search term included liver cirrhosis/ or biliary cirrhosis/ or compensated liver cirrhosis/ or decompensated liver cirrhosis/ or primary biliary cirrhosis AND gastrointestinal hemorrhage/ or duodenum bleeding/ or intestinal bleeding/ or melena/ or rectum hemorrhage/ or upper gastrointestinal bleeding/. Subsequently, articles cited in the identified literature were reviewed and included as appropriate. Where adequate recent evidence could not be identified, or where evidence was deemed to be foundational or paediatric-focused, earlier studies have been included.

Reference	**Evidence level (I-VII)**	**Methods, key findings, outcomes or recommendations**
Attard, T.M., Miller, M., Pant, C. & Thomson, M. (2017). Readmission after Gastrointestinal Bleeding in Children: A Retrospective Cohort Study. *Journal of Pediatrics*. May 2017, 184: 106-113.e4 DOI 10.1016/j.jpeds.2017.01.044	IV	This Retrospective Cohort Study compared the demographic, clinical, and therapeutic characteristics in a cohort of patients presenting to the emergency department with acute gastrointestinal bleeding. The researchers also looked at patients who represented with further gastrointestinal bleeding within 30 days. Data was obtained from 49 tertiary children's hospitals in the US for children aged 1-21 years of age admitted with acute gastrointestinal bleeding, between January 2007 and September 2015. The primary outcomes in this study were 30-day inpatient readmission through the ED and 30-day return to the ED only. Unadjusted, univariate followed by multivariable analysis of the associations between patient characteristics and treatment course at the index encounter using the R statistical package, v. 3.2.3. The study identified 9902 patients with acute gastrointestinal bleeding; with 16.1% representing to the ED and 9% being readmitted; 69% within 2 weeks of discharge. Readmission was most frequently associated with portal hypertension or oesophageal variceal haemorrhage. The study found a decreased likelihood of readmission with endoscopy (OR 0.77, 95% CI, 0.661, 0.906) during the initial admission. Multiple comorbidities, longer initial stay and the early proton pump inhibitor therapy were associated with higher likelihood of readmission.
Chavez-Tapia, N., Barrientos-Gutierrez, T., Tellez-Avila, F., Soares-Weiser, K., Mendez-Sanchez, N., Gluud, C. & Uribe, M. (2011). Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding - an updated Cochrane review. *Alimentary Pharmacology and Therapeutics, 34*(5): 509-518.	I	Systematic review of 17 RCTs to compare the all-cause mortality and infection mortality, between cirrhotic (adult) patients with upper gastrointestinal bleeding receiving antibiotic prophylaxis or no intervention/placebo. Some of the RCTs were single-centre, some multi-centre. The trials excluded patients with known infections. RCTs took place in Australia, Czech Republic, France, Germany, Greece, Korea, Spain, Taiwan and the United Kingdom. Most were not blinded. Twelve trials (1241 patients) evaluated antibiotic prophylaxis compared with placebo or no intervention. Antibiotic prophylaxis compared with placebo or no intervention was associated with significant reduction in bacterial infections (RR 0.36, 95% CI 0.27 to 0.49), rebleeding (RR 0.53, 95% CI 0.38 to 0.74), days of hospitalisation (MD -1.91, 95% CI -3.80 to -0.02), bacteraemia (RR 0.25, 95% CI 0.15 to 0.40), pneumonia (RR 0.45, 95% CI 0.27 to 0.75), spontaneous bacterial peritonitis (RR 0.29, 95% CI 0.15 to 0.57), and urinary tract infections (RR 0.23, 95% CI 0.12 to 0.41). The few number of trials included in the analysis were not enough to conclude a significant beneficial effect of prophylaxis on mortality. Another five trials (650 patients) compared different antibiotic regimens. Data could not be combined as each trial used different antibiotic regimen; Quinolone (Norfloxacin, Ofloxacin); Cephalosporin (Ceftriaxone) Ampicillin and sul- bactam. None of the examined antibiotic regimen was superior to the control regimen regarding mortality or bacterial infections. No antibiotic treatment was associated with significant adverse effects. The meta-analysis found that use of prophylactic antibiotics in cirrhotic patients with upper gastrointestinal bleeding significantly reduce bacterial infections, incidence of rebleeding events, and length of hospitalisation. These benefits were

Reference	Evidence level (I-VII)	Methods, key findings, outcomes or recommendations
		observed independent of which antibiotic was administered. The findings of the meta-analysis support current treatment guidelines for adults, insofar as they consider antibiotic prophylaxis as standard of care (Garcia-Tsao 2007; Bosch 2008; Bendtsen, 2008; El Shabrawi, 2011; Franchis, 2005). However these guidelines recommend antibiotics based on the beneficial effects reported on mortality and this effect is not well-supported by this analysis, compared to the effect of prophylaxis to prevent bacterial infections, rebleeding and reduce days of hospitalisation. The review did find that all the examined trials had methodological weaknesses with high risk of bias. Lack of blinding and lack of proper sample size calculations were the most common sources of bias. In the paediatric setting, the frequency of bacterial infections in children with cirrhosis and upper gastrointestinal bleeding is not known. In their expert consensus report, Shneider et al. (2012) recommend precautionary antibiotics be administered to children with variceal bleeds, but that analyses of the prevalence of bacterial infection needs to be performed to determine whether antibiotic therapy will provide the same benefits as it does to adults. It is possible that as children generally have immature immune systems, this therapy will be more beneficial in the paediatric population. In the earlier consensus report (Shneider et al., 2006), antibiotic prophylaxis directed at intestinal flora (such as ceftriaxone) is reported is an integral part of therapy for children, from a risk/benefit perspective.
Chiou. F.K. & Abdel-Hady, M. (2017). Portal hypertension in children. *Paediatrics and Child Health*, December 2017 27(12): 540-545.	VII	This symposium paper describes the pathophysiology and causes of paediatric portal hypertension. The authors outline possible clinical presentations and treatments for major complications arising from portal hypertension, including gastrointestinal and variceal bleeds. Management options relating to a bleed, outlined in the paper include: Intravenous fluid resuscitation, crystalloid fluids, Red blood cell transfusion: target haemoglobin of 70–80 g/L, Nil by mouth, nasogastric tube on free drainage, Correct coagulopathy (Vitamin K, fresh frozen plasma) and thrombocytopenia (if less than 20 × 10 9 /L), Empiric broad-spectrum antibiotics, Monitor vital signs, urine output, conscious level, blood sugar and haemoglobin levels, IV Octreotide: 1–5 mcg/kg/hour continuous infusion, IV Omeprazole: 1 mg/kg/dose od, or IV Ranitidine 1–3 mg/kg/dose tds, NG/PO Sucralfate: 250 mg–1000 mg qds, PO Lactulose: 0.5 ml/kg/dose tds, Endoscopic variceal ligation and Endoscopic sclerotherapy. No references are provided in the paper.
D'Amico, G., Pagliaro, L., Pietrosi, G. & Tarantino, I. (2010). Emergency sclerotherapy versus vasoactive drugs for bleeding oesophageal varices in cirrhotic patients. *Cochrane Database Of Systematic Reviews*, Mar	I	Systematic review of RCTs comparing benefits and harms of sclerotherapy with vasoactive drugs (vasopressin, terlipressin, somatostatin or octreotide) for acute variceal bleeding in adult cirrhotic patients (regardless of the aetiology and the severity of cirrhosis). Seventeen RCTs including 1817 patients were reviewed, comparing sclerotherapy with vasopressin (one trial), terlipressin (one trial), somatostatin (five trials), and octreotide (ten trials). None of the included trials were blinded, however, the reviewers conclude that this would not lead to biased conclusions in the trials. No significant differences were found when comparing drugs. Combining all the trials irrespective of the drug, the risk differences (95% CI) were failure to control bleeding -0.02 (-0.06 to 0.02), five-day failure rate -0.05 (-0.10 to 0.01), rebleeding 0.01 (-0.03 to 0.05), mortality -0.02 (-0.06 to 0.02), and transfused blood units-0.24 (-0.54 to 0.07). Adverse events 0.08 (0.03 to 0.14) and serious adverse events 0.05

Reference	Evidence level (I-VII)	Methods, key findings, outcomes or recommendations
17(3):CD002233. DOI: 10.1002/14651858.CD002233.pub2.		(0.02 to 0.08) were significantly more frequent with sclerotherapy. The meta-analysis found no convincing evidence to support the use of emergency sclerotherapy for variceal bleeding in cirrhosis as the first, single treatment compared to vasoactive drugs. The limitations identified by the authors of this meta-analysis are that the question of sclerotherapy compared with vasoactive drugs appears to be superseded by current guidelines and recent consensus conferences that recommended combination therapy as a first-line treatment for acute variceal bleeding (De Franchis, 2005; Garcia-Tsao, 2007). Other studies report band ligation to be superior to sclerotherapy for acute variceal bleeding (Avgerinos et al., 2004; Villanueva et al., 2006). The authors also report that the methodological quality of the included trials was generally unsatisfactory, with only five trials reporting adequate control of selection bias. Another limitation, which is not discussed by the authors, is that four of the RCTs in the analysis have not been obtained in full; only abstracts have been read. Thus methodologies and limitations of these four studies cannot have been reasonably scrutinised. Despite the review's inherent limitations, and the fact that the data relates only to adults with variceal bleeds secondary to cirrhosis, there is no identified physiological reason that the results of the study could not be replicated in the cirrhotic paediatric population. Ten of the trials in the review considered octreotide (although two of these were examined only by abstract) and concluded octreotide had a similar efficacy with fewer side effects to sclerotherapy. The findings of this study are supported by paediatric studies (Eroglu, Emerick, Whitington & Alonso, 2004; Duche et al., 2008; Lam, Aters & Tobias, 2001). Of note, not all children with portal hypertension and variceal bleeds have liver cirrhosis as the cause. Therapies in non-cirrhotic patients are not addressed by this meta-analysis.
D'Antiga, L. (2012). Medical management of esophageal varices and portal hypertension in children. *Seminars in Pediatric Surgery*, August 2012, 21(3): 211-218.	V	This paper includes a summary of PHT and draws from a range of research papers, including RCTs, cohort studies and reports of expert committees. It also describes an institutional series of children with EHPVO within the Italian hospital within which the author is based (Osperdali Riuniti di Bergamo). The author explains that much of the paediatric treatment has been derived from adult research, even though paediatric varices are generally derived from non-cirrhotic PHT – a very different scenario to adults (211). There is little evidence on the efficacy of NSBBs, endoscopy, or shunts in children (p212). Children with EHPVO have high morbidity affecting QOL, such as frequent bleeding episodes, splenomegaly and hypersplenism, growth retardation and neurocognitive impairment (212). The paper recommends the following, with regard to management of acute variceal bleeding: Monitor vital signs, obtain venous access, FBC, INR, LFTs, UECs, crossmatch. PRBCs to maintain Hb 7g/dL, carefully avoiding a rebound fluid overload which would lead to rebleeding.

Reference	Evidence level (I-VII)	Methods, key findings, outcomes or recommendations
		Plasma, NGT placement, and vasoactive drugs as bridge to endoscopy (214).
Duche, M., Ducot, B., Ackermann, O., Guerin, F., Jacquemin, E. & Bernard, O. (2017). Portal hypertension in children: High-risk varices, primary prophylaxis and consequences of bleeding. *Journal of Hepatology,* February 2017, 66(2): 320-327.	IV	Large retrospective study of 1300 children between 1989 and 2014, looking at the efficacy of primary surgical or endoscopic prophylaxis in children with portal hypertension. Endoscopic features were recorded; high-risk varices were defined as: grade 3 oesophageal varices, grade 2 varices with red wale markings, or gastric varices. Two hundred forty-six children bled spontaneously and 182 underwent primary prophylaxis. The results of primary prophylaxis were reviewed as well as bleed-free survival, overall survival and life-threatening complications of bleeding. The study found high-risk varices in 96% of children who bled spontaneously and in 11% of children who did not bleed without primary prophylaxis (p <0.001), regardless of the cause of portal hypertension. Life-threatening complications of bleeding were recorded in 19% of children with cirrhosis and high-risk varices who bled spontaneously. Ten-year probabilities of bleed-free survival after primary prophylaxis in children with high-risk varices were 96% and 72% for non-cirrhotic causes and cirrhosis respectively. Ten-year probabilities of overall survival after primary prophylaxis were 100% and 93% in children with non-cirrhotic causes and cirrhosis respectively. The authors thus concluded that prevention of the first bleed in children with high-risk varices can be achieved by surgery or endoscopic treatment, and decreases mortality and morbidity.
Erdoğan, M.Ö., Öztürk, E., Erdoğan, B., Mehmet Tahir Gökdemir, M., Çolak, S., Murat Orak, M. & Güloğlu, C. (2014). Predictors of Emergency Blood Transfusion in Esophageal Variceal Bleeding *Journal of Academic Emergency Medicine*. 13: p35-38. http://www.akademikaciltip.com/sayilar/235/buyuk/45-48.pdf	VI	This retrospective analysis explored the attributes of patients presenting to a Turkish hospital emergency department with oesophageal variceal bleeding between the years 2000 and 2009, to determine predictors of the need for emergency blood transfusions in this patient cohort. Of the 54 patients identified, the researchers considered attributes including age, co-morbidities, time before admission to ward, vital signs, haemocrit, INR and albumin levels, medications, transfusions, time before endoscopy, and mortality. The paper concluded that patients who are over 60 years old, tachycardic and have low albumin are more likely to require transfusion. Given the analysis was of adult patients and the small size the study, no conclusions could reliably be applied to the clinical guideline under development. No higher-quality paediatric trials could be found relating to blood transfusion.
Giouleme, O. & Theocharidou, E. (2013). Management of	VII	This review paper describes portal vein thrombosis aetiology, clinical presentation, diagnosis, and treatment of portal

Reference	Evidence level (I-VII)	Methods, key findings, outcomes or recommendations
Portal Hypertension in Children With Portal Vein Thrombosis. *Journal of Pediatric Gastroenterological Nutrition*, October 2013, 57(4): 419-425. DOI: 10.1097/MPG.0b013e3182a1cd7f		hypertension, including pharmacologic, endoscopic and surgical options. Key points of relevance to the guideline review include: *PVT is a common cause of PH, variceal bleeding and splenomegaly are the two most common initial manifestations (p419).* *Extrahepatic portal vein obstruction (EHPVO) is a major cause of PH in children (419).* *Oesophageal varices are present in 90-95% of patients with PVT, with PV occlusion leading to vasodilation of the hepatic artery and formation of collateral vessels (419) Anorectal varices are also common.* *GI bleeding is better tolerated in patients with PVT compared to cirrhosis because the former usually maintains better liver function (419).* *The use of non-selective beta-blockers to prevent variceal bleeding in adults is established and comparable to EVL Some small case-series paediatric studies have been undertaken (421).* *In the setting of an acute variceal bleed event, beta blockers may inhibit the protective effect of tachycardia - a crucial compensatory mechanism for shock in children (421).* *Vasoactive agents such as vasopressin and somatostatin induce splachnic vasoconstriction, thereby decreasing portal venous inflow (421)* *2 paediatric studies suggest use of Octreotide (dose 1 -2 mcg/kg/hr) may be effective but reported rebleeding rates were high (50%).* *Sclerotherapy and EVL are highly effective in paediatric variceal bleed management (422).*
Gugig, R. & Rosenthal, P. (2012). Management of portal hypertension in children. *World Journal of Gastroenterology*. 18(11):1176-1184. DOI: 10.3748/wjg.v18.i11.1176	V	Well-resourced systematic review describing the best practice management of portal hypertension in children, (including primary and secondary prophylaxis, Emergency therapy of variceal bleeding, Pharmacology, Endoscopy, Sengstaken-Blackmore tubes Surgical and interventional radiology and Sclerotherapy and ligation therapy) with a strong evidence base included and limitations of the evidence base discussed. While the evidence in the paper is now outdated, practice remains unchanged, as far as can be determined. Key points of relevance to the guideline review include: *The initial management of variceal bleeding is stabilization of the patient.* *Patients on beta blocker therapy may not manifest the usual compensatory tachycardia and are at higher risk of developing*

Reference	Evidence level (I-VII)	Methods, key findings, outcomes or recommendations
		significant hypotension. *Conservative fluid resuscitation in the form of crystalloid initially, followed by red blood cell transfusion, is critical to avoid overfilling the intravascular space and increasing portal pressure.* *Nasogastric tube placement is safe and may be an essential part of the management of these patients. It allows documentation of the rate of ongoing bleeding and removal of blood, a protein source that may precipitate encephalopathy. In addition, blood in the stomach increases splanchnic blood flow and could aggravate portal hypertension and ongoing bleeding.* *Platelets should be administered for levels less than 50 × 109/L, and coagulopathy corrected with vitamin K and fresh frozen plasma.* *There may be a value to the use of recombinant factor VIIa in severe coagulopathy as the fluid requirements may be diminished.* *Intravenous antibiotic therapy should be considered for all patients with variceal bleeding in light of the high risk of potentially fatal infectious complications.* *Once the patient is stabilized, endoscopy should be performed to document that hemorrhage is indeed from variceal rupture. The Sengstaken-Blackmore tube (SSBT) was designed to stop hemorrhage by mechanically compressing esophageal and gastric varices. The device consists of a rubber tube with at least two balloons. It is passed into the stomach, where the first balloon is inflated and pulled up snug against the gastroesophageal junction. Once the tube is secured in place, the second balloon is inflated in the esophagus at a pressure (60-70 mmHg) that compresses the varices without necrosing the esophagus. A channel in the rubber tube allows gastric contents to be sampled for evidence of bleeding. This therapy is very effective in controlling acute bleeding but is associated with significant number of complications and high incidence of re-bleeding when the tube is removed. Its use in children requires significant sedation. Use of the SSBT increases the risk of aspiration pneumonia, which can be a life threatening complication in a patient with liver failure. Re-bleeding has been reported in 33%-60% of patients. Given these problems it is reserved for severe uncontrollable haemorrhage and generally serves as a temporizing measure until a more definite procedure can be performed.*

Reference	Evidence level (I-VII)	Methods, key findings, outcomes or recommendations
Gulati, R., Radhakrishnan K. R., Hupertz, V., Wyllie, R., Alkhouri, N., Worley, S. & Feldstein, A.E. (2013). Health-Related Quality of Life in Children With Autoimmune Liver Disease. *Journal of Pediatric Gastroenterological Nutrition*, October 2013, 57(4):444-50. DOI: 10.1097/MPG.0b013e31829ef82c	VI	This cross-sectional qualitative study assessed the health related quality of life (HRQOL) of 30 children (aged 0-21 years) with autoimmune liver disease from the Cleveland Clinic. The study used a 7- point Likert-scale questionnaire directed at children or their parents as proxy, and asked about physical, emotional, social and mental health domains. The researchers compared their cohort's scores to children with type 1 diabetes mellitus, moderate to severe asthma, juvenile rheumatoid arthritis, obesity and healthy children. The study found that HRQOL scores in their cohort were comparable to those living with asthma, juvenile rheumatoid arthritis and obesity, but worse than children with type 1 diabetes. Ascites, joint and abdominal pain, itching, xanthomas, bone fractures, fatigue, high rates of hospitalisation and worry about transplant were factors adversely affecting scores. While the study provides some insight into ways children with liver disease and their families might be better supported by health care professionals, the study's limitations include its small size and one-time assessment of QOL indicators.
Hussey, S., Kelleher, K.T. & Ling, S. (2010). Emergency Management of Major Upper Gastrointestinal Hemorrhage in Children. *Clinical Pediatric Emergency Medicine*, September 2010; 11(3): 207-216.	VII	This paper makes recommendations for the acute management of major upper intestinal bleed in children, including securing the airway, obtaining IV access, blood investigations, fluid resuscitation; pharmacological therapies (treatment of coagulopathies, acid suppression, somatostatin analogues and antibiotics) and subsequent management with endoscopy and surgery. The recommendations are based on adult-derived systemic reviews, randomised control trials and controlled trials and experimental or anecdotal paediatric evidence. The paper contains a useful algorithm (p209) for management of a patient with a significant GI bleed in children, which is comparable to the algorithm in the 2013 RCH Clinical Guideline. Key points of relevance to the guideline include: *Determine the presence of shock and haemodynamic instability (p208)* *Support for and reestablishment of an effective circulating volume is a resuscitation priority (p208) – recommend 20ml/kg NaCl bolus then blood products* *At cannulation, obtain Group & Hold and crossmatch, FBE, coags, LFTs, albumin, UECs, blood gas and lactate, BCs (p210)* *Vitamin K could be administered empirically and INR corrected with FFP (p212)* *Some clinicians prescribe H2 receptor antagonists. The use of PPIs is not without controversy, given they require liver*

Reference	Evidence level (I-VII)	Methods, key findings, outcomes or recommendations
		metabolism, however no paediatric data available to suggest they are unsafe (p212). *Whether bacterial translocation occurs as sequela or plays a role in pathogenesis of haemorrhage is unclear. Usual choice is ampicillin and cefotaxime (p212).* *Somatostatin analogues (eg octreotide, 1-2mcg/kg bolus followed by 1-5mcg/kg/hr).* *Evidence based management of GI bleeds in children have been hampered by a lack of controlled management of therapeutic trials in children (p215).*
Kochar, R. & DuPont, A.W. (2010). Primary and secondary prophylaxis of gastric variceal bleeding. Medicine Reports 2(26) - *Wiley Online Library*, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2948400/pdf/1757-5931-0002-0000000026.pdf. DOI: 10.1111/j.1440-1746.2010.06572.x	VII	This review paper discusses primary and secondary prophylaxis but also summarises acute management steps. The authors make some relevant statements about treatment options and provide a useful acute management algorithm. Key points of relevance to the guideline review include: *Variceal bleeding is the most common lethal complication of cirrhosis, with a mortality rate of 20% (page 1)* *Large, well conducted trials comparing treatment modalities are lacking, therefore management of varices is based on recent prospective and retrospective studies, expert consensus and opinion and professional experience. (page 1)* *Endoscopic therapy and TIPS are considered first line treatments, however current guidelines favour endoscopy (band ligation, tissue adhesives, thrombin, sclerotherapy) as the preferred intervention (page 2).* *Useful algorithm (page 2) – recommends octreotide and 3rd generation cephalosporin antibiotic treatment, then endoscopic treatment (cyanocryalate)* *Initial steps in acute management – maintain airway, gain IV access and provide prompt haemodynamic resuscitation, commence vasoactive medications (to reduce portal pressure by splenic vasoconstriction), administer prophylactic antibiotics , followed by diagnostic and therapeutic endoscopy (page 3)*
Koul, P.B., Totapally, B.R. & Raszynski, A. (2012). Continuous octreotide infusion for treatment of upper gastrointestinal bleeding due to portal hypertension in children: An observational study from pediatric intensive	TBA	*Abstract only.* This retrospective single hospital study evaluated the use of octreotide for the control of acute upper gastrointestinal bleeding in children with portal hypertension. Case notes of 18 encounters in 13 children were reviewed. Seven of the 13 children reviewed received a loading dose (1.27 ± 0.76 µg/kg), and the remaining five children received a median starting dose of 1.44 ± 1.19 µg/kg/h. The mean maximum dose was 1.68 ± 1.38 µg/kg/h. Re-bleeding occurred in one third; hemostasis was eventually achieved in all. The study found that octreotide infusion appears to be safe and effective in

Reference	Evidence level (I-VII)	Methods, key findings, outcomes or recommendations
care unit. *Journal of Pediatric Intensive Care*. 01(02): 099-103. DOI: 10.3233/PIC-2012-017		controlling pediatric upper gastrointestinal bleeding due to portal hypertension.
Lacroix, J., Hebert, P.C., Hutchison, J.S., Hume, H.A., Tucci, M., Ducruet, T., Gauvin, F., Collet, J.P., Toledano, B.J., Robillard, P., Joffe, A., Biarent, D., Meert, K. & Peters, M.J. (2007). Transfusion strategies for patients in pediatric intensive care units. *New England Journal of Medicine,* 356: 1609–1619.	II	In this prospective, randomised, controlled, single-centre non-inferiority trial, the researchers hypothesized that a restrictive PRBC transfusion strategy would be as safe as a liberal transfusion strategy, as judged by the outcome of multiple-organ dysfunction. The study included 637 stable, critically ill children who had haemoglobin concentrations below 9.5g/dL within seven days after admission to ICU. Patients were randomly allocated to the restrictive or the liberal strategy group. Those in the restrictive-strategy group (320 patients) were given a haemoglobin threshold of 7g/dL for PRBC transfusion, with a target range of 8.5–9.5g/dL and those in the liberal-strategy group (317 patients) were given a threshold of 9.5g/dL with a target range of 11–12g/dL. Only leukocyte depleted PRBCs were used in this study. Each protocol was applied for up to 28 days of the ICU stay, or until death. Haemoglobin concentrations were maintained at a mean (±SD) level that was 2.1±0.2g/dL lower in the restrictive-strategy group than in the liberal-strategy group (lowest average levels, 8.7±0.4 and 10.8±0.5 g/dL, P<0.001). New or progressive multiple-organ dysfunction syndrome developed in 38 patients in the restrictive-strategy group, as compared with 39 in the liberal-strategy group (12% in both groups) (absolute risk reduction with the restrictive strategy, 0.4%; 95% confidence interval, — 4.6 to 5.4). There were 14 deaths in each group within 28 days after randomisation. No significant differences were found in other outcomes, including adverse events. The researchers conclude from the trial that in stable, critically ill children a haemoglobin threshold of 7g/dL for PRBC transfusion can decrease transfusion requirements without increasing adverse outcomes. Non-inferiority trials are sometimes necessary when a placebo group cannot be ethically included, but these trials have a number of weaknesses including: No internal demonstration of assay sensitivity; No single conservative analysis approach; and Lack of protection from bias by blinding. However, blinding was not appropriate for this trial and methodology and analysis was robust. The patients were adequately randomised and the patient groups were similar in terms of demographic,

Reference	Evidence level (I-VII)	Methods, key findings, outcomes or recommendations
		severity of illness, organ dysfunction, septic state, haemoglobin levels and prior transfusion exposure, for instance. The researchers did not control for other therapeutic interventions and did not discuss interventions that might have affected haemoglobin levels, such as blood tests or invasive procedures. The conclusion of the trial support haemoglobin thresholds stated in paediatric guidelines and recommendations for variceal bleeds (Shneider et al., 2102; Costaguta & Alvarez, 2012; El-Shabrawi & Kamal, 2011). Based on the results of this trial, it appears to be safe to use either a conservative or liberal transfusion threshold for stable children in PICU. It is not known if the conclusion of the study could appropriately be applied to the patient with acute variceal bleed, in the active blood loss phase. It would be difficult to determine in a RCT what the safe transfusion threshold is for unstable patients. However it is expected that in the ICU environment, the patient can tolerate haemoglobin of 7g/dL for short periods of time and that using a lower transfusion threshold could decrease the number of blood transfusions and support the adjuvant aim of conservative blood volume restitution (Shneider et al., 2006; Garcia-Tsao, Sanyal, Grace & Carey, 2007; De Franchis 2005).
Lam, J.C., Aters, S.S., & Tobias, J.D. (2001). Initial Experience with Octreotide in the Pediatric Population. *American Journal Of Therapeutics,* 8: 409-416.	IV	A retrospective review of all patients 18 years of age or less who had received octreotide at a single-centre. The sample included 10 patients aged from 14 days to 17 years (five boys and five girls). The effectiveness of octreotide was evaluated by criteria based on the indication for its use. In patients with gastrointestinal bleeding, transfusion requirements before and after octreotide therapy and the clinical evidence of ongoing bleeding were evaluated. For patients with pancreatitis, data were collected on pain and amylase and lipase levels before and after octreotide therapy. For hypoglycaemia, glucose requirements pre and post octreotide were assessed. In cases of chylothorax/ chyloperitoneum, the evaluation was based on chest tube output and abdominal girth. The indications for octreotide included pancreatitis (three patients), gastrointestinal bleeding (four patients) chylothorax (two patients) and hypoglycaemia (one patient). In the four patients with gastrointestinal bleeding, two had oesophageal bleeding and the other two had lower gastrointestinal bleeding. All of the patients with gastrointestinal bleeding received continuous infusion. Three of the four patients with gastrointestinal bleeding were treated with an initial bolus of 1mcg/kg prior to continuous infusion. All four received continuous infusion of 1mcg/kg/hr.

Reference	Evidence level (I-VII)	Methods, key findings, outcomes or recommendations
		Two of these patients (one with Crohn's and one with oesophageal varices) did not require any further transfusions after octreotide therapy. Two patients had rebleeding when octreotide was stopped, which responded to restarting the infusion. One patient received sclerotherapy for their varices. The other patient with oesophageal varices was subsequently discharged with no surgical intervention. No adverse events were observed in the gastrointestinal group. The only adverse effect that could potentially be attributed to octreotide was the occurrence of hyperglycaemia in a patient with pancreatitis. Based on their study and review of other small paediatric and adult studies, the authors conclude that octreotide is a viable medication in children with gastrointestinal bleeding, pancreatitis, hypoglycaemia, and chylous ascites/ peritoneum because of its low risk profile and apparent effectiveness. They recommend further evaluation of octreotide in RCTs to make definitive conclusions and determine optimal dosing. The study was a very small, single-centre, retrospective study with no control or comparison group. The journal article is very brief on details and offers little interpretation of its findings or potential biases. This makes it impossible to determine whether octreotide improved the patient's status or resulted in less favourable clinical outcomes. The article spends more time discussing results from other studies than its own, unconvincingly drawing parallels between its findings and those of other small studies. Only three of the ten patients considered in this rather dated (12 year-old) study had oesophageal bleeds. This not only makes for a marginal study size, but the age of the patients with oesophageal bleeds (14 and 17 years) also means their physiology is more adult than paediatric. Given the weaknesses in the study, no conclusions could reliably be applied to the clinical guideline under review. Unfortunately no higher-quality paediatric trials could be found (other than in abstract-form only) that investigated the use of octreotide.
Ling, S.C., Walters, T., McKiernan, P.J., Schwarz, K.B., Garcia-Tsao, G. & Shneider, B.L. (2011). Primary Prophylaxis of Variceal Hemorrhage in Children With	VII	This paper outlines primary prophylaxis and is therefore not relevant for acute management, however it has some relevant up-to-date statistics on frequency of variceal occurrence and mortality so may be useful in Clinical Guideline background/ introduction. Key points of relevance to the guideline review include: *Mortality rate of 19% has been reported within 35 days of variceal bleeding episodes in North American children with liver*

Reference	Evidence level (I-VII)	Methods, key findings, outcomes or recommendations
Portal Hypertension: A Framework for Future Research. *Journal of Pediatric Gastroenterology and Nutrition*, March 2011 52(3): 254–261. DOI: 10.1097/MPG.0b013e318205993a		*disease (p255)* *A variceal bleed is associated with significant adverse sequelae, including the requirement for blood transfusion and ICU admission (p255)* *Two studies showed that 5% and 15% (respectively) of children with biliary atresia and variceal haemorrhage would die (p255)* *More than 50% of cirrhotic children have varices (p255)* *3% of children with biliary atresia will have a variceal bleed in the first 2 years of life (p255)*
Mileti, E. & Rosenthal, P. (2011). Management of portal hypertension in children. *Current Gastroenterology Reports.* 13(1): 10-16.	VII	This paper describes the pathophysiology of portal hypertension and makes recommendations for the prevention and management of variceal bleeding in children. The paper makes a number of recommendations, many of which are the same as other papers, however, some are new and are not supported by in-text references. For example, the authors assert that nasogastric tube placement and gastric lavage are helpful in confirming that the site and extent of bleeding is in the upper gastrointestinal tract. “Gastric lavage is usually done with room-temperature saline or sterile water and helps to evacuate the blood from the stomach, which allows for better visualization of the mucosa at the time of endoscopy”. Discussion with RCH’s Head of Gastroenterology in July 2018 indicate that this technique is outdated. The paper mentions two tubes that can be used to achieve balloon tamponade, which are not mentioned in any other literature reviewed: a Linton tube and a Minnesota tube. “The Linton tube is a single-balloon tube used to stop the bleeding from gastric varices; the Minnesota and Sengstaken-Blakemore tubes have two balloons, one for the stomach for gastric varices, and the other for esophageal varices”. The paper provides some useful discussion on balloon tamponade and complications: “The length of the esophageal balloon limits the use of the Minnesota and Sengstaken-Blakemore tubes to children weighing more than 40kg.” “Bleeding can be stopped in almost 90% of cases by balloon tamponade; however, the tubes are only temporizing measures and cannot be kept in place for more than 24h [9]. “ “Tube placement should be attempted only by individuals who have been trained and are comfortable with their use, because

Reference	Evidence level (I-VII)	Methods, key findings, outcomes or recommendations
		complication rates are high when the tubes are not properly placed. Complications include esophageal perforation, aspiration, mucosal ischemia, and airway obstruction [9,10]. When balloon tamponade is required, there should be a low threshold for intubation, and intubation is highly recommended."
Pimenta, J.R., Ferreira, A.R., Fagundes, E., Queiroz, T., Baptista, R. de Araújo Moreira, E.G., de Resende, C.B., Bittencourt, P., Carvalho, S.D., Neto, J. & Penna, F.J. (2017). Factors Associated With Bleeding Secondary to Rupture of Esophageal Varices in Children and Adolescents With Cirrhosis. *Journal of Pediatric Gastroenterology and Nutrition*. February, 64(2): e44–e48	IV	This cross-sectional single centre study included 103 children and adolescents diagnosed with PHT and liver cirrhosis. 35 patients who had an upper GI bleed secondary to oesophageal varices rupture and 68 patients with varices without a history of upper GI bleeding, were evaluated. The most prevalent diagnoses in the study group were biliary atresia (33%), and autoimmune hepatitis (32%). Patients with BA who had an UGIB had the bleed at a median age of 2.9 years. The autoimmune hepatitis group with UGIB had the bleed at median age 8.4 years (e46). The study found that statistically significant risk factors for UGIB include the presence of red spots on varices and the presence of gastric varices, consistent with other studies identified by the study authors (e47).
Sarin, S.K. & Khanna, R. (2014). Non-cirrhotic portal hypertension—diagnosis and management. *Journal of Hepatology*. 60(2):421-441.	V	This paper describes the pathophysiology of Non-cirrhotic portal hypertension and discusses clinical features and management strategies of its associated complications. The authors review and discuss the Baveno V consensus and summarise key research as it pertains to evidence for practice in this field, specifically EVL, EST and TIPS and beta-blockers as secondary prophylaxis.

Reference	Evidence level (I-VII)	Methods, key findings, outcomes or recommendations
Shaheen, N.J., Stuart, E., Schmitz, S.M., Mitchell, K.L., Fried, M.W., Zacks, S., Russo, M.W., Galanko, J. & Shrestha, R. (2005). Pantoprazole reduces the size of postbanding ulcers after variceal band ligation: a randomized, controlled trial. *Hepatology*, 41(3): 588-594.	II	This double-blinded, randomised, placebo-controlled trial of assessed the efficacy of the proton pump inhibitor (PPI), pantoprazole, as an adjunct to elective endoscopic variceal ligation (EVL). Participants were patients presenting at a single US hospital between 200 and 2003 with portal hypertension, varices and a history of prior variceal haemorrhage, aged 18 to 80 years. Subjects in the PPI arm received 40mg pantoprazole intravenously after EVL followed by 40mg oral pantoprazole for 9 days. Control subjects received intravenous and oral placebo. Subjects underwent upper endoscopy 10 to 14 days after banding. Primary outcomes included the size and number of ulcers and the subjects' reports of dysphagia, chest pain, and heartburn. Forty-two of 42 completed the protocol. At follow-up endoscopy, the mean number of ulcers was similar in the two groups. However, the ulcers in the pantoprazole group were half as large as in the placebo group (37mm2 vs. 82 mm2, P < .01). Chest pain, dysphagia, and heartburn scores were not significantly different. Four subjects, all in the placebo group, had adverse outcomes, including three who bled from post-banding ulcers and one with sepsis. The RCT concluded that subjects receiving pantoprazole after elective EVL leads to a 50% reduction in the size of post-banding ulcers at follow-up endoscopy compared to placebo. This study had several strengths. Methodology and priori outcomes were clearly defined. Blinding was complete and no potential for bias could be identified. Monitoring during and after treatment was compulsive, and no subject was lost to follow-up. Compliance was high with the intervention. Because of the infrequency of rebleeds post EVL, the researchers could not use this variable as a primary outcomes of the effect of the PPI on improved mortality cannot be measured with the sample size used in this study (3000 participants would be necessary to achieve 80% power). The focus instead is on reducing the size and number of ulcers and the subjects' quality of life reports (dysphagia, chest pain, and heartburn). No research could be identified that looked more fundamentally at whether PPIs improve clinical outcomes when administered on their own, without being used as an adjunct to EVL. However, it is expected that the results of this RCT could be replicable in a paediatric trial where EVL is indicated (with PPI dosing appropriate for weight). Further, if PPIs reduce ulceration size by half, it is anticipated that when used independently of surgical intervention, their use should help maintain

Reference	Evidence level (I-VII)	Methods, key findings, outcomes or recommendations
		oesophageal mucosal integrity and reduce the risk of further bleeding episodes.
Shava, U., Srivastava, A., Jagdisan, B., Yachha, S.K. & Poddar, U. (2013). Safety and efficacy of endoscopic variceal ligation for primary prophylaxis of variceal bleeding in children. *Journal of Clinical and Experimental Hepatology*. March 2013, 3(1): S98	IV	This paper describes treatment and outcomes of 70 children with high risk varices, who received prophylactic Endoscopic variceal ligation in a hospital in Lucknow, India, between 2005 and 2011. No control or comparison group was considered. The retrospective study concluded that EVL is feasible in children aged 3-5 years, for those with intra or extra-hepatic PHT. They found EVL in this patient group was associated with only mild complications in 8% of patients and a recurrence rate of 16% over 1 year. Given the brevity of the paper, and the fact that EVL was used prophylactically, rather than in patients who had experienced a bleed, no conclusions can reliably be applied to the clinical guideline under review. Given the weaknesses in the study, no conclusions could reliably be applied to the clinical guideline under review. No higher-quality paediatric trials could be found relating to EVL.
Singhi, S., Jain, P., Jayashree, M. & Lal, S. (2013); Approach to a child with upper gastrointestinal bleeding. *Indian Journal of Pediatrics*, April 2013; 80(4): 326-333.	VII	Developed by staff in the Department of Pediatrics, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research in Chandigarh, India; this paper was presented at the Symposium on PGIMER Management Protocols in Gastrointestinal Emergencies. It describes the more frequent aetiologies of GI bleeding in Indian children and treatment and management pathways for these children. The references within the paper are a mix of journal articles describing randomised control trials, controlled trials without randomisation and reports of expert committees. The paper contains a useful algorithm (p328) for management of a patient with a significant GI bleed, which is comparable to the algorithm in the 2013 RCH Clinical Guideline.
Shneider, B.L., Bosch, J., de Franchis, R., Emre, S.H., Groszmann, R.J., Ling, S.C., Lorenz, J.M., Squires, R.H., Superina, R.A., Thompson,	VII	In 2011, an international panel of experts revised and developed the Baveno V Consensus Report into a paediatric-specific commentary. This article reports the recommendations of the panel. It describes the methodology of diagnosis and therapy in paediatric portal hypertension and its complications. Recommendations for therapeutic management include preventing the formation of varices, preventing a bleed, acute management of a variceal bleed and preventing a second bleed. Recommendations relevant to acute variceal bleeds include:

Reference	Evidence level (I-VII)	Methods, key findings, outcomes or recommendations
A.E., & Mazariegos, G.V. (2012). Portal Hypertension in Children: Expert Pediatric Opinion on the Report of the Baveno V Consensus Workshop on Methodology of Diagnosis and Therapy in Portal Hypertension. *Pediatric Transplantation*, 16: 426–437.		Prevention of the first bleeding episode; Blood volume restitution; Antibiotic prophylaxis; Timing of endoscopy; Pharmacological and endoscopic treatment; Use of balloon tamponade; Management of treatment failures; and Prevention of rebleeding. The panel concluded there was insufficient data to make any recommendations on the prevention of hepatic encephalopathy, or post-variceal bleed prognosis. They identified that areas requiring urgent further study include: Clinical course (haemodynamic, biochemical, and haematologic parameters); Responses to various vasoactive therapies; Determination of prognostic markers (to identify high risk bleeding episodes where early TIPSS might be advantageous); Analysis of infectious risks and potential role of antibiotic prophylaxis; and Responses to transfusion practices. This report is authoritative in its definitions for a bleeding episode, but for therapeutic management of a variceal bleed, it is less conclusive. The panel reports that given the very limited number of randomised trials in paediatric liver disease, the recommendations in the report are not graded on the basis of type of evidence. Most of the statements are expert opinion or are derived from case series or cohorts. More research is required for the development of definitive paediatric management guidelines. The panel comprised representative specialists from Children's hospitals in the USA (Pittsburgh, Yale, and Chicago); Spain (Barcelona); Italy (Milan) and Canada (Toronto). The specialists' qualifications are not described although it is assumed they are gastroenterologists and/or hepatoligists. It is possible given the small number of hospitals and countries represented by the expert panel, that other experts have reached different conclusions for diagnosis and management of this patient group. No critique of the panel report was however, identified. It is also noteworthy that the recommendations in the report are relevant primarily to pre-pubescent children, where physiologic parameters are most distinct from adults (Shneider et al., 2012).
de Ville de Goyet, J. D'Ambrosio, G. & Chiara Grimaldi, C. (2012). Surgical	VII	This review paper outlines surgical management strategies for managing paediatric patients with PHT, which are different depending on the classification of the PHT. This paper is likely to be highly relevant to RCH theatres and surgical teams, but

Reference	Evidence level (I-VII)	Methods, key findings, outcomes or recommendations
management of portal hypertension in children. *Seminars in Pediatric Surgery*, August 2012, 21(3): 219-232.		less so for a clinical guideline addressing acute management of a variceal bleed. This paper makes clear however, that preliminary assessments in the emergency department should establish the cause of PHT if possible. Appropriate preoperative care includes assessment of the patient's coagulation profile (p224).
Vogel, C.B. (2-17). Pediatric portal hypertension: A review for primary care. *The Nurse Practitioner*, 12 May 201742(5): 35–42. DOI: 10.1097/01.NPR.0000515427.91649.91	VII	This review paper outlines primary care requirements for health practitioners to consider, when caring for children with portal hypertension. It describes aetiology of disease, pathophysiology, clinical presentation, diagnostics, primary, secondary and tertiary treatment and management, including clinical pathways for referral if complications arise. Complications discussed in the paper include haemorrhage from varices, ascites, hepato-pulmonary syndrome, porto-pulmonary hypertension, and hepatic encephalopathy (p39). *Variceal bleeding is the most serious complication of portal hypertension, which can occur from venous collaterals in the stomach or oesophagus. Varices and ascites are seen when portal pressure is 12 mm Hg or greater. This is not a subtle finding, as there is a 30% mortality with variceal bleeding (p 39).* This paper draws from much of the literature RCH's 2013 guideline used. It has a useful table, outlining the causes of paediatric portal hypertension, including intra-hepatic, pre-hepatic and post-hepatic (p 36). Acute management strategies listed in the paper include: octreotide, PPIs, PRBCs and/or platelets, and endoscopy (referencing the Baveno v consensus workshop).
Wanty, C.,Helleputte, T., Smets, F., Sokal, E.M. & Stephenne, X. (2013). Assessment of risk of bleeding from esophageal varices during management of biliary atresia in children. *Journal of Pediatric Gastroenterology and*	IV	This retrospective study reviewed clinical, ultrasonographic, endoscopic, and laboratory data of 83 patients with biliary atresia from the beginning of medical management up to the occurrence of an upper gastrointestinal bleeding event. In patients with no bleeding, data was analysed until liver transplantation, endoscopic treatment of EV was performed, or last follow-up. Risk factors were investigated using univariate and multivariate statistical analyses. The researchers found that 20% of the patients had a gastrointestinal bleed incident, with a median age of 9.5 months (6-50 months). In univariate and multivariate analyses, high-grade EV, red color signs on endoscopic examination, and low fibrinogen levels, at first endoscopy, were identified as risk factors for bleeding. When tested in >10,000 different models, these 3 variables appeared to play the most significant role in predicting bleeding.

Reference	Evidence level (I-VII)	Methods, key findings, outcomes or recommendations
Nutrition, 56(5): 537–543. DOI:10.1097/MPG.0b013e318282a22c		
Zhao X., Shi Y. & Gao, P. (2017). The selection and prognosis of transfusion strategy in acute upper gastrointestinal bleeding. Hepatology International. Conference: 26th Annual Conference of the Asian Pacific Association for the Study of the Liver, APASL 2017. China. 11 (1 Supplement 1) (pp S344).	IV	This retrospective study undertaken at the First Hospital of Jilin University, Changchun, China aimed to compare that prognosis of different transfusion strategy in adult patients admitted with acute non-massive upper gastrointestinal bleeding in 2012.The study included 166 patients, all of whom underwent endoscopy and received red-cell transfusion while hospitalized. The patients were assigned to two groups in accordance with the haemoglobin levels before transfusion: a restrictive strategy (transfusion when the haemoglobin level fell below 70 g/L) and a liberal strategy (transfusion when the haemoglobin fell between 70 and 90 g/L). The common aetiology of haemorrhage were peptic ulcer (87 cases, 51%), oesophago-gastric variceal bleeding (49 cases, 30%), erosive gastritis or esophagatis (16 cases, 10%), Mallory Weiss Syndrome (8 cases, 5%), gastric cancer (6 cases, The study found that the mortality at 4 weeks was significantly lower in the restrictive strategy group than in the liberal strategy group (5.5 vs 7.1%, p\0.05). The rate of further bleeding was significantly lower in the restrictive strategy group than in the liberal strategy group (9.1 vs 19.6%, p \ 0.05). In the subgroup of patients with cirrhosis, the risk of death and further bleeding were significantly lower in the restrictive transfusion strategy than in the liberal transfusion between two groups. Incidence of adverse events: the overall rate of adverse events was significantly lower in the restrictive strategy group than in the liberal strategy group (31.8 vs 46.4%, p\0.05).