Occult upper gastrointestinal mucosal abnormalities in critically ill patients

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Background: The objectives of this study were to estimate the frequency of occult upper gastrointestinal abnormalities, presence of gastric acid as a contributing factor, and associations with clinical outcomes.

Methods: Data were extracted for study participants at a single centre who had an endoscopy performed purely for research purposes and in whom treating physicians were not suspecting gastrointestinal bleeding. Endoscopic data were independently adjudicated by two gastroenterologists who rated the likelihood that observed pathological abnormalities were related to gastric acid secretion using a 3-point ordinal scale (unlikely, possible or probable).

Results: Endoscopy reports were extracted for 74 patients [age 52 (37, 65) years] undergoing endoscopy on day 5 [3, 9] of ICU admission. Abnormalities were found in 25 (34%) subjects: gastritis/erosions in 10 (14%), nasogastric tube trauma in 8 (11%), oesophagitis in 4 (5%) and non-bleeding duodenal ulceration in 3 (4%). The contribution of acid secretion to observed pathology was rated 'probable' in six subjects (rater #1) and five subjects (rater #2). Prior to endoscopy, 39 (53%) patients were receiving acid-suppressive therapy. The use of acid-suppressive therapy was not associated with the presence of an endoscopic abnormality (present 15/25 (60%) vs. absent 24/49 (49%); $P = 0.46$). Haemoglobin concentrations, packed red cells transfused and mortality were not associated with mucosal abnormalities ($P = 0.83$, $P > 0.9$ and $P > 0.9$ respectively).

Conclusions: Occult mucosal abnormalities were observed in one-third of subjects. The presence of mucosal abnormalities appeared to be independent of prior acid-suppressive therapy and was not associated with reduced haemoglobin concentrations, increased transfusion requirements, or mortality.

Editorial Comment

Acid-suppressive treatment during critical illness is controversial. This observational study examined occult abnormalities in the upper gastrointestinal mucosa in a mechanically ventilated, critically ill ICU cohort. The findings confirmed the idea that morphological findings often do not match other clinical factors or treatments concerning upper gastrointestina bleeding.

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In 1842, Curling documented a case series of 12 patients who died from either gastrointestinal haemorrhage or peritonitis during convalescence from burn injuries and were found on autopsy to have a duodenal ulcer.[1] A century later, following the introduction of intensive care units to provide prolonged advanced life support for critically ill patients, a number of case series were published describing patients who died of gastrointestinal haemorrhage and were observed during post-mortem, surgical or endoscopic examination to have lesions of the gastroduodenal mucosa.[2–4]

Occult gastroduodenal mucosal abnormalities are thought to occur frequently in the critically ill, with historical data suggesting more than 50% have occult abnormalities of the upper gastrointestinal mucosa observed at endoscopy.[5,6] Presumably in the hope of reducing the morbidity and mortality burden that may occur if these occult lesions progress to cause clinically significant gastrointestinal bleeding, many clinicians empirically prescribe acid-suppressive drugs to critically ill patients as routine practice.[7,8] Comparing the two largest prospective cohort studies, published 20 years apart (1994 and 2015), it appears that while the use of acid-suppressive drugs has increased dramatically, the prevalence of clinically important gastrointestinal bleeding remains fairly steady.[9,10] However, the increased use of acid-suppressive drugs may be relevant to patient outcomes, as there is considerable evidence that excessive use of these medications increases the likelihood of adverse events and this may result in net harm.[11–14] Accordingly, there is considerable interest in re-evaluating the role of routine prophylactic acid suppressive therapy in critical illness.[13,15]

As large randomised controlled trials of acid-suppressive therapy have either commenced or are being planned,[16] we sought to describe the occurrence of occult gastrointestinal abnormalities in contemporary practice, particularly those that may be caused or exacerbated by gastric acid. For this reason, we performed a retrospective analysis of all patients at our institution that had an upper gastrointestinal endoscopy for research purposes.[17–21]

Our primary objective was to estimate the proportion of mechanically ventilated critically ill patients with occult upper gastrointestinal abnormalities. Our secondary objectives were to evaluate whether: (1) acid-suppressive drugs were associated with a reduced frequency of occult lesions; (2) the presence of gastric acid may have been a contributing factor for the presence of occult abnormalities; and (3) occult abnormalities were associated with adverse patient outcomes.

Methods

Data were extracted for all study participants who had an endoscopy performed purely for research purposes (i.e. there was no indication to perform endoscopy because of symptoms or signs of gastrointestinal bleeding) while mechanically ventilated in the Royal Adelaide Hospital Intensive Care Unit from 2004 to 2014 inclusive. The Royal Adelaide Hospital Intensive Care Unit is a 42-bed mixed medical-surgical closed Intensive Care Unit with research interests in gastrointestinal function and nutrition in the critically ill. Each prospective study was approved by the Research Ethics Committee of the Royal Adelaide Hospital, as was this retrospective analysis (Royal Adelaide Hospital Human Research Ethics Committee approval number R20160623). Selection criteria for participation in these studies are reported.[17–21] Patients were identified by hand searching patient enrolment records from the Royal Adelaide Hospital Intensive Care Unit research database.

Data extraction

Participant demographic and ICU admission data were extracted from the local Australia and New Zealand Intensive Care Society Adult Patient Database (ANZICS-APD).[22] Participant medical records from the index admission were then extracted and hand-searched, with laboratory values extracted from the hospital electronic data warehouse. Haemoglobin concentrations were recorded for day of ICU admission, day of endoscopy and day of ICU discharge. Estimated glomerular filtration rate was categorised into functional sub-groups (> 90, 60–90, 30–60, and < 30 ml/min).

The following data were collected: patient demographics, admission diagnosis, severity of illness (Acute Physiology and Chronic Health Evaluation (APACHE II) score), timing of initiation of enteral feeding,[23] risk factors for gastrointestinal bleeding; including administration of non-steroidal anti-inflammatory greater than 'low-dose' aspirin, corticosteroid use prior to and/or during the index admission, vasoactive drug administration (noradrenaline, adrenaline, or vasopressin) in the 48 h preceding endoscopy,[24] 'haemostatic dysfunction' on day of endoscopy (defined as International Normalised Ratio > 1.5, Activated Partial Thromboplastin Time > 40 s or platelet count < 100,000/μl),[21] previous diagnosis of peptic ulcer disease (defined as diagnosis recorded on any patient discharge summary or admission record), and the use of acid-suppressive drugs prior to and/or during the index admission (proton-pump inhibitor or histamine receptor antagonist). Furthermore, the patient-centred outcomes of transfusion of packed red cells throughout ICU admission and hospital mortality were extracted. Presence of *Clostridium difficile* infection required a positive *Clostridium difficile* toxin microbiology report during the index hospitalisation.[25]

Endoscopy data

Patient reports were extracted from the Royal Adelaide Hospital endoscopy databases (Endoscribe™ and ProVation®). Endoscopy reports and images were independently adjudicated by two senior gastroenterologists/endoscopists (NQN and CKR). They estimated the likelihood that gastric acidity contributed to the observed pathology using an ordinal scale: (1) gastric acid unlikely to have contributed to abnormalities observed; (2) gastric acid possibly contributed to abnormalities observed; and (3) gastric acid probably contributed to abnormalities observed. In addition, based upon these findings, they selected a recommendation from four treatment options: (1) cease or avoid commencing an acid suppressive drug; (2) continue histamine receptor antagonist or commence if not receiving acid suppressive therapy; (3) continue proton pump inhibitor or commence if not receiving acid suppressive therapy; or (4) commence high-dose proton pump inhibitor therapy.

Statistical analysis

Data are described as number (%), mean (SD) or median [IQR] as indicated. Factor associations were assessed by Fisher's exact test throughout due to low cell frequencies. Continuous variables were compared using either Wilcoxon's rank-sum test [median, IQR] or *t*-test (mean, SD) as indicated. Inter-rater reliability for ordinal classification was assessed using Cohen's kappa. Rate estimates are presented as (%, 95% exact binomial confidence interval). Haemoglobin profiles over time were compared using a mixed-effects linear model, incorporating subject as a random effect and red cell transfusion as a fixed covariate. Profiles pre/post-endoscopy were compared setting $t = 0$ at endoscopy and including a linear spline.

Results

Endoscopy reports were extracted for 74 subjects from five studies. Demographic data are summarised (Table 1). Four subjects (5%) had been previously diagnosed with peptic ulcer disease that was unrelated to the index hospitalisation. Prior to endoscopy, 39 (53%) subjects were receiving acid-suppressive drugs (proton pump inhibitor $n = 30$ and histamine receptor antagonist $n = 9$), 6 (8%) subjects had been exposed to non-steroidal anti-inflammatory drugs and 17 (23%) to steroids. In the 48 h prior to endoscopy, 41 (55%) subjects received vasoconstrictor drugs and 73 (99%) received enteral nutrition prior.

Endoscopic findings

Abnormalities were found in 25 (34%; 95% CI 23% to 46%) subjects; including gastritis/erosions in 10 (14%), nasogastric tube trauma in 8 (11%) and oesophagitis in 4 (5%). Three (4%) subjects had non-bleeding ulceration of the duodenum, with the remaining 49 (66%) subjects having normal mucosa.

Interpretation of endoscopic findings

The contribution of acid to the pathology was rated 'probable' in six subjects by rater #1 and in five subjects by rater #2 (Table 2). Based on

Table 1 Features at baseline and on day of endoscopy and outcomes of subjects

Baseline	
Age (years)	51 (18)
Sex (*n*)	
Male	58 (78%)
APACHE II score	19 [16 to 24]
Haemoglobin concentration (g/l)	116 (27)
Primary ICU diagnostic category	
Respiratory	23 (31%)
Trauma	23 (31%)
Neurological	11 (15%)
Sepsis	4 (5%)
Other	13 (18%)
At Endoscopy	
Endoscopy performed day of ICU admission	5 [3 to 9]
Haemoglobin concentration (g/l)	91 (15)
Haemostatic dysfunction	19 (26%)
International Normalised Ratio > 1.5	2 (3%)
Activated Partial Thromboplastin Time > 40 s	12 (16%)
Platelet count < 100,000/μl	10 (14%)
Estimated glomerular filtration rate	
< 30 ml/min	7 (9%)
30–60 ml/min	16 (22%)
60–90 ml/min	31 (42%)
> 90 ml/min	20 (27%)
Post endoscopy clinical outcome	
Duration of ICU admission (days)	16 [11 to 25]
Duration of hospital admission (days)	33 [17 to 54]
Survived to hospital discharge	
Yes	54 (73%)

Data are mean (SD), Median [IQR] or *n* (%). Haemostatic dysfunction was defined as INR > 1.5 or APTT > 40 s or platelets < 100,000/μl on day of endoscopy and patients could be assigned to multiple categories. Using the serum creatinine on the day of endoscopy, the estimated glomerular filtration rate was calculated with the Cockcroft-Gault formula.

endoscopy reports, rater #1 would have recommended starting or continuing a proton pump inhibitor for 14 and rater #2 for 12 subjects (Table 2). The inter-rater reliability was substantial for both the likelihood that the pathology was acid-related (observed agreement 88%, kappa 0.81) and whether an acid-suppressive drug should be commenced or ceased based on the endoscopy result (agreement 76%, kappa 0.60).

Clinical Outcomes

No subject was diagnosed with *Clostridium difficile* infection. Forty-one (55%) subjects had received a blood transfusion with a median of 7 [2 to 13] packed red cell units administered during their ICU stay.

Table 2 Assessment of acid-related pathology and recommended treatment by raters.

	Rater #1	Rater #2	Inter-rater agreement (%)	Kappa1
Likelihood of Acid-related Pathology, *n* (%)				
Unlikely	11 (44)	11 (44)	88	0.813
Possible	8 (32)	9 (36)		
Probable	6 (24)	5 (20)		
Recommended Treatment Plan for Acid Suppressive Therapy, *n* (%)				
Cease current therapy	11 (44)	13 (52)	76	0.595
Start/continue therapy	14 (56)	8 (32)		
High-dose therapy	–	4 (16)		

[1]Cohen's kappa statistic for inter-rater agreement.

Relationships between patient characteristics and endoscopic findings

The presence of an endoscopic abnormality was not associated with the prior use of acid-suppressive therapy (present 15/25 (60%) vs. absent 24/49 (49%); $P = 0.46$); individually, proton pump inhibitors (present 13 (52%) vs. absent 17 (35%); $P = 0.21$) and histamine receptor antagonists (present 2 (8%) vs. absent 7 (14%); $P = 0.71$). For other risk factors, the proportion exposed in those with and without observed endoscopic abnormality were as follows; non-steroidal anti-inflammatory drugs [1/25 (4%) vs. 5/49 (10%); $P = 0.66$], steroids [8 (32%) vs. 9 (18%); $P = 0.25$], coagulopathy [7 (28%) vs. 12 (25%); $P = 0.78$] and inotropes [14 (56%) vs. 27 (55%); $P > 0.9$]. Of the three subjects who were found to have duodenal ulceration, two had been receiving proton pump inhibitors since admission to the intensive care unit. Diagnostic category was not associated with the presence of an abnormality ($P = 0.42$). None of the laboratory variables were associated with the presence of an endoscopic abnormality.

Relationships between endoscopic findings and outcomes

The presence of an occult upper gastrointestinal mucosal abnormality was not associated with

transfusion of packed red cells ($P > 0.9$) or the number of units administered (Fig. 1A). Haemoglobin concentrations were similar on the day of ICU admission, day of endoscopy and day of ICU discharge (Fig. 1B). When using a mixed effects linear model of change in haemoglobin concentration over time, incorporating packed red cells transfused, there was a change in slope (linear spline) between the pre- and post-endoscopy periods but no difference in mean haemoglobin profiles between those with and without occult upper gastrointestinal mucosal abnormality (Fig. 1C). Hospital mortality was similar in subjects with and without a detected gastrointestinal abnormality [7/25 (28%) vs. 13/49 (27%); $P > 0.9$].

Discussion

The key observations from our study include that occult abnormalities of the upper gastrointestinal mucosa occurred in approximately one in three mechanically ventilated critically ill patients, with gastritis and nasogastric tube mucosal erosions the most frequently observed abnormalities. While duodenal ulcers were observed in three subjects, two of these were already established on acid suppressive medication. Gastrointestinal mucosal abnormalities were observed with similar frequency in subjects who were and who were not receiving acid suppressive therapy. Acid production was rated as a probable contributing factor in only one quarter of abnormalities. Last, the presence of occult abnormalities was not associated with any adverse measured clinical outcomes.

Our estimate of the proportion of critically ill patients who have occult gastrointestinal abnormalities suggests that the true prevalence with modern-day practice may be less than the estimates of prevalence from historical reports. In 1974, Czaja and colleagues performed endoscopies in 32 of 77 consecutively admitted adult patients with burn injury to more than 25% of body surface area and reported that 78% of those studied had gastroduodenal mucosal abnormalities. While erosive gastritis was the most frequently observed abnormality, almost half the patients had either gastric or duodenal ulceration or both.[5] However, this study represented a very unwell cohort; the mean area of burn injury was

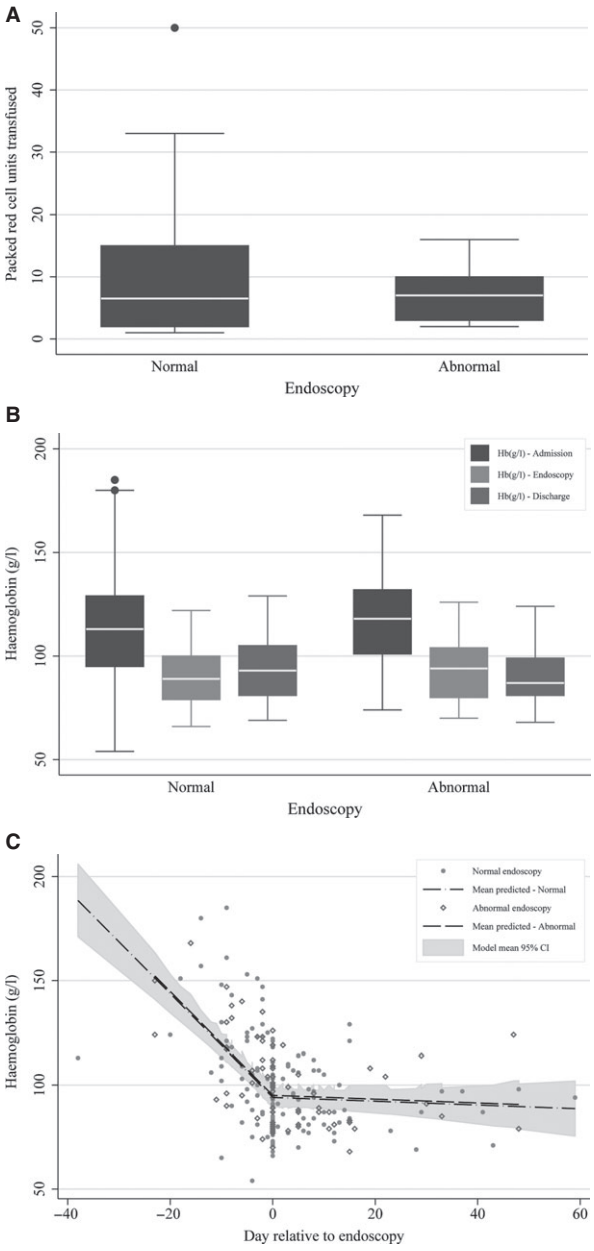

Fig. 1. A. Haemoglobin concentrations on day of ICU admission, day of endoscopy and day of ICU discharge. B. Packed red cell units transfused by occult upper gastrointestinal mucosal abnormalities ($P = 0.83$, Wilcoxon rank-sum test; The median value is represented by the middle line with the upper and lower quartile values represented by the hinges of the box. The vertical whiskers represent data points closest to but within 1.5 times the IQR beyond the 25th and 75th percentiles and the open circle the outlier data point. C. Mixed effects model with linear spline at day of endoscopy with means as dashed line and 95% confidence intervals of haemoglobin concentrations represented as shadow for patients with (— —) and without (— • —) abnormality of gastrointestinal mucosal.

57%, over a quarter developed a substantial complication of their ulceration, 22% developed gastrointestinal bleeding that required > 3 units of packed red cells in a 24 h period, 6% developed perforation necessitating operative repair, and ICU mortality was 75%. In the early 1980s, Peura and Johnson [6] recruited 39 patients who were admitted to a medical ICU with an illness of sufficient severity that at least 5 days in ICU was anticipated. Endoscopy was performed within 18 h of admission and the investigators observed that 74% of patients had gastroduodenal mucosal abnormalities, with almost half of the abnormalities (14/29) categorised as ulceration, signs of bleeding, or both.[6] Kamada and colleagues reported observations from endoscopies performed in 47 head-injured patients at a trauma ICU in Osaka, Japan, during a 2-year period.[26] They reported that 75% of their cohort had mucosal abnormalities, with erosive gastritis the most frequently reported lesion and gastric and duodenal ulceration in 23% and 6% of patients, respectively. However, the criteria for selection for endoscopy were not stated in the latter study and 47% developed clinically significant gastrointestinal bleeding during their ICU admission, which suggests that there may have been selection bias.

Even when previous studies have focussed on the group of patients who develop clinically significant bleeding and have an endoscopy performed, a proportion will have no upper gastrointestinal mucosal abnormalities. In the multi-centre cohort study conducted by the Canadian Critical Care Trials Group, 33 of 2252 consecutively admitted patients were deemed to have clinically significant gastrointestinal bleeding, of which less than half had upper gastrointestinal ulcer disease demonstrated at endoscopy or surgery, representing 0.5% (95% CI 0.2% to 0.8%) of the study population.[9] More recently, in a multi-centre period-prevalence study, 27 of 1034 patients admitted across 97 ICUs developed clinically significant gastrointestinal bleeding,[10] with only two patients (0.19%; 95%CI, 0% to 0.46%) proven to have bleeding attributable to gastrointestinal ulceration diagnosed at endoscopy.[10] Taken together, these data suggest that episodes of clinically significant gastrointestinal bleeding are rarely associated with upper gastrointestinal mucosal pathology that is caused or exacerbated by gastric acid. Our data are in keeping with this hypothesis, as the use of acid suppressive therapy was not associated with the presence of occult abnormalities of the upper gastrointestinal mucosa. Therefore, our findings support current calls to conduct high quality randomised controlled trials of empiric acid suppressive medication in the critically ill.[27]

Potential mechanisms underlying a reduction in proportion of patients with occult abnormalities

The apparent reduced prevalence of occult abnormalities, we observed may be a result of a number of factors. In our study, only one subject had remained fasted from time of ICU admission until endoscopy. This is likely to be relevant as enteral nutrition buffers gastric acid,[28] increases mesenteric blood flow,[29] and induces the secretion of protective prostaglandins and mucus.[30,31] Furthermore, changes in clinical practice, such as judicious fluid resuscitation or lung protective ventilation, may attenuate the insult of critical illness to the gastrointestinal epithelium.[32,33] Finally, the prevalence of *Helicobacter pylori*, at least in high-income countries, has decreased in recent years,[34,35] which may also contribute.

One strength of our study is that it is the largest reported series to date of endoscopies performed in critically ill patients without symptoms of gastrointestinal bleeding. This allows estimation of the frequency and clinical outcomes associated with occult upper gastrointestinal mucosal lesions in this group. Nonetheless, there are important limitations with this study design, including that the sample size may have been too small to detect meaningful associations between occult lesions and outcomes.[36,37] While our study capitalised on an existing endoscopic database, it was retrospective and included a heterogeneous cohort of critically ill patients in a single ICU. We acknowledge the potential risk of unmeasured confounders and selection biases inherent to the original studies. We wish to emphasise that patients with recent or current clinically significant GI bleeding would have been excluded from participation in all of these studies. Moreover, the cohort of 74 patients represents only a small proportion of the total number of patients that would have been ventilated in our ICU (~ 1000

per year) over this period. Any reported associations, or lack thereof, should therefore be considered hypothesis generating and an accurate estimate of prevalence of upper gastrointestinal mucosal abnormalities requires endoscopic examination in consecutively admitted patients.

In summary, critically ill patients as subjects undergoing endoscopy solely for research purposes, and in whom, there was no clinical suspicion of gastrointestinal bleeding were assessed for occult abnormalities of the upper gastrointestinal mucosa, and these were found in approximately one in three mechanically ventilated ICU subjects. The proportion of subjects with abnormalities was not associated with prior acid-suppressive medication, and only one-quarter of abnormalities were rated as likely to be related to gastric acid secretion. Accordingly, when present, occult abnormalities of the upper gastrointestinal mucosa do not appear to be associated with adverse patient outcomes.

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