Appropriateness of colonoscopy in Europe (EPAGE II)
Chronic diarrhea and known inflammatory bowel disease

Background and study aims: To summarize the published literature on assessment of appropriateness of colonoscopy for investigation of chronic diarrhea, management of patients with known inflammatory bowel disease (IBD), and for colorectal cancer (CRC) surveillance in such patients, and to report report appropriateness criteria developed by an expert panel, the 2008 European Panel on the Appropriateness of Gastrointestinal Endoscopy, EPAGE II.

Methods: A systematic search of guidelines, systematic reviews, and primary studies regarding the evaluation of chronic diarrhea, the management of IBD, and colorectal cancer surveillance in IBD was performed. The RAND/UCLA Appropriateness Method was applied to develop appropriateness criteria for colonoscopy for these conditions.

Results: According to the literature, colonoscopic evaluation may be justified for patients aged > 50 years with recent-onset chronic diarrhea or with alarm symptoms. Surveillance colonoscopy for CRC should be offered to all patients with extensive ulcerative colitis or colonic Crohn’s disease of 8 years’ duration, and to all patients with less extensive disease of 15 years’ duration. Intervals for surveillance colonoscopy depend on duration of evolution, initial diagnosis, and histological findings. The EPAGE II criteria also confirmed the appropriateness of diagnostic colonoscopy for diarrhea of > 4 weeks’ duration. They also suggest that, in addition to assessing extent of IBD by colonoscopy, further colonoscopic examination is appropriate in the face of persistent or worsening symptoms. Surveillance colonoscopy in IBD patients was generally appropriate after a lapse of 2 years. In the presence of dysplasia at previous colonoscopy, it was not only appropriate but necessary.

Conclusions: Despite or perhaps because of the limitations of the available published studies, the panel-based EPAGE II (http://www.epage.ch) criteria can help guide appropriate colonoscopy use in the absence of strong evidence from the literature.
New biological treatments now aim at halting the progression of the disease and at attaining complete mucosal healing as well as clinical remission. Therapeutic approaches to IBD are presented in a companion article [19].

Long-standing ulcerative colitis and Crohn’s disease are associated with development of colorectal dysplasia and cancer, but the exact magnitude of the risk is not clearly defined [20 – 32] (see also Results section Surveillance colonoscopy in known IBD). Recent studies suggest that colorectal cancer (CRC) in IBD may be less frequent than was previously believed. This could partly be due to effective therapy and prevention strategies [33, 34]. The main established risk factors for CRC in IBD include prolonged due to effective therapy and prevention strategies [33, 34]. The less frequent than was previously believed. This could partly be also Results section Surveillance colonoscopy in known IBD).

Methods

The literature review process included a systematic search of websites issuing guidelines and of Medline (1997 – February 2008) to select published guidelines, systematic reviews, and primary studies assessing the use of colonoscopy in patients with chronic diarrhea and in known IBD. With the exception of certain relevant articles, the literature published before 1997 is presented in the previous literature review [47, 48].

The application of the RAND/UCLA Appropriateness Method is described in a companion article in this issue [50]. Briefly, the RAND process is a formal explicit expert panel method that allows classification of each indication into one of the following categories of appropriateness: inappropriate, uncertain, appropriate, and both appropriate and necessary (i.e. the indication mandates colonoscopy). To simplify the graphical presentation of the appropriateness results, these four categories were consolidated into two clusters: “Appropriate” (comprising the two categories appropriate and appropriate and necessary) and “Not appropriate” (comprising categories inappropriate and uncertain). In addition to simplification and enhanced clarity of presentation, the rationale for this choice was that in many instances in the case of a nonappropriate scenario, whether it be uncertain or inappropriate, the decision for not proposing the colonoscopy should be specifically discussed and shared with the patient. All clinical indications and their ratings are available on the EPAGE website (www.epage.ch).

Results: Literature review

Chronic diarrhea

A total of 18 primary studies investigating the diagnostic yield of colonoscopy in patients presenting chronic diarrhea and published between 1997 and February 2008 were identified. Nine guidelines published over the same period and giving recommendations on the use of colonoscopy for diagnostic purposes in these patients were retrieved.

Primary studies [51 – 68] investigating the diagnostic yield of lower gastrointestinal endoscopy in chronic diarrhea (Table e1) show wide variation in rates, with findings ranging from 15 % up to 70% of the cases. Microscopic colitis [64, 69] (both collagenous colitis and lymphocytic colitis) was diagnosed in 10% – 14% of patients investigated endoscopically for chronic diarrhea. Guidelines [1, 2, 70 – 74] (Table e2) offer no clear consensus on the appropriateness of endoscopic procedures in chronic diarrhea. If an endoscopic procedure is performed, it is not clear whether the initial procedure should be sigmoidoscopy or colonoscopy, although some guidelines clearly recommend colonoscopy at > 50 years of age [70]. In the event of an endoscopic investigation, multiple biopsies should be taken – including in the ileum, except when the latter is macroscopically normal – but there is no clear consensus on the exact location and on the number of biopsies to be taken. There seems to be a trend towards the taking of multiple biopsies, ideally in the descending colon, especially when looking for microscopic colitis [69, 75].

Practitioners might consider performing colonoscopy in the presence of chronic diarrhea mainly with the aim of excluding CRC. In the retrieved primary studies [76 – 78] (Table e3), chronic diarrhea does not appear to constitute an indicator or a risk factor for colonic neoplasia. Some CRC screening/surveillance guidelines [70, 71, 74] do cite diarrhea as a possible symptom which might indicate CRC, while the majority of the retrieved screening/surveillance guidelines do not even mention diarrhea [79 – 88]. Only the French guidelines from ANAES (Agence Nationale d’Accréditation et d’Évaluation en Santé) [70] recommend that, for patients with diarrhea of recent onset and unresponsive to treatment, a total colonoscopy be performed to identify a potential colonic neoplasm if symptoms appear in an individual > 50 years of age, or if symptoms appear at younger than < 50 years of age and if symptomatic treatment is not effective.
Known inflammatory bowel disease (IBD)

Nine guidelines on the use of colonoscopy for clinical management of patients with known IBD and published between 1997 and February 2008 were identified. For the same period, 19 guidelines were retrieved on the use of colonoscopy for surveillance of patients with known IBD. Guidelines [5, 6, 9, 18, 89 – 92] issuing recommendations on the use of colonoscopy for surveillance purposes (surveillance excluded) in known ulcerative colitis and Crohn’s disease are presented in Table e4 and Table e5. In management of known ulcerative colitis, sigmoidoscopic rather than colonoscopic evaluation may be used to define disease activity or assess superimposed colitis. However, the appropriateness of this detection mode depends upon the evolution of the disease and on the potential consequences in terms of therapeutic approach. A colonoscopy is useful in the elective preoperative phase. Management of known Crohn’s disease does not systematically require colonoscopic procedures, either for evaluation of treatment, or after a new relapse. Colonoscopic procedures are useful for the examination or for the management of short accessible strictures and of bleeding; a colonoscopy is useful in the elective preoperative phase.

Surveillance colonoscopy in known IBD. According to the retrieved guidelines [5, 6, 9, 18, 21, 70, 73, 80, 81, 83, 88 – 91, 93 – 97] (Table e6), surveillance colonoscopy should be offered:

- to all patients with extensive ulcerative colitis or colonic Crohn’s disease of 8 years’ duration;
- to all patients with less extensive disease of 15 years’ duration;
to all patients with IBD-associated primary sclerosing cholangitis.

The literature appears to favor surveillance colonoscopy every 3 years for 10 years, every 2 years for 10 years, and then annually, depending on the decade of evolution. This procedure should include at least 4 biopsies taken randomly every 10 cm throughout the colon plus biopsy of any macroscopic lesion. Meta-analyses, reviews and studies on the association between IBD and CRC are shown in Table e7.

Results: EPAGE II panel

Of the 463 indications examined by the EPAGE II panel, 6 concerned chronic diarrhea, 27 the evaluation of ulcerative colitis, 23 the evaluation of Crohn’s disease, and 43 the use of colonoscopy for CRC surveillance in IBD. The number of scenarios (indications) considered inappropriate in each of these clinical categories was 2, 15, 9 and 15 respectively. Frank disagreement among the expert panelists was low (11% of scenarios). Indications considered necessary (mandating colonoscopy) were concentrated mainly in the group of CRC surveillance, especially when previous colonoscopy had revealed any grade of dysplasia or in presence of long-standing disease.

Table 8 shows the definitions used for the clinical categories. Fig. 1a, 2a, 3a, and 4a summarize appropriateness of colonoscopy consolidated into two categories: “Not appropriate” (comprising categories uncertain and inappropriate) versus “Appropriate” (including necessary).

As in the literature review, the EPAGE II panel criteria confirmed the appropriateness of diagnostic colonoscopy for diarrhea of at least 4 weeks’ duration (Fig. 1a). They also recommend that in addition to assessment of the extent of IBD by colonoscopy, colonoscopic examination is appropriate in the face of persistent or worsening symptoms (Figs. 2a and 3a), with some nuances for ulcerative colitis depending on the existence and nature of prior sigmoidoscopy findings. The indication for surveillance co-

Table 8
Colonoscopy in IBD patients (Fig. 4a) was generally appropriate after a period of 2 years. In the presence of dysplasia at previous colonoscopy, it was not only appropriate but necessary (mandating colonoscopy). More detailed results presenting the four main categories of appropriateness (inappropriate, uncertain, appropriate, and both appropriate and necessary, that is, mandating colonoscopy) can be found online (Figs. e1b, e2b, e3b, e4b).

Conclusions: Literature review

Chronic diarrhea

Caution is necessary in the interpretation of results from the literature on the appropriateness of colonoscopy for patients with chronic diarrhea. Primary studies are of modest quality. Most of them have a small sample size and are retrospective case series, without a control group. Variations in results can be explained by the heterogeneity existing in the studies in outcomes measured, study design, definitions, indications for colonoscopy, and/or inclusion criteria, thus reflecting the discrepancies in and the evolution of the definition of chronic diarrhea. Direct comparison of results between studies is therefore difficult and hence guidelines on this must be interpreted with caution, being mainly based on modest evidence, expert opinion, and consensus. The role of diagnostic colonoscopy thus remains uncertain but, if this procedure is performed and findings are macroscopically normal, multiple biopsies should be taken to exclude microscopic colitis.

The literature review also highlights the fact that despite the modest quality of evidence, and although the presence of these symptoms probably does not enhance the pick-up rate of CRC per se, recommendations tend to consider screening purposes together with clinical symptoms as an indication for performing an evaluation colonoscopy. Colonoscopic evaluation may thus be justified for patients aged > 50 years with recent-onset chronic diarrhea or for any patients with such a complaint in association with alarm symptoms.

Known IBD

Assessment of the appropriateness of colonoscopy in management of known ulcerative colitis and Crohn's disease relies on modest evidence. Available primary studies in patients with
known IBD are aimed at evaluating the efficiency of specific treatments, rather than the general impact of colonoscopy on patient outcome. Expert opinion and consensus play an important role in the recommendations on colonoscopy in IBD [45,98]. Guidelines on the use of colonoscopy for surveillance in ulcerative colitis and Crohn’s disease provide remarkably uniform recommendations, mostly relying on past studies [99] on CRC risk. The available evidence remains, however, modest. Considerable variation in the reported association between IBD and CRC might be due to differences in referral patterns, in follow-up, to differences in the methods of evaluating cancer risk, and to biological differences among the patients studied [45,100]. Surveillance of CRC in IBD has important limitations [98,100 – 102], including the possibility of a lead-time bias [100], limited patient compliance [103], variable endoscopic quality [104,105], poor interobserver agreement in histopathological interpretation, and disagreement in the management of dysplasia [45]. Although knowledge on the risk of CRC in ulcerative colitis and Crohn’s disease does reveal some discrepancies, guidelines issue similar surveillance recommendations for both IBDs.

The appropriateness of colonoscopy in the management of known ulcerative colitis and Crohn’s disease is in many cases debatable and depends on the evolution of the disease and on the therapeutic approach. Colonoscopy is useful in the preoperative phase and in the therapeutic management of short accessible strictures and of bleeding. In the future, endoscopic procedures might be indicated and systematically performed in order to monitor mucosal healing in patients where biological treatments are planned and/or under way [106,107]. Literature data support CRC surveillance in IBD, while at the same time recognizing its limitations. In the future, new techniques such as endomicroscopy and chromoendoscopy might considerably improve detection procedures for colonic dysplasia [108,109].

Conclusions: EPAGE II panel

The EPAGE II panel criteria confirmed the appropriateness of diagnostic colonoscopy for diarrhea of at least 4 weeks’ duration. They also suggest that, in addition to assessing the extent of IBD by colonoscopy, further colonoscopic examination is appropriate in the face of persistent or worsening symptoms. The indication for surveillance colonoscopy in IBD patients is generally considered appropriate after a lapse of 2 years; in the presence of dysplasia at previous colonoscopy, it is not only appropriate but necessary.

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Appendix: The EPAGE II Study Group

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References

2 Fine KD, Schiller LR. AGA technical review on the evaluation and management of chronic diarrhea. Gastroenterology 1999; 116: 1464 – 1486
14 Best WR, Becktel JM, Singleton JW. Redefined values of the eight coefficients of the Crohn’s Disease Activity Index (CDAI). Gastroenterology 1979; 77: 843 – 846
17 Konikoff MR, Denson LA. Role of fecal calprotectin as a biomarker of intestinal inflammation in inflammatory bowel disease. Inflamm Bowel Dis 2006; 12: 524 – 534

* See Appendix: The EPAGE II Study Group

Schusselé Filliettaz S et al. EPAGE II: Chronic diarrhea and known IBD... Endoscopy 2009; 41: 218 – 226
Rubio CA, Befrits R. Low-grade dysplasia in flat mucosa in ulcerative colitis. Gastroenterology 2004; 126: 1494–1495
66 Shah RJ, Fenoglio-Reiser C, Bleau BL et al. Usefulness of colonoscopy with biopsy in the evaluation of patients with chronic diarrhea. Am J Gastroenterol 2001; 96: 1091–1095
The following figures and tables are available online:
www.thieme-connect.com/media/endoscopy/200903-supmat/endo843.pdf

**Fig. e1b** Appropriateness ratings of clinical indications for performing colonoscopy in patients with uncomplicated chronic diarrhea (full decision tree).

**Fig. e2b** Appropriateness ratings of clinical indications for performing colonoscopy in patients for the evaluation of known ulcerative colitis, excluding surveillance for colorectal cancer (full decision tree).

**Fig. e3b** Appropriateness ratings of clinical indications for performing colonoscopy in patients for the evaluation of known Crohn’s disease, excluding surveillance for colorectal cancer (full decision tree). SBFT, small-bowel follow through; CT/MRI, computed tomography/magnetic resonance imaging.

**Fig. e4b** Appropriateness ratings of clinical indications for performing colonoscopy for surveillance for colorectal cancer in patients with known inflammatory bowel disease (full decision tree).

**Table e1** Studies investigating the diagnostic yield of colonoscopy in chronic diarrhea (1997 – February 2008).

**Table e2** Guidelines on the appropriateness of diagnostic colonoscopy in chronic diarrhea.

**Table e3** Studies investigating the association between diarrhea and colorectal cancer (CRC), 1997 – February 2008.

**Table e4** Guidelines/reviews on the appropriateness of colonoscopy for the clinical management of known ulcerative colitis.

**Table e5** Guidelines/reviews on the appropriateness of colonoscopy for the clinical management of known Crohn’s disease.

**Table e6** Guidelines/reviews on the use of colonoscopic surveillance for colorectal cancer (CRC) in patients with inflammatory bowel disease (IBD).

**Table e7** Meta-analyses, reviews, and studies investigating the association between inflammatory bowel disease (IBD) and colorectal cancer (CRC) (1997 – February 2008).