REVIEW

Acute endoscopic intervention in non-variceal upper gastrointestinal bleeding

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Upper gastrointestinal bleeding is one of the commonest emergencies encountered by general physicians. Once haemodynamic stability has been achieved, therapeutic endoscopy is vital in control and arrest of bleeding. Various methods are available and the evidence is reviewed as to the most optimal approach. Clinical parameters including timing of endoscopy, risk stratification, and predictors of failure will also be discussed together with a summary of recommendations based on current available evidence.

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Its annual incidence is estimated at 50 to 150 per 100 000 of the population while highest among the lowest socioeconomic groups.[1] In 1957, the reported hospital mortality was 16%[2] while in 1997 after a large audit of acute gastrointestinal bleeding in England, this was 11%.[3] This striking lack in improvement in mortality may simply reflect an aging population with multiple comorbidity in whom upper gastrointestinal bleeding (UGIB) has been shown to have poorer outcome.

Table 1 lists the causes of UGIB, with peptic ulcer bleeding accounting for most cases. The control and arrest of bleeding is vital and in most cases this is achieved using therapeutic endoscopic intervention. Most (80%) of bleeds (haemodynamically stable) do not re-bleed and thus do not require urgent endoscopic intervention. However, patients with actively bleeding peptic ulcer and non-bleeding visible vessel have 80% and 50% risk of re-bleeding respectively.[1] It follows from these findings that endoscopic therapeutic haemostatic measures should be delivered in the first instance. Failure of such measures may require surgical intervention.

CLINICAL ASSESMENT

General management of patients presenting with acute UGIB requires immediate clinical evaluation, and resuscitation. This entails stabilisation of the systemic blood pressure and restoration of the intravascular volume. If there is any concern of airway compromise or if there is failure to respond after initial resuscitation, anaesthetic support should be sought early. Patients should be risk stratified according to low and high risk for rebleeding and mortality based on the Rockall score[3] (table 2). This comprises five categories (age, signs of shock, comorbidities, endoscopic findings, and description) and has been validated as predictors of rebleeding and mortality.[4]

ENDOSCOPY: WHAT TO LOOK FOR ON THE REPORT

Endoscopy in the hands of a skilled operator is the most sensitive and specific diagnostic procedure for determining cause and site of UGIB.[5] Information from endoscopic examination should include (a) location (b) bleeding rate (oozing compared with spurting) (c) source of bleeding if multiple and (d) presence of stigmata of recent haemorrhage (SRH). SRH is more likely to be found if endoscopy is performed within 12–18 hours of hospital admission.[6] Certain endoscopic characteristics of SRH are important in predicting rebleeding (table 3). A clean ulcer base without SRH is a reliable indicator that the ulcer is not likely to rebleed. Such patients are deemed low risk and do not require prolonged hospital admission.[7]

TIMING OF ENDOSCOPY

Early endoscopy (within 24 hours), permits safe and prompt discharge of patients classified as low risk, while those at high risk would seem to have an improved outcome.[7] Most centres in the UK are able to provide such a service while in some regions there is an on call bleed rota to provide a service out of hours.

ENDOSCOPIC MANAGEMENT

Needless to say, appropriate skill and training together with a competent assistant are prerequisites to achieve effective endoscopic haemostasis. Several techniques exist, which will be reviewed individually and in combination together with their relative merits and efficacy. Trials evaluating the different endoscopic modalities are varied in populations studied and trial design making direct comparisons difficult. Furthermore, some studies have small sample size and hence poor statistical power with regards to defined outcomes. In addition, as these techniques are technically demanding, there is danger in interpreting and extrapolating published trial data without taking into consideration the available local expertise. Clear defined outcome measures should include rates of rebleeding, surgery, and mortality, and to a lesser extent transfusion requirements or length of hospital stay. Table 4 shows categories of the available modalities.

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Table 1 Causes of acute upper gastrointestinal haemorrhage[1]

Diagnosis	Approximate %
Peptic ulcer	35–50
Gastroduodenal erosions	8–15
Oesophagitis	5–15
Varices	5–10
Mallory Weiss tear	15
Upper gastrointestinal malignancy	1
Vascular malformation	5
Others	5

Table 3 Endoscopic characteristics of stigmata of recent haemorrhage (SRH)[1]

Endoscopic features of SRH	Rebleeding (%)
Pulsatile arterial bleeding	85
Adherent clot	40
Pigmented protuberance	20
Flat blood spot on ulcer base	5–10

Table 4 Endoscopic management

Modality	Type
Injection	Adrenaline (epinephrine)
	Sclerosants
	Alcohol
	Thrombin
	Fibrin glue
Thermal	Heater probe
	Electrocoagulation
	Nd-Yag laser
	Argon plasma coagulation (APC)
Mechanical	Haemoclips
	Banding
	Staples
	Sutures

INJECTION

This method is simple, widely used, and the cheapest available haemostatic modality. Proposed mechanisms of action include tamponade, vasoconstriction, end arteritis, and possibly direct effect on clotting process at the site of arterial defect.

Adrenaline (epinephrine)

Chung et al in 1988[8] reported 100% primary haemostasis in patients with active ulcer bleeding injected with 1:10 ?000 dilute adrenaline. Rebleeding still occurred (24%) implying only a temporary vasoconstrictive effect but the need for surgery was subsequently reduced.

Sclerosants such as polidocanol, 5% ethanolamine oleate, 3% sodium tetradecyl sulphate, and cyanoacrylate (tissue glue) have been used with varying results. To date no direct comparisons have been made with conservative treatment and only one (in abstract) with adrenaline.[9] It stands to reason however, that the addition of a sclerosant agent, may achieve better rates of rebleeding. Table 5 shows some of the various combinations.

It is worthy of note that most of the above trials had small numbers and some were not powered to show mortality differences. Chung's controlled trial in 1996 comparing adrenaline and adrenaline with alcohol was the largest; 97.5% primary haemostasis was achieved with adrenaline alone while it was 94.9% with the combination—both impressive figures. In addition, hospital stay and time for ulcer healing was similar. The addition of alcohol does not confer any advantage.

However, complications can occur with sclerosants as reported in animal studies[14] and also in case reports. Experimental studies in dogs showed no advantage individually between adrenaline (1:10 000), ornipressin, 1% polidoconal, thrombin, or fibrin in heparin induced bleeding. However, the mucosal and submucosal injury (necrosis) was greatest in ethanol followed by polidoconal and thrombin sealants. Two case reports[15 16] have confirmed this and even reported a fatality. Adrenaline caused the least damage. Such severe reactions have not been reported with adrenaline or its effects on systemic circulation. Adrenaline injection seems to be safe.

Until recently, the ideal volume of injection had not been evaluated. Lin et al[17] have compared large (13–20 ml) with small (5–10 ml) volume of injection of adrenaline. Primary haemostasis was achieved in all 156 patients randomised.

Table 2 Rockall score

	Score 0	Score 1	Score 2	Score 3
Age (y)	<60	60–79	80	
Shock	Pulse <100	Pulse >100	Pulse >100	
	Systolic BP >100	Systolic BP >100	Systolic <100	
Comorbidity	Nil major		Heart failure	Renal failure
			Ischaemic heart disease	Liver failure
			Any other illnesses	Disseminated cancer
Endoscopic stigmata	None		Blood in GIT	
	Dark spot		Adherent clot	
			Visible/spurting vessel	
Diagnosis	Mallory Weiss	All other diagnosis	Upper GI cancer	
	No lesion seen			
Pre-endoscopy score	**Risk of death (%)**	**Post-endoscopy score**	**Risk of death (%)**	**Risk of rebleeding (%)**
7	75 (45–100)	8+	40 (30–51)	37 (27–47)
6	62 (50–73)	7	23 (15–31)	37 (28–46)
5	35 (27–43)	6	12 (6–17)	27 (20–34)
4	21 (17–25)	5	11 (6–15)	25 (19–31)
3	12 (9–16)	4	8 (4–12)	15 (10–21)
2	6 (3–9)	3	2 (0–4)	12 (7–17)
1	3 (0.6–5)	0–2	0 (0–1)	6 (3–8)
0	0 (0–1.2)			

Table 5 Combinations of agents for injection

Group	Study	Number	Rebleeding (%)	Surgery (%)	Mortality (%)	Transfusion (units)
Choudari, 1994[10]	Adrenaline + alcohol	52	14	8	0	8
	Adrenaline alone	55	15	7	2	9
Villanueva, 1993[11]	Adrenaline + polidoconal	33	21	15	3	2
	Adrenaline alone	30	10	13	6	2
Lazo, 1992[12]	Alcohol	25	8	4	–	–
	Conservative	14	57	50	–	–
Chiozzini, 1989[9]	Alcohol	16	13			
	Adrenaline	19	2			
Chung SC, 1996[13]	Adrenaline + alcohol	79	8	11	9	2
	Adrenaline	81	11	15	5	3

Rebleeding was lower by 15.4% in the large volume group compared with 30.8% in the small volume group. Numbers requiring surgery, transfusion requirements, or mortality were similar. Thus injecting large volumes (>13 ml) can reduce the rate of rebleeding.

A primary role for tamponade in haemostasis with injection therapy has been suggested. The question as to whether tamponade alone was sufficient was addressed in a study by Laine et al.[18] Patients were randomised to receive either saline solution (mean volume 30 ml) or bipolar electrocoagulation (BiPEC). Rebleeding was noted in 29% of saline group compared with 12% in the BiPEC group. In addition, number of units of blood transfused was higher (2 compared with 0) in the BiPEC group. Mortality was significantly different. From this one study, injection therapy seems to work by mechanisms other than tamponade alone.

In summary, endoscopic injection is of confirmed value but its mechanisms of action still remain unclear. For peptic ulcers, large volumes of adrenaline are required and combination with sclerosants confers no advantage.

Fibrin glue and thrombin

Table 6 shows studies comparing combinations of adrenaline and thrombin and adrenaline and fibrine with adrenaline alone.

The study by Kubba et al[19] (table 6) compared a combination of adrenaline and thrombin with adrenaline alone. This study showed a statistical significance in reduction of rebleeding and mortality in the combination group but no difference was seen in surgery or transfusion requirements. Mortality as expected was high particularly those with already pre-existing comorbidities. Pescatore et al[20] however compared a combination of fibrin (fibrin glue is a combination of fibrin and thrombin) with adrenaline compared with adrenaline alone. This study showed no difference between the two modalities. Comorbidities in this study were better stratified. More recently, Lin et al[21] have made a direct comparison between adrenaline and fibrin although with smaller numbers (n = 26 each group). They showed rebleeding was higher in the adrenaline group (14 compared with 4) but transfusion requirements, surgery, and

mortality were similar. However, numbers eventually treated were small.

Based on current evidence, there is no clear advantage of either fibrin or thrombin alone or in combination with adrenaline. No adverse effects have been reported with thrombin on systemic coagulation. In terms of cost, a 10 ml 1:10 000 vial of adrenaline is £2.36 inclusive of VAT while a 0.5 ml vial fibrin glue (Histoacryl) costs £7.49 inclusive of VAT.

THERMAL

Thermal methods have the advantage of target irrigation, good coaptive coagulation, portability, and are comparatively economic once established but may incur initial capital cost. Several such methods are discussed below.

Heater probe

The heater probe transmits energy via a Teflon tipped catheter. Studies have shown it to be superior compared with conservative treatment in terms of reduction of rebleeding, surgery, and transfusion requirements.[22 23] Church et al[23] showed similar efficacy with bipolar electrocoagulation (BiCAP) with overall low complication rates. More recently,[24] a randomised trial of 247 patients was performed comparing heater probe plus thrombin with heater probe alone. Ninety seven per cent primary haemostasis was achieved with no difference seen in rebleeding and emergency surgery. The authors concluded this combination conferred no addition advantage. Overall the heater probe is user friendly and while perforations can occur they are rare. The usual energy setting is 20 W but there has been no trial to date comparing the various energy settings.

Electrocoagulation

Haemostasis is achieved by heat and also through a tamponade effect. Monopolar coagulation has fallen into disrepute with early case series showing perforation and death. Alternatively, results with BiCAP have been more encouraging. BiCAP has eight separate electrodes over its surface. Electrical energy travels between the adjacent electrodes. Compared with placebo it is superior in terms of

Table 6 Fibrin glue and thrombin

	Kubba et al 1996		Pescatore et al 2002	
	Adrenline+thrombin	Adrenaline alone	Adrenaline+fibrin	Adrenaline alone
Outcome	n = 70	n = 70	n = 70	n = 65
Rebleed	3	14	21	16
Transfusion number	7	5	2	2
Emergency surgery	3	5	4	6
Mortality	0	7	2	2

Table 7 Combination therapy trials

	Chung S 1997[37]			Lin HJ 1999[38]					Gevers AM 2002[39]					Chun HC 2003[40]		
	Adr+HP	v	Adr	Adr	v	BiPEC	v	Adr+BipEC	Adr	v	Clip	v	Adr+Clip	Adr+HP	v	Adr+APC
Number	136		134	32		32		32	34		35		32	97		88
Primary haemostasis	135		131	31		30		30	33		30		29	93		86
Rebleed	5		12	11		9		2	5		13		8	21		15
Transfusion	3		2	3		2		1	5		4		4	2		2
Surgery	8		4	5		2		1						9		4
Mortality	8		7	3		1		1	0		0		8	6		5

reduced rebleeding, emergency surgery, and transfusion requirements.[25][26] It seems to be at least comparable to heater probe.[24] When compared with saline to evaluate the tamponade theory, Laine *et al* showed saline solution injection (mean volume 30 ml) was less effective compared with BiCAP.[18]

Laser
Nd-Yag laser compared with argon laser has been the most studied. Results have been conflicting with Swain *et al*[27] showing reduction in rebleeding, emergency surgery, and even mortality in the laser treated group. Another group[28] a year later who had a similar number of patients however showed a poorer outcome compared with controls. What was striking was that in the study by Swain *et al*, a single experienced endoscopist delivered all therapy. Thus for this therapeutic modality, outcome seems very much dependent on the skill of an endoscopist who is familiar with this technique. This has also been shown to be true in managing palliative gastrointestinal malignancy where there was good outcome when managed by a single endoscopist.[29] On a practical level, this approach is technically difficult and expensive. Other equally and perhaps more efficient methods are readily available and thus this technique has gone out of favour.

Argon plasma coagulation
Argon plasma coagulation that is based on coagulation through a jet of argon gas alone is not sufficient in controlling spurting haemorrhage, and potentially dangerous for large non-bleeding vessels. This is because the thermal damage is superficial and hence more applicable to mucosal or superficial bleeding lesions such as gastric antral vascular ectasia. One trial[30] has shown comparable efficacy with heater probe therapy in ulcer haemostasis (non-spurting). However, a later trial[31] in combination with adrenaline, achieved 98.1% primary haemostasis with 9.6% rebleed rate. Despite these two studies, most experts would not advocate its use in active or spurting bleeding for the reasons outlined above.[1]

MECHANICAL
Haemoclips
Mechanical devices such as haemoclips have been used to aid in the control of primary haemostasis and rebleeding. Various comparisons have been made[32][33] but only Nishiaki *et al*,[34] Lin HY *et al*,[35] and Chung *et al*[36] have made direct comparisons. Chung *et al* have shown haemoclips, heater probe, and adrenaline to be of equal efficacy in primary haemostasis. Chung *et al* also showed less rebleeding in the group treated with haemoclips alone. Like laser therapy, this device is very much operator dependent. It can be technically challenging especially in patients with "difficult to approach" peptic ulcer bleeding. In this instance, injection therapy or thermal methods are more suitable. However, where there is active

spurting applying at least two haemoclips at right angles is helpful to gain immediate arrest of bleeding. Several clips may need to be applied occasionally to gain complete haemostasis.

COMBINATION THERAPY
As the mechanisms for achieving primary haemostasis differ with injection and thermal methods, it is thus rational to investigate whether combining such modalities may offer an advantage.

Chung *et al*[37] and later confirmed by Lin *et al*[48] have shown in well designed trials that combining thermal methods with adrenaline injection reduced rebleeding rates compared with adrenaline injection alone. Data remain discordant regarding combination of injection therapy with haemoclip. Gevers *et al*[39] found haemoclip inferior to adrenaline but Chung *et al*[36] who studied 124 patients found that in the subgroup with spurting vessel, haemoclip alone or in combination with adrenaline injection, was better at achieving haemostasis. Thus at present, combination therapy using adrenaline injection combined with either a thermal or mechanical method seems most efficacious.

Table 7 list some of the various combination trials.

MEDICAL TREATMENT
A comprehensive review of pharmacotherapy in UGIB is beyond the scope of this review however, there is good evidence to support the use of continuous high dose intravenous proton pump inhibitor (PPI) infusion (omeprazole 80 mg bolus followed by 8 mg/h) for 72 hours. When used as an adjunct to endoscopic treatment, there was reduction in rates of rebleeding, blood transfusion requirements, and also hospital stay. Although there was a reduction in mortality seen this did not reach statistical significance.[41] In addition, its role in those patients with adherent clots is somewhat controversial. The one large study that researched this issue showed minimal difference only and used intravenous boluses of PPI,[42] which is not sufficient to maintain pH above 6.[43][44]

FAILURE OF ENDOSCOPIC THERAPY
Precise timing for surgery is still much debated. With newer haemostatic modalities available and improving skills of the endoscopist, surgery is seen as a last resort when managing patients with UGIB. Not unreasonably, there is concern that persistence in repeated endoscopy will have adverse outcome on patients. Unfortunately, we cannot predict accurately who will fail to respond to endoscopic therapeutic intervention. Two studies however, have shown failure in treatment in patients with active bleeding, large ulcers, and those situated in the posterior duodenal wall.[45][46] More recently, Wong *et al*[47] have shown that shocked patients requiring large volumes to resuscitate and haemoglobin <1 g/l at presentation are more likely to fail to achieve primary haemostasis endoscopically.

Retreatment (second look) endoscopy of patients who failed primary therapeutic endoscopic measures, remains controversial. Lau et al[48] have shown in 3473 patients where they achieved a remarkable 98.5% primary haemostasis, endoscopic retreatment rather than immediate surgery should be undertaken in patients who rebleed. Complications were higher in the surgery group with no differences in transfusion requirements or 30 day mortality. However, routine second look endoscopy is generally not recommended,[49] except in those patients whose initial endoscopic examination was incomplete because of technical reasons (for example, excessive blood). Furthermore, the cost effectiveness of routine second look endoscopy has not been established.[50]

More recently, another group[51] have advocated early elective surgery for posterior duodenal wall bleeding ulcers, in high risk patients. However, only 22 patients were treated with only eight in the surgical arm after primary endoscopic treatment. Similarly, another study of 55 patients,[52] showed an usually high rebleeding rate of 50% in the endoscopic retreatment arm but no difference in mortality compared with those who had early elective surgery. One explanation is that the endoscopic modality used was fibrin glue, which as shown above has a higher rebleeding rate compared with established injection therapy. The authors acknowledge this and thus the comparison is not ideal. Thus, it still remains impossible to accurately identify the subgroup of patients who will benefit from early surgical treatment after failed primary endoscopic haemostasis.[46 47] What is clear however, is that patients should be stratified individually based on their endoscopic findings, clinical status, and associated comorbidities. Early discussions with the surgeon should be undertaken as to appropriateness of early surgical intervention, if, at all. Some advocate the establishment of a dedicated gastrointestinal bleed unit, similar to a coronary care unit. Several such units have been reported in the UK with impressive results.[53 54]

Box 1 Predictors of failure of endosocpic treatment

- On going active bleeding
- Large ulcers >1 cm
- Site—posterior duodenal wall
- Shocked
- Large volume resuscitation (at presentation)
- Hb <1 g/l

CONCLUSIONS
Because of the differences in study design and populations treated, ranking of techniques from most to least effective is not possible. However, based on current literature combination therapy with adrenaline injection and thermal probes (preferably BiCAP) for actively bleeding peptic ulcers is the best option. For active spurting vessels, use of the haemoclip alone or in combination with adrenaline injection is recommended. For vascular mucosal lesions such as angiodysplasia, APC is safe and efficacious either alone or in combination with adrenaline injection. Finally, the endoscopist must always use the technique or modality with which they have the most experience and with which they are most confident of achieving primary haemostasis.

Box 2 Management of patients with UGIB—What to do:

- Resuscitate patient
- If airway insecure—involve anaesthetist early
- Rockall scoring before and after endoscopy
- Liaise with endoscopist (if out of hours service available contact endoscopist; if not liaise with general surgeon on-call)
- If endoscopy not possible urgently, consider starting intravenous omeprazole infusion (NB not evidence based)

Endoscopist
- Active bleeding peptic ulcer—combination of adrenaline injection and BiPEC
- Spurting vessel—haemoclip in combination with adrenaline injection
- Superficialvascular lesion—APC alone or in combination with adrenaline injection

Key references for further reading:
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SELF ASSESSMENT QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AT END OF REFERENCES)

1. Which of the statements relating to upper gastrointestinal bleeding (UGIB) is true?

(A) There has been significant improvement in mortality rates over the past half century.
(B) Oesophagitis is the commonest cause for UGIB
(C) Most cases do not rebleed after endoscopic therapeutic intervention
(D) Patients who have pulsatile arterial bleeding at endoscopy are at high risk of rebleeding.
(E) An anaesthetist should always be involved when endoscoping patients with UGIB

2. Which of these statements are correct?

(A) The thermal methods of endoscopic management achieve primary haemostasis by heat effect alone.
(B) Nd-Yag laser therapy is the most effective and widely available tool in the endoscopic management of UGIB
(C) APC is ideal for mucosal vascular malformations but not for control of spurting vessels.
(D) Fibrin is a combination of fibrinogen and thromboplastin
(E) Fibrin glue on its own is more effective when combined with adrenaline

3. In the management of patients with UGIB

(A) Endoscopic therapy is by far the most important treatment even before the adequate resuscitation has taken place

(B) Elderly, shocked patients with a low haemoglobin have the best chance of achieving successful haemostasis with endoscopy alone.

(C) Surgical input should be sought early even if successful haemostasis has been achieved.

(D) The best combination of endoscopic therapy is with ethanol injection and laser

(E) Haemoclips are technically simple and inexpensive and hence should be attempted first as an endoscopic therapy regardless of site of ulcer.

4. In the management of patient with upper gastrointestinal bleeding

(A) Endoscopic therapy using thermal methods alone is ideal and most appropriate treatment

(B) If primary haemostasis fails, then it is not worth a second attempt as the chances of success at second attempt endoscopy are extremely low.

(C) The role and timing of surgery is clearly defined and usually superseded by endoscopy

(D) Mortality in the elderly population is much higher in those having surgery compared with those having a therapeutic endoscopy

(E) Primary haemostasis with combination therapy (injection + thermal) is achieved in most cases over 90% of the time.

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ANSWERS

1. (A) F, (B) F, (C) T, (D) T, (E) F; 2. (A) F, (B) F, (C) T, (D) F, (E) F; 3. (A) F, (B) F, (C) T, (D) F, (E) F; 4. (A) F, (B) F, (C) F, (D) T, (E) T.

FILLER ....

Drug companies' smartest and most flexible tool!

My pen is from Pfizer and my post-it notes from Astra Zeneca and each time I use them I try to convince myself that they don't influence my prescribing decisions. Sadly I am only fooling myself. The messages from the drug companies must get through—otherwise they wouldn't use these tools. But of course the main tool that they are using is me.

The pens and post-it notes have got smaller and less useful over the years and drug companies may eventually get rid of them altogether. I wonder will they do the same to their smartest and most flexible tool—the doctor who takes their gifts. Roy Lilley writing for *Pharmaceutical Marketing* says that drug companies should ''try linking treatment and drugs with therapy delivery and sell a new service. Put the people with the pill and learn about adding value to the medicine.'' (http://www.pmlive.com/pharm_market/opinion.cfm?showArticle = 1&ArticleID = 3074)

What could he mean by this? Does he mean bypassing the independent prescriber altogether and getting drug companies to run asthma clinics and allow their employees to prescribe inhalers? This idea may not be as outlandish as you think. Drug companies have long employed people to explain to patients how to take certain injections—expensive ones like interferon, that is. But increasingly we may see employees of drug companies prescribing medications too.

In the past they gave you the pen and the paper and the folder: are we just a small step away from them doing the prescribing for you as well? It could happen unless pretty soon someone shouts STOP.

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