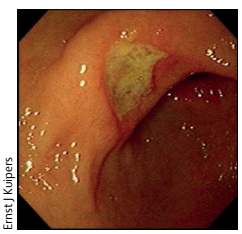
PPIs for prevention and treatment of peptic ulcer



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The incidence and mortality of peptic ulcer rose markedly during the 19th century,[1] peaking in the generation born at the end of the century, and then steadily decreasing. In recent decades, the main ulcer aetiology has shifted in many countries from *Helicobacter pylori* to non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin. Use of other drugs such as steroids, aldosterone antagonists, and selective serotonin reuptake inhibitors can contribute to gastroduodenal ulceration and its complications.[2] This combination of factors explains why upper gastrointestinal bleeding remains the most common gastrointestinal emergency globally. In the USA, gastrointestinal bleeding led to 796 000 emergency department visits and 435 000 admissions in 2012, comprising 20% of gastrointestinal emergency admissions that year.[3] Peptic ulcer is the predominant bleeding source, accounting for around 40% of upper gastrointestinal bleeds. Many occur in elderly people with comorbidity and multidrug use, which, combined with frequent presentation with shock, explains why ulcer bleeding remains associated with a 5–10% mortality despite improvements in management and care.

This situation calls for primary prevention of ulcer formation and ulcer bleeding, improved management of a bleed, and prevention of rebleeding. Many studies have therefore focused on the effect of gastroprotection, in particular by means of proton-pump inhibitors (PPIs) as well as histamine-2 receptor antagonists and prostaglandin analogues. However, the abundance of studies and treatment regimens makes the effects of gastroprotection difficult to quantify.

This challenge underlines the importance of the thorough, high-quality systematic review and meta-analysis[4] of gastroprotectant drug trials published in *The Lancet Gastroenterology & Hepatology*. Benjamin Scally and colleagues analysed 1212 randomised trials of gastroprotectant drugs, including 849 trials of 142 485 participants that compared a gastroprotectant with control. All included trials focused on the effect of gastroprotection on peptic ulcer prevention, ulcer healing, and upper gastrointestinal bleeding. Scally and colleagues report substantial benefits, in particular with PPI treatment, in all three areas. Importantly, these effects were of similar magnitude in NSAID users and non-users, and did not differ between PPIs. PPI treatment was associated with an odds ratio of 0·20 (95% CI 0·17–0·23) for development of an endoscopic ulcer, of 0·21 (0·12–0·36) for an ulcer bleed, and of 5·22 (4·00–6·80) for ulcer healing. The comprehensive analysis also allowed an investigation of the effects of PPIs on further bleeding and complications. PPI treatment significantly reduced the risk of further bleeding, and the need for blood transfusion, endoscopic intervention, and surgery, with ORs ranging between 0·56 and 0·67. Previous individual trials have been unable to show any benefit of gastroprotection on all-cause mortality in bleeding patients, which is confirmed in this systematic review (OR 0·90, 95% CI 0·72–1·11).

Scally and colleagues' findings support guideline recommendations for management of patients with upper gastrointestinal bleeding, including use of intravenous PPIs while awaiting (but not delaying) upper endoscopy, oral or intravenous PPIs immediately after endoscopy, and oral PPI maintenance in patients at high risk for rebleeding.[5–7] Do these findings also provide definite answers to all clinical issues regarding gastroprotectants? The answer is no. Despite the large number of trials, the median number of patients per trial was only 78 (IQR 44·0–210·5) and the median duration only 1·4 months (IQR 0·9–2·8).[4] These small numbers explain why the number of events in subgroup analyses was low for some of the outcomes. These outcomes included rare complications such as complicated ulcer disease in non-NSAID users, but also events such as further bleeding, blood transfusion, and need for endoscopic and surgical intervention when analysed by drug class. The very short, 3-day median duration of the acute upper gastrointestinal bleeding trials probably also influenced the results. Furthermore, the analyses did not allow firm conclusions to be reached on the effect of high-dose PPIs when given orally or intravenously in patients with bleeding ulcers. Although initial studies focused on high-dose continuous intravenous therapy, recent data suggest that intermittent intravenous or frequent oral dosing are similarly effective.[8,9] The latest update of the Asia-Pacific guideline on upper gastrointestinal bleeding concluded that high-dose

oral PPIs (defined as ≥80 mg daily) can be used to prevent rebleeding (unpublished data), albeit with the warning that available studies were relatively small and underpowered. The optimum method of dosing requires further study.

In conclusion, the thorough meta-analysis by Scally and colleagues provides relevant information for many clinicians. It confirms that gastroprotection, in particular by means of PPIs, is associated with a roughly five times reduced risk of ulcer incidence as well as ulcer bleeds when compared with no protection, and a five times improvement in ulcer healing. It also points to areas that require further study, in particular the need to understand whether oral and intravenous PPIs are similarly effective in patients with bleeding ulcers to prevent rebleeding and to reduce the need for intervention including endoscopic treatment, transfusion, surgery, and prolonged admission.

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I declare no competing interests.

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When should feeding begin in patients undergoing colorectal surgery?

Although there have been major improvements in the management of patients undergoing colorectal surgery, particularly with the introduction of enhanced recovery after surgery (ERAS) pathways and laparoscopic surgery, prolonged postoperative ileus remains one of the most common complications experienced by these patients. Well conducted, prospective clinical studies with clear definitions have consistently identified postoperative ileus in more than 20% of patients after colorectal resection.[1,2] The cause of postoperative ileus is multifactorial and includes trauma to both the abdominal wall and the bowel itself, activation of inflammatory pathways, fluid and electrolyte disturbances, and use of medications that alter bowel motility. We desperately need new preventative and therapeutic interventions in this perplexing field.

In a systematic review and meta-analysis[3] of 13 randomised controlled trials with almost 1200 patients, early enteral feeding was compared with standard postoperative feeding in intestinal surgery. A significant reduction in mortality associated with feeding within 24 h of surgery was reported. However, the reductions in pneumonia, anastomotic leakage, and wound infection were not statistically significant. Lubbers and colleagues[4] proposed a possible mechanism whereby early feeding of lipid-rich formula might have an effect on the motility of the intestine via a cholecystokinin-induced indirect stimulation of the vagus nerve. In a single-centre randomised controlled trial of 123 patients with rectal cancer, Boelens and colleagues[5] compared early enteral tube feeding with parenteral nutrition both starting 8 h after completion of surgery. The findings


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