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Proton pump inhibitors for upper gastrointestinal bleeding

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ABSTRACT

Acute upper gastrointestinal bleeding (UGIB) remains a public health burden with a persistent high mortality despite advances in modern day management. Proton pump inhibitors (PPI) as medical therapy is an attractive adjuvant to endoscopic treatment in UGIB but the method and dose of PPI therapy remains controversial. This chapter aims to describe the current evidence addressing acute PPI use in the management of UGIB. It will explore the evidence behind the timing, the dosage and the mode of administration of PPI during initial UGIB management, prior to and immediately following endoscopy, as well as in the short-term following discharge.

Introduction

Acute upper gastrointestinal bleeding (UGIB) remains a common cause of hospitalization with an annual incidence of 78/100′000 population and a reported mortality that decreased in the United States over the last 2 decades from 4.7% to 2.1% [1,2]. UGIB can be categorized into variceal and non-variceal UGIB (NVUGIB) causes, as there are important differences in management strategies. Peptic ulcer (PU) disease remains the most common cause of NVUGIB and hospital admission diagnosis in 2012 among all gastro-intestinal related disorders in the United States [3]. Despite advances in modern day management of UGIB, including optimized use of endoscopic therapy, the morbidity and mortality associated with UGIB remains significant, as does its health economic burden [1,2,4,5]. Medical therapy is an attractive adjuvant to endoscopic treatment in UGIB and acid suppression with the use of high-dose proton pump inhibitors (PPI) remains a cornerstone in the medical management of acute UGIB; the optimal route of administration and dosing however remain controversial [6].

This review summarizes the protective pathophysiological mechanisms and the current evidence pertaining to the efficacy and cost-effectiveness of PPI therapy in the management of UGIB. It will discuss the timing, dosage and the route of administration of PPI during the initial management of UGIB prior and immediately following, as well as in the short-term following discharge.

Proton pump inhibitor and the role of acid suppression

In vitro data have explored the important role of acid in impairing hemostasis and causing clot digestion [7], highlighting the important therapeutic role of acid suppressive drugs in the acute setting of UGIB. Maintenance of a high intragastric pH (above 6.0) during the management of UGIB is indeed warranted, as the ability for platelets to form the primary hemostatic platelet plug is deeply impaired by an acid environment, being reduced by 75% at a pH of 6.8 relative to a pH of 7.4. When the pH falls to 5 or 4, platelets start to disaggregate (Fig. 1). Low pH levels also alter the platelet aggregation response to ADP, collagen and adrenaline by both inhibiting initial platelet aggregation and causing disaggregation [8]. Acid suppression may also be beneficial in preventing fibrinolysis in patients with upper GI bleeding and ensuring the integrity of the mucus/bicarbonate barrier.

For a long time, available agents did not permit such a sustained targeted elevation in gastric pH. It has been postulated that this is why studies using H2-receptor antagonists did not demonstrate significant improvements in important patient outcomes, such as rebleeding, surgery or mortality [8].

Since the approval of omeprazole by the US Food and Drug Administration (FDA) in 1991, PPI have been extensively used to treat a variety of conditions in the upper gastrointestinal tract, including peptic ulcer bleeding as they are capable of producing profound acid suppression in the stomach. Due to their generic

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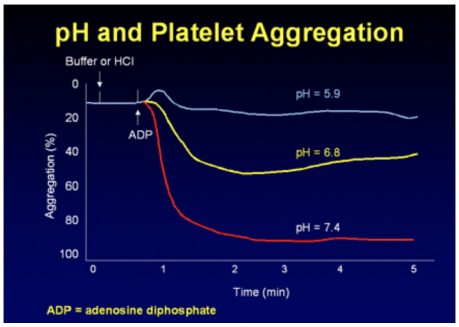

Fig. 1. pH and Platelet aggregation (adapted from Ref. [9]).

mechanism of action, their use was extended to include all non-variceal causes of UGIB [10,11]. All currently approved PPI are benzimidazole derivatives, heterocyclic organic molecules that include both a pyridine and benzimidazole moiety linked by a methylsulfinyl group(12).

They are specifically designed to interact with the proton pump of gastric parietal cells to induce profound and sustained acid inhibition. Dexlansoprazole, esomeprazole, omeprazole, lansoprazole, rabeprazole and pantoprazole are the most commonly available worldwide as oral preparations; omeprazole, esomeprazole and pantoprazole are also available in i.v. form(12) (Table 1).

PPI interact by covalent binding with the proton pump of the parietal cell, thereby causing an irreversible inhibition of acid secretion. Consequently, only a *de novo* synthesis of proton pumps will enable the parietal cell to further produce acid [8]. Theoretically, maximal acid inhibition should be obtained with a proton pump inhibitor if a significant amount of drug is available at the precise moment the parietal cells become activated. Rationally, this is obtainable by continuous, not intermittent, i.v. administration of a PPI. However, the mode of administration has been recently challenged by the publication of a meta-analysis supporting the non-inferiority of intermittent (oral or iv) vs continuous iv PPI administration with regards to rebleeding rate and mortality [13]. Eventually, the rationale behind acid-suppressive therapy in UGIB is to rapidly increase the intragastric pH above 6.0 and so maintain it for 3–4 days. Although every PPI has different substitutions on the pyridine and/or benzimidazole rings, in general they are all remarkably similar in their pharmacological properties. Besides, head-to-head data are few and taken overall do not suggest significant differences(10). Therefore, any benefit of the PPI is assumed to be a class effect in the setting of UGIB.

PPI therapy prior endoscopy

Current evidence

The guidance on whether to administer PPI therapy prior to endoscopy is conflicting. In 2007, a randomized trial (n = 638 patients) by Lau et al. reported the benefit of a high-dose bolus followed by continuous infusion of omeprazole before patients underwent endoscopy. The mean (±SD) duration of infusion before endoscopy was 14.7 ± 6.3 h in the omeprazole group and 15.2 ± 6.2 h in the placebo group. Endoscopic treatment was required in 19.1% of patients who received omeprazole compared to 28.4% of patients who received placebo (P = .007). Similarly, among patients with peptic ulcer disease, active bleeding was significantly less common in patients who received omeprazole (6.4% vs 14.7%; P = .01), and clean-based ulcers were found more often (64.2% vs 47.4%; P = .001) [14]. Notably, rebleeding rate and mortality within 30 days were not reduced in patients receiving omeprazole (11% vs 8%, p = .49 and 8% vs 7% p = .78, respectively). A subsequent Cochrane meta-analysis of 6 randomized trials (n = 2223 patients) evaluating the use of a PPI before endoscopic evaluation also found that PPI therapy prior to endoscopy (using different doses and varying routes of administration) did not significantly reduce mortality (odds ratio [OR] = 1.12; 95% CI, 0.72–1.73), rebleeding (OR = 0.81; 95% CI, 0.61–1.09), or the requirement for surgery (OR = 0.96; 95% CI, 0.68–1.35) [15]. There was only a significantly lower proportion of peptic ulcers with high-risk stigmata at endoscopy (OR = 0.67; 95% CI, 0.54–0.84) and significantly lower rates of endoscopic treatment performed (OR = 0.68; 95% CI, 0.50–0.93).

Given these data and along with the favorable risk profile of early PPI use, the 2012 American college of Gastroenterology (ACG) guidelines and the 2015 European Society of Gastrointestinal Endoscopy (ESGE) guidelines recommend the use of PPI prior endoscopy in order to decrease the proportion of patients with ulcers with high-risk stigmata and the requirement for endoscopic treatment(16, 17). In contradistinction, as PPI use prior endoscopy does not affect rates of rebleeding, surgery, or mortality NICE recommendations in UK did not recommend routine PPI administration prior to endoscopy(18). Likewise, the 2018 Asia-Pacific working group consensus on NVUGIB PPI rejects indiscriminate use of iv PPI in stable patients with suspected NVUIGB prior to endoscopy as there is no proven value(19).

Route of administration

Several trials of repeated bolus administration have demonstrated that an initial loading dose of 80 mg omeprazole or pantoprazole is preferable to 40 mg in achieving fast and sustained increases in intragastric pH, without additional influence if using a larger loading dose [8].

Intravenous administration prior endoscopy seemed legitimate as the aim of acid-suppressive therapy in UGIB is to rapidly increase the intragastric pH above 6.0 and people are often fasting awaiting upper endoscopy. Despite their high bioavailability, iv PPI route should be then preferred, where indication before endoscopy is appropriate. The 2012 ACG guidelines and the 2015 ESG guidelines for NVUGIB recommend the iv route of PPI administration with 80 mg bolus following by a continuous perfusion (8 mg/h) while awaiting an early endoscopy, based on the best evidence [16,17].

Table 1
Pharmacological difference between different proton pump inhibitors (PPI) [12]

PPI	Equivalent oral dose	Routes of administration	Time to peak plasma level (tmax, hr)	Bioavailability (%)
Omeprazole	20 mg	oral/IV/DR	0.5–3.5	30–40
Esomeprazole	20 mg	oral/IV/DR	1.5	64–90
Pantoprazole	40 mg	oral/IV/DR	2–3	77
Lansoprazole	30 mg	oral/DR	1.7	80–85
Dexlansoprazole MR	30 mg	oral/DR	1-2; 4-5	na
Rabeprazole	20 mg	oral/DR	12.1	52

IV: intravenously; DR: delayed release; MR = produces two distinct releases of drug, na = not available.

Cost-effectiveness consideration of PPI use prior to endoscopy

Cost-effectiveness analyses of PPI therapy prior endoscopy have shown mixed results.

Cost-effectiveness considerations are important because most of randomized trials assessing PPI prior endoscopy found no statistically significant between-group differences in rebleeding, surgery, or mortality rates. Tsoi et al. provided an important economic analysis on the use of PPI while awaiting an early endoscopy [20]. Overall, 631 patients were recruited, and 377 were eventually found to be bleeding from ulcers. Among these, 60 (19.1%) patients in the PPI and 90 (28.4%) patients in the placebo group required endoscopic hemostasis at the time of gastroscopy (performed on average 14–15 h after the onset of PPI administration). Authors tabulated direct costs and overall average per patient costs were U.S. $2813 for the intravenous PPI (80 mg bolus followed by 8 mg/h infusion till the endoscopy), and U.S. $2948 in the placebo group. PPI administration also reduced endoscopic therapy by 7.4% and was thus both less costly and more effective than placebo, making it a dominant strategy in economic terms.

However, the conclusions of an economic analysis can vary according to the choice of unit of effectiveness or utility that in turn usually reflects a clinically meaningful outcome. Another economic analysis assessing the cost-effectiveness of using PPI prior to endoscopy concluded this strategy was slightly more effective and costlier than no administration(21). In a Canadian economic environment, this approach becomes dominant as the duration of hospitalization for high-risk ulcer patients increases or that of low-risk ulcer patients decreases(21). This economic analysis also suggested that PPI use pre-endoscopy is most cost-effective if endoscopy is to be delayed for more than 16 h or in patients most likely to be bleeding from a non-variceal UGIB cause, or a source likely to be exhibiting a high-risk lesion [21].

Pragmatically, if endoscopic evaluation has to be delayed or cannot be performed, PPI therapy should be continued to reduce the risk of further bleeding. A Cochrane meta-analysis of randomized trials (n = 4373 patients) of patients with UGIB who did not consistently receive endoscopic hemostatic therapy reported that PPI therapy was associated with reduced rebleeding (OR = 0.38; 95% CI, 0.18–0.81) and surgery (OR = 0.62; 95%, CI 0.44–0.88), but not mortality [22]. This suggests that if endoscopy will be delayed or cannot be performed, PPI therapy may improve clinical outcomes. Therefore, the above-mentioned observed lesion downstaging attributable to PPI therapy prior endoscopy may be even more beneficial in situations in which early endoscopy may be delayed or when available endoscopic expertise may be suboptimal.

Additional data that are required to better determine the cost-effectiveness of indiscriminate PPI administration before endoscopy including the relationship between duration of PPI administration before endoscopy and subsequent endoscopic severity of the lesion (Forrest class), the effects of differing drug doses, regimens, and the determination of any possible effect of PPI on patients bleeding from non-ulcer lesions [21,23]. Efforts should be made to better identify subgroups of patients or situations in which this use will be more likely to be cost-effective.

Practice points

PPI prior endoscopy

- PPI started prior to endoscopy only decrease the proportion of patients with high-risk stigmata ulcers and the requirement for endoscopic treatment but do not affect rebleeding or mortality
- If endoscopic evaluation has to be delayed or cannot be performed, PPI therapy should be started and continued to reduce the risk of further bleeding.
- When PPI are considered, the high dose iv (80 mg) followed by 8 mg/h should be the preferred regimen
- Additional data are required to better determine the efficacy and cost-effectiveness of PPI prior to endoscopy and the subgroup of patients more likely to benefit from such an approach

PPI therapy after endoscopy

Current evidence in non-variceal bleeding

It is important to contrast the pre-endoscopy from post-endoscopic hemostasis uses of PPI in patients with high risk stigmata bleeding ulcers. The use of intravenous high-dose PPI has become standard practice in the management of ulcer UGIB as it is effective and less costly in most settings [10,16,17,19,24]. As mentioned above, increased gastric pH has been linked with improved clot stability. A landmark placebo-controlled randomized trial from Hong Kong showed that the administration of continuous omeprazole infusion (80 mg intravenous bolus followed by 8 mg/h for 72 h) after endoscopic therapy for bleeding peptic ulcers was superior to placebo in reducing recurrent bleeding, transfusion requirements and hospital stay [25]. Subsequently, a meta-analysis of randomized trials of intravenous PPI therapy (80 mg bolus followed by 8 mg/h continuous infusion) vs. placebo/no treatment for 72 h after endoscopic therapy of high-risk stigmata revealed a significant reduction in further bleeding (RR = 0.40; 95% CI 0.28–0.59), surgery (RR = 0.43; 95% CI 0.24–0.76), and mortality (RR = 0.41; 95% CI 0.20–0.84) [26]. The improvement in mortality was specifically in patients having first undergone successful endoscopic hemostasis. Those authoritative data have been replicated in other meta-analysis [24,27] and unanimously incorporated into guidelines addressing the post-endoscopic management of NVUIGB [10,16,17].

Notably, in a large randomized trial of bolus followed by continuous infusion PPI vs. placebo after successful endoscopic hemostasis, subgroup analysis of patients with oozing bleeding showed a very low rebleeding rate with placebo (8/163 (4.9%)). The results of this subgroup analysis suggest that intensive PPI therapy may not be needed for a subgroup of lesions exhibiting oozing without other stigmata of recent hemorrhage [28], and that the Forrest classification of Ia lesions may need revisiting.

Route of administration

It is recommended that after endoscopy, the route of administration and PPI dosing should be tailored to the identified source of bleeding(10).

Low risk stigmata

Hemodynamically stable patients without serious comorbid conditions who exhibit low-risk endoscopic lesions and therefore do not require endoscopic hemostasis (e.g., clean-based, flat, pigmented spots) can be discharged on a once-daily oral PPI (40 mg) [10,16]. Indeed, once-daily PPI therapy has demonstrated effective ulcer healing for patients with peptic ulcer disease in short term use [29]. Recommendations on duration of treatment remain disparate, varying between 4 and 8 weeks, depending on the cause of bleeding: 4 weeks for duodenal ulcer and 8 weeks for gastric ulcer or until endoscopic reassessment [10,16]. These recommendations are based on expert opinion, as only one trial has studied different regimens and duration of treatment, finding that twice-daily oral dosing for the first 11 days may be preferable in patients at high risk of rebleeding. In this trial, patients with a Rockall

score ≥6 who were given a twice−daily oral PPI had a lower rebleeding rate than those who received a once-daily oral PPI (11 versus 29% at 28 days) [30].

High risk stigmata

Conversely, patients with evidence of high-risk stigmata after successful endoscopic hemostasis benefit from a higher-dosing of PPI therapy for 72 h but the optimal regimen remains controversial [10,16,17]. Based upon previously published metanalyses, evidence-based guidelines on NVUGIB have recommended that PPI therapy be given as an 80 mg intravenous bolus followed by 8 mg/h continuous infusion for 72 h to reduce rebleeding, surgery, and mortality in patients with high risk ulcers that had undergone successful endoscopic hemostasis [10,16,17]. In comparison to H(2)-receptor antagonist or placebo, the benefits of PPI seem to persist regardless of the route of administration (iv or oral) and the dose (high dose, defined as 80 mg bolus followed by 8 mg/h for 72 h, or lower dose) [24].

More recently, high-dose infusion of PPI (80 mg iv bolus following by a continuous perfusion (8 mg/h) for 72 h has been challenged by meta-analyses [13,31−33]. Indeed, these have suggested non-inferiority in rebleeding risk and other clinical outcomes including the need for blood transfusion, surgery, length of hospital stay and mortality, when comparing continuous vs intermittent IV doses [13,31−33]. These results however are hampered by poor methodological quality in the intermittent bolus studies and a confusion in concluding equivalence when only non-inferiority can be surmised [34].

Furthermore, additional data have suggested that a high dose oral PPI regimen (40 mg every 12 h for 3 days) are non-inferior in preventing recurrent bleeding from peptic ulcers when comparted to iv regimens [13,31−33,35]. Generalizability of those results coming mainly from Asian studies are however limited due to differences in underlying bleeding etiologies, genetic cytochrome polymorphisms in the metabolism of PP, and the higher prevalence of *H.pylori* in Asian populations. Additionally, most of the included trials informing these meta-analyses were relatively small and rates of rebleeding were overall low (3−14%).

There is no formal consensus regarding the different PPI regimens according to international recommendations that favour high-dose PPI infusion post-endoscopic therapy. For patients who receive endoscopic hemostasis and for patients with an adherent clot not receiving endoscopic hemostasis, the 2015 ESGE guidelines suggest considering PPI therapy as intermittent intravenous bolus dosing (at least twice-daily) for the 72 h following endoscopy. If the patient's condition permits, high dose oral PPI may also be an option in those able to tolerate oral medications(16). The NICE guidelines recommend routine administration of PPI to patients with NVUGIB and stigmata of recent hemorrhage shown at endoscopy, but do not specify the route, dosage or duration of administration [18]. The recent 2018 Asia-Pacific working group consensus on NVUGIB have included intermittent high-dose oral PPI for 3 days following endoscopic therapy as an approach to prevent rebleeding [19].

Even if the intermittent regimen warrants further investigation before becoming treatment of choice, future guidelines should be clearer as to the possible recommended use of high dose PPI infusion versus bolus IV dosing, and the possible more widespread adoption of high dose oral PPIs, although the highest-quality data remain those favoring the PPI high-dose IV infusion (8 mg/h for 72 h).

Cost-effectiveness considerations addressing PPI use after endoscopic hemostasis

In patients with UGIB who have undergone successful endoscopic hemostasis, classical administration of high-dose intravenous PPI therapy for 3 days has proven to be both more effective and less costly than not doing so, as demonstrated by numerous economic analyses [36−38]. PPI treatment initiated after endoscopy is cost-effective as it significantly reduces the incidence of re-bleeding and the need for surgery compared with placebo or other antacid drugs [27]. High-dose intravenous PPI therapy is a dominant strategy mainly because the cost of the medications is relatively lower than the incremental expenses of one additional rebleeding episode. Cost analyses should be repeated if additional high-quality data become available on oral PPI use after UGIB. Indeed, the administration of intravenous PPI requires nursing supervision leading to high costs, while oral administration is attractive due to widespread availability, ease of implementation and economical [31].

Based on the results of an economic model, the strategy of administering oral PPI both before and after endoscopy with endoscopic therapy in NVUIGB would likely to be the most cost-effective but warrants further investigations [27]. A significant consideration in such economic suppositions needs however to be the non-evidence based and questionable safety of premature discharge from hospital before the usual 72-h post-endoscopy period that represents the conventional highest risk period for ulcer rebleeding following endoscopic hemostasis.

Current evidence in variceal bleeding

The best available evidence supports the use of short-course oral once-daily dose PPI for 10 days post-endoscopic variceal ligation to reduce ulcer size if ulcer healing is a concern as a complication of sclerotherapy or variceal ligation [39].Practices such as high-dose infusion and prolonged use should be discouraged unless evidence of such additional attributable benefits becomes available [39,40].

Practice points

- Authoritative guidelines support use of high dose PPI for 3 days after successful endoscopic hemostasis for NVUGIB, in particular high risk peptic ulcer bleeding
- Additional data are required to prove non-inferiority, let alone equivalence of intermittent (oral/iv) dosing in comparison to continuous infusion of PPI
- PPI after endoscopy in NVUGIB is a dominant strategy in economic terms, i.e.: more efficacious and less costly
- In variceal UGIB, only a short 10-day course of a once-daily oral PPI following endoscopic banding may be reasonable

Concerns associated with PPI use

Safety concern

In a recent systematic review, Vaezi et al. summarize the evidence for the various proposed complications of PPI therapy [41]. The authors found moderate strength of evidence to suggest that PPI use may be associated with bacterial enteric infections, including *Clostridium difficile* [42]. However, the remaining associations, including myocardial infarction, hepatic encephalopathy, hospital-acquired pneumonia and spontaneous bacterial peritonitis were weak and were most likely explained by residual confounding due to study design limitations. These data are supported, with regards to short-term PPI use, by a recent randomized trial addressing the value of PPI prophylaxis for gastrointestinal bleeding in the ICU [43]. In this study comparing pantoprazole vs placebo, no difference was found in the new-onset rate of adverse events (pneumonia or *Clostridium difficile*) but the follow-up was

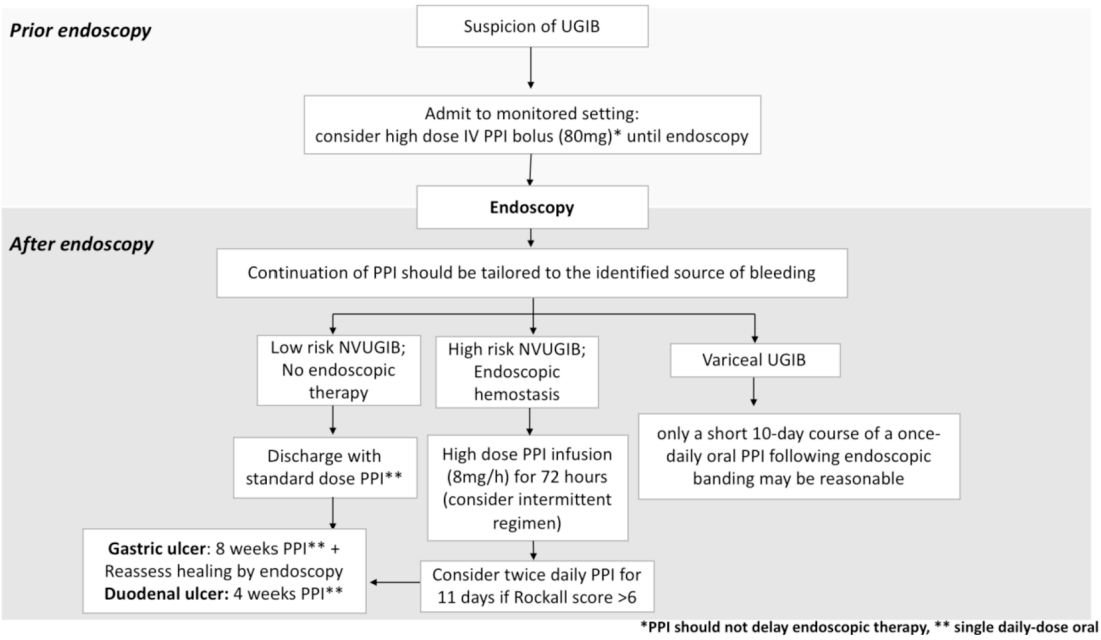

Fig. 2. Algorithm: Therapeutic management of UGIB with PPI.

only 90 days [43]. Eventually, these drugs seem generally safe with a favorable risk-benefit profile, assuming they are being given for an appropriate indication.

Cost concern

In addition to safety concerns, inappropriate overuse of PPI also has economic repercussions. In USA, the annual cost was $ 14 billion and $ 24 billion worldwide [44]. In the state of New Jersey, the additional cost due to inappropriate PPI prescribing at one of their institutions in 2014 was estimated at approximately $ 1 million [45]. Inappropriate use of PPI is still common even as iv administration [46]. The main reasons for this overuse of PPI are the prevention of gastro-duodenal ulcers in low-risk patients or, arguably perhaps in stress ulcer prophylaxis [47]. Anemia with no evidence of digestive bleeding was also identified as an important inappropriate indication [48]. Reducing inappropriate PPI use has become a priority and is one of the privileged themes of the *Choosing Wisely* campaign across the world that seeks to help physicians and patients engaging in conversations about unnecessary tests, treatments and procedures [49]. A PPI deprescribing tool uploaded into an electronic medical record of a Canadian Hospital has been studied as a reminder to guide reassessment and deprescribing. This tool permitted to reassess 93% of PPI prescription, resulting in 26% of patients having their PPI safely and successfully deprescribed [50].

Conclusion

Adherence to evidence-based practice and ensuring robust quality assurance of UGIB management are crucial for optimizing patient outcomes (Fig. 2). Clear guidelines for adequate PPI use in order to standardize best practices are urgenty required. Although high-dose PPI after endoscopy is unanimously incorporated into guidelines for management of NVUGIB, many gaps persist in our knowledge of best practice for PPI use prior endoscopy and to determine the optimal dosing regimen once the iv regimen is completed.

We should focus our efforts atbetter identifying subgroups of patients or situations in which this use will be more likely to be cost-effective so that authoritative recommendations can be confidently issued, based on best evidence.

Research agenda

- Cost effectiveness analysis for PPI use prior endoscopy and better identify who can benefit
- Additional trials to assess whether intermittent regimens are equivalent to continuous iv PPI use
- To determine the optimal dosing regimen once the iv PPI regimen is completed in patients with acute NVUGIB undergoing successful hemostasis

Conflicts of interest

None.

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