

10. Appropriateness of Colonoscopy: Diarrhea¹

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Introduction

The number of potential causes of diarrhea is very large. The easiest and most useful method of classifying diarrhea is according to its duration. The majority of cases of acute diarrhea are mild and caused by self-limiting infections or other processes, and thus no diagnostic intervention is indicated.

For patients with chronic diarrhea, diagnostic testing is usually indicated, but although endoscopy may be useful for patients with chronic diarrhea, it is unclear whether the initial procedure should be a flexible sigmoidoscopy or colonoscopy.

In November 1998, a multidisciplinary European expert panel convened in Lausanne, Switzerland, to discuss and develop criteria for the appropriate use of gastrointestinal endoscopy, a widely-used procedure, regarded as highly accurate and safe. The RAND appropriateness method was chosen for this purpose, because it allows the development of appropriateness criteria based on published evidence and supplemented by explicit expert opinion. A detailed description of the RAND appropriateness method, including the literature search process [1], and of the whole process, as well as the global results of the panel [2], are published as separate articles in this issue of the Journal. The literature review was based on a systematic search of Medline, Embase and the Cochrane Library conducted up to the end of 1997 and completed with some key articles published in 1998. Updating and revision of the literature review is currently ongoing.

This article presents a literature review on diarrhea that was provided to the panelists for study and comment prior to the panel meeting to support their ratings of appropriateness of use of colonoscopy in diarrhea. This article further-

more presents an overview of the main panel results related to diarrhea and a summary of published evidence and panel-based appropriateness criteria.

1. Literature Review

Acute Diarrhea

Definitions

It is important that there should be a consensus of opinion concerning definitions of diarrhea. The definition used by the EPAGE project was that diarrhea means the passage of abnormally loose or liquid stools with a greater than normal frequency of defecation, usually three or more stools daily. By “uncomplicated” is meant that an infectious or malabsorption origin has been excluded and no inflammatory bowel disease is known. Acute diarrhea was taken to mean episodes with a rapid onset, most being self-limiting within 3 to 5 days. Persistent (or chronic) diarrhea was considered to mean the passage of loose stools over a period of 14 days or more.

Natural History

A prospective study [3] showed that about 25% of patients had diarrhea which persisted for more than 3 months, compatible with IBS, following an episode of acute gastroenteritis, and nearly 20% for more than 6 months, in the absence of any evidence of lactose intolerance.

Etiology

Acute diarrhea usually results from gastrointestinal infection, mainly by transmission of pathogenic microorganisms to the gastrointestinal tract [4]. A wide variety of pathogens (bacteria, viruses, protozoa, etc.) have been found to cause

acute diarrhea. There is no doubt that bacteria are the most common agents at the origin of diarrhea in travellers and that Enterotoxigenic *E. Coli* (ETEC) is the single most frequently detected species. Other bacterial pathogens commonly found in the gastrointestinal tract include *Shigella*, *Salmonella* and *Campylobacter*.

Although viruses are a common cause of diarrhea in adults and children alike worldwide, they are less common as a cause of diarrhea in travellers than bacterial agents.

Diagnosis

The American College of Gastroenterology (ACG) guidelines on acute infectious diarrhea in adults [5] do not recommend the routine use of endoscopy and consider that endoscopy should be carried out only in homosexual males with diarrhea and in any patients with persistent diarrhea which has not responded to a course of empirical therapy. In immunocompromised patients, rectosigmoidoscopy is proposed as a measure in patients meeting certain criteria: tenesmus, a dysenteric syndrome, leukocytes and blood in the stools, and stools of low bulk.

Persistent, Chronic or Non-Specific Diarrhea

In contrast to the measures recommended in the event of acute diarrhea, some authors feel that colonoscopy may contribute useful information in patients with chronic diarrhea, particularly if stool studies, sigmoidoscopy and barium enema have failed to identify an etiology [6,7]. Donowitz et al. propose a two-fold regimen for the evaluation of patients with chronic diarrhea, with colonoscopy being undertaken first, with ileoscopy being recommended as a second step in the event that stool and blood analyses, standard abdominal radiography, high-quality barium studies of the upper gastrointestinal tract, small intestine and colon, as well as sigmoidoscopy with biopsy, are negative [8].

Neugut et al. [9] prospectively studied 154 patients who underwent colonoscopy to evaluate a change in bowel habits (constipation or diarrhea). Even though 90% of the patients were aged 45 years or older, colonoscopy identified no lesion in 74%, polyps in 20%, and cancer in 6%.

In a retrospective study of 205 patients undergoing lower GI endoscopy (sigmoidoscopy or colonoscopy) and biopsy for hemoccult-negative diarrhea as the sole symptom (HIV-negative patients only), Patel [10] reported a diagnostic yield of 18% (37/205). In the majority of these patients (32/37), clinically significant pathologies requiring therapeutic measures were found (pseudo-membranous colitis 7/37, chronic inflammatory bowel disease 7/37, other forms of colitis (microscopic, collagenous, ischemic, indeterminate) 8/37, Melanosis coli 5/37, villous adenoma 3/37, others).

Kalra et al. [11] reported a diagnostic yield of 38% in patients with diarrhea, namely polyps, colitis, diverticula or cancer (proportions not specified). The yield attained 91% in patients with diarrhea and bleeding. Another study reported only one cancer in a cohort of 117 patients with non-bleeding lower abdominal symptoms, but the authors did not, however, report the percentage of patients who complained of diarrhea only [12]. Studies concerning screening colonoscopy in asymptomatic patients have reported a higher prevalence rate of neoplasms than that reported in patients with chronic diarrhea [13,14]. Diarrhea on its own does not thus appear to constitute a clear indicator of colonic neoplasia, nor is initial evaluation by colonoscopy justified in order to rule out malignancy as a cause.

Patients with Diarrhea and Macroscopically Normal Mucosa

The diagnostic yield in diarrhea patients with macroscopically normal mucosa has only to date been analysed in retrospective studies with varying inclusion/exclusion criteria. The percentages reported as regards macroscopically normal mucosa and abnormal histology (mainly microscopic colitis) ranged from 10% [10] to 19% [15,16]. The clinical outcome of such patients was, however, reported to be benign and careful follow-up without any specific medical treatment may be sufficient as a therapeutic measure [10]. Rams et al. [17] and Prior et al. [16] were in favour of biopsy for patients with such indications, whereas Marshall et al. [18] found that the yield of biopsies in diarrhea patients with macroscopically normal colons at endoscopy is low. We may thus conclude that these retrospective studies, with widely differing inclusion/exclusion criteria, do not permit a decision to be made as to which patients with macroscopically normal mucosa should be biopsied.

Diagnostic Yield in Routine Ileoscopy

One prospective study [19] in 136 consecutive patients scheduled for colonoscopy, including 28 patients with diarrhea (no further details given), reported a positive diagnosis in eight cases (6% of all patients, 29% of diarrhea patients and in four out of six HIV-positive patients with diarrhea). In four of these eight cases, the diagnosis was made on the basis of ileoscopy alone (3% of all patients and 14% of diarrhea patients). Although the yield reported in asymptomatic patients was low (2.7%), ileoscopy in patients complaining of diarrhea (especially HIV-positive patients) seems valid as a measure. Another prospective study [20] of routine ileoscopy in an unselected series of 295 consecutive patients did, however, find that 1.8% (4/213) had macroscopic abnormalities, a quarter of which had an abnormal histology (0.5%) of the ileal mucosa. The interpretation of these percentage rates is problematical because no information is given concerning the indication for colonoscopy and the patients' symptoms. Ileoscopy was not associated with complications in either study. The

significant difference in success rates reported (95% by Zwas and 71% by Kundrotas) for ileal intubation may be due to the differing levels of expertise of the endoscopists. Routine ileoscopy seems to be indicated in patients with chronic diarrhea, especially in those who are HIV-positive.

Donowitz et al. [8] suggest a two-stage outpatient evaluation in patients with chronic diarrhea, which relies initially on patient history and physical examination to dictate the course of further investigation, with, if necessary, a third inpatient evaluation stage.

The initial examination and a limited colorectal evaluation often indicate the etiology of the diarrhea. If the cause of the diarrhea is not obvious after this evaluation, then several investigations should be undertaken in the following order (stage 1): stool studies, blood studies, radiological studies, sigmoidoscopy with biopsy. In the event that the etiology still remains unclear, a second series of more costly and more invasive tests are then performed (stage 2).

Irritable Bowel Syndrome (IBS)

Diarrhea attributable to IBS usually refers to the passing of small quantities of loose stools. Stool evacuation is often preceded by urgency or tenesmus. The stools passed initially may be normal in consistence but rapidly followed by a softer, unformed stool. IBS affects 14–24% of women and 5–19% of men. Up to 70% of persons with IBS symptoms do not seek medical attention but it does, in fact, account for 12% of patients seen in primary care and 28% of patients seen in a gastroenterological practice. A historical cohort study [21] of 112 patients with IBS (mean follow-up period 29 years) showed a good long-term prognosis with a normal (as expected) survival rate and a low likelihood of evolution towards organic disease. Diagnosis relies principally on the patient's clinical history [22, 23] and is rarely confirmed by a structured evaluation. Camilleri et al. [24] recommend in their review that sigmoidoscopy be carried out in order to exclude colitis, combined with barium enema in patients over age 40, followed by an empirical treatment trial in patients with suspected irritable bowel syndrome [24] and they argue that the risk and expense of colonoscopy are rarely justified given the disorder's benign natural history. The AGA recommends flexible sigmoidoscopy or colonoscopy, or a barium enema in patients over 50 years of age [23].

Microscopic Colitis

Definition

Microscopic colitis was described by Read [25] as a condition characterised by longstanding diarrhea and mild inflammation in the colonic mucosa with negative macroscopic findings. Histological changes include a thickened subepithelial band of collagen (mandatory for the diagnosis of collagenous colitis and absent in lymphocytic colitis), non-specific inflammation in the mucosa, inflammatory

cells in the surface epithelium and preservation of crypt architecture [26], but other authors disagree about the definitions of collagenous, lymphocytic and microscopic colitis [27,28]. A unitary nosological concept does, however, seem to predominate with microscopic colitis as a general term, including collagenous, lymphocytic and other rarer forms of colitis [29].

Prevalence, Incidence and Etiology

In a well-designed population-based epidemiological study in Sweden (in an area of mixed urban/rural type with limited migration and nearly 170,000 inhabitants) conducted between 1984 and 1993, Bohr et al. [30] reported a prevalence rate of 15.7/10⁵ for collagenous colitis (CI95: 9.8–21.6) and a mean annual incidence of 1.8/10⁵ (CI95: 1.2–2.4) inhabitants. The female: male ratio was 9:1, the median age at diagnosis was 64 years.

The etiology of collagenous colitis is unclear although its association with other autoimmune disorders suggests a possible immunologically mediated response to an unidentified stimulus [26]. Use of non-steroidal anti-inflammatory drugs may precipitate or exacerbate the condition [31,32].

Symptoms and Diagnosis

Symptoms include intermittent watery diarrhea (100%), predominantly nocturnal (68%), abdominal pain (79%), incontinence and mild weight loss (42%) [26]. No consensus of opinion exists concerning the optimal initial screening modality: sigmoidoscopy or total colonoscopy [28]. The percentage of cases missed at sigmoidoscopy ranged from 5% [33] to 29% [34], but due to a more dense collagen deposit in the proximal colon, colonoscopy seems to represent the best diagnostic tool [30].

Treatment

No randomised trials of treatment are available and although no reliable reports of effective therapy exist, the best response to treatment has been described with steroid use [26] and sulfasalazine [27] use.

Clostridium Difficile-Associated Diarrhea (CDAD)

Prevalence

Antibiotic-associated diarrhea is caused by *Clostridium difficile* in only 15–20% of cases and is of unknown origin in most of the remaining cases. Antibiotic-associated diarrhea not caused by *C. difficile* is relatively mild and self-limiting [35]. *C. difficile* remains the most frequently identified cause of nosocomial diarrhea [36]. About 5–25% of *C. difficile* detected do not produce toxins and do not cause colitis or diarrhea [35].

Symptoms

Typical symptoms include profuse watery, greenish, foul-smelling or bloody diarrhea and cramping abdominal pain [37]. Symptoms can range from mild to life-threatening. Katz et al. [38] reported a clinical decision rule (with prior antibiotic use as long as 6–8 weeks before and a history of significant diarrhea) to identify patients at high risk of having CDAD, with a sensitivity of 80% and a specificity of 45%, a positive predictive value of 18% and a negative predictive value of 94%.

Diagnosis

It is difficult to establish a definitive diagnosis of *C. difficile*-associated diarrhea (CDAD), since there is no true gold standard. A guideline endorsed by the American College of Gastroenterology for the diagnosis and treatment of *C. difficile*-associated diarrhea and colitis was recently published [35,38]. Although endoscopy with biopsy represents the best and the quickest means of diagnosing *Clostridium difficile* colitis, it is expensive and should be reserved for the following situations only: severely ill patients, negative tests but high suspicion of *C. difficile* diarrhea; other colonic pathologies which can be diagnosed by endoscopy are included in the differential diagnosis.

Colonoscopy is preferred by certain authors since the pseudomembranes may be restricted to the right colon [39]. In a prospective study, as many as 9% (2/22) of PMC cases were not detected if flexible sigmoidoscopy alone, but not colonoscopy, was performed [40]. The macroscopic appearance of the colonic mucosa varies from that of non-specific micro- or macroscopic colitis to that of pseudomembranous colitis (50% of patients undergoing sigmoidoscopy because of diarrhea and *C. difficile* cytotoxins had organisms in their stools [36]).

2. Panel Results

The experts of the European panel on appropriateness of gastrointestinal endoscopy (EPAGE) considered the above literature review as well as their own clinical expertise in evaluating the appropriateness of colonoscopy for uncomplicated diarrhea. Definitions of terms, clinical variables used, general and specific panel results related to uncomplicated diarrhea are presented.

Definitions

The definitions used by the European panel on gastrointestinal endoscopy to assess appropriateness of colonoscopy in uncomplicated diarrhea are listed in Table 1.

Clinical Variables

Table 2 shows the clinical variables and their level of detail that were used to create and rate patient scenarios to assess

Table 1 Definitions of terms

<i>Uncomplicated Diarrhea</i>	Diarrhea with one or more of the following: ≥ 3 loose stools/day, nocturnal diarrhea, hypokaliemia, dehydration.
<i>Infectious work-up</i>	Stool culture of enteric pathogens and examination for ova and parasites, immunoassay for <i>Clostridium difficile</i> toxin if patient was taking antibiotics within 2 weeks prior to onset of diarrhea.
<i>Potential diarrhea source identified</i>	One or more of the following: pseudo-membranes with positive <i>Clostridium difficile</i> toxin, biopsy consistent with inflammatory bowel disease, biopsy consistent with microscopic colitis or collagenous colitis.
<i>Empirical IBS therapy</i>	At least 2 weeks of daily treatment with fiber (psyllium- or methylcellulose-containing preparations) or antispasmodics (dicyclomine, propantheline, hyscosamine, loperamide, diphenoxylate).
<i>Lower GI evaluation</i>	Sigmoidoscopy: flexible tube (60 cm) Barium enema: double contrast technique

Table 2 Clinical variables used in uncomplicated diarrhea

Variables	Number of categories	Categories
Age	2	– age < 50 years – age ≥ 50 years
Duration of diarrhea	2	– < 3 weeks – ≥ 3 weeks
Indicators of systemic inflammation	2	– no indicator of inflammation – indicator(s) of inflammation present
Lower GI evaluation	3	– no lower GI investigation done – sigmoidoscopy done and negative – barium enema done and negative
Response to empirical irritable bowel therapy	3	– no IBS therapy – no or only partial response to IBS therapy – positive response to IBS therapy

the use of colonoscopy in patients with uncomplicated diarrhea.

General Panel Results

Uncomplicated diarrhea was assessed by 38 clinical scenarios. Of the 38 scenarios, the panel rated 13/38 (34%) as inappropriate, 12/38 (32%) as uncertain and 13/38 (34%) as appropriate.

Table 3 Description of appropriateness of indications for colonoscopy for uncomplicated diarrhea

Clinical situation

In individuals with uncomplicated diarrhea of less than 3 weeks' duration, indication for colonoscopy is
inappropriate

In individuals < 50 years of age with uncomplicated diarrhea for more than 3 weeks and no indicator of systemic inflammation, indication for colonoscopy is
inappropriate if no IBS therapy had been prescribed or if there was a positive response to IBS therapy
uncertain in absence of response to IBS therapy unless sigmoidoscopy had been performed and was negative (*inappropriate*)

In individuals < 50 years of age with uncomplicated diarrhea for more than 3 weeks and presence of indicator(s) of systemic inflammation, indication for colonoscopy is
appropriate in absence of response to IBS therapy
uncertain if no IBS therapy had been prescribed or if there was a positive response to IBS therapy unless no LGI investigation was performed (*appropriate*)

In individuals aged 50 years or more with uncomplicated diarrhea for more than 3 weeks, and no indicator of systemic inflammation, indication for colonoscopy is
inappropriate in the case of a positive response to therapy generally
uncertain in the absence of IBS therapy generally
appropriate in the absence of response to IBS therapy

In individuals aged 50 years or more with uncomplicated diarrhea for more than 3 weeks, and presence of indicator(s) of systemic inflammation, indication for colonoscopy is
appropriate if no lower GI investigation had been done or if there is no response to IBS therapy
uncertain if there was a positive response to IBS therapy

Specific Clinical Panel Results

Main results are expressed as overall statements representing over 90% of the clinical scenarios for the appropriateness of use of colonoscopy in patients with diarrhea (Table 3). In some cases, the same scenario may apply to more than one statement. Detailed appropriateness and necessity criteria are available in a computerized form accessible *via* Internet (<http://www.epage.ch>) which readers are encouraged to consult. No indication for the use of colonoscopy in patients with diarrhea was judged necessary (crucial).

3. Conclusions

The literature indicated that, in acute diarrhea, colonoscopy is generally not indicated and adds little to the information already gained at history-taking, physical examination and stool analysis. In contrast, colonoscopy may contribute to the diagnosis and management of some cases of chronic diarrhea, when there is a strong suspicion of a colonic process or when the presence of IBD is suspected. In addition, colonoscopy can contribute principally to the diagnosis and management of some cases of chronic diarrhea with negative stool tests, especially in patients with suspected CDAD in whom a rapid diagnosis is essential.

The results of the European panel indicate that performing colonoscopy was inappropriate for diarrhea of less than 3 weeks' duration. In diarrhea of 3 weeks' duration but without indicators of systemic inflammation, it was most often inappropriate or uncertain. When indicators of systemic inflammation were present, colonoscopy was judged appropriate most of the time.

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