflammatory Chronic Diarrhea. Patients with chronic diarrhea with blood and pus in the stool should undergo barium X-ray or sigmoidoscopy or colonoscopic biopsy. Stool culture and analysis of Clostridium difficile toxins may provide help in determination of infectious causes of the inflammation.
4. Evaluation of Fatty Chronic Diarrhea. Patients with steatorrhea should undergo conventional small-bowel barium follow through/enteroclysis to exclude structural disorder. Small intestine endoscopic mucosal biopsy should also be carried out. Some tests for pancreatic exocrine insufficiency, such as secretin test (direct) and bentiromide test (indirect) can be performed; while Schilling test is rarely carried out. **Table 4** summarizes laboratory work-up performed in evaluating chronic diarrhea.

MANAGEMENT

In general, the management of chronic diarrhea can be divided into two groups, i.e. supportive and pharmacological treatment, both for infectious and non-infectious causes.[8] Pharmacological treatment is also subdivided into two classes including symptomatic and causal treatment. Causal treatment can be done through empirical therapy.

Table 3. Physical findings and conditions associated with diarrhea[8]

Conditions	Possible physical findings
Nutritional deficiency	
- Calorie, fat, and protein	Weight loss including signs of malnutrition
- Protein	Edema and muscle hypertrophy, hair loss
- Iron, folic acid, and vitamin B12	Anemic signs such as pale conjunctiva
- Nicotinic acid	Glositis and dermatitis
- Vitamin B1 and B12	Paresthesia and peripheral neuritis
- Vitamin K	Easy bruising and bleeding
- Potassium, sodium, magnesium	Body weakness
- Calcium	Tetany, bone pain
- Zinc	Hair loss
Pancreatitis, pancreatic cancer	Abdominal pain
Celiac Disease	Dermatitis herpetiformis, small sized body, late menarche, mouth ulcer, eruption and itching skin
Whipple's Disease	Polyarthritis with skin pigmentation
Mesenteric Ischemia, Crohn Disease	Abdominal angina, mouth ulcer, perianal ulcer / fistula, sub-acute intestinal obstruction, abdominal mass, lymphoma, lymphadenopathy
Biliary cirrhosis and sclerosing cholangitis	Jaundice
Post gastrectomy	Abdominal scar, with or without blind loop
Inflammatory bowel disease	Chronic bleeding diarrhea, abdominal pain, intra-abdominal mass (Crohn), fistula, intestinal stricture, extra-intestinal manifestation (arthritis, stomatitis, gangrenous pyoderma, episcleritis), toxic megacolon complication.

Empirical therapy for chronic diarrhea, according to American Gastroenterological Association (AGA) guidelines is used in three conditions: (1) as an initial or temporary therapy prior to diagnostic testing; (2) when the diagnostic testing has failed to confirm a diagnosis; and (3) when a diagnosis has been established, but no specific treatment is available or it fails to provide any therapeutic effect. Empirical antibiotic treatment may be justified if the prevalence of bacterial infection is high in a specific location and it can be customized to the pattern of bacterial resistance. However, other empirical therapy of bile acid-binding resin such as cholestyramine (rarely used in Indonesia) can be used for bile acid-induced diarrhea.[3]

Adequate fluid (hydration) is still anessential part in the management of chronic diarrhea, for example by administering oral rehydration solutions. Intravenous fluid administration is provided when oral rehydration is not possible. Supportive treatment can be useful including providing education, avoid unnecessary medication or food intake that may cause chronic diarrhea, good nutrition which is not irritative to gastrointestinal tract, either by oral or parenteral route. It should be noted that the nutrition is supposed to be customized with the possible etiology of chronic diarrhea, for example oral nutrition of fat restriction (e.g. milk containing short-chain peptides) for diarrhea cases with steatorrhea.[3,8]

Pharmacological therapy can also be addressed for symptomatic treatment, e.g. by giving symptomatic antidiarrheal drugs. These drugs are aimed to reduce fluid loss due to diarrhea. Symptomatic anti-diarrheal drugs include: (1) inhibitor of intestinal motility and secretion such as diphenoxylate, loperamide, codeine HCl/phosphate, atropine sulfate; (2) stool bulking agents such as kaolin-morphine and toxic absorber such as activated charcoal, kaolin-pectin, atapulgite and smectite; (3) antisecretory drugs such as ocreotide (somatostatin analogues) or natural somatostatin.

Other symptomatic treatment are antiemetic drugs, vitamin and mineral, extract of pancreatic enzymes, aluminium hydroxide, phenotiazine, nicotinic acid.[8] In addition, causative treatment is customized with possible causes, both for infectious (by administering antibiotics, antifungal, antiprotozoal, and antihelminthics) and non-infectious causes (e.g. in IBD, radiation colitis, etc).

Table 4. Laboratory work-up to evaluate chronic diarrhea

Blood Tests	Stool Tests	Others
Usually includes routine tests such as complete peripheral blood count, albumin level, erythrocytes sedimentation rate, liver and kidney function tests, glucose level, and electrolytes level. The presence of iron deficiency anemia may guide us to Celiac disease, although it is not specific. Serological test including IDT for amoeba, widal, gall culture, HIV, CD4, CD8, antibody against Giardia, antigliadin, anti endomysial antibodies and others as indicated	Routine stool tests 3x (evaluation on the presence of blood and leukocytes in the stools) Fecal occult bleeding test also must be done when malignancy is suspected. Parasitology tests and microbiologic stool culture are performed to identify the microorganisms causing chronic diarrhea. Moreover, it can also evaluate antibiotic sensitivity and resistance. Fecal pH test is carried out to exclude lactose intolerance (fecal pH < 5.5) only if sample is obtained when the patient does not take antibiotic treatment Fecal electrolytes, evaluating fecal osmotic gap to distinguish secretory from osmotic diarrhea. Test for fecal calprotectin levels, a marker of neutrophil activity that can be useful to detect IBD. Test for Clostridium difficile toxin in the stools, which should be performed for patients with diarrhea symptom after hospitalization or following antibiotic treatment Gastrointestinal analysis, fecal fat quantitative and qualitative analysis with specific staining techniques whenever there is a suspicion of malabsorption.	Hydrogen breath test, abdominal ultrasonography, abdominal CT-scan, endoscopic biopsy (esogastroduodenoscopy, sigmoidoscopy, colonoscopy), small-bowel conventional follow through/enteroclysis, ERCP, MRCP, endoscopic capsules

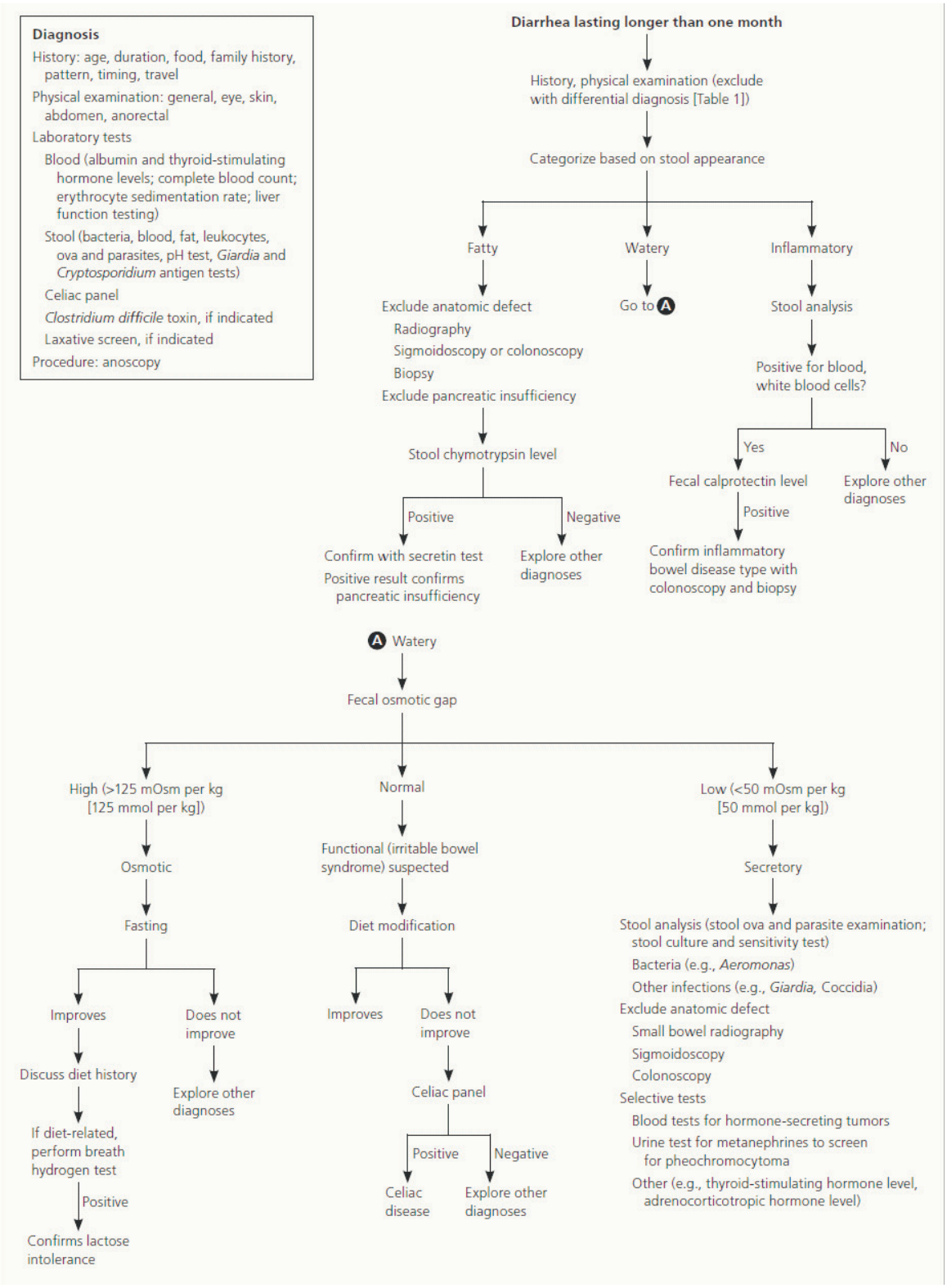

Figure 1. Algorithm for the diagnosis of chronic diarrhea.[1]

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