Taking the tension out of portal hypertension

Bleeding from oesophageal varices is the most serious complication of portal hypertension and accounts for most cirrhosis-related deaths.[1] A quarter of high-risk cirrhotic patients with liver decompensation who present with a first major variceal bleed die as a consequence of the bleed.[2] After control of the index bleed, there is a 70% chance of rebleeding with a similar mortality if further effective treatment is not given.[3] Mortality is related to several factors, including failure of rapid control of initial bleeding, early rebleeding, presence and severity of underlying liver disease and functional hepatic reserve.[4] Optimal emergency management requires an efficient and organised team to provide accurate initial assessment of the patient, effective resuscitation, rapid endoscopic diagnosis, successful intervention with control of bleeding, and prevention of early rebleeding as well as the anticipated complications of liver decompensation including spontaneous bacterial peritonitis, progressive liver and renal failure and hepatic encephalopathy.[5] The modern management of acute, persistent variceal bleeding is therefore best accomplished by a skilled, knowledgeable and well-equipped team that can offer the full spectrum of treatment options.[6]

The treatment of variceal haemorrhage has evolved markedly in the past decade.[4,7] Substantive advances in the control of acute variceal bleeding have included new and effective drugs,[8] improved endoscopic tools and techniques and refinements in variceal ligation equipment.[9,10] The selective use of radiologically inserted transjugular intrahepatic portosystemic shunts as salvage intervention for intractable bleeding,[11,12] a diminishing role of narrow-diameter polytetrafluoroethylene interposition portacaval shunts[13] and the exponentially increasing demand for liver transplantation[14] in patients with progressive hepatic decompensation and intractable variceal bleeding have further improved survival. Despite these advances in treatment, uncontrolled or recurrent bleeding from varices and the consequences of progressive liver failure remain the commonest causes of early death in cirrhotic patients,[15] emphasising the need for medical staff to act swiftly and decisively as soon as the patient reaches hospital.[16]

Several important clinical considerations influence the choice of therapy as well as the prognosis in individual patients. These include the natural history of the disease causing the portal hypertension, location and extent of the bleeding varices, residual hepatic function, presence of associated systemic disease, continuing alcohol abuse, patency of major splanchnic veins and response to each specific treatment.[4] The natural history of cirrhosis is dependent on the degree of functional liver decompensation, the magnitude of variceal bleeding and the presence of additional complications such as ascites, spontaneous bacterial peritonitis, portal vein thrombosis or hepatocellular carcinoma.[17] Progressive liver decompensation occurs more rapidly in patients with alcoholic cirrhosis than in those with cirrhosis caused by viral hepatitis B or C and is often associated with super-added alcoholic hepatitis. Once decompensation occurs in cirrhotic patients, mortality without organ replacement is as high as 85% over 5 years.[18] Defining prognosis is an essential part of the assessment of cirrhosis and forms the basis of any future treatment decisions.[19]

The spectrum of interventions required to control recurrent variceal bleeding and achieve efficient and successful treatment of the severe and potentially life-threatening complications of portal hypertension have become increasingly invasive, resource-dependent and sophisticated and often require advanced specialist skills.[20] Selection of the appropriate intervention is critical as the rational treatment of oesophageal varices requires a full appreciation of the haemodynamic consequences of variceal bleeding and a clear understanding of the risks of rebleeding and the response to each specific intervention.[21] The ideal treatment of portal hypertension and bleeding varices should be universally effective, safe, easy to administer and inexpensive. As no such panacea exists, and no single treatment is applicable to all patients, knowledge of the alternatives allows the well-informed surgeon, gastro-enterologist, hepatologist or intensivist to choose the appropriate therapy for each clinical situation.

The advent of modern endoscopic therapy has moved the endoscopist to centre stage in the initial management of variceal bleeding.[22] Because diagnostic endoscopy is key to the confirmation of bleeding varices, the endoscopist's role as gatekeeper is pivotal in variceal management.[23] Sustained control of acute bleeding is critical for survival because marginal liver function worsens inexorably with each subsequent major bleed.[7] An analysis of the incidence of death due to uncontrolled variceal bleeding in 8 combined studies involving 1 488 patients reported an 8% mortality for exsanguination within 48 hours of admission to hospital,[24] while in another survey death due to uncontrolled bleeding occurred in 6.2% of patients.[15] Even when initial control of variceal bleeding is successful, there is a significant chance of rebleeding. Early rebleeding is a strong predictor of mortality and recurrent variceal bleeding substantially increases the risk of complications which further contribute to mortality,[24] emphasising that rapid and lasting control of variceal bleeding remains the principal imperative of endoscopic intervention.[7]

The extent and urgency of initial therapy for variceal bleeding depends on the magnitude and severity of the bleeding episode.[4] Establishment and maintenance of a secure airway, and prompt resuscitation with restoration of circulating blood volume, are vital and precede any diagnostic studies.[5] Both intravenous and central venous access may be necessary, the latter preferably after correction of existing coagulopathy. While blood is being cross-matched, crystalloid solution is rapidly infused until the blood pressure is restored

and urine output is adequate. Saline infusions may aggravate ascites and should be avoided, and overzealous expansion of circulating blood volume may cause a rebound increase in portal pressure and precipitate further bleeding.[15] Patients who are haemodynamically unstable, elderly or who have cardiac or pulmonary disease should be monitored using a pulmonary artery catheter because injudicious administration of fluids combined with vaso-active drugs may lead to rapid onset of oedema, ascites and hyponatraemia.[4] Clotting factors are often deficient and fresh blood, fresh-frozen plasma and vitamin K_1 are frequently required.[5] Platelet transfusions may be necessary. Sedatives should be avoided to prevent worsening of incipient encephalopathy. All patients with cirrhosis and upper gastro-intestinal bleeding should receive short-term prophylactic antibiotics to prevent serious infectious complications.[25]

Empirical pharmacological therapy has a critical advantage in that special technical expertise for administration and monitoring is not required. Most endoscopy units recommend that pharmacological therapy be started when a diagnosis of variceal bleeding is suspected and before emergency endoscopy is performed.[25] This policy has the theoretical advantage of controlling bleeding before the initial endoscopy, which makes both diagnosis and immediate endoscopic therapy easier. The selection of vaso-active therapy depends on local resources. Glypressin (terlipressin), the synthetic analogue of vasopressin, is the vasoconstrictor of choice, with few side-effects and the added advantage of being effective in 2 mg intravenous bolus doses administered 4-hourly, simplifying administration. Early administration of glypressin has shown to improve survival.[25] Somatostatin and its synthetic analogues, octreotide and vapreotide, stop variceal bleeding in up to 80% of patients, and because of their excellent safety profile can be used without special monitoring. Beta-blockade is ineffective and contraindicated in patients who are actively bleeding and are shocked.[25]

Variceal band ligation is as effective as injection sclerotherapy and is the endoscopic intervention of choice both for acute variceal bleeding and long-term variceal eradication therapy.[9] Most endoscopists prefer immediate intervention during the diagnostic endoscopy with application of bands at and above the bleeding site. Balloon tamponade is a useful temporary bridge in the case of massive uncontrolled or recurrent bleeding. Continued life-threatening variceal bleeding after two endoscopic procedures requires escalation of therapy.[1] The introduction of minimally invasive, radiologically placed transjugular intrahepatic portosystemic shunts (TIPS) is a valuable rescue therapy for patients with uncontrolled or refractory variceal bleeding unresponsive to standard pharmacological and endoscopic therapy. TIPS placement has a mortality rate of less than 1% and morbidity rates less than 10% in skilled hands in selected patients. The major disadvantages after TIPS are stent dysfunction and hepatic encephalopathy.[2,13]

All patients are at high risk for rebleeding after control of the first variceal bleed. Either endoscopic variceal band ligation or pharmacological treatment with β-adrenergic blockers is an accepted first-line therapy to prevent variceal rebleeding. Non-selective, i.e. blocking both β-1 cardiac and β-2 vascular receptors, β-adrenergic blockers should be used.[8] The major disadvantages of β-adrenergic blockers in clinical practice are the substantial number of cirrhotic patients (up to 20%) who have contraindications precluding the use of β-blockers and an additional 5% of patients who develop intolerance to treatment that results in withdrawal of the medication. A further significant disadvantage is that only 40% of patients receiving long-term β-blockers achieve the desired therapeutic reduction in portal pressure of 20% from baseline or to levels less than 12 mmHg.[26] Failure to achieve these haemodynamic targets is the strongest independent predictor of variceal rebleeding.[26] More recently, β-blockers in combination with isosorbide mononitrates, which enhance the reduction in portal pressure, have been used.

Several studies have sought to identify prognostic indicators associated with early variceal rebleeding. Multivariate analyses have demonstrated that active bleeding at emergency endoscopy,[27-31] variceal size,[32] Child-Pugh grade,[27,30-34] Child-Pugh score,[28,30,35,36] haematocrit levels,[27,35] bacterial infection,[30,35,37,38] encephalopathy,[28] portal vein thrombosis,[27] platelet count,[28] hepatocellular carcinoma,[32,35] continued alcohol abuse,[28,32,35] hypo-albuminaemia[30] and a hepatic venous pressure gradient >20 mmHg[35,39-42] measured shortly after admission have been identified as independent prognostic factors for early rebleeding[30] and significant predictors of risk for 5-day failure to control bleeding.[40,43] However, the conclusions in these studies are often discordant and the predictive value of the results difficult to assess from the data. Differences in these studies include an absence of rigorous endoscopic criteria for defining variceal rebleeding, lack of standardisation of time of entry and wide differences in patient sampling (percentage of alcoholics, percentage of Child-Pugh grade of patients, active bleeding at endoscopy) which question the validity of these data and the relevance and applicability to other population groups.

There is a wide variation in the reported mortality rates after the first episode of variceal bleeding related in particular to differences in the interpretation of time 'zero' and the inclusion of patients beyond the first 48 hours of onset of initial bleeding. In addition, some studies include patients who have had a first bleed as well as patients who present with subsequent variceal bleeds. In these selected groups, mortality rates differ markedly. Published studies also include widely differing proportions of alcoholic and Child-Pugh grade C patients.[44] The most frequently reported predictive factors associated with an increased mortality at 6 weeks are active bleeding at endoscopy,[45] variceal size,[46] hypovolaemic shock,[33,47,48] units of blood transfused,[49] early rebleeding,[28,33,50] Child-Pugh grade,[33,34,51-53] model for end-stage liver disease (MELD) score >15,[54] HVPG >20 mmHg,[47] renal failure,[47,55] blood urea or creatinine,[28,35,56-59] total bilirubin,[57,59,60] international normalised ratio (INR),[49,56,57] ascites,[60] hepatic encephalopathy,[28,49,56,61] albumin,[52,62] bacterial infection,[53] hepatocellular carcinoma,[46,47,54,59,60] continued alcohol abuse[46] and age.[48,61] Unfortunately the consistency of these results is variable and conflicting because of small sample sizes, potential referral bias, dissimilar study end-points, differences in patient selection, causes of cirrhosis and techniques of endoscopic intervention and they have not found general utility in current portal hypertensive literature.

Several studies have attempted to develop a classification that can both characterise the degree of liver injury and predict the prognosis of patients with cirrhosis on the basis of clinical and laboratory variables.[18] Because of its simplicity and ease of use, the Child-Pugh classification has been widely used to predict survival in cirrhotic patients and the development of complications such as variceal bleeding and

response to surgical intervention.[63] The major limitations in the Child-Pugh classification are lack of inter-observer concordance and clinical subjectivity in assessing the degree of ascites and encephalopathy and the poor discrimination in patients with Child-Pugh scores between 10 and 15 in class C. The MELD score, which was originally designed to assess the prognosis of cirrhotic patients having a transjugular intrahepatic portosystemic shunt, is a continuous score relying on three objective variables.[64] MELD has replaced the Child-Pugh score in Europe and the USA for prioritising liver donor allocation according to a 'sickest first' policy.[15] MELD is based on creatinine, bilirubin, and the INR and is considered more reproducible because the components do not include subjective variables such as ascites and encephalopathy.[64] However, both the Child-Pugh and MELD scores can vary substantially if single variables are modified by medical treatment such as an albumin infusion, ascitic paracentesis, or over-zealous diuretic therapy, which can increase serum creatinine. MELD best predicts 3-month survival of cirrhotic patients, irrespective of cause. In studies by Bambha *et al.*,[65] Chalasani *et al.*[58] and Amitrano *et al.*[54] MELD was a clinically useful and objective predictor of short-term survival after acute variceal bleeding. However, current interest in prognostic scoring in acute variceal bleeding continues to evolve, and modified versions of both the original Child-Pugh and MELD scores are now available.[66]

Substantial progress in the treatment of variceal bleeding has occurred since the review 'Taking the tension out of the portal system' by the Kings College Liver Group.[67] However, despite the plethora of randomised controlled trials in portal hypertensive bleeding, there is considerable variation in the quality of studies with regard to selection, assessment and attrition bias, with consequent deficiencies leaving unanswered questions. Understanding the problems inherent in the design, execution and interpretation of clinical trials in portal hypertension is critical in deciding whether the results apply to the care of a specific patient.[22] For example, when assessing endoscopic control of bleeding and survival in patients with varices, trials with a large proportion of alcoholic patients who have advanced cirrhosis and liver decompensation are less likely to show a difference in bleeding control as death from recurrent bleeding is replaced by early death from liver failure in a high-risk population.[22] The implications for future research into portal hypertension are that adequately powered, adequately conducted, properly reported multicentre trials need to continue to address unresolved issues. As patient trial recruitment becomes an increasing impediment, future studies will require uniform and internationally accepted protocols to facilitate aggregate analyses and future meta-analyses. In addition, the ever-increasing demand for medical fiscal discipline and logistic efficiency requires that cost factors be adequately addressed in prospective studies. These issues have been raised at the Baveno Consensus Conferences.[47,68-70] Identification and knowledge of accurate prognostic factors predicting early rebleeding should ideally provide a powerful tool to identify at an early stage those patients in whom conventional treatment is likely to be unsuccessful and who require urgent implementation of an aggressive salvage strategy. Future prospective studies incorporating and evaluating the full spectrum of prognostic factors including clinical variables, liver biochemistry, endoscopic intervention, portal pressures and comparative MELD and Child-Pugh assessment will be valuable advances in improving the effective and rational management of patients with bleeding oesophageal varices and portal hypertension.

J. E. J. Krige

Surgical Gastroenterology
Department of Surgery
University of Cape Town

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