Ectopic varices CME

Majid Abdulrahman Almadi, MBBS, MSc, FRCPC, Abdulqader Almessabi, MBBS, FRCPC, Philip Wong, MD, MSc, FRCPC, Peter M. Ghali, MD, MSc, FRCPC, Alan Barkun, MDCM, MSc, FRCPC

Montreal, Quebec, Canada; Riyadh, Kingdom of Saudi Arabia; Abu Dhabi, United Arab Emirates

One manifestation of portal hypertension, gastroesophageal varices, accounts for significant morbidity and mortality caused by bleeding in this patient population. Although uncommon, ectopic varices can involve any other part of the GI tract and are challenging for clinicians to identify, diagnose, and manage. Missing or misinterpreting these lesions can carry grave consequences, and the management options for these lesions are unclear in the literature. In this article, we review the vascular anatomy of the portal venous system, the etiologies of portal hypertension, and the parts of the GI tract that could be involved with ectopic varices. Different diagnostic modalities as well as pharmacologic, endoscopic, angiographic, and surgical management options are discussed.

INTRODUCTION

Portal hypertension (PHT) exhibits many manifestations. One of the most clinically serious is the development of portosystemic shunts in the form of GI varices. Bleeding from a variceal source represents 6%[1] to 14%[2] of upper GI bleeding. Although the majority of cases originate from varices located at the gastroesophageal junction or the fundus of the stomach,[3,4] they do occur at other sites throughout the GI tract. The term ectopic varices (ECV) has been used[5] to describe variceal veins other than those found in the esophagus and stomach. Such lesions, although rare, represent a clinical challenge because they are more difficult to locate, occur at distal sites, and, when identified, the choice of therapeutic intervention is unclear. The consequences of missing or misinterpreting these lesions can be grave, with a mortality rate reaching 40%.[6,7]

Abbreviations: ECV, ectopic varices; PHT, portal hypertension; OR, odds ratio; PSC, primary sclerosing cholangitis; PVT, portal vein thrombosis; SMV, superior mesenteric vein; TIPS, transjugular intrahepatic portosystemic shunt; VCE, video capsule endoscopy.

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The majority of the literature is limited to case reports and small series because of the rarity of these lesions. This article addresses the different diagnostic modalities used for the identification of ECV, as well as the pharmacologic, endoscopic, angiographic, and surgical management options for ECV.

Most of the quoted prevalences,[8-14] prognoses, and therapies for ECV are based on series that predated current endoscopic technology such as video capsule endoscopy (VCE). Estimates have varied greatly in the literature[8,11,12,15,16] because of the heterogeneous patient populations, significant interobserver variability,[17,18] differing underlying etiology for PHT,[15,19,20] and variability in the diagnostic modality used. In addition, the majority of these reports originate from tertiary care centers with highly selected patient populations. All of these factors make it difficult to appreciate the true prevalence of these lesions. Different areas of ECV are the duodenum, jejunum, ileum, colon, rectum, peristomal, biliary tree, peritoneum, umbilicus, falciform ligament, bare area of the liver, splenic ligament, urinary bladder, right diaphragm, ovary, vagina, and testis.[21]

VASCULAR ANATOMY OF THE PORTAL VENOUS SYSTEM

The venous drainage of the GI tract from the distal esophagus to the proximal rectum is mainly through the portal venous system that flows to the liver and subsequently to the systemic venous system through the hepatic veins to the inferior vena cava. These veins start from the capillaries that form a dense submucosal venous plexus in the GI wall and then short veins that penetrate the muscular layer of the intestine, mainly on the mesenteric border and subsequently into major veins.[22]

The veins composing the portal venous system as well as the organs that are drained by those veins are shown in Table 1.

ETIOLOGIES OF VARICOSE VEINS IN THE GI TRACT

Portosystemic collaterals are present in the normal state, but because of their small size and the high vascular resistance in this venous bed compared with the low-pressure system of the portal venous system, blood flows

TABLE 1. The portal venous system and the organs that are drained by those veins

	Major branches	Second-order branches		Organs
Portal vein	Splenic vein	Short gastric		Fundus Left part of the greater curvature of the stomach
		Left gastroepiploic		Anterosuperior and posteroinferior surfaces of the stomach Greater omentum
		Pancreatic		Body and tail of the pancreas
		Inferior mesenteric	Left colic	Descending colon
			Superior rectal	Hemorrhoidal plexus of the rectum
	Superior mesenteric vein	Right gastroepiploic		Lower parts of the anterosuperior and posteroinferior surfaces of the stomach Greater omentum
		Pancreaticoduodenal		Pancreas Duodenum
		Jejunal		Jejunum
		Ileal		Ileum
		Middle colic		Transverse colon
		Right colic		Ascending colon
		Ileocolic (appendicular)		Ileum Cecum
	Direct draining veins	Cystic		Gallbladder
		Left gastric/esophageal		Lesser curvature of the stomach Lower esophagus
		Right gastric		Lesser curvature of the stomach
		Paraumbilical		Veins of the anterior abdominal wall

preferentially in a hepatopetal manner. In the case of PHT and because the portal vein contains no valves, the blood flows around the liver through collaterals with the lowest resistance. The areas where major shunts occur between the portal and systemic venous system are shown in Table 2 and are commonly the gastroesophageal junction, rectum, paraumbilical, and retroperitoneal areas. In PHT, the deep intrinsic veins in the mucosa of the GI tract become massively enlarged and develop into the tortuous variceal channels.[22] Furthermore, the number and size of vessels in the lamina propria are increased,[23] and the meshwork of the superficial venous plexus that is present in the normal state is replaced by a more longitudinal arrangement of veins in patients with varices[22]; this could indicate that they are acting as collateral channels.[22] Individuals with gastric varices tend to have large gastrorenal shunts,[24] lower portal venous pressures,[24] not related to the degree of hepatic dysfunction[17] compared with those with esophageal varices; this demonstrates the variability in hemodynamics in patients with PHT.[24] The structure of the venous system also differs among segments of the GI tract,[25] which affects the development of varices.

ECV can also develop when segmental blockages in veins of the portal system occur in the absence of PHT. There have been observations that ECV may develop after obliteration of esophageal varices either by sclerotherapy or banding; this is thought to occur because of shunted blood opening other collaterals between the portal and systemic circulations. There is, in addition, a familial form of ECV that involves the entire GI tract.[26-28]

DUODENAL VARICES

In duodenal varices, the afferent vessel originates either from the superior mesenteric vein (SMV) or from the portal vein trunk via either the superior or inferior pancreaticoduodenal vein, whereas the efferent vein drains into the inferior vena cava.[10] A single-center retrospective review of 5664 endoscopic procedures performed over 4 years found the prevalence of duodenal varices to be 1 in every

TABLE 2. Anatomic sites of common portosystemic anastomoses in portal hypertension

Anatomic site	Portal	Systemic
Gastroesophageal junction	Coronary and short gastric veins	Superior vena cava via the azygos vein
Rectum	Superior hemorrhoidal	Middle and inferior hemorrhoidal
Paraumbilical (caput medusae)	Left portal via a recannulated umbilical vein	Epigastric venous plexus of the abdominal wall
Retzius veins	Retroperitoneal veins connecting the abdominal viscera	Intercostal, phrenic, lumbar, and renal veins

435 endoscopic procedures; 69% had concomitant esophageal varices, whereas the rest were isolated duodenal varices.[9] Results of a survey for ECV conducted over 5 years in Japan identified 57 cases of duodenal varices; they were located in the duodenal bulb in 3.5%, the descending part in 82.5%, and the transverse part in 14.0%[29] (Fig. 1A).

Recognition of these lesions as a source of bleeding can be challenging, with as many as 5 repeated EGDs needed to make the diagnosis.[30]

On percutaneous US, a thickened duodenal wall with a slow, constant blood flow on color Doppler imaging is suggestive of duodenal varices, and when thrombosis of the confluence of the splenic vein and the SMV is detected, duodenal varices should also be suspected.[31]

SMALL-BOWEL VARICES

The diagnosis of small-bowel lesions has been limited in the past because of inaccessibility to advanced imaging modalities, specifically VCE and enteroscopy. Because of this technology, we have come to appreciate the contribution of small-bowel pathology in patients with PHT. The prevalence is estimated to be from 1.9% to 8.7% in patients evaluated for obscure GI bleeding by either VCE and/or enteroscopy,[11,12] whereas in patients with PHT, enteroscopy and VCE demonstrated that 69% had small-bowel varices.[32] In those with persistent anemia, 16% to 26% had small-bowel varices when evaluated by VCE.[33,34] Terminal ileal varices were found in 18% of patients with PHT when the terminal ileum was systematically intubated on colonoscopy.[35]

In patients with GI bleeding and PHT, the presence of esophageal varices without stigmata of bleeding may be the presumed bleeding source; however, a significant proportion of these patients also exhibit small-bowel varices that may in fact have been the origin of bleeding.[36]

Jejunal and ileal varices occur when collaterals form between the SMV, inferior mesenteric vein, and the retroperitoneal systemic venous system, but have also been described in anatomic locations in proximity to surgical anastomoses or adhesions. The usual presentation of hematochezia or melena can occur without PHT, as in the case of splenic vein or segmental mesenteric vein thrombosis, or in congenital vascular malformations.[37]

COLONIC VARICES

The term PHT colopathy (Fig. 2) has been used to describe angiodysplasias and varices in the colon in patients with PHT.[38]

The prevalence of colonic varices has been found to be 34% to 46% in patients with cirrhosis.[13,39,40]

In a case-control study, these lesions were more likely to be found in patients with portal hypertensive gastropathy (odds ratio [OR] 5.64; 95% CI, 3.39-9.41), large esophageal varices (OR 4.76; 95% CI, 2. 78-8.15), and Child-Pugh class C cirrhosis (OR 2.64; 95% CI, 1.40-4.97). They were less common in patients receiving β-blockers (OR 0.23; 95% CI, 0.13-0.40).[41] However, these variables were not found to be statistically significant in other series[16,40] and need validation in larger studies.

RECTAL VARICES

These result from communication between the superior hemorrhoidal vein (draining into the portal system via the inferior mesenteric vein) and the middle or inferior hemorrhoidal vein that drains into the systemic vasculature via the internal iliac veins to the inferior vena cava.

Rectal varices (Fig. 3A,B) have been defined as variceal veins extending more than 4 cm above the anal verge,[19] are dark blue in color, and do not prolapse into the proctoscope on examination. In contrast, hemorrhoids are vascular cushions composed of arterial and venous anastomoses that do not communicate with the portal venous system, often prolapse into the proctoscope, are purple in color, and do not extend proximal to the dentate line.[42,43]

Failure to differentiate between rectal varices and hemorrhoids could delay appropriate management and result in preventable mortality.[44]

A case-control study demonstrated that among patients with PHT, those without cirrhosis were more likely to have anorectal varices compared with those with cirrhosis (89% and 56%, respectively).[15] Rectal varices have been found more frequently in the presence of portal vein thrombosis (PVT) compared with those with cirrhosis or noncirrhotic PHT (80%, 28%, and 30%, respectively),[19] whereas another case series of patients with PHT did not find such an association.[16]

Figure 1. A patient with duodenal varices confirmed by EUS with Doppler imaging and treated endoscopically. **A,** An image of a duodenal varix in the descending, second part of the duodenum appearing as a spherical bulge. **B,** The same duodenal varix that bled. There is a visible vessel in the ulcer; this resulted from a previous band ligation of the varix. **C,** The same varix in the duodenum that has been clipped successfully. **D,** The same varix in **B** and **C** 1 week after endoscopic hemostasis using clips. Most authors recommend banding or injection therapy. **E,** EUS image of the duodenal varix in **A** through **D**.

GALLBLADDER AND COMMON BILE DUCT VARICES

Gallbladder varices develop when shunting occurs between the cystic vein (a branch from the portal vein) and either anterior abdominal wall veins that represent the systemic circulation or the portal vein branches within the liver itself.[45]

It is thought that they are more prevalent in cases of PVT than in other causes.

In the majority of cases, they are incidental findings, but, if unrecognized, may result in significant morbidity in the event of elective or urgent surgeries (ie, cholecystectomies).

On cholangiography, bile duct varices may be visualized as multiple, smooth, mural filling defects with narrowing and irregularity resulting from compression of the portal vein and

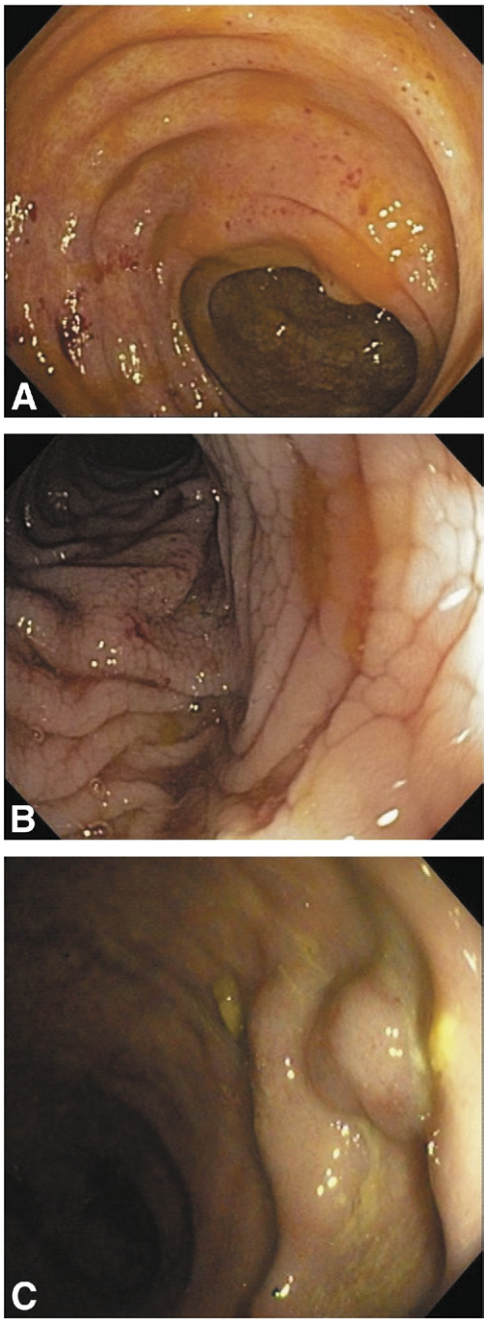

Figure 2. A, Portal hypertensive colopathy as evident by edematous mucosa with red spots. **B,** Mosaic-like reticular pattern of the mucosa of the colon. **C,** A colonic varix manifested as a localized prominence.

the collateral vessels. They may mimic primary sclerosing cholangitis (PSC) or cholangiocarcinoma (pseudocholangiocarcinoma[46]). Extrahepatic biliary obstruction, cholangitis, and hemobilia have been described.

STOMAL VARICES

These varices develop in the mucocutaneous junction of a stoma in patients with coexisting PHT[47,48] or in the area proximal to the stoma.[49]

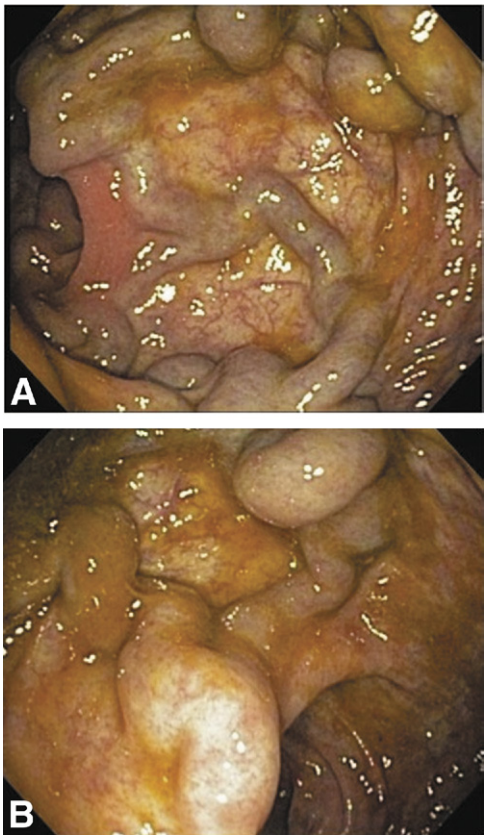

Figure 3. A and **B,** Rectal varices appearing as serpiginous, dilated, blue-colored veins.

In patients with PSC who had undergone a colectomy for associated pancolitis, peristomal varices developed in 27%.[50]

In another case series of 117 patients with chronic liver disease who had colon surgery with either a surgical stoma or primary colonic anastomosis, stomal and/or esophageal varices developed in 31% of patients with a stoma compared with 15% of those with a primary anastomosis. Furthermore, patients who bled from peristomal varices rebled more frequently and required more transfusions, despite the presence or absence of bleeding from esophageal varices, compared with those who bled only from esophageal varices. However, because the incidence of rebleeding was similar between both groups, these differences could be related to the underlying severity of liver disease that precluded the creation of a primary colonic anastomosis.[51]

When the bleeding site with suspected peristomal varices cannot be seen on visual inspection, US should be performed to confirm the presence of stomal varices as well as to evaluate the cause of PHT.[52]

Risk factors for the development of peristomal varices in patients with PSC who had undergone a colectomy for ulcerative colitis were splenomegaly, esophageal varices, advanced histological stage at liver biopsy, low serum albumin, thrombocytopenia, and an increased prothrombin time.[50]

MANAGEMENT OF AN ECTOPIC VARICEAL RUPTURE

As in any patient with hemorrhage, general supportive measures are critical and include appropriate resuscitation with crystalloid or other blood products, management of altered level of consciousness if present, and admission to a monitored setting. In the case of patients with cirrhosis, extrapolating from the esophageal varices literature, initiation of prophylactic antibiotics should not be overlooked[53] to prevent sepsis.

PHARMACOLOGIC INTERVENTIONS

Based on published practical guidelines for the optimal treatment of gastroesophageal varices and variceal bleeding, initiation of somatostatin or its analogs may be beneficial when a variceal source of bleeding is suspected and continued for 3 to 5 days after confirmation.[53] Octreotide has been shown to be effective in the control of bleeding colonic varices.[54]

ENDOSCOPIC INTERVENTIONS

Endoscopy provides both diagnostic information and the potential for therapy. Guidelines for the management of gastroesophageal varices, and variceal bleeding state that endoscopy should be performed within 12 hours of presentation[53]; adherence to such recommendations is expected to be beneficial with any suspected variceal source of bleeding. In areas beyond the reach of conventional endoscopic procedures, enteroscopy can be performed electively.[36]

Injection sclerotherapy has been used successfully in controlling bleeding varices in the duodenum[55,56] and small bowel and in controlling peristomal varices with no injury to the stoma from the sclerosant used.[52] Materials used for injection have included bucrylate,[57-59] thrombin,[60,61] ethanolamine,[61] and *N*-butyl-2-cyanoacrylate (Histoacryl; TissueSeal, Ann Arbor, MI).[56,62,63] This modality, although simple, has the potential to cause systemic bacteremia or, in the case of Histoacryl injection, embolization.

Band ligation,[21,65-67] although successful in halting bleeding, is of limited use when the ECV is larger than 15 mm. Furthermore, it does not obliterate the feeding vessel, and its application may be difficult in the acute setting because of limited visibility from the banding hood, and accidental banding of the major papilla has been reported, causing biliary obstruction.[68]

Clipping can be easily applied but has the potential of further potentiating bleeding while having drawbacks similar to those of banding[69] (Fig. 1B-D).

The success rate of these procedures has not been studied in controlled trials, so the choice of endoscopic therapy is dependent on individual expertise, location of the ECV, and the technical feasibility.[69]

EUS can be used to better localize and differentiate ECV from other bleeding mucosal lesions (Fig. 1E).[67,70,71] In patients with rectal varices, EUS is a more sensitive diagnostic study than conventional white light endoscopy because it demonstrates the ECV as round or ovoid, tortuous, anechoic structures with an increase in the size of submucosal and perirectal vessels without associated wall thickness or without necessarily detecting the presence of perforating veins.[14,39,72] Furthermore, EUS can be used to apply a sclerosant or coils when adequate visualization is not possible with conventional endoscopy.[64,73] EUS is also useful to follow up therapy of the varix after therapy.

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT

Transjugular Intrahepatic Portosystemic Shunt (TIPS) has been successful in decompressing the portal system and controlling variceal bleeding in patients with ECV.[52,74-77] In a case series, TIPS resulted in a decreased need for repeated procedures in patients with ECV, including peristomal varices, with rebleeding rates in this group averaging 23% and 31% at 1 and 2 years, respectively.[78] Depending on the cause of PHT, TIPS carries the risk of hepatic decompensation and encephalopathy[79] and may not be suitable for patients with isolated gastric varices (for whom splenectomy would be more appropriate) or in cases of ECV caused by focal venous obstruction.

The outcome of TIPS is worse in patients with more advanced Child-Pugh scores[79,80] and is contraindicated in patients with PVT or advanced cardiac or renal disease. The stent may also occlude, either spontaneously or in patients with gastrorenal or splenorenal shunts, requiring reintervention.[79,81]

ROLE OF RADIONUCLEOTIDE SCANS AND ANGIOGRAPHIC INTERVENTIONS

In patients in which the primary site of bleeding could not be localized on initial endoscopy, radionucleotide scans,[82] or angiography can be used based on the expected rate of bleeding.

Angiography can provide both diagnosis and therapeutic intervention. The angiographic evaluation of ECV can be performed via either direct visualization of the venous system through transhepatic portography or indirect visualization of the venous phase after splenic and/or mesenteric arteriography. It provides information about splenic vein patency, and transhepatic portal venography has been used to confirm ECV by finding abnormal splanchnic vessels feeding from either the SMV or the inferior mesenteric vein with a hepatofugal flow.[83]

Balloon-occluded retrograde transvenous obliteration, although initially developed for the management of gastric varices, has been used with success in occlusion of the feeding vessels in ECV.[67,75,84-87]

After an initial angiographic intervention, embolization of the veins draining into the ECV with coils, 100% alcohol, or Gelfoam (Pfizer, New York, NY) or a combination of these is indicated when the ECV persist despite a portosystemic pressure gradient decrease to less than 12 mm Hg or 25% to 50% reduction from baseline measurement or if bleeding from the ECV recurs.[83,88]

SURGICAL INTERVENTIONS

In instances in which all other approaches have failed, surgical resection or ligation remains an option in controlling the bleeding ECV.[89,90]

In patients with ECV secondary to splenic vein thrombosis from chronic pancreatitis, some have advocated splenectomy because the risk of variceal bleeding exceeds that of surgery.[91]

In patients with peristomal varices, local measures to control bleeding are usually effective with the initial application of pressure and when positioning the patient in a recumbent position. If the bleeding vessel can be visualized, ligation or cautery is effective.[52] If surgical revision or relocation of the stoma is attempted, recurrence of bleeding is common.[52] Portosystemic shunt surgery has been used successfully to control bleeding[47,48] and has the lowest incidence of both rebleeding and need for additional procedures compared with other interventions.[92] This approach, however, is associated with an increased operative risk from underlying liver disease and a potential for hepatic decompensation.

In rectal varices, surgical staples have been used successfully.[93,94]

Extrapolating from existing guidelines for variceal bleeding, depending on the cause and degree of liver dysfunction, liver transplantation may be the last resort for correcting the underlying PHT with restoration of normal liver function.[53]

In the rare case of rupture of an intraperitoneal varix, a high index of suspicion is required. These patients usually present with hemodynamic instability, increased abdominal distention, a decrease in hemoglobin, and bloody ascites. Surgical exploration attempting to locate and ligate the bleeding varix may represent the only option.[95]

PROGNOSIS

The mortality associated with ECV bleeding is unclear because of the limited literature and short follow-up of what are most often highly selected patients. It is undoubtedly affected by the underlying severity of liver disease.

PRIMARY AND SECONDARY PREVENTION OF BLEEDING FROM ECV

It is unclear whether the management of ECV should differ from that of esophageal varices. The management options that have been recommended for patients with PHT and esophageal varices,[53] although not formally studied in patients with ECV, appear reasonable. In the case of peristomal varices, a systematic review found that the use of β-blockers as monotherapy was associated with recurrent bleeding, but there were no reports on the use of octreotide in this setting.[52]

CONCLUSIONS

The diagnosis of ECV requires a high index of suspicion and may require multimodality imaging or repeated endoscopies. The management of ECV rupture is poorly characterized but includes traditional pharmacological, endoscopic, and angiographic methods with surgery for highly selected cases. Additional data are required to better define the optimal tailored management and prognosis of these patients.

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Current affiliations: Division of Gastroenterology (M.A., A.A, P.W., P.M.G., A.B.), McGill University and the McGill University Health Centre, Montreal, Quebec, Canada, Division of Gastroenterology (M.A.), King Khalid University Hospital, King Saud University, Riyadh, Kingdom of Saudi Arabia, The Division of Hepatology (A.A.), Mafraq Hospital, Abu Dhabi, United Arab Emirates.

Reprint requests: Dr. Majid Abdulrahman Almadi, MBBS, FRCPC, Division of Gastroenterology, McGill University Health Center, Royal Victoria Hospital, 687 Pine Avenue West, Montreal, QC H3A 1A1, Canada.