MANAGEMENT OF PATIENTS WITH UPPER GASTROINTESTINAL BLEEDING

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Upper gastrointestinal bleeding (UGIB) is a serious clinical problem, which is fatal in 6-10% of the cases (1, 2, 3). The incidence of acute massive UGIB is estimated at 40-150 episodes per 100 000 per year (1, 2, 3). The mortality rate increases with age and the number of co-morbidities, especially renal and liver failure, heart disease and neoplasms (1, 2, 3). Mortality seems to be lower in specialist centres, which is a consequence of following the adopted management standards rather than the possession of advanced equipment. Gastric or duodenal peptic ulcer is the most common cause of UGIB, accounting for 35-50% of the cases. Other causes of bleeding include gastric or duodenal erosion (8-15%), oesophagitis (5-15%), oesophageal varices (5-10%), Mallory-Weiss syndrome (15%), vascular malformations (5%), neoplasms (1%). Other rare causes account for 5% of the cases.

Risk groups and resuscitation

Approximately 80% of UGIB cases stop spontaneously (4). Serious complications and death occur in the remaining 20% of the patients with persistent or recurrent bleeding (4). The main goal of management should therefore be the identification of high-risk patients based on clinical, laboratory and endoscopy data. Among the systems identifying such patients, the most commonly employed one is the Rockall score, ranking the severity of bleeding based on the clinical data and endoscopy findings, and the Forrest classification of the severity of bleeding based on endoscopic evaluation (tab. 1, 2 and 3) (5, 6). Patients with mild to moderate bleeding, a pulse rate below 100 bpm, blood pressure above 100 mm Hg, haemoglobin concentration above 10 g/dL, without significant co-morbidities, less than 60 years of age are at a low risk of recurrent bleeding and

Table 1. The Forrest classification of the severity of bleeding from the ulcer and the risk of rebleeding depending on the endoscopic picture

<table>
<thead>
<tr>
<th>Grade</th>
<th>Endoscopic picture</th>
<th>Risk of rebleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>active haemorrhage</td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>spurtng</td>
<td>85-100%</td>
</tr>
<tr>
<td>IB</td>
<td>oozing</td>
<td>10-27%</td>
</tr>
<tr>
<td>II</td>
<td>signs of recent haemorrhage</td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>visible vessel</td>
<td>50%</td>
</tr>
<tr>
<td>IIB</td>
<td>adherent clot</td>
<td>30-35%</td>
</tr>
<tr>
<td>IIC</td>
<td>haematin covered flat spot (dark spot)</td>
<td>&lt; 8%</td>
</tr>
<tr>
<td>III</td>
<td>no signs of haemorrhage – clean bed of ulcer</td>
<td>&lt; 3%</td>
</tr>
</tbody>
</table>
of more than 100 bpm, blood pressure below 100 mm Hg, haemoglobin concentration below 10 g/dL, over 60 years of age should be admitted to a multi-specialist intensive care unit (anaesthetist, endoscopist, gastrologist, surgeon) providing constant monitoring (7-11). In these patients an intensive fluid resuscitation should be carried out to stabilise their haemodynamic status (tab. 4) (12). If resuscitation is carried out correctly, the hourly urine output exceeds 30 ml and the central venous pressure is 5-10 cm H2O (7). In patients with severe bleeding, soon after their general condition has been stabilised, an endoscopy should be performed. In certain cases of intensive active bleeding, an emergency endoscopy should be considered when the patient couldn’t be stabilised haemodynamically despite intensive resuscitation. These patients should be given erythromycin 30-60 min prior to endoscopy at a dose of 3-mg/kg bodyweight (250 mg in practice) in a single intravenous injection or a 30-min drip infusion. Erythromycin demonstrates potent gastrokinetic properties. Administration of erythromycin prior to emergency endoscopy causes the stomach to empty from blood and blood clots, impro-

Table 2. The Rockall scoring system of bleeding severity

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt; 60</td>
<td>60-79</td>
<td>≥ 80</td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td>pulse &lt; 100</td>
<td>pulse &gt; 100</td>
<td>pulse &gt; 100</td>
<td>BP &lt; 100</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>brak / none</td>
<td>circulatory failure</td>
<td>corona artery disease</td>
<td>renal failure</td>
</tr>
<tr>
<td>Endoscopic signs of bleeding</td>
<td>none</td>
<td>blood</td>
<td>adherent clot</td>
<td>visible or spurting vessel</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Mallory-Weiss syndrome</td>
<td>no patholgy</td>
<td>all other diagnoses</td>
<td>malignancy of the upper GI tract</td>
</tr>
</tbody>
</table>

Table 3. The risk of rebleeding and death in patients with UGIB according to the Rockall score

<table>
<thead>
<tr>
<th>Score</th>
<th>Risk of rebleeding %</th>
<th>Risk of death %</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 8</td>
<td>37 (27-47)</td>
<td>40 (30-51)</td>
</tr>
<tr>
<td>7</td>
<td>37 (28-46)</td>
<td>23 (15-31)</td>
</tr>
<tr>
<td>6</td>
<td>27 (20-34)</td>
<td>12 (6-17)</td>
</tr>
<tr>
<td>5</td>
<td>25 (19-31)</td>
<td>11 (6-15)</td>
</tr>
<tr>
<td>4</td>
<td>15 (10-21)</td>
<td>8 (4-12)</td>
</tr>
<tr>
<td>3</td>
<td>12 (7-17)</td>
<td>2 (0-4)</td>
</tr>
<tr>
<td>0-2</td>
<td>6 (3-8)</td>
<td>0 (0-1)</td>
</tr>
</tbody>
</table>

dead, and may be managed at a general ward (7-11). In these patients, endoscopy should be performed at the next available elective date, and in the absence of signs of recent bleeding, varices or neoplasms on endoscopy the patient may be discharged early (7-11). Until now few institutions have presented their prospectively collected outcomes when applying a similar early management strategy.

Patients with severe bleeding, a pulse rate of more than 100 bpm, blood pressure below 100 mm Hg, haemoglobin concentration be-

Table 4. Hypovolemic shock: manifestations and fluid resuscitation

<table>
<thead>
<tr>
<th>Blood loss (ml)</th>
<th>&lt; 750</th>
<th>750-1500</th>
<th>1500-2000</th>
<th>&gt;2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood loss (%bw)</td>
<td>&lt;15%</td>
<td>15-30%</td>
<td>30-40%</td>
<td>&gt;40%</td>
</tr>
<tr>
<td>Pulse</td>
<td>&lt;100</td>
<td>100-120</td>
<td>120-140</td>
<td>&gt;140</td>
</tr>
<tr>
<td>BP</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&lt;100</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Pulse volume</td>
<td>normal</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Respiration rate</td>
<td>14-20</td>
<td>20-30</td>
<td>30-35</td>
<td>&gt;35</td>
</tr>
<tr>
<td>Hourly urine output</td>
<td>&gt;30</td>
<td>20-30</td>
<td>&lt;20</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Mental status</td>
<td>marked anxiety</td>
<td>mild anxiety</td>
<td>anxiety confusion</td>
<td>confusion drowsiness</td>
</tr>
<tr>
<td>Fluid therapy</td>
<td>crystalloids</td>
<td>crystalloids</td>
<td>crystalloids colloids blood</td>
<td>crystalloids colloids blood</td>
</tr>
</tbody>
</table>
ves the quality of the examination, shortens its duration and considerably reduces the need for repeat endoscopy due to insufficient visualisation of changes in the upper gastrointestinal tract (8, 9, 11).

The role of endoscopy is pivotal and the earlier it is carried out the more information is gained. The therapeutic options effected by endoscopy are undisputed and suffice to mention that by this therapy has not only reduced the risk of re-bleeding been also the ensuing mortality. In fact this is the only therapeutic modality, which has proven to reduce mortality in patients with upper G-I haemorrhage. Among the many known risk factors for an unfavourable outcome that of prevention of re-bleeding emerges as one of those with the greatest impact and potential to improve the outcome for each individual patient. This review aims at presenting the background for the cornerstones in the clinical assessment and management of these patients and to present the evidence for one specific therapeutic concept i.e. to control intragastric pH in order to prevent re-bleeding. This is an area where considerable amount of data have been captured over recent years and also a management concept, which has potential to even further improve the ultimate outcome.

Endoscopic diagnosis and treatment

Endoscopy in patients with UGIB is an effective tool in the diagnosis and treatment of most causes of bleeding. It reduces the need for blood transfusions, the duration of hospitalisation at the intensive care unit and the duration of hospital stay (13). The higher effect on the number of transfusions and the duration of hospital stay is associated with early endoscopy, i.e. endoscopy performed within 24 hours of admission (14). Endoscopy performed at the admission room allows to identify up to 46% of haemodynamically stable patients with minor endoscopic signs of past bleeding, who can well be managed in the outpatient setting (15, 16).

Endoscopic treatment is indicated in patients with endoscopically revealed active bleeding in the form of blood spurting out of a visible vessel or oozing from the surface of the ulcer and in the case of a non-bleeding visible vessel, often in the form of a pigmented protuberance in the ulcer bed (8-11). If a blood clot covering the ulcer is revealed, an attempt to remove it and initiate appropriate treatment depending on the lesion discovered underneath the blood clot should be made (8-11, 17). In these situations, endoscopic treatment allows to reduce the incidence of recurrent bleeding, the need for surgical intervention and mortality (18). Endoscopic methods of bleeding control include injection methods, thermal methods and mechanical methods. In the injection methods, the haemostatic effect mainly results from a tamponade due to increased pressure inside the tissues following injection of various solutions around the bleeding vessel. Such additional substances as adrenaline, which causes vasoconstriction and accelerates platelet aggregation and activation, sclerosing agents (polidocanol, alcohol), which trigger inflammation and the formation of thrombus in the lumen of the vessel, or substances which seal the bleeding site, such as thrombin, fibrin or tissue glue, additionally enhance the tamponade effect.

Thermal contact methods (heater probe, mono- and bipolar coagulation probes) or non-contact methods (argon plasma coagulation, Nd-YAG laser) haemostasis results from coagulation, which closes the bleeding vessel and causes superficial destruction of the pathological tissue. Mechanical methods of bleeding control include endoscopically applied clips and rubber bands or endoscopic loops. They elicit the effect of a mechanical tamponade and pressure, which close the bleeding vessel. The most commonly utilised endoscopic method of bleeding control is the injection of 1:10 000 solution of adrenaline in saline around the site of bleeding. The injection is made in four quadrants around the site of bleeding and into the bleeding vessel, which involves the administration of a total of 4-16 ml of the solution. This allows achieving primary haemostasis in 95% of the patients with the expected rebleeding rate of 15-20% of the patients (19). The addition of sclerosing substances contributes to the increased incidence of complications in the form of inflammatory injury to the gastrointestinal wall without a clear effect on the effectiveness of haemostasis (20-23). Meta-analyses comparing the efficacy of individual injection methods failed to demonstrate the superiority of any one method over the other (24, 25). Similarly, meta-analyses which compared the efficacy of the individual thermal methods of upper gastrointestinal bleeding control sho-
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...no superiority of one method over another (24, 25). Also the comparison of the efficacy of injection methods versus thermal methods suggests their equivalence (26). Management combining injection with thermal methods has proved to be more effective in preventing rebleeding and reducing the mortality compared to injection methods and thermal methods alone or drug therapy (27, 28). Placement of haemostatic clips may be a promising form of endoscopic treatment of bleeding in the case of a visible or spurting vessel (29, 30, 31). The variable efficacy of this method is mainly due to the technical difficulties associated with the correct placement of the clips on the vessel (29-32). In light of the available data it seems that the selection of the method of endoscopic control of upper gastrointestinal bleeding should first of all be based on the availability of the individual methods and expertise of the centre as well as the skill and experience of the endoscopist in using the various endoscopic management modalities (8-11).

Pharmacotherapy

Over the years data have accumulated to show that acid plays a key role in a variety of processes leading to mucosal damage or in the continuation and aggravation of already existing mucosal defects. Clinical trials have consistently shown that effective acid secretory control by proton pump inhibition is very effective not only in preventing mucosal damage induced by selective and unselective COX inhibitors but also in healing established ulcers caused by this family of drugs (33, 34, 35). It is a reasonable assumption, which now has been supported by clinical trial data that there exists a dose response relationship between these protective-healing effects and the level by which acid secretion is controlled. H2 receptor antagonists (H2RA) are, in these respects, less effective than e.g. omeprazole and esomeprazole (36, 37). Furthermore experimental studies have demonstrated that there is a close responsive relationship between the pH of gastric juice and the acute damage inflicted by NSAID compounds on the gastroduodenal mucosal.

When it comes to peptic ulcer bleeding two issues are relevant regarding pharmacologic control and deviation of gastric pH. Firstly the question comes up whether constant elevation of pH can arrest ongoing bleeding and secondly whether this can prevent further–recurrent haemorrhage though stabilisation of the clot.

In vitro at pH 6.4, plasma coagulation and platelet aggregation are compromised by 50%; at pH less than 6.4 platelets disaggregate; at pH 5.4 plasma coagulation and platelet aggregation are virtually abolished; at pH 4 fibrin clots are dissolved. Pepsin can further inhibit coagulation in an acid environment, since it has maximal proteolytic at pH 2 but negligible activity at a pH above 5 (38, 39). H2RA:s cannot maintain intragastric pH around 6 for more than at the most 24 hours not even when large doses are given as infusion. This is due to rapid development of tolerance (tachyphylaxis). It is therefore interesting, and at the same time predictable, that clinical trials have been unable to show a consistent beneficial effect to prevent re-bleeding in patients with peptic ulcer haemorrhage. In an meta-analysis of 24 randomised studies with 1062 patients, the use of intravenous H2-receptor antagonists was associated with a reduction of rebleeding risk by 7.2%, the need for surgery by 6.7% and the risk of death by 3.2% (39). The use of H2-receptor antagonists is therefore not recommended in the management of UGIB (8-11).

PPI:s have been shown to maintain intragastric pH over 6 for 72 hours when given in adequate doses. A bolus injection is required, in the magnitude of 80 mg, followed by infusion of 8 mg per hour. High doses of PPIs, which irreversibly bind to ATPase secreting hydrogen ions in the parietal cells of the stomach, are capable of maintaining pH within the lumen of the upper GI tract on a level, which favours the normal haemostatic processes (38). The efficacy of the first drug in this class has been demonstrated in randomised studies (40), large prospective multicentre studies (41, 42) and meta-analyses (38). PPIs are superior to H2-receptor antagonists, reducing the time to haemostasis in patients managed for UGIB from 6.75 to 1.86 days (p<0.005) (38). In a study conducted by Lau et al., omeprazole at a dose of 80 mg in a bolus followed by an infusion at the rate of 8 mg/h reduced the risk of rebleeding following endoscopic treatment by 70%, significantly reduced the rate of repeat endoscopies and the need for blood transfusions as well as reducing the duration of hospital stay with a clear trend to reduce mortality (41). In a large meta-analysis including 1244 patients from 15 countries in 155 centres, Barkun et al.
demonstrated superior efficacy of pantoprazole versus ranitidine in the treatment of UGIB (42). In meta-analysis of 29 studies comparing PPIs with H2-receptor antagonists in over 4000 patients, Martin et al. observed a reduction of rebleeding risk by 56%, of surgery risk by 31%, of the need for re-endoscopies by 41% and of the need for transfusion by 33% (43). Bardou et al. demonstrated that high doses of intravenous PPIs in high-risk patients, in addition to lowering the incidence of rebleeding by 20%, significantly reduced the risk of death by 2.4% (48).

Therefore most comprehensive reviews within the field conclude that PPI administration as indicated above can reduce the risk for recurrent bleeding after successful endoscopic therapy and the need for reintervention. There are, however, some caveats in the form of potential ethnic differences in the efficacy of this therapeutical concept. Accordingly all metaanalyses have demonstrated a stronger effect of PPIs in Asian study cohorts than been possible to elucidate in Caucasians. This issue is currently explored in huge clinical trials with esomeprazole i.v., which exerts the most potent inhibitory effect on the secretion of hydrochloric acid and thereby have the greatest potential to be clinically valuable in this setting (44, 45).

We have also tried to extract information from the literature if corresponding pharmacologic treatment (i.e. i.v. PPI) may even stop ongoing haemorrhage from bleeding PU and if so a management algorithm can be constructed to guide the clinicians towards the most effective management of these patients from the very first presentation of the patient. First of all we have to realise that the vast majority of upper GI haemorrhages are caused by acid related disorders (see above). This fact forms the rational of initiating the acid inhibitory therapy as early as possible (including NSAID induced lesions). Secondly there are three studies which offer indirect evidence that immediate iv PPS may be beneficial (38, 46, 47). Similar circumstantial evidence suggests that maintained elevated intragastric pH may arrest ongoing bleeding and facilitate and stabilise clot formation. Parenteral administration of high doses of PPIs leads to a reduced percentage of patients with active bleeding during endoscopy and the need for endoscopic haemostasis (41, 43). Provided that iv PPIs have a favourable safety profile (which seems to be the case), there are no reasons to withhold this therapy from the very beginning of the management strategy (fig. 1). No doubt robust data will be gained to further substantiate the efficacy of this strategy but at Karolinska University Hospital we have already introduced this as a routine therapy. In fact this has also been found to offer a favourable health economic profile compared to a more conservative “wait and see” strategy (Barkun et al 2004 (25, 48, 49).

Another drugs used in the management of UGIB, both systemically and locally, include the following substances or drug classes: neutralising and gastroprotective agents, sucralfate, H2RA, proton pump inhibitors (PPIs), somatostatin, vasopressin, drugs used in the eradication of Helicobacter pylori as well as â-blockers, adrenaline, Cyclonamine (ethamsylate), Gastrothrombina and vitamin K.

Prevention of bleeding from stress ulceration

A special form of UGIB is a bleeding caused by stress ulceration (SRMD – stress-related mucosal damage). In this pathology, the erosive process affects the mucous membrane of the upper gastrointestinal tract and occurs in abnormal physiological conditions, such as trauma, surgery, organ failure, sepsis, burns (36). The onset is usually sudden (within several hours) and is associated with mucosal defects ranging from superficial erosions to deep ulcerations, most commonly multifocal and affecting the fundus of the stomach (36).

Factors that predispose to the development of stress ulceration include multiple local interactions resulting from changes in the mucosal protective mechanisms, impaired production of mucus, bicarbonate and prostaglandins, impaired regenerative abilities of the epithelium, alterations in the motility of the upper GI tract (most commonly decreased motility), changes in the composition of the gastric juice (increased content of hydrochloric acid and pepsin), impaired mucosal microcirculation accompanied by a limitation of gas and nutrient exchange and reduced epithelial and non-epithelial buffering activity (36). The risk factors of bleeding in SRMD include artificial ventilation of more than 48 hours’ duration, coagulopathy (INR > 1.5), thrombocytopenia (PLT < 50 × 10^9), hospitalisation at the intensive care unit for more than 7 days, shock, renal and hepatic failure, burns of over 35% of
the body surface area, multiorgan injury, kidney and liver transplantation, head and/or spinal injury, systemic metabolic acidosis, steroid therapy (hydrocortisone > 250 mg/day). With the presence of one risk factor, the risk of bleeding is small. However, every next risk factor increases the risk by another 10% (36). The following are regarded as the absolute indications for SRMD prophylaxis: burns, shock, multiorgan injury, coagulopathies in ICU patients, a history of peptic ulcer and/or UGIB in ICU patients in the past year, mechanical ventilation > 48 h, presence of at least two risk factors.

The drugs used in SRMD prophylaxis commonly include H$_2$-receptor antagonists, antacids and sucralfate. The recent years have seen an increasing number of studies demonstrating a high efficacy and superiority of PPIs over the remaining agents which elevate gastric pH (36). These drugs that are used most commonly in everyday clinical practice for SRMD prevention.

Summary

In patients with UGIB manifestations an immediate assessment of haemodynamic status should be performed and fluid resuscitation initiated. The placement of a nasogastric tube should be considered, as the nature of secretion has prognostic significance and may determine further management. Based on the clinical data patients should be classified into those at high and at low risk of rebleeding and death. In high risk patient’s immediate parenteral administration of high doses of PPIs may lead to a reduced percentage of patients with active bleeding during endoscopy and the need for endoscopic haemostasis. Endoscopy should be performed within the first 24 hours of pa-
tient’s presentation. Early endoscopy allows to rationally dividing patients into those requiring observation and treatment at the intensive care unit or at the general ward, and those who may be discharged soon and managed in the outpatient setting.

Endoscopic treatment is indicated in patients with active bleeding on endoscopy and with a non-bleeding visible vessel, which often takes the form of a pigmented protuberance in the ulcer bed. In order to reduce the risk of rebleeding following the successful endoscopic treatment, drug therapy should be continued with high-dose intravenous PPIs for 72 hours.

Patients with UGIB should also be examined for the presence of Helicobacter pylori infection and eradication therapy started if the result is positive. In the case of rebleeding a repeat endoscopic treatment should be attempted. Surgery should be considered in the case of active bleeding that could not be controlled endoscopically, following haemostasis during the first or alternatively re-endoscopy, particularly if the ulceration is localised on the posterior wall of the duodenum or high on the minor curvature in patients at high risk of rebleeding and in the case of rebleeding following two courses of endoscopic treatment.

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