SAJS

Review

Complications of endoscopic variceal therapy

J. E. J. KRIGE, M.B. CH.B., F.A.C.S., F.R.C.S. (ED.), F.C.S. (S.A.)
P. C. BORNMAN, M.B. CH.B., F.R.C.S. (ED.), F.R.C.S. (GLASG.), F.C.S. (S.A.), M.MED. (SURG.)
J. M. SHAW, M.B. B.CH., F.C.S. (S.A.)
C. APOSTOLOU, M.B. CH.B., F.C.S. (S.A.)

Department of Surgery, University of Cape Town, MRC Liver Research Centre and Surgical Gastroenterology Unit, Groote Schuur Hospital, Cape Town

Bleeding from oesophageal varices is the most serious complication of portal hypertension and is the leading cause of cirrhosis-related deaths.[1-3] One-quarter of cirrhotic patients who present with a first major variceal bleed die as a consequence of the bleed.[3] After control of the index bleed, there is a 70% chance of rebleeding with a similar mortality.[4-6] Survival after variceal bleeding depends largely on the rapidity and efficacy of control of the initial bleed, the presence and severity of underlying liver disease, and hepatic functional reserve.[7,8]

Endoscopic injection sclerotherapy became an established method of controlling variceal bleeding worldwide following the initial prospective studies[9,10] which were started in Cape Town in 1975, and the subsequent first randomised trial initiated in our unit.[11] Endoscopic injection of tissue adhesive was pioneered by Gotlib and Zimmerman[12] in 1984 and Soehendra in Germany in 1986.[13] Endoscopic variceal ligation was introduced by Stiegmann[14] in 1986 in Denver, Colorado.

Endoscopic treatment remains the principal first-line intervention in patients with bleeding oesophageal varices, both during the acute event and for long-term prevention of recurrent bleeding.[2,15] Endoscopic haemostasis of actively bleeding varices has a greater inherent potential for major complications compared with other endoscopic procedures.[16-21] In this article, peer-reviewed publications were assessed to evaluate the incidence, spectrum, consequences and prevention of complications of endoscopic treatment for bleeding oesophageal and gastric varices. An electronic and manual literature search was conducted to identify relevant articles. The electronic search accessed Medline from 1977 to October 2005, Embase from 1980 to October 2005 and the Cochrane Library for randomised controlled trials using a predetermined search strategy. Relevant review articles and the bibliographic references were examined for potential sources.

Endoscopic techniques

Endoscopic sclerotherapy

Endoscopic injection sclerotherapy (EIS) of oesophageal varices is designed to control the initial bleed and prevent subsequent bleeding by thrombosing the veins or thickening the mucosa overlying the veins in this area.[22] EIS using flexible endoscopy may be accomplished by injecting sclerosant directly into the venous channel (intravariceal) or into the submucosa adjacent to a varix (paravariceal), or a combination of both.[23] Most endoscopists perform sclerotherapy without accessories ('freehand technique').[24] Sclerotherapy is performed with different levels of skill and protocols using variable frequencies of injections and endoscopic surveillance.[24] Several technical variables may affect the outcome of any individual sclerotherapy session or clinical trial.[25] These variables include the type and concentration of the sclerosant solution, the injection site, injection volume and frequency of injections.[23] Despite the widespread popularity of the procedure for control of acute variceal bleeding, sclerotherapy technique remains, to a great extent, empiric and individualised. Several basic issues of methodology remain largely unanswered.[26] It is therefore not surprising that controlled trials comparing sclerotherapy with other specific therapies, including variceal ligation, have yielded conflicting results.[27]

A variety of sclerosants are used with different mechanisms of action and varying complication rates.[1,2,5] Tetradecyl sodium (1 - 3% solution), sodium morrhuate (5% solution) and ethanolamine oleate (5% solution) are the most commonly used sclerosant agents in the USA.[21] Outside North America, 5% ethanolamine oleate and 1% polidocanol are used; polidocanol is usually used for paravariceal injections. The ideal sclerosant and the best route of administration have yet to be defined, although the few controlled trials available favour ethanolamine oleate for intravariceal and combined therapy.[27]

Endoscopic tissue adhesive injection

Since their discovery in 1949, cyanoacrylates have been used as a tissue adhesive, embolisation material, and haemostatic agents in a broad range of medical specialties including orthopaedics, plastic and facial surgery, vascular surgery and interventional radiology.[28,29] Tissue reactivity and toxicity of the short-chain cyanoacrylate monomers led to the synthesis of less histotoxic long-chain monomers, of which Histoacryl is the least histotoxic of the cyanoacrylate polymers available commercially. Two types of tissue adhesives, Histoacryl and Bucrylate, have been used to treat variceal bleeding[28] (Fig. 1). These have proved effective in the control of bleeding with a 90% success rate.[2] The fundamental technique of tissue

adhesive injection using *N*-butyl-2-cyanoacrylate (Histoacryl) is the same as sclerotherapy. Gotlib and Zimmerman first described the use of Bucrylate for endoscopic obliteration of oesophageal varices,[12] and Soehendra *et al*. reported its use for gastric varices.[13] The cyanoacrylate polymers have a viscosity and appearance similar to water. Polymerisation occurs on contact with water to form a solid complex tightly bound to underlying tissue. Polymerisation is almost immediate in blood. Experimental and clinical studies have shown that cyanoacrylate polymers have both bacteriostatic and haemostatic activity.[28] Patients and personnel working with Histoacryl require eye protection or goggles as a precaution against inadvertent spraying of tissue adhesive during injection. Since the liquid tissue adhesive solidifies rapidly, any delay in withdrawing the injection needle from the varix after injecting the adhesive may result in the needle being trapped in the solidified cyanoacrylate mass. Leakage of adhesive may block the working channel of the endoscope and irreparably damage the instrument. This can be avoided by lubricating the insertion tube liberally with silicone oil and aspirating oil through the working channel. To prevent premature solidification during injection, Histoacryl is diluted with the oily contrast agent Lipiodol.

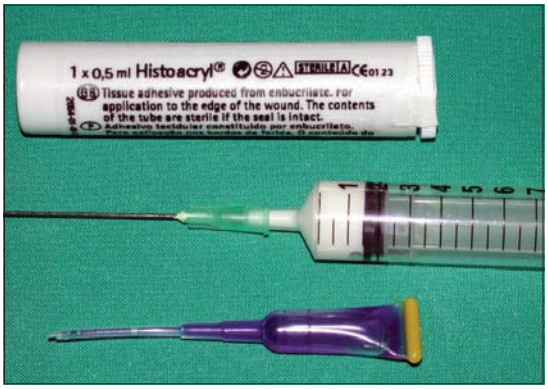

Fig. 1. Histoacryl tissue adhesive for endoscopic intravariceal injection.

Endoscopic variceal ligation

Endoscopic variceal ligation (EVL) was developed as an alternative endoscopic method of treating oesophageal varices with the anticipation that EVL would be as effective as EIS, but with fewer complications.[14] EVL uses small elastic 'O' bands which are stretched and loaded onto a cylinder attached to the tip of an end-viewing endoscope[30] (Fig. 2). The varix is sucked into the cylinder, ensnared when the band is dislodged, and strangulated, leading to necrosis and sloughing of the thrombosed varix and band about a week later (Fig. 3). Six to eight elastic bands can be applied to the variceal columns during each endoscopy session.[31]

Compared with sclerotherapy, EVL is less invasive because no sclerosant or sclerotherapy needle is used.[32] However, there are technical drawbacks with EVL. The original single-band ligating device required repeated removal of the endoscope for reloading and reinsertion each time a new band was applied.[33] An oesophageal overtube facilitated reintroduction but increased patient discomfort. Reloading the single-band ligator also prolonged the procedure, which was problematic especially during active bleeding or with poor patient tolerance. The single-band ligator has been replaced in most centres by the multiple-band ligator which carries six to ten bands (Fig. 4) and avoids the use of an overtube.[34] A practical limitation of EVL is the suction cap on the tip of the endoscope, which reduces the field of vision by 30% and is a disadvantage when treating actively bleeding varices as blood and clot may pool in the suction cap and further reduce visibility. The new transparent caps have improved visibility. The standard disposable multiband ligators release individual bands by shortening the towlines around a rotating spindle mounted in the accessory port. In contrast, the recently available Euroligator[15] is re-usable and releases each band by turning a wheel on the driver which applies tension to incrementally withdraw a flexible metal shaft.

Fig. 2. Single-band endoscopic ligator. Inner banding cylinder illustrated with loaded 'O' ring ready for deployment.

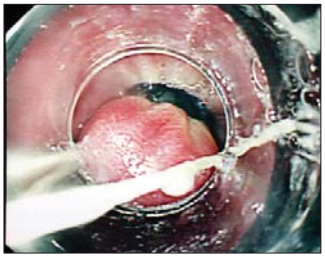

Fig. 3. Banded varix viewed through a multiband suction cap.

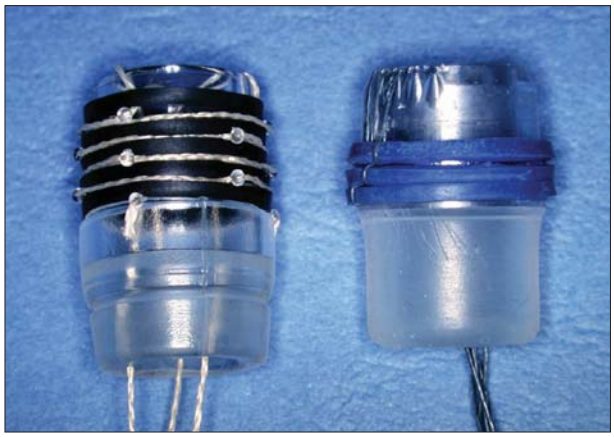

Fig. 4. Loaded 'O' rings on multiband ligator application caps.

Incidence of complications after endoscopic therapy

There is no consensus regarding the definition or classification of the complications that occur after the endoscopic treatment of oesophageal and gastric varices, and consequently the incidence varies widely in reported studies.[21] Much of the published data are flawed because the reporting process is often biased with subjective and retrospective information, and complication rates are generally operator dependent.[35] Comparative analyses of complication rates are hampered by variations in patient population, type and severity of liver disease and endoscopic technique used.[21] In

addition, differences in study design introduce a covert selection bias which may influence results. These biases include sampling and selection bias (specialist centres, expert endoscopists, different patient populations) confounding bias (emergency versus elective procedures) and measurement bias[35] (incomplete reporting, delayed complications).

Many patients undergoing endoscopic variceal intervention have a limited prognosis, and therefore complications may not be identified or treated aggressively. The debilitated state of many patients undergoing endoscopic therapy contributes to the medical difficulties they encounter, often making differentiation of a true complication of the procedure difficult.[36] Complication rates are also higher when carefully documented in prospective studies, while some studies express complication rates in terms of incidence per patient treated or per procedure performed.[21] In long-term studies, repeated intervention also increases the cumulative risk of endoscopic-related complications in the individual patient.[37] The most reliable data indicate that 10 - 15% of patients undergoing endoscopic variceal intervention will develop a major complication, but fewer than 1% of patients die as a direct result of the procedure.[21]

Classification of endoscopic complications

Endoscopic-related complications have been categorised as (*i*) local effects involving the oesophagus, including ulceration, stricture and perforation; (*ii*) regional respiratory and cardiovascular effects; and (*iii*) distant or systemic consequences.[21] Minor events have been defined as those that are self-limiting and do not require specific treatment, and do not interfere with the regular injection programme. Major complications are serious or life-threatening events that prolong hospitalisation.[21]

Endoscopic injection sclerotherapy

Important factors influencing the complication rate are the experience of the endoscopist, the specific injection technique employed, the use of ancilliary devices including overtubes or balloon tamponade, and whether sclerotherapy is performed as an emergency or elective procedure.[21] Other interrelated anatomical factors are the close proximity of the oesophagus to vital mediastinal structures, repetitive breaching of the mucosa, and the potential for pulmonary and systemic spread of sclerosant through portal venous collaterals.[2,15,21,27]

Oesophageal complications

Morphological changes

Oesophageal complications of EIS are invariably the consequence of excessive sclerosant-induced submucosal or transmural necrosis.[21] The few studies that have examined the local histopathological effects of sclerosant on the oesophageal wall in detail have been based on autopsy studies. Although the injection techniques, type and volume of sclerosant used, and intervals between injections vary in these studies, the histopathological findings are remarkably similar and provide a time-dependent morphological profile of the effects of EIS on the oesophagus.[38-41]

The earliest changes in the oesophageal wall, which occur during the initial 48 hours after injection of sclerosant, are thrombosis in superficial veins, submucosal oedema, and minor areas of tissue necrosis.[38] Mucosal ulceration is uncommon during this early phase.[42] After 48 hours, progressive tissue necrosis occurs, predominantly in the superficial layers and to a lesser extent in the deeper tissues (Fig. 5). During the first week, mucosal ulceration and a marked acute polymorphonuclear leucocyte inflammatory response occur, which is followed by an intense macrophage and fibroblast infiltration.[38,43] Some residual varices remain patent while others contain thrombi in the early stages of endothelial and fibroblastic organisation.[40,44] The extent of sclerotherapy-induced ulceration varies from small linear superficial defects to extensive ulcers.[40] While most ulcers are limited to the submucosa or inner layer of the muscularis propria, a few extend more deeply into the muscularis propria. A quarter of autopsy specimens show transmural necrosis, which may progress to mediastinitis.[40]

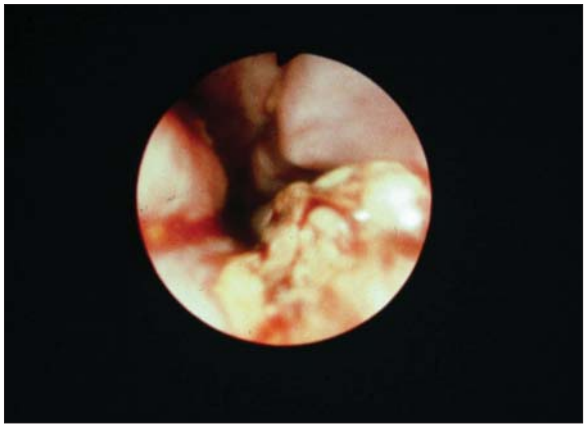

Fig. 5. Mucosal slough at the site of a recent sclerotherapy injection.

The later chronic reaction is characterised by an evolution from granulation tissue to mature collagen with an accompanying chronic inflammatory cell infiltrate that becomes less prominent with time.[43] Necrosis and ulceration may persist for up to 3 weeks. Organised thrombi and fibrosis become evident 1 month after injection.[39,40] Fibrosis is usually limited to the submucosa and the inner muscularis propria but may occur as a localised transmural breach in muscle or as diffuse transmural fibrosis encasing residual varices.[43] Marked thickening of the oesophageal wall is present in some specimens.[42]

Ulceration

Small areas of superficial mucosal ulceration are a common finding in the lower oesophagus after EIS.[43-46] Some reports consider ulceration to be an inevitable and necessary consequence of effective sclerotherapy.[47,48] The prevalence and extent of ulceration is related to the type[49,50] and volume[51,52] of sclerosant injected, method of injection,[53] interval between injections[54-56] and size of varices.[57] Ulceration is reported to occur more frequently in Child's C patients and after injection of large varices.[57] There is evidence that increasing volumes of sclerosant may be implicated in deep ulceration, and the incidence increased with the associated use of balloon tamponade.[58,59]

In a randomised study comparing the two injection techniques, no significant difference was found in the incidence of ulceration between paravariceal and intravariceal injections using 50% ethanol.[53] The risk of ulceration may be related more to the intensity of the sclerotherapy programme

than to the specific injection technique.[53,54] In most instances, minor areas of superficial ulceration are asymptomatic and heal rapidly without the need for specific treatment.[21]

To prevent sclerotherapy-induced ulcers and their complications, sucralfate, H_2-receptor blockers and antacids, alone or in combination, have been used.[60-63] While sucralfate may reduce rebleeding from ulceration, the frequency and extent of ulcers are similar in patients who had not received sucralfate.[63] A controlled trial suggested that ulcer healing may be accelerated by sucralfate, especially in patients with deep ulceration.[61] Ulcers healed more slowly in patients with a serum albumin level less than 3 g/dl.[64]

A small proportion of sclerotherapy-induced ulcers persist, despite prolonged treatment with high-dose H_2-receptor antagonists and sucralfate (Fig. 6). In a small group of patients with complicated chronic ulcers, complete healing was achieved in all after an 8-week course of 40 mg omeprazole daily.[65] The rapid healing of resistant ulcers with omeprazole suggests that such ulcers may be perpetuated by mucosal damage from continuing gastroesophageal reflux. It is suggested that consideration be given to earlier use of omeprazole for post-sclerotherapy ulcers complicated by symptoms or bleeding.[21]

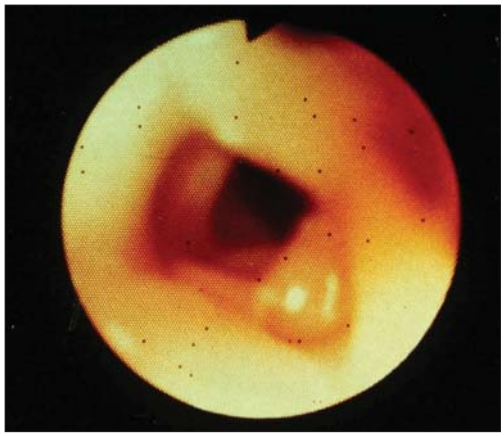

Fig. 6. Mucosal ulceration involving one quadrant of the oesophagus.

Bleeding

Minor bleeding may occur from the needle puncture site after intravariceal injection of large varices, but it usually stops spontaneously. Bleeding that persists can be controlled by an adjacent small-volume submucosal injection or by direct tamponade using the side of the flexed tip of the endoscope. More severe bleeding results from inadvertent variceal laceration or accidental entry of the needle sheath into the varix in a restless or heaving patient. This can be prevented by withdrawing the needle into the sheath between injections.[21]

Early recurrent major bleeding is the most common life-threatening event after sclerotherapy and occurs in 20 - 35% of patients. Urgent endoscopy is important to establish whether recurrent bleeding is from a varix, sclerosant-induced ulceration, oesophagitis, or another source. If recurrent bleeding is variceal in origin, further sclerotherapy is indicated. Although control of acute variceal bleeding is usually achieved with a single injection session in 70% of patients, some require further injections.[66] If variceal bleeding recurs despite two apparently adequate injections, mortality increases exponentially and some other definitive procedure should be used.[67,68]

Bleeding from ulceration after EIS may be particularly troublesome and occurs in up to 13% of patients.[17,69,70] It may be difficult to exclude a variceal component aggravating the bleeding because of the complex venous anatomy of the lower oesophagus.[71] Further injection of sclerosant is inappropriate if deep ulceration or oesophagitis is present, and may compound the problem. In most ulcers, bleeding is self-limiting or stops with the addition of octreotide and sucralfate.[18,62] The small number of patients who continue to bleed pose a major management problem. Balloon tamponade increases the risk of pressure necrosis and perforation. Oesophageal transection may be hazardous after several previous injection sclerotherapy sessions and shunt surgery is inappropriate in cirrhotic patients with poor liver function.[72] In this difficult situation, the Liverpool group were able to control severe bleeding in 20 of 22 patients using intravenous somatostatin.[73]

Perforation

In a small cohort of patients deep ulceration with transmural necrosis may progress to a localised or contained perforation without mediastinitis or communication with the pleural cavity.[18,74] Confined perforations should be suspected in patients who have persistent pain and pyrexia after EIS. The diagnosis is confirmed on gastrografin swallow. Treatment is conservative with intravenous antibiotics, parenteral hyperalimentation or enteral feeding via a fine-bore silastic nasoduodenal tube.[18] Subsequent sclerotherapy should be delayed for 2 months until complete healing has occurred.[21]

Free perforation occurs in 2 - 3% of patients and has a prohibitive mortality, especially in patients with advanced liver disease. Perforation occurred more frequently with the rigid oesophagoscope and was due to instrumental injury.[75] Perforation after flexible injection sclerotherapy is usually delayed and is the result of deep ulceration and transmural necrosis.[76] The risk of perforation is highest in patients who require repeated injections for uncontrolled or recurrent bleeding during the index admission.[77,78] During these sessions, cumulative volumes of sclerosant are often used, and the risk of inadvertent misplaced, deep injections is greatest.[79,80] Possible aggravating factors predisposing to delayed perforation include concurrent balloon tamponade, impairment of healing secondary to poor liver function, mucosal ischaemia associated with infusion of vasopressin, prolonged nasogastric intubation and colonisation of the ulcer base with *Candida*.[80,81]

Oesophageal perforation generally presents 10 - 14 days after the index injection session.[82] Analysis of patients in whom detailed clinical information is available reveals a prodrome with several features in common.[82-86] The majority developed deep local ulceration at the injection site following urgent or emergency sclerotherapy during their index admission. Most patients had severe, prolonged retrosternal and pleuritic chest pain, fever, an exudative pleural effusion and worsening encephalopathy.[21,82] The effusions were initially sterile, but invariably became infected with a variety of organisms. Gram-negative septicaemia, shock and deteriorating liver function with multi-organ failure was a common outcome despite surgical or tube drainage. Some

patients may not manifest the clinical features of an oesophageal leak but present with subtle signs of sepsis, worsening encephalopathy or deteriorating liver function, and the diagnosis is only made at autopsy.[21,78,87]

Free oesophageal perforation poses a major management problem.[21] Oesophageal necrosis, mediastinal venous collaterals and sepsis with multiple organ failure preclude conventional treatment for oesophageal perforation.[21] At thoracotomy the tissues are friable and oedematous, making repair difficult and likely to break down.[82] In most reports, the majority of perforations were managed conservatively with tube thoracostomy and had a high mortality.[82-87] This reflects the reluctance to institute major operative treatment in high-risk patients who have already been considered to have a poor prognosis.[21,82]

Intramural haematoma

Intramural haematoma of the oesophagus is a rare complication of EIS and has a reported incidence of 0.3 - 1.6%.[88] The precise pathogenesis is speculative. Tissue necrosis extending into the submucosa and muscularis may be the initiating event and may be compounded by repeated injections.[88] Raised portal pressure and coagulation defects[89] may aggravate intramural dissection and extension of blood and sclerosant both longitudinally and circumferentially in the oesophageal wall.[90,91] Tissue necrosis is at its most severe during the first 3 - 4 days after sclerotherapy and this may explain the early manifestation of this complication.[92] Other factors implicated in the pathogenesis include the different injection techniques (paravariceal versus intravariceal injection), the type of sclerosant solution, the volume of sclerosant given per injection, the interval between treatments and the occurrence of retching or prolonged valsalva during or shortly after injection sclerotherapy.[89,92]

An intramural oesophageal haematoma should be suspected in a patient who presents with the triad of sudden-onset dysphagia, odynophagia and haematemesis or bloodstained sputum occurring soon after variceal sclerotherapy.[93-95] There may however be no evidence of blood loss or haematemesis if the haematoma is contained within the oesophageal wall or submucosa and the mucosa has not been breached, in contrast to patients with a Mallory-Weiss tear, who present with upper gastrointestinal bleeding with or without pain and no dysphagia.[96] Associated retrosternal chest pain is common and is due to epithelial separation by the expanding intramural haematoma. The absence of subcutaneous emphysema in the neck differentiates this condition from the more serious complication of oesophageal perforation.[88]

In a patient who has recently had EIS and has a clinical presentation compatible with an intramural haematoma of the oesophagus, contrast studies provide the simplest way of confirming the diagnosis and excluding an oesophageal perforation (Fig. 7).[88] The contrast study may reveal a 'double-barrel' oesophagus in which contrast material can be seen in both the lumen of the oesophagus and the intramural cavity.[97,98] An elongated radiolucent filling defect with a smooth outline is another radiological feature.[94,96] Oesophagoscopy is helpful in establishing the diagnosis but should be reserved for inconclusive cases because of the invasive nature of the investigation.[88] If performed, endoscopy usually shows a characteristic dark blue intramural bulge of mucosa[94] (Fig. 8). Other imaging studies include computed tomography (CT) scan, magnetic resonance imaging (MRI) and oesophageal echo-endoscopy.

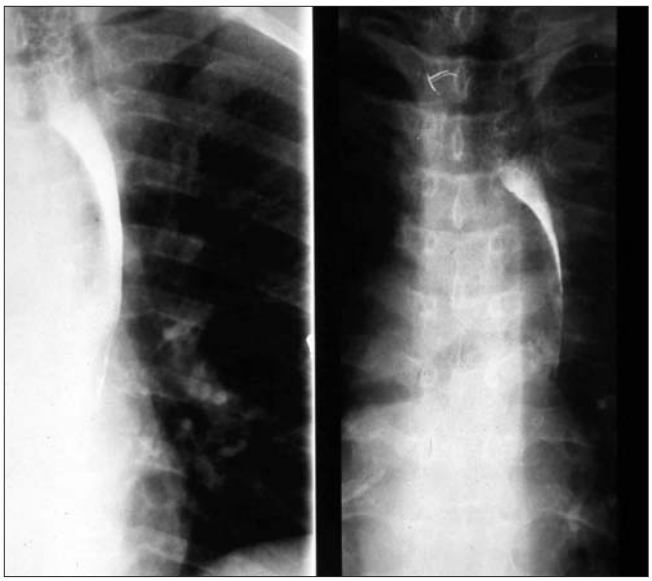

Fig. 7. Barium swallow showing an oesophageal intramural haematoma.

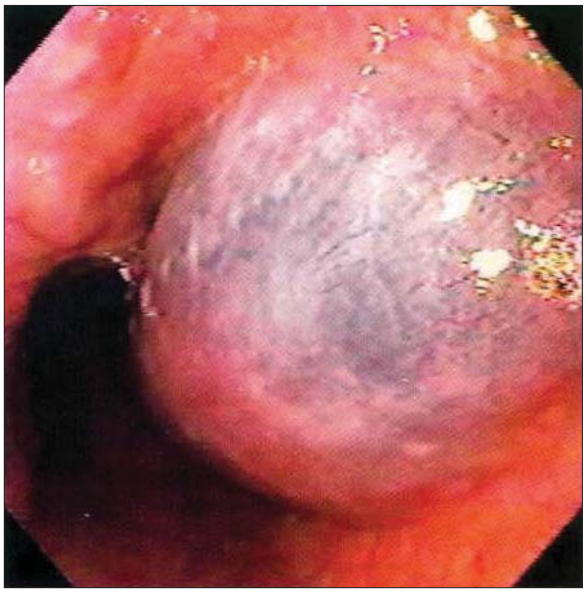

Fig. 8. Sclerotherapy-induced intramural oesophageal haematoma.

Treatment depends on a definitive diagnosis of intramural oesophageal haematoma.[88] In contrast to patients with oesophageal perforation after EIS, which has a poor prognosis and who may require urgent surgical intervention, patients with intramural haematoma have a good prognosis.[21] The initial treatment of intramural haematoma should be conservative.[99] Symptoms usually begin to resolve spontaneously within 36 - 72 hours and disappear completely in 2 - 3 weeks.[100] Patients should be kept nil per mouth and receive intravenous fluids. Oral feeds are introduced gradually as tolerated.[88] Resolution of the intramural haematoma occurs by reabsorption without disruption of the mucosal surface in patients with small haematomas, or sloughing of the overlying mucosa may occur if the intramural haematoma is large.[94,101] No adverse long-term sequelae have been reported after intramural haematoma formation and in most cases oesophageal varices had disappeared and were absent on follow-up oesophagoscopy.[88]

Stricture

The incidence of oesophageal strictures after EIS ranges from 10% to 15%. In 204 patients undergoing long-term sclerotherapy, 1 in 10 developed a stricture.[37] While some reports have not found a direct relationship with the number of previous EIS sessions, volume or type of sclerosant and site of injection,[102-105] Sorensen and the Cape Town group demonstrated a clear relationship between frequency and cumulative volume of injection and an association with pre-existing ulceration.[106,107] Patients who developed a stricture had received more injections and larger volumes of sclerosant and a significantly greater number had preceding mucosal necrosis.[21]

Sclerotherapy-induced strictures are usually short and localised to the lower 5 cm of the oesophagus[21] (Fig. 9). Most strictures are easily dilatable and two to three dilatation sessions suffice in 85% of patients.[105] Persistent oesophageal dysmotility may explain the refractory dysphagia which occurs in some patients despite adequate dilatation. Dilatation does not precipitate bleeding from partially treated varices and although the stricture may temporarily delay eradication of varices, the EIS programme can be continued successfully after stricture dilatation.[21] For short symmetrical strictures, Maloney mercury-filled rubber dilators allow easy and safe dilatation while tighter and longer strictures require fluoroscopically controlled dilatation over an endoscopically placed guidewire with Savary dilators.[21]

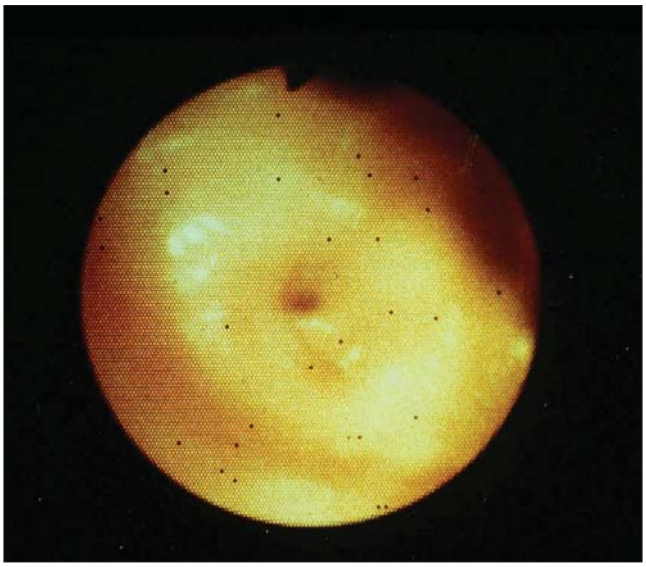

Fig. 9. High-grade oesophageal stricture after sclerotherapy.

Motility disorders

Several studies have evaluated both the short- and long-term effects of sclerotherapy on oesophageal motor function and gastroesophageal reflux.[108-110] Serial evaluation of motility patterns in the oesophagus before sclerotherapy, 3 days after sclerotherapy and 6 months later has demonstrated that the length of the high-pressure zone, peristaltic velocity and swallow-wave symmetry are markedly affected. The length of the high-pressure zone increased significantly after the initial sclerotherapy session owing to intense inflammation in the distal oesophagus. The normal waveform pattern and symmetry are altered substantially by sclerotherapy. Double- and triple-peak waveforms, dropped swallow waves in the distal oesophagus and simultaneous and spontaneous contractions have been documented.[109-111] Oesophageal function after eradication of varices using oesophageal scintigraphy has shown increased transit times compared with controls.[112] These changes increase after sequential treatment, and this effect is probably a manifestation of sclerosant-induced oesophagitis, intramural inflammatory response or fibrotic changes in the oesophageal wall.[113]

Injection sclerotherapy does not substantially affect lower oesophageal sphincter pressure.[109,110] There is some disagreement concerning the incidence and severity of gastroesophageal reflux after EIS and its effect on oesophageal acid clearance.[109,110,111,114,115] Reilly *et al*. found that gastroesophageal reflux, as determined by standard reflux tests, become more prevalent after sclerotherapy and suggested that reflux contributed to stricture formation.[109] In contrast, Ogle *et al.* found no instance of acid reflux into the oesophagus but patients who received sclerotherapy did have impaired acid clearance.[111] The magnitude of these changes is not thought to be severe enough to promote pathological gastroesophageal reflux.

A variety of other unusual local oesophageal complications have been reported after sclerotherapy. Pneumatosis intestinalis and pneumoperitoneum may occur due to intramural air entering through a small mucosal tear in the oesophageal wall and dissecting distally into the stomach, small bowel and colon. Rupture into the peritoneum produces free intraperitoneal air. The condition is benign and resolves spontaneously.[116] Other rare complications include pseudo-diverticula,[117] mucosal bridges,[118] and perioesophageal granulomas.[119] These are usually incidental findings and require no specific therapy.

Cardiorespiratory effects

Cardiac complications specifically related to EIS are rare. Anecdotal reports of coronary artery spasm,[120] persistent bradyarrhythmia,[121] and heart failure due to polidocanol[122,123] have been reported. Seven cases of pericarditis after sclerotherapy have been described.[124,125] The onset is heralded by fever, chest pain and dyspnoea and a pericardial friction rub is present with electrocardiographic and echocardiographic evidence of a pericardial effusion. If pericarditis remains undiagnosed, progression to cardiac tamponade or constrictive pericarditis may occur.[126,127]

Pulmonary complications are common and range from minor asymptomatic changes found incidentally on routine chest radiographs to aspiration or bronchopneumonia, pleural effusions, lobar collapse or consolidation and adult respiratory distress syndrome.[119,128] It is often difficult to determine to what extent respiratory changes are directly attributable to EIS as aspiration, sepsis, pulmonary congestion due to fluid shifts after vigorous resuscitation with crystalloids, massive transfusion, and diaphragmatic splinting by tense ascites are additional factors that may contribute to a deterioration in pulmonary function.[21,129]

Several studies have investigated the distribution and potential damaging effects of sclerosant solutions on the respiratory system.[130-132] There is evidence that sclerosant dissemination to the pulmonary and systemic circulation after intravariceal EIS occurs through oesophagogastric collaterals and the azygous-hemiazygous systems.[21] Entry of sclerosant

into the pulmonary circulation has been demonstrated to occur by positive uptake on lung scan of technetium-99m (Tc99m)-tagged STS and SM solutions when injected into oesophageal varices.[21] Systemic dissemination has also been demonstrated to occur with ethanolamine-Tc99m sodium pertechnetate, but the frequency and consequences appear to be minor.[130-132]

Since premedication and passage of an endoscope may contribute to aspiration pneumonitis or hypoxaemia, the incidence of respiratory dysfunction in patients receiving EIS should be compared with that in patients undergoing endoscopy for other reasons. In a controlled study no difference was found in either the short- or long-term effects on lung function and gas exchange after EIS in patients with cirrhotic portal hypertension compared with a similar group undergoing diagnostic endoscopy only.[133] In contrast, patients complaining of post-injection retrosternal pain 24 hours after EIS had a larger fall in vital capacity and forced expiratory volume than patients without pain.[134] One-third of cirrhotic patients with oesophageal varices were shown to have pre-existing pulmonary interstitial oedema and arterial hypoxaemia (PAO_2 < 80 mmHg). In these patients injection of 5% ethanolamine oleate may lead to a further deterioration of pulmonary function and a decrease in arterial oxygen content.[134]

Pulmonary and mediastinal abnormalities are frequently found on routine chest radiographs and CT when performed within 48 hours after EIS. These changes may be explained by peri-oesophageal inflammation and the lack of serosa covering the oesophagus. Saks *et al.* found radiological changes in up to 79% of patients.[135] Pleural effusions and mediastinal soft-tissue densities are the most common findings, while atelectasis, linear lung shadows and retrocardiac soft-tissue densities are demonstrated less often.[135,136] Chest pain and effusions occur more frequently in patients who develop deep ulceration and is due to an intense peri-oesophageal, mediastinal and pleural inflammatory reaction.[39,43] Most effusions are small and resolve spontaneously.

Aspiration is the most serious respiratory complication and occurs most frequently during EIS for acute bleeding.[21] Aspiration pneumonia is avoidable if the stomach is emptied by suction before sclerotherapy and an assistant scrupulously clears the mouth and hypopharynx with a suction catheter during injection. Excessive sedation, hepatic encephalopathy, and a prolonged procedure without adequate or effective airway protection during active bleeding are contributing factors if bleeding is massive. In this situation endotracheal intubation before endoscopy is essential to avoid this potentially lethal complication.[21] Other uncommon pulmonary complications reported after EVS are bronchoesophageal fistula,[137] pneumothorax,[138] subcutaneous emphysema[119] and chylothorax.[139]

Systemic complications

Septicaemia and bacteraemia

Transient fever after sclerotherapy occurs in a quarter of patients due to an acute local inflammatory response or chemical phlebitis. If a fever persists for more than 2 days, a search for a septic or local oesophageal complication is mandatory. Anecdotal reports have incriminated EIS as a cause of meningococcal and *Streptococcus pneumoniae* septicaemia,[140] infective endocarditis,[141] pyogenic meningitis,[142] brain[143-146] and perinephric abscesses[147] and bacterial peritonitis.[148,149] These reports have raised the question whether the incidence of septic complications is increased as a consequence of EIS-induced bacteraemia.

There are several possible sources of bacterial contamination during injection sclerotherapy.[21] The spectrum of organisms associated with bacteraemia and the predominance of alpha-haemolytic streptococcus strongly suggest oropharyngeal flora as the source of contamination. During sclerotherapy these organisms may be introduced by the endoscope or injector needle and enter the bloodstream. The length of the needle injector and a contaminated water supply have been implicated in EIS-associated bacteraemia.[150,151] The incidence of bacteraemia after EIS ranges from 0% to 50%.[150-159] A variety of injection techniques and sclerosant solutions and different lengths of injection needles were used in these studies. An increased incidence of bacteraemia occurs during and up to 5 minutes after EVS. Because blood cultures were drawn during both these periods in fewer than half of the studies, the extent of bacteraemia in some studies may have been underestimated.[21] Inherent in all studies using positive blood cultures is the difficulty of determining true bacteraemia from contaminants.[21] Some investigators have isolated common skin commensals and in one study, 23% of isolates were coagulase-negative staphylococcus[155] which may originate from the skin during venepuncture.

Most previous data on bacteraemia after sclerotherapy have been obtained from blood cultures during elective EIS.[21] The risk of bacteraemia may be higher during technically more demanding and traumatic emergency sclerotherapy and in the presence of venous and urine catheters and endotracheal tubes. In addition, alcoholic cirrhotics may develop bacteraemia spontaneously owing to decreased reticulo-endothelial system function, impaired neutrophil chemotaxis, low levels of serum complement and impaired cell-mediated immunity.[159] The clinical importance of blood culture isolates after sclerotherapy remains questionable. In none of the prospective studies have organisms (other than probable commensals) been isolated more than 30 minutes after sclerotherapy, suggesting that bacteraemia is always transient. Furthermore, no infective complications have been reported following bacteraemia in these studies. Previous recommendations advising routine antibiotic prophylaxis are no longer valid and most authorities now recommend prophylaxis only for patients with specific vascular risk factors, such as prosthetic valves or previous endocarditis.[158] Strict attention to routine equipment cleaning and disinfection to avoid contamination of endoscopes and the water supply are essential.[21]

Haemodynamic and thrombotic effects

Potential effects of repeated long-term EIS and obliteration of oesophageal varices are an increase in portal pressure, the development of other compensatory collaterals and bleeding from varices at remote sites.[160-162] Despite an improvement in laboratory and clinical parameters of hepatic function, the portal venous pressure gradient increased by a third in cirrhotic patients after eradication of oesophageal varices.[161] Six of 15 patients (40%) with non-alcoholic portal hypertension developed spontaneous spleno-adreno-renal shunts following sclerotherapy.[163] The same mechanism may explain the increased incidence of portal hypertensive

gastropathy after repeated EVS[164] and the phenomenon of bleeding from varices at other sites, including duodenum, ileum, colon, rectum and bowel-related adhesions.[160,162,165-168]

Changes and direction of flow in the coronary and azygos systems are complex in portal hypertension. Phasic retrograde oesophageal collateral flow has been demonstrated during EIS using fluoroscopy and endoscopic Doppler flow techniques.[169] Intra-operative portography has demonstrated that flow may be hepatofugal, to and fro or hepatopedal.[170] There is concern that altered venous flow, endothelial damage and a hypercoagulable state after repeated intravariceal EIS may promote excessive local venous thrombosis with propagation into the splanchnic venous system and thrombosis of the portal and splenic veins. Some authors claim that a local endothelial inflammatory response after EIS is the initiating event, while others have shown that hypercoagulable states may be induced by sclerosant.[171-173] In an umbilical cord model designed to simulate variceal blood flow, brief exposure to even low concentrations of STS produces damage and stripping of endothelium which exposes highly thrombogenic factor VIII-rich subendothelium.[173] The effects of STS on coagulation and platelet function are dependent on sclerosant concentration. Dilute STS induces a hypercoagulable state by selective inhibition of protein C, and promotion of platelet aggregation. Activation of systemic blood coagulation in cirrhotics after sclerotherapy, which may be aggravated by vasopressin infusion, may promote venous thrombosis in the splanchnic bed. In experimental studies higher concentrations of STS inactivate the coagulation cascade and cause lysis of platelets.[173]

Since EIS may lead to thrombosis of gastric varices,[42] it is conceivable that thrombus may extend and initiate thrombosis in the splanchnic venous system. Portal vein thrombosis is a well-recognised complication of cirrhosis and portal hypertension. The reported incidence ranges from 0.5% to 21%.[174-176] Acute portal or mesenteric venous thrombosis in association with EIS is, however, uncommon. Seven cases of portal or mesenteric venous infarction have been reported following EIS or intravenous vasopressin.[177-180] Stoltenberg *et al.*, in an autopsy series, demonstrated extension of thrombus from oesophageal varices into the portal and mesenteric venous systems resulting in small-intestinal infarction and hepatic failure.[181] In 2 cases splenic vein thrombosis and splenic infarction occurred suggesting propagation of clot via both coronary and left gastric veins.

Distant histological effects due to sclerosant, including intimal damage and fibrosis in the portal vein, have been reported after obliteration of oesophageal varices. Hunter *et al.* found substantial changes when comparing the morphology of portal and splenic veins in patients who had received EIS with those who had not.[182] In addition to the loss of smooth muscle and elastin fibres and medial fibrosis present in patients with portal hypertension, those who had received EIS also had disruption of normal venous architecture with loss of elastic fibres, smooth-muscle bundles and an increase in fibrous tissue. Changes in splenic vein histology have been demonstrated in patients undergoing splenorenal shunt after EIS which included increased fibrosis, intimal and medial destruction and microthrombi.[183] Retrograde flow, flow through collateral pathways or abnormal responses of the perivenous lymphatic vessels to the sclerosant may, alone or in combination, account for the changes seen.[182]

An increased incidence of thrombosis of the portal vein or its major tributaries after long-term sclerotherapy has been disputed. In the Emory controlled trial comparing EIS with distal splenorenal shunt, all patients underwent angiographic assessment of the portal, splenic and superior mesenteric veins before and after treatment.[184] Those who received chronic EIS provided a unique group in whom the incidence of thrombosis could be assessed. Despite frequent injections (mean 6.5) and large volumes (mean 62 ml), no patient developed splenic or portal vein thrombosis.[184]

Tissue adhesive injection

Endoscopic obliterative therapy with Histoacryl is now the first-choice treatment for emergency control of acute gastric variceal bleeding.[13,185,186] Histoacryl polymerises immediately on contact with blood, resulting in rapid haemostasis.[28] The major complications related to tissue adhesive injection are damage to endoscopic equipment due to premature hardening of cyanoacrylate, local mucosal ulceration at the injection site and embolisation of liquid adhesive before polymerisation has occurred.[29] Cementation and fixation of the injection needle in the glued varix is a serious complication.[187] Endoscopic extraction of an adherent injector is difficult. Laser disintegration[188] of the solidified Histoacryl mass or amputation of the catheter above the impacted needle are two suggested retrieval options before operative removal is considered.

Common minor complications of the procedure include fever and chest pain due to the inflammatory response.[189] Major complications include ulceration and recurrent bleeding.[28,29] Acute and chronic inflammatory changes secondary to Histoacryl injection include perivascular inflammation and vessel-wall necrosis with a foreign body reaction. Perigastric abscesses may follow perivascular inflammation with infection.[189] Endoscopic obliteration of varices with bucrylate was found to cause acute ulcerations of the oesophageal wall in autopsy studies. However, no ulceration has been documented when Histoacryl injections are strictly intravariceal, in contrast to inadvertent paravariceal injection, which can cause extensive ulceration. Approximately 1 week after intravariceal injection of Histoacryl, the mucosa overlying the obliterated varix begins to slough. The solid tissue adhesive is treated as a foreign body and is gradually extruded into the lumen. Several months may elapse before the Histoacryl is completely eliminated from the stomach wall. This usual sequence of events following Histoacryl injection is not associated with increased bleeding or other adverse events.[28,29]

Serious complications such as embolisation to the portal vein, lung and spleen have been reported.[190,191] Rare complications include splenic infarction and splenic abscess, bacterial pericarditis, leakage through the gastro-renal shunt into the left renal vein and inferior vena cava, systemic embolisation including pulmonary, cerebral and coronary embolisation, portal and splenic vein thrombosis.[192-195] Other complications include bacteraemia and visceral fistulas. Risk factors for extravariceal embolisation with Histoacryl treatment include a large injection volume, the dilution of radiolucent Histoacryl with radiopaque Lipiodol and the existence of shunts.[192] In 140 patients who had Histoacryl

injection for bleeding gastric varices, radiographically evident pulmonary emboli were observed in 6 (4.3%).[196] In comparison with patients without emboli, these patients received a higher mean volume of injection (4.2 v. 1.8 ml) (p = 0.0011). Four of the 6 patients with pulmonary emboli had respiratory symptoms. Chest radiographs and CT scans showed unusual tubular or nodular, radiopaque pulmonary emboli along the pulmonary vessels. Multiple peripheral, wedge-shaped, subsegmental perfusion defects were seen on perfusion lung scans. In 5 of 6 patients the radiographic abnormalities showed complete or partial resolution. There were no fatalities directly associated with pulmonary emboli.[196]

A prospective randomised study compared the efficacy and complications of cyanoacrylate injection and band ligation in cirrhotic patients with gastric variceal bleeding.[197] Group A, who received cyanoacrylate injection, comprised 31 patients and group B, who had band ligation, 29 patients. Active bleeding was present in 15 patients in group A and 11 patients in group B. Treatment was repeated regularly until obliteration of gastric varices. Initial haemostasis (defined as no bleeding for 72 hours after treatment) was 87% in group A and 45% in group B (p = 0.03). The sessions required to achieve variceal obliteration and obliteration rates were similar in both groups. However, rebleeding rates were significantly higher in group B (54%) than group A (31%) (p = 0.0005). Treatment-induced ulcer bleeding occurred in 2 patients (7%) in group A and 8 patients (28%) in group B (p = 0.03). The amount of blood transfusion required was higher in group B than group A (4.2 ± 1.3 v. 2.6 ± 0.9 units) ($p < 0.01$). Nine patients in group A and 14 patients in group B died (p = 0.05). The data suggested that endoscopic control and subsequent eradication using cyanoacrylate was more effective and safer than band ligation in patients with bleeding gastric varices.[197]

Endoscopic variceal ligation

The initial technical complications of variceal ligation related to the use of the overtube that facilitated extraction and re-insertion of the endoscope with the use of the original single-shot ligator which required removal to load each new 'O' ring. Complications associated with the use of the overtube include oesophageal mucosal tears, variceal rupture with massive bleeding, oesophageal perforation and separation of the overtube from the bite block.[33,34] Placement of the overtube caused injury to the oesophagus by pinching mucosa between the gastroscope and the edge of the overtube when the endoscope was used as an obturator to facilitate introduction of the overtube or with repeated reinsertion of the gastroscope.[33,34,198] Specific precautions are now recommended when an overtube is used and important modifications in the design and technique have reduced the risk of overtube trauma. Design changes in the overtube include a smoothly tapered distal end to reduce the risk of pinching oesophageal mucosa, a precurved shape to fit the pharynx and a change in the shape of the mouthpiece to prevent rotation of the overtube. Many endoscopists use an oesophageal bougie dilator, which completely fills the lumen of the overtube as an obturator. The development of a multiple-band ligator has eliminated the need for an overtube.[32] Separation of the plastic barrel of the multi-band ligation set has occurred if the silastic collar loosens, or the ligator cap may dislodge if there is a size mismatch between the ligator cap and the endoscope.[199] Grasping forceps or a balloon catheter are useful tools to retrieve the dislodged component from the oesophagus or stomach.

Oesophageal ulcers caused by EVL are more superficial and resolve faster than sclerotherapy-induced ulcers.[31,32] A prospective randomised clinical study by Young *et al.*[200] compared ulcers induced by sclerotherapy with those caused by ligation. Sclerotherapy-induced ulcers were significantly deeper than those induced by ligation (1.8 mm v. 0.6 mm). However, the ligation-induced ulcers were significantly larger in surface area and more circular than the linear lesions induced by sclerotherapy. Ligation-induced ulcers healed at a mean of 14 days compared with 21 days for those resulting from sclerotherapy. These findings confirm earlier clinical and laboratory observations that the majority of ligated sites (whether in the stomach or oesophagus) slough and produce consistent shallow ulcerations from 3 to 7 days after application.

Oesophageal band ligation-induced bacteraemia occurs far less often than with sclerotherapy and is associated with fewer significant infectious sequelae such as spontaneous bacterial peritonitis or pneumonia. Berner *et al.*[201] studied the short-term risks of bacteraemia, changes in pulmonary and coagulation functions, oesophageal motility, and gastroesophageal reflux in a prospective randomised trial of sclerotherapy versus variceal ligation. Although the numbers of patients were small, there were no significant differences with respect to pulmonary and coagulation parameters or bacteraemia. However, oesophageal dysmotility and evidence of reflux were more common in patients undergoing sclerotherapy. Patient acceptance of ligation procedures was better than for sclerotherapy sessions.

Comparative efficacy and complications of endoscopic variceal treatment

EVL compared with EIS

Data from 13 peer-reviewed prospective randomised controlled trials comparing the efficacy and complications of EVL and EIS have been published in full and are summarised in Table I. The first study by Stiegmann *et al.* found band ligation to have improved survival and fewer complications.[32] Laine *et al.* reported a significant reduction in local complications but no difference in rebleeding or mortality.[202] Gimson *et al.* reported that band ligation obliterated the varices more rapidly and reduced the incidence of rebleeding but without affecting mortality or complications.[203] Lo *et al.* documented that ligation reduced rebleeding, mortality and complications and achieved obliteration more rapidly.[204] Hou *et al.* found that EVL was superior to EIS in reducing rebleeding and complications but not mortality.[205] Eradication was achieved in fewer treatment sessions in the trials reported by Sarin *et al.*[206] and Baroncini *et al.*[207] with clear benefit in terms of fewer procedure-related complications. Avgerinos *et al.* found that EVL eradicated varices more swiftly than EIS and with fewer complications.[208] Masci *et al.* recorded significantly more major complications with EIS (36% v. 10%).[209]

De la Pena *et al.* found similar rates of variceal eradication, but eradication was accomplished sooner and with fewer complications in patients undergoing EVL.[210] In 84 patients

TABLE I. RANDOMISED TRIALS COMPARING ENDOSCOPIC SCLEROTHERAPY WITH BAND LIGATION

Author (year) (total number)	Patients	Group	Sessions	Rebleed (%)	Variceal bleeding	Complications (%)	Recurrence (%)	Eradication (%)	Survival (%)
Stiegmann[32] (1992) (*N* = 129)	**65**	**EIS**	**5 ± 2**	**48**	**52**	**22**	**50**	**56**	**55**
	64	**EVL**	**4 ± 2**	**36**	**48**	**2**	**33**	**55**	**72**
Laine[202] (1993) (*N* = 77)	**39**	**EIS**	**6.2 ± 0.4**	**44**	**31**	**56**	**NA**	**69**	**85**
	38	**EVL**	**4.1 ± 0.3**	**26**	**24**	**24**	**NA**	**59**	**89**
Gimson[203] (1993) (*N* = 103)	**49**	**EIS**	**4.90**	**53**	**51**	**57**	**NA**	**71**	**37**
	53	**EVL**	**3.40**	**30**	**24**	**67**	**NA**	**82**	**52**
Lo[204] (1995) (*N* = 120)	**59**	**EIS**	**6.5 ± 1.2**	**51**	**36**	**19**	**NA**	**63**	**68**
	61	**EVL**	**3.8 ± 0.4**	**33**	**13**	**3**	**NA**	**74**	**84**
Hou[205] (1995) (*N* = 134)	**67**	**EIS**	**4.6 ± 1.6**	**33**	**43**	**22**	**30**	**79**	**84**
	67	**EVL**	**3.5 ± 1.6**	**18**	**38**	**5**	**48**	**87**	**79**
Sarin[206] (1997) (*N* = 95)	**48**	**EIS**	**5.2 ± 1.8**	**21**	**NA**	**50**	**8**	**92**	**94**
	47	**EVL**	**4.1 ± 1.2**	**6**	**NA**	**45**	**29**	**96**	**94**
Baroncini[207] (1997) (*N* = 111)	**54**	**EIS**	**4.0 ± 0.1**	**19**	**30**	**31**	**13**	**93**	**78**
	57	**EVL**	**3.5 ± 0.1**	**16**	**22**	**11**	**30**	**93**	**79**
Avgerinos[208] (1997) (*N* = 77)	**40**	**EIS**	**5.8 ± 2.7**	**47**	**25**	**60**	**44**	**97**	**80**
	37	**EVL**	**3.7 ± 1.9**	**27**	**14**	**35**	**31**	**93**	**78**
Hou[220](1999) (*N* = 168)	**84**	**EIS**	**5.1 ± 2.2**	**38**	**32**	**NA**	**NA**	**86**	**NA**
	84	**EVL**	**3.7 ± 1.7**	**24**	**43**	**NA**	**NA**	**88**	**NA**
Masci[209] (1999) (*N* = 100)	**50**	**EIS**	**5.3**	**42**	**10**	**38**	**27**	**82**	**NA**
	50	**EVL**	**3.4**	**12**	**14**	**18**	**32**	**88**	**NA**
De la Pena[210] (1999) (*N* = 88)	**46**	**EIS**	**5.3 ± 1.6**	**50**	**30**	**41**	**28**	**71**	**78**
	42	**EVL**	**6.6 ± 2.4**	**31**	**12**	**14**	**25**	**79**	**81**
Fakhry[211] (2000) (*N* = 84)	**41**	**EIS**	**4.8 ± 0.9**	**15**	**10**	**65**	**20**	**NA**	**NA**
	43	**EVL**	**2.8 ± 0.5**	**16**	**12**	**2**	**21**	**NA**	**NA**
***Zargar[212] (2005) (*N* = 73)**	**36**	**EIS**	**7.7 ± 3.3**	**19**	**19**	**22**	**9**	**92**	**NA**
	37	**EVL**	**3.7 ± 1.2**	**3**	**3**	**3**	**11**	**95**	**NA**

*Extrahepatic portal venous obstruction.
NA = data not available.
Significant differences between EVL and EIS are underlined.

with schistosomal and post-hepatitic cirrhosis, Fakhry *et al.* required significantly fewer treatment sessions to eradicate varices and fewer complications with EVL.[211] In 73 adult patients with bleeding oesophageal varices due to extrahepatic portal vein obstruction Zargar *et al.* found that EVL achieved variceal eradication with significantly fewer endoscopic sessions and fewer complications than EIS.[212]

A meta-analysis[213] of the seven initial randomised trials concluded that EVL reduced the rebleeding rate (odds ratio (OR) 0.52; 95% confidence interval (CI) 0.37 - 0.74), mortality rate (OR 0.67; Cl 0.46 - 0.98), and rate of death due to bleeding (OR 0.49; Cl 0.24 - 0.996) compared with EIS. Oesophageal strictures occurred less frequently with EVL (OR 0.10; Cl 0.03 - 0.29). The number of endoscopic treatment sessions required to achieve variceal obliteration was lower with EVL than with EIS. On the basis of lower rates of rebleeding, mortality, and complications and the need for fewer endoscopic treatments, EVL should be considered the endoscopic treatment of choice for patients with bleeding oesophageal varices.[213]

EVL compared with combination therapy (EVL plus EIS)

EIS of large oesophageal varices may be technically demanding and generally requires greater sclerosant volumes, more commonly results in needle puncture bleeding, and requires more endoscopy sessions with an increased risk of serious complications. In contrast, banding is ideally suited to large varices but becomes progressively more difficult with each subsequent session as varices reduce in size and less variceal tissue is available to trap in the 'O' rings.[33] The combination of EVL and small-volume EIS therefore has the potential advantage of augmenting the benefits of both techniques by achieving more rapid variceal eradication and less chance of variceal recurrence, thus reducing the likelihood of later rebleeding.[34]

(a) Synchronous combination (EVL + EIS) therapy

The combination of EVL and synchronous EIS should theoretically achieve more rapid variceal eradication, as the sclerosant is injected into a stagnant varix above the ligation site. Laine *et al.*[214] compared EVL

TABLE II. RANDOMISED TRIALS COMPARING ENDOSCOPIC BAND LIGATION WITH LIGATION PLUS SIMULTANEOUS SCLEROTHERAPY

Author (year) (patient numbers)	Patients	Group	Sessions	Re-bleed	Variceal bleeding	Complications	Eradication (recurrence)	Survival
Laine[214] (1996)	**20**	**EVL**	**2.7 (0.4)**	**30%**	**25%**	**10%**	**60%**	**85%**
(N = 41)	**21**	**EVL/EIS**	**4.9 (0.6)**	**29%**	**19%**	**29%**	**71%**	**86%**
Saeed[215] (1997)	**25**	**EVL**	**3.3 (0.4)**	**25%**	**86%**	**25%**	**(16%)**	**84%**
(N = 47)	**22**	**EVL/EIS**	**4.1 (0.6)**	**36%**	**63%**	**65%**	**(23%)**	**64%**
Umehara[216] (1999)	**26**	**EVL**	**2.3 ± 0.5**	**NA**	**NA**	**46%**	**81%**	**91%**
(N = 51)	**25**	**EVL/EIS**	**3.5 ± 1.0**	**NA**	**NA**	**68%**	**84%**	**100%**
Al Traif[217] (1999)	**31**	**EVL**	**3.6 ± 0.4**	**23%**	**10%**	**34%**	**81%**	**77%**
(N = 60)	**29**	**EVL/EIS**	**3.8 ± 0.5**	**17%**	**7%**	**29%**	**86%**	**90%**
Djurdjevic[218] (1999)	**51**	**EVL**	**2.3 ± 0.7**	**14%**	**10%**	**2%**	**92% (26%)**	**88%**
(N = 103)	**52**	**EVL/EIS**	**2.4 ± 0.7**	**20%**	**14%**	**6%**	**88% (24%)**	**87%**
Argonz[219] (2000)	**41**	**EVL**	**3.9 ± 0.3**	**NA**	**31.7%**	**7.3%**	**65.8%**	**61%**
(N = 80)	**39**	**EVL/EIS**	**3.8 ± 0.3**	**NA**	**23.1%**	**30.8%**	**74.4%**	**69%**
Hou[220] (2001)	**47**	**EVL**	**3.7 ± 1.2**	**23%**	**NA**	**NA**	**(40%)**	**87%**
(N = 94)	**47**	**EVL/EIS**	**3.8 ± 1.4**	**28%**	**NA**	**NA**	**(25%)**	**85%**

NA = data not available.
Significant differences between EVL and EIS are underlined.

TABLE III. RANDOMISED TRIALS COMPARING ENDOSCOPIC BAND LIGATION WITH LIGATION PLUS CONSECUTIVE SCLEROTHERAPY

Author (year) (patient numbers)	Patients	Group	Sessions	Re-bleed	Variceal bleeding	Complications	Eradication (recurrence)	Survival
Bhargava[222] (1996)	**21**	**EVL**	**4.3 ± 1.8**	**NA**	**19%**	**31%**	**24%**	**NA**
(N = 50)	**23**	**EVL/EIS**	**5.9 ± 2.3**	**NA**	**22%**	**44%**	**87%**	**NA**
Lo[223] (1998)	**35**	**EVL**	**3.7 ± 0.9**	**31%**	**5.4%**	**NA**	**(43%)**	**NA**
(N = 72)	**37**	**EVL/EIS**	**3.4 ± 1.1**	**8%**	**23%**	**NA**	**(14%)**	**NA**
Masumoto[224] (1998)	**20**	**EVL**	**2.3 ± 0.8**	**0%**	**0%**	**5%**	**65%**	**100%**
(N = 41)	**21**	**EVL/EIS**	**4.1 ± 0.9**	**0%**	**0%**	**10%**	**86%**	**100%**

NA = data not available.
Significant differences between EVL and EIS are underlined.

TABLE IV. RANDOMISED TRIALS COMPARING INJECTION SCLEROTHERAPY WITH LIGATION PLUS SCLEROTHERAPY

Author (year) (patient numbers)	Patients	Group	Sessions	Re-bleed	Complications	Recurrence	Survival
Iso[225] (1997)	30	EIS	4.1 (0.8)	0%	91%	8%	NA
(N = 61)	31	EVL/EIS	3.0 (0.5)	4%	22%	39%	NA
Masumoto[224] (1998)	18	EIS	4.7 ± 1.4	0%	50%	95%	100%
(N = 39)	21	EVL/EIS	4.1 ± 0.9	0%	10%	86%	100%
Nishikawa[228] (1999)	14	EIS	3.9 ± 0.8	0%	7%	50%	79%
(N = 28)	14	EVL/EIS	2.3 ± 0.5	0%	14%	45%	64%
Garg[226] (1999)	34	EIS	6.6 ± 2.9	16%	20%	85% (5.8%)	91%
(N = 69)	35	EVL/EIS	7.9 ± 3.3	3%	3%	80% (14.2%)	89%
Shigemitsu[227] (2000)	12	EIS	2.8 ± 0.6	NA	41%	48%	100%
(N = 24)	12	EVL/EIS	2.4 ± 0.7	NA	83%	82%	100%

NA = data not available.
Significant differences between EVL and EIS are underlined.

sclerotherapy (EVL/EIS) in 41 patients. Twenty-one patients randomised to EVL/EIS had their oesophageal varices ligated then 1 ml of sclerosant (1.5% sodium tetradecyl sulfate) injected into the varix immediately above the ligature. However, the anticipated benefits were not realised in this study, which reported similar eradication, rebleeding and death rates in the two groups (Table II). More treatment sessions (rather than fewer) were required to achieve eradication in the combined treatment arm, which caused more complications than EVL alone. Similar results were reported by Saeed *et al.*,[215] Umehara *et al.*,[216] Al Traif *et al.*,[217] Djurdjevic *et al.*,[218] Argonz *et al.*[219] and Hou *et al.*,[220] who reported that control of acute bleeding, rebleeding rates, variceal eradication rates, and mortality were similar in the two treatment groups (Table II). However, more endoscopy sessions were required to achieve eradication with combination therapy, which was associated with a higher incidence of deep mucosal ulceration, dysphagia and oesophageal strictures.

A meta-analysis[221] found no significant differences between EVL and EIS combined versus EVL alone in terms of oesophageal rebleeding (relative risk (RR) 1.05; 95% CI 0.67 - 1.64; $p = 0.83$), death (RR 0.99; 95% CI 0.68 - 1.44; $p = 0.96$) or number of endoscopic sessions to variceal obliteration (RR 0.23; 95% CI 0.055 - 0.51; $p = 0.11$). However, the incidence of oesophageal strictures was significantly higher in the EVL plus EIS group than in the EVL-alone group. The meta-analysis of these studies suggests that little is to be gained by the addition of low-dose sclerotherapy to standard ligation techniques. Based on the available evidence, synchronous treatment with EVL and EIS provides no additional benefit and is associated with higher patient morbidity.

(b) Sequential combination (EVL + EIS) therapy

Recognising the technical limitations of EVL and synchronous EIS, Bhargava and Pokharna[222] adopted a more pragmatic approach to combination therapy (Table III). Patients were randomised to either EVL alone, or to the combination of EVL and sequential EIS. Combination therapy used repeated EVL until the varices were reduced in size to grade II, followed by weekly small-volume sclerotherapy to achieve complete eradication. Overall the combined treatment cohort required more endoscopic sessions (5.9 ± 2.3 v. 4.3 ± 1.8; $p < 0.05$), but re-bleeding rates (19% v. 22%) and complication rates were similar in the two groups. This study suggested that a staged approach to combination therapy was better, as it achieved 100% variceal eradication without the associated high rate of iatrogenic complications normally associated with EIS. In their study Lo *et al.*[223] found that eradication and number of sessions needed were similar in both groups. However, the mortality (2.7% v. 8.6%), rebleeding (8% v. 31%) and variceal recurrence (14% v. 43%) rates were lower with combination therapy than with EVL alone. Masumoto *et al.* found no difference in their study.[224]

EIS alone compared with combined EVL and EIS therapy

Iso *et al.*[225] compared EIS alone with a step-wise combination of EVL as initial treatment followed by weekly EIS (Table IV). There were significantly fewer iatrogenic complications with the combined EVL/EIS strategy.[225] Garg *et al.*[226] found that more complications (20% v. 3%) and rebleeding (16% v. 3%) occurred with sclerotherapy alone. In the study by Shigemitsu *et al.*[227] eradication was achieved with significantly less sclerosant in the combined EVL/EIS group (17 v. 25 ml, $p < 0.05$). Nishikawa *et al.*[228] found that the number of treatment sessions for eradication was significantly lower (2.3 v. 3.9, $p < 0.001$) for EVL and EIS, and that in total less sclerosant was used.

Strategies to prevent endoscopic-related complications

Endoscopic therapy is an established and integral part of the management of acute variceal bleeding and the long-term treatment of patients after a variceal bleed. Although complications after endoscopic therapy for variceal bleeding are common, most are minor and do not interrupt the treatment programme. In a small group of patients, however, the success of therapy is compromised by recurrent bleeding and serious procedure-related complications.[21] Most of the serious complications related to endoscopic therapy occur in patients with severe liver disease in whom control of bleeding is difficult. It is not the complication that is a breach of optimal care, but rather the failure to anticipate or recognise it and respond appropriately. Mature clinical judgement is necessary in acute problematic or complex cases, and careful supervision of trainees or assistance by an experienced endoscopist becomes essential when critical decisions are required. Early and close multidisciplinary consultation is often useful in demanding cases to facilitate appropriate therapy and optimal management.[15,21]

A number of critical generic precautions are important to avoid both local and systemic complications, regardless of the type or technique of endoscopic intervention used to control acute bleeding.[21] Effective resuscitation should precede endoscopy in patients with evidence of recent major bleeding. Diagnostic and therapeutic endoscopy should be performed in a well-equipped unit with competent assistance and careful monitoring. It is prudent to perform endoscopy with the minimum sedation needed for a safe procedure. High-risk patients and those with significant cardiopulmonary disease need only topical oropharyngeal anaesthetic spray and the minimum intravenous sedation. In a frail patient, a benzodiazepine alone may be safer than the combination of a benzodiazepine and an opiate. Medications used for sedation should be titrated to the desired level of sedation using small, incremental doses. Flumazenil, a benzodiazepine antagonist, and naloxone, an opiate antagonist, must be available should a cardiopulmonary complication occur. Meticulous attention should be given to suctioning of the mouth and hypopharynx by a dedicated assistant to avoid aspiration.[22,23]

Early endotracheal intubation is crucial if major bleeding occurs. Precise and accurately placed injections are essential.[23] To ensure adequate visibility during active bleeding, a large or double-channel endoscope with vigorous irrigation should be used with the head elevated. Uncontrolled blind, large-volume injections during active bleeding must be avoided. The sclerotherapy needle should not exceed 5 mm in length and a short bevel reduces the risk of deep injections. Recurrent bleeding after EIS requires careful evaluation and repeat endoscopy to determine the source. If variceal bleeding continues or recurs during the index admission despite two adequate injections, other definitive therapy should be instituted.[22,23]

If ulceration involves more than one oesophageal quadrant, further injections should be delayed until healing has occurred.[21] Treatment with H_2-blockers or sucralfate does not prevent ulceration, but may accelerate healing. Omeprazole has been effective in the treatment of chronic ulcers. Special care should be taken in patients with deep ulceration and persistent pain, fever, an increasing pleural effusion and deterioration of liver function, which suggest transmural necrosis and impending perforation. Motility abnormalities are usually transient in nature and of minor clinical consequence and most symptomatic strictures respond effectively to dilatation.[21]

In countries where cyanoacrylate adhesive is available and licensed for endoscopic use, damage to the endoscopic equipment, ulceration and pulmonary embolism are the main potential complications that restrict its use. Damage to the endoscope is preventable if specific precautions are taken.[28] There have been documented cases of cerebral, pulmonary and portal embolism.[195] These complications appear to be related to the volume of cyanoacrylate injected. The volume should be limited to 4 - 6 ampoules (2.0 - 3.0 g) per session. Cerebral and pulmonary embolism appears to depend on the presence of an abnormal right-left vascular communication.[229]

Variceal eradication with EVL requires fewer endoscopic treatment sessions, and causes substantially fewer oesophageal complications.[15,33,34] Although the incidence of early gastrointestinal rebleeding is reduced by EVL in most studies, this does not result in an overall survival benefit relative to EIS. Simultaneous combination therapy (EVL + EIS) of large varices confers no advantage over EVL alone.[221] A staged approach with initial EVL followed by EIS when varices are small requires further evaluation as the sequential combination may prove to be the optimal method of minimising variceal recurrence.[15] Overall, current data demonstrate clear advantages for using EVL in preference to EIS. EVL should therefore be regarded as the endoscopic technique of choice in the treatment of oesophageal varices.[15,33,34]

The range of treatment options for bleeding oesophageal varices has expanded markedly during the past two decades. The treatment of acute bleeding and prevention of recurrent variceal bleeding is best accomplished by a skilled, knowledgeable, and well-equipped team using a multidisciplinary integrated approach. Optimal management should provide the full spectrum of treatment options, which include pharmacological therapy, endoscopic treatment, interventional radiological procedures, surgical shunts and liver transplantation.[15]

This review is based in part on an invited lecture by Professor J. E. J. Krige at the Inaugural Tri-Nations Gastroenterology Meeting on 'Current Topics in Gastroenterology' at Bunker Bay, Margaret River, Western Australia, on 8 March 2005 and a chapter on 'Complications of endoscopic sclerotherapy' by J. E. J. Krige *et al.*[21]

REFERENCES

1. Bornman PC, Krige JEJ, Terblanche J. Management of oesophageal varices. *Lancet* 1994; **343:** 1079-1084.
2. Krige JE, Bornman PC. Endoscopic treatment of oesophageal varices. *S Afr J Surg* 2000; **38:** 82-88.
3. Krige JE, Beckingham IJ. Portal hypertension: varices. *BMJ* 2001; **322:** 348-351.
4. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. *Hepatology* 1995; **22:** 332-354.
5. Terblanche J, Burroughs AK, Hobbs KEF. Controversies in the management of bleeding esophageal varices. *N Engl J Med* 1989; **320:** 1393-1398.
6. Terblanche J, Burroughs AK, Hobbs KEF. Controversies in the management of bleeding esophageal varices. *N Engl J Med* 1989; **320:** 1469-1475.
7. Terblanche J, Krige JEJ, Bornman PC. Endoscopic sclerotherapy. *Surg Clin North Am* 1990; **70:** 341-359.
8. Bosch J, Garcia-Pagan JC. Prevention of variceal rebleeding. *Lancet* 2003; **361:** 952-954.
9. Terblanche J, Northover JMA, Bornman P. A prospective controlled trial of sclerotherapy in the long-term management of patients after oesophageal variceal bleeding. *Surg Gynecol Obstet* 1979; **148:** 323-333.
10. Terblanche J, Northover JMA, Bornman PC, *et al*. A prospective

evaluation of injection sclerotherapy in the treatment of acute bleeding from esophageal varices. *Surgery* 1979; **85:** 239.
11. Terblanche J, Bornman PC, Kahn D, Jonker MA, Campbell JA, Wright J. Failure of repeated injection sclerotherapy to improve long-term survival after oesophageal variceal bleeding. A five-year prospective, controlled clinical trial. *Lancet* 1983; **2:** 1328-1332.
12. Gotlib JP, Zimmerman P. Une nouvelle technique de traitement endoscopique des varices oesophagiennes: l'obliteration. *Endosc Dig* 1984; **7:** 10-12.
13. Soehendra N, Nam VC, Grimm H, Kempeneers I. Endoscopic obliteration of large esophagogastric varices with bucrylate. *Endoscopy* 1986; **18:** 25-26.
14. Stiegmann GV, Cambre T, Sun J. A new endoscopic elastic band ligating device. *Gastrointest Endosc* 1986; **32:** 230-233.
15. Krige JEJ, JM Shaw, Bornman PC. The evolving role of endoscopic treatment for bleeding esophageal varices. *World J Surg* 2005; **29:** 966-973.
16. Sanowski RA, Waring JP. Endoscopic techniques and complications in variceal sclerotherapy. *J Clin Gastroenterol* 1987; **9:** 504-513.
17. Schuman BM, Beckman JW, Tedesco FJ, Griffin JW, Assad RT. Complications of endoscopic injection sclerotherapy: A review. *Am J Gastroenterol* 1987; **82:** 823-830.
18. Kahn D, Jones B, Bornman PC, Terblanche J. Incidence and management of complications after injection sclerotherapy: A ten-year prospective evaluation. *Surgery* 1989; **105:** 160-165.
19. Baillie J, Yudelman P. Complications of endoscopic sclerotherapy of esophageal varices. *Endoscopy* 1992; **24:** 284-291.
20. Muhldorfer SM, Kekos G, Hahn EG, Ell C. Complications of therapeutic gastrointestinal endoscopy. *Endoscopy* 1992; **24:** 276-283.
21. Krige JEJ, Bornman PC, Terblanche J. Complications of sclerotherapy. In: Sivak MV, ed. *Gastrointestinal Endoscopy*. 2nd ed. New York: WB Saunders, 2000: 860-876.
22. Krige JEJ, Terblanche J. Endoscopic sclerotherapy and variceal band ligation in the management of bleeding esophageal varices. In: Blumgart L, Fong Y, eds. *Surgery of the Liver and Bile Ducts*. 3rd ed. Baltimore: WB Saunders, 1885-1906.
23. Terblanche J, Krige JEJ. Endoscopic therapy in the management of esophageal varices: injection sclerotherapy and variceal ligation. In: Baker RJ, Fischer JE, eds. *Mastery of Surgery*. 4th ed. Philadelphia: Lippincott, Williams & Wilkins, 2001: 1384-1398.
24. Krige JEJ, Terblanche J. Injection sclerotherapy of oesophageal varices. In: Jamieson GG, DeBas HT, eds. *Rob and Smith's Operative Surgery. Surgery of the Upper Gastrointestinal Tract*. 5th ed. London: Chapman & Hall Medical, 1994: 10-20.
25. Krige JEJ, Terblanche J. Injection sclerotherapy of oesophageal varices. In: Carter D, Russell RCG, Pitt H, Bismuth H, eds. *Rob and Smith's Operative Surgery. Surgery of the Liver, Pancreas and Bile Ducts*. 5th ed. London: Chapman & Hall Medical, 1996: 163-172.
26. Matloff DS. Treatment of acute variceal bleeding. *Gastroenterol Clin North Am* 1992; **21:** 103-117.
27. Terblanche J, Stiegmann G, Krige JEJ, Bornman PC. Long-term management of variceal bleeding: The place of varix injection and ligation. *World J Surg* 1994; **18:** 185-192.
28. Binmoeller KF, Soehendra N. 'Superglue': the answer to variceal bleeding and fundal varices? *Endoscopy* 1995; **27:** 392-396
29. Binmoeller KF. Glue for gastric varices: some sticky issues. *Gastrointest Endosc* 2000; **52:** 298-301.
30. Stiegmann GV, Yamamoto M. Endoscopic techniques for the management of active variceal bleeding. *Gastrointest Endosc Clin North Am* 1994; **2:** 59-74.
31. Stiegmann GV. Endoscopic management of esophageal varices. In: Green FL, Ponsky JL, eds. *Endoscopic Surgery*. Philadelphia: WB Saunders, 1996: 113-124.
32. Stiegmann GV, Goff JS, Michaletz-Onody PA, *et al*. Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. *N Engl J Med* 1992; **326:** 1527-1632.
33. Tait IS, Krige JEJ, Terblanche J. Endoscopic band ligation of oesophageal varices. *Br J Surg* 1999; **86:** 812-817.
34. Krige JEJ, Botha JF, Bornman PC. Endoscopic variceal ligation for bleeding esophageal varices. *Digestive Endoscopy* 1999; **11:** 315-320.
35. Baillie J. Complications of endoscopy. *Endoscopy* 1994; **26:** 185-203.
36. Chan MF. Complications of upper gastrointestinal endoscopy. *Gastrointest Endosc Clin N Am* 1996; **6:** 287-303.
37. Krige JEJ, Bornman PC, Goldberg PA, Terblanche J. Variceal rebleeding and recurrence after endoscopic injection sclerotherapy: a prospective evaluation in 204 patients. *Arch Surg* 2000; **135:** 1315-1322.
38. Helpap B, Bollweg L. Morphological changes in the terminal oesophagus with varices following sclerosis of the wall. *Endoscopy* 1981; **13:** 229-233.
39. Evans DMD, Jones DB, Cleary BK, Smith PM. Oesophageal varices treated by sclerotherapy: A histopathological study. *Gut* 1982; **23:** 615-620.
40. Papadimos D, Kerlin P, Harris OD. Endoscopic sclerotherapy: lessons from a necropsy study. *Gastrointest Endosc* 1986; **32:** 269-273.
41. Pushpanathan C, Idikio H. Pathological findings in the esophagus after endoscopic sclerotherapy for variceal bleeding. *Am J Gastroenterol* 1986; **81:** 9-13.
42. Kage M, Korula J, Harada A, Mucientes F, Kanel G, Peters RL. Effects of sodium tetradecyl sulfate endoscopic sclerotherapy on the esophagus. *J Clin Gastroenterol* 1987; **9:** 635-643.
43. Ayres SJ, Goff JS, Warren GH. Endoscopic sclerotherapy for bleeding oesophageal varices: Effects and complications. *Ann Intern Med* 1983; **98:** 900-903
44. Soehendra N, de Heer K, Kempeneers I, Frommelt L. Morphological alterations of the esophagus after endoscopic sclerotherapy of varices. *Endoscopy* 1983; **15:** 291-296.
45. Terabayashi H, Ohnishi K, Tsunoda T, *et al*. Prospective controlled trial of elective endoscopic sclerotherapy in comparison with percutaneous transhepatic obliteration of esophageal varices in patients with nonalcoholic cirrhosis. *Gastroenterology* 1987; **93:** 1205-1209.
46. Low DE, Kozarek RA, Ball TJ, Beebe HG. Endoscopic variceal sclerotherapy as primary treatment for bleeding esophageal varices. *J Clin Gastroenterol* 1989; **11:** 253-259.
47. Sarin SK, Nanda R, Vij JC, Anand BS. Oesophageal ulceration after sclerotherapy – a complication or an accompaniment? *Endoscopy* 1986; **18:** 44-45.
48. Kitano S, Koyanagi N, Iso Y, Higashi H, Sugimachi K. Prevention of recurrence of esophageal varices after endoscopic injection sclerotherapy with ethanolamine oleate. *Hepatology* 1987; **7:** 810-815.
49. Kitano S, Iso Y, Koyanagi N, Higashi H, Sugimachi K. Ethanolamine oleate is superior to polidocanol for endoscopic injection sclerotherapy of esophageal varices: a prospective randomized trial. *Hepatogastroenterology* 1989; **34:** 19-23.
50. Kitano S, Iso Y, Yamaga H, Hashizume M, Higashi H, Sugimachi K. Trial of sclerosing agents in patients with oesophageal varices. *Br J Surg* 1988; **75:** 751-753.
51. Neeman A, Leiser A, Kadish U. Treatment of esophageal varices: low versus high dose of 5% ethanolamine oleate. *Am J Gastroenterol* 1991; **86:** 1182-1184.
52. Iso Y, Kitano S, Iwanaga T. A prospective randomized study comparing the effects of large and small volumes of the sclerosant 5% ethanolamine oleate injected into esophageal varices. *Endoscopy* 1988; **20:** 285-288.
53. Sarin SK, Nanda R, Sachdev G, Chari S, Anand BS, Broor SL. Intravariceal versus paravariceal sclerotherapy: a prospective controlled randomised trial. *Gut* 1987; **28:** 657-662.
54. Westaby D, Melia WM, Macdougall BRD, Hegarty JE, Williams R. Injection sclerotherapy for oesophageal varices: a prospective randomised trial of different treatment schedules. *Gut* 1984; **25:** 129-132.
55. Sarin SK, Sachdev G, Nanda R, Batra SK, Anand BS. Comparison of the two time schedules for endoscopic sclerotherapy: a prospective randomised controlled study. *Gut* 1986; **27:** 710-713.
56. Higashi H, Kitano S, Hashizume M, Yamaga H, Sugimachi K. A prospective randomized trial of schedules for sclerosing esophageal varices. 1 versus 2 week intervals. *Hepatogastroenterology* 1989; **36:** 337-340.
57. Choudhuri G, Agrawal BK, Tantry BV. Post-sclerotherapy esophageal ulcers: a prospective analysis of their behaviour. *Indian J Gastroenterol* 1989; **8:** 19-21.
58. Robertson CS, Womack C, Robson K, Morris DL. A study of the local toxicity of agents used for variceal injection sclerotherapy. *HPB Surg* 1989; **1:** 149-154.
59. Madonia S, Traina M, Montalbano L, *et al*. Variceal ulceration following sclerotherapy: normal consequence or complication. *Gastrointest Endosc* 1990; **36:** 76-77.
60. Tamura S, Shiozaki H, Kobayashi K, *et al*. Prospective randomized study on the effect of ranitidine against injection ulcer after endoscopic injection sclerotherapy for esophageal varices. *Am J Gastroenterol* 1991; **86:** 477-480.
61. Pacquet KJ, Koussouris P, Keinath R, Rembach W, Kalk JF. A comparison of sucralfate with placebo in the treatment of esophageal ulcers following therapeutic endoscopic sclerotherapy of esophageal varices – a prospective controlled randomized trial. *Am J Med* 1991; **91:** suppl 2A, 147-150.
62. Roark G. Treatment of post sclerotherapy esophageal ulcers with sucralfate. *Gastrointest Endosc* 1984; **30:** 9-10.
63. Polson RJ, Westaby D, Gimson AE. Sucralfate for the prevention of early rebleeding following injection sclerotherapy for esophageal varices. *Hepatology* 1989; **10:** 279-292.
64. Singal A, Sarin SK, Sood GK, Broor SL. Ulcers after intravariceal sclerotherapy: correlation of symptoms and factors affecting healing. *J Clin Gastroenterol* 1990; **12:** 250-254.
65. Gimson A, Polson R, Westaby D, Williams R. Omeprazole in the management of intractable esophageal ulceration following injection sclerotherapy. *Gastroenterology* 1990; **99:** 1829-1831.
66. Kahn D, Bornman PC, Terblanche J. A 10-year prospective evaluation of balloon tube tamponade and emergency injection sclerotherapy for actively bleeding oesophageal varices. *HPB Surg* 1989; **1:** 207-219.
67. Bornman PC, Terblanche J, Kahn D, Jonker MAT, Kirsch RE. Limitations of multiple injection sclerotherapy sessions for acute variceal bleeding. *S Afr Med J* 1986; **70:** 34-36.
68. Burroughs AK, Hamilton G, Philips A, Mezzanotte G, McIntyre N, Hobbs KEF. A comparison of sclerotherapy with staple transection of the esophagus for the emergency control of bleeding from esophageal varices. *N Engl J Med* 1989; **321:** 857-862.

69. Sauerbruch T, Weinzierl M, Kopcke W, Paumgartner G. Long-term sclerotherapy of bleeding esophageal varices in patients with liver cirrhosis. An evaluation of mortality and rebleeding risk factors. *Scand J Gastroenterol* 1985; **20:** 51-58.
70. Palani CK, Abuabara S, Kraft AR, Jonasson O. Endoscopic sclerotherapy in acute variceal hemorrhage. *Am J Surg* 1981; **141:** 164-168.
71. Kitano S, Terblanche J, Kahn D, Bornman PC. Venous anatomy of the lower oesophagus in portal hypertension: practical implications. *Br J Surg* 1986; **73:** 525-531.
72. Durtschi MB, Carrico CJ, Johansen KH. Esophageal transection fails to salvage high risk cirrhotic patients with variceal hemorrhage. *Am J Surg* 1986; **150:** 18-23.
73. Jenkins SA, Shields R, Jaser N, *et al*. The management of gastrointestinal haemorrhage by somatostatin after apparently successful endoscopic sclerotherapy for bleeding oesophageal varices. *J Hepatol* 1991; **12:** 296-301.
74. Shemesh E, Bat L. Esophageal perforation after fibreoptic endoscopic injection sclerotherapy for esophageal varices. *Arch Surg* 1986; **121:** 243-245.
75. Bornman PC, Kahn D, Terblanche J, Worthley C, Spence RAJ, Krige JEJ. Rigid versus fibreoptic endoscopic injection sclerotherapy – A prospective randomized controlled trial in patients with bleeding esophageal varices. *Ann Surg* 1988; **208:** 175-178.
76. McGrew W, Goodin J, Stuck W. Fatal complication of endoscopic sclerotherapy: Serratia marcescens bacteremia with delayed esophageal perforation. *Gastrointest Endosc* 1985; **31:** 329-331.
77. Pillay P, Starzl TE, Van Thiel DH. Complications of sclerotherapy for esophageal varices in liver transplant candidates. *Transplant Proc* 1990; **22:** 2149-2151.
78. Bacon BR, Camara DS, Duffy MC. Severe ulceration and delayed perforation of the esophagus after endoscopic variceal sclerotherapy. *Gastointest Endosc* 1987; **33:** 311-315.
79. Grobe JL, Kozarek RA, Sanowski RA. Venography during endoscopic injection sclerotherapy of esophageal varices. *Gastrointest Endosc* 1984; **30:** 6-8.
80. Soderlund C, Weichel KL. Oesophageal perforation after sclerotherapy for variceal haemorrhage. *Acta Chir Scand* 1983; **149:** 491-495.
81. Barthel JS, Sprouse RF, Dix JD, Sunderrajam EV. Fatal candida esophageal abscess and sepsis complicating endoscopic variceal sclerotherapy. *Gastrointest Endosc* 1987; **33:** 107-110.
82. Goldberg PA, Krige JEJ, Bornman PC, Terblanche J. Oesophageal perforation following injection sclerotherapy. *Diseases of the Oesophagus* 1995; **8:** 188-192.
83. Vickers CR, O'Connor HJ, Quintero GA, Aerts RJP, Elias E, Neuberger JM. Delayed perforation of the esophagus after variceal sclerotherapy and hepatic transplantation. *Gastrointest Endosc* 1989; **35:** 459-461.
84. Huizinga WKJ, Keenan JP, Marszalek A. Sclerotherapy for bleeding oesophageal varices – a fatal complication. *S Afr Med J* 1984; **65:** 436-438.
85. Shibuya S, Takase Y, Aoyagi K, Chikamori F, Orii K, Iwasaki Y. Esophageal perforation after endoscopic sclerotherapy for esophageal varices: a case report with review of the literature. *Diseases of the Oesophagus* 1989; **3:** 203-208.
86. Perino LE, Gholson CF, Goff JS. Esophageal perforation after fibreoptic variceal sclerotherapy. *J Clin Gastroenterol* 1987; **9:** 286-289.
87. Korula J, Pandya K, Yamada S. Perforation of esophagus after endoscopic variceal sclerotherapy. Incidence and clues to pathogenesis. *Dig Dis Sci* 1989; **34:** 324-329.
88. Van Beljon J, Krige JEJ, Bornman PC. Intramural esophageal hematoma after endoscopic injection sclerotherapy for bleeding varices. *Digestive Endoscopy* 2004; **16:** 62-66
89. Low DE, Patterson DJ. Complete esophageal obstruction secondary to dissecting intramural hematoma after endoscopic variceal sclerotherapy. *Am J Gastroenterol* 1988; **83:** 435-438.
90. Jones DB, Frost RA, Goodacre RL. Intramural hematoma of the esophagus – a complication of endoscopic injection sclerotherapy. *Gastrointest Endosc* 1986; **32:** 239-240.
91. Mosimann F, Bronnimann B. Intramural haematoma of the oesophagus complicating sclerotherapy for varices. *Gut* 1994; **35:** 130-131.
92. Salomez D, Ponette E, Van Steenbergen W. Intramural hematoma of the esophagus after variceal sclerotherapy. *Endoscopy* 1991; **3:** 299-301.
93. Korula J. Pseudotumor of the esophagus: an unusual complication of esophageal variceal sclerotherapy. *Am J Gastroenterol* 1985; **12:** 954-956.
94. Ou Tim L, Segal I, Mirwis J. Intramural haematoma of the oesophagus. The role of endoscopy. *S Afr Med J* 1982; **61:** 798-800.
95. Shay SS, Berendson RA, Johnson LF. Esophageal hematoma. Four new cases, a review, and proposed etiology. *Dig Dis Sci* 1981; **26:** 1019-1024.
96. Thompson NW, Ernst CB, Ery WJ. The spectrum of emetogenic injury to the esophagus and stomach. *Am J Surg* 1987; **113:** 13-26.
97. Benjamin B, Hanks TJ. Submucosal dissection of the oesophagus due to haemorrhage. A new radiographic finding. *J Laryngol* 1965; **79:** 1032-1038.
98. Marks IN, Keet AD. Intramural rupture of the oesophagus. *BMJ* 1968; **3:** 536-537.
99. Reed AR, Michell WL, Krige JE. Mechanical tracheal obstruction due to an intramural esophageal hematoma following endoscopic variceal sclerotherapy. *Am Surg* 2001; **67:** 690-692.
100. Van Steenbergen W, Fevery J, Broeckaert L, Ponette E, Bacert A, Groote JD. Intramural hematoma of the esophagus: unusual complication of variceal sclerotherapy. *Gastrointest Radiol* 1984; **9:** 293-295.
101. McGrath JP, Walsh TN, Hennessy TP. Total dysphagia from intramural haematoma following sclerotherapy for oesophageal varices. *Br J Surg* 1992; **79:** 781.
102. Waring JP, Sanowski RA. Food impaction and stricture after sclerotherapy of esophageal varices. *Am J Gastroenterol* 1988; **83:** 1245-1247.
103. Haynes WC, Sanowski RA, Foutch PG, Bellapravula S. Esophageal strictures following endoscopic variceal sclerotherapy: clinical course and response to dilatation therapy. *Gastrointest Endosc* 1986; **32:** 202-205.
104. Snady H, Korsten MA. Prevention of dysphagia and stricture formation after endoscopic sclerotherapy. *Gastroenterology* 1984; **86:** 1258.
105. Kochhar R, Goenka MK, Mehta SK. Esophageal strictures following endoscopic variceal sclerotherapy. *Dig Dis Sci* 1992; **37:** 347-352.
106. Sorensen T, Burcharth F, Pedersen ML, Findahl F. Oesophageal stricture and dysphagia after endoscopic sclerotherapy for bleeding varices. *Gut* 1984; **25:** 473-477.
107. Farrell RJ, Goldberg PA, Krige JEJ, Kottler EP, Bornman PC, Terblanche J. Oesophageal stricture following variceal sclerotherapy in portal hypertension. *S Afr Med J* 1992; **81:** 98-99.
108. Sauerbruch T, Wirsching R, Liesner B, Weinzierl M, Pfahler M, Paumgartner G. Esophageal function after sclerotherapy of bleeding varices. *Scand J Gastroenterol* 1982; **17:** 745-751.
109. Reilly JJ, Schade RR, Van Thiel DH. Esophageal function after injection sclerotherapy: pathogenesis of esophageal stricture. *Am J Surg* 1984; **147:** 85-88.
110. Larson GM, Vandertoll DJ, Netscher DT, Polk HC. Esophageal motility: effects of injection sclerotherapy. *Surgery* 1984; **96:** 703-709.
111. Ogle SJ, Kirk CJC, Bailey RJ, Johnson AG, Williams R, Murray-Lyon IM. Oesophageal function in cirrhotic patients undergoing injection sclerotherapy for oesophageal varices. *Digestion* 1978; **18:** 178-185.
112. Spence RAJ, Smith JA, Isaacs S, Terblanche J. Disturbed oesophageal motility after eradication of varices by chronic sclerotherapy – a scintigraphic study. *S Afr Med J* 1990; **77:** 138-140.
113. Snady H, Korsten MA. Esophageal acid-clearance and motility after endoscopic sclerotherapy of esophageal varices. *Am J Gastroenterol* 1986; **81:** 419-422.
114. Cohen LB, Simon C, Korsten MA, *et al*. Esophageal motility and symptoms after endoscopic injection sclerotherapy. *Dig Dis Sci* 1985; **30:** 29-32.
115. Shoenut JP, Micflikier AB. Retrosternal pain subsequent to sclerotherapy. *Gastrointest Endosc* 1986; **32:** 84-87.
116. DeMarino GB, Sumkin JH, Leventhal R, Van Thiel DH. Pneumatosis intestinalis and pneumoperitoneum after sclerotherapy. *AJR* 1988; **151:** 953-954
117. Scherl EJ, Fabry TL. Pseudo diverticula secondary to injection sclerotherapy. *J Clin Gastroenterol* 1983; **5:** 401-403.
118. Gottfried EB, Goldberg HJ. Mucosal bridge of the distal esophagus after esophageal variceal sclerotherapy. *Gastrointest Endosc* 1985; **31:** 267-269.
119. Barsoum MS, Mooro HA, Bolous FI, Ramzy AF, Rizk-Allah MA, Mahmoud FI. The complications of injection sclerotherapy of bleeding oesophageal varices. *Br J Surg* 1982; **69:** 79-81.
120. Charng MJ, Wang SP, Change MS. Coronary spasm complicating sclerotherapy of esophageal varices. *Chest* 1988; **93:** 204-205.
121. Perakos PG, Cirbus JJ, Camara DS. Persistent bradyarrhythmia after sclerotherapy for esophageal varices. *South Med J* 1984; **77:** 531-532.
122. Paterlini A, Salmi A, Buffoli F, Lombardi C. Heart failure and endoscopic sclerotherapy of variceal bleeding. *Lancet* 1984; **6:** 1241.
123. Imperiali G, Terruzzi V, Spotti D. Heart failure as a side effect of polidocanol given for oesophageal variceal sclerosis. *Endoscopy* 1986; **18:** 207.
124. Knauer CM, Fogel MR. Pericarditis: complication of esophageal sclerotherapy. Report of three cases. *Gastroenterology* 1987; **93:** 287-290.
125. Caletti GC, Brocchi E, Labriola E, Gassarrini G, Barbara L. Pericarditis: a probably overlooked complication of endoscopic variceal sclerotherapy. *Endoscopy* 1990; **22:** 144-145.
126. Brown DL, Luchi RJ. Cardiac tamponade and constrictive pericarditis complicating endoscopic sclerotherapy. *Arch Intern Med* 1987; **147:** 2169-2171.
127. Tabibian N, Schwartz JT, Smith JL, Graham DY. Cardiac tamponade as a result of endoscopic sclerotherapy: report of a case. *Surgery* 1987; **102:** 546-547.
128. Baydur A, Korula J. Cardiorespiratory effects of endoscopic esophageal variceal sclerotherapy. *Am J Med* 1990; **89:** 477-482.
129. Zeller FA, Cannan CR, Prakash UBS. Thoracic manifestations after esophageal variceal sclerotherapy. *Mayo Clin Proc* 1991; **66:** 727-732.
130. Sukigara M, Omuta R, Tatsuya M. Systemic dissemination of ethanolamine oleate after injection sclerotherapy for esophageal varices. *Arch Surg* 1985; **120:** 833-836.
131. Conners AF, Bacon BR, Miron SD. Sodium morrhuate delivery to the lung during endoscopic variceal sclerotherapy. *Ann Intern Med* 1986; **105:** 539-542.
132. DePuey EG, Richards WO, Milikan WJ. Scintigraphic detection of pulmonary embolization of esophageal variceal sclerosant. *Endoscopy* 1988; **20:** 91-94.

133. Korula J, Baydur A, Sassoon C, Sakimura I. Effect of esophageal variceal sclerotherapy (EVS) on lung function. *Arch Intern Med* 1986; **146:** 1517-1520.
134. Kitano S, Iso Y, Yamaga H, Hashizume M, Wada H, Sugimachi K. Temporary deterioration of pulmonary functions after injection sclerotherapy for cirrhotic patients with esophageal varices. *Eur Surg Res* 1988; **20:** 298-303.
135. Saks BJ, Kilby AE, Dietrich PA, Coffin LH, Krawitt EL. Pleural and mediastinal changes following endoscopic injection sclerotherapy of esophageal varices. *Radiology* 1983; **149:** 639-642.
136. Mauro MA, Jaques PF, Swantkowski TM, Staab EV, Bozynski EM. CT after uncomplicated esophageal sclerotherapy. *J Roentgenol* 1986; **147:** 57-60.
137. Carr-Locke DL, Sidky K. Broncho-oesophageal fistula: a late complication of endoscopic variceal sclerotherapy. *Gut* 1982; **23:** 1005-1007.
138. Alwmark A, Bengmark S, Borjesson B. Emergency and longterm transesophageal sclerotherapy of bleeding esophageal varices. *Scand J Gastroenterol* 1982; **17:** 409-412.
139. Gertsch P, Mosimann R. Chylothorax complicating sclerotherapy for bleeding oesophageal varices. *Br J Surg* 1983; **70:** 562-566.
140. Van Zaanen HCT, Schotborgh RH, Chamuleau RAFM. Meningococcus septicemia: a complication of endoscopic injection sclerotherapy. *Gastrointest Endosc* 1990; **85:** 631-632.
141. Baskin G. Prosthetic endocarditis after endoscopic variceal sclerotherapy: a failure of antibiotic prophylaxis. *Am J Gastroenterol* 1989; **84:** 311-312.
142. Kumar P, Mehta SK, Devi I, *et al.* Pyogenic meningitis and cerebral abscesses after endoscopic injection sclerotherapy. *Am J Gastroenterol* 1991; **86:** 1672-1674.
143. Wang WM, Chen CY, Jan CM, Chen LT, Wu DC. Central nervous system infection after endoscopic injection sclerotherapy. *Am J Gastroenterol* 1990; **85:** 865-867.
144. Robert JY, Raoul JL, Bretagne JF, *et al.* Unusual presentation of a case of brain abscess after endoscopic injection sclerotherapy of esophageal varices. *Endoscopy* 1991; **23:** 237-238.
145. Hassig WM, Dekovich AA. Brain abscess after sclerotherapy. *Am J Gastroenterol* 1992; **87:** 679 (L).
146. Cohen FL, Koerner RS, Taub SJ. Solitary brain abscess following endoscopic injection sclerosis of esophageal varices. *Gastrointest Endosc* 1985; **31:** 331-333.
147. Ritchie MT, Lightdale CJ, Botet JF. Bilateral perinephric abscesses: a complication of endoscopic injection sclerotherapy. *Am J Gastroenterol* 1987; **82:** 670-673.
148. Barnett JL, Elta G. Bacterial peritonitis following endoscopic variceal sclerotherapy. *Gastrointest Endosc* 1987; **33:** 316-317.
149. Tam F, Chow H, Prindiville T, *et al.* Bacterial peritonitis following esophageal injection sclerotherapy for variceal hemorrhage. *Gastrointest Endosc* 1990; **36:** 131-133.
150. Snady H, Korsten MA, Waye JD. The relationship of bacteremia to the length of injection needle in endoscopic variceal sclerotherapy. *Gastrointest Endosc* 1985; **31:** 243-246.
151. Gerhartz HH, Sauerbruch T, Weinzierl M. Nosocomial septicemia in patients undergoing sclerotherapy for variceal hemorrhage. *Endoscopy* 1984; **16:** 129-130.
152. Cohen LB, Korsten MA, Scherl EJ, Velez ME, Fisse RD, Arons EJ. Bacteraemia after endoscopic injection sclerosis. *Gastrointest Endosc* 1983; **29:** 198-200.
153. Camara DS, Gruber M, Barde CJ, Montes M, Caryana JA, Chung RS. Transient bacteremia following endoscopic injection sclerotherapy of oesophageal varices. *Arch Intern Med* 1983; **143:** 1350-1352.
154. Brayko CM, Kozarek RA, Sanowski RA, Testa AW. Bacteremia during oesophageal variceal sclerotherapy: its cause and prevention. *Gastrointest Endosc* 1985; **31:** 10-12.
155. Sauerbruch T, Holl J, Ruckdeschel G. Bacteraemia associated with endoscopic sclerotherapy of oesophageal varices. *Endoscopy* 1985; **17:** 170-172.
156. Low DE, Shoenut JP, Kennedy JK, Harding GKM, Den Boer B, Micflikier AB. Infectious complications of endoscopic injection sclerotherapy. *Arch Intern Med* 1986; **146:** 569-571.
157. Hegnhoj J, Andersen JR, Jarlov JO, Bendtsen F, Rasmussen HS. Bacteraemia after injection sclerotherapy of oesophageal varices. *Liver* 1988; **8:** 167-171.
158. Lorgat F, Madden MV, Kew G, *et al.* Bacteremia after injection of esophageal varices. *Surg Endosc* 1990; **4:** 18-19.
159. Ho H, Zuckerman MJ, Wassem C. A prospective controlled study of the risk of bacteremia in emergency sclerotherapy of esophageal varices. *Gastroenterology* 1991; **101:** 1642-1648.
160. Manzione NC, Das KM, Wolkoff AW, Carnevale N. Unusual sites of upper gastrointestinal variceal bleeding. *J Clin Gastroenterol* 1989; **9:** 40-42.
161. Korula J, Ralls P. The effects of chronic endoscopic variceal sclerotherapy on portal pressure in cirrhotics. *Gastroenterology* 1991; **101:** 800-805.
162. Foutch PG, Sivak MV. Colonic variceal hemorrhage after endoscopic injection sclerosis of esophageal varices: a report of three cases. *Am J Gastroenterol* 1984; **79:** 756-760.
163. Dilawari JB, Raju GS, Chawla YK. Development of large spleno-adreno-renal shunt after endoscopic sclerotherapy. *Gastroenterology* 1989; **97:** 421-426.
164. D'Amigo G, Montalbano L, Triana M, *et al.* Natural history of congestive gastropathy in cirrhosis. *Gastroenterology* 1990; **99:** 1558-1564.
165. Keane RM, Britton DC. Massive bleeding from rectal varices following repeated injection sclerotherapy of oesophageal varices. *Br J Surg* 1986; **73:** 120.
166. Fry RD, Fischer KC, Susman N, Shatz BA, Hulbert B. Adhesion-related variceal hemorrhage following sclerosis of esophageal varices. *Arch Surg* 1988; **123:** 94-95.
167. Arst HF, Reynolds JDH. Acute ileal variceal hemorrhage secondary to esophageal sclerotherapy. *J Clin Gastroenterol* 1986; **8:** 603-606.
168. Elefthenadis E. Duodenal varices after sclerotherapy for esophageal varices. *Am J Gastroenterol* 1988; **83:** 439-441.
169. McCormack TT, Smith PM, Rose JD, *et al.* Perforating veins and blood flow in oesophageal varices. *Lancet* 1983; **2:** 1442-1444.
170. Aoki H, Hasumi A, Shimazu M. The hemodynamics of esophagogastric varices: significance of esophagogastric arterial inflow in their information. In: Idezuki Y, ed. *Treatment of Esophageal Varices*. New York: Elsevier, 1988: 315-328.
171. Kang JH, Kambayashi J, Sakon M, *et al.* Mechanism of the haemostatic effect of ethanolamine oleate in the injection sclerotherapy for oesophageal varices. *Br J Surg* 1987; **74:** 50-53.
172. Musso R, Longo A, Triolo A, *et al.* Polidocanol may directly activate the contact phase of blood coagulation during sclerotherapy. *Gastrointest Endosc* 1987; **33:** 400-401.
173. Jacobson BF, Franz RC, Hurly EM, *et al.* Mechanism of thrombosis caused by sclerotherapy of esophageal varices using sodium tetradecyl sulphate. *Surg Endosc* 1992; **6:** 4-9.
174. Sarfeh IJ. Portal vein thrombosis associated with cirrhosis. Clinical importance. *Arch Surg* 1979; **114:** 902-905.
175. Okuda K, Ohnishi K, Kimura K. Incidence of portal vein thrombosis in liver cirrhosis. An angiographic study on 708 patients. *Gastroenterology* 1985; **89:** 279-286.
176. Belli L, Sansalone CV, Aseni P. Portal vein thrombosis in cirrhosis. A retrospective analysis. *Ann Surg* 1986; **203:** 286-291.
177. Thatcher BS, Sivak MV, Ferguson DR, Petras REl. Mesenteric venous thrombosis as a possible complication of endoscopic sclerotherapy: a report of two cases. *Am J Gastroenterol* 1986; **81:** 126-129.
178. Goldberg H, Fabry TL. Mesenteric thrombosis following sclerotherapy during vasopressin infusion: mechanism and therapeutic implications. *J Clin Gastroenterol* 1989; **11:** 56-57.
179. Ashida H, Kotoura Y, Nishioka A, *et al.* Portal and mesenteric venous thrombosis as a complication of endoscopic sclerotherapy. *Am J Gastroenterol* 1989; **84:** 306-310.
180. Deboever G, Elegeert I, Defloor E. Portal and mesenteric venous thrombosis after endoscopic injection sclerotherapy. *Am J Gastroenterol* 1989; **84:** 1336-1337.
181. Stoltenberg PH, Goodale RL, Silvis SE. Portal vein thrombosis following combined endoscopic variceal sclerosis and vasopressin therapy for bleeding varices. *Am J Gastroenterol* 1987; **82:** 1297-1300.
182. Hunter GC, Steinkirchner T, Burbige EJ, Guernsey JM, Putnam CW. Venous complications of sclerotherapy of esophageal varices. *Am J Surg* 1988; **156:** 497-501.
183 Chaudhary A, Tatke M, Aranya RC. Endoscopic sclerotherapy: the far and near effects. *Br J Surg* 1990; **77:** 963.
184. Kawasaki S, Henderson JM, Riepe SP, Brooks WS, Hertzler G. Endoscopic variceal sclerosis does not increase the risk of portal venous thrombosis. *Gastroenterology* 1992; **102:** 206-215.
185. Sato T, Yamazaki K, Toyota J, Karino Y, Ohmura T, Suga T. Inflammatory tumor in pancreatic tail induced by endoscopic ablation with cyanoacrylate glue for gastric varices. *J Gastroenterol* 2004; **39:** 475-478.
186. Lee YT, Chan FK, Ng EK, *et al.* EUS-guided injection of cyanoacrylate for bleeding gastric varices. *Gastrointest Endosc* 2000; **52:** 168-174.
187. Bhasin DK, Sharma BC, Prasad H, Singh K. Endoscopic removal of sclerotherapy needle from gastric varix after N-butyl-2-cyanoacrylate injection. *Gastrointest Endosc* 2000; **51:** 497-498.
188. Lorenz A, Stadtler N, Schulz HJ. Laser disintegration of cyanoacrylate clot with successful endoscopic removal of sclerotherapy needle from gastric varix. *Endoscopy* 2002; **34:** 670-672.
189. Akahoshi T, Hashizume M, Shimabukuro R, *et al.* Long-term results of endoscopic Histoacryl injection sclerotherapy for gastric variceal bleeding: a 10-year experience. *Surgery* 2002; **131:** 1 Suppl, S176-S181.
190. Yu LK, Hsu CW, Tseng JH, Liu NJ, Sheen IS. Splenic infarction complicated by splenic artery occlusion after N-butyl-2-cyanoacrylate injection for gastric varices: case report. *Gastrointest Endosc* 2005; **61:** 343-345.
191. Wahl P, Lammer F, Conen D, Schlumpf R, Bock A. Septic complications after injection of N-butyl-2-cyanoacrylate: report of two cases and review. *Gastrointest Endosc* 2004; **59:** 911-916
192. Kok K, Bond RP, Duncan IC, *et al.* Distal embolization and local vessel wall ulceration after gastric variceal obliteration with N-butyl-2-cyanoacrylate: a case report and review of the literature. *Endoscopy* 2004; **36:** 442-446.

193. Turler A, Wolff M, Dorlars D, Hirner A. Embolic and septic complications after sclerotherapy of fundic varices with cyanoacrylate. *Gastrointest Endosc* 2001; **53:** 228-230.
194. Huang YH, Yeh HZ, Chen GH, *et al.* Endoscopic treatment of bleeding gastric varices by N-butyl-2-cyanoacrylate (Histoacryl) injection: long-term efficacy and safety. *Gastrointest Endosc* 2000; **52:** 160-167.
195. Roesch W, Rexroth G. Pulmonary, cerebral and coronary emboli during bucrylate injection of bleeding fundic varices. *Endoscopy* 1998; **30:** S89-S90.
196. Hwang SS, Kim HH, Park SH, *et al.* N-butyl-2-cyanoacrylate pulmonary embolism after endoscopic injection sclerotherapy for gastric variceal bleeding. *J Comput Assist Tomogr* 2001; **25:** 16-22.
197. Lo GH, Lai KH, Cheng JS, Chen MH, Chiang HT. A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. *Hepatology* 2001; **33:** 1060-1064
198. Nevens F, Rutgeerts P. Variceal band ligation in the management of bleeding oesophageal varices: an overview. *Dig Liver Dis* 2001; **33:** 284-287.
199. Tuncer K, Ozutemiz O. An unusual complication of esophageal variceal band ligation: iatrogenic esophageal foreign body. *Endoscopy* 2003; **35:** 460.
200. Young MF, Sanowski RA, Rasche R. Comparison and characterization of ulcerations induced by endoscopic ligation of esophageal varices versus endoscopic sclerotherapy. *Gastrointest Endosc* 1993; **39:** 119-122.
201. Berner JS, Gaing AA, Sharma R, Almenoff PL, Muhlfelder T, Korsten MA. Sequelae after esophageal variceal ligation and sclerotherapy: a prospective randomized study. *Am J Gastroenterol* 1994; **89:** 852-858.
202. Laine L, El Newihi HM, Migikovsky B, Sloane R, Garcia F. Endoscopic ligation compared with sclerotherapy for the treatment of bleeding esophageal varices. *Ann Intern Med* 1993; **119:** 1-7.
203. Gimson AES, Ramage JK, Panos MZ, *et al.* Randomised trial of variceal banding ligation versus injection sclerotherapy for bleeding esophageal varices. *Lancet* 1993; **342:** 391-394.
204. Lo GH, Lai KH, Cheng JS, *et al.* A prospective, randomized trial of sclerotherapy versus ligation in the management of bleeding esophageal varices. *Hepatology* 1995; **22:** 466-471.
205. Hou MC, Lin HC, Kuo BIT, Chen CH, Lee FY, Lee SD. Comparison of endoscopic variceal injection sclerotherapy and ligation for the treatment of esophageal variceal hemorrhage: A prospective randomized trial. *Hepatology* 1995; **21:** 1517-1522.
206. Sarin SK, Govil A, Jain AK, *et al.* Prospective randomized trial of endoscopic sclerotherapy versus variceal band ligation for esophageal varices: influence on gastropathy, gastric varices and variceal recurrence. *Hepatology* 1997; **26:** 826-832.
207. Baroncini D, Milandri GL, Borioni D, *et al.* A prospective randomized trial of sclerotherapy versus ligation in the elective treatment of bleeding esophageal varices. *Endoscopy* 1997: **29:** 235-240.
208. Avgerinos A, Armonis A, Manolakopoulos S, *et al.* Endoscopic sclerotherapy versus variceal ligation in the long-term management of patients with cirrhosis after variceal bleeding. A prospective randomised study. *J Hepatol* 1997; **26:** 1034-1041.
209. Masci E, Stigliano R, Mariani A, *et al.* Prospective multicenter randomized trial comparing banding ligation with sclerotherapy of esophageal varices. *Hepatogastroenterology* 1999; **46:** 1769-1773.
210. de la Pena J, Rivero M, Sanchez E, Fabrega E, Crespo J, Pons-Romero F. Variceal ligation compared with endoscopic sclerotherapy for variceal hemorrhage: prospective randomized trial. *Gastrointest Endosc* 1999; **49:** 417-423.
211. Fakhry S, Omar M, Gannam M, *et al.* Endoscopic sclerotherapy versus endoscopic variceal ligation in the management of bleeding esophageal varices: a prospective randomized study in schistosomal hepatic fibrosis. *Endoscopy Arab Edition* 2000; **1:** 39-44.
212. Zargar SA, Javid G, Khan BA, *et al.* Endoscopic ligation vs. sclerotherapy in adults with extrahepatic portal venous obstruction: a prospective randomized study. *Gastrointest Endosc* 2005; **61:** 58-66.
213. Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding. A meta-analysis. *Ann Intern Med* 1995; **123:** 280-287.
214. Laine L, Stein C, Sharma V. Randomized comparison of ligation versus ligation plus sclerotherapy in patients with bleeding esophageal varices. *Gastroenterology* 1996; **110:** 529-533.
215. Saeed ZA, Stiegmann GV, Ramirez FC, *et al.* Endoscopic variceal ligation is superior to combined ligation and sclerotherapy for esophageal varices: A multicenter prospective randomized trial. *Hepatology* 1997; **25:** 71-74.
216. Umehara M, Onda M, Tajiri T, Toba M, Yoshida H, Yamashita K. Sclerotherapy plus ligation versus ligation for the treatment of esophageal varices: a prospective randomized study. *Gastrointest Endosc* 1999; **50:** 7-12.
217. Al Traif I, Fachartz FS, Al Jumah A, *et al.* Randomized trial of ligation versus combined ligation and sclerotherapy for bleeding esophageal varices. *Gastrointest Endosc* 1999; **50:** 1-6.
218. Djurdjevic D, Janosevic S, Dapcevic B, *et al.* Combined ligation and sclerotherapy versus ligation alone for eradication of bleeding esophageal varices: a randomized and prospective trial. *Endoscopy* 1999; **31:** 286-290.
219. Argonz J, Kravetz D, Suarez A, *et al.* Variceal band ligation and variceal band ligation plus sclerotherapy in the prevention of recurrent variceal bleeding in cirrhotic patients: a randomized, prospective and controlled trial. *Gastrointest Endosc* 2000; **51:** 157-163.
220. Hou MC, Lin HC, Kuo BI, Lee FY, Chang FY, Lee SD. The rebleeding course and long-term outcome of esophageal variceal hemorrhage after ligation: comparison with sclerotherapy. *Scand J Gastroenterol* 1999; **34:** 1071-1076.
221. Karsan HA, Morton SC, Shekelle PG, *et al.* Combination endoscopic band ligation and sclerotherapy compared with endoscopic band ligation alone for the secondary prophylaxis of esophageal variceal hemorrhage: a meta-analysis. *Dig Dis Sci* 2005; **50:** 399-406.
222. Bhargava DK, Pokharna R. Endoscopic sclerotherapy versus endoscopic variceal ligation and endoscopic sclerotherapy: a prospective randomized study. *Am J Gastroenterol* 1997; **92:** 950-953.
223. Lo GH, Lai KH, Cheng JS, *et al.* The additive effect of sclerotherapy to patients receiving repeated endoscopic variceal ligation: a prospective, randomized trial. *Hepatology* 1998; **28:** 391-395.
224. Masumoto H, Toyonaga A, Oho K, Iwao T, Tanikawa K. Ligation plus low-volume sclerotherapy for high-risk esophageal varices: comparisons with ligation therapy or sclerotherapy alone. *J Gastroenterol* 1998; **33:** 1-5.
225. Iso Y, Kawanaka H, Tomikawa M, Matsumata T, Kitano S, Sugimachi K. Repeated injection sclerotherapy is preferable to combined therapy with variceal ligation to avoid recurrence of esophageal varices: A prospective randomized trial. *Hepatogastroenterology* 1997; **44:** 467-471.
226. Garg PK, Joshi YK, Tandon RK. Comparison of endoscopic variceal sclerotherapy with sequential endoscopic band ligation plus low-dose sclerotherapy for secondary prophylaxis of variceal hemorrhage: a prospective randomized study. *Gastrointest Endosc* 1999; **50:** 369-373.
227. Shigemitsu T, Yoshida T, Harada T, Takeo Y, Nakamura H, Okita K. Endoscopic injection sclerotherapy with ligation versus endoscopic injection sclerotherapy alone in the management of esophageal varices: a prospective randomized trial. *Hepatogastroenterology* 2000; **47:** 733-737.
228. Nishikawa Y, Hosokawa Y, Doi T, *et al.* Evaluation of endoscopic injection sclerotherapy with and without simultaneous ligation for the treatment of esophageal varices. *J Gastroenterol* 1999; **34:** 159-162.
229. Maluf-Filho F, Sakai P, Ishioka S, Matuguma SE. Endoscopic sclerosis versus cyanoacrylate endoscopic injection for the first episode of variceal bleeding: a prospective, controlled, and randomized study in Child-Pugh class C patients. *Endoscopy* 2001; **33:** 421–427.