

Chromoendoscopy

The ASGE Technology Committee provides reviews of existing, new or emerging endoscopic technologies that have an impact on the practice of gastrointestinal endoscopy. An evidence-based method is used, with a MEDLINE literature search to identify pertinent clinical studies on the topic and a MAUDE (Food and Drug Administration Center for Devices and Radiological Health) database search to identify the reported complications of a given technology. Both are supplemented by accessing the "related articles" feature of PubMed and by scrutinizing pertinent references cited by the identified studies. Controlled clinical trials are emphasized, but in many cases data from randomized controlled trials are lacking. In such cases, large case series, preliminary clinical studies, and expert opinions are used. Technical data are gathered from traditional and Web-based publications, proprietary publications, and informal communications with pertinent vendors.

Technology Status Evaluation Reports are drafted by 1 or 2 members of the ASGE Technology Committee, reviewed and edited by the committee as a whole, and approved by the Governing Board of the ASGE. When financial guidance is indicated, the most recent coding data and list prices at the time of publication are provided. For this review the MEDLINE database was searched through September 2006 for articles and references within related to endoscopic tissue staining by using the keywords "chromoscopy," "chromoendoscopy," and "endoscopy" paired with "acetic acid," "congo red," "crystal violet," "indigo carmine," "lugol's," "methylene blue," "phenol red," and "toluidine blue." Practitioners should continue to monitor the medical literature for subsequent data about the efficacy, safety, and socioeconomic aspects of these technologies.

Technology Status Evaluation Reports are scientific reviews provided solely for educational and informational purposes. Technology Status Evaluation Reports are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment or payment for such treatment.

BACKGROUND

Chromoendoscopy, or chromoscopy, refers to the topical application of stains or dyes at the time of endoscopy in an effort to enhance tissue characterization, differentiation, or diagnosis. Chromoendoscopy is distinguished from endoscopic tattooing, which involves the injection of a long-lasting pigment (eg, India ink) into tissue for future localization. Endoscopic tattooing has been reviewed in a separate status evaluation report.¹

TECHNICAL CONSIDERATIONS

Classification of stains

The stains that are used for chromoendoscopy are classified as absorptive (or vital), contrast, or reactive (Table 1). Absorptive stains, such as Lugol's solution and methylene blue, identify specific epithelial cell types by preferential absorption or diffusion across the cell membrane. Contrast stains, such as indigo carmine, seep through mucosal crevices and highlight surface topography and mucosal irregularities. Reactive stains, such as congo red and phenol red, undergo chemical reactions with specific cellular constituents, resulting in a color change akin to a pH indicator.

Accessories for staining

The staining agents are generally inexpensive, readily available, and can be purchased from several vendors. None of them are specifically cleared by the Food and Drug Administration (FDA) for performance of chromoendoscopy, however. Stain preparation and dilution of the stock solution, when necessary, must be done in house because the reagents are not specifically marketed for chromoendoscopy.

For most chromoendoscopic applications, a spray catheter is used to apply a uniform mist of the staining agent onto the mucosa. Several disposable and reusable spray catheters are available for this purpose (Table 2).

The delivery of certain dyes mixed in a colonic lavage solution, in an enema, or in pill form has also been described.^{2,3}

STAINING INDICATIONS AND TECHNIQUES

General considerations

Certain chromoendoscopic techniques require pretreatment of the mucosa with a mucolytic agent to disrupt

TABLE 1. Staining agents for chromoendoscopy

Stains	Mechanism of action	Main applications
Absorptive stains		
Lugol's solution (iodine + potassium iodide)	Glycogen-containing normal squamous epithelium is stained dark brown; inflammation, columnar mucosa, dysplasia, and cancer remain unstained	Esophageal squamous cell cancer and dysplasia Barrett's esophagus
Methylene blue (methylthioninium chloride)	Absorptive epithelial cells of the small bowel, colon, and intestinal metaplasia at any site are stained blue; dysplasia and cancer is variably stained or unstained	Barrett's esophagus Gastric intestinal metaplasia and cancer Chronic ulcerative colitis
Toluidine blue (tolonium chloride)	Nuclei of malignant cells are stained blue	Oral and esophageal squamous cell cancer
Crystal violet (methylrosaniline chloride)	Absorbed into intestinal and neoplastic cells; nuclear stain	Barrett's esophagus Colonic neoplasms
Contrast stains		
Indigo carmine (indigotindisulfonate sodium)	Nonabsorbed dark bluish dye highlighting mucosal topography	Colonic neoplasms Chronic ulcerative colitis
Reactive stains		
Congo red (biphenylenaphthadene sulfonic acid)	Color change from red to dark blue/black in presence of acid at pH <3	Ectopic gastric mucosa Gastric cancer Adequacy of vagotomy
Phenol red (phenolsulfonephthalein)	Color change from yellow to red in presence of alkali (eg, from hydrolysis of urea to ammonia and carbon dioxide by urease-producing <i>H pylori</i>)	<i>H pylori</i> infection

TABLE 2. Spray catheters for chromoendoscopy

Manufacturer	Name	Length (cm)	Minimum accessory channel (mm)	Specific features	Use	U.S. list price (11/2006)
Hobbs Medical, Inc	Mistifier	260	2.8	Compatible with power irrigators	Single	\$225/box (box of 5)
Wilson-Cook Medical, Inc	Glo-Tip (GT-7-SPRAY)	240	2.8	Radiopaque tip	Single	\$67
Olympus, Inc	PW-6P-1	190	2.0		Reusable	\$208
	PW-5L-1	165	2.8		Reusable	\$208
	PW-5V-1	240	2.8		Reusable	\$208

and remove excess mucus from the mucosal surface. A 10% *N*-acetylcysteine (Mucomyst; Apoteco Inc, Princeton, NJ) solution is most commonly used for this purpose. The amount to be sprayed depends on the surface area being examined.

Depending on the staining objectives, targeted spraying (eg, colon polyp) or spraying the entire surface of the organ (eg, Barrett's esophagus) with the dye is performed. The amount of reagent needed varies according to the surface area to be stained, but in principle the smallest volume necessary should be used. Atropine or glucagon

may be administered just before staining to minimize gut contractions and uneven spraying. A spray catheter is inserted down the working channel of the endoscope and extends 2 to 3 cm beyond the distal end of the endoscope. Pan staining is performed by directing the spray catheter tip toward the mucosa and spraying the dye while rotating the shaft of the endoscope in a repeated clockwise-counterclockwise fashion and simultaneously slowly withdrawing the endoscope. A water rinse is typically carried out 1 to 2 minutes after staining to remove excess dye, except when contrast stains are used. The additional

time needed for tissue staining and interpretation is variable (2-20 minutes), depending on the indication and lesion or organ to be stained.

Chromoendoscopy is not technically demanding, but interpretation of the staining patterns requires familiarity, may not always be straightforward, and is subject to observer variation.^{4,6} Classification of mucosal staining patterns and related lesions has been described for various conditions stained by specific agents⁷⁻¹² but is not yet standardized or validated sufficiently for routine endoscopic practice.

Specific staining techniques

Lugol's solution: Lugol's solution is an iodine-based absorptive stain that has an affinity for glycogen in nonkeratinized squamous epithelium. It is used primarily for identifying squamous dysplasia and early squamous cell cancer of the esophagus (Fig. 1).¹³⁻²¹ Approximately 20 to 30 mL of 1.5% to 3% Lugol's solution is sprayed onto the esophageal mucosa.²² On staining, the normal esophagus promptly undergoes a dark green-brown to black discoloration that gradually fades over several minutes. Glycogen-depleted areas such as dysplasia, squamous cell carcinoma, Barrett's epithelium, and inflammation remain unstained or weakly stained.

Methylene blue: Methylene blue stains the normal absorptive epithelium of the small intestine and colon. The absence of staining in these tissues usually indicates the presence of metaplastic, neoplastic, or inflammatory change. Methylene blue also stains absorptive intestinal-type metaplasia of the esophagus⁸ and stomach.²³ Methylene blue has been used primarily in Barrett's esophagus²⁴ and, to a lesser extent, for the detection of gastric intestinal metaplasia²⁵ and dysplasia in chronic ulcerative colitis.²⁶

The application of methylene blue in the upper GI tract involves pretreating the mucosa with a mucolytic agent, spraying of the dye (typically 0.5% methylene blue) followed by a dwell time of 1 to 2 minutes, and vigorously washing the excess dye with tap water until persistent blue staining remains.^{25,27,28} The staining effect fades away within 24 hours. Positive staining for Barrett's intestinal metaplasia is defined as the presence of dark blue-stained mucosa that persists despite vigorous irrigation,^{27,29} whereas staining pattern heterogeneity and decreased stain intensity suggest Barrett's high-grade dysplasia or cancer (Fig. 2).⁹ The use of methylene blue staining in conjunction with magnification or high-resolution endoscopy may improve the diagnostic yield,^{11,30} whereas inadequate staining technique and inflammation may contribute to errors in interpretation.

For pancolon staining, the colon is sprayed with 0.1% methylene blue and evaluated in a segmental fashion (20-30 cm of colon at a time), starting at the cecum. Once a segment has been sprayed, excess dye is suctioned after a dwell time of 1 minute, and the colonoscope is

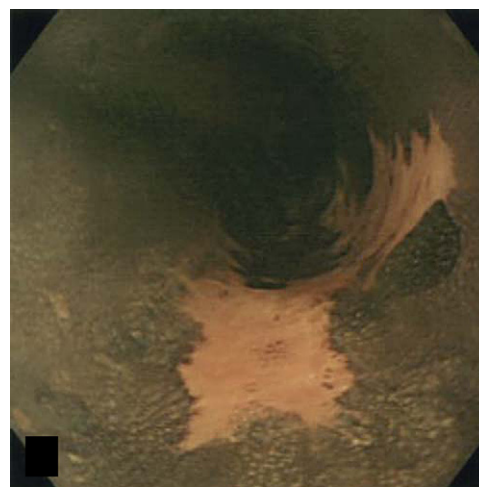


Figure 1. Chromoendoscopy with Lugol's solution. Unstained area defines extent of biopsy-confirmed squamous cell carcinoma of the esophagus. (From Katada C, Muto M, Manabe T, et al. Local recurrence of squamous-cell carcinoma of the esophagus after EMR. *Gastrointest Endosc* 2005;61:219-25.)

reinserted to the proximal extent of the segment to commence evaluation.²⁶

Toluidine blue: Toluidine blue is a basic absorptive dye that stains cell nuclei and can identify malignant cells, in part because of their increased mitotic activity and nuclear/cytoplasmic ratio.³¹ Toluidine blue staining has been used primarily for the detection of squamous dysplasia and carcinoma of the oral cavity^{32,33} and, to a lesser extent, the esophagus.³⁴⁻³⁷ The staining technique involves prewashing the mucosa with 1% acetic acid followed by the application of 10 to 20 mL of a 1% aqueous solution of toluidine blue. After 1 minute, rewashing with 1% acetic acid is performed to remove excess dye. Abnormal areas are stained royal blue.^{34,36} Inflammatory and fibrotic lesions may retain the dye, leading to false-positive staining.

Crystal violet: Crystal violet, or gentian violet, is best known as a topical antimicrobial agent that irreversibly binds microbial DNA and directly inhibits cell replication.³⁸ Crystal violet stains cell nuclei and has been applied recently in the esophagus for the detection of Barrett's intestinal metaplasia and dysplasia³⁹ and in the colon for enhancing visualization of the pit patterns.⁴⁰ The staining technique is similar to that of methylene blue, although a smaller amount of a 0.05% to 0.1% crystal violet solution is used to avoid excessive darkening of the stained surface.³⁹ A double-dye staining technique consisting of methylene blue staining followed by crystal violet staining has also been described in the esophagus (Fig. 3).^{41,42} In the colon, a comparable technique involves the application of indigo carmine to delineate lesion contour, followed by crystal violet staining with magnification endoscopy for pit pattern analysis.⁴³

Indigo carmine: Indigo carmine is a deep-blue contrast stain that is used primarily in the colon for enhancing

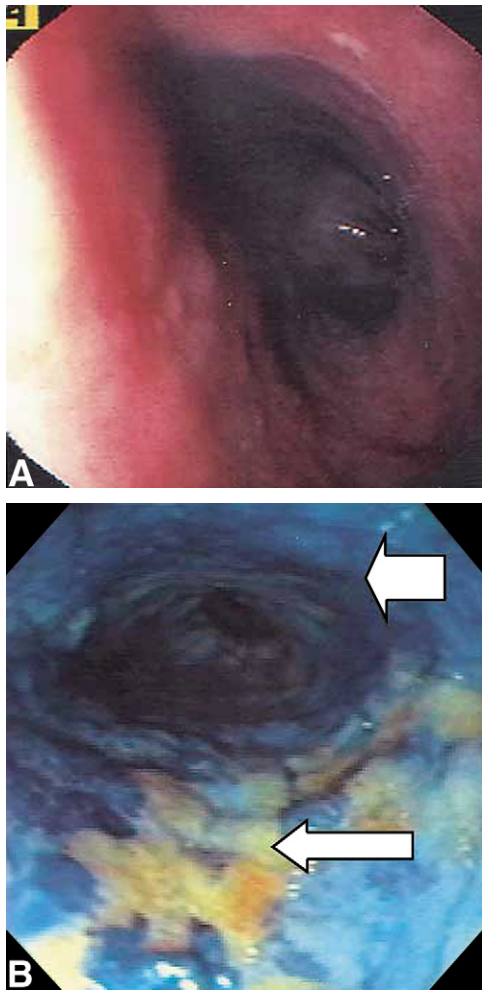


Figure 2. **A**, Endoscopic image of long-segment Barrett's esophagus (BE) with no apparent cancer obtained before the use of 4-quadrant jumbo random biopsy technique. Biopsy specimens revealed only focal high-grade dysplasia. **B**, Endoscopic image of long-segment BE from the same patient at a separate procedure after methylene blue (MB) staining. Intramucosal adenocarcinoma was diagnosed by MB-directed biopsy specimens from the unstained BE seen in the bottom half of the image (*long thin arrow*). Note the normal dark-blue-stained mucosa on the opposite wall (*short thick arrow*). (From Canto MIF, Setrakian S, Willis J, et al. Methylene blue-directed biopsies improve detection of intestinal metaplasia and dysplasia in Barrett's esophagus. *Gastrointest Endosc* 2000;51:560-8.)

the detection or differentiation of colorectal neoplasms. Indigo carmine staining is often used in conjunction with high-resolution or magnification endoscopy.^{44,45} The staining technique consists of either pancolonics or lesion-targeted spraying of 0.1% to 0.8% indigo carmine, followed by immediate observation of mucosal irregularities and pit patterns. The staining patterns are generally categorized according to the Kudo pit pattern classification; nonneoplastic tissues are characterized by regular, rounded, or stellar pits, whereas neoplastic tissues are characterized by irregular, tubular, or villous pits (Fig. 4).⁷

Congo red: Congo red is a reactive stain that changes color from red to dark blue or black in the presence of

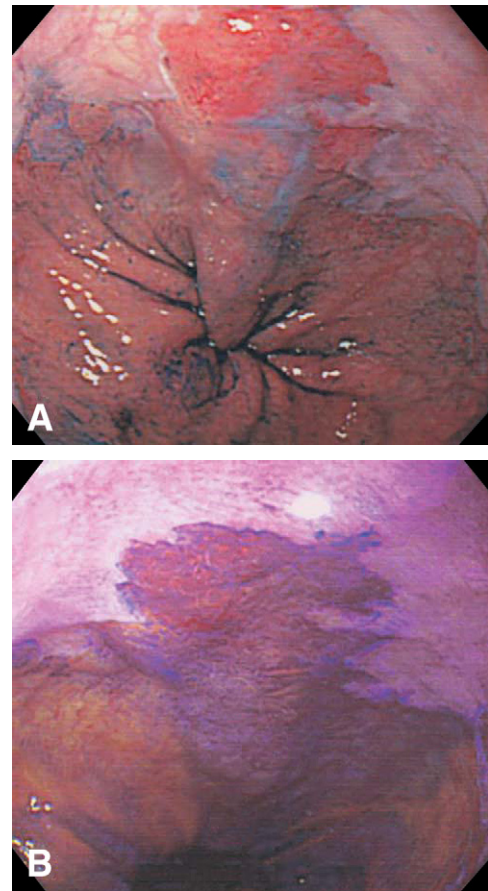


Figure 3. **A**, Chromoendoscopic view (methylene blue) showing non-staining of small round lesion with reddish, irregular surface. **B**, Chromoendoscopy view (crystal violet) showing strong staining of lesion that has irregularly arranged villous pits. Biopsy specimen confirmed adenocarcinoma. (From Amano Y, Komazawa Y, Ishimura N, et al. Two cases of superficial cancer in Barrett's esophagus detected by chromoendoscopy with crystal violet. *Gastrointest Endosc* 2004;59:143-6.)

acid at pH < 3. Congo red staining is rarely performed currently, although it has been used previously to assess the adequacy of vagotomy⁴⁶⁻⁴⁸ and to detect ectopic gastric mucosa^{49,50} or early gastric cancer.^{51,52} Variations in staining technique have been reported, but a general approach consists of administering a secretagogue (eg, pentagastrin 5 µg/kg) to stimulate acid production, rinsing the mucosa with 0.5% to 5% sodium bicarbonate solution to neutralize gastric juice at the surface, and spraying the mucosa with 0.3% to 0.5% congo red. Acid-secreting areas become black within minutes.

Phenol red: Phenol red is a reactive dye that changes color from yellow to red in the presence of an alkaline milieu.⁵³ Phenol red has been used to detect and map the gastric distribution of *Helicobacter pylori* during endoscopy because the urease-producing bacterium causes hydrolysis of urea to ammonia (alkali) and carbon dioxide.^{54,55} The staining technique involves reduction of gastric acid secretion with a proton pump inhibitor the day before (or intravenous injection of an H₂ blocker 30

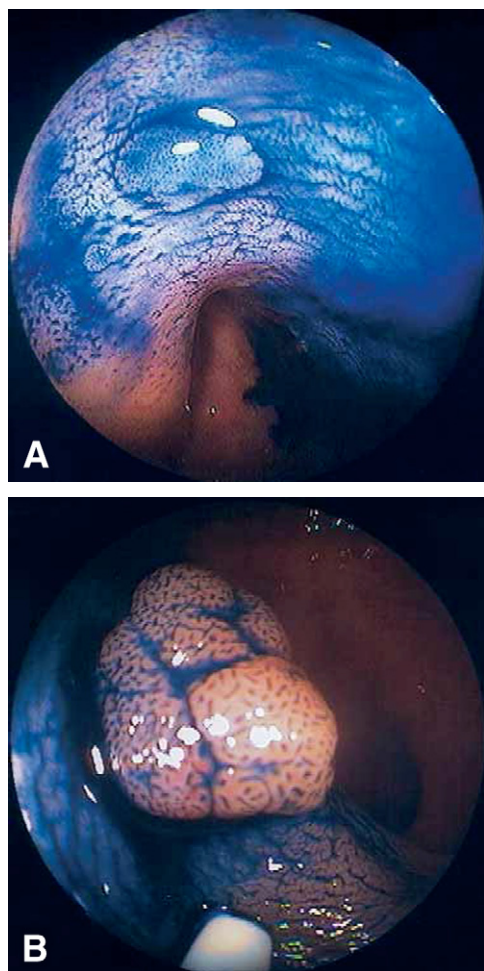


Figure 4. **A,** Colonoscopic view of hyperplastic polyp stained with 0.9% indigo carmine dye. **B,** Colonoscopic view of adenomatous polyp stained with 0.9% indigo carmine dye. (From Eisen GM, Kim CY, Fleischer DE, et al. High-resolution chromoendoscopy for classifying colonic polyps: a multicenter study. *Gastrointest Endosc* 2002;55:687-94.)

minutes before) endoscopy, ingestion of an antifoaming mucolytic agent (dimethylpolysiloxane) to remove gastric mucus, and injection of an anticholinergic drug to reduce gastric motility immediately before endoscopy. A 0.1% phenol red solution containing 5% urea is then sprayed over the entire surface of the stomach. Positive staining from yellow to red, indicative of *H pylori*, occurs within 2 to 3 minutes after dye spraying and persists for at least 15 minutes.⁵⁶ A false-positive reaction may result from bile reflux.⁵⁴

Acetic acid: The use of acetic acid at the time of endoscopy is not considered a chromoscopic technique per se because acetic acid is not a coloring agent, but the end result is similar to that achieved with a contrast agent. Acetic acid is a weak acid that breaks the disulfide bonds of glycoproteins that make up the mucus layer and causes reversible denaturation of intracellular cytoplasmic protein. It is known for its use during colposcopy where it whitens dysplastic squamous lesions of the

cervix. Acetic acid is used for contrast enhancement of the surface epithelium, and enhanced magnification endoscopy (EME) is the term commonly used to describe the combined use of magnification endoscopy and acetic acid instillation in the GI tract. The role of EME has been assessed primarily in Barrett's esophagus.

The technique involves spray instillation of approximately 10 mL of 1.5% to 3% acetic acid onto the esophageal mucosa. Pretreatment of the mucosa with a mucolytic agent is not needed, but a small wash (~5 mL of water) is typically performed after acetic acid spray. Initially, a whitish discoloration of both esophageal and gastric epithelia is noted. After 2 to 3 minutes, the normal esophagus remains white, whereas Barrett's and gastric columnar epithelia take on a reddish hue.⁵⁷ The mucosal effect, however, lasts only 2 to 3 minutes and repeated applications of acetic acid may be necessary. Round and reticular pit patterns typically predict gastric epithelium, whereas villous and ridged patterns predict Barrett's epithelium (Fig. 5).⁵⁷

CLINICAL APPLICATIONS AND EFFICACY

Esophageal squamous neoplasia

Lugol's solution is the most commonly used stain for enhancing the detection of esophageal squamous dysplasia and early squamous cell carcinoma in persons considered to be at risk for these conditions, including tobacco and alcohol abusers, head and neck cancer patients, and those living in endemic regions for the disease.¹³⁻²¹ Squamous lesions are detected with 91% to 100% sensitivity and 40% to 95% specificity after Lugol staining.²¹ The extent and delineation of these lesions are also more accurately defined after staining,^{18,21} hence the use of Lugol's solution to guide endoscopic mucosal resection (EMR) of early stage squamous cell carcinoma and to detect recurrences at the EMR sites.⁵⁸

Toluidine blue staining may be useful for improving the detection of early squamous cell carcinoma, but experience with this agent is limited.³⁴⁻³⁶ A double staining method using toluidine blue and Lugol's solution has been described to assess tumor extent and aid the EMR of early cancer.³⁷

Barrett's esophagus

Most chromoendoscopic studies in Barrett's esophagus have evaluated the role of methylene blue, although the utility of this agent, either for the diagnosis of Barrett's metaplasia or for the detection of Barrett's dysplasia and early cancer, remains controversial because of a wide range of diagnostic sensitivities (32%-98%) and specificities (23%-100%) reported.^{5,8,9,11,27-29,30,39,59-68} Also, a high level of interobserver variability was found among 4 examiners (all $\kappa < 0.4$) regarding the interpretation of the methylene blue staining pattern in a prospective, blinded study.⁵ Two of 3 randomized, controlled, crossover trials showed an

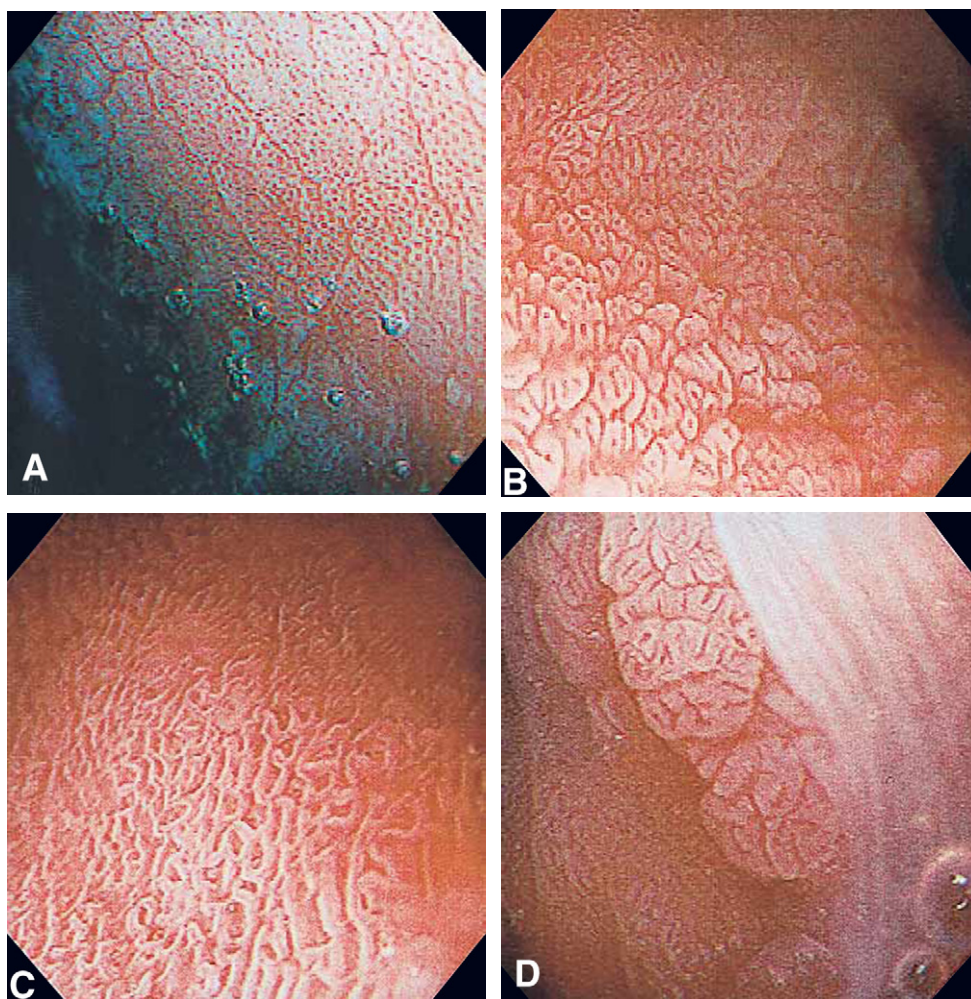


Figure 5. Endoscopic views after acetic acid instillation; 4 different patterns of the mucosal surface were observed. **A**, Pattern I: round pits with a characteristic pattern of regular and orderly arranged circular dots. **B**, Pattern II: reticular pits that are circular or oval and are regular in shape and arrangement. **C**, Pattern III: villous with no pits present but a fine villiform appearance with regular shape and arrangement is evident. **D**, Pattern IV: ridged with no pits present but a thick villous convoluted shape with a cerebriform appearance with regular shape and arrangement is evident. (From Guelrud M, Herrera I, Essenfeld H, et al. Enhanced magnification endoscopy: a new technique to identify specialized intestinal metaplasia in Barrett's esophagus. *Gastrointest Endosc* 2001;53:559-65.)

increased yield in the diagnosis of Barrett's metaplasia with methylene blue-directed biopsy compared with random biopsy.^{27,29,68} Some studies reported an increased detection rate of Barrett's dysplasia and early adenocarcinoma with methylene blue staining,^{9,27} whereas others did not.^{29,59,61,65,68} Potential factors contributing to the discrepant findings include differences in staining technique, operator experience, and staining interpretation.²⁴

The clinical experience with other staining agents, including Lugol's solution, crystal violet, and indigo carmine, in Barrett's esophagus remains limited. Lugol staining has been used to enhance delineation of the squamocolumnar interface and improve identification of Barrett's esophagus⁶⁹ or residual islands of Barrett's tissue within neosquamous mucosa after mucosal ablative therapy. Staining with 0.05% crystal violet identified Barrett's epithelium with 88% accuracy and detected dysplastic and

cancerous Barrett's lesions with 100% sensitivity and 67% specificity in one prospective study.³⁹ Indigo carmine staining was found to be helpful in distinguishing nondysplastic (ridged/villous pattern) from dysplastic (irregular/distorted pattern) Barrett's tissue.¹⁰

Initial experience regarding the use of EME with acetic acid in identifying Barrett's metaplasia reported a diagnostic yield of 87% to 100% when the villous-ridged pit patterns were seen as opposed to 0% to 11% for the round-reticular pit patterns.⁵⁷ Interobserver agreement, however, has been found to be poor (all κ values <0.4) regarding pit pattern assessment in several studies.^{5,70} The diagnostic accuracy of EME with acetic acid for Barrett's metaplasia has ranged from 52% to 90% in several prospective studies,^{5,71-75} and the use of acetic acid for identifying Barrett's dysplasia and early cancer has not been established. Acetic acid instillation has also been used to

identify remnant islands of Barrett's epithelium after mucosal ablative therapy. Residual islands not seen before acetic acid instillation were identified in 52% of patients in one study.⁷⁶

Gastric neoplasia

Several stains have been applied in the stomach, either alone or in combination, to detect or delineate gastric intestinal metaplasia, dysplasia, and early cancer.^{4,23,77,78}

Methylene blue staining with magnification endoscopy detected gastric intestinal metaplasia and dysplasia with 84% and 83% accuracy, respectively, in a study involving 136 patients.⁴

Congo red staining may be useful for the detection of gastric intestinal metaplasia and cancer because these conditions are associated with decreased or absent acid production.⁷⁹⁻⁸¹ A double staining technique using methylene blue and congo red identified early gastric cancers as "bleached" areas of mucosa that did not stain with either methylene blue or congo red, in contrast to the red or blue-red colored mucosa of noncancerous areas.^{51,52} The detection of synchronous early gastric cancers increased from 28% under standard white-light imaging to 89% after methylene blue–congo red staining.⁵¹ The technique also facilitated the detection of carcinomatous foci 4 to 10 mm in size that were not visible with conventional endoscopy.⁵²

Phenol red staining has been used to detect and map the distribution of *H pylori*, given its role in gastric carcinogenesis. Phenol red staining achieved 92% to 100% sensitivity and 85% to 95% specificity in detecting *H pylori* compared with biopsy as the gold standard.^{54,56}

Colorectal neoplasia

Pancolonic or targeted indigo carmine staining, with or without magnification or high-resolution endoscopy, is the most widely used chromoendoscopic technique for the detection or differentiation of colon polyps and neoplasms.

In uncontrolled studies, indigo carmine staining increased the detection rate of small, flat, or depressed colonic lesions that were overlooked by conventional colonoscopy.^{43,82,83} Three prospective, randomized, controlled trials have compared pancolonic indigo carmine chromoendoscopy with standard colonoscopy^{84,85} or targeted indigo carmine chromoendoscopy.⁸⁶ Although the detection rate for nonneoplastic polyps and diminutive or flat adenomas was increased in all 3 trials, the overall detection rate for adenomas was not significantly increased in 2 studies.^{84,85} Patients with ≥ 3 adenomas were more readily identified in the panchromoendoscopy group than in the conventional colonoscopy or targeted chromoscopy groups,^{84,86} although staining increased procedure time by 2- to 3-fold,^{84,85} thereby limiting its practicality.

The sensitivities and specificities of indigo carmine chromoendoscopy for predicting polyp histology (adenomatous vs hyperplastic) were 82% to 95% and 64% to 95%, respectively.⁸⁷⁻⁹¹ Relative to standard colonoscopy, indigo carmine chromoendoscopy with magnification increased the accuracy for polyp differentiation from 84% to 96% in one study.⁹² High-resolution indigo carmine chromoendoscopy only marginally increased the accuracy from 81% to 83% in another study.⁹¹ Indigo carmine staining is not currently considered a substitute for histologic diagnosis.^{88,91}

Indigo carmine staining combined with magnification endoscopy appears to be a useful technique for the detection of aberrant crypt foci in the rectum, a potential biomarker for proximal flat colonic neoplasia.⁹³ In high-risk conditions, such as hereditary nonpolyposis colorectal cancer syndrome, the use of indigo carmine staining significantly increased the detection rate of adenomas, particularly in the proximal colon, relative to conventional colonoscopy in 2 back-to-back colonoscopy studies.^{94,95}

A double-staining technique using indigo carmine and crystal violet with magnification endoscopy predicted incomplete EMR of flat, sessile colonic neoplasms with high accuracy,⁹⁶ although the use of indigo carmine staining to assess depth of invasion was found to be inaccurate.⁹⁷

Chronic ulcerative colitis

Prospective and randomized trials have shown indigo carmine and methylene blue chromoendoscopy to be of benefit in enhancing the detection of dysplasia in chronic ulcerative colitis (CUC).^{26,98-102} In one prospective, back-to-back colonoscopy surveillance study involving 100 patients with CUC, an indigo carmine–targeted biopsy protocol required fewer biopsies yet trended toward a significant increase in dysplasia detection compared with conventional colonoscopy and random biopsy.⁹⁹

In a prospective, randomized, controlled trial involving 263 patients with CUC, pancolonic staining with 0.1% methylene blue with magnification endoscopy did not alter cancer detection but yielded a 3-fold improvement in the detection of dysplasia (32 vs 10) relative to standard colonoscopic surveillance. Sensitivity and specificity were both 93% for differentiating neoplastic from nonneoplastic lesions.²⁶

SAFETY

Chromoendoscopy is perceived to be a safe procedure, with the stains considered to be nontoxic at the concentrations used.

Potential side effects of Lugol staining include retrosternal burning and nausea.¹⁰³ The application of 5% sodium thiosulfate is useful to neutralize residual iodine and reduce adverse symptoms after the staining evaluation has

been completed.¹⁰³ Rare instances of intense chemical esophagitis¹⁰⁴ and gastritis¹⁰⁵ responding to conservative management have been described. Lugol staining should be avoided in patients with iodine hypersensitivity and hyperthyroidism, and severe allergic reactions, such as bronchospasm, have been reported.⁶⁹

Methylene blue may cause a harmless, transient blue-green discoloration of the urine and feces. In Barrett's esophagus, methylene blue has been shown to induce oxidative DNA damage when exposed to white light,¹⁰⁶ although there have been no reports of clinically relevant toxicity or enhanced cancer risk associated with this agent.

No significant local or systemic toxicity has been reported with the topical use of the other staining agents.

A search of the MAUDE database did not identify any reported complications related to chromoendoscopy. Risks associated with the techniques used in dye spraying are negligible but may include aspiration during esophageal use. Common personal protective precautions should be used by staff to prevent inadvertent external exposure. Staining of clothing can occur with many of the agents discussed.

FINANCIAL CONSIDERATIONS

The accessories needed to perform tissue staining are readily available and relatively inexpensive. Costs for the spray catheters are included in Table 2. There is no specific Current Procedural Terminology (CPT)* code for billing and reimbursement for the time and effort added to the endoscopic procedure.

SUMMARY

Chromoendoscopy is inexpensive, safe, and relatively easy to perform, although the method is not standardized for several stains and the staining patterns are subject to observer interpretation. There is a need to build consensus on the staining techniques and terminology of the mucosal patterns for most applications, in addition to proving efficacy and reproducibility in high-quality, randomized, controlled trials before chromoendoscopy can be incorporated into routine clinical practice. The cost-effectiveness of tissue staining for various GI conditions has not been established, and its stance relative to commercially avail-

able, competing, and less cumbersome "chromoendoscopy without dye" techniques, such as narrow-band imaging,¹⁰⁷ remains to be seen.

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