Nonvariceal upper gastrointestinal bleeding (UGIB) remains a common emergency for gastroenterologists with an annual incidence of 50 to 150 per 100,000 of the population. Mortality from UGIB is around 10%, and may reach 35% in patients hospitalized with another medical condition. Serious comorbidity remains an independent risk factor for UGIB mortality, which is often attributable to increasing age and associated illnesses [1]. A recent time trend analysis by a Dutch group has demonstrated a decrease in incidence of UGIB (from 61.7 per 100,000 per year in 1993–1994 to 47 per 100,000 per year in 2000), but has not demonstrated a reduction in mortality or rebleeding rates [2], even though there have been significant advances in medical and endoscopic management of serious UGIB. An ageing population with potentially serious comorbidities helps to explain the lack of concordance between the overall population incidence and mortality rate for UGIB. Patients over 80 years of age now account for around 25% of all UGIB and 33% of UGIB occurring in hospitalized patients [1].

**ETIOLOGY OF NONVARICEAL UPPER GASTROINTESTINAL BLEEDING**

The causes and historically quoted frequencies of nonvariceal UGIB are shown in Table 1. There is controversy regarding the relative contribution of peptic ulcer bleeding to overall UGIB rates. Recent data from the Clinical Outcome Research Initiative suggest that the frequency of peptic ulcer as a cause of UGIB may have been overestimated. In 7822 endoscopies performed for UGIB, peptic ulcer was the likely cause in only 1610 patients (20.6%) [3]. Data from the Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy, however, identified peptic ulcers in 50% of patients presenting to community and tertiary care institutions between 1999 and 2002 [4]. Regardless of the historical frequency of peptic ulcer bleeding, the
The incidence of peptic ulcer disease should decline with more widespread Helicobacter pylori eradication. In addition, widespread use of cyclooxygenase-2–specific nonsteroidal anti-inflammatory drugs may also affect peptic ulcer risk, although prescription of this particular class of drugs worldwide has been severely affected by recent statements by the US Food and Drug Administration and other national drug monitoring organizations.

**CLINICAL RISK ASSESSMENT**

One of the major challenges of managing UGIB involves identifying patients who are at high risk of rebleeding and death; conversely, identifying patients who are suitable for early discharge and outpatient endoscopy is also important for effective resource use. Several clinical scoring systems have been developed to help predict outcome for patients with a view to improving patient management and promoting cost-effective use of resources. In most published scoring systems, a combination of clinical, laboratory, and endoscopic variables are weighted to produce a score that predicts the risk of mortality, recurrent hemorrhage, need for clinical intervention, or suitability for early discharge. The most commonly used systems (Rockall score, the Baylor bleeding score, the Cedars-Sinai Medical Centre Predictive Index, and the Blatchford score) were recently excellently reviewed by Das and Wong [5]. Several factors are associated with poor outcome from UGIB and may be related to the patient’s presentation and comorbidities, or to the behavior of the ulcer:

- Shock
- Melena
- Anemia at presentation
- Significant fresh blood in vomit, gastric aspirate, or rectum
- Concurrent sepsis
- General poor health
- Liver, renal, cardiac disease
- Large ulcer size
- Persistent bleeding despite endoscopic therapy
- Recurrent bleeding

Inclusion of endoscopic stigmata of recent hemorrhage (SRH) that relate to increased risk of rebleeding and death into scoring systems increases the

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcer</td>
<td>30–50</td>
</tr>
<tr>
<td>Mallory-Weiss tear</td>
<td>15–20</td>
</tr>
<tr>
<td>Erosive gastritis or duodenitis</td>
<td>10–15</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>5–10</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1–2</td>
</tr>
<tr>
<td>Angiodysplasia or vascular malformations</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
</tr>
</tbody>
</table>
sensitivity for predicting patients at high or low risk of adverse events compared with nonendoscopic assessments [6,7]. In addition, early endoscopy-based triage (within 12 hours of admission) may allow safe and early discharge of low-risk patients with no increased rate of rebleeding or mortality [8]. Risk stratification using nonendoscopic parameters has the advantage that it can be performed readily on initial presentation in the emergency department, however, and if early endoscopy, which requires skilled staff and resources, is not available, appropriate initial risk assessment can be made. Clearly, more studies are required to clarify the role of endoscopy in early risk assessment. More generally, care must be taken when applying a risk stratification scoring system to any patient population not represented by the original studies, because racial, cultural, or ethnic factors may affect a populations’ risk [9].

**INITIAL MANAGEMENT**

Resuscitation and optimization of comorbid conditions are vital in the initial management of patients before endoscopy. Transfusion of blood and blood products may be necessary and patients often require management in an intensive care setting. Endotracheal intubation remains controversial in significant nonvariceal UGIB. The endoscopist’s task is made easier and the risk of massive aspiration in a patient with reduced level of consciousness is reduced if a patient is intubated; however, evidence of a reduction in acquired pneumonia or cardiopulmonary events is lacking [10,11]. The presence of blood-stained nasogastric aspirate can be used to predict the presence of high-risk lesions and nasogastric tube insertion should be considered for some patients [12]. The optimum timing of endoscopy remains a balance between clinical need and resources, but endoscopy performed within 24 hours of hospital admission has been shown to reduce the length of hospital stay and may reduce the likelihood of rebleeding or surgical intervention in the highest risk patients [13].

**ENDOSCOPIC ASSESSMENT**

Endoscopic SRH [14] associated with a higher risk of rebleeding, surgical intervention, and death have been well defined. High-risk lesions, such as actively bleeding ulcers, nonbleeding visible vessels (NBVV), and adherent clots [15], require aggressive intervention because ulcer rebleeding is associated with a 5- to 16-fold increase in mortality [16], and effective endoscopic management can substantially reduce this risk. The rebleeding rate of ulcers with a clean base or red or blue spots is low [17,18], and endoscopic intervention is usually not recommended [9].

Although actively bleeding vessels are consistently identified by endoscopists, this is not the case for other SRH, particularly NBVV and flat pigmented spots [19]. Attention has turned to alternative approaches to assess lesions more objectively. Doppler examination of ulcers was assessed as a means of obtaining objective evidence of rebleeding risk in 100 patients admitted with UGIB but not bleeding at the time of index endoscopy. Doppler findings were compared with the Forrest classification of the ulcer [20]. Ulcers were assessed for
the presence of blood vessels and were considered to be Doppler-positive if a vessel no deeper than 1 mm was identified. Doppler-positive ulcers and those in the Forrest group with adherent clot or visible vessels were treated endoscopically. There was agreement between the Forrest classification and Doppler in only 58% of cases. Rebleeding, requirement for surgery, and mortality rate were all significantly lower in the Doppler-assessed group. The authors suggest that Doppler assessment can guide appropriate endoscopic intervention for patients with NBVV. Technical and resource limitations, however, mean this technique is unlikely to be widely available for some time.

Not infrequently, excessive blood in the upper gastrointestinal tract may preclude an accurate endoscopic diagnosis. A retrospective study by Cheng and coworkers [21] identified 25 of (1.7%) 1459 patients where a diagnosis could not be made endoscopically because of blood obscuring the examination field. Not surprisingly, these patients had a significantly higher rate of complications, rebleeding, need for surgery, and mortality. The authors stress the importance of good preparation along with the removal of blood during the procedure. Bolus administration of intravenous erythromycin before endoscopy has been shown to clear the stomach of blood, thereby increasing the likelihood of successful hemostasis and reducing the need for further interventions [22,23].

ENDOSCOPIC MANAGEMENT
Endoscopic intervention is beneficial in high-risk patients with UGIB, reducing the rate of rebleeding, need for surgical intervention, and mortality [24]. It is likely that most hemostatic techniques are equally effective when used alone. Recent research has focused on the role of combination therapies and newer mechanical means of homeostasis. Most of the following text refers to peptic ulcer bleeding but may be applicable in other causes of nonvariceal UGIB.

Injection Therapy
Injection of dilute (1:10,000) adrenaline in 1-mL aliquots around the bleeding points results in hemostasis in up to 100% of patients with bleeding peptic ulcers, probably by a combination of vascular tamponade and vasoconstriction, with a concomitant reduction in rebleeding rates from 40% to 15% [25,26]. The dose of adrenaline required to achieve hemostasis is probably dependent on the individual patient; however, in a study of 156 patients with Forrest type I or IIa lesions a larger volume (13–20 versus 5–10 mL) resulted in less rebleeding (15.4% versus 30.8%) [27]. Although injection with adrenaline is successful in achieving initial hemostasis, the published rebleed rates of 15% to 36% remains relatively high [28,29]. Attention has focused on alternative techniques (eg, heat or mechanical) or combination therapy to determine if there is any additional benefit.

Sclerosants, such as ethanol, polidocanol, and ethanolamine, have been used to promote vessel thrombosis, but evidence to date suggests these agents are no better, and may have more risk, than adrenaline [28,30–32]. In one study, ethanol injection alone was shown to have a rebleeding rate as low as 4% [33];
however, most other published studies have demonstrated similar or worse rates of hemostasis than adrenaline alone. A combination of adrenaline and ethanol may improve hemostasis and shorten duration of hospital stay for patients with spurring hemorrhage [31].

Thrombin-fibrinogen mixture (fibrin-sealant glue) does not seem to confer any additional benefit beyond adrenaline alone when used in a one-off basis in combination with adrenaline injection for patients with high-risk peptic ulcers, although it may be of particular use in patients with active bleeding [34]. A study involving 51 patients with active bleeding or NBVV demonstrated lower rebleeding rates with a single treatment with combination adrenaline and fibrin sealant compared with adrenaline alone, although there was no difference in mortality, transfusion requirements, surgery, or duration of hospital stay [35]. Repeated injection of fibrin glue following treatment with dilute adrenaline in patients with active bleeding or NBVV was subsequently compared with single application of fibrin glue or polidocanol following adrenaline injection. Patients underwent daily endoscopy until the ulcer base was clean or covered in hematin. Patients in the repeat treatment group had significantly higher rates of hemostasis with less rebleeding compared with the polidocanol group, although mortality rates were not reduced [36]. The major drawback of this schedule is the cost incurred by repeated daily procedures. In another study, endoscopic intervention with a combination of adrenaline injection and 600 to 1000 IU human thrombin has been shown to be more effective than injection of adrenaline alone, with a reduction in rebleeding (4.5% versus 20%), transfusion requirement, and mortality [37].

Injection with \(N\)-butyl-2-cyanoacrylate has been shown to be effective for control of variceal bleeding [38], but its role in nonvariceal UGIB remains uncertain. In a small study of 32 cases it was no more effective than injection with dilute adrenaline for control of bleeding ulcers [28]. More recently, Lee and coworkers [39] showed significantly lower rebleeding rate for patients with Forrest type Ia lesions treated with \(N\)-butyl-2-cyanoacrylate compared with injection with hypertonic saline-adrenaline injection. There was no overall benefit in the use of \(N\)-butyl-2-cyanoacrylate with regards to hemostasis rates, emergency surgery, or mortality. Arterial embolization is a recognized complication of this treatment, and occurred in 2 of 63 patients in the treatment group. The authors recommend \(N\)-butyl-2-cyanoacrylate injection only as a measure of last resort before surgery because of potentially fatal adverse effects.

**Thermal Techniques**

Several thermal techniques have been used for the control of nonvariceal UGIB. Homeostasis is achieved by compression of the artery during heating (coaptation) and the effect of heat on tissue.

**Noncontact thermal techniques**

Laser (neodymium:yttrium-aluminum-garnet) and argon plasma coagulation are the only noncontact thermal therapies currently available. Argon plasma coagulation causes hemostasis by conducting a high-frequency electrical
current through a beam of ionized argon gas, resulting in superficial tissue damage and coagulation. Although the technique is generally safe and relatively straightforward, the efficacy has yet to be fully determined. A prospective observational study into the use of argon plasma coagulation in 254 patients with nonvariceal UGIB revealed initial hemostasis rates of 75.9% and rebleeding rates of 5.7% with argon plasma coagulation alone [40]. When a second endoscopic technique was added, initial hemostasis was achieved in 99.6%. In the only comparative randomized trial involving argon plasma coagulation in nonvariceal UGIB, rates of hemostasis, rebleeding, emergency surgery, and 30-day mortality were comparable with the heater probe, although the numbers in this study (N = 41) were too small to detect a difference [41]. Chau and coworkers [42] compared combination treatment with adrenaline and heater probe with adrenaline and argon plasma coagulation in a prospective, randomized, controlled trial involving 185 patients with bleeding peptic ulcers. There was no significant difference in primary hemostasis, procedure duration, rebleeding, requirement for surgery, 30-day mortality, or ulcer healing at 8 weeks, suggesting that combination therapy with adrenaline and argon plasma coagulation is as effective as heater probe in high-risk patients with bleeding ulcers.

Laser therapy has been shown to be as effective as injection with epinephrine-polidocanol [43], but because of technical constraints of the technique, laser therapy is not routinely used in the management of nonvariceal UGIB.

Contact thermal techniques
Bipolar electrocoagulation and heater probe thermocoagulation use thermal contact to achieve hemostasis by compression of the vessel and coaptation. A bipolar electrocoagulation device may include an injector-irrigator component (eg, Gold probe, Boston Scientific, Boston, MA) to allow injection of adrenaline and irrigation of the culprit lesion. Bipolar electrocoagulation has been shown to reduce the rebleeding rate when compared with normal saline injection in high-risk bleeding ulcers [44], and in combination with adrenaline in type IIb ulcers [45].

Combination therapy with heater probe thermocoagulation and adrenaline in the treatment of actively bleeding peptic ulcers resulted in hemostasis in up to 98.6%, with rebleeding in 8.2% [46]. In another study, however, there was no significant difference in rates of rebleeding, requirement for surgery, and length of hospital stay when compared with adrenaline alone [29]. Subgroup analysis, however, did illustrate benefit in patients with Forrest Ia lesions, with dual therapy resulting in significantly lower rebleeding rates and nonsignificant reductions in emergency surgery and length of hospital stay. When used alone, heater probe thermocoagulation was not superior to combination treatment with adrenaline and polidocanol in patients with Forrest type I, IIa, and IIb ulcers [47]. Heater probe thermocoagulation (HPC) in combination with thrombin was compared to HPC and placebo in 247 patients with bleeding peptic ulcers and was found to confer no benefit when compared with the placebo arm with regards to hemostasis, rebleeding rates, requirement for surgery, adverse events, or mortality [48].
Mechanical Techniques

Mechanical methods of achieving hemostasis are often used in variceal UGIB. Endoloops and particularly clips (eg, the Hemoclip [Teleflex Medical, Research Triangle Park, NC]), however, are likely to play an increasing role in the control of nonvariceal UGIB. Hemostasis using endoclips involves deployment of a clip to achieve vascular compression. So far the Hemoclip has been safe and effective, achieving homeostasis rates of up to 100% [49]. Comparative studies with other endoscopic techniques suggest lower rebleeding rates than adrenaline injection [50], ethanol [51], or hypertonic saline-epinephrine [52]. The additional benefit of adrenaline with a mechanical method is unclear [53]. A randomized comparative study of injection of epinephrine-polidocanol and Hemoclip versus Hemoclip alone, however, showed clipping to be inferior to combination Hemoclip–adrenaline injection therapy in the treatment of bleeding peptic ulcers [54]. Chung and coworkers [52] found the Hemoclip to be an effective method for hemostasis and safer than hypertonic saline-epinephrine, and combination treatment with injection therapy and Hemoclips was equivalent to either treatment alone for control of bleeding. Rebleeding rates and the need for surgery were higher, however, in the adrenaline group. A potential limitation of the Hemoclip is the technical difficulty in applying the clips to difficult-to-reach lesions, particularly those high on the gastric lesser curve or posterior wall of the duodenum. This was demonstrated in a comparative study of Hemoclip with heater probe thermocoagulation in which the overall rates of hemostasis were 85% and 100%, respectively. In the subgroup of difficult-to-approach lesions the homeostasis rate fell to 30% and 82%, respectively. Rotatable and more versatile endoclips may help to lessen this problem. In addition, devices that can deploy multiple or stronger clips are needed. Two small studies have evaluated the role of Hemoclips for control of bleeding caused by Dieulafoy’s lesion. Hemostasis was generally successful and there was a trend toward reduction in the need for repeat procedures [55,56].

Endoscopic band ligation is currently technically easier to use than endoclips and has been shown to be safe and effective for control of small lesions in 19 patients with acute peptic ulcer bleeding [57]. Rubber band ligation has recently been assessed in a small group of patients with UGIB secondary to Dieulafoy’s lesion and found to be as effective as injection with or without thermal therapy [58].

Adherent Clots

Special mention needs to be made regarding the problem of adherent clots. A subgroup analysis of patients with adherent clots in early endoscopic studies demonstrated little or no benefit of endoscopic therapy for ulcers with adherent clots [59–62]. A subsequent meta-analysis showed significant benefit only in patients with active bleeding or NBVV [24]. A randomized controlled trial to assess endoscopic intervention in patients with severe UGIB and adherent clot randomized 32 patients to medical or combination therapy following irrigation of the clot [45]. Endoscopic therapy consisted of adrenaline injection,
shaving of the clot with cold guillotine, and bipolar coagulation of the under-
lying stigmata. Combination therapy was shown to be safe with significantly
less early rebleeding compared with medical therapy, although the small sam-
ple size, unexpectedly low rebleed rates in the treatment group (0%), and un-
equal distribution of confounding factors in the two groups means that
cautions need to be taken when extrapolating the results. In addition, various
studies have shown intraobserver variation in the labeling of SRH, and the
degree of clot adherence may vary depending on the extent of clot irrigation
[63,64]. For instance, in one study 5 minutes of irrigation by a bipolar probe
was found to remove clot in 43% of patients, whereas irrigation with a syringe
only removed 9% of the clot [65]. In another study, 10 seconds of irrigation
with WaterPik (Teledyne, Fort Collins, CO) removed clots in a further 26%
of patients [66]. Placement of a newly designed transparent irrigating hood
that allows forceful irrigation yet maintains a reasonable endoscopic view
may prove useful for clot removal. Early experience suggests that total pro-
cedure time may be reduced when using this device [67,68]. Although the opti-
imum technique for clot removal is unclear, the value of clot removal is clear,
because high-risk SRH may be exposed in the underlying ulcer in a further
30% of patients. Rebleeding rates for untreated ulcers with adherent clot
are reported as 20% and in the group where clots remained was 8%, which
is similar to that expected in low-risk lesions, such as flat pigmented spots
[15]. Current practice among experienced endoscopists involves targeted irri-
gation of an adherent clot to dislodge it, if possible, followed by treatment of
the underlying lesion [45].

SECOND-LOOK ENDOSCOPY AND ENDOSCOPIC RETREATMENT
Several studies investigating the role of routine second-look endoscopy follow-
ing endoscopic treatment have shown no benefit with regards to clinically signif-
icant outcomes for unselected patient populations [69], although there may be a
role in high-risk patients [70,71]. Repeat endoscopy is indicated if there is clinical
evidence of rebleeding or if the initial procedure was unsuccessful or partially
successful, although this depends on local endoscopic and surgical expertise
[9,72]. In expert centers, endoscopic retreatment is associated with fewer
complications, less need for surgery, and no increased mortality risk compared
with surgery [73].

FUTURE DIRECTIONS IN ENDOSCOPY
Endoscopic Suturing
A variety of endoscopic suturing devices have been developed primarily for
gastroplication in patients with gastroesophageal reflux. Endoscopic suturing
for UGIB is an attractive prospect, but further development of new devices
is required before suturing for UGIB can be widely adopted. Such issues as
the device size and maneuverability, and precise control of suture depth,
need to be addressed.
Cryotherapy
Application of heat to bleeding or potentially bleeding lesions has drawbacks, such as the requirement for contact, expense, lack of control of depth of injury, and difficulty in treating multiple or diffuse lesions. Cryosurgery involves freezing tissue to achieve a therapeutic response. Gastric freezing to achieve hemostasis during variceal and nonvariceal bleeding has been possible for several decades, although evidence of therapeutic benefit from the original techniques was lacking [74]. More recently, delivery systems for liquid nitrogen or nitrous oxide have made endoscopic cryotherapy possible for bleeding and other applications [75–77]. Delivery of nitrous oxide to result in cryotherapy relies on the Joule-Thompson effect: rapid expansion of compressed gas results in a drop in temperature of the gas. This allows noncontact therapy to localized or diffuse vascular lesions. The technique remains experimental, but it seems to be safe and effective for radiation proctitis and vascular malformations, and there may be potential use in other gastrointestinal vascular lesions.

PROTON PUMP INHIBITORS
In vitro studies of the effect of gastric pH on platelet aggregation and coagulation provide the rationale for acid suppression in UGIB. If gastric pH is maintained above pH6 (by infusional proton pump inhibitors), platelet aggregation is optimized and fibrinolysis relatively inhibited, thereby potentially improving the likelihood of clot stability at an ulcer site. Individual trials of H2 receptor antagonists have generally failed to demonstrate a clinical benefit in UGIB [78,79], although a meta-analysis has suggested a weak effect [80]. Several studies have evaluated intravenous proton pump inhibitors for nonvariceal UGIB; unfortunately, these trials are heterogeneous in terms of patient population, regimen of proton pump inhibitor, and timing or type of endoscopic intervention, making comparisons difficult. Five meta-analyses of proton pump inhibitors in nonvariceal UGIB have now shown a benefit, however, in terms of rebleeding and need for surgery, but not for mortality [81–85]. The usual intravenous regime for omeprazole therapy in the more robust studies was an 80-mg intravenous bolus of omeprazole followed by a continuous infusion of 8 mg/h for up to 72 hours. This regimen resulted in a reduction of rebleeding from 22.5% to 6.7%, representing a number needed to treat (NNT) of 6 to prevent one person bleeding within 30 days [84]. Subsequent studies using lower intravenous doses of omeprazole [86] or high-dose oral omeprazole [87–89] also demonstrated a reduction in rebleeding rate. Further study is required to determine the optimum dose and schedule of proton pump inhibitors in UGIB. It seems reasonable, however, to treat patients with high-risk SRH with intravenous or high-dose oral proton pump inhibitors after endoscopic therapy has been administered.

SUMMARY
Nonvariceal UGIB remains a significant cause of morbidity and mortality. Many patients require intensive supportive therapy and aggressive management of medical comorbidities. Age and concurrent medical conditions remain
major determinants of morbidity. Most UGIB stops spontaneously. Appropriate therapy for patients who continue to bleed, or in patients who rebleed after initial hemostasis has been achieved, includes aggressive endoscopy, usually with a combination of thermal and injection therapy, followed by intravenous or high-dose oral proton pump inhibitor. Mechanical endoscopic devices are promising for achieving hemostasis in peptic ulcer bleeding. Patients at high risk of rebleeding can usually be identified by clinical and endoscopic means and treated appropriately.
The algorithm used for management of nonvariceal UGIB at the authors’ institution is summarized in Fig. 1. It is their policy to include gastroenterologists, intensive care physicians, surgeons, and radiologists at an early stage of the admission and decision-making process to optimize care of potentially ill patients. The value of regular and repeated clinical assessment, adequate resuscitation, and appropriate multidisciplinary input cannot be overstated.

References


