Gastroenterology guideline: Terlipressin

1. INTRODUCTION

Terlipressin is a vasopressin analogue, which acts a vasoconstrictor predominantly in the splanchnic circulation. It is licensed to treat variceal bleeding[1], but is also used to treat hepatorenal syndrome although it is unlicensed for this indication[2]. In March 2023, the MHRA provided new guidance on the use of terlipressin for hepatorenal syndrome[3] – see section 3 for further details.

Terlipressin should only be used with caution and under strict monitoring of the patients in the following cases[1]:

- Septic shock
- Bronchial asthma, respiratory deficiencies
- Uncontrolled hypertension
- Electrolyte derangements or if the patient is taking other medicines with a risk of hypokalaemia or hyponatraemia
- Cerebral or peripheral vascular diseases
- Cardiac arrhythmias, including QT prolongation or if patients are on other medicines that could prolong the QT interval
- Chronic renal insufficiency
- Acute coronary syndrome, coronary deficiencies or previous myocardial infarction
- Elderly patients >70 years as experience is limited in these groups
- Pregnancy or breastfeeding – seek specialist advice

Adverse effects and monitoring requirements

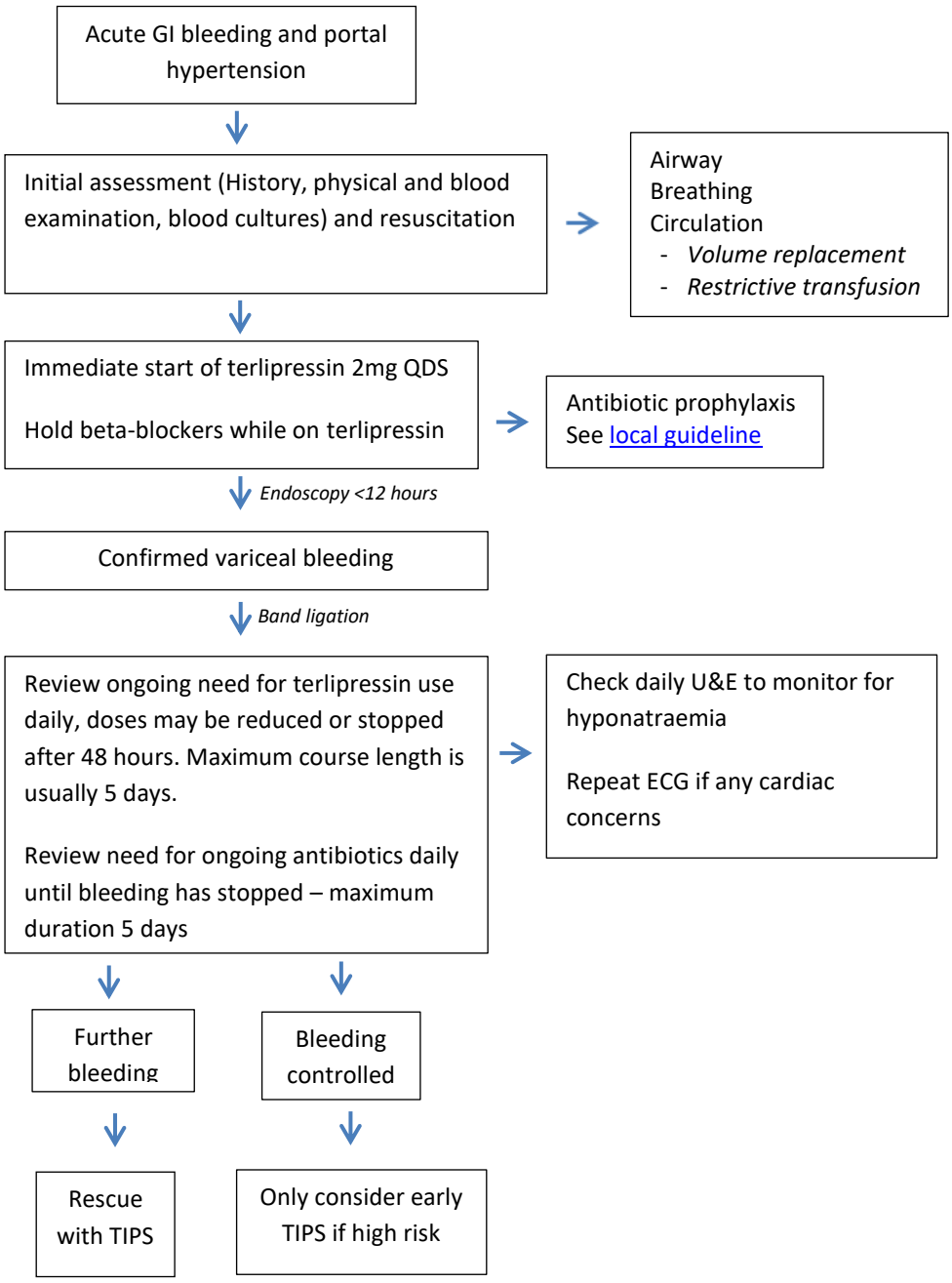
- Monitor daily U and E as terlipressin can cause hyponatraemia via weak anti-diuretic hormone effect
- An ECG must be checked before starting treatment
- As terlipressin can cause hyper and hypotension, peripheral vasoconstriction, bronchospasm and cardiac ischaemia, patients must be closely monitored and an ECG repeated if any adverse effects arise.
- GI adverse effects, including abdominal cramps and diarrhoea can occur but these are usually transient[1]

2. VARICEAL HAEMORRHAGE

Variceal haemorrhage is caused by rupture of variceal walls due to excessive wall tension and is one of the most immediate life-threatening complications in patients with cirrhosis. 70% of GI bleeding events in patients with portal hypertension are due to variceal bleeds[4]. Terlipressin has been shown to improve mortality in variceal bleeding compared to placebo and is as effective as endoscopic therapy at reducing mortality, haemostasis and preventing re-bleeding[5].

Presentation of acute upper gastrointestinal bleeding [4]

Immediate action is required



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2. HEPATORENAL SYNDROME

Hepatorenal syndrome (HRS) is defined as renal failure in people with cirrhosis and ascites in the absence of [6-7]:

- Pre-renal causes
- History of nephrotoxic drugs
- History of shock (acute tubular necrosis)
- Proteinurea +/- haematuria (parenchymal renal disease)

Clinical trials have shown terlipressin to be effective at reversing HRS-AKI but also showed that patients who received terlipressin were more likely to die by day 90 (largely due to respiratory disorders) than those who received placebo. There were also more serious respiratory events and cases of sepsis or septic shock in those who received terlipressin than in those who received placebo[3]

Contraindications to terlipressin for hepato-renal syndrome (MHRA Drug Safety Update March 2023)[3]

- Patients with advanced renal dysfunction (baseline serum creatinine at or above 442 micromol/L (5.0mg/dl) unless the benefit is judged to outweigh the risks
- Patients with severe liver disease (defined as acute-on-chronic liver failure (ACLF) Grade 3, a model for end-stage liver disease (MELD) score ≥ 39, or both) unless the benefit is judged to outweigh the risks (locally a UK end-stage liver disease (UKELD) score may also be used).

The classifications of HRS were changed in 2018[5, 7]

Old classification	New classification		Diagnostic criteria
HRS-1	**HRS-AKI (acute kidney injury)**		a) Absolute increase in serum Cr ≥0.3mg/dL (27micromol/L within 48 hours) And/or b) Urinary output ≤0.5ml/kg ≥6 hours Or c) Percent increase in serum Cr ≥50% using the lowest available value of outpatient serum Cr within 3 months as the baseline value
HRS-2	**HRS-NAKI (no acute kidney injury)**	**HRS-AKD (acute kidney disease)**	a) eGFR <60ml/min for <3 months in the absence of other (structural) causes b) Percent increase in serum Cr <50% using the last available value of outpatient serum Cr within 3 months as the baseline value
		HRS-CKD (chronic kidney disease)	a) eGFR <60ml/min for ≥3 months in the absence of other (structural) causes

Precautions when using terlipressin for hepatorenal syndrome[3]

- Stabilise patients with new-onset breathing difficulties or worsening of existing respiratory disease before administering terlipressin and monitor closely during treatment
- Consider a reduction in albumin dose in patients with signs or symptoms of respiratory failure or fluid overload; discontinue terlipressin if symptoms are severe or do not resolve
- Monitor patients daily for signs and symptoms of infection
- Monitor blood pressure, heart rate, oxygen saturation, serum sodium and potassium levels, and fluid balance; terlipressin may induce myocardial ischaemia and pulmonary vascular congestion, especially in those with pre-existing cardiopulmonary disease
- Terlipressin can be administered as a continuous intravenous infusion as an alternative to bolus injection as infusion may be associated with lower rates of severe adverse events than bolus injection (see below)
- Patients receiving terlipressin for hepatorenal syndrome should be counselled on the benefits and risks, even if circumstance necessitates that counselling occurs after treatment with terlipressin is given

Terlipressin dosing in hepatorenal syndrome[3]

Refer to HRS management algorithm

IV infusion:

Continuous IV infusions should be prescribed on paper with a "See additional chart" order added to EPMA

Terlipressin dose	Volume of 0.9% sodium chloride or 5% glucose	Infusion time
2mg	100ml	24 hours
4mg	250ml	24 hours
6mg	250ml	24 hours
8mg	250ml	24 hours
10mg	250ml	24 hours

References

1. Flynn Pharma Ltd. Summary of Product Characteristics Terlipressin Acetate 1mg Solution for Injection. Last updated on the eMC 22/09/2022.
2. National Institute for Health and Clinical Excellence (2016). Cirrhosis. NICE Clinical Guideline NG50.
3. Medicines and Healthcare Regulatory Agency (2023); Terlipressin: new recommendations to reduce risks of respiratory failure and septic shock in patients with type 1 hepatorenal syndrome; *Drug Safety Update*
4. European Association for the Study of the Liver (2018); EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis; *J Hepatol*; https://doi.org/10.1016/j.jhep.2018.03.024
5. Nevens F, Bittencourt P et al (2018); Recommendations on the Diagnosis and Initial Management of Acute Variceal Bleeding and Hepatorenal Syndrome in Patients with Cirrhosis; *Digestive Diseases and Sciences*; 64; p1419-1431

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6. Best LMJ, Freeman SC, Sutton AJ et al. (2019); Treatment for hepatorenal syndrome in people with decompensated liver cirrhosis: a network meta-analysis; *Cochrane Database of Systematic Reviews*; Issue 9. Art. No.: CD013103
7. Angeli, P. Guadalupe, GT, Mitra, NK et al. (2019); News in pathophysiology, definition and classification of hepato-renal syndrome: A step beyond the International Club of Ascites (ICA) consensus document; *Journal of Hepatology;* vol. 71; 811–822.