Received Date : 29-Aug-2016

Revised Date : 18-Oct-2016

Accepted Date : 15-Nov-2016

Article type : Clinical investigation

Full title

Occult upper gastrointestinal mucosal abnormalities in critically ill patients

Authors

Christopher Ovenden¹, Mark P Plummer^{1,2}, Shane Selvanderan¹, Timothy A Donaldson³, Nam Q Nguyen^{5,6,7}, Luke M Weinel⁴, Mark E Finnis^{1,4}, Matthew J Summers⁴, Yasmine Ali Abdelhamid¹, Marianne J Chapman^{1,4,5}, Christopher K Rayner^{5,6,7} and Adam M Deane^{1,4,8}

¹Discipline of Acute Care Medicine, University of Adelaide, Adelaide, Australia

²Neurosciences Critical Care Unit, Addenbrooke's Hospital, Cambridge, United Kingdom

³Department of Anaesthesia, Royal Adelaide Hospital, Adelaide, Australia

⁴Department of Critical Care Services, Royal Adelaide Hospital, Adelaide, Australia

⁵Centre for Research Excellence in Translating Nutritional Science to Good Health

⁶Discipline of Medicine, University of Adelaide, Adelaide, Australia

⁷Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, Adelaide, Australia

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/aas.12844](https://doi.org/10.1111/aas.12844)

This article is protected by copyright. All rights reserved

⁸ Intensive Care Unit, The Royal Melbourne Hospital, Parkville, Australia

Name and location of the institution where the work was carried out

Intensive Care Unit, Royal Adelaide Hospital, Adelaide, Australia

Short title of no more than 40 letters and spaces

Occult gastrointestinal abnormalities

Word count

2,654 words

Corresponding author

Adam M Deane

Intensive Care Unit, The Royal Melbourne Hospital, Grattan Street, Parkville, Victoria,
Australia 3050 Ph: +61 3 9342 9249

Email: adam.deane@adelaide.edu.au

Keywords

Critical illness; endoscopy; gastrointestinal diseases; gastrointestinal haemorrhage; intensive care; peptic ulcer

ABSTRACT

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 6 subjects (rater #1) and 5 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 gastrointestinal bleeding.

INTRODUCTION

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 twenty 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: (i) acid-suppressive drugs were associated with a reduced frequency of occult lesions; (ii) the presence of gastric acid may have been a contributing factor for the presence of occult abnormalities; and (iii) 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 hours preceding endoscopy [24], 'haemostatic dysfunction' on day of endoscopy (defined as International Normalised Ratio > 1.5, Activated Partial Thromboplastin Time > 40 seconds or platelet count < 100,000/ μ L) [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). Further, 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. Additionally, 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 6 studies (Table 1). Demographic data are summarised (Table 2). 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 hours prior to endoscopy 41 (55%) subjects received vasoconstrictor drugs and 73 (99%) received enteral nutrition prior.

Laboratory findings

~~The haemoglobin was 116 (27) g/L on admission, and 91 (15) g/L on the day of endoscopy. Nineteen (26%) patients had 'haemostatic dysfunction' (2 (3%) International Normalised Ratio > 1.5, 12 (16%) Activated Partial Thromboplastin Time > 40 seconds and 10 (14%) platelets < 100x10⁹/L). The estimated glomerular filtration rate was > 90 mL/min in 20~~

~~(27%), 60-90 mL/min in 31 (42%), 30-60 mL/min in 16 (22%) and < 30 mL/min in 7 (9%) patients.~~

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 6 subjects by rater #1 and in 5 subjects by rater #2 (table 1). Based on endoscopy reports, rater #1 would have recommended starting or continuing a proton pump inhibitor for 14 and rater #2 for 12 subjects (table 1). 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.

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 (Figure 1A). Haemoglobin concentrations were similar on the day of ICU admission, day of endoscopy and day of ICU discharge (Figure 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 (Figure 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. Lastly, 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 out 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 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 hour 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 hours 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 two-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 (~ 1,000 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.

Funding: CO was supported by a University of Adelaide Summer Research Scholarships, MPP was supported by a National Health and Medical Research Council Postgraduate Scholarship, YA is supported by a Royal Adelaide Hospital A.R. Clarkson Scholarship, and AMD is supported by a National Health and Medical Research Council Early Career Fellowship.

All authors have no conflicts of interest

Author Manuscript

References

1. Curling TB: On acute ulceration of the duodenum, in cases of burn. *Med Chir Trans* 1842;25:260-281
2. Fogelman MJ, Garvey JM: Acute gastroduodenal ulceration incident to surgery and disease. Analysis and review of eighty-eight cases. *Am J Surg* 1966;112:651-656
3. Skillman JJ, Bushnell LS, Goldman H, Silen W: Respiratory failure, hypotension, sepsis, and jaundice. A clinical syndrome associated with lethal hemorrhage from acute stress ulceration of the stomach. *Am J Surg* 1969;117:523-530
4. Lucas CE, Sugawa C, Riddle J, Rector F, Rosenberg B, Walt AJ: Natural history and surgical dilemma of "stress" gastric bleeding. *Arch Surg* 1971;102:266-273
5. Czaja AJ, McAlhany JC, Pruitt BA, Jr.: Acute gastroduodenal disease after thermal injury. An endoscopic evaluation of incidence and natural history. *N Engl J Med* 1974;291:925-929
6. Peura DA, Johnson LF: Cimetidine for prevention and treatment of gastroduodenal mucosal lesions in patients in an intensive care unit. *Ann Intern Med* 1985;103:173-177
7. Eastwood GM, Litton E, Bellomo R, Bailey MJ, Festa M, Beasley RW, Young PJ: Opinions and practice of stress ulcer prophylaxis in Australian and New Zealand intensive care units. *Crit Care Resusc* 2014;16:170-174
8. Shears M, Alhazzani W, Marshall J, Muscedere J, Hall R, English SW, Dodek PM, Lauzier F, Kanji S, Duffett M, Barletta J, Alshahrani M, Arabi Y, Deane AM, Cook DJ: Stress Ulcer Prophylaxis In Critical Illness: A National Survey. *Canadian Journal of Anesthesia* 2016;
9. Cook DJ, Fuller HD, Guyatt GH, Marshall JC, Leasa D, Hall R, Winton TL, Rutledge F, Todd TJ, Roy P, et al.: Risk factors for gastrointestinal bleeding in critically ill patients. Canadian Critical Care Trials Group. *N Engl J Med* 1994;330:377-381
10. Krag M, Perner A, Wetterslev J, Wise MP, Borthwick M, Bendel S, McArthur C, Cook D, Nielsen N, Pelosi P, Keus F, Guttormsen AB, Moller AD, Moller MH: Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. *Intensive Care Med* 2015;41:833-845
11. Krag M, Perner A, Wetterslev J, Moller MH: Stress ulcer prophylaxis in the intensive care unit: is it indicated? A topical systematic review. *Acta Anaesthesiol Scand* 2013;57:835-847

12. MacLaren R, Reynolds PM, Allen RR: Histamine-2 receptor antagonists vs proton pump inhibitors on gastrointestinal tract hemorrhage and infectious complications in the intensive care unit. *JAMA Intern Med* 2014;174:564-574
13. Krag M, Perner A, Wetterslev J, Wise MP, Borthwick M, Bendel S, McArthur C, Cook D, Nielsen N, Pelosi P, Keus F, Guttormsen AB, Moller AD, Moller MH: Stress ulcer prophylaxis in the intensive care unit: an international survey of 97 units in 11 countries. *Acta Anaesthesiol Scand* 2015;59:576-585
14. Buendgens L, Koch A, Tacke F: Prevention of stress-related ulcer bleeding at the intensive care unit: Risks and benefits of stress ulcer prophylaxis. *World J Crit Care Med* 2016;5:57-64
15. Krag M, Perner A, Wetterslev J, Wise MP, Hylander Moller M: Stress ulcer prophylaxis versus placebo or no prophylaxis in critically ill patients. A systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. *Intensive Care Med* 2014;40:11-22
16. Krag M, Perner A, Wetterslev J, Wise MP, Borthwick M, Bendel S, Pelosi P, Keus F, Guttormsen AB, Schefold JC, Moller MH: Stress ulcer prophylaxis with a proton pump inhibitor versus placebo in critically ill patients (SUP-ICU trial): study protocol for a randomised controlled trial. *Trials* 2016;17:205
17. Nguyen NQ, Fraser RJ, Chapman M, Bryant LK, Holloway RH, Vozzo R, Feinle-Bisset C: Proximal gastric response to small intestinal nutrients is abnormal in mechanically ventilated critically ill patients. *World J Gastroenterol* 2006;12:4383-4388
18. Nguyen NQ, Fraser RJ, Bryant LK, Chapman M, Holloway RH: Proximal gastric motility in critically ill patients with type 2 diabetes mellitus. *World J Gastroenterol* 2007;13:270-275
19. Burgstad CM, Besanko LK, Deane AM, Nguyen NQ, Saadat-Gilani K, Davidson G, Burt E, Thomas A, Holloway RH, Chapman MJ, Fraser RJ: Sucrose Malabsorption and Impaired Mucosal Integrity in Enterally Fed Critically Ill Patients: A Prospective Cohort Observational Study. *Crit Care Med* 2013;
20. Deane AM, Rayner CK, Keeshan A, Cvijanovic N, Marino Z, Nguyen NQ, Chia B, Summers MJ, Sim JA, van Beek T, Chapman MJ, Horowitz M, Young RL: The effects of critical illness on intestinal glucose sensing, transporters, and absorption. *Crit Care Med* 2014;42:57-65
21. Selvanderan SP, Summers MJ, Finnis ME, Plummer MP, Ali Abdelhamid Y, Anderson MB, Chapman MJ, Rayner CK, Deane AM: Pantoprazole Or Placebo for stress Ulcer

Prophylaxis (POPUP): Randomized double blind exploratory study Critical Care Medicine 2016;

22. Plummer MP, Finnis ME, Horsfall M, Luy M, Kar P, Ali Abdelhamid Y, Deane AM: Prior exposure to hyperglycaemia attenuates the relationship between glycaemic variability during critical illness and mortality Critical Care and Resuscitation 2016;
23. Marik PE, Vasu T, Hirani A, Pachinburavan M: Stress ulcer prophylaxis in the new millennium: a systematic review and meta-analysis. Crit Care Med 2010;38:2222-2228
24. Bardou M, Quenot JP, Barkun A: Stress-related mucosal disease in the critically ill patient. Nat Rev Gastroenterol Hepatol 2015;12:98-107
25. Buendgens L, Bruensing J, Matthes M, Duckers H, Luedde T, Trautwein C, Tacke F, Koch A: Administration of proton pump inhibitors in critically ill medical patients is associated with increased risk of developing Clostridium difficile-associated diarrhea. J Crit Care 2014;29:696 e611-695
26. Kamada T, Fusamoto H, Kawano S, Noguchi M, Hiramatsu K, Masuzawa M, Sato N: Acute gastroduodenal lesions in head injury. An endoscopic study. Am J Gastroenterol 1977;68:249-253
27. Krag M, Perner A, Moller MH: Stress ulcer prophylaxis in the intensive care unit. Curr Opin Crit Care 2016;22:186-190
28. Hurt RT, Frazier TH, McClave SA, Crittenden NE, Kulisek C, Saad M, Franklin GA: Stress prophylaxis in intensive care unit patients and the role of enteral nutrition. JPEN J Parenter Enteral Nutr 2012;36:721-731
29. Sim JA, Horowitz M, Summers MJ, Trahair LG, Goud RS, Zaknic AV, Hausken T, Fraser JD, Chapman MJ, Jones KL, Deane AM: Mesenteric blood flow, glucose absorption and blood pressure responses to small intestinal glucose in critically ill patients older than 65 years. Intensive Care Med 2013;39:258-266
30. Plummer MP, Blaser AR, Deane AM: Stress ulceration: prevalence, pathology and association with adverse outcomes. Crit Care 2014;18:213
31. Alshamsi F, Belley-Cote E, Cook D, Almenawer SA, Alqahtani Z, Perri D, Thabane L, Al-Omari A, Lewis K, Guyatt G, Alhazzani W: Efficacy and safety of proton pump inhibitors for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis of randomized trials. Crit Care 2016;20:120
32. Barletta JF, Bruno JJ, Buckley MS, Cook DJ: Stress Ulcer Prophylaxis. Crit Care Med 2016;44:1395-1405

33. Liew VY, Chapman MJ, Nguyen NQ, Cousins CE, Plummer MP, Chapple LA, Abdelhamid YA, Manton ND, Swalling A, Sutton-Smith P, Burt AD, Deane AM: A prospective observational study of the effect of critical illness on ultrastructural and microscopic morphology of duodenal mucosa. *Crit Care Resusc* 2016;18:102-108
34. Mitchell H, Katelaris P: Epidemiology, clinical impacts and current clinical management of *Helicobacter pylori* infection. *The Medical journal of Australia* 2016;204:376-380
35. Roberts SE, Morrison-Rees S, Samuel DG, Thorne K, Akbari A, Williams JG: Review article: the prevalence of *Helicobacter pylori* and the incidence of gastric cancer across Europe. *Alimentary pharmacology & therapeutics* 2016;43:334-345
36. Deane AM, Guyatt GH: Primum non nocere and challenging conventional treatment. *Intensive Care Med* 2015;41:933-935
37. Cook DJ, Griffith LE, Walter SD, Guyatt GH, Meade MO, Heyland DK, Kirby A, Tryba M: The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients. *Crit Care* 2001;5:368-375

Figure 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.

Table 1.

	Rater #1	Rater #2	Inter-rater agreement (%)	Kappa ¹
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%)		

Table 1 Assessment of acid-related pathology and recommended treatment by raters.

¹ Cohen's kappa statistic for inter-rater agreement

Table 2

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 sec	12 (16%)
	Platelet count < 100,000/uL	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 seconds or platelets < 100,000/uL 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.

aas_12844_f1a.tif

aas_12844_f1b.tif

aas_12844_f1c.tif

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Ovenden, C;Plummer, MP;Selvanderan, S;Donaldson, TA;Nguyen, NQ;Weinel, LM;Finnis, ME;Summers, MJ;Abdelhamid, YA;Chapman, MJ;Rayner, CK;Deane, AM

Title:

Occult upper gastrointestinal mucosal abnormalities in critically ill patients

Date:

2017-02-01

Citation:

Ovenden, C., Plummer, M. P., Selvanderan, S., Donaldson, T. A., Nguyen, N. Q., Weinel, L. M., Finnis, M. E., Summers, M. J., Abdelhamid, Y. A., Chapman, M. J., Rayner, C. K. & Deane, A. M. (2017). Occult upper gastrointestinal mucosal abnormalities in critically ill patients. *ACTA ANAESTHESIOLOGICA SCANDINAVICA*, 61 (2), pp.216-223. <https://doi.org/10.1111/aas.12844>.

Persistent Link:

<http://hdl.handle.net/11343/292221>