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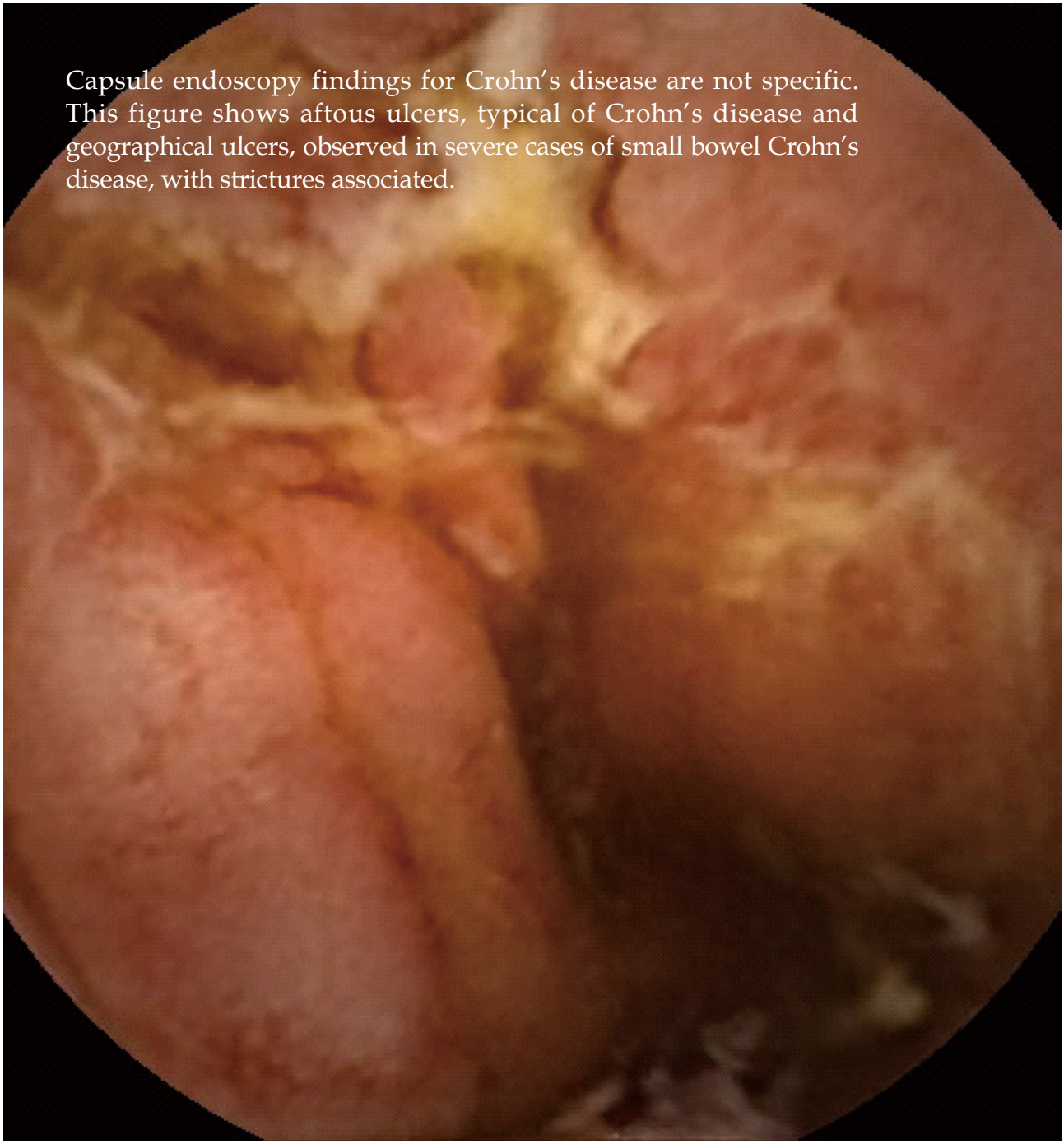

Capsule endoscopy findings for Crohn's disease are not specific. This figure shows aftous ulcers, typical of Crohn's disease and geographical ulcers, observed in severe cases of small bowel Crohn's disease, with strictures associated.

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EDITORIAL

Can we improve the diagnostic yield of small bowel video-capsule endoscopy?

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Abstract

Video-capsule endoscopy has revolutionized the examination of small bowel mucosa. However, this modality is relatively young and its diagnostic yield is low. Herein, we discuss different approaches to improve examination's diagnostic yield. There are strong data supporting some of them while there is speculation about the rest. As capsule endoscopy continues to evolve there is also a strong belief that technology will overcome at least some of the obstacles that hamper capsule endoscopy's diagnostic yield sometime in the near future.

Key words: Video-capsule endoscopy; Small bowel; diagnostic yield

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INTRODUCTION

Small bowel video-capsule endoscopy (VCE) is a powerful, patient friendly and expensive method to examine the small bowel. It has been shown to be superior to any other modality for the examination of small bowel mucosa with a diagnostic yield (DY) around 50%[1,2]. VCE DY is hampered by the presence of food residue, air bubbles and turbid or green viscous intraluminal fluid. Failure of the capsule to visualize the whole small bowel due to delayed gastric (GTT) or small bowel transit time (SBTT) also results in incomplete examinations. Moreover, the technical characteristics of the available capsule endoscopes are not optimal yet and since wireless capsule endoscopy is an evolving technology it is expected that the forthcoming capsule generations may successfully address some of the above issues. Until then, several methods have been proposed in order to increase examination's DY including use of cathartics and prokinetics, changing body posture, repeating a negative exam etc. with varying results[2].

The lack of established and validated objective measures and criteria to evaluate VCE DY adds further difficulties for the improvement of examination's DY. Until recently, investigators have used different subjective, unvalidated outcome measures to examine VCE DY and there is no accepted and validated scale to evaluate bowel cleanliness[2,3]. Moreover, many studies are published in abstract form and randomized controlled, adequately powered studies are still in a minority[2].

The vast majority of the information provided in this manuscript refers to published data using the Given Imaging Ltd (Israel) capsule. Given Imaging first delivered wireless capsule endoscopy in 2001. More recently, Olympus (Japan) delivered the Endocapsule, Intro-Medic Co, Ltd (Korea) developed the MiRoCam and finally, Chongqing Jinshan Science and Technology Group (China) launched the OMOM capsule for small bowel examination. Actually, few data are available in the literature concerning the Endocapsule (none regarding

our topic) and even less concerning the other two systems (one study regarding VCE completion rate is discussed below).

PURGATIVE BOWEL PREPARATION

The preparation suggested by the capsule manufacturer for VCE (Given Imageing, Yokneam, Israel) is an only clear liquids diet and 8 h fast. However, there is currently strong evidence from a recent meta-analysis that small bowel purgative preparation (polyethylene glycol solution or sodium phosphate) improves examination's DY[3]. Rokkas *et al*[3] evaluated data from 12 eligible studies and showed that VCE DY was superior in patients prepared with purgative *vs* those prepared with a clear liquids diet only [OR (95 % CI) = 1.813 (1.251 - 2.628), P = 0.002]. Increased VCE DY was the result of better quality of mucosa visualization [OR (95 % CI) = 2.113 (1.252 - 3.566), P = 0.005] in patients receiving purgatives. The study did not detect any advantage of purgative bowel preparation regarding VCE completion rate, VCE GTT and VCE SBTT.

While there is evidence of the benefit of bowel preparation for VCE, there is no consensus on the preparation regimen yet. Several investigators favour a half dose of purgative in the evening before the examination[3], other investigators prefer colonoscopy-like preparation[3] while some advocate the administration of the preparation during the examination[4-6]. The meta-analysis of Rokkas *et al*[3] showed marginal superiority of sodium phosphate over polyethylene glycol regarding the quality of VCE images. However a formal comparison between these two regimens has not been performed yet and a non-randomized prospective study evaluating the quality of small bowel preparation with sodium phosphate or polyethylene glycol did not detect any difference[7].

Bowel purge for VCE might be associated with adverse events and patient intolerance but this has not been reported yet[2]. Moreover, the meta-analysis on bowel preparation for VCE has not detected clinically significant adverse events related to bowel preparation[3].

SIMETHICONE

It has been consistently shown in randomized controlled trials that simethicone improves small bowel mucosa visibility at least in the proximal part of VCE recording by wiping out air bubbles from bowel lumen, either given alone[8-11] or in conjunction with purgatives[4,12,13]. None of the trials showed any benefit of simethicone use regarding VCE completion rate.

PROKINETICS

VCE completion rate is about 80%[1-3]. Retrospective studies have identified factors like inpatient status[14,15], previous abdominal surgery[15,16], poor bowel cleansing[15] and prolonged GTT[15] to predict incomplete small bowel VCE examination. There is still controversy whether advanced age[14,17,18] and diabetes mellitus[15,19,20] predict incomplete VCE studies.

In order to improve VCE completion rate, the use of prokinetics has been studied. The initial studies of oral erythromycin[21] and oral metoclopramide[22] showed marked reduction of the GTT but later studies showed no benefit of using these prokinetics either alone[23-26] or in conjunction with purgatives[13] regarding improving VCE completion rate.

Recent prospective randomized trials with mosapride[27], lubiprostone[28] and bisacodyl[29] also failed to show any benefit regarding the completion rate of the examination and new powerful prokinetics are not on the horizon after the withdrawal of tegaserod.

OTHER INTERVENTIONS

Another approach to improve VCE completion rate could be the follow-up of the capsule in the stomach by using the real-time viewer (Given Imaging, Yoqneam, Israel) which offers real-time inspection of the alimentary lumen peri-procedurally. In case of delayed GTT, intervention with endoscopic advancement of the capsule in the duodenum could be applied[5,30]. Moreover, the use of the real time viewer to optimize the timing for the administration of bowel preparation in order to improve the quality of bowel preparation is promising[5] but it has not been studied extensively yet.

Investigators also studied placing the patient in the right lateral position after swallowing the capsule in order to decrease the GTT but this approached has reached conflicting results; one study in favor and one against[31,32].

In an elegant prospective, randomized, single-blinded controlled trial, 93 consecutive patients were randomized to either use chewing-gum or not in order to determine whether chewing-gum increases the ability of VCE to reach the cecum[33]. Complete VCE examination rate was higher in the chewing-gum group compared with controls (83.0% *vs* 71.7% respectively, P = 0.19) and both GTT and SBTT were significantly shorter in the chewing-gum *vs* control group[33]. These data suggest a potential positive role of sham feeding to accelerate the passage of the capsule to the cecum.

One prospective randomized controlled study from China[34] examined the hypothesis that reduction of the image capture rate in the stomach saves battery's life and thus allows the operating capsule to reach the cecum. Fifty patients who underwent the OMOM [Chongqing Jinshan Science & Technology (Group) Co., Ltd, Chongqing, China] small bowel capsule-endoscopy were randomized into 2 groups: modified image capture rate (initially set at 0.5 frames per second and then modified to 2 frames per second once the capsule passed the pylorus) group and the control group (image capture rate set at 2 frames per second during the entire recording). VCE completion rate was 100% in the modified image capture rate *vs* 72% in the control group (P = 0.014)

showing the impact of technological improvement for the completion of the examination[34].

When there is strong evidence for the presence of small bowel mucosa lesions despite a negative VCE examination, there are several approaches for further evaluation including enteroscopy, radiology or a second capsule endoscopy. Patients with occult gastrointestinal bleeding with nondiagnostic VCE underwent a "second-look VCE" if they manifested a new bleeding episode or a drop in hemoglobin $\geqslant$ 2 g/dL[35]. "Second-look VCE" was diagnostic in those patients whose presentation changed from occult to overt or those whose hemoglobin dropped $\geqslant$ 4 g/dL showing that a certain proportion of patients with a negative VCE may benefit from the repetition of the examination[35]. However, it has not been tested yet if this approach is cost-effective.

CONCLUSION

Capsule endoscopy is a useful modality to evaluate small bowel mucosa lesions. However, examination's DY is low. Until the development of new generation capsules equipped with technology that will overcome obstacles such as poor mucosa visibility and limited life span of the battery, purgative bowel preparation and simethicone use are essential to improve the DY of the examination. Dual-camera small bowel capsule endoscopy might also increase DY but it has not been formally tested[36]. Prokinetic use and changing body posture are useless while sham feeding e.g. chewing-gum, might be helpful in order to increase the completion rate of VCE.

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GUIDELINES FOR CLINICAL PRACTICE

Lower gastrointestinal bleeding in the elderly

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Abstract

Lower gastrointestinal bleeding (LGIB) is an important worldwide cause of morbidity and mortality in the elderly. The incidence of LGIB increases with age and corresponds to the increased incidence of specific gastrointestinal diseases that have worldwide regional variation, co-morbid diseases and polypharmacy. The evaluation and treatment of patients is adjusted to the rate and severity of hemorrhage and the clinical status of the patient and may be complicated by the presence of visual, auditory and cognitive impairment due to age and co-morbid disease. Bleeding may be chronic and mild or severe and life threatening, requiring endoscopic, radiologic or surgical intervention. Colonoscopy provides the best method for evaluation and treatment of patients with LGIB. There will be a successful outcome of LGIB in the majority of elderly patients with appropriate evaluation and management.

Key words: Lower gastrointestinal bleeding; Lower gastrointestinal tract hemorrhage; Colonic hemorrhage; Colonic bleeding; Elderly

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INTRODUCTION

Lower gastrointestinal bleeding (LGIB) is a significant worldwide cause of morbidity and mortality in the elderly. The incidence of LGIB increases with age and is more common in men than women. There are worldwide regional differences in the causes of LGIB. For example, in the countries of Western Europe and the United States diverticulosis coli is common and is also one of the most common causes of LGIB. In Asia, however, diverticulosis coli is not common and is a much less common cause of LGIB. In the United States the incidence of LGIB ranges from 20.5 to 27 per 100 000 persons per year with a greater than 200 fold increase from the third to the ninth decade of life[1]. With projections of ever increasing numbers of the elderly population in the future, health care costs will rise, because the elderly patients tend to increase healthcare costs through longer hospital stays and more utilization of resources[2]. Therefore, one can expect that the worldwide incidence and importance of LGIB will also continue to rise.

The increase in incidence of LGIB in the elderly corresponds to three factors more common in the elderly: the increased incidence of gastrointestinal disease specific to elderly patients, co-morbid diseases and polypharmacy. Gastrointestinal diseases that cause LGIB that are more common in the elderly include diverticulosis coli, vascular ectasia, ischemic colitis and colonic neoplasms. After hemorrhage, the presence of a serious concurrent illness is the second most important factor in predicting mortality among patients with LGIB[2]. Co-morbid

diseases more common in the elderly that are associated with an increased incidence and severity of LGIB include cardiovascular disease, cirrhosis, renal disease, diabetes mellitus, and malignancy. Polypharmacy is common in the elderly with the increased use of anticoagulants and non-steroidal anti-inflammatory drugs (NSAIDS) that increase the risk of LGIB[3].

PATHOPHYSIOLOGY OF LGIB

LGIB can be acute, occult or obscure in nature. Acute LGIB presents as melena or hematochezia. Melena is the passage of black, tarry, foul-smelling stools as a result of degradation of blood to hematin. The source of melena is most often from the upper GI tract. However, it may also be from the small intestine or the right colon. Hematochezia is the passage of bright red blood per rectum, with or without stool. Occult bleeding is bleeding not apparent to the patient and is usually detected with stool guaiac testing[3]. It is the most common presentation of LGIB in the elderly, occurring in 10 % of the adult population. Remarkably, patients can loose up to 100 mL of blood per day and still have grossly normal appearing stools[4]. Obscure bleeding is bleeding in which the source of bleeding is difficult to detect on routine endoscopic and radiologic examinations. The source of bleeding is unidentified in approximately 5 % of patients who present with GI bleeding[5].

GASTROINTESTINAL DISEASES CAUSING LGIB (TABLE 1)

There are many gastrointestinal diseases that cause LGIB in the elderly. There are worldwide regional differences in the causes of LGIB. In the countries of Western Europe and the United States the most common causes of LGIB are diverticular disease and vascular ectasias. Less common causes of LGIB are inflammatory diseases of the colon, neoplasms, postpolypectomy hemorrhage, hemorrhoids, stercoral ulcer and solitary rectal ulcer. Rare causes include Dieulafoy's lesion and colo-rectal varices[6,7]. In Asia, however, the most common causes of LGIB are hemorrhoids, anal fissures and malignant colorectal neoplasms. Less common causes are benign colorectal neoplasms, ulcerative colitis, infectious colitis, ischemic colitis and radiation colitis. Diverticulosis coli is remarkably a rare cause of LGIB in Asia[8].

Diverticulosis coli

The incidence of diverticulosis coli increases with age from approximately 5% of individuals at age 40% to 65% of individuals at age 85 in the countries of Western Europe and the United States[9]. Although most patients with diverticulosis coli are asymptomatic, it is the most common cause of LGIB. LGIB occurs in approximately 3% to 5% of patients with diverticular disease, usually in the form of hematochezia[10]. The incidence of LGIB ranges from 15% to 48%, depending upon the series. Diverticular hemorrhage can be severe with significant morbidity and a mortality rate of 10% to 20%. Risk factors for LGIB in the elderly include the use of NSAIDS and hard stools due to lack of dietary fiber and constipation[11,12].

Table 1 Causes of LGIB in the elderly

Diverticulosis coli
Vascular ectasia (telangiectasia)
Inflammatory disease of the colon
Neoplasms
Post-polypectomy bleeding
Hemorrhoids
Stercoral ulcer
Solitary ulcer syndrome
Dieulafoy's lesion
Colo-rectal varices

LGIB: Lower gastrointestinal bleeding.

A colonic diverticulum is a sac-like protrusion that herniates through the colonic wall through the spaces weakened by the vasa recta. It is postulated that the vasa recta drape over the dome of the thinned-out colonic wall and become more prone to injury[13]. Factors that increase injury include NSAIDS and hard stool. Although about 90% of colonic diverticula are in the left colon, 50%-90% of diverticular LGIB occurs from right-sided colonic diverticula[14]. The increased frequency and severity of right sided diverticular hemorrhage may be due to the fact that right-sided diverticula appear to have wider domes and necks, exposing the vasa recta to injury over a greater length of the vessel. Diverticula may also arise in the small intestine where they may be source of obscure bleeding, such as from a small bowel diverticulum or Meckel's diverticulum.

LGIB from diverticula presents as painless, acute hematochezia. However, maroon colored stools or melena may occur in bleeding from right sided colonic diverticula and small bowel diverticula. Diverticular LGIB usually ceases spontaneously, with less than 1% of patients requiring greater than four units of blood[9]. However, bleeding can become more hemodynamicaly significant in elderly patients. Factors that increase hemorrhage are co-morbid conditions, such as cardiovascular disease and the use of anticoagulants or NSAIDS[3].

Vascular ectasia

Vascular ectasia, also termed angiodysplasia can occur in the colon and small intestine. Vascular ectasia occurs with much greater frequency in the elderly than telangiectasia, hemangiomas or congenital arteriovenous malformations. Vascular ectasia is a degenerative lesion of previously normal blood vessels that may occur anywhere in the colon, but more commonly in the cecum and right colon. Small bowel vascular ectasia is the most common source of obscure GI bleeding, occurring up to 60% of cases in Western Europe and the

United States[15,16]. On careful histologic examination, these lesions are noted to be ectatic, distorted veins, venules and capillaries, lined only by endothelium and occasionally by a small amount of smooth muscle[17,18]. The mechanism of injury appears to be from repeated episodes of colonic distention associated with transient increases in both luminal pressure and size that result in multiple episodes of increased wall tension and obstruction of submucosal venous outflow, especially at the point where vessels pierce the muscle layers of the colon. After many years, this process leads to dilatation of venules and capillaries with the development of vascular ectasia occurs[18]. Colonic lesions occur most commonly in the right colon because the right colon region has the largest luminal diameter with the highest resting wall tension. Colonic vascular ectasia is noted in over 25% of asymptomatic individuals over the age of 60[19]. There is an association of vascular ectasia and heart disease, specifically aortic stenosis[20]. Vascular ectasia causes LGIB in 12% to 40% of patients, depending upon the study. The bleeding from vascular ectasia is usually subacute, but can be chronic and recurrent, especially in small bowel lesions. LGIB may present as iron deficiency anemia and occult blood positive stools, but may be massive in up to 15% of patients.

Inflammatory diseases of the colon

LGIB can occur from inflammatory diseases of the colon. The various types of inflammatory diseases of the colon can be indistinguishable upon initial presentation. The findings of abdominal pain, LGIB, fever and dehydration are common to all. Endoscopically, the mucosa may appear edematous, friable and ulcerated in any type of colitis, although certain characteristics can aide in diagnosis as discussed below. The most common forms of inflammatory bowel disease in the elderly are ischemic colitis, infectious colitis, idiopathic inflammatory bowel disease and post irradiation colitis.

Ischemic colitis

Ischemic colitis accounts for 3% to 9% of all cases of LGIB in the elderly[1,21]. Colonic atherosclerosis is almost universal in the elderly and predisposes to ischemic colitis. Ischemic colitis results from reduced blood supply to the colon from a variety such factors as hypotension and vascular embolic events. Although the precipitating event or factors leading to the lesion may not be identified, a history of a hypotension supports the diagnosis. Patients often present with lower abdominal cramping type of pain followed by hematochezia or bloody diarrhea. LGIB is rarely severe. Ischemic colitis commonly involves the watershed areas of the colon which are the right colon, splenic flexure and recto-sigmoid junction. Although usually acute, some patients may develop a chronic colitis resembling idiopathic inflammatory bowel disease. It is most often segmental in nature with rectal sparing, simulating the appearance of Crohn's disease. It is often unresponsive to standard colitis treatment and may be complicated by perforation or stricture formation that requires surgical intervention[22].

Infectious colitis

The elderly have a greater risk for infectious colitis and its complications such as LGIB[23]. The mortality from infectious colitis increases with age[24]. LGIB is rarely massive in patients with infectious colitis. Hematochezia is noted in less than 10% of cases[24]. The most common causes of enteric infections in the elderly are Campylobacter, Salmonella, Shigella, E. Coli 0157: H7 and Clostridium difficile[25]. *C. difficile* must be considered in elderly patients in long-term care facilities and hospitals and in patients who have recently been treated with antibiotics. Infectious colitis often presents with a history of undercooked fish or meat consumption and during outbreaks of bloody diarrhea in the community and in long term care facilities or hospitals. E. Coli 0157: H7 can cause significant complications, such as acute thrombotic thrombocytopenic purpura and death in the elderly[26].

Idiopathic inflammatory bowel disease

Idiopathic inflammatory bowel disease (IBD) occurs in the elderly, although with much less frequency than in younger populations. There is a bi-modality in IBD, with a second peak occurring between the ages of 60 and 70[27]. Approximate 15% of all patients with IBD develop symptoms after the age of 65[28,29]. Although LGIB is common with IBD, severe hematochezia is infrequent. LGIB in IBD accounts for hospitalizations in 6% of patients with Crohn's disease and 1.4% to 4.2% of patients with ulcerative colitis[30,31].

Post irradiation colitis

Post irradiation colitis is a source of LGIB in the elderly because of their higher incidence of malignancy requiring irradiation. It occurs in patients treated for genitourinary cancer, such as prostate cancer and gynecological malignancies. LGIB can be massive or occult with chronic iron deficiency anemia. It can develop acutely or many years after treatment[30].

Neoplasms

Benign and malignant neoplasms of the colon and rectum are a cause of LGIB in 10% to 20% of cases of LGIB[31]. Neoplasms most often present as a change in stool frequency, a change in stool caliber or weight loss. LGIB is the initial presenting symptom in up to 26% of patients with colorectal neoplasms[32,33]. Although LGIB from colorectal neoplasms is usually occult or mild, it can be massive LGIB if there is erosion into a large vessel or if patients are taking anticoagulants or NSAIDS.

Post-polypectomy bleeding

The incidence of colonic polyps and thus the necessity of colonoscopic polypectomy rises with advancing age. LGIB is a complication of colonoscopic polypectomy in approximately 0.7% to 2.5% of cases[34,35]. Post-poly-

pectomy hemorrhage is the source of LGIB in approximately 3% of patients. It more commonly follows sessile polyp removal and presents as hematochezia with or without abdominal pain soon after polypectomy. However, it may be delayed in some cases for up to one week after the procedure[36].

Hemorrhoids

Hemorrhoids are a common source of LGIB in elderly patients. LGIB presents with intermittent low-volume hematochezia, which often coats the stool[37].

Stercoral ulcer and solitary rectal ulcer syndrome

Stercoral ulcers and the solitary rectal ulcer syndrome can be a source of massive LGIB in the elderly. Stercoral ulcers are the result of mucosal damage by hard impacted stool in the rectum, from manipulation or foreign body injury, such as from a rectal tube in the hospitalized patient. The solitary rectal ulcer syndrome is due to rectal prolapse and mucosal damage from constipation and straining[38].

RARE CAUSES OF LGIB

Rare causes of LGIB are Dieulafoy's lesion and colonic or rectal varices. Dieulafoy's lesion is a source of obscure LGIB. It is a large superficial artery underlying a mucosal defect, which is rare and difficult to find when not bleeding[39]. Portal hypertension can cause varices outside the esophagus, including the colon and rectum[40].

FACTORS INCREASING THE SEVERITY OF LGIB IN THE ELDERLY (TABLE 2)

Two factors that directly affect morbidity and mortality in elderly patients with LGIB are co-morbid disease and polypharmacy. Co-morbid diseases, such as cardiovascular disease, diabetes mellitus and malignancy, have a significant impact on the incidence and severity of LGIB[2]. Polypharmacy with the use of NSAIDS and anticoagulants increases bleeding in patients with LGIB[3].

Co-morbid disease

Co-morbid diseases directly impact LGIB to increase morbidity and mortality in the elderly patient[2]. After hemorrhage, the presence of serious concurrent illness is the second most important factor in predicting mortality among patients with LGIB[2]. Co-morbid diseases that are associated with an increased incidence and severity of LGIB include cardiovascular disease, hypertension, renal disease, diabetes mellitus and malignancy. Atherosclerotic cardiovascular disease affecting the splanchnic circulation is a cause of ischemic bowel disease[22]. Atrial fibrillation is associated with embolic events to the intestine leading to ischemic bowel disease[22]. Aortic valvular disease is associated with vascular ectasia of the colon[20]. Cerebrovascular disease, diabetes mellitus and malignancy profoundly affect the response to LGIB, with prolonged hospitalization due to increased morbidity and an increase in mortality[2].

Table 2 Factors affecting the severity of LGIB in the elderly

Co-morbid diseases
Cardiovascular disease
Cerebrovascular disease
Diabetes mellitus
Renal disease
Cirrhosis
Hypertension
Neoplasia
Polypharmacy
Anticoagulants
NSAIDS

NSAIDS: Non-steroidal anti-inflammatory drugs.

Polypharmacy

Polypharmacy, the use of multiple medications, is common in the elderly population[3]. Medications more commonly used by the elderly that can cause or aggravate LGIB are anticoagulants and NSAIDS. Elderly patients with arthritis use NSAIDS to a significant degree. NSAIDS not only cause upper GI ulceration, but also ulceration of the small intestine and colon. Elderly patients with cerebrovascular disease and atherosclerotic heart disease are often given anticoagulants and aspirin for prevention of embolic events, ischemia, myocardial infarction and stroke. NSAIDS and anticoagulants increase LGIB morbidity and mortality from hemorrhage due to their effect on blood clotting factors[11,12].

CLINICAL COURSE AND DIAGNOSTIC EVALUATION OF LGIB

The clinical course of LGIB can vary widely in elderly patients from occult bleeding to massive life-threatening hemorrhage and death. Therefore, the evaluation of these patients must be adjusted to the rate and severity of hemorrhage and the clinical status of the patient. The history and physical examination is important, but may be complicated by the presence of visual, auditory and cognitive impairment due to age and co-morbid disease. It may be necessary to call the primary care provider, caregiver and perhaps even the pharmacist to obtain history, such as extent of bleeding, duration of symptoms, presence of co-morbid disease, prior surgical history, drug allergies and recent and current use of medication such as Clopidogrel, warfarin and NSAIDS.

Common presenting symptoms of LGIB may not be evident in the elderly. For example, in elderly patients who are taking NSAIDS, abdominal pain may not be present. Painless hemorrhage that may even be life-threatening can occur[41]. Physical examination to assess the severity of bleeding and status of the patient is important, with emphasis on the presence of orthostatic changes, signs of cardiopulmonary compromise, stigmata of chronic

liver disease and evidence of coagulopathy. Orthostatic changes in blood pressure imply a 20% to 40% loss of circulatory volume. In cognitively impaired patients, a mini mental status exam as a measure of cognitive function is indicated on or after admission, if feasible.

Informed consent to procedures may be difficult to obtain in patients who suffer from cognitive dysfunction, since they cannot sufficiently participate in the informed consent process. With the exception of a true life-threatening emergency, every attempt should be made to obtain consent for testing procedures from the patient, if competent, or the surrogate. In the case when a guardian cannot be reached, administrative consent should be obtained[42].

The timing of tests and the type of intervention should be custom tailored, depending upon the patient's functional status, the impact on clinical outcome and the available diagnostic strategies. This is most important in the frail elderly patient. However, intervention should not be withheld because of age alone[1-3].

Resuscitation efforts are a cornerstone in the successful management of patients with acute LGIB after the initial evaluation. In the majority of cases, LGIB stops spontaneously with appropriate resuscitation and supportive care. However, LGIB may be severe and life threatening. Endoscopic, radiologic or even surgical intervention may be necessary.

In patients with mild, chronic or occult bleeding with or without iron deficiency anemia, workup can be performed in hospital or as an outpatient, depending upon the clinical state of the patient. If LGIB is severe, the patient should be hospitalized, placed in an intensive care unit, given intravenous fluids and blood transfusions and provided with an adequate airway and oxygenation, as necessary. Laboratory data, including complete blood count, comprehensive metabolic profile, blood typing and cross matching, cardiac enzymes, prothrombin time, a PTT, stool for occult blood, electrocardiogram and chest x-ray should be obtained. In the appropriate setting, evaluation for infection must be done. Most organisms causing infectious colitis can be identified on stool culture. *C. difficile* colitis is most often diagnosed with stool assay for toxin A and B.

Approximately 10% to 15% of patients presenting with hematochezia may have an upper GI source of bleeding. Therefore, it is important to rule out an upper GI bleeding source[43]. One should perform an NG lavage and confirm the presence of bilious or non-bloody aspirate in elderly patients presenting with hematochezia to help rule out an upper GI source of bleeding[42]. If the NG lavage is positive or there is any suspicion of an upper GI source of hemorrhage, upper GI endoscopy should be performed as the first endoscopic procedure.

Plain x-ray films of the abdomen, CT scan of abdomen and barium enema are most often not helpful in the acute setting for the evaluation of LGIB. However, plain x-ray films of the abdomen may reveal evidence for obstruction or perforation. In patients with severe ischemic bowel disease the "thumb printing" sign may be seen. In the evaluation of more chronic bleeding, flexible sigmoidoscopy and barium enema may be helpful if the patient cannot undergo a complete colonoscopy. When further investigation of intra-abdominal structures is warranted, CT scan of the abdomen may be helpful.

Table 3 Endoscopic and radiologic modalities for the investigation of LGIB

Colonoscopy
Radionuclide scan
Abdominal angiography
Wireless capsule endoscopy
Push enteroscopy
Double balloon enteroscopy

ENDOSCOPIC AND RADIOLOGIC METHODS OF EVALUATION OF LGIB (TABLE 3)

Urgent colonoscopy performed within 24 h of hospitalization following a rapid purge is the best test for evaluation of LGIB, once the patient has been resuscitated and hemodynamically stabilized[44]. Polyethylene sulfate purge causes less associated water and electrolyte abnormalities and may be preferable to saline purge for colonoscopic preparation in the elderly patient with comorbid renal or cardiovascular disease. If the patient is unable to take the purgative by mouth, the placement of an NG tube for its administration may be necessary. The diagnostic accuracy of colonoscopy in the setting of acute LGIB ranges from 72% the 86% with cecal intubation achieved in 95% patients[41,45,46]. Colonoscopy can reveal the bleeding lesion, such as a bleeding diverticulum, vascular ectasia, or neoplasm. Colonoscopic evaluation in inflammatory bowel disease often reveals edematous, friable and ulcerated mucosa. Differential diagnosis may therefore require careful interpretation of pathologic findings to obtain an accurate diagnosis. Unfortunately, colonoscopy for evaluation of LGIB in the elderly patient may give erroneous results in some cases of vascular ectasia. Vascular ectasia may be confused with traumatic mucosal lesions from the procedure or may not be seen due to volume depletion or administration of meperidine for sedation, which can cause vascular spasm and poor filling of vascular lesions[22].

In patients with active LGIB where colonoscopy is not feasible due to massive bleeding, radionuclide imaging and abdominal angiography may identify the source of bleeding. For visualizing the bleeding source, radionuclide imaging requires that the bleeding rate be 0.1 to 0.5 mL per minute and abdominal angiography requires greater than 1 mL per minute[47,48]. Accuracy rates for these procedures vary greatly. The accuracy of radionuclide imaging is 24% to 78% and the accuracy of abdominal angiography is 27% to 77% for bleeding localization, depending upon the series[7].

There are important considerations involving the evaluation of elderly patients with LGIB[49]. lder patients are more likely to have cardiac pacemakers with or without defibrillators, given the high incidence of cardiovascular disease in this age group. Recommendations for management of patients who require endoscopy and have pacemakers and internal defibrillators are not well defined. Cardiology consultation may be indicated. Pacemaker dependent patients should be driven to automatic pacing by placing a magnet on the skin overlying the device whenever monopolar electrosurgical devices are used. The patients who are not in a continuously paced rhythm should be monitored, with a magnet available for continuous pacing if needed. If the status of the patient's rhythm is not known, great care should be used during electrocautery with EKG monitoring. Intracardiac defibrillators should be inactivated prior to the use of electrocautery. Continuous rhythm monitoring until the defibrillator is reactivated following the procedure must be preformed. Alternative means of tissue removal, destruction or hemostasis should be considered to simplify management of patients with LGIB and defibrillators to control hemorrhage, such as hemo-clips, ligation devices and injection of epinephrine and sclerosing agents. The general dictum of geriatric pharmacology of starting with low doses of medication and slowly advancing to larger doses is all the more important in the sedation of the elderly patient during endoscopy. As in younger adults, midazolam and narcotics are generally used. Initial dosages should be lower and titration should be more gradual[50]. IV sedation guided by ASA criteria can be performed, especially in clinical settings when deeper sedation is required in the elderly patient.

It is estimated that 5% patients with GI bleeding, whether occult or overt, will have a negative upper GI endoscopy and colonoscopy[5]. The scenario of obscure bleeding is more common in elderly patients. Obscure overt bleeding is characterized by persistent and recurrent visible evidence of bleeding, whereas obscure occult GI bleeding is defined as a positive fecal occult blood test after a negative upper GI endoscopy, colonoscopy, and routine small bowel radiographic study. Radionuclide scanning and abdominal arteriography may be helpful when bleeding is sufficient to reveal a lesion[51].

Newer endoscopic methods are available for evaluation of patients with obscure bleeding. These methods visualize the small intestine, which may be an important source of either overt or occult bleeding in the elderly patient. Wireless capsule endoscopy has become an important tool for the diagnosis of obscure GI Bleeding, being able to non-invasively visualize the entire small intestine[52,53]. Push enteroscopy and double balloon enteroscopy are modalities that provide for both the evaluation and treatment of obscure GI bleeding from the small intestine[54].

Treatment of LGIB (Table 4)

Hemorrhage from LGIB can be controlled in the vast majority of patients. Colonoscopy provides the best method for controlling LGIB as it provides many methods for control of hemorrhage. These include heater probe or bipolar probe thermal coagulation, band ligation, argon plasma coagulation, metallic clips, epinephrine and sclerosing agent injection, and application of fibrous glue[13,23,36,44,45].

Table 4 Modalities for the treatment of LGIB

Colonoscopy
Thermal coagulation, band ligation, metallic clips, epinephrine injection, sclerosing agent injection, fibrous glue
Abdominal angiography
Vasopressin infusion, embolization
Surgery

Abdominal angiography not only permits the identification of the bleeding source but offers the potential of treatment with intra-arterial infusion of vasopressin or embolization of the bleeding vessel. For persistent bleeding not amenable to control by colonoscopic methods, abdominal angiography with infusion of vasopressin or embolization of the bleeding vessel is successful in about 90% of cases. Intra-arterial vasopressin infusion is successful in controlling the bleeding in up to 90% of patients with diverticular disease and vascular ectasia. However, intolerance to the cardiovascular complications of vasopressin is common in the elderly. Embolization with polyvinyl alcohol particles or microcoils provides a more definitive means of controlling hemorrhage, but may be complicated by intestinal infarction in up in to 20% of patients[55]. Unfortunately, bleeding recurrence can occur in up to 50% of patients, depending upon the series[56,57].

Patients who fail angiographic or endoscopic therapy for control of LGIB require surgery. Every effort should be made to identify the bleeding source prior to referral for surgery, which often requires segmental colectomy. Blind resection is associated with very high rebleeding and mortality rates in the elderly and should only be reserved for the very rare instance of exsanguinating colonic bleeding where immediate life-saving surgery is required[9,58-61]. Blind segmental resection is associated with a re-bleeding rate of 47% and morbidity and mortality rate of 83% and 57% respectively[62]. Localization of bleeding by a positive preoperative angiogram reduces the risk of rebleeding[57]. Surgery may be necessary in up to 24% of patients with massive LGIB from diverticular disease[63].

Treatment of LGIB in patients with infectious colitis depends on the type of infection and the source of bleeding. Specific antimicrobial therapy is based upon the organism identified. Radiation proctitis can be treated with a variety of agents, including argon plasma coagulation, formalin application, sucralfate enemas and hyperbaric oxygen therapy[31,55,64,65]. Comparative controlled data are limited and it is unknown which therapy is most effective.

In the majority of patients with LGIB treatment is

successful. Bleeding is controlled or ceases spontaneously, with less than 1% of patients requiring a transfusion of greater than four units of blood[11]. Jensen and Machicado reported no rebleeding during a 30 mo follow up after endoscopic therapy when compared to a 53% rebleeding rate in patients treated with conservative medical therapy alone[24]. Despite improvements in localization and treatments of LGIB, the mortality rate for severe LGIB remains 10%[1].

There are specific issues in the elderly patient with co-morbid disease and polypharmacy. For example, Metronidazole used to treat *C. difficile* colitis may interfere with oxidation of warfarin and induce excessive anticoagulation. General principles for treatment of elderly patients with IBD are the same as for younger patients, although no studies specific to the elderly population are available. However, significant treatment associated complications occur in elderly patients with IBD. For example, osteoporosis is a significant problem in elderly IBD patients on corticosteroids. Older patients with IBD on these agents must be evaluated for osteoporosis and offered prophylaxis with such agents as calcium and vitamin D supplementation and biphosphonates[66].

CONCLUSION

In conclusion, LGIB is a significant worldwide cause of increased morbidity and mortality in the elderly. The incidence of LGIB increases with age and corresponds to the increased incidence of specific gastrointestinal diseases that have worldwide regional variation, co-morbid diseases and polypharmacy that occur more common in the elderly. In the majority of elderly patients with LGIB appropriate evaluation and management will lead to a successful outcome.

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GUIDELINES FOR CLINICAL PRACTICE

Endoscopic placement of enteral feeding tubes

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Abstract

Malnutrition is common in patients with acute and chronic illness. Nutritional management of these malnourished patients is an essential part of healthcare. Enteral feeding is one component of nutritional support. It is the preferred method of nutritional support in patients that are not receiving adequate oral nutrition and have a functioning gastrointestinal tract (GIT). This method of nutritional support has undergone progression over recent times. The method of placement of enteral feeding tubes has evolved due to development of new feeding tubes and endoscopic technology. Enteral feeding can be divided into methods that provide short-term and long-term access to the GIT. This review article focuses on the current range of methods of gaining access to the GIT to provide enteral feed.

Key words: Enteral feeding; Nutrition; Gastro-intestinal tract; Percutaneous; Jejunostomy; Gastrostomy

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INTRODUCTION

Malnutrition and undernutrition

Malnutrition is defined as a state of nutrition in which there is a deficiency or excess of energy, protein and other nutrients causing measurable adverse effects on tissue/body form, function and clinical outcome[1]. It is recognised that 30% of in-hospital patients are malnourished (undernourished) on admission and the majority of these will lose further weight while in hospital[2]. Consequences of malnutrition include reduced muscle mass, impaired immune function, poor tissue viability, poor clinical outcome and psychosocial effects[3]. Enteral feeding is one of the treatment options available to treat malnourished patients and prevent poor outcomes. See Tables 1 and 2 for enteral feeding indications and contraindications.

Hospital patients at risk of malnutrition should be identified by screening methods such as MUST (Malnutrition Universal Screening Tool), SGA (Subjective Global Assessment), MNA (Mini Nutritional Assessment) and or NRS (Nutrition Risk Score). Further nutritional assessment involves dietary history, anthropometrics, biochemical testing, and clinical methods. Patient energy requirements are calculated using: Basal Metabolic Rate equations (e.g. Schofield, Harris Benedict, Ireton Jones), Stress Factors, Combined Factor for Activity Level and Diet Induced Thermogenesis, Weight loss/gain or Physical Activity Levels.

Malnourished patients require nutritional support. This can be provided in different forms including dietary modification, dietary supplements, enteral feeding (standard 1kcal/mL; with or without fibre) or higher energy (1.2-2.0 kcal/mL; with or without fibre) or

parenteral feeding. The development of parenteral nutrition in the 1960's meant that feeding was possible even in patients who did not have a functioning gastrointestinal tract[4].

Enteral feeding is used to provide either supplementary or complete nutrition to patients who are unable to maintain adequate nutrition by oral route. It is only likely to benefit malnourished patients or those at risk of malnutrition. This includes patients that have had a failed trial of diet modification or supplementary feeds or patients at pulmonary aspiration risk from oral nutrition.

This review will focus on various techniques available for endoscopically placed feeding tubes as a means of delivering enteral feeds to the gastrointestinal tract (GIT).

ENTERAL VERSUS PARENTERAL FEEDING

Enteral feeding is more physiological, less costly and easier to administer than parenteral feeding. Enteral feeding produces GIT luminal contents that can decrease gut atrophy. Maintaining a normal intestinal mucosa reduces the hazard of bacteria and toxins crossing the GIT wall and therefore can decrease proinflammatory mediator levels. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis[5]. Hernandez *et al*[6] have shown that enteral feeds decrease gut mucosal atrophy in critically ill patients. A meta-analysis has shown that in acute pancreatitis, use of EN was associated with a significant reduction in infectious morbidity, hospital length of stay, and a trend toward reduced organ failure when compared with use of parenteral nutrition (PN)[7]. However it is important to note that many of the studies involving parenteral nutrition had full dose daily calorie intake whereas enteral feeding studies were less likely to reach estimated energy requirements. This is significant since ill stressed patients should not be given full calorie energy requirements in the first 24-48 h of commencing feeding. Therefore the parenteral feeding groups were disadvantaged in that the patients were overfed initially and received excess energy calorie intake. Indeed early parenteral studies reported that outcomes were improved with standard care (intravenous fluids and dextrose) compared with parenteral nutrition[8]. Complications of enteral feeding can be related directly to tube, formula or pulmonary aspiration[9]. Enteral tubes can directly damage nose, pharynx or oesophagus. Enteral tubes can also be misplaced intracranially, intra-abdominally or into the tracheobronchial tree. Formula related problems include nausea, vomiting and diarrhea. Nutrient imbalances secondary to enteral feed include hyperglycaemia, electrolyte disturbance, volume overload and refeeding syndrome. See Table 2 for enteral feeding contraindications.

The National Institute of Clinical Excellence states that parenteral nutrition is only to be used in patients with "inadequate or unsafe oral and/or enteral nutritional intake and a non-functional, inaccessible or perforated (leaking) gastrointestinal tract"[9]. These guidelines also state that PN can be associated with risks due to line placement, infection and thrombosis that do not occur with enteral feeding[9].

In summary, although the enteral versus parenteral nutrition trials have involved heterogeneous groups of patients and varying types of nutrition, it is recommended that in patients with a functioning gut enteral feeding is preferable to parenteral feeding.

Table 1 Enteral feeding indications[74]

Unconscious patient: Head injury, ventilated patient
Swallowing disorder: MS, MND, bulbar and pseudobulbar palsies, huntington's disease, post-stroke (early feeding < 7 d beneficial)
Physiological anorexia: Liver disease
Partial intestinal failure: Postoperative ileus, IBD, short bowel syndrome
Increased nutritional requirements: Cystic fibrosis, renal disease
Psychological problems: Severe depression, anorexia nervosa

Table 2 Enteral feeding relative contraindications[75][a]

Intestinal obstruction
Ileus
High output small bowel fistula
High doses positive inotropic agents
Hypotension

[a]Patients with intestinal failure due to ileus, dysmotility, or subacute obstruction and who cannot tolerate oral intake are recognized to be suitable to receive some form of enteral nutrition.

SHORT-TERM ENTERAL FEEDING

Short-term enteral access feeding tubes are typically placed when enteral feeding is expected to be less than 30 d duration[10]. Pre-pyloric tubes naso-gastric tubes (NG) are the most frequent type of NET used. These NG tubes deliver enteral feed to the stomach reservoir and are the most physiological method of enteral feeding. NG tube placement requires little training and is the preferred method of enteral feeding for the majority of patients provided there is no stomach dysfunction. An additional advantage of NG feeding is that the stomach can tolerate higher feeding rates and increased density feeds compared to post-pyloric feeding. Feeding can be bolus or continuous *via* NG tube. However, general disadvantages of NET tubes include tube dislocation and clogging. They can also cause patient discomfort, irritation, ulceration and bleeding.

NG tube placement: NG tube placement typically occurs at the patient's bedside. The NG tube is negotiated from the naris to be distally placed in stomach. It is typically small diameter NG tubes (5-8 French gauge) that are utilized. The correct position of the NG tube is confirmed by ensuring that the aspirate suctioned has

Table 3 Management of post-pyloric NETs

Flushed immediately after each intermittent feeding bolus infusion
Flushed every 6 to 8 h during continuous feeding
Flushed immediately after installation of any medications
Only use liquid/completely dissolved medications

a pH < 5. The use of a stethoscope to auscultate for gastric gurgling while injecting air will not determine that NG tube is in correct position. A chest X-ray can also be performed to determine definite placement position.

Unfortunately NET tubes are frequently removed accidentally. Reinserting these feeding tubes exposes the patient to risk and consumes hospital resources including replacement time and radiology time. Nasal bridles are easily placed at bedside and essentially fix the NET in position at the naris. A recent small study has suggested that a nasal bridle can prevent NET dislodgement[11]. Only 10% patients in nasal bridle group had NET displacement versus 36% in the tape group[11].

Pre-pyloric endoscopic NET placement

Peroral endoscopic NG tube placement: Endoscopic NG tube placement may be valuable if there is any obstruction in the oesophagus (such as oesophageal stricture) that prevents bedside NG tube placement. In these circumstances the gastroscope is passed to the stricture and the NG tube is then passed through the stricture using direct vision. The length of NG tube to be inserted can be estimated by measuring, using a NET placed externally, from the tip of the patient's nose to the earlobe and then to the xiphoid process (sternum)[12]. Another option for placing pre-pyloric NETs is the use of an ultrathin gastroscope. This small diameter gastroscope is transversed through the oesophageal stricture and allows access to the stomach. A guidewire is then placed through the gastroscope into the stomach and the gastroscope is removed with the guidewire remaining in-situ. A NET tube can then be placed over the guidewire into the stomach. This method however will require a difficult mouth-to-nose transfer step. A further method of peroral NG tube placement is dilation of tight malignant oesophageal strictures using balloon dilatation[13]. This allows access to the stomach and placement of the NG tube, with a normal gastroscope. However balloon dilatation of malignant oesophageal strictures carries an oesophageal perforation risk of 6.4%[13].

Transnasal endoscopic NG tube placement: A transnasal method of NG tube placement in oesophageal cancer patients has been described[14]. The ultrathin gastroscope is used to intubate the oesophagus *via* the nasal cavity and then position the guidewire into the stomach through the oesophageal stricture. The gastroscope is then retracted *via* the nasal cavity. The NG tube is subsequently inserted over the guidewire using fluoroscopic methods. Lin *et al* achieved a 99% success rate of NG placement in oesophageal cancer patients that had previously failed NG placement. However 30% of the patients required oesophageal stricture dilation, to allow passage of the ultrathin gastroscope, before placement of NG tube[14].

Post-pyloric endoscopic NET placement

Post-pyloric enteral feeding has a long history and was first described in 1858[15]. In patients where gastric feeding had failed (large residual gastric volumes, vomiting or regurgitation) post-pyloric NET placement is another option to allow enteral feeding[16-18]. See Table 3 for management of post-pyloric NETs.

It is known that ill patients can have slow gastric emptying but that small bowel motility is usually preserved. Therefore feeding post-pylorically, in such individuals, may decrease gastro-oesophageal reflux and resulting pulmonary aspiration[19]. There is however varying data available regarding the risk of pneumonia in prepyloric feeding versus post-pyloric feeding. One meta-analysis showed no significant difference in the rates of pneumonia[20]. A study in a group of critically ill patients did however show a significantly increased gastro-oesophageal reflux in a pre-pyloric feeding group compared to post-pyloric feeding group. The patients who had gastro-oesophageal reflux also had increased rates of pulmonary aspiration[21]. Therefore post-pyloric feeding should be considered in patients with gastric feed aspiration, severe gastro-oesophageal reflux, gastrocuteaneous fistula or gastroparesis. For Intensive Care Units, the American Society for Parenteral and Enteral Nutrition and the American Society of Critical Care Medicine have revised their guidelines to suggest that gastric residual volume up to 500 mL is allowed and only levels greater than this increase the risk of pulmonary aspiration[22]. The requirement for post-pyloric feeding in acute severe pancreatitis is debatable. There is evidence that NG feeding has no increased complications compared to NJ feeding in patients with objectively graded severe acute pancreatitis[23,24].

The decision to use a post-pyloric NET necessitates specific instructions regarding its care. Post-pyloric NETs have smaller diameters than those of pre-pyloric NETs. They are therefore more prone to clogging and blockage. If the post-pyloric NET is placed beyond the Ligament of Treitz pancreatic enzymes may not be released. However, this may result in mal-digestion. Post-pyloric feeding requires prescription of elemental feeds[4]. Post-pyloric feeding also bypasses the gastric acid and therefore there is increased risk of bacterial contamination. Therefore feeds have to be given as a closed system. Continuous feeding is used since bolus feeding cannot be tolerated by the small bowel lumen[4].

Non-endoscopic post-pyloric NET placement: The possibility that standard post-pyloric feeding tubes, placed at the bedside, will reach the small bowel is 30%[25]. A modification of the standard tube is the self-propelling feeding tube. These can be inserted at the bedside. One

Table 4 Endoscopic methods of peroral post-pyloric NET placement

Drag and pull	Sutured distal end of NET is pulled down small bowel using grasping forceps
Over the guidewire	Guidewire placed in small bowel and NET placed over guidewire. Involves difficult oro-pharyngeal exchange
Push technique	NET stiffened using guidewire(s). Grasping forceps used to push into small bowel
Through scope	240 cm NET used to allow exchange. Involves oro-pharyngeal exchange

Table 5 Principles/techniques of post-pyloric NET placement[67]

Decompress stomach to reduce gastroscope looping within stomach
Liberal lubrication needs to be applied to lower friction between guidewire/NET/gastroscope
A stiff shaft guidewire will help direct NET insertion along longitudinal axis

study, using this type of NET, with air insufflation, intravenous erythromycin and electrocardiogram monitoring of the stomach, achieved an 88% post-pyloric placement in an intensive care setting[25]. A further study compared spiral and straight-tip post-pyloric NETs[26]. In those patients with normal gastric emptying, successful placement at 24 h was achieved in 78% (spiral tube) versus 14% (straight tube)[26]. Unfortunately both of these post-pyloric NET placement techniques require experience and are relatively slow to perform. Post-pyloric NET placement using fluoroscopy is also possible. It does however need radiological equipment and this can result in delays. Post-pyloric tubes that have an electromagnetic tip which can be imaged in real-time are available. Sensors on the lower chest wall are able to image the tip of the NET and provide an image on a mobile screen. This has been shown to eliminate lung placement[27].

Peroral endoscopic post-pyloric NET placement: Endoscopic post-pyloric NET placement is a frequent referral to the endoscopy team. Experience of such endoscopic techniques however varies widely among endoscopists. Indeed, training programs are generally lacking in teaching trainee endoscopists the relevant techniques of post-pyloric NET placement.

There are four major different techniques of peroral endoscopic post-pyloric NET placement (See Tables 4 and 5): (1) Drag and pull technique: This is the earliest technique. A suture is placed at the distal tip of the NET. The NET is then passed via naris to the stomach. The gastroscope is then navigated perorally into the stomach. Biopsy forceps grab the suture and drag the NET as far down the small bowel as possible. The grasping forceps are released and the gastroscope is withdrawn slowly. The biopsy forceps release grasp and then re-grasp to keep pushing the NET further down the small bowel while the gastroscope is retracted. Unfortunately the friction of the gastroscope against the NET often causes retraction of the NET into the stomach on endoscope removal. Indeed it is this difficulty that discourages endoscopists from this technique. One group however has claimed a 93% success rate with this method[28]. A further technique has been developed that entails using a mucosal clip to attach the distal NET to small bowel wall mucosa[29]. In this small study this prevented retrograde dislodgement of the NET; (2) Over-the-guidewire technique: The gastroscope is advanced perorally into the small bowel. A guidewire is then advanced down the biopsy channel into the small bowel and the gastroscope is removed leaving the guidewire in-situ. The guidewire exits orally and needs to be changed to achieve nasal exit. A nasopharyngeal catheter is placed via the nose into the pharynx. The distal tip of the catheter is grabbed using forceps to allow the distal end to exit orally. The guidewire is fed through this catheter to exit at the nose. Next the catheter is retracted nasally to leave guidewire in-situ. At this point a NET can be fed over the guidewire to the small bowel; (3) Push technique: The NET is stiffened using 2 guidewires. One 0.052 inch or two 0.035 inch guidewires are placed through the NJ tube without exiting the tip of the tube. This "stiffened" tube is then navigated through the nose and into the stomach. The NET is then grabbed by biopsy forceps and pushed into the small bowel with advancement of the gastroscope[30]. The stiffened NET is thought less likely to migrate proximally on removal of the endoscope. Wiggins *et al* had a 97.6% successful positioning rate using this technique with a mean procedure time of 11.6 min[31]. A separate study reported a success rate for NET placement of 94% performed in an average of 12 min[32]. This preliminary placement of the tube through the nose into the small bowel avoids the difficult oral-nasal transfer; (4) Therapeutic gastroscope method: A small diameter NET can be fed through the biopsy channel of a large diameter therapeutic scope. This allows direct placement the large diameter gastroscope into the small bowel. A 240 centimetre 8 or 10 French guage NET is placed through the endoscope. The scope is removed once the distal end of the NET is in a suitable position. The extended length of the NET allows the NET to remain in position as the scope is exchanged/removed over the NET. The NET is then cut to the desired length. The next step is an oro-nasal transfer as described above. A feeding adaptor is subsequently placed at the proximal end of the NET. Bosco *et al*[33] had a 90% success rate, with this technique, with a mean procedure time of 19 min. A separate study reported successful NET placement in the jejunum in 90% of cases with an average procedure time of 15 min[34].

Transnasal endoscopic post-pyloric NET placement: A transnasal endoscopic post-pyloric NET placement method has been described in both critically ill and non-

Table 6 Types of endoscopic placed feeding tubes

Short-term enteral feeding	
Pre-pyloric endoscopic NET placement	Peroral pre-pyloric NET
	Transnasal pre-pyloric NET
Post pyloric endoscopic NET placement	Peroral post-pyloric NET
	Transnasal post-pyloric NET
Long-term enteral feeding	
Pre-pyloric feeding	Endoscopic PEG
Post-pyloric feeding	Endoscopic PEGJ
	Endoscopic D-PEJ

critically ill patients. It was first described as a method of viewing the upper gastrointestinal tract (GIT) in 1987[35]. The advent of small diameter gastroscopes has allowed a transnasal method of post-pyloric NET placement. The technique involves application of intranasal anaesthesia to a patient naris. One benefit of this method is that no intravenous sedation is required which may be important especially if patient is unwell. This method also negates the need for the difficult mouth to nose wire transfer associated with some peroral NET placement techniques. An ultrathin gastroscope is passed transnasally into the upper GI tract[36]. The gastroscope is then advanced as far as possible into the duodenum. A soft-tipped guidewire is placed through the working channel. The guidewire is advanced as far as possible into the small bowel. The gastroscope is withdrawn with the guidewire remaining in-situ. The NET is passed over the guidewire which is subsequently removed. Distal NET position is confirmed by fluoroscopy. If NET position is not satisfactory the whole procedure is repeated. Unfortunately, excessive gastric looping of the thin gastroscope is common-especially if altered duodenal anatomy is present. In one study, in a non-critically ill group, only 36.8% had NET placement in the jejunum (the endoscopists had little previous experience) although 86.3% did have post pyloric NET placement[36]. In a separate study in critically ill patients a 133 cm long small calibre prototype gastroscope was used[37]. Wildi *et al* had a 93.6% post-pyloric NET placement. The group did however comment that duodenal intubation was a difficult component of the procedure.

There have been very few randomised studies comparing transnasal NET placement versus peroral technique. One randomised trial did show that procedure time and sedation doses were lower in the transnasal group compared to the peroral group[38]. The post-pyloric NET placement rate was the same in both groups with an overall 85% post-pyloric placement[38]. The overall NET placement, distal to the Ligament of Treitz, was however only 30% with no significant difference between the groups[38]. This transnasal method also eliminates the risk of endoscopist finger injury during mouth-to-nose guidewire transfer[39].

A separate study which compared transnasal versus fluoroscopic NET placement in critically ill patients showed no significant differences between post-pyloric NET placement rates[40]. 90% of procedures achieved a post-duodenal bulb placement[40]. The procedure duration was again shorter in the transnasal group[40]. The importance of endoscopist experience of previous transnasal endoscopy was highlighted by this study. Jejunal NET placement improved from 60% to 100% between the first and last ten procedures[40]. Overall however there are conflicting reports regarding actual jejunal NET placement by the transnasal method[36,38,41].

Double-lumen tube NETs: In patients with gastric outlet obstruction a NET with a proximal port for gastric decompression and a distal port for jejunal feeding may be beneficial. These specialised NETs have an outer gastric decompression tube and a thin inner jejunal feeding tube. The gastric decompression port may decrease vomiting and risks associated with post-pyloric feeding tubes.

LONG-TERM ENTERAL FEEDING

Long-term enteral feeding requires the achievement of permanent access in the stomach or small bowel. Long-term enteral feeding is required if the indication for enteral feeding is likely to be greater than 30 d. The effect of the timing and method of enteral tube feeding for dysphagic stroke patients has been studied in a large multi-centre randomised controlled trial. In the early PEG feeding (versus early NG tube placement) there was an increased risk of death or poor outcome of 7.8% ($P = 0.05$)[42]. General indications for long-term enteral tube insertion include patients who are unable to adequately meet nutritional requirements orally. Patients also need a functioning gastro-intestinal tract. See Table 6 for specific indications for long-term enteral feeding. It is however important to note that long-term enteral feeding medicalises a normal activity of everyday living. Ideally the decision to place long-term enteral feeding should be taken by the Nutrition Support Team or Percutaneously Placed Enteral Tube Feeding Service[43]. Each hospital should have a defined referral pathway. The Nutrition Support Team is also responsible for post-procedure and long-term follow up.

Endoscopic PEG placement

Technique: The usual method for PEG tube insertion is the "pull through" method. A routine gastroscopy is performed. Duodenal intubation is performed to ensure there is no gastric outlet obstruction. Two operators are usually involved but one operator PEG insertion is possible and safe[44]. In the "two operator" method the first operator controls the gastroscope. The gastroscope light is then transilluminated through the anterior abdominal wall. The second operator applies finger pressure on the anterior abdominal wall. This diaphanoscopy should result in indentation of the gastric mucosa. The abdominal wall is then aseptically cleaned. The needle aspiration test is utilized. This technique can decrease the risk of overlying small or large bowel

perforation[45]. Local anaesthetic is injected along tract into the stomach lumen. Next a short incision is made at the puncture site and a trocar needle is inserted into the stomach lumen. A guidewire is placed *via* trocar into the stomach, grabbed by forceps and then retracted through the mouth while removing the gastroscope. The PEG tube is then attached to the guidewire and is pulled *via* the mouth to the abdominal wall exit site. The external booster should be positioned 1-2 cm from the external abdominal wall. No dressings should be placed at the exit site. The external booster should not be sutured.

There is a significantly lower frequency of regurgitation with PEG comparedto NG feeding (20.3% versus 40.7%)[46] Another benefit of PEG feeding is that the patient receives higher levels of prescribed enteral feeding[47].

Sedation: Commonly, conscious sedation is used. Occasionally general anaesthesia may be required if the patient cannot be safely sedated using conscious sedation. In some patients with chronic progressive neuromuscular disease the risk of sedation means that anaesthetist support is required.

Prophylactic antibiotics: The British Society of Gastroenterology guidelines suggest intravenous antibiotics for all patients prior to PEG tube insertion (and jejunostomy tube insertion)[48]. Commonly, a single dose of intravenous co-amoxiclav is given in the hour before the procedure. Cefuroxime is an alternative but should be avoided, where possible, in regions with a high incidence of Clostridium difficile infection or infections due to extended spectrum Beta-lactamase-producing organisms. Patients already receiving broad-spectrum antibiotics do not require additional prophylaxis for PEG. The choice of antibiotic for patients with a history of serious penicillin allergy has not been established but teicoplanin is a logical alternative. One meta-analysis has shown an advantage of one dose of antibiotic previous to PEG insertion[49]. A further meta-analysis showed that rates of infection post PEG-tube insertion were 8% in the antibiotic prophylaxis group and 26% in the no antibiotic group[50]. The emergence of Methicillin Resistant Staphylococcus Aureus (MRSA) bacteria causing local infection at the PEG tube site has led some centres to reappraise infection prophylaxis. A recent study has revealed that MRSA colonisation increases the risk of PEG site MRSA infection[51]. Oral MRSA eradication treatment may be beneficial[52].

Diaphanoscopy and needle aspiration test: The transillumination of gastroscopy light through the abdominal wall was until recently considered essential before proceeding with PEG placement. Recent data has however shown that diaphanoscopy is not essential[53]. Ponsky *et al* used the negative needle aspiration test as an alternative to diaphanoscopy with no complications recorded. In this method a 5 mL syringe is filled with 5 mL of normal saline. The syringe is then held in continuous aspiration as it is passed into the stomach. If air is aspirated before the needle reaches the stomach this suggests that the needle has passed through an overlying loop of bowel. In this situation PEG insertion is abandoned.

Anticoagulants and antiplatelets: Recent guidelines from the BSG suggest that aspirin can be continued during PEG. Warfarin should be stopped but the possible requirement for low molecular weight heparin depends on whether there is a low or high thromboembolism risk. Clopidogrel should also be stopped but if the cardiac condition is high-risk there is a need to liase with cardiology specialists[54].

Repeat gastroscopy to confirm PEG-tube position: There is no requirement for a second pass of the gastroscope to verify position of the internal bumper in the majority of procedures[55].

When to commence feeding? Early feeding (< 4 h) post PEG insertion has been shown to be safe, well tolerated and reduces cost by reducing hospital stay times[56]. Interestingly, however, early feeding is rarely practiced and most endoscopists withhold feeding for at least 12 h.

Early dislodgement of PEG-tube (< 2 wk): There is some evidence that immediate replacement of the PEG-tube through the tract is possible[57]. Pofahl *et al* immediately replaced PEG tubes in patients who had early dislodgement with no complications. However the main risk of blind reinsertion of a replacement tube, in a gastro-cutaneous track that is not adequately mature, is inadvertent insertion into the peritoneal cavity. However, urgent replacement can be attempted either endoscopically or radiologically. If endoscopic replacement is attempted then air insufflation should be avoided to minimise tract disruption. Further treatment options that allow the tract to heal include a period of nasogastric suction with intravenous antibiotics and observation[58]. Repeat PEG placement can then be considered at D 7-10.

Pre-procedure coagulation parameters: Data suggests that platelets should be greater than 50 000 and international normalised ratio less than 1.4 prior to PEG insertion[59].

Complications: Data from the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) published in 2008 gave results relating to the cause of all deaths within 30 d post-PEG insertion in all UK hospitals[60]. Over a one-year period there were 719 deaths. Death was due to cardiovascular disease (n = 175), respiratory disease (n = 508), central nervous system disease (n = 358), renal disease (n = 38), and hepatic failure (n = 11). In 136 cases (19%) the NCEPOD

expert panel regarded the procedure as futile[60]. 10% patients required a reversal agent post-procedure which indirectly indicates oversedation[60]. Other evidence shows that serious complications requiring treatment occur in approximately 1%-4% of PEG-tube insertion cases[60]. Severe acute complications, such as perforation, serious abdominal haemorrhage or peritonitis, occur in less than 0.5% of cases[61,62]. PEG tube related complications are more likely to occur in elderly patients with co-morbid illness[62].

PEG site metastasis: Untreated head and neck cancer patients can develop metastatic disease at the abdominal wall due to PEG-tube placement. In one study this risk was approximately 1%[63] although the use of an overtube may decrease this risk[64]. PEG tube metastasis have also occurred in patients with oesophageal adenocarcinoma. Introducer PEG-gastropexy (or Russell method) may be useful in this situation as there is no PEG-tube journey through the oro-pharynx. If it is expected that the patient is going to undergo surgery with curative intent then techniques that may cause seeding of tumour along the skin puncture site should be avoided.

Button/low-profile PEG: These are usually placed once the PEG tract has formed but can also be inserted in a single step endoscopically. Button PEG-tubes are low profile devices and are less socially stigmatising. They are usually used in young persons who find normal PEG-tube protrusion socially unacceptable. However, button PEG-tubes however need replaced every 6 mo and are also more expensive.

Transnasal PEG-tube placement: Unsedated transnasal PEG placement using small diameter gastroscopes is possible. Results show a PEG placement rate of > 90%[65,66]. These operators were however skilled in performing diagnostic transnasal gastroscopy.

Endoscopic PEGJ placement

Endoscopic PEGJ placement permits post-pyloric feeding. Theoretically, small bowel feeding deceases the risk of gastro-oesophageal reflux and aspiration. There is however limited evidence regarding this and reported rates of aspiration with PEG-J feeding vary from 17%-60%[67].

Endoscopic PEGJ placement indications include recurrent aspiration with gastric enteral feeding (either PEG or NG), severe gastric-oesophageal feed reflux, gastroparesis and insufficient gastric remnant after surgery (i.e. not possible to place pre-pyloric feeding access). Therefore in patients who have not tolerated pre-pyloric enteral tube feeding it would seem appropriate to use percutaneous post-pyloric feeding if long-term feeding is required.

Techniques: The first description involved dragging a PEGJ tube *via* a previously formed gastrostomy site. The PEGJ tube was then dragged into the small bowel by means of a gastroscope and snare/forceps. Unfortunately the PEGJ tube habitually migrated proximally upon removal of the scope and the snare/forceps. More recent techniques allow jejunostomy tubes (J-tube) to be placed through PEG-tubes. The consequence of this is that a smaller diameter feeding tube must be used. This over-the-wire technique necessitates a wire being positioned through the PEG tube into the stomach. The wire is then grabbed by forceps and pulled as far possible into the small bowel using the gastroscope. The gastroscope and forceps are removed with the guidewire remaining in the small bowel. A J-tube is then fed over the guidewire into position. A third technique involves passage of an ultrathin endoscope through a PEG site. The gastroscope is then placed into the small bowel. A guidewire is advanced distally, as far as possible, and the gastroscope removed while keeping the guidewire in place. A gastrojejunal tube is then passed over the guidewire into the small bowel[68]. A supplementary measure is that the distal end of the PEGJ tube (suture attached) can be secured to the small bowel wall using a hemoclip.

Endoscopic D-PEJ placement

Jejunal feeding tubes can be placed directly into the small bowel. A paediatric colonoscope or an enteroscope is employed since gastroscopes are not long enough to reach the jejunum (unless there has been a prior gastrectomy). When the endoscope reaches the jejunum, diaphanoscopy and finger indentation, is performed. Next the negative needle aspiration test is performed. Access to the small bowel is achieved using a trocar needle. The guidewire is then positioned through the trocar needle. The D-PEJ is then inserted using a "pull" technique as used with PEG insertion. D-PEJ tubes (18-20 French guage) are larger in diameter than PEG-J tubes (9-12 French guage). However the expertise required to insert a DPEJ may not be as widely available as that for PEG-J insertion. Repeated intubation of the jejunum may be required to identify possible puncture site. Fluoroscopy may also be required.

In one large retrospective study (307 procedures) the success rate of D-PEJ was 68%[69]. Failure was mostly due to gastric outlet/small bowel obstruction or inability to perform diaphanoscopy. In this study there was 5% risk of serious adverse events including bowel perforation, jejunal volvuli, major bleeds and aspiration[69]. 1 death occurred out of the 286 patients in the study.

It is known that obesity has a negative effect on the success rate of DPEJ insertion. In one study where the overall success rate of DPEJ insertion was 81% the success rate in those patients with BMI > 30 kg/m^2 was only 60%[70]. Given the increasing obesity epidemic this problem will be of increasing importance. This same study also highlighted increased complications in obese patients.

Studies have shown that D-PEJ tubes have lower rates of reintervention (due to less kinking/clogging/retrograde jejunal tube migration) and increased tube longevity compared to PEGJ[71,72]. In one study the reintervention

rate was as high as 75% for PEGJ, compared to 31% for DPEJ[73].

CONCLUSION

Malnutrition and undernutrition are common in hospitals. The methods that we have to screen and treat malnutrition have improved greatly over recent times. Parenteral nutrition is a viable option in patients who require nutrition but have a non-functioning gastrointestinal tract. Numerous methods have evolved which aim to achieve GIT access to allow enteral feeding. The development of hospital nutrition teams with specialist interest in enteral feeding will allow enteral feeding in a wider group of patients. The advanced technology that allows many methods of enteral feeding is important but the implementation of these methods is also vital. Enteral feeding should be patient centred and individualized for each patient.

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REVIEW

Endoscopic retrograde cholangiopancreatography associated pancreatitis: A 15-year review

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Abstract

The aim of this article is to review the literature regarding post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. We searched for and evaluated all articles describing the diagnosis, epidemiology, pathophysiology, morbidity, mortality and prevention of post-ERCP pancreatitis (PEP) in adult patients using the PubMed database. Search terms included endoscopic retrograde cholangiopancreatography, pancreatitis, ampulla of vater, endoscopic sphincterotomy, balloon dilatation, cholangiography, adverse events, standards and utilization. We limited our review of articles to those published between January 1, 1994 and August 15, 2009 regarding human adults and written in the English language. Publications from the reference sections were reviewed and included if they were salient and fell into the time period of interest. Between the dates queried, seventeen large (> 500 patients) prospective and four large retrospective trials were conducted. PEP occurred in 1%-15% in the prospective trials and in 1%-4% in the retrospective trials. PEP was also reduced with pancreatic duct stent placement and outcomes were improved with endoscopic sphincterotomy compared to balloon sphincter dilation in the setting of choledocholithiasis. Approximately 34 pharmacologic agents have been evaluated for the prevention of PEP over the last fifteen years in 63 trials. Although 22 of 63 trials published during our period of review suggested a reduction in PEP, no pharmacologic therapy has been widely accepted in clinical use in decreasing the development of PEP. In conclusion, PEP is a well-recognized complication of ERCP. Medical treatment for prevention has been disappointing. Proper patient selection and pancreatic duct stenting have been shown to reduce the complication rate in randomized clinical trials.

Key words: Cholangiopancreatography endoscopic retrograde; Adverse effects; Pancreatitis; Prevention and control/therapy; Risk assessment; Risk factors; Ampulla of vater; Sphincter of oddi; Humans

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INTRODUCTION

The first endoscopic pancreatogram was obtained in 1968, and in 1974, biliary sphincterotomy was first described[1-2]. This was followed by the first report of

Table 1 Clinical trials evaluating the incidence of overall complications and post-ERCP pancreatitis

Author	Country	Year published	*n*	No. ERCP	Overall complications (%)	Post-ERCP pancreatitis (%)
Large prospective trials						
Wang[20]	China	2009	2691	3178	7.92	4.31
Kapral[62]	Austrian	2008	NR[a]	3132	12.60	5.10
Dundee[23]	Australia	2007	563	700	5.71	3.71
Williams[24]	United Kingdom	2007	4561	5234	5.00	1.60
Bhatia[25]	India	2006	1497	1497	NR[a]	3.80
Cheng 2006 and Sherman 2003[b][111,154]	United States	2006	1115	NR[a]	NR[a]	15.10
Andriulli[59]	Italy	2004	1127	1050	NR[a]	4.80
Christensen[13]	Denmark	2004	NR[a]	1177	15.90	3.80
Barthet	France	2002	658	1159	NR[a]	3.50
Vandervoort[10]	United States	2002	1223	1223	11.20	7.20
Freeman[58]	United States	2001	NR[a]	1963	NR[a]	6.70
Masci[35]	Italy	2001	2103	2044	4.95	1.80
DePalma[27]	Italy	1999	535	NR[a]	NR[a]	5.30
Deans[11]	United Kingdom	1997	958	1000	2.40	1.00
Johnson[28]	United States	1997	1979	NR[a]	NR[a]	10.40
Freeman[29]	United States and Canada	1996	2347	NR[a]	9.80	5.40
Loperfido[12]	Italy	1995	2769	NR[a]	4.00	1.30
Large retrospective trials						
Cotton[29]	United States	2009	11497	NR[a]	4.00	2.60
Lukens[30]	United States	2009	2606	3924	3.12	0.97
Andriulli[31]	Italy	2007	16855	NR[a]	6.85	3.47
Cheon[60]	United States	2007	9872	14331	NR[a]	4.00

[a]Not reported; [b]Same patient cohort; ERCP: Endoscopic retrograde cholangiopancreatography.

papillotomy for the management of choledocholithiasis[3] and in subsequent years, numerous endoscopic techniques evolved to address pancreaticobiliary disease. As computerized axial tomography and magnetic resonance imaging have improved, endoscopic retrograde cholangiopancreatography (ERCP) has evolved from primarily a diagnostic procedure into primarily a therapeutic procedure.

As the indications for ERCP have increased, a greater focus on recognizing and preventing complications has emerged. Asymptomatic hyperamylasemia, cardiopulmonary depression, hypoxia, aspiration, intestinal perforation, bleeding, cholangitis, adverse medication reactions, sepsis, acute pancreatitis and death all are recognized complications of ERCP. Post-ERCP pancreatitis (PEP) remains the leading cause of morbidity and mortality post procedure and has been at the center of studies designed to improve procedural outcomes[4-9].

Over the last 15 years, in large prospective trials the overall and pancreatitis complication rates following ERCP have ranged from 2.4% to 15.9%[10-13] and 1.0% to 15.1%[14-16] respectively. Some studies have suggested that lower rates of PEP can be achieved; however the incidence of pancreatitis remains high particularly in at-risk patient populations. Pancreatitis continues to be the major cause of post-procedure morbidity and mortality[17-22] (Table 1).

DIAGNOSIS OF PEP

PEP has been defined as the presence of new pancreatic-type abdominal pain associated with at least a threefold increase in serum amylase concentration occurring 24 h after an ERCP, with pain severe enough to require admission to the hospital or to extend an admitted patient's length of stay. This definition was developed in 1991 based upon approximately 15 000 procedures evaluated during a consensus workshop. The severity of PEP was defined according to length of stay (mild pancreatitis 2-3 d, moderate pancreatitis 4-10 d and severe pancreatitis more than 10 d or intensive care admission or local complications secondary to pancreatitis)[23]. This consensus definition has not been uniformly adopted and many studies published after 1991 have used different criteria to define PEP and classify severity.

Several studies have challenged the serum amylase threshold of three times the upper limit of normal, arguing that this definition is not always consistent with the clinical and morphological features of pancreatitis[24-30]. Variations in the published studies regarding the criteria for serum amylase elevationhave included twice[28-31], four times[10,32-33] and five times[25-26,33-35] the upper limit of the normal.

In regard to the severity of PEP, there is also heterogeneity in criteria used in published studies. Some authors have used the Atlanta criteria published in 1993 to define severity[36-38]. The Atlanta criteria incorporate systemic complications of PEP by integrating the Acute Physiologic and Chronic Health Evaluation (APACHE) Ⅱ classification and the Ranson's criteria to define the severity[38-40]. An APACHE Ⅱ score greater than 8 or a Ranson's score with 3 or more of 11 criteria would be defined as severe PEP. Some studies have used the APACHE Ⅱ classification alone to grade the severity of PEP[41]. Other studies have used combinations of criteria to define the presence and severity of PEP or have

Table 2 Patient and procedural risk factors associated with post-ERCP pancreatitis

Patient related factors
Female sex
Young age
History of or suspected sphincter of oddi dysfunction
History of pancreatitis, recurrent pancreatitis or post-ERCP pancreatitis
Procedure related factors
Difficult or multiple cannulation attempts
Multiple pancreatic contrast injections
Pancreatic acinarization
Precut sphincterotomy
Endoscopic papillary balloon dilation
Sphincter of oddi manometry
Distal common bile duct diameter ≤ 1 cm
Presence of a pancreatic stricture
Procedures not involving stone removal

established unique definitions[31,36,42-45]. The heterogeneity of criteria in the literature on PEP hinders direct comparison of the published clinical trials.

PATHOPHYSIOLOGY OF PEP

The pathophysiology of PEP is not well understood. Mechanical, hydrostatic, chemical, enzymatic, allergic, thermal, cytokine and microbiological factors have all been proposed as causes[37,46-49]. Many studies suggest that PEP results from mechanical trauma with injury of the papilla or pancreatic sphincter causing swelling of the pancreatic duct and obstruction to the flow of pancreatic enzymes. This hypothesis remains controversial and no consensus related to the pathogenesis of PEP has been established.

The cascade of events leading to acute pancreatitis has been characterized in three phases. The first phase is characterized by premature activation of trypsin within the pancreatic acinar cells[50]. The second phase is characterized by intrapancreatic inflammation. The third phase is characterized by extrapancreatic inflammation[50]. Inflammation in the second and third phases has been described in a four step process with (1) activation of inflammatory cells; (2) chemoattraction of activated inflammatory cells; (3) activation of adhesion molecules resulting in binding of inflammatory cells to the endothelium; and (4) migration of activated inflammatory cells into areas of inflammation[50]. Recent studies have evaluated proinflammatory markers (TNF, IL-1, IL-6, IL-8, PAF and IL-10) in the setting of PEP[51-54]. While three randomized control trials suggested a protective effect using low and high dose (4 μg/kg and 20 μg/kg) interleukin 10 given intravenously 15-30 min prior to ERCP[14], subsequent studies using similar IL-10 protocols did not support these findings[55-56]. Though not demonstrated to date, modulation of proinflammatory pathways could represent an appealing goal for studies evaluating PEP and the systemic inflammatory response.

PROCEDURAL RELATED FACTORS ASSOCIATED WITH PEP

Although the triggers of the inflammatory cascade are not yet well understood, procedural and patient- related factors have been clearly associated with the incidence of PEP. ERCP is the most technically difficult endoscopic procedure performed in both inpatient and outpatient settings by trainees and experienced endoscopists. While trauma to the duodenum or papilla during endoscopy without cannulation rarely causes pancreatitis, cannulation of the papilla, especially in moderate to difficult cases, has been associated with high rates of PEP[7]. Procedures involving multiple (> 1-4) or failed attempts at cannulation, multiple pancreatic injections (≥ 2-5), pancreatic acinarization and prolonged cannulation time (> 10 min) have been associated with PEP. Operator experience, ampullary balloon dilation, pre-cut access sphincterotomy, endoscopic sphincterotomy (ES), sphincter of Oddi manometry, distal common bile duct diameters of ≤ 1 cm, presence of a pancreatic stricture, papillectomy and procedures not involving stone removal have also been associated with higher risks for developing PEP[10,12,20,29,35,46,57-60] (Table 2).

OPERATOR EXPERIENCE

While there is no established mandate for procedure volume for competence in ERCP, a prospective study published in 1996 to evaluate the number of supervised ERCPs a physician must perform to achieve procedural competence was reported to be at least 180 procedures[61]. In the United States, the American Society for Gastrointestinal Endoscopy and the American College of Gastroenterology have published quality indicators for ERCP. It is expected that competent endoscopists will be able to perform sphincterotomy, clear the common bile duct of stones, provide relief of biliary obstruction and successfully place stents for bile leaks in ≥ 85% of cases[62].

There have been few studies published in regard to operator experience in ERCP and this issue remains controversial. A recent study in Austria demonstrated a case volume exceeding 50 ERCPs per year had higher success and lower overall complication rates[63]. It is generally agreed that the case mix at high volume and academic referral centers may include a greater proportion of difficult and high-risk cases which may confound the relationship between experience and complication rates.

While operator experience is felt to be critical for high quality outcomes, many large prospective and retrospective trials have not shown consistent data correlating inexperience with PEP. Higher rates of bleeding have been reported after endoscopic sphincterotomy with a mean case volume of < 1 per wk[19] and trainee involvement was associated with severe or fatal complications in a recent retrospective analysis[64].

Table 3 Frequency of post-ERCP pancreatitis - conventional contrast based cannulation versus guide-wire cannulation in randomized trials

Author	Year published	Country	*n*	Rate of pancreatitis		*P* value
				CC (%)	GWC (%)	
Lee[72]	2009	Korea	300	11.30	2.00	0.001
Bailey[73]	2008	Australia	430	7.90	6.20	0.48
Artifon[70]	2007	Brazil and United States	300	16.60	8.60	0.037
Lella[69]	2004	Italy	392	4.10	0.00	< 0.01
Cortas[68]	1999	Canada	47	10.30	5.60	NR[a]

n: Patients included in final analysis; GWC: Guide-wire cannulation (papillotome with guide-wire assistance); CC: Conventional cannulation (papillotome with contrast injection); [a]Not reported.

A large prospective trial however, found that case volume had no effect on the incidence of PEP[29]. A prospective survey of ERCP in the United Kingdom in 2007 based on self reported surveys demonstrated that 15% of all credentialed endoscopists performed less than 50 ERCPs per year as compared to 61% of those in training with 11% of deaths with endoscopists performing less than 50 ERCPs per year. Although the rates of PEP were low at 1.5%, the success rates for bile duct stone extraction and biliary stent placement were 62% and 73% respectively. The authors summarized that in the UK there is a need for fewer operators and greater experience in those performing therapeutic endoscopy[65]. In the same year, a study in France showed no risk associated with operator inexperience[66].

CANNULATION TECHNIQUES

Cannulation techniques to access the pancreatic and biliary ducts include the use of sphincterotomes or straight or curved catheters with guide-wires or contrast injection. When an initial attempt at cannulation fails, access may be achieved after placement of a pancreatic guide-wire or stent to help guide the endoscopist towards the common bile duct and away from the pancreatic duct. Precut access papillotomy is frequently employed in referral centers when conventional approaches fail. Rare or experimental techniques such as the use of endoscopic scissors or endoscopic dissection with a cotton swab have been reported but are rarely employed in clinical practice[67].

Compared to standard catheters, the use of sphincterotomes may reduce failed attempts to obtain biliary access, decrease time required to cannulate the common bile duct and decrease the rate of PEP[68-69]. Selective sphincterotome cannulation with a guide wire may be associated with a reduced rate of PEP compared to cannulation with contrast injection[68-72] (Table 3). In 2008, a large prospective controlled trial randomized 430 patients into sphincterotome plus guide-wire versus conventional cannulation arms. The series demonstrated a significantly higher rate of cannulation with guide-wires but failed to show a significant difference in the rate of PEP between the two approaches[73]. The authors reported an 8.8%-14.9% increased risk of PEP after greater than 4 attempts at the papilla, highlighting the importance of cannulation with fewer attempts. These findings are consistent with previous studies[10,73].

PANCREATIC DUCT INJECTION

Multiple pancreatic duct injections (≥ 2-5)[10,20,29,59] and pancreatic acinarization[12,20,35] have been recognized as risk factors for PEP. Differences in the osmolality and ionicity of contrast media have been studied with varying results in terms of impact on PEP[30,33,60,74-76]. A recent meta-analysis of thirteen randomized controlled trials indicated there was no significant difference between high and low- osmolality contrast media[76]. Earlier studies suggested that there was a decreased risk of PEP with the use of non–ionic contrast agents[74], however this has not been consistently demonstrated[75]. One large retrospective analysis of 14 331 ERCPs suggested that less opacification of the pancreatic duct, head versus tail, resulted in significantly lower rates of PEP[60]. Although there is heterogeneity, clinical trial data suggest that hydrostatic pressure may play a role in the development of pancreatitis.

PANCREATIC DUCT STENTING

The theory that PEP is caused by pancreatic duct obstruction is supported by the majority of randomized controlled trials that demonstrate a decreased incidence of pancreatitis in high risk patients with the placement of a pancreatic duct stent[18,77-84]. In the three largest studies published to date evaluating the rate of pancreatitis with pancreatic duct stent placement, there were significant differences with decreased rates of PEP of 10.4%, 14.8% and 52.3%[17,78-79]. While pancreatic duct stenting has been shown to decrease the risk of PEP, it has not been able to prevent it. Despite stent placement, pancreatitis occurs in 2.0%-14% of cases[78-79,81,83-84] and some studies fail to demonstrate a statistically significant protective effect[60,83-84] (Table 4).

BILIARY STONE EXTRACTION

In the setting of choledocholithiasis, endoscopic papillary balloon dilatation (EPBD), ES and mechanical

Table 4 Randomized controlled trials evaluating the effect of pancreatic duct stenting on prevention of post-ERCP pancreatitis

Author	Country	Year published	*n*	Rate of post-ERCP pancreatitis		*P* value
				Without stent (%)	With stent (%)	
Tsuchiya[84]	Japan	2007	64	12.50	3.10	NR[a]
Sofuni[78]	Japan	2007	201	13.60	3.20	0.02
Harewood[77]	United States	2005	19	33.00	0.00	0.02
Fazel[85]	United States	2003	74	28.00	5.00	< 0.05
Tarnasky[18]	United States	1998	80	26.00	7.00	0.03
Smithline[87]	United States	1993	93	18.00	14.00	0.299

n: Patients included in final analysis; [a]Not reported.

Table 5 Frequency of post-ERCP pancreatitis - endoscopic sphincterotomy *vs* endoscopic papillary balloon dilation in randomized studies

Author	Year published	Country	*n*	Rate of pancreatitis		*P* value
				ES (%)	EPBD (%)	
DiSario[98][b]	2004	United States	237	0.83	15.38	< 0.05
Fujita[87]	2003	Japan	282	2.80	10.90	< 0.05
Vlavianos[92]	2003	United Kingdom	202	1.01	4.86	NR[a]
Arnold[89]	2001	Germany	60	10.00	20.00	NR[a]
Bergman[99]	1997	The Netherlands	202	6.93	6.93	NR[a]

n: Patients included in final analysis; ES : Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; [b]Multi-centered; [a]Not reported.

lithotripsy are the techniques used to extract obstructing stones. There have been multiple studies that have established the increased rate of PEP with EPBD ranging from 4.9%-20.0% versus 0.42%-10.0% with ES[85-88]. Prospective trials support this observation; however it is difficult to generalize the findings given the many factors that contribute to procedural complications[89-93] (Table 5). Balloon dilation may also be required in some clinical settings. If a patient has had a prior sphincterotomy and has limited remaining tissue for incision, balloon dilation may be necessary to enlarge the bile duct insertion and enable stone extraction.

PATIENT-RELATED RISK FACTORS ASSOCIATED WITH PEP

Given the high risk of PEP in certain populations, identifying a clear indication is critical in reducing the complication rate. It has been well recognized that ERCP is riskiest in patients who need it the least[21,94]. Large prospective trials have demonstrated that female gender, age less than 60-70 years, suspected SOD and recurrent or prior PEP were associated with a higher risk of PEP[10,12,20,29,35,57,95] (Table 2). Though widely accepted, there has been some heterogeneity across studies. For example, one smaller trial suggested an age of less than 50 as a significant risk factor[95]. A recent large retrospective study of 16 855 patients demonstrated the highest rates of PEP were associated with patients with SOD but there was no significant increase in younger patients or in women[64]. Alternatively, a meta-analysis evaluating five patient- related risk factors demonstrated a relative risk of SOD of 4.09 (95% CI 1.93 to 3.12; $P < 0.001$) and female gender of 2.23 (95% CI 1.75 to 2.84; $P < 0.001$)[96]. One study demonstrated a 10 fold increase in the development of PEP in patients with SOD[97].

Some factors may be protective as well. Studies have suggested that the absence of chronic pancreatitis[58], the presence of obesity[98], older age (> 80)[99] and a history of alcohol consumption or cigarette smoking may be associated with a decreased risk of PEP[100]. Proper patient selection and identification of patients at higher risk is the most effective means of reducing the incidence of PEP.

PHARMACOLOGIC AGENTS EVALUATED IN PREVENTION/REDUCITON OF PEP

There has been great interest in the affect of pharmacologic agents on PEP. Preventing cellular injury and pancreatic tissue auto-digestion may involve blocking the premature activation of proteolytic enzymes within the acinar cells[19,101-109]. Though conceptually straightforward, the goal of blocking this activation has been difficult to achieve. Multiple trials have been performed with a goal of reducing the incidence or severity of PEP. Approximately 34 (Table 6) pharmacologic agents and procedures (e.g. topical application of pharmacologic agents injected or sprayed on to the papilla) have been evaluated for potential prevention of PEP in controlled trials. Most clinical trials have been disappointing and a minority of studies has demonstrated benefit (Table 7)[14,15,31,34,42-45,55,56,59,96,110-161].

Allopurinol has been shown in two of five pro-

Table 6 Pharmacologic agents evaluated for potential reduction/prevention of post-ERCP pancreatitis

Pharmacologic agent	RCT showed benefit
Allopurinol	Yes
Cephtazidime	Yes
Diclofenac	Yes
Gabexate	Yes
Glyceryl trinitrate	Yes
Hydrocortisone	Yes
Indomethacin	Yes
Interleukin-10 (IL-10)	Yes
Nafamostat mesylate	Yes
Octreotide	Yes
Somatostatin	Yes
Ulinastatin	Yes
Anticholinergic drugs	No
Aprotinin	No
Botulinum toxin	No
Calcitonin	No
Epinephrine	No
Fresh frozen plazma	No
Glucagon	No
H-2 Blocker	No
Heparin	No
Lidocaine	No
Methylprednisolone	No
N-aceytyl cysteine (NAC)	No
Natural beta-carotene	No
Nifedipine	No
Nitroglycerin	No
Parenteral nutrition	No
Pentoxifylline	No
Prednisone	No
Recombinant PAF acetylhydrolase (rPAF-AH)	No
Selenium	No
Semapimod	No

spective trials to decrease the incidence of PEP[110,112]. In these trials showing benefits, allopurinol was given in 300 mg or 600 mg doses at 15 h and 3 h prior to ERCP. When reviewing other studies of allopurinol, these effects were not significant in patients dosed on a different 4 h and 1 h regimen and with varying dose concentrations of allopurinol[111,113,114]. This may suggest that not only the dose but timing of allopurinol administration is important in the reduction of PEP. Diclofenac, a non steroidal anti-inflammatory drug, was evaluated in three trials. With diclofenac 100 mg PR dosed immediately after ERCP, the incidence of PEP was decreased[44,131] but a trial evaluating diclofenac 50 mg PO at 30-90 min prior to ERCP and up to 4-6 h post ERCP showed no decrease in PEP[132]. In regard to glyceryl trinitrate[129], hydrocortisone[118] and interleukin-10[14], all agents were shown in one randomized control trial to show benefit. However in studies with larger numbers of patients[31,56,128] these findings were found to be statistically insignificant.

Gabexate[145,146,148], octreotide[135,136], somatostatin[156,159] and ulinastatin[152] have all been reported to show a reduction in PEP. However there have been studies evaluating each of these agents with similar designs that report no significant reduction in the incidence of PEP. These differences could be explained by the selection of patients, number of patients, clinical presentation and timing of administration or dosage of the agent under investigation.

While the use of allopurinol, cephtazidime, diclofenac, gabexate, glyceryl trinitrate, hydrocortisone, indomethacin, interleukin-10, nafamostat mesylate, octreotide, somatostatin and ulinastatin have shown promise in clinical trials, there is currently no accepted pharmacologic intervention to prevent pancreatitis and in some cases (gabexate, nafamostat and somatostatin) the pharmacologic agent is not approved for use in some countries. Nevertheless, pharmacologic prevention remains an active area of research.

MANAGEMENT OF PEP

Once mild or moderate PEP has occurred it usually quickly resolves with conservative therapy. Although there are no specific guidelines for the treatment of PEP, a recent study demonstrated that a protocol-based management strategy was associated with less severe pancreatitis, shorter lengths of hospital stay, need for fewer imaging studies and less use of antibiotics[102]. Practice guidelines for acute pancreatitis treatment are available and may be applicable to PEP as well[50].

In patients with persistent or severe PEP, two important markers of severity are multisystem organ failure and pancreatic necrosis, both of which require aggressive management[23]. Early identification of organ failure, pancreatic necrosis, perforation (especially in the setting of endoscopic sphincterotomy), biliary damage/leak and pancreatic fluid collections are important clinical branch points, potentially requiring more intensive intervention. Checking serum transaminases, amylase and lipase is not routinely recommended post-ERCP. If assessed, elevations are commonly observed post procedure. These elevations are likely secondary to intermittent biliary, pancreatic or papillary obstruction. 46% of patients in a recent study were reported to have elevated liver test elevations after ERCP and only 5.4% of them had PEP[103]. Asymptomatic elevations are not an indication for a change in management and repeat ERCP is performed only with a clear indication.

Although there is controversy related to enteral feeding during treatment of acute pancreatitis, patients who are unlikely to resume oral nutrition within five days require nutritional support which can be provided *via* TPN or enteral routes. There appears to be some advantages to enteral feeding and a recent study found that initiating oral nutrition after mild acute pancreatitis with a low fat soft diet appeared to be safe but did not result in a shorter length of hospitalization[104].

CONCLUSION

Acute pancreatitis is the most common complication after ERCP. The pathophysiology is not well understood

Table 7 Randomized controlled trails of pharmacologic agents evaluated for reduction or prevention of post-ERCP pancreatitis

Agent	Author	Factor studied	*n*	Rate of post-ERCP pancreatitis (%)			*P* value
				Overall	Control	Intervention	
Allopurinol							
	Martinez-Torres[110]	Allopurinol 300 mg PO at 15 h; 300 mg PO at 3 h before ERCP	170	NR[a]	9.40	2.30	0.049
	Romagnuolo[111]b	Allopurinol 300 mg PO at 1 h before ERCP	586	NR[a]	4.10	5.50	0.440
	Katsinelos[112]	Allopurinol 600 mg PO at 15 h; 600 mg PO at 3 h before ERCP	243	10.20	17.80	3.20	< 0.001
	Mosler[113]	Allopurinol 600 mg PO at 4 h; 300 mg PO at 1 h before ERCP	346	12.55	12.14	12.96	0.520
	Budzynska[114]	Allopurinol 200 mg PO at 15 h; 200 mg PO at 3 h before ERCP	300	10.70	7.90	12.10	0.320
Beta-carotene							
	Lavy[115]	Natural beta-carotene 2 g at 12 h before ERCP	321	9.60	9.60	10.00	NR[a]
Botulinum toxin							
	Gorelick[116]	Botulinum toxin injection after biliary sphincterotomy	26	NR[a]	43.00	25.00	0.340
Cephtazidime							
	Raty[117]	Cephtazidime 2g Ⅳ 30 min before ERCP	321	NR[a]	9.38	2.58	0.009
Hydrocortisone							
	Kwanngern[118]	Hydrocortisone 100 mg Ⅳ at 1 h before ERCP	120	6.67	11.86	1.64	0.031
	Manolakopoulos[119]b	Hydrocortisone 100 mg Ⅳ at 30 min before ERCP	340	10.00	13.00	7.10	0.380
	De Palma[31]	Hydrocortisone 100 mg Ⅳ immediately before ERCP	529	5.30	4.90	5.70	NS
Prednisone							
	Sherman[120]b	Prednisone 40 mg PO at 15 h and at 3 h before ERCP	1115	15.07	13.60	16.60	0.190
	Budzynska[114]	Prednisone 40 mg at 15 h; 40 mg at 3 h before ERCP		10.70	7.90	12.00	0.330
Methylprednisolone							
	Dumot[43]	Methylprednisolone 125 mg Ⅳ immediately before ERCP	286	NR[a]	8.70	12.40	0.340
Heparin							
	Barkay[42]	Unfractionated heparin 5000 IU SC 20-30 min before ERCP	106	NR[a]	7.40	7.80	NS
	Rabenstein[121]	Low molecular weight heparin Certoparin 3000 IU SC the day before ERCP	448	8.50	8.81	8.14	0.870
Interlukin-10							
	Sherman[56]b	IL-10 8 μg/kg Ⅳ 15-30 min before ERCP	305	17.38	14.30	15.40	0.830
		IL-10 20 μg/kg Ⅳ 15-30 min before ERCP				22.00	0.140
	Deviere[14]	IL-10 4 μg/kg Ⅳ 30 min before ERCP	144	29.90	24.40	10.41	0.046
		IL-10 20 μg/kg Ⅳ 30 min before ERCP				6.81	0.017
	Dumot[55]	IL-10 8 μg/kg Ⅳ 15 min before ERCP	200	10.00	9.10	10.90	0.650
N-acetyl cystine							
	Milewski[122]	NAC 600 mg Ⅳ BID × 2 d after ERCP	106	9.43	11.76	7.27	NS
	Katsinelos[123]	NAC 70 mg/kg 2 h before and 35 mg/kg 4 h intervals for 24 h after procedure	249	10.80	9.60	12.10	> 0.500
Nifedipine							
	Prat[124]	Nifedipine 20 mg PO 3-6 h before ERCP	155	15.50	17.70	13.20	NS
	Sand[125]	Nifedipine 20 mg PO q 8 h the day of ERCP	166	3.61	4.00	4.00	NR[a]
Nitroglycerin							
	Hao[126]	Glyceryl trinitrate 5 mg Ⅳ and 100 mg vitamin C 5 min before ERCP maneuvers	74	16.20	25.00	7.90	0.012
	Beauchant[127]b	Nitroglycerin bolus of 0.1 mg, then 35 g/kg/min Ⅳ for 6 h after ERCP	208	12.00	15.00	10.00	0.260
	Kaffes[128]	Transdermal glyceryl trinitrate patch (15 mg) precordial area 30-40 min before ERCP	318	NR[a]	7.40	7.70	NS
	Moreto[129]	Transdermal glyceryl trinitrate patch (15 mg) precordial area 30-40 min before ERCP	144	9.00	15.00	4.00	0.030
	Sudhindran[130]	Glyceryl trinitrate 2 mg SL 5 min before ERCP	186	13.00	18.00	8.00	< 0.050
Diclofenac							
	Khoshbaten[131]	Diclofenac 100 mg PR immediately after ERCP	100	15.00	26.00	4.00	< 0.010
	Cheon[132]	Diclofenac 50 mg at 30-90 min before and at 4-6 h after ERCP	207	16.40	16.70	16.20	NS
	Murray[44]	Diclofenac 100 mg PR immediately after ERCP	220	11.00	15.45	6.36	0.049
Indomethacin							
	Sotoudehmanesh[133]	Indomethacin 100 mg PR after ERCP	442	4.98	6.78	3.16	OR 0.4 (0.2 - 1.1)

Octreotide							
	Kisli[134]	Octreotide 0.1 mg gtt 60 min before ERCP and continued during and after ERCP	120	NR[a]	11.49	15.15	NS
	Li[135]b	Octreotide 0.3 mg gtt 1 h before -6 h after ERCP; then 0.1 mg SC; 12 h later 0.1 mg SC	832	3.85	5.26	2.42	0.046
	Thomopoulos[136]	Octreotide 500 μg TID starting 24 h before ERCP	201	10.89	8.90	2.00	0.03
	Testoni[137]b	Octreotide 200 μg TID × 24 h before ERCP	114	NR[a]	14.30	12.00	NS
	Hardt[138]	Octreotide 200 μg SC the night before ERCP	94	NR[a]	NR[a]	NR[a]	NS
	Duvnjak[139]	Octreotide 0.5 mg SC 60 min before ERCP	209	NR[a]	9.52	3.85	NS
	Arvanitidis[140]	Octreotide 0.1 mg SC 30 min before; 8 h and 16 h after ERCP	73	10.95	11.11	10.81	NS
	Tulassay[45]b	Octreotide 0.1 mg SC 45 min after ERCP	1199	7.84	6.00	5.90	NS
	Arcidiacono[141]	Octreotide 0.1 mg SC 120 and 30 min before; 4 h after ERCP	151	6.62	NR[a]	NR[a]	NS
	Baldazzi[142]	Octreotide 0.1 mg SC 45 min before; 6 h after ERCP	100	NR[a]	NR[a]	NR[a]	NR[a]
	Testoni[143]	Octreotide 0.2 mg SC before ERCP	60	NR[a]	NR[a]	NR[a]	NS
	Testoni[34]	Octreotide 200 μg TID × 3 d before ERCP	60	NR[a]	NR[a]	NR[a]	NS
Gabexate							
	Ueki[144]	Gabexate 600 mg Ⅳ 60-90 min before and 22 h after ERCP	68	2.90	NR[a]	2.90	NS
	Manes[145]b	Gabexate mesylate 500 mg within 1 h before ERCP	608	5.60	9.40	3.90	< 0.01
		Gabexate mesylate 500 mg within 1h after ERCP				3.40	< 0.01
	Xiong[146]	Gabexate 300 mg Ⅳ 30 min before gtt until 4 h after ERCP	200	6.70	10.50	3.10	0.04
	Fujishiro[151]b	Gabexate 900 mg/1500 mL gtt for 13 h beginning 1 h before ERCP	139	NR[a]	NR[a]	4.30	NS
	Andriulli[59]b	Gabexate 500 mg 30 min before gtt until 6 h after ERCP	1127	5.60	4.80	5.80	NS
	Masci[96]b	Gabexate 500 mg Ⅳ 30 min before gtt until 6.5 h after ERCP and 1 g Ⅳ for 13 h after ERCP	434	1.80	2.20	1.40	NS
	Andriulli[147]b	Gabexate 500 mg Ⅳ 30 min before and 2 h after ERCP	579	8.60	6.50	8.10	NS
	Cavallini[148]b	Gabexate 1 g Ⅳ 30-90 min before gtt until 12 h after ERCP	418	5.00	8.00	2.00	0.03
Nafamostat mesylate							
	Choi[149]	Nafamostat mesylate 20 mg gtt 1 h before and for 24 h after ERCP	704	5.40	7.40	3.30	0.018
Ulinastatin							
	Yoo[150]	Ulinastatin 100 000 U gtt after ERCP for 5.5 h	227	6.20	5.60	6.70	0.715
	Ueki[144]	Ulinastatin 150 000 units 60-90 min before & for 22 h after ERCP	68	2.90	2.90	2.90	NS
	Fujishiro[151]b	Ulinastatin 150 000 units 1 h before, during; 11 h after ERCP				6.50	NS
		Ulinastatin 50 000 units				8.50	NS
	Tsujino[152]b	Ulinastatin 150 000 U gtt 10 min before ERCP	406	5.17	7.40	2.90	0.041
Pentoxifylline							
	Kapetanos[153]	Pentoxifylline 400 mg PO TID before ERCP	320	4.38	3.00	5.60	0.28
Recombinant PAF acetylhydrolase							
	Sherman[154]b	Recombinant PAF acetylhydrolase (rPAF-AH) 1 mg/kg gtt < 1 h before ERCP	600	17.60	19.60	17.50	0.59
		Recombinant PAF acetylhydrolase (rPAF-AH) 5 mg/kg gtt < 1 h before ERCP				15.90	0.34
Semapimod							
	van Westerloo[155]	Semapimod Ⅳ 50 mg/100 mL glucose gtt 1 h before ERCP	242	11.98	14.88	9.09	0.117
Somatostatin							
	Lee[156]b	Somatostatin 3 mg in 500 mL NS gtt 12 h starting 30min before ERCP	391	6.65	9.60	3.60	0.02
	Andriulli[59]b	Somatostatin 750 μg Ⅳ 30 min before and continued for 6 h after ERCP				6.30	NS
	Arvanitidis[157]	Somatastatin 4 μg/kg gtt 12 h on identification of the papilla and before introduction of the catheter	372	NR[a]	9.80	1.70	< 0.05
		Somatostatin 3 mg gtt 12 h on identification of the papilla and before introduction of the catheter				1.70	< 0.05

	Poon[158]	Somatostatin 250 mg IV bolus immediately after ERCP	270	NR[a]	13.30	4.40	0.01
	Andriulli[147][b]	Somatastatin 750 μg IV 30 min before and 2 h after ERCP				11.50	NS
	Poon[159]	Somatostatin 3 mg in 500 mL NS gtt for 12 h starting 30 min before ERCP	220	5.91	10.00	3.00	0.03
	Bordas[160]	Natural somatostatin 4 mg/kg IV on identification of the papilla and before introduction of the catheter	160	NR[a]	10.00	2.50	< 0.05
Topical spray on papilla							
	Matsushita[15]	Epinephrine (10 mL of 0.02%) sprayed on papilla before cannulation	370	1.10	2.16	0.00	0.123
	Schwartz[161]	Lidocaine (10 mL of 1%) sprayed on the major papilla before cannulation	294	4.08	3.04	4.32	0.73

PEP: Post-ERCP pancreatitis; ERCP: Endoscopic retrograde cholangiopancreatography; IL-10: Ingerlukin-10; NAC: N-acetyl cystine; NS: Not significant; [a]Not reported/unable to acquire primary data from publication; [b]Multi-centered.

but theories regarding mechanical, hydrostatic, chemical, enzymatic, allergic, thermal, cytokine and microbiological factors have been proposed. While trauma during endoscopy without cannulation rarely causes pancreatitis, procedural factors involving cannulation, access and pancreaticobiliary drainage have been associated with PEP. Although operator experience is important in high quality outcomes, many large prospective and retrospective trials have not shown consistent data associating inexperience with increased incidence, perhaps due to the importance of case-mix in outcome. Patient-related risk factors are well recognized with Sphincter of Oddi dysfunction and a history of PEP conferring additional risk in the post-procedure setting. However, obesity, older age, alcohol consumption and cigarette smoking may be protective. Approximately 34 pharmacologic agents have been evaluated and 63 clinical trials have been performed in an effort to identify an agent to prevent PEP. Over the last 15 years, no pharmacologic agent has been accepted in reducing PEP due to a lack of reproducibility, heterogeneity in outcomes and/or limitations in study design. Proper patient selection and identification of risk factors pre-procedure is the most effective means of reducing the incidence of PEP.

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REVIEW

Role of wireless capsule endoscopy in inflammatory bowel disease

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Abstract

Capsule endoscopy (CE) offers state-of-the-art imaging of the small bowel. In Crohn's disease its clinical role is still uncertain. This report analyses the usefulness of CE in patients with suspected Cronh's disease, in patients with established Crohn's disease (when assessing severity, occult gastrointestinal bleeding and/or as a guide to therapy), in patients with inflammatory bowel disease unclassified (IBDU), and in individuals with ulcerative colitis. The first item in this group is the most important although there is no strong evidence to establish the position of CE in the diagnostic workup. In patients with established Crohn's disease, recently developed activity scores are promising tools for an accurate assessment of severity. As a guide to therapy, CE should be focused on patients with unexplained symptoms when other investigations are inconclusive. In postoperative Crohn's Disease, international consensus recommended considering CE only if ileocolonoscopy is contraindicated or unsuccessful. In the case of IBDU, studies have shown a significant proportion of patients reclassified with Crohn's disease. In this setting, CE could have a role determining small bowel involvement. The role of CE in ulcerative colitis is limited. Some authors advocate CE before colectomy for refractory cases in order to exclude Crohn's disease. In summary, CE offers a new horizon in inflammatory bowel disease, and a better knowledge of mucosal abnormalities that could offer a paradigm shift: changing from symptom-based disease activity estimation to direct mucosal healing monitoring. Nevertheless, randomized controlled studies are still needed to provide stronger evidence in this setting.

Key words: Wireless capsule endoscopy; Crohn's disease; Ulcerative colitis; Inflammatory bowel disease

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INTRODUCTION

The history of gastrointestinal endoscopy is one of striking technical advances. From the first rigid instrument developed by Kussmaul in Germany, or the semi-flexible instruments designed by Rudolf Schindler in Chicago, to the current video endoscopes, a more accurate visualization of the gastrointestinal tract offers increasing knowledge of gastrointestinal disease and better therapeutic possibilities. However, endoscopic assessment of the small bowel has remained a challenge, because its length and tortuosity determines a major

difficulty for its exploration with flexible endoscopes. Sonde and push enteroscopes provided a significant advance in this field[1-3].

Capsule endoscopy (CE) was initially marketed in 2001, and, to date, has been the greatest advance in the field of small bowel exploration. The procedure provides state-of-the-art imaging of the small intestine, and is recommended as the third test to be used in the investigation of obscure gastrointestinal bleeding, after colonoscopy and upper endoscopy[4]. Nevertheless, in small bowel Crohn's disease, the role of capsule endoscopy is not clear, but despite this, there have been some papers which have addressed this issue[5-16]. A meta-analysis of eleven studies which included 223 patients and compared CE to other imaging modalities for inflammatory bowel disease, established that CE has an incremental diagnostic yield of 25%-40% over other methods, such as barium studies or CT scanning[17]. However, some other well designed papers have limited the role of CE in comparisons with other procedures as CT enterography, ileocolonoscopy or small bowel follow-through[18]. Indeed, in the setting of Crohn's disease, it is widely recognized that its clinical role remains uncertain[14,19].

When evaluating the importance of this new technology in inflammatory bowel disease, several issues regarding its role present themselves[20]: (1)The suspected Crohn's disease, when the usual diagnosis workup in negative or non diagnostic; (2) Assessment of severity of small bowel Crohn's disease; (3) Study of the patient with IBD and a gastrointestinal bleeding of obscure origin; (4) CE as a guide to therapy; (5) Unclassified IBD; and (6) The role of CE in Ulcerative Colitis (UC).

Nowadays, the first item is most frequently encountered, and the one which has given rise to greater contention, given the widespread use of CE for diagnostic purposes. Nevertheless, these indications have already been established, but remain subjects of research, and the number of papers focused on each of these issues is increasing. In the following pages, the evidence will be examined in order to suggest a recommendation for each indication.

ROLE OF CE IN SUSPECTED CROHN'S DISEASE

To date, there is no single gold standard diagnostic test for Crohn's disease[14]. The diagnosis is based on a composite of findings, including the clinical history and physical examination of the patient, and biochemical, endoscopic, radiologic and pathologic findings[20]. Until the implementation of CE, the diagnosis was made on the basis of small bowel radiology and ileocolonoscopy, and was seldom aided by push enteroscopy. Histological confirmation of the disease is still possible only in a minority of those patients, and an image-based diagnosis is the usual setting[18].

However, the main question, when using CE in this case, is in which position of the diagnostic workup it can be performed in order to optimize the use of what is an expensive and time consuming technology. Previously, suspicion of Crohn's disease was left to the expertise of the treating physician, and the diagnostic protocol was triggered when a patient had abdominal pain or diarrhea. The diagnostic yield of CE is low when performed in patients with abdominal pain alone, or in patients with abdominal pain and diarrhea[21,22]. When other criteria are present, this yield increases. These criteria are inflammatory serum markers (ESR, C reactive protein, thrombocytosis or leukocytosis). In an interesting paper by Fireman, which enrolled patients with abdominal pain, diarrhea, anemia and weight loss with an average symptom duration of 6.3 years, and all of them having presented with normal colonoscopies, upper endoscopies and small bowel follow-through, Crohn's disease was found by CE in 12 of the 17 patients[23,24].

Recently, an international OMED and ECCO consensus confirmed a previous recommendation in this group of patients: ileocolonoscopy and small bowel imaging should generally precede CE. the choice of the radiographic procedure depends on local availability[20]. Furthermore, some of those radiologic methods have shown a similar sensitivity to CE, which supports the initiation of the diagnostic work-up as recommended[18]. A previously established consensus panel, the ICCE, agreed to expand their definition of patients who should be considered as being suspected of having Crohn's disease. An algorithm was formulated, which included symptoms as well as extraintestinal manifestations, inflammatory markers or abnormal imaging studies[25] (Figure 1). Moreover, a recent follow-up study including 102 patients with suspected Crohn's disease observed small bowel inflammatory changes in 35% of patients, and a prevalence of Crohn's disease after 12 mo follow-up of 13%. A poor positive predictive value was observed (31%), although it increased by up to 50% when more stringent criteria were required for the diagnosis of Crohn's disease by CE, as well as when ICCE clinical criteria (Figure 1) where considered as a guide to patient selection[14]. In summary, it seems obvious that the addition of more than one suggestive clinical symptom increases the adequacy of CE for the diagnosis of Crohn's disease[9,19,20].

Another controversial issue is the position of CE in the diagnostic algorithm of suspected Crohn's disease. Although, as mentioned above, it is widely accepted to perform it after ileocolonoscopy and a small bowel radiographic method (as SB series), in view of the results of the Mayo Clinic trial[18], the authors recommend the performance of CT-enterography after ileocolonoscopy but before CE. Indeed, they had a similar sensitivity but a higher specificity rate for CT enterography compared to CE. In the discussion, they finally state that the algorithm ought to be adapted to local availability and expertise[18]. On the other hand, the same group has

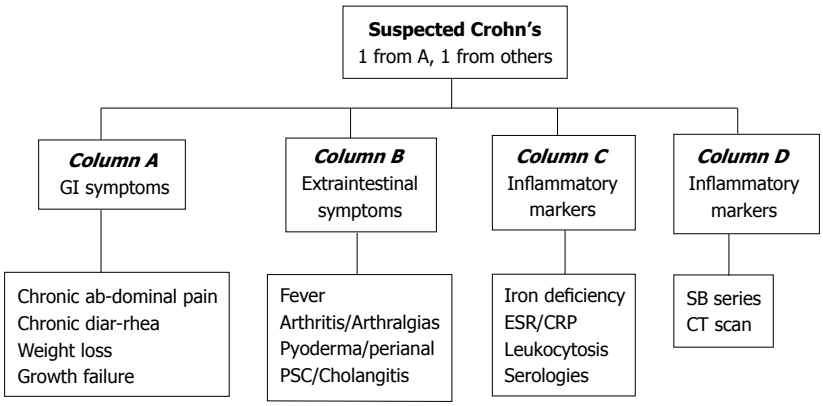

Figure 1 Criteria for suspected Crohn's disease. (Mergener *et al*[18]) (PSC: Primary sclerosing cholangitis; ESR: Erythrocyte sedimentation rate; CRP: C reactive protein; SB series: Small bowel series; CT scan: Computed tomography scan).

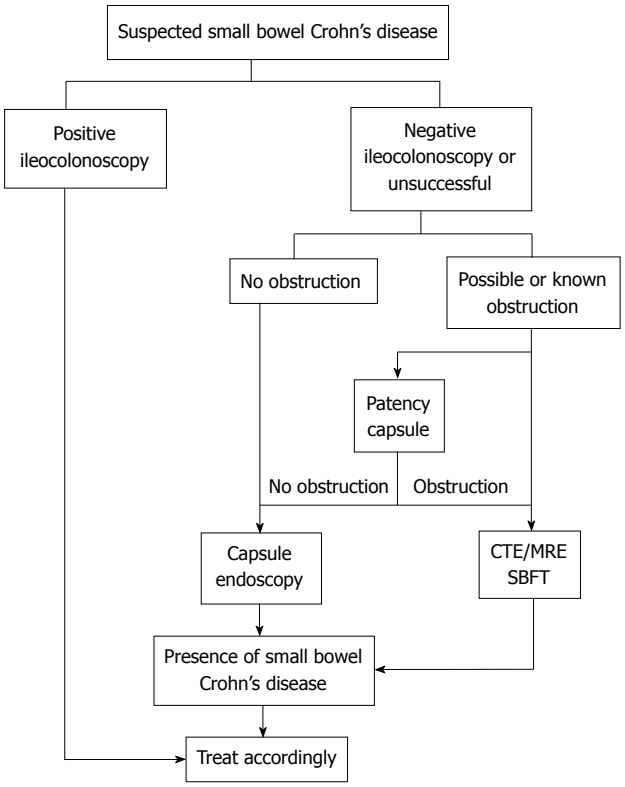

Figure 2 Algorithm for approaching suspected Crohn's disease. (Leighton *et al*[19]).

published a recent paper showing economic benefits when CE is performed after ileocolonoscopy, but before small bowel series[12]. Furthermore, the vast majority of centers still follow the algorithm in which CE is a first line diagnostic tool in Crohn's disease[26-30] (Figure 2). A meta-analysis has demonstrated that CE is superior to small bowel radiology, ileocolonoscopy, and CT-enterography in the evaluation of suspected Crohn's disease patients[11]. The main concern with CE as a diagnostic tool is the absence of a confident gold standard test to which it may be compared. This has led to a majority of studies in which the concept of diagnostic yield is the main outcome variable, providing evidence that is not easily applicable to daily clinical practice. The diagnostic yield can be defined as the likelihood of a positive finding. However, it is not the same as sensitivity, that is, the likelihood of a positive test given true disease (based on a criterion standard). The diagnostic yield is the first step in determining what finding a test is capable of producing; nevertheless, the diagnostic yield does not provide the technical accuracy specifications of sensitivity and specificity. Indeed, a lower threshold for positive findings lead to a high diagnostic yield[19]. This tendency is changing, with some new studies which are trying to determine diagnostic accuracy with a gold standard represented by a panel of investigators with expertise in the diagnostic tools compared in the study[18,31]. Moreover, other authors established a follow-up period in which patients were considered as having established Crohn's disease if they met the current clinical and radiological criteria during this period, despite CE findings[14]. Although somewhat artificial, these research designs mark a promising research field in which the exact accuracy of the procedure, and therefore its position in the diagnostic workup, will eventually be defined.

But not only the aforementioned issues are controversial. When the CE yields a finding, there are no validated diagnostic criteria for the diagnosis of Crohn's disease. Many of the lesions described in studies of suspected Crohn's disease are unspecific, and this could explain the variability of the diagnostic yield[20] (Figure 3). To date, the presence of more than three ulcerations, in the absence of NSAIDs ingestion, constitutes the most commonly used diagnostic criterion[7,14]. The lesson to be learned from this uncertainty is that clinical history, including the ingestion of NSAIDs, is the basis of the diagnostic workup. Physicians have to take into account that minimal mucosal leaks can be of no significance. Evidence suggests that up to 13% of normal, asymptomatic individuals can have mucosal breaks and other minor lesions of the small bowel detected by CE[27]. Nevertheless, it is obviously urgent to define criteria or scores for the diagnosis and for assessing both the activity and severity of Crohn's disease by CE.

Despite all these concerns, CE has changed the diagnosis and management of small bowel Crohn's disease, and it has been recognized as a cost-effective diagnostic tool in these patients[12,30].

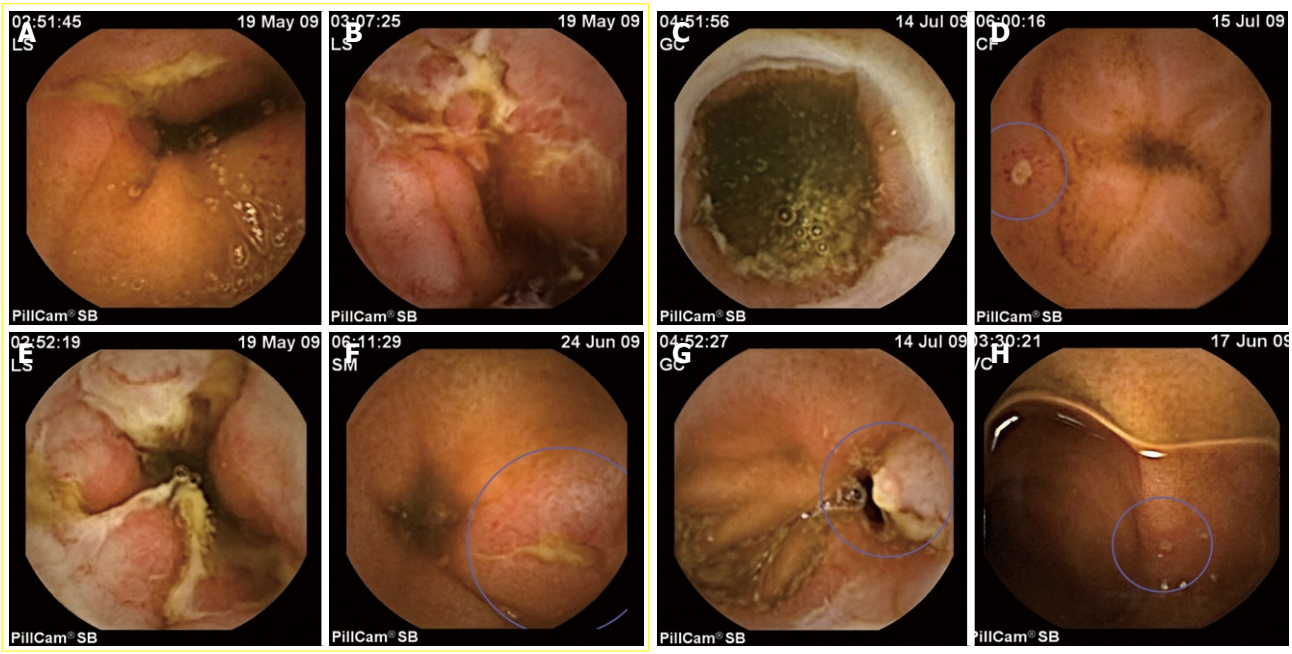

Figure 3 CE findings for Crohn's disease are not specific. In the images, only the ones included inside the yellow square are confirmed cases of Crohn's disease. The other four were NSAIDs related lesions. A, B: Aftous ulcers, typical of Crohn's disease; B, E: Geographical ulcers, observed in severe cases of small bowel Crohn's disease, with strictures associated. D, H: Very small aftae, quite often observed in normal people, but, in these cases, in patients with a recent NSAIDs therapy. C: A typical ring-shaped stricture associated to NSAIDs. G: An ulcer in a patient with anemia and in treatment with high doses of NSAIDs for arthritis.

ASSESSMENT OF SEVERITY OF SMALL BOWEL CROHN'S DISEASE

Regarding the activity of the disease, valuable results have been demonstrated in two studies proposing and validating a CE score (CECDAI)[27,28]. The CECDAI has been validated but still has to be tested in further prospective trials. The attempt to reach a consensus in the score index has provided other potential benefits: (1) The score, in conjunction with clinical data, is an important tool for the diagnosis in suspected cases; (2) It establishes a more objective method for following up mucosal healing; (3) It could help to individualize the treatment in each subject; and (4) A score tends to unify terminology and improves scientific communication between investigators[24]. While waiting for a definitive validation, its use can improve the procedure's accuracy when assessing severity.

CE AS A GUIDE TO THERAPY

Endoscopy plays an important role in the evaluation and monitoring of established Crohn's disease. Ileocolonoscopy and upper endoscopy have well-established roles for this purpose, but the exact position of CE still needs to be defined[32].

Therefore, international consensus states that in established Crohn's disease, CE should be focused on patients with unexplained symptoms when other investigations are inconclusive, if this option may change management[20]. In this case, it is mandatory to assess the absence of evident strictures in the bowel prior to CE by radiographic methods. Although most patients with Crohn's disease have lesions accessible to ileocolonoscopy, sometimes there are patients with unexplained symptoms and inconclusive radiographic imaging on ileocolonoscopy, who may well have subtle small bowel lesions. CE allows the detection of these superficial lesions with a relevant influence on therapeutic management[16,20].

A recent paper[9] has also studied whether symptoms represented flares in disease activity. CE yielded negative findings in approximately 48% of symptomatic patients, which, the authors interpreted as symptoms caused by other diseases (bacterial overgrowth, irritable bowel syndrome, etc.) CE yielded negative findings in approximately 48% of symptomatic patients, which the authors interpreted as symptoms caused by other diseases (bacterial overgrowth, irritable bowel syndrome …). Accordingly, they believe that the use of CE avoided unnecessary treatments, and recommended that every patient with Crohn's disease should undergo CE early in the evolution of the disease, in order to have an accurate evaluation of disease extension. Nevertheless, this study has a retrospective design and does not describe a follow up, so the results must be interpreted with caution[19].

Another major advantage of CE is that being comparable to other radiographic methods in the assessment of activity in patients with established Crohn's disease[17], it offers of no radiation exposure[33].

Capsule endoscopy may also be useful to determine early postoperative recurrence of Crohn's disease. In one prospective study, CE was more sensitive in the detection of proximal lesions, but ileocolonoscopy was more sensitive overall[34]. Accordingly, the ICCE consensus

recommended to consider CE only if ileocolonoscopy is contraindicated or unsuccessful[20].

INFLAMMATORY BOWEL DISEASE-UNCLASSIFIED

Population-based studies have shown that in 4%-10% of adult patients with inflammatory bowel disease affecting the colon, it is impossible to distinguish between Crohn's disease and ulcerative colitis using current diagnostic techniques. In children, this group accounts up to 30% of patients. The determination of the definitive diagnosis has implications in terms of medical and surgical therapy, as well as in the clinical outcomes[35,36]. Obviously, when a total colectomy is being considered, this differentiation is essential. Therefore, CE can be helpful in this setting, although a negative study does not exclude a future diagnosis of Crohn's disease[20].

Nevertheless, the papers published in this field are all retrospective and have enrolled only a small number of patients, with neither control groups nor a systematic exclusion of CMV infection. The authors used the Mow criteria for the diagnosis, which cannot reliably exclude a future diagnosis of Crohn's disease[37,38]. These concerns make the conclusions established in these papers weak, and firm recommendations can not be offered.

Nonetheless, in the most important of these studies[37], 10% of patients were previously diagnosed with ulcerative colitis with atypical symptoms, 9% of patients with refractory ulcerative colitis, 33% of patients with a previous colectomy and new symptoms, and 17% with Inflammatory bowel disease unclassified (IBDU) who were reclassified as Crohn's disease patients. In view of these results, a better presurgical diagnosis is critical in this situation.

ROLE OF CE IN UC

The diagnosis of UC does not require a CE. Nevertheless, some experts advocate small bowel imaging in patients with ulcerative colitis prior to elective colectomy for medically refractory cases. CE may also be indicated in UC patients with unexplained anemia or abdominal symptoms[20,38]. Minimal mucosal abnormalities in patients with UC after an ileal pouch-anal anastomosis do not predict the outcome, with no clear clinical significance[20].

Despite the absence of strong evidence, it seems reasonable to perform CE in patients with ulcerative colitis who experience atypical symptoms or have medically refractory disease, if there are no contraindications to the procedure[38,39].

COMPLICATIONS OF CE IN PATIENTS WITH CROHN'S DISEASE

Contraindications for CE include having a known or suspected gastrointestinal tract obstruction and/or known small bowel strictures, because of the increased risk of capsule retention in such patients[40]. The overall rate of retention is variable between the different studies, but it has been estimated in 1.8%-5.8% of the procedures for any indication[20]. The retention rate is low in patients with suspected Crohn's disease, but it can increase up to 13% in patients with known Crohn's disease, despite a normal radiographic study[41,42]. For this reason, in cases were there are doubts about the possible presence of a stricture, it is recommended to prevent possible capsule retention with a patency capsule. The patency capsule is a self-dissolving capsule that is the same size as the video capsule. It contains a radiofrequency identification tag that allows it to be detected by a scanning device placed on the abdominal wall. The tag can also be seen easily with a plain abdominal film. When its passage is blocked by a stenosis, the patency capsule dissolves 40-80 h after ingestion. If strictures are indentified, an alternative method, as enteroscopy, should be considered[20].

A retained capsule endoscopy does not usually cause obstruction, and can remain intact for up to 4 years[7,24]. However, single cases of acute obstruction have been reported, with perforation in some cases[20]. The usual approach for the removal of the retained CE is surgery, but double balloon enteroscopy can be an alternative. An option in patients with known Crohn's disease and strictures might be a medical therapy with steroids or infliximab, but nowadays there is no evidence about the appropriateness of this alternative. Retention should be suspected when the capsule does not reach the colon in the recorded study[24]. In this situation, it is advisable to follow up with a self report of CE excretion or a plain abdominal film after 2 wk. Visualization of the cecum might be a reliable measure for excluding retained CE[20].

FUTURE OF CE IN INFLAMMATORY BOWEL DISEASE

It is fairly clear that capsule endoscopy identifies the earliest inflammatory changes in the small bowel. CE therefore offers the opportunity to diagnose Crohn's disease earlier than ever before, but it remains unclear whether an early diagnosis provides any benefit to the patient. It is currently thought that an earlier diagnosis will bring a better outcome[24]. Another paradigm shift is the change from a symptom-based disease activity estimation to direct monitoring of mucosal healing, with the resulting CE scores activity indexes plus fecal and serum biomarkers, endoscopy and radiology[24].

A better definition of specific lesions in inflammatory bowel disease, indications of the procedure in patients with unspecific symptoms, validation of activity scores, and the technical modifications to allow biopsy sampling are some of the main unresolved questions that will probably be addressed in upcoming papers.

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CASE REPORT

Endoscopic removal of multiple duodenum foreign bodies: An unusual occurrence

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Abstract

Deliberate single foreign body ingestion is a scenario that many gastroenterologists commonly see in psychiatric units and prisons. However, multiple foreign body ingestions, especially located in the duodenum, provide the endoscopist with unique challenges for management and treatment. Although most foreign objects pass spontaneously, one should have a low threshold of intervention for multiple objects, especially those that are wide, sharp and at risk of perforation. Diagnosis is typically made when there is a history of ingestion coupled with corresponding radiographic verification. The symptoms tend to be non-specific although some patients are able to delineate where the discomfort level is, correlating with the site of impaction. Most foreign bodies pass spontaneously; however when multiple sharp objects are ingested, the gastroenterologist should perform endoscopic procedures to minimize the risks of bowel perforation. We describe here a successful case of multiple ingested foreign bodies retrieved across the C-loop of the duodenum and the pharynges-esophageal curve via endoscopy and review the literature of multiple foreign body ingestion.

Key words: Foreign bodies; Multiple; Duodenum; Management; Foreign body ingestions

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INTRODUCTION

Foreign body ingestions are a common feature of many patients who are young, alcoholic or have psychiatric conditions and it is a common scenario many primary care physicians or gastroenterologists see. The dilemma is whether to allow the foreign body to pass spontaneously or to remove it either endoscopically or surgically. We report a case of a schizophrenic prisoner with a history of bowel resection due to past foreign body ingestions who came to the emergency room after swallowing multiple spoons and a ballpoint pen. These were successfully retrieved endoscopically. In this report we review the literature on multiple foreign body ingestions located in the duodenum and possible interventions for endoscopic management.

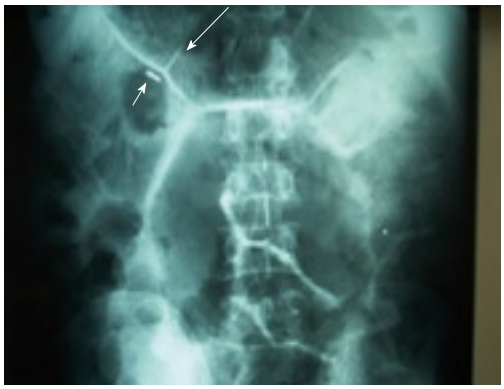

Figure 1 Abdominal X-ray demonstrating the metal part of the pen (short white arrow) and outlines of multiple plastic spoons (long white arrows).

Figure 2 Successful extraction of all the duodenal foreign bodies.

CASE REPORT

A 62-year-old male prisoner with schizophrenia was brought to the emergency room with severe abdominal pain and recurrent vomiting. He has a previous history of several instances of uneventful foreign body ingestions. However, three years ago one such episode resulted in bowel perforations that eventually required colectomy and end ileostomy. Currently he reported ingestion of multiple plastic spoons and a ballpoint pen three days previously. He had dry oral mucosa, normal vital signs and a mildly distended abdomen with no signs of obstruction or peritonitis. Serial abdominal radiographs showed linear outlines of the ingested foreign bodies in the subhepatic region that have not changed in position (Figure 1). These were presumed to be in the second and third parts of duodenum. He had hypokalemia (2.9 mEq/dL) that was corrected with intravenous fluids and potassium supplementation. An upper endoscopy was performed under monitored anesthesia care. Multiple plastic spoons and a ballpoint pen were impacted in the distal C-loop of duodenum. All the spoons were oriented with their handles directed proximally. Using a polypectomy snare to grasp the distal handle of the most accessible spoon, it was gently disimpacted and brought into the stomach. There the snare was reoriented to align the spoon vertically grasping the distal handle about 1 cm from the tip. Then it was gradually brought out across the GE junction up to the pharyngo-esophageal curve where maneuvering the rigid, non-yielding foreign body was difficult. To accomplish the maneuver, the foreign body was held with the snare as far up in the hypopharynx as possible by the endoscopist while the anesthetist introduced grasping forceps through the mouth aided by a direct laryngoscope. The tip of the spoon was grasped with the forceps and gently maneuvered across the hypopharynx without trauma. Four spoons and a ballpoint pen were successfully retrieved by this method, one after the other (Figure 2). Post-procedure check endoscopy showed no significant mucosal trauma or bleeding and a repeat abdominal x-ray confirmed that all the foreign bodies were removed. The patient was counseled against foreign body ingestion and care was transferred to the psychiatry service.

DISCUSSION

In adults, most foreign body ingestion occurs in certain populations: the elderly, mentally disabled, alcoholics, prisoners and psychiatric patients[1-3]. Most foreign bodies will pass spontaneously through the gastrointestinal tract without any complications[1]; in fact, once past the esophagus the majority of foreign bodies ingested will move uneventfully throughout the alimentary canal[4,5]. However, non-operative interventions are still necessary in 10%-20% of patients and surgery in 1%[1], especially in the cases of ingested multiple sharp and long objects.

Timely diagnosis can be difficult as the ingestion goes unreported until the onset of symptoms which may be remote from the actual time of ingestion[6,7]. Radiograph films can identify most foreign objects; however, they do not readily detect fish or chicken bones, wood, plastic, most glass and thin metals objects[8]. Contrast examinations with barium should not be performed routinely because coating the foreign body and esophageal mucosa can compromise the subsequent endoscopy[9]; they should be performed cautiously if symptoms are not clear in order to clarify the presence of a foreign body[10]. CT scans, though commonly used, can be negative with radiolucent objects though their yield can be enhanced with 3D reconstruction[11,12].

Management decision for patients depend on a variety of factors including age, the object ingested, the location of the ingested object, the urgency of removal, the number of objects swallowed and the skill of the endoscopist. The timing should be contingent on the perceived risks of obstruction and/or perforation. Most physicians would prefer the endoscopic route since it avoids surgery, has reduced costs, is relatively accessible, allows simultaneous diagnosis of other diseases and has a low rate of mortality[3]. Endoscopic removal of foreign objects should be performed by experienced endoscopists using accessories such as snares, Dormia baskets or strong-toothed graspers[13]. Objects longer

than 6 to 10 cm such as spoons and toothbrushes should be removed using a longer (> 45 cm) overtube that extends beyond the gastroesophageal junction. The object can be grasped with a snare or basket and maneuvered into the overtube[1]. The entire apparatus, foreign body, overtube and endoscope can then be withdrawn in one motion, avoiding losing grasp of the object in the overtube itself[14]. The endoscopic retrieval of sharp objects is accomplished using retrieval forceps (rat-tooth, biopsy or alligator jaws) or a snare. The risk of mucosal injury during sharp-object retrieval can be minimized by orientating the object with the point trailing during the extraction with an overtube[13]. In the presented case, endoscopic retrieval could have been facilitated by using an overtube but all prison systems are not equipped for advanced endoscopic interventions and lack of it did not deter successful retrieval of the multiple swallowed objects.

Urgent retrieval is necessary to avoid complications of the object ingested. Those patients with a past history of gastrointestinal tract surgery or congenital gut malformations are at an increased risk of obstruction or perforation. Our patient had a past history of gastrointestinal operations, mitigating the possibility of spontaneous evacuation. Additionally, the properties of the objects themselves determine the degree of complications associated with ingestion. Long, slender items have a more difficult time transversing the tortuous gastrointestinal tract; hence they are more likely to stay lodged[4,15]. This is further complicated by ingesting multiple long, slender objects each of which carries the risk of obstruction or perforation. In general, objects wider than 2 cm do not pass though the pylorus and tend to lodge in the stomach while objects longer than 5 cm tend to get caught in the duodenal sweep[16,17]. Additionally, it is recommended that sharp-pointed objects like pens in this case, should be removed even if the patient is asymptomatic[13] as the mortality and the risk of perforations increases with these objects[1,2,5] leading to peritonitis, abscess formation, inflammatory mass formation, obstruction, fistulae, hemorrhage or even death[15,18].

Complicating the clinical picture in this case were the multiple foreign bodies lodged in the duodenum. In reviewing the literature, several retrospective case series did not delineate a clear approach to multiple foreign bodies obstructed in the duodenum. One series involving a retrospective analysis of foreign body ingestions in Greece noted only 2.6% of ingested foreign bodies were lodged in the duodenum[19]; none of these cases involved multiple objects. Similarly a comparison of 1088 cases in China showed that most of the foreign body ingestions were located in the esophagus (53%) while only 4.5% were found in the duodenum[3]. Other series of foreign body ingestions in Italy[20], Bulgaria[15], the United States[21], Korea[22], Jordan[23] and Greece[24] showed similar findings with singular objects ingested. We were able to successfully retrieve multiple objects via endoscopy by manipulating the snare carefully while gently maneuvering the gasping forceps onto the objects, thereby easing the foreign bodies through the hypopharynx individually and avoiding a surgical procedure.

Deliberate ingestion of foreign bodies by prison inmates and psychiatry patients pose unique challenges for endoscopic removal. Though most objects can pass spontaneously, the presentation of symptoms necessitated a treatment option. It is important to evaluate each individual case with respect to the comfort level of the endoscopist and the emergent nature of the intervention. Attempt at endoscopic retrieval is the current standard of care for foreign body ingestions in the absence of features of perforation or major vessel penetration. Impaction of multiple long, rigid objects in the duodenum and their successful retrieval across the C-loop of the duodenum and the pharynges-esophageal curve are the unique features in this reported case.

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CASE REPORT

Choledochal varices bleeding: A case report

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Abstract

Choledochal varices are a rare cause of hemobilia associated with chronic portal vein thrombosis. We present a case of chronic portal vein thrombosis complicated with bleeding from choledochal varices. The presentation, clinical manifestations and management are described.

Key words: Bile duct varices; Portal hypertensivebiliopathy; Common bile duct dilatation; Extrahepatic portal vein obstruction; Endoscopic ultrasound; Hemobilia; Portal vein thrombosis

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INTRODUCTION

Choledochal varices should be considered as a possible cause of obstructive jaundice in patients with history of portal vein thrombosis or hypertension. Diagnosis of choledocal varices can be easily missed by the usual imaging procedures. Unrecognized choledochal varices can lead to bleeding during endoscopic biliary tract procedures. We report a case of bleeding choledochal varices with biliary tree obstruction secondary to chronic portal vein thrombosis. The contribution of endoscopic ultrasound findings towards making a prompt diagnosis is emphasized.

CASE REPORT

A 53 year old man was admitted to hospital with splenomegaly and thrombocythemia in 2001. Ultrasound examination of the abdomen revealed splenomegaly and the absence of blood flow in the main portal vein which suggested portal vein thrombosis. Bone marrow biopsy showed trilineage hyperplasia which suggested myeloproliferative disease. He experienced an episode of esophageal varices bleeding in 2001 which was controlled with multiple banding ligations. He was followed up in the hematology clinic and given hydroxyurea 500 mg daily and propanolol 20 mg three times daily. His regular surveillance endoscopy did not show recurrence of esophageal varices.

In May 2008 he presented with a 2 d history of rectal bleeding. On admission, he was afebrile and hemodynamically stable. Physical examination showed only splenomegaly and a fresh blood clot in the rectum. Blood tests revealed hemoglobin 10.6 g/dL (reference level 13-18 g/dL), platelets 225 × 10^9/L (reference level 150 - 400 × 10^9/L) and total bilirubin 61 μmol/L (reference level 2-23 μmol/L). Serum alanine transferase, alkaline phosphatase and prothrombin time were normal. An upper esophageal gastroduodenoscopy was performed one day after admission. There were three columns of small esophageal varices with no evidence of recent bleeding. No gastric varix was detected. However, active spurting through the ampulla of Vater was noted. Computer tomography (CT) of the abdomen showed mild biliary tree dilatation

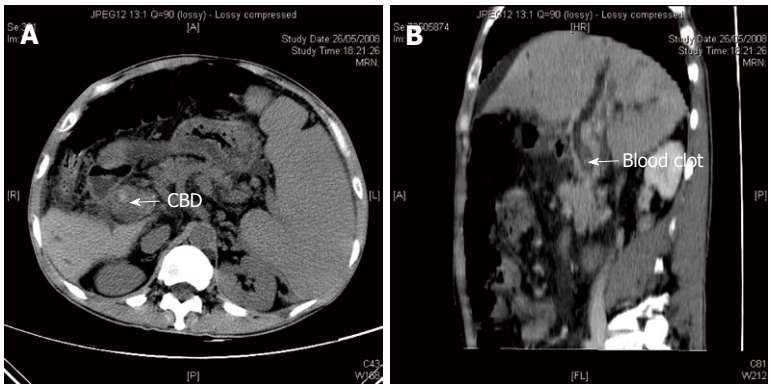

Figure 1 Abdominal computer tomography. A: Non-contrast CT scan showing a hyperdense lesion inside the common bile duct causing upstream biliary dilatation; B: Contrast enhanced CT scan (sagittal view) showed a non-enhanced lesion inside the common bile duct.

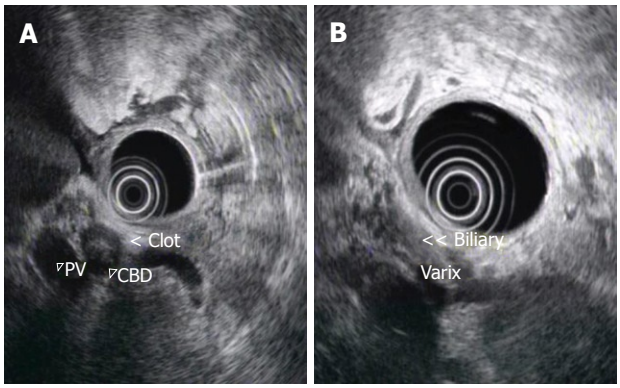

Figure 2 Endoscopic Ultrasound. A: Endoscopic ultrasound image showing the CBD was completely obstructed by the hypoechoic clot; B: Endoscopic ultrasound image showing multiple small anechoic tubular structures around the CBD, consistent with varices.

with intraluminal hyperdensities that suggested a blood clot (Figure 1A and B). Features of chronic portal hypertension which include ascites, splenomegaly, portal venous thrombosis and portasystemic collaterals were seen. No definite liver mass suggestive of a liver tumor was seen. He was given intravenous terlipressin injections and the bleeding subsided after medical therapy. Four days after admission, endoscopic ultrasound (EUS) of the biliary system showed echogenic material with acoustic shadow, consistent with a blood clot inside the common bile duct (Figure 2A). In addition, there were multiple collaterals around the duodenum and common bile duct (Figure 2B) and the main portal vein was occluded. There was no pancreatic mass and no mass extension outside the common bile duct. The splenic vein and superior mesenteric vein were patent. However, he developed a fever, chill and shock on the same day after the EUS. Blood tests showed evidence of cholangitis and disseminated intravascular coagulation. His clinical course was complicated by acute respiratory distress syndrome and multiple organ failure despite percutaneous biliary tree drainage. He died 9 d after admission.

DISCUSSION

We described a man with chronic extrahepatic portal vein thrombosis and choldedochal varices secondary to an underlying haematological thrombotic tendency. He had bleeding from bile duct varices complicated by obstructive jaundice. He died due to cholangitis and multi-organ failure.

There are several causes of hemobilia. Experience from Green's series[1] indicate that trauma during medical procedures is the most common etiology of haemobilia. Other causes include inflammation, gallstone disease, vascular abnormalities and tumor. Bleeding from bile duct varices is relatively rare and to our knowledge, less than 10 case series have been reported[2,3].

Bile duct varices result from abnormal venous dilatation of the bile duct wall when the pressure within the main portal vein is elevated. This is particularly observed in the presence of portal vein obstruction. The extrahepatic bile duct is surrounded by two venous systems, namely the paracholedochal veins of Petren[4] and the epicholedochal venous plexus of Saint[5]. The paracholedochal veins are extrinsic to the bile duct wall so dilatation of these veins results in extrinsic compression on the common bile duct. Saint plexus on the other hand, is a fine reticular venous network covering the outer surface of the common hepatic and bile duct. When the portal vein is obstructed, these plexus dilate and bypass the occlusion. Occasionally this abnormal dilated venous structure may bleed and cause mechanical obstruction.

Although choledochal varices may be an incidental finding of imaging, its occurrence can result in several clinical consequences. Firstly, case reports reveal that unrecognized bile duct varices may lead to excessive hemorrhage during surgery of bile duct[6]. Secondly, choledocal varices may compress the bile duct lumen and result in obstruction and jaundice[7]. Moreover, bleeding from the bile duct can be fatal and can be spontaneous or secondary to endoscopic procedure. The possibility of procedure induced bleeding was highlighted by a report of a case of severe bleeding resulting from endoscopic bile duct dilatation[8]. Finally, the variable appearance of choledochal varices on cholangiogram can lead to a diagnostic dilemma. Classically, choledocal varices appear as smooth extrinsic compression on cholangiogram. However, an appearance resembling primary sclerosing cholangitis has been reported. Liver biopsy of these patients showed features of small bile duct disease. One

possible explanation is a direct compressive injury to the bile duct by porta cavernoma or ischaemic injury secondary to poor venous drainage. In addition, bile duct angulation and displacement (pseudo cholangiocarcinoma sign) has been reported in the case of bile duct varices which render its differentiation from malignant biliary stricture difficult.

Diagnosis of choledochal varices relies on high clinical suspicion, typical cholangiogram appearances and evidence of extrahepatic portal venous obstruction and collateral venous circulation on imaging. The role of endoscopic ultrasound in diagnosis had been described by Palazzo *et al*[9]. It is advantageous over other imaging modalities by allowing better visualization of the portal vein and bile duct anatomy and the relationship of the dilated venous collaterals or varices with the bile duct and duodenum. Besides, EUS can also detect unrecognized malignant tumors in patients with extrahepatic portal venous obstruction of undetermined origin or thrombosis that has not been previously recognized in a CT scan[10].

Treatment is usually offered when complications develop. For patients with jaundice due to obstruction by bile duct varices, treatment options include portosystemic shunting and hepaticojejunostomy. Portosystemic shunting can be achieved by transjugular or surgical methods. Regression of bile duct varices following transjugular intrahepatic portosystemic shunting has been reported[11]. For a patient presenting with variceal bleeding, both endoscopic sclerotherapy and portasystemic shunting are an effective treatment of choice[12].

In conclusion, we report a case of haemobilia due to choledochal varices complicated with common bile duct obstruction and cholangitis. Choledochal varices should be included in the differential diagnosis of haemobilia or unexplained CBD stricture, especially in the presence of portal hypertension. It is particularly important since unrecognized choledochal varices may result in hemorrhage during endoscopic procedures involving the bile duct.

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January 25-29
Waikoloa, HI, United States
Selected Topics in Internal Medicine

January 26-27
Dubai, United Arab Emirates
2nd Middle East Gastroenterology Conference

February 11-13
Fort Lauderdale, FL, United States
21th Annual International Colorectal Disease Symposium

February 26-28
Carolina, United States
First Symposium of GI Oncology at The Caribbean

March 05-07
Peshawar, Pakistan
26th Pakistan Society of Gastroenterology & Endoscopy Meeting

March 12-14
Bhubaneswar, India
18th Annual Meeting of Indian National Association for Study of the Liver

March 25-28
Beijing, China
The 20th Conference of the Asian Pacific Association for the Study of the Liver

March 27-28
San Diego, California, United States
25th Annual New Treatments in Chronic Liver Disease

April 07-09
Dubai, United Arab Emirates
The 6th Emirates Gastroenterology and Hepatology Conference, EGHC 2010

April 14-17
Landover, Maryland, United States
12th World Congress of Endoscopic Surgery

April 14-18
Vienna, Austria
The International Liver Congress™ 2010

April 28-May 01
Dubrovnik, Croatia
3rd Central European Congress of surgery and the 5th Croatian Congress of Surgery

May 01-05
New Orleans, LA, United States
Digestive Disease Week Annual Meeting

May 15-19
Minneapolis, MN, United States
American Society of Colon and Rectal Surgeons Annual Meeting

June 04-06
Chicago, IL, United States
American Society of Clinical Oncologists Annual Meeting

June 16-19
Hong Kong, China
ILTS: International Liver Transplantation Society ILTS Annual International Congress

June 20-23
Mannheim, Germany
16th World Congress for Bronchoesophagology-WCBE

August 28-31
Boston, Massachusetts, United States
10th OESO World Congress on Diseases of the Oesophagus 2010

September 10-12
Montreal, Canada
International Liver Association's Fourth Annual Conference

September 11-12
La Jolla, CA, United States
New Advances in Inflammatory Bowel Disease

September 16-18
Prague, Czech Republic
Prague Hepatology Meeting 2010

September 23-26
Prague, Czech Republic
The 1st World Congress on Controversies in Gastroenterology & Liver Diseases

October 07-09
Belgrade, Serbia
The 7th Biannual International Symposium of Society of Coloproctology

October 15-20
San Antonio, TX, United States
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October 23-27
Barcelona, Spain
18th United European Gastroenterology Week

October 29-November 02
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Acknowledgments

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

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No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http//www.cdc.gov/ncidod/EID/eid.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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Write as mean ± SD or mean ± SE.

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