



## **Draft PMB definition guideline for Gastric or intestinal ulcers with haemorrhage or perforation**

## Disclaimer

*The benefit definition for gastric or intestinal ulcers with haemorrhage or perforation has been developed for the majority of standard patients. These benefits may not be sufficient for outlier patients. Therefore Regulation 15(h) and 15(l) may be applied for patients who are inadequately managed by the stated benefits. The benefit definition does not describe specific in-hospital management such as theatre, anaesthetists, anaesthetics, nursing care and allied professional services. However, these interventions form part of care and are prescribed minimum benefits.*

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## Abbreviations

CMS	Council for Medical Schemes
CT	Computerized Tomography
DSPs	Designated Service Providers
DTP	Diagnosis Treatment Pairs
ECG	Electrocardiogram
ESGE	European Society of Gastrointestinal Endoscopy
FBC	Full Blood Count
INR	International Normalized Ratio
LFT	Liver function test
NSAIDs	Non-steroidal anti-inflammatories
OTSCs	Over-the-scope clips
PMB	Prescribed Minimum Benefit
PPIs	Proton Pump Inhibitors
PUD	Peptic ulcer disease
U&E	Urea and Electrolytes
YLD	Years Lived With Disability

## 1. INTRODUCTION

- 1.1. The legislation governing the provision of the Prescribed Minimum Benefits (PMBs) is contained in the Regulations enacted under the Medical Schemes Act, 131 of 1998 (the Act). In respect of some of the Diagnosis Treatment Pairs (DTPs), medical scheme beneficiaries sometimes find it difficult to know their entitlements in advance. In addition, medical schemes interpret these benefits differently, resulting in a lack of uniformity of benefit entitlements.
- 1.2. The benefit definition project is coordinated by the Council for Medical Schemes (CMS) and aims to define the PMB package, as well as to guide the interpretation of the PMB provisions by relevant stakeholders.

## 2. SCOPE AND PURPOSE

- 2.1 This is a recommendation for the diagnosis, treatment and care of individuals with gastric ulcers with haemorrhage and perforation in any clinically appropriate setting as outlined in the Act.
- 2.2 The purpose is to improve clarity in respect of funding decisions by medical schemes, taking into consideration evidence-based medicine, affordability and cost-effectiveness.

**Table 1: Possible ICD10 codes for identifying gastric or intestinal ulcers with haemorrhage or perforation**

<b>ICD-10 Code</b>	<b>ICD-10 Description</b>
K25.0	Gastric ulcer, acute with haemorrhage
K25.1	Gastric ulcer, acute with perforation
K25.2	Gastric ulcer, acute with both haemorrhage and perforation
K25.4	Gastric ulcer, chronic or unspecified with haemorrhage
K25.5	Gastric ulcer, chronic or unspecified with perforation
K25.6	Gastric ulcer, chronic or unspecified with both haemorrhage and perforation
K26.0	Duodenal ulcer, acute with haemorrhage
K26.1	Duodenal ulcer, acute with perforation
K26.2	Duodenal ulcer, acute with both haemorrhage and perforation
K26.4	Duodenal ulcer, chronic or unspecified with haemorrhage
K26.5	Duodenal ulcer, chronic or unspecified with perforation
K26.6	Duodenal ulcer, chronic or unspecified with both haemorrhage and perforation
K27.0	Peptic ulcer, site unspecified, acute with haemorrhage

K27.1	Peptic ulcer, site unspecified, acute with perforation
K27.2	Peptic ulcer, site unspecified, acute with both haemorrhage and perforation
K27.4	Peptic ulcer, site unspecified, chronic or unspecified with haemorrhage
K27.5	Peptic ulcer, site unspecified, chronic or unspecified with perforation
K27.6	Peptic ulcer, site unspecified, chronic or unspecified with both haemorrhage and perforation
K28.0	Gastrojejunal ulcer, acute with haemorrhage
K28.1	Gastrojejunal ulcer, acute with perforation
K28.2	Gastrojejunal ulcer, acute with both haemorrhage and perforation
K28.4	Gastrojejunal ulcer, chronic or unspecified with haemorrhage
K28.5	Gastrojejunal ulcer, chronic or unspecified with perforation
K28.6	Gastrojejunal ulcer, chronic or unspecified with both haemorrhage and perforation

### 3. EPIDEMIOLOGY AND BURDEN OF DISEASE

- 3.1. Peptic ulcer disease (PUD) refers to ulceration into the submucosa of either the stomach (gastric ulcer) or duodenum and is one of the most common gastrointestinal conditions. PUD is predominantly due to either *Helicobacter pylori* infection or use of medicines such as the non-steroidal anti-inflammatories (NSAIDs) and aspirin. Whilst the incidence and prevalence of PUD has increased by around 4.8% over the past decade, the age standardised prevalence rates and years lived with the disability (YLD) have reduced by 17% and 19.5% respectively (Vos, Allen, Arora, Barber, Bhutta, Brown, Carter, et al, 2015.). This is presumably due to the reduction of *H pylori* infections and introduction of new treatments (Rickard, 2016).
- 3.2. The most common complications of gastric ulceration are bleeding, perforation or obstruction. Although the incidence of upper gastrointestinal bleeding or perforation due to gastric ulcer is declining, the mortality rate remains steady at around 5-10% for bleeding and as high as 20% for perforation (Rickard, 2016). Not all patients presenting with upper gastrointestinal bleeding require hospitalisation and endoscopic or surgical treatment, with many cases spontaneously resolving or responding to oral treatment. However, there are patients with clinically significant bleeding or at high risk of recurrent bleeding, who will require more intensive intervention (Lanas and Chan, 2017).

#### 4. RESUSCITATION AND PRE-DIAGNOSTIC WORK UP

**Table 2: Resuscitation and pre-diagnostic work up basket for gastric or intestinal ulcers with haemorrhage or perforation**

Intervention	Description	Comment
Consultations	General Practitioner / primary care practitioner (including emergency physician and family physicians)	1 consult – will refer to Gastroenterologist or Surgeon
	Gastroenterologist/Surgeon	1 consult
Laboratory investigations	International Normalized Ratio (INR)	
	Urea and Electrolytes (U&E)	
	Full Blood Count (FBC)	
	Arterial Blood Gas	
	ABO and Rh compatibility testing	
Radiology: Imaging	Chest x-ray	
	Abdominal x-ray	
Resuscitation	Blood products	As indicated
	Intravenous fluids	
	Supplemental oxygenation	

- 4.1. The initial investigation and management of a patient with bleeding or perforation begins with an assessment of their haemodynamic stability and requirements for resuscitation. Risk stratification of patients into low and high risk categories will assist in determining which patients require urgent intervention.
- 4.2. Prompt fluid replacement, initially with crystalloid solutions, is necessary to reduce mortality in patients with acute haemorrhage (Gralnek, Dumonceau, Kuipers, Lanas, Sanders, Kurien, Rotondano, Hucl, Dinis-Ribeiro & Marmo, 2015).
- 4.3. Red Blood Cell (RBC) transfusions may be required, as indicated, to maintain a haemoglobin level of  $\geq 7\text{g/dl}$  (Gralnek et al., 2015; Laine and Jensen, 2012; NCGC, 2016).
- 4.4. ABO and Rhesus compatibility testing are necessary in the event of patients requiring a blood transfusion due to excessive bleeding.

## 5. INVESTIGATIONS AND DIAGNOSIS

**Table 3: Diagnostic basket for gastric or intestinal ulcers with haemorrhage or perforation**

	Description	Comment
Laboratory investigations		
	FBC	
	U&E	
	Blood gas	
	Liver function test (LFT)	
	Amylase or lipase	Either amylase or lipase – not both
	INR	
	ABO and Rh compatibility testing	
Imaging radiology and procedures		
For gastric ulcers with perforation	Chest x-ray	
	Abdominal x-ray	
	Contrast Computerized Tomography (CT) scan	Priority over barium meal.
	Ultrasound (including whole abdomen and pelvic organs)	
For gastric ulcers with haemorrhage	Chest x-ray	
	Abdominal x-ray	
	Ultrasound (including whole abdomen and pelvic organs)	Only one ultrasound- Primary practitioner or radiologist
	Gastro-intestinal endoscopy	
Histopathology		
	Biopsy	Not routine in the event of perforation
	H. Pylori	
Other	Electrocardiogram (ECG)	
Exclusions		
Diagnostic laparoscopy for perforation	If unsure - Specialist to perform a CT scan to confirm diagnosis	



- 5.1. All laboratory tests indicated in the above table should not be repeated if already carried out as part of the primary diagnosis. If any of the tests are clinically indicated following resuscitative measures then they will be included as PMB level of care.
- 5.2. Diagnosis of bleeding or perforation of a gastric ulcer should include chest and abdominal x-rays. CT scans are considered the gold standard as they are more sensitive and specific than plain radiography (Cahalane, 2016).
- 5.3. Endoscopy (Early) within 24 hours is recommended in stable patients. Very Early endoscopy (within 12 hours) is recommended in unstable patients with features such as tachycardia or hypotension despite resuscitation attempts or with nasogastric aspirate or bloody emesis (Gralnek et al., 2015).
- 5.4. Amylase or lipase testing is useful in determining other causes of upper gastrointestinal disorders such as pancreatitis.
- 5.5. An INR is indicated in patients with active bleeding and those on anticoagulants.
- 5.6. Testing for *H. pylori* by biopsy is recommended during endoscopy (Chey, Leontiadis, Howden & Moss, 2017), however routine biopsy is not warranted in duodenal ulcers.
- 5.7. The evidence supporting ultrasonography in the detection of pneumoperitoneum in cases of perforation is limited, with CT generally considered to be more accurate. However there may be role for ultrasonography in patients where CT may not be appropriate, specifically in pregnant women or children (Coppolino, Gatta, Di Grezia, Reginelli, Iacobellis, Vallone, Giganti & Genovese, 2013).

## 6. MANAGEMENT AND TREATMENT

### 6.1. Medical management

**Table 4: Medical management of gastric or intestinal ulcers with haemorrhage or perforation**

Haemostatic interventions	Adrenaline injections
	Endoscopy clips
	Thermal ablation
Eradication of H-Pylori	Antibiotics
Acid suppression	Proton Pump Inhibitors (PPIs) – Oral or IV
Prokinetic agent	Erythromycin or Metoclopramide - only if the patient cannot tolerate erythromycin

- 6.1.1. Erythromycin, used as a prokinetic agent, given intravenously in a single 250mg dose 30-120 minutes prior to endoscopy has been shown to improve endoscopic visualisation, particularly in patients with severe or active bleeding and large amounts of blood in their stomach (Gralnek et al., 2015). Two recent meta-analyses have shown that pre-endoscopy erythromycin shortens hospital length of stay and reduces the need for a repeat endoscopy, however no difference in mortality has been proven (Bai, Guo & Li, 2011; Gralnek et al. 2015; Rahman, Nguyen, Sohail, Almashhrawi, Ashraf, Puli & Bechtold, 2016).
- 6.1.2. PPI therapy is widely recommended as the foundation of treatment for stabilising blood clots by increasing pH levels, however the evidence for PPI therapy prior to endoscopy remains inconsistent (CADTH, 2016). Intravenous PPI infusion prior to endoscopy is recommended in the 2015 European Society of Gastrointestinal Endoscopy (ESGE) guideline based on the evidence from a 2010 Cochrane Systematic Review which showed that PPIs pre-endoscopy reduced the incidence of stigmata of recurrent risk as well as the need for endoscopic haemostasis, however, there was no difference in clinical outcomes such as reduced re-bleeding or the need for additional endoscopic treatments or surgery or improvements in mortality (Gralnek et al., 2015). Other guidelines such as the NICE 2016 updated guidelines on acute upper gastrointestinal bleeding specifically recommend not to use PPIs pre-endoscopically in NVUGB (NCGC, 2016). The use of PPIs pre-endoscopy is therefore not recommended as PMB level of care.
- 6.1.3. The risk of re-bleeding or persistent bleeding is high in patients with spurting or oozing bleeding or with a non-bleeding visible vessel and therefore endoscopic haemostasis is recommended (Gralnek et al., 2015; Satoh, Yoshino, Akamatsu, Itoh, Kato, Kamada, Takagi, Chiba, Nomura, Mizokami, Murakami, Sakamoto, Hiraishi, Ichinose, Uemura, Goto, Joh, Miwa, Sugano & Shimosegawa, 2016)
- 6.1.4. A combination of adrenaline injection plus a second haemostasis modality has been shown to have statistically significantly reduced bleeding rates when compared to the use of adrenaline alone; therefore adrenaline should not be used as monotherapy (Gralnek et al., 2015; Vergara, Bennett, Calvet & Gisbert, 2014)
- 6.1.5. A recent meta-analysis by Baracat et al (2016) showed that while there was no difference in initial haemostasis or mortality rates with haemoclip compared to injection, there was a statistically significant improvement with the use of haemoclip in re-bleeding rates, and the need for emergency surgery with NNTs of 7 and 20 respectively, was also notably reduced. Haemostasis with haemoclip in combination with injection compared to haemoclip alone did not show any differences; whereas haemoclip in combination with injection compared to injection alone showed improvements in re-bleeding and emergency surgery with numbers needed to treat (NNTs) of 10 and 9 respectively (Baracat,F., Moura, Bernardo, Pu, Mendonça, Moura, Baracat, R. & Ide, 2016).

- 6.1.6. Thermocoagulation was also evaluated in this meta-analysis. Thermocoagulation compared to haemoclip was no different in terms of re-bleeding, emergency surgery or mortality. A benefit over haemoclip was noted in initial homeostasis, however these results should be viewed with caution due to the high levels of heterogeneity in the studies used (Barakat et al., 2016).
- 6.1.7. When assessing thermocoagulation compared to injection or in combination with injection versus injection alone, or thermocoagulation in combination with injection versus thermocoagulation alone, there was no statistically significant difference in any of the endpoints with the exception of improvements in emergency surgery rates when thermocoagulation is used in conjunction with injections, compared to injection alone (Barakat et al., 2016; Laine and Jensen, 2012)
- 6.1.8. Although over-the-scope clips (OTSCs) have been in use since around 2006, the evidence for their use has been limited to largely single centre, observational studies. A large retrospective analysis of 100 cases in Germany in 2016 showed that primary failure to achieve haemostasis was significantly reduced when OTSC was used as first line therapy (FLET), compared to second line therapy (SLET) (Richter-Schrag, Glatz, Walker, Fischer & Thimme, 2016). The high cost of OTSCs and lack of cost-effectiveness data limits their use.

## 6.2. Surgical Management

**Table 5: Surgical management for gastric or intestinal ulcers with haemorrhage or perforation**

Intervention	Comment
Laparoscopy	In selected patients, subject to designated service providers, formularies and protocols to ensure affordability
Laparotomy	
Omental Patch closure	For perforation
Antrectomy or gastrectomy +/- vagotomy	
Ulcer excision and patch	

- 6.2.1. Laparotomy with or without an omental patch is the gold standard of surgical treatment for perforated peptic ulcer (Søreide, K., Thorsen, Harrison, Bingener, Møller, Ohene-Yeboah & Søreide, J. A. 2015)
- 6.2.2. Laparoscopic surgery for perforated peptic ulcer has been increasingly used. A number of recent meta-analyses have concluded that non-randomised trials may suggest a benefit in reduced hospital stay and fewer post-operative complications. The data from currently published non-inferiority randomised controlled trials shows similar outcomes for a laparoscopic approach compared to a conventional open repair (Antoniou, S. A., Antoniou, G. A., Koch, Pointner & Granderath, 2013; Ge, Wu, Chen, Q., Chen, Q., Lin, Liu & Huang, 2016; Sanabria, Villegas, & Morales Uribe, 2013 ; Zhou, Wang, W., Wang, J., Zhang, X., Zhang, Q., Li & Xu, 2015).
- 6.2.3. Studies have shown that the total costs of laparoscopic treatments compared to open surgery are most dependent on the cost of consumable (disposables), length of stay and theatre time (Ge et al., 2016 and Wright, Davis, Koehler & Scheeres, 2014).
- 6.2.4. Laparoscopic surgery for perforated peptic ulcer is considered PMB level of care subject to designated service providers (DSPs), formularies and protocols. This is to ensure that the costs of disposables used for the procedure make this procedure cost effective and affordable.

## 7. Post-operative and follow up care

**Table 6: Post-operative and follow up care in gastric or intestinal ulcers with haemorrhage or perforation**

Repeat endoscopy within approximately 6 weeks post biopsy for gastric ulcers (not duodenal ulcers). Second scope in follow-up only on motivation to rule out gastric cancer or need for surgery
Repeat eradication therapy if necessary
Maintenance PPI (only if patient continues with NSAID, anti-thrombotic use or ongoing symptoms of dyspepsia)
Follow up consultation within 6 weeks; then 3 months later (unless indicated for earlier)

- 7.1. In the event of failure of first-line therapy for *H. pylori*, eradication therapy should be repeated but avoiding antibiotics from the first-line regimen already used (Chey et al., 2017). Following *H. pylori* eradication, it is not necessary to continue with ongoing PPI therapy unless the patient continues with NSAID or antithrombotic use (Gisbert, Calvet, Cosme, Almela, Feu, Bory, Santolaria, Aznarez, Castro, Fernandez, Garcia-Gravalos, Benages, Canete, Montoro, Borda, Perez-Aisa & Pique, 2012; Laine & Jensen, 2012; Laine, 2016) or if the patient remains symptomatic.
- 7.2. PPI therapy is recommended for 72 hours post-endoscopy to prevent re-bleeding. There is no difference in clinical outcomes between continuous IV or intermittent (every 12 hours) IV treatment (Sachar et al., 2014). Furthermore, no statistically significant difference in clinical outcomes has been shown comparing the use of IV to oral PPIs; and the oral formulation is likely to be more cost-effective (Jiang, Chen & Gao, 2016; NCGC, 2016; Tringali, Manta, Sica, Bassotti, Marmo & Mutignani, 2017). Therefore, oral treatment should be considered except in patients who are unable to take oral formulations, for example, if they are vomiting or fasting.
- 7.3. Patients who are diagnosed positive for *H. pylori* should receive eradication therapy (Chey et al., 2017; Laine and Jensen, 2012; Satoh et al., 2016). The risk of re-bleeding is considerably reduced with effective eradication therapy (Gisbert et al., 2012).
- 7.4. Choice of antibiotic therapy is dependent on the patient's previous exposure to antibiotics and sensitivity of the *H. pylori* strain to available antibiotics (Chey et al., 2017).

***This guideline will be due for update on 31 August 2019***

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