UPPER GASTROINTESTINAL BLEEDING IN SEVERELY BURNED PATIENTS: INCIDENCE, RISK FACTORS AND OUTCOME

HÉMORRAGIE DIGESTIVE HAUTE CHEZ LES GRANDS BRULÉS: INCIDENCE, FACTEURS DE RISQUE ET RETENTISSEMENT

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SUMMARY. Upper gastrointestinal bleeding (UGIB) is a rare complication of the ICU stay. Our objective was to study the epidemiological, clinical manifestations, and evolutionary characteristics of UGIB, and identify its risk factors in severely burned patients. This is a retrospective case-control study of burned patients in the ICU in Tunisia over a period of 6 years, including all adult patients with severe burns who presented at least one episode of gastrointestinal bleeding. The control group consisted of severely burned patients with no gastrointestinal bleeding during their ICU stay. The two groups were matched according to age, gender and extent of burns. The incidence of gastrointestinal bleeding was 2.3% with an average time of onset of 19±17 days. Esophagogastroduodenoscopy was performed in 45 patients showing bulbar ulcer, gastric ulcer, and oesophageal ulcerations in respectively 28, 8 and 3 patients. In the multivariate study, acute kidney injury (OR 13.8, CI [2.9-67], p=0.001), fluid intake <2 ml/kg/%TBSA over the first 24h (OR 10, IC [1.5-68.5], p=0.019), and length of ICU stay >10 days (OR 48.2, IC [4.4-530], p=0.002) were independent risk factors for the occurrence of gastrointestinal bleeding. Mortality in the UGIB group was higher (55.8% vs 25%, p=0.001). Upper gastrointestinal bleeding is a serious complication of a burn patient's ICU stay. Acute renal failure, low fluid intake in the first 24h, and a long duration of ICU stay were independent risk factors for its occurrence.

Keywords: gastrointestinal haemorrhage, burns, complications, risk factors

RÉSUMÉ. *L'hémorragie digestive haute est une complication du séjour en réanimation. Notre objectif était d'étudier les caractéristiques épidémiologiques, cliniques et évolutives de l'hémorragie digestive et d'identifier ses facteurs de risque chez les brûlés graves. Etude rétrospective cas-témoins dans l'unité de réanimation des grands brûlés de Tunis sur une période de 6 ans, incluant tous les adultes gravement brûlés ayant présenté au moins un épisode d'hémorragie digestive. Les témoins sont des patients gravement brûlés n'ayant pas présenté d'hémorragie digestive pendant l'hospitalisation. Les deux groupes étaient appariés en fonction de l'âge, du sexe et de l'étendue des brûlures. L'incidence de l'hémorragie digestive était de 2,3%, avec un délai moyen d'installation 19±17 jours. Une fibroscopie œsogastroduodénale réalisée chez 45 patients, a montré un ulcère bulbaire, un ulcère gastrique et des ulcérations œsophagiennes chez respectivement 28, 8 et 3 patients. Dans l'étude multivariée, l'agression rénale aiguë OR 13,8, IC [2,9-67], p=0,001, l'apport liquidien <2 ml/kg/%TBSA sur les 24 premières heures OR 10, IC [1,5-68,5], p=0,019, et un séjour en USI >10 jours OR 48,2, IC [4,4-530], p=0,002, étaient des facteurs de risque indépendants pour la survenue d'une hémorragie digestive. L'hémorragie digestive est une complication grave du séjour d'un patient brûlé en réanimation. L'agression rénale aiguë, un faible volume de perfusion sur les 24 premières heures et une longue durée de séjour étaient des facteurs de risque indépendants de l'hémorragie digestive.*

Mots-clés : *hémorragie gastro-intestinale, brûlures, complications, facteurs de risque*

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Introduction

Acute gastrointestinal bleeding (AGIB) in critically ill patients has been described in the literature since the 1800s. It is mainly related to severe physiologic stress, which results from shock, sepsis, trauma and severe medical illnesses. In fact, the reported incidence of stress-related mucosal damage varies from 6% to 100% in critically ill patients. It is caused by mucosal abnormality that varies from sub-mucosal haemorrhage and erosion to multiple ulceration, and may be found in the oesophagus, stomach and duodenum.[1,2] Endoscopically evident gastritis or ulceration may be noted in up to 100% of patients, and clinically evident bleeding in 20%, with increased morbidity and mortality.[3]

Determining the true frequency of clinically important bleeding is complicated by the heterogeneity of the patient populations.[4]

In severely burned patients, Curling reported in 1823 a specific form of stress ulcer that results from reduced plasma volume and leads to ischemia and cell necrosis of the gastrointestinal (GI) mucosa.[5] More often associated with perforation and haemorrhage than other forms of stress ulcer, incidence of GIB in burns is rare and varies from 1.5 to 4%. It constitutes the most frequent life-threatening GI complication in burn patients, with a mortality rate reaching 50% according to the literature.[1,6,7]

While stress ulcer has been subject to much research and meta-analysis,[8] risk factors to develop stress ulcer and then AGIB in burn patients are not well elucidated. Several articles studied this subject from 1960 to 1980 and since then, only a few have been published.

The aim of our study was to determine the incidence, clinical characteristics, causes, risk factors and outcome of burned patients who developed AGIB during their ICU stay.

Patients and methods

We conducted a monocentric, retrospective, observational case control comparative study in an intensive burn care department in Tunis, during the period from January 2016 to July 2022. We included all severely burned patients who developed at least one episode of AGIB more than 48 hours after admission. Children aged under 18 years, non-burned patients and those with incomplete medical records were excluded.

AGIB was defined by the occurrence of exteriorized digestive bleeding (melena, hematemesis) and/or acute deglobulisation without further explanation with nasogastric lavage positive for bright red blood.

Deglobulisation was defined as an acute decrease in haemoglobin level of more than 2 g/dl in 24 hours without any specific reason.[1]

To determine the risk factors for the onset of GI bleeding, cases were compared with the control population made up of hospitalized patients who did not develop AGIB during the study period, matched according to age, gender and total burned surface area (TBSA).

All patients' records were thoroughly reviewed and several clinical and paraclinical parameters were recorded. Clinical data were age, sex, co-morbidities, information about characteristics of burns including mechanism and TBSA, severity scores, information about the initial management and resuscitation procedures including fluid management and enteral feeding, and systematic stress ulcer prophylaxis, onset and clinical manifestations of GI bleeding and associated complications, specific management, and the final issue.

A survivor was defined as a patient discharged from the ICU alive.

The data were analysed using the SPSS Base 20 statistical software package. Quantitative data were expressed as mean ± standard deviation (SD) or median [IQR 25-75] according to the normality or not of the variables. Quantitative variables were expressed as percentage. The association of potential risk factors with GI bleeding was determined by calculating odds ratios (OR) and 95% confidence intervals (CI). Variables that were significantly associated with GI bleeding ($P < 0.05$) were entered into a multivariate, forward stepwise logistic regression analysis. ROC curve and logistic regression have been adopted to find the cut off for the initial fluid management quantity, the delay of enteral feeding initiation, and the length of hospital stay. A p value of less than 0.05 was considered statistically significant.

Results

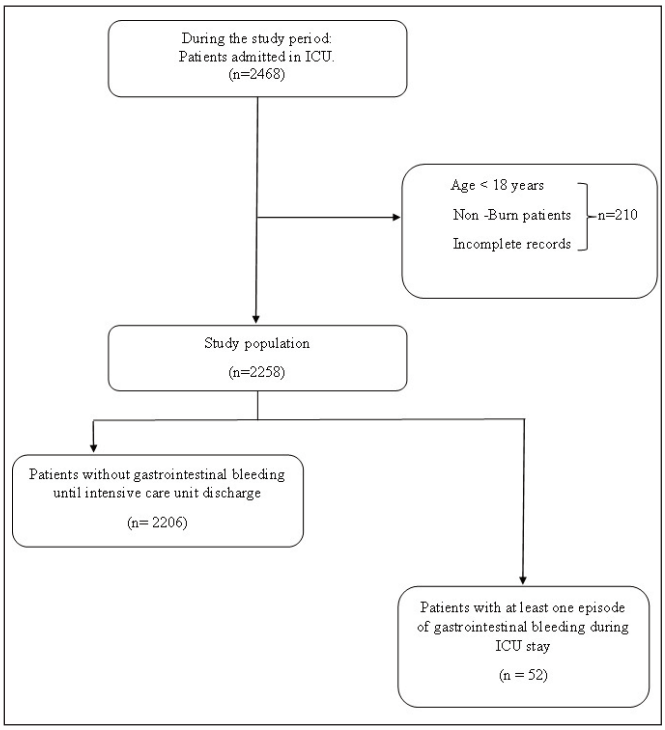
During the study period, 2468 patients were admitted to the ICU, 2258 were severely burned adult patients. Among them, 52 were diagnosed with at least one episode of AGIB with an incidence of 2.3% (*Fig. 1*).

Patients who developed GI bleeding (n=52) have a mean age of 38 ± 22 years, a genre ratio of 2,2 and a mean TBSA of 35 ± 14%. The mean ABSI was 6,2 ± 2,6. A history of gastrointestinal ulcer was found in five cases. Burns were thermal in the majority of cases (43/52), caused by domestic accident in 62% of cases (*Table 1*).

The mean time to onset GI bleeding was 13 days.

There was clinical presentation of epigastric pain in 28 cases (53.5%), followed by hematemesis (n=19) and melena (n=19) and both hematemesis and melena were found in 7 cases. Haemorrhagic shock was noted in 22 cases (*Table II*).

Deglobulisation was found in 44 cases, raising suspicion of the diagnosis of GI bleeding.



ICU: Intensive care unit

Fig. 1 - Flow diagram

Table I - Clinical characteristics of patients

	Gastrointestinal bleeding group (n=52)	Control group (n=52)	p value
Age (years)	38 ± 22	40 ± 19	0.66
Sex ratio (M/F)	2.2 (36/16)	2.2 (36/16)	-
Comorbidities:			
- **Arterial hypertension**	6	6	-
- **Diabetes**	2	5	0.44
- **Chronic kidney failure**	0	0	-
- **Gastrointestinal ulcer**	4	3	-
Total body surface area burned (TBSA)	35 ± 14	32.5 ± 17	0.35
Abbreviated burn severity index (ABSI)	6 ± 2.6	5 ± 2.6	0.09
Unit burn standard (UBS)	68 ± 52	43.1 ± 34.5	0.05
Baux score	72.5 ± 23	70 ± 28	0.62
Burn circumstances:			
- **Domestic accident**	32 (62%)	29 (56%)	
- **Work accident**	8 (15.5%)	8 (15.4%)	
- **Suicide attempt**	12 (24%)	15 (29%)	
Mechanisms of injury:			
- **Thermal injury**	43 (82.7%)	47 (91%)	
- **Electric injury**	9 (17.3%)	5 (10%)	

Table II - Gastrointestinal bleeding symptoms

Symptoms	N=52
Deglobulisation with blood in nasogastric lavage	44 (84.6%)
Haemorrhagic shock	22 (42.3%)
Hematemesis	12 (23.1%)
Melena	12 (23.1%)
Hematemesis and melena	7 (13.5%)

Esophagogastroduodenoscopy was performed in 45 (86.5%) patients, was normal in 6 (13%) cases and showed bulbar ulcer in 28 (62%) cases, gastric ulcer in 8 (18%) cases and oesophageal ulcer in 3 (7%) cases (*Fig. 2*).

Different factors for AGIB have been studied. No significant difference has been reported regarding the systematic prophylactic proton pump inhibitor treatment and invasive mechanical ventilation. Fluid intake during the first 24 hours <2 ml/Kg/% TBSA, a delayed enteral feeding, sepsis, hemodynamic shock, acute kidney injury, and a prolonged hospitalization for more than 10 days were the evolutionary statistically significant parameters for GIB in the univariate study *(Table III)*.

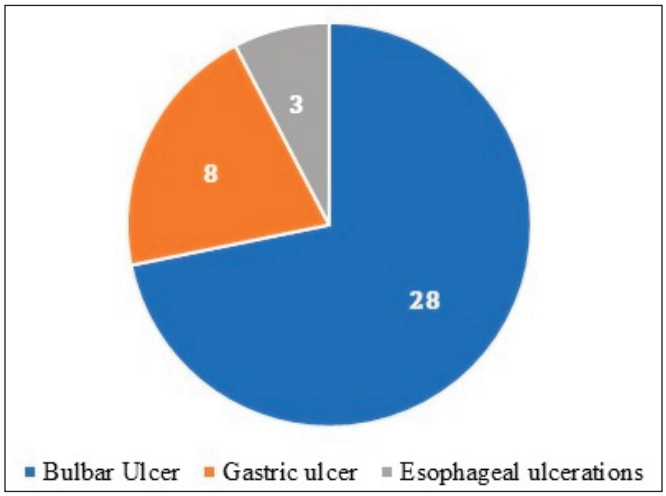


Fig. 2 - Esophagogastroduodenoscopy abnormalities

Table III - Risk factors for gastrointestinal bleeding: univariate study

	Gastrointestinal bleeding group (n=52)	Control group (n=52)	p value
Prophylactic proton pump inhibitor treatment	8 (15.4%)	8 (15.4%)	1
Invasive mechanical ventilation	16 (31%)	14 (27%)	0.66
Sepsis	49 (94%)	36 (69%)	0.001
Hemodynamic shock	22 (42%)	12 (23%)	0.037
Acute kidney injury	23 (44%)	5 (10%)	$< 10^{-3}$
Fluid intake during first 24 hours <2 ml/Kg/%TBSA	15 (29%)	2 (4%)	0.01
Enteral feeding initiation time since burn (hours)	24 ± 19	17 ± 11	0.024
Duration of intensive care unit stay >10 days	51 (98%)	36 (69%)	$< 10^{-3}$

TBSA: Total body surface area burned

In multivariate analysis, acute kidney failure, fluid intake during first 24 hours <2 ml/Kg/%BSA (AUC=0,693; 95% CI: 0.593 - 0.793), and duration of intensive care unit stay >10 days (AUC=0,693; 95% CI: 0.593 - 0.793) were found to be independent risk factors for GIB (*Table IV*) (*Figs. 3, 4*).

All patients received proton pump inhibitor systemic treatment. Thirty-four patients (65%) required blood transfusion. Endoscopic treatment with installation of clips was indicated in 6 cases and surgery was necessary in 9 cases.

No difference has been reported in ventilatory nor in hemodynamic support between the two groups. The mortality rate was significantly higher in patients developing GIB (29/52 versus 13/52, p: 0.001) (*Table V*).

Discussion

In our study, we report AGIB in 52 out of 2258 patients. An incidence of 2.3%. The same findings have been reported by Prasad et al. in 1987[9] and by Kim et al. 27 years later.[10] A recent Chinese study (1093 burn patients) shows an incidence of 3.2%.

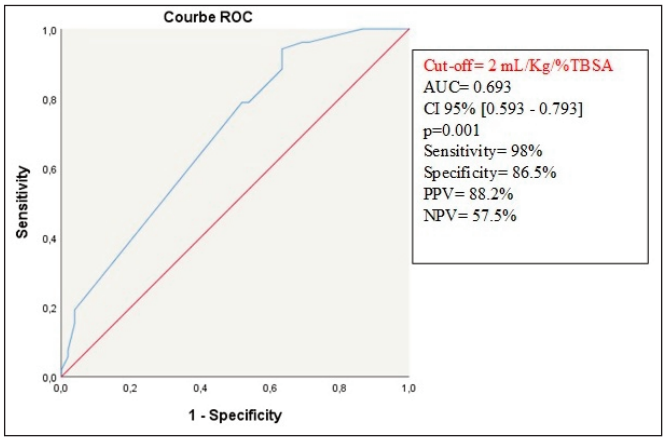
Upper gastrointestinal bleeding is not a specific complication of severely burned patients. It appears to be as frequent as in other medico surgical intensive care patients. Krag et al. studied this problem in a prospective multicentric study in 11 countries regrouping mixed intensive care unit patients and reported an incidence of 4.8%.[11]

UGIB diagnosis was based on clinical and bio-

Table IV - Risk factors for gastrointestinal bleeding: multivariate study

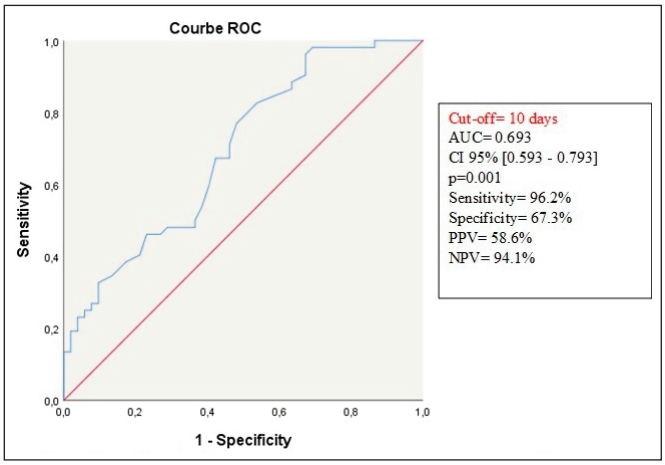
	Gastrointestinal bleeding group (n=52)	Control group (n=52)	OR	IC (95%)	p value
Acute kidney injury	23 (44%)	5 (10%)	13.8	2.9 – 67	0.001
Fluid intake during first 24 hours <2 ml/Kg/%TBSA	15 (29%)	2 (4%)	10	1.5 – 68.5	0.019
Duration of intensive care unit stay >10 day	51 (98%)	36 (69%)	48.2	4.4 – 530	0.002

TBSA: total body surface area burned; OR: odds ratio; CI: confidence interval



TBSA: total burned surface area; AUC: area under the curve; CI: confidence interval; PPV: positive predictive value; NPP: negative predictive value

Fig. 3 - Performance of the quantity of fluid intake during first 24 hours (in mL/Kg/%BSA) in the prediction of upper gastrointestinal bleeding occurrence



AUC: area under the curve; CI: confidence interval; PPV: positive predictive value; NPP: negative predictive value

Fig. 4 - Performance of the duration of intensive care unit stay in the prediction of upper gastrointestinal bleeding occurrence

Table V - Impact of gastrointestinal bleeding

	Gastrointestinal bleeding group (n=52)	Control group (n=52)	p value
Patients requiring blood transfusion	34 (65.4%)	6 (11.5%)	$< 10^{-3}$
Ventilatory support requirement (days)	12.8 ± 12.8	12.5 ± 12.7	0.95
Norepinephrine requirement (days)	8 ± 5.5	5.5 ± 2.5	0.1
Mortality	29 (58%)	13 (26%)	0.001

logical signs. Thus, we report hematemesis and/or melena in 38 cases, shock in 22, and acute anaemia with haemoglobin level <8 g/dl in 44 patients, which seem to be the most sensitive and specific signs for diagnosis.[12] Epigastric pain was the most frequent symptom in our study, similar to the study of Choi et al. showing that 35.3% of ulcer burned patients complained of epigastric pain.[13]

Esophagogastroduodenoscopy was performed in 45 patients and bulbar ulcer was reported in 28 patients. The predominance of the duodenal localization was also reported in burned patients in the endoscopic findings of Kim et al..[10] Kumar et al. conclude that GIB in severely burned patients was more from the ulcers than the erosions and more from the duodenum than the stomach.[14]

Proton pump inhibitor treatment reduces gastric acid secretion. It represents the most commonly used drug to prevent gastrointestinal bleeding in severely ill patients.[15] In our cases, systematic proton pump inhibitor treatment was prescribed only in patients with a medical history of gastroduodenal ulcer or in those aged more than 65 years old. According to our protocol, 8 patients in the peer group were under prophylactic treatment. Thus, it seems not to interfere with GIB occurrence. Many studies highlighted prophylactic proton pump inhibitor treatment and its role in stress ulcer prophylaxis. Systematic proton pump inhibitor treatment prescription in intensive care patients did not prove superior in mortality nor in occurrence of gastrointestinal bleeding in this population in international, blinded, placebo-controlled, randomized trial.[16] A comparative study of two groups of patients with and without ulcer prophylaxis was carried out, and according to this study, anti-ulcer prophylaxis does not influence the rate of clinically significant GIB in intensive care, even in patients having one or more risk factors.[17]

Invasive mechanical ventilation (MV) has long been incriminated as a risk factor for stress ulcer and associated GIB. In our study, we did not find that MV exposes to the risk of occurrence of GIB. Our findings are concomitant to those recently published in a meta-analysis involving 8 large studies with more than 73,379 mixed intensive care ventilated patients, where MV was not incriminated as a risk factor for upper gastrointestinal bleeding.[8]

In our study, several evolutive parameters were incriminated as risk factors for UGIB in the univariate study. Forty-nine (94%) of our GIB group patients presented at least one sepsis during their hospitalisation compared to 69% in the control group. And 42.3% vs 23.1% presented shock. Sepsis has been incriminated in the occurrence of GIB in critically ill patients in three out of eight studies included.[8] The same meta-analysis incriminates also hemodynamic shock in four. While burns are responsible for vascular leak and fluid creep, sepsis and shock worsen the situation. They are responsible for a relative hypovolemic state, a microcirculatory decrease in the gastrointestinal tract and stress-related mucosal damage.

Early enteral feeding was proposed as a preventive measure of gastrointestinal bleeding due to stress ulceration, especially in burn patients. Early enteral feeding has been shown to raise gastric pH

and enhance regional distribution of gastrointestinal blood flow. It also helps to maintain intestinal barrier function and, as such, prevents bacterial translocation across the gut wall.[18,19] In our study, we report delayed enteral feeding in the GIB group. Our results are similar to those reported by Raff et al. in a comparative retrospective study of 526 burns patients, as a preventive measure against GIB in burned patients, with two groups with enteral feeding compared to total parenteral nutrition and cimetidine with or without antacids. In this series, the enterally fed group had a significantly lower incidence of GI bleeding.[20]

In our multivariate study, we reported three independent risk factors for GIB. With non-elucidated physio pathological mechanisms, acute kidney injury is a well-known risk factor for GIB in intensive care patients.[8] In our study regarding burn patients, acute kidney injury was an independent risk factor for UGIB. The burn injury is responsible for an important fluid loss and patients are in a hypovolemic state. Ellison et al. have shown that acute kidney injury multiplies the risk of GIB by 3.[21]

Fluid intake during the first 24 hours <2 ml/Kg/% TBSA was also found to be an independent risk factor for GIB. In fact, insufficient fluid therapy during the early phase majors the hypovolemic state and associated complications. It is responsible for splanchnic vasoconstriction that leads to ischemia and cell necrosis of the gastrointestinal mucosa exposing to Curling ulcer and GIB.[22]

Prolonged intensive care unit stay is associated with several gastrointestinal mucosa irritative factors: enteral feeding discontinuation, pain, hyperprotidic metabolism and adverse treatments effects. In our study, we reported that duration of intensive care unit stay >10 days is an independent risk factor for GIB.

We did not show a difference in organ support techniques needed between the two groups. All patients received intra venous proton pump inhibitor treatment. Forty-four patients in the GIB group presented an acute anaemia with haemoglobin level <8 g/dL so blood transfusion requirements were significantly elevated. Endoscopic treatment remains the treatment of choice. Nevertheless, surgical treatment is indicated in cases of refractory gastrointestinal bleeding (8 to 15%) that does not respond to endoscopic treatment, if the hemodynamic state is unstable, or there is a need to transfuse more than six packed red blood cells to maintain haematocrit at 30%.[23] In our series, surgery was necessary in nine patients who had hemodynamic instability.

Patients who develop GIB had a worse prognosis than other patients, with a mortality rate that varies from 10 to 40% in unburned patients and from 10 to 50% in burned patients.[21] In our study, GIB was associated with a high mortality rate of up to 56%. These patients were more severe on admission with higher prognostic scores.

We estimate that we add some interesting data to the literature concerning AGIB in burn patients and associated risk factors, which contributes to better discerning this complex pathology. The relatively small, retrospective and monocentric design may be considered as limitations.

Conclusion

Our study showed that AGIB is rare in burn patients, with an incidence of 2.3%. It occurs on the 13th day on average. Diagnosis was based on clinical signs with epigastric pain and/or GI bleeding symptom (melena and/or hematemesis) and/or deglobulisation in the majority of cases. Bulbar ulcer was the most observed lesion on esophagogastroduodenoscopy (in 62% of cases). Fluid intake during the first 24 hours <2 ml/Kg/% TBSA, delayed enteral feeding, sepsis, hemodynamic shock, acute kidney injury, and a prolonged hospitalization for more than 10 days have been identified as risk factors for occurrence of haemorrhage. All patients received proton pump inhibitor systemic treatment. Thirty-four patients required blood transfusion. Endoscopic treatment with installation of clips was indicated in six cases and surgery was necessary in nine cases. AGIB was associated with a high mortality rate of up to 56%. Adequate initial fluid resuscitation and early enteral feeding are necessary to prevent this complication.

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