Variceal Bleeding

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At the conclusion of this presentation it is hoped you will have a greater understanding of:

- Portal and hepatic vascular anatomy
- Some of the causes of portal hypertension and chronic liver disease/cirrhosis
- The pathophysiology of portal hypertension and how it contributes to many of the clinical manifestations of chronic liver disease
- General and specific management strategies for portal hypertension and oesophageal variceal bleeding
- Variceal banding being appropriate for oesophageal varices but that glue injection is more appropriate for gastro-oesophageal and isolated gastric varices
- The importance of antibiotic prophylaxis in acute variceal bleeding and the benefit that a restrictive transfusion approach brings
What are varices?

- Engorged veins that carry a greater than normal **volume** of blood under higher than normal **pressure**
- Commonly encountered in the GI tract in association with **Portal Hypertension** in the setting of chronic liver disease/cirrhosis
- GI varices can occur for reasons other than CLD/cirrhosis
- Varices can occur outside the GI tract (eg varicose veins of the legs)
Historical Aspects (1)

- **1543** – Vesalius\(^1\) maps the portal venous system
- **1719** – Morgagni\(^2\) describes ‘a portal hypertensive bleeding’
- **1841** – Raciborski\(^3\) discovers that collaterals form between the systemic and portal circulations through the abdominal wall, short gastric and haemorrhoidal veins
- **1859** – Sappey\(^4\) describes oesophageal varices
- **1877** - Nikolai Eck\(^5\) creates porto-caval shunts in animals to treat ‘mechanical ascites’ (the ‘Eck Fistula’)
- **1903** – Vidal\(^6\) successfully establishes an ‘Eck Fistula’ in a man with ascites

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1. Vesalius A. De Humani Corporis Fabrica Basileae. 1543
Historical Aspects (2)

1. **1906** – Gilbert & Villaret\(^1\) coin the term ‘Portal Hypertension’ (‘d’Hypertensionportale’)

2. **1936** – Rousselot\(^2\), working on patients with ‘Banti’s Syndrome’ sheds light on elevated portal pressure

3. **1940** – Schatzki\(^3\) published observations made in early 1930’s on barium x-ray’s in patients with gastric and oesophageal varices. The first description of varices was “dilated veins that bulge into the lumen, producing uneven worm like surface of the inside of oesophagus”

4. **1937** – Thomson and colleagues\(^4\) performed portal pressure measurements during celiotomy procedures clarifying the role of portal hypertension in the development of oesophageal varices

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2. Rousselot LM. The role of congestion (portal hypertension) in so-called Banti’s Syndrome: clinical and pathologic study of thirty-one cases with late results following splenectomy. *JAMA* 1936;107:1788–93.
Historical Aspects (3)

1804 – Philip Bozzini created a special tube, named a ‘lichtleiter’ or ‘light-guiding instrument’ for examining the urinary tract. This was later re-named ‘Endoscope’ by French Surgeon Antoine Jean Desormeaux

1868 – Adolph Kussmaul first utilised the endoscope to examine the inside of the stomach of a living person

1881 – Johann von Mikulicz, a Polish-Austrian Surgeon, created and used the ‘gastroscope’, specifically for examination of the oesophagus, stomach and small intestine

1932 – Rudolph Schindler introduced the flexible gastroscope; the improved ‘gastro-camera’ appeared in the 1950’s

1936 – Crafoord and Freckner, two Swedish Surgeons, first reported their use of rigid gastroscopes to visually inspect bleeding varices and stop the bleed utilizing injection sclerotherapy with quinine-urethane solution

Lichtleiter – the proto-endoscope
Hepatic Venous Pressure Gradient (HVPG)

- **Wedged Hepatic Venous Pressure (WHVP)**
  - used to estimate the portal venous pressure by reflecting not the actual hepatic portal vein pressure but the hepatic sinusoidal pressure
  - determined by wedging a catheter in a hepatic vein, to occlude it, and then measuring the pressure of proximal static blood (which is reflective of pressure in the sinusoids)

- **Hepatic Venous Pressure Gradient (HVPG)**
  - a clinical measurement of the pressure gradient between the WHVP and the free hepatic venous pressures, and thus is an estimate of the pressure gradient between the portal vein and the inferior vena cava
  - HVPG of ≥5 mmHg defines portal hypertension, and if the measurement exceeds 10 mmHg it is called clinically significant portal hypertension. Above 12 mmHg, variceal haemorrhaging may occur

Hepatic Venous Pressure Gradient (HVPG)

\[ \text{HVPG} = \text{WHVP} - \text{FHVP} \]

\[ \text{HVPG (19)} = \text{WHVP (23)} - \text{FHVP (4)} \]
Portal Hypertension

- Defined as an increased portosystemic pressure gradient (difference between pressures in the portal vein and the IVC) – as reflected in the HVPG (>5mmHg)
- The risk of developing varices and clinical complications of decompensated liver disease (e.g. ascites, variceal bleeding, encephalopathy) occurs when HVPG rises to >10mmHg
- Thus HVPG >10mmHg is termed “Clinically Significant Portal Hypertension”¹
- Portal hypertension due to chronic liver disease = sinusoidal portal hypertension
- There are other causes of portal hypertension
  - Schistosomiasis
  - Portal and splenic vein thrombosis
  - Budd-Chiari syndrome
  - Less frequent conditions causing pre-sinusoidal or post-sinusoidal blockage

Portal Hypertension

- Portal hypertension is the most severe and frequent complication of chronic liver disease
- It is the cause of most of the severe clinical symptoms of cirrhosis:
  - Bleeding from gastro-oesophageal varices
  - Bleeding from portal hypertensive gastropathy
  - Ascites
  - Spontaneous bacterial peritonitis (SBP)
  - Hepato-renal syndrome (HRS)
  - Hepatic encephalopathy (HE)
  - Hepato-pulmonary and porto-pulmonary syndrome
  - Bacteraemia
  - Hypersplenism
Gastro-oesophageal varices

- At diagnosis, up to half of patients with compensated cirrhosis have varices
- Varices are even more frequent if the patient has severely impaired liver function (Child-Pugh class B/C)\(^1\)
- Varices develop with an annual incidence of 5%-9% in patients without varices at diagnosis\(^2,3\)
- The rate of progression from small varices to large varices is similar

**Gastro-oesophageal varices**

- The risk of a first variceal bleed increases with:
  - Impairment of liver function
  - Size of varices
  - Presence of red colour signs over the varices (red wales, red spots, diffuse redness)
- Annual bleeding risk is about 12% (5% for small varices; 15% for large varices)\(^1,2\)

Oesophageal varices
Gastro-oesophageal varices

- Bleeding from a ruptured gastro-oesophageal varix is a major medical emergency
  - 6 week mortality ~ 15%
  - Poorer mortality outcome in those with poorer liver function
- In many cases death is not due to bleeding but rather to infection, hepato-renal syndrome and liver failure
- In the last 30 years improvement in treatments have halved the mortality rates from variceal bleeding

Gastric varices
Non-Selective β-blockers (NSBB’s)

Standard NSBB’s (propanolol, nadolol, timolol) decrease portal pressure by reducing portal-collateral blood flow by:
- Reducing the cardiac index (via β1-receptor blockade)
- Splanchnic vasoconstriction (via β2-receptor blockade)\(^1,2\)

Carvedilol is more effective than standard NSBB’s at lowering portal hypertension – it has intrinsic anti-α-adrenergic activity in addition to β1/β2 receptor blocking ability\(^3\)

For >30yrs NSBB’s have been shown to effectively prevent a first variceal bleed, to lower recurrence of re-bleeding and to reduce bleeding-associated mortality\(^4,5\)

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Non-Selective β-blockers (NSBB’s)

- NSBB’s also increase intestinal transit time, reduce bacterial translocation and lower risks of SBP
- To effectively prevent variceal bleeding HVPG should be reduced to <12mmHg or by at least 20% from baseline
- However, a long-term satisfactory haemodynamic response is only seen in 33%-50%
- In non-responders the addition of Isosorbide Mononitrate (a NO-donor) can further reduce portal pressure, but at the cost of more side-effects
- Consider temporarily ceasing β-blockers in the setting of decompensated patients with refractory ascites, hepato-renal syndrome, spontaneous bacterial peritonitis, severe arterial hypotension, hyponatraemia and acute kidney injury

Current Treatments for Portal Hypertension

Terlipressin

- A long-acting synthetic vasopressin analogue
- Potent splanchnic vasoconstrictor
- Also has systemic circulatory effects – increases arterial pressure, increases systemic vascular resistance and reduces cardiac output
- Can be given by infusion or repeated i.v. injections every 4 hrs
- In practice duration of therapy is usually 3-5 days after a variceal bleed or for 1-2 weeks in the setting of Type-1 Hepato-renal syndrome (HRS)
- Potential ischaemic and arrythmic complications (avoid in those with cerebrovascular, cardiovascular, peripheral or visceral arterial diseases)
- Caution in the elderly and those with hypertension

Somatostatin and analogues

Somatostatin and long-acting analogues (eg Octreotide) are effective splanchnic vasoconstrictors.
- They reduce portal pressure through inhibition of glucagon and other vasoactive peptides and facilitate adrenergic vasoconstriction\(^1,2\)
- Short half-life means continuous IV infusion required (50μg/hr Octreotide → reduces HVPG and porto-collateral blood flow\(^3\))
- The reduction in portal pressure induced by Somatostatin and analogues is not maintained over time - reduced portal pressure only partly explains why Octreotide successfully controls variceal bleeding\(^4\)

Current Treatments for Portal Hypertension

**New Drugs**

- **Statins**
  - Improve endothelial dysfunction in many vascular diseases
  - In experimental models of cirrhosis, Statins (simvastatin, atorvastatin):
    - Reduce hepatic vascular resistance
    - Improve endothelial dysfunction
    - Decrease fibrosis
  - In patients with cirrhosis, Statins moderately lower HVPG (even in those on NSBB’s) and improve quantitative liver function tests, but do not influence the systemic circulation
  - In a recent trial of patients surviving an episode of variceal bleeding, adding Simvastatin to the standard of care (NSBB + variceal banding) did not reduce variceal re-bleeding rates but did improve survival
  - Large epidemiological surveys have shown that progression of liver disease is reduced and mortality decreased in patients receiving Statins

Current Treatments for Portal Hypertension

- **New Drugs**
  - **Renin-Angiotensin-Aldosterone inhibitors**
    - ACE inhibitors/ARB’s lower the HVPG and appear safe in those with good liver function (Child-Pugh A)\(^1\)
    - Role in preventing variceal bleeding and safety in acute decompensated liver disease requires more study
  - **Aetioologic treatments**
    - Successful treatment of the specific cause of the liver disease (e.g. Hep B, Hep C, haemochromatosis, alcohol) can markedly reduce portal hypertension
    - Probably takes longer in those who are clinically decompensated

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Current Treatments for Portal Hypertension

New Drugs

Antifibrotic Drugs

Obeticholic Acid – suppresses bile acid synthesis and increases bile acid transport from the liver to the canaliculi. Improves liver biochemistry in PBC and histologic features in those with NASH. Trials ongoing.

Simtuzumab – monoclonal antibody against lysyl oxidase-like 2 enzyme (LOXL2). Reduced liver fibrosis in a mouse model. Trials ongoing.

Emricasan – an anti-apoptotic agent with anti-inflammatory and anti-fibrotic properties. Shown to reduce portal pressure in a recent pilot study in patients with cirrhosis as well as in experimental models.

Current Treatments for Portal Hypertension

- **Endoscopic treatments - Banding and Glue Injection**
  - Classification of Gastro-oesophageal and isolated gastric varices according to Sarin and choice of endoscopic therapy

Current Treatments for Portal Hypertension

Endoscopic Variceal Band Ligation (EVBL) – ‘Banding’

- Treatment of choice for oesophageal varices – it is safer and more effective than endoscopic injection sclerotherapy
- Once EVBL is begun for acute bleeding or as scheduled primary/secondary prophylaxis it should be repeated every 2-4 weeks until the varices are ‘eradicated’
- Once varices have been eradicated occasional endoscopic surveillance is required to ensure varices do not reform

Endoscopic therapy for gastric varices

- Isolated gastric varices (IGV1 and 2) and type 2 gastro-oesophageal varices (GOV2) should be treated by intra-variceal injection of a tissue adhesive (e.g., Histoacryl glue)
- This has been shown to be more effective than banding in the setting of acute bleeding
- A second glue injection 2-4 weeks later can be considered to further reduce bleeding risk
- Thrombin has been used instead of glue\(^1\)

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Duodenal Varix (A – CT scan) and after glue injection (B – plain x-ray)
Histoacry glue injection of gastric varices - embolisation to the brain
Interventional radiology treatments

Transjugular intrahepatic portosystemic shunt (TIPSS)

- Minimally invasive fluoroscopic-guided procedure that creates a shunt between a hepatic vein and the intrahepatic portal vein, sustained by a metal stent
- Ideally the shunt is large enough to reduce portal pressure (ideally HVPG of 10-12mmHg) but not so large as to cause liver failure or hepatic encephalopathy
- TIPSS has almost completely replaced surgical shunts because they are safer but with similar efficacy
- Main indication is acute variceal bleeding when other therapies have failed and for refractory ascites
- In practice hepatic encephalopathy is a limiting factor (occurring in a third of patients, severely in 6%-10%)¹²

Current Treatments for Portal Hypertension

Transjugular Intrahepatic Portosystemic Shunt (TIPSS)
Interventional radiology treatments

Balloon-occluded retrograde transvenous obliteration (BRTO)

- Minimally invasive procedure
- Gastric or mesenteric varices retrogradely accessed from the femoral vein (via a spontaneous spleno-renal shunt) and occluded with tissue adhesives or thrombogenic vascular coils
- Very efficient at controlling bleeding gastric varices but no randomised controls performed
- Consider if a patient has failed medical and endoscopic therapy and is not a good candidate for TIPSS¹

Acute Oesophageal Variceal Bleeding

- Most immediately dangerous complication of cirrhosis
- Even with modern treatment, mortality ~ 15%
  - In the first 5 days death is usually due to blood loss
  - In the ensuing 6 weeks death is due to multiple organ dysfunction

- Important predictors of poor outcomes are:
  - Hepatic Venous Pressure Gradient (HVPG) > 20mmHg
  - Severe liver failure
  - Impaired renal function
  - Bacterial infection
  - Hypovolaemic shock
  - Active variceal bleeding during endoscopy
  - Early bleeding relapse and need for >4 units packed red cells transfused
  - Hepatocellular carcinoma
  - Portal vein thrombosis

2. Rajoriya N, Tripathi D. Historical overview and review of current day treatment in the management of acute variceal haemorrhage. World J Gastroenterol 2014;20:6481-94
Oesophageal varices
Bleeding oesophageal varix
Acute Oesophageal Variceal Bleeding

General management

Resuscitation

- ABC (Airway, Breathing, Circulation)
- Consider intubation if ↓LOC/haematemesis
- Restrictive transfusion policy – give packed red cells to maintain target [Hb] 70g/L (less restrictive policy of target [Hb] 90g/L associated with higher mortality\(^1\), except perhaps in those with Child-Pugh C status, rapid ongoing bleeding and those with ischaemic cardiovascular disease)

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Acute Oesophageal Variceal Bleeding

🌿 General management

🌿 Antibiotics

🌿 Early prophylactic antibiotics should be given – this reduces incidence of infections after a bleeding episode and reduces mortality\(^1,2\)

🌿 Encephalopathy

🌿 Lactulose po or via NG tube or rectally is recommended to reduce likelihood of encephalopathy

🌿 Rifaximin may be effective but has not been evaluated in this situation

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Acute Oesophageal Variceal Bleeding

- **Vasoactive Drugs**
  - Intravenous vasoactive therapy (eg Terlipressin, Octreotide) should be started as soon as variceal bleeding is recognised – usually in ED
  - The vasoactive drugs are thought to be equally effective in controlling bleeding and preventing re-bleeding within 5 days, but the quality of evidence varies and is best for Terlipressin¹
  - Vasoactive drug infusion is usually maintained for 2-5 days.

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Acute Oesophageal Variceal Bleeding

Endoscopic therapy

- Emergency endoscopy should be performed as soon as possible, ideally no later than 12 hours after presentation.
- Consider administering Erythromycin 250mg i.v. 30mins beforehand to accelerate gastric emptying and improve visibility\(^1\).
- Banding is indicated immediately if a variceal bleed is confirmed (or in the case of IGV/GOV-1 – glue injection).
- The combination of vasoactive drugs, endoscopic therapy and prophylactic antibiotics results in 5-day successful bleeding control in 85%-90% of cases.
- After this period NSBB’s could be started as secondary prophylaxis.

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Banded Oesophageal Varices
Failure of Standard Therapy

- **Treatment of patients that fail standard therapy (“Rescue Therapy”)**
  - Failure to control variceal bleeding with vasoactive drugs/endoscopic therapy is a very demanding situation.
  - Consider emergency TIPSS if there is available expertise and no contraindication.
    - However, mortality in this situation is high (~40%) – probably because there is marked deterioration in liver function during uncontrolled bleeding whilst TIPSS being arranged.
  - If bleeding is recurrent and not severe there is the option of continuing vasoactive drugs and having a second attempt at endoscopic therapy.
  - BRTO (balloon-occluded retrograde transvenous obliteration) is a consideration in the case of bleeding gastric varices and a contraindication to TIPSS.
Failure of Standard Therapy

- **Treatment of patients that fail standard therapy (“Rescue Therapy”)**
  - **Oesophageal Tamponade**
    - Balloon tamponade with a Sengstaken-Blakemore tube or similar may rarely be used
    - Massive exsanguinating bleeding or recurrent bleeding as a bridge to TIPSS or other more definitive therapy
  - **Oesophageal self-expanding metallic stents** have been shown to be very effective\(^1\) and a recent RCT showed oesophageal stents are as effective but safer than balloon tamponade\(^2\)

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Oesophageal Balloon Tamponade
Having concluded this presentation it is hoped you have a greater understanding of:

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- The pathophysiology of portal hypertension and how it contributes to many of the clinical manifestations of chronic liver disease
- General and specific management strategies for portal hypertension and oesophageal variceal bleeding
- Variceal banding being appropriate for oesophageal varices but that glue injection is more appropriate for gastro-oesophageal and isolated gastric varices
- The importance of antibiotic prophylaxis in acute variceal bleeding and the benefit that a restrictive transfusion approach brings
LIVER

EMPLOYEE OF THE MONTH

Thank you liver 💘