Clinical Practice Guideline For the Endoscopic Management of Non-variceal Non-peptic Ulcer Upper Gastrointestinal Bleeding

Authors

Alan N Barkun[1], Loren Laine[2], Grigorios I Leontiadis[3], Ian M Gralnek[4,5], Nicholas Carman[6], Mostafa Ibrahim[7], Michael Sey[8,9], Ali A Alali[10,11], Matthew W Carroll[12], Lawrence Hookey[13], Mark Borgaonkar[14], David Armstrong[3], James YW Lau[15], Nauzer Forbes[16], Rapat Pittayanon[17], Frances Tse[3]

Affiliations

1. Division of Gastroenterology and Hepatology, McGill University Health Centre, McGill University, Montreal, Quebec, Canada.
2. Section of Digestive Diseases, Yale School of Medicine, New Haven, Connecticut; Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut.
3. Department of Medicine and Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, Ontario, Canada.
4. Institute of Gastroenterology and Hepatology, Emek Medical Center, Afula, Israel.
5. Rappaport Family Faculty of Medicine, Technion Israel Institute of Technology, Haifa, Israel.
6. SickKids Inflammatory Bowel Disease Centre, Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children (SickKids), Toronto, ON, Canada.
7. Department of Gastroenterology and Hepatology, Theodor Bilharz Research Institute, Cairo, Egypt.
8. Lawson Health Research Institute, London Health Sciences Centre, London, ON, Canada.
9. Division of Gastroenterology, Western University, London, ON, Canada.
10. Department of Medicine, Faculty of Medicine, Kuwait University, Jabriya, Kuwait.
11. Thunayan Alghanim Gastroenterology Center, Amiri Hospital, Sharq, Kuwait.

12. Division of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada.
13. Division of Gastroenterology, Department of Medicine, Queen's University, Kingston, Ontario, Canada.
14. Department of Medicine, Memorial University, St Johns, Newfoundland, Canada.
15. Surgery, The Chinese University of Hong Kong, New Territories, Hong Kong.
16. Medicine, University of Calgary, Calgary, Canada.
17. Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

Correspondence

Frances Tse, MD, MPH, FRCPC, AGAF, CAGF
Methods Co-Chair, non-variceal non-peptic ulcer upper gastrointestinal bleeding clinical practice guideline
Professor of Medicine
McMaster University, Department of Medicine, Division of Gastroenterology
Farncombe Family Digestive Health Research Institute
Hamilton Health Sciences Centre
1280 Main St. West
Suite 2F53, Hamilton, Ontario, Canada, L8S4K1
Phone: 905 521-2100
Email: tsef@mcmaster.ca

Alan N Barkun, MD, CM, FRCPC, FACP, FACG, AGAF, MSc (Clinical Epidemiology)
Clinical Co-Chair, non-variceal non-peptic ulcer upper gastrointestinal bleeding clinical practice guideline
Professor of Medicine
Douglas G. Kinnear Chair in Gastroenterology
McGill University and the McGill University Health Centre
1650 Cedar Avenue
D7.346, Montreal, Quebec, Canada, H3G 1A4
Phone: 514 934-8233
Email: alan.barkun@muhc.mcgill.ca

Guideline funding

The Canadian Association of Gastroenterology (CAG), a non-profit medical specialty society representing gastroenterologists, entirely funded the development of these guidelines. CAG staff facilitated panel appointments and coordinated meetings but had no role in selecting guideline questions or formulating recommendations. The panellists volunteered their expertise without receiving any payments, and the methodologists received funding support from the CAG.

Conflict of interest (COI) statement

The conflicts of interest (COI) of all participants were managed according to the CAG policies (https://www.cag-acg.org/_Library/clinical_cpgs_position_papers/CAG_Conflict_of_Interest_Policy_Nov17_2019.pdf), which are based on the recommendations of the Institute of Medicine (now the National Academy of Medicine)[1] and the Guidelines International Network.[2] Detailed COI management methods are in *Appendix 1*.

Author contributions to the manuscript

The steering committee (AB, LL, GL, FT) drafted the PICO questions, which were reviewed and approved by all panel members. Methodologists performed evidence synthesis, assessed the certainty of evidence, developed evidence profiles and evidence-to-decision frameworks, and facilitated panel discussions. Panelists formulated the recommendations. The steering committee prepared the initial manuscript, which was later revised with input from all panel members. Additionally, two patients with a history of gastrointestinal bleeding reviewed the PICO questions and provided feedback on the final manuscript.

Abbreviations

AE = adverse effects

APC = argon plasma coagulation

ARR = absolute risk reduction

CI = confidence interval

COI = conflict of interest

DEP = Doppler endoscopic probe

DL = Dieulafoy's lesion

EBL = endoscopic band ligation

ECOG = Eastern Cooperative Oncology Group

EtD = Evidence to Decision framework

GAVE = gastric antral vascular ectasia

GI = gastrointestinal

GIN = Guideline International Network

HR = hazard ratio

MD = mean difference

MWT = Mallory-Weiss Tear

NVNPUB = non-variceal non-peptic ulcer bleeding

PICO = patient population, intervention, comparator, outcome

PPI = proton pump inhibitor

RCT = randomized controlled trial

RFA = radiofrequency ablation

RR = risk ratio

UGI = upper gastrointestinal

UGIB = upper gastrointestinal bleeding

THA = topical hemostatic agents

TTSC = through-the-scope clip

VG = visually guided

ABSTRACT

Background: Non-variceal, non-peptic ulcer bleeding (NVNPUB), arising from etiologies such as malignant tumours, Mallory-Weiss tears (MWT), Dieulafoy's lesions (DL), and gastric antral vascular ectasia (GAVE), constitutes a significant and increasing proportion of UGIB cases.

Objective: These evidence-based guidelines, developed by the Canadian Association of Gastroenterology (CAG) with international collaboration, are the first to specifically address the endoscopic management of these conditions, aiming to support patients, clinicians and others in making informed decisions.

Methods: CAG formed a guideline panel with a balanced representation to minimize potential bias from conflicts of interest. The Cochrane Gut Group supported the guideline-development process, including conducting literature searches and performing systematic reviews. The panel prioritized clinical questions and outcomes according to their importance for clinicians and adult patients. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used, including developing GRADE Evidence-to-Decision frameworks, which underwent public comment.

Results: The panel formulated 19 conditional recommendations for adult patients with NVNPUB due to malignant tumours, MWT, DL, and GAVE.

Conclusions: For patients with active bleeding from malignant tumours, the panel suggested topical hemostatic agents over conventional endoscopic hemostatic therapy; it also suggested the administration of oncologic therapy following the endoscopic intervention. In patients with active bleeding from MWT (oozing and spurting), the panel suggested endoscopic band ligation (EBL) or endoscopic through-the-scope clip (TTSC) over epinephrine injection alone. For non-bleeding MWT with visible vessels, adherent clots, flat pigmented spots, or clean-based ulcers, the panel suggested against endoscopic hemostatic therapy. For DL, the panel suggested mechanical modalities with EBL or TTSC, contact thermocoagulation, or injection of sclerosants over epinephrine injection alone. For patients with GAVE, the panel suggested EBL over argon plasma coagulation.

KEYWORDS

gastrointestinal neoplasms; Mallory-Weiss syndrome; Dieulafoy's lesions; gastric antral vascular ectasia; gastrointestinal hemorrhage; practice guidelines; GRADE

Summary of recommendations

Background

Upper gastrointestinal bleeding (UGIB) accounts for over 300,000 hospital admissions annually in the United States (US).[3] While peptic ulcer disease causes 30-50% of UGIB cases, there has been a notable rise in non-variceal non-peptic ulcer bleeding (NVNPUB), accounting for more than one-third to two-thirds of UGIB cases and, sometimes surpassing peptic ulcer bleeding (PUB).[4-9] NVNPUB can result from various causes, including malignant tumours, Mallory-Weiss tears (MWT), Dieulafoy's lesions (DL), gastric antral vascular ectasia (GAVE), esophagitis, gastritis, duodenitis, and other vascular lesions. Recent US data indicates a 30% decrease in hospitalizations for PUB, while hospitalizations for malignancy, DL and angiodysplasia increased by 50%, 33%, and 32%, respectively.[9]

Endoscopic hemostatic interventions play a crucial role in managing NVNPUB. Most previous guidelines on non-variceal UGIB primarily focused on PUB, often overlooking or grouping other causes with peptic ulcers.[10-14] This guideline is the first to specifically address endoscopic management of NVNPUB, providing healthcare professionals with evidence-based strategies that address the distinct challenges posed by NVNPUB. This guideline was based on original systematic reviews of evidence and was conducted under the auspices of the Canadian Association of Gastroenterology (CAG) with international collaborators. The panel followed best practices for guideline development recommended by the Institute of Medicine (IOM) and the Guidelines International Network (GIN).[2, 15-17] The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of the evidence and formulate recommendations.[18-24]

Interpretation of strong and conditional recommendations

The strength of a recommendation is categorized as either strong, indicated by the phrase "the guideline panel recommends…", or conditional, indicated by "the guideline panel suggests…". Table 1 provides GRADE's interpretation of strong and conditional recommendations by patients, clinicians, healthcare policymakers, and researchers.

Recommendations

The list of recommendations is provided in Table 2.

Values and preferences

The guideline panel rated further bleeding as critical for decision-making regarding malignant UGIB, MWT, and DL. This composite outcome includes the failure to achieve immediate hemostasis and any rebleeding. For GAVE, the panel rated the number of units of blood transfusions needed and changes in hemoglobin levels as critical for decision-making, as this condition typically results in anemia related to chronic blood loss rather than acute bleeding. These outcomes are highly valued, and a strong emphasis is placed on interventions that can effectively address them.

Explanations and other considerations

These recommendations also consider cost and cost-effectiveness, impact on health equity, acceptability, and feasibility.

Introduction

Aim of this guideline and specific objectives

This guideline aims to provide evidence-based recommendations for the endoscopic management of adults with non-variceal, non-peptic ulcer upper gastrointestinal bleeding (NVNPUB), with a focus on malignant upper gastrointestinal bleeding (UGIB), Mallory-Weiss tears (MWT), Dieulafoy's lesions (DL), and gastric antral vascular ectasia (GAVE). Other causes of NVNPUB have been excluded from this iteration. The target audience includes healthcare providers managing UGIB, patients, and decision-makers. Policymakers involved in developing local, national, or international programs for optimizing the management of NVNPUB will also find these guidelines valuable. This document can also serve as a basis for adaptation by local, regional, or national guideline panels.

Description of the health problem(s)

Malignant upper gastrointestinal bleeding (UGIB) is associated with high morbidity and mortality.[5, 25, 26] It can arise from primary tumours, locally invasive tumours from adjacent structures, or metastases. GI malignancies account for up to 5% of UGIB cases, with gastric cancer being the most common.[27-29]

Bleeding can vary from occult to overt and may be the first sign of a malignancy.[27, 28] Unfortunately, by the time bleeding is evident, metastatic disease is often already present, which significantly limits treatment options.[27, 28, 30] Endoscopic treatment presents unique challenges due to factors such as tumour friability and diffuse bleeding that lack a clear therapeutic target. Additionally, the patient's overall health status is often complicated by multiple comorbidities. These factors make achieving effective and sustained hemostasis particularly challenging.

Mallory-Weiss tears (MWT), often caused by forceful retching or vomiting, account for approximately 5-15% of UGIB cases.[31, 32] While most bleeding from MWTs resolves spontaneously with a relatively low death rate of 1-3%, certain factors such as active bleeding, advanced age, and significant comorbidities can increase mortality risk. [5, 9, 33] Given the differences in the pathophysiology, clinical presentation, and disease course from peptic ulcer bleeding, a systematic assessment of endoscopic management strategies for MWTs is crucial to optimize patient outcomes and avoid unnecessary or potentially harmful interventions.

Dieulafoy's lesion (DL) is characterized by an abnormally large submucosal artery eroding through a small mucosal defect.[34] While most commonly located in the proximal stomach, DL can also occur anywhere in the GI tract.[35, 36] Despite accounting for only 1-2% of UGIB cases, DL is likely under-recognized due to its small size, subtle appearance, and intermittent bleeding.[37, 38] Nevertheless, it can cause significant and recurrent bleeding, posing serious risks of morbidity, prolonged hospitalization, and mortality if not promptly treated.[38] Mortality rates have decreased from 80% to 4-10% in recent years, likely due to advances in endoscopic management and reduced need for surgical intervention.[36, 39, 40] Given the severity and high rebleeding risks associated with DL, the option of no endoscopic therapy was not considered by the guideline panel.

Gastric antral vascular ectasia (GAVE) is characterized by vascular dilation in the muscularis mucosa, predominantly in the antrum with a striped pattern, but it can also appear in other parts of the stomach with nodular or diffuse punctate patterns.[41] GAVE accounts for about 4% of non-variceal UGIB cases and 6% of GIB in patients with cirrhosis.[42-44] Clinical presentations range from occult to overt bleeding, with up to 60% of patients remaining transfusion-dependent.[45, 46] This condition is associated with various conditions, including liver disease and portal hypertension, chronic kidney disease, and connective tissue disorders.[42, 43] Despite its impact, large population-based epidemiological studies are lacking, and its

prevalence remains unknown. A screening study in cirrhotic patients estimated a prevalence of 12%.[47] Furthermore, misdiagnosis of GAVE as portal hypertensive gastropathy, gastritis, or other conditions is common.[48, 49] In the US, hospitalizations for GAVE have increased by 75% over 11 years, particularly in cases without active bleeding, significantly raising healthcare costs.[42]

Methods

The guideline panel developed and graded the recommendations and assessed the certainty of the evidence following the GRADE approach.[22, 50] The overall guideline-development process, including funding, panel formation, management of conflicts of interest, internal and external review, and organizational approval, was guided by CAG policies and procedures derived from the GIN-McMaster Guideline Development Checklist and was intended to meet recommendations for trustworthy guidelines by IOM and the GIN.[2, 15-17]

Organization, Panel Composition, Planning and Coordination

The CAG coordinated the work of this panel, with project oversight managed by a steering committee (AB, LL, GL, FT) reporting to the CAG Guideline Committee. The CAG was also responsible for selecting and appointing members to the guideline panel and vetting and retaining methodologists (FT, NF, MC, NC) to conduct systematic reviews and coordinate the guideline development process using the GRADE approach. Details on panel membership are provided in *Appendix 1*.

The international panel included gastroenterologists and a surgeon with clinical and research expertise on the guideline topic from Canada, the United States (US), Hong Kong, Thailand, Israel, Egypt and Kuwait. It also included methodologists with expertise in evidence appraisal and guideline development. One of the panel co-chairs (AB) was a content expert, while the other (FT) was an expert in guideline-development methodology. The panel also incorporated input from two patient representatives who reviewed and provided feedback on the PICO questions and the recommendations. The panel's activities were facilitated through a combination of Web-based tools (https://www.slido.com and www.gradepro.org) and online meetings.

Guideline funding and management of conflicts of interest

The development of these guidelines was funded by the CAG, a non-profit medical specialty society representing gastroenterologists. CAG staff facilitated panel appointments and meetings but did not participate in selecting guideline questions or formulating recommendations. The panellists volunteered their expertise, while the methodologists received funding support from the CAG. Conflicts of interest of all participants were managed according to CAG policies, following the recommendations of the IOM and GIN.[1, 51] Before appointment to the panel, individuals disclosed financial and nonfinancial interests, which were reviewed by the CAG Guideline Committee to identify and manage potential conflicts, as detailed in *Appendix 1*.

Recusal was used to manage conflicts of interest. Panel members with a current direct financial interest in commercial entities that could be impacted by the guidelines were recused from making judgments about relevant recommendations. The Evidence-to-Decision (EtD) framework for each recommendation specifies which individuals were recused. Methodologists with material interest in commercial entities potentially impacted by the guidelines were recused from performing systematic reviews or rating the certainty of evidence related to those products.

Selection of questions and outcomes of interest

The steering committee brainstormed the questions, which the panel prioritized as outlined in Table 3. The questions address all types of endoscopic therapies with published studies relevant to the conditions in question, including RCTs and observational studies. Some questions have been divided into sub-questions to compare different modalities.

The panel selected outcomes of interest for each question *a priori*, following the GRADE approach.[52] For malignant UGIB, MWT, and DL, the panel rated further bleeding as critical for decision-making. This composite outcome includes the failure to achieve immediate hemostasis and any rebleeding. An International Consensus Panel has emphasized the importance of using further bleeding as the primary endpoint for RCTs on UGIB management, highlighting its vital role as the primary clinical goal for patients with UGIB.[53] For GAVE, which commonly presents as chronic GI bleeding leading to anemia,[54-56] the panel rated the number of units of blood transfusion and changes in hemoglobin levels as critical for decision-making. Table 4 outlines the critical and important outcomes for all questions.

Evidence Review and Development of Recommendations

The Cochrane Gut Group at McMaster University conducted systematic searches of the published English-language literature, including MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials from inception through March 6, 2024. Search strategies and the PRISMA flow diagram are included in *Appendix 2*. The search aimed to identify studies assessing any endoscopic hemostatic therapy for NVNPUB, including malignant UGIB, MWT, DL, and GAVE.

Methodologists performed duplicate screening, data extraction, and risk of bias assessment. RCTs, meta-analyses, and observational studies were sought to address the guideline questions. RCTs that included patients with non-variceal UGIB were considered, provided they offered subgroup data specifically for the conditions. Observational studies with fewer than ten patients for any specific type of endoscopic therapy were excluded to ensure the reliability and robustness of the evidence being synthesized. Evidence on values, preferences, and costs was also sought.

We performed our systematic reviews and assessed the risk of bias following the Cochrane Handbook for Systematic Reviews of Interventions.[57] The risk of bias was assessed at the outcome level using the Cochrane Collaboration's risk of bias tool for randomized trials or the modified Newcastle-Ottawa Scale for nonrandomized studies.[57, 58] The certainty ("quality") of evidence was assessed for each outcome based on GRADE domains: risk of bias, imprecision, inconsistency, indirectness, risk of publication bias, presence of large effects, dose-response, and residual confounding. The certainty of the evidence was categorized as very low, low, moderate, or high.[20-22]

For each question, the methodologists prepared evidence profiles and Etd frameworks, summarizing the systematic review results *(Appendices 3-6*).[18, 19, 24] The EtD table addressed the magnitude of the effects of interventions, patients' values and preferences, the balance between desirable and undesirable effects, resource utilization, health equity, acceptability, and feasibility. The guideline panel reviewed draft EtD tables for accuracy and completeness.

During a two-day online meeting, the panel developed recommendations based on the evidence summarized in the EtD frameworks. For each recommendation, the panel took an individual patient

perspective and reached a consensus on every domain of the EtD table. Recommendations were agreed upon by consensus with at least 75% voting agreement. The manuscript was prepared following the McMaster GRADE guidance for transparent and complete reporting of guidelines.[59] All panel members reviewed and approved the final guideline manuscript.

Interpretation of Strong and Conditional Recommendations

According to the GRADE approach, recommendations are categorized as "strong" or "conditional." For strong recommendations, the words "the guideline panel recommends" are used, and for conditional recommendations, "the guideline panel suggests." Table 1 provides GRADE's interpretation of strong and conditional recommendations.

Document review

All panel members reviewed and revised the draft recommendations before making them available online on *[date]* for external review by stakeholders, including allied organizations, medical professionals, patients, and the public. *[Number]* comments were received, and while relevant feedback was addressed, the recommendations remain unchanged. On *[date]*, the CAG Guideline Committee confirmed adherence to the guideline-development process, and on *[date]*, the CAG Executive Board approved the submission of the guidelines for publication under the imprimatur of CAG. The guidelines were then subjected to peer review by *Gastroenterology*.

How to use this guideline

This guideline is intended to aid clinicians in selecting endoscopic treatment options while also supporting policymaking, education, advocacy, and identifying future research needs. Patients may find them useful as well. It is not intended to define a standard of care. Clinicians should make decisions based on each patient's clinical presentation, ideally through a shared decision-making process that considers the patient's values and preferences. Decision-making may be influenced by specific clinical settings and available resources. This guideline may not cover all suitable care methods, and recommendations may become outdated as new evidence emerges. Each recommendation includes statements about its underlying values and preferences, along with qualifying remarks that are essential for accurate interpretation and should be included when the guideline is quoted or translated. The

guideline is further supported by EtD frameworks and summary-of-findings tables, enhancing their usability.

Recommendations

Malignant upper gastrointestinal bleeding (UGIB)

Question 1: Should patients with active bleeding from malignant upper gastrointestinal (UGI) tumours receive endoscopic hemostatic therapy versus no endoscopic hemostatic therapy?

Recommendations:

1a: In patients with active bleeding from malignant UGI tumours, we suggest conventional endoscopic hemostatic therapy (e.g. injection, thermal devices, mechanical devices, or a combination thereof) over no endoscopic hemostatic therapy (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).

1b: In patients with active bleeding from malignant UGI tumours, we suggest topical hemostatic agents over no endoscopic hemostatic therapy (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).

1a. Conventional Endoscopy Hemostatic Therapy vs. No Endoscopic Hemostatic Therapy

Evidence summary

We found no RCTs or observational studies that directly addressed this question. Six comparative cohort studies were excluded due to seriously biased comparisons between patients treated for active bleeding and those untreated due to inactive bleeding.[25-27, 30, 60, 61] Twelve cohort studies provided data on the outcomes of treating malignant UGIB with various conventional endoscopic therapies, including injection therapy (epinephrine, saline, sclerosant, ethanol, fibrin glue), thermocoagulation (argon plasma coagulation (APC), heater probe, bipolar devices, coagulation forceps, Nd-YAG laser), and mechanical devices (through-the-scope clips), either alone or in combination.[25-27, 30, 60-67] The majority of patients (62%) received APC in these studies.[25-27, 30, 60-67] Yet, most studies did not provide subgroup data for each intervention. The validity of subgroup comparisons was further compromised by the small sample sizes and selection bias present in these non-randomized studies. Due to significant heterogeneity in populations, interventions, outcomes, duration of follow-up and study designs, a proportional meta-analysis of these studies was deemed inappropriate and potentially misleading. Instead, we summarized the results as ranges and presented them in forest plots without pooled

estimates, following the recommendations of the Cochrane Non-Randomized Studies Methods Group.[57] These details, along with the EtD framework, are provided in *Appendix 3.*

Benefits, harms, and burden

Based on data from 12 single-arm cohort studies, outcomes for patients treated with conventional endoscopic therapies were variable: 30-day further bleeding occurred in 22% to 87% of patients (about 50% for most studies), failure to achieve immediate hemostasis in 0% to 69% (about 20% for most studies), 30-day rebleeding in 17% to 53% (about 30% for most studies), and mortality in 13% to 93%, with most studies reporting 30-day mortality.[25-27, 30, 60-67] Two studies reported 0% adverse effects in 81 patients treated with APC.[26, 67]

Without comparative data, estimating the effects of conventional endoscopic therapies compared to no therapy was impossible. To address this, an expert evidence survey was conducted using the GRADE expert evidence approach.[68] The panel estimated that patients with active bleeding from malignant UGI tumours who do not receive endoscopic therapy have a risk of further bleeding of at least 85%, failure to achieve immediate hemostasis of at least 50%, and 30-day rebleeding of at least 35% for those who stopped bleeding spontaneously. The panel judged that conventional endoscopic hemostatic therapies likely have variable magnitudes of desirable and undesirable effects.

Certainty in the evidence of effects

Very low certainty of evidence due to serious risk of bias, serious inconsistency, and serious imprecision.

Other EtD criteria and considerations

There was no research evidence on patients' values and preferences in the context of malignant UGIB. The panel agreed, based on their experience, that patients place a high value on reducing further bleeding (critical outcome) to avoid prolonged or repeated hospitalizations, additional interventions, and decreased quality of life. However, the panel recognized possible variability and uncertainty in patients' values and preferences regarding blood transfusions and 6-month mortality, influenced by their overall prognosis and care goals. Patients may prefer less invasive procedures if their goal is comfort care, while those aiming for extended survival might choose more aggressive treatments. Costs may vary depending on the intervention. There was no research evidence on cost-effectiveness. The panel judged conventional endoscopic therapies as probably acceptable and feasible with no adverse impact on equity-deserving groups.

Conclusions and research needs

The panel judged that the balance of effects likely favours conventional endoscopic hemostatic therapy in patients with active bleeding from malignant UGI tumours. As a result, the panel issued a conditional recommendation for conventional endoscopic hemostatic therapies over no endoscopic hemostatic therapy, recognizing that the certainty of the evidence was very low. This conditional recommendation would be more applicable to tumours with spurting bleeding rather than those with diffuse oozing. When tumours are diffusely oozing over a large area, conventional endoscopic therapies can be challenging to apply, and some (e.g., thermocoagulation, sclerosants) may lead to further tissue injury. Therefore, some patients with diffusely oozing tumours may not be suitable for conventional endoscopic hemostatic intervention. Future research should focus on well-designed RCTs or observational studies comparing conventional endoscopic therapy with no endoscopic therapy, potentially in combination with other hemostatic interventions such as radiation, embolization, or surgery. Additionally, research on patient values and preferences would enhance shared decision-making.

1b. Topical Hemostatic Agents (THA) vs. No Endoscopic Hemostatic Therapy

Evidence Summary

We found no RCTs that directly addressed this question.

Nineteen studies provided single-arm cohort-type data that addressed this question, including four RCTs and 15 observational studies.[69-82] Fourteen studies exclusively used TC-325 (588 patients),[69-82] while others involved Endoclot™ (15 patients),[83-85] Ankaferd Blood Stopper (10 patients),[86] and UI-EWD (41 patients).[87] Despite the differences in composition, all these agents function as mechanical barriers to control bleeding, justifying their inclusion in pooled proportional meta-analyses. These results, along with the EtD framework, are detailed in *Appendix 3.*

Benefits

A comparative cohort study suggested that THA when compared to no endoscopic therapy, may reduce 30-day rebleeding (RR 0.67, 95% CI 0.14 to 3.17; ARR 99 fewer per 1000, 95% CI 258 fewer to 651 more) and 6-month mortality (RR 0.33, 95% CI 0.04 to 2.69; ARR 201 fewer per 1000, 95% CI 288 fewer to 507 more), but these estimates were very imprecise.[79]

30-day further bleeding with THA was reported in 18 studies, with a pooled proportion of 26% (95% CI 20% to 32%).[62, 69-84, 87] Failure to achieve immediate hemostasis was reported by 19 studies, with a pooled proportion of 5% (95% CI 3% to 7%).[62, 69-84, 86, 87] 30-day rebleeding was reported by 18 studies, with a pooled proportion of 23% (95% CI 18% to 28%).[62, 69-84, 87] Mortality was reported by 13 studies, with a pooled proportion of 29% (95% CI 20% to 39%).[62, 69, 71, 72, 74, 76-81, 83, 87] Most studies reported 30-day mortality, while five reported 6-month mortality.[69, 72, 78, 80, 87] Most deaths were not related to GI bleeding. Estimating the effects of THA versus no endoscopic therapy was challenging due to limited comparative data. To address this, expert survey results from PICO 1a were applied, and the panel concluded that THA likely has large desirable effects over no endoscopic therapy.

Harms and Burden

A comparative cohort study suggested THA, compared to no endoscopic therapy, may increase blood transfusions (MD 5.60 units, 95% CI 4.59 fewer to 15.79 more) and length of hospitalization (MD 4.40 days, 95% CI 10.85 fewer to 19.65 more).[79] However, the data were skewed, and these outcomes can be subjective, influenced by factors such as the health system's structure, institutional protocols, clinical judgment, and patient-specific factors.[79] Few studies reported adverse effects related to THA, but a systematic review of THAs in UGIB, including patients with malignant UGIB, found a pooled adverse event rate of 2% (95% CI 1% to 3%).[88] The panel judged that THA likely has moderate undesirable effects over no endoscopic therapy.

Certainty in the evidence of effects

Very low certainty of evidence due to serious risk of bias and serious imprecision.

Other EtD criteria and considerations

No research evidence was available on patients' values and preferences, but the panel assumed that avoiding further bleeding is critical to patients. The panel considered the cost of THA to be high. There was no research evidence on the cost-effectiveness of THA compared to no endoscopic therapy. The panel judged THA probably acceptable with no adverse impact on equity-deserving groups, but its feasibility may vary due to access challenges in some countries.

Conclusions and research needs

The panel judged that the balance of effects likely favours THA in patients with active bleeding from malignant UGI tumours (oozing or spurting). Thus, the panel issued a conditional recommendation for THA over no endoscopic hemostatic therapy, recognizing the very low certainty of the evidence, which was predominantly based on TC-325. If TC-325 is chosen as a THA, it is crucial that TC-325 only be applied to actively bleeding lesions. The panel highlighted the need for more comparative studies, potentially in combination with other hemostatic interventions such as radiation, embolization, or surgery. Since most evidence was derived from TC-325, further research on other THAs is needed.

Question 2: Should patients with active bleeding from malignant UGI tumours receive one conventional endoscopic hemostatic therapy versus another conventional endoscopic hemostatic therapy?

Recommendations:

2: In patients with active bleeding from malignant UGI tumours, we were unable to reach a recommendation for or against any specific type of conventional endoscopic hemostatic therapy over another.

2. Specific Type of Conventional Endoscopic Therapy vs. Another Type of Conventional Endoscopic Therapy

Evidence Summary

We did not find any studies that directly compare various conventional endoscopic hemostatic therapies with each other.

Conclusions and research needs

Due to the lack of evidence, the panel was unable to reach a recommendation for or against any specific type of conventional endoscopic therapy over another in patients with active bleeding from malignant UGI tumours. Since current evidence suggests that THA may be more effective than conventional hemostatic therapies for malignant UGIB, the panel did not consider clinical trials comparing conventional endoscopic therapies a high research priority.

Question 3: Should patients with active bleeding from malignant UGI tumours receive topical hemostatic agents versus conventional endoscopic hemostatic therapies?

Recommendations:

3: In patients with active bleeding from malignant UGI tumours, we suggest topical hemostatic agents over conventional endoscopic hemostatic therapy (conditional recommendation, very low certainty of evidence ⊕⊖⊖⊖).

3. Topical Hemostatic Agents (THA) vs. Conventional Endoscopic Hemostatic Therapy

Evidence Summary

We identified two systematic reviews that indirectly addressed this question.[88, 89] One review performed proportional meta-analyses of 16 studies that provided single-arm cohort-type data on THA in malignant GIB.[89] The other review assessed THA in UGIB of any etiology but provided subgroup analyses for malignancy-related bleeding, including data from two RCTs.[88] An individual patient data meta-analysis, published after our search period, included three RCTs and found TC-325 more effective than conventional endoscopic therapy in malignant GIB.[90]

We conducted a systematic review that included four RCTs.[72, 75, 76, 78] Three RCTs compared TC-325 with conventional endoscopic hemostatic therapies for malignancy-related GIB, while the fourth RCT focused on acute non-variceal UGIB and provided subgroup data for malignancy-related cases.[72, 75, 76, 78] Two RCTs included both upper and lower GI tumours.[72, 78] Most (81.1%) patients in the 4 RCTs had UGI tumours. All RCTs evaluated TC-325, with none examining other THAs. The conventional endoscopic hemostatic therapies for comparison included injection techniques, contact and non-contact thermal coagulation methods, and mechanical devices. However, no subgroup data were provided for these interventions.

We found one retrospective comparative cohort study that compared THA (TC-325 or Endoclot™) with conventional endoscopic hemostatic therapy (epinephrine injection combined with APC and/or through-the-scope clips) in patients with GI bleeding and reported subgroup data on malignant bleeding.[83]

The EtD framework is available in *Appendix 3.*

Benefits

Meta-analyses of four RCTs suggested that TC-325, when compared with conventional endoscopic hemostatic therapies, may reduce 30-day further bleeding (RR 0.31, 95% CI 0.08 to 1.23; ARR 296 fewer per 1000, 95% CI 394 fewer to 99 more), failure to achieve immediate hemostasis (RR 0.10, 95% CI 0.03 to 0.37; ARR 231 fewer per 1000, 95% CI 249 fewer to 162 fewer), 30-day rebleeding (RR 0.50, 95% CI

0.14 to 1.77; ARR 119 fewer per 1000, 95% CI 205 fewer to 183 more), and blood transfusions (MD -0.09 units, 95% CI -0.93 to 0.74), but these estimates were very imprecise.[72, 75, 76, 78] THA appeared to have little or no impact on 6-month mortality (RR 0.94, 95% CI 0.69 to 1.29, ARR 23 fewer per 1000, 95% CI 118 fewer to 110 more).[72, 75, 76, 78]

One comparative cohort study also showed that THA may reduce 30-day further bleeding (RR 0.82, 95% CI 0.42 to 1.60; ARR 120 fewer per 1000, 95% CI 387 fewer to 400 more) and failure to achieve immediate hemostasis (RR 0.07, 95% CI 0.0046 to 1.13; ARR 543 fewer per 1000, 95% CI 581 fewer to 76 more), but these estimates were very imprecise.[83]

The panel judged that THA likely has large desirable effects compared to conventional endoscopic hemostatic therapy.

Harms and Burden

Compared to conventional endoscopic hemostatic therapies, THA may increase the length of hospitalization (MD of 4.28 days, 95% CI -0.27 to 8.82).[72, 75, 78] Two RCTs reported more adverse effects associated with THA (RR 1.27, 95% CI 0.83 to 1.94; ARR 53 more per 1000, 95% CI 33 fewer to 183 more).[75, 76] However, these estimated effects were very imprecise. A systematic review of THAs in UGIB, including patients with malignant GIB, found a pooled adverse event rate of 2% (95% CI 1% to 3%).[88]

A comparative cohort study suggested that THA may increase 30-day rebleeding (RR 6.55, 95% CI 0.93 to 46.12; ARR 462 more per 1000, 95% CI 6 fewer to 1000 more), but the estimate was very imprecise.[83] Notably, the 30-day rebleeding outcome may be affected by other hemostatic therapies, such as embolization, radiation, and surgery. Due to inherent selection bias in this observational study, the panel prioritized the effect estimates from the systematic review of four RCTs.[72, 75, 76, 78]

The panel judged that THA likely has moderate undesirable effects compared to conventional endoscopic hemostatic therapy.

Certainty in the evidence of effects

Very low certainty of evidence due to serious risk of bias, serious inconsistency, and very serious imprecision. The evidence was not downgraded for indirectness because most patients had bleeding from UGI tumours, as opposed to lower GI tumours.

Other EtD criteria and considerations

No research evidence existed on patients' values and preferences, but the panel assumed that avoiding further bleeding was critical for decision-making for patients. A cost minimization study published after our search period found that using THA, compared to standard endoscopic therapy, resulted in a cost-saving of US$1613 for malignant UGIB, considering device-related costs, incremental facility costs and additional physician and staff time.[91] Additionally, a cost-utility analysis published later also found that using TC-325 as first-line treatment for malignant GIB in the UK resulted in a cost-saving of £245.88 compared to standard endoscopic therapy.[92] The panel judged THA likely to be acceptable with no adverse impact on equity-deserving groups, though its feasibility may vary due to access challenges in some countries.

Conclusions and research needs

The panel judged that the balance of effects likely favours THA in patients with active bleeding (oozing or spurting) from malignant UGI tumours. The data on hospitalization length were skewed and may not be generalizable to all settings. As a result, the panel prioritized the potential benefits of reducing further bleeding over the potential burden and costs. Therefore, the panel issued a conditional recommendation for THA over conventional endoscopic hemostatic therapy, recognizing the very low certainty of the evidence, which was predominantly based on TC-325. The panel emphasized the need for more comparative studies to increase the certainty of the evidence. Additionally, RCTs should compare the efficacy and safety of THAs with other non-endoscopic hemostatic therapies.

Question 4: Should patients with active bleeding from malignant UGI tumours receive oncologic therapy after endoscopic hemostatic therapy versus no oncologic therapy after endoscopic hemostatic therapy?

Recommendations:

4: In patients with active bleeding from malignant UGI tumours, we suggest administering oncologic therapy following endoscopic hemostatic therapy rather than not providing oncologic therapy after endoscopic hemostatic therapy (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).

4. Oncologic Therapy vs. No Oncologic Therapy Following Endoscopic Hemostatic Therapy

Evidence Summary

We defined oncologic therapies as surgery, chemotherapy, and radiation therapy. The goals of these therapies can vary based on cancer type, stage, and the patient's overall health, but generally include

curative intent, disease control, symptom management, palliative care, prolongation of survival, and prevention of complications, such as bleeding. While radiologic embolization is not typically considered a primary oncologic therapy for UGI cancers, it can play a crucial role in a multi-modal approach.

We did not find any RCTs directly addressing this question. However, there were observational data from an RCT and a multi-center retrospective cohort study.[78, 80] In the RCT, patients with malignant GI bleeding were randomized to receive TC-325 or standard endoscopic treatment.[78] The proportion of patients undergoing additional non-endoscopic hemostatic or oncologic treatments, such as surgery, chemotherapy, radiation, embolization, or a combination thereof, within a month following the initial endoscopy was similar in the two arms (50.9% in the TC-325 arm vs. 62.7% in the standard endoscopic treatment arm).[78] The high rate of additional treatment was likely due to the good performance status of the included patients (ECOG 0-2).[78] Both studies reported on 6-month overall mortality (critical outcome) and 30-day rebleeding but not on 6-month further bleeding (critical outcome).[78, 80] No studies provided direct evidence of adverse effects from oncologic therapy following endoscopic hemostatic therapy compared to without it. Three systematic reviews of non-comparative cohort studies provided indirect evidence on the toxicity of palliative radiotherapy for symptomatic locally advanced gastric cancer, chemotherapy in advanced gastric cancer, and complications after surgical resection in patients with gastric cancer.[93-95] The EtD framework is available in *Appendix 3.*

Benefits

In a post-hoc observational analysis of an RCT, multivariable analysis identified the Charlson comorbidity index (HR 1.17, 95% CI 1.05 to 1.32) and the receipt of additional non-endoscopic hemostatic treatment(s) or oncologic treatment(s) such as surgery, chemotherapy, radiation, embolization, or a combination of these (HR 0.16, 95% CI 0.06 to 0.43), as independent predictors of 6-month survival, after adjustment for ECOG score, Glasgow-Blatchford score, and upper GI lesions; TC-325 application was not an independent predictor.[78] Receiving additional non-endoscopic hemostatic treatment(s) or oncologic treatment(s) did not predict 30-day rebleeding (HR 1.1, 95% CI 0.24 to 5.06).[78]

In the retrospective cohort study, factors associated with 6-month survival included low ECOG scores 0 to 2 (HR 0.14, 95% CI 0.04 to 0.47), cancer stage 1 to 3 (HR 0.31, 95% CI 0.01 to 0.96), and receipt of definitive hemostatic treatments, including surgery, chemotherapy, radiotherapy, or radiological

embolization (HR 0.24, 95% CI 0.09 to 0.59), after adjusting for comorbidity, type of cancer bleeding, and coagulopathy.[80]

However, these observational analyses are prone to residual confounding as the comparison was not randomized. The association between oncologic treatments following endoscopic hemostatic therapy and improved 6-month survival may be confounded by baseline health and cancer stage. Nevertheless, the panel judged that oncologic therapies likely have large desirable effects over no oncologic therapies.

Harms and Burden

A systematic review of seven cohort studies involving 161 patients with symptomatic locally advanced gastric cancer found Grade 3 to 4 toxicities in up to 15% of those treated with radiotherapy alone and up to 25% with chemoradiotherapy.[94] Another systematic review of 60 RCTs involving 11,698 patients receiving systemic chemotherapy for advanced gastric cancer reported treatment discontinuation due to toxicity ranging from 8% to 21%.[95] Additionally, a systematic review of single-arm cohort studies including 32,067 patients who underwent gastrectomy for gastric cancer reported postoperative complication rates between 12.5% and 51.0%, with infectious complications, anastomotic leakage, and pneumonia being the most common.[93] The panel judged that oncologic therapies likely have moderate undesirable effects over no oncologic therapies.

Certainty in the evidence of effects

Very low certainty of evidence due to serious risk of bias, serious indirectness from different types and early stages of GI cancers and the inclusion of both oncologic treatments and radiologic embolization as the intervention, as well as very serious imprecision.

Other EtD criteria and considerations

There was no research evidence on patients' values and preferences regarding oncologic therapies, but the panel assumed patients might have variable views on adverse effects from these therapies, particularly when considering improving quality of life versus increasing survival.[96, 97] In the context of malignant GI bleeding, patients may choose interventions that align with their personal goals—opting for less invasive procedures if prioritizing quality of life or more aggressive treatments for prolonged survival. Therefore, engaging patients in shared decision-making is crucial. The cost of oncologic therapies can vary widely due to factors such as tumour location, specific treatments, and individual

patient circumstances (e.g. staging, comorbidities). No data existed on the cost-effectiveness of oncologic therapies following endoscopic hemostatic therapies. Although the panel judged that oncologic therapies were probably acceptable and feasible, they could increase inequity due to cancer health disparities. Factors such as race, gender, age, geography, socioeconomic status, cultural beliefs, social support, and health literacy could impact equitable access to these treatments.[98] To address cancer health disparities, it is crucial to ensure equitable access to treatment for all populations. This involves culturally sensitive community outreach, policy changes to reduce socio-economic barriers, and investment in research focused on underserved groups.[98]

Conclusions and research needs

For patients with active bleeding from malignant UGI tumours, the panel determined that oncologic therapies after endoscopic hemostatic therapy likely offer a net benefit despite the very low certainty of the evidence. As a result, the panel issued a conditional recommendation in favour of administering oncologic therapy following endoscopic hemostatic therapy, as opposed to not providing it. This conditional recommendation placed a higher value on the potential reduction in 6-month mortality (critical outcome) over the potential burdens, harms, costs and negative impact on equity. The panel highlighted the importance of shared decision-making with patients, involving them in discussions about the risks and benefits of oncologic therapies tailored to their individual circumstances and preferences. Given the ethical and practical challenges of conducting an RCT on this topic, the panel emphasized the need for well-designed observational studies to determine optimal timing for oncologic therapy and called for more comparative studies to strengthen the evidence.

Mallory Weiss Tears

Question 5: Should patients with active bleeding from Mallory-Weiss tears (spurting or oozing) receive endoscopic hemostatic therapy versus no endoscopic hemostatic therapy?

Recommendations:

5: In patients with active bleeding from Mallory-Weiss tears (spurting or oozing), we suggest endoscopic hemostatic therapy over no endoscopic hemostatic therapy (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).

5. Endoscopic Hemostatic Therapy vs. No Endoscopic Hemostatic Therapy

Evidence Summary

We identified two RCTs that addressed this question. One included patients with UGIB from Mallory Weiss Tears (MWT) with "active bleeding" or non-bleeding visible vessels, comparing epinephrine and polidocanol injections with no endoscopic hemostatic therapy.[99] Only the "active bleeding" subgroup was included in our systematic review.[99] Another RCT included patients with UGIB and provided data on a subgroup of patients with MWT with spurting or oozing bleeding, comparing multi-polar electrocoagulation with no endoscopic hemostatic therapy.[100] No study provided data for further bleeding (critical outcome). One study reported failure to achieve immediate hemostasis,[100] while the other provided data for rebleeding.[99] All rebleeding occurred within 7 days. To avoid double-counting 7-day and 30-day outcomes, we included the rebleeding outcomes as 7-day results only. This approach was based on our *a priori* decision that 7-day further bleeding was the critical outcome. One study provided data for the length of hospitalization.[99] Both studies provided data on adverse effects.[99, 100] Only two outcomes—blood transfusions and 30-day mortality—could be pooled for meta-analyses.

Four comparative cohort studies evaluated endoscopic hemostatic therapy versus no endoscopic hemostatic therapy in patients with UGIB due to MWT.[101-104] Meta-analyses of these studies were deemed inappropriate as they compared patients with active bleeding who received endoscopic therapy to those without active bleeding who did not receive endoscopic treatment.

The EtD framework is available in *Appendix 4.*

Benefits

Meta-analyses of two RCTs suggested that endoscopic hemostatic therapy, compared to no endoscopic hemostatic therapy, may reduce failure to achieve immediate hemostasis (RR 0.06, 95% CI 0.004 to 0.91; ARR 823 fewer per 1000, 95% CI 871 fewer to 79 fewer), 7-day rebleeding (RR 0.20, 95% CI 0.03 to 1.58; ARR 174 fewer per 1000, 95% CI 211 fewer to 126 more), blood transfusions (MD -2.20 units, 95% CI -5.23 to 0.84), and length of hospitalization (MD -2.10 days, 95% CI -2.20 to 2.00), but these effects were very imprecise.[99, 100] Endoscopic hemostatic therapy may have little or no impact on 30-day mortality (RR 0.24, 95% CI 0.03 to 2.05; ARR 58 fewer per 1000, 95% CI 75 fewer to 81 more), but the effect was very imprecise.[99, 100] Given the natural history of MWT with relatively low rebleeding rates, the panel

prioritized failure to achieve immediate hemostasis over 7-day rebleeding and judged that endoscopic hemostatic therapy likely has large desirable effects compared to no endoscopic hemostatic therapy.

Harms and Burden

Both RCTs reported no adverse effects, with or without endoscopic hemostatic therapy, making relative and absolute effects non-estimable.[99, 100] The panel judged that endoscopic hemostatic therapy likely has trivial undesirable effects. This assessment was also supported by indirect evidence from peptic ulcer bleeding.[10, 13]

Certainty in the evidence of effects

Very low certainty of evidence due to serious risk of bias and very serious imprecision.

Other EtD criteria and considerations

There was no research evidence on patients' values and preferences in the context of MWT. However, the panel assumed there is probably no important uncertainty or variability in how much patients value the main outcomes, such as avoiding failure to achieve immediate hemostasis or rebleeding. The costs of endoscopic hemostatic therapy were considered moderate. Although cost-effectiveness studies were lacking, the panel considered endoscopic hemostatic therapy for actively bleeding MWT as likely cost-effective by achieving immediate hemostasis, reducing rebleeding rates, and decreasing blood transfusions and length of hospitalization. The panel judged endoscopic hemostatic therapy as likely acceptable and feasible with no adverse impact on equity-deserving groups.

Conclusions and research needs

For patients with active bleeding (oozing or spurting) from MWT, the panel judged that endoscopic hemostatic therapy likely offers a net benefit over no endoscopic hemostatic therapy despite very low certainty of evidence. Therefore, the panel issued a conditional recommendation for endoscopic hemostatic therapy over no endoscopic hemostatic therapy. The panel highlighted the need for more comparative studies to increase the certainty of the evidence. Additionally, future RCTs should compare the efficacy and safety of different endoscopic hemostatic therapies and stratify randomization based on stigmata.

Question 6: Should patients with active bleeding from Mallory-Weiss tears (spurting or oozing) receive one endoscopic hemostatic therapy versus another endoscopic hemostatic therapy?

Recommendations:

6a: In patients with active bleeding from Mallory-Weiss tears (spurting or oozing), we suggest endoscopic band ligation or endoscopic through-the-scope clip (TTSC) placement over epinephrine injection alone (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).

6b: In patients with active bleeding from Mallory-Weiss tears (spurting or oozing), we suggest endoscopic band ligation or endoscopic through-the-scope clip (TTSC) placement (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).

6a. Mechanical Modalities (Endoscopic Band Ligation (EBL) / Endoscopic Through-the-scope Clip (TTSC) Placement) vs. Epinephrine Injection Alone

Evidence Summary

We identified three RCTs that addressed this question.[102, 105, 106] Two studies included only patients with active bleeding stigmata (spurting or oozing),[105, 106] while one study included both active and non-active bleeding stigmata but provided subgroup data for active bleeding stigmata.[102] All three studies reported further bleeding, rebleeding, and overall mortality. [102, 105, 106] Two studies reported a follow-up period of 30 days, noting that all rebleeding occurred within 7 days.[105, 106] One study did not specify a follow-up period or the timing of rebleeding.[102] To avoid double-counting 7-day and 30-day outcomes, we considered all rebleeding and further bleeding outcomes as 7-day outcomes. One study reported failure to achieve immediate hemostasis and length of hospitalization.[106] Two studies reported units of blood transfused and adverse effects.[105, 106]

No comparative cohort studies addressing this question were identified.

We also conducted proportional meta-analyses of single-arm cohort-type data from seven studies on EBL/TTSC and four studies on epinephrine injection alone.[102, 104-110] The results of the proportional meta-analyses were provided as supplementary data in the Evidence Profile Table but were not included in the EtD framework due to the absence of direct comparison. The EtD framework is in *Appendix 4.*

Benefits

Meta-analyses of 3 RCTs suggested that EBL/TTSC, compared with epinephrine injection alone, may reduce the risk of 7-day further bleeding (RR 0.32, 95% CI 0.06 to 1.64; ARR 95 fewer per 1000, 95% CI

131 fewer to 89 more) and 7-day rebleeding (RR 0.31, 95% CI 0.03 to 3.13; ARR 80 fewer per 1000, 95% CI 103 fewer to 248 more), with no significant subgroup differences between EBL, TTSC, or EBL/TTSC.[102, 105, 106] However, these estimates were very imprecise due to small sample sizes and very low event rates.[102, 105, 106] Due to zero events in the EBL/TTSC group for failure to achieve immediate hemostasis, calculating the risk ratio and confidence interval with continuity corrections introduced instability and potential bias.[106] However, when considering the opposite outcome (immediate hemostasis), EBL/TTSC appeared to have no impact compared to epinephrine injection alone (RR 1.01, 95% CI 0.94 to 1.09).[106] 30-day mortality was not estimable due to double-zero events.[102, 105, 106] Overall, the panel judged that EBL/TTSC likely has moderate desirable effects compared to epinephrine injection alone.

Harms and Burden

Compared to epinephrine injection, EBL/TTSC may increase blood transfusions (MD 0.85 units, 95% CI -0.34 to 2.04) and length of hospitalization (MD 0.80 days, 95% CI 0.13 to 1.47).[105, 106] These estimates were very imprecise and were not considered clinically meaningful by the panel. Additionally, the outcomes related to blood transfusion requirements and length of hospitalization can be subjective and influenced by individual clinical practices. We were unable to assess the adverse effects of EBL/TTSC compared to epinephrine injection alone due to double-zero events.[105, 106] The panel judged that EBL/TTSC likely has trivial undesirable effects compared to epinephrine injection alone.

Certainty in the evidence of effects

Very low certainty of evidence due to serious risk of bias and very serious imprecision.

Other EtD criteria and considerations

The panel assumed patients likely do not have important uncertainty or variability in valuing the critical outcome of further bleeding. Costs of EBL/TTSC were considered moderate, but no studies have assessed its cost-effectiveness compared to epinephrine injection alone in MWT. The panel judged EBL/TTSC as likely acceptable, feasible, and unlikely to adversely impact equity-deserving groups.

Conclusions and research needs

For patients with active bleeding from MWT (oozing or spurting), the panel judged that EBL/TTSC likely offers a net benefit over epinephrine injection alone despite the evidence being of very low certainty. This conditional recommendation placed a higher value on the potential benefits of reducing 7-day

further bleeding than the potential burden and costs. The panel stressed the importance of conducting more comparative studies to increase the certainty of the evidence. Additionally, future RCTs should investigate how different stigmata (oozing, spurting) and the size of MWT respond to each intervention. Cost-effectiveness analyses should also be performed to assess the economic impact of each treatment option.

6b. Endoscopic Band Ligation (EBL) vs. Endoscopic Through-the-scope Clip (TTSC) Placement

Evidence Summary

We found one RCT and one comparative cohort study that addressed this question.[107, 111] Both studies reported further bleeding and all the important outcomes.[107, 111] Since all rebleeding occurred within 7 days, we included all rebleeding and further bleeding outcomes as 7-day outcomes.

We also conducted proportional meta-analyses using single-arm cohort-type data from five studies on EBL and five studies on TTSC.[102, 105-111] The results were provided as supplementary data in the Evidence Profile Table but were not included in the EtD framework due to the lack of direct comparative data. The EtD framework is in *Appendix 4.*

Benefits, harms, and burden

Based on one RCT, the relative and absolute effects of EBL compared to TTSC on 7-day further bleeding and 7-day rebleeding were highly uncertain (RR 2.10, 95% CI 0.21 to 21.39; ARR 52 more per 1000, 95% CI 38 fewer to 971 more).[107] The relative effects for failure to achieve immediate hemostasis, overall mortality, and adverse effects were not estimable due to double-zero events.[107] For "immediate hemostasis," EBL appeared to have no impact compared to TTSC (RR 1.00, 95% CI 0.91 to 1.10).[107] The estimates for blood transfusions (MD 1.30 units, 95% CI -0.36 to 2.96) and length of hospitalization (MD 0.60 days, 95% CI -2.02 to 3.22) were very imprecise and were not deemed clinically meaningful by the panel.[107]

A comparative cohort study also found highly uncertain effects of EBL compared to TTSC on 7-day further bleeding and 7-day rebleeding (Risk Difference [RD] -0.19, 95% CI -0.34 to 0.03; ARR 190 fewer per 1000, 95% CI 340 fewer to 30 more).[111] The relative effects for failure to achieve immediate hemostasis, overall mortality, and adverse effects were not estimable due to double-zero events.[111] EBL appeared to have no impact on "immediate hemostasis" compared to TTSC (1.00, 95% CI 0.95 to

1.06).[111] For units of blood transfused, the MD was 0.00 (95% CI -1.31 to 1.31),[111] and for the length of hospitalization, the MD was -0.10 (95% CI -1.67 to 1.47).[111]

Due to the low event rates and the fragility of results in both the RCT and observational study, the panel judged that there was very serious imprecision, rendering the relative and absolute effects of EBL compared to TTSC for active bleeding MWT highly uncertain. Nevertheless, both EBL and TTSC appeared to be highly effective in achieving "immediate hemostasis" with low rates of failure to achieve immediate hemostasis, 7-day rebleeding and 7-day further bleeding (critical outcome).

Certainty in the evidence of effects

Very low certainty of evidence due to serious risk of bias and very serious imprecision.

Other EtD criteria and considerations

The panel assumed there is no important uncertainty or variability in how patients value the critical outcome of avoiding further bleeding. The panel considered the relative costs negligible. No published cost-effectiveness analyses were available. The panel judged EBL, compared to TTSC, as probably acceptable and feasible and unlikely to negatively affect equity-deserving groups.

Conclusions and research needs

For patients with active bleeding from MWT (oozing or spurting), the panel could not determine whether the balance of effects favoured EBL or TTSC due to the very low certainty of the evidence. Consequently, the panel made a conditional recommendation for either EBL or TTSC. The panel emphasized the need for more comparative studies to increase the certainty of the evidence.

Question 7: Should patients with no active bleeding from Mallory-Weiss tears (non-bleeding visible vessels, adherent clots, flat pigmented spots, clean-based ulcers) receive endoscopic hemostatic therapy versus no endoscopic hemostatic therapy?

Recommendations:

7a: In patients with Mallory-Weiss tears with non-bleeding visible vessels, we suggest against endoscopic hemostatic therapy (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).

7b: In patients with Mallory-Weiss tears with non-bleeding adherent clots, we suggest against endoscopic hemostatic therapy (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).

7c: In patients with Mallory-Weiss tears with non-bleeding clean based ulcers or flat pigmented spots, we suggest against endoscopic hemostatic therapy (conditional recommendation, very low certainty of evidence ⊕⊖⊖⊖).

7a. Endoscopic Hemostatic Therapy vs. No Endoscopic Hemostatic Therapy in Non-bleeding Visible Vessels

7b. Endoscopic Hemostatic Therapy vs. No Endoscopic Hemostatic Therapy in Adherent Clots

Evidence Summary

We found one RCT and two retrospective cohort studies that addressed the above two questions.[99, 102, 103] The RCT included patients with MWT with non-bleeding visible vessels and compared epinephrine and polidocanol injections against no endoscopic hemostatic therapy.[99] Both cohort studies included patients with various stigmata of MWT and compared endoscopic hemostatic therapies (epinephrine injection, EBL, TTSC, or fibrin glue injection) to medical treatment for UGIB due to MWT, providing subgroup data on non-bleeding visible vessels or adherent clots.[102, 103] Patients who received endoscopic treatment had more severe bleeding, as indicated by higher rates of transfusion.[103] Since these were non-randomized studies, there may be inherent selection bias that could influence the results.

None of the studies provided data on the critical outcome of further bleeding or the important outcomes of mortality, units of blood transfusions and length of hospitalization. However, all studies provided data on 7-day rebleeding. One RCT reported adverse effects.[99]

We also conducted a proportional meta-analysis of single-arm cohort-type data from three studies for 7-day rebleeding.[99, 102, 103] As indirect evidence of the adverse effects of endoscopic hemostatic therapy in patients with non-bleeding stigmata, we performed a proportional meta-analysis of nine studies involving patients with bleeding MWT who received endoscopic hemostatic therapy.[99-101, 105-108, 110, 112] Additionally, to assess the adverse effects of no endoscopic hemostatic therapy, we performed a proportional meta-analysis using single-arm cohort-type data from three studies involving patients with flat-pigmented spot or clean-based ulcers who did not receive this therapy.[99-101] The results of the proportional meta-analyses were provided as supplementary data in the Evidence Profile Table. The EtD framework is available in *Appendix 4.*

Benefits, harms, and burden

Based on one RCT, the relative and absolute effects of endoscopic hemostatic therapy compared to no endoscopic hemostatic therapy on 7-day rebleeding in patients with MWT and visible vessels were highly uncertain due to the small sample size and very low event rates (RR 0.30, 95% CI 0.04 to 2.31; ARR 262 fewer per 1000; 95% CI 360 fewer to 491 more).[99] A systematic review of two comparative cohort studies also found highly uncertain effects of endoscopic hemostatic therapy compared to no endoscopic hemostatic therapy on 7-day rebleeding in patients with non-bleeding visible vessels or adherent clots due to very low event rates with zero event in the group receiving no endoscopic hemostatic therapy (RD 0.03, 95% CI -0.06 to 0.11; ARR 30 more per 1000, 95% CI 60 less to 110 more).[102, 103] In one study, none of the patients experienced rebleeding, regardless of whether they received endoscopic hemostatic therapy or medical treatment.[102] In the other study, there was one case of rebleeding in a patient with a non-bleeding visible vessel who had undergone endoscopic hemostatic therapy.[103] In contrast, no rebleeding cases occurred in patients with adherent clots.[102, 103] Proportional meta-analyses of single-arm cohort-type data suggested that no endoscopic hemostatic therapy was associated with very low 7-day rebleeding rates (pooled rebleeding rates of 6% for non-bleeding visible vessels and 0% for adherent clots).[99, 102, 103]

Based on one RCT, adverse effects related to endoscopic hemostatic therapy were not estimable due to double-zero events.[99] Based on proportional meta-analyses of single-arm cohort-type data, the pooled rate of adverse effects with endoscopic hemostatic therapy was 5% (95% CI 2% to 12%),[99-101, 105-108, 110, 112] and without endoscopic hemostatic therapy was 0% (95% CI 0% to 0.04%).[99-101]

The panel judged these effect estimates as highly uncertain due to low event rates and the fragility of the RCT and observational data. For non-bleeding visible vessels in MWT, the panel determined that the desirable and undesirable effects of endoscopic hemostatic therapy compared to no therapy were unclear. For adherent clots, the panel determined that both the desirable and undesirable effects of endoscopic hemostatic therapy were trivial.

Certainty in the evidence of effects

Very low certainty of evidence due to serious risk of bias and very serious imprecision.

Other EtD criteria and considerations

The panel assumed patients likely do not have important uncertainty or variability in valuing the main outcome of rebleeding. The costs of endoscopic hemostatic therapy were deemed moderate, yet no studies have assessed its cost-effectiveness compared to no endoscopic hemostatic therapy. The panel judged endoscopic hemostatic therapy likely to be acceptable, feasible, and unlikely to adversely impact equity-deserving groups.

Conclusions and research needs

For patients with MWT with non-bleeding visible vessels, the panel could not determine whether the balance of effects favoured endoscopic hemostatic therapy or no endoscopic hemostatic therapy due to very low certainty evidence and the fragility of results. For patients with MWT with adherent clots, the panel judged that the balance of effects does not favour either endoscopic hemostatic therapy or no endoscopic hemostatic therapy. Notably, the rebleeding rates were very low without endoscopic hemostatic therapy. Therefore, the panel did not anticipate a significant benefit from endoscopic hemostatic therapy for either non-bleeding visible vessels or adherent clots in the context of MWT and expressed concerns about potentially aggravating bleeding with such therapy.

Given the uncertainty surrounding the benefits and the potential harms of endoscopic hemostatic therapy and its moderate costs, the panel issued a conditional recommendation against endoscopic hemostatic therapy for MWT with non-bleeding vessels or adherent clots. This decision aligns with peptic ulcer bleeding guidelines concerning adherent clots, which advise against endoscopic intervention for lesions with similarly low rebleeding rates.[10, 13] However, for non-bleeding visible vessels, this recommendation diverges from peptic ulcer bleeding guidelines, as the rebleeding risk in MWT appears to be much lower, thereby justifying the decision against endoscopic therapy. The panel highlighted the need for more comparative studies to increase the certainty of the evidence. Additionally, understanding the natural history of visible vessels or adherent clots in the context of MWT, especially in the era of proton pump inhibitor (PPI) treatment, is crucial.

7c. Endoscopic Hemostatic Therapy vs. No Endoscopic Hemostatic Therapy in Clean-based Ulcers or Pigmented Spots

Evidence Summary

We did not find any RCT that addressed this question. One comparative cohort study included 52 patients who did not receive endoscopic hemostatic therapy and only two who did, making comparative analysis unfeasible.[103] Proportional meta-analyses of single-arm cohort-type data were conducted on two studies involving patients with MWT who had flat pigmented spots or clean-based ulcers and received endoscopic hemostatic therapy and on four studies involving those who did not receive endoscopic hemostatic therapy.[101, 103, 113, 114] Overall, six patients received endoscopic hemostatic therapy, and 154 did not.[101, 103, 113, 114] None of the studies provided data on the critical outcome of further bleeding, nor important outcomes of mortality, units of blood transfusions received and the length of hospitalization. However, all studies provided data on 7-day rebleeding.

There was no direct evidence of adverse effects from endoscopic hemostatic therapy in patients with MWT with flat-pigmented spots or clean-based ulcers. Therefore, indirect evidence was obtained through proportional meta-analyses of single-arm cohort-type data from nine studies on patients with bleeding MWT who underwent endoscopic hemostatic therapy.[99-101, 105-108, 110, 112] A proportional meta-analysis was also performed of single-arm cohort-type data from three studies on patients with flat-pigmented spot or clean-based ulcers who did not receive endoscopic hemostatic therapy.[99-101] The EtD framework is in *Appendix 4.*

Benefits, harms, and burden

The pooled rebleeding rate for patients who received endoscopic hemostatic therapy was 0% (95% CI 0% to 0.5%; range 0% to 0%).[103, 114] For those who did not receive endoscopic hemostatic therapy, the pooled rebleeding rate was also 0% (95% CI 0% to 0.02%; range 0% to 0%).[101, 103, 113, 114] The pooled rate of adverse effects with endoscopic hemostatic therapy was 5% (95% CI 2% to 12%),[99-101, 105-108, 110, 112] and without endoscopic hemostatic therapy was 0% (95% CI 0% to 0.04%).[99-101] The panel judged that the desirable effects of endoscopic hemostatic therapy were trivial, and the undesirable effects were small.

Certainty in the evidence of effects

Very low certainty of evidence due to serious risk of bias, very serious imprecision, and serious indirectness due to the lack of comparative data.

Other EtD criteria and considerations

The panel assumed patients likely do not have important uncertainty or variability in valuing the main outcome of rebleeding. The costs of endoscopic hemostatic therapy were deemed moderate. There was no published cost-effectiveness analysis. However, when benefits are minimal, even modest procedure costs can lead to poor cost-effectiveness ratios. The panel judged endoscopic hemostatic therapy likely to be acceptable, feasible, and unlikely to adversely impact equity-deserving groups.

Conclusions and research needs

For patients with MWT with flat pigmented spots or clean-based ulcers, the panel determined that the balance of desirable and undesirable effects probably favours no endoscopic hemostatic therapy. These patients have a very low risk of rebleeding, which significantly reduces the potential benefits and increases the potential harms of endoscopic intervention. As a result, the panel issued a conditional recommendation against endoscopic hemostatic therapy based on very low certainty evidence. This aligns with peptic ulcer bleeding guidelines, which advise against endoscopic intervention for such lesions.[10, 13]

Dieulafoy's Lesion (DL)

Question 8: Should patients with upper gastrointestinal bleeding (UGIB) from Dieulafoy's lesion receive one endoscopic hemostatic therapy versus another endoscopic hemostatic therapy?

Recommendations:

8a: In patients with UGIB from Dieulafoy's lesion, we suggest either endoscopic band ligation with or without epinephrine injection or endoscopic through-the-scope clip (TTSC) placement with or without epinephrine injection (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).

8b: In patients with UGIB from Dieulafoy's lesion, we suggest either mechanical devices (endoscopic band ligation or endoscopic through-the-scope clip (TTSC) placement) with or without epinephrine injection or contact thermal devices (heater probe, bipolar electrocoagulation) with or without epinephrine injection (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).

8c: In patients with UGIB from Dieulafoy's lesion, we cannot make a recommendation for or against the use of cap-mounted clips over conventional endoscopic hemostatic therapy.

8d: In patients with upper GI bleeding from Dieulafoy's lesion, we suggest either mechanical devices (endoscopic band ligation or endoscopic through-the-scope clip (TTSC) placement) with or without epinephrine injection or injection of sclerosants with or without epinephrine injection (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).

8a. Endoscopic Band Ligation (EBL) with or without epinephrine injection vs. Endoscopic Through-the-scope-clip (TTSC) Placement with or without epinephrine injection

Evidence Summary

We identified two systematic reviews that addressed this question.[115, 116] The first review combined observational data with RCT data in its meta-analyses, introducing potential bias due to the inherent differences in study designs.[115] The second review included one RCT relevant to this question.[116] To provide a more robust comparison between EBL and TTSC in patients with DL, we conducted our own systematic reviews and meta-analyses that included two RCTs and two comparative cohort studies, analyzed separately.[117-120] Epinephrine injection was used in some patients in both groups to reduce active bleeding and improve visualization, but no subgroup data for patients treated with and without epinephrine were available.[117-120] One comparative cohort study included in the first review was excluded from our meta-analyses as it only provided data for three patients treated with EBL and nine patients treated with TTSC, falling below our predetermined threshold of 10 patients for each treatment group.[121] All studies reported further bleeding, failure to achieve immediate hemostasis, rebleeding, and mortality.[117-120] Since all rebleeding episodes occurred within seven days, we classified all rebleeding and further bleeding events as 7-day outcomes to avoid double counting 7-day and 30-day outcomes. One RCT did not report the need for additional hemostatic therapy.[119] One RCT reported adverse effects.[120]

Additionally, we conducted proportional meta-analyses of single-arm cohort-type data from ten studies on EBL[117-120, 122-127] and 13 studies on TTSC.[40, 117-120, 128-136] The results of the proportional meta-analyses were presented as supplementary data in the Evidence Profile Table but were not included in the EtD framework due to the lack of direct comparison. The EtD framework is in *Appendix 5.*

Benefits, harms, and burden

Based on meta-analyses of two RCTs, the relative and absolute effects of EBL compared to TTSC on 7-day further bleeding and rebleeding in patients with DL were highly uncertain due to the small sample size and very low event rates (RR 0.66, 95% CI 0.09 to 5.03; ARR 22 fewer per 1000; 95% CI 59 fewer to 260 more).[119, 120] 30-day mortality and adverse effects were not estimable due to double-zero events. Failure to achieve immediate hemostasis was also not estimable due to double-zero events. When considering "immediate hemostasis," EBL showed no difference compared to TTSC (RR 1.00, 95% CI 0.92 to 1.09; ARR 1 fewer per 1000, 95% CI 1 fewer to 1 fewer). EBL also appeared to have no impact on additional hemostatic therapy (RR 1.00, 95% CI 0.07 to 14.34; ARR 0 fewer per 1000, 95% CI 72 fewer to 1000 more), although this estimate was very imprecise.[120]

A systematic review of two comparative cohort studies suggested that EBL may reduce 7-day further bleeding, rebleeding, and additional hemostatic therapy in patients with DL.[117, 118] The risk ratio (RR) was the same for all three outcomes (RR 0.22, 95% CI 0.05 to 0.95, ARR 166 fewer per 1000, 95% CI 202 fewer to 11 fewer).[117, 118] Failure to achieve immediate hemostasis and 30-day mortality were not estimable due to double-zero events. Compared to TTSC, EBL showed no difference in achieving immediate hemostasis (RR 1.00, 95% CI 0.95 to 1.06; ARR 1 fewer per 1000, 95% CI 1 fewer to 1 fewer).[117, 118]

The panel prioritized the systematic review of RCTs over cohort studies, given the limitations and inherent selection bias with the latter. They judged the effect estimates of 7-day further bleeding and rebleeding highly uncertain due to low event rates and the fragility of the RCT and observational data. Yet, both EBL and TTSC appeared highly effective in achieving immediate hemostasis. Therefore, the desirable effects of EBL compared to TTSC remain unclear, while the undesirable effects of EBL relative to TTSC were deemed trivial.

Certainty in the evidence of effects

Very low certainty of evidence due to serious risk of bias and very serious imprecision.

Other EtD criteria and considerations

There was no research evidence on patients' values and preferences in the context of DL. However, the panel assumed patients likely do not have important uncertainty or variability in valuing the critical

outcome of further bleeding. The cost difference between EBL and TTSC was considered negligible, with no cost-effectiveness studies comparing the two. The panel judged EBL probably acceptable, feasible, and unlikely to adversely impact equity-deserving groups.

Conclusions and research needs

For patients with UGIB from DL, the panel could not determine whether the balance of effects favoured EBL or TTSC due to very low certainty evidence. Consequently, the panel issued a conditional recommendation for either EBL or TTSC, both of which can be performed with or without epinephrine injection. They highlighted the need for more comparative studies. However, conducting RCTs on DL is challenging due to their rarity, intermittent nature of bleeding, and interobserver variability in diagnosis, as they may be misdiagnosed as small ulcers. Until more evidence becomes available, clinicians should consider individual patient factors (e.g. lesion location, accessibility), the availability of devices, and clinician expertise when choosing between these two interventions. The panel expressed concerns that TTSC might be less effective than EBL, as EBL can aspirate and ligate vessels originating from the submucosal layers.

8b. Mechanical Modalities (Endoscopic Band Ligation (EBL) / Endoscopic Through-the-scope Clip (TTSC) Placement) With or Without Epinephrine Injection vs. Contact Thermocoagulation With or Without Epinephrine Injection

Evidence Summary

We did not find any RCTs addressing this question. Two comparative cohort studies compared mechanical versus contact thermal therapies in patients with UGIB from DL.[125, 137] One prospective cohort study compared EBL with bipolar electrocoagulation in patients with non-variceal UGIB and provided subgroup data on DL.[125] Another study provided subgroup data from two RCTs and prospective cohort studies, comparing Doppler endoscopic probe (DEP) guided treatments versus visually guided hemostasis (VG).[137] This study included 77 patients who were treated with either mechanical modalities such as TTSC or cap-mounted clips or thermal modalities like heater probe or multipolar electrocoagulation, regardless of DEP use.[137] Only seven patients received cap-mounted clips, and no subgroup data was provided to differentiate between TTSC or cap-mounted clips.[137] Patients in the DEP cohort were more likely to undergo mechanical treatments than the VG cohort (100% vs. 49.2%;

p<0.001), which could introduce a confounding factor.[137] Epinephrine injection was used in some patients in both groups, but no subgroup data was provided.[125, 137]

One study provided data on 7-day further bleeding, 7-day rebleeding, and failure to achieve immediate hemostasis,[125] while another reported 30-day rebleeding and adverse effects.[137] Both studies reported additional hemostatic therapy, but neither reported mortality.[125, 137]

We performed proportional meta-analyses using single-arm cohort-type data from ten studies on EBL,[117-120, 122-127] 13 studies on TTSC,[40, 117-120, 128-136] and four studies on thermal modalities.[125, 138-140] The results were provided as supplementary data in the Evidence Profile Table. However, due to the lack of direct comparative data, they were not included in the EtD framework, which is available in *Appendix 5.*

Benefits, harms, and burden

Based on one cohort study, the relative and absolute effects of mechanical modalities (EBL) compared to thermal modalities on 7-day further bleeding (RD -0.21, 95% CI -0.45 to 0.02; ARR 210 fewer per 1000, 95% CI 450 fewer to 20 more), failure to achieve immediate hemostasis (RD -0.14, 95% CI -0.36 to 0.07; ARR 140 fewer per 1000, 95% CI 360 fewer to 70 more), and 7-day rebleeding (RD -0.07, 95% CI -0.25 to 0.11; ARR 70 fewer per 1000, 95% CI 250 fewer to 110 more) were highly uncertain due to the small sample size and very low event rates.[125] Based on one cohort study, the relative and absolute effects of mechanical modalities (TTSC) compared to thermal modalities on 30-day rebleeding were also highly uncertain (RR 0.81, 95% CI 0.40 to 1.64; ARR 61 fewer per 1000, 95% CI 194 fewer to 206 more).[137] A meta-analysis of the 2 cohort studies suggested that mechanical modalities may reduce the need for additional hemostatic therapy, with surgery being the most common form (RR 0.14, 95% CI 0.03 to 0.77; ARR 153 fewer per 1000, 95% CI 172 fewer to 41 fewer), but the effect estimate was very imprecise.[125, 137] For adverse effects, mechanical modalities appeared to have little to no impact compared to thermal modalities (RR 1.35, 95% CI 0.13 to 14.23; ARR 11 more per 1000, 95% CI 28 fewer to 427 more), but the effect estimate was very imprecise.[137]

The panel judged the desirable and undesirable effects of mechanical modalities as uncertain compared to contact thermal modalities.

Certainty in the evidence of effects

Very low certainty of evidence due to serious risk of bias and very serious imprecision. The evidence was not further downgraded for indirectness related to the small number of patients who received cap-mounted clips.

Other EtD criteria and considerations

The panel assumed patients likely do not have important uncertainty or variability in valuing the critical outcome of further bleeding. The cost difference between mechanical and thermal modalities was considered negligible, and no cost-effectiveness studies were found. The panel judged mechanical modalities as probably acceptable, feasible, and unlikely to adversely impact equity-deserving groups.

Conclusions and research needs

For patients with UGIB from DL, the panel was unable to ascertain whether the balance of effects favoured mechanical (EBL/TTSC) or contact thermal modalities due to very low certainty evidence from cohort studies and highly imprecise results. Since both modalities appeared effective and safe, the panel issued a conditional recommendation for using either mechanical or contact thermal modalities, with or without epinephrine injection. The panel emphasized the need for more comparative studies.

8c. Cap-mounted Clip vs. Conventional Endoscopic Hemostatic Therapy

Evidence Summary

We found one RCT comparing cap-mounted clips to conventional endoscopic hemostatic therapy (TTSC or bipolar electrocoagulation) in patients with non-variceal UGIB.[141] A small subgroup of patients had DL (two in the cap-mounted clip group and three in the standard endoscopic treatment group), but the data was insufficient for meaningful analysis.[141]

Most evidence for cap-mounted clips in treating DL came from case series and case reports, with those involving fewer than ten patients excluded from this guideline's evidence synthesis. A retrospective cohort study evaluated cap-mounted clips for non-variceal UGIB, perforations, and fistulas.[142] This study also used propensity score matching to compare cap-mounted clips with "standard endoscopic therapy" for DL, although it did not define the latter, aside from excluding epinephrine injection as a monotherapy.[142] Further bleeding, failure to achieve immediate hemostasis, mortality, and the need for additional hemostatic therapy were not reported for the "standard endoscopic therapy" group. All

rebleeding occurred within five days and was the only outcome available for comparative analysis.[142] Adverse effects were not reported.[142]

Another cohort study included patients from two RCTs and prospective cohort studies, comparing Doppler endoscopic probe (DEP) guided treatments to visually guided hemostasis (VG).[137] It included 77 patients with DL treated with either mechanical modalities like TTSC or cap-mounted clips or thermal modalities such as heater probe or bipolar electrocoagulation, regardless of DEP use.[137] However, only seven patients received cap-mounted clips, and no subgroup data were provided.[137] This study was excluded from our evidence synthesis as it did not meet our pre-defined threshold of 10 patients per treatment group.[137]

A large retrospective study provided indirect evidence regarding the safety of cap-mounted clips in 1517 patients with refractory bleeding, perforation, fistula, and anastomotic dehiscence.[143]

The EtD framework is in *Appendix 5.*

Benefits, harms, and burden

Based on data from a comparative cohort study, the relative and absolute effects of cap-mounted clips versus conventional endoscopic therapy on 7-day rebleeding in patients with DL were highly uncertain due to the small sample size and very low event rates (RR 0.50, 95% CI 0.14 to 1.73; ARR 150 fewer per 1000, 95% CI 258 fewer to 219 more).[142] Among the 20 patients treated with cap-mounted clips for DL, 15.0% had 7-day further bleeding, none failed to achieve immediate hemostasis, and 10.0% required additional hemostatic therapy.[142]

Based on one cohort study, the overall and severe adverse event rates of cap-mounted clips were 1.7% and 0.59%, respectively.[143]

The panel judged the effect estimate of 7-day rebleeding as highly uncertain due to low event rates, small sample size, and the inherent bias associated with observational design. As a result, the desirable effects of cap-mounted clips over conventional endoscopic hemostatic therapy remained unclear. Due to a lack of comparative data, the undesirable effects of cap-mounted clips were also uncertain.

Certainty in the evidence of effects

Very low certainty of evidence due to serious risk of bias, very serious imprecision, and serious indirectness due to the lack of a clear definition for "standard endoscopic therapy" in the cohort study.

Other EtD criteria and considerations

The panel assumed that patients likely do not have important uncertainty or variability in valuing the critical outcome of further bleeding. The costs of cap-mounted clips compared to conventional endoscopic therapy were considered moderate. There were no cost-effectiveness studies. The panel deemed cap-mounted clips to be probably acceptable and unlikely to adversely impact equity-deserving groups. Nevertheless, feasibility may vary depending on access and training to ensure the safe and effective application of these systems, as well as proper management of any complications or failures.

Conclusions and research needs

For patients with UGIB from DL, the panel was unable to ascertain whether the balance of effects favoured cap-mounted clips or conventional endoscopic therapy due to very low certainty evidence from a cohort study and highly imprecise results. The panel also expressed concerns about the higher upfront costs of the cap-mounted clips and the challenges involved in retrieval if misapplication occurs. Consequently, the panel was unable to make a recommendation for or against the use of cap-mounted clips over conventional endoscopic hemostatic therapy for DL. They emphasized the need for well-designed RCT.

8d. Mechanical Modalities (Endoscopic Band Ligation (EBL) / Endoscopic Through-the-scope Clip (TTSC) Placement) With or Without Epinephrine Injection vs. Injection of Sclerosants With or Without Epinephrine

Evidence Summary

We did not identify any RCTs that compared EBL with injection of sclerosants. One RCT included 107 patients with UGIB due to DL and compared aethoxysklerol injection with TTSC placement alone or combined with aethoxysklerol injection.[144] Epinephrine injection was not used in this study. The study defined "successful endoscopic hemostasis" as the cessation of bleeding during the index endoscopy without subsequent rebleeding and "unsuccessful endoscopic hemostasis" as any rebleeding occurring within 48 hours post-index endoscopy. The study did not provide outcome data for further bleeding, failure to achieve immediate hemostasis, the need for additional hemostatic therapy, mortality, or

adverse effects.[144] All rebleeding cases occurred within 48 hours and were considered in the 7-day rebleeding outcome.[144]

No comparative cohort study was identified.

We performed proportional meta-analyses using single-arm cohort-type data from 13 studies on TTSC[40, 117-120, 128-136] and three studies on injection of sclerosants,[132, 145, 146] with some patients in both groups receiving epinephrine injections. The results were provided as supplementary data in the Evidence Profile Table but were not included in the EtD framework due to the lack of direct comparative data. The EtD framework is in *Appendix 5.*

Benefits, harms, and burden

Based on data from one RCT, the relative and absolute effects of TTSC versus injection of sclerosants on 7-day rebleeding in patients with DL were highly uncertain due to the small sample size and very low event rates (RR 0.80, 95% CI 0.36 to 1.77; ARR 57 fewer per 1000, 95% CI 181 fewer to 218 more).[144] No comparative data were available for other outcomes.

The study also reported a higher risk of 7-day rebleeding with TTSC alone compared to when combined with sclerosant injection (RR 6.77, 95% CI 0.80 to 51.80; ARR 192 more per 1000, 95% CI 4 fewer to 1000 more).[144] However, the effect estimate was very imprecise due to very low event rates and the small sample size.[144] As this comparison was not part of our predefined question and the study had serious risk of bias—such as unclear allocation sequence generation and concealment—the panel deemed it inappropriate to draw conclusions regarding the effects of combining TTSC with sclerosant injection over either treatment alone.

Proportional meta-analyses of single-arm cohort-type data suggested that both TTSC and injection of sclerosants had similar 7-day further bleeding rates (14%, 95% CI 11% to 19% vs. 14%, 95% CI 8% to 23%) and adverse effects (0%).[40, 117-120, 128-136, 145, 146]

The panel judged the effect estimates as highly uncertain due to low event rates, small sample size, and high risk of bias. As a result, the desirable effects of TTSC over injection of sclerosants remained unclear. Due to a lack of comparative data, the undesirable effects of TTSC compared to injection of sclerosants were also uncertain.

Certainty in the evidence of effects

Very low certainty of evidence due to serious risk of bias and very serious imprecision. Specifically, the panel expressed concerns about the lack of reporting of allocation sequence generation and baseline characteristics of the included patients in the RCT.[144]

Other EtD criteria and considerations

The panel assumed patients likely do not have important uncertainty or variability in valuing the main outcome of rebleeding. The costs of TTSC compared to injection of sclerosants were considered negligible. There were no cost-effectiveness studies. The panel judged TTSC to be probably acceptable, feasible, and unlikely to adversely impact equity-deserving groups.

Conclusions and research needs

For patients with UGIB from DL, the panel was unable to determine whether the balance of effects favoured mechanical modalities (EBL / TTSC) or injection of sclerosants due to very low certainty evidence from an RCT and highly imprecise results. Since both interventions appeared to be effective and safe, the panel issued a conditional recommendation for using either mechanical modalities or injection of sclerosants, with or without epinephrine injection. The panel highlighted the need for more comparative studies.

Question 9: Should patients with upper GI bleeding from Dieulafoy's lesion receive injection of epinephrine alone versus other endoscopic hemostatic therapies?

Recommendations:

9a: In patients with upper GI bleeding from Dieulafoy's lesion, we suggest against epinephrine injection alone over mechanical devices (endoscopic band ligation (EBL) or endoscopic through-the-scope clip (TTSC) placement) (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).

9b: In patients with upper GI bleeding from Dieulafoy's lesion, we suggest against epinephrine injection alone over thermal devices (heater probe, bipolar or multipolar electrocoagulation) (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).

9a. Epinephrine Injection Alone vs. Mechanical Modalities (Endoscopic Band Ligation (EBL) / Endoscopic Through-the-scope Clip (TTSC) Placement)

Evidence Summary

We identified three RCTs that addressed this question.[121, 123, 133] One RCT compared epinephrine injection alone to EBL, another compared epinephrine injection alone to endoscopic TTSC placement, and the third compared epinephrine injection alone with either EBL or TTSC.[121, 123, 133] We conducted meta-analyses of these three RCTs. [121, 123, 133] Two of them reported further bleeding, failure to achieve immediate hemostasis, and mortality,[121, 133] while all three reported rebleeding and the need for additional hemostatic therapy. Notably, only one detailed the timing of the rebleeding, noting that all rebleeding events occurred within 48 hours after the initial endoscopy.[123] To avoid double-counting of 7-day and 30-day outcomes, we classified all rebleeding cases under the 7-day outcome. Adverse effects associated with the interventions were reported in only one RCT.[133]

We also found two comparative cohort studies that compared epinephrine injection alone with EBL or TTSC in DL.[147, 148] However, both studies were excluded from evidence synthesis as they involved fewer than ten patients for a specific type of endoscopic therapy.

The EtD framework is in *Appendix 5.*

Benefits, harms, and burden

Meta-analyses of three RCTs suggested that epinephrine injection alone may increase the risk of 7-day further bleeding (RR 4.37, 95% CI 1.43 to 13.33; ARR 361 more per 1000, 95% CI 46 more to 1000 more), failure to achieve immediate hemostasis (RR 2.49, 95% CI 0.52 to 11.82; ARR 106 more per 1000, 95% CI 34 fewer to 773 more), 7-day rebleeding (RR 7.46, 95% CI 1.81 to 30.76; ARR 170 more per 1000, 95% CI 21 more to 783 more), and additional hemostatic therapy (RR 10.47, 95% CI 2.62 to 41.86; ARR 249 more per 1000, 95% CI 43 more to 1000 more), with no significant subgroup differences between EBL, TTSC, or EBL/TTSC.[121, 123, 133] 30-day mortality and adverse effects were not estimable due to double-zero events.

The panel judged the desirable effects of epinephrine injection alone, when compared to EBL or TTSC, as trivial, while the undesirable effects were large.

Certainty in the evidence of effects

Very low certainty of evidence due to serious risk of bias and very serious imprecision.

Other EtD criteria and considerations

The panel assumed patients likely do not have important uncertainty or variability in valuing the critical outcome of further bleeding. The costs of epinephrine injection alone compared to EBL or TTSC were considered negligible. No cost-effectiveness studies were found. The panel judged epinephrine injection alone to be probably acceptable and feasible and unlikely to adversely impact equity-deserving groups.

Conclusions and research needs

For patients with UGIB from DL, the panel judged that the balance of effects likely favoured EBL or TTSC over epinephrine injection alone. As a result, the panel made a conditional recommendation against epinephrine injection alone over mechanical modalities (EBL or TTSC). While this conditional recommendation serves as guidance for current clinical practice, there is a need for more well-designed comparative studies to improve the precision of available data for the formulation of a stronger recommendation.

9b. Epinephrine Injection Alone vs. Thermocoagulation

Evidence Summary

We did not identify any RCTs that addressed this question. We found one comparative cohort study involving 21 patients with DL, which compared epinephrine injection alone with epinephrine injection and heater probe coagulation.[138] All rebleeding cases occurred during hospitalization, though the exact timing was not specified. For consistency and to prevent double counting between 7-day and 30-day outcomes, we classified these rebleeding events under the 7-day outcome.

We did not identify any study that assessed non-contact thermocoagulation in DL.

The EtD framework is available in *Appendix 5.*

Benefits, harms, and burden

Based on one cohort study, epinephrine injection alone may increase the risk of 7-day further bleeding (RD 0.45, 95% CI 0.15 to 0.76; ARR 450 more per 1000, 95% CI 150 more to 760 more), failure to achieve immediate hemostasis (RD 0.27, 95% CI -0.01 to 0.56; ARR 270 more per 1000, 95% CI 10 fewer to 560

more), 7-day rebleeding (RD 0.18, 95% CI -0.08 to 0.44; ARR 180 more per 1000, 95% CI 80 fewer to 440 more), and the need for additional hemostatic therapy (RD 0.45, 95% CI 0.15 to 0.76; ARR 450 more per 1000, 95% CI 150 more to 760 more).[138] However, these effect estimates were very imprecise. Adverse effects were not estimable due to double-zero events.[138] Epinephrine injection alone may have little to no impact on 30-day mortality (RD 0.09, 95% CI -0.13 to 0.31; ARR 90 more per 1000, 95% CI 130 fewer to 310 more), but the estimate was also very imprecise.

The panel judged the desirable effects of epinephrine injection alone, when compared to contact thermocoagulation, as trivial, while the undesirable effects were large.

Certainty in the evidence of effects

Very low certainty of evidence due to serious risk of bias and very serious imprecision.

Other EtD criteria and considerations

The panel assumed patients likely do not have important uncertainty or variability in valuing the critical outcome of further bleeding. The costs of epinephrine injection alone compared to contact thermocoagulation were considered negligible. No cost-effectiveness studies were found. The panel judged epinephrine injection alone to be probably acceptable and feasible and unlikely to adversely impact equity-deserving groups.

Conclusions and research needs

For patients with UGIB from DL, the panel judged that the balance of effects likely favoured contact thermocoagulation over epinephrine injection alone. As a result, the panel made a conditional recommendation against epinephrine injection alone over contact thermocoagulation. Although this conditional recommendation serves as guidance for current clinical practice, there is a need for well-designed comparative studies to improve the precision of available data, thereby facilitating the formulation of a stronger recommendation. Additionally, RCTs comparing thermocoagulation with mechanical modalities are needed to inform clinical decision-making, as both modalities appear superior to epinephrine injection alone.

Gastric Antral Vascular Ectasia (GAVE)

Question 10: Should patients with gastric antral vascular ectasia (GAVE) receive one endoscopic hemostatic therapy versus another endoscopic hemostatic therapy?

Recommendations:

10: In patients with gastric antral vascular ectasia (GAVE), we suggest against radiofrequency ablation (RFA) over argon plasma coagulation (APC) (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).

Evidence Summary

We identified five RCTs that compared EBL with APC in patients with GAVE (presented in PICO 11).[149-153] No RCTs were found for comparing one endoscopic hemostatic therapy versus another.

We identified one retrospective comparative cohort study that compared RFA with APC.[154] The study included 77 patients with GAVE, of whom 27 (33%) had cirrhosis.[154] Among these patients, 24 were treated with APC alone, 28 with RFA alone, and 25 received both modalities across multiple sessions.[154] Outcomes assessed were changes in hemoglobin level and the number of treatment sessions, evaluated 18 months before and after the index endoscopy.[154] Transfusion requirements, mortality, and adverse effects were not reported. It is possible that patients with more severe GAVE were preferentially selected for RFA due to its higher cost compared to APC.[154] No other comparative studies on different endoscopic hemostatic therapies for GAVE were found.

We identified a systematic review that included 33 non-comparative cohort studies on either RFA or APC.[155] However, this review did not include the comparative cohort study identified by our search.[154] Due to methodological concerns associated with comparing pooled results from single-arm non-comparative studies, this review was excluded from our evidence synthesis.[155]

We performed proportional meta-analyses of single-arm cohort-type data from five studies involving RFA in patients with "refractory" GAVE who had persistent anemia or gastrointestinal bleeding despite prior APC, EBL, or Nd-YAG laser treatments.[156-160] We also performed proportional meta-analyses of single-arm cohort-type data from nine studies involving APC in patients with GAVE.[46, 161-168] The results of these analyses were presented as supplementary data in the Evidence Profile Table but were not included in the EtD framework due to the lack of direct comparison. The EtD framework is in *Appendix 6.*

We also found six single-arm cohort studies on Nd:YAG laser,[56, 169-173] one on heater probe,[174] and two on cryotherapy[175, 176] in patients with GAVE, each with more than ten patients. However, the absence of

comparative studies led the panel to conclude that there was insufficient evidence to form recommendations regarding these interventions. The results of these studies are summarized in *Appendix 6.*

Benefits, harms, and burden

Non-cirrhotic patients treated with RFA alone underwent a mean of 2.2 treatment sessions, resulting in a mean hemoglobin (Hgb) increase of 0.7 g/L.[154] Cirrhotic patients treated with RFA alone averaged 2.4 sessions but showed no change in mean Hgb level (MD 0 g/L).[154] In contrast, non-cirrhotic patients treated with APC alone underwent a mean of 2.4 sessions, with a mean Hgb increase of 1.1 g/L, whereas cirrhotic patients averaged 2.7 sessions, with a mean Hgb increase of 0.3 g/L.[154] No data were available on the change in blood transfusion requirements, mortality, number of hospitalizations, or adverse effects.[154]

The minimally important difference (MID) in Hgb level in patients with GAVE is unknown. However, based on indirect evidence from two studies that assessed health-related quality of life in post-menopausal women and patients with arthritis, a 2g/dL decrease was found to be associated with a statistically significant and clinically meaningful decline in health utility.[177, 178] Consequently, the panel used a MID of 2g/dL as our decision threshold.

The panel judged that the desirable effects of RFA, in terms of fewer treatment sessions, and its undesirable effects, in terms of change in Hgb level (a critical outcome) compared to APC in GAVE, were trivial.

Certainty in the evidence of effects

Very low certainty of evidence due to serious risk of bias, very serious imprecision, and serious indirectness, particularly concerning the surrogate outcome of change in hemoglobin level in relation to the patient-important outcome of transfusion requirements.

Other EtD criteria and considerations

There is no research evidence on patients' values and preferences in the context of GAVE. However, the panel assumed patients likely do not have important uncertainty or variability in valuing the critical outcomes of change in hemoglobin levels and the units of blood transfused, as well as important outcomes like the number of endoscopy sessions and hospitalizations. The costs of RFA compared to

APC were considered large. There were no cost-effectiveness studies in patients with GAVE who had not failed prior APC treatments. The panel judged RFA probably acceptable and unlikely to adversely impact equity-deserving groups. However, feasibility may vary based on accessibility and expertise.

Conclusions and research needs

The panel judged that the balance of effects does not favour either RFA or APC in patients with GAVE. However, considering the large costs associated with RFA and its variable feasibility due to expertise and accessibility, the panel made a conditional recommendation against RFA over APC, particularly in patients who have not failed other treatments. The panel emphasized the need for RCTs that compare the effectiveness and safety of RFA versus APC or EBL in GAVE patients, focusing on long-term outcomes such as recurrence rates and transfusion requirements. These studies should also examine healthcare resource utilization, including hospitalization, transfusion requirements, and follow-up procedures associated with each treatment. Additionally, research should assess quality-adjusted life years and patient-important outcomes to better understand the impact of endoscopic interventions on quality of life.

Question 11: Should patients with gastric antral vascular ectasia (GAVE) receive endoscopic banding ligation versus other endoscopic hemostatic therapies?

Recommendations:

11: In patients with gastric antral vascular ectasia (GAVE), we suggest endoscopic band ligation over argon plasma coagulation (APC) (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).

Evidence Summary

We identified five RCTs that addressed this question, involving patients with cirrhosis or portal hypertension.[149-153] Among these, four trials included adult patients, while one included only pediatric patients.[149-153] Most patients (69%) presented with symptoms of overt bleeding. In two studies, endoscopic appearances were described: 13.2% of cases showed the watermelon stripe pattern, whereas 86.8% exhibited the diffuse punctuate pattern.[149, 151] Only one RCT confirmed GAVE through biopsy.[152] All studies followed their patients for six months. In accordance with the Cochrane policy for managing potentially problematic studies,[179] we did not include three of the RCTs in our systematic review because of internal data reliability issues that are further described in Appendix 6.[150, 152, 153]

A systematic review and meta-analysis of two RCTs compared EBL and APC in patients with GAVE.[149, 151] Both studies reported changes in hemoglobin levels, the units of blood transfusions needed, the number of endoscopic sessions required to obliterate lesions, and adverse effects.[149, 151] One study reported on the number of hospitalizations, while neither study provided data on mortality.[151]

We also performed a meta-analysis of five comparative cohort studies comparing EBL and APC in GAVE.[180-184] In these studies, 46% of the patients had cirrhosis, while 49% presented with overt bleeding.[180-184] Only one study provided data on endoscopic patterns, indicating that patients showed either the watermelon stripe pattern or the diffuse punctate pattern, each occurring in 50% of cases.[180] The mean follow-up across these studies ranged from 10 to 26 months.[180-184] None of the studies conducted adjusted analyses to account for variations in prognostic factors between groups that could potentially affect the outcomes.

The details of our assessment of these studies and the EtD framework are in *Appendix 6.*

Benefits

Meta-analyses of two RCTs suggested that compared to APC, EBL may increase hemoglobin (Hgb) level by 0.7 g/dL (95% CI 0.08 lower to 1.49 higher) over 6 months.[149, 151] EBL may also reduce the units of blood transfusions (MD 3.30 lower, 95% CI 4.45 lower to 2.15 lower), decrease the number of endoscopic sessions required for the obliteration of lesions (MD 1.51 lower, 95% CI 4.69 lower to 1.66 more), and lower the number of hospitalizations (MD 1.30 lower, 95% CI 2.24 lower to 0.36 lower).[149, 151] However, these estimates were very imprecise.[149, 151]

Similarly, meta-analyses of five comparative cohort studies suggested that EBL may increase Hgb level by 0.54 g/dL (95% CI 0.30 higher to 0.77 higher).[180-184] EBL may also reduce the units of blood transfusions (MD 1.90 lower, 95% CI 5.74 lower to 1.94 higher), decrease the number of endoscopic sessions required for the obliteration of lesions (MD 1.53 lower, 95% CI 3.94 lower to 0.89 more), and reduce the number of hospitalizations (MD 2.10 lower, 95% CI 3.82 lower to 0.38 lower), but these estimates were very imprecise.[180-184] EBL appeared to have little to no impact on mortality (RR 0.69, 95% CI 0.31 to 1.58; ARR 93 fewer per 1000, 95% CI 207 fewer to 174 more).[181, 183, 184]

The panel judged that the desirable effects of EBL compared to APC were small.

Harms and Burden

Meta-analyses of two RCTs suggested that EBL, compared to APC, may increase the risk of adverse effects (RD 0.16, 95% CI -0.29 to 0.61; ARR 160 more per 1000, 95% CI 290 fewer to 610 more).[149, 151] Similarly, meta-analyses of five RCTs also suggested that EBL may increase the risk of adverse effects (RR 1.93, 95% CI 0.60 to 6.18; ARR 32 more per 1000, 95% CI 14 fewer to 179 more). [180-184] However, these estimates were very imprecise due to low event rates. The adverse effects associated with EBL included post-banding ulcers, hypertrophied polyps, abdominal pain, nausea and vomiting. The panel considered these adverse effects to be minor. As a result, the panel judged that the undesirable effects of EBL compared to APC were small.

Certainty in the evidence of effects

Very low certainty of evidence due to serious risk of bias, very serious imprecision, and serious indirectness. The indirectness relates to using change in hemoglobin level as a surrogate outcome. Also, the RCTs included patients only with cirrhosis, who mostly presented with overt bleeding rather than occult bleeding with a diffuse punctate endoscopic pattern.

Other EtD criteria and considerations

The panel assumed patients likely do not have important uncertainty or variability in valuing the critical outcomes and important outcomes. The costs of EBL compared to APC were considered negligible. No cost-effectiveness studies were found. The panel judged EBL to be probably acceptable and feasible and unlikely to adversely impact equity-deserving groups.

Conclusions and research needs

The panel judged that the balance of effects probably favoured EBL over APC in patients with GAVE. Consequently, the panel issued a conditional recommendation for EBL over APC. The panel stressed the importance of conducting large, high-quality RCTs. Future research should also explore potential subgroup differences, focusing on different endoscopic patterns and patients with and without cirrhosis. These studies should prioritize long-term outcomes, such as recurrence rates and the durability of treatment effects in maintaining hemoglobin levels and reducing transfusion requirements. Additionally, they should also examine healthcare resource utilization, including hospitalization, transfusion requirements, and follow-up procedures associated with each treatment.

What are others saying and what is new in this guideline?

This guideline is the first to specifically address the endoscopic management of non-variceal non-peptic ulcer bleeding caused by conditions such as malignant UGIB, Mallory-Weiss tears (MWT), Dieulafoy's lesions (DL), and gastric antral vascular ectasia (GAVE). Also, this guideline, in contrast to many, is entirely based on high-quality systematic reviews and adopts the GRADE approach with evidence profiles and EtD framework for each recommendation, thereby enhancing the transparency and trustworthiness of the decision-making process.

Recent guidelines from the US, Canada, Europe and Asia on non-variceal UGIB have primarily focused on peptic ulcer bleeding and have not specifically addressed these conditions.[10, 11, 13, 14] The European Society of Gastrointestinal Endoscopy (ESGE) 2015 guidelines suggested consideration of endoscopic hemostasis for malignant UGIB, actively bleeding MWT, DL, and upper GI angioectasias, but no specific modalities were recommended due to insufficient evidence.[12] The older American Society of Gastrointestinal Endoscopy (ASGE) 2004 guidelines advised endoscopic therapy for vascular abnormalities such as DL and vascular malformations, as well as for ongoing or severely bleeding MWT, but they did not specify particular modalities or provide recommendations for malignant UGIB.[185]

Limitations of this guideline

The limitations of this guideline are inherent in the very low certainty of the evidence available for the questions addressed. For two recommendations concerning malignant UGIB (PICO 1a and 1b), there was no published direct or relevant indirect evidence. Consequently, the panel was surveyed to gather unpublished collective data to inform the decision-making process. It is important to note that the interpretation of these survey data is limited by factors such as recall bias and variations in individual provider practices. This process is explicitly noted for relevant recommendations. Furthermore, this guideline focuses on the endoscopic management of these conditions and does not cover pre- and post-endoscopic management. We acknowledge that not all aspects of managing these conditions are included in this guideline. The panel prioritized questions where there was clinical uncertainty or where new information might guide decision-making. Future updates could include new recommendations as evidence becomes available. The panel suggested actions based on the best evidence available when developing these guidelines. Some recommendations may change as new evidence emerges. Finally, the

recommendations are intended to help clinicians and patients make informed decisions, but they should not replace careful consideration of the individual clinical circumstances and patients' values and preferences.

Revision or adaptation of this guideline

Plans for updating this guideline

After this guideline is published, the CAG will maintain it by monitoring new evidence, reviewing it with experts, and revising it regularly.

Updating or adapting recommendations locally

While this guideline is developed for global application, adaptation will be necessary in many circumstances based on resource availability, feasibility, and acceptability of interventions. The EtD frameworks and the "Adolopment" model should guide adaptations.[186] Local guideline groups may leverage the evidence already gathered and appraised in these frameworks. By adding relevant local information, they can efficiently create local recommendations, requiring fewer resources than developing a guideline de novo.

Acknowledgments

The authors acknowledge Yuhong Yuan for supporting the literature search but not qualifying for authorship, and Nosheen Maqsood from the Canadian Association of Gastroenterology for administrative support of these guidelines.

Authorship

Contribution: F.T. wrote the first draft of the manuscript and revised the manuscript based on the authors' suggestions. Methodologists (F.T., N.F., M.C., N.C.) contributed evidence summaries to the guidelines, checked the manuscript's accuracy and coordinated the systematic reviews. All authors approved the content. A.N.B. and F.T. were the chair and co-chair of the panel. A.N.B., L.L. and F.T. led the panel meetings.

Appendices

Appendix 1: Disclosures and management of conflicts of interest

Appendix 2: Literature search strategies and PRISMA flow diagram

Appendix 3: Evidence Profiles and EtD Framework for upper gastrointestinal bleeding due to malignant tumours

Appendix 4: Evidence Profiles and EtD Framework for upper gastrointestinal bleeding due to Mallory-Weiss tears

Appendix 5: Evidence Profiles and EtD Framework for upper gastrointestinal bleeding due to Dieulafoy's lesion

Appendix 6: Evidence Profiles and EtD Framework for upper gastrointestinal bleeding due to gastric antral vascular ectasia

Tables

Table 1. Interpretation of strong and conditional recommendations

Implications for	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policy makers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation, according to the guideline, could be used as a quality criterion or performance indicator.	Policymaking will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision-making is appropriate.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the	This recommendation will likely be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and

	recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.	the related judgments, research evidence, and additional considerations) that determined the conditional recommendation will help identify possible research gaps.

Table 2. List of recommendations with strength of recommendation and certainty of evidence

Malignant Upper Gastrointestinal Bleeding	
1a.	In patients with active bleeding from malignant UGI tumours, we suggest conventional endoscopic hemostatic therapy (e.g. injection, thermal devices, mechanical devices, or a combination thereof) over no endoscopic hemostatic therapy (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).
1b.	In patients with active bleeding from malignant UGI tumours, we suggest topical hemostatic agents over no endoscopic hemostatic therapy (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).
2.	In patients with active bleeding from malignant UGI tumours, we cannot make a recommendation for or against any specific type of conventional endoscopic hemostatic therapy over another.
3.	In patients with active bleeding from malignant UGI tumours, we suggest topical hemostatic agents over conventional endoscopic hemostatic therapy (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).
4.	In patients with active bleeding from malignant UGI tumours, we suggest administering oncologic therapy following endoscopic hemostatic therapy rather than not providing oncologic therapy after endoscopic hemostatic therapy (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).
Mallory-Weiss Tears	
5.	In patients with active bleeding from Mallory-Weiss tears (spurting or oozing), we suggest endoscopic hemostatic therapy over no endoscopic hemostatic therapy (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).
6a.	In patients with active bleeding from Mallory-Weiss tears (spurting or oozing), we suggest endoscopic band ligation (EBL) or endoscopic through-the-scope clip (TTSC) placement over epinephrine injection alone (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).
6b.	In patients with active bleeding from Mallory-Weiss tears (spurting or oozing), we suggest endoscopic band ligation (EBL) or endoscopic through-the-scope clip (TTSC) placement (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).
7a.	In patients with Mallory-Weiss tears with non-bleeding visible vessels, we suggest against endoscopic hemostatic therapy (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).
7b.	In patients with Mallory-Weiss tears with non-bleeding adherent clots, we suggest against endoscopic hemostatic therapy (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).
7c.	In patients with Mallory-Weiss tears with non-bleeding clean based ulcers or flat pigmented spots, we suggest against endoscopic hemostatic therapy (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).
Dieulafoy's Lesions	

8a.	In patients with upper GI bleeding from Dieulafoy's lesion, we suggest either endoscopic band ligation (EBL) with or without epinephrine injection or endoscopic through-the-scope clip (TTSC) placement with or without epinephrine injection (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).
8b.	In patients with upper GI bleeding from Dieulafoy's lesion, we suggest either mechanical devices (endoscopic band ligation (EBL) or endoscopic through-the-scope clip (TTSC) placement) with or without epinephrine injection or contact thermal devices (heater probe, bipolar or multipolar electrocoagulation) with or without epinephrine injection (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).
8c.	In patients with upper GI bleeding from Dieulafoy's lesion, we cannot make a recommendation for or against the use of cap-mounted clips over conventional endoscopic hemostatic therapy.
8d.	In patients with upper GI bleeding from Dieulafoy's lesion, we suggest either mechanical devices (endoscopic band ligation (EBL) or endoscopic through-the-scope clip (TTSC) placement) with or without epinephrine injection or injection of sclerosants with or without epinephrine injection (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).
9a.	In patients with upper GI bleeding from Dieulafoy's lesion, we suggest against epinephrine injection alone over mechanical devices (endoscopic band ligation (EBL) or endoscopic through-the-scope clip (TTSC) placement) (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).
9b.	In patients with upper GI bleeding from Dieulafoy's lesion, we suggest against epinephrine injection alone over thermal devices (heater probe, bipolar electrocoagulation) (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).
Gastric Antral Vascular Ectasia	
10.	In patients with gastric antral vascular ectasia (GAVE), we suggest against radiofrequency ablation (RFA) over argon plasma coagulation (APC) (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).
11.	In patients with gastric antral vascular ectasia (GAVE), we suggest endoscopic band ligation over argon plasma coagulation (APC) (conditional recommendation, very low certainty of evidence ⨁⊖⊖⊖).

Table 3. Clinical questions formulated and prioritized

Malignant Upper Gastrointestinal Bleeding	
1.	Should patients with active bleeding from malignant UGI tumours receive endoscopic hemostatic therapy versus no endoscopic hemostatic therapy?
2.	Should patients with active bleeding from malignant UGI tumours receive one conventional endoscopic hemostatic therapy versus another conventional endoscopic hemostatic therapy?
3.	Should patients with active bleeding from malignant UGI tumours receive topical hemostatic agents versus conventional endoscopic hemostatic therapies?
4.	Should patients with active bleeding from malignant UGI tumours receive oncologic therapy after endoscopic hemostatic therapy versus no oncologic therapy after endoscopic hemostatic therapy?
Mallory-Weiss Tears	
5.	Should patients with active bleeding from Mallory-Weiss tears (spurting or oozing) receive endoscopic hemostatic therapy versus no endoscopic hemostatic therapy?
6.	Should patients with active bleeding from Mallory-Weiss tears (spurting or oozing) receive one endoscopic hemostatic therapy versus another endoscopic hemostatic therapy?

7.	Should patients with no active bleeding from Mallory-Weiss tears (non-bleeding visible vessels, adherent clots, flat pigmented spots, clean based ulcers) receive endoscopic hemostatic therapy versus no endoscopic hemostatic therapy?
Dieulafoy's Lesions	
8.	Should patients with upper GI bleeding from Dieulafoy's lesion receive one endoscopic hemostatic therapy versus another endoscopic hemostatic therapy?
9.	Should patients with upper GI bleeding from Dieulafoy's lesion receive injection of epinephrine alone versus other endoscopic hemostatic therapies?
Gastric Antral Vascular Ectasia	
10.	Should patients with gastric antral vascular ectasia (GAVE) receive one endoscopic hemostatic therapy versus another endoscopic hemostatic therapy?
11.	Should patients with gastric antral vascular ectasia (GAVE) receive endoscopic banding ligation (EBL) versus other endoscopic hemostatic therapies?

GI = gastrointestinal

Table 4. Critical or important outcomes for decision-making

Malignant Upper Gastrointestinal Bleeding	
1-3.	• Further bleeding (30-day) - critical • Overall mortality (6-month) - important • Failure to achieve immediate hemostasis - important • Rebleeding (30-day) - important • Number of units of blood transfusions needed - important • Length of hospitalization - important • Readmissions - important • Adverse effects – important
4.	• Further bleeding (30-day, 6-month) - critical (only 6-month) • Overall mortality (6-month) - critical • Failure to achieve immediate hemostasis - important • Rebleeding (30-day) - important • Number of units of blood transfusions needed - important • Length of hospitalization - important • Readmissions - important • Adverse effects - important
Mallory-Weiss Tears	
5-7.	• Further bleeding (7-day, 30-day) - critical (only 7-day) • Overall mortality - Important • Failure to achieve immediate hemostasis - Important • Rebleeding (7-day, 30-day) - important • Number of units of blood transfusions needed - Important • Length of hospitalization - Important • Adverse effects - important

Dieulafoy's Lesions	
8-9.	• Further bleeding (7-day, 30-day) – critical (only 7-day) • Failure to achieve immediate hemostasis - Important • Overall mortality – Important • Rebleeding (7-day, 30-day) - important • Adverse effects – Important • Additional hemostatic therapy (e.g. repeat endoscopic hemostatic therapy, radiologic embolization, surgery) - important
Gastric Antral Vascular Ectasia	
10-11.	• Change in units of blood transfusions needed - critical • Change in Hemoglobin level - critical • Overall mortality - Important • Number of endoscopic sessions required for obliteration of lesions - Important • Adverse effects – important

References

1. Institute of Medicine (US) Committee on Conflict of Interest in Medical Research E, and Practice. Conflict of Interest in Medical Research, Education, and Practice. In: B. L, M.J. F, eds. National Academies Press, 2009.
2. Schunemann HJ, Al-Ansary LA, Forland F, et al. Guidelines International Network: Principles for Disclosure of Interests and Management of Conflicts in Guidelines. Ann Intern Med 2015;163:548-53.
3. Peery AF, Crockett SD, Murphy CC, et al. Burden and Cost of Gastrointestinal, Liver, and Pancreatic Diseases in the United States: Update 2021. Gastroenterology 2022;162:621-644.
4. Barkun A, Sabbah S, Enns R, et al. The Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy (RUGBE): Endoscopic hemostasis and proton pump inhibition are associated with improved outcomes in a real-life setting. Am J Gastroenterol 2004;99:1238-46.
5. Hearnshaw SA, Logan RF, Lowe D, et al. Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. Gut 2011;60:1327-35.
6. Jairath V, Kahan BC, Gray A, et al. Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial. Lancet 2015;386:137-44.
7. Park HW, Jeon SW. Clinical Outcomes of Patients with Non-ulcer and Non-variceal Upper Gastrointestinal Bleeding: A Prospective Multicenter Study of Risk Prediction Using a Scoring System. Dig Dis Sci 2018;63:3253-3261.

8. Sey MSL, Mohammed SB, Brahmania M, et al. Comparative outcomes in patients with ulcer- vs non-ulcer-related acute upper gastrointestinal bleeding in the United Kingdom: a nationwide cohort of 4474 patients. Aliment Pharmacol Ther 2019;49:537-545.

9. Wuerth BA, Rockey DC. Changing Epidemiology of Upper Gastrointestinal Hemorrhage in the Last Decade: A Nationwide Analysis. Dig Dis Sci 2018;63:1286-1293.

10. Barkun AN, Almadi M, Kuipers EJ, et al. Management of Nonvariceal Upper Gastrointestinal Bleeding: Guideline Recommendations From the International Consensus Group. Ann Intern Med 2019;171:805-822.

11. Gralnek IM, Camus Duboc M, Garcia-Pagan JC, et al. Endoscopic diagnosis and management of esophagogastric variceal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2022;54:1094-1120.

12. Gralnek IM, Dumonceau JM, Kuipers EJ, et al. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2015;47:a1-46.

13. Laine L, Barkun AN, Saltzman JR, et al. ACG Clinical Guideline: Upper Gastrointestinal and Ulcer Bleeding. Am J Gastroenterol 2021;116:899-917.

14. Sung JJ, Chiu PW, Chan FKL, et al. Asia-Pacific working group consensus on non-variceal upper gastrointestinal bleeding: an update 2018. Gut 2018;67:1757-1768.

15. Committee on Standards for Developing Trustworthy Clinical Practice Guidelines BoHCSGR, Mancher M, Wolman DM, Greenfield S, Steinberg E, eds. Clinical Practice Guidelines We Can Trust: Washington, DC: National Academic Press

16. Qaseem A, Forland F, Macbeth F, et al. Guidelines International Network: toward international standards for clinical practice guidelines. Ann Intern Med 2012;156:525-31.

17. Schunemann HJ, Wiercioch W, Etxeandia I, et al. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. CMAJ 2014;186:E123-42.

18. Alonso-Coello P, Oxman AD, Moberg J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. BMJ 2016;353:i2089.

19. Alonso-Coello P, Schunemann HJ, Moberg J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. BMJ 2016;353:i2016.

20. Atkins D, Eccles M, Flottorp S, et al. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. BMC Health Serv Res 2004;4:38.

21. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383-94.

22. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.

23. Schunemann HJ, Best D, Vist G, et al. Letters, numbers, symbols and words: how to communicate grades of evidence and recommendations. CMAJ 2003;169:677-80.

24. Schunemann HJ, Mustafa R, Brozek J, et al. GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health. J Clin Epidemiol 2016;76:89-98.

25. Maluf-Filho F, Martins BC, de Lima MS, et al. Etiology, endoscopic management and mortality of upper gastrointestinal bleeding in patients with cancer. United European Gastroenterol J 2013;1:60-7.

26. Abu-Sbeih H, Szafron D, Elkafrawy AA, et al. Endoscopy for the diagnosis and treatment of gastrointestinal bleeding caused by malignancy. J Gastroenterol Hepatol 2022;37:1983-1990.

27. Sheibani S, Kim JJ, Chen B, et al. Natural history of acute upper GI bleeding due to tumours: short-term success and long-term recurrence with or without endoscopic therapy. Aliment Pharmacol Ther 2013;38:144-50.

28. Schatz RA, Rockey DC. Gastrointestinal Bleeding Due to Gastrointestinal Tract Malignancy: Natural History, Management, and Outcomes. Dig Dis Sci 2017;62:491-501.

29. Savides TJ, Jensen DM, Cohen J, et al. Severe upper gastrointestinal tumor bleeding: endoscopic findings, treatment, and outcome. Endoscopy 1996;28:244-8.

30. Allo G, Burger M, Chon SH, et al. Efficacy of endoscopic therapy and long-term outcomes of upper gastrointestinal tumor bleeding in patients with esophageal cancer. Scand J Gastroenterol 2023;58:1064-1070.

31. Di Fiore F, Lecleire S, Merle V, et al. Changes in characteristics and outcome of acute upper gastrointestinal haemorrhage: a comparison of epidemiology and practices between 1996 and 2000 in a multicentre French study. Eur J Gastroenterol Hepatol 2005;17:641-7.

32. Mertens A, Essing T, Roderburg C, et al. A Systematic Analysis of Incidence, Therapeutic Strategies, and In-hospital Mortality of Mallory-Weiss Syndrome in Germany. J Clin Gastroenterol 2024;58:640-649.

33. Ljubicic N, Budimir I, Pavic T, et al. Mortality in high-risk patients with bleeding Mallory-Weiss syndrome is similar to that of peptic ulcer bleeding. Results of a prospective database study. Scand J Gastroenterol 2014;49:458-64.

34. Juler GL, Labitzke HG, Lamb R, et al. The pathogenesis of Dieulafoy's gastric erosion. Am J Gastroenterol 1984;79:195-200.

35. Norton ID, Petersen BT, Sorbi D, et al. Management and long-term prognosis of Dieulafoy lesion. Gastrointest Endosc 1999;50:762-7.

36. Ali H, Bolick NL, Pamarthy R, et al. Inpatient outcomes of Dieulafoy's lesions in the United States. Proc (Bayl Univ Med Cent) 2022;35:291-296.

37. Chakinala RC, Solanki S, Haq KF, et al. Dieulafoy's Lesion: Decade-Long Trends in Hospitalizations, Demographic Disparity, and Outcomes. Cureus 2020;12:e9170.

38. Wang Y, Bansal P, Li S, et al. Dieulafoy's lesion of the upper GI tract: a comprehensive nationwide database analysis. Gastrointest Endosc 2021;94:24-34 e5.

39. Baxter M, Aly EH. Dieulafoy's lesion: current trends in diagnosis and management. Ann R Coll Surg Engl 2010;92:548-54.

40. Parra-Blanco A, Takahashi H, Mendez Jerez PV, et al. Endoscopic management of Dieulafoy lesions of the stomach: a case study of 26 patients. Endoscopy 1997;29:834-9.

41. Thomas A, Koch D, Marsteller W, et al. An Analysis of the Clinical, Laboratory, and Histological Features of Striped, Punctate, and Nodular Gastric Antral Vascular Ectasia. Dig Dis Sci 2018;63:966-973.

42. Kichloo A, Solanki D, Singh J, et al. Gastric Antral Vascular Ectasia: Trends of Hospitalizations, Biodemographic Characteristics, and Outcomes With Watermelon Stomach. Gastroenterology Res 2021;14:104-111.

43. Patel U, Desai R, Desai J, et al. Predictors of blood transfusion and in-hospital outcomes in patients with gastric antral vascular ectasia (GAVE): a nationwide population-based analysis. Ann Transl Med 2019;7:46.

44. Dulai GS, Jensen DM, Kovacs TO, et al. Endoscopic treatment outcomes in watermelon stomach patients with and without portal hypertension. Endoscopy 2004;36:68-72.

45. Gretz JE, Achem SR. The watermelon stomach: clinical presentation, diagnosis, and treatment. Am J Gastroenterol 1998;93:890-5.

46. Sebastian S, McLoughlin R, Qasim A, et al. Endoscopic argon plasma coagulation for the treatment of gastric antral vascular ectasia (watermelon stomach): long-term results. Dig Liver Dis 2004;36:212-7.

47. Yamada M, Ichikawa M, Takahara O, et al. Gastroduodenal vascular ectasia in patients with liver cirrhosis. Dig Endosc 1999;11:241-245.

48. Aryan M, Jariwala R, Alkurdi B, et al. The misclassification of gastric antral vascular ectasia. J Clin Transl Res 2022;8:218-223.

49. Schaube J, Herz R, Stolte M. [Water melon stomach or antrum gastritis--differential diagnostic aspects]. Z Gastroenterol 1994;32:493-6.

50. Langer G, Meerpohl JJ, Perleth M, et al. [GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables]. Z Evid Fortbild Qual Gesundhwes 2012;106:357-68.

51. Schunemann HJ, Osborne M, Moss J, et al. An official American Thoracic Society Policy statement: managing conflict of interest in professional societies. Am J Respir Crit Care Med 2009;180:564-80.

52. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol 2011;64:395-400.

53. Laine L, Spiegel B, Rostom A, et al. Methodology for randomized trials of patients with nonvariceal upper gastrointestinal bleeding: recommendations from an international consensus conference. Am J Gastroenterol 2010;105:540-50.

54. Ghrenassia E, Avouac J, Khanna D, et al. Prevalence, correlates and outcomes of gastric antral vascular ectasia in systemic sclerosis: a EUSTAR case-control study. J Rheumatol 2014;41:99-105.

55. DeLoughery TG, Jackson CS, Ko CW, et al. AGA Clinical Practice Update on Management of Iron Deficiency Anemia: Expert Review. Clin Gastroenterol Hepatol 2024;22:1575-1583.

56. Gostout CJ, Viggiano TR, Ahlquist DA, et al. The clinical and endoscopic spectrum of the watermelon stomach. J Clin Gastroenterol 1992;15:256-63.

57. Cochrane Handbook for Systematic Reviews of Interventions version 6.5 (updated August 2024). In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds, 2024.

58. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Ottawa, ON: Ottawa Hospital Research Institute, 2011.

59. Nieuwlaat R, Wiercioch W, Brozek JL, et al. How to write a guideline: a proposal for a manuscript template that supports the creation of trustworthy guidelines. Blood Adv 2021;5:4721-4726.

60. Martins BC, Wodak S, Gusmon CC, et al. Argon plasma coagulation for the endoscopic treatment of gastrointestinal tumor bleeding: A retrospective comparison with a non-treated historical cohort. United European Gastroenterol J 2016;4:49-54.

61. Park H, Ahn JY, Jung HY, et al. Can Endoscopic Bleeding Control Improve the Prognosis of Advanced Gastric Cancer Patients?: A Retrospective Case-Control Study. J Clin Gastroenterol 2017;51:599-606.

62. Kim YI, Choi IJ, Cho SJ, et al. Outcome of endoscopic therapy for cancer bleeding in patients with unresectable gastric cancer. J Gastroenterol Hepatol 2013;28:1489-95.

63. Koh KH, Kim K, Kwon DH, et al. The successful endoscopic hemostasis factors in bleeding from advanced gastric cancer. Gastric Cancer 2013;16:397-403.

64. Loftus EV, Alexander GL, Ahlquist DA, et al. Endoscopic treatment of major bleeding from advanced gastroduodenal malignant lesions. Mayo Clin Proc 1994;69:736-40.

65. Song IJ, Kim HJ, Lee JA, et al. Clinical Outcomes of Endoscopic Hemostasis for Bleeding in Patients with Unresectable Advanced Gastric Cancer. J Gastric Cancer 2017;17:374-383.

66. Suzuki H, Miho O, Watanabe Y, et al. Endoscopic laser therapy in the curative and palliative treatment of upper gastrointestinal cancer. World J Surg 1989;13:158-64.

67. Thosani N, Rao B, Ghouri Y, et al. Role of argon plasma coagulation in management of bleeding GI tumors: evaluating outcomes and survival. Turk J Gastroenterol 2014;25 Suppl 1:38-42.

68. Mustafa RA, Garcia CAC, Bhatt M, et al. GRADE notes: How to use GRADE when there is "no" evidence? A case study of the expert evidence approach. J Clin Epidemiol 2021;137:231-235.

69. Arena M, Masci E, Eusebi LH, et al. Hemospray for treatment of acute bleeding due to upper gastrointestinal tumours. Dig Liver Dis 2017;49:514-517.

70. Cahyadi O, Bauder M, Meier B, et al. Effectiveness of TC-325 (Hemospray) for treatment of diffuse or refractory upper gastrointestinal bleeding - a single center experience. Endosc Int Open 2017;5:E1159-E1164.

71. Chen YI, Barkun A, Nolan S. Hemostatic powder TC-325 in the management of upper and lower gastrointestinal bleeding: a two-year experience at a single institution. Endoscopy 2015;47:167-71.

72. Chen YI, Wyse J, Lu Y, et al. TC-325 hemostatic powder versus current standard of care in managing malignant GI bleeding: a pilot randomized clinical trial. Gastrointest Endosc 2020;91:321-328 e1.

73. Haddara S, Jacques J, Lecleire S, et al. A novel hemostatic powder for upper gastrointestinal bleeding: a multicenter study (the "GRAPHE" registry). Endoscopy 2016;48:1084-1095.

74. Hussein M, Alzoubaidi D, O'Donnell M, et al. Hemostatic powder TC-325 treatment of malignancy-related upper gastrointestinal bleeds: International registry outcomes. J Gastroenterol Hepatol 2021;36:3027-3032.

75. Lau JYW, Pittayanon R, Kwek A, et al. Comparison of a Hemostatic Powder and Standard Treatment in the Control of Active Bleeding From Upper Nonvariceal Lesions : A Multicenter, Noninferiority, Randomized Trial. Ann Intern Med 2022;175:171-178.

76. Martins BC, Abnader Machado A, Scomparin RC, et al. TC-325 hemostatic powder in the management of upper gastrointestinal malignant bleeding: a randomized controlled trial. Endosc Int Open 2022;10:E1350-E1357.

77. Meng ZW, Marr KJ, Mohamed R, et al. Long-Term Effectiveness, Safety and Mortality Associated with the Use of TC-325 for Malignancy-Related Upper Gastrointestinal Bleeds: A Multicentre Retrospective Study. J Can Assoc Gastroenterol 2019;2:91-97.

78. Pittayanon R, Khongka W, Linlawan S, et al. Hemostatic Powder vs Standard Endoscopic Treatment for Gastrointestinal Tumor Bleeding: A Multicenter Randomized Trial. Gastroenterology 2023;165:762-772 e2.

79. Pittayanon R, Prueksapanich P, Rerknimitr R. The efficacy of Hemospray in patients with upper gastrointestinal bleeding from tumor. Endosc Int Open 2016;4:E933-6.

80. Pittayanon R, Rerknimitr R, Barkun A. Prognostic factors affecting outcomes in patients with malignant GI bleeding treated with a novel endoscopically delivered hemostatic powder. Gastrointest Endosc 2018;87:994-1002.

81. Ramirez-Polo AI, Casal-Sanchez J, Hernandez-Guerrero A, et al. Treatment of gastrointestinal bleeding with hemostatic powder (TC-325): a multicenter study. Surg Endosc 2019;33:2349-2356.

82. Rodriguez de Santiago E, Burgos-Santamaria D, Perez-Carazo L, et al. Hemostatic spray powder TC-325 for GI bleeding in a nationwide study: survival and predictors of failure via competing risks analysis. Gastrointest Endosc 2019;90:581-590 e6.

83. Paoluzi OA, Cardamone C, Aucello A, et al. Efficacy of hemostatic powders as monotherapy or rescue therapy in gastrointestinal bleeding related to neoplastic or non-neoplastic lesions. Scand J Gastroenterol 2021;56:1506-1513.

84. Vitali F, Naegel A, Atreya R, et al. Comparison of Hemospray((R)) and Endoclot() for the treatment of gastrointestinal bleeding. World J Gastroenterol 2019;25:1592-1602.

85. Kim YJ, Park JC, Kim EH, et al. Hemostatic powder application for control of acute upper gastrointestinal bleeding in patients with gastric malignancy. Endosc Int Open 2018;6:E700-E705.

86. Kurt M, Akdogan M, Onal IK, et al. Endoscopic topical application of Ankaferd Blood Stopper for neoplastic gastrointestinal bleeding: A retrospective analysis. Dig Liver Dis 2010;42:196-9.

87. Shin J, Cha B, Park JS, et al. Efficacy of a novel hemostatic adhesive powder in patients with upper gastrointestinal tumor bleeding. BMC Gastroenterol 2021;21:40.

88. Alali AA, Moosavi S, Martel M, et al. Topical hemostatic agents in the management of upper gastrointestinal bleeding: a meta-analysis. Endosc Int Open 2023;11:E368-E385.

89. Karna R, Deliwala S, Ramgopal B, et al. Efficacy of topical hemostatic agents in malignancy-related GI bleeding: a systematic review and meta-analysis. Gastrointest Endosc 2023;97:202-208 e8.

90. Alali AA, Pittayanon R, Martel M, et al. TC-325 Superiority in Malignant Gastrointestinal Bleeding: An Individual Patient Data Meta-Analysis of Randomized Trials. Am J Gastroenterol 2024.

91. Shah ED, Law R. Valuing innovative endoscopic techniques: hemostatic powder for the treatment of GI tumor bleeding. Gastrointest Endosc 2024;100:49-54.

92. Cooper DM, Norton B, Hawkes ND, et al. Hemostatic powder TC-325 as first-line treatment option for malignant gastrointestinal bleeding: a cost-utility analysis in the United Kingdom. Endoscopy 2025.

93. Chen G, Wang J, Chen K, et al. Relationship Between Postoperative Complications and the Prognosis of Gastric Carcinoma Patients Who Underwent Surgical Resection: A Systematic Review and Meta-Analysis. Cancer Control 2021;28:10732748211011955.

94. Tey J, Soon YY, Koh WY, et al. Palliative radiotherapy for gastric cancer: a systematic review and meta-analysis. Oncotarget 2017;8:25797-25805.

95. Wagner AD, Syn NL, Moehler M, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 2017;8:CD004064.

96. Meropol NJ, Egleston BL, Buzaglo JS, et al. Cancer patient preferences for quality and length of life. Cancer 2008;113:3459-66.

97. Weeks JC, Cook EF, O'Day SJ, et al. Relationship between cancer patients' predictions of prognosis and their treatment preferences. JAMA 1998;279:1709-14.

98. Patel MI, Lopez AM, Blackstock W, et al. Cancer Disparities and Health Equity: A Policy Statement From the American Society of Clinical Oncology. J Clin Oncol 2020;38:3439-3448.

99. Llach J, Elizalde JI, Guevara MC, et al. Endoscopic injection therapy in bleeding Mallory-Weiss syndrome: a randomized controlled trial. Gastrointest Endosc 2001;54:679-81.

100. Laine L. Multipolar electrocoagulation in the treatment of active upper gastrointestinal tract hemorrhage. A prospective controlled trial. N Engl J Med 1987;316:1613-7.

101. Bataller R, Llach J, Salmeron JM, et al. Endoscopic sclerotherapy in upper gastrointestinal bleeding due to the Mallory-Weiss syndrome. Am J Gastroenterol 1994;89:2147-50.

102. Chung IK, Kim EJ, Hwang KY, et al. Evaluation of endoscopic hemostasis in upper gastrointestinal bleeding related to Mallory-Weiss syndrome. Endoscopy 2002;34:474-9.

103. Lee S, Ahn JY, Jung HY, et al. Effective endoscopic treatment of Mallory-Weiss syndrome using Glasgow-Blatchford score and Forrest classification. J Dig Dis 2016;17:676-684.

104. Peng YC, Tung CF, Chow WK, et al. Efficacy of endoscopic isotonic saline-epinephrine injection for the management of active Mallory-Weiss tears. J Clin Gastroenterol 2001;32:119-22.

105. Huang SP, Wang HP, Lee YC, et al. Endoscopic hemoclip placement and epinephrine injection for Mallory-Weiss syndrome with active bleeding. Gastrointest Endosc 2002;55:842-6.

106. Park CH, Min SW, Sohn YH, et al. A prospective, randomized trial of endoscopic band ligation vs. epinephrine injection for actively bleeding Mallory-Weiss syndrome. Gastrointest Endosc 2004;60:22-7.

107. Cho YS, Chae HS, Kim HK, et al. Endoscopic band ligation and endoscopic hemoclip placement for patients with Mallory-Weiss syndrome and active bleeding. World J Gastroenterol 2008;14:2080-4.

108. Higuchi N, Akahoshi K, Sumida Y, et al. Endoscopic band ligation therapy for upper gastrointestinal bleeding related to Mallory-Weiss syndrome. Surg Endosc 2006;20:1431-4.

109. Shimoda R, Iwakiri R, Sakata H, et al. Endoscopic hemostasis with metallic hemoclips for iatrogenic Mallory-Weiss tear caused by endoscopic examination. Dig Endosc 2009;21:20-3.

110. Yamaguchi Y, Yamato T, Katsumi N, et al. Endoscopic hemoclipping for upper GI bleeding due to Mallory-Weiss syndrome. Gastrointest Endosc 2001;53:427-30.

111. Lecleire S, Antonietti M, Iwanicki-Caron I, et al. Endoscopic band ligation could decrease recurrent bleeding in Mallory-Weiss syndrome as compared to haemostasis by hemoclips plus epinephrine. Aliment Pharmacol Ther 2009;30:399-405.

112. Dwivedi M, Misra SP. Mallory-Weiss syndrome: clinical features and management. J Assoc Physicians India 1999;47:397-9.

113. Inaspettato G, Prattico F, Rodella L, et al. Mallory-Weiss syndrome: retrospective analysis of 97 cases. Giornale Italiano di Endoscopia Digestiva 1996;19:113-118.

114. Bharucha AE, Gostout CJ, Balm RK. Clinical and endoscopic risk factors in the Mallory-Weiss syndrome. Am J Gastroenterol 1997;92:805-8.

115. Barakat M, Hamed A, Shady A, et al. Endoscopic band ligation versus endoscopic hemoclip placement for Dieulafoy's lesion: a meta-analysis. Eur J Gastroenterol Hepatol 2018;30:995-996.

116. Yuan Y, Wang C, Hunt RH. Endoscopic clipping for acute nonvariceal upper-GI bleeding: a meta-analysis and critical appraisal of randomized controlled trials. Gastrointest Endosc 2008;68:339-51.

117. Ahn DW, Lee SH, Park YS, et al. Hemostatic efficacy and clinical outcome of endoscopic treatment of Dieulafoy's lesions: comparison of endoscopic hemoclip placement and endoscopic band ligation. Gastrointest Endosc 2012;75:32-8.

118. Ji JS, Kim HK, Kim SS, et al. Clinical outcome of endoscopic management of duodenal Dieulafoy's lesions: endoscopic band ligation versus endoscopic hemoclip placement. Surg Endosc 2016;30:3526-31.

119. Liu D, Lu F, Ou D, et al. [Endoscopic band ligation versus endoscopic hemoclip placement for bleeding due to Dieulafoy lesions in the upper gastrointestinal tract]. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2009;34:905-9.

120. Park CH, Joo YE, Kim HS, et al. A prospective, randomized trial of endoscopic band ligation versus endoscopic hemoclip placement for bleeding gastric Dieulafoy's lesions. Endoscopy 2004;36:677-81.

121. Chung IK, Kim EJ, Lee MS, et al. Bleeding Dieulafoy's lesions and the choice of endoscopic method: comparing the hemostatic efficacy of mechanical and injection methods. Gastrointest Endosc 2000;52:721-4.

122. Akahoshi K, Yoshinaga S, Fujimaru T, et al. Hypertonic saline-epinephrine injection plus endoscopic band ligation therapy for gastric Dieulafoy's lesion. J Gastroenterol 2003;38:911-2.

123. Alis H, Oner OZ, Kalayci MU, et al. Is endoscopic band ligation superior to injection therapy for Dieulafoy lesion? Surg Endosc 2009;23:1465-9.

124. Krishnan A, Velayutham V, Satyanesan J, et al. Role of endoscopic band ligation in management of non-variceal upper gastrointestinal bleeding. Trop Gastroenterol 2013;34:91-4.

125. Matsui S, Kamisako T, Kudo M, et al. Endoscopic band ligation for control of nonvariceal upper GI hemorrhage: comparison with bipolar electrocoagulation. Gastrointest Endosc 2002;55:214-8.

126. Mumtaz R, Shaukat M, Ramirez FC. Outcomes of endoscopic treatment of gastroduodenal Dieulafoy's lesion with rubber band ligation and thermal/injection therapy. J Clin Gastroenterol 2003;36:310-4.

127. Nikolaidis N, Zezos P, Giouleme O, et al. Endoscopic band ligation of Dieulafoy-like lesions in the upper gastrointestinal tract. Endoscopy 2001;33:754-60.

128. Ding YJ, Zhao L, Liu J, et al. Clinical and endoscopic analysis of gastric Dieulafoy's lesion. World J Gastroenterol 2010;16:631-5.

129. Jiang Y, Hu J, Li P, et al. A Retrospective Analysis of Cyanoacrylate Injection versus Hemoclip Placement for Bleeding Dieulafoy's Lesion in Duodenum. Gastroenterol Res Pract 2018;2018:3208690.

130. Lara LF, Sreenarasimhaiah J, Tang SJ, et al. Dieulafoy lesions of the GI tract: localization and therapeutic outcomes. Dig Dis Sci 2010;55:3436-41.

131. Ljubicic N. Efficacy of endoscopic clipping and long-term follow-up of bleeding Dieulafoy's lesions in the upper gastrointestinal tract. Hepatogastroenterology 2006;53:224-7.

132. Massinha P, Cunha I, Tome L. Dieulafoy Lesion: Predictive Factors of Early Relapse and Long-Term Follow-Up. GE Port J Gastroenterol 2020;27:237-243.

133. Park CH, Sohn YH, Lee WS, et al. The usefulness of endoscopic hemoclipping for bleeding Dieulafoy lesions. Endoscopy 2003;35:388-92.

134. Park SH, Lee DH, Park CH, et al. Predictors of Rebleeding in Upper Gastrointestinal Dieulafoy Lesions. Clin Endosc 2015;48:385-91.

135. Sone Y, Kumada T, Toyoda H, et al. Endoscopic management and follow up of Dieulafoy lesion in the upper gastrointestinal tract. Endoscopy 2005;37:449-53.

136. Yamaguchi Y, Yamato T, Katsumi N, et al. Short-term and long-term benefits of endoscopic hemoclip application for Dieulafoy's lesion in the upper GI tract. Gastrointest Endosc 2003;57:653-6.

137. Nulsen B, Jensen DM, Kovacs TOG, et al. Outcomes in Severe Upper GI Hemorrhage from Dieulafoy's Lesion with Monitoring of Arterial Blood Flow. Dig Dis Sci 2021;66:3495-3504.

138. Cheng CL, Liu NJ, Lee CS, et al. Endoscopic management of Dieulafoy lesions in acute nonvariceal upper gastrointestinal bleeding. Dig Dis Sci 2004;49:1139-44.

139. Iacopini F, Petruzziello L, Marchese M, et al. Hemostasis of Dieulafoy's lesions by argon plasma coagulation (with video). Gastrointest Endosc 2007;66:20-6.

140. Stark ME, Gostout CJ, Balm RK. Clinical features and endoscopic management of Dieulafoy's disease. Gastrointest Endosc 1992;38:545-50.

141. Jensen DM, Kovacs T, Ghassemi KA, et al. Randomized Controlled Trial of Over-the-Scope Clip as Initial Treatment of Severe Nonvariceal Upper Gastrointestinal Bleeding. Clin Gastroenterol Hepatol 2021;19:2315-2323 e2.

142. Qiu J, Xu J, Zhang Y, et al. Over-the-Scope Clip Applications as First-Line Therapy in the Treatment of Upper Non-variceal Gastrointestinal Bleeding, Perforations, and Fistulas. Front Med (Lausanne) 2022;9:753956.

143. Kobara H, Mori H, Fujihara S, et al. Outcomes of gastrointestinal defect closure with an over-the-scope clip system in a multicenter experience: An analysis of a successful suction method. World J Gastroenterol 2017;23:1645-1656.

144. Cui J, Huang LY, Liu YX, et al. Efficacy of endoscopic therapy for gastrointestinal bleeding from Dieulafoy's lesion. World J Gastroenterol 2011;17:1368-72.

145. Asaki S, Sato H, Nishimura T, et al. Endoscopic diagnosis and treatment of Dieulafoy's ulcer. Tohoku J Exp Med 1988;154:135-41.

146. Yilmaz M, Ozutemiz O, Karasu Z, et al. Endoscopic injection therapy of bleeding Dieulafoy lesion of the stomach. Hepatogastroenterology 2005;52:1622-5.

147. Katsinelos P, Paroutoglou G, Mimidis K, et al. Endoscopic treatment and follow-up of gastrointestinal Dieulafoy's lesions. World J Gastroenterol 2005;11:6022-6.

148. Yanar H, Dolay K, Ertekin C, et al. An infrequent cause of upper gastrointestinal tract bleeding: "Dieulafoy's lesion". Hepatogastroenterology 2007;54:1013-7.

149. Abd Al-Wahab N, Amer K, Ibrahim A. Argon plasma coagulation versus endoscopic band ligation in treatment of gastric vascular ectasia in cirrhotic patients in Zagazig university. Afro-Egypt J Infect Endem Dis 2019;9:176-184.

150. Abdel Ghaffar M, Abd El Maguid H. Endoscopic band ligation versus argon plasma coagulation in management of bleeding from gastric antral vascular ectasia in patients with portal hypertension. J Med Sci Res 2019;2:214-219.

151. Abdelhalim H, Mostafa I, Abdelbary M, et al. Endoscopic band ligation versus argon plasma coagulation for the treatment of gastric antral vascular ectasia in Egyptian patients with liver cirrhosis. World Journal of Medical Sciences 2014;10:357-361.

152. Elhendawy M, Mosaad S, Alkhalawany W, et al. Randomized controlled study of endoscopic band ligation and argon plasma coagulation in the treatment of gastric antral and fundal vascular ectasia. United European Gastroenterol J 2016;4:423-8.

153. Ghobrial C, Rabea M, Mohsen N, et al. Gastric antral vascular ectasia in portal hypertensive children: Endoscopic band ligation versus argon plasma coagulation. J Pediatr Surg 2019;54:1691-1695.

154. St Romain P, Boyd A, Zheng J, et al. Radiofrequency ablation (RFA) vs. argon plasma coagulation (APC) for the management of gastric antral vascular ectasia (GAVE) in patients with and without cirrhosis: results from a retrospective analysis of a large cohort of patients treated at a single center. Endosc Int Open 2018;6:E266-E270.

155. McCarty TR, Rustagi T. Comparative Effectiveness and Safety of Radiofrequency Ablation Versus Argon Plasma Coagulation for Treatment of Gastric Antral Vascular Ectasia: A Systematic Review and Meta-Analysis. J Clin Gastroenterol 2019;53:599-606.

156. Dray X, Repici A, Gonzalez P, et al. Radiofrequency ablation for the treatment of gastric antral vascular ectasia. Endoscopy 2014;46:963-9.

157. Magee C, Lipman G, Alzoubaidi D, et al. Radiofrequency ablation for patients with refractory symptomatic anaemia secondary to gastric antral vascular ectasia. United European Gastroenterol J 2019;7:217-224.

158. Markos P, Bilic B, Ivekovic H, et al. Radiofrequency ablation for gastric antral vascular ectasia and radiation proctitis. Indian J Gastroenterol 2017;36:145-148.

159. McGorisk T, Krishnan K, Keefer L, et al. Radiofrequency ablation for refractory gastric antral vascular ectasia (with video). Gastrointest Endosc 2013;78:584-8.

160. Senzolo M, Realdon S, Zanetto A, et al. Endoscopic radiofrequency ablation for the treatment of severe gastric antral vascular ectasia in patients with cirrhosis. Eur J Gastroenterol Hepatol 2021;33:1414-1419.

161. Bhatti MA, Khan AA, Alam A, et al. Efficacy of argon plasma coagulation in gastric vascular ectasia in patients with liver cirrhosis. J Coll Physicians Surg Pak 2009;19:219-22.

162. Boltin D, Gingold-Belfer R, Lichtenstein L, et al. Long-term treatment outcome of patients with gastric vascular ectasia treated with argon plasma coagulation. Eur J Gastroenterol Hepatol 2014;26:588-93.

163. Fuccio L, Zagari RM, Serrani M, et al. Endoscopic argon plasma coagulation for the treatment of gastric antral vascular ectasia-related bleeding in patients with liver cirrhosis. Digestion 2009;79:143-50.

164. Kwan V, Bourke MJ, Williams SJ, et al. Argon plasma coagulation in the management of symptomatic gastrointestinal vascular lesions: experience in 100 consecutive patients with long-term follow-up. Am J Gastroenterol 2006;101:58-63.

165. Lecleire S, Ben-Soussan E, Antonietti M, et al. Bleeding gastric vascular ectasia treated by argon plasma coagulation: a comparison between patients with and without cirrhosis. Gastrointest Endosc 2008;67:219-25.

166. Naga M, Esmat S, Naguib M, et al. Long-term effect of argon plasma coagulation (APC) in the treatment of gastric antral vascular ectasia (GAVE). Arab J Gastroenterol 2011;12:40-3.

167. Probst A, Scheubel R, Wienbeck M. Treatment of watermelon stomach (GAVE syndrome) by means of endoscopic argon plasma coagulation (APC): long-term outcome. Z Gastroenterol 2001;39:447-52.

168. Roman S, Saurin JC, Dumortier J, et al. Tolerance and efficacy of argon plasma coagulation for controlling bleeding in patients with typical and atypical manifestations of watermelon stomach. Endoscopy 2003;35:1024-8.

169. Bourke MJ, Hope RL, Boyd P, et al. Endoscopic laser therapy for watermelon stomach. J Gastroenterol Hepatol 1996;11:832-4.

170. Calamia KT, Scolapio JS, Viggiano TR. Endoscopic YAG laser treatment of watermelon stomach (gastric antral vascular ectasia) in patients with systemic sclerosis. Clin Exp Rheumatol 2000;18:605-8.

171. Liberski SM, McGarrity TJ, Hartle RJ, et al. The watermelon stomach: long-term outcome in patients treated with Nd:YAG laser therapy. Gastrointest Endosc 1994;40:584-7.

172. Mathou NG, Lovat LB, Thorpe SM, et al. Nd:YAG laser induces long-term remission in transfusion-dependent patients with watermelon stomach. Lasers Med Sci 2004;18:213-8.

173. Pavey DA, Craig PI. Endoscopic therapy for upper-GI vascular ectasias. Gastrointest Endosc 2004;59:233-8.

174. A DEC, Aviani Fulvio G, Bordin A, et al. The GRIM Test could be useful in detecting fabricated data. Minerva Anestesiol 2024.

175. Cho S, Zanati S, Yong E, et al. Endoscopic cryotherapy for the management of gastric antral vascular ectasia. Gastrointest Endosc 2008;68:895-902.

176. Patel AA, Trindade AJ, Diehl DL, et al. Nitrous oxide cryotherapy ablation for refractory gastric antral vascular ectasia. United European Gastroenterol J 2018;6:1155-1160.

177. Harrow BS, Eaton CB, Roberts MB, et al. Health utilities associated with hemoglobin levels and blood loss in postmenopausal women: the Women's Health Initiative. Value Health 2011;14:555-63.

178. Strand V, Cryer B, Luo X, et al. Effect of blood loss on physical function in arthritis patients: a pooled analysis. Health Outcomes Research in Medicine 2011;2:e27-e38.

179. Boughton SL, Wilkinson J, Bero L. When beauty is but skin deep: dealing with problematic studies in systematic reviews. Cochrane Database Syst Rev 2021;6:ED000152.

180. Fabian A, Bor R, Szabo E, et al. Endoscopic treatment of gastric antral vascular ectasia in real-life settings: Argon plasma coagulation or endoscopic band ligation? J Dig Dis 2021;22:23-30.

181. Keohane J, Berro W, Harewood GC, et al. Band ligation of gastric antral vascular ectasia is a safe and effective endoscopic treatment. Dig Endosc 2013;25:392-6.

182. O'Morain NR, O'Donovan H, Conlon C, et al. Is Endoscopic Band Ligation a Superior Treatment Modality for Gastric Antral Vascular Ectasia Compared to Argon Plasma Coagulation? Clin Endosc 2021;54:548-554.

183. Sato T, Yamazaki K, Akaike J. Endoscopic band ligation versus argon plasma coagulation for gastric antral vascular ectasia associated with liver diseases. Dig Endosc 2012;24:237-42.

184. Wells CD, Harrison ME, Gurudu SR, et al. Treatment of gastric antral vascular ectasia (watermelon stomach) with endoscopic band ligation. Gastrointest Endosc 2008;68:231-6.

185. Adler DG, Leighton JA, Davila RE, et al. ASGE guideline: The role of endoscopy in acute non-variceal upper-GI hemorrhage. Gastrointest Endosc 2004;60:497-504.

186. Schunemann HJ, Wiercioch W, Brozek J, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. J Clin Epidemiol 2017;81:101-110.