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REVIEW

Portal hypertension: pathophysiology, diagnosis and management

S. Bloom,[1] W. Kemp[2] and J. Lubel[1]

[1]Gastroenterology and Hepatology, Eastern Health and [2]Gastroenterology and Hepatology, Alfred Health, Melbourne, Victoria, Australia

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Correspondence
John Lubel, Level 2, 5 Arnold Street, Box Hill, Vic. 3128, Australia.
Email: john.lubel@monash.edu.au

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Abstract

Portal hypertension is an important complication of liver disease. As a result of elevated pressures within the portal vein several complications can arise, including the development of oesophageal and gastric varices, ascites, hepatic encephalopathy as well as complications secondary to circulatory dysfunction, such as hepatorenal syndrome, portopulmonary syndrome and hepatopulmonary syndrome. This review outlines the pathogenesis and diagnosis of portal hypertension and outlines the management of these various important clinical sequelae. The management of oesophageal and gastric varices is particularly important, and both the emergency management together with prophylactic management of this condition are described.

Introduction

Many of the clinically significant complications of cirrhosis arise as a consequence of increased portal hypertension (PHT). This is defined as hepatic venous pressure gradient (HVPG) greater than 5 mmHg, with complications arising once this exceeds 10 mmHg. Portal hypertensive complications are associated with high morbidity and mortality and include variceal bleeding, portal hypertensive gastropathy, ascites and hepatic encephalopathy. These conditions present a challenge to the Australian health system with the economic costs associated with treating liver disease estimated to be higher than that of type 2 diabetes and chronic kidney disease combined.[1] Over the past decade, our understanding of portal hypertension has increased dramatically allowing for optimisation of management and new therapeutic approaches.

Portal hypertension pathophysiology

The portal vein acts as the major outflow tract for the splanchnic circulation. The portal system is a low pressure, low resistance system. In the healthy state, considerable post-prandial increases in portal venous blood flow do not significantly alter portal pressure due to the highly compliant nature of this system. The normal portal vein pressure is 5 mmHg or less and is a product of blood flow (Q) and resistance (R) according to Ohm's law:

$$\text{Portal Pressure} = \text{Q (blood flow)} \times \text{R (portal resistance)}$$

The aetiology of increased portal resistance is commonly categorised according to anatomical location into pre-hepatic, intra-hepatic and post-hepatic causes (Table 1). In the western world, sinusoidal PHT secondary to cirrhosis is the most common cause of PHT.

In cirrhosis, the architectural changes associated with fibrosis and nodule formation result in a fixed alteration to sinusoidal blood flow. In contrast to this fixed hepatic resistance, there is a dynamic component which arises from contraction of myofibroblasts within the space of Disse.[2] These myofibroblasts originate from hepatic stellate cells, which in the healthy state are the predominant storage site for vitamin A. In the presence of inflammation, cytokines released from injured hepatocytes stimulate the recruitment and transdifferentiation of hepatic stellate cells into contractile myofibroblasts with the capacity to deposit collagen. An excess of locally produced vasoconstrictor peptides together with a relative depletion in hepatic nitric oxide

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Table 1 Classification of portal hypertension by anatomical location

Post-hepatic	Luminal vascular obstruction
	• Budd–Chiari syndrome
	• Myeloproliferative disorders
	• Genetic prothrombotic predisposition (JAK2, anti-phospholipid syndrome, factor 5 Leiden, prothrombin gene mutation)
	• Congenital webs
	• Thrombosis
	• Vena cava syndrome
	Extraluminal vascular compression
	Congestion
	• Right heart failure, constrictive pericarditis, pulmonary hypertension
Intra-hepatic	Pre-sinusoidal
	• Early schistosomiasis, primary biliary cirrhosis
	• Idiopathic portal hypertension
	• Cystic fibrosis
	Sinusoidal
	• Acute/chronic viral hepatitis
	• Acute alcoholic hepatitis
	• Nodular regenerative hyperplasia
	• Infiltrative disorders (e.g. lymphoproliferative and myeloproliferative diseases)
	Post-sinusoidal
	• Veno-occlusive disease (sinusoidal obstruction syndrome)
	• Graft versus host disease
	• Chemotherapeutic agents used prior to haematopoietic stem transplantation
	• 6 – mercaptopurine, oxalliplatin, tacrolimus and aziathioprine
Pre-hepatic	Congenital portal vein atresia
	Intraluminal obstruction (thrombus, neoplasia)
	• Thrombosis
	• Malignancy
	• Myeloproliferative disorders
	• Genetic pro-thrombotic predisposition
	• Inflammatory event (pancreatitis)
	• Intra-abdominal infection
	Extraluminal vascular compression
	• Pancreatitic malignancy
	• Retroperitoneal fibrosis

(NO) contribute to this dynamic component of hepatic resistance. These reversible components may represent up to 30% of the total resistance to portal blood flow.[3]

The increased pressure within the portal venous system induces shear stresses in the splanchnic vessels, and together with translocation of bacterial lipopolysaccharides results in excessive systemic NO production.[4] The subsequent systemic vasodilatation activates several homeostatic regulatory systems, such as the renin-angiotensin-aldosterone system (RAAS) and antidiuretic hormone (ADH) causing sodium and water retention. These events result in an increase in splanchnic vasodilation and blood flow with resultant increase in flow into the portal venous system further exacerbating PHT.[2]

Detection of portal hypertension

The presence of portal hypertension may be clinically silent; however, findings such as splenomegaly, ascites and abdominal wall collaterals (caput medusae) strongly suggest its presence. Radiological imaging, such as Doppler ultrasound and computed tomography may demonstrate the presence of collateral vessels, alterations in portal venous flow, splenomegaly and ascites, thereby supporting the diagnosis of portal hypertension. Despite this, the first presentation of portal hypertension may be with variceal haemorrhage, and this needs to be urgently excluded in any patient with suspected liver disease who has significant gastrointestinal haemorrhage.

Direct measurement of portal venous pressures is invasive and requires significant procedural experience. This technique involves the introduction of a balloon catheter through the jugular or femoral vein into the hepatic vein. The HVPG is derived from subtracting free hepatic vein pressure (FHVP) from wedge hepatic vein pressure (WHVP):

$$\text{HVPG} = \text{WHVP} - \text{FHVP}$$

PHT is defined by an HVPG > 5 mmHg. Clinically significant PHT is defined as an HVPG ≥ 10 mmHg. This threshold is required for the development of complication of PHT, such as porto-systemic collaterals, varices, ascites and circulatory dysfunction. Variceal haemorrhage is associated with HVPG greater than 12 mmHg and when HVPG is greater than 20 mmHg following variceal haemorrhage, the risk of death increases fivefold.[5] Likewise, the risk for development of hepatocellular carcinoma increases to sixfold when the HVPG is >10 mmHg.[6]

The routine use of HVPG in clinical practice is generally limited to specialist centres. The role that less invasive methods of predicting PHT, such as liver stiffness measurement (LSM) using transient elastography, is yet to be established. The ideal LSM to determine significant PHT requires further validation; however an LSM of >20 kpa appears to have a high specificity (92.3%), while an LSM > 13 kpa has a high sensitivity for PHT (94%).[7,8] The use of a ratio of spleen size and platelet count in combination with LSM may overcome these limitations with recent literature demonstrating a combined sensitivity and specificity greater than 80% for detection of significant PHT.[9]

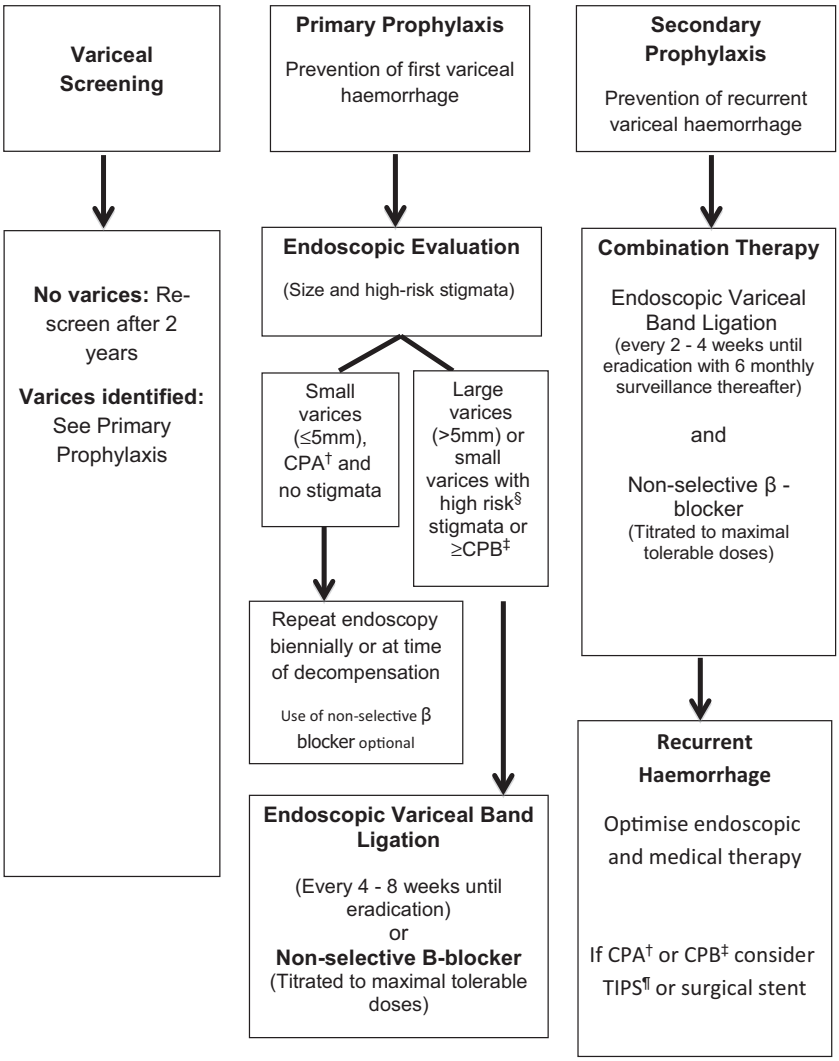

Figure 1 Modern variceal haemorrhage prophylaxis. †Child–Pugh A (CPA) score. ‡Child–Pugh B (CPB) score. §Red spots, wheals and stigmata of recent bleeding. ¶Transjuglar intrahepatic portosystemic shunt.

Complications of portal hypertension

Gastrointestinal haemorrhage

Oesophageal varices

Oesophageal varices are present in 40% of patients with an initial diagnosis of Child–Pugh A cirrhosis and in 60% of patients with signs of decompensation.[10,11] Those without varices at initial assessment develop them at an incidence of 7% per year.[11] Seven per cent of small varices (<5 mm) will bleed over a 2-year period compared with 30% of large varices.[11] The risk of subsequent haemorrhage is determined by the degree of underlying hepatic dysfunction, size of varices and presence of high-risk stigmata at endoscopy.

Primary prophylaxis The treatment of varices before a bleeding episode has occurred is referred to as primary prophylaxis (Fig. 1). It is recommended to perform a gastroscopy to determine the presence and size of oesophageal or gastric varices at the time of diagnosis of cirrhosis or at the time of new onset hepatic decompensation. In those with absent or only small varices, biennial surveillance is recommended. Non-selective beta blockade (NSBB) does not appear to prevent variceal development,[12,13] but may be used in patients with large varices or those with stigmata associated with high bleeding risk, as an alternative to endoscopic variceal band ligation (EVBL). NSBB reduce portal pressure by reducing cardiac output and splanchnic vasodilatation (Table 2). At 2 years, the bleeding risk is reduced from 25% to 15%, with a reduction in mortality from 27% to 23%.[10] The doses are typically aimed at reducing the resting pulse rate by 25% or to 55 b.p.m.; however, only 30–40% of patients reduce HPVG by the recommended 20% or to <12 mmHg.[16] The combination of nitrates and NSBB

Table 2 Vasoactive agents in portal hypertension

Agent	Mechanism of action	Indication	Dosage	Evidence	Side-effects
Propanolol	Reduces portal vein blood flow and pressure by: • Reduced cardiac output (β1 blockade) • Reduced splanchnic vasodilation (β2 – blockade)	1) Primary prophylaxis in patient with oesophageal varices >5 mm 2) Secondary Prophylaxis for recurrent variceal haemorrhage 3) Secondary prophylaxis for Portal Hypertensive Gastropathy	10 mg twice daily titrated to maximal tolerated dose Aim for reduction of heart rate by 25% or resting heart rate of 55 bpm	Primary prophylaxis 10% reduction in 2 year bleeding risk[10] 4% 2 year Mortality reduction[10] Secondary prophylaxis 40% decrease in re-bleeding[10] Mortality reduction of 25%[10]	• Fatigue • Lethargy • Postural hypotension • Refractory ascites • Bronchospasm • Impotency • Nightmares
Carvedilol	1) α1 blockade reducing intra-hepatic resistance 2) NSBB (as above)	Secondary Prophylaxis for recurrent variceal haemorrhage	6.25 mg titrated to blood pressure and heart rate (55 bpm or 25% reduction)	• Improved proportion meeting HVPG targets compared with NSBB (50% v 16% $P < 0.05$)[14] • Possibly lower rates of first variceal bleeding compared with EBVL (10% v 23%)[14]	• Greater decrease in mean arterial pressures than NSBB (11% v 5%)[14]
Isosorbide mononitrate	Systemic and splanchnic vasodilation reduces portal blood flow	Not currently recommended in primary or secondary prophylaxis	10 mg nocte titrated to blood pressure (>95 mmHg systolic)	Reduces HVPG when added to NSBB	• Hypotension • Increase 6-year mortality
Octreotide	Splanchnic vasoconstriction and inhibition of vasodilatory peptides (glucagon) release	Management of acute suspected or proven variceal haemorrhage	50 mcg bolus followed by 50 mcg/h infusion for 2–5 days	• Improved haemostasis (80%) at time of endoscopy • Reduced re-bleeding rates	• Minimal • Tachyphylaxis
Terlipressin	Splanchnic vasoconstriction reducing portal blood flow.	1) Management of acute suspected or proven variceal haemorrhage 2) Type I Hepatorenal syndrome	1–2 mg IV per 4–6 hourly for 24 h and reduced to 1 mg 4 hourly Total treatment of 2–5 days	Variceal bleeding • Increases haemostasis (80%) at time of endoscopy[15] • Reduced all cause mortality (RR 0.65 CI 0.49–0.88)[15] Hepatorenal • Improved creatinine and urine output • No effect on mortality	• Hypertension • Myocardial and peripheral ischaemia • Bowel ischemia

EBVL, endoscopic variceal band ligation; HVPG, hepatic venous pressure gradient; NSBB, non-selective beta blockade; RR, relative risk.

reduces HVPG, but without any additional reduction in mortality or haemorrhage rate compared with NSBB alone.[17] Carvedilol may be more effective at reducing portal pressure and has shown superiority to EVBL for primary prevention.[14] However, worsening of resistant ascites and hypotension limits widespread use.[14] Unfortunately, the dose of NSBB required to reduce portal pressure adequately may lead to unacceptable fatigue, dizziness and shortness of breath, symptoms that contribute to a 15% discontinuation rate.[14] EVBL appears equivalent to NSBB for primary prophylaxis, with importantly no difference in survival between the two strategies. Thus, the choice between NSBB and EVBL is highly dependent on available resources as well as patient tolerance and compliance with pharmacological therapy.

Acute variceal haemorrhage Following an acute variceal haemorrhage, spontaneous cessation of bleeding occurs in 40–50%, presumably secondary to hypovolaemia and subsequent splanchnic vasoconstriction.[18] Excessive transfusion may elevate portal pressure and a restrictive transfusion protocol, aiming for haemoglobin of 80 g/L has demonstrated improved survival and decreased re-bleeding in Child–Pugh A and B patients.[19]

Management of coagulation dysfunction can be challenging. Elevation in international normalised ratio (INR) is an important measure of hepatic dysfunction. However, it is now well recognised that in cirrhosis there is dysregulation of both prothrombotic and anti-thrombotic systems. This reduces the predictive value of INR for bleeding tendency in these patients. Typically, correction of coagulation abnormalities requires the administration of fresh frozen plasma (FFP) and prothrombinex. The volume expansion associated with these products has the potential to increase portal pressure and trigger re-bleeding. Furthermore, significant amounts of FFP are required to correct INR in cirrhotic patients without any evidence for benefit.[20] Correction of platelet count to greater than 70×10^9/L appears sufficient to control bleeding, whereas counts $> 50 \times 10^9$/L are thought to be safe for invasive procedures.[21] Due to a lack of evidence regarding efficacy, excessive correction of coagulation abnormalities should be discouraged.

The use of short-term antibiotics following variceal haemorrhage, with or without ascites, has been shown to improve mortality through decreased rates of re-bleeding and spontaneous bacterial peritonitis (SBP).[22,23] In the setting of severe liver disease, evidence supports the use of ceftriaxone 1g intravenously daily.[22] Antibiotics should be commenced on presentation and continued for a period of 7 days. Switching to an oral quinolone antibiotic may be appropriate once the patient is stable (Table 3).

Table 3 Acute and prophylactic antibiotics in portal hypertension

Agent	Mechanism of action	Indication	Dosage	Evidence
Ceftriaxone	Gram-negative bactericidal agent	1) Prophylaxis with post-variceal haemorrhage	1g daily for 5 days	Decreases re-bleeding and spontaneous bacterial peritonitis rates following variceal haemorrhage
		2) Spontaneous bacterial peritonitis		Higher rate of infection resolution in Child–Pugh C patients
Norfloxacin	Gram negative Bacteriostatic agent	1) Primary treatment of spontaneous bacterial peritonitis	400 mg BD	50% decrease in spontaneous bacterial peritonitis incidence SBP episodes[24]
		2) Secondary Prophylaxis of spontaneous bacterial peritonitis	400 mg daily indefinitely	Reduced hepatorenal syndrome incidence (↓13%)[24] Improved 17% improvement in 12 month survival[24]
Trimethoprim sulfamethizole	Broad spectrum Bacteriostatic agent	Secondary prophylaxis of spontaneous bacterial peritonitis (if norfloxacin contraindicated norfloxacin)	160 mg/800 mg daily indefinitely	Equivalent efficacy to norfloxacin

SBP, spontaneous bacterial peritonitis.

The vasoactive agents, terlipressin and octreotide play a major role in controlling acute oesophageal variceal haemorrhage. These agents can achieve initial haemostasis in 60–80% of cases.[18] Terlipressin reduces portal pressure through splanchnic vasoconstriction. The intact molecule causes immediate vasoconstriction, followed by a delayed effect due to enzymatic breakdown of terlipressin into vasopressin.[18] Terlipressin is the only vasoactive agent that has been demonstrated to decrease mortality in acute variceal haemorrhage on meta-analysis and is generally given for a minimum of 5 days.[18] Caution should be taken in individuals with vascular disease because of potential to cause ischaemia. Octreotide, a somatostatin analogue, has inhibitory effects on exocrine and endocrine hormones and decreases portal pressures. In combination with EVBL there is evidence suggesting equivalent efficacy of octreotide and somastatin to terlipressin on re-bleeding rates, transfusion requirement and mortality (8.8% vs 8.9% vs 8.0%, respectively; $P = 0.929$).[25]

Timely definitive endoscopic treatment is recommended with significant benefits in regards to re-bleeding and mortality. Failure to proceed to endoscopic treatment within 15 h is associated with higher mortality.[26] A meta-analysis of 10 randomised controlled trials demonstrated that EVBL was superior to sclerotherapy in controlling bleeding (RR 0.53 CI 0.28–1.01.).[27] Failure to control bleeding or lack of available expertise may require balloon tamponade through insertion of a Sengstaken–Blakemore tube or equivalent, until more definite treatment is available. Tamponade can control bleeding in over 80% of patients, but is associated with a risk of aspiration and perforation.[27] Initial HVPG measurement greater than 20 mmHg predicts those at increased risk of early and late re-bleeding.[28] Initial treatment failure can be managed with repeat endoscopic treatment or transjugular intrahepatic portosystemic shunt (TIPS) (Fig. 2). TIPS in this setting decreases bleeding rates, however, it appears to have no effect on long-term survival and is associated with increased rates of encephalopathy.[29] The early use of TIPS in a select group of patients with severe liver disease (Child–Pugh B or C), who have endoscopically confirmed variceal haemorrhage, may improve the prognosis and shorten the acute hospital stay compared with a more conventional combination of pharmacotherapy and EVBL.[29]

Secondary prophylaxis Mortality from an initial haemorrhage is between 5% and 8%, however the mortality at 6 weeks approaches 20%.[10] Mortality associated with re-bleeding approaches 40% with the majority of events occurring in the first 5 days.[10] Without adequate prophylactic therapy, the risk of recurrent variceal haemorrhage is as high as 80% within the first year with an associated mortality of 33%.[18] Severe initial bleeding, as defined by active bleeding at endoscopy, haemoglobin less than 80 g/L and gastric variceal bleeding, is associated with increased re-bleeding rates.

Secondary prophylaxis is the management of varices following an index bleed. Management comprises EVBL and NSBB. NSBB has been demonstrated to reduce re-bleeding by 40% with a reduction in mortality of 25%.[18] On meta-analysis of 23 randomised controlled trials, combination therapy was associated with a significantly lower rate of re-bleeding (12% reduction) and recurrence (RR 0.64 CI 0.53 to 0.77) compared with EVBL alone.[30] EVBL should be repeated until varices are eradicated, which typically requires three to five sessions. Ongoing surveillance is recommended on a 3 to 6 monthly basis thereafter. Combination therapy with nitrates and NSBB is associated with improved mortality; however, high rates of discontinuation secondary to side-effects.[17] Nitrates alone may be associated with higher long-term mortality particularly in those over 50 years of age.[31] The use of TIPS for secondary prophylaxis reduces re-bleeding events by 28% compared with endoscopic therapy alone.[32] However, there is increased morbidity secondary to encephalopathy and no clear survival benefit.

Gastric varices

While less common and associated with lower rates of bleeding compared with oesophageal varices (25% vs 64%),[33] haemorrhage associated with gastric varices is often more severe with increased transfusion requirements and higher re-bleeding rates. Gastric varices can be classified by anatomical location (Fig. 3). This classification can assist the prediction of bleeding and directs treatment strategies. Pharmacological therapy of gastric varices is identical to that of oesophageal varices (Table 2). Gastro-oesophageal varices (GOV) 1 are considered extensions of oesophageal varices and can be treated in a similar fashion. Isolated gastric varices (IGV) 1 are less common, but are more likely to bleed, whereas IGV2 rarely bleed.[33] Endoscopic therapy of non-GOV 1 varices utilises tissue adhesives injected directly into the lesion. Tissue adhesives are preferred given the superiority in reducing long-term re-bleeding rates (24% reduction).[34] Risks associated with tissue adhesives are systemic emboli with reports of splenic infarction, pulmonary emboli and cerebral strokes. Only three studies have compared tissue adhesives with TIPS demonstrating equal control of initial haemorrhage, but favouring TIPS in the prevention of re-bleeding.[27] NSBB are less effective than tissue adhesives for secondary prophylaxis.[35]

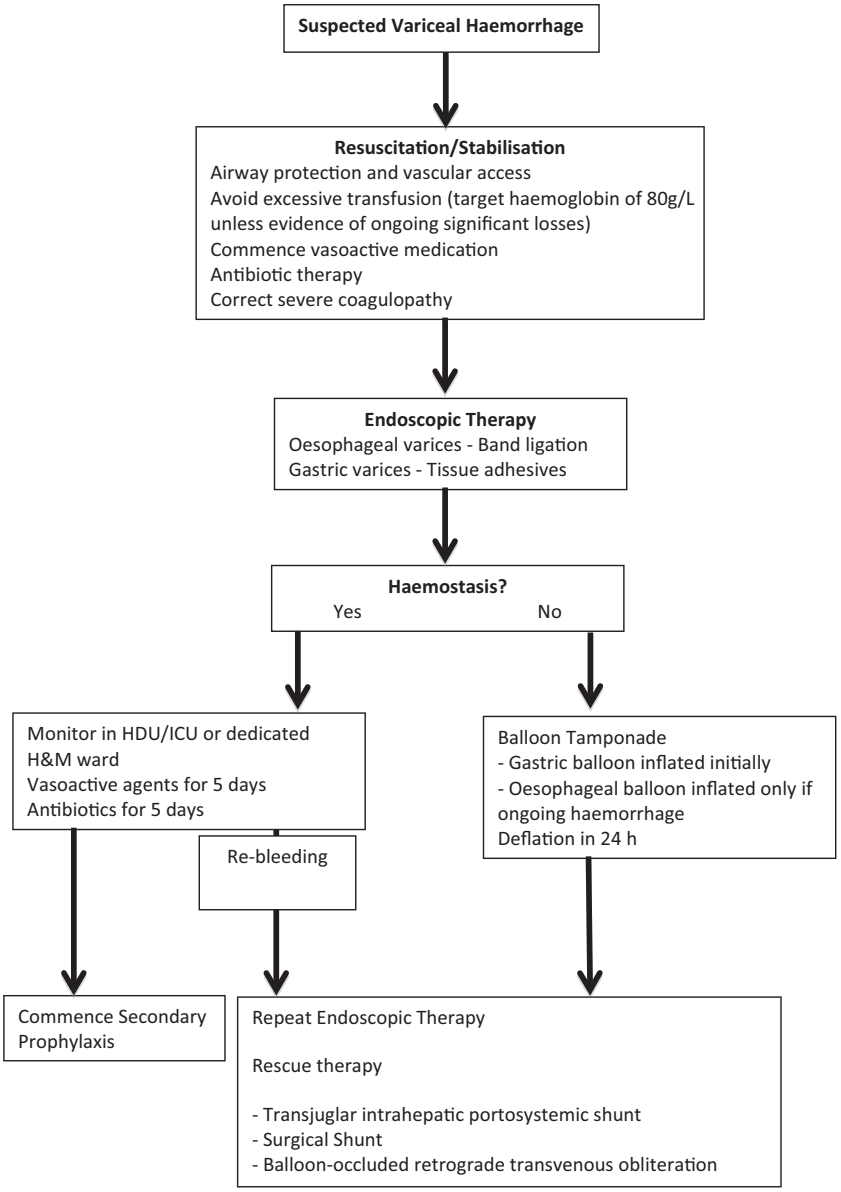

Figure 2 Acute management of variceal haemorrhage.

Portal hypertensive gastropathy

Portal hypertensive gastropathy (PHG) is characterised by the endoscopic appearance of 'snake scale'-like mucosal changes in the stomach. Rarely does it present with acute gastrointestinal haemorrhage (2.5%), but it can be a cause of chronic anaemia (10%) in cirrhosis.[36] While requiring PHT, it does not appear to be directly correlated to the severity of PHT, the degree of underlying liver disease or presence of oesophageal varices.[36] The pathology of PHG is incompletely understood, but appears to result from a combination of alteration in gastric blood flow, hypoxia and impairment of gastric mucosal defences.[37] Long-term NSBB reduces recurrent bleeding, and vasoconstrictive therapy appears to be effective in acute bleeding episodes. TIPS may be beneficial with one study demonstrating a reduction in incidence of 90%, but data are limited.[36]

Haemodynamic complications of portal hypertension

Ascites

Ascites is the accumulation of fluid in the peritoneal cavity and occurs in 50% of cirrhotic patients within 10 years.[38] As a consequence of the vasodilatory and a hyperdynamic circulatory response to PHT, the RAAS

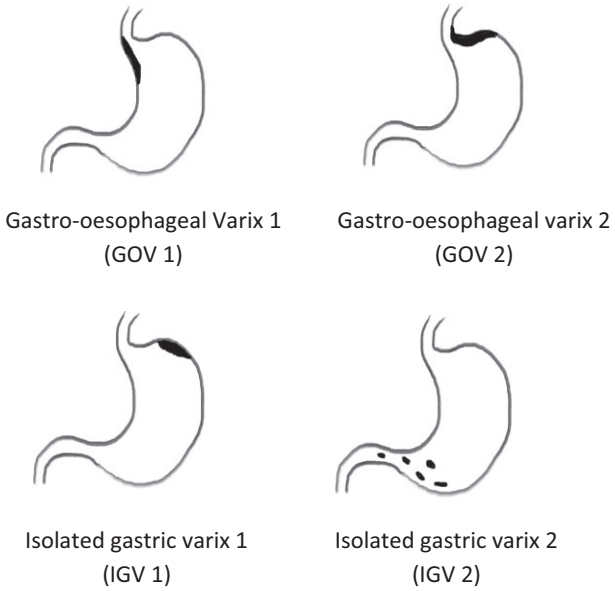

Figure 3 Classification of gastric varices according to sarin.

and ADH drive inappropriate retention of salt and water. In the setting of hypoalbuminaemia, it has been postulated that excessive volume leaks directly from the splanchnic capillaries and the hepatic sinusoids.

Abdominal ultrasound can demonstrate even a small volume of ascites, whereas moderate accumulation of fluid can be confirmed by clinical examination alone. Diagnostic paracentesis is recommended with the initial presentation of ascites or if clinical deterioration suggests SBP. Analysis of the serum ascites albumin gradient (SAAG) has replaced the use of protein concentration for determination of aetiology. A SAAG equal to or greater than 11 g/L is diagnostic of PHT-related ascites with an accuracy of 97%.[38] SBP may present with worsening hepatic encephalopathy, sudden onset of abdominal pain and fever. Polymorphonuclear count can be used to confirm the presence of SBP with counts greater than 250/mm^3 being diagnostic.[39] If SBP is confirmed, treatment is initiated with a third generation cephalosporin until further antibiotic sensitivities are known. Aminoglycosides should be avoided given the risk of renal impairment. Four randomly controlled trials support the use of albumin in SBP with a reduction in renal failure (22% reduction) and mortality (19.4% reduction).[40] It is recommended that patients receive 1.5g albumin/kg within 6 h of presentation and 1g/kg on day 3.[41] Daily norfloxacin or trimethoprim/sulfamethoxazole is recommended prophylaxis for those with prior episodes of SBP (Table 3).[41]

Dietary salt restriction to less than 2000 mg/day appears to be effective in only 10% of patients.[41] Commonly, patient will accept additional medication rather than further dietary salt reduction. Caution should be taken when using NSBB in these patients because of increasing evidence suggesting a worse survival in the setting of resistant ascites.[14] NSBB should be ceased in patients who have SBP as there is an associated reduced survival in this cohort. Angiotensin-converting enzyme inhibitors and non-steroidal anti-inflammatory drugs should be avoided to prevent worsening renal function.[39] Spironolactone and furosemide are recommended diuretic therapies. In isolation, spironolactone is more effective with more controlled weight loss, but at the risk of hyperkalaemia. The addition of furosemide allows better sodium excretion with control of serum potassium concentration. Doses of 100 mg of spironolactone and 40 mg of furosemide can be safely initiated, with maximal doses of 400 mg and 160 mg respectively. Spironolactone may not be tolerated because of painful gynaecomastia, and in these instances amiloride may be substituted. Compliance and titration of dose can be monitored through assessment of 24 h urinary sodium or conveniently by a spot ratio of $[Na^+]/[K^+] > 1$.[41] Diuretics should be ceased in the setting of severe renal impairment or severe hyponatraemia (<120 mmol/L).[39] Diuretic intolerant or resistant patients can be managed with regular paracentesis or can be considered for TIPS.

Hepatorenal syndrome

Hepatorenal syndrome (HRS) is defined by marked reduction in renal function in the presence of cirrhosis complicated by ascites in the absence of other causes. Alterations in renal blood flow are thought to be the precipitating event. This results in a reduction in glomerular filtration rate and sodium and water retention. The syndrome itself is characterised by oliguria, low urinary sodium output (<20 mmol) and hyponatraemia.[42] Hepatorenal syndrome is classified as type I HRS, when there is rapid deterioration of renal function over a 2-week period and type II HRS when onset is more prolonged. Type I is typically associated with a precipitating factor, such as SBP, large volume paracentesis without albumin replacement or gastrointestinal bleeding.

The diagnosis of HRS is one of exclusion requiring cessation of nephrotoxic agents, treatment of possible underlying infection and hypovolaemia. Albumin replacement is recommended initially at a dose of 1 gram per kilogram for a 48-h period. Terlipressin is recommended following failure of volume expansion at 1–2 mg 4–6 hourly. Prognosis of Type I HRS is poor in the absence of liver transplantation with only 10% leaving hospital.[42]

Hepatopulmonary/portopulmonary syndromes

Hepatopulmonary syndrome is characterised by a triad of portal hypertension, pulmonary vasodilation/shunting and impaired oxygenation as defined by a widened A-a gradient. The pathophysiology, while not completely understood, involves excessive NO and Endothelin-1 production secondary to inflammation from hepatic injury and translocation of gastrointestinal bacteria.[43] Clinical features can include clubbing and platypnea-orthodeoxia (dyspnoea and deoxygenation induced by upright posture). Mortality arises from liver failure rather than hypoxia. In the absence of liver transplantation, survival at 5 years is 23%.[43] Portopulmonary syndrome refers to pulmonary hypertension in the presence of PHT without alternative causes. Traditional therapies for pulmonary hypertension may have benefit, but liver transplantation can be curative.

Hepatic encephalopathy

Hepatic encephalopathy is a neuropsychiatric complication of PHT. Through the development of collateral vessel and obstruction of hepatic blood flow, neuroactive peptides are shunted in the systemic circulation rather than detoxified by the liver. Theories suggest ammonia, inflammatory cytokines and hyponatraemia act synergistically resulting in cerebral oedema, astrocyte swelling and alternations in astrocyte mitochondrial function.[44]

The severity of presentation, classified by the West Haven criteria (Table 4), can range from subtle alterations in mood to overt coma. Biochemical measurement of ammonia to diagnose encephalopathy is debatable given the fact that this condition relies on clinical diagnosis and can occur in the absence of elevated ammonia levels. Initial therapy should be aimed at correcting possible aetiologies, such as infection, electrolyte imbalances (such as hypokalaemia) and gastrointestinal bleeding.

Current therapies target the absorption and production of ammonia. Lactulose alters gastrointestinal pH favouring lactobacilli over urease-containing bacteria and enhances production of non-absorbable ammonia. Furthermore, these laxatives enhance faecal nitrogen excretion.[44] In small placebo studies, lactulose appeared more effective in controlling hepatic encephalopathy and preventing recurrent episodes, but had no effect on mortality.[44] Dosing is generally titrated to the number of bowel action aiming for two to three loose actions, although there is little evidence to support this. In the comatose patient, nasogastric administration or 200 mL enemas of lactulose may be required.

Table 4 West Haven encephalopathy criteria

Grade 1	Lack of awareness
	Depression
	Anxiety
	Sleep disturbance
	Impaired psychometric testing
	Shortened attention span
Grade 2	Lethargy
	Disorientation to time and place
	Personality changes
	Inappropriate behaviour
	Slurred speech
	Asterixis
Grade 3	Ataxia
	Altered reflexes
	Nystagmus
	Confusion
	Somnolence
Grade 4	Coma

Neomycin was the first antibiotic to demonstrate effectiveness in hepatic encephalopathy, but its use has been limited because of ototoxicity and nephrotoxicity.[44] Rifaximin (550 mg BD), a minimally absorbable oral antibiotic is currently available in Australia for use in lactulose resistance encephalopathy. When used in conjunction with lactulose, rifaximin has been shown to reduce recurrent encephalopathy and hospitalisation.[45]

Conclusion

The management of PHT has improved dramatically over the past decade. This improvement has come on the background of technical advancements and enhanced understanding of the pathophysiology. Future therapies will target additional pharmacological sites not yet utilised. Endothelial receptor blockade appears promising in animal models of pre- and intra-hepatic PHT; however, further human studies are required. Statins are thought to increase NO synthase selectively in the liver, limiting the systemic side-effects that hamper nitrate use. Preliminary data have demonstrated a statistical significant increased survival in Child–Pugh A and B patients presenting with variceal haemorrhage.[11] Blockade of angiotensin-mediated hepatic vasoconstriction and fibrosis can reduce HVPG, however, the effects appear equivalent to NSBB and are non-additive with increased renal impairment and hypotension common as liver function worsens. Ultimately addressing the cause of PHT and prevention will be the most effective therapy.

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ORIGINAL ARTICLES

Blood oxygen equilibration time after cessation of supplemental oxygen in chronic respiratory disease

A. M. C. Stone,[1] K. K. H. Wong[1,2,3] and D. J. Barnes[1,2]

[1]Department of Respiratory and Sleep Medicine, Royal Prince Alfred Hospital, [2]Medical School, University of Sydney and [3]The Woolcock Institute of Medical Research, Sydney, New South Wales, Australia

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hypoxaemia, chronic respiratory disease, arterial blood gas, supplemental oxygen, oximetry.

Correspondence
Andrew M. C. Stone, Department of Respiratory and Sleep Medicine, Royal Prince Alfred Hospital, Missenden Road, Camperdown, NSW 2050, Australia.
Email: astone@med.usyd.edu.au

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Abstract

Background: Measurement of the arterial partial pressure of oxygen (PaO_2) while breathing air is an informative investigation in patients with hypoxaemia due to chronic respiratory disease, but there are a lack of published data on the time needed for blood oxygen levels to equilibrate after cessation of supplemental oxygen (O_2) in such patients.

Aim: To determine the blood oxygen equilibration time after cessation of O_2 and thereby provide guidance on best timing of baseline arterial blood gas analysis in this population.

Methods: Medically stable subjects with chronic respiratory disease were administered O_2 at a constant concentration. Continuous pulse oximetry was recorded from before cessation of O_2 to beyond the point of oxygen saturation (SpO_2) equilibration. Data were fitted to an exponential decay model. Blood oxygen equilibration time was defined as the t90, the time taken for SpO_2 to fall 90% of the difference between initial (on O_2) and final (on air) values.

Results: Eighty-two (82) subjects with a mean age of 66 years were included. The largest diagnostic category was chronic obstructive pulmonary disease (37), followed by interstitial lung disease (15) and bronchiectasis (12). The median t90 was 6 min 18 s (interquartile range: 4 min 32 s–10 min 30 s). The 95th centile t90 value was 20 min.

Conclusion: In the majority of patients with chronic respiratory disease, a time delay of 20 min between cessation of supplemental O_2 and PaO_2 measurement allows confidence that the result is a true baseline value.