Endoscopic management of gastric varices: Efficacy and outcomes of gluing with N-butyl-2-cyanoacrylate in a North American patient population

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BACKGROUND: Gastric variceal bleeding is associated with significant morbidity and mortality in patients with portal hypertension. Outside of North America, gastric variceal injection of N-butyl-2-cyanoacrylate has been shown to be safe and effective. The majority of studies on this mode of therapy are in Asian populations in which the etiology of portal hypertension differs from North America.

AIM: To assess the safety and efficacy of gastric variceal glue injection in a North American population.

METHODS: Consecutive patients that underwent glue injection of gastric varices in the Calgary Health Region from 2001 to 2006 were assessed.

RESULTS: Thirty-four patients (19 men, 15 women) underwent a total of 47 separate gluing procedures. Of those presenting with active bleeding at endoscopy, immediate hemostasis was achieved in 93.8% of patients. Rebleeding within 48 h of gluing was observed after four procedures. Gastric varices were eradicated in 84.0% of cases. Complications included superior mesenteric vein thrombosis in one patient. Twenty-eight (82.4%) patients were alive at the end of follow-up. The treatment failure-related mortality rate was 2.1%.

CONCLUSIONS: The present study is one of the few to assess the role of gastric variceal gluing in a North American population. Glue injection with cyanoacrylate is safe and effective in the treatment of bleeding gastric varices.

Key Words: Endoscopic therapy; Gastric varices; Gluing, N-butyl-2-cyanoacrylate; Portal hypertension

Gastric variceal hemorrhage is an important cause of gastrointestinal bleeding in patients with portal hypertension. Approximately 20% of unselected patients with portal hypertension have associated gastric varices (1,2). Isolated gastric varices have a reported prevalence of 5% to 12% (1,3,4) compared with esophageal gastric varices, which range from 10% to 50% (1,2,4,5).

Although bleeding from gastric varices is less common than from esophageal varices, the bleeding is more severe and more difficult to treat, carrying a higher morbidity and mortality (1,6). Reported rates of bleeding range from 10% to 36% (7-9).

Variceal bleeding is the complication that carries the highest mortality in end-stage liver disease, with rates ranging from 40% to 70% after the first bleeding episode (10,11).

Outside of North America, one treatment modality that appears to be effective in achieving hemostasis, preventing rebleeding and obliterating gastric varices is the injection of a tissue adhesive or glue, such as N-butyl-2-cyanoacrylate (NBCA) (Histoacryl, B Braun, Germany), directly into a varix under endoscopic guidance (3-5,7,8,12,13). This liquid adhesive polymerizes and hardens on contact with blood, which results in near immediate solidification of the varices and

HISTORIQUE: Les hémorragies causées par des varices gastriques s’associent à une importante morbidité et à une importante mortalité chez les patients ayant une hypertension portale. À l’extérieur de l’Amérique du Nord, il est démontré que l’injection de N-butyl-2-cyanoacrylate pour oblitterer les varices gastriques est sécuritaire et efficace. La majorité des études sur ce mode de thérapie ont eu lieu auprès de populations asiatiques, pour qui l’étiologie de l’hypertension portale diffère de celles d’Amérique du Nord.

OBJECTIF: Évaluer la sécurité et l’efficacité de l’obliteration des varices gastriques à la colle au sein d’une population nord-américaine.

MÉTHODOLOGIE: Les auteurs ont évalué des patients consécutifs de la région sanitaire de Calgary qui ont reçu une injection de colle dans des varices gastriques entre 2001 et 2006.

RÉSULTATS: Trente-quatre patients (19 hommes, 15 femmes) ont subi un total de 47 interventions distinctes d’obliteration à la colle. Ainsi, 93,8 % des patients qui présentaient une hémorragie active à l’endoscopie sont parvenus à une hémostasie immédiate. On a observé la reprise de l’hémorragie dans les 48 heures suivant l’injection de colle après quatre interventions. Les varices gastriques ont été éradiquées dans 84,0 % des cas.

Les complications ont inclus une thrombose de la veine mésentérique supérieure chez un patient. Vingt-huit (82,4 %) patients étaient vivants à la fin du suivi. Le taux de mortalité relatif à l’échec du traitement s’élevait à 2,1 %.

CONCLUSIONS: La présente étude est l’une des rares à évaluer le rôle de l’obliteration des varices gastriques à la colle au sein d’une population nord-américaine. L’injection de colle contenant du cyanoacrylate est sécuritaire et efficace dans le traitement d’hémorragies causées par des varices gastriques.
minimizes the risk for embolization or bleeding from the puncture site. Other traditional endoscopic treatments have been tried, including sclerotherapy and banding, but none are as effective as NBCA gluing (3-7,8,12-15).

There is no published literature systematically describing the efficacy and outcomes of this procedure in Canada, although it has been used in a number of centres since the late 1990s. To date, this mode of therapy is not approved for use in the United States and thus there are only three published articles (two of which are small pilot studies) on this management approach in a North American population (16-18). Because the epidemiology and etiology of liver disease in North America is different from that in Asia and India, where most of these studies have been conducted, validation of this therapeutic intervention in the North American population is warranted.

In the present study, the clinical characteristics, efficacy, complications and outcomes of patients with bleeding gastric varices that have been treated with direct variceal injection of NBCA are reported.

PATIENTS
The Calgary Health Region (CHR) in southern Alberta provides medical and surgical care to over one million residents of the city of Calgary and over 20 nearby smaller cities (19). Approximately 80% of CHR residents are Caucasian, 10% are Asian, 3% are Native Canadians and the remainder consist of a wide diversity of ethnicities that is representative of many other North American urban centres (19). The two tertiary care centres in the CHR record all endoscopic procedures in an electronic endoscopy database (Endopro; Pentax Inc, USA). Institutional ethics approval was obtained from the Conjoint Health Ethics Research Board of the University of Calgary.

METHODS
All endoscopic procedures recorded in the database between January 1, 2001 and August 31, 2006, were searched to identify consecutive patients who had gastric varices as a finding at endoscopy. All such reports were manually reviewed to further identify those patients who underwent endoscopic therapy with glue injection. In addition to the endoscopy report, all identified patients had their hospital and clinical charts reviewed to collect data on clinical characteristics, outcomes and follow-up. Patients were then categorized according to the indication for gluing as active bleeding (ongoing bleeding visualized at endoscopy), recent bleeding (hematemesis or melena at the time of presentation but signs of recent bleeding visualized at endoscopy, such as red wale markings or gastric varices believed to be the culprit lesion by the performing endoscopist) or nonbleeding (planned secondary prophylactic procedure in seven (14.9%) patients. The distribution of Child-Pugh class scores was: A: 28.0%, B: 56.0% and C: 16.0%. Seven patients had alcoholic liver cirrhosis (50%). Of patients with available data (n=25), the distribution of Child-Pugh class scores was: A: 28.0%, B: 56.0% and C: 16.0%. Seven patients had alcoholic liver cirrhosis (50%). Of patients with available data (n=25), the distribution of Child-Pugh class scores was: A: 28.0%, B: 56.0% and C: 16.0%.

Outcomes of gastric variceal gluing in the present population are summarized in Table 2. Of the 16 patients with active bleeding at the end of the endoscopic procedure; and

3. Obliteration of gastric varices as the lack of visible gastric varices at follow-up endoscopy.

Follow-up information was obtained through a review of medical records, with end of follow-up defined as the last contact with the CHR or death. Proportions for rebleeding and complications were described with 95% binomial CIs (Stata version 7.0, Stata Corp, USA). Immediate bleeding control and procedural complications were analyzed at a per-procedure level; rebleeding and other outcomes were assessed at a per-patient level.

RESULTS
Between January 2001 and August 2006, 29,419 upper gastrointestinal endoscopies for all indications were performed at our two tertiary care facilities. Thirty-four patients underwent 47 gastric variceal gluing procedures by 12 different gastroenterologists (Table 1). For glue injection, a forward-viewing video endoscope (Pentax Inc, USA) was used in all cases with a standard sclerotherapy injection kit. A standard protocol was used to prepare for glue injection. The working channel and tip of the endoscope were lubricated with silicone by passing a coated wire brush in and out of the channel. The injector needle and plastic catheter were primed with Lipiodol (Laboratoire Guerbet, France). NBCA was mixed with lipiodol in a 1:1 mixture by drawing up 0.5 mL of each component into the same 3 mL syringe. The primed injection catheter was inserted through the working channel. Suction was disconnected before injecting to prevent inadvertent suctioning of glue material into the endoscope channel. At the discretion of the endoscopist, a varix was selected and injected with 1 mL to 2 mL of the glue mixture. If 2 mL was injected, the needle was left in the varix while the assistant attached a second syringe with a prepared glue mixture to the injection system. The needle was then flushed with 1 mL to 2 mL of lipiodol as the needle was withdrawn from the varix. There were minor variations in technique among the gastroenterologists. Fluoroscopy was not used in any of the cases and postprocedure x-rays were not routinely obtained to look for embolization of glue material.

Among the 19 male and 15 female patients, the mean age was 54.5 years (range 25 to 74 years); 82.3% were Caucasian (Table 1). The most common cause of portal hypertension was alcohol-induced liver cirrhosis (50%). Of patients with available data (n=25), the distribution of Child-Pugh class scores was: A: 28.0%, B: 56.0% and C: 16.0%. Seven patients had alcoholic liver cirrhosis (50%). Of patients with available data (n=25), the distribution of Child-Pugh class scores was: A: 28.0%, B: 56.0% and C: 16.0%.

The indications for gluing were: active bleeding in 16 (34.0%), recent bleeding in 24 (51.1%) and as a secondary prophylactic procedure in seven (14.9%) patients. The distribution of Child-Pugh class scores was: A: 28.0%, B: 56.0% and C: 16.0%. Seven patients had alcoholic liver cirrhosis (50%). Of patients with available data (n=25), the distribution of Child-Pugh class scores was: A: 28.0%, B: 56.0% and C: 16.0%.

The mean number of glue injections per procedure was 2.5 (median 2; range 1 to 5) with a mean volume of 3.6 mL of glue mixture injected (median 4 mL; range 1 mL to 8 mL). Concurrent portal hypertensive gastropathy was noted in 15 cases.

Outcomes of gastric variceal gluing in the present population are summarized in Table 2. Of the 16 patients with active
bleeding at the time of endoscopy, immediate hemostasis was achieved in 15 (93.8%). Early rebleeding (within 48 h of gluing) occurred after four procedures (10.0%); in three patients, successful hemostasis was achieved with repeat glue injections. One patient presented with active bleeding at endoscopy and died from uncontrolled bleeding. One additional patient with recently bleeding gastric varices had uncontrollable bleeding after an attempted glue injection into a nonbleeding varix; the patient required a Linton tube and subsequent transjugular intrahepatic portosystemic shunt (TIPS) creation to control the bleeding. Thus, the immediate procedure complication rate was 4.3%.

Follow-up data beyond 48 h were available for all but one patient who was transferred to the University of Calgary health sciences centre for gluing only, then hospitalized elsewhere. For the remaining 33 patients, the median follow-up period was 11 months (range five days to 52 months). Eight patients (24.2%; 95% CI 12.9% to 41.2%) rebled from varices at some time during follow-up. Thus, the overall treatment failure rate (lack of immediate control [n=2]) or any rebleeding during follow-up [n=8]) was 21.3% (95% CI 12.0% to 35.0%). Twenty-five patients had at least one follow-up endoscopy at a median of two months. Of those, 21 patients (84.0%; 95% CI 65.1% to 93.4%) had complete obliteration of gastric varices as evidenced by no varices or only hardened varices visualized at endoscopy. Newly recognized PHG portal hypertensive gastropathy was noted in nine patients.

The complications of variceal gluing in the present population are presented in Table 3. In the five cases of fever (higher than 38°C), blood cultures were drawn in three patients but were negative; the fever resolved in all patients within 48 h. The three patients found to have ulceration at the site of gluing required supportive care only, including a blood transfusion in two. One patient presented to hospital with acute abdominal pain 48 h after variceal gluing. A computed tomography (CT) scan of her abdomen revealed acute superior mesenteric vein thrombosis (Figure 1). There were no glue emboli noted on imaging. The patient required anticoagulation with heparin followed by coumadin for three months and had no further problems over the 14-month follow-up period.

No symptomatic glue emboli were confirmed. One patient developed acute shortness of breath 1 h postprocedure, but a chest x-ray did not reveal any radiopaque glue material. The patient had a history of asthma and the dyspnea resolved with administration of a bronchodilator; no further investigations were pursued.

Six (17.6%) of the 34 patients were deceased at the end of follow-up. One patient died from uncontrolled variceal bleeding (described above); the others died of liver disease (n=2) or malignancy (two pancreatic, one hepatocellular carcinoma).

**DISCUSSION**

Compared with esophageal varices, treatment modalities for acutely bleeding gastric varices are less well-established. Nonendoscopic methods, such as TIPS and surgical portosystemic shunt creation, are often effective in treating gastric varices but are technically difficult, more invasive and have complication rates of 10% to 30%. This includes serious
complications such as hepatic encephalopathy, intra-abdominal hemorrhage and death (20-23).

Traditional endoscopic therapies used for esophageal varices, such as band ligation and injection of sclerosing agents, have also been trialed in gastric varices with limited success with respect to hemostasis, rebleeding and obliteration of gastric varices (3,6,8,24,25). These small nonrandomized trials involved diverse populations and varied with respect to the types of gastric varices and techniques making comparisons across studies difficult.

There are only a small number of randomized, prospective studies that have compared gluing with traditional endoscopic methods. Sarin et al (3) compared cyanoacrylate with alcohol injection and found a higher rate of hemostasis (78% versus 38%; P<0.05) and variceal obliteration (100% versus 44%; P<0.05) in the gluing group. Two studies have compared glue injection with gastric variceal band ligation in patients with acutely bleeding gastric varices (8,15). Lo et al (8) found glueing to be more effective in achieving immediate hemostasis (87% versus 45%; P=0.03) and in preventing rebleeding (69% versus 46%; P<0.005). In addition, this group found that the number of blood transfusions required was significantly lower in patients managed using glue injection (2.3 units versus 4.2 units; P<0.01) (8). Tan et al (15) reported no difference in controlling active bleeding in the two groups but a significantly lower rebleeding rate in the gluing group (22% versus 44%; P<0.05). Lo et al (26) have recently compared glue injection with TIPS in the management of gastric variceal bleeding. Variceal obliteration was achieved in 51% of the glue injection group compared with 20% in the TIPS group. However, there was a higher rate of rebleeding in those who had glue injection (38%) compared with those treated with TIPS (11%) over a mean follow-up period of 33 months (26). Thus, TIPS represents another form of therapy but it is associated with other complications including hepatic encephalopathy, which occurred in nine of 35 (25.7%) TIPS patients in the Lo et al (26) study.

Our results confirm the safety and efficacy of gluing gastric varices in a North American population. Although this mode of therapy was first pioneered in Germany (27), the vast majority of published studies to date, with the exception of three American-based studies (16-18), have examined cohorts from southeast Asia and India. In those studies, the most common etiology of portal hypertension was viral hepatitis-induced cirrhosis, ranging from 45% to 95% of patients. Furthermore, most of these studies involved few or no patients with noncirrhotic causes of portal hypertension. In contrast, our results evaluated a population of which 82.4% are Caucasian and only 5.9% are of Asian descent. In the present cohort, the most common etiology of portal hypertension was cirrhosis, but alcoholism represents nearly one-half of the underlying causes; viral hepatitis was present in less than one-quarter. In addition, 20.6% of our sample had noncirrhotic portal hypertension.

Despite these differences, the findings in the present study are comparable with the published literature from outside of North America (Table 4). Our rate of initial hemostasis in acutely bleeding varices was 93.8% compared with 87% to 100% in the literature. Furthermore, variceal obliteration was successful in 84.0% of patients, which is similar to the 80% to 100% rate previously published after one injection session. Our rebleeding rate following initial hemostasis was 24%, similar to other all other studies reporting rates from 10% to 31% (3,8,12). As in the present cohort, most rebleeding responded to repeat endoscopic glue injection. The literature reports a treatment failure-related mortality rate of 2% to 4% (3,8,12), which again is similar to the present study (2.1%). The management of esophageal varices in the setting of coexisting gastric varices is controversial and there is no general consensus or available randomized evidence on the best strategy. In our centre, most endoscopists will recommend eradication of gastric varices with glue injection before banding of esophageal varices.

In the United States, Greenwald et al (16) performed a pilot study from, and cost-analysis for, the use of NBCA for bleeding gastric varices. This prospective study enrolled 44 patients and compared them with historical controls. Hemostasis was

![Figure 1](https://example.com/fig1.png)

**Figure 1** Coronal oblique reformation of the abdomen from an oral and intravenous contrast-enhanced computed tomography scan acquired in the portal venous phase. Extensive hypo-attenuating material filling the slightly dilated superior mesenteric vein (arrows) and several feeding branches is consistent with acute thrombosis.

### Table 4

Comparison of studies evaluating N-acetyl-2-cyanoacrylate injection for recently bled or actively bleeding gastric varices

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Hemostasis, %</th>
<th>Rebleeding, %</th>
<th>Obliteration, %</th>
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<td>47</td>
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<td>23.10</td>
<td>84.00</td>
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<td>92</td>
<td>100</td>
<td>21.70</td>
<td>–</td>
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<td>Lo et al (26)</td>
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<td>37.80</td>
<td>51</td>
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<tr>
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<td>93.30</td>
<td>22.40</td>
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<tr>
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<td>44</td>
<td>100</td>
<td>25</td>
<td>100</td>
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<tr>
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<td>174</td>
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<td>75</td>
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<td>29</td>
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<tr>
<td>Lo et al (8)</td>
<td>31</td>
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<td>31</td>
<td>51</td>
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<tr>
<td>Huang et al (7)</td>
<td>90</td>
<td>94.40</td>
<td>23.30</td>
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Rebleeding from gastric varices at any time during published follow-up
Gluing of gastric varices

achieved in all patients with active bleeding at endoscopy, early rebleeding (within 72 h) occurred in 9.1%, rebleeding at any time in 25% and varices were obliterated in all patients after an average of 2.8 gluing sessions (16). In the other pilot study from the United States (18), the use of a very similar compound (2-octyl cyanoacrylate) achieved immediate hemostasis in 100% of 25 patients with active or recent gastric variceal bleeding. Rebleeding occurred in one patient, resulting in death. The largest North American study to date was published recently by Caldwell et al (17). In 80 patients with ing in death. The largest North American study to date was published recently by Caldwell et al (17). In 80 patients with portal hypertension, rebleeding occurred in only 5% within 72 h and in 17% of patients from three months to one year following the procedure. Serious embolization was noted in 2% of their patients. Due to the relative paucity of North American data, the 2005 updated American Society for Gastrointestinal Endoscopy guidelines (28) for endoscopic management of gastric variceal hemorrhage concluded that there were insufficient data to recommend any specific endoscopic treatment, including gluing, for gastric varices.

The main limitation of the present study is its retrospective design. Other considerations in interpreting these data include completeness and accuracy of endoscopy reports, variations in gluing techniques among gastroenterologists, as well as differences in gluing techniques across comparison studies. Our follow-up is sufficient to detect serious complications and should encompass all rebleeding episodes.

Although the efficacy of this technique appears well-established, the main controversy surrounds potential complications of the procedure. Fever and epigastric pain are common and usually resolve spontaneously within a few hours. Transient bacteremia is also possible, reported in up to 50% of patients following endoscopic sclerotherapy for esophageal varices with either glue or ethanol, and likely occurs with most gastric variceal therapeutic approaches (29,30). The risk factors identified for the occurrence of bacteremia in these case series were the volume of blood transfused and Child-Pugh score. Mediastinitis and peritonitis have also been reported as a complication after glue injection (31). We had no documented cases of bacteremia or clinically significant infection in our patients.

Furthermore, a well-established complication is that of systemic embolization of the glue material postinjection. Emboli to every part of the body including the limbs, intestines, spleen, lungs, coronary arteries and brain have been published as case reports (32-36). However, considering all the patients in the trials mentioned in Table 4, documented glue embolism is rare and only occurred in two cases (0.2%) and was suspected in five other cases (0.7%) of a total of 726 procedures (thus, seven suspected and confirmed cases of emboli of a total of 726 cases = 0.92%) (3-5,7,8,12,13,17,26). Akahoshi et al (5) followed all patients with a computed tomography scan after glue injection and found no embolization of glue material in 52 patients over a 10-year period. Symptomatic distant embolization did not occur in any of our patients and the upper limit of this 95% CI (0.0% to 7.4%) suggests this is uncommon. However, asymptomatic emboli were not systematically sought radiographically and it is possible that small subclinical emboli may have occurred.

Embolization to the portal system leading to portal vein and splenic vein thrombosis has also been reported (37). Our study includes the first report of superior mesenteric vein thrombosis as a complication of gastric variceal gluing. Because no radiopaque glue material was noted on imaging, the mechanism of this complication is unclear and may represent embolization or alternatively, phlebitis. Mesenteric venous thrombosis has been reported as a complication of ethanol sclerotherapy for esophageal varices (38,39). Similar to sclerosants, glue emboli may serve as a nidus for thrombus formation, accessing the portal system via gastrorenal shunts. This patient had a congenital absence of the portal vein with previous splenectomy and splenorenal and mesocaval shunts. Our patient’s unique portovenous anatomy may have been the predisposing factor that led to the thrombosis. The other factor that clearly may increase the risk of local vessel thrombosis, distinct from the possibility of glue thrombi, is the gastric inflammation resulting from the NBCA administration and gastric variceal thrombosis.

On the horizon, two radiological techniques involving transcatheter embolotherapy are showing promise in the management of bleeding or high risk gastric varices. Balloon-occluded retrograde transvenous obliteration (BRTO) takes advantage of spontaneous splenorenal shunts to access gastric varices. Percutaneous transhepatic obliteration requires cannulation of afferent gastric veins. Obliteration is achieved by injection of sclerosants or cyanoacrylate glue. Reported rebleeding rates range from 2% to 3% with an obliteration rate of 86% to 97% (40,41). An extension of these techniques is balloon-occluded endoscopic injection therapy. This involves transvenous insertion of coils into all veins except the supplying vein of the gastric varix, the occlusion of that vein with an intravenous balloon as in BRTO. The varix is then injected under endoscopic and fluoroscopic guidance with cyanoacrylate glue. Preliminary studies indicate equal efficacy to BRTO, but larger trials with longer follow-up are required (42).

CONCLUSIONS

The present study is only the third in a North American population assessing the role of cyanoacrylate in the endoscopic management of gastric varices. The present cohort is distinct from previous, predominately Asian, study populations. Our study indicates that this modality is safe and highly effective for the treatment of actively bleeding gastric varices or varices that have recently bled. Gluing can achieve a high rate of hemostasis, often with obliteration of varices altogether. The rate of complications is acceptably low, but the consequences can be severe. However, the rates of adverse events and their consequences appear lower, or comparable with, the alternatives of surgery, TIPS and other modalities. With further such experience in the use of NBCA variceal gluing in the North American population, there likely will be wider acceptance of this therapeutic intervention for patients with portal hypertension.

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