Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

(7.8%) versus those not using it (6.9%; N Engl J Med 2020;382:1018–1028). Based on the results of this study, there is now 1 more piece of relevant evidence justifying a thorough discussion among experts on the regular use of low-dose aspirin in CHB or CHC patients.

LUCA G. GUIDOTTI
Division of Immunology, Transplantation and Infectious Diseases
IRCCS San Raffaele Scientific Institute
Vita-Salute San Raffaele University
Milan, Italy

CARLO LA VECCHIA
Department of Clinical Sciences and Community Health
University of Milan
Milan, Italy

MASSIMO COLOMBO
Liver Center
IRCCS San Raffaele Hospital
Milan, Italy

Conflicts of interest
The authors have made the following disclosures: Luca G. Guidotti is a member of the Board of Directors for Genenta Science, and Epsilen Bio; a consultant for Gilead Sciences; and a CLV consultant for Teofarma. Massimo Colombo is a member of the speakers bureau for Gilead Sciences, MSD, Roche, Bayer, Intercept, and Wasserman; and a consultant for Target HCC, Exelixis, and Galapagos.

Acute Upper GI Bleeding: Good Night, Sleep Tight, Endoscopy Can Wait until Morning Light

Lau JYW, Yu Y, Tang RSY, et al. Timing of Endoscopy for Acute Upper Gastrointestinal Bleeding. N Engl J Med 2020;382:1299–1308.

Gastrointestinal hemorrhage is the leading cause of hospitalization in gastroenterology (Gastroenterology 2019;156:254–272). Prognostic scoring systems for acute upper GI bleeding (AUGIB), such as the Glasgow-Blatchford score (GBS) or Rockall score, can help to predict which patients require intervention (Lancet 2000;356:1318–1321; Gut 1996;38:316–321). Evidence does not strongly favor 1 particular index, but the GBS has good sensitivity for detecting patients at high risk of rebleeding and death. Nevertheless, mortality in AUGIB remains essentially unchanged over the past 2 decades. Despite advances in endoscopic and pharmacological therapies, case fatality is approximately 5%–10% globally (BMJ 1995;311:222–226). Historically, a major focus to improve outcome has centered on performing timely endoscopy to achieve early hemostatic control.

Three randomized controlled trials investigating the clinical impact of the timing of therapeutic endoscopy yielded somewhat conflicting results, but overall failed to provide a clear evidence that early intervention improves outcomes. Two of the trials, which included low-risk patients assigned to either early (<2 hours) or later (<6 hours) endoscopy, did not demonstrate any difference in mortality (Gastrointest Endosc 2004;60:1–8; Gastrointest Endosc 1999;50:755–761). The third trial, which included a significant proportion of high-risk patients presenting with shock, showed benefit of early endoscopy in patients with bloody aspirate in terms of need for transfusion and length of stay, but found no difference in mortality (J Clin Gastroenterol 1996;22:267–271). However, a nationwide cohort study in high-risk AUGIB patients suggested that early endoscopy performed between 6 and 24 hours has the lowest mortality rate compared with very early (<6 hours) or delayed (>24 hours) endoscopy (Gastrointest Endosc 2017;85:936–944). To date, no prospective trial has examined the effect of endoscopy timing in a cohort of patients presenting with AUGIB and high-risk features for adverse outcome. Lau et al have set out to fill this gap in our knowledge with a well-designed randomized controlled trial.

This trial recruited 516 patients presenting with AUGIB and a GBS of ≥ 12, who were allocated to receive either urgent (<6 hours) or early (6–24 hours) endoscopy. Notably, the trial excluded those patients remaining in refractory shock despite resuscitation (32 of 598 patients with a GBS of ≥ 12), whom were treated with an emergency endoscopy. The primary end point of the study was all-cause mortality within 30 days. Secondary end points included rebleeding, transfusion requirements and length of stay. In this cohort of patients the main cause for bleeding was peptic ulceration, accounting for $>60\%$ of cases, with variceal bleeding representing $<10\%$. Although urgent endoscopy identified more ulcers with active bleeding or visible vessels requiring hemostatic treatment, this difference did not translate into an improvement in mortality or other clinical outcomes. Overall, the present study, therefore, provides much-needed evidence that, in patients who respond to hemodynamic resuscitation urgent endoscopy within 6 hours from presentation does not offer significant benefits over early endoscopy within 24 hours.

Comment. Active bleeding at endoscopy is associated with a poor prognosis in AUGIB, suggesting that successful endoscopic hemostasis might improve clinical outcomes. Systematic reviews have assessed the role of endoscopic therapy in patients with high-risk stigmata of peptic ulcer bleeding (Gastrointest Endosc 2009;69:786–799; Clin Gastroenterol Hepatol 2009;7:33–47). These reviews have necessarily integrated data from individually small and potentially underpowered studies. Meta-analyses demonstrate consistent superiority for endoscopic versus sole pharmacologic therapy in terms of rebleeding. However the impact of endoscopic therapy on mortality is not unequivocally proven, only reaching significance in aggregated analyses of all forms of endoscopic therapy versus various pharmacological therapies (H2 receptor antagonists or proton pump inhibitors [PPIs]). To date there is no randomized controlled evidence that endoscopic therapy is superior to high-dose PPI therapy in preventing death. Nevertheless endoscopic treatment forms the basis of medical management of AUGIB.

In clinical practice, the timing of intervention is often based on the clinical risk features, including hemodynamic instability and hemoglobin levels. Emergency endoscopy has the potential to resolve the bleeding event and allow quicker recovery. However, proceeding to immediate endoscopy raises potential safety concerns, including inadequate resuscitation and the risks of out-of-hours endoscopy when fewer resources and support are available. In addition, many episodes of AUGIB might otherwise resolve with supportive and pharmacologic therapies alone without requiring endoscopic intervention. Until now, the decision-making process regarding endoscopy timing in this high-risk group has lacked robust evidence. In the present study, Lau et al provide a compelling demonstration of the noninferiority of early (6–24 hours) versus urgent (<6 hours) endoscopy. Furthermore, the investigators adopted a pragmatic approach of performing next morning endoscopy in their early arm, which would be readily applicable in most hospital settings. A minor proportion of patients randomized to the early endoscopy arm (20 of 258 patients) developed signs of shock or fresh bleeding that prompted emergency endoscopy within 6 hours. Thus, this group of patients nonetheless requires careful monitoring. However, the outcome of this study raises wider questions regarding AUGIB endoscopic management and our understanding of bleeding-associated mortality.

The results of this trial are particularly timely to the current novel coronavirus disease-2019 (COVID-19) pandemic era, during which endoscopy services have been severely curtailed (Endoscopy 2020;52:483–490). This circumstance has necessitated careful consideration and selection of cases requiring urgent endoscopy, as opposed to conservative management with intravenous PPI and fluid resuscitation. The health consequences of this approach have been retrospectively analyzed in a cohort of patients presenting with GI bleeding at 2 hospitals in New York (Gastroenterology 2020), a city heavily affected by severe acute respiratory disease coronavirus 2. As expected, during COVID the number of admission for upper GI bleeding decreased by nearly 30%. After adjusting for confounding variables, such as COVID-19 diagnosis, admission during the pandemic was associated with an increased length of stay (odds ratio [OR], 2.46; 95% confidence interval [CI], 1.13–5.34) and the probability of having ≥1 blood transfusion (OR, 2.86; 95% CI, 1.25–6.55), but a decreased odds of having an endoscopy (OR, 0.32; 95% CI, 0.15–0.72) compared with admission before the pandemic outbreak. Nevertheless, no change in mortality was observed. Overall, this result indicates that, although endoscopy is an important triaging tool for early discharge, it may not necessarily affect patient outcome.

Consistent with the notion that endoscopic intervention may not always yield substantial mortality benefit, the majority (>80%) of deaths in the context of AUGIB are not related to exsanguination but rather to decompensation of a comorbid illness. Indeed, Sung et al identified multiorgan failure, cardiopulmonary conditions, and terminal malignancy as the most common causes of death from peptic ulcer bleeding (Am J Gastroenterol 2010;105:84–89). Therefore, perhaps not unsurprisingly, age and comorbidity represent the most important independent risk factors for mortality after AUGIB. Of some concern is that, although overall incidence of peptic ulcers has been declining, time trend analyses indicate an increasing incidence amongst the elderly (Eur J Gastroenterol Hepatol 2004;16:177–182). This comorbid population, with concomitant higher rates of aspirin and other nonsteroidal anti-inflammatory drug use, may present an increasing challenge to the satisfactory management and outcome in AUGIB. Mortality among this population may be connected to frailty, a state of increased vulnerability to a noxious insult owing to an age-related, multisystem physiologic decline. Under these circumstances, further reducing AUGIB-associated mortality through endoscopy alone may be impossible. It may instead require pre-event intervention, such as early cancer detection, optimizing treatment of underlying diseases, and decreasing the progression of organ dysfunction.

In the remaining cases for whom AUGIB represents an eminently reversible pathology, the present study provides evidence that urgent endoscopy is unlikely to offer additional benefit over early endoscopy. Optimal management of those patients presenting with refractory shock, and not included in this trial, still needs to be established and merits further investigation. There may be a role for strategies similar to those used for major bleeding after trauma, including restricted volume replacement and permissive hypotension. Nevertheless, for the majority patients, this work prompts consideration of the possibility that endoscopy might be safely further deferred beyond 24 hours, or not required at all, as might become evident in the current COVID-era management approach. To an extent, this practice has already been adopted in the use of ambulatory pathways and facilitated discharge for those patients with a low GBS. However, should this approach be more widely extended after COVID, additional thought may need to be given to the cost implications of potentially longer hospital stays or readmission rates. Future studies addressing all these issues will be important in refining the most efficient use of endoscopy in AUGIB, with important ramifications for service design and out-of-hours provision.

M. ZAEEM CADER
Cambridge Institute of Therapeutic Immunology and Infectious Disease
Jeffrey Cheah Biomedical Centre
University of Cambridge *and*
Division of Gastroenterology and Hepatology
Department of Medicine
University of Cambridge
Addenbrooke's Hospital
Cambridge, UK

MASSIMILIANO DI PIETRO
MRC Cancer Unit
University of Cambridge
Cambridge, UK