GI Endoscopic Emergencies

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Editors
Louis M. Wong Kee Song, M.D., F.R.C.P.C., F.A.S.G.E.
Division of Gastroenterology and Hepatology
Mayo Clinic
Rochester, MN, USA

Emmanuel C. Gorospe, M.D., M.P.H., F.A.C.P.
Division of Gastroenterology and Hepatology
Mayo Clinic
Rochester, MN, USA

Todd H. Baron, M.D., F.A.S.G.E.
Division of Gastroenterology and Hepatology
University of North Carolina
Chapel Hill, NC, USA

Center for Digestive Health
Prevea Health & Hospital Sisters Health System
Green Bay, WI, USA

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Contents

Contributors

Douglas G. Adler Division of Gastroenterology and Hepatology, Department of Internal Medicine, Huntsman Cancer Center, University of Utah School of Medicine, Salt Lake City, UT, USA

Hisham Aldahab Division of Gastroenterology, The McGill University Health Center, Montreal General Hospital Site, Montreal, QC, Canada

Andrea Anderloni Gastroenterology and Digestive Endoscopy, Nuovo Regina Margherita Hospital, Rome, Italy

Bryan L. Balmadrid Department of Gastroenterology, Virginia Mason Medical Center, Seattle, WA, USA

Alan Barkun Division of Gastroenterology, The McGill University Health Center, Montreal General Hospital Site, Montréal, QC, Canada

Department of Epidemiology, Biostatistics and Occupational Health, McGill University Health Center, McGill University, Montreal, QC, Canada

Todd H. Baron Division of Gastroenterology and Hepatology, University of North Carolina, Chapel Hill, NC, USA

Kenneth F. Binmoeller Paul May and Frank Stein Interventional Endoscopy Center, California Pacific Medical Center, San Francisco, CA, USA

Michael Y. Chan Division of Gastroenterology, University of California, San Diego, San Diego, CA, USA

Disaya Chavalitdhamrong Division of Gastroenterology, Hepatology, and Nutrition, University of Florida, Gainesville, FL, USA

Yen-I. Chen Division of Gastroenterology, The McGill University Health Center, Montreal General Hospital Site, Montréal, QC, Canada, Montreal, QC, Canada

Peter V. Draganov Division of Gastroenterology, Hepatology, and Nutrition, University of Florida, Gainesville, FL, USA

John C. Fang Division of Gastroenterology, Hepatology and Nutrition, University of Utah School of Medicine, Salt Lake City, UT, USA

Ashley L. Faulx Division of Gastroenterology and Liver Disease, University Hospitals Case Medical Center, Cleveland, OH, USA

Lauren B. Gerson Division of Gastroenterology, California Pacific Medical Center, San Francisco, CA, USA

Emmanuel C. Gorospe Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

Center for Digestive Health, Prevea Health & Hospital Sisters Health System, Green Bay, WI, USA

Ian M. Gralnek Department of Gastroenterology and Hepatology, Ha'Emek Medical Center, Afula, Israel

Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Ian Grimes Division of Gastroenterology, University of Wisconsin Medical School, Madison, WI, USA

Chris Hamerski Paul May and Frank Stein Interventional Endoscopy Center, California Pacific Medical Center, San Francisco, CA, USA

Cesare Hassan Gastroenterology and Digestive Endoscopy, Nuovo Regina Margherita Hospital, Rome, Italy

Shayan Irani Department of Gastroenterology, Virginia Mason Medical Center, Seattle, WA, USA

Prasad G. Iyer Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

Amir Klein Department of Gastroenterology, Rambam Health Care Campus, Haifa, Israel

Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Linda S. Lee Department of Gastroenterology and Hepatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Yidan Lu Division of Gastroenterology, The McGill University Health Center, Montreal General Hospital Site, Montreal, QC, Canada

Paresh P. Mehta Department of Gastroenterology and Hepatology, Digestive Disease Institute, Cleveland Clinic, Cleveland, OH, USA

Klaus Mönkemüller Division of Gastroenterology and Hepatology, Basil Hirschowitz Endoscopic Center of Excellence, University of Alabama at Birmingham, Birmingham, AL, USA

Alison E. Oakes Division of Gastroenterology, Hepatology and Nutrition, University of Utah School of Medicine, Salt Lake City, UT, USA

Shajan Peter Division of Gastroenterology and Hepatology, Basil Hirschowitz Endoscopic Center of Excellence, University of Alabama at Birmingham, Birmingham, AL, USA

Patrick R. Pfau Division of Gastroenterology, University of Wisconsin Medical School, Madison, WI, USA

Thomas C. Queen Division of Gastroenterology and Hepatology, Department of Internal Medicine, Huntsman Cancer Center, University of Utah School of Medicine, Salt Lake City, UT, USA

Alessandro Repici Digestive Endoscopy Unit, Department of Gastroenterology, Instituto Clinico Humanitas, Milan, Italy

Wajeeh Salah Department of Gastroenterology, Mayo Clinic Health System – Eau Claire, Eau Claire, WI, USA

John R. Saltzman Department of Gastroenterology and Hepatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Shiv K. Sarin Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India

Thomas J. Savides Division of Gastroenterology, University of California, San Diego, San Diego, CA, USA

Janak N. Shah Paul May and Frank Stein Interventional Endoscopy Center, California Pacific Medical Center, San Francisco, CA, USA

Kapil Sharma Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India

Robert J. Summerlee Division of Gastroenterology, Hepatology, and Nutrition, University of Florida, Gainesville, FL, USA

Joseph J.Y. Sung Institute of Digestive Disease, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

James H. Tabibian Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

Raymond S.Y. Tang Institute of Digestive Disease, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

John J. Vargo Department of Gastroenterology and Hepatology, Digestive Disease Institute, Cleveland Clinic, Cleveland, OH, USA

C. Mel Wilcox Division of Gastroenterology and Hepatology, Basil Hirschowitz Endoscopic Center of Excellence, University of Alabama at Birmingham, Birmingham, AL, USA

Louis M. Wong Kee Song Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

Angelo Zullo Digestive Endoscopy Unit, Department of Gastroenterology, Instituto Clinico Humanitas, Milan, Italy

Triage, Sedation and Monitoring

1

Paresh P. Mehta and John J. Vargo

Introduction

Endoscopic emergencies provide a variety of challenges to the endoscopist as patients are often critically ill with multiple comorbidities and thus are at higher risk for significant adverse events [1]. The most common etiology for emergent endoscopic intervention is gastrointestinal bleeding. Other emergencies, such as food impaction, colonic obstruction, acute cholangitis, and post-procedure complications (e.g., perforation), occur less frequently. The triage of patients to appropriate levels of care, timing of endoscopic intervention, use of appropriate sedative agents, and monitoring are important components of the initial care process. When the appropriate evaluation and triage of these patients occur at levels of care that can successfully manage these emergent clinical situations, including in an intensive care unit (ICU), endoscopy suite, or operating room (OR), the endoscopist practices in a controlled environment, which promotes a higher degree of successful intervention and outcomes.

P.P. Mehta, M.D. • J.J. Vargo, M.D., M.P.H. (✉)
Department of Gastroenterology and Hepatology, Digestive Disease Institute, Cleveland Clinic, 9500 Euclid Avenue, Desk A31, Cleveland, OH 44195, USA
e-mail: vargoj@ccf.org

Triage

Endoscopic emergencies differ significantly from the controlled environment that most gastroenterologists are accustomed to performing routine diagnostic and therapeutic endoscopy. After an initial assessment and appropriate resuscitation based on the type of emergency encountered, the decision on when and where the endoscopic intervention should take place is the next step in management. Factors that should be taken into account, regardless of the emergency encountered, include a history and physical examination and when feasible, a more detailed history of cardiopulmonary disease (including coronary artery disease, heart failure, chronic pulmonary obstructive disease), obstructive sleep apnea or sleep-related disorders, history of prior reactions to sedatives or anesthetics, current medications, and history of substance use or abuse (alcohol, tobacco, illicit drugs) [2]. The physical examination should include evaluation of vital signs, succinct cardiac and pulmonary auscultation, and evaluation of upper airway anatomy (including neck circumference, cervical spine dysfunction, and facial anatomy) [3]. The use of this active medical information allows patients to be categorized according to the American Society of Anesthesiologists Physical Status (ASA PS) classification, which was specifically designed to risk stratify patients prior to undergoing sedation (Table 1.1). A Clinical Outcomes Research

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Table 1.1 Continuum of the depth of sedation

	Minimal sedation (anxiolysis)	Moderate sedation/ analgesia	Deep sedation/analgesia	General anesthesia
Responsiveness	Normal response to verbal stimuli	Purposeful response to verbal or tactile stimulation	Purposeful response after repeated/painful stimulation	No response, even with painful stimulation
Airway	Unaffected	Unaffected	Intervention may be required	Intervention often required
Spontaneous respiration	Unaffected	Unaffected	May be inadequate	Intervention often required
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May require intervention

Adapted from Gross JB et al. American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology 2002;98:1005

Initiative (CORI) database study, which included over 1.5 million endoscopic procedures, showed that increasing ASA PS was associated with an increased rate of serious adverse events during esophagogastroduodenoscopy (EGD) and colonoscopy [4]. Emergent scenarios may require some or all of the required history to be obtained from family members, prior medical chart documentation, or other medical team members. This should also be used to determine the timing of recent liquid or food intake as this may determine if the patient should undergo endotracheal intubation prior to endoscopy [3] to avoid pulmonary aspiration.

As with other aspects of medical care, endoscopic emergencies need to be evaluated on a case-by-case basis with regard to timing (early vs. late) and location of the procedure in order to optimize procedural safety and success. As an example, patients presenting with upper GI bleeding (UGIB) who undergo early endoscopic intervention (within 24 h) appear to spend less days as inpatients in the ICU [5] and hospital [6]. More recent evidence suggests that delay in performing endoscopic retrograde cholangiopancreatography (ERCP) within 48 h of the index presentation for acute cholangitis leads to increased 30-day readmission rates [7]. Timing of intervention for foreign body ingestion and food impaction is related to the clinical presentation, type of object ingested, and ability to handle secretions [8], with early intervention advocated when signs of high-grade obstruction are present.

Sedation

Several sedatives and anesthetic agents are available for administration during procedures. Endoscopists should be familiar with the depth of sedation these agents provide, their duration of action, side effects, and if available, appropriate reversal agents. This information is even more important during emergent endoscopic procedures as patients may already be at higher risk for cardiopulmonary adverse events. The degree of sedation needed to successfully complete a procedure ranges from moderate sedation to general anesthesia (Table 1.1). The decision on optimizing the depth of sedation should be made from the type of emergency encountered and, more importantly, the patient's medical comorbidities. As sedation depth is a continuum with no clearly defined boundaries, endoscopists must be prepared for managing deeper levels of sedation than planned [3, 9].

Utilization of the ASA PS prior to endoscopy should assist in the choice of agents used and determine if the support of a dedicated anesthesia team is indicated. In non-emergent situations, ASA PS 1 and 2 patients are considered appropriate candidates for moderate sedation, whereas ASA PS 3 patients should be carefully evaluated for requirement of anesthesia support, and ASA PS 4 and 5 patients will require anesthesia assistance. In emergent situations, the risk for pulmonary aspiration and cardiopulmonary adverse events should also be taken into account, regardless of ASA PS.

Table 1.2 Selected pharmacological agents for sedation and analgesia

Drug	Onset of action, min	Peak effect, min	Duration of effect, min	Pharmacological antagonist	Side effects
Midazolam	1–2	3	15–80	Flumazenil	Respiratory depression
Diazepam	2–3	3–5	360	Flumazenil	Respiratory depression
Fentanyl	1–2	3–5	30–60	Naloxone	Respiratory depression
Meperidine	3–6	5–7	60–180	Naloxone	Respiratory depression
Propofol	<1	1–2	4–8	None	Respiratory depression, hypotension

Adapted from Vargo JJ et al. Multisociety sedation curriculum for gastrointestinal endoscopy. Gastrointest Endosc. 2012;76:e1–25

Pharmacologic Therapy

There are a variety of sedative, analgesic, and hypnotic agents available for use in endoscopy. In the United States, most patients receive a combination of benzodiazepine and an opioid for routine EGD or colonoscopy [10]. The most commonly utilized benzodiazepine is midazolam due to its shorter duration and onset of action; however, other benzodiazepine agents can be used as adjuvant or primary sedative therapy. Opioids that are commonly used include fentanyl and meperidine, the choice of which is generally made at the discretion of the endoscopist. Propofol, a short-acting drug with sedative, amnestic, and hypnotic properties, can be used alone or in combination with other agents. The choice of which medications to use is for the most part influenced by institutional privileges (e.g., propofol), endoscopist preference, and type of intervention to be performed. Table 1.2 summarizes the pharmacological agents that are more likely to be used in emergent scenarios [11].

Benzodiazepines

Moderate sedation with benzodiazepines (in combination therapy with opioids) is the most common form of sedation used in endoscopic procedures around the world [12] and can be used in many emergent endoscopic scenarios. In a randomized control trial that compared three groups (diazepam only, midazolam only, or no sedation) in patients undergoing EGD, midazolam increased patient tolerance and had a higher amnestic effect than in patients who received diazepam [13]. Moreover, midazolam is generally favored over diazepam due to its shorter duration of action. The popularity of benzodiazepines is due to their relatively low cost, wide availability, and desired effects, including sedation, hypnosis, retrograde amnesia, and muscle relaxation [2]. Also, the synergistic effect with other sedatives and opioids is a key characteristic that can be used to decrease undesired effects associated with higher doses of each individual agent. Prior to administration in emergent scenarios, the endoscopist should be aware of the dose-dependent effect of benzodiazepines on ventilatory depression and their ability to alter hemodynamics by inducing hypotension and tachycardia [14]. Due to their metabolism and excretion patterns, the use of benzodiazepines in the geriatric population [15] and in patients with known hepatic or renal dysfunction requires dose adjustments.

Opioids

Opioid administration in endoscopy primarily provides analgesia with some mild sedative effects. When used in combination with benzodiazepines, an optimal combination of sedation and analgesia can be achieved, although depth of

sedation must be monitored closely. In one study, the combination therapy of meperidine and midazolam in ASA PS 1 and 2 patients targeting moderate sedation in routine and advanced endoscopic procedures lead to deep sedation in 68 % of cases [9]. This should be emphasized in the setting of emergent endoscopic procedures where airway management is critical and close monitoring of depth of sedation by the endoscopy team is essential. In regard to opioid agents, fentanyl shortened total procedure and recovery times when compared to meperidine during routine endoscopy in one study; however, patients felt less overall pain during the procedure when meperidine was used [16]. Both meperidine and fentanyl can cause depression of central ventilatory drive, which may lead to sentinel cardiopulmonary adverse events. It should also be noted that meperidine has an active metabolite *normeperidine*, which may add to the drug's longer effect when compared to fentanyl. Therefore, diligent airway monitoring during emergent endoscopic procedures for which these agents are utilized is necessary.

Propofol

Propofol (2,6-diisopropylphenol) is an ultrashort-acting hypnotic agent with sedative, antiemetic, hypnotic, and amnestic effects [2]. Propofol has no analgesic effect and, due to preparation methods, is contraindicated in patients with egg or soybean allergies. Recovery is fast, usually within 10–20 min of discontinuation, regardless of the total dose administered [17]. The primary disadvantages of propofol are the inability to easily titrate to desired levels of sedation without inducing general anesthesia and the lack of available pharmacological antagonists. In most areas of the United States, propofol must be administered with the assistance of an anesthesiologist, although there are data supporting the safety profile of endoscopist and nurse-administered propofol sedation. During emergent endoscopic procedures, it must be noted that propofol can induce dose-dependent hypotension; this occurs more frequently during bolus administration, and slow initial administration is therefore advised. Airway management is also critical with propofol sedation, and the endoscopy team must be able to rescue a patient who is unable to protect his or her airway or loses spontaneous respiratory function [2]. Propofol can be used in combination with benzodiazepines or opioids, allowing for more optimal control of dose-dependent adverse effects of all agents administered. This is optimal as studies have shown that combination therapy with propofol and fentanyl or midazolam allows moderate sedation to be achieved [18, 19].

Monitoring

The standard of care for patients undergoing any form of endoscopic evaluation that requires sedation includes cardiopulmonary monitoring prior to, during, and after the procedure. This generally includes pulse oximetry, continuous electrocardiographic (ECG) monitoring, and automated blood pressure monitoring [20]. These monitoring devices and the trained endoscopy personnel who are assessing the patient's cardiorespiratory status are critical during endoscopic emergencies. In elective endoscopy, unplanned adverse events are rare, occurring in 1.4 % of procedures [1]. Based on an assessment of the CORI database to evaluate the occurrence of cardiopulmonary adverse events in 324,737 procedures completed with moderate sedation, risk factors included inpatient status, advanced age, and higher ASA PS classification [1]. Patients undergoing inpatient procedures were found to be sicker (56 % with ASA PS $\geq$ 3), and inpatient procedures were often more complex. This exemplifies the type of scenario where the majority of emergent endoscopic interventions will occur, and diligent safety monitoring in this population becomes even more critical.

Pulse Oximetry and Supplemental Oxygen

Pulse oximetry measures oxygenation through a microprocessor that converts absorption patterns of hemoglobin and oxyhemoglobin into estimated

oxygen saturations [21]. Pulse oximetry assesses changes in oxygen saturation but does not measure ventilation status or hypercarbia. In a systematic review of randomized trials evaluating the efficacy of pulse oximetry to prevent adverse outcomes in the perioperative period, pulse oximetry was found to be of questionable value [22]. Nevertheless, societal guidelines recommend that all patients undergoing endoscopic procedures should undergo pulse oximetry monitoring based on critical event analysis data showing hypoxemia related to respiratory depression as the precipitating event [23, 24]. In emergent bleeding patients who are in the midst of resuscitation with probable central hypovolemia, the pulse oximetry probe should preferably be placed on an earlobe for more accurate readings [21]. Supplemental oxygen use has been shown to decrease rates of hypoxemia in patients undergoing endoscopy with moderate sedation [25, 26]. Although there is no available evidence that directly evaluates the use of supplemental oxygen in emergent endoscopy, it should be implemented prior to administration of sedation in these cases, and there may be a direct benefit in patients with unrecognized ischemic heart disease [26].

Automated Sphygmomanometers

Sedatives can have negative effects on hemodynamics, including hypotension and tachycardia, which, in emergent endoscopy cases, may compound an already altered hemodynamic state. The ASA practice guideline for sedation and analgesia by non-anesthesiologists states that there is insufficient evidence to reach a conclusion about hemodynamic monitoring, but since sedative and analgesic agents blunt appropriate responses from procedure-related stress, detection of early changes in blood pressure may enable practitioners to detect problems earlier and intervene in a timely fashion [3]. All emergent cases should be completed with blood pressure monitoring using standard automated sphygmomanometers, which continuously display and intermittently measure blood pressure [21].

ECG Monitoring

Continuous ECG monitoring should be implemented with other monitoring devices to provide real-time evaluation of the patient's cardiac status. In a prospective cohort study evaluating cardiovascular risk of ERCP, new ECG changes occurred in 24 % of patients >65 years of age and in 9.3 % of patients under the age of 65 [27]. This risk may be higher during emergent endoscopic procedures where patients are more vulnerable to adverse events due to the hemodynamic stress.

Capnography

Capnography utilizes the near-infrared spectrophotometric absorption spectrum of carbon dioxide (CO_2) at 420 nm to provide graphic assessment of the ventilation status via the partial pressure of CO_2 during the respiratory cycle [28]. Previous studies have shown capnography to improve safety by detecting early indicators of hypoxia and/or signs of alveolar hypoventilation. Vargo et al. showed that, when targeting deep sedation in advanced endoscopic procedures utilizing capnography, the latter was superior to pulse oximetry alone in detecting respiratory depression [29]. In a randomized controlled trial of 247 subjects undergoing ERCP and endoscopic ultrasonography (EUS), utilization of capnography significantly decreased the incidence of hypoxia versus standard monitoring, with the procedural team blinded to the capnography data (132 blinded vs. 49 open, $p < 0.001$). Rates of hypoxia (69 % blinded vs. 46 % open, $p < 0.001$) were also significantly lower with capnography monitoring [30]. To date, there is no evidence to support the use of capnography in routine EGD or colonoscopy utilizing moderate sedation in adults. However, patients who are undergoing advanced endoscopic procedures are likely to benefit from the use of capnography for more complete respiratory monitoring.

Advanced Airway Management and Anesthesiology Involvement

Although most emergent endoscopic interventions can be performed safely without endotracheal intubation, patients undergoing advanced interventions or with a compromised cardiorespiratory status may benefit from endotracheal intubation and anesthesiology involvement for sedation administration. In two separate retrospective studies evaluating the role of endotracheal intubation for UGIB, there were no significant differences in cardiopulmonary adverse events, including total ICU days or acquired pneumonia [31, 32], between the intubated and non-intubated groups. However, patients who are at risk for pulmonary aspiration, such as those with active hematemesis and hepatic encephalopathy, are likely to benefit from endotracheal intubation prior to endoscopic intervention [33].

Procedural considerations and the possibility of adverse events contribute significantly in the decision to involve the anesthesia team in endoscopic cases. The most significant factor is an ASA PS of 4 or higher, as this group has been shown to be at higher risk for cardiopulmonary adverse events [4] and dedicated anesthesia monitoring may improve outcomes. Other factors to consider include prolonged therapeutic procedures in which deep sedation or general anesthesia is needed, history of intolerance or allergy to routine sedation regimens, history of severe sleep apnea, and abnormal facial, oral, neck, and/or jaw abnormalities [11].

Conclusion

Endoscopic emergencies provide a unique challenge to the endoscopist and endoscopy team due to the higher level of patient acuity and increased risk for adverse events during the procedure. There is lack of robust evidence-based data regarding the optimal triage and sedation management of these patients, which can vary significantly between the types of emergent situations encountered. The endoscopy team should utilize known predictive factors for increased risk of cardiopulmonary adverse events, such as a higher ASA PS, and utilize advanced airway management with the assistance of a dedicated anesthesia team, as appropriate.

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Periprocedural Management of Antithrombotic Agents

2

Michael Y. Chan and Thomas J. Savides

Abbreviations

ACC	American College of Cardiology
ACCP	American College of Chest Physicians
ACS	Acute coronary syndrome
ACT	Activated clotting time
ADP	Adenosine diphosphate
AF	Atrial fibrillation
AHA	American Heart Association
aPTT	Activated partial thromboplastin time
AT	Antithrombin
BMS	Bare-metal stent
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
CI	Confidence interval
COX	Cyclooxygenase
DBE	Double-balloon enteroscopy
DES	Drug-eluting stent
DIC	Disseminated intravascular coagulation
EGD	Esophagogastroduodenoscopy
ERCP	Endoscopic retrograde cholangiopancreatography
EUS	Endoscopic ultrasound
FDA	Food and Drug Administration
FFP	Fresh frozen plasma
FNA	Fine-needle aspiration
GIB	Gastrointestinal bleeding
GPI	Glycoprotein IIb/IIIa inhibitor
HITT	Heparin-induced thrombocytopenia and thrombosis
INR	International normalized ratio
ISTH	International Society of Thrombosis and Haemostasis
IU	International units
IV	Intravenous
LMWH	Low-molecular-weight heparin
LVAD	Left ventricular assist device
MI	Myocardial infarction
NSAID	Nonsteroidal anti-inflammatory drug
NSTEMI	Non-ST elevation myocardial infarction
OR	Odds ratio
OS	Orthopedic surgery
PCI	Percutaneous coronary interventions
PDE	Phosphodiesterase
PEG	Percutaneous endoscopic gastrostomy
PGI_2	Prostacyclin
PO	Per oral
PPB	Post-polypectomy bleeding
PPI	Proton-pump inhibitor
rFVIIa	Recombinant activated factor VII
SC	Subcutaneous
SEMS	Self-expanding metal stent
STEMI	ST elevation myocardial infarction
TF	Tissue factor
TIMI	Thrombolysis in Myocardial Infarction
TXA_2	Thromboxane A_2

M.Y. Chan, M.D., M.P.H. • T.J. Savides, M.D. (✉)
Division of Gastroenterology, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093, USA
e-mail: michaelchan78@yahoo.com; tsavides@ucsd.edu

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UA Unstable angina
UFH Unfractionated heparin
UGI Upper gastrointestinal
VKA Vitamin K antagonist
VTE Venous thromboembolism

Introduction

Cardiovascular diseases affect approximately one-third of all adults and account for 800,000 deaths each year in the United States [1]. As a result, many patients are on antithrombotic therapies to reduce their risk of thromboembolic complications and pose a dilemma for providers who perform endoscopy due to lack of well-designed studies investigating the optimal approach in managing these agents in patients who require procedures. There is much reliance on retrospective studies and expert opinion that formulate guidelines for management of antithrombotic therapies in the periprocedural setting [2–4].

Management of antithrombotic medications at the time of endoscopy involves balancing the risk of thromboembolic events from interruption of these agents versus the risk of procedure-related bleeding and related complications from continuation of therapy. In general, patients who undergo procedures considered low risk for causing bleeding can continue their antithrombotic medications, regardless of their risk for thromboembolism (Table 2.1). Patients at low risk for thromboembolism but who undergo procedures with higher bleeding risk can temporarily discontinue antithrombotic medications and remain in a subtherapeutic range in the periprocedural period. Patients at moderate-to-high risk for thromboembolic events who are undergoing procedures with high bleeding risk are a challenge to manage. Providers need to be familiar with the bleeding risks of planned procedures, identify those at highest risk for thromboembolism, recognize the need for bridging therapy, and know when to interrupt and reinitiate antithrombotic therapy.

Table 2.1 Management recommendations based on risks of thromboembolism and procedure-related bleeding

Procedural bleeding risk	Thromboembolism risk	
	Low	High
Low	Continue antithrombotic medications	Continue antithrombotic medications
High	Temporarily discontinue antithrombotic medications without bridging therapy	Continue antithrombotic medications or temporarily discontinue antithrombotic medication with bridging therapy

Bleeding Risk of Endoscopic Procedures

Overview

Procedures considered high risk for bleeding (Table 2.2) are those associated with ≥1 % risk of causing clinically significant hemorrhage (i.e., requiring hospitalization, transfusion, endoscopic treatment, or surgery) [4, 5]. Low-risk procedures include diagnostic endoscopy with or without biopsy, endoscopic retrograde cholangiopancreatography (ERCP) without sphincterotomy, endoscopic ultrasound (EUS) without fine-needle aspiration (FNA), and capsule endoscopy. High-risk procedures include polypectomy at any location (≥1 cm), ERCP with biliary/pancreatic sphincterotomy, and endoscopic hemostasis, among others. The bleeding risk associated with enteral stent placement but without dilation and ERCP with papillary balloon dilation but without sphincterotomy remains controversial. As a general rule, elective high-risk procedures should be delayed until the patient's risk for thromboembolism is reduced and/or antithrombotic medications are optimized to minimize bleeding complications. In the setting where emergent endoscopic intervention is required, every effort should be made to conservatively manage these patients (e.g., transfusions) until their periprocedural bleeding and thromboembolic risks are reduced.

Table 2.2 Bleeding risks of endoscopic procedures

Low-risk procedures (<1 %)	Controversial	High-risk procedures (≥1 %)
Diagnostic (EGD, colonoscopy, flexible sigmoidoscopy, BAE) ± biopsy	Enteral stent placement without dilation	Polypectomy (any location, ≥1 cm)
ERCP ± stenting without sphincterotomy	ERCP papillary balloon dilation without sphincterotomy	ERCP with biliary/pancreatic sphincterotomy
EUS without FNA		EUS with FNA
Capsule endoscopy		PEG placement
		Therapeutic BAE
		Pneumatic or bougie dilation
		Endoscopic hemostasis
		Treatment of varices
		Cystogastrostomy
		EMR, ESD, ampullectomy
		Ablation of tumor or vascular lesion by any technique

BAE balloon-assisted enteroscopy, *EGD* esophagogastroduodenoscopy, *ERCP* endoscopic retrograde cholangiopancreatography, *EUS* endoscopic ultrasound, *FNA* fine-needle aspiration, *PEG* percutaneous endoscopic gastrostomy, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection

Endoscopic Sphincterotomy

The majority of ERCP-related bleeding is intraluminal and is primarily related to sphincterotomy, including precut papillotomy. In a pooled analysis of 21 prospective cohort studies involving 16,855 patients who underwent ERCP, clinically significant bleeding occurred in 226 patients (1.34 %, 95 % confidence interval [CI] 1.16–1.52 %) [6]. Independent predictors of post-ERCP hemorrhage include sphincterotomy, coagulopathy before the procedure (partial thromboplastin or prothrombin time >2 s above normal, platelet count <80,000 mm^3, or ongoing hemodialysis), anticoagulant therapy within 3 days post procedure (oral warfarin or intravenous heparin), cholangitis before the procedure, intraprocedural bleeding (ranging from oozing to requiring endoscopic hemostasis), precut papillotomy, obstruction/stenosis of the orifice of the papilla of Vater, low endoscopist case volume (≤1 sphincterotomy/week), and low center volume (<200 ERCPs/year) [7–9]. Freeman et al. showed that while cirrhosis was not an independent predictor of post-sphincterotomy bleeding ($p=0.06$), the two patients with fatal bleeding complications had Child–Pugh class C cirrhosis [7]. Neither extension of previous sphincterotomy nor the size of sphincterotomy was associated with increased post-sphincterotomy bleeding [7].

Evidence is conflicting as to the risk of post-sphincterotomy bleeding in the setting of recent aspirin or nonsteroidal anti-inflammatory drug (NSAID) use. Freeman et al. showed no increased risk of bleeding if aspirin or NSAID was used within 3 days of endoscopic sphincterotomy [7]. In another case–control study, there was no increased risk of clinically significant bleeding related to the use of antiplatelet agents [10]. Conversely, one study demonstrated an increased incidence of post-sphincterotomy bleeding in aspirin users relative to nonusers (9.7 % vs. 3.9 %, $p=0.01$), and the withholding of aspirin for 7 days prior to endoscopic sphincterotomy did not decrease the risk for bleeding (9.5 % vs. 3.9 %, $p=0.01$) [11]. Unfortunately, data are lacking regarding the safety of endoscopic sphincterotomy in patients on dual antiplatelet agents and/or anticoagulants or in those who are coagulopathic due to cirrhosis or hemodialysis.

In one study, endoscopic balloon dilation of the biliary sphincter was as effective as biliary sphincterotomy for the removal of common bile duct stones, with significantly reduced bleeding complications (0 % vs. 2.0 %, $p=0.001$) [12]. However, the rate of post-ERCP pancreatitis was

higher in the balloon dilation group (7.4 % vs. 4.3 %, $p=0.05$). Therefore, it cannot be advocated for routine use [12]. There are no well-designed, head-to-head comparisons of the two methods at this time in patients who are on antithrombotic therapy.

An endoscopist performing ERCP on an emergent basis is likely already dealing with a patient at high risk for post-procedural bleeding. Based on current evidence, ERCP can be performed with low risk of post-procedural bleeding if sphincterotomy is not necessary or can be deferred until the patient's bleeding risk is reduced. If the patient is medically stable, transfer to a high-volume center for ERCP should be considered.

Endoscopic Hemostasis

Contribution of Antithrombotic Medications to Gastrointestinal Bleeding

In the setting of antiplatelet use, recurring patient-related risk factors for gastrointestinal bleeding (GIB) include prior history of GIB, history of *H. pylori* infection, and advanced age. Concurrent use of anticoagulants, steroids, or NSAIDs is also a consistent predictor of GIB. GIB risk increases with the number of risk factors present in the patient [13]. Among patients using low-dose aspirin (75–325 mg daily), a meta-analysis of placebo-controlled trials for vascular protection demonstrated a relative risk of 2.07 (95 % CI, 1.61–2.66), conferring an increased annual incidence of 0.12 % (95 % CI 0.07–0.19 %) for major GIB attributed to low-dose aspirin use [14].

The risk of GIB with combination antithrombotic agents is increased when compared with low-dose aspirin alone. A meta-analysis showed an increased risk of major GIB when aspirin was combined with clopidogrel (odds ratio [OR] 1.86, 95 % CI, 1.49–2.31) or with an anticoagulant (OR 1.93, 95 % CI, 1.42–2.61) compared with aspirin alone [15]. In the same study, proton-pump inhibitor (PPI) therapy significantly reduced the risk of GIB events in patients given low-dose aspirin [15]. The routine use of PPI with clopidogrel is controversial due to impairment of antiplatelet effects of clopidogrel by PPI in in vitro studies [13]. Although findings from clinical studies are inconsistent, product labeling of omeprazole and esomeprazole includes warnings about possible interactions with clopidogrel.

Patients who undergo careful monitoring of anticoagulant intensity have a 0.3–0.5 % increased annual risk of major bleeding compared with controls [16]. Independent predictors of anticoagulant-related bleeding include intensity of anticoagulant effect, age >75, concomitant use of antiplatelets, and length of therapy [17].

Holster et al. performed a meta-analysis of 43 randomized trials comparing bleeding risk of the new oral anticoagulants versus standard therapy [18]. While all the studies included bleeding events as a safety outcome, only 19 of these trials assessed GIB as a separate subgroup (Table 2.3). The overall OR for GIB among patients taking the new oral anticoagulants was 1.45 (95 % CI, 1.07–1.97), and the OR for clinically relevant bleeding (as defined by the International Society of Thrombosis and Haemostasis [ISTH] and Thrombolysis in Myocardial Infarction [TIMI] study group) was 1.16 (95 % CI, 1.00–1.34). Subgroup analyses demonstrated significantly

Table 2.3 Bleeding risk of new oral anticoagulants [18]

Group	OR (95 % CI)
Clinically relevant bleeding	1.2 (1.0–1.3)
Gastrointestinal bleeding	1.5 (1.1–2.0)
Indication	
ACS	5.2 (2.6–10.5)
Venous thrombosis	1.6 (1.0–2.4)
AF	1.2 (0.9–1.6)
OS thromboprophylaxis	0.8 (0.3–2.0)
Drug-specific GIB[a]	
Dabigatran	1.6 (1.3–1.9)
Rivaroxaban	1.5 (1.2–1.8)
Apixaban	1.2 (0.6–2.7)
Edoxaban	0.3 (0.0–7.7)

OR odds ratio, *CI* confidence interval, *ACS* acute coronary syndrome, *AF* atrial fibrillation, *OS* orthopedic surgery, *GIB* gastrointestinal bleeding

[a]Results based on three studies for dabigatran, five studies for rivaroxaban, eight studies for apixaban, and one study for edoxaban

increased bleeding risk of the new oral anticoagulants versus standard therapy if the indications included acute coronary syndrome (ACS) and treatment of venous thrombosis, but not atrial fibrillation (AF) or thromboprophylaxis after orthopedic surgery (OS). Dabigatran and rivaroxaban were also associated with significantly increased risk for GIB. The meta-analysis was limited by substantial heterogeneity between studies with an I^2 of 60.8 % ($p<0.05$) for studies assessing GIB and I^2 of 83.5 % ($p<0.05$) for studies assessing clinically relevant bleeding. Further studies assessing specific GIB-related outcomes in patients taking the new oral anticoagulants are warranted.

Considerations Regarding Hemostatic Techniques

Most studies evaluating endoscopic hemostasis in anticoagulated patients are retrospective in nature. In these studies, identifying the site of GIB was successful in >80 % of patients [19, 20]. Gastroduodenal ulcers and erosions accounted for >50 % of lesions causing upper GIB. Studies evaluating specific lower GI sources of bleeding are lacking, although common causes include polyps, diverticula, and angiodysplasia. Among patients with GIB on antiplatelets or anticoagulants, 17–29 % will have no mucosal abnormality on endoscopic evaluation [21].

Endoscopic clips are safe and effective in the treatment of bleeding peptic ulcers, Dieulafoy lesions, and Mallory–Weiss tears, as well as for prophylaxis or treatment of post-polypectomy bleeding and diverticular hemorrhage [22]. Clip placement has been demonstrated to be superior to injection alone and comparable to thermal coagulation for the treatment of non-variceal upper gastrointestinal bleeding [23]. Endoscopic clip placement, when technically feasible, may be preferable to thermal therapies in patients on antithrombotic therapy for several reasons. Thermal therapies induce or extend ulcer formation and may exacerbate bleeding from tissue injury. Clips have the theoretical advantage of applying mechanical compression to bleeding lesions and can be applied with minimal tissue injury. Additionally, clips can serve as angiographic or surgical markers if bleeding cannot be controlled endoscopically. Clips achieve high rates of primary hemostasis (85–100 %) with low rebleeding rates (2–20 %), although their effectiveness in the setting of antithrombotic therapy is unclear [22]. Studies comparing the different modalities for endoscopic hemostasis in patients on antithrombotic agents are lacking.

Polypectomy

Polypectomy is usually performed in the elective setting with outpatient antithrombotic medications optimized prior to the procedure. Moreover, immediate post-polypectomy bleeding (PPB) can usually be treated effectively with traditional hemostatic techniques. However, severe delayed PPB (1–14 days post procedure) may require emergent endoscopic intervention and often occurs in patients on antithrombotic therapy [24, 25]. Independent predictors of delayed PPB include resumption of anticoagulation following polypectomy, polyp diameter (≥10 mm), number of polyps removed, proximal colonic location, history of cardiovascular disease, and hypertension [24–28].

Aspirin/NSAID use alone has not been shown to increase the risk of delayed PPB [24, 29]. Current data suggest that there is an increased risk of PPB in patients who continue clopidogrel alone or in combination with aspirin, with an event rate ranging from 2.4 to 3.5 % [27, 28, 30]; however, bleeding was controlled without the need for angiographic or surgical intervention. Thus, in patients who are at high risk for cardiovascular complications, such as those with recent ACS or stent placement, continuation of dual antiplatelet therapy may be reasonable.

Endoscopic clip placement over the polypectomy defect may decrease the risk of delayed PPB. In the only randomized controlled trial to evaluate this intervention, no difference was seen in the rates of delayed PPB in the prophylactic clip placement group compared with the group that received no clip; however, the polyps removed were generally low-risk, small (mean size 7.8 ± 4.0 mm) lesions [31]. On the other hand, a large retro-

spective study of patients with resected polyps of ≥2 cm showed that prophylactic clip closure significantly reduced the risk of PPB compared with no clip closure (1.8 % vs. 9.7 %) [32].

Data are limited on the effectiveness of prophylactic clip placement after polypectomy in the setting of uninterrupted anticoagulation. A small retrospective study of 21 patients (41 polypectomies) on uninterrupted warfarin (mean international normalized ratio [INR] 2.3, range 1.4–4.9) who underwent hot snare resection of small polyps (≤10 mm) had no PPB events when one or two clips were placed immediately after polyp resection. Warfarin was withheld for 36 h before the procedure, while patients remained on a modified diet to avoid supra-therapeutic INR and without concomitant antiplatelet agents. Warfarin was resumed according to the patient's standard schedule [33]. Prophylactic clip placement after polypectomy may be effective in preventing PPB in select patients on uninterrupted anticoagulation, although confirmatory data are needed.

Left Ventricular Assist Devices

Left ventricular assist devices (LVADs) are increasingly being used in patients with advanced cardiac failure as a bridge to cardiac transplantation or destination therapy (i.e., ineligible for transplantation). Bleeding complications after LVAD implantation are common, with 30 % requiring surgery and 50–80 % requiring at least 2 units of packed red blood cells [34, 35]. Risk factors for GIB after LVAD implantation include use of nonpulsatile device and history of GIB prior to device placement [36, 37]. Retrospective studies show rates of GIB varying from 8 to 40 %, likely due to differences in the definition of GIB, and rebleeding is common [37–41]. Endoscopy is safe in LVAD patients and identifies the etiology of GIB in 60–70 % of cases, with peptic ulcer bleeding and vascular malformations of the upper GI tract being the more common sources [39, 42]. Endoscopic hemostasis is generally successful, but data are limited to small studies [42]. The cardiologist and/or cardiac surgeon should be involved in any plan to modify antithrombotic medications.

Endoscopic Bleeding Risks for Other Situations

Foreign Body Ingestion/Food Impaction

Data from two large retrospective studies found bleeding related to endoscopic foreign body removal ranging from 1 to 3 % [43, 44]. Bleeding associated with endoscopic esophageal food disimpaction ranged from 0 to 1 % in two retrospective studies [45, 46].

Colonic Decompression

The risk of causing bleeding from endoscopic decompression of colonic pseudo-obstruction is uncommon [47].

Luminal Stents

A systematic review of gastroduodenal self-expanding metal stents (SEMS) found a 0.5 % risk of bleeding in a pooled analysis of 606 patients [48]. Data regarding bleeding complications from placement of esophageal and colonic SEMS are scant.

Assessing Risk for Thromboembolism

Bleeding complications from endoscopy can be problematic but are rarely catastrophic. Conversely, thromboembolic events are associated with high rates of morbidity and mortality. The following is an approach to risk stratify patients according to their risk of thromboembolic events. Patients with prosthetic heart valves, AF, and venous thromboembolism (VTE) frequently require chronic anticoagulation therapy. A strategy has been proposed for risk stratifying patients susceptible to perioperative thromboembolism according to indication for anticoagulant therapy (Table 2.4) [49]. Patients

Table 2.4 Proposed perioperative risk stratification for patients at risk for thromboembolism on anticoagulation [49]

	Annual risk for thromboembolism		
Condition	Low (<5 %)	Moderate (5–10 %)	High (>10 %)
Mechanical heart valve	– Bileaflet aortic valve without atrial fibrillation or risk factors[a]	– Bileaflet aortic valve with at least 1 risk factor[a]	– Any mechanical mitral valve – Older aortic mechanical valve (caged ball, tilting disk) – Recent (<6 months) stroke/TIA
Atrial fibrillation	– $CHADS_2$ score 0–2 without previous stroke/TIA	– $CHADS_2$ score 3 or 4	– $CHADS_2$ score 5 or 6 – Rheumatic or severe valvular disease – Recent (<3 months) stroke/TIA
Venous thromboembolism	– VTE >12 months previously without other risk factors	– VTE within the past 3–12 months – Non-severe thrombophilia[b] – Recurrent VTE – Active cancer (diagnosis <6 months or undergoing treatment)	– Recent (<3 months) VTE – Severe thrombophilia[c]

$CHADS_2$ score (range 0–6): congestive heart failure, hypertension, age >75 years, and diabetes mellitus are assigned 1 point apiece, while previous stroke or TIA is assigned 2 points

$CHADS_2$ cardiac failure–hypertension–age–diabetes–stroke, *TIA* transient ischemic attack, *VTE* venous thromboembolism

[a]Risk factors for stroke without atrial fibrillation: congestive heart failure, hypertension, age >75 years, diabetes, prior stroke/TIA

[b]Non-severe thrombophilia: heterozygous factor V Leiden or prothrombin gene G20210A mutation

[c]Severe thrombophilia: deficiency of protein C, protein S, or antithrombin, antiphospholipid syndrome (presence of antiphospholipid antibodies or lupus anticoagulant), homozygous for factor V Leiden, homozygous for prothrombin gene G20210A, compound heterozygous mutations of latter two genes

with a >10 % annual risk for thromboembolism are classified as "high risk," 5–10 % annual risk as "moderate risk," and <5 % annual risk as "low risk." While this classification system can provide some guidance for the risk of developing a thromboembolic event, a patient's risk assessment should be individualized according to patient- and procedure-related factors.

Atrial Fibrillation

In patients with AF, the $CHADS_2$ score is useful to risk stratify a patient's annual risk for stroke, although it has not been validated in the perioperative setting [50]. The $CHADS_2$ score scheme is based on a scale of 0–6. Congestive heart failure, hypertension, age >75 years, and diabetes mellitus are assigned 1 point apiece, while previous stroke or transient ischemic attack (TIA) is assigned 2 points. Patients with AF at highest risk for stroke (>10 % annual stroke risk) include a $CHADS_2$ score of 5 or 6, recent (<3 months) ischemic stroke or TIA, or the presence of rheumatic or severe valvular heart disease. Patients with a $CHADS_2$ score of 3 or 4 are considered moderate risk (5–10 % annual risk) and 0–2 are low risk (<5 % annual risk) for stroke [49].

Mechanical Heart Valves

Patients with mechanical heart valves who are at high risk for thromboembolic events include a prosthesis in the mitral position, any caged-ball or tilting disk aortic valve prosthesis, and recent

(<6 months) ischemic stroke or TIA. Patients with bileaflet aortic valve prostheses with one or more risk factors, including AF, prior stroke or TIA, hypertension, diabetes, congestive heart failure (CHF), or age >75 years, are at moderate risk. Patients with bileaflet aortic valve prostheses without AF or other risk factors for stroke are at low risk [49].

Deep Vein Thrombosis/Pulmonary Emboli

Patients with recent (<3 months) VTE and severe thrombophilia are considered high risk for additional thromboembolic events. Those at moderate risk are patients with VTE within the past 3–12 months, recurrent VTE, active cancer (diagnosis < 6 months or undergoing treatment), and non-severe thrombophilia. Remote VTE (>12 months) with no other risk factors is considered low risk (Table 2.4) [49].

Coronary Stents and Recent Acute Coronary Syndrome

Dual antiplatelet therapy with combination aspirin and thienopyridine has been shown to reduce adverse events in patients receiving coronary artery stents. Premature discontinuation of antiplatelet therapy is associated with increased risk of stent thrombosis, myocardial infarction, and death. Stent thrombosis can have catastrophic consequences, with incidence of death ranging from 20 to 45 % and myocardial infarction in up to 64 % of cases [51]. Patients at highest risk for stent thrombosis are those with bare-metal stents (BMS) placed within 6 weeks and drug-eluting stents (DES) placed within 12 months [3]. Guidelines vary in regards to when dual antiplatelet therapy can be interrupted (while aspirin is continued) for elective procedures: 4–6 weeks after placement of BMS and 6–12 months after placement of DES [2–5]. Individuals at higher risk for thrombotic events (diabetes, renal failure, cancer, heart failure, complex coronary disease, or history of coronary stent thrombosis) or with stent placement in the setting of ACS may need longer periods of uninterrupted dual antiplatelet therapy prior to elective/urgent procedures [52]. Dual antiplatelet therapy should be resumed after bleeding risk is minimized from the endoscopic intervention and continued for the recommended duration (up to 12 months for patients with BMS and at least 12 months for patients with DES) [53].

Non-cardioembolic Stroke and Transient Ischemic Attack Prevention

Risk factors for non-cardioembolic stroke include hypertension, diabetes, and hyperlipidemia. Aggressive control of risk factors and lifestyle changes (smoking and alcohol cessation) are recommended to prevent a stroke [54]. Aspirin reduces the risk for secondary stroke by 15 % (95 % CI, 6–23 %) compared with placebo. Aspirin monotherapy, combination aspirin/dipyridamole, and clopidogrel monotherapy are all acceptable options for stroke prevention. Use of an antiplatelet agent is preferred over oral anticoagulants for non-cardioembolic stroke prevention [54].

Left Ventricular Assist Devices

LVADs induce hypercoagulability and persistent platelet activation through various mechanisms, frequently requiring combination anticoagulation and antiplatelet therapy depending on the device implanted [55]. Two randomized controlled trials investigating one of the most common LVADs (HeartMate II, Thoratec, Pleasanton, CA) found low rates of thrombotic complications (ischemic stroke ranging from 3 to 8 %; device thrombosis ranging from 2 to 4 %) in patients on combination warfarin and aspirin [34, 35]. Ischemic strokes are more common with lower INR (<1.5), and hemorrhagic strokes are more common with higher INR (>3.0) [56].

Management of Antithrombotic Medications

Anticoagulants

Overview of Anticoagulants

Indications for anticoagulation therapy encompass a heterogeneous group of conditions that have varying risks of developing into thromboembolism, including patients with prosthetic heart valves, AF, VTE, and hypercoagulable states (e.g., thrombophilia, active cancer). Anticoagulants exert their effects at various points in the coagulation cascade, which include coagulation initiation and propagation, as well as fibrin formation (Fig. 2.1). An overview of currently available anticoagulants is provided in Table 2.5.

Vitamin K antagonists (VKAs), such as warfarin, are the mainstay of chronic anticoagulation therapy. VKAs inhibit γ-carboxylation of vitamin K epoxide reductase in the liver, which inhibits the production of factors II, VII, IX, and X in the coagulation cascade. While VKAs are effective at reducing thromboembolic events, they have several limitations, including slow onset of action (~5 to 7 days to therapeutic INR), need for regular monitoring, variability in drug metabolism, narrow therapeutic window (usually an INR between 2.0 and 3.0), and several drug and dietary interactions. Approximately 5 days are needed for the INR to normalize after VKA cessation. The effects of VKAs can be reversed more rapidly with administration of vitamin K and fresh frozen plasma (FFP) primarily.

Unfractionated heparin (UFH) can be administered in intravenous (IV) and subcutaneous (SC) forms. Its mode of action is through antithrombin (AT) III-mediated inhibition of factor Xa and thrombin (factor IIa) of the coagulation cascade. Intravenous formulations are used for

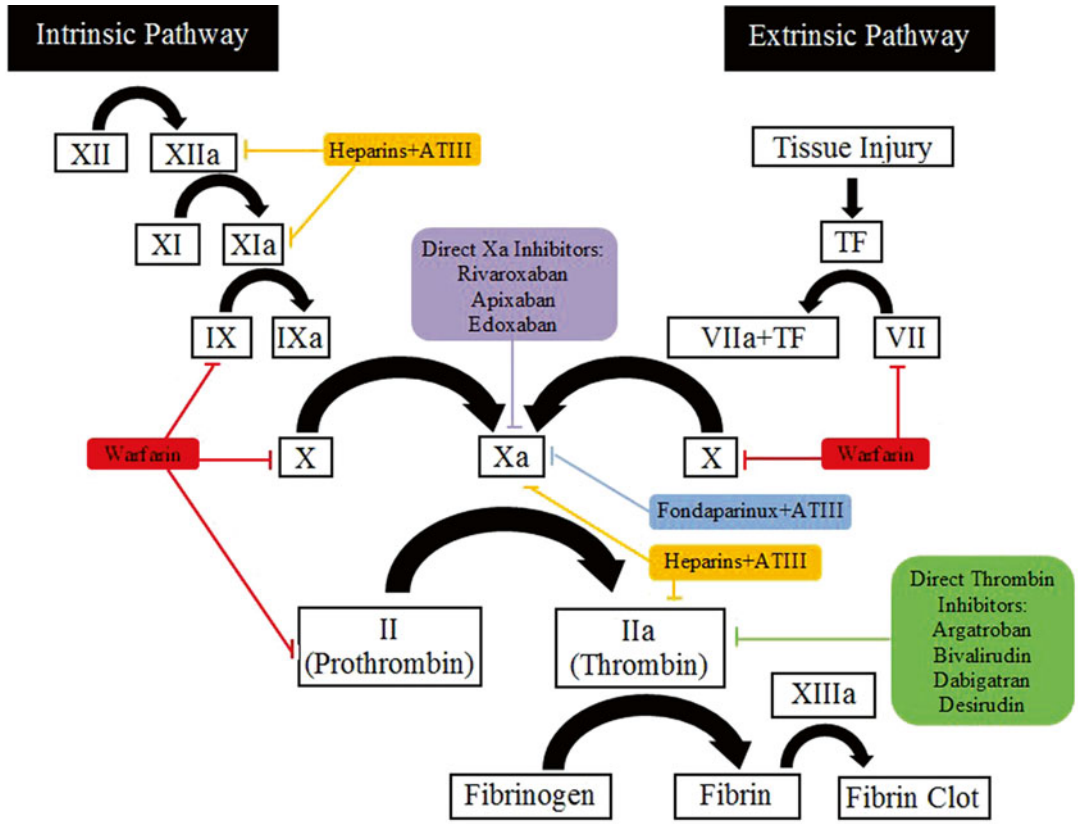

Fig. 2.1 Simplified diagram of coagulation cascade with sites targeted by anticoagulant drugs

Table 2.5 Current anticoagulant agents

Drug	Main indications	Route	Mechanism of action	Time to maximal effect	Elimination half-life[a]	Return of normal coagulation after cessation	Reversal agent or antidote
Warfarin (Coumadin, Bristol-Myers Squibb) [57–59]	VTE treatment; AF, post-MI, mechanical valve, bioprosthetic valve, others	PO	Vitamin K-dependent inhibition of clotting factors II, VII, IX, and X	5–7 days for therapeutic INR	36–42 h	~5 days to normalize INR	Vitamin K, FFP, PCC, rFVIIa
Unfractionated heparin (Fresenius Kabi USA) [60, 61]	ACS, VTE treatment or prophylaxis, bridge therapy for AF/cardioversion	IV or SC	AT-mediated indirect inhibition of factors XIIa, IXa, XIa, and Xa and thrombin	Immediate (IV) Within 6 h (SC)	30–120 min	4 h	Hold or protamine sulfate
Low-molecular-weight heparin (enoxaparin [Lovenox, Sanofi Aventis], dalteparin [Fragmin, Eisai]) [60, 62, 63]	ACS, VTE treatment or prophylaxis, bridge therapy for AF/cardioversion	SC	AT-mediated indirect inhibition of factors XIIa, IXa, XIa, and Xa and thrombin	3–5 h	3–6 h	24 h	Hold or protamine sulfate
Fondaparinux (Arixtra, GlaxoSmithKline) [60, 64]	VTE treatment and prophylaxis	SC	AT-mediated indirect inhibition of factor Xa	3–5 h	17–21 h	2–4 days	No antidote; consider rFVIIa
Bivalirudin (Angiomax, The Medicines Company) [60, 65]	PCI; ACS; HITT treatment and prophylaxis	IV	Reversible direct thrombin inhibition	Immediate	20–30 min	1 h	No antidote; consider hemodialysis
Desirudin (Iprivask, Canyon Pharmaceuticals) [66, 67]	VTE prophylaxis	SC	Reversible direct thrombin inhibition	60–90 min	2–3 h	16–36 h	No antidote; consider hemodialysis
Argatroban (Eagle Pharmaceuticals) [60, 68]	PCI (patients with heparin allergy); HITT treatment and prophylaxis	IV	Reversible direct thrombin inhibition	Immediate	40–50 min	2–4 h	No antidote; consider hemodialysis

Dabigatran (Pradaxa, Boehringer Ingelheim) [57, 58, 69]	Non-valvular AF	PO	Reversible direct thrombin inhibition	0.5–2 h	12–17 h	24–36 h	No antidote; charcoal for overdose (ingestion <2 h); consider hemodialysis (~60 % removal), rFVIIa, PCC, or FEIBA
Rivaroxaban (Xarelto, Janssen Pharmaceuticals) [57, 58, 70]	VTE treatment and prophylaxis; non-valvular AF	PO	Reversible direct factor Xa inhibition	1–4 h	5–13 h	24 h	No antidote; charcoal for overdose (ingestion <2 h); consider PCC
Apixaban (Eliquis, Bristol-Myers Squibb) [71]	Non-valvular AF; phase III studies: VTE treatment and prophylaxis	PO	Reversible direct factor Xa inhibition	1–4 h	8–15 h	24 h	No antidote; charcoal for overdose (ingestion <2 h); consider PCC
Edoxaban (Daiichi Sankyo) *(investigational)* [72, 73]	Phase III studies: VTE treatment and prophylaxis (Japan); non-valvular AF (USA)	PO	Reversible direct factor Xa inhibition	1–2 h	6–11 h	24–36 h	No antidote; charcoal for overdose (ingestion <2 h); consider PCC

VTE venous thromboembolism, *AF* atrial fibrillation, *MI* myocardial infarction, *PO* per oral, *INR* international normalized ratio, *FFP* fresh frozen plasma, *PCC* prothrombin complex concentrates, *rFVIIa* recombinant activated factor VIIa, *ACS* acute coronary syndrome, *IV* intravenous, *SC* subcutaneous, *AT* antithrombin, *PCI* percutaneous coronary intervention, *HITT* heparin-induced thrombocytopenia and thrombosis

[a]*Note*: elimination half-life is dose dependent

treatment of VTE, ACS, and bridging anticoagulation for AF and cardioversion. Subcutaneous formulations are used for VTE prophylaxis. The IV UFH anticoagulant response is monitored by measuring the activated partial thromboplastin time (aPTT) at 6 h intervals. UFH is favored over low-molecular-weight heparin (LMWH) in certain clinical situations given its short half-life, reversal capabilities, and safe use in patients with renal dysfunction. Urgent reversal can be achieved with protamine sulfate [57].

LMWHs have increased bioavailability over UFH when administered subcutaneously. LMWHs inhibit factor Xa and, to a lesser degree, thrombin (IIa) to achieve their anticoagulant effects. Laboratory monitoring is usually not needed, but anti-Xa assays are used in select patients. Clinical indications are similar to UFH, and urgent reversal of anticoagulant effects can partially be achieved with protamine sulfate [57].

Fondaparinux is administered subcutaneously and inhibits factor Xa [57, 60]. This agent is approved for use in the prophylaxis and treatment of VTE and may be employed in situations where UFH and LMWH cannot be used, such as in the setting of heparin-induced thrombocytopenia and thrombosis (HITT). Monitoring is not usually necessary, but an anti-Xa assay may be used to identify if activity is present [74]. Recombinant activated factor VII (rFVIIa) can be considered for emergent reversal [60].

Bivalirudin and desirudin are synthetic analogs of r-hirudin. They reversibly bind to the enzymatic catalytic site and anion binding site of thrombin [57]. The short half-life of bivalirudin enables its use in the periprocedural setting. It is an accepted alternative anticoagulant to UFH for percutaneous coronary interventions (PCI) and ST elevation myocardial infarction (STEMI), as well as in select patients with unstable angina (UA) and non-ST elevation myocardial infarction (NSTEMI) [53, 75]. There is some evidence that bleeding complications are lower with bivalirudin than with combination UFH and glycoprotein IIb/IIIa inhibitors (GPI) in the setting of ACS [53, 76]. Bivalirudin may be monitored by activated clotting time (ACT) [74]. Desirudin has been used mainly for VTE prophylaxis [66]. Monitoring can be done by following the aPTT [74]. Serious bleeding complications with desirudin are comparable to SC UFH and LMWH [66]. There are no known reversal agents for bivalirudin and desirudin.

Argatroban is an IV anticoagulant derived from the amino acid arginine and reversibly binds to the thrombin active site. It has a short half-life, and coagulation parameters normalize within hours of infusion cessation but may take longer in patients with hepatic impairment. The aPTT or ACT should be followed for appropriate dosing. It is used primarily in the management of HITT and as a potential alternative to UFH during PCI in patients with heparin allergy [52, 57, 60]. There is no known reversal agent for argatroban.

Several novel oral anticoagulants have recently been marketed for use or are in late phases of clinical trials. These new agents provide the convenience of oral administration and avoid many of the limitations of warfarin. However, there are reports of increased clinically relevant bleeding complications, including GIB, with the new oral anticoagulant agents compared with standard therapies [18]. Dabigatran is a direct thrombin inhibitor approved for use in non-valvular AF [77]. Time to maximal effect is 0.5–2 h with a terminal half-life of 12–17 h at steady-state levels [58]. There is no specific reversal agent. Because dabigatran is a direct thrombin inhibitor, administration of FFP or prothrombin complex concentrate (PCC) may not be completely effective in reversing its effects. Hemodialysis may be effective at removing dabigatran (~60 %) from the bloodstream, and activated charcoal may be helpful in the setting of overdose [77]. Rivaroxaban is a direct factor Xa inhibitor and is approved for treatment and prophylaxis of VTE and stoke prevention in the setting of non-valvular AF [57, 58]. Time to maximal inhibition is 1–4 h. Its half-life is 5–13 h [58]. There is no specific reversal agent. Activated charcoal may be useful in the setting of overdose. However, given that rivaroxaban is highly protein bound, hemodialysis will not be effective in removing it from plasma. As it is an

upstream inhibitor of coagulation, administration of FFP, PCC, or rFVIIa may reverse its effects [57]. Apixaban (recently FDA approved) and edoxaban(in phase III clinical trials) are both direct factor Xa inhibitors with similar indications and pharmacologic properties as rivaroxaban [57].

Bridging Therapy

Once it is determined that a patient's thromboembolic risk and procedure-related bleeding risk warrant a change in antithrombotic therapy, the ultimate goal is to minimize the interval that a patient remains off anticoagulation. Anticoagulation interruption may be performed with or without "bridging." Bridging therapy usually refers to the administration of a short-acting anticoagulant, usually IV UFH or SC LMWH, during interruption of warfarin [49]. The following sections will discuss which patients need bridging anticoagulation, when to stop and restart anticoagulants in the periprocedural setting, and methods of reversing anticoagulation.

Patients at high risk for developing thromboembolism are recommended to receive bridging therapy (Table 2.4) [49]. In moderate-risk patients, the decision to proceed with bridging therapy should be based on individual patient- and procedure-related factors. Bridging therapy is not recommended for low-risk patients [49].

Interruption of Anticoagulants before Procedure

Patients requiring temporary interruption of warfarin before endoscopy should stop a minimum of 5 days prior to the procedure; shorter time intervals are discouraged [49]. Patients receiving therapeutic dose IV UFH should stop the agent at least 4–6 h before the procedure [49]. Patients on therapeutic dose SC LMWH should receive their last dose a minimum of 24 h prior to the procedure [49]. Because reversal agents are not available for the new oral anticoagulants (i.e., dabigatran, rivaroxaban, apixaban, and edoxaban), these agents should be held at least 1–2 days prior to the procedure and even longer in the setting of renal impairment.

Resumption of Anticoagulants after Procedure

Patients may resume warfarin within 12–24 h after endoscopy as long as the procedure was completed with adequate hemostasis [49]. UFH and LMWH should not be resumed at a fixed time after the procedure without consideration of anticipated bleeding risk or adequacy of post-procedural hemostasis. Following procedures with low bleeding risk, patients receiving therapeutic dose IV UFH or SC LMWH (whether for bridging purposes or not) may resume therapy approximately 24 h after the procedure. Following procedures with high bleeding risk, resumption of therapeutic dose IV UFH or SC LMWH (whether for bridging purposes or not) should be delayed for 48–72 h at which time adequate hemostasis has been assured [49]. When resuming IV UFH, it should be done without bolus injection and at the same infusion rate used prior to the procedure [49]. If bleeding continues beyond 72 h, use of low-dose heparin bridging regimens and resumption of warfarin alone without post-procedural bridging are therapeutic options [49].

Reversal

If reversal of anticoagulation status is necessary, the severity of bleeding and urgency of reversal will often dictate the method of anticoagulation reversal, selection of reversal agent, and dosing of the agent. Table 2.6 provides a general overview of reversal agents when urgent reversal is needed or in the setting of severe bleeding. Of note, anticoagulation reversal guidelines are institution specific, taking into account the institution's clinical experience and formulary availability. One can seek the guidance of a hospital's hematology, pharmacy, or anticoagulation service to assist with anticoagulation reversal.

Protamine sulfate is the antidote for heparin-based anticoagulants and can be used for emergent reversal. For treatment of UFH overdose, 1 mg of protamine sulfate per 100 units of heparin is usually administered (not to exceed 50 mg in a single dose) [60]. Given the short half-life of IV UFH (60–90 min), the dose of protamine sulfate given should be calculated based on the amount of UFH adminis-

Table 2.6 Antithrombotic reversal agents [5, 17, 60, 78–80]

Reversal agent	Antithrombotic agents	Dosage	Contraindications	Notes
Protamine sulfate	UFH, LMWH	1 mg protamine sulfate per 100 units of heparin (not to exceed 50 mg in single dose) 1 mg per 1 mg enoxaparin or 100 units dalteparin in previous 8 h (not to exceed 50 mg in single dose) [60]	• Allergy to protamine sulfate	• Patients who previously received protamine sulfate-containing insulin, undergone vasectomy, or have known sensitivity to fish are at increased risk of preformed antibodies and allergic reactions • 60–80 % reversal of LMWH
Vitamin K	Vitamin K antagonist	10 mg IV infusion over 20–30 min	• Allergy to vitamin K	• AHA and ACC recommend FFP over high-dose vitamin K (10 mg) in patients with mechanical valves requiring emergent reversal given the risk of creating a hypercoagulable condition with vitamin K [78] • IV more rapid onset than oral; SC injection not recommended
FFP	Vitamin K antagonist	10–30 mL/kg (1 unit = ~250 ml)	• Should not be given for vitamin K deficiency or nonurgent vitamin K antagonist reversal	• Replaces all coagulation factors but cannot fully correct • May need repeat after 6 h for continued bleeding • 15–20 min to thaw each unit • Requires ABO compatibility testing • Risk of intravascular volume overload
PCC Three-factor PCC (Bebulin, Baxter; Profilnine, Grifols) Four-factor PCC (Kcentra, CSL Behring)	Off-label use: vitamin K antagonist, dabigatran, rivaroxaban, apixaban	25–50 IU/kg IV sufficient in most patients	• DIC • HITT • Hypersensitivity to any components in the product	• Derived from human plasma • Factors require activation via coagulation cascade • Rapid correction of INR in warfarin patients • Small-volume infusion over 10–30 min • Risk of thrombosis 1.4 % • May need repeat dose after 6 h • Consider adding FFP if three-factor PCC used

(continued)

Table 2.6 (continued)

Reversal agent	Antithrombotic agents	Dosage	Contraindications	Notes
rFVIIa (NovoSeven RT, Novo Nordisk)	Off-label use: vitamin K antagonist, fondaparinux, dabigatran	15–90 μg/kg IV bolus every 2–6 h until hemostasis achieved	• None known	• Non-plasma-derived form • Rapid infusion of small volume • Rapid INR correction of warfarin but may not correct bleeding because only restores rFVIIa • Risk of thrombosis 5–10 %
Factor VIII inhibitor bypass activity (FEIBA NF, Baxter)	Off-label use: vitamin K antagonist, dabigatran	50–100 units/kg every 6–12 h, depending on indication (not to exceed single dose of 100 units/kg and daily dose of 200 units/kg	• Known anaphylactic or severe systemic reactions • Normal coagulation mechanism • Treatment of bleeding episodes resulting from coagulation factor deficiencies in the absence of inhibitors to coagulation factor VII or IX • DIC • Acute thrombosis or embolism (including MI)	• Derived from human plasma
Platelets	Aspirin, thienopyridines, ticagrelor	1 apheresis unit		• Each unit raises platelet count by 30×10^9/L
Desmopressin (DDAVP, Sanofi Aventis)	Off-label use: aspirin, thienopyridines	0.3–0.4 μg/kg IV	• Hypersensitivity to drug or components • CrCl <50 ml/min • History of hyponatremia	

UFH unfractionated heparin, *LMWH* low-molecular-weight heparin, *IV* intravenous, *SC* subcutaneous, *AHA* American Heart Association, *ACC* American College of Cardiology, *FFP* fresh frozen plasma, *PCC* prothrombin complex concentrate, *IU* international units, *DIC* disseminated intravascular coagulation, *HITT* heparin-induced thrombocytopenia and thrombosis, *rFVIIa* recombinant activated factor VII, *MI* myocardial infarction

tered over the previous several hours. Rapid administration of protamine sulfate can cause severe hypotension or anaphylaxis. Protamine sulfate is not as effective in reversing the anticoagulant effects of LMWHs. The American College of Chest Physicians (ACCP) recommends that if LMWH is given within 8 h, protamine sulfate should be given in a dose of 1 mg per 100 anti-Xa units of LMWH (not to exceed 50 mg in a single dose) [60]. One milligram of enoxaparin is equivalent to approximately 100 anti-Xa units. If bleeding continues, a second dose of protamine sulfate at 0.5 mg per 100 anti-Xa units can be given [60].

Recommendations for reversing anticoagulation in patients on VKA therapy vary according to differences in society guidelines. The ACCP recommends reversal with vitamin K (10 mg) by slow IV infusion (over 30 min) in all patients with serious bleeding and elevated INR, supplemented with FFP, PCC, or rFVIIa, depending on the urgency of the clinical situation [17]. Repeat vitamin K infusion may be given every 12 h, as needed, for persistent INR elevation [17]. In patients with life-threatening bleeding (e.g., intracranial hemorrhage), administration of FFP, PCC, or rFVIIa is recommended, supplemented with vitamin K (10 mg) by slow IV infusion [17]. The American Heart Association and American College of Cardiology recommend FFP over high-dose

vitamin K (10 mg) in patients with mechanical valves requiring emergent reversal due to the risk of creating a hypercoagulable state with the use of the latter. Low-dose vitamin K (1 mg) IV may be a safe alternative [78].

There are no known reversal agents for the newer oral anticoagulant agents, which include direct factor Xa inhibitors (i.e., rivaroxaban, apixaban) and direct thrombin inhibitors (i.e., dabigatran). The use of FFP, PCC, rFVIIa, and FEIBA for anticoagulation reversal can be considered, but data are limited to anecdotal experience and small studies (Table 2.6).

PCCs come in three-factor or four-factor concentrates. Three-factor PCCs have therapeutically useful levels of factors II, IX, and X, but only small amounts of factor VII [81]. There are currently two three-factor PCCs available in the United States: Bebulin (Baxter) and Profilnine (Grifols). Four-factor PCCs contain factors II, VII, IX, and X, as well as proteins C and S. Kcentra (CSL Behring) is the only four-factor PCC approved for use in the United States. Because three-factor PCCs lack factor VII, their use alone for reversing VKA-induced coagulopathy may not be completely effective [81]. When comparing four-factor PCCs with FFP for reversing VKA-induced coagulopathy, the former delivers a higher concentration of coagulation factors more rapidly and in a smaller volume than FFP, although at significant expense [81].

Algorithm

Figure 2.2 is a proposed algorithm for the management of anticoagulants in the periprocedural period.

Antiplatelets

Overview of Antiplatelets

Antiplatelet agents are used for the management of atherosclerotic thrombotic diseases, a spectrum of conditions that includes stroke, ACS, and peripheral vascular disease, as well as in patients undergoing cardiac surgery and PCI [82]. An overview of current antiplatelet drugs is shown in Table 2.7.

Aspirin is an irreversible inhibitor of cyclooxygenase (COX), causing decreased production of thromboxane A_2 (TXA_2) and prostacyclin (PGI_2) and leading to impaired platelet aggregation [82]. The thienopyridines are a class of drugs that include clopidogrel, ticlopidine, and prasugrel. They are prodrugs whose active metabolites bind to platelet $P2Y_{12}$ receptor to form disulfide bridges between extracellular cysteine residues that irreversibly inhibit adenosine diphosphate (ADP)-induced platelet aggregation [82]. In patients treated with aspirin or thienopyridines, normal platelet function returns with the production of new platelets, which usually occurs over a period of 5–10 days.

Dipyridamole is a phosphodiesterase (PDE) inhibitor that causes an increase in cyclic adenos-

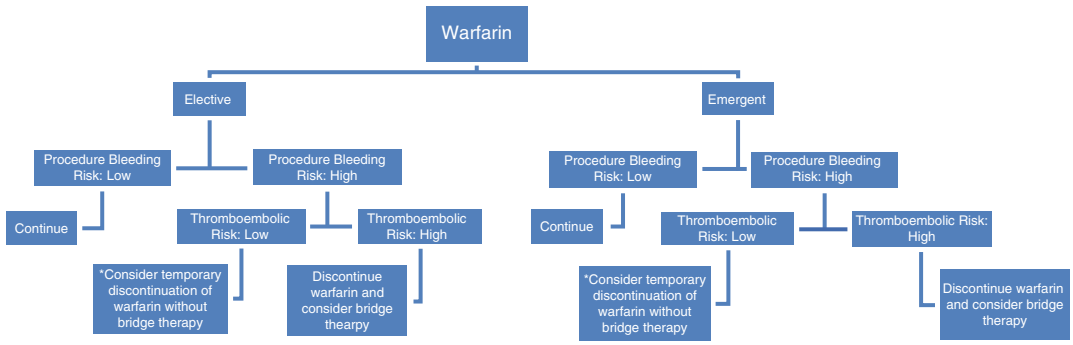

Fig. 2.2 Anticoagulant therapy management algorithm

Table 2.7 Current antiplatelet agents

Drug	Main indications	Route	Mechanism of action	Time to maximal IPA	Elimination half-life[a]	Return of platelet function after cessation	Reversal agent or antidote
Aspirin (generic) [49, 83]	ACS, PCI, stroke treatment and prophylaxis, MI prophylaxis, others	PO	Irreversible inhibition of COX → ↓ thromboxane A_2 and prostacyclin	Minutes to hours (delayed with enteric coating)	6 h 15–20 min (plasma half-life)	5–10 days (lifespan of platelet)	Platelet transfusion ± desmopressin
Clopidogrel (Plavix, Sanofi Aventis) [49, 84]	ACS, PCI, stroke, peripheral arterial disease	PO	Irreversible inhibition of $P2Y_{12}$ ADP receptor	12–15 h after loading dose 5–10 days after maintenance dose	8 h	7–10 days	Platelet transfusion ± desmopressin
Ticlopidine (Ticlid, Apotex) [83, 85]	Stroke, PCI	PO	Irreversible inhibition of $P2Y_{12}$ ADP receptor	8–11 days after maintenance dose	24–36 h	7–10 days	Platelet transfusion ± desmopressin
Prasugrel (Effient, Eli Lilly) [86]	ACS, PCI	PO	Irreversible inhibitor of $P2Y_{12}$ ADP receptor	4 h after loading dose	~7 h (range 2–15 h)	7–9 days	Platelet transfusion ± desmopressin
Dipyridamole + aspirin (Aggrenox, Boehringer Ingelheim) [87–89]	Stroke prophylaxis (combined with aspirin); prosthetic heart valve thromboembolism prophylaxis adjunct	PO	PDE3/5 inhibition → ↑ cAMP/cGMP in platelets → ↓ platelet aggregation through multiple mechanisms	Hours	9–12 h	See aspirin	Platelet transfusion ± desmopressin
Cilostazol (Pletal, Otsuka Pharmaceutical) [87, 90–92]	Intermittent claudication (USA); peripheral arterial disease (Japan)	PO	PDE3 inhibition → ↑ cAMP in platelets → ↓ platelet aggregation through multiple mechanisms	6–8 h	11–13 h	24–48 h	Platelet transfusion ± desmopressin
Ticagrelor (Brilinta, AstraZeneca) [93]	ACS, PCI	PO	Reversible inhibition of $P2Y_{12}$ ADP receptor	1–2 h after loading dose	9 h	5 days	Platelet transfusion ± desmopressin
Cangrelor (The Medicines Company) (*investigational*) [94]	Phase III studies: ACS, PCI	IV	Reversible inhibition of $P2Y_{12}$ ADP receptor	30 min	3–6 min	60–90 min	Rapid reversal with cessation

(continued)

Table 2.7 (continued)

Drug	Main indications	Route	Mechanism of action	Time to maximal IPA	Elimination half-life[a]	Return of platelet function after cessation	Reversal agent or antidote
Abciximab (ReoPro, Eli Lilly) [95, 96]	PCI with STEMI or high-risk UA/NSTEMI Treatment of patients undergoing PCI. Treatment of patients with UA not responding to conventional medical therapy when PCI is planned within 24 h.	IV	Noncompetitive, irreversible inhibition of GP IIb/IIIa	2 h	10–30 min	24–48 h	Platelet transfusion ± desmopressin
Eptifibatide (Integrilin, Merck) [95, 97]	PCI with STEMI or high-risk UA/NSTEMI Treatment of ACS managed medically or with PCI. Treatment of patients undergoing PCI	IV	Competitive, reversible inhibition of GP IIb/IIIa	Immediate	2.5 h	<4 h	Platelet transfusion ± desmopressin
Tirofiban (Aggrastat, Medicure) [95, 98]	PCI with STEMI or high-risk UA/NSTEMI	IV	Competitive, reversible inhibition of GP IIb/IIIa	Immediate	2 h	4–8 h	Platelet transfusion ± desmopressin

IPA inhibition of platelet aggregation, *ACS* acute coronary syndrome, *PCI* percutaneous coronary intervention, *MI* myocardial infarction, *PO* per oral, *IV* intravenous, *COX* cyclooxygenase, *ADP* adenosine diphosphate, *PDE* phosphodiesterase, *STEMI* ST segment elevation myocardial infarction, *UA* unstable angina, NSTEMI non-ST segment elevation myocardial infarction, *GP* glycoprotein

[a]Note: elimination half-life is dose dependent

ine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) in platelets, leading to a decrease in platelet aggregation through multiple mechanisms [87]. Dipyridamole is frequently used in combination with aspirin for secondary prophylaxis of non-cardioembolic transient ischemic attacks or stroke. Dipyridamole alone is not associated with increased bleeding risk but, when used in combination with aspirin, may require 5–10 days for platelet function to return. Cilostazol is a PDE3 inhibitor that also causes an increase in cAMP in platelets, leading to inhibited platelet aggregation. It is approved for use in the treatment of intermittent claudication [87]. Cilostazol has not been associated with increased bleeding risk in clinical studies [87].

Agents with reversible effects on the $P2Y_{12}$ receptor include ticagrelor and cangrelor. Ticagrelor, a cyclopentyltriazolopyrimidine, is an oral reversible $P2Y_{12}$ receptor inhibitor with more rapid onset and return of platelet function than clopidogrel and is approved for use in ACS and PCI [82]. Compared with clopidogrel, ticagrelor is associated with a higher rate of major bleeding not related to coronary artery bypass grafting surgery [99]. Cangrelor is an intravenously administered reversible $P2Y_{12}$ receptor inhibitor currently in phase III clinical trials for treatment of ACS. Unlike other $P2Y_{12}$ receptor inhibitors, cangrelor has a rapid onset of action (maximal inhibition of ADP-induced platelet aggregation at 30 min) as well as rapid return of platelet function (within 60 min) [94]. Overall bleeding complications related to cangrelor are low and comparable to clopidogrel [100].

Both prasugrel and ticagrelor now form part of ACS management algorithms, based on data from head-to-head comparison trials demonstrating reduced cardiovascular events relative to clopidogrel, but at the expense of increased bleeding complications [53, 99, 101].

GPIs prevent the binding of fibrinogen to GP IIb/IIIa receptors, interfering with interplatelet bridging mediated by fibrinogen, which is the final common pathway of platelet aggregation. GPIs primarily serve as adjunctive therapy when used in combination with dual antiplatelet and anticoagulant (UFH or bivalirudin) therapy at the time of PCI in the setting of STEMI or high-risk UA/NSTEMI [53, 75]. Abciximab is a monoclonal antibody fragment that exerts noncompetitive, irreversible inhibition of GP IIb/IIIa. Although the plasma half-life of abciximab is short (few min), its platelet-bound half-life lasts hours. Therefore, it may take 24–48 h for platelet function to return in the absence of platelet transfusion [83]. Eptifibatide and tirofiban are small-molecule GPIs which exert competitive inhibition of GP IIb/IIIa. Their effects on platelet aggregation are closely related to plasma concentrations, and return of platelet function occurs within hours (~4 h) of stopping infusion [83]. Bleeding complications are higher with the use of GPIs [102].

Bridging Therapy

There are currently no proven bridging therapies for patients who must consider discontinuing dual antiplatelet therapy. The use of anticoagulants has not been satisfactory in this regard and there are no data supporting the use of GPIs in this situation [103]. Given the lack of uniform guidelines in regard to the discontinuation and resumption of antiplatelet agents in the periprocedural period, endoscopists should consult with the appropriate specialist for the optimal management of these high-risk patients.

Interruption of Antiplatelets before Procedure

In general, patients on aspirin monotherapy may proceed with most endoscopic procedures without interruption in the absence of pre-existing bleeding disorders [2–4]. Exceptions may include endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), ampullary resections, EUS-FNA of large cystic lesions, and ERCP with combination sphincterotomy and large papillary balloon dilation [4]. Patients at low risk for cardiovascular events who are receiving aspirin monotherapy should stop the drug 7–10 days pre-procedure; those on clopidogrel monotherapy should stop the drug 5–10 days pre-procedure [5, 49].

In patients with coronary stents who are receiving dual antiplatelet therapy and require an endoscopy, it is recommended to defer endoscopy, if feasible, for at least 4–6 weeks after placement of

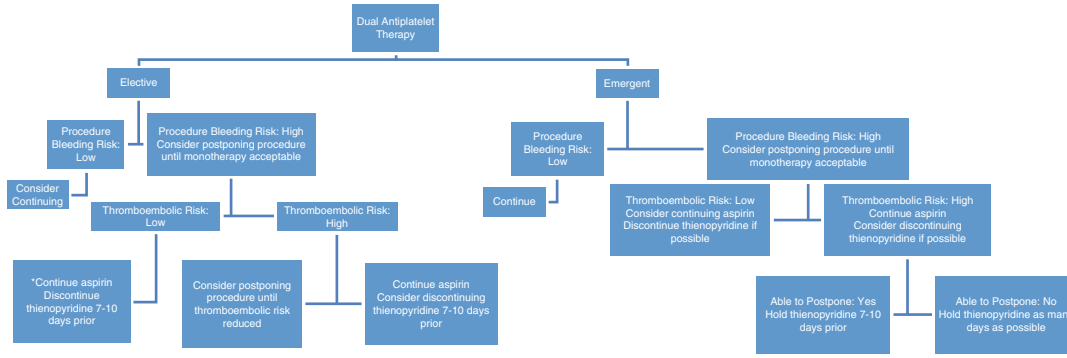

Fig. 2.3 Dual antiplatelet therapy management algorithm

a BMS and for at least 6–12 months after placement of a DES [2–5, 49]. In patients who require a procedure within 6 weeks of placement of a BMS or within 6 months of placement of a DES, it is recommended that dual antiplatelet therapy be continued at the time of the procedure [49].

Resumption of Antiplatelets after Procedure

In general, dual antiplatelet therapyshould be resumed after the bleeding risk is minimized from the endoscopic intervention and continued for the recommended duration. Platelet inhibition is rapid with aspirin (minutes to hours) compared with maintenance-dose clopidogrel, which may take 5–10 days to reach maximal inhibition of platelet function [49]. Aspirin and maintenance-dose clopidogrel can usually be resumed within 24 h post procedure (similar to warfarin) [5, 49]. Loading-dose clopidogrel has a more rapid onset and can be considered if bleeding risk is low [5]. The optimal timing regarding resumption of prasugrel and ticagrelor is unclear, but likely more than 24 h post procedure [5].

Reversal

The effects of antiplatelet agents with irreversible inhibition of platelet aggregation will last for the lifespan of the platelets, and function will return after the platelet pool is replenished (~7–10 days). Patients requiring reversal of antiplatelet effects may require platelet infusion and, in some cases, desmopressin to help restore platelet function. The GPIs have short half-lives and may only require supportive care and holding the infusion.

Algorithm

Figure 2.3 is a proposed algorithm for the management of antiplatelet therapy in the periprocedural period.

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Approach to Suspected Nonvariceal Upper Gastrointestinal Bleeding

3

Yen-I. Chen, Yidan Lu, Hisham Aldahab, and Alan Barkun

Introduction

Acute nonvariceal upper gastrointestinal bleeding (NVUGIB) is one of the most common causes for hospitalization worldwide. In the United States, there are 250,000–300,000 hospital admissions and 15,000–30,000 deaths each year as a result of NVUGIB [1]. Peptic ulcer disease is the most prevalent source of NVUGIB and accounts for approximately 50 % of all cases. Less common causes of NVUGIB include esophagitis, erosive gastropathy, angiodysplasia, tumor, Dieulafoy lesion, and Mallory-Weiss syndrome [2]. The incidence of NVUGIB ranges from 48 to 160 cases per 100,000 adults per year. In 2004, the mean length of stay for patients admitted with NVUGIB in the United States ranged from 2.7 to 4.4 days, and the associated costs varied from $3402 to $5532 per hospitalization [3]. Recent data have shown that the mortality rate from NVUGIB is trending down to 2.4–5 %, and the hospitalization rate has decreased from 78.4/100,000 to 60.6/100,000 [4–6]. This may be explained, in part, by better risk stratification and advances in peri-endoscopic medical management and endoscopic therapy.

Herein, we will highlight the pre- and post-endoscopic medical management of NVUGIB, including initial resuscitation, risk stratification, pre- and post-endoscopic use of proton pump inhibitors, use of nasogastric (NG) tube insertion and promotility agents, indications and timing for endoscopy, predictors of rebleeding, second-look endoscopy, eradication of *H. pylori*, and use of aspirin, nonsteroidal anti-inflammatory agents (NSAIDs), and antithrombotic agents. Specific endoscopic techniques for hemostasis of NVUGIB will be addressed in a separate chapter.

Suspected Nonvariceal Upper GI Bleeding

Initial Approach and Resuscitation

Patients presenting with acute upper gastrointestinal bleeding (UGIB) are at risk of hemodynamic shock and airway compromise. Therefore,

Y.-I. Chen • Y. Lu • H. Aldahab
Division of Gastroenterology, The McGill University Health Center, Montreal General Hospital Site, 1650 Cedar Avenue, Room D7.346, Montreal, QC H3G 1A4, Canada

A. Barkun, M.D. (✉)
Division of Gastroenterology, The McGill University Health Center, Montreal General Hospital Site, 1650 Cedar Avenue, Room D7.346, Montreal, QC H3G 1A4, Canada

Department of Epidemiology, Biostatistics and Occupational Health, McGill University Health Center, McGill University, Montréal, QC H3G 1A4, Canada
e-mail: alan.barkun@muhc.mcgill.ca

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the first priority is to assess the adequacy of the airway, as well as the patient's breathing and circulation. Intubation is clearly indicated if the airway is compromised, while prophylactic intubation may be considered in severe UGIB although current data supporting such practice are limited [7, 8]. Venous access should be achieved with at least two large-bore cannulas, and patients with active bleeding should be monitored in an intensive care unit (ICU) with pulse oximetry and cardiac monitoring. All patients should be blood-typed and cross-matched for packed red blood cells (RBC), with blood sent for hemoglobin, hematocrit, platelets, coagulation profile, creatinine, urea, and electrolytes [9]. Hemodynamic shock is associated with increased mortality; therefore, prompt resuscitation should be initiated with either crystalloid or colloid fluids [10, 11].

The value of RBC transfusion in massively exsanguinating NVUGIB is self-evident, and the small proportion of patients requiring massive transfusion should be managed in accordance with institutional major hemorrhage protocols in close liaison with hospital transfusion teams. Otherwise, the benefits of blood transfusion for NVUGIB must be weighed against its detrimental effects. Some data suggest that RBC transfusion may worsen bleeding by disrupting splanchnic vasoconstriction associated with hypovolemia, thereby increasing splanchnic blood pressure, which may impair clot formation [12, 13]. Transfusions may also directly induce abnormalities in coagulation properties [14]. Current evidence supports a restrictive transfusion strategy with a hemoglobin threshold of <7 g/dL [2], although transfusion policy should be individualized and take into account other factors, such as age, comorbidities, hemodynamic status, and active bleeding. A restrictive transfusion strategy has been associated with improved outcomes, with decreased in-hospital mortality in critically ill patients [15], as well as better 6-week survival and decreased rebleeding in patients with UGIB [16], when compared to a more liberal transfusion approach targeting hemoglobin levels above 9–10 g/dL. However, it is important to note that the favorable findings regarding the restrictive strategy pertain primarily to patients with UGIB in the context of chronic liver disease (Child's grades A and B) and that such benefits in patients with NVUGIB without liver disease require confirmatory data.

Correction of Coagulopathy and Platelet Count

In the Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy (RUGBE) cohort of 1869 patients, an international normalized ratio (INR) >1.5 was associated with an almost twofold increased risk in mortality (OR 1.95, 95 % CI 1.13–3.41) without increased risk of rebleeding [17]. Data using a historical cohort as comparison showed that the correction of INR to <1.8, as part of intensive resuscitation, led to lower mortality and fewer myocardial infarctions in the intervention group [18]. Current guidelines on the management of NVUGIB support the correction of coagulopathy, although this should not delay endoscopy [2]. This consensus recommendation is based on recognition of the benefits of early endoscopic intervention, coupled with decreased tissue injury associated with nonthermal hemostatic techniques, such as endoscopic clips or hemostatic powders. Moreover, limited observational data suggest that endoscopic hemostasis can be performed safely in patients with an INR <2.5 [19].

The use of prothrombin complex concentrate (PCC) should be considered for the reversal of warfarin-induced coagulopathy in patients presenting with life-threatening hemorrhage. Unlike fresh frozen plasma (FFP), PCC does not need to be frozen during storage and therefore can be administered without delay. In addition, PCC can be administered more rapidly at lower infusion volumes than FFP and may be more effective in reversing warfarin-induced coagulopathy [20]. However, it is important to note that PCC may not be effective, or possibly even harmful, in the management of non-warfarin-induced coagulopathy (e.g., due to chronic liver disease), which

would require the use of FFP. Finally, the emergence of direct thrombin and factor Xa inhibitors poses a new challenge in the management of GI bleeding, since neither FFP nor PCC has been proven effective in the reversal of such agents. However, PCC use may still be considered in severe bleeding based on its variable success in animal and in vitro studies, as well as in healthy human volunteers [21, 22]. The development of specific antidotes for these novel agents is currently underway.

In contrast to INR, the platelet count has not been shown to be a predictor of either rebleeding or mortality. There are no evidence-based data to guide platelet transfusion thresholds, although maintaining a platelet count of 50×10^9/L and above has been proposed in most patients with suspected platelet dysfunction or significant thrombocytopenia in the setting of acute GI bleeding [23].

Risk Stratification

In parallel with resuscitation, the stratification of patients into high- and low-risk categories using established prognostic scales should be performed in order to assist the decision-making process with regard to hospitalization versus early discharge, timing of endoscopy, and other interventions [2, 24].

The Rockall score uses both pre-endoscopic and post-endoscopic variables (Table 3.1). It uses clinical variables such as age, comorbidities, the presence of shock, along with endoscopic findings to predict further bleeding and mortality [25]. Patients with risk scores of 0 and 1 have low incidences of rebleeding and no associated mortality, and these patients at low risk for complications can be considered for early discharge [25]. The Glasgow-Blatchford risk score (GBS) predicts the risk of requiring interventions (i.e., transfusion, surgical, and endoscopic therapy) (Table 3.2). It incorporates only pre-endoscopic variables, including hemoglobin and blood urea nitrogen (BUN), heart rate and systolic blood pressure, history of syncope and melena, and heart failure or liver disease [27]. A GBS of 0 is associated with a 0.5 % risk for needing subsequent intervention. Using this cutoff to direct early discharge with outpatient endoscopy led to reduced hospitalization without increased complications [28].

The GBS area under its receiver-operator curve (AUC) (0.90, 95 % CI 0.88–0.93) outperformed the full Rockall score (0.81, 96 % CI

Table 3.1 Numerical scoring system for complete Rockall score

Score	Age	Shock	Comorbidities	Diagnosis	Evidence of recent bleeding
0	<60	No shock	No major comorbidity	Mallory-Weiss, no bleeding or lesion identified	None or dark spot only
1	60–79	Pulse >100 bpm SBP >100 mmHg		Other diagnoses	
2	>80	Hypotension SBP <100 mmHg	Ischemic heart disease, cardiac failure, any major comorbidity	Malignancy of the upper GI tract	Active bleeding, oozing, non-bleeding visible vessel, adherent clot, or blood in the GI tract
3			Renal and/or liver failure, disseminated malignancy		

Adapted from Rockall et al. [25]

Table 3.2 Full and modified Glasgow-Blatchford risk score

	Clinical parameters			Score
Modified GBS	Heart rate (beats/min)	≥100		1
	Systolic blood pressure (mmHg)	100–109		1
		90–99		2
		<90		3
	Blood urea nitrogen (mg/dL)	19–22.3		2
		22.4–27.9		3
		28.0–69.9		4
		≥70.0		6
	Hemoglobin (g/dL)	Men	Women	
		12.0–12.9	10–12	1
		10.0–11.9		3
		<10	<10	6
Subjective findings [26]	Comorbidities	Liver disease		2
		Heart failure		2
	Presentation	Syncope		2
		Melena		1

Adapted from Blatchford et al. [27]

0.77–0.84) and pre-endoscopic Rockall score (0.70, 95 % CI 0.65–0.75) when predicting the need for intervention or death [28]. Prospectively, the pre-endoscopic Rockall does not readily identify low-risk patients [29]. A modified GBS that omits the presence of syncope and the blood urea value has been validated [30]. Another modified GBS, which eliminates subjective components (presence of hepatic and cardiac disease, melena, and syncope), performed as well as the standard GBS in a prospective comparison by Cheng et al. (Table 3.2) [26]. For both, scores of ≤1 had significantly lower rates of rebleeding and mortality. Other scoring schemes have also been proposed, including the Baylor bleeding score and the Cedars-Sinai Medical Center predictive index. However, the Rockall score and GBS remain the more commonly used risk assessment tools [31].

Consensus recommendations support the use of one of the validated scales for risk stratification [32, 33]. The modified GBS may be the preferred method when used to identify patients for early discharge and outpatient endoscopy given its ease of use, absence of subjectivity, and lack of need for an endoscopic score. The pre-endoscopic Rockall score appears to be the least reliable among the commonly used scoring schemes.

Pre-endoscopic Use of Proton Pump Inhibitors

Proton pump inhibitors (PPI) play an important role in the stabilization of clot formation, especially in bleeding peptic ulcers, through pH-dependent factors by raising the pH to 6 and improving platelet aggregation [34]. Raising the pH may also decrease pepsin-mediated clot lysis and fibrinolytic activity.

A Cochrane systematic review and meta-analysis of six randomized controlled trials (2223 patients) comparing PPI with either placebo or histamine-2 (H2) receptor antagonists found no evidence that pre-endoscopic administration of PPI led to a reduction in rebleeding, mortality, or need for surgery [35]. However, the use of pre-endoscopic PPI may obviate the need for endoscopic intervention by downstaging high-risk

Table 3.3 Identification of bleeding stigmata with associated prevalence and outcomes

Stigmata of recent hemorrhage		Forrest classification	Prevalence in NVUGIB (modified from Barkun et al. [36]) (%)	Rate of ongoing bleeding (modified from Laine et al. [37]) (%)
Spurting	High-risk stigmata	IA	3	55
Oozing		IB	22	
Non-specified active bleeding			2	
Non-bleeding visible vessel		IIA	10	43
Adherent clot		IIB	7	22
Flat pigmented spot	Low-risk stigmata	IIC	5	10
Clean base		III	47	5

Adapted from Lu and Barkun [38]

endoscopic stigmata (Forrest classification) into low-risk lesions (Table 3.3). Given its safety profile and beneficial effect on the need for endoscopic therapy, the use of PPI in the setting of acute NVUGIB is useful, especially in patients with high-risk stigmata. Moreover, the administration of PPI may prove advantageous when early endoscopy is not feasible or local expertise is limited. Pre-endoscopic PPI, however, should not be used to delay or replace endoscopy [39]. Intravenous administration may be preferred to oral dosing on the basis of evidence supporting the former; it may also be more conducive for patients who are at risk for emesis. An initial bolus of 80 mg of omeprazole or pantoprazole, followed by an infusion of 8 mg/h, is recommended, although a lower dosage may also be effective [9, 40].

In the absence of an impact on major clinical endpoints, cost may be a more relevant variable. Cost-effectiveness analysis in US and Canadian settings reveals that pre-endoscopic PPIs are slightly more costly but effective than no administration [41]. Such conclusions may vary depending on the elapsed time to endoscopy (early versus delayed), the underlying stigmata of recent bleeding (favoring HRS), and the proportion of patients with variceal bleeding [39].

Pre-endoscopic Use of Nasogastric Tube and Prokinetic Agents

The role of the nasogastric tube (NGT) in the initial assessment of patients presenting with suspected UGIB remains controversial. Its insertion is recommended in selected patients [32], at least for sampling purposes, as it carries prognostic value in identifying endoscopic HRS [42]. However, NGT aspirates can be negative in up to 15 % of cases with UGIB, especially when bleeding stems from a duodenal source [42]. The presence of fresh blood in the NGT aspirate is an independent predictor of adverse outcome on multivariate analysis [43] and a predictor of high-risk lesions in patients who are hemodynamically stable without hematemesis. In the Canadian RUGBE study, a bloody NGT aspirate exhibited a specificity of 75.8 % for endoscopic HRS, whereas a clear NGT aspirate had a predictive value of 85.3 % for low-risk endoscopic lesions [42].

Therefore, pre-endoscopic use of NGT in selected, stable patients without hematemesis may be beneficial in predicting high-risk lesions at endoscopy and may aid the clinician in selecting patients for prompt endoscopy and pre-endoscopic administration of high-dose PPI. However, caution must be taken when using the

NGT as a prognostic tool since high-risk lesions located in the duodenum may yield a clear nasogastric aspirate.

The use of nasogastric lavage is no longer indicated, especially with evidence supporting the use of prokinetics in this setting. Meta-analyses show that erythromycin is associated with a decrease need for repeat endoscopy in patients with evidence of ongoing bleeding or suspected retained blood in the stomach (hematemesis, coffee ground vomitus, or bloody NGT aspirate) [44]. However, it failed to change outcomes in terms of length of stay (LOS), transfusion requirements, and need for surgery [45]. The data stem from a limited number of studies and patients, and, thus, the robustness of these conclusions needs validation in larger trials. Current guidelines do not recommend the routine administration of prokinetic agents but support their use in selected patients with evidence of active bleeding and/or suspected blood in the stomach [2]. In terms of dosing, erythromycin should be administered intravenously 20–120 min prior to endoscopy at a dose of 250 mg over 5–30 min [45]. Since erythromycin is known to prolong the QT interval, an electrocardiogram prior to its use is advisable. Metoclopramide may be used as an alternative prokinetic agent, although data on the administration of erythromycin are more robust [45].

Timing of Endoscopy

Practice guidelines recommend early endoscopy (defined as within 24 h of presentation) in most patients with NVUGIB [2]. In randomized trials, very early endoscopy (<12 h) did not appear to confer any additional benefits in terms of rebleeding, need for surgery, or mortality in unselected patients with NVUGIB when compared to early endoscopy (>12 h to <24 h) [46–48]. However, a recent observational study suggested that endoscopy within 13 h of presentation was associated with lower mortality in selected high-risk patients, defined as GBS >12 [49]. In accordance with previous studies, there was no benefit in mortality rate when endoscopy was performed within 13 h in low-risk subjects. Despite confounding bias, these data highlight the importance of proper risk stratification and its potential impact on the selection of individuals for very early endoscopy. Moreover, another observational study recently demonstrated that endoscopy performed within 12 h was associated with increased efficiency of care and improved control of hemorrhage in high-risk patients [50], supporting a recent UK guideline that recommends endoscopy immediately following resuscitation in patients at increased risk of negative outcomes [51].

In accordance with current international consensus guidelines, we advocate early endoscopy (within 24 h of presentation) in most patients with NVUGIB [2]. Although the evidence does not support very early endoscopy (within 12 h of presentation) on a routine basis, high-risk patients, as predicted by prognostic scales, may be considered for more urgent endoscopy, although such an approach needs validation from larger trials. Of note, however, guidelines do recommend endoscopy within 12 h of presentation in patients with suspected variceal bleeding, based on limited high-quality data [52].

Efficacy of Endoscopic Therapy

Endoscopic therapy is indicated in patients presenting with NVUGIB and HRS, as defined by the Forrest classification: active spurting (Ia), active oozing (Ib), non-bleeding visible vessel (IIa), and adherent clot (IIb) (Table 3.3) [37]. Meta-analyses have demonstrated that endoscopic therapy (injection or thermal) of ulcers with these features significantly improved the rates of rebleeding, surgery, and/or mortality [53, 54]. Low-risk lesions, such as ulcers with flat, pigmented spots (Forrest IIc) and clean-based ulcers (Forrest III), are associated with lower incidences of rebleeding, and endoscopic therapy has not been shown to be beneficial in this setting [37, 55].

In terms of endoscopic hemostasis, clip placement, thermocoagulation, and sclerosant

injection are effective modalities in treating ulcers with HRS [2]. These modalities, when used as monotherapy or in combination with epinephrine injection, are superior to epinephrine injection alone in terms of initial hemostasis and rebleeding rates (mono vs. epinephrine OR (odds ratio) 0.3 [0.22–0.41]; combo vs. epinephrine OR 0.53 [0.40–0.69]), need for surgery (mono vs. epinephrine OR 0.44 [0.20–0.98]; combo vs. epinephrine OR 0.64 [0.46–0.90]), and, in some studies, mortality (mono vs. epinephrine OR 0.37 [0.10–1.37]; combo vs. epinephrine OR 0.51 [031–0.84]) [56, 57]. Thus, epinephrine injection alone is not recommended as definitive treatment. When combination therapy was compared to monotherapy with clips, thermocoagulation, or sclerosant injection, both were shown to be equally efficacious [56–60]. At present, there are insufficient data to recommend one modality over the other; however, contact thermal devices, clips, and combination therapy may have the strongest evidence for use [2]. The following summarizes the five meta-analyses that assessed the efficacy of different endoscopic modalities in NVUGIB.

The meta-analysis by Calvet et al. encompassed 16 studies and compared the use of epinephrine injection alone to epinephrine injection followed by a second endoscopic therapy (1673 patients) [56]. The hemostatic modalities included injection therapies (epinephrine, thrombin, ethanolamine, ethanol, sodium tetradecyl sulfate, polidocanol, and fibrin glue), thermal modalities (laser, heat probe, bipolar electrocoagulation), and clips. The analysis concluded that the addition of a second endoscopic modality, irrespective of the type, after epinephrine injection decreased further bleeding (OR 0.53 [040–0.69]), mortality (OR 0.51 [0.31–0.84]), and emergency surgery (OR 0.64 [0.46–0.90]) compared to epinephrine injection alone.

Marmo et al. compared combination therapy (injection plus thermal or mechanical) versus monotherapy for the treatment of high-risk bleeding peptic ulcers in an analysis that included 22 studies (2474 patients) [59]. Compared to epinephrine injection alone, combination therapy was associated with significantly lower rates of recurrent bleeding (OR 0.33 [0.17–0.63]) and need for surgery (OR 0.21 [0.07–0.60]), but not mortality (OR 0.99 [0.20–4.96]). Combination therapy was not significantly better than either thermal or mechanical monotherapy.

Sung et al. assessed 15 randomized trials (1156 patients) in a meta-analysis that compared clips vs. injection alone, clips plus injection vs. injection alone, and clips vs. thermocoagulation, with or without injection [60]. Although a high degree of heterogeneity was noted across the trials, the use of clips, with or without injection, was associated with decreased rebleeding (OR 0.47 [0.28–0.76]) and need for surgery (OR 0.23 [0.08–0.70]), but not mortality (OR 1.35 [0.25–7.14]), relative to injection therapy alone. No significant differences were noted between thermocoagulation and clips.

Barkun et al. performed a meta-analysis of 41 trials (4261 patients) using endotherapy in patients with high-risk bleeding ulcers [58]. Endoscopic therapy using any modality outperformed pharmacotherapy at reducing the rebleeding rate (OR 0.35 [0.27–0.46]), but not surgery or mortality. Injection therapy was inferior to all other endoscopic modalities, except for thermal coagulation, in which a trend favored the latter but failed to reach significance. Data were insufficient to support the combined use of injection with thermal or mechanical therapy. On the basis of the study findings and subgroup analyses, the authors concluded that thermal therapy or endoscopic clips should be used alone or in combination with epinephrine injection in NVUGIB with HRS.

The meta-analysis by Laine et al. yielded similar conclusions by analyzing randomized trials that used rebleeding as the primary outcome while excluding those that incorporated second-look endoscopy (re-treatment when needed). Endoscopic therapy, when compared to pharmacotherapy, was associated with decreased rates of rebleeding and need for surgery, except in the adherent clot subgroup where no differences were detected. Epinephrine injection alone was inferior at reducing further bleeding compared to

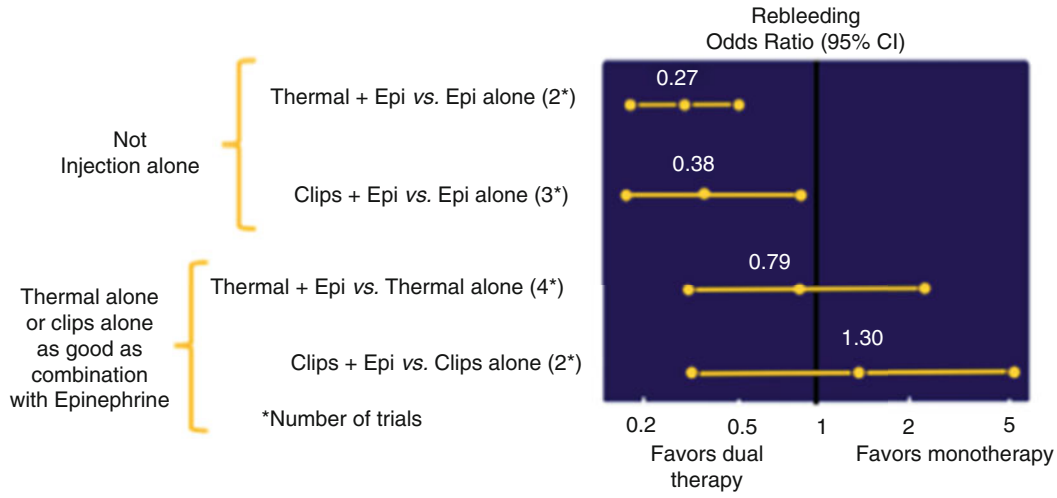


Fig. 3.1 Combination therapy vs. monotherapy in terms of their effectiveness in reducing rates of rebleeding

other modalities. In accordance with other studies, endoscopic clip placement and thermal therapy were equally efficacious, with or without injection therapy (Fig. 3.1).

The Adherent Clot

The approach to the adherent clot first involves irrigation in an attempt to dislodge the clot and expose the underlying stigmata [2]. Aggressive irrigation for up to 5 minutes successfully exposes a HRS in 33–43 % of lesions [61, 62]. Failure to do so defines an adherent clot. In two randomized trials, endoscopic treatment of the adherent clot decreased the rebleeding rate compared to medical therapy alone [63, 64], whereas other studies have demonstrated no added benefit of endotherapy [65–67]. A single randomized controlled trial using high-dose IV PPI bolus followed by infusion reported no rebleeding in the acid suppression-only group [67]. One meta-analysis suggested significant improvement in outcomes attributable to endoscopic treatment in the subset of patients with adherent clots [68], although the study was criticized because of statistical shortcomings [69]. Another meta-analysis found no benefit in clinical outcomes, although significant heterogeneity was noted among the trial populations [57].

With regard to the ulcer with an adherent clot, we agree with current recommendations supporting initial vigorous irrigation followed by consideration for endotherapy, especially in high-risk patients, while acknowledging that high-dose IV PPI may be adequate in certain populations [2, 24].

Novel Endoscopic Hemostatic Powders

Recently, novel endoscopic topical hemostatic powders, such as the Ankaferd Blood Stopper™ (ABS) and TC-325, have been adapted to digestive endoscopy for the management of GI bleeding. ABS (Ankaferd Health Products Ltd., Istanbul, Turkey) is an herbal extract derived from five different plants that achieves hemostasis by promoting the formation of a protein network serving as an anchor for erythrocyte aggregation [70]. This agent, however, is not available in North America. TC-325 (Hemospray™, Cook Medical, Winston-Salem, NC, USA) is composed of a proprietary biologically inert powder that becomes coherent and adhesive upon contact with moisture in the GI tract, thus serving as a mechanical barrier for hemostasis (Fig. 3.2) [71]. In addition, it provides a scaffold that enhances platelet aggregation and possibly the activation of clotting factors [72]. A prospective pilot study described 20 patients with nonmalignant UGIB who underwent treatment with TC-325, resulting in initial hemostasis in 95 % of cases [73]. In a prospective cohort involving 71 subjects from nine institutions with NVUGIB, acute

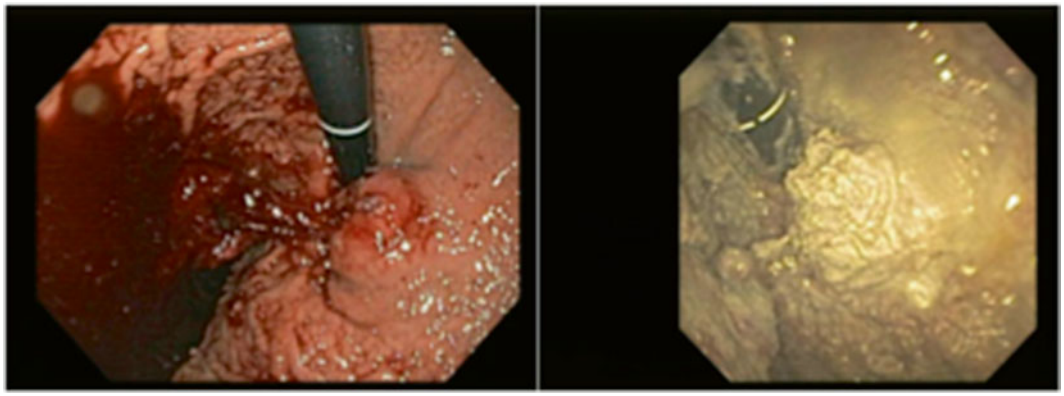


Fig. 3.2 Pre- and post-TC-325 hemostasis in bleeding gastric cardia mass

hemostasis was achieved in 92 % of patients with TC-325 used as the sole approach. The rebleeding rate at 1 week was 15 % [74]. Although preliminary data on topical agents for endoscopic hemostasis are encouraging, additional trials are needed to further define its efficacy and safety.

In summary, endoscopic therapy is indicated in patients presenting with NVUGIB and HRS at endoscopy. Endoscopic clip placement, thermal coagulation, and sclerosant injection can be used alone or in combination with epinephrine injection. Epinephrine injection as sole therapy is not recommended. The approach to the ulcer with an adherent clot involves an attempt at dislodging the clot with vigorous irrigation to reveal underlying HRS, if any, which can then be treated either by endoscopic therapy or high-dose PPI. Hemostatic powders appear promising, but they require further study.

Post-endoscopic Proton Pump Inhibitor Therapy

It is recommended that high-dose intravenous PPI therapy (e.g., a PPI at a dose of 80 mg bolus dose followed by 8 mg/h infusion) should be administered to patients with HRS who underwent successful endoscopic therapy [2]. In terms of duration, high-dose PPI should be continued for 72 h post-endoscopic therapy based on the understanding that most high-risk lesions require 3 days to evolve to a low-risk lesion and that, consequently, the majority of rebleeding will occur during this time period [75]. These recommendations are based on a meta-analysis of randomized controlled trials encompassing 5792 patients in whom PPI therapy reduced the incidence of rebleeding (OR 0.45, 95 % CI 0.36–0.57) and need for surgery (OR 0.56, 95 % CI 0.45–0.70), but not mortality (OR 0.90, 95 % CI 0.67–1.19) [75–82]. Subgroup analysis of trials from Asia and a meta-analysis by Laine and McQuaid, however, showed that the administration of high-dose intravenous PPI following successful endoscopic therapy improved mortality [57]. Low-dose PPI has been shown to exhibit similar effectiveness to high-dose PPI, although this approach is not favored in consensus statements due to significant methodological limitations in reported studies [2, 83]. In terms of cost-effectiveness, the use of high-dose PPI following successful endoscopic therapy is more effective and less costly than no PPI [84–86]: the cost of PPI therapy is relatively lower than the incremental expenses attributable to one additional rebleeding episode. All patients should be on a single oral dose of a PPI daily at the time of discharge. The duration of PPI is determined by the underlying etiology of the bleeding etiology, with consideration for double-dose oral PPI if bleeding was the result of esophagitis [2].

Predictors of Rebleeding

Rebleeding after initial hemostasis occurs in 10–20 % of patients [36, 87, 88] and is in and of itself a predictor of mortality [89]. Predictors of rebleeding include comorbid illnesses, hemodynamic instability, active bleeding at endoscopy, large ulcer size (>2 cm), ulcer location (posterior duodenal wall and lesser gastric curvature), hemoglobin <10 g/dL, and transfusion requirements [88, 89].

Second-Look Endoscopy

A pre-planned second-look endoscopy at 16 to 48 hours should not be routinely performed. Earlier meta-analyses show that second-look endoscopy decreases rebleeding [90–92] and surgery [92]. The applicability of these findings are limited in contemporary practice. Indeed, the studies included sub-optimal endoscopic hemostatic methods, and did not employ, for the most part, post-endoscopic IV PPI [93]. Furthermore, the benefits of a second-look endoscopy were less apparent when very-high risk patients were excluded, and when considering the economic burden it creates [92, 94]. Although we do not routinely recommend second-look endoscopy, it may be considered in patients at an especially high risk for rebleeding [2, 24].

Rebleeding

Endoscopy should be repeated in the setting of rebleeding [2, 24]. A second attempt at endoscopic hemostasis can be successful in 73 % of patients and, when compared to surgery, is associated with lower complications without increased mortality [95]. Surgery and interventional radiology consultations should be considered with a second episode of rebleeding and are used increasingly as salvage therapies for cases that fail endotherapy. Surgical intervention and transarterial angiographic embolization (TAE) may be required in 2.3 % and 13 % of patients, respectively [96]. In this non-randomized study, mortality was noted to be higher with surgery than TAE (29 % vs. 10 %), suggesting that TAE may be the safer rescue therapy for rebleeding (Fig. 3.3) [96]. Other retrospective studies support TAE after failed endoscopic treatment, which appears comparable to surgery with regard to complications, without adversely affecting mortality [97–99].

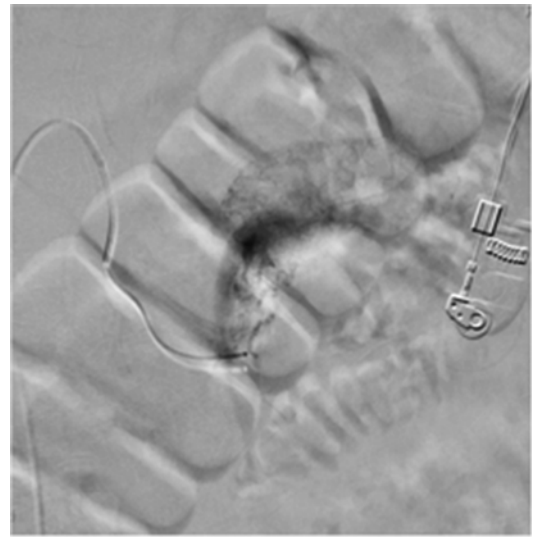


Fig. 3.3 Image from a subtracted angiogram showing contrast extravasation in the proximal jejunum. Bleeding artery is a jejunal branch of the SMA. Embolized with 500–700 μm particles to slow flow end point with resolution of bleeding. Courtesy of Dr. David A. Valenti, Department of Radiology, McGill University

In summary, a repeat attempt at endoscopic hemostasis is favored in the setting of rebleeding. Surgical and angiographic interventions are considered rescue therapies when endoscopic hemostasis fails or is infeasible, with emphasis on the radiological approach given its association with lower mortality relative to surgery [2].

Helicobacter pylori Testing

All patients with bleeding peptic ulcers should be tested for *H. pylori* and receive eradication therapy, if positive [2]. A meta-analysis demonstrated that eradication of *H. pylori* was signifi-

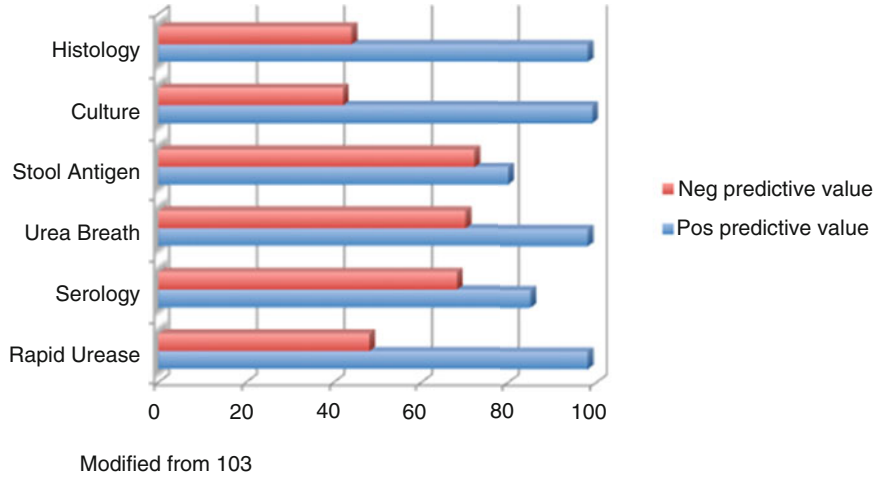


Fig. 3.4 Diagnostic performance of *H. pylori* in acute NVUGIB

cantly more effective than PPI therapy alone in preventing rebleeding from peptic ulcer disease [100]. If *H. pylori* is not detected in the acute setting, repeat testing is indicated on the basis of a systematic review of 23 studies showing that diagnostic tests for *H. pylori* infection (including serology, histology, urea breath test, rapid urease test, stool antigen, and culture) demonstrate high positive predictive value (0.85–0.99) but low negative predictive value (0.45–0.75) in the setting of acute GI bleeding, with 25–55 % of *H. pylori*-infected patients yielding false-negative results (Fig. 3.4) [101]. The biological explanation for this high false-negative rate in the setting of acute bleeding remains unclear [102].

Use of Nonsteroidal Anti-inflammatory Agents Post NVUGIB

In patients with previous ulcer bleeding, alternatives to nonsteroidal anti-inflammatory drugs (NSAIDs) should be considered, but if required, a combination of COX-2 inhibitor along with a PPI is recommended [103, 104]. Data suggest that adding a PPI to a traditional NSAID or using a COX-2 inhibitor alone reduces the risk for upper gastrointestinal complications. However, the reduction in complications was greater with the combination of a COX-2 inhibitor and a PPI [102]. Evidence from randomized controlled trials demonstrates that COX-2 inhibitor plus PPI, when compared to COX-2 inhibitor alone, further decreases the risk of rebleeding following an episode of acute peptic ulcer hemorrhage [105–107]. On the other hand, COX-2 inhibitors may increase the risk for cardiovascular events, as shown by two meta-analyses [108, 109]. With regard to reinstituting NSAID therapy following NVUGIB, the clinician must weigh the cardiovascular risk relative to that of GI complications on a case-by-case basis. In sum, we recommend the use of a COX-2 inhibitor along with a PPI if an alternative replacement to NSAID therapy is not feasible.

Acute Management of Antithrombotic Agents in NVUGIB

In the context of acute NVUGIB, ASA can be withheld although prolonged discontinuation should be avoided. In one meta-analysis, nonadherence or withdrawal of ASA was associated with a threefold increase in major cardiac events

[110]. Recently, a retrospective cohort study from Sweden showed that prolonged discontinuation of ASA for secondary cardiovascular prophylaxis following acute GI bleeding resulted in a sevenfold increase in cardiovascular events or death [111]. The time to thrombosis is usually between 7 and 30 days, which is consistent with the inhibited platelet circulation time of about 10 days [112, 113]. Controlled data suggest that cardiovascular benefits attributable to early reintroduction of ASA outweigh the risks of GI adverse events [114]. Based on these findings, consensus guidelines recommend that, in patients who receive low-dose ASA and develop acute ulcer bleeding, ASA therapy should be withheld and restarted as soon as the risk for cardiovascular complication is thought to outweigh the risk for bleeding [2].

We recommend that ASA be reintroduced within 3–5 days of the index bleed after consultation with the interested disciplines, including general practitioners, internists, cardiologists, neurologists, gastroenterologists, and intensivists. Data on the optimal management of clopidogrel and dual antiplatelet therapy in the context of acute bleeding are lacking, whereas the management of patients on oral anticoagulant is discussed below.

Long-Term Antiplatelet Therapy and Gastroprotective Strategies Following NVUGIB

Peptic ulcer bleeding is a common complication of long-term ASA administration for cardiothrombotic prophylaxis [115, 116]. Both H2-receptor antagonist (H2RA) and PPI have been explored as possible gastroprotective agents in this setting. A randomized trial showed that famotidine 20 mg twice daily reduces the incidence of peptic ulcer and erosive esophagitis compared to placebo in patients on ASA at low risk of developing GI complications [117]. Furthermore, this was an endoscopic study with the primary endpoint being the presence of peptic ulcer or erosions on repeat EGD at 12 weeks. Clinical outcomes were not assessed. In another randomized trial comparing famotidine 40 mg twice a day with pantoprazole 20 mg daily, the latter was superior to H2RA in terms of reducing not only dyspepsia but also upper GI bleeding events in patients on long-term ASA and with a history of peptic ulcer disease (PUD), with or without bleeding [118]. We concur with current consensus guidelines recommending PPI prophylaxis in patients on ASA and high-risk features for GI complications, such as a previous history of PUD and/or ulcer bleeding [2].

In addition to PPI prophylaxis, patients who require long-term ASA following acute NVUGIB should undergo testing and eradication of *H. pylori* [2]. Controlled data show that eradication of *H. pylori* following ulcer bleeding is as effective as the administration of PPI in preventing recurrent bleeding while on ASA [119]. In addition, *H. pylori* eradication leads to very low rebleeding rates even after a period of 10 years [120]. In contrast, one study demonstrated a high rebleeding rate on ASA despite an attempt at *H. pylori* eradication [121], though many patients in this study failed eradication therapy. Therefore, given the variable success in treating *H. pylori*, we recommend *H. pylori* testing/eradication and the use of long-term PPI in patients requiring prolonged ASA use following an ulcer bleed [2].

Clopidogrel administration following peptic ulcer bleeding is also associated with high rebleeding rates (9–14 %) [122, 123], and coadministration of a PPI should be considered. A randomized trial comparing PPI with placebo in patients on clopidogrel with a history of PUD showed a decreased incidence of recurrent ulcer disease on endoscopy at 6 months follow-up [124]. In addition, data on the gastroprotective effect of PPI in the setting of dual antiplatelet therapy (DAPT) is well documented by the COGENT trial [125], showing a significant reduction in GI bleeding (HR 0.34 (0.18–0.63)). Thus, PPI gastroprotection is indicated in patients on clopidogrel alone when there is a history of PUD, while patients on DAPT should

receive PPI routinely regardless of previous PUD status [115, 116, 126].

Of note is the potential for PPI to decrease the antiplatelet effect of clopidogrel, as suggested by pharmacokinetic studies [127–129]. Several observational studies have also demonstrated this interaction although they are confounded by covariate imbalance and statistical bias. Indeed, the attenuating effect of PPI on clopidogrel seems to be limited following multivariate adjustment [130, 131]. In addition, the COGENT trial comparing DAPT (ASA and clopidogrel) and PPI versus DAPT and placebo showed no significant difference in major cardiovascular events, although the study was terminated prematurely with a median follow-up time of 133 days [125]. Lastly, three systematic reviews assessing best quality observational studies did not show any significant interaction between PPI and clopidogrel with regard to major cardiovascular complications [131–133].

Based on available data, most societal guidelines recommend that patients continue with their current medical regimen, unless advised otherwise by their health-care providers. Furthermore, the initiation of PPI, with or without clopidogrel, should be guided by the risk for GI complications [2].

Long-Term Anticoagulation Therapy and Gastroprotective Strategies Following NVUGIB

Warfarin therapy is associated with significant risk of bleeding due to its vitamin K antagonist effect and its narrow therapeutic window. Systematic reviews show a rate of major hemorrhage (bleeding from any source) ranging from 1 % to 7.4 % per year [134–136]. The benefit of PPI therapy in preventing GI bleeding in patients on warfarin has not been studied in randomized controlled trials. A population-based, nested, control study evaluating gastroprotective agents in patients using antiplatelet therapies and/or oral anticoagulants showed an overall decrease in GI bleeding. A subgroup analysis of patients on warfarin trended toward less bleeding, but did not reach statistical significance (OR 0.48 [022–1.04]) [137]. Nevertheless, PPI coadministration should be considered in patients on warfarin and with a history of peptic ulcer bleeding or other causes of NVUGIB.

Triple therapy consisting of DAPT and an oral anticoagulant is indicated in patients who are at high risk for cardiothrombotic and embolic events. Warfarin combined with DAPT increases the risk of GI bleeding substantially, with a hazard ratio (HR) of 5.0 (1.4–17.8) relative to DAPT alone in one study [138]. In a randomized controlled trial comparing PPI to H2RA as gastroprotective agents, patients who presented with acute coronary syndrome and treated with DAPT and enoxaparin or a thrombolytic agent had a significant reduction in GI bleeding in favor of esomeprazole over famotidine [139]. Given the high risk of bleeding, we recommend that all patients on triple therapy receive PPI prophylaxis, regardless of previous history of peptic ulcer or GI bleeding.

Novel Anticoagulants and the Risk of Bleeding

Warfarin is limited by the need for routine monitoring of INR due to its narrow therapeutic window. Novel anticoagulants (nOAC), including direct thrombin and factor Xa inhibitors, have the advantage of not requiring such monitoring. Several agents, such as dabigatran, rivaroxaban, apixaban, and edoxaban, are currently in use or undergoing large-scale evaluation in patients with atrial fibrillation, deep vein thrombosis (DVT), pulmonary embolism, and DVT prophylaxis. Controlled data demonstrate an increased risk for GI bleeding with these novel agents [140, 141]. A recent systematic review encompassing 43 trials showed a modest but significant increase risk for GI bleeding with the use of nOAC relative to standard of care (warfarin and/or unfractionated (UFH)/low-molecular-weight heparin (LMWH)) [142]. The pooled OR for dabigatran was 1.58 (95 % CI 1.29–1.93) with a

Table 3.4 Risk of GI bleeding on antiplatelets and oral anticoagulants (OAC) with suggested gastroprotection strategies

Antiplatelet/OAC	Risk of GIB OR, 95 % CI	Routine PPI	PPI with Hx of PUD or NVUGIB	*H. pylori* testing/ eradication following PUD/NVUGIB
ASA low dose	2.07 (1.61–2.66) vs. placebo [143]		+ [2, 24, 126]	+ [2, 24, 126, 144, 145]
Clopidogrel	1.67 (1.27–2.20) vs. no treatment [146]		+ [126]	+ [2, 24, 144, 145]
DAPT	3.90 (2.78–5.47) vs. no treatment [146]	+ [125][a]		+ [115, 144]
Warfarin	1.94 (1.61–2.34) vs. no treatment [146]		+ [126]	+ [2, 24, 144, 145]
Triple therapy: ASA/Plavix/OAC	5.0 (1.4–17.8) vs. DAPT [138]	+ [139][a]		+ [2, 24, 144, 145]
Novel OAC	1.45 (1.07–1.97) vs. warfarin and/or UFH/LMWH [142]		+[b]	+ [2, 24, 144, 145]

Recommendations based on expert consensus guidelines
OAC oral anticoagulants, *ASA* aspirin, *DAPT* dual antiplatelet therapy, *PPI* proton pump inhibitor, *GIB* gastrointestinal bleeding, *PUD* peptic ulcer disease, *NVUGIB* nonvariceal upper gastrointestinal bleeding, *UFH* unfractionated heparin, *LMWH* Low-molecular-weight heparin
[a]No guideline, refers to the highest-level evidence available
[b]Recommendations by the authors based on existing evidence discussed in the text

number needed to harm (NNH) of 83, whereas the pooled OR for rivaroxaban was 1.48 (95 % CI 1.21–1.82). Neither apixaban nor edoxaban was associated with increased GI bleeding. It is important to note that no direct comparisons have been carried out among these agents. It is, therefore, premature to label a particularly nOAC that is associated with the lowest risk for GI bleeding.

GI bleeding related to nOAC will become increasingly important with the widespread use of these agents. To date, the nOAC trials have not included patients at high risk for GI complications, such as a previous history of GI bleeding or PUD. Furthermore, data on the severity of GI bleeding with nOAC compared to warfarin are lacking, which is particularly relevant in the absence of proven reversal agents. In terms of gastroprotection, PPI prophylaxis in the setting of nOAC use has not been studied. Despite the lack of evidence-based data, we recommend PPI use in patients on nOAC with a history of PUD (Table 3.4).

Summary

NVUGIB is a common source for hospital admissions that is associated with significant mortality and morbidity. Initial management begins with appropriate resuscitation and airway protection, transfusion of packed RBC to a threshold of 7–8 g/dL in non-massively exsanguinating patients, correction of coagulopathy without delaying endoscopy, and risk stratification (Fig. 3.5). The use of an NGT remains controversial but can be useful in select patients for prognostic purposes. Prokinetic agents may be used to improve endoscopic visualization, particularly in patients in whom a stomach full of blood is suspected. Pre-endoscopic high-dose PPI may downgrade lesions with high-risk stigmata but does not appear to have any major impact on clinical outcomes. The administration of PPI following successful endoscopic therapy is recommended since it is associated with decreased mortality, rebleeding, and need for surgery. Endoscopic therapy is indicated when high-risk

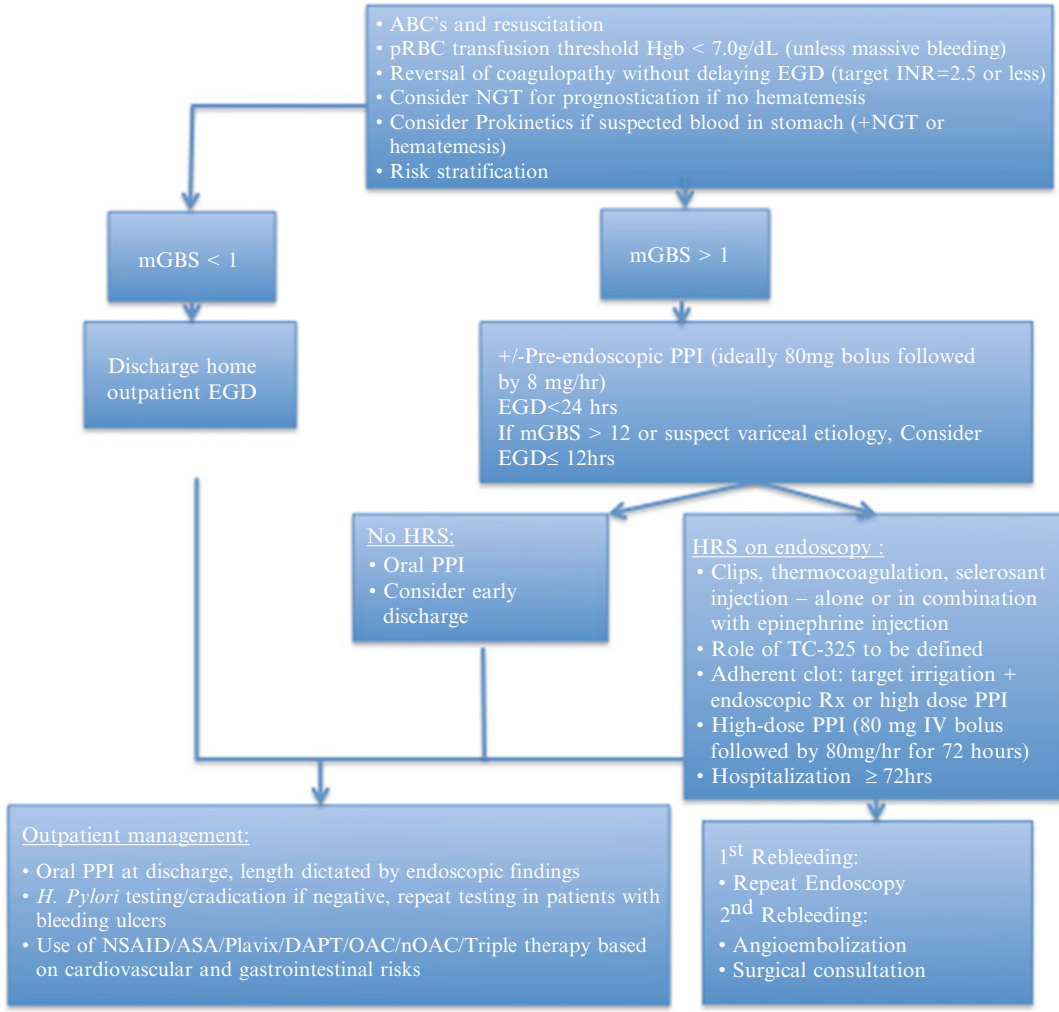
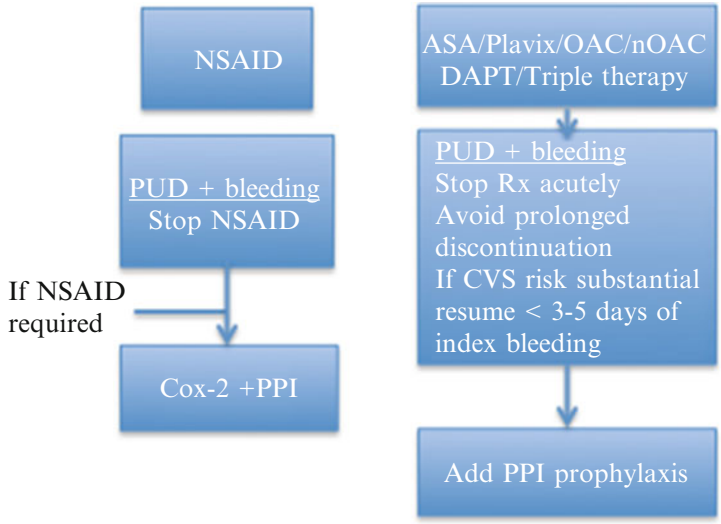


Fig. 3.5 Suggested Management Algorithm for NVUGIB

stigmata are present, and modalities include clips, thermal coagulation, and sclerosant injection, alone or in combination with epinephrine injection. Epinephrine injection is no longer recommended as sole modality of treatment. Hemostatic powders appear promising, although more data are needed to determine ideal indications and optimal application. Routine second-look endoscopy is not recommended but may be considered in selected patients at very high risk of rebleeding. All patients presenting with NVUGIB should be tested for *H. pylori* with subsequent eradication, if positive. Caution should be taken with negative testing in the setting of acute NVUGIB due to high false-negative rates, and repeat testing should be performed. The use of NSAID, ASA, and clopidogrel should be based on careful assessment of the risks for major cardiovascular events relative to the risks of recurrent GI bleeding complications. The role of gastroprotection prophylaxis in the setting of nOAC use requires further study (Fig. 3.6).



OAC: oral anticoagulant, nOAC: novel oral anticoagulant DAPT: dual antiplatelet therapy, Triple Therapy: DAPT + OAC

Fig. 3.6 NSAID/antiplatelet/oral anticoagulant use in peptic ulcer disease, complicated or not

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Approach to Suspected Variceal Bleeding

4

Kapil Sharma and Shiv K. Sarin

Introduction

Variceal hemorrhage is an important cause of upper gastrointestinal (UGI) bleeding. Hepatic venous pressure gradient (HVPG) thresholds of 10 mmHg and 12 mmHg are required for the development and rupture of esophageal varices, respectively. Esophageal varices develop at a rate of 5–15 % per year and enlarge at a rate of 4–10 % per year in patients with cirrhosis. Their presence is related to the severity of liver disease, with prevalence ranging from 40 % in patients with Child's A cirrhosis to 85 % in Child's C cirrhosis [1]. The most important predictor of variceal hemorrhage is the size of the varices, with the risk of first variceal bleeding as high as 15 % per year in patients with large varices [2]. Advanced cirrhosis (Child's B/C) and the presence of red color signs on endoscopy are other risk factors for variceal bleeding. Variceal bleeding stops spontaneously in 40–50 % of cases. An HVPG >20 mmHg (measured within 24 h of variceal hemorrhage) is the most important factor predicting failure to control initial bleeding (83 % vs. 29 %), early rebleeding within the first week of admission (50 % vs. 12 %) and higher 1-year mortality (64 % vs. 20 %) [3]. Delayed rebleeding is seen in 60 % of untreated patients, usually within 2 years following the index bleed.

K. Sharma, M.D., D.M.
S.K. Sarin, M.D., D.M., D.Sc., F.N.A. (✉)
Department of Hepatology, Institute of Liver and Biliary Sciences (ILBS), New Delhi, India
e-mail: shivsarin@gmail.com

Initial Assessment

History

A patient with known or suspected liver disease, or a chronic alcohol abuser, who presents with hematemesis and/or melena should focus the initial evaluation and management toward suspected acute variceal hemorrhage. However, an inquiry about prior episodes of UGI bleeding is important since up to half of patients with a history of UGI hemorrhage are bleeding from the same lesion. Nonvariceal bleeding etiologies in the cirrhotic patient might be entertained based on the patient's presenting symptoms, such as a peptic ulcer in the setting of epigastric pain and use of nonsteroidal anti-inflammatory agents (NSAIDs) and a Mallory-Weiss tear in the context of forceful retching, vomiting, or coughing. A thorough medication history should be obtained, with particular attention to the use of NSAIDs, antiplatelet agents, and anticoagulants. The use of iron and bismuth compounds discolors the stool black, which can mimic melena.

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Physical Examination

Variceal hemorrhage should be suspected in all patients presenting with acute UGI bleeding and physical signs suggestive of liver disease, namely, jaundice, spider angiomas, palmar erythema, Dupuytren's contractures, parotid enlargement, testicular atrophy, loss of secondary sexual characteristics, ascites, and encephalopathy. Splenomegaly is an important clue to the presence of portal hypertension, and the presence of ascites makes the presence of esophageal varices even more likely. Caput medusae is often suggestive of an intrahepatic cause of portal hypertension. In Budd-Chiari syndrome, by contrast, veins are dilated in the flanks and back, and blood flows in a cephalic direction [4]. A bruit may be heard in the left or right upper abdominal quadrant in the presence of a splanchnic arteriovenous fistula. A venous hum may be heard in the epigastric region of a patient with portal hypertension, representing collateral flow in the falciform ligament.

Laboratory Tests

Laboratory studies frequently reveal evidence of hepatic synthetic dysfunction, including prolongation of the prothrombin time (INR), hypoalbuminemia and hyperbilirubinemia, as well as anemia. Thrombocytopenia and leukopenia, reflecting hypersplenism (and bone marrow suppression in alcoholics), may be noted. Patients with severe bleeding may present with hypovolemic shock and renal insufficiency. Abdominal imaging studies, such as ultrasound or CT, frequently reveal splenomegaly, collateral vessels, abnormal liver echotexture and contour, and ascites.

Diagnosis and Classification of Varices

The diagnosis of varices and variceal hemorrhage is established at the time of upper endoscopy. A definite or presumed diagnosis of variceal hemorrhage is made when the following features are observed at endoscopy: active bleeding from a varix (Fig. 4.1), fibrin plug or "white nipple" over a varix (Fig. 4.2), adherent clot over a varix, or presence of esophageal and/or gastric varices with no other identifiable sources of UGI bleeding, particularly when the varices are large and exhibit red color signs (Fig. 4.3). Acute bleeding may be attributed to concomitant severe portal hypertensive gastropathy in the absence of definite bleeding stigmata involving the varices, although the presentation is less acute and bleeding less severe in this setting than that of variceal etiology. When endoscopy is performed early (within hours of presentation), active variceal

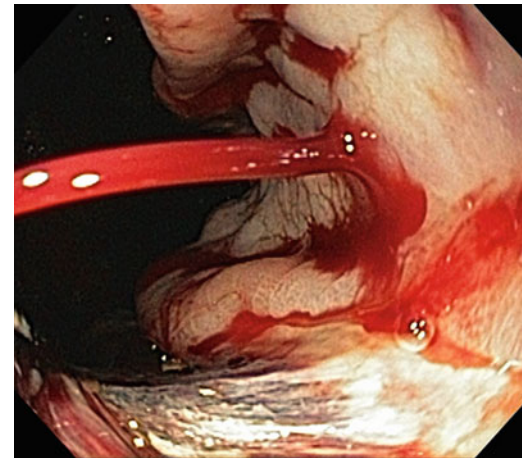

Fig. 4.1 Active variceal bleeding at the gastroesophageal junction

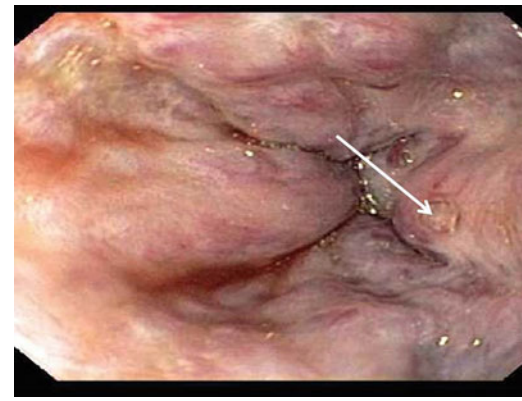

Fig. 4.2 Acute variceal hemorrhage with "fibrin plug" identified on a varix (arrow)

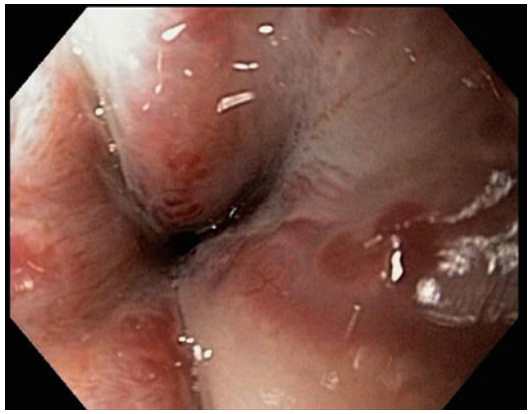

Fig. 4.3 Large esophageal varices with red color signs

Table 4.1 Classification of esophageal varices per the Japanese Society for portal hypertension

Parameter		Finding
Color (C)	Cw	White varices
	Cb	Blue varices
Length (l)	ll	Long length
	lm	Medium length
	ls	Short length
Form (F) Shape and size	F0	Lesions assuming no varicose appearance
	F1	Straight small-caliber varices
	F2	Moderately enlarged, beady varices
	F3	Markedly enlarged, nodular, or tumor-shaped varices
Red color sign (RC) Red wale markings, cherry red spots, hematocystic spots	RC0	Absent
	RC1	Small in number and localized
	RC2	Intermediate between 1 and 3
	RC3	Large in number and circumferential

bleeding is seen in 39–44 % of patients, stigmata of recent hemorrhage (white nipple or clot over the varices) are seen in 34–44 % of patients, and the remaining cases (12–28 %) have no definite stigmata of recent hemorrhage.

Several classifications of esophageal varices have been proposed (Tables 4.1 and 4.2), although these classifications are subject to interobserver and intraobserver variations [5–7]. The simplest and most commonly used classification consists of categorizing the varices as small (≤5 mm) or large (>5 mm) [8]. The presence of red signs, such as red wale marks and cherry red spots, is also described, which increases the risk of variceal hemorrhage. The size of the varices can be overestimated in a partially collapsed lumen, and so assessment of variceal size should be performed with the esophageal lumen distended and the stomach decompressed.

Table 4.2 Paquet's classification of esophageal varices

Grade 0	No varices
Grade I	Venectasia, disappearing with insufflation
Grade II	Larger, clearly visible, usually straight varices, not disappearing with insufflation
Grade III	More prominent varices, locally coil-shaped and partly occupying the lumen
Grade IV	Tortuous, sometimes grape-like varices occupying the esophageal lumen

The classification by Sarin is the most widely used classification system for gastric varices since it is simple to use and guides therapy. Gastric varices are classified on the basis of their location in the stomach and relationship with esophageal varices (Fig. 4.4).

Preprocedural Management

The initial management of variceal bleed is aimed at controlling the present episode as well as preventing further rebleeding, a phenomenon common in the first week and associated with increased mortality.

Resuscitation

It is the cornerstone to the success of endotherapy and survival. Initial resuscitative measures include protection of airway, breathing, and circulation. Resuscitation efforts should be initiated at the same time as initial assessment in the emergency department and continued during the patient's hospitalization. Most patients with suspected variceal bleeding should be admitted

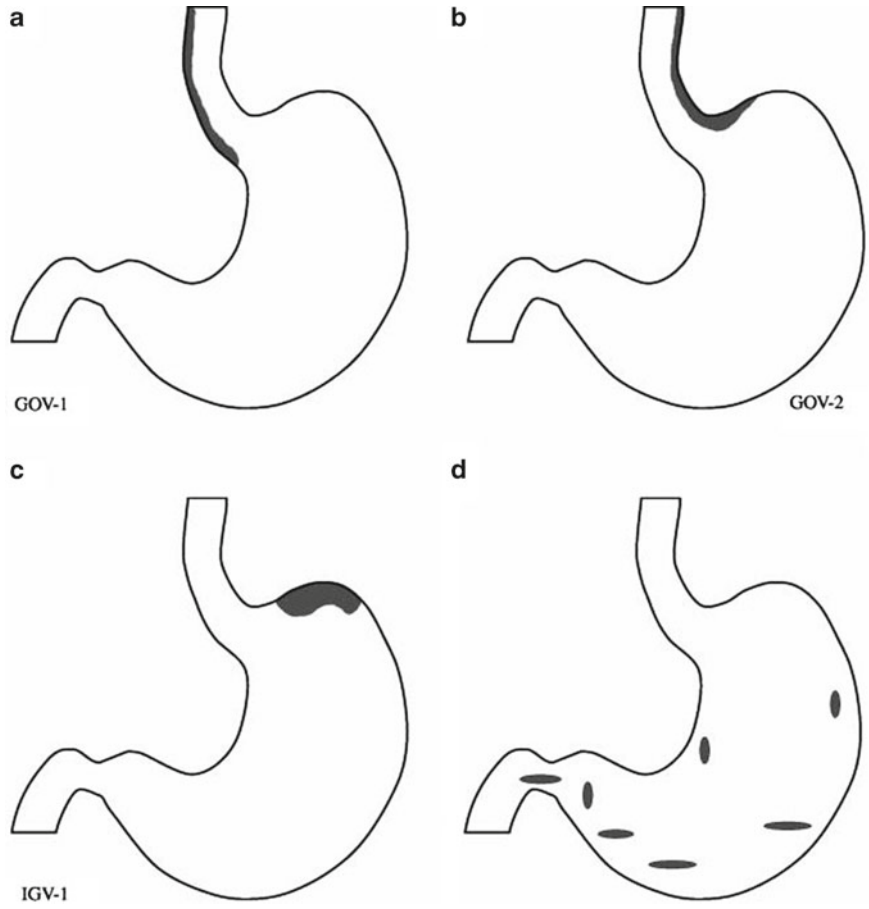

Fig. 4.4 Sarin classification of gastric varices. (**a**) Type 1 gastroesophageal varices (GOV 1) are typically a continuation of esophageal varices into the lesser curvature of the stomach. (**b**) Type 2 gastroesophageal varices (GOV 2) are esophagogastric varices extending into the fundus. (**c**) Type 1 isolated gastric varices (IGV 1) are gastric fundal varices without the presence of esophageal varices. (**d**) Type 2 isolated gastric varices (IGV 2) are varices at ectopic sites in the stomach outside the cardiofundal region

to a monitored intensive care setting. At least one large-bore (16 or 18 G) catheter should be placed intravenously (IV), and two IV lines should be placed when the patient has ongoing bleeding. Arterial blood gas analysis should be performed, with continuous pulse oximetry monitoring. Preprocedural endotracheal intubation for airway protection is required in the presence of active hematemesis, grade III and IV hepatic encephalopathy, anticipated difficulties with airway (e.g., short, thick neck) or sedation (e.g., active alcohol abuser), and other factors that predispose to aspiration [8]. Otherwise, the need for airway protection should continuously be assessed during endoscopy, with prompt temporary termination of the procedure if the risk for aspiration is deemed high (e.g., large-volume blood and clots retained in the stomach).

Gastrointestinal hemorrhage is poorly tolerated in cirrhotics compared to non-cirrhotics, and these patients are prone to renal failure. Colloids are preferred for volume resuscitation. The aims of volume replacement are to maintain a systolic blood pressure around 90–100 mmHg, a heart rate <100 beats per minute, a central venous pressure (CVP) of 1–5 mmHg, and minimum urine output of 40 mL/h. Blood transfusion

in variceal hemorrhage should be initiated early, but a restrictive transfusion strategy is recommended. Overtransfusion leads to a rebound increase in portal pressure and increases the risk of rebleeding. Transfusion of packed red blood cells (PRBCs) should be done with the goal of maintaining the hematocrit level between 25 and 30 % and the hemoglobin level around 7–8 g/dL [9], although transfusion policy should be individualized and consider additional factors, such as age, comorbidities, hemodynamic instability, and ongoing bleeding. There are insufficient data to make specific management recommendations regarding coagulopathy and thrombocytopenia, and utilization of INR is not a reliable gauge of the coagulation status in cirrhotic patients. In practice, however, transfusion of platelets and plasma products to maintain a platelet count >40,000 and INR <2.5, respectively, in the peri-endoscopic period are reasonable thresholds. The use of recombinant activated factor VII (rFVIIa) in cirrhotic patients with acute variceal bleeding is not recommended. The promising role of thromboelastogram (TEG) in the peri-transplant period can be extrapolated for TEG-guided correction of coagulopathy.

Administration of Vasoactive Agents

The administration of a vasoactive drug to control variceal bleeding in cirrhotics was first used in clinical practice in 1962. Vasopressin was the agent used. Presently, various agents are available, and the selection of a particular vasoactive drug depends upon availability, local resources, and cost. In a patient with suspected variceal bleeding, the administration of a vasoactive agent is initiated at the time of admission and can be discontinued should subsequent endoscopy reveal a nonvariceal cause for the acute episode of hemorrhage.

Vasopressin and Its Analogs

Vasopressin is the most powerful splanchnic vasoconstrictor, decreasing blood flow to all splanchnic organs, with resultant decrease in portal venous inflow and thus the portal pressure. Because of its short half-life, vasopressin is given as a continuous infusion of 0.2–0.4 U/min IV, which can be increased to a maximum of 0.8 U/min. Bosch et al. demonstrated a decrease in HVPG of 23 % and decrease in intravariceal pressure of 14 % [10]. Due to its vasoconstrictive action in various vascular beds, the use of vasopressin is hampered by multiple side effects, including cardiac events (e.g., myocardial ischemia, arrhythmia), hypertension, bowel ischemia, limb gangrene, and cerebrovascular accidents. These adverse effects can lead to drug withdrawal in up to 25 % of patients [11]. To decrease the risk of complications, vasopressin should be used at the lowest effective dose for no more than 24 h and should always be combined with a vasodilator, such as nitroglycerin, to decrease its systemic hemodynamic effects. Because of the frequency and potential for serious side effects, as well as the availability of safer drug alternatives, the use of vasopressin has practically been abandoned.

Terlipressin is a synthetic analog of vasopressin with a longer biological half-life and significantly less side effects. It has an immediate vasoconstricting action, followed by a delayed effect due to slow transformation of terlipressin into vasopressin by the enzymatic cleavage of triglycyl residues. A single bolus of 2 mg of terlipressin decreased HVPG by 21 % and azygous blood flow by 25 %, which lasted for up to 4 h [12]. The overall efficacy of terlipressin in controlling variceal bleeding is 75–80 % at 48 h [13] and 67 % at 5 days [14]. Terlipressin has been shown to significantly improve control of bleeding and survival when compared to placebo [13, 15] and is the only vasoactive drug that has been shown to improve survival. However, terlipressin can provoke ischemic complications and severe dysrhythmia. Therefore, it should be used with caution or avoided altogether in select patients with a history of ischemic heart or cerebrovascular disease, limb or gut vasculopathy, or heart rhythm disorders.

Terlipressin is given as a 2 mg bolus IV every 4 h during the first 2 days. The dose is halved

after bleeding is controlled and can be maintained for up to 5 days. Terlipressin is not available in the USA, but is commonly used in other countries in the setting of acute variceal bleeding. The administration of terlipressin at low dose in a continuous infusion has been tested in cirrhotic patients and septic shock with promising results [16, 17], but its use in acute variceal bleeding remains indeterminate and cannot be recommended as of yet.

Somatostatin and Its Analogs

Somatostatin and its analogs are potent vasoconstrictors by decreasing release of vasodilators (mainly glucagon) and by a direct splanchnic vasoconstrictive effect. Their main advantage over vasopressin is that they are relatively safe and can be used continuously for 5 days or even longer. Randomized trials and meta-analyses [18, 19] have demonstrated that somatostatin significantly improves control of bleeding when compared to placebo, but not survival [20]. On the other hand, its beneficial effect on the control of bleeding and early rebleeding is similar to that of terlipressin and with a better safety profile. Despite its favorable side-effect profile, intravenous infusion of somatostatin has been shown to predispose to renal vasoconstriction with subsequent reduction in glomerular filtration rate, free water clearance, and sodium excretion in patients with cirrhosis with ascites. Major side effects are rare and minor side effects include nausea, vomiting, and hyperglycemia, which occur in nearly one-third of patients. Because of its short half-life, somatostatin is given as a bolus injection of 250 μg followed by a continuous infusion of 250 μg/h IV [21]. *Octreotide* is a synthetic analog of natural somatostatin with a similar mechanism of action but a longer half-life. However, this does not result in longer hemodynamic effects [22, 23], probably due to the development of tachyphylaxis or rapid desensitization [24]. Octreotide is administered as a 50 μg bolus followed by a continuous infusion of 50 μg/h for 3–5 days.

Antibiotic Prophylaxis

Bacterial infection is a well-known serious complication of cirrhosis. Up to 20 % of cirrhotic patients who are hospitalized due to GI bleeding present with bacterial infections, and an additional 50 % will develop an infection while in hospital [25]. This risk is especially high in those patients with poor liver function (i.e., Child's class B and C) [26]. Among infections, spontaneous bacterial peritonitis (SBP) is most common, followed by urinary tract infections, pneumonia, and multisite infections. In cirrhotic patients presenting with acute GI bleeding and ascites, a diagnostic tap of the ascites is required. Enteric flora is responsible for the majority of infections, and *E. coli* is the pathogen most commonly responsible. The infections probably impair coagulation and, hence, contribute to failure to control initial bleeding or early rebleeding. Antibiotic prophylaxis in cirrhotic patients with upper GI bleeding favorably impacts the rates of acute bacterial infections, rebleeding, and mortality. If oral intake is feasible, the recommended antibiotic is norfloxacin 400 mg twice daily for 7 days. Norfloxacin is a poorly absorbed quinolone that selectively inhibits gram-negative bacteria in the gut, which is the source of infection. An intravenous fluoroquinolone can be given if oral administration is not an option.

In a study involving patients with advanced cirrhosis and gastrointestinal hemorrhage (69 % variceal in nature), IV ceftriaxone at a dose of 1 g/day was found to be more effective than oral norfloxacin in preventing infections (11 % vs. 33 %, $p=0.003$) and in preventing SBP (2 % vs. 12 %, $p=0.03$) [27]. However, the prevalence of fluoroquinolone resistance was not stated in this study. As per the Baveno V guidelines [28], an oral quinolone is the recommended antibiotic, which should be administered for 5–7 days or until discharge. However, in patients with advanced cirrhosis, on previous quinolone prophylaxis, or living in regions with known high prevalence of quinolone resistance, intravenous ceftriaxone 1 g/day for 5–7 days or until discharge is recommended.

Endoscopy

Timing

A study by Sarin et al. [29] assessing the timing of endoscopy with respect to UGI bleeding did not show a significant difference in need for surgery or mortality when endoscopy was performed within 6 h, at 6 to 24 h, or beyond 24 h. However, urgent endoscopy (within 12 h of presentation) is indicated in patients with severe bleeding (i.e., patients presenting with hematemesis and/or melena and hemodynamic instability, a hemoglobin level <8 g/dl or drop ≥2 g/dl within 12 h, requirement of ≥2 units of PRBCs, and/or high probability of variceal bleeding). Ideally, endoscopy should be performed within 6 h in the presence of severe bleeding, as per the APASL guidelines [8].

Procedural Considerations

The use of a therapeutic channel (3.7–6 mm) endoscope is advised to enable rapid suction and cleaning of retained blood and clots. Repositioning the patient, such as in the right lateral decubitus position or head of the bed elevation, can be helpful to allow visualization of areas covered by pooling of bloody material (e.g., fundus).

The technical aspects of endoscopic modalities available for hemostasis of variceal bleeding are discussed in detail in separate chapters. Here, the outcomes and adverse events related to the commonly used modalities for variceal hemostasis are highlighted.

Endoscopic Sclerotherapy

Endoscopic variceal sclerotherapy involves injecting a sclerosant into (intravariceal) or adjacent (paravariceal) to esophageal varices. The most commonly used sclerosants are ethanolamine oleate, sodium tetradecyl sulfate, sodium morrhuate, and ethanol. Prospective, randomized trials have shown mixed results, but suggest improved immediate hemostasis and a reduction in rebleeding with sclerotherapy compared with medical therapy alone for bleeding esophageal varices [30]. Initial hemostasis is achieved in 85–95 % of cases, with a rebleeding rate of 25–30 %. Sclerotherapy-related complications include chest pain, esophageal ulcers (which can bleed or perforate), esophageal strictures, mediastinitis, fistulas, pleural effusions, aspiration pneumonia, acute respiratory distress syndrome, fever, and bacteremia. In part due to its associated complications, sclerotherapy is generally reserved as second-line therapy when endoscopic band ligation is deemed unfeasible or fails at controlling esophageal variceal bleeding.

Endoscopic Band Ligation

Prospective, randomized, controlled trials have shown that endoscopic band ligation (EBL) is as effective as sclerotherapy in achieving initial hemostasis and reducing the rate of rebleeding from esophageal varices (Fig. 4.5). Acute hemostasis is achieved in 80–90 % of cases, with a rebleeding rate of 25–30 %.

In a prospective, randomized trial of endoscopic sclerotherapy versus EBL for esophageal varices [31], both techniques were equally effective in controlling the acute bleeding episode. EBL achieved faster variceal obliteration in fewer treatment sessions than sclerotherapy, as well as a significantly lower rate for the development of portal hypertensive gastropathy and rebleeding. However, esophageal variceal recurrence was higher after EBL than sclerotherapy. A meta-analysis has shown that EBL reduces the rates of rebleeding, bleeding-related death, and overall mortality compared with sclerotherapy [32].

Endoscopic Cyanoacrylate Injection

Endoscopic variceal obliteration of gastric varices is generally achieved using tissue adhesives, such as n-butyl-2-cyanoacrylate and 2-octyl-cyanoacrylate (Fig. 4.6). Endoscopic cyanoacrylate injection is considered the treatment of choice for gastric varices because of high rates of initial hemostasis and low rebleeding rates and is comparable to transjugular intrahepatic portosystemic shunt (TIPS) in terms of bleeding outcomes. The technique is performed on an off-label basis in the USA. Adverse events related to cyanoacrylate injection are rare and include thromboembolic phenomena involving various organs (e.g., splenic,

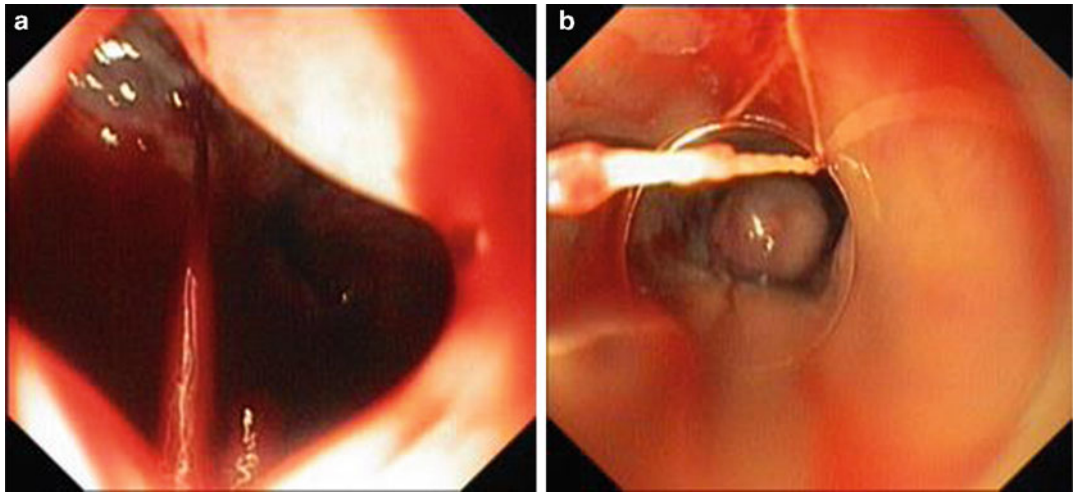

Fig. 4.5 (**a**) Active esophageal variceal bleeding. (**b**) Hemostasis achieved following endoscopic band ligation

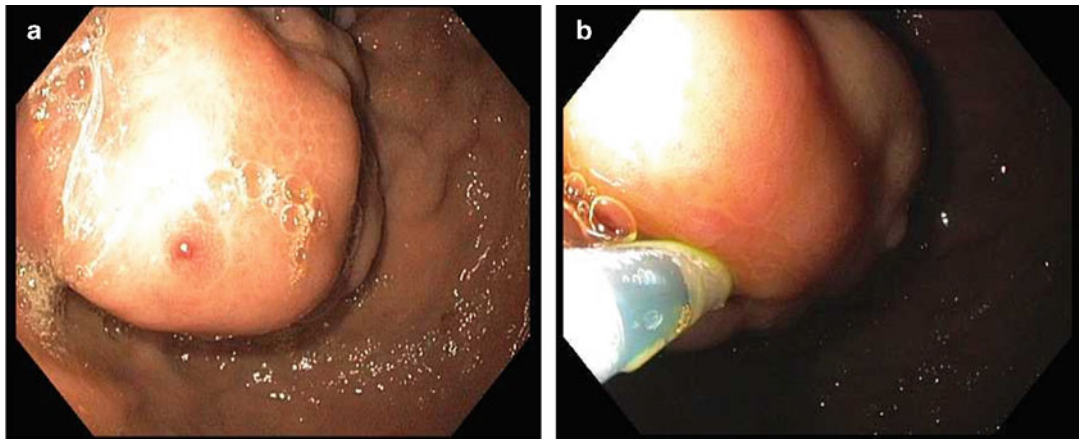

Fig. 4.6 (**a**) Type 1 isolated gastric varices with stigmata of recent bleeding. (**b**) Performance of endoscopic cyanoacrylate injection

renal, pulmonary, cerebral, spinal, and coronary), needle entrapment in the varix, gastric ulceration, retro-gastric abscess, visceral fistula formation, and bacteremia/sepsis [33]. A wide range of rebleeding rates has been reported after cyanoacrylate injection, although the rates are <10 % in large series, and rebleeding is often seen in patients with associated portal vein thrombosis.

Rescue Therapies

Variceal bleeding cannot be controlled or early rebleeding occurs in 10–20 % of patients despite optimum endoscopic and pharmacologic therapy. An HVPG >20 mmHg measured within 24 h of presentation is predictive of treatment failure.

Balloon Tamponade

Balloon tamponadeof varices is seldom required to temporarily control active variceal bleeding that is not manageable during endoscopy. It enables stabilization of the patient with massive bleeding prior to definitive therapy (e.g., TIPS or relook endoscopy with therapeutic intent). Three types of tamponade balloons are available. The Sengstaken-Blakemore tube has gastric and esophageal balloons, with a single aspirating port in the stomach. The Minnesota tube also has gastric and esophageal balloons, but with aspiration ports both in the esophagus and stomach. The Linton-Nicholas tube has a single large gastric balloon and aspiration ports in the stomach and esophagus and is used primarily for tamponade of fundal variceal hemorrhage. Balloon tamponade provides initial control of bleeding in 85 % to 98 % of cases, but variceal rebleeding occurs soon after the balloon is deflated in 21 % to 60 % of patients [34]. The major issue with balloon tamponade is a 30 % rate of serious adverse events, such as aspiration pneumonia, esophageal rupture, and airway obstruction. Patients should be endotracheally intubated before placement of a tamponade balloon to minimize the risk of pulmonary complications, and the balloon(s) should not remain inflated for more than 24 h to lessen the risk of tissue necrosis.

Stent Tamponade

Stent placement is a promising alternative to balloon tamponade for the control of active esophageal variceal hemorrhage. A stent dedicated for this purpose is available in some countries (SX-ELLA Stent Danis; ELLA-CS, Hradec Kralove, Czech Republic), but is not approved for use in the USA (Fig. 4.7). The device is a fully covered self-expanding metal stent with atraumatic edges and radiopaque markers at both ends and at the midpoint to easily assess its position by a plain chest X-ray or fluoroscopy. It also has retrieval loops with gold markers at both stent's ends for atraumatic endoscopic extraction using a specifically designed system. The stent can be left in place for as long as 2 weeks. The efficacy and safety of the SX-ELLA Stent Danis are currently limited to a few case series [35, 36], but the stent offers several advantages (e.g., ability for oral intake) and with a perceived better safety profile relative to balloon tamponade.

Transjugular Intrahepatic Portosystemic Shunt

TIPS is an interventional radiologic procedure where a tract is created between the hepatic vein and portal vein and kept open by placement of a stent, which diverts blood from the portal circulation through the hepatic parenchyma to the systemic circulation (Fig. 4.8). TIPS is indicated in the setting of acute variceal bleeding as rescue therapy and to prevent recurrent bleeding after initial endotherapy. TIPS is successful in more than 90 % of patients with active variceal bleeding. TIPS may precipitate or worsen encephalopathy in about 25 % of patients. The later complication of TIPS stenosis or dysfunction occurs to a lesser extent with utilization of polytetrafluoroethylene (PTFE)-covered stents.

Balloon-Occluded Retrograde Transvenous Obliteration

BRTO is a vascular interventional radiologic technique performed in patients with bleeding gastric varices who have a gastro-renal shunt (GRS), in which a balloon-occlusion catheter is advanced via a transfemoral (or transjugular) approach and positioned in the GRS near its base in the left renal vein. Following balloon occlusion of the GRS, sclerosant is injected, and stagnation of the sclerosant within the shunt and gastric varices results in obliteration of the varices. Preprocedural imaging (e.g., CT) is important to assess for the presence of a shunt [37]. Where available, BRTO is an effective treatment option in patients with bleeding gastric varices and GRS who have failed endoscopic therapy for control of acute gastric variceal bleeding or who are poor candidates for salvage TIPS, such as

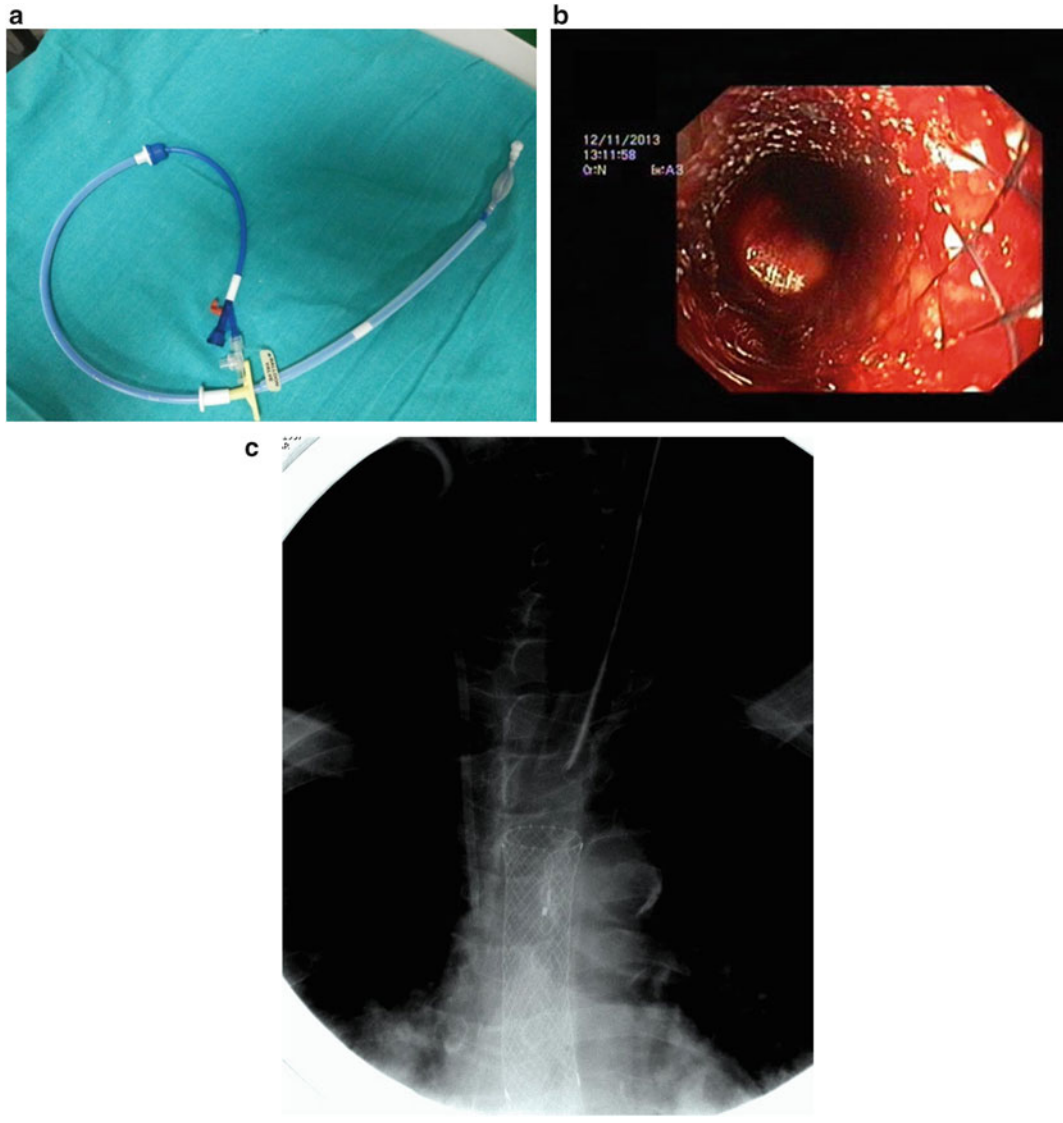

Fig. 4.7 (**a**) Dedicated covered self-expanding metal stent for tamponade of esophageal variceal hemorrhage. (**b**) Endoscopic view of deployed stent for variceal tamponade. (**c**) Fluoroscopic view of stent for variceal tamponade

patients with a thrombosed portal vein, hepatic encephalopathy, or a low HVPG. BRTO-related adverse events include hemoglobinuria, abdominal pain, transient fever, pleural effusion, transient worsening in liver biochemistry, shock, and atrial fibrillation. Delayed events include the development or worsening of esophageal varices in up to 50 % of patients, the appearance of ectopic intestinal or rectal varices, and extension of thrombus to the portal vein and renal vein.

Surgery

Surgery is a last resort in patients with variceal bleeding when endoscopic and interventional radiologic procedures have failed or deemed unfeasible. The shunt operations can be total or selective, depending on whether they decompress the entire portal system (total) or selectively decompress the gastroesophageal varices and spleen but maintain portal inflow to the liver. Non-shunt procedures are

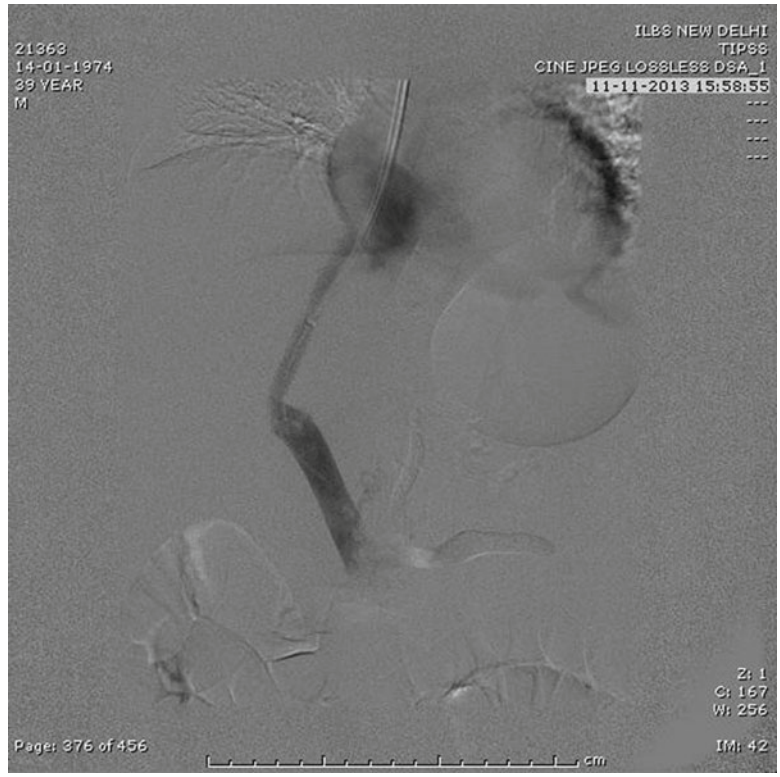

Fig. 4.8 TIPS placement as salvage therapy for esophageal variceal hemorrhage

primarily devascularization procedures, which include splenectomy, gastric and esophageal devascularization, and, in some cases, esophageal transection. With the increasing availability of TIPS and high morbidity associated with surgery, however, surgical procedures are rarely used.

Prevention of Recurrent Variceal Bleeding

The risk factors for recurrent variceal bleeding include severe index bleeding with hemoglobin <8 mg/dl, gastric variceal bleeding, active bleeding at the time of endoscopy, and high HVPG. Cirrhotic patients who survive an episode of variceal bleeding should receive therapy to prevent recurrence of variceal hemorrhage (secondary prophylaxis). Combined nonselective beta-blocker and EBL is the best option for secondary prophylaxis of esophageal variceal hemorrhage. EBL should be repeated every 2–4 weeks until obliteration, with the first surveillance endoscopy performed 1–3 months after obliteration and then every 6–12 months thereafter to assess for variceal recurrence. TIPS should be considered in patients with Child's A or B cirrhosis who experience recurrent variceal hemorrhage despite combination pharmacologic and endoscopic therapy. In centers where the expertise is available, surgical shunt can be considered in Child's A patients. Patients who are otherwise liver transplant candidates should be referred to a transplantation center for evaluation [38].

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Approach to Suspected Small Intestinal Bleeding

5

Lauren B. Gerson

Introduction

In patients presenting with acute gastrointestinal (GI) hemorrhage, the presence of a small bowel source will be a relatively uncommon occurrence. Based on prior literature, the bleeding source will originate from the upper GI tract, the colon, and the small bowel in 85, 10, and 5 % of cases, respectively [1]. For this reason, current guidelines recommend that gastroenterologists consider "second-look" endoscopic examinations of the upper and lower GI tracts prior to initiation of an evaluation for a small bowel source (Fig. 5.1). While repeat upper and lower examinations are not routinely recommended for all patients presenting with acute bleeding, these tests should be strongly considered in patients who underwent initial testing with poor preparation of the colon or blood found in the GI tract on upper endoscopy, particularly during retroflexion. This chapter will outline the diagnostic approach to patients with suspected small bowel hemorrhage. Specific endoscopic treatment of sources responsible for small intestinal bleeding will be covered in a separate chapter.

Role for "Second-Look" Endoscopic Examinations

Approximately 20–30 % of patients with acute GI bleeding who undergo capsule endoscopy and/or deep enteroscopy will have sources of bleeding within reach of standard upper or lower endoscopic examinations that might have been missed upon initial testing. In one study published in 2009, the prevalence of lesions outside the small bowel in patients undergoing double-balloon enteroscopy (DBE) was assessed. The study examined 143 DBE procedures in 107 patients over an interval of 3.5 years [2]. The patients presented with either obscure overt or obscure occult bleeding. The direction of the DBE examination was guided by prior video capsule endoscopy (VCE) findings, if available. In the absence of a VCE study, an anterograde approach was used for patients presenting with melena, whereas patients with hematochezia underwent initial retrograde examinations. Bidirectional enteroscopy was performed if no source was found on the initial DBE approach. Small bowel pathology was detected in 69 (65 %) patients and included angiodysplastic lesions in

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L.B. Gerson (✉)
Division of Gastroenterology, California Pacific Medical Center, 2340 Clay Street, 6th Floor, San Francisco, CA 94115, USA
e-mail: GersonL@sutterhealth.org

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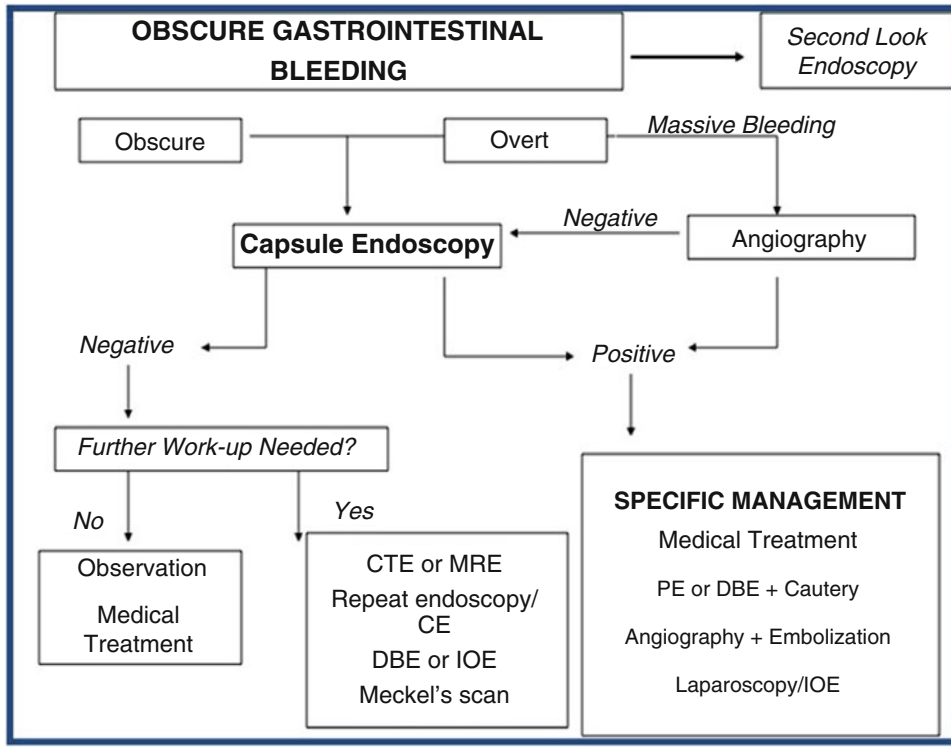

Fig. 5.1 Algorithm for obscure gastrointestinal bleeding (Reprinted with permission) [38]

34 (32 %), ulcerations in 12 (11 %), and small bowel neoplasms in 6 (6 %), in addition to other etiologies.

In order to classify bleeding lesions as "definite" versus "probable," the authors used a classification system based on clinical action where A1 was a lesion requiring immediate hemostasis and A2 was a lesion where close observation was recommended. In addition, none of the following lesions were considered as definite causes of bleeding, including grade A–B erosive esophagitis, small esophageal varices without stigmata of bleeding or red wale signs, nonspecific duodenitis, minimal gastric antral vascular ectasia (GAVE), single non-bleeding colonic angiodysplasias, and hemorrhoids without stigmata of bleeding. If the patient presented with occult GI bleeding, any lesion was categorized as a possible source of bleeding except for colonic diverticulosis without signs of hemorrhage, esophageal varices, and/or hemorrhoids.

The authors found a possible cause of bleeding in 51 (48 %) patients. These sources included colonic diverticulosis in 11, gastric or duodenal ulcerations in 6, non-bleeding colonic angiodysplastic lesions in 5, GAVE in 5, Cameron erosions in 2, and other sources in 18 patients. Twenty-six (24 %) patients were considered to have definite sources of hemorrhage detected, including gastric and/or duodenal ulcerations ($n=6$), Cameron erosions ($n=2$), GAVE ($n=4$), radiation ileitis ($n=3$), angiodysplastic lesions ($n=4$), diverticulosis ($n=3$), colonic Crohn's disease ($n=1$), anastomotic ulceration ($n=1$), and hemorrhoids ($n=1$). Based on these findings, the authors suggested that second-look endoscopic examinations be performed prior to small bowel evaluation, particularly if there was inadequate mucosal visualization or lack of documentation of landmarks on the initial examination.

The authors from another study published in 2008 queried whether repeat endoscopic exami-

nations within 6 months of a VCE procedure were necessary when initial examinations were negative [3]. At the time of the study, the investigators were required to repeat standard upper and lower endoscopic examinations within 6 months of a VCE study for the purposes of obtaining Medicare reimbursement for the VCE study. Of the 198 patients referred for investigation of obscure GI bleeding, 50 underwent repeat endoscopic examinations solely to enable Medicare reimbursement. The average duration of obscure bleeding was 50 months, and the most recent upper and/or lower endoscopic exams had been performed 19 months prior to the VCE study. The authors found only two patients with probable causes of bleeding (GAVE and gastric ulceration). On the subsequent VCE study, probable bleeding sources were identified in 24 (51 %) patients and possible sources in 5 (11 %) patients, including angiodysplastic lesions ($n=17$), mass lesions ($n=2$), nonsteroidal anti-inflammatory drug enteropathy ($n=2$), Cameron erosions ($n=2$), and Crohn's disease ($n=1$). The authors concluded that repeat endoscopic examinations prior to VCE were associated with a low diagnostic yield. Differences between this study and the aforementioned 2009 study may be explained by the fact that the population in the 2009 study was referred for deep enteroscopy and the quality of the prior endoscopic examinations not rigorously assessed as in the 2008 study.

Video Capsule Endoscopy: The Third Test

Once the decision is made to pursue a small bowel source of hemorrhage, the next recommended test is VCE testing. VCE was initially approved by the United States Food and Drug Administration in 2001 as an adjunctive test for the evaluation of small bowel disorders and then as a first-line modality for small bowel evaluation in 2003.

Currently available VCE systems in the United States include the PillCam SB (Given Imaging, Inc., Yokneam, Israel) and the Olympus Endocapsule (Olympus Corp., Center Valley, PA). Both capsule systems capture two frames per second and have a field of view of 160°. The PillCam SB is now available with a 12-h battery life, which may increase completion rates to the cecum. The Olympus Endocapsule has an 8-h battery life. The current capsules measure 11×26 mm in dimensions and contain a lens, white light-emitting diodes for illumination, silver oxide batteries, and an ultrahigh frequency band radio telemetry transmitter. The camera for the PillCam SB capsule is a complementary metal oxide semiconductor (CMOS) chip, whereas the Olympus Endocapsule uses a charge-coupled device (CCD) chip. A capsule-loading device is available to directly deliver the capsule into the duodenum and may be considered in patients with significant dysphagia secondary to esophageal motility disorders and gastroparesis, inpatients with limited mobility, patients on chronic narcotics, pediatric patients, and subjects unable to ingest large pills. For patients who are unsure about the ability to swallow the capsule, particularly children or young adolescents, the "jelly bean" test can be administered as a trial before attempting to swallow the capsule endoscope.

The video capsule endoscope requires activation prior to ingestion. A flashing light will be apparent when the device is ready for usage. Sensors are placed on the patient's chest and abdomen in order to capture quadrant location for the VCE device; while recent software does not require sensor placement, most VCE readers find this information to be useful, and studies have demonstrated accuracy of the quadrant locator in the setting of subsequent surgical interventions. After capsule ingestion, the patient is able to leave the endoscopy unit wearing the waist belt holding the data recorder. For inpatients, ingestion can occur directly at the bedside. The patients are allowed to ingest a liquid meal 2 h later and a regular diet after 4 h.

Meta-analyses have demonstrated the efficacy of administering a purgative preparation prior to the VCE examination [4]. The studies have demonstrated that the administration of 2 l of polyethylene glycol (PEG) is equivalent to 4 l and results in improved small bowel visualization and diagnostic yield. In a 2009 meta-analysis encompassing 12 studies (6 prospective, 6 retrospective), the

diagnostic yield was significantly improved in patients who received purgative preparations compared to those maintained on clear liquids alone (263 vs. 213 patients; odds radio (OR) 1.8, 95 % CI 1.3–2.6, $p=0.002$). The quality of small bowel visualization was also significantly improved (OR 2.1, 95 % CI 1.3–3.6, $p=0.005$). The administration of purgatives did not affect overall completion rates to the cecum or transit times in the stomach or small bowel.

For inpatients, the yield of VCE has been shown to exceed 90 % when administered within 48 h of hospital admission [5]. However, usage of VCE in the inpatient setting, while associated with higher diagnostic yields, carries increased rates of gastric retention (mainly due to the use of narcotics and other medications, in addition to the immobility state) and incomplete examinations to the cecum [6]. For inpatients undergoing VCE studies with a higher risk of incomplete studies, measures to avoid gastric retention include endoscopic placement of the capsule into the small bowel; use of promotility agents, such as intravenous metoclopramide or erythromycin before and during the study; and cessation of narcotics, if possible. If the patient is being discharged from the hospital, it may be advantageous to wait until discharge for the VCE study to occur so that the examination can occur while the patient is more active in an outpatient setting.

VCE is advantageous with a diagnostic yield of 25–50 % compared to the yields demonstrated using traditional small bowel radiography (3–20 %) [7, 8], push enteroscopy (3–30 %) [9–11], and elective angiography (5–15 %) [12, 13]. In patients with a negative capsule endoscopy, the usage of multidetector computed tomographic (CT) or magnetic resonance (MR) enterography has been shown to detect pathology in some patients, particularly if bleeding is related to an underlying neoplasm [14].

Timing of the VCE examination correlates with diagnostic yield in patients with overt obscure GI hemorrhage. In the landmark study by Pennazio et al., the diagnostic yield in 100 patients undergoing VCE was 92 % in those with ongoing overt hemorrhage, 13 % in patients with bleeding that had stopped (intervals ranging between 10 days and 1 year), and 44 % in the iron-deficiency anemia cohort [11]. Subsequent studies reported higher diagnostic yields when VCE was performed within 2 weeks of an overt bleeding episode (detection rate 91 %) compared to 34 % when the VCE occurred more than 2 weeks later [15]. Similarly, higher diagnostic yields have been demonstrated when deep enteroscopy is performed within 2 weeks of an overt bleeding episode [16].

In a recent retrospective study from a tertiary medical center, inpatients with overt obscure GI bleeding undergoing VCE studies were analyzed for diagnostic and therapeutic yields in relation to timing of VCE administration. The diagnostic yield was significantly higher for inpatients (66 %) compared to outpatients (53 %) and greater if the VCE was administered within 3 days of hospitalization (yield for active bleeding and/or angiodysplasia of 44 % versus 28 % for VCE studies performed after 3 days, $p=0.05$). If the VCE was administered early, the length of stay was shorter (6 versus 10 days, $p<0.0001$), and there was a greater rate of therapeutic intervention (19 % versus 7 %, $p=0.05$) [17].

Repeat Video Capsule Endoscopy

When the VCE study is negative, a decision should be made whether to pursue ongoing diagnostic evaluation for a small bowel source or wait until another episode of bleeding occurs. The argument for the latter decision is that the diagnostic yield is higher within 2 weeks of a bleeding episode, so that waiting for another episode of hemorrhage to occur can be useful if the patient is stable. On the other hand, if the patient continues to demonstrate overt bleeding and/or require transfusions, then ongoing evaluation should occur.

Multiple studies have demonstrated increased diagnostic yields when VCE studies are repeated after an initial negative evaluation. In the study by Viazis et al., the investigators followed patients with initial nondiagnostic VCE studies and performed repeat VCE when the patients had recurrent overt bleeding or a drop in hemoglobin ≥ 2 mg/dl [18]. Of 104 patients with an initial nondiagnostic VCE followed for a mean of 25 months, 76 (73 %) received a second VCE study due to

recurrent bleeding. Thirty-seven (49 %) subjects had positive findings on repeat VCE, with angiodysplastic lesions being the most common finding. On logistic regression analysis, significant predictors for an abnormal repeat study included change in bleeding type from occult to overt hemorrhage and drop in hemoglobin levels ≥ 4 mg/dl.

In another retrospective study, the authors analyzed 82 of 676 patients undergoing repeat VCE studies from 2001 to 2009 [19]. Overall, the diagnostic yield of repeat VCE was 55 %, leading to a change in management in 39 % of the cohort. Reasons for repeat VCE studies included incomplete initial VCE ($n = 22$, yield of repeat VCE 45 %), screening for polyposis syndromes ($n = 4$, yield 50 %), ongoing gastrointestinal symptoms ($n = 26$, yield 38 %), and prior VCE studies leading to therapeutic interventions but with ongoing symptoms ($n = 30$, yield 77 %).

Based on the abovementioned studies, close follow-up is advised in patients with an initial normal VCE study who remain clinically stable. If the patient has ongoing acute hemorrhage, urgent repeat VCE could be considered versus other options, including deep enteroscopy, CT or MR enterography, or angiography. If the patient remains stable without bleeding, the recommendation would be to consider repeat VCE study when hemoglobin falls or the patient experiences recurrent overt bleeding.

Angiography: Is There Ever a Role?

The diagnostic yield of mesenteric angiography in patients with obscure GI bleeding traditionally has been low, in the range of 5–15 % [13]. The question, therefore, arises whether there currently is a role for angiography and, if so, in what subset of patients.

The diagnostic algorithm suggests angiography for patients with "massive bleeding" (Fig. 5.1). The amount of hemorrhage required for a positive angiographic examination is in the order of ≥1 ml/min or bleeding in the setting of hemodynamic instability (hypotension and/or tachycardia). Angiography has typically been performed in patients with suspected ongoing diverticular hemorrhage where a source could not be identified during colonoscopy, or in patients with significant bleeding from mucosal or submucosal vascular lesions, where embolization might be an effective treatment modality (Videos 5.1 and 5.2).

A recent randomized controlled trial compared angiography ($n = 30$) to VCE ($n = 30$) in patients with obscure overt GI bleeding [20]. VCE was diagnostic in 16 (53 %) patients compared to 6 (20 %) patients undergoing angiography ($p < 0.005$). Findings on VCE examinations included tumors ($n = 3$), active bleeding ($n = 4$), ulcerations ($n = 6$), and active gastric bleeding ($n = 3$). Lesions found on angiography included Meckel's diverticulum ($n = 1$), tumor ($n = 1$), and angiodysplastic lesions in the small bowel and/or colon ($n = 4$). None of the patients in the angiography group underwent embolization. Four patients continued to bleed after angiography and underwent VCE demonstrating diverticular hemorrhage in three patients (two small intestinal and one colonic). Five patients underwent surgical resection for tumors and Meckel's diverticulum. Over a mean follow-up of 48 months, rebleeding occurred in 25 % of the overall cohort, mainly due to vascular lesions and diverticular disease. There were no significant differences between groups in terms of hospitalization or death rates. A limitation of the study was that it was likely underpowered to detect meaningful differences in diagnostic yields and outcomes.

In summary, angiography cannot be recommended as the first test in the setting of obscure overt GI bleeding, although it may be considered in the patient who presents with hemodynamic instability.

Push Enteroscopy

Push enteroscopy (using endoscopes up to 250 cm in length) was introduced in the 1990s. The technique is hampered by looping of the enteroscope resulting in patient discomfort and limiting the extent of the examination to 50–150 cm of visualized small bowel (corresponding to proximal jejunum) despite the use of an overtube [21]. The

reported diagnostic yield of push enteroscopy in patients with obscure GI bleeding ranges from 15 to 75 %, with arteriovenous malformations being the most common lesions identified [22]. However, in 10–60 % of push enteroscopic examinations, detected lesions were described to be within reach of a standard endoscope. Push enteroscopy examinations can still be useful in patients with suspected bleeding of the proximal small bowel but have largely been replaced by utilization of VCE and deep enteroscopy. Push enteroscopy can be considered in patients requiring a "second look" examination of the upper digestive tract prior to video capsule endoscopy.

Deep Enteroscopy

Options for deep enteroscopy include balloon and/or spiral examinations. Double-balloon enteroscopy (DBE) was introduced into the United States in 2004 after Yamamoto in Japan described the ability to advance deep in the small bowel using an enteroscope with a balloon at the scope tip and a second balloon on a 140-cm overtube [23]. The overtube balloon could be inflated to grip the intestinal wall, so that the enteroscope could be advanced without loop formation. Subsequently, with both balloons close together, the apparatus could be withdrawn with reduction of any loops that might have formed. Using this technique from the anterograde and retrograde approaches, total enteroscopy could be achieved.

For the single-balloon technique, introduced into the United States in 2007, the tip of the enteroscope in a hooked position was used in lieu of the balloon at the end of the enteroscope tip. With the tip deflected and the overtube balloon inflated, reduction maneuvers could be performed [24]. Spiral enteroscopy, introduced into the United States in 2008, described usage of an overtube with a spiral apparatus at its end that could be placed over an enteroscope [25]. Once advancement into the jejunum was achieved, the overtube would be locked into place, and rotations of the spiral could occur until maximal advancement was achieved.

Compared to VCE, deep enteroscopy requires a longer examination time (1–1.5 h on average). While complete small bowel visualization has been described in case reports, the DBE instrument can typically be advanced to the mid-distal jejunum using the anterograde approach and to the proximal ileum from the retrograde route (approximately 250 cm and 130 cm, respectively, based on prior studies) [26–30].

A meta-analysis published in 2008 demonstrated equivalent diagnostic yields for VCE and deep enteroscopy [31]. Because VCE is less invasive and associated with lower complication rates, it usually precedes deep enteroscopy, even in patients with acute suspected small bowel hemorrhage (Fig. 5.2 and Video 5.3).

Initial usage of deep enteroscopy can be considered, however, in certain clinical settings. First, if VCE is not available and a patient has a normal upper and lower endoscopic examination, empiric deep enteroscopy is reasonable, with an anterograde approach in the setting of melena and/or a suspected bleed in the proximal two-thirds of the small bowel or a retrograde approach in the setting of hematochezia. It should be noted that retrograde deep enteroscopy examinations are typically associated with a 20–30 % failure rate to intubate the terminal ileum, usually in the setting of poor colonic preparation and/or prior appendectomy or pelvic surgery [32]. Second, empiric deep enteroscopy without VCE may be considered in actively bleeding patients with a high suspicion of small bowel hemorrhage. For example, if a patient has had angiodysplastic lesions detected on upper and lower endoscopic examinations that were treated and the patient continues to bleed, deep enteroscopy may be performed without VCE since the clinical suspicion for small bowel vascular angioectasias is high. In addition, if a patient has an abnormality on a prior imaging test, such as a finding suspicious for a small bowel neoplasm, then subsequent deep enteroscopy for diagnosis and biopsy is appropriate. If a patient undergoes a VCE study demonstrating blood without a discrete source, subsequent enteroscopy is appropriate to determine the cause of bleeding (Fig. 5.3).

As mentioned above, with the current generation of capsule endoscopes, the miss rates for mucosal lesions are between 20 and 30 % [33, 34].

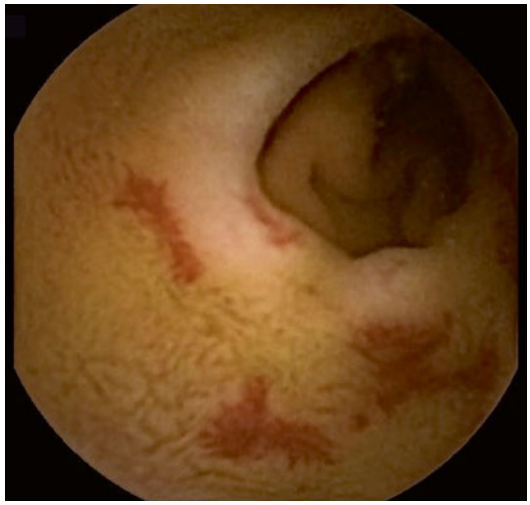

Fig. 5.2 Diffuse angiodysplastic lesions on VCE study. A 67-year-old woman with transfusion-dependent anemia and a history of GI bleeding presented with a 2-day history of melena and crampy abdominal pain. Her past medical history was notable for CREST syndrome, coronary artery disease, factor V Leiden thrombophilia with multiple deep venous thromboses on warfarin therapy, peripheral vascular disease, chronic obstructive pulmonary disease, and congestive heart failure. On physical examination, telangiectasias were apparent on the lips, chest, and mucous membranes. Laboratory data included hemoglobin of 4.4 g/dl with an MCV of 76, INR of 6.0, and BUN of 37. Prior upper endoscopy and colonoscopy demonstrated small vascular ectasias in the gastric fundus and body, as well as in the colon, which were treated with argon plasma coagulation therapy. However, there were no changes in transfusion requirements after endoscopic therapy. A capsule endoscopy study was performed demonstrating multiple confluent angiodysplastic lesions throughout the small bowel that were not actively bleeding. Since the number of angiodysplastic lesions in the small bowel was too numerous for endoscopic therapy, treatment was initiated with intravenous octreotide, with transition to subcutaneous injection. The patient's transfusion requirements improved following initiation of subcutaneous octreotide administration

In the setting of a normal VCE study, a subsequent enteroscopy study is not recommended unless there is a high clinical suspicion that lesions have been missed on the VCE study. If the VCE study is normal, the next recommended test for a patient with obscure GI bleeding should be an enterography examination.

Magnetic Resonance or Computed Tomographic Enterography

Recent advances in MR and CT imaging have enhanced the role of these examinations for patients with obscure GI bleeding. MR enterography (MRE) and CT enterography (CTE) examinations, which entail giving the patient up to 1800 ml of neutral volume contrast to enhance the bowel wall, allow visualization of submucosal pathology that could be missed on VCE and/or deep enteroscopic examinations. While the sensitivity and specificity of VCE remain superior to MRE and CTE in patients with obscure GI bleeding, these examinations can be useful as complementary tests.

The role of MRE and CTE in patients with obscure GI bleeding is evolving. Currently, small bowel enterography examinations can be considered for the following indications: (1) patients presenting with obscure bleeding in the presence of abdominal pain or obstructive symptoms. Enterography examinations are recommended prior to VCE examination to exclude the presence of a stricture that would lead to VCE retention. Enterography examinations have demonstrated equal sensitivity to the patency capsule for this indication [35], (2) patients presenting with GI hemorrhage with known or suspected small intestinal Crohn's disease. While meta-analyses have demonstrated superior ability of VCE to diagnose Crohn's disease compared to CTE, the risk of capsule retention can exceed 10 % [36], and, therefore, MRE or CTE is recommended as the first test in patients with symptoms suggestive of small bowel obstruction; (3) prior studies have demonstrated that patients with negative VCE studies have high rates of rebleeding. While the yield of repeat VCE can approach 50 % as discussed above, enterography examinations should be considered to exclude submucosal pathology that can be missed by VCE as they have demonstrated superior sensitivity for the detection of small bowel neoplasms and other vascular lesions (Fig. 5.4) [37].

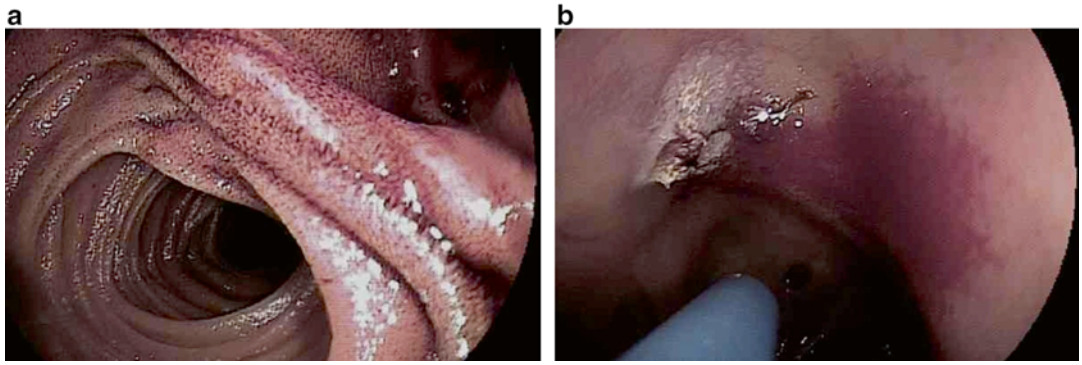

Fig. 5.3 Example of VCE-directed DBE examination. A 69-year-old woman with chronic arthritis on ibuprofen 600 mg daily presented with dark maroon stools requiring multiple transfusions. Her upper endoscopy and colonoscopy were negative. Subsequent VCE examination demonstrated blood without a discrete source seen on 2 frames at 4 h. The overall small bowel transit time was 7.5 h. Anterograde enteroscopy was performed due to ongoing bleeding and demonstrated a bleeding jejunal diverticulum (**a**) treated with argon plasma coagulation therapy (**b**)

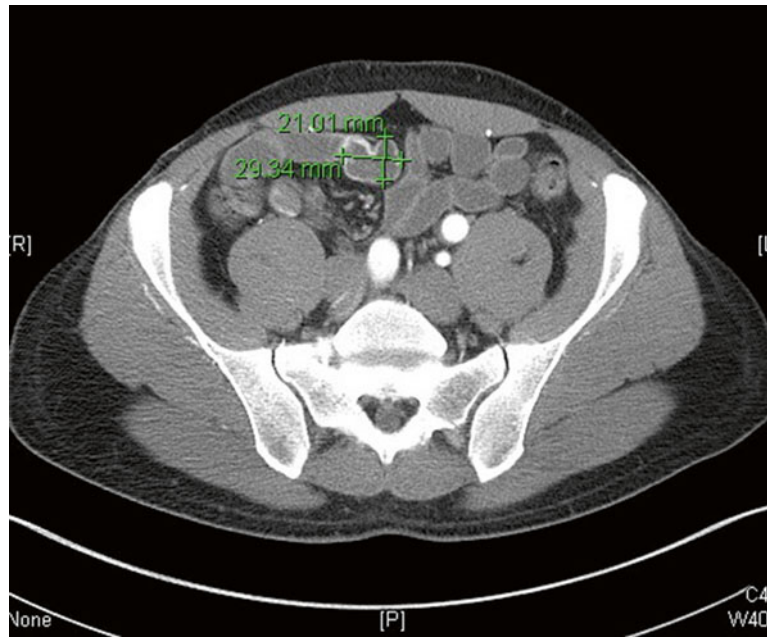

Fig. 5.4 Case of obscure GI bleeding diagnosed by CT enterography. A 35-year-old man presented with hemoglobin of 6 mg/dl and hematochezia. Colonoscopy, upper endoscopy, and VCE were negative for a bleeding source. Push enteroscopy identified a possible polypoid lesion at 70 cm that was not removed. The patient underwent anterograde DBE with the finding of a 4-mm jejunal tubular adenoma that was biopsied. Due to ongoing bleeding, a CT enterography was performed, which demonstrated a Meckel's diverticulum. The patient underwent segmental small bowel resection with cessation of bleeding

Conclusion

While acute small bowel hemorrhage is a relatively rare event, it has been associated with significant patient morbidity and costs of care. After negative standard endoscopic examinations, VCE is recommended as the next diagnostic test in most patients. Decisions regarding second-look upper and lower endoscopic examinations should be based on the quality of these examinations, ongoing symptoms such as hematemesis,

and any associated findings. In patients with suspected obstruction or abdominal pain, CT or MR enterography should be performed prior to the VCE study. A patency VCE study is another option to exclude the presence of stricturing disease. In general, deep enteroscopy should be reserved for patients with findings on VCE suggestive of a small bowel source of bleeding that warrant further diagnosis or therapy, but empiric enteroscopy can be considered in patients with a high pretest probability of small bowel pathology. Angiography should be reserved for patients presenting with hemodynamic instability in the setting of presumed active small bowel bleeding. If the initial VCE examination is normal and the patient continues to bleed, further testing includes a repeat VCE study, deep enteroscopy, or an enterography (MR or CT) examination, depending upon the clinical presentation.

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Approach to Suspected Lower Gastrointestinal Bleeding

6

Wajeeh Salah and Ashley L. Faulx

Introduction

Acute lower gastrointestinal bleeding (LGIB), previously defined as bleeding that occurs distal to the ligament of Treitz, accounts for approximately 20 % of all cases of gastrointestinal (GI) bleeding. With the advent of deep enteroscopy and increased recognition of the small bowel as an important source of GI bleeding (mid-gastrointestinal bleeding), LGIB currently refers to bleeding that originates from the colon and rectum.

The incidence of LGIB increases with age and, in the elderly, may surpass that of upper GI bleeding [1]. A recent study from Spain showed that over a decade the incidence of lower GI complications had increased by more than 50 %, while the incidence of upper GI complications had decreased by almost 50 %. Additionally, patients with lower GI complications had a longer length of hospital stay, greater resource utilization (more diagnostic tests performed), and higher mortality than patients with upper GI complications [2].

In the United States, diverticular bleeding is the most common cause of severe LGIB and accounted for approximately $1.3 billion in healthcare costs in 2001. The incidence is approximately 20–27 cases per 100,000 individuals annually [3]. A detailed and accurate clinical history is a crucial first step in determining the source of LGIB. Many of the common causes of LGIB have characteristic clinical features, and a careful history can provide vital clues, allowing for more rapid identification of the bleeding source. The presence or absence of abdominal pain, as well as other physical exam findings, can help risk stratify the patient and provide an early prediction of severity. The advent of new types of endoscopes and endoscopic hemostatic devices, as well as new techniques, can be added to the endoscopist's toolbox during the evaluation and management of suspected LGIB.

Causes and Severity of Lower GI Bleeding

The most common causes of acute hematochezia are listed in Table 6.1 [4].

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W. Salah (✉)
Department of Gastroenterology, Mayo Clinic Health System – Eau Claire, Eau Claire, WI 54703, USA
e-mail: Wajeeh.Salah@gmail.com

A.L. Faulx
Division of Gastroenterology and Liver Disease, University Hospitals Case Medical Center, Cleveland, OH 44106, USA

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Table 6.1 Etiologies of acute lower gastrointestinal bleeding

Bleeding lesion	Frequency (%)
Diverticulosis	5–42
Ischemia	6–18
Anorectal (hemorrhoids, anal fissures, rectal ulcers)	6–16
Neoplasia (polyps and cancers)	3–11
Angioectasia	0–3
Postpolypectomy	0–13
Inflammatory bowel disease	2–4
Radiation colitis	1–3
Other colitis (infectious, antibiotic associated, colitis of unclear etiology)	3–29
Massive upper GI bleeding	3–13
Other causes	1–9
Unknown cause	6–23

LGIB can be categorized as severe, moderate, and scant and is manifested by hematochezia. The chronic passage of intermittent bright red blood, often associated with a bowel movement, with streaks of blood on the stool or toilet paper is common and can usually be attributed to hemorrhoids, anal fissures, or a slow-growing neoplastic lesion. Patients over the age of 40 or those with a strong family history of colon cancer should undergo a high-quality colonoscopic evaluation. In younger, healthy patients, a digital rectal exam, in addition to flexible sigmoidoscopy, may be sufficient for evaluation if a rectal outlet source of bleeding is identified. Moderate hematochezia is a frequent GI cause for hospitalization and usually requires inpatient evaluation and management. Severe acute hematochezia is the least common but potentially life-threatening condition. In this high-risk group, rapid diagnosis and therapy are essential to avoid associated morbidity and mortality. Massive upper GI bleeding can also manifest with hematochezia, and so exclusion of an upper GI source is important in the right clinical scenario. Hematochezia associated with upper GI bleeding is often accompanied by hemodynamic instability, with possible concurrent hematemesis and upper GI symptoms. Up to 15 % of patients presenting with massive hematochezia have been found to have an underlying upper GI bleeding source.

Clinical History and Clues as to the Source of Bleeding

The initial evaluation of a suspected LGIB source starts with a careful history and physical examination. Often, the patient history can provide vital clues as to the etiology of bleeding and help to risk stratify the patient and plan the initial management. For example, a patient presenting with hematochezia within 2 weeks of undergoing a colonoscopy with polypectomy may not require urgent endoscopic evaluation, since postpolypectomy bleeding is frequently self-limited. A visual inspection of the external anal opening and a digital rectal examination can identify bleeding rectal outlet lesions, such as hemorrhoids and anal fissures, as well as to confirm stool color and consistency.

Diverticular Bleeding

Diverticular bleeding typically presents in elderly patients (>60 years old) and is associated with a "painless gush" of bright red blood per rectum. Patients with diverticular hemorrhage commonly provide a history of rectal bleeding that is large in volume and sudden in onset. Diverticulosis is the most common cause of acute LGIB, accounting for 42–56 % of cases (Fig. 6.1). Diverticula occur in areas of weakness within the wall of the colon. Bleeding occurs when the thin diverticular wall herniates into an arterial blood vessel (usually in the dome of the diverticulum or at its antimesenteric margin). In Western countries, 75 % of diverticula occur in the left colon, and, when right-sided diverticula do occur, they are usually associated with concurrent left-sided diverticula. Right-sided diverticular bleeding may be more severe than left-sided diverticular bleeding. Diverticular bleeding ceases spontaneously in about 80 % of cases. Although endoscopic therapies to treat a bleeding diverticulum, such as epinephrine injection and/or clip application (Video 6.1), are effective, recurrent bleeding has been reported in up to 40 % of patients despite endoscopic therapy [5]. For this reason, we advocate application of an endoscopic tattoo to mark the

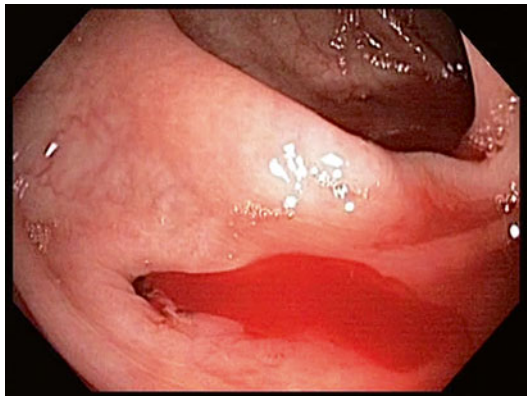

Fig. 6.1 Actively bleeding colonic diverticulum located in the sigmoid colon

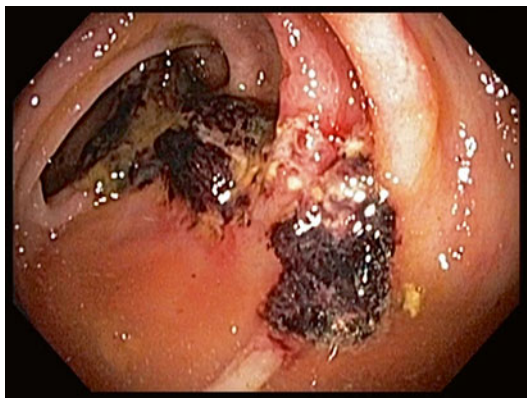

Fig. 6.2 Ischemic colitis at the splenic flexure in a hospitalized patient with hypotension and sepsis

site of bleeding anytime an actively bleeding diverticulum is identified, so as to facilitate endoscopic or surgical localization should rebleeding occur. Recent studies have identified factors, such as nonsteroidal anti-inflammatory drugs (NSAIDs), antiplatelet drugs, and hypertension, that may be associated with a higher rate of recurrence of colonic diverticular bleeding [6].

Ischemic Colitis

Ischemic colitisusually manifests with abdominal pain and hematochezia, typically in an elderly patient. Historical features that raise the suspicion for colonic ischemia include small to medium volume passage of blood per rectum and antecedent hypotension. The colitis tends to be segmental (Fig. 6.2) and more commonly affects areas of the colon where the blood supply from two vascular territories do not overlap ("watershed areas"), such as the splenic flexure (Video 6.2). The likelihood of colonic ischemia as the cause of hematochezia also increases in patients who are critically ill or have a history of severe peripheral vascular disease. A common clinical scenario for the occurrence of colonic ischemia is in the critically ill patient who is in an intensive care unit and who suddenly develops hematochezia. Obtaining an accurate history regarding current medications (e.g., vasopressor therapy) and trending the patient's blood pressure measurements in the period leading up to the episode of hematochezia are key determinants.

Vascular Ectasias

Bleeding vascular ectasias, or angioectasias, can present with either melena (from a right colon source) or bright red blood per rectum (from a left colon source). They more commonly present with painless bleeding in elderly patients (Fig. 6.3), and the severity of bleeding is variable. Angioectasias can be acquired through aging and their formation has been associated with chronic renal failure as well as aortic stenosis. Angioectasias are flat lesions in the GI tract and, as a result, can be easily obscured by retained

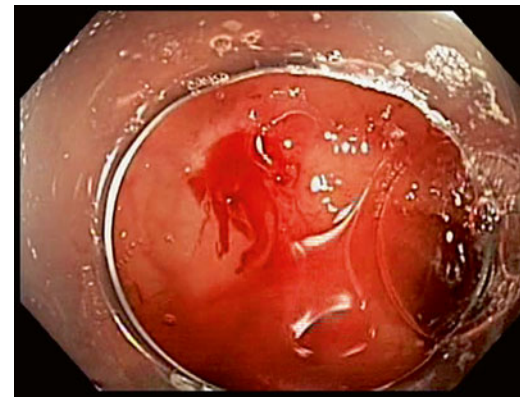

Fig. 6.3 Actively bleeding colonic angioectasia hidden between mucosal folds at the hepatic flexure identified using a cap-fitted colonoscope

colonic material or remain hidden between the colonic folds. In these situations, the use of an endoscopic cap may help locate an actively bleeding colonic angioectasia and facilitate endoscopic therapies, such as epinephrine injection, clip application, and/or argon plasma coagulation (Video 6.3). Angioectasias should be suspected in patients with recurrent overt LGIB where the source of bleeding has not been identified on previous colonoscopic examinations or other diagnostic studies. Colonoscopy with a good quality bowel preparation and careful examination of the colonic mucosa is essential for the detection and treatment of these lesions.

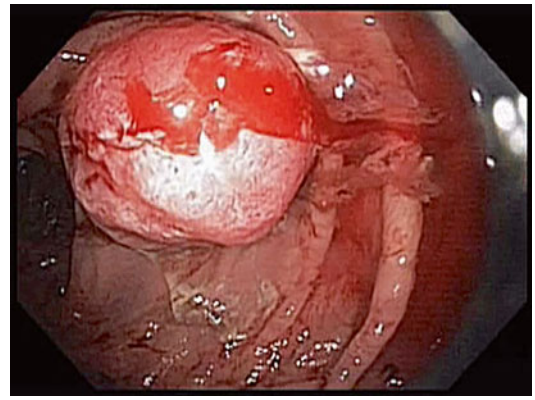

Fig. 6.4 Actively bleeding colonic neoplasia in the descending colon

Neoplasia

Overt LGIB due to colonic neoplasia is a relatively rare occurrence. Bleeding due to colonic neoplasia (Fig. 6.4) occurs more commonly in elderly patients and is more often a source of occult blood loss. Bleeding is usually of small volume and painless and tends to occur as a result of tumor neovascularization (Video 6.4). LGIB from colonic neoplasia can present as intermittent melena (from a right-sided colonic neoplasia) or hematochezia (from a more distal neoplasia). Factors that raise the suspicion for colonic neoplasia as the source of LGIB include a history of iron-deficiency anemia, weight loss, and a change in stool caliber.

Anorectal Lesions

Hemorrhoidal bleeding is a relatively common source of LGIB and can be seen in patients of any age. Small-volume hematochezia, characterized by bright red blood after a bowel movement with dripping into the toilet or streaking on the toilet paper, is most commonly caused by hemorrhoids, especially in patients under the age of 50. Hemorrhoidal bleeding tends to be of low volume and intermittent in nature and may be associated with constipation.

Anal fissures are typically associated with pain upon defecation and small volume bleeding. These

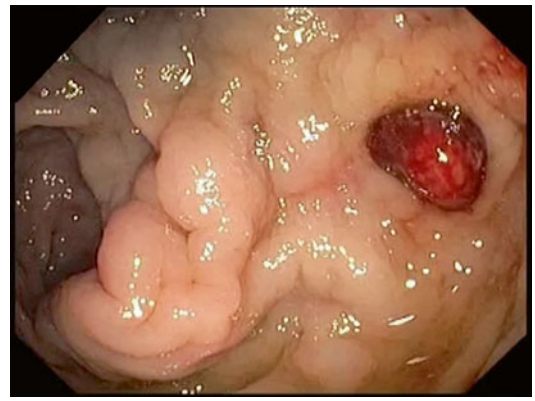

Fig. 6.5 Distal rectal ulcer with a visible vessel and large overlying clot

may be associated with constipation and the passage of hard stools. There may also be a history of anal trauma antecedent to the episode of bleeding.

Rectal ulcers can be caused by severe or prolonged pressure and irritation within the rectum. This can be due to constipation and hard stool (stercoral ulcer) or by pressure from fecal management systems. Due to the rich blood supply of the rectum, bleeding from rectal ulcers (Fig. 6.5) can be severe if the ulcer erodes into an arterial vessel. This type of bleeding lesion may require multiple endoscopic modalities, such as epinephrine injection and clip application, in order to provide durable hemostasis (Video 6.5). The diagnosis of an anorectal source of LGIB requires a thorough examination of the anal canal, both internally and externally. A careful inspection of

the external anal opening and a digital rectal exam should be performed. It is also imperative to perform a high-quality retroflexed endoscopic examination of the rectum when evaluating for potential anorectal sources of LGIB.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) can present with abdominal pain and/or pain with defecation. Patients with IBD can present with either small or large volume of rectal bleeding and tends to occur in younger patients. In patients with IBD, bleeding is usually due to diffuse inflammation of the colonic mucosa, and the severity of bleeding is correlated to the degree of mucosal inflammation. LGIB in a patient with IBD may be the initial presenting symptom of the disease and may be associated with weight loss, anemia, inflammatory biomarkers, and extraintestinal manifestations or a family history of IBD.

Miscellaneous Causes

Bleeding due to radiation proctopathy typically presents with the passage of bright red blood per rectum, which may be associated with tenesmus. A history of previous radiation exposure (i.e., radiation for prostate cancer in men or for uterine cancer in women) is essential in making the presumptive diagnosis of bleeding due to radiation proctopathy.

Patients with bleeding due to NSAID-induced colonic ulceration (Fig. 6.6) can present with either melena or hematochezia. In contrast to ischemic ulcers, NSAID-induced colonic ulcers may be isolated and can occur in any part of the colon. NSAID-induced ulcers generally are clean-based and resolve following cessation of the offending drug (Video 6.6).

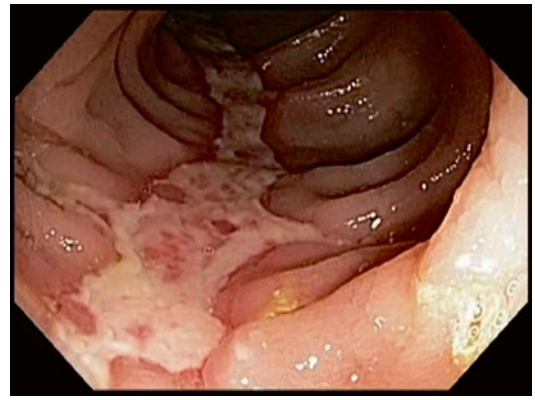

Fig. 6.6 NSAID-induced colonic ulcer in the descending colon. Note the long, linear, and clean-based appearance of the ulcer

Table 6.2 Risk factors for prediction of severity in acute lower GI bleeding[a]

Risk factors	Odds ratio	95 % CI
Heart rate >100/min	3.7	1.8–7.6
Systolic blood pressure ≤115 mmHg	3.5	1.5–7.7
Syncope	2.8	1.1–7.5
Non-tender abdominal examination	2.4	1.2–4.9
Rectal bleeding within the first 4 h of evaluation	2.3	1.3–4.2
Aspirin use	2.1	1.1–3.8
>2 comorbid illnesses	1.9	1.1–3.4

[a]Adapted from Strate L. et al. Arch Int Med 2003;163:838–43

Early Predictors of Severity in Acute Lower GI Bleeding

Although there have been multiple studies designed to evaluate prognostic factors of severity in patients with upper GI bleeding, few have evaluated predictive factors of severity in LGIB (Table 6.2) [4]. In one study, important hemodynamic predictors of severity in patients with upper GI bleeding, such as tachycardia and hypotension, were also key predictors in patients with LGIB [4]. This study also found that the abdominal examination can be predictive of severity. Severe LGIB was associated with a non-tender abdomen on palpation (e.g., diverticular hemorrhage).

Preprocedural Assessment

The preprocedural steps involved in the care of the patient who presents with suspected LGIB include obtaining a careful history, physical examination, and appropriate laboratory tests,

initiating resuscitative measures (intravenous fluids and blood transfusions, as appropriate), correcting coagulopathy, and triaging the patient to the appropriate level of care (outpatient vs. ward vs. intensive care unit) based on severity of bleeding and comorbidities. As outlined above, clues in the history can direct toward a probable cause of bleeding, such as postpolypectomy hemorrhage in a patient who recently underwent polypectomy, diverticular bleeding in a patient presenting with painless large-volume hematochezia and known diverticulosis on prior colonoscopy, and ischemic colitis in an elderly patient with arteriosclerosis presenting with sudden onset abdominal pain followed by bloody diarrhea. The presence of hematochezia combined with hemodynamic instability and risk factors, such as a prior history of upper GI bleeding and NSAID use, should raise concern for a brisk upper GI bleeding source. In this situation, an emergent upper endoscopy should be performed. The alternative of placing a nasogastric tube is controversial since a negative aspirate for blood does not necessarily rule out an upper GI source (e.g., post-pyloric duodenal bleeding ulcer).

The optimal thresholds regarding the international normalized ratio (INR) and platelet count for the safe and effective use of colonoscopy in the setting of acute LGIB have not been determined, although correction of coagulation defects with fresh frozen plasma (target INR <2) and platelet transfusion (target platelet count >40,000) are reasonable thresholds. Patients with mechanical heart valves and/or coronary stents on anticoagulation and/or antiplatelet therapy at the time of presentation should be managed in conjunction with a cardiology specialist.

Although colonoscopy is the recommended initial test for acute LGIB, bleeding may rarely be so massive with risk of exsanguination that emergent alternatives are required. Prompt angiography with therapeutic intent (embolization) is usually the next step, with emergent salvage surgery considered only as a last resort since the morbidity and mortality associated with "blind" subtotal colectomy is significantly higher than segmental resection of a preoperatively identified bleeding site.

Endoscopic Approach to Lower GI Bleeding

As mentioned above, colonoscopy is the preferred initial test in patients with LGIB. It is a relatively safe procedure with a reported adverse event rate of less than 2 %. Colonoscopy can identify a definitive bleeding source in 40–80 % of patients and a probable source in 80–100 % [7]. Endoscopic therapy can be performed once the source is identified. The various hemostatic modalities available for treatment of LGIB are reviewed in a separate chapter.

The data regarding timing and utility of colonoscopy remain controversial. Some studies have suggested that early colonoscopy is more likely to find a definitive source of bleeding compared to elective colonoscopy. Even if hemostasis is not permanently achieved (i.e., rebleeding occurs), identification of the bleeding site can aid the interventional radiologist or surgeon for subsequent therapy. In the patient requiring surgical management, the morbidity and mortality associated with subtotal colectomy are significantly higher than a segmental resection, the latter rendered possible by prior endoscopic identification and marking (tattoo placement ± clip application). Endoscopic evaluation should be undertaken only after the patient has been adequately resuscitated and should be performed in a monitored care setting if the patient is presenting with severe active bleeding, hemodynamic compromise, significant coagulopathy, advanced age, and/or multiple comorbid conditions.

Early Versus Elective Colonoscopy

Over the past 15 years, several studies have promoted the value of early or urgent colonoscopy (variably defined as colonoscopy within 6–24 h of admission) in the diagnosis and management of LGIB. Jensen et al. prospectively evaluated 121 patients with severe diverticular bleeding who underwent urgent colonoscopy after rapid purge with 4–8 l of a standard polyethylene glycol solution. Stigmata of recent hemorrhage were identified in 20 % of patients, with a reported 0 % rate for continued or recurrent bleeding in treated

patients, which compared favorably to historical controls [8]. In two retrospective studies, early colonoscopy was associated with a shorter hospital length of stay in patients with acute LGIB [9, 10]. In another randomized study which compared urgent colonoscopy (within 12 h) to elective colonoscopy (within 72 h), a higher rate for positive diagnoses was found in the urgent group (42 %) as opposed to the elective group (24 %). Therapy was performed more commonly in the urgent group (35 %) than in the elective group (0 %), although there were no differences in clinically meaningful outcomes between the two groups [11]. Similarly, the study by Laine et al., which compared urgent colonoscopy (within 12 h) to delayed colonoscopy (within 74 h), found a higher rate for positive diagnoses in the urgent group, but no differences in outcomes between the two groups [12]. Although there may be a benefit for early colonoscopy in acute LGIB with regard to some outcomes, data from larger randomized trials are needed.

From a practical perspective, in patients with acute LGIB necessitating hospitalization, we proceed with colonoscopic evaluation within 12–24 h of presentation. Colonoscopy in an unprepped colon has been advocated by some, though the limited visibility and potential increased risk of adverse events (e.g., perforation) due to blind maneuvers through bloody material preclude this approach in most cases. A rapid colon purge with 4–6 l of a polyethylene glycol (PEG)-based solution given at a rate of 1 l every 30 min can be considered in a patient with presumed active LGIB in need of urgent colonoscopy. If oral ingestion of the solution is not tolerated, it can be administered by nasogastric tube. A prokinetic agent (e.g., metoclopramide 10 mg intravenously) can also be administered prior to the purge to accelerate bowel transit and control nausea and vomiting. Colonoscopy can generally be performed within 1–2 h upon completion of the prep and the start of liquid discharge, since diluted blood and clots can be readily cleared from view. In an inpatient whose bleeding seems to have stopped, the colon preparation can be administered in a standard fashion, with colonoscopy performed the following day.

New Endoscopic Tools to Aid in the Diagnosis of Lower GI Bleeding Sources

The field of endoscopy is one of rapid changes, and the tools and techniques used in the diagnosis of LGIB lesions are continually evolving and improving. The last decade has seen the development of an ever-growing number of new endoscopic tools. The advent of tools, such as high-definition colonoscopes, water-jet irrigation systems, large-bore mechanical suction devices, endoscopic distal attachment caps, and endoscopic through-the-scope (TTS) Doppler ultrasound systems, has the ability to improve the identification of small or flat lesions in the colon and thus provide the opportunity for therapeutic intervention.

High-Definition Endoscopes

The latest generation of colonoscopes has been designed to improve visualization of the colonic mucosa, as well as providing a wider angle of view. The introduction of high-definition and high-resolution endoscopic imaging systems makes it possible to visualize small or flat lesions in the setting of acute GI hemorrhage. This can potentially improve detection of difficult to identify sources of lower GI hemorrhage, such as bleeding diverticula, angioectasias, and Dieulafoy lesions.

Water-Jet Irrigation Systems

The successful identification of a source of lower GI hemorrhage is highly dependent on the quality of the bowel preparation, as well as the ability to visualize the underlying mucosa. In patients presenting with severe LGIB, the ability to adequately assess the colonic mucosa can be impaired by either retained stool or blood. Additionally, inadequate bowel preparation can contribute to missed procedure-related adverse events. The development of water-jet irrigation systems (Fig. 6.7) has greatly improved the ability of the endoscopist to effectively and efficiently clear a large segment of colonic mucosa so that underlying lesions can be identified. Most of the newer generations of colonoscopes contain built-in channels that are specifically designed for water-jet irrigation systems.

Large-Bore Suction Devices

Fig. 6.7 Water-jet irrigation system for large-volume irrigation to improve visualization

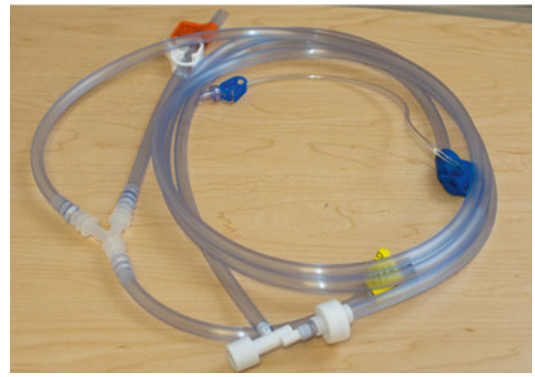

Fig. 6.8 Large-bore mechanical suction device for rapid clearance of large clots and stool

Fig. 6.9 Disposable distal attachment (endoscopic cap) fitted at the tip of an endoscope to improve mucosal visualization and provide mechanical leverage for endoscopic therapy

The ability to remove a large clot or fragment of stool during colonoscopy can greatly improve the chances of successfully identifying a bleeding lesion. An actively bleeding lesion may be concealed by a large overlying clot making identification and treatment of the underlying lesion difficult. Sources of severe and brisk LGIB, such as diverticula and angioectasias, can be buried by a large overlying clot that is difficult to clear through the standard colonoscope suction channel. Large-bore mechanical suction devices (Fig. 6.8) have been developed, which are designed to bypass suction from the endoscope's control head. This allows for more rapid clearance of a large volume of clot or other material that may otherwise clog the instrument's working channel.

Endoscopic Caps

The use of a disposable distal attachment, or endoscopic cap, can assist in the identification of the source of LGIB. An endoscopic cap is a soft, short, transparent, hollow tube (Fig. 6.9) that is fitted at the tip of the endoscope. A short cap typically extends 2–4 mm from the tip of the endoscope. This creates a fixed focal distance that allows for improved mucosal visualization. The use of the cap can provide several advantages in both the diagnosis and treatment of bleeding lesions. The cap enables spreading of the mucosal folds for better visualization, and this is especially useful in identifying flat bleeding lesions (i.e., angioectasias) or bleeding lesions that are located within a diverticulum, around flexures or in angulated portions of the bowel. The cap can also be used to stabilize the endoscope position and align the bleeding point for therapeutic interventions.

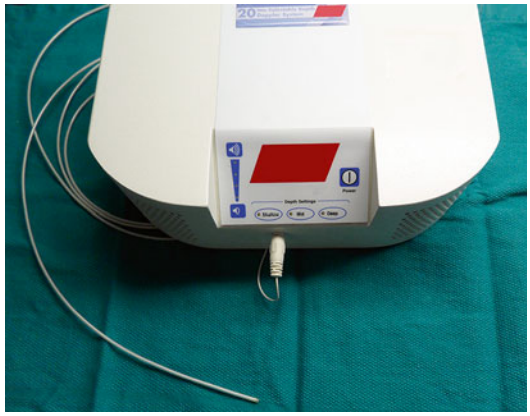

Fig. 6.10 Through-the-scope audible Doppler ultrasound system (processor and disposable through-the-scope ultrasound probe)

Through-the-Scope Doppler Ultrasound Systems

Endoscopic TTS Doppler ultrasound systems can be added to the endoscopist's armamentarium of tools for the diagnosis of bleeding lesions in the lower GI tract. TTS Doppler systems utilize a standalone receiver and a miniaturized Doppler ultrasound probe (Fig. 6.10) that is advanced under direct vision to the site of the lesion. The TTS Doppler ultrasound system is portable, requires minimal training to use, and can be rapidly deployed to provide an audible Doppler signal. This can be particularly useful for lesions in the GI tract, such as ulcers or diverticula, with indeterminate stigmata of hemorrhage. TTS Doppler ultrasound probes can be used to identify the precise location of underlying arterial feeding vessels to ulcers, diverticula, and Dieulafoy lesions, among others. The audible Doppler signal can also be used to trace the course of the vessel and create an "acoustic map" of its course, thus defining the precise location to apply targeted endoscopic hemostasis, as well as providing an objective endpoint in determining when adequate hemostasis has been achieved.

Unprepared Hydroflush Colonoscopy

Traditionally, the accepted standard of care for patients presenting with severe LGIB has been to perform urgent colonoscopy within 6–24 h of admission. The main limitation of urgent colonoscopy is the need for rapid oral administration of a large volume of a PEG-based bowel preparation, which can delay the procedure for several hours. A newer approach to the endoscopic evaluation of LGIB has been investigated by Repaka et al. [13], and a feasibility study has recently been published. This method, termed "unprepared hydroflush colonoscopy," entails preparing the patient immediately with three tap water enemas prior to colonoscopy. In patients with severe LGIB, the brisk flow of blood traveling through the lower GI tract can act as a cathartic agent and decrease residual stool volume. This can potentially eliminate the need for a large amount of oral purgative preparation. In addition, this method makes use of a water-jet irrigation pump (Fig. 6.7) attached to the accessory port of a standard adult colonoscope to clear any residual colonic blood or stool. Furthermore, the endoscopist is able to utilize a large-bore mechanical suction device (Fig. 6.8), as needed, for evacuation of large clots or stool from the colon to further improve visualization. By eliminating the standard oral purgative, the placement of a nasogastric tube to deliver the prep (required in up to 50 % of patients) can be avoided. An added advantage in curtailing the oral administration of a bowel prep is that an upper endoscopy can be performed (if there is a concern for an upper GI source), immediately followed by colonoscopy in the same session, further expediting the delivery of care.

Using this method, investigators found that endoscopic visualization was adequate for definitive (38 %) or presumptive diagnosis in all procedures, and none required repeat colonoscopy for inadequate preparation. Rebleeding occurred in 25 % of patients, all in patients who did not have a definitive diagnosis on initial colonoscopy. All patients interviewed at 7 days expressed a preference for tap water enemas versus a rapid oral purge. Robust data are not yet available to support this approach, although it is not uncommon at our institution to perform an unprepared hydroflush colonoscopy. We also make an effort to involve our colleagues in the emergency department and intensive care unit in this alternative endoscopic management, which may decrease time to colo-

noscopy and possibly improve clinical outcomes in these patients.

Conclusion

The incidence of acute LGIB has risen over the past decade. It is associated with substantial morbidity and mortality, especially in the elderly population, which accounts for the majority of patients hospitalized with LGIB. The presenting clinical characteristics of the various causes of LGIB can be helpful in guiding initial management. The institution of resuscitative measures and triage of the patient are directed, in part, by the severity of bleeding and associated comorbidities. Colonoscopy is generally the initial step in the evaluation of patients presenting with acute LGIB (Fig. 6.11) [14]. The advent of newer endoscopic tools, such as high-definition endoscopes, water-jet irrigation systems, large-bore mechanical suction devices, endoscopic distal attachement caps, and TTS endoscopic Doppler ultrasound systems, has improved the ability of endoscopy to locate, diagnose, and treat bleeding lesions in the lower GI tract. In the event that

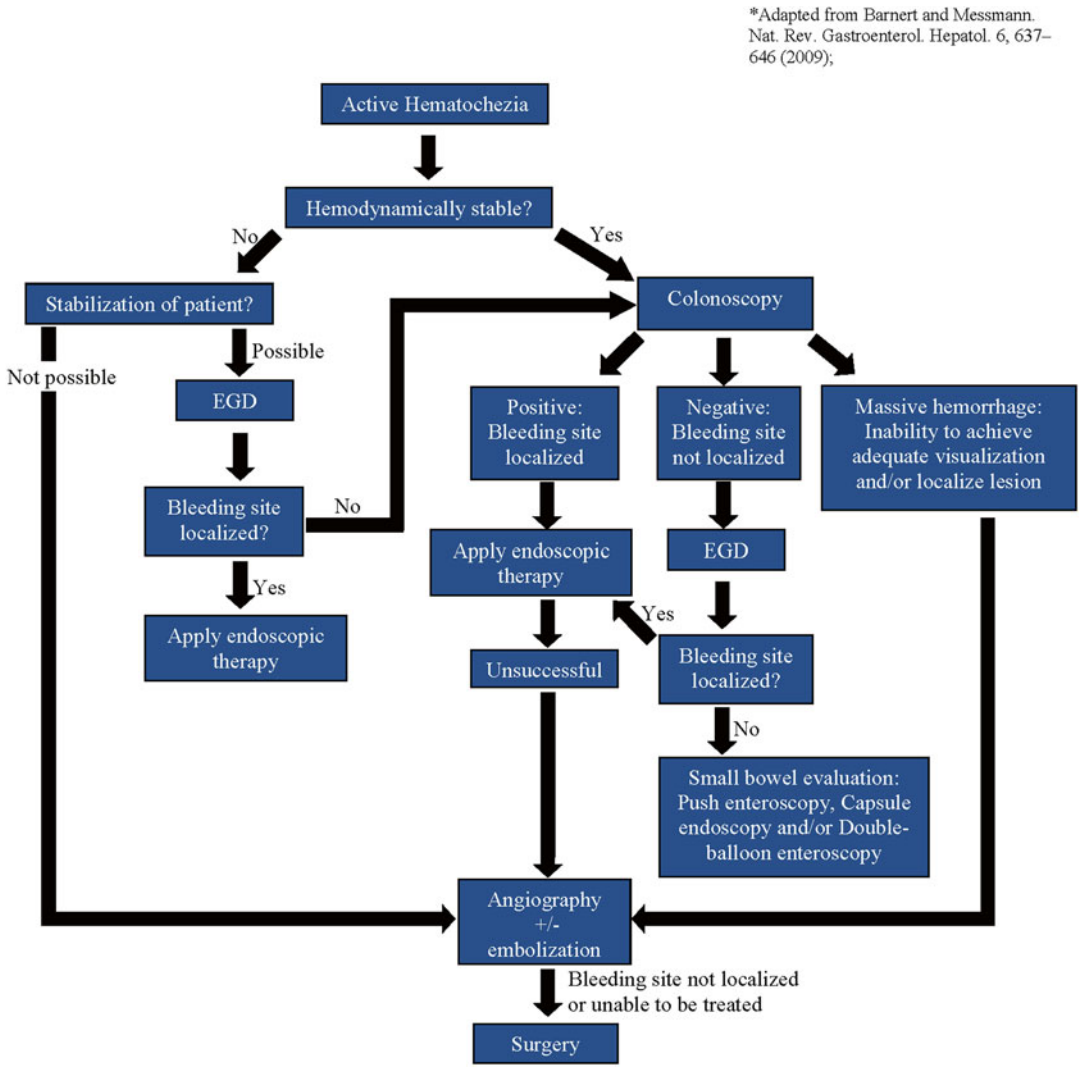

Fig. 6.11 Proposed algorithm for the evaluation of suspected lower GI bleeding

endoscopic hemostasis fails, endoscopy is still an invaluable tool to identify and mark the bleeding site for salvage surgical or interventional radiologic modalities. New methods, such as the unprepared hydroflush colonoscopy technique, are being developed to make use of the available tools in order to expedite the delivery of endoscopy and potentially improve the efficiency of patient care. Further studies are needed to determine the optimal timing of colonoscopy in the setting of acute LGIB and its role relative to alternative radiologic and therapeutic options.

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7 Approach to Foreign Body Ingestion, Food Impaction, and Caustic Injury

Emmanuel C. Gorospe, Louis M. Wong Kee Song, and Prasad G. Iyer

Foreign Body Ingestion

Foreign body ingestions are common medical emergencies. There is an abundance of literature on the many types of foreign bodies that are accidentally or intentionally ingested. Fortunately, the morbidity and mortality rates attributed to foreign body ingestion appear to be low [1]. The epidemiology, diagnosis, management, and outcomes of foreign body ingestions are based primarily on single case reports, case series, and retrospective chart reviews [2]. Most foreign body ingestions traverse the gastrointestinal (GI) tract uneventfully. About 10–20 % of patients will require endoscopic intervention and less than 1 % will require surgery [3, 4]. A significant proportion of foreign body ingestions occur in children primarily as a result of their propensity for placing objects in their mouths. In this young population, coins are most frequently ingested [5]. Among adults, the groups at risk for foreign body ingestions include those who are intoxicated, patients with psychiatric or cognitive impairments, and incarcerated individuals seeking secondary gains from inducing a medical emergency [6, 7]. The management of these individuals can be challenging as they are prone to repeat these behaviors and may present with multiple ingested foreign objects (Fig. 7.1).

Initial Assessment

In most adults, the history provided by the patient is most helpful in identifying the characteristics and quantity of the ingested foreign object(s). Children, patients with intentional ingestion for secondary gain, and those with psychiatric comorbidities may not cooperate or provide accurate clinical histories. Foreign body ingestion in cognitively impaired patients and children should be suspected if they show telltale signs and symptoms, such as refusal to eat, painful swallowing, blood-tinged oral secretions, drooling, choking, and vomiting. Without imaging or endoscopy, localizing ingested foreign objects in the GI tract is difficult. Table 7.1

Electronic supplementary material: The online version of this chapter (doi:10.1007/978-1-4939-3085-2_7) contains supplementary material, which is available to authorized users. Videos can also be accessed at http://link.springer.com/chapter/10.1007/978-1-4939-3085-2_7.

E.C. Gorospe (✉)
Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Center for Digestive Health, Prevea Health & Hospital Sisters Health System, 1726 Shawano Ave, Green Bay, WI 54307, USA
e-mail: gorospe@alumni.mayo.edu

L.M. Wong Kee Song • P.G. Iyer
Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

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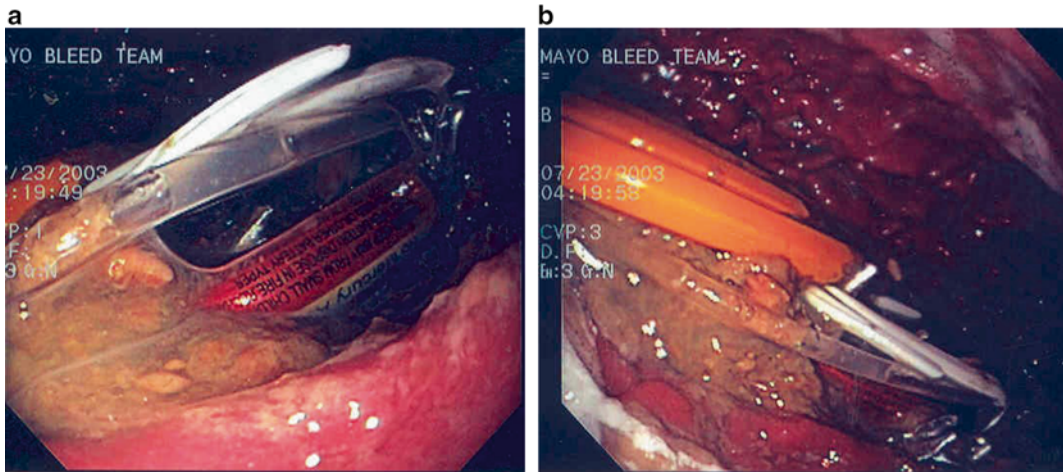

Fig. 7.1 Various foreign bodies in the stomach, including pencils, plastic silverware, soda can pop tops, and cylindrical batteries

Table 7.1 Anatomical site for possible food or foreign body impaction

Anatomy	Site of possible obstruction
Esophagus	– Post-cricoid
	– Aortic arch
	– Aberrant right subclavian artery
	– Left main bronchus
	– Diaphragmatic pinch
	– Pathologic narrowing or stricture (e.g., Schatzki's ring, peptic stricture, malignant stricture, eosinophilic esophagitis)
Stomach	– Pylorus
Small bowel	– Junction of descending and horizontal duodenal segment
	– Ileocecal valve
	– Pathologic narrowing or stricture (e.g., surgical adhesions, NSAID-induced diaphragm disease, Crohn's stricture)

summarizes the various physiologic and pathologic anatomical points in the GI tract where a delay in food transit or foreign body retention is most likely to occur [8]. The utilization of the site of pain or sensation of obstruction is an inaccurate means to assess location. For example, neck or chest pain may persist with the foreign body (e.g., fish bone) having already migrated into the stomach or the small bowel.

The initial physical assessment should search for signs of complications. Examination findings, such as neck swelling and crepitus, suggest esophageal perforation. The presence of abdominal guarding, rebound tenderness, and severe pain suggests perforation or peritonitis, warranting imaging (e.g., abdominal CT) and prompt surgical evaluation. The need for airway protection and the risk of aspiration should also be assessed prior to and during endoscopy [1].

Posterior-anterior and lateral films of the neck, chest, and/or abdomen should be obtained based on the swallowed object(s) and clinical presentation (Fig. 7.2). The lateral film is particularly important in identifying a faintly radiopaque foreign body that can easily be missed on posterior-anterior projection (e.g., partially calcified bone fragment overlying the spine). This is particularly useful for objects lodged in the esophagus. Some foreign objects, such as fish bones, plastic, aluminum, and wood, are translucent and may not readily be seen. In general, contrast material should be avoided due to the risk of aspiration and coating of the foreign body, which makes subsequent endoscopic retrieval difficult. CT scan is useful in selected cases but false negatives can occur with small or thin objects. In symptomatic patients and in those with suspected foreign body impaction in the esophagus, endoscopy should not be delayed despite a negative radiographic assessment [3].

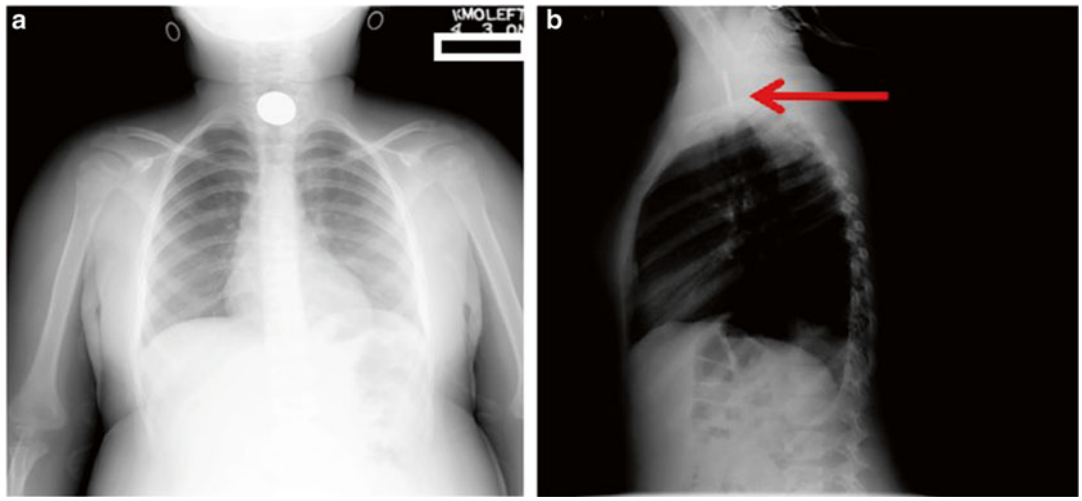

Fig. 7.2 (**a**) Posterior-anterior chest radiograph in a child shows a rounded metallic object (coin). (**b**) Lateral view confirms the object to be lodged in the esophagus (*arrow*), not the trachea

Management Overview of Specific Types of Foreign Bodies

The initial approach to ingested foreign bodies will depend on their type, size, and shape. Based on current guidelines and previous management algorithms by Selivanov and Henderson, an approach to ingested foreign bodies is proposed in Fig. 7.3 [1, 9, 10]. The management of specific types of ingested foreign objects is described below.

The type and timing of intervention is largely influenced by the patient's age, comorbidities, surgical history, clinical presentation, and location and characteristics of the ingested foreign body. Table 7.2 is a simplified matrix to guide the decision-making process in determining the timing of endoscopy based on the anatomical site of retention [1]. Most ingested foreign bodies can be retrieved via flexible endoscopy under moderate sedation. Foreign body retrieval under general anesthesia is generally required in small children, uncooperative patients, anticipated lengthy procedures, need to retrieve multiple ingested objects, and use of rigid endoscopes or overtubes. Objects impacted in the hypopharynx or cricopharyngeal region may best be managed by an otorhinolaryngologist using a rigid endoscope [7].

A number of endoscopic accessories should be readily accessible, including short and long (≥55 cm gastric length) overtubes, snares, forceps (e.g., rat tooth, alligator), baskets, retrieval nets, and a protector hood for sharp objects [1, 3]. If endoscopic retrieval is contemplated, practicing and planning of endoscopic maneuvers on similar objects before the actual procedure may be helpful in rehearsing the appropriate maneuvers and identifying the best accessories for successful extraction [11].

Blunt Objects

Coins are the most common blunt objects swallowed by children [12]. A coin impacted in the esophagus can be readily removed with a retrieval net, a basket, or an alligator or rat-tooth forceps. Indiscriminate removal of coins and other radiopaque esophageal foreign bodies with a balloon catheter under fluoroscopic guidance and without airway protection is not recommended. Because of the confined working space, objects in the esophagus may be difficult to grasp. They can be pushed into the stomach where they can be manipulated with ease and safely extracted afterwards (Fig. 7.4). If already in the stomach, coins and other small blunt objects (<2.5 cm in diameter) tend to pass through the pylorus and

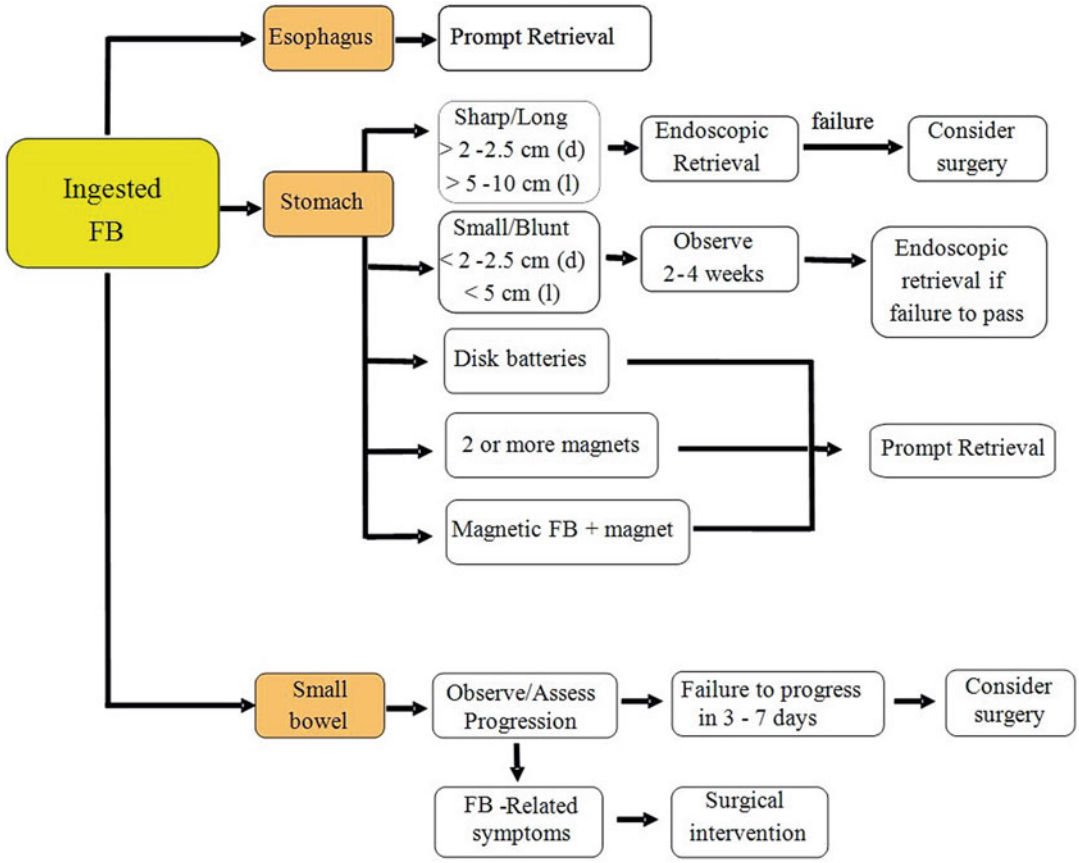

Fig. 7.3 Suggested management algorithm for ingested foreign bodies (FB) (*d* diameter; *l* length)

Table 7.2 Recommended timing of endoscopy for foreign body ingestion[a]

	Emergent endoscopy	Urgent endoscopy	Nonurgent endoscopy
Esophagus	– Completely obstructing food bolus – Disk batteries – Sharp-pointed objects	– Incompletely obstructing food bolus – Blunt objects – Magnetic objects	– Coins may be observed for 12–24 h before removal if asymptomatic
Stomach	None specified	– Sharp-pointed objects – Magnetic objects	– Objects >2.5 cm diameter – Disk and cylindrical batteries may be observed up to 48 h
Duodenum	None specified	– Sharp-pointed objects – Objects >6 cm length – Magnetic objects	None specified

[a]Adapted from Ikenberry SO et al. ASGE guideline: management of ingested foreign bodies and food impactions. Gastrointest Endosc 2011;73:1085–91. The exact timing of emergent and urgent endoscopy was not specified in the ASGE guideline. We define emergent endoscopy as within 1 h and urgent endoscopy as within 12 h of presentation

may progress down the GI tract uneventfully. A 2–4-week period of observation with interval radiographic imaging is suitable, unless the potential for small bowel retention exists, such as in patients with a history of intestinal obstruction, adhesions, or strictures [1]. It is reasonable to remove foreign objects in patients with prior GI tract surgery as adhesions may complicate safe

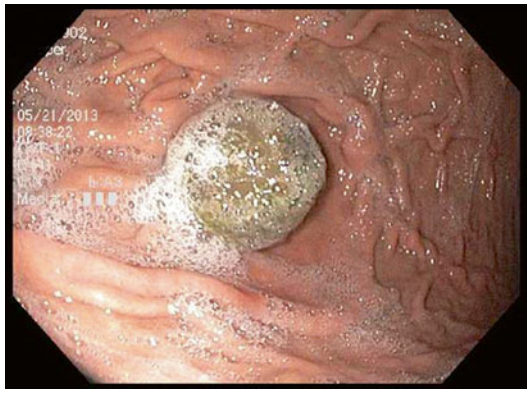

Fig. 7.4 Coin in gastric body

passage of ingested foreign bodies. Endoscopic retrieval is indicated for blunt objects that fail to pass the stomach after a week interval or in patients who are symptomatic [1].

Long Objects

Long objects (>6 cm), such as pencils, toothbrushes, spoons, and other plastic utensils, usually cannot pass through the duodenal sweep and should be endoscopically removed [13]. The use of any promotility agent to promote passage is not effective or safe in these cases. Retrieval of these objects can be challenging, particularly if the ends of the object are impacted against the gastric wall in a position perpendicular to the long axis of the esophagus. As a general approach, endoscopic retrieval of long objects may require patient repositioning, maximum air insufflation, and manipulation of the object with a large alligator forceps to free one of its ends so that it can be grasped with a snare, forceps, or basket, with or without the aid of a gastric-length overtube (Fig. 7.5).

Sharp Objects

This category includes items, such as fish bones, toothpicks, nails, needles, and open safety pins. These types of foreign bodies impacted in the hypopharynx or cricopharyngeus are best managed by an otorhinolaryngologist, using laryngoscopy or a rigid endoscope. For initial diagnosis, most metallic sharp objects can be demonstrated with either a chest or abdominal x-ray (Fig. 7.6). If x-rays are unrevealing as to the location of the object(s), endoscopy must be still performed to rule out an esophageal impaction in the presence of symptoms [14]. Any sharp-pointed object lodged in the esophagus should be removed without delay due to the high risk of complications, including perforation and fistula formation (e.g., aortoesophageal or bronchoesophageal fistula) [1]. Although most foreign bodies pass through the GI tract uneventfully, the incidence of perforation attributed to sharp-pointed objects has been as high as 35 % in reported case series [15]. For this reason, it is recommended that sharp objects be removed endoscopically from the stomach or duodenum, if feasible. If sharp foreign objects are beyond the reach of the endoscope and fail to progress through the remainder of the GI tract within 3–7 days, surgical exploration and retrieval must be considered [1]. Immediate surgical intervention is warranted if obstructive symptoms, bleeding, peritonitis, or perforation develops.

Batteries

Ingestion of batteries, especially disk batteries, represents an emergency that requires prompt endoscopic retrieval. Children are at highest risk of swallowing batteries with subsequent toxicity from chemical injury [16]. Batteries that are more than 20 mm in diameter can embed in the esophagus, cause liquefaction necrosis, and lead to fistula formation or perforation. This process can occur within hours after ingestion. In contrast to disk or button batteries, cylindrical batteries that have migrated into the stomach need not be removed unless they are several in number, they do not traverse the pylorus within 48 h (Fig. 7.7), or the patient becomes symptomatic [1, 17]. The use of Ipecac syrup to promote expulsion of the battery via vomiting is considered ineffective and unsafe. This may lead to migration and impaction of the battery from the stomach into the esophagus [1].

Magnets

Ingestion of magnets deserves special attention given its unique property to attract another magnet or other ingested metallic objects. The intraluminal attachment of magnetic objects may

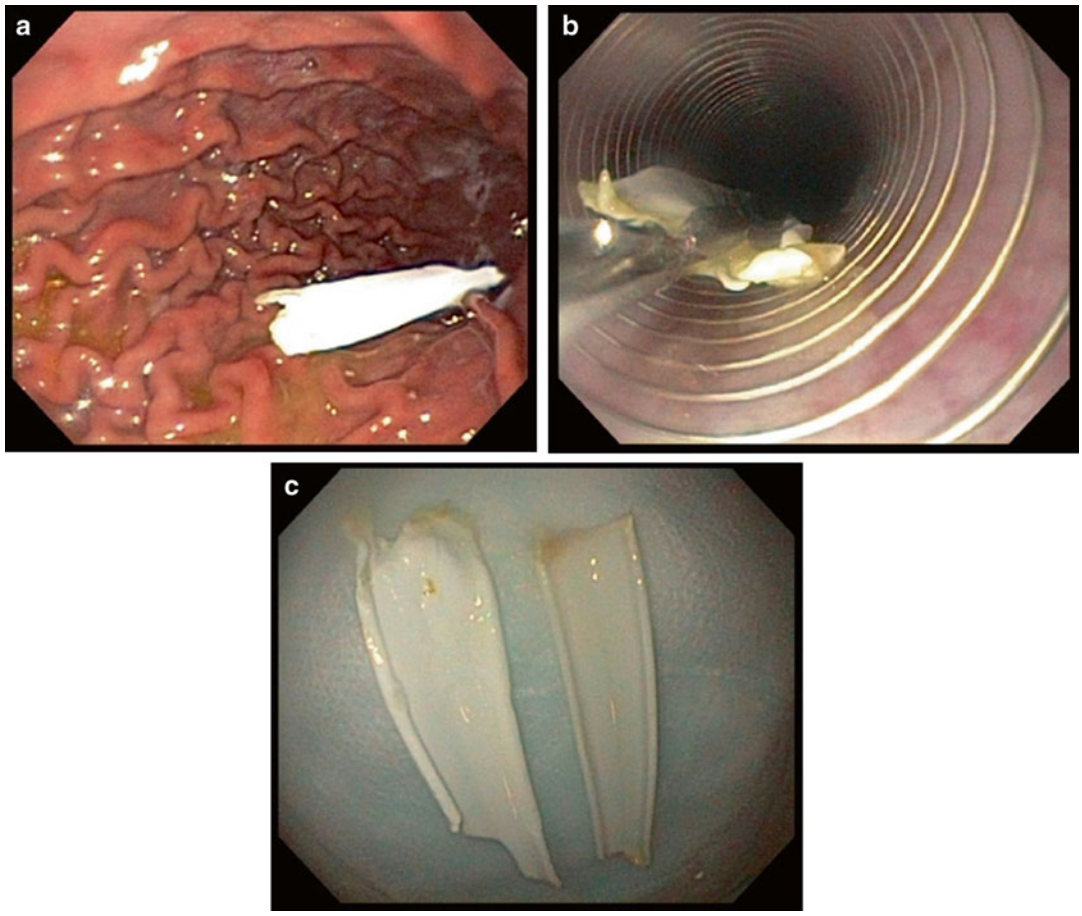

Fig. 7.5 (**a**) Fragmented pieces of a long plastic foreign body with sharp ends. (**b**) Safe extraction performed using a forceps through a gastric-length overtube. (**c**) Removed foreign body

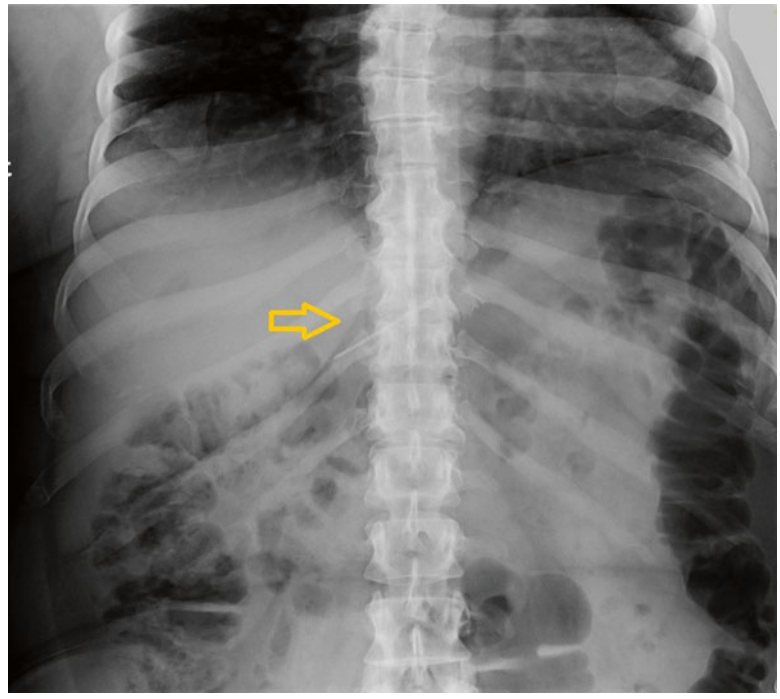

Fig. 7.6 Straight pin detected on abdominal x-ray

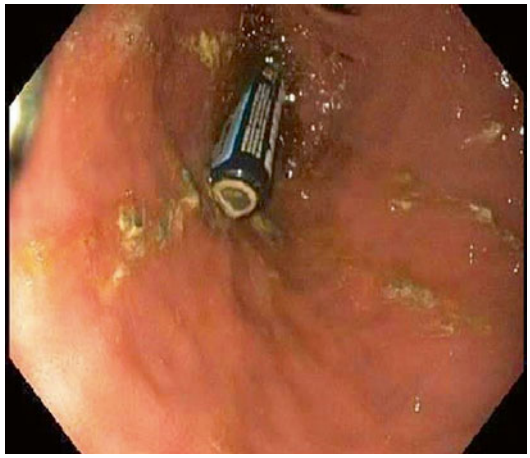

Fig. 7.7 Cylindrical battery retained in the stomach more than 48 h requiring endoscopic retrieval due to risk of chemical leakage

cause pressure necrosis in the intervening luminal tissue [18]. The degree of pressure necrosis will depend on the strength of the magnetic interaction. Multiple magnets clumped together will cause more serious consequences as compared to few magnets that are separated in different locations in the bowel. There are multiple case reports on complications related to magnet ingestion, including perforation, obstruction, fistula formation, volvulus, and GI bleeding [19–22].

A chest and abdominal x-ray should be obtained to verify the location and number of ingested magnet(s) and other metallic objects. Prompt removal is warranted if more than two magnets or other metallic objects are found in the esophagus or the stomach. A single small magnet may pass through the gut without causing problems. If several magnets are found in separate locations in the small bowel, the patient should be admitted and kept nil per os and undergo serial abdominal imaging. Surgical exploration and retrieval of the magnets should be performed with the onset of symptoms or failure to progress [23].

Drug Packets

"Body packers" are persons used to inconspicuously transport illicit drugs by ingesting packed substances [24]. A number of drugs have been smuggled this way, including cocaine, heroin, and ecstasy. Accidental leakage or rupture of drug packets can result in fatal toxicity. Nowadays, body packers are less prone to accidental packet leakage or rupture due to enhancements in the packaging process. Materials, such as latex, rubber, and other sealed wrappers, have been used for better handling. As a result, these drug packets are more likely to present with obstructive symptoms than toxicity [25].

Patients suspected or confirmed of body packing should be monitored for spontaneous passage of the packets. Diagnostic endoscopy may be helpful in selected instances, such as to document the presence of drug packets in the stomach when a high index of suspicion exists in the setting of an unreliable history and equivocal radiologic assessment. In asymptomatic patients, gut decontamination with activated charcoal and whole-bowel irrigation with a polyethylene glycol solution to promote evacuation are usually attempted [25]. Surgery is indicated in individuals with suspected packet rupture and cocaine toxicity, failure of the packets to progress, intestinal obstruction, or perforation [26]. Endoscopic removal of drug packets is ill advised as the risk of rupture during retrieval of the packets usually outweighs the benefit [27].

Lead

Ingestion of lead-containing products can cause acute lead toxicity and other chronic symptoms, such as abdominal pain, lethargy, and neurologic impairment, in addition to the risk of the actual foreign body ingestion [28]. Lead is particularly hazardous in children due to its toxic effects on the developing nervous system [29]. Common foreign objects with lead include lead weights, toys with leaded paint, and rifle pellets. There are multiple reports of ingestion of innocuous-looking products that are actually tainted with lead, resulting in lead poisoning in children [30–32]. After ingestion, the acidic gastric environment facilitates lead dissolution and absorption in the gut. Ingested foreign objects with high lead content in the esophagus or stomach should be removed to prevent further lead exposure.

Elevated blood lead levels have been reported within 2 h of ingestion [33]. While waiting for endoscopic retrieval, administration of a proton pump inhibitor may decrease the rate of metallic dissolution and lead absorption [34]. Blood lead levels should be measured if there is suspicion of acute lead poisoning, especially in children.

Small Intestinal Foreign Bodies

Once foreign objects have migrated into the small bowel, there is very limited medical intervention that can be done in case symptomatic retention or obstruction occurs. In select cases, deep enteroscopy (e.g., double-balloon enteroscopy) can be considered for retrieval of obstructing foreign bodies as opposed to surgery [35, 36]. The use of deep enteroscopy for retrieval of small intestinal foreign objects should be assessed on an individual basis. It may be a reasonable approach for attempted removal of a retained capsule endoscope, but not for a sharp-pointed object since reduction maneuvers during deep enteroscopy may actually instigate perforation by the object at the site of impaction. Intensive care monitoring and prompt medical (e.g., antidote) intervention may be warranted for foreign objects that may leach toxic substances, such as in the case of drug packets, to curtail potentially lethal toxicity [37].

Retained Capsule Endoscopy

Unlike other foreign body ingestions, capsule ingestion is intended to be a diagnostic procedure for small bowel diseases. Given its rising utility in clinical practice, a detailed discussion on retained capsule merits a separate section. Capsule retention can be confirmed by abdominal imaging at least 2 weeks after ingestion (Figs. 7.8 and 7.9) [38]. Capsule retention in the small bowel can be of significant concern due to its potential to cause intestinal obstruction. There is a wide range of reported incidence rates for capsule retention. Studies have reported incidence rates of 0–15 % depending on the patient population and indication for the procedure [39–41]. Capsule retention in the small bowel has been reported in patients with Crohn's disease, small bowel adhesions, NSAID-induced enteropathy, surgical anastomosis, small bowel tumors, and, rarely, radiation enteritis [41–43]. In the event of capsule retention, medical therapy is largely ineffective. Prokinetic agents as

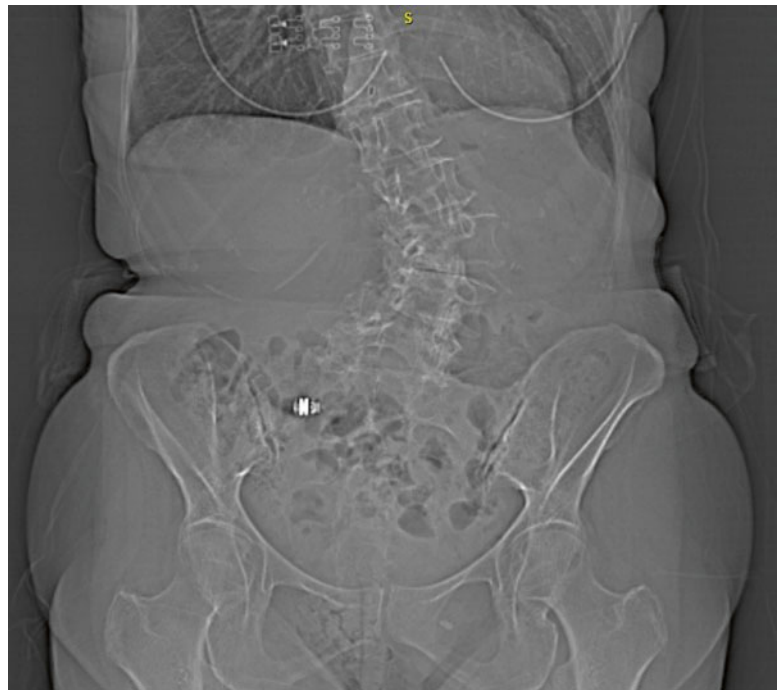

Fig. 7.8 Retained capsule on abdominal x-ray in a patient with NSAID-induced strictures

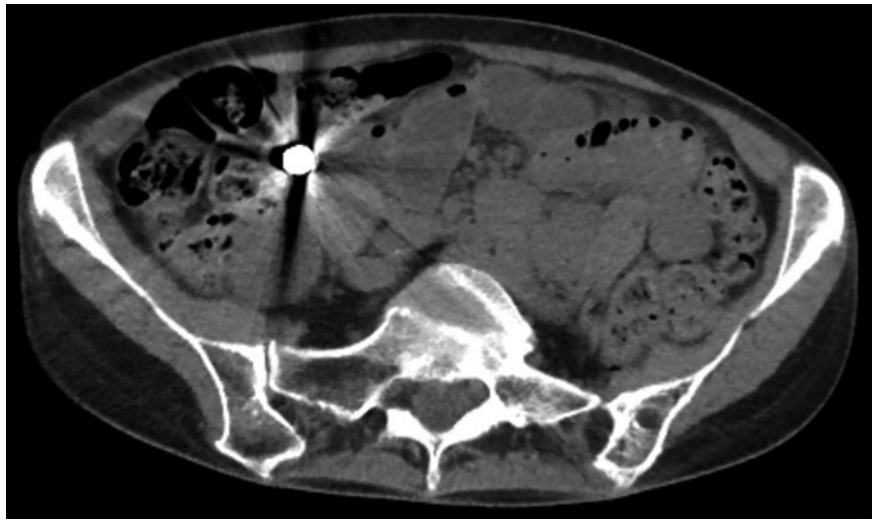

Fig. 7.9 Retained capsule on abdominal CT in a patient with an indeterminate stricture

well as treatment with infliximab for strictures associated with Crohn's disease have been tested with limited effectiveness [40, 41]. Endoscopic therapy, specifically double-balloon enteroscopy (Fig. 7.10 and Video 7.1), and surgery have been shown to be effective options for the retrieval of retained capsules [42, 44].

Food Bolus Impaction

Food bolus impaction is a common medical emergency. A survey from a national insurance database estimates an annual incidence rate of 13 per 100,000 with a male-to-female ratio of 1.7:1 [45]. The incidence seems to increase with age. Persons at risk for food impaction include those who are intoxicated, with swallowing disorders, difficulty in mastication, inadequate palatal sensation, and underlying esophageal motility disorder [46]. Impaction of food products (e.g., meat, nutshells, bones) and true foreign objects tend to occur at either physiologic and pathologic sites of narrowing or angulation in the esophagus [3]. The most common food bolus is meat based on several population-based surveys [6, 45].

Initial Assessment

The initial evaluation of most patients presenting with food bolus impaction is similar to that for foreign body ingestion. Special attention should be given regarding any underlying swallowing disorders. Prior history of intermittent food impaction in a young male with a history of allergies should raise suspicion for underlying eosinophilic esophagitis (Fig. 7.11) [47]. An elderly male with unexplained weight loss and progressive solid food dysphagia may prompt evaluation for an underlying esophageal malignancy or worsening esophageal strictures [48]. In contrast, a first-time episode of food bolus impaction while binging on alcohol is likely to be an acute event precipitated by intoxication [1].

Management

Radiographic assessment prior to endoscopy is recommended in cases where the food bolus may contain bone or sharp calcified fragments to prevent further injury during extraction [14]. Several pharmacologic agents have been tried to facilitate relaxation of the lower esophageal sphincter

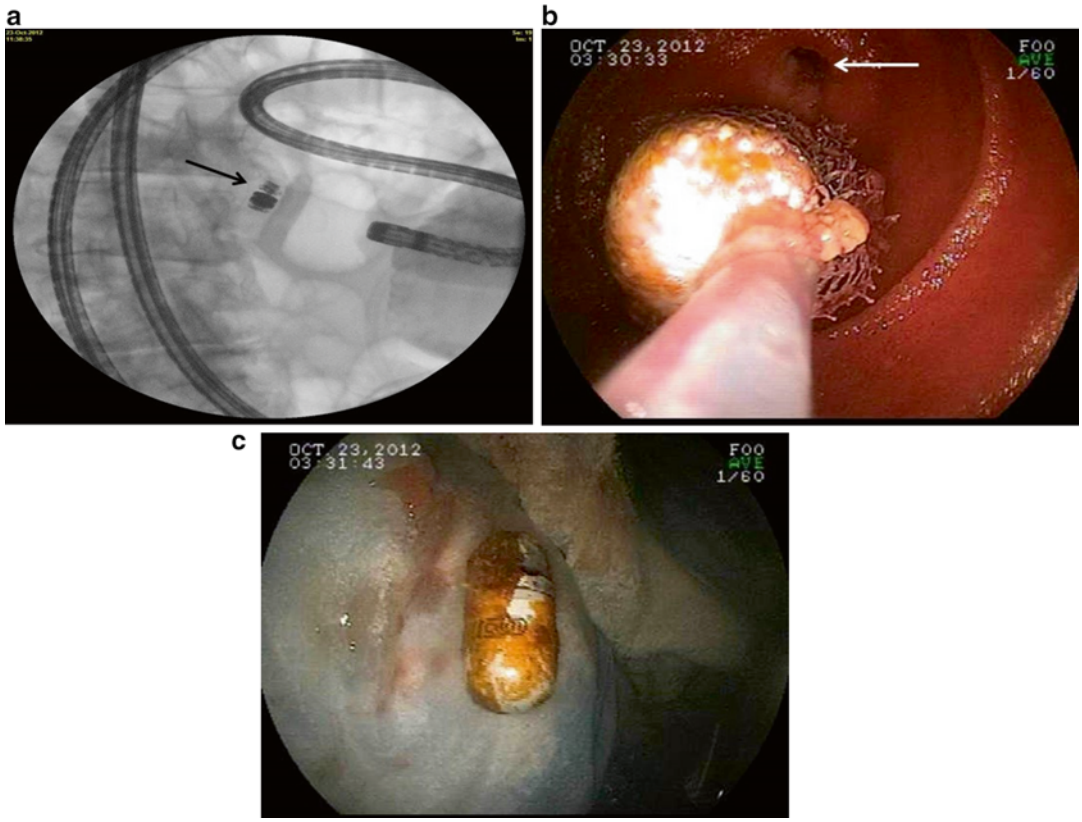

Fig. 7.10 (**a**) Fluoroscopic view of retained capsule (*arrow*) in ileum, accessed by a double-balloon enteroscope. (**b**) Capsule retrieval using a net with visualization of ileal stricture (*arrow*). (**c**) Retrieved capsule endoscope

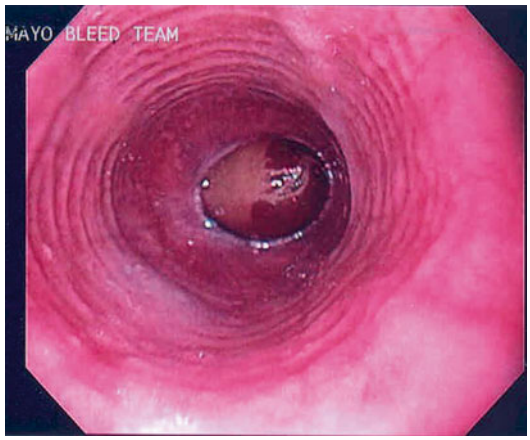

Fig. 7.11 Impacted grape at the gastroesophageal junction in the setting of eosinophilic esophagitis (feline esophagus)

and passage of an impacted food bolus. These include glucagon, nifedipine, sublingual nitroglycerin, and benzodiazepines. Among these, glucagon is the most widely used agent [49]. A trial of glucagon at a dose of 1 mg intravenously is generally safe to administer upon presentation [50]. If successful, the patient may be dismissed from the emergency department and scheduled for elective endoscopy to assess for an underlying esophageal pathology. The results have been mixed regarding the effectiveness of glucagon for food bolus impaction [51]. Patients who are unable to handle their oral secretions due to high-grade obstruction are unlikely to respond to glucagon and should undergo prompt endoscopy due to the risk of aspiration. Patients without distressing symptoms and high-grade obstruction may undergo endoscopy at a more convenient time within 12–24 h [3]. Postponing endoscopy to more than 24 h, however, may prolong the patient's anxiety and lead to maceration of the food bolus. This process can make en bloc retrieval of the fragmented bolus unfeasible.

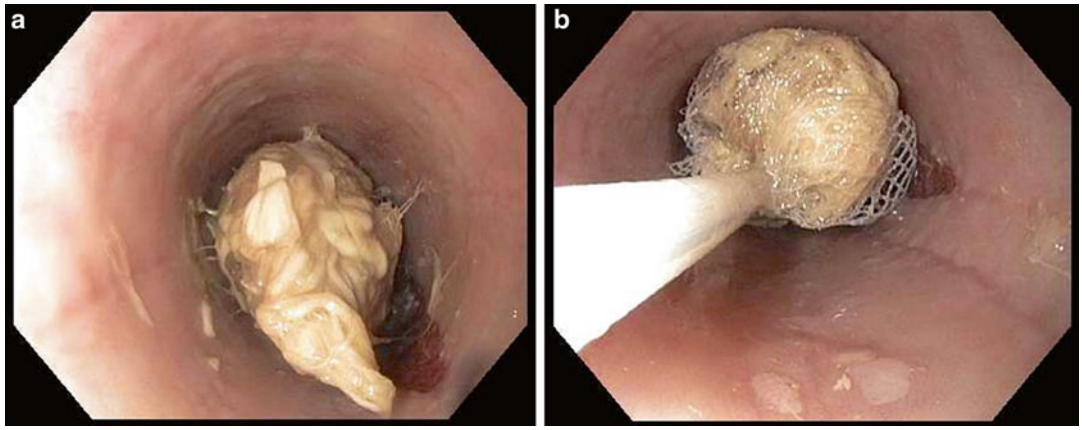

Fig. 7.12 (**a**) Food impaction in the distal esophagus. (**b**) Removal of food bolus using a retrieval net

Thus, it is our practice to perform endoscopy as soon as feasible upon the patient's presentation with food impaction.

At endoscopy, the location and characteristics of the food bolus should be noted. A bolus high in the esophagus can be problematic and the airway should be protected if a difficult disimpaction is anticipated. Most food impactions, however, are located in the distal esophagus. Glucagon can be repeated at this stage to reduce esophageal spasm and improve visualization [52]. A careful attempt can be made at maneuvering the endoscope around the food bolus and into the stomach. If successful, the cause of the obstruction can be assessed and the food bolus can be gently pushed into the stomach. Although reported as safe and effective, the non-fluoroscopic wire-guided Savary dilator push method and the practice of blindly pushing the bolus into the stomach should be performed with great caution due to the risk of perforation or deep mucosal tears [53, 54].

If the push technique fails or appears impractical, the food bolus can be safely extracted en bloc using a snare, basket, Roth net, or suction cap as long as it is solid and compact in its consistency (Fig. 7.12 and Video 7.2) [55]. If not, the food bolus can be retrieved in a piecemeal fashion using one or a combination of accessories (e.g., snare and/or wide-pronged forceps) with the aid of an overtube to allow for multiple passages of the endoscope. Following disimpaction, the cause for the obstruction should be examined. Dilation of strictures can be performed safely if reflux or stasis-induced esophagitis is mild. Otherwise, it is prudent to defer dilation for 2–4 weeks, at which time the inflammatory changes would have subsided, allowing for a more accurate assessment. During this time interval, patients are advised to eat slowly, chew well, and properly select their foods. A prescription for a proton pump inhibitor is also reasonable to help promote healing of any underlying esophagitis. Patients with documented eosinophilic esophagitis (EE) on biopsy should preferably be treated and followed on an outpatient basis as eosinophilic esophagitis tends to be a chronic relapsing disease [56]. Those patients with EE and recurrent food impaction or significant dysphagia despite medical therapy may undergo dilation, which should be performed carefully due to the increased risk for dramatic esophageal tears during dilation [57]. A suggested algorithm for the management of food bolus impaction is shown in Fig. 7.13.

Caustic Ingestions

The degree of caustic injury depends on the amount, concentration, and contact time with the corrosive substance [58]. The injury can be particularly severe in children. In contrast to adults whose ingestion of caustic substances is usually suicidal in intent, caustic ingestion in children is mostly accidental [59]. In 2009, a representative

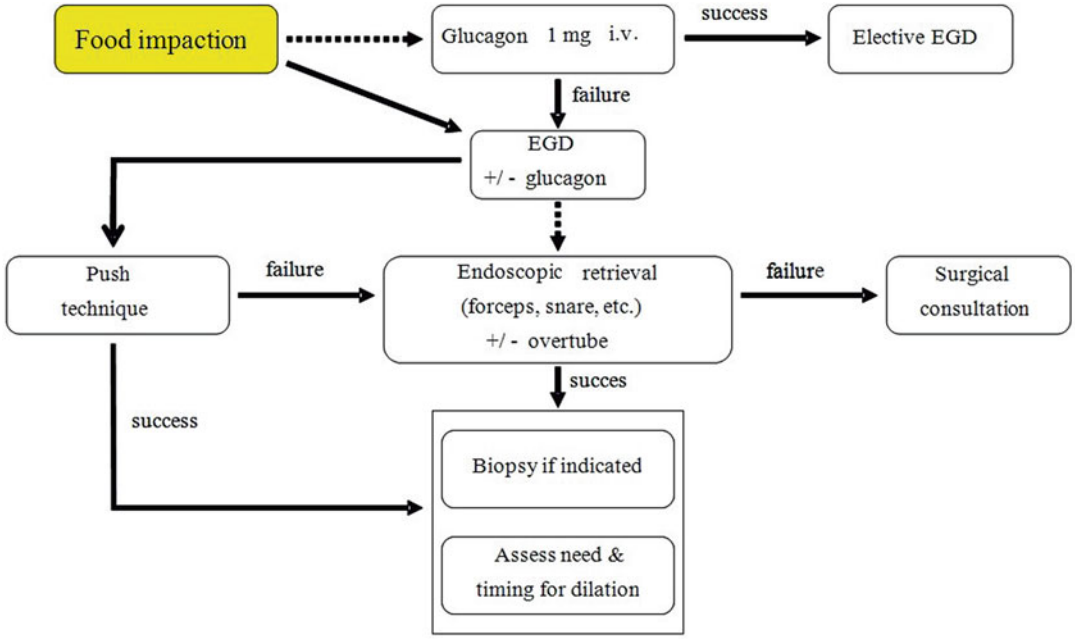

Fig. 7.13 Suggested management algorithm for food bolus impaction

sampling of a national hospital database approximated 800 annual pediatric caustic ingestions in the USA, which resulted in an economic burden of $22 million [60]. Caustic ingestions carry long-term health-care burden from late complications, such as oropharyngeal injury, esophageal strictures, fistulas, carcinoma, and pyloric stenosis.

Alkali and acid cause tissue injury by different mechanisms. Alkaline agents with a pH of 11 or higher cause the most severe injury through liquefaction necrosis [61]. Occasionally, penetration through the esophageal wall can occur due to liquefaction of the tissue structure, facilitating deeper organ damage [62]. Acidic solutions are corrosive and they cause injury by coagulation necrosis. The newly formed coagulum can attenuate further tissue destruction [63]. Therefore, acids generally produce less tissue damage compared to alkali substances.

Initial Assessment

Caustic ingestion can present with a wide range of symptoms. Some patients may even be asymptomatic after ingestion. More serious exposure may result in dysphagia and oropharyngeal or retrosternal pain. There may be hemoptysis, drooling, stridor, or hoarseness with involvement of the upper airways [64]. In the early phase of injury, the degree of tissue damage may not correlate with the symptoms. Epiglottitis may occur in toddlers in whom tracheal intubation may be required in order to protect the airway [65]. In extensive injuries, hemodynamic instability may develop [66]. The absence of oropharyngeal injury does not exclude the presence of upper GI tract injury. Flexible upper endoscopy is needed to assess the extent of injury within 24–48 h of ingestion (Video 7.3) [67]. The degree of injury can be classified using the Hollinger classification, which was developed to standardize endoscopic reporting in esophageal caustic injuries (Table 7.3 and Fig. 7.14) [68].

Table 7.3 Hollinger classification of esophageal caustic injuries

Grade	Endoscopic findings
0	Normal
I	Superficial mucosal desquamation and edema
II	Sloughing of mucosa with hemorrhages and exudates
III	Sloughing of tissue with deep ulcerations or necrosis

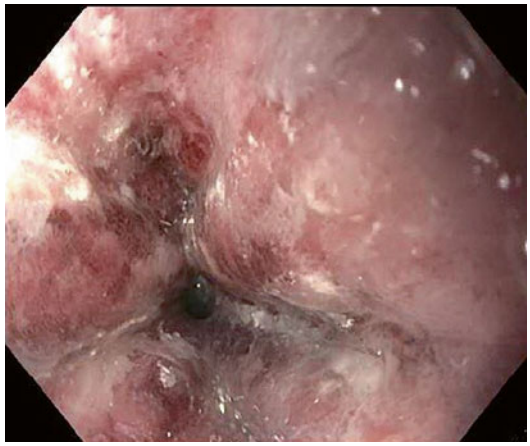

Fig. 7.14 Grade III esophageal caustic injury due to lye ingestion from suicidal intent

The timing of endoscopy is important as endoscopic evaluation immediately after ingestion may not reveal the actual extent of injury [69]. In contrast, endoscopy after 3–4 days may increase the risk of perforation in the setting of necrotic esophageal mucosa [70]. The development of hemodynamic instability, severe respiratory distress, or obvious oropharyngeal necrosis is a contraindication for performing endoscopy [67]. The role of radiologic imaging is mostly limited to the assessment of suspected perforation and for follow-up to detect stricture formation as a late complication of caustic ingestion [71].

Management

The current management strategies for caustic ingestion are largely conservative and based on clinical experience and published case series [72]. Many prefer to admit patients with caustic ingestion in a monitored setting, such as an intensive care unit. Patients should be kept fasting but with adequate intravenous hydration. Serial abdominal exam and chest and abdominal films should be performed while the patient remains in the critical setting. It is reasonable to start intravenous proton pump inhibitors to aid ulcer healing. In the initial hours of admission, the emphasis is to prevent aspiration and emesis. The use of emetics is not recommended as it would re-expose the esophagus and stomach to caustic injury. The use of neutralizing solutions has been associated with more thermal injury from chemical reaction, without any therapeutic benefit [73]. There is no consensus regarding the empiric administration of corticosteroids and broad-spectrum antibiotics. In general, nasogastric tubes are avoided as they may induce emesis and cause esophageal perforation with blind insertion into the damaged esophageal mucosa.

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8 Non-endoscopic Management of Acute Mechanical Colonic Obstruction and Pseudo-obstruction

Alison E. Oakes and John C. Fang

Introduction

Ogilvie's syndrome or acute colonic pseudo-obstruction was first described by Sir William Ogilvie in 1948 when he reported two patients with sudden onset of abdominal pain, constipation, and dilation of the large bowel. Both patients had retroperitoneal tumor invasion of the celiac plexus and prevertebral sympathetic ganglia. From this eponym, the definition has evolved to the clinical signs and symptoms of large bowel obstruction and colonic dilation on radiographic imaging, but without an identifiable source of mechanical obstruction [1–3].

In contrast, mechanical colonic obstruction is due to anatomic obstruction of the colon causing distension proximal to the blockage. Subsequent intestinal transit is impaired leading to clinical symptoms. Partial obstruction allows some gas and liquid stool to pass, while complete obstruction does not. Herein, we describe the presentation, diagnosis, evaluation, and non-endoscopic management of acute colonic pseudo-obstruction (ACPO) and mechanical colonic obstruction (MCO). The endoscopic management of these conditions is reviewed in a separate chapter.

Clinical Presentation

The clinical presentation of both conditions is similar. ACPO typically presents with abdominal pain and distension. Distension is progressive and the timing ranges from 24 h to 7 days before treatment is sought. Abdominal pain is typically non-colicky and may be only mild to moderate in severity despite significant distension. Nausea and vomiting are often present. Although patients generally complain of constipation, up to 40 % of patients may continue to pass stool or flatus [1–5].

In complete mechanical obstruction, the passage of fecal material is rare and these patients are often obstipated. In contrast to ACPO, abdominal pain is cramping or colicky in nature and more frequently localized in the hypogastric or periumbilical regions. Symptom course varies widely based on the etiology of obstruction. MCO due to malignancy or stricture can display a gradual progression with predominance of constipation and/or distension, while volvulus tends to be more sudden

A.E. Oakes, M.D.
Division of Gastroenterology, Hepatology and Nutrition, University of Utah School of Medicine, Salt Lake City, UT 84132, USA

University of Utah HSC,
30 N 1900 E, Salt Lake City, UT 84132, USA
e-mail: alison.oakes@hsc.utah.edu

J.C. Fang, M.D. (✉)
Division of Gastroenterology, Hepatology and Nutrition, University of Utah School of Medicine, Salt Lake City, UT 84132, USA
e-mail: john.fang@hsc.utah.edu

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in onset and acutely painful [5]. Sigmoid volvulus can present with intermittent pain reflecting spontaneous resolution and recurrence of volvulus [6]. Cecal volvulus can cause pain ranging from hours to days. Distension, nausea, and vomiting are also typical. When the obstruction is distal, nausea tends to occur later in the clinical course [7]; earlier onset nausea and emesis are more consistent with small bowel obstruction. Dehydration may result from emesis and/or poor oral intake.

On physical examination, bowel sounds may be present, absent, or abnormal with either pathology and are not particularly useful diagnostically. A palpable mass on rectal exam is concerning for rectal neoplasm causing obstruction, but this is rare. The presence of fever, abdominal rigidity, guarding, shock, or signs of sepsis is concerning for ischemia, peritonitis, and/or colonic perforation. Severe abdominal distension is seen more commonly in ACPO and can even cause respiratory compromise due to ventilatory restriction [1].

Table 8.1 Predisposing factors for acute colonic pseudo-obstruction (ACPO)

Predisposing factor	Percent of ACPO patients[a]
Surgery	35–52
OB/gynecology	9.8–10
Abdominal/pelvic	9.3–10
Orthopedic	7–7.3
Other (urologic, thoracic, neurosurgery)	11.8
Trauma	11–11.3
Infection	10
Cardiac	10
Neurologic	9–9.3
Medical conditions	30
Medications	
Electrolyte derangements	
Liver or renal failure	
Neoplasia	
Alcohol abuse	
Mechanical ventilation	

[a]Percentages do not sum to 100 % due to category overlap

Etiology and Predisposing Factors

Acute Colonic Pseudo-obstruction

Patients presenting with ACPO often have multiple predisposing factors and a single cause is challenging to identify. It is important to rule out toxic megacolon due to *Clostridium difficile* infection, which can present similarly [2]. Patients with toxic megacolon typically have numerous watery bowel movements, marked leukocytosis, and a history of recent antibiotic exposure or healthcare contact. Infection can be excluded by stool toxin or *C. difficile* PCR testing. As noted earlier, ACPO and MCO can be difficult to distinguish on clinical grounds and mechanical obstruction should be excluded before rendering a diagnosis of ACPO.

ACPO is responsible for about 20 % of all large bowel obstructions [3]. Pseudo-obstruction is more common in males older than age 60 and the risk increases with longer hospital stays. Numerous surgical, medical, and neurological conditions have been identified as predisposing factors, as well as certain medications and metabolic derangements (Table 8.1) [2–4, 8, 9]. The most common associated surgical factors include orthopedic and gynecologic surgery, trauma (surgical and nonsurgical), and burns [3]. Cesarean section and hip procedures are the most frequently implicated gynecologic and orthopedic surgeries, respectively [3, 5]. In a UK hospital, ACPO affected about 1 % of all post-orthopedic surgery patients. In this series, patients recovering from hip replacement represented about 60 % of ACPO cases, whereas knee replacement accounted for 30 % and lumbar decompression for 10 % of cases [10]. In another case series, over 50 % of patients had spine or retroperitoneal manipulations [8].

Predisposing medical conditions include systemic or intra-abdominal infection, myocardial infarction and congestive heart failure, alcohol abuse, liver or renal failure with related metabolic disturbances, diabetes, respiratory pathology (including pneumonia and mechanical ventilation), leukemia, retroperitoneal tumors or history of pelvic radiation, and herpes zoster infection. Less commonly associated factors include chronic neurologic conditions, such as Parkinson's disease, Alzheimer's disease,

Table 8.2 Medications associated with ACPO

Opiates
Anticholinergics
Histamine-2 blockers
Calcium-channel blockers
Tricyclic antidepressants
Phenothiazines (chlorpromazine, prochlorperazine)
Steroids
Epidural anesthesia
Antiparkinsonian drugs (dopamine agonists, anticholinergics)
Clonidine
Benzodiazepines

multiple sclerosis, and cerebrovascular accidents [2–5, 8, 11].

Medications that impair intestinal motility are often implicated in ACPO, including opiates, antihistamines, antipsychotics, tricyclic antidepressants, corticosteroids, and epidural anesthesia. In addition to Parkinson's disease being a risk factor for ACPO, drugs used to treat the condition, such as dopamine agonists and anticholinergics, have been linked to ACPO (Table 8.2). Metabolic derangements are commonly present in ACPO patients and may be inciting or aggravating factors. Hypothyroidism, hyponatremia, hypocalcemia, hypokalemia, hypomagnesemia, and elevated urea nitrogen have all been described in association with ACPO (Table 8.1) [2–5, 8, 11].

Mechanical Colonic Obstruction

The specific etiology of MCO is usually more definitive (Table 8.3). The most common cause is colorectal cancer, accounting for 33–60 % of mechanical obstructions [1, 12–14], with three-quarters of these cancers being adenocarcinomas [4]. Overall, 10–30 % of colorectal cancer patients will develop obstruction [1, 4, 15]. Volvulus causes about 10–15 % of obstructions and chronic diverticular disease (abscess and stricture) accounts for 10 % [15]. In addition to primary colorectal cancers, metastatic tumors to the abdomen, including ovarian and uterine cancers, can lead to extrinsic compression of the colonic lumen [14]. Benign strictures due to ischemia, diverticular disease, diverticulitis and inflammatory bowel disease (secondary to acute inflammation or chronic strictures), nonsteroidal anti-inflammatory agents (NSAIDs), and high-dose pancreatic enzymes can cause MCO [12, 15–19]. Intussusception, adhesions, hernia, fecal impaction, and endometriosis are less frequent causes [12, 15, 20]. Very rarely, infectious sources, including *Actinomyces*, *Taenia saginata*, botulism, and *Salmonella*, have been reported to cause mechanical colonic obstruction [15].

Table 8.3 Etiologies of mechanical colonic obstruction

Etiology	Percent of colon obstruction[a]
Primary colorectal cancer	53–60
Volvulus	15–17
Sigmoid	76
Cecal	22
Diverticular disease	10
Extrinsic tumor compression	6
Other	9
Ischemic stricture	
Anastomotic stricture	
Inflammatory bowel disease	
Intussusception	
Fecal impaction	
Adhesion	
Infection	

[a]Percentages do not sum to 100 % due to category overlap

Pathophysiology

Acute Colonic Pseudo-obstruction

The exact pathophysiology of ACPO has not been fully elucidated. In the gastrointestinal (GI) tract, parasympathetic innervation stimulates motility while sympathetic innervation inhibits peristalsis. Sir Ogilvie hypothesized that destruction of sympathetic ganglia caused relative parasympathetic overdrive leading to bowel spasm and clinical signs of obstruction [3, 8, 21]. In recent years, the successful treatment of ACPO with acetylcholinesterase inhibitors has substantially modified this original theory.

Acetylcholinesterase inhibitors prevent the breakdown of the enteric neurotransmitter acetylcholine, leaving more stimulatory neurotransmitter available at the synapse. This enhances blood flow and smooth muscle contraction, stimulating bowel motility [8, 21]. Thus, the success of acetylcholinesterase inhibitors in treatment of ACPO may imply that decreased parasympathetic innervation (rather than increased activity as Ogilvie first hypothesized) is the main factor resulting in ACPO. In a case series of chronic colonic pseudo-obstruction, biopsies showed reduced number of myenteric (parasympathetic and sympathetic inputs) and submucosal (parasympathetic) ganglion cells in 4 of 6 patients.

Rather than decreased parasympathetic input to the bowel, an alternative hypothesis is that ACPO results from increased sympathetic drive due to tonic hyperactivity of inhibitory neurons. Animal models of postoperative ileus show sympathetic overactivity and leukocyte migration into the lamina propria [3]. Taken as a whole, these findings support the presence of autonomic dysfunction and imbalance of sympathetic (antimotility) and parasympathetic (promotility) inputs to the large bowel in ACPO. In addition, the colocolic reflex may also play a role in persistence of ACPO. In this case, distension of the distal colon sends inhibitory signals to the proximal GI tract, further inhibiting motility [2]. Once distension has progressed, it may be more difficult to resolve due to this negative feedback inhibition.

Mechanical Colonic Obstruction

MCO is, by definition, mechanical or anatomic in nature, whether internal or external to the bowel lumen. Compromise of blood flow leading to ischemia can occur due to increased intraluminal pressure, twisting of the mesentery (as in volvulus), or direct extrinsic compression of the vasculature [15]. Local inflammation and edema can cause or contribute to mechanical obstruction, as in endometriosis, inflammatory bowel disease, diverticulitis, or diverticular abscess [12, 15].

Mechanisms of Injury

Patients with ACPO and MCO are at risk for ischemia and/or perforation as wall tension increases. With increasing wall tension, venous congestion occurs and results in impaired blood flow. As intraluminal pressures continue to rise above diastolic blood pressure, arterial flow slows. Ischemia results when pressures exceed systolic blood pressure and ischemic bowel tissue is predisposed to perforation. Luminal stasis can cause bacterial overgrowth and translocation through the gut lumen, which may lead to peritonitis in the absence of perforation [15]. Laplace's law states that wall tension is proportional to the intraluminal pressure and radius of the bowel [4, 15]. Therefore, the location at highest risk of perforation in ACPO is usually the cecum due to its larger diameter. However, there is an imperfect association with increased diameter and perforation and other factors, including the rate and duration of colonic dilation, are important as well [2]. In MCO, the presence of a closed-loop obstruction due to volvulus or obstruction with a competent/closed ileocecal valve is more likely to result in perforation due to increased intraluminal pressure [12].

Diagnosis and Evaluation

Radiographic imaging is .critical in the diagnosis and management of either type of colonic obstruction. In ACPO, plain abdominal X-ray typically reveals massive gas-filled dilation of colon without air-fluid levels and little or no small bowel dilation (Figs. 8.1 and 8.2). Stool and gas can be seen distal to the dilated segment since a mechanical obstruction is not present [22]. Careful attention should be paid to the amount of stool in the rectal vault to exclude distal stool impaction, which would be managed differently than ACPO. The cecum and right colon are usually the sites showing dilation of the largest diameter, averaging 10–16 cm on radiographs and conferring the highest risk of perforation due to Laplace's law [5, 23]. In MCO, plain abdominal films reveal dilation proximal to the obstruction with air-fluid levels in the colon and small bowel. Distal to the

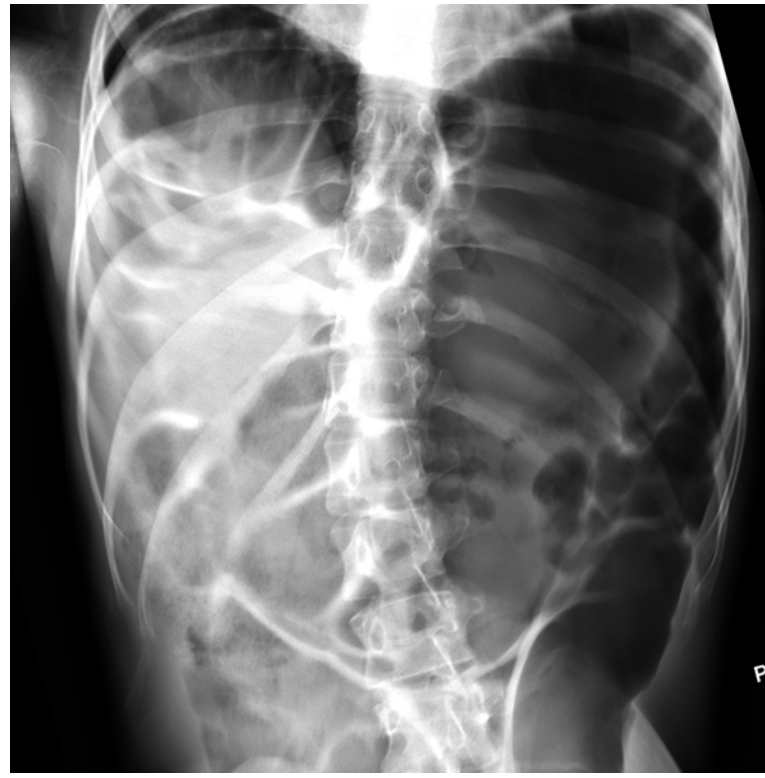

Fig. 8.1 Acute colonic pseudo-obstruction. Abdominal X-ray reveals diffusely dilated loops of small and large bowel

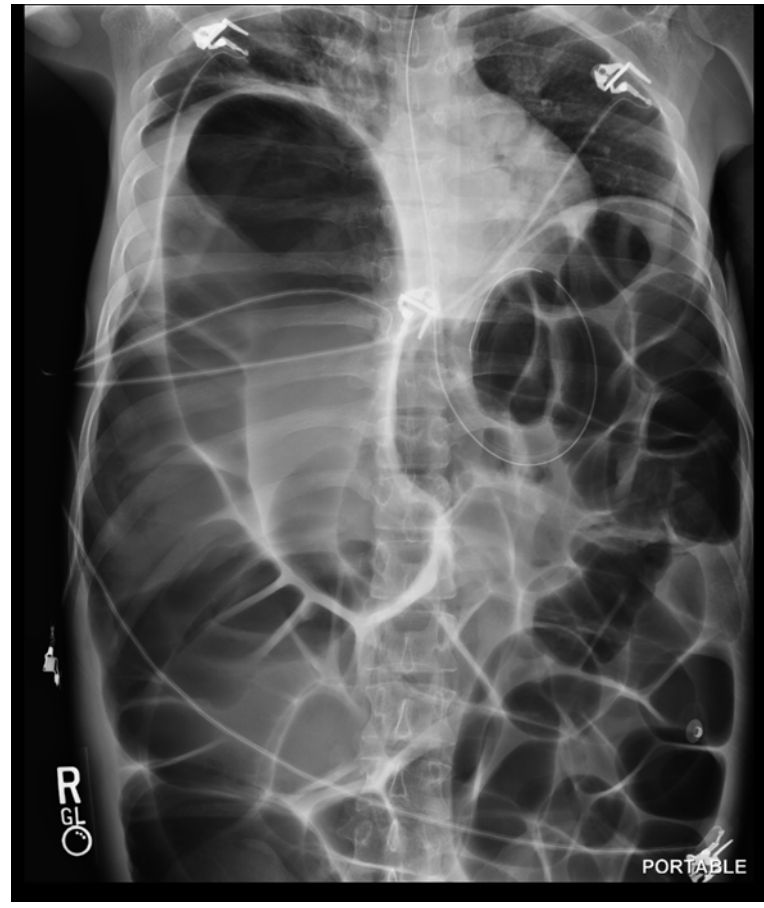

Fig. 8.2 Acute colonic pseudo-obstruction. Abdominal X-ray reveals diffuse gaseous distension of small bowel loops and colon causing diaphragm elevation bilaterally

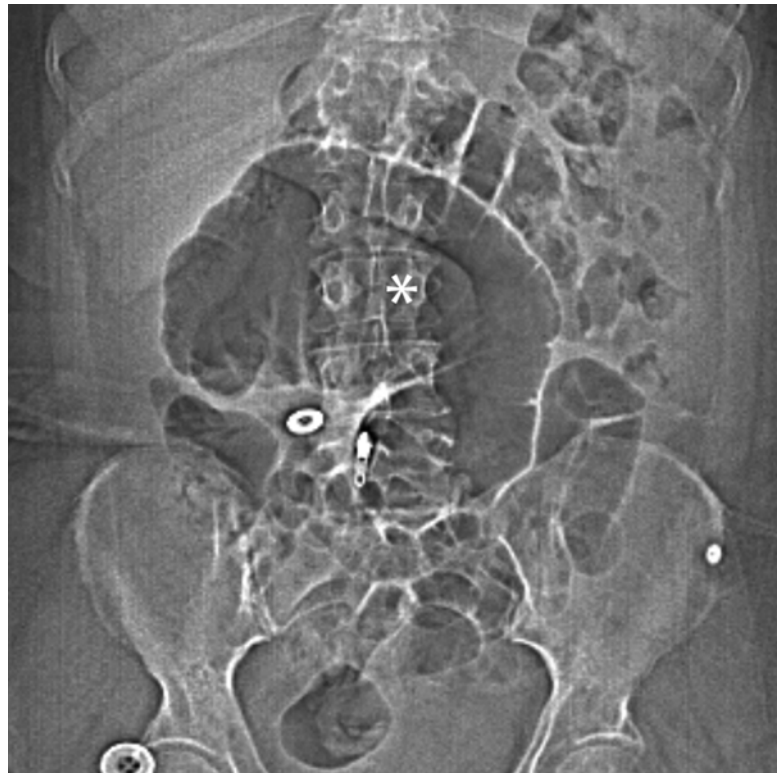

Fig. 8.3 Cecal volvulus. CT topogram with * indicating marked dilation of the cecum

obstruction, the colon is decompressed and devoid of stool and air [12]. Cecal volvulus typically displays a markedly distended loop of large bowel extending from the right lower quadrant to the epigastrium or left upper abdomen (Fig. 8.3). Sigmoid volvulus can present with an inverted-U or a coffee bean shape on X-ray due to massive dilation (Fig. 8.4) [24]. Upright abdominal and chest films are more useful than supine films in determining if free air due to perforation is present. If bowel ischemia is present, plain films may reveal thumbprinting due to mucosal edema and submucosal hemorrhage [5].

Unfortunately, plain radiographs have poor sensitivity in diagnosing colonic obstruction. In a study of 120 patients, the sensitivity was only 33 % while the specificity was 100 %; subsequent CT imaging increased the sensitivity to 67 % [25]. In another series of 140 cases, plain abdominal X-ray alone had an 84 % sensitivity and 72 % specificity for colonic obstruction [15]. Plain abdominal imaging may also not be reliable in differentiating between ACPO and MCO. In another series, 30 % of patients diagnosed with MCO on plain X-ray actually had ACPO, whereas 20 % of those diagnosed with ACPO had mechanical obstruction [15].

CT with oral or rectal contrast is advised in all suspected cases to differentiate ACPO from mechanical obstruction and to assess for evidence of complications (Fig. 8.5). Contrast CT studies have the added ability to characterize bowel mucosa for signs of ischemia or perforation [3]. Water-soluble contrast enema is preferred over barium enema due to the risk of barium impaction at the site of obstruction and barium peritonitis if perforation is present [4]. CT findings that are characteristic of ACPO include preserved haustral markings and luminal dilation in the absence of an obstructive lesion [23]. If mechanical colonic obstruction is present, the source is very likely to be seen on these studies (Fig. 8.6). Volvulus can be diagnosed by the presence of a bird's beak pattern on contrast studies. On CT imaging, sigmoid volvulus is characterized by limbs of the twisted loop con-

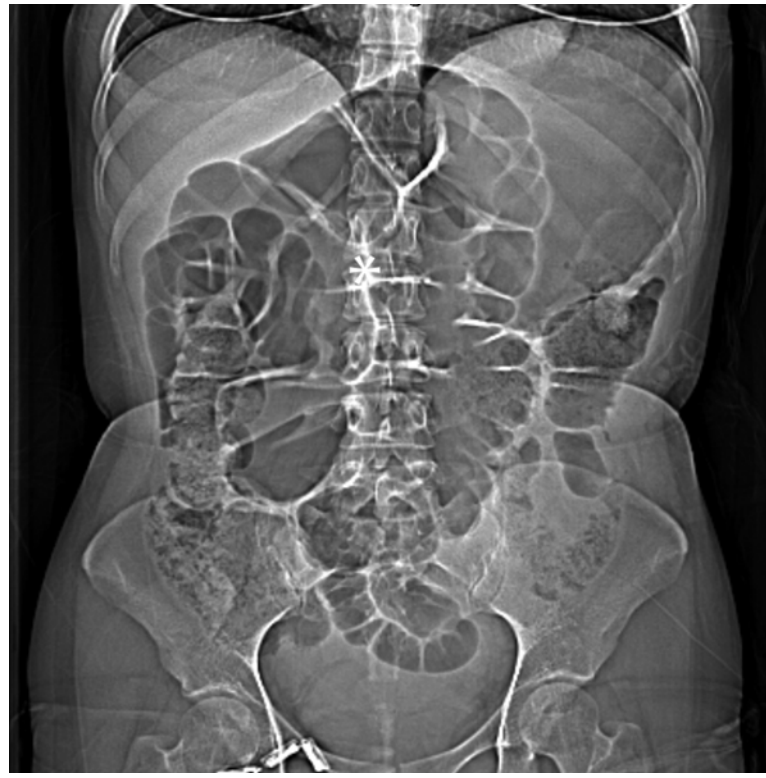

Fig. 8.4 Sigmoid volvulus. Abdominal X-ray with * indicates classic coffee bean appearance

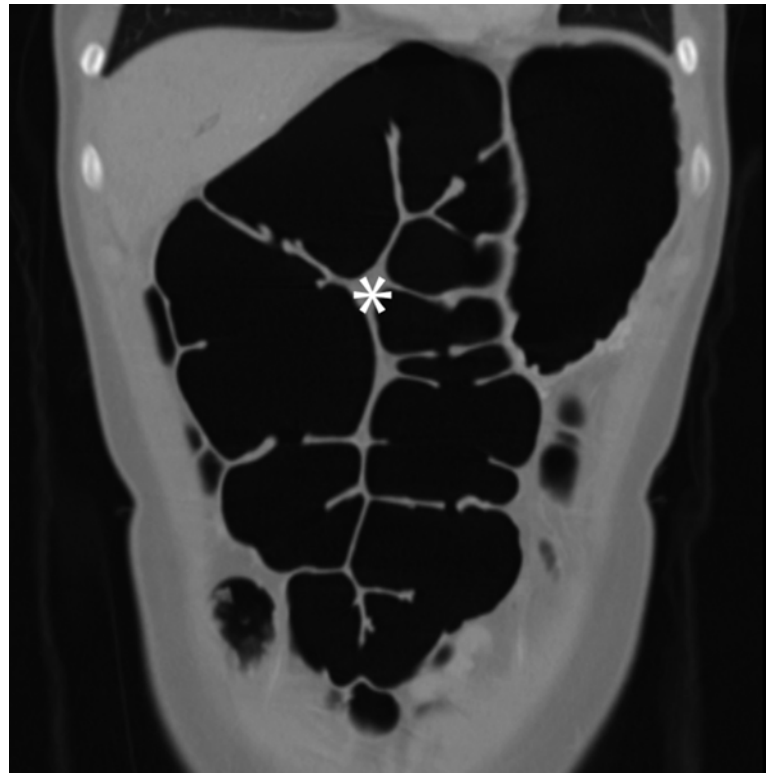

Fig. 8.5 Sigmoid volvulus. CT topogram with * indicates classic coffee bean appearance

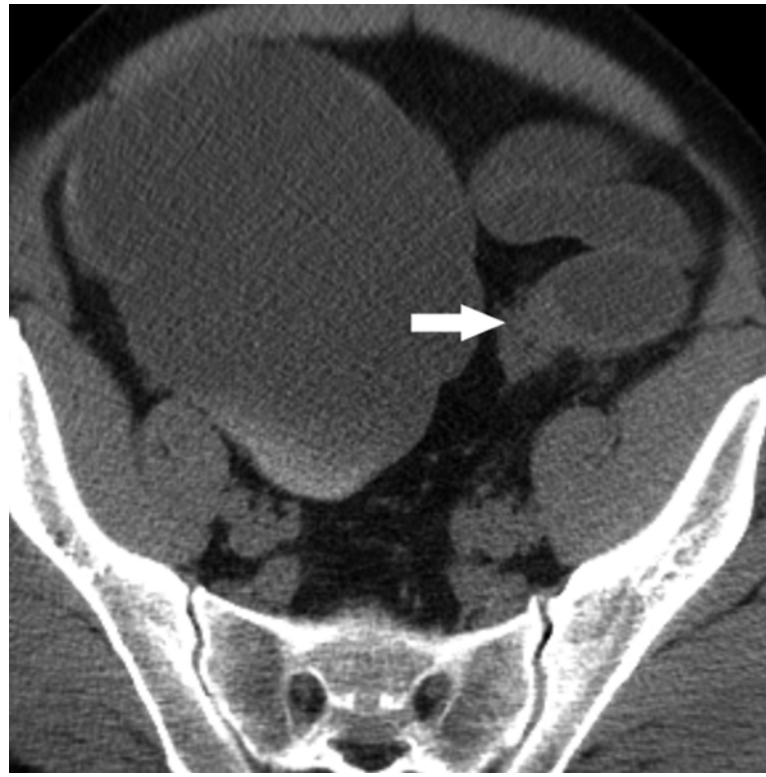

Fig. 8.6 Malignant sigmoid colon obstruction. CT with arrow indicating abrupt transition from dilated to decompressed sigmoid colon in the setting of cancer involving the proximal sigmoid colon

verging toward a fulcrum point, which appears as a "whirl sign" when the view plane is orthogonal to the rotation axis of the loop. In most cases, the whirl sign is found in the left lower abdomen with a craniocaudal axis (Fig. 8.7). The rectum and the upstream colon are usually flat, whereas the twisted loop is highly distended and located in the anterior part of the abdomen. Cecal volvulus is the torsion of a mobile cecum around its own mesentery, which often results in a closed-loop obstruction; twisted terminal ileum, distended cecum, and twisted ascending colon are seen. Cecal volvulus may occur by three mechanisms: type 1 develops from clockwise axial torsion or twisting of the cecum around its mesentery; type 2 loop volvulus develops from counterclockwise axial torsion of the cecum around its mesentery; and type 3 or cecal bascule involves upward folding of the cecum as opposed to axial twisting [24]. In most cases of cecal volvulus, the whirl sign is found in the right part of the abdomen with a lateral or an anteroposterior axis (Fig. 8.8). Pneumatosis or gas in mesenteric veins in concert with bowel wall thickening strongly suggests that bowel infarction has occurred [5, 24].

Management

Initial management of .ACPO and MCO is conservative unless there is significant concern for present or impending complications. Endoscopic interventions are central to the management of both MCO and ACPO and are detailed in a separate chapter. ACPO can often be managed conservatively, with reported success rates ranging widely from 20 to 92 % [2–4, 8]. Cases unresponsive to conservative measures after 24–48 h, symptom duration more than 3–4 days, and colonic diameter more than 10–12 cm warrant further treatment [8]. MCO can also be managed conservatively for a short time interval while preparing for more definitive endoscopic or

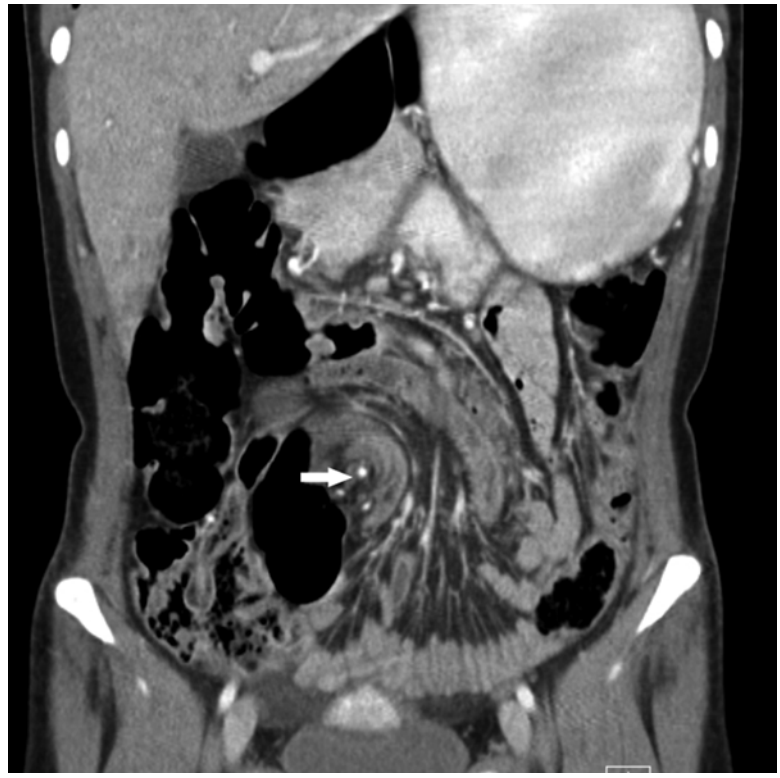

Fig. 8.7 Sigmoid volvulus. CT with swirling mesentery or "whirl sign" in the lower abdomen in the setting of a sigmoid volvulus

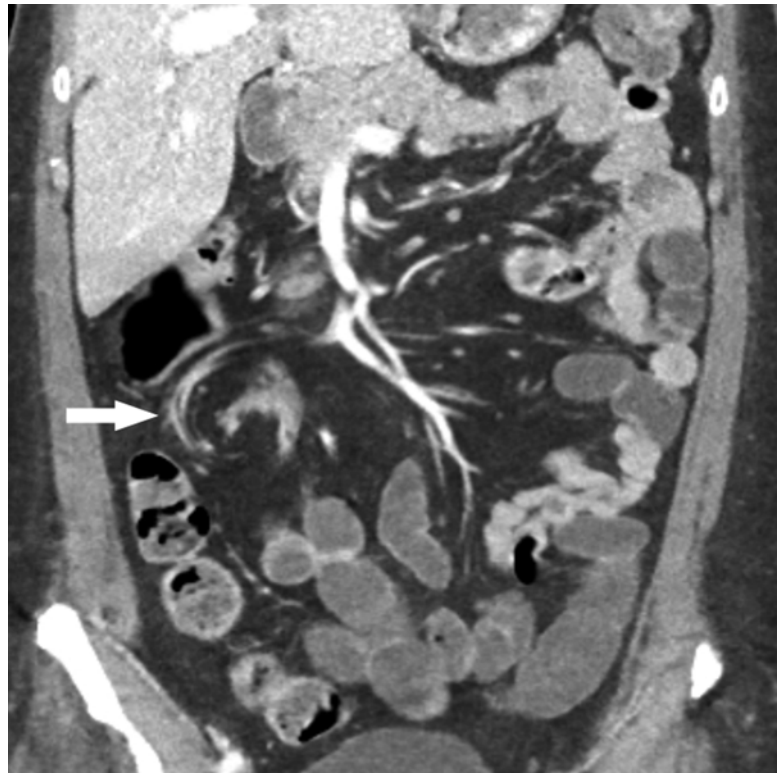

Fig. 8.8 Cecal volvulus. CT with arrow indicating swirling of the mesentery or "whirl sign" within the right lower quadrant of the abdomen

surgical therapy. Close monitoring with serial abdominal examination and plain abdominal radiographs obtained every 12–24 h should be performed to monitor for peritoneal signs suggestive of ischemia or impending perforation while conservative measures are being instituted [2].

Conservative Measures

Initial conservative management of ACPO consists of noting by mouth, intravenous fluids, placement of a nasogastric tube to intermittent suction for proximal decompression, and rectal tube placement to gravity drainage. Metabolic and/or electrolyte imbalances should be corrected and any underlying associated condition(s) treated. All medications that can worsen GI motility should be discontinued whenever possible [2, 3, 8].

Positional maneuvers are also advised, when feasible, including knee-to-chest position, prone position with hips elevated on a pillow, and hourly rotation to right and left lateral decubitus positions [4]. Laxatives should not be given to relieve constipation, specifically lactulose, as this sugar provides substrate for enteric bacterial fermentation and can worsen gas [8]. Water-soluble (e.g., Gastrografin) enema can be performed if there is concern for distal obstruction or fecal impaction; this will also act as a laxative agent to relieve fecal impaction, if present. Conservative management of mechanical colonic obstruction is similar except that rectal tubes are not indicated as the colon distal to the obstruction is typically decompressed [12, 14, 15].

Pharmacologic Therapy

The most effective pharmacologic treatment for pseudo-obstruction is neostigmine, an acetylcholinesterase inhibitor, with success rates ranging from 50 to 94 % (Table 8.4) [26–33]. The mechanism of action is thought to be indirect stimulation of muscarinic parasympathetic receptors in the gut [8]. Neostigmine has a rapid onset of action and the effect is short-lived. Intravenous (IV) dosing is advised due to variable oral absorption; doses range from 2 to 2.5 mg IV. In the setting of a partial response or relapse after an initial response, a second dose may be administered. The most common adverse effect is mild to moderate abdominal cramping and most common significant side effect is bradycardia. Neostigmine is contraindicated in the presence of mechanical bowel obstruction, perforation, pregnancy, arrhythmia, renal failure, and bronchospasm. Cardiac monitoring and atropine present at the bedside are recommended due to the possibility of bradycardia [21].

To date, there are no large studies on the utilization of neostigmine in pseudo-obstruction.

Table 8.4 Studies using neostigmine in the treatment of acute colonic pseudo-obstruction (ACPO)

Author	Study design	Dose (mg IV)	Responders n (%)	Time to response
Hutchinson and Griffiths [44]	Prospective cohort	2.5	8/11 (73)	Range 1–10 min
Stephenson et al. [45]	Prospective observational	2.5	12/12 (100)	Range 3–20 min
Turgano-Fuentes et al. [46]	Prospective observational	2.5	13/16 (81)	Range 20 min–4 h
Ponec et al. [27]	Randomized controlled	2	17/18 (94)	Median 3–4 min
Althausen et al. [47]	Prospective observational	2	6/7 (85)	5 min
Paran et al. [48]	Prospective observational	2.5	9/11 (81)	Mean 90 min
Trevisani et al. [49]	Prospective observational	2.5	26/28 (93)	Range 30 s–10 min
Abeyta et al. [50]	Retrospective observational	2	9/10 (90)	Mean 22 min
Loftus et al. [51]	Retrospective observational	2	11/18 (61)	30 min
Mehta et al. [30]	Prospective observational	2	16/19 (84)	Median 14 h
Tsirline et al. [29]	Retrospective observational	0.5–4	30/45 (67)	N/A

The only randomized, case-controlled study included 21 subjects with ACPO who were given 2 mg IV of neostigmine [27]. Efficacy endpoints were defined as passage of flatus/stool and improved abdominal distension. Ten of eleven patients in the treatment group achieved a clinical response with median time to response of 4 min. None of the 10 controls had symptom resolution. However, all 7 of the control subjects who were later treated with open-label neostigmine exhibited a clinical response. Overall, 17 of 18 (94 %) patients receiving treatment with neostigmine had rapid clinical improvement, characterized by passage of gas and stool and decrease in colon diameter by a median of 7 cm. Two of the seventeen responders had recurrent symptoms that required colonoscopic decompression, with one eventually requiring subtotal colectomy. Significant bradycardia requiring atropine administration was observed in 2 patients; other side effects were mild and included emesis, sialorrhea, and abdominal cramping. In one of the largest prospective observational study of neostigmine in ACPO, 26 of 28 ACPO patients given 2.5 mg IV neostigmine had total resolution of clinical symptoms within 10 min of administration.

Overall, neostigmine has been reported to be successful in 157 of 195 (81 %) patients with ACPO, with recurrence rates of 11–33 % [26–33]. However, one study found neostigmine to be much less successful than endoscopic intervention. In their retrospective observational study, a 75 % (39 of 52) success rate was seen with colonoscopic decompression compared to 56 % (25 of 45) in those who received up to 2 doses of neostigmine [29]. Postsurgical patients have been found to be more likely to respond to neostigmine compared to patients with electrolyte imbalances or those receiving antimotility agents [30].

Erythromycin is a motilin receptor agonist that stimulates GI motility. It can relieve ACPO at doses of 250–500 mg administered either IV or orally, though success with this agent is limited to anecdotal case reports and, thus, cannot be routinely recommended. Methylnaltrexone, a recently approved enteric specific opiate antagonist, has been reported to relieve ACPO in a patient who did not respond to 2 doses of neostigmine [31]. Further studies are required before this agent can be recommended [32]. One small, prospective, randomized, placebo-controlled trial reported that daily administration of polyethylene glycol solution significantly decreased the relapse rate (33 % vs. 0 %) after successful pharmacologic or endoscopic decompression [2]. There are case reports in patients with refractory ACPO demonstrating success with continuous infusion or daily scheduled neostigmine treatment [26, 33].

In the presence of colonic obstruction, opiates and anticholinergics can be used for pain relief, but may worsen motility. Antiemetics may be used, but metoclopramide is not advised due to its prokinetic properties. Corticosteroids have been shown to relieve nausea and inflammation but do not improve mortality. Small studies have also reported clinical improvement with administration of octreotide [14, 34].

Surgical Therapy

Surgical management of .ACPO is reserved for patients who fail medical and endoscopic management and for those who develop signs or symptoms concerning for peritonitis or perforation. Risk factors for perforation include the absolute size of colonic distension (>12–14 cm) and longer duration of illness (>2 days), but the most important factor may be the rate of cecal distension [5, 8]. Surgical options depend on whether perforation has occurred. If the bowel has not perforated, cecostomy or right hemicolectomy with primary anastomosis may be performed. If perforation has occurred, total colectomy with ileostomy and Hartmann's procedure may be required. Fortunately, surgery is rarely required and it carries greater morbidity and mortality than either medical or endoscopic treatment.

MCO is ultimately treated by surgical treatment of the anatomic abnormality. Right- and left-sided colonic tumors are treated with right and left hemicolectomy, respectively [1]. Diverticular strictures may be treated with either sigmoidectomy or left hemicolectomy depending

on the extent and severity of disease [15]. Sigmoid volvulus is best managed in clinically stable patients with initial endoscopic detorsion followed by surgical resection [35]. Recurrence rates for sigmoid volvulus are 50–60 %. If the patient is a good surgical candidate, elective resection can be undertaken with mesosigmoidopexy and primary anastomosis after successful endoscopic decompression [36, 37]. If gangrene and/or perforation has occurred, then a Hartmann's procedure may be required; bowel reanastomosis may be performed at a later date [1, 38]. The initial treatment of cecal volvulus is surgical detorsion with resection by right hemicolectomy or ileocolic resection [1]. Cecopexy or colopexy may also be performed [39]. Endoscopic detorsion of cecal volvulus is technically challenging with very high failure rates and is not routinely recommended [1]. As with ACPO, surgical intervention is also indicated for any cause of MCO whenever there is significant concern for ischemia, peritonitis, or perforation and after failed pharmacologic/endoscopic interventions [1, 12, 13, 15]. Finally, small case series have shown successful decompression with simple surgical loop colostomy for palliation in frail patients [13].

Interventional Radiology

Percutaneous intervention can be considered for patients who fail conservative, pharmacologic, and endoscopic measures and are poor surgical candidates. ACPO can be managed with percutaneous cecostomy performed either radiologically, surgically, or endoscopically. Radiologically placed cecostomy has been reported in case reports and small case series using fluoroscopic or CT guidance, with or without T-fasteners, with high success rates after failure of conventional treatment [40, 41]. MCO can be treated symptomatically with venting percutaneous gastrostomy tube placed radiographically or endoscopically [1, 12, 13, 15].

Complications

The most significant complications for both MCO and ACPO are ischemia and perforation. Perforation or ischemia occurs in 3–15 % of ACPO cases [8]. ACPO has an overall mortality of 25–31 % [3]. However, if complications develop, mortality increases to 40–50 % [2, 8]. Mortality as a result of MCO varies widely based on etiology, presence of complications, and patient comorbidities. MCO due to colon cancer carries a perforation rate of 1–11 % and mortality rates ranging from <1 % to 50 %, depending on comorbidities [1, 42]. In sigmoid volvulus, gangrenous colon is present in 10–20 % of patients, with reported mortality rates of 12–45 % [42, 43]. In a case series of cecal volvulus, perforation and gangrenous colon were present in about 20 % of cases with an overall mortality of 17 % [7, 43].

Conclusion

Acute colonic obstruction is divided into ACPO and MCO. Both conditions may present with similar clinical features. Radiologic imaging is essential for both diagnosis and differentiation of ACPO and MCO. The evaluation and management of ACPO include careful review and modification of predisposing factors, metabolic derangements, and medications that impair motility. Endoscopic and surgical interventions are often definitive therapy for colonic obstruction from either ACPO or MCO, though conservative measures and pharmacologic treatment may be employed as adjuncts or prior to these more invasive interventions. Surgical and interventional radiologic management are also employed for endoscopic failures or when complications occur. An algorithmic approach to the management of acute colonic obstruction is proposed (Fig. 8.9). A multidisciplinary approach that involves gastroenterologists, surgeons, and interventional radiologists enables optimization of patient care and outcomes.

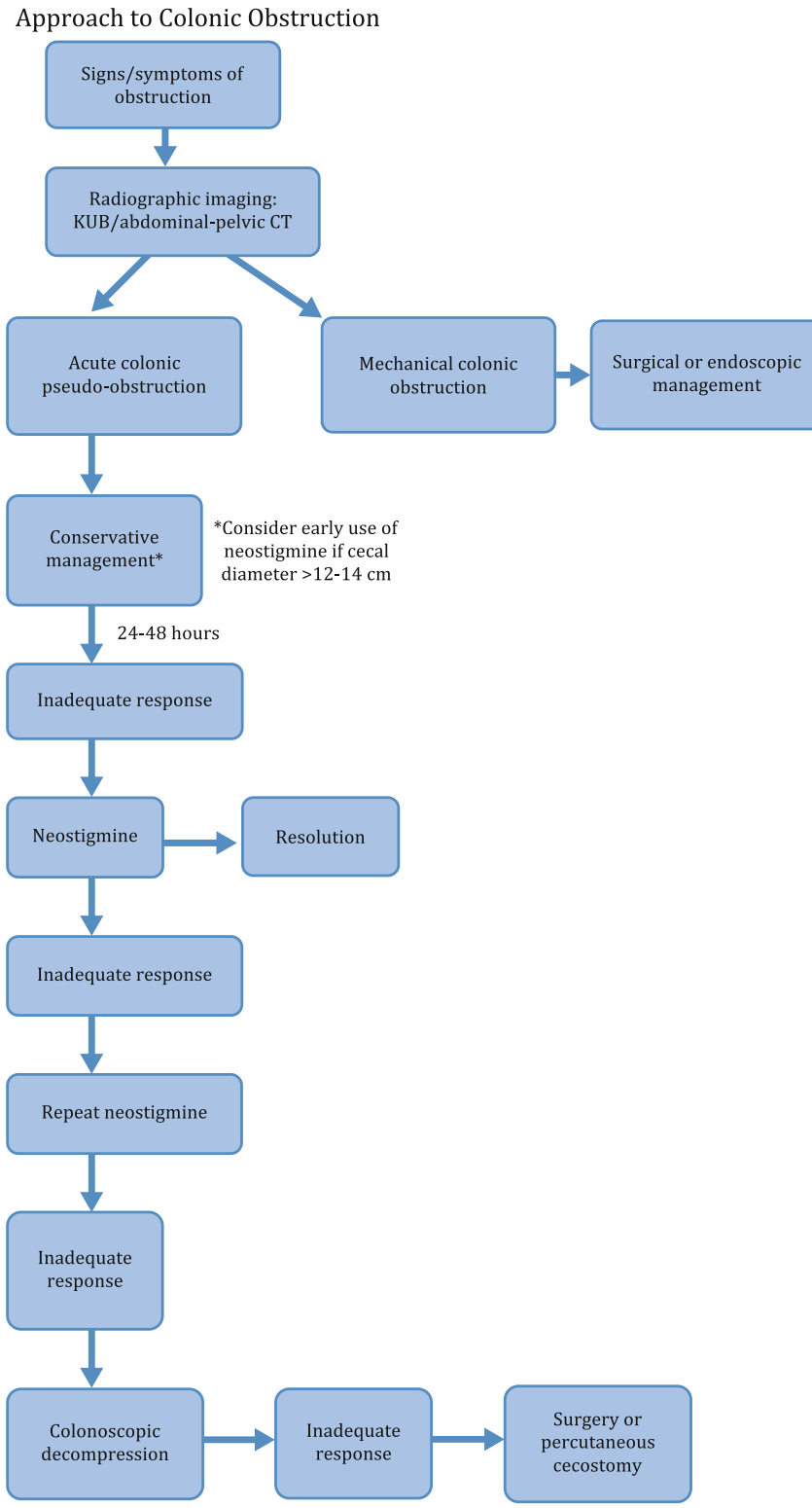

Fig. 8.9 Algorithmic approach to the management of acute colonic obstruction

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Approach to Acute Cholangitis

9

Bryan L. Balmadrid and Shayan Irani

Introduction

Acute bacterial cholangitis is a bacterial infection of the biliary tree classically presenting as fever, jaundice, and abdominal pain. Jean-Martin Charcot (1825–1893) first described this triad of symptoms as associated with biliary infection [1]. Herein, the pathogenesis, clinical features, diagnosis, and management of acute bacterial cholangitis, with emphasis on antimicrobial therapy, are discussed. The endoscopic therapy of acute biliary obstruction is highlighted, but discussed in more detail in a separate chapter.

Pathogenesis

The pathogenesis of acute cholangitis involves bacterial invasion into the biliary system, leading to infection. There are protective mechanisms in place to prevent this, as well as risk factors that compromise these mechanisms.

Normally, bile is sterile, and there are several mechanisms protecting it from invasion by intestinal bacteria (Table 9.1). The sphincter of Oddi acts as a gross mechanical barrier to prevent reflux into the biliary system, while the tight junctions between hepatocytes serve as a barrier at the cellular level. The continuous bile flow and biliary mucus prevent bacteria from adhering to the bile duct wall. Bile salts have a bacteriostatic effect. Kupffer cells in the liver and immunoglobulins (specifically IgA) provide an immunological barrier [2]. Normal intraductal biliary pressure ranges between 7 and 14 cm of H_2O, but can rise upward of 20–30 cm of H_2O in biliary obstruction. This can disrupt the host protective mechanisms by adversely affecting the hepatic tight junctions, bile flow, Kupffer cell function, and immunoglobulin A production [2]. High pressures, along with bacterial colonization, can lead to cholangiovenous reflux of infected bile and endotoxins, leading to bacteremia and potentially sepsis [3, 4]. Less commonly, high biliary pressures can lead to bacterial migration from the portal circulation into the biliary tract and cholangitis [5].

Bacterial colonization (bactobilia) most commonly occurs in an ascending manner from the small bowel and less frequently from hematogenous spread via the portal vein. Foreign bodies, such as stones and stents, in the biliary tree can serve as a nidus for bactobilia (Fig. 9.1). Biliary lithiasis, the most common cause of acute cholangitis in Western countries [6], acts both as a bacterial and an obstructive source [7, 8].

Biliary stasisalone can lead to bacterial colonization and stone formation. Fibrocystic

B.L. Balmadrid • S. Irani (✉)
Department of Gastroenterology, Virginia Mason Medical Center, Buck Pavillion 3rd Floor, Seattle, WA 98101, USA
e-mail: shayan.irani@vmmc.org

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Table 9.1 Protective mechanism from acute cholangitis

Protective mechanism	Risk factors compromising protective mechanism
Mechanical	
Sphincter of Oddi	Sphincterotomy, biliary stents
Tight junction	Increased intrabiliary pressures
Bacteriostatic	
Bile flow	Increased intrabiliary pressures
Bile mucus	Bile stasis
Bile salts	–
Immunologic	
Kupffer cells	Increased intrabiliary pressures
Immunoglobulin	Increased intrabiliary pressures

diseases of the liver, such as choledochal cysts (types I–V), are especially prone to developing biliary stasis (Fig. 9.2). The cyst wall is composed of dense fibrous tissue, with little or no muscle or elastic tissue, and is often without an epithelial lining.

Both benign and malignant strictures can increase the risk of developing acute cholangitis in the right setting. Malignant and benign strictures alone are infrequently the cause of cholangitis. However, these pathologies usually lead to interventions (e.g., contrast injection, stent placement), which can lead to bacterial infections (Fig. 9.3). Other risk factors that increase the susceptibility to cholangitis include advanced age (>70 years) and smoking [9].

Bacteria have been isolated from gallstones to study their role in the pathogenesis of acute cholangitis. Organisms grown in culture from brown pigment stones are those commonly seen in cholangitis (enterococci—40 %, *Escherichia coli*—17 %, *Klebsiella* species—10 %) [10]. *Escherichia coli* is a coliform bacterium with external pili that facilitate adherence to foreign bodies, such as stones and stents. It is the most commonly isolated organism (25–50 %). Other coliform organisms include *Klebsiella* (15–20 %) and *Enterobacter* species (5–10 %) [10]. Enterococcal species are the most common gram-positive organisms identified (10–20 %). Anaerobic organisms, such as *Bacteroides* and *Clostridia*, are rare and usually seen in the setting of a mixed infection. These organisms are also more likely present in the setting of repeated infections and prior biliary surgery and among elderly patients (Table 9.2) [11]. Cultures from bile stones or occluded stents are positive in >90 % and are often polymicrobial relative to blood cultures obtained in patients with acute cholangitis [6, 12].

Clinical Manifestations

The clinical presentation of acute bacterial cholangitis ranges from mild illness to septic shock. Fever is the most common clinical symptom, followed by right upper quadrant abdominal pain and jaundice (Table 9.3). However, the classic Charcot's triad occurs in only 50–75 % of patients [6]. It is seen less frequently in the elderly and immunocompromised patients [13]. Hypotension and altered mental status occur in less than 14 % of patients and suggest suppurative cholangitis, which is associated with morbidity and mortality rates as high as 50 % [14]. The addition of hypotension and altered mental status to Charcot's triad is known as Reynolds' pentad.

Acute renal failure and intrahepatic abscesses are the two most common complications of cholangitis, with abscesses usually occurring later in the course of the disease [15]. The 30-day mortality of ineffectively treated patients with cholangitis approximates 10 % [16]. In a study assessing 449 episodes of cholangitis over 20 years, seven factors were found to independently predict mortality: acute renal failure, female gender, age, cholangitis associated with liver abscess or cirrhosis, and cholangitis secondary to high biliary strictures or after transhepatic cholangiography [17]. Further risk factors predicting complications and overall mortality are addressed below.

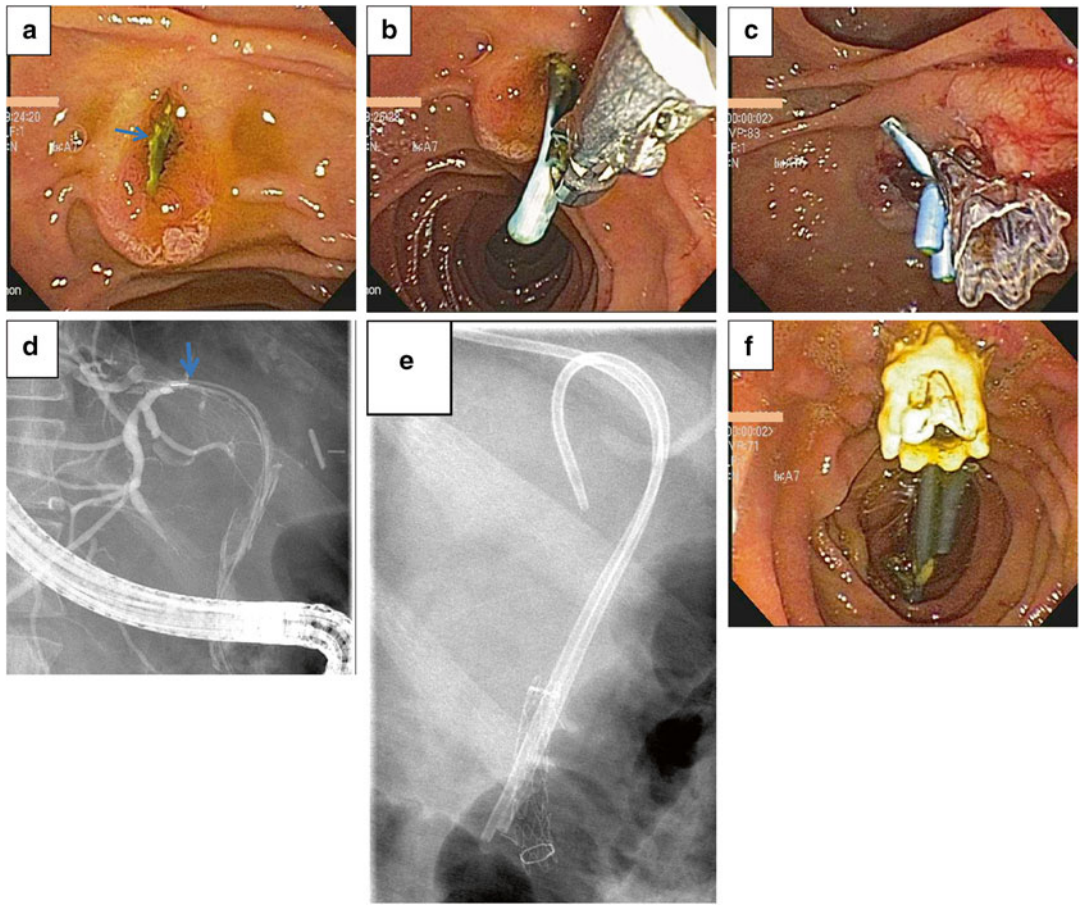

Fig. 9.1 (**a**) Proximally migrated plastic biliary stents causing biliary obstruction, resulting in cholangitis. (**b**) Migrated stents removed with a rat-toothed forceps. (**c–e**) Two plastic stents placed into the left intrahepatic duct beyond hilar stricture (*arrow*) followed by a fully covered self-expandable metal stent to anchor the plastic stents and prevent recurrent proximal migration. (**f**) Some distal migration of plastic stents noted at 4 months, although they still functioned well

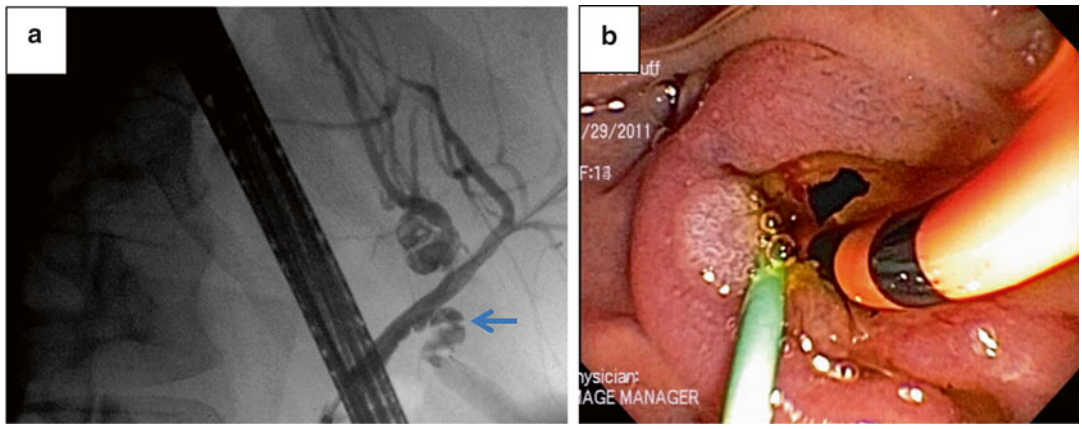

Fig. 9.2 (**a**) Type 5 choledochal cyst (Caroli's disease) involving segment 8 of the liver (*arrow points to the cystic duct*). (**b**) Multiple intrahepatic *black pigment stones* removed. Surgical resection of the affected liver segment was performed subsequently with resolution of recurrent bouts of cholangitis

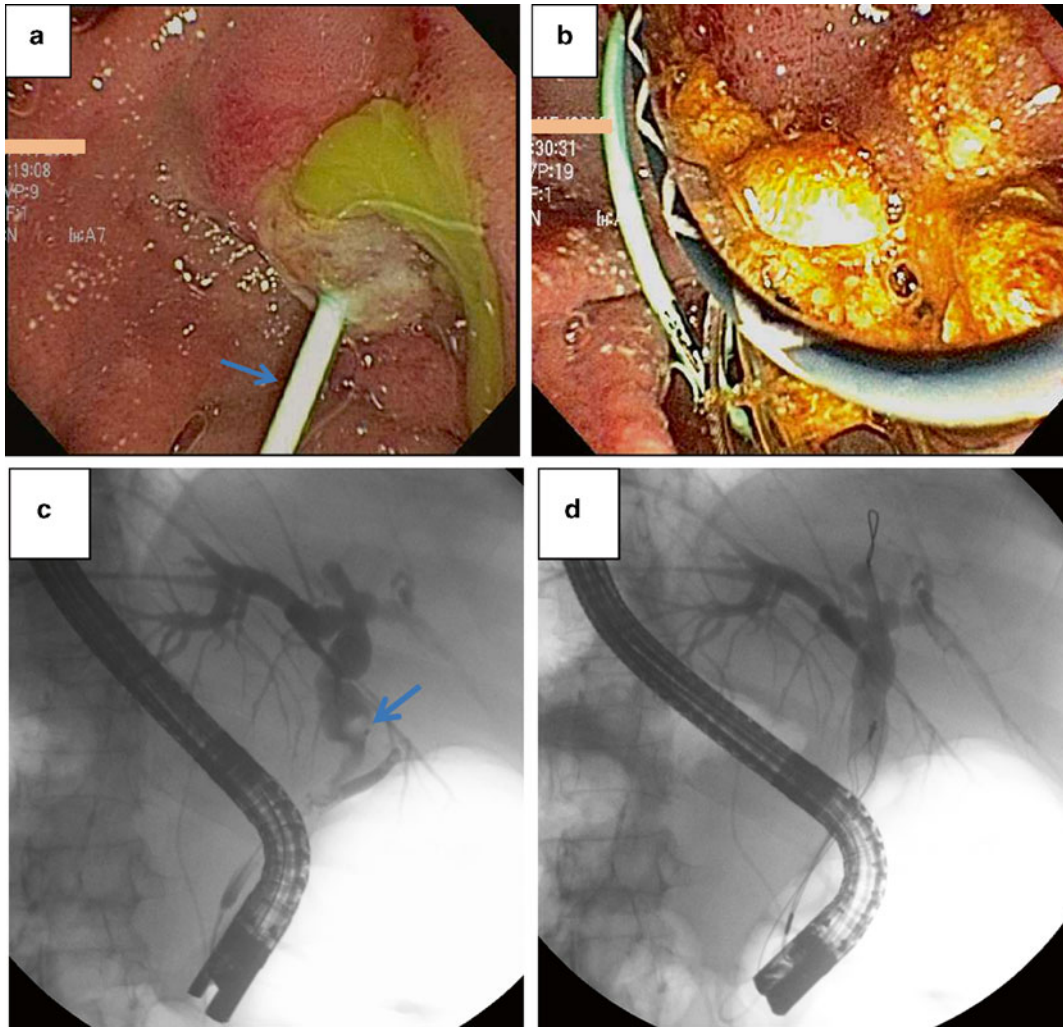

Fig. 9.3 Patient with a prior orthotopic liver transplant on immunosuppression presenting with cholangitis after a recent ERCP. (**a**) Note prior pancreatic stent (*small arrow*) with purulence emerging from biliary sphincterotomy. (**b**) Anastomotic stenosis and proximal choledocholithiasis (*arrow*) at choledocho-choledochostomy. (**c** and **d**) Stone removal with extraction basket followed by 10 mm fully covered self-expandable metal stent placement (not shown) to treat the anastomotic stenosis

Diagnosis

Laboratory Tests

Laboratory results help distinguish a biliary source of sepsis from other causes. Eighty percent of patients will have a serum bilirubin greater than 2.0 mg/dL [18]. However, a normal bilirubin does not rule out acute cholangitis, especially early in the disease process. Eighty percent of patients will have an elevated white blood count (WBC), and, in those with a normal WBC, the peripheral blood smear usually reveals a "left" shift to immature neutrophils. A classic cholestatic pattern with elevations in the serum alkaline phosphatase from biliary origin is seen in the majority of patients. With increasing pressure to the biliary system, concomitant transaminase elevation is also observed. Rarely will the

Table 9.2 Organisms associated with acute bacterial cholangitis[a]

Microorganism	Percent (%)
Gram-negative organisms	
Escherichia Coli	25–50
Klebsiella spp.	15–20
Enterobacter spp.	5–10
Pseudomonas spp.	0.5–19
Gram-positive organisms	
Enterococcus spp.	10–20
Streptococcus spp.	2–10
Anaerobes	4–20
Fungal	Rare

[a]Adapted from Gomi H et al. J Hepatobiliary Pancreat Sci. 2013;20:60–70 [35]

Table 9.3 Clinical presentation of acute cholangitis[a]

Symptom	Percent	Syndrome
Fever	90	Charcot's triad involves first three
Abdominal pain	70	
Jaundice	60	
Hypotension	30	Reynolds' pentad involves all five
Altered mental status	20	

[a]Adapted from Murray, Fibrocystic Diseases of the Liver (2010)

transaminase levels increase to 1000 IU/L as in the case of hepatic ischemia, drug-induced liver injury, or fulminant viral hepatitis. During an episode of acute cholangitis, the hepatic synthetic function is usually preserved, but repeated episodes of obstruction and cholangitis may eventually lead to chronic hepatic failure [19].

Pancreatic enzymes can be elevated in cases of biliary pancreatitis. Other nonspecific markers of inflammation, such as C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR), are also usually elevated.

Imaging

Transabdominal ultrasonography is a rapid, readily available, noninvasive first modality of choice that can quickly assess for biliary ductal dilation and choledocholithiasis. Its limitations include decreased image quality in the setting of large body habitus and decreased sensitivity with small stones and in non-dilated ducts.

Magnetic resonance cholangiopancreatography (MRCP) is more sensitive and specific than ultrasound for biliary dilation and choledocholithiasis and can provide a useful "road map" prior to endoscopic retrograde cholangiopancreatography (ERCP). This is especially important in patients with suspected intrahepatic biliary obstruction (i.e., fibrocystic diseases, primary sclerosing cholangitis (PSC), hilar and intrahepatic cholangiocarcinoma). In addition, MRCP can help evaluate for hepatic abscesses. In a recent meta-analysis, MRCP was shown to have excellent sensitivity and specificity for demonstrating the presence and level of biliary obstruction. It was, however, less sensitive at detecting choledocholithiasis and for differentiating benign from malignant obstruction when compared to endoscopic ultrasound (EUS) and ERCP [20]. In the presence of a dilated common bile duct (CBD), MRCP has 90–95 % concordance with ERCP in diagnosing CBD stones over 1 cm in diameter [21, 22]. In high-risk patients with low to moderate suspicion for cholangitis, MRCP can be very useful prior to proceeding to an ERCP. In the setting of obvious and severe cholangitis, however, a therapeutic ERCP with drainage of the obstruction should not be delayed.

Computerized tomographic (CT) scan of the abdomen does not have the same resolution in defining the anatomy of the biliary tree compared to MRCP, but is more often obtained due to wider availability and lower cost. In addition, a CT scan can evaluate for other diagnoses and associated complications, such as pancreatitis and liver abscesses. CT findings of papillitis and marked early inhomogeneous enhancement of the liver have been found to be associated with acute suppurative cholangitis [22].

EUS is valuable in diagnosing the cause of cholangitis in select cases. Two large meta-analyses have shown high sensitivities (89–94 %) and specificities (94–95 %) for EUS in detecting choledocholithiasis when compared to ERCP and intraoperative cholangiogram as the gold standard [23, 24]. Although EUS is a minimally

invasive procedure that requires sedation, it can be performed prior to consideration of an ERCP and in the right clinical context to confirm passage of a CBD stone and, thus, avoid an unnecessary ERCP.

ERCP remains the gold standard for the diagnosis and management of acute cholangitis. With cross-sectional imaging modalities and ultrasound almost universally available, ERCP should be regarded as a therapeutic procedure. However, an ERCP could be the first step in the evaluation and treatment of cholangitis in the right clinical scenario, such as in patients with indwelling stents or established biliary obstruction.

Differential Diagnosis

The differential diagnosis includes liver abscess, cholecystitis, hepatolithiasis, biliary leaks, Mirizzi's syndrome (which can cause cholangitis as well), severe pancreatitis, hepatitis, and right lower lobe pneumonia/empyema. Laboratory testing and imaging studies are helpful in sorting out these diagnoses from cholangitis. Cholecystitis can coexist with cholangitis and should be considered in patients who are not responding to definitive treatment of cholangitis.

Management

The management of cholangitis is based on two tenants: antibiotics and decompression of the biliary tree. In addition to antimicrobial therapy and biliary decompression, supportive measures in the form of fluid resuscitation, correction of coagulopathy, and close monitoring for evidence of sepsis are essential.

Classification of the Severity of Acute Cholangitis

The Tokyo Guidelinesconsist of a three-stage classification system to categorize patients with suspected acute cholangitis and determine management strategies (Table 9.4).

Table 9.4 Severity of acute cholangitis

	Grade 2 (moderate)	Grade 3 (severe)
Grade 1 (mild)	Any two of the following	Any organ dysfunction below
Does not meet any of	1. WBC >12,000 or <4000	1. Cardiovascular dysfunction
Grade 2 or grade 3 criteria	2. Fever: T >39 °C	2. Neurologic dysfunction
	3. Age >75 years	3. Respiratory dysfunction
	4. Total bilirubin >5 mg/dL	4. Renal dysfunction
	5. Albumin <2.8 g/dL	5. Hepatic dysfunction
		6. Hematological dysfunction

Grade 1—mild acute cholangitis: a stable patient who is clinically diagnosed with acute cholangitis and does not meet criteria for grade 2 or 3.

Grade 2—moderate acute cholangitis: any two of the following criteria need to be fulfilled: WBC >12,000 or <4000, total bilirubin >5 mg/dL, albumin <2.8 g/dL, higher fevers (>39 °C), and older age (>75 years).

Grade 3—severe acute cholangitis: this involves end-organ dysfunction, such as cardiovascular dysfunction (e.g., hypotension), neurologic dysfunction (e.g., altered mental status), respiratory dysfunction (e.g., decreased oxygen saturation), renal dysfunction (e.g., elevated creatinine >2.0 mg/dL), and hepatic dysfunction (e.g., INR >1.5) [25, 26].

Antibiotics

Biliary and Blood Cultures

In suspected cholangitis, blood cultures are obtained, and empiric antibiotics are started prior to any biliary intervention. Cultures should also be obtained from bile and/or stents removed at ERCP since the yield for positive cultures is higher [26]. Biliary and blood culture results tailor the antibiotic regimen [11]. However, the clinical benefit of blood cultures has been questioned. In 2010, the

Surgical Infection Society and the Infectious Diseases Society of America [27] have recommended against routine collection of blood cultures based on a large retrospective study showing only a 5 % true positivity for blood cultures, with most patients not requiring any change in antibiotic therapy despite the culture results. On the other hand, positive blood culture results would be useful in patients who are responding poorly to the initial choice of antibiotics. In our practice, we recommend the collection of blood cultures prior to the initiation of antibiotics and make every effort to obtain bile cultures as well. In patients who are responding to the initial antimicrobial regimen, there usually is no need to alter the antibiotics. However, in patients who fail to respond appropriately despite adequate biliary drainage, the culture results can help tailor the antibiotic regimen.

Antibiotic Regimens

There is no established consensus on the initial choice of antibiotics due to lack of prospective data [11, 12, 28]. Based on the known bacterial profile of cholangitis, the initial regimen selected should have adequate gram-negative coverage and biliary penetration. Intravenous antibiotics should be used initially in patients presenting with sepsis and/or severe cholangitis.

The choice of initial antimicrobial therapy should be based on local epidemiology and bacterial sensitivities. Beta-lactam-based monotherapies appear to be as effective as and less toxic than the combination of a beta-lactam antibiotic (ampicillin) and an aminoglycoside (gentamicin) [29]. Fluoroquinolones have excellent biliary penetration [12], and in a prospective randomized study, ciprofloxacin monotherapy was as effective as triple therapy with ceftazidime, ampicillin, and metronidazole [30]. Moxifloxacin has been shown to be safe and non-inferior to ceftriaxone plus metronidazole [31] as well as piperacillin/tazobactam followed by amoxicillin/clavulanic acid [32]. Other initial options include a fluoroquinolone with metronidazole, a beta-lactam/beta-lactamase inhibitor, a third-generation cephalosporin with or without metronidazole, and monotherapy with a carbapenem (Table 9.5). For patients with bilio-enteric anastomoses, elderly patients, and those with recurrent infections, one should consider anaerobic coverage upfront. In our practice, we initially start with a fluoroquinolone alone (levofloxacin 500 mg daily).

Table 9.5 Antimicrobial selection for acute cholangitis

Antimicrobial	Adult dosage
IV formulation (recommended for initial use with any signs of sepsis)	
Beta-lactam-based therapy	
Piperacillin-tazobactam	3.375 g or 4.5 g every 6 to 8 h
Ticarcillin-clavulanate	3.1 g every 4 to 6 h
Ampicillin-sulbactam	3 g every 6 h
Third-generation cephalosporin	
Ceftriaxone ± Metronidazole	1 g every 24 h 500 mg every 8 h
Fluoroquinolones	
Levofloxacin ± Metronidazole	500 mg or 750 mg every 24 h 500 mg every 8 h
Ciprofloxacin ± Metronidazole	400 mg every 12 h 500 mg every 8 h
Carbapenem	
Imipenem-cilastatin	500 mg every 6 h
Meropenem	1 g every 8 h
Ertapenem	1 g every 24 h
Oral formulation (after patient has stabilized)	
Fluoroquinolones	
Levofloxacin ± Metronidazole	500 mg every 24 h 500 mg every 8 h
Ciprofloxacin ± Metronidazole	400 mg every 12 h 500 mg every 8 h
Beta-lactam	
Amoxicillin-sulbactam	875 mg/125 mg every 12 h

Antibiotic Resistance

Over the last decade, the prevalence of extended-spectrum beta-lactamase (ESBL)-producing *E. coli* and *Klebsiella* [33] has increased, and these microorganisms are not reliably susceptible to cephalosporins, penicillin derivatives, or fluoroquinolones [34]. If these organisms are suspected, piperacillin/tazobactam and carbapenems are an appropriate initial choice.

For enterococcal infections, vancomycin should be used in severe (grade 3) acute cholangitis, although the emergence of vancomycin-resistant

enterococcus (VRE) is a concern. If VRE is confirmed in cultures, linezolid or daptomycin would be appropriate drugs of choice [35]. Antibiotic resistance will likely continue to increase, and the current recommendations must be adjusted based on upcoming data. In case of poor response to initial antibiotic therapy, both inadequate biliary drainage and antibiotic resistance should be considered. A periodic review of one's hospital and regional biliary culture data is helpful in adjusting to the reality of increasingly resistant organisms.

Duration of Antibiotics

At this time, there are insufficient prospective data to provide definitive recommendations regarding the optimal duration of antimicrobial therapy after biliary decompression. There is evidence that once biliary drainage is achieved, antibiotics can be discontinued soon thereafter. In a small, prospective, single-arm study of 18 patients with moderate or severe cholangitis, all patients underwent biliary drainage within 24 h of presentation. Antibiotics were stopped 24 h after resolution of fever. After a 3-day follow-up, none developed recurrent cholangitis or cholangitis-related complications. The majority (78 %) of patients had discontinued antibiotics within 4 days, with the remaining patients requiring 7 days or less of antibiotic therapy [36]. Similarly, a retrospective study of 80 patients showed that a 3-day course of antibiotics was as effective as a longer course in patients who underwent prompt biliary drainage with resolution of fever [37]. Currently, expert opinion suggests an antimicrobial duration of 4–7 days after the infection has been controlled, regardless of the severity of cholangitis. For enterococcal and streptococcal bacteremia, antibiotics should be extended to 2 weeks due to the risk of infective endocarditis. The presence of factors, such as Caroli's disease (biliary cystic disease), malignant biliary obstruction, indwelling biliary stents, immunosuppression, older age, prosthetic valves, and other comorbidities, probably warrants longer duration of antibiotics [35].

Fungal Cholangitis

Fungal cholangitis is rare and can be difficult to treat. *Candida* species are part of the normal gastrointestinal tract microbial flora and are the most common causes of fungal cholangitis. Fungal cholangitis is usually associated with an immunosuppressive state, including chemotherapy, immunosuppressive drugs (e.g., corticosteroids), malignant hematologic diseases, acquired immune deficiency syndrome (AIDS), and diabetes mellitus. Broad-spectrum antibiotic use is also an important risk factor. The diagnosis of fungal cholangitis is based on clinical history and bile cultures [38]. The fungal organisms can create fungal masses or "balls" resulting in recurrent biliary obstruction (Fig. 9.4). Treatment may require repeated biliary drainage in the form of percutaneous or nasobiliary drains with intrabiliary administration of antifungals in addition to systemic antifungals. The prognosis in this clinical setting is poor [39]. Fluconazole is an appropriate first choice when fungal cholangitis is suspected, although it is important to monitor the patient's clinical response and follow up with culture sensitivities due to increasing drug resistance [38].

Biliary Decompression

Due to the relative safety and efficacy of ERCP, it is the treatment of choice for biliary decompression [40]. Although the technical details of the procedure for acute biliary obstruction are discussed in a separate chapter, we provide our insights regarding the use of biliary decompression modalities for acute cholangitis.

The goal of ERCP is to assess the cause of the biliary obstruction and provide effective drainage, which often involves placement of an intrabiliary stent and/or a sphincterotomy. Historically, nasobiliary drains were recommended alongside biliary stents but are rarely used nowadays (Fig. 9.4) based on two randomized controlled trials showing no significant difference in the success rate, effectiveness, or morbidity compared to

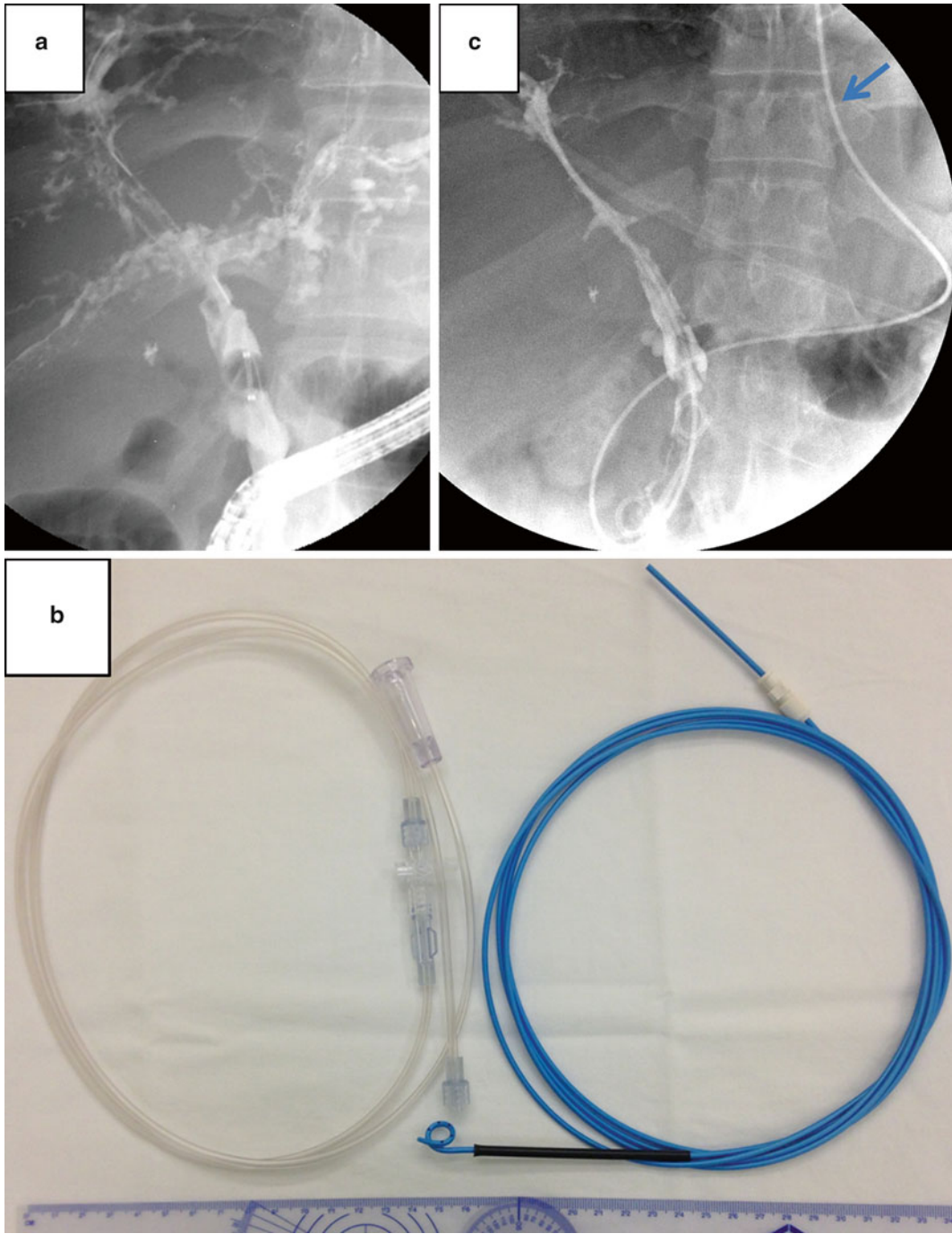

Fig. 9.4 Fungal cholangitis. Diabetic patient with recurrent cholangitis treated with multiple courses of broad-spectrum antibiotics and stent exchanges. (**a**) ERCP shows multiple filling defects consistent with fungal ball formation. (**b** and **c**) A nasobiliary drain was used to provide irrigation and administration of intrabiliary antifungals

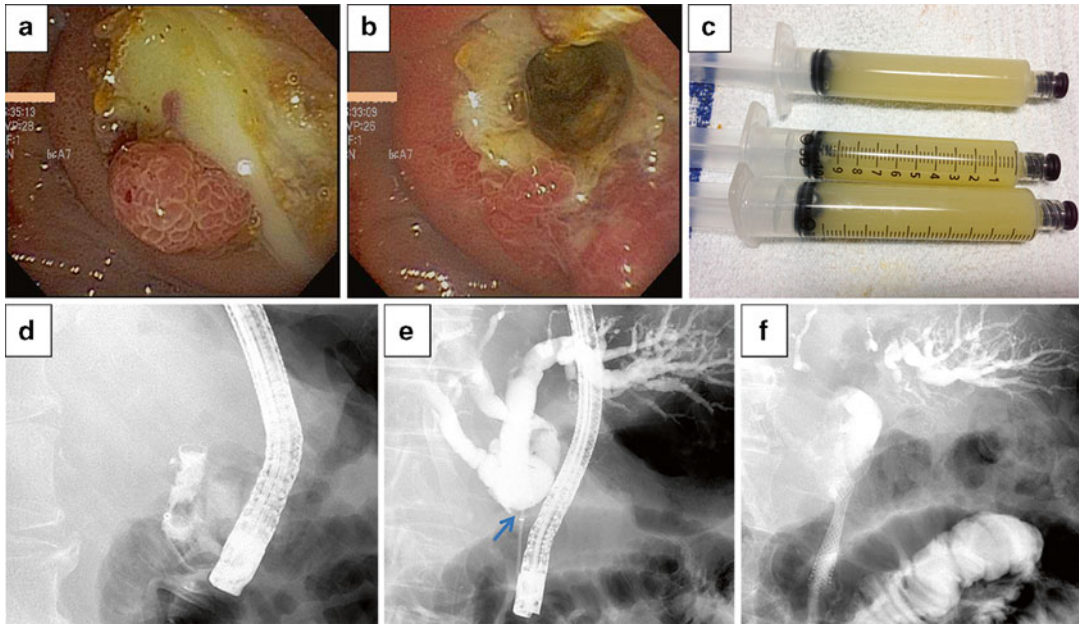

Fig. 9.5 Patient with pancreatic adenocarcinoma and biliary obstruction, previously treated with a fully covered self-expanding metal stent (FCSEMS), presented with cholangitis. (**a** and **b**) Purulent discharge from the major papilla with an occluded FCSEMS. (**c**) 30 mL of purulent bile aspirated and sent for culture prior to cholangiogram. (**d** and **e**) Cholangiogram demonstrating filling defects within the stent and a high-grade stricture at proximal end of the stent with resultant biliary obstruction. (**f**) New uncovered self-expandable metal stent (SEMS) placed across the stricture with resultant decompression

intrabiliary stents [41, 42]. Nasobiliary drains are still effective, however, in fungal cholangitis, which requires frequent irrigation.

It is important to prioritize the goals of ERCP, especially in an unstable patient (i.e., severe cholangitis). The primary goal is biliary access with some form of drainage, which usually entails a stent. The secondary goal is to determine the source of obstruction with an attempt to relieve it (e.g., choledocholithiasis extraction). Slow and sparing injection of non-diluted contrast or a wire-guided biliary cannulation helps reduce the risk of cholangiovenous reflux and intraprocedural bacteremia. Once deep cannulation is achieved, aspiration of 20–40 mL of bile will help with both biliary decompression and provision of a culture sample (Fig. 9.5) [43]. A complete cholangiogram can then be performed to investigate and address the source of the obstruction. Although larger plastic stents (10 Fr) theoretically provide more effective drainage, one randomized controlled study comparing 10 Fr to 7 Fr stents in 40 patients (all with endoscopic sphincterotomy) showed no difference in symptom and lab improvement, complications, or failure rates [44].

The role of routine endoscopic sphincterotomy (EST) is not as clear at this time. There are no randomized controlled trials comparing EST alone versus EST with stent placement versus stent placement alone. Two case series examined the effect of adding EST to nasobiliary drainage or stent placement. There was no added benefit to EST, with an increase in complications, especially bleeding [45, 46]. On the other hand, a more recent retrospective study evaluating 363 cases showed that in the setting of suspected choledocholithiasis, EST during the initial ERCP was safe and effective [47]. Since choledocholithiasis is the most common cause of acute cholangitis, EST plays a major role overall in cholangitis management. The success rate of

CBD stone removal is 90–95 % after EST. In critically ill patients requiring emergent drainage, however, stent placement without sphincterotomy may be preferable, with definitive treatment postponed at a later date.

Antimicrobial therapy has been shown to be effective in stabilizing patients and has allowed for ERCP to be performed electively. There is no difference in mortality and morbidity with regard to mild to moderate acute cholangitis when ERCP is performed within 72 h compared to a more emergent ERCP [48, 49]. However, delaying an ERCP beyond 72 h has been shown to have worse outcomes [50]. If a patient has not responded to antibiotics after 6 h or if the patient meets criteria for severe (grade 3) acute cholangitis, an urgent ERCP should be performed. In a more recent retrospective study of choledocholithiasis-induced acute cholangitis, clinical and technical success rates in mild to moderate cholangitis were similar in the urgent (within 24 h) versus elective (>24 h) group, with fewer days in the hospital in the urgent group [48].

If ERCP is unsuccessful or the expertise is unavailable, percutaneous transhepatic biliary drainage (PTBD) can be performed with biliary access gained using ultrasound or fluoroscopic guidance. The procedural risks include intra-abdominal and puncture site bleeding, bile leak, pneumothorax, hemothorax, and catheter occlusion and dislodgement. Due to these risk factors and the inconvenience and discomfort of a percutaneous drain, ERCP is the preferred treatment modality in most clinical settings, although there are no head-to-head comparisons between PTBD and ERCP to date. Technical and clinical success rates for PTBD are high in most studies (82–98 %), with higher success rates (95–98 %) when the biliary tree is dilated [51]. Morbidity (5–7 %) and mortality rates are low [52, 53]. PTBD is a reasonable first choice in a patient with altered anatomy, such as prior gastric bypass surgery or prior failed attempts at ERCP.

Surgical decompression and open drainage are rarely required and usually a last resort when ERCP and PTBD are unsuccessful. T-tube placement can be performed for biliary drainage, with emphasis on a quick operation without significant time being spent on definitive therapy [54]. Compared to ERCP and PTBD, complication rates are significantly higher, including T-tube malfunction and delayed bile duct strictures. Cholecystectomy should be considered in a patient with cholelithiasis and/or choledocholithiasis, but after resolution of the acute cholangitis.

Surgery may play a role in recurrent or refractory cholangitis. If the extrahepatic biliary system continues to be a source of obstruction, biliary diversion, such as a hepatico- or choledochoduodenostomy or choledochojejunostomy, can be performed. A partial hepatectomy can also be considered in selected cases of recurrent intrahepatic obstructions, especially those who fail endoscopic treatment [55]. Recurrent cholangitis can lead to cirrhosis and chronic liver failure, thus necessitating consideration for liver transplantation in some patients.

Conclusion

Acute cholangitis is caused by a microbial infection in the bile ducts, usually due to an obstruction, foreign object (e.g., stent), or manipulation of the biliary tree. Symptoms and signs of cholangitis include the classic Charcot's triad of fever, jaundice, and abdominal pain. In severe cases, acute cholangitis can lead to hypotension, mental status changes, and end-organ damage. Medical management relies on antimicrobial therapy. Most cases of acute cholangitis can be stabilized on antibiotic therapy and sometimes managed with antibiotics alone if there is no ongoing biliary obstruction. Antibiotic selection and duration depend on the clinical history, patient stability, local drug resistance profile, and other risk factors. A 4–7-day course of antibiotics is usually recommended after adequate biliary drainage has been achieved. Bile cultures are helpful in guiding selection of antimicrobial therapy and should be routinely obtained at ERCP. Severe cholangitis should be treated urgently with biliary drainage via ERCP or PTBD. For patients who fail to respond appropriately to initial antibiotics and biliary

decompression, considerations should be given for ongoing biliary obstruction, resistant organisms, fungal infections, and complications, such as abscesses.

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Approach to Endoscopic Adverse Events

10

Disaya Chavalitdhamrong, Robert J. Summerlee, and Peter V. Draganov

Introduction

The term "complication" has unfortunate medico-legal connotations and is perhaps better avoided. The description of deviations from the intended outcome as "unplanned events" fits nicely within the principles of informed consent, although the American Society for Gastrointestinal Endoscopy (ASGE) consensus statement favors the use of the term "adverse events" [1]. Adverse events can occur before endoscopy (e.g., reaction to prophylactic antibiotics or bowel preparation), during the procedure, immediately post-procedurally, and have even been reported to be delayed beyond 14 days when they are clearly related to the procedure [1]. Factors increasing the risk of an adverse event include the patient's comorbidities, present illnesses, urgent or emergent setting, need for therapeutic interventions, and lack of expertise of the endoscopist.

The incidence of adverse events can be decreased, but some are inevitable, and as a result, a predetermined strategy to manage them should be planned ahead of time. The specific management strategy should consider patient-, procedure-, and endoscopist-related factors and should take into account the available local resources. Therefore, the following recommendations may not apply or be feasible in all settings, which even further emphasize the need for a predetermined institution-specific plan and management protocol. Management of endoscopy-related adverse events is divided to three periods: pre-procedural, intra-procedural, and post-procedural.

Pre-procedural management includes review of the patient's medical history and physical examination, proper indication for the procedure, risk stratification, informed consent, antibiotic prophylaxis (when necessary), the management of anticoagulation and antiplatelet therapy, ensuring nil per os (NPO) or bowel preparation, and formulation of the sedation plan. Possible side effects and adverse events should be readily disclosed during informed consent of the patient.

Intra-procedural management includes completeness of the examination and completion of therapeutic procedures involving photo-documentation, comprehensive knowledge regarding the procedure and the devices used, patient monitoring, and documentation of medications administered. Increasingly, adverse events such as perforation are detected during the procedure and can be successfully managed with endoscopic techniques at the same session.

The post-procedural period includes recognition, documentation, and management of adverse events.

D. Chavalitdhamrong • R.J. Summerlee
P.V. Draganov, M.D. (✉)
Division of Gastroenterology, Hepatology, and Nutrition, University of Florida, 1329 SW 16th Street, Suite 5251, Gainesville, FL 32608, USA
e-mail: dragapv@medicine.ufl.edu

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Prompt recognition and immediate response to endoscopic adverse events are vital for a successful outcome. Optimal communication with patients and families and demonstration of empathy following an adverse event will enhance the physician-patient relationship and reduce the likelihood of medico-legal claims. Even if the patient is transferred to another service (e.g., surgery), an ongoing follow-up by the endoscopist, including documentation in the chart of the encounters, is essential. Ultimately, endoscopic adverse events will occur. Accordingly, the endoscopist must have a predetermined plan of action to expeditiously address potential adverse events, as outlined below.

Procedure-Related Pain

Psychosocial, neurophysiologic, anatomic, and pathologic factors influence the patient's perception and tolerance of pain. Pain is the most common side effect of endoscopy. This can immediately be reported during the procedure in patients under moderate sedation or after recovery from deep sedation. A prospective study on the incidence of hospital visits within 14 days of outpatient endoscopy (upper endoscopy and colonoscopy) revealed that the most common reasons for endoscopy-related emergency department visits were abdominal pain (47 %), gastrointestinal bleeding (12 %), and chest pain (11 %) [2].

Pre-procedural Considerations

Insufflation with carbon dioxide instead of air during colonoscopy, balloon-assisted enteroscopy, and ERCP decreases abdominal discomfort and bowel distention, without any additional adverse reactions, hence warranting routine clinical use [3–5]. The use of carbon dioxide insufflation has been reported to decrease post-procedural hospital admissions [6]. Carbon dioxide insufflation should be strongly considered for anticipated prolonged and difficult procedures, such as deep enteroscopy, endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD) [6].

Intra-procedural Considerations

Decreasing the amount of air insufflation and suctioning intraluminal air at the end of the procedure should be performed routinely. Switching from air to carbon dioxide insufflation during a procedure should be considered for difficult and prolonged cases. In addition, it is recommended to switch to carbon dioxide insufflation if a perforation occurs during the procedure and endoscopic closure is attempted [7].

Changing to a pediatric colonoscope is an option for those patients with difficult sigmoid angulations and intra-abdominal adhesions impeding passage of the adult colonoscope. The use of ScopeGuide™ (Olympus America, Center Valley, PA, USA) during difficult colonoscopies may potentially lead to less patient discomfort by allowing the endoscopist to see loops that require reduction before further advancement of the colonoscope.

Post-procedural Considerations

Upon discharge from the endoscopy unit, the patient should be provided with contact information for the endoscopy unit, on-call endoscopist, or emergency department. The potential causes of post-endoscopy pain are numerous (Table 10.1). Some are benign in nature (e.g., bowel distention with air), while others can have catastrophic consequences (e.g., perforation). Other causes of post-procedural pain, such as myocardial infarction and pulmonary embolism, should not be overlooked. A history of heart disease, lower blood pressure or hemoglobin level on arrival, and persistent shock before endoscopy were found to be associated with increased risk for procedure-related myocardial infarction [8]. Initial evaluation consists of a targeted history and physical examination. Abdominal examination, including auscultation of bowel sounds, observation of abdominal distention, gentle percussion, and palpation, is essential. A high index of suspicion for bowel perforation or pancreatitis is needed especially in high-risk procedures, such as difficult or therapeutic colonoscopy, and in patients with risk

Table 10.1 Potential causes of post-procedural pain

Endoscopy related	Other causes
Air insufflation	Myocardial infarction
Post-polypectomy syndrome	Pulmonary embolism
Perforation/abdominal compartment syndrome	Pneumonia/aspiration
Post-ERCP pancreatitis	Diabetic ketoacidosis
Endoscopic therapy-related conditions (e.g., post-band ligation, post-stent placement, post-polypectomy syndrome, post-APC treatment)	Takotsubo cardiomyopathy
Post-ERCP cholangitis	
Intramural hematoma	
Bowel ischemia	
Splenic laceration and rupture	
Acute appendicitis	
Volvulus	
Ogilvie's syndrome (acute colonic pseudo-obstruction)	
Chilaiditi's syndrome (interposition of large bowel between the liver and diaphragm)	

factors for post-ERCP pancreatitis, respectively. Initial laboratory tests, including complete blood count with differential, electrolytes, liver function panel, amylase, and lipase, are warranted in patients with severe pain or signs/symptoms of perforation or peritonitis. Administration of analgesic medications should not be avoided because effective analgesia does not compromise diagnostic evaluation [9]. Radiologic investigations, including abdominal x-ray and computed tomography (CT), are important tools for diagnosis and to guide further treatment. There are no firm guidelines on when to consider radiologic evaluation, but the decision usually is based on balancing the likelihood of a serious adverse event, such as perforation (e.g., very unlikely with diagnostic procedure versus more likely after large-area polypectomy), and the patient's clinical presentation. Furthermore, the choice for a particular test (e.g., abdominal series versus CT) should be individualized based on specific features (e.g., CT will be more useful than abdominal x-ray in the case of suspected retroperitoneal perforation following ERCP or post-polypectomy syndrome). The CT protocol for evaluating post-procedural acute abdominal pain should be tailored to the specific situation. For example, if pain occurs after an upper endoscopy, CT should be done with both oral (water-soluble) and intravenous contrast medium unless contraindications exist [10]. For suspected perforation after ERCP, the use of non-contrast CT to verify any extraluminal contrast originating from the endoscopic procedure is recommended. Whenever a retroperitoneal perforation is suspected, administration of oral contrast is indicated since its leakage is diagnostic of a duodenal perforation [10]. Water-soluble contrast enema can help detect a perforation or confirm a concealed perforation in a patient presenting with pain after colonoscopy [11].

Procedure-Related Bleeding

The risk of bleeding from endoscopy is related to both patient and procedural factors. Low-risk procedures include upper endoscopy, colonoscopy, ERCP without sphincterotomy, and endoscopic ultrasound (EUS) without fine needle aspiration. Polypectomy, sphincterotomy, percutaneous endoscopic gastrostomy, and dilation therapy are high-risk procedures. The decision to hold antithrombotic agents should be titrated to the patient's risk for a thromboembolic event and is discussed in detail in a separate chapter. The two more common bleeding adverse events after high-risk endoscopy (i.e., post-polypectomy and post-sphincterotomy bleeding) are reviewed below.

Post-polypectomy Bleeding

Bleeding following colonoscopy is usually related to polypectomy. The incidence of post-polypectomy bleeding ranges from 0.6 % to 8.6 %, depending on the setting and the definition of bleeding [12]. Delayed post-polypectomy bleeding has been reported up to 16 days after colonoscopy [12]. The morphology, size and location of colorectal polyps, number of polyps removed, and post-polypectomy anticoagulation have been associated with the risk of post-polypectomy bleeding [12–14]. The role of various therapeutic techniques and their incidence on post-polypectomy bleeding remain controversial. Endoscopic mucosal resection (EMR) is a useful technique for removing large colon polyps, but it is associated with increased risk of bleeding (6–7 %) and perforation (1–2 %) [15]. Failure to create a sufficiently large submucosal fluid safety cushion using saline (or other) lift technique is the usual cause of EMR-related complications [16].

Pre-procedural Considerations

Peri-procedural anticoagulation and antiplatelet management is discussed in a separate chapter. A careful medical history and physical examination may help determine patients with risk factors (such as anticoagulation use and certain comorbidities) and help guide the proper management plan. Endoscopists should perform pre-procedural coagulation testing (platelet count, INR, partial thromboplastin time) selectively on the basis of the patient's medical history (bleeding, liver disease, malabsorption, malnutrition), physical examination (bruising or petechiae), and associated risk factors (anticoagulation, prolonged antibiotic use) [12]. Platelet transfusion should be considered in patients with platelets less than 50,000/μL.

Desmopressin acetate (DDAVP®) should be considered in patients with platelet function disorders, such as von Willebrand disease. Eltrombopag, a thrombopoietin receptor agonist, reduces the need for platelet transfusions and should be considered in patients with chronic liver disease or idiopathic thrombocytopenic purpura with platelets less than 50,000/μL [17]. Post-polypectomy bleeding risk seems to be increased in patients taking warfarin or resuming warfarin or heparin within 1 week after polypectomy. Clopidogrel and warfarin should be discontinued 5–10 days and 3–5 days, respectively, before the procedure, or the endoscopy should ideally be postponed if the procedure is an elective one [18].

Intra-procedural Considerations

Post-polypectomy bleeding tends to be associated with the removal of large polyps, use of cutting rather than coagulation current, and transection of a stalk or neck of tissue without cautery or with insufficient cautery [16]. Coagulation (or blended) current instead of cutting current is typically used [12]. When a large polyp with a thick stalk is encountered, epinephrine or saline submucosal injection, placement of a detachable snare (EndoLoop™, Olympus America, Center Valley, PA, USA), and/or endoscopic clip placement may be considered [16, 19]. When a visible vessel is present following polypectomy, clips should be applied [12]. There is no defined "standard of care" in this situation [18]. Nine randomized studies have compared various techniques in the prevention of post-polypectomy bleeding. All studies to date have limitations and, therefore, the results should be interpreted with caution.

In summary, (1) the submucosal injection of saline-epinephrine solution prior to polyp resection can prevent early but not delayed bleeding; (2) loop placement can prevent bleeding, especially in large polyps, but mostly early bleeding; (3) clips may prevent delayed post-polypectomy hemorrhage, but this has not been proven in a randomized trial; and (4) combination modalities may be more effective than a single technique [12].

Post-procedural Considerations

Patients who undergo uneventful polypectomy need to be informed that delayed post-polypectomy bleeding can occur up to 14 days after their procedure. Resuscitation takes priority when assessing a patient with post-procedural bleeding. The abdomen should be examined for

evidence of peritoneal signs. Complete blood count, coagulation parameters, and blood type and crossmatch should be obtained. Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and anticoagulants should be stopped, if feasible. Patients on warfarin may require reversal with prothrombin complex concentrate or fresh frozen plasma.

Delayed post-polypectomy bleeding most commonly stops spontaneously. If bleeding does not stop, then repeat colonoscopy should be performed. Most post-polypectomy bleeding can be controlled endoscopically. The skill set of any endoscopist who performs colonoscopy must include the ability to achieve hemostasis. Injection of the polypectomy site with dilute epinephrine solution is helpful for persistent venous oozing [16]. Mechanical hemostatic methods, such as hemoclip and EndoLoop™ placement, seem to be effective and are favored over thermal therapies, but controlled data are insufficient to make firm recommendations [12, 16]. The main premise to preferably use mechanical hemostatic devices is to avoid further thermal damage to the post-polypectomy area and potentially decrease the risk of perforation (Fig. 10.1). Band ligation has been successfully applied in a few case reports [20–22]. Careful discharge instructions and extended observation are necessary. Aspirin, NSAIDs, and clopidogrel should be discontinued for 7–10 days, and warfarin should be withheld for at least 48–72 h, if possible [16].

Blood transfusion, hospitalization, and multidisciplinary involvement (GI, interventional radiology, and surgery) may be required in complicated cases. In our institution, we have developed a GI bleeding protocol with multidisciplinary involvement. The protocol is used for any GI bleeding, including post-endoscopy bleeding. The key concepts of our GI bleeding protocol are as follows:

1. Multidisciplinary involvement should be considered in any patient with hemodynamic instability, transfusion requirements of more than 4 units packed red blood cell over 24 h or 8 units in total, rebleeding, no clear source of bleeding identified on initial endoscopy, high risk for rebleeding, and difficult to match blood type or who is a Jehovah's witness. If any of the above factors is present, the "GI bleeding protocol" is activated.
2. The first step in the bleeding protocol is to conduct a conference call that includes the senior staff from GI, surgery, interventional

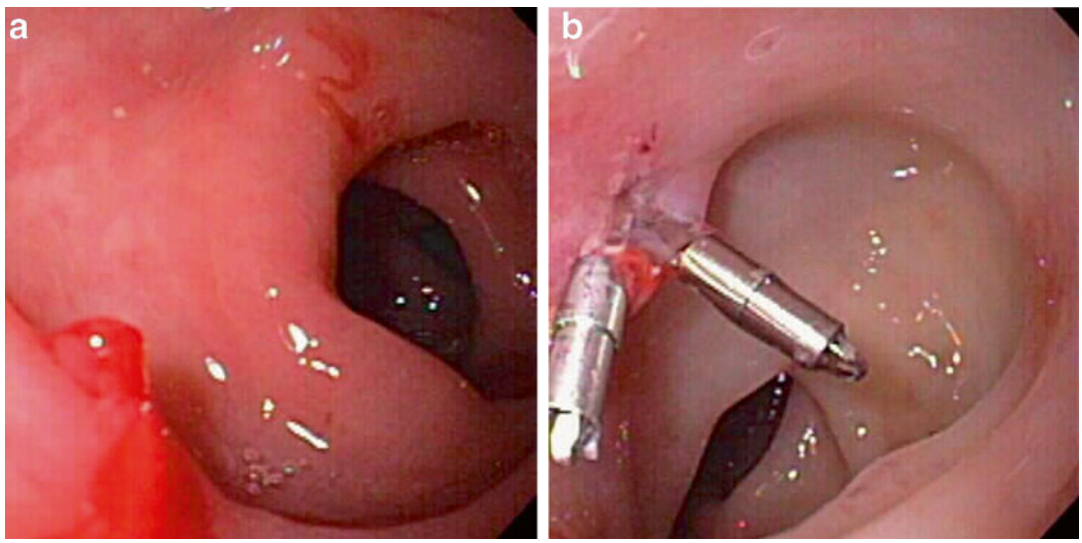

Fig. 10.1 (**a**) Post-polypectomy bleeding site with visible vessel. (**b**) Hemostasis secured with clip placement

radiology, and intensive care unit specialties. Any service can initiate the protocol, but typically this is done most commonly by the GI attending. The hospital telephone operators have an established process to page all the appropriate physicians covering the four respective services at that particular moment and place them individually on hold in a "virtual room" until all services have responded. Once all four services have been reached, a conference call is carried out, and a decision is made for the most appropriate next step in management.

3. One person is designated to be in charge of communicating to the patient the recommended management strategy. This is typically the GI staff because, as a rule, he or she already has been involved in the case and has an established rapport with the patient and family.

The implementation of this GI bleeding protocol has greatly improved communication and has streamlined patient care at our institution. Importantly, we are no longer caught up in a vicious cycle of one provider recommending a specific therapy (e.g., GI team recommends angiography to be done by interventional radiology) and another provider recommending an alternative strategy (e.g., interventional radiology recommends a bleeding radionuclide scan first instead of angiography). Furthermore, the patient and family do not receive conflicting information. Most importantly, the patient is treated with the agreed upon consensus therapy in a timely manner. We believe that every institution should strongly consider the establishment of such a GI bleeding protocol. The specific criteria to initiate the protocol and the following steps may be different than those described above based on local resources and expertise. The establishment of a multidisciplinary management strategy, however, tends to be labor-intensive. Nevertheless, a multidisciplinary predetermined plan will improve patient care and facilitate communication between physicians and the patient.

Post-ERCP Bleeding

Bleeding complications of ERCP are usually related to sphincterotomy. The incidence of post-endoscopic sphincterotomy bleeding is 0.5–2 % and has been reported in up to 12 % of cases [23]. A number of risk factors for post-ERCP bleeding have been identified, which are related to patient comorbidities (hemodialysis, cholangitis before the procedure, coagulopathy, Billroth II anatomy) and intervention (length of sphincterotomy, precut sphincterotomy, anticoagulation within 3 days after procedure, endoscopist's low case volume) [24, 25]. Immediate bleeding at the time of sphincterotomy is also a known risk factor for delayed bleeding [26]. The risk of bleeding can be minimized by identifying patients at risk and optimizing coagulation abnormalities and attention to technique.

Pre-procedural Considerations

Identifying patients at risk and optimizing coagulation abnormalities are mandatory. Controversy remains regarding the appropriate use of platelet and coagulation factor transfusions in high-risk patients, and data are limited. Recommendations regarding warfarin and clopidogrel are similar to those mentioned in the post-polypectomy section [18].

Intra-procedural Considerations

Hemorrhage can be limited by careful technique, including proper orientation of the wire, avoidance of unnecessarily long cuts, and judicious use of the electrosurgical current. The use of pure-cut current has been shown to increase the risk of bleeding. Blended or coagulation current reduces the bleeding risk but may increase the risk of post-ERCP pancreatitis [26]. The Endocut™ mode (ERBE USA, Marietta, GA, USA) or Pulse mode™ (Olympus America, Center Valley, PA, USA) provides computerized control of the electrosurgical generator, and these modes are commonly used due to relative safety in bleeding reduction and a lower incidence of pancreatitis compared to blended current [27]. Balloon dilation of the native papilla is associated

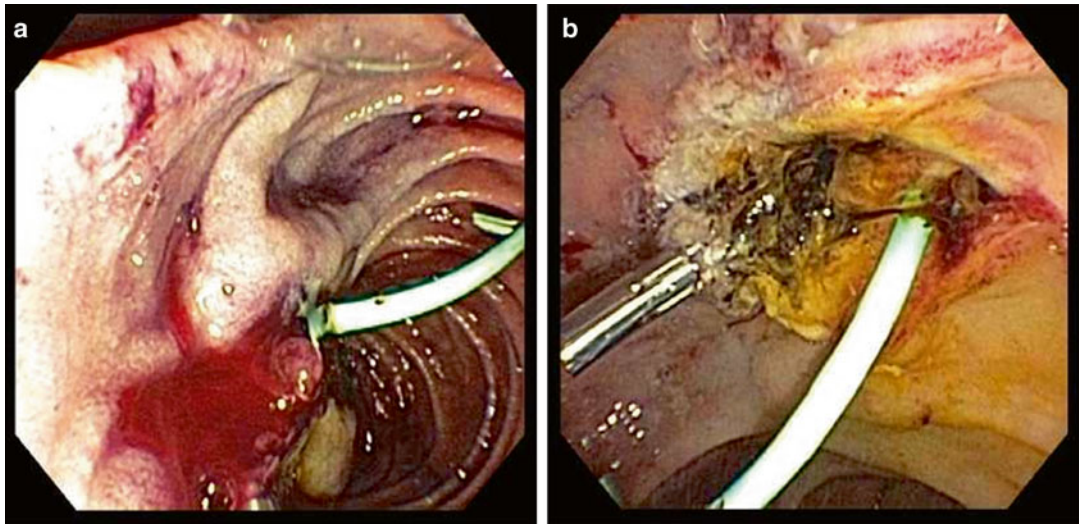

Fig. 10.2 (**a**) Active post-sphincterotomy bleeding. (**b**) Hemostasis achieved with combined bipolar coagulation and clip placement

with a decreased rate of bleeding, but is to be avoided because of well-documented increased risk of post-ERCP pancreatitis. It may be considered in highly selected cases where sphincterotomy is particularly risky. Specific examples include patients with bile duct stones and significant coagulopathy that cannot be easily corrected and those in whom location of the papilla makes sphincterotomy technically difficult (e.g. intradiverticular papilla or Billroth II anatomy) [28]. Endoscopic papillary large balloon dilation (EPLBD) following limited endoscopic sphincterotomy is a relatively new technique which has been shown to be effective and safe for the removal of large biliary duct stones [29–31]. Importantly, the use of EPLBD can not only facilitate the extraction of difficult stones, but has not been associated with increased risk of post-ERCP pancreatitis. The use of a covered sphincterotome and prophylactic submucosal injection of hypertonic saline-epinephrine have also been reported to decrease the risk of post-sphincterotomy bleeding, but these techniques have not been incorporated into routine practice [32, 33].

Post-procedural Considerations

Post-sphincterotomy bleeding often stops spontaneously, except in patients with a bleeding diathesis. Delayed bleeding is defined as occurring after the completion of ERCP, which can happen up to several weeks after the procedure. With delayed bleeding, repeat endoscopic evaluation is recommended before using other modalities. Most immediate and delayed bleeding can be managed with medical treatment and/or endoscopic therapy. Endoscopic techniques include injection therapy with dilute epinephrine, mechanical hemostasis with hemoclip, balloon tamponade or temporary fully covered self-expandable metal stent, and thermal methods (Fig. 10.2). Angiography with embolization or surgery is reserved for patients with refractory bleeding.

Procedure-Related Perforation

Perforations of the GI lumen are relatively uncommon but are considered one of the most serious and potentially life-threatening adverse events in endoscopy. The incidence of esophageal dilation-related perforation is about 0.1–0.4 % and is associated with a mortality rate of up to 20 % [34, 35]. Malignant perforations, sepsis, mechanical ventilation at presentation, and high burden of comorbidities have been reported to

impact the overall survival in patients with esophageal perforation [36]. Colonic perforation rates vary from 0.01 % to 0.8 % for diagnostic procedures and up to 5 % for therapeutic procedures [11]. Risk factors include advanced age, female gender, multiple comorbidities, diverticulosis, prior abdominal surgery, colonic obstruction, and therapeutic interventions [11, 37]. The ERCP-related perforation rate is less than 1 % in patients with normal anatomy [34]. The reported incidence of ERCP-related perforations varies (0.3–1.3 %), appears to be related to the indication for the procedure and the technical skill of the endoscopist, and carries a mortality rate as high as 25 % [38].

The rarity of endoscopic perforation makes it a challenging clinical problem. It is difficult for an endoscopist to build an extensive individual experience that is backed by firm scientific evidence with regard to patient management. A predetermined plan of action can help streamline the management process in order to reduce morbidity and mortality. The choice of the appropriate management protocol, however, remains controversial [38, 39]. Surgical treatment remains an important option. Improved endoscopic visualization and endoscopic closure devices have permitted nonsurgical management as a viable option in a significant proportion of cases, particularly if the perforation is recognized at the time of endoscopy. Colonic perforations related to therapeutic procedures (e.g., EMR) tend to be smaller and more amenable to endoscopic closure than diagnostic-related perforations (e.g., cecal barotrauma) [40].

Pre-procedural Considerations

The patient should be informed with the overall rate of perforation and cited an increased risk of perforation with specific therapeutic interventions. A thorough understanding of the various devices available for endoscopic closure of perforations is of paramount importance. These devices tend to be rarely used, and, as a result, the endoscopist and assistant typically are not as proficient with their setup and operation compared with devices that are utilized on a routine basis. Periodic in-service training can help to maintain competency and lessen technical mishaps in device deployment. Since perforations are rare occurrences, a predetermined plan of action that is developed as a unit policy is highly advisable. We have developed an endoscopic perforation management strategy at our institution and have reported our experience in the hope that it may form a useful framework for other endoscopists [7].

Patient Work-Up

The pain associated with perforation is usually acute and sudden in onset [35]. About 25 % of patients with esophageal perforation have associated vomiting and shortness of breath [35]. Cervical esophageal perforation causes neck pain and may result in subcutaneous crepitus. Management differs based on whether the perforation is detected during the procedure or is diagnosed at a later time.

Perforation Detected at the Time of Endoscopy

Colonic perforation is obvious when a mural tear with visualization of intra-abdominal organs or serosal fat is seen at endoscopy. Failure to maintain adequate visualization of the lumen due to poor distention may be due to perforation and leakage of air into the peritoneum. It is important to recognize markers, such as the target sign following EMR (Fig. 10.3), and close the defect accordingly [41]. Careful analysis of the post-EMR specimen and resection defect may reveal a target sign, which is an endoscopic finding of inadvertent muscularis propria resection and potential perforation [41]. Recognition of this endoscopic sign allows for prompt endoscopic treatment.

An important physical sign is tension pneumoperitoneum, which might require needle decompression to alleviate cardiorespiratory compromise. Fine needle decompression using a 14-gauge angiocatheter needle is an effective means of relieving intra-abdominal hypertension in acute abdominal compartment syndrome [42].

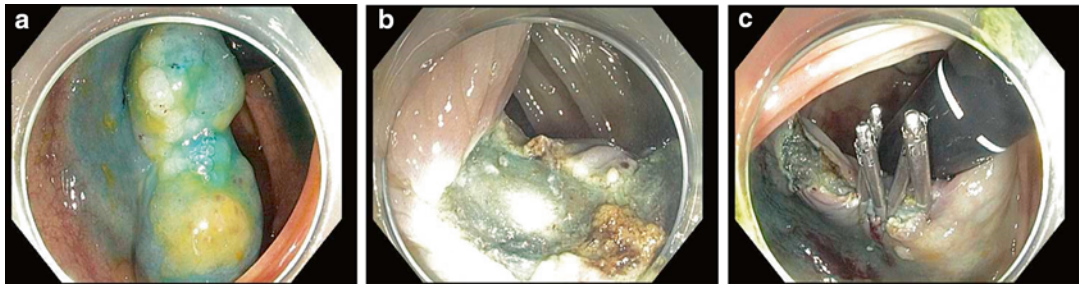

Fig. 10.3 (**a**) Appearance of large flat colon polyp following submucosal dye-assisted fluid injection. (**b**) Target sign seen following hot snare resection of lesion. (**c**) Clip closure of target sign defect

The utilization of carbon dioxide insufflation, if available, during endoscopy will alleviate the problem related to abdominal compartment syndrome because carbon dioxide is reabsorbed approximately 100 times faster than room air. If room air is used during a procedure, switching to insufflation with carbon dioxide, if available, when a perforation is detected is highly advisable, particularly if endoscopic closure is to be attempted. Small colonic perforations are generally more difficult to recognize endoscopically and could present with clinical signs and symptoms of peritonitis within several hours after the completion of colonoscopy. A high index of suspicion must be maintained for possible colonic perforation when post-procedural patients present with delayed onset progressive abdominal pain, especially when therapeutic interventions have been performed.

The decision between surgery and endoscopic closure is based on the type, location and accessibility of injury, quality of the bowel preparation, underlying pathology, clinical stability of the patient, available devices, and expertise. Endoscopic treatment with minimal air insufflation is suitable for small perforations, with prompt diagnosis, and in the presence of a good bowel preparation. Endoscopic closure using through-the-scope (TTS) and over-the-scope (OTS) clips has been reported as a feasible and effective method [43–45]. The Ovesco® OTS clip (Ovesco Endoscopy AG, Tubingen, Germany) enables more durable closure than TTS clips because of its ability to grasp more tissue (by pulling the defect into the cap prior to clip deployment) and to apply a greater compression force for full-thickness closure (Fig. 10.4). The OverStitch™ (Apollo Endosurgery, Austin, TX, USA) endoscopic suturing system is a promising tool for closure of defects, although there are limited studies on its efficacy and safety for closure of perforations.

The clinical approach at the time of perforation recognition is complicated by the need to involve multiple specialty providers and reach consensus to accomplish a number of tasks and interventions in a relatively short period of time. As such, a management strategy that focuses only on the final end point (e.g., surgical versus endoscopic closure) can oftentimes be suboptimal. Before this final end point is reached, however, a multiple-step process occurs that requires dynamic coordination between multiple services, including GI endoscopy, surgery, and radiology. The need for management algorithms in situations which call for multiple urgent interventions by multiple providers from different specialties has been recognized and used in various areas of medicine (e.g., management of cardiorespiratory arrest). Therefore, we believe that each institution should have a perforation management algorithm that takes into account local expertise and resources. Some specific questions that need to be addressed include:

- Should a nasogastric tube be placed? When should that occur (during the endoscopic procedure, after the procedure in the recovery area, at a later point in time after other evaluation has taken place)?

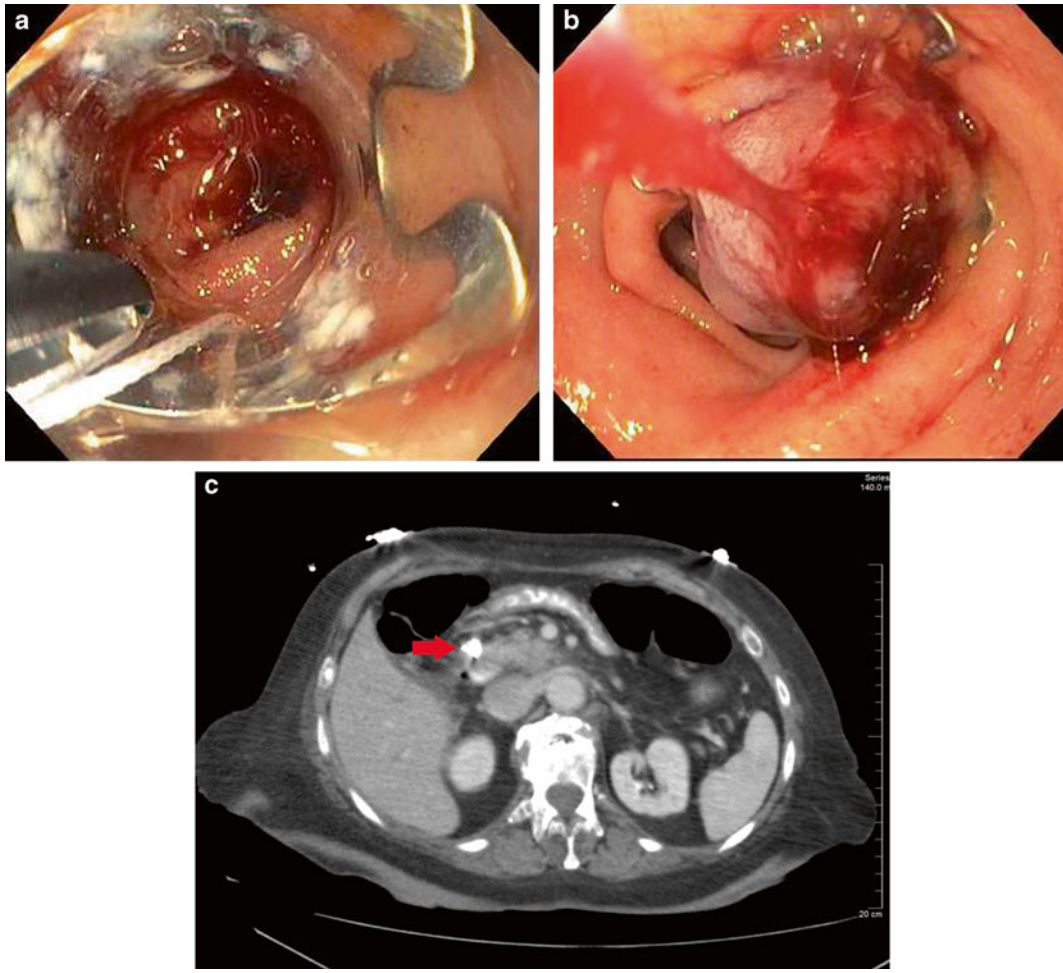

Fig. 10.4 (**a**) Over-the-scope clip closure of iatrogenic duodenal perforation by tip of duodenoscope during ERCP. (**b**) Successful closure of perforation with the over-the-scope clip device. (**c**) CT abdomen obtained post-endoscopic closure shows the over-the-scope clip (*arrow*) and small foci of retroperitoneal air

- Is there a need to obtain blood work for evaluation? If so, what specific blood tests should be ordered and when?
- Is there a need to obtain a radiographic study to confirm the perforation even if there is no doubt that a perforation has occurred (e.g., the endoscope enters the peritoneal cavity)?
- If radiologic studies are required, what is the preferred diagnostic modality (plain flat view film versus acute abdominal series including flat upright film versus CT)?
- If CT is ordered, should one order the study with intravenous contrast, oral contrast, both, or neither? If oral contrast is given, how long prior to the study should contrast be administered?
- What type of antibiotic should be given?
- Should routine electrocardiogram (EKG) be obtained?
- Should a surgical consultation be obtained if the perforation is closed endoscopically?
- If surgical consultation is deemed necessary, what is the best timing for the consultation (immediately when the perforation is recognized or after some supportive evidence, such as radiologic study, is available) and which surgical specialty should be consulted?

- If the perforation is closed successfully by endoscopic means, to which service should the patient be admitted (surgical versus medical service)?
- Who is going to communicate with the family in the hectic time following the adverse event?
- It is typical for the endoscopist involved with the perforation to have other cases scheduled for the day. Who is going to cover these cases?

These questions do not necessarily have right or wrong answers, but preferably should be addressed prior to the occurrence of the adverse event. This may provide for a more organized experience where all participating services have clearly assigned responsibilities, resulting in a less stressful environment and more efficient achievement of the needed tasks.

Perforation Detected at a Later Time

Nothing by mouth status, intravenous fluids, empiric antibiotics, and appropriate pain management should be initiated when perforation is suspected. Diagnostic work-up should be performed immediately. A prompt diagnosis is the most powerful predictor of outcome following perforation, with significant morbidity and mortality associated with delayed diagnosis beyond 24 h [46]. Diagnosis of a perforation relies on radiographic evidence (x-ray and/or CT) [35]. Management depends largely on the site and severity of the perforation and the time lapse between the perforation and initiation of therapy [35]. In patients with limited injury and contained leakage without systemic symptoms, supportive treatment may be sufficient. Antibiotics are recommended (ciprofloxacin and metronidazole are recommended as first-line therapy, whereas ticarcillin-clavulanate is recommended in patients who are allergic to the first-line medications) [7]. CT scan without intravenous contrast, but with oral or rectal water-soluble contrast, is the preferred test for upper GI or lower GI perforation, respectively [7]. This protocol can avoid contrast-induced nephropathy, while there is significantly added value on contrast study. Right lateral decubitus positioning is recommended if duodenal perforation is suspected. A prior discussion on a predetermined plan with the surgical team is preferred once perforation is suspected. If endoscopic closure is attempted with stent (for esophageal perforation) or clip placement and the CT does not show extravasation, continued medical management is the preferred approach. In the case of overt contrast extravasation, surgical approach should be given first consideration. The suggested site-specific management algorithms for perforation are outlined in Figs. 10.5, 10.6, and 10.7 [7].

The management of ERCP-related perforations remains controversial [38]. Clinical and radiographic features can be used to determine either surgical or conservative treatment [47]. The mortality rate increases dramatically with delayed treatment [47]. ERCP and endoscopic sphincterotomy carry the risk of perforation of the bile duct, pancreatic duct, or duodenum [38]. Luminal perforation (free bowel wall perforation) and perforation at the esophagus, the stomach, the liver, and the afferent limb of a Billroth II anastomosis have been reported [48–50]. Proposed classification of ERCP-related perforations includes type I for duodenal wall perforations, type II for periampullary perforations, type III for ductal or duodenal perforations due to endoscopic instruments, and type IV for guidewire perforations with the presence of retroperitoneal air on x-ray [38, 51]. The need for operative intervention should be based on the type of injury, clinical findings, and radiographic features [51]. Type I perforations are usually large and should be treated surgically. Type II and type III perforations may be treated conservatively if contrast leak is minimal and no associated fluid collections are present. Type IV perforations usually do not require surgery [38, 51]. Endoscopic treatment, including self-expandable metal stents, TTS clips, and OTS clips, have been used with success [52]. The suggested management algorithm for ERCP-related perforations is outlined in Fig. 10.8.

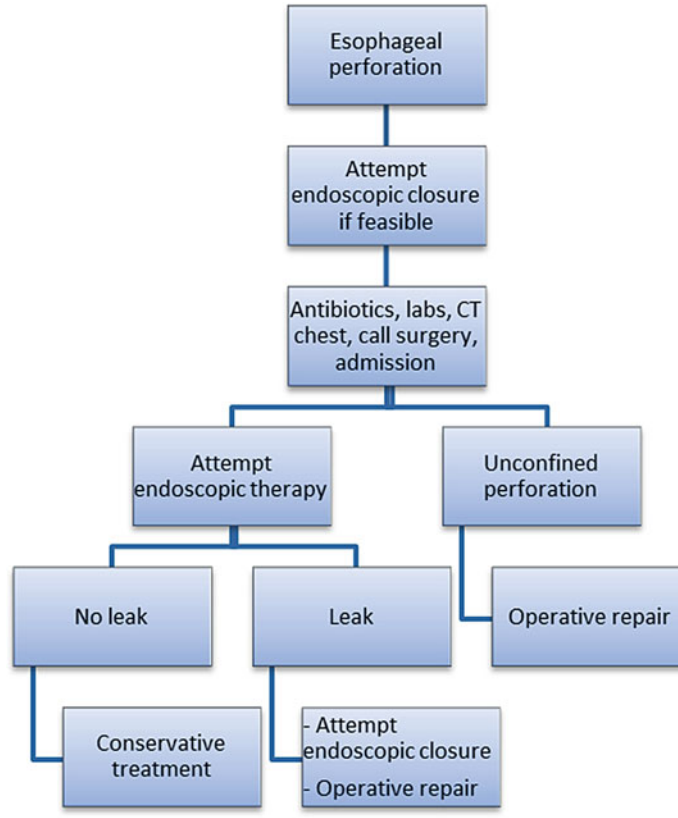

Fig. 10.5 Suggested management algorithm for esophageal perforation

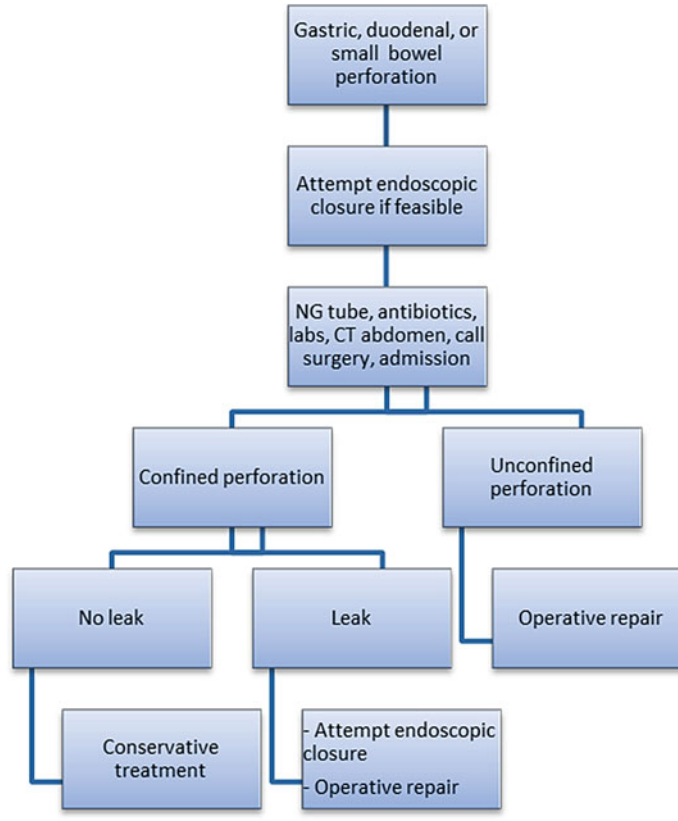

Fig. 10.6 Suggested management algorithm for gastric, duodenal, or small bowel perforation

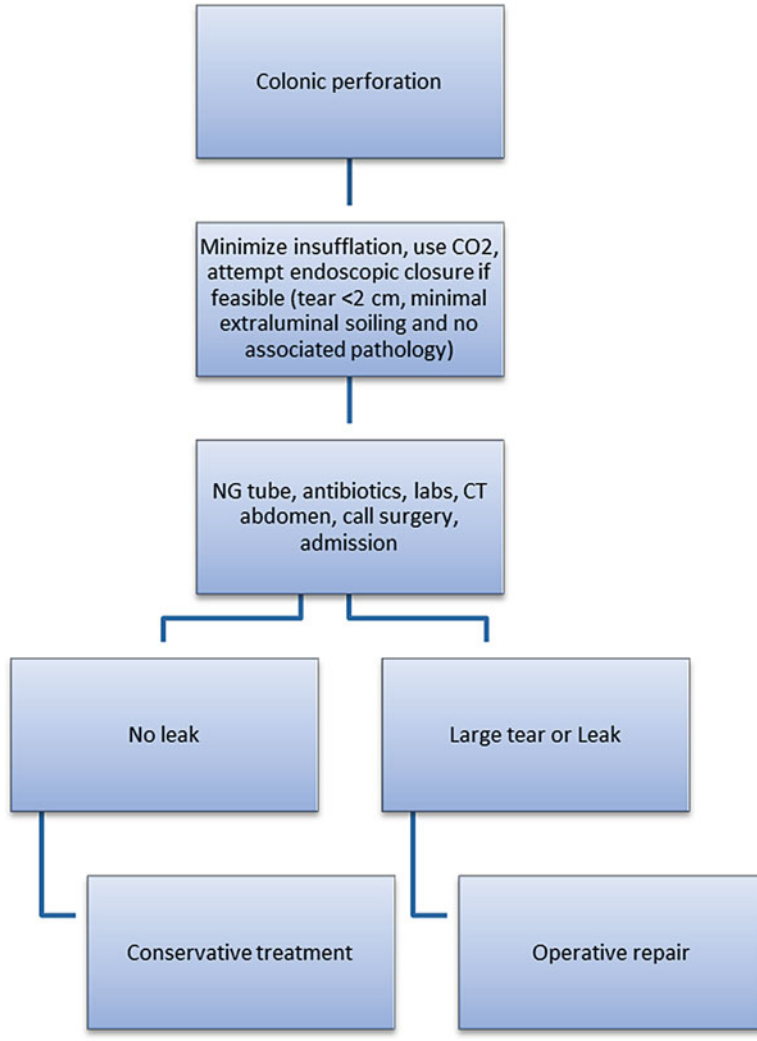

Fig. 10.7 Suggested management algorithm for colonic perforation

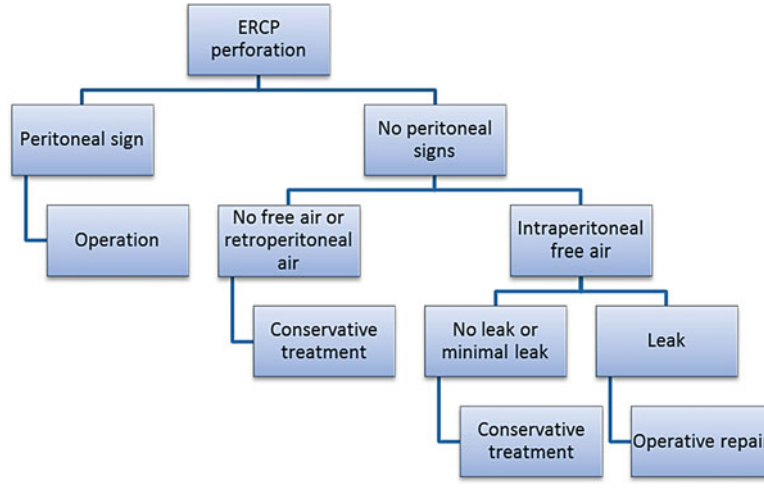

Fig. 10.8 Suggested management algorithm for ERCP-related perforation

Summary

Endoscopic adverse events are inevitable. Careful attention to high-risk patients, appropriate patient preparation and planning, proper procedural techniques, and close post-complication monitoring are critical. Procedural benefits should clearly justify the anticipated procedural risks. Early recognition and prompt treatment are key determinants to minimize suboptimal outcomes. The goal in managing endoscopic adverse events remains in the timely recognition and efficient evaluation and therapy of the unplanned event in order to optimize patient outcomes. To this end, institution-specific and multidisciplinary advanced planning protocols are recommended to establish expedited evaluation and management of patients with endoscopic adverse events.

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Hemostasis of Acute Nonvariceal Upper Gastrointestinal Bleeding

11

Amir Klein and Ian M. Gralnek

Introduction

The causes of acute non-variceal upper gastrointestinal bleeding (NVUGIB) include gastroduodenal peptic ulcer (20–50 %), gastrointestinal erosions (8–15 %), erosive esophagitis (5–15 %), Mallory-Weiss tear (8–15 %), angiodysplasia/gastric antral vascular ectasia (GAVE) (5 %), and benign and malignant tumors of the upper gastrointestinal (GI) tract (5 %) [1–3]. Upper endoscopy in patients presenting with acute NVUGIB is effective for both diagnosis of the bleeding cause and for therapy, as indicated. Endoscopic hemostasis significantly reduces rebleeding rates, blood transfusions, length of hospital stay, need for surgery, and/or mortality [4–13]. Furthermore, early upper endoscopy, performed within 24 h of presentation, improves patient outcomes [5]. This chapter will highlight the role of endoscopic evaluation and risk stratification, as well as the various endoscopic modalities available for hemostasis of acute NVUGIB.

Timing of Endoscopy in Acute NVUGIB

After correction of coagulopathy and hemodynamic stabilization with intravenous fluid resuscitation, patients with presumed acute upper GI bleeding should undergo early endoscopy [6, 7]. Early endoscopy is defined as esophagogastroduodenoscopy (EGD) performed within 24 h of patient presentation. Although early endoscopy is advocated in most patients, select high-risk patients, such as those with severe coagulopathy, acute coronary syndrome, or suspected bowel perforation, should have their upper endoscopy examination deferred until the clinical situation is fully evaluated and stabilized. In contrast, low-risk patients, identified by clinical pre-endoscopy risk stratification scores (e.g., Glasgow-Blatchford Bleeding Score or the Clinical Rockall Risk Score), may be considered for outpatient management [11–13].

Very early or emergent upper endoscopy (defined as within 2–12 h of patient presentation) has not been shown to confer additional benefit or

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A. Klein, M.D.
Department of Gastroenterology, Rambam Health Care Campus, Haifa, Israel

Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

I.M. Gralnek, M.D. M.S.H.S., F.A.S.G.E. (✉)
Department of Gastroenterology and Hepatology, Ha'Emek Medical Center, Afula, Israel

Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
e-mail: ian_gr@clalit.org.il

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alter patient outcomes. A review of meta-analyses on the subject found no significant difference between urgent (1–12 h) and early (>12 h) endoscopy in terms of rebleeding rates, need for surgery, or mortality [8]. One controlled study, however, reported significantly shorter hospital length of stay and lower costs in favor of very early (1–2 h) as opposed to elective (1–2 days) upper endoscopy [14]. Endoscopy performed within hours of presentation will likely reveal more high-risk bleeding stigmata, such as active bleeding, a non-bleeding visible vessel, or an adherent clot. However, these endoscopic findings, which invariably lead to more therapeutic interventions, are not clearly beneficial with regard to patient outcomes [14, 15].

Early upper endoscopy may actually confer additional risk to the patient when the procedure is performed during off hours (nights and weekends). An increased risk in oxygen desaturation has been described in patients undergoing urgent (within 2 h) versus early (2–24 h) endoscopy [16]. Moreover, a large cohort study from the United Kingdom showed a strong correlation between increased mortality and the practice of after-hours endoscopy [17].

Endoscopic Hemostatic Modalities for NVUGIB

A variety of endoscopic devices for hemostasis exists for the management of acute NVUGIB, including injection therapies, thermal modalities, mechanical devices, or a combination thereof. This section will focus on the technical aspects and applications of these various techniques.

Injection Therapy

The primary mechanism of action of injection therapy is local tamponade resulting from the volume effect. The addition of epinephrine (1:10,000 or 1:20,000 dilution) in saline solution has a secondary pharmacological effect that produces local vasoconstriction [18]. Agents, such as normal saline or dilute epinephrine, are usually injected in 1–2-ml aliquots around the bleeding stigmata in a 4-quadrant fashion, if feasible. There are data to suggest that higher injected volumes of dilute epinephrine (>10–20-ml total) are superior to small volume injection for achieving hemostasis in peptic ulcer bleeding (Video 11.1) [19]. Care is needed, however, to avoid over-injection on the side of the lesion closest to the tip of the endoscope as this may elevate the lesion away from the field of view and hamper access for subsequent therapy.

Sclerosing agents, such as ethanol, ethanolamine, and polidocanol, produce hemostasis by causing direct tissue injury and vascular thrombosis. However, the injection of a sclerosant is associated with an unpredictable depth of injury, which can lead to delayed perforation. Sclerosing agents are not commonly used for NVUGIB due to the availability of safer and equally effective alternatives for hemostasis. Tissue adhesives, such as thrombin, fibrin sealant, and cyanoacrylates, are another class of injectable agents that can be used to create a primary seal at the site of bleeding. These agents, however, are not commonly used in the treatment of NVUGIB and are not approved by the US Food and Drug Administration (FDA) for this purpose.

Endoscopic injection is performed using catheter needles, which consist of an outer sheath and an inner hollow-core needle (19–25 gauges). By actuating a handle on the end of the sheath, the endoscopist or assistant can retract the needle into the sheath for safe passage through the working channel of the endoscope. With the catheter needle in position near the site of bleeding, the needle is extended out of the sheath, and the agent is injected using a syringe attached to the catheter handle after needle puncture into the submucosal space [18]. Table 11.1 lists available injection needles.

Thermal Therapy

Thermal devices used in the treatment of GI bleeding include contact and noncontact modalities (Table 11.2). Contact thermal devices include heater probes, which generate heat directly at the tip of the probe, and bipolar electrocoagulation

Table 11.1 Injection needles[a]

Manufacturer	Device name	Sheath diameter (French)	Sheath length (cm)	Needle gauge	Needle length (mm)
Boston Scientific (Natick, MA)	Interject sclerotherapy needle	7	200, 240	23, 25	4, 6
ConMed Endoscopic Technologies (Chelmsford, MA)	Click-Tip injection needle	7	180, 230	19, 22, 25	4, 6
	Flexitip disposable sclerotherapy needle	7	180, 230	4, 5	
	Sure shot injection needle	7	160, 230	5	
Cook Medical (Winston-Salem, NC)	Acujet variable injection needle	7	220	23, 25	
	Injectaflow variable injection needle	7	220	23, 25	
Olympus America (Center Valley, PA)	Injector force injection needle	7	230	21, 23, 25	4, 5, 6, 8
US Endoscopy (Mentor, OH)	Articulator injection needle	7	160, 230, 350	25	4,5
	Carr-Locke injection needle	7	230	25	5
	Vari-Safe injection needle	7	230	23	4, 5, 7
Kimberly-Clark (Roswell, GA)	Injection needle catheter	7	160, 200, 240	23, 25	4, 6
Telemed Systems (Hudson, MA)	Sure-Stop sclerotherapy needle	5,7	160, 240	25	4, 5

[a]Adapted from Conway JD, Adler DG, et al. Endoscopic hemostatic devices. Gastrointest Endosc 2009;69:987–96

Table 11.2 Contact and noncontact thermal devices[a]

Manufacturer	Device name	Sheath diameter (French)	Sheath length (cm)	Special features
Boston Scientific (Natick, MA)	Gold probe	7, 10	300, 350	
	Injector gold probe	7, 10	210	Integrated injection needle
ConMed Endoscopic Technologies (Chelmsford, MA)	Bicap superconductor, multielectrode bipolar probe	5, 7, 10	200, 300, 350	
	Palladium tip bipolar hemostasis probe	7, 10	300	
	Beamer argon probe	5, 7, 10	160, 230, 320	
Cook Medical (Winston-Salem, NC)	Quicksilver bipolar probe	7, 10	350	
Olympus America (Center Valley, PA)	Solar probe	7, 10	350	
	Heat probe	7, 10	230, 300	Reusable
	Coagrasper	7	165	
US Endoscopy (Mentor, OH)	Bipolar hemostasis probe	7, 10	350	
Canady (Hampton, VA)	Canady plasma GI probe	5, 7	230, 340	Straight, side fire
ERBE (Marietta, GA)	APC probe	5, 7, 10	50, 220, 300	Straight
	FiAPC probe	5, 7, 10	50, 220, 300	Side circumferential fire

[a]Adapted from Conway JD, Adler DG, et al. Endoscopic hemostatic devices. Gastrointest Endosc 2009;69:987–96

probes, which generate heat indirectly by passage of an electrical current between closely spaced electrodes at the tip of the probe. Noncontact thermal devices include argon plasma coagulation and laser therapy, although the latter is rarely used nowadays.

Heat generated from these thermal devices leads to edema, coagulation of tissue proteins, contraction of vessels, and indirect activation of the coagulation cascade, resulting in a hemostatic bond [18, 20]. Heater and bipolar probes also benefit from local tamponade (mechanical pressure of the probe tip directly onto the bleeding site) combined with heat or electrical current to coagulate blood vessels, a process known as "coaptive coagulation." This process minimizes the heat sink effect, whereby energy is lost due to blood flow through a non-compressed vessel.

The heater probe consists of a Teflon-coated hollow aluminum cylinder with an inner heating coil. A thermo-coupling device at the tip of the probe maintains a constant temperature. A foot pedal controls heat activation as well as water-jet irrigation through the probe. Heater probe activation delivers energy to the diode in the probe tip. Once the pulse has been initiated, the duration of activation is predetermined and cannot be stopped until the entire amount of preselected energy is delivered [21]. A setting of 30 J is suggested for peptic ulcer bleeding (Video 11.1) and gastric Dieulafoy lesions. A setting of 15 J is recommended for other lesions, such as a bleeding Mallory-Weiss tear and vascular ectasias.

The bipolar probe delivers thermal energy by completion of an electrical circuit between positive and negative electrodes on the tip of the probe as current flows through non-desiccated tissue. In contrast to monopolar devices, the electrical circuit is confined to the tip of the probe, and so no grounding pad is required. As the targeted tissue desiccates, there is decrease in electrical conductivity, thereby limiting the maximum temperature, depth, and area of tissue injury. A foot pedal controls the delivery of the energy in watts [20]. The usual setting for peptic ulcer bleeding and gastric Dieulafoy lesions is 20 W delivered in 7–10 s application (referred to as tamponade stations) prior to removal of the probe. Several applications, with moderate to firm probe-tissue contact pressure, may be required until active bleeding is controlled and/or white coagulum formation with shallow cavitation of the treated site is observed. A lesser amount of energy (12–15 W) and shorter application duration (3–5 s) are recommended for other lesions, such as a bleeding Mallory-Weiss tear and vascular ectasias. Similar to the heater probe, built-in water-jet irrigation in the bipolar probe facilitates identification and precise targeting of the actively bleeding point prior to coagulation and aids in sliding the probe off the coagulated, sticky tissue.

Argon plasma coagulation (APC), a noncontact device, uses high-frequency monopolar alternating current conducted to the target tissue through a stream of ionized argon gas to achieve coagulation of superficial tissue [22]. As the coagulated tissue surface loses its electrical conductivity, the plasma stream shifts to adjacent non-desiccated (conductive) tissue, which again limits the depth of tissue injury [18]. If the APC catheter is too far from the target tissue, there is no ignition of the gas, and depression of the foot pedal results only in flow of inert argon gas. Coagulation depth is dependent on the generator power setting, duration of application, and distance from the probe tip to the target tissue [22, 23]. The optimal distance between the probe and target tissue ranges from 2 to 8 mm [24]. Commercially available APC systems (ERBE USA, Marietta, GA; ConMed Electrosurgery, Centennial, CO; Canady Technology, Pittsburgh, PA; Genii, St. Paul, MN) include a specialized electrosurgical generator capable of high-frequency monopolar current, an activation foot pedal, an argon gas cylinder, disposable grounding pads, and flexible single-use APC probes. An adjustable gas flowmeter allows argon gas flow rates of 0.5–7 l/min. APC probes are composed of Teflon with a ceramic tip encasing the tungsten electrode and are available as end-firing, side-firing, and circumferential-firing probes. APC is primarily used for the treatment of superficial mucosal vascular lesions, such as vascular ectasias and GAVE (Video 11.2). Suggested settings are a power of 30–45 W (depending on the APC generator utilized) and an argon flow rate of 1 l/min.

Table 11.3 Clipping devices[a]

Manufacturer	Device name	Sheath diameter (French)	Sheath length (cm)	Jaw opening width (mm)	Special features
Boston Scientific (Natick, MA)	Resolution clip	7	155, 235	11	2-prong clip
Cook Medical (Winston-Salem, NC)	Triclip	7,8	207	12	3-prong clip
	Instinct clip	7	230	16	2-prong clip rotatable
Olympus America (Center Valley, PA)	Quickclip 2	7	165, 230	9	2-prong clip rotatable
	Quickclip 2 long	7	165, 230	11	2-prong clip rotatable
	QuickClipPro	7	165, 230	11	2-prong clip rotatable

[a]Adapted from Conway JD, Adler DG, et al. Endoscopic hemostatic devices. Gastrointest Endosc 2009;69:987–96

Mechanical Therapy

Endoscopic mechanical therapies include clips (Table 11.3) and band ligation devices. Through-the-scope (TTS) endoscopic clips are deployed directly onto the bleeding site (e.g., active bleeding, non-bleeding visible vessel) and typically fall off within days to weeks after placement [1, 25]. All endoscopic clipping devices have three primary components: a metallic double- or triple-pronged preloaded clip, a delivery catheter, and a handle to operate and deploy the clip. Clips are available in a variety of jaw lengths and opening widths. The delivery catheter consists of a metal cable with or without a protective sheath. The tip of the metal cable has a hook onto which the clip is attached. The handle consists of two sliding components: the first allows advancement of the metal cable holding the clip out of the protective sheath, if present, and the second is the plunger that controls the opening, closing, and deployment of the clip. After insertion of the clip through the working channel of the endoscope, the clip is extended out of the sheath, if one is present. The clip is then positioned over the target area and opened with the plunger handle. A rotation mechanism on the handle is available on some commercially available clips, and this allows the endoscopist to change the orientation of the clip at the site of bleeding. The jaws of the clip are applied with pressure and closed onto the target tissue by using the device handle [25, 26]. Some clips have reopening capabilities and can be repositioned, whereas others are permanently deployed and released upon clip closure. Similarly, some clips are automatically released on deployment, while others require repositioning of the plunger handle to release the deployed clip from the catheter. Hemostasis is achieved by mechanical compression of the bleeding site (Video 11.3). Both the operator and assistant should be well acquainted with the various clip deployment mechanisms so as to facilitate easy and efficient utilization. Clip selection is mostly dependent on device availability, operator preference, and familiarity with a particular clip.

Emerging data suggest that the over-the-scope clip (OTSC; Ovesco, Tübingen, Germany), developed for closure of small mural defects, may also be effective for the management of focal nonvariceal GI bleeding lesions (e.g., peptic ulcer, Dieulafoy lesion, post-polypectomy bleeding site) (Figs. 11.1 and 11.2) [27–29]. The OTSC may prove superior to standard TTS clips because of its ability to grasp more surrounding tissue and apply a greater compressive force (Video 11.4). However, no comparative data are available at this time. The OTSC device includes an applicator cap carrying the clip, a memory-shaped nitinol clip in the form of a bear claw when released, and a rotating hand wheel for clip deployment. The applicator cap with the mounted nitinol clip is affixed to the tip of the endoscope in a manner similar to that of a variceal band ligation device. Caps are available in three sizes to accommodate various endoscope diameters: 11 mm (designed for endoscope diameters 9.5–11 mm), 12 mm (for endoscope diameters 10.5–12 mm), and 14 mm (for endoscope diameters 11.5–14 mm). Caps are also available in two depths (3 and 6 mm) to allow variation in the amount of tissue desired during

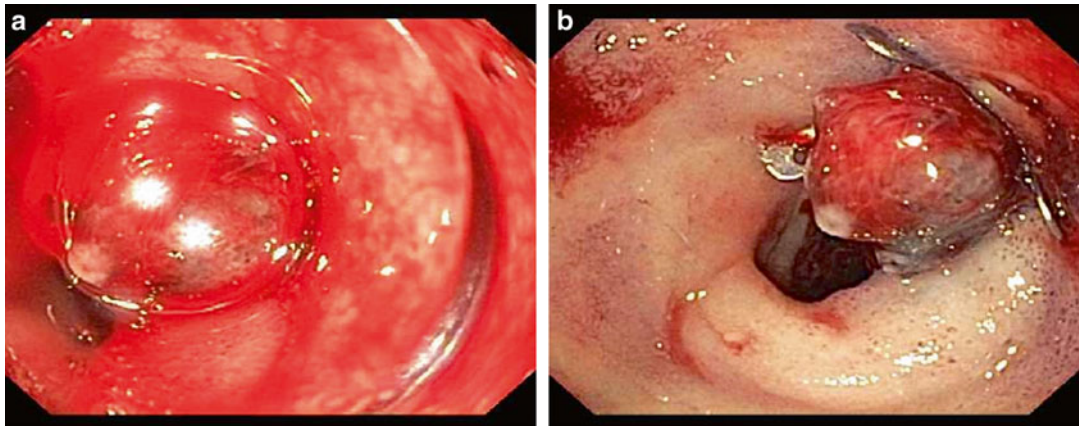

Fig. 11.1 (**a**) Cap-assisted access to an actively bleeding duodenal ulcer in a difficult location. (**b**) Successful hemostasis achieved with placement of an over-the-scope clip

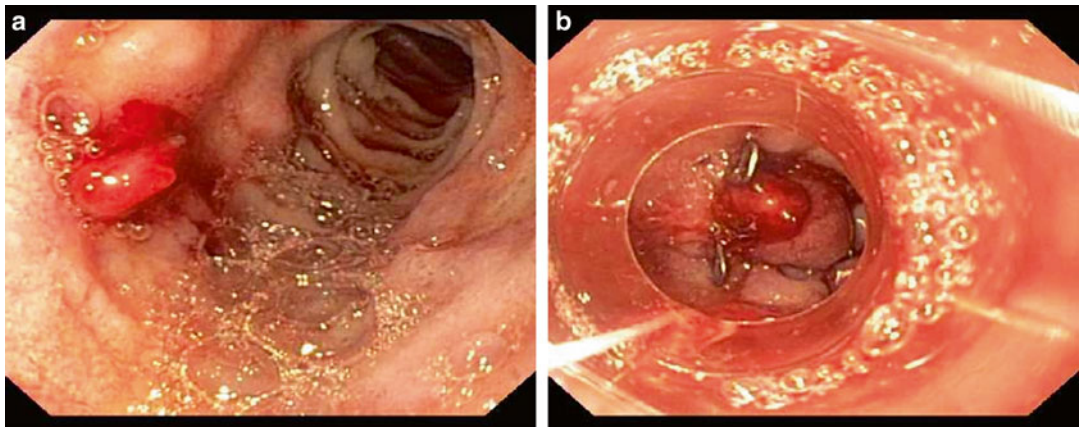

Fig. 11.2 (**a**) Duodenal Dieulafoy lesion. (**b**) Hemostasis achieved with placement of an over-the-scope clip

suction. Clips come in three different sizes to match the cap sizes and also in three different shapes of teeth: type A (rounded teeth), type T (pointed teeth), and type GC (longer pointed teeth). Clips with rounded teeth are used when the goal is tissue compression for hemostasis, particularly in the thinner-walled esophagus and colon. The applicator cap incorporates a clip release thread, which is pulled retrograde through the working channel of the endoscope and fixed onto a hand wheel mounted on the working channel access port of the endoscope. The clip is released by turning the hand wheel, in a manner similar to deploying a variceal ligation band [27].

Endoscopic band ligation (EBL) devices, commonly used in esophageal variceal bleeding, can also be effective at treating select NVUGIB lesions. EBL involves placement of elastic bands under the suctioned target tissue to produce mechanical compression and tamponade (e.g., Dieulafoy lesion) (Fig. 11.3 and Video 11.5) [30].

Emerging Endoscopic Techniques for NVUGIB

Video Capsule Endoscopy

Recently, video capsule endoscopy has been shown to be an effective method to identify acute upper GI bleeding in the emergency department. Capsule endoscopy identified gross blood in the

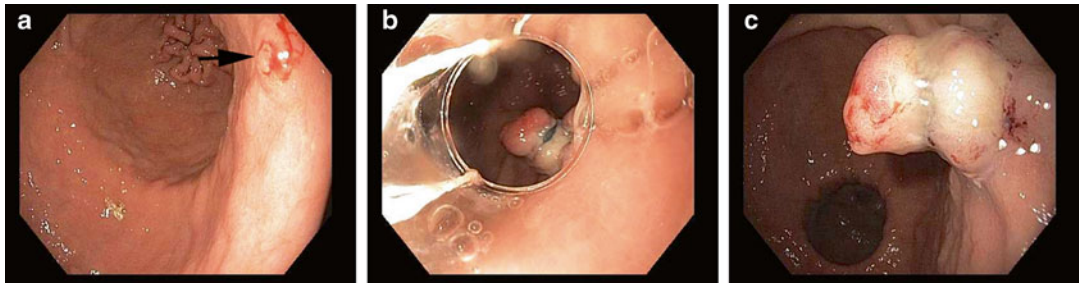

Fig. 11.3 (**a**) Gastric Dieulafoy lesion. (**b**) Band ligation performed. (**c**) Post band ligation appearance

upper GI tract, including the duodenum, significantly more often than nasogastric tube aspiration, and identified inflammatory lesions to a similar degree as EGD. Capsule endoscopy may also facilitate patient triage and earlier endoscopy but at this point in time should not be considered a substitute for EGD [31].

Capsule endoscopy only offers diagnostic capabilities and cannot offer the dual diagnostic and therapeutic advantage of EGD in the hands of a skilled endoscopist for the treatment of NVUGIB. The role of real-time capsule endoscopy might be in a setting where endoscopic services are not readily available and to ascertain the presence of upper GI bleeding before a patient is referred to a tertiary facility.

Topical Hemostatic Agents

Hemostatic sprays have been used thus far in a limited number of patients with acute upper and lower GI bleeding, with good results overall [32]. The advantages of noncontact spray catheter delivery of hemostatic agents include ease of use, lack of need for precise lesion targeting, access to lesions in difficult locations, and the ability to treat a larger area (Video 11.6). Various granules or powders have been used in military combat situations to treat compressible external hemorrhage in battlefield casualties. One of these compounds, TC-325 (Hemospray; Cook Medical Inc., Winston-Salem, NC), is currently undergoing evaluation as a hemostatic agent for endoscopic use [32, 33]. TC-325 is a proprietary, inorganic, absorbent powder that rapidly concentrates clotting factors at the bleeding site, forming an adherent coagulum. Hemospray is a handheld device consisting of a pressurized CO2 canister for delivery of the powder, a TTS delivery catheter, and a reservoir for the powder cartridge. The powder is delivered via push button in 1–2-s bursts until hemostasis is achieved. The maximum amount of TC-325 that can be safely administered during a single treatment session has not yet been established [32]. The coagulum typically sloughs within 3 days and is naturally eliminated. Hemospray has received regulatory clearance in some countries but is not yet approved by the US FDA.

Hemostatic sprays derived from plant products have also been evaluated. Clinical experience with these agents for endoscopic hemostasis is currently limited to the off-label use of the Ankaferd Blood Stopper (ABS; Ankaferd Health Products Ltd, Istanbul, Turkey), a mixture of extracts from several plants that is approved in Turkey for topical treatment of dental and postsurgical external bleeding [34–39]. ABS promotes formation of a protein mesh that acts as an anchor for erythrocyte aggregation without significantly altering coagulation factors or platelets. The ABS solution, available in 2-mL vials, is delivered onto the bleeding site via an endoscopic spray catheter until an adherent coagulum is formed [35]. EndoClot (EndoClot Plus Inc., Santa Clara, CA) consists of absorbable modified polymers and is intended to be used as an adjuvant hemostatic agent to control bleeding in the GI tract. It is a biocompatible, non-pyogenic, starch-derived compound that rapidly absorbs water from serum and concentrates platelets, red blood cells, and coagulation proteins at the

bleeding site to accelerate the clotting cascade. The particles are subsequently cleared from the bleeding site with no remaining residue a few hours to days later. There are only scant data on this product's safety or efficacy [35]. The current limited data demonstrate the potential for hemostatic sprays to be used as definitive or bridge therapy. The efficacy of these agents is unknown in brisk arterial bleeding and may be limited because of the rapid "wash-away" effect of the hemostatic agent by ongoing blood flow. The exact role and overall safety of hemostatic sprays remain to be delineated. Additional data and prospective comparative studies involving a larger number of subjects are needed.

Preprocedural Considerations

In addition to fluid resuscitation and correction of coagulopathy, as previously mentioned, an assessment should be made for preemptive endotracheal intubation for airway protection, particularly in the setting of active hematemesis, encephalopathy, and/or difficult airway (e.g., short, thick neck). The procedure should also be aborted temporarily if a large amount of retained blood and clots is found in the stomach at the time of endoscopy to enable airway protection for prevention of aspiration.

A dual channel or therapeutic channel (3.7 mm) upper endoscope is recommended for the assessment of acute upper GI bleeding. The larger working channel enables better suction capability and the passage of large (10 Fr) rather than small (7 Fr) diameter thermal probes for hemostasis. A pedal-activated water-jet irrigation device coupled to the entrance port of the working channel or built in the endoscope facilitates washing the mucosa of adherent bloody material and aids in precisely identifying the actively bleeding point for targeted hemostasis.

Common Causes of NVUGIB

Peptic Ulcer

Gastroduodenal ulcer remains the leading cause of acute NVUGIB. Mortality rates associated with peptic ulcer bleeding are still about 5–10 %. Endoscopic findings in peptic ulcer bleeding associated with increased morbidity and mortality include ulcer location (e.g., high lesser gastric curve, posterior duodenal bulb), ulcer size $\geq$ 2 cm, pulsatile arterial bleeding, and large bleeding vessel ($\geq$2 mm) [6, 9]. Endoscopic assessment and risk stratification prior to application of a specific hemostatic technique are essential in guiding the appropriate endoscopic treatment of patients with acute upper GI bleeding due to peptic ulcer.

The endoscopic stigmata of an ulcer provide prognostic information regarding the risk of ongoing bleeding or rebleeding and the necessity for therapeutic intervention (Table 11.4). In Europe and Asia, the Forrest classification for stigmata of recent hemorrhage (Fig. 11.4) is

Table 11.4 Rates of rebleeding before and after endoscopic therapy and rates of surgery and mortality with no endoscopic therapy, stratified by endoscopic stigmata

Endoscopic stigmata	Forrest classification	Prevalence (%)	Persistent bleeding or rebleeding with no endoscopic treatment (%)	Rebleeding after endoscopic hemostasis (%)	Surgery for bleeding with no endoscopic treatment (%)	Mortality with no endoscopic treatment (%)
Active bleeding	I	12–18	55–90	15–30	35	11
Non-bleeding visible vessel	IIa	8–22	43–50	15–30	34	11
Adherent clot	IIb	8–17	22–33	0–5	10	7
Flat pigmented spot	IIc	16–20	8–10	NA	6	3
Clean base	III	42–55	5	NA	0.5	2

Data from Refs. [1, 6, 10, 40]

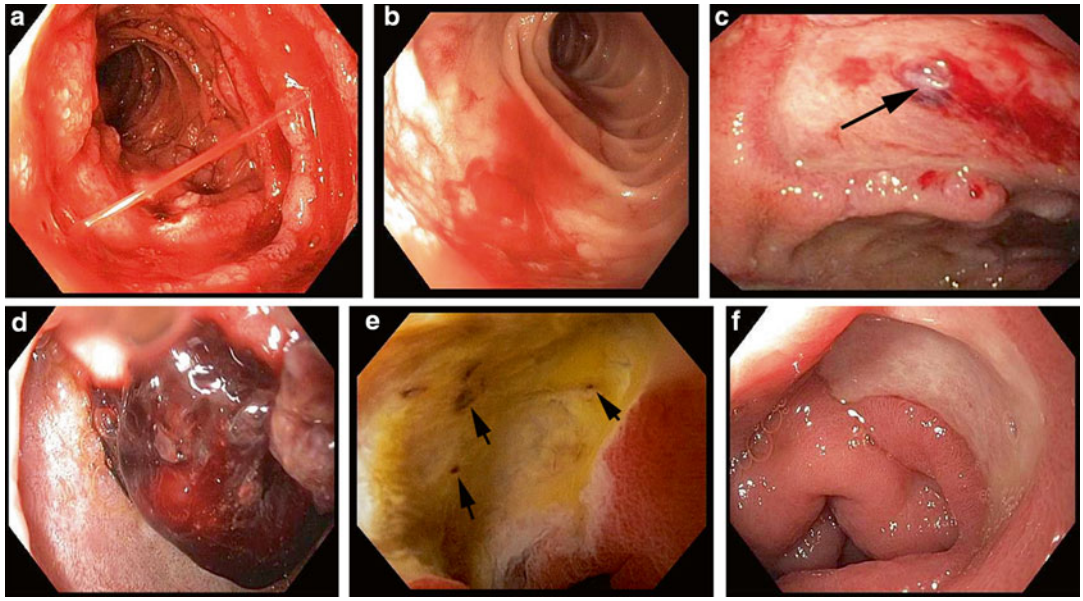

Fig. 11.4 Endoscopic stigmata of bleeding peptic ulcer. High-risk lesions include (**a**) Forrest 1A, spurting blood; (**b**) Forrest 1B, oozing blood; (**c**) Forrest IIA, non-bleeding visible vessel; (**d**) Forrest IIB, adherent clot. Low-risk lesions include (**e**) Forrest IIC, flat pigmented spots, and (**f**) Forrest III, clean base

commonly used, whereas in North America, descriptive terms are the norm. Most patients with ulcer bleeding have low-risk stigmata (flat pigmented spot or clean base) and thus do not require endoscopic hemostasis. High-risk stigmata (active bleeding, non-bleeding visible vessel, or adherent clot) are encountered in up to 35 % of patients with acute peptic ulcer bleeding [10, 40]. Active bleeding is subcategorized as spurting or oozing, although most studies of prevalence have combined these categories into "active ulcer bleeding" [41]. Results from prospective trials, however, suggest they should likely be viewed separately because the risk of further bleeding with spurting bleeding is higher than with oozing bleeding [42, 43].

Deeply penetrating, indurated ulcers with high-risk stigmata are problematic to treat endoscopically. They are usually located in the high lesser curve of the stomach or the posteroinferior wall of the distal duodenal bulb, supplied by large vessels originating from the left gastric artery or gastroduodenal artery, respectively (Video 11.7). Furthermore, these are difficult locations to access at endoscopy. In some cases, a clear cap placed at the tip of the endoscope aids in maintaining a more stable position and provides a working window for passage of hemostatic accessories. This technique is particularly helpful for accessing lesions at the duodenal angle in the setting of an edematous, shortened duodenal bulb. However, the application of firm tamponade pressure using a thermal probe on a (usually large) vessel within a penetrating ulcer base may result in perforation. Clip placement is also of limited value in this setting since the clip does not have sufficient compression force to close the indurated ulcer base. Moreover, an attempt at clip closure may result in avulsion of the vessel and precipitation of torrential bleeding (Fig. 11.5). Thus, ulcers with high-risk stigmata in deeply fibrotic bases are generally not amenable to endoscopic therapy and should be referred for angiographic embolization or surgical intervention.

Esophagitis

Erosive esophagitis can cause up to 8 % of acute upper GI bleeding. It is more commonly seen in patients who are already in hospital for another reason and with an indwelling nasogastric tube.

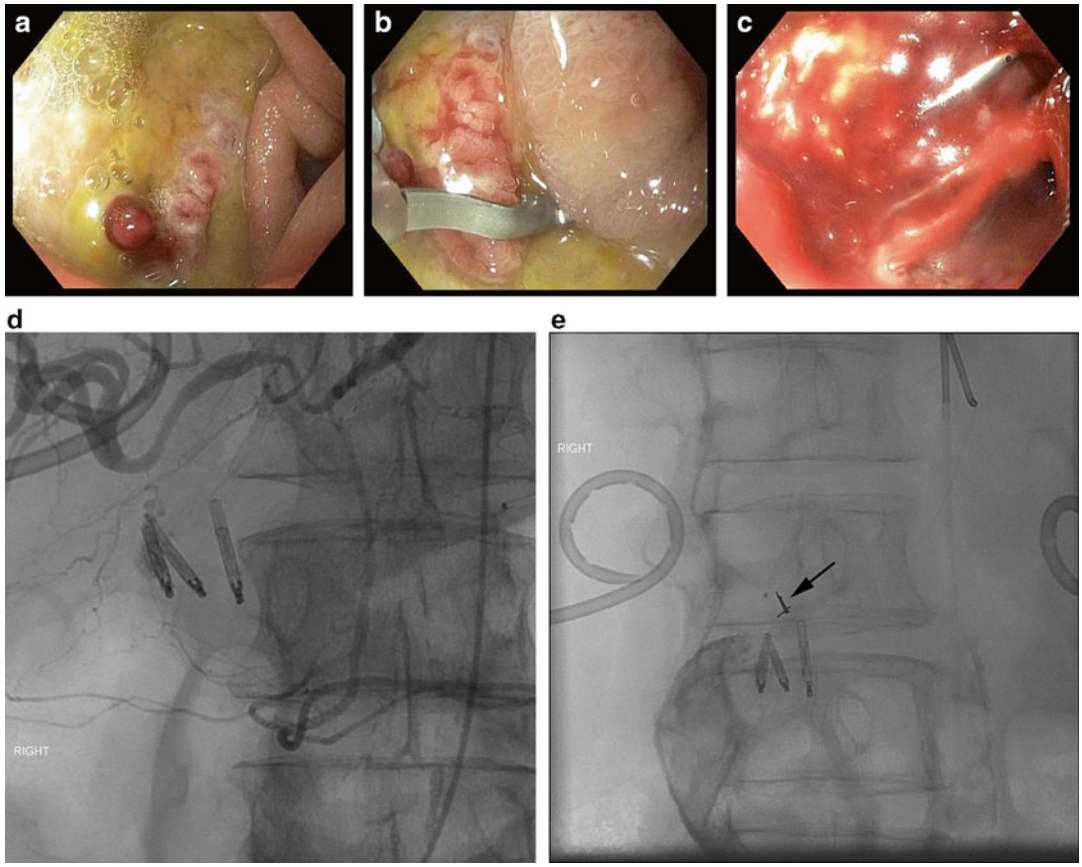

Fig. 11.5 (**a**) Large penetrating duodenal ulcer with prominent visible vessel. (**b**) Attempted clip closure of visible vessel in a fibrotic base. (**c**) Failed clip placement with precipitation of torrential bleeding. (**d**) Emergent angiogram performed for superselective embolization, aided by visualization of endoscopic clips. (**e**) Coil embolization of feeding vessel (*arrow*)

Upper endoscopy is important for diagnosis, although endoscopic hemostasis is rarely required unless a focal ulcer with high-risk stigmata of recent hemorrhage is found. The application of a thermal probe (e.g., bipolar probe at 15 W for 3–5 s with moderate contact pressure) and placement of clips are reasonable endoscopic treatment options. These patients should be treated with a proton pump inhibitor (PPI) for 8–12 weeks, followed by repeat endoscopy to rule out underlying Barrett's esophagus [10].

Mallory-Weiss Tear

A mucosal laceration at the gastroesophageal junction (more often located on the gastric side as seen on retroflex endoscopic view) is usually, but not always, due to antecedent vomiting or retching. Bleeding is usually self-limited and the rate of rebleeding approximates 10 % [10, 44]. Patients with active bleeding require endoscopic therapy. Bipolar coagulation and clips (Video 11.8), with or without epinephrine injection, as well as band ligation have all been used successfully [45–49]. In patients with portal hypertension and/or concomitant esophageal varices, band ligation is the preferred modality.

Dieulafoy Lesion

A Dieulafoy lesion is a large submucosal artery (1–3 mm in size) that protrudes through the mucosa and can be a cause of massive upper GI bleeding. The lesion is usually located in the

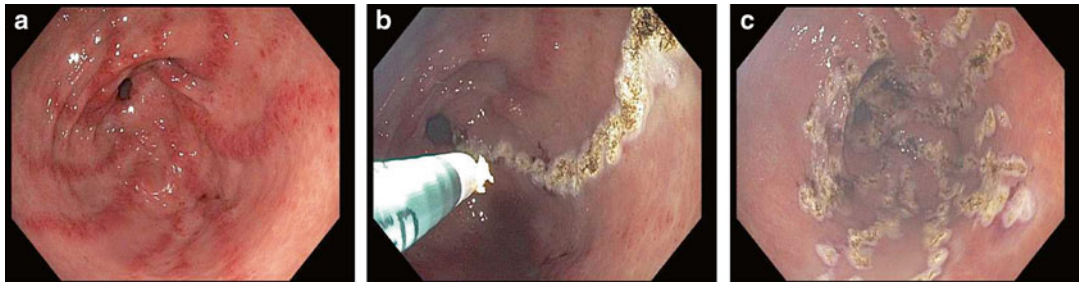

Fig. 11.6 (**a**) Gastric antral vascular ectasia (watermelon stomach). (**b**) Ablation of the stripes of vascular ectasias using argon plasma coagulation. (**c**) Endoscopic appearance following argon plasma coagulation

stomach, most often in the fundus, but can be present anywhere in the GI tract [10]. It may be difficult to locate a Dieulafoy lesion by the time upper endoscopy is performed because the lesion can retract back into the mucosa leaving no telltale sign. Dieulafoy lesions can be managed successfully by a variety of endoscopic techniques, including band ligation (Video 11.5), clip placement, contact thermal coagulation, sclerosant injection, and cyanoacrylate injection. Epinephrine injection alone is not recommended since it is associated with high rates of rebleeding [50, 51].

Sporadic Vascular Ectasias and Gastric Antral Vascular Ectasia

These mucosal vascular lesions are more likely to cause chronic blood loss with resulting iron deficiency anemia rather than overt upper GI bleeding. They can be isolated or associated with comorbidities such as cirrhosis, chronic renal failure, collagen vascular disease, valvular heart disease, and Osler-Weber-Rendu syndrome. Although these lesions can be treated by a variety of hemostatic techniques, APC is usually the preferred treatment modality due to ease of use (Fig. 11.6) [52–54].

Upper Gastrointestinal Tumors

Benign or malignant tumors of the upper GI tract are responsible for up to 5 % of cases of acute upper GI bleeding. Endoscopic hemostasis is less effective in this setting, with higher rates of rebleeding compared to bleeding from peptic ulcer [55–58]. Various endoscopic treatment modalities have been described with no clear recommendations [1]. Endoscopic control of bleeding is usually short-lived, and these lesions generally require angiographic embolization, radiotherapy, or surgical intervention for definitive hemostasis. Successful preliminary experience with Hemospray for tumor bleeding has been reported, although long-term efficacy remains to be seen [59].

Comparison of Available Techniques

Studies comparing various modalities for NVUGIB have focused mostly on peptic ulcer bleeding. The following, therefore, relates primarily to ulcer hemostasis.

Injection Therapy

Epinephrine

Dilute epinephrine is comparable to other monotherapies in achieving primary hemostasis of active bleeding. However, a meta-analysis of three trials with 212 patients, without second-look endoscopy, revealed that epinephrine was inferior in preventing rebleeding and surgery when compared to bipolar coagulation, clips, or fibrin glue [8]. Furthermore, when epinephrine was combined with another modality—an

injectable sclerosant, bipolar electrocoagulation, heater probe, thrombin glue, or fibrin glue—there was a significant reduction in rebleeding and surgery compared with epinephrine injection alone. A combined analysis of epinephrine plus another modality (bipolar coagulation, sclerosant, or clip) was shown to be significantly more effective in reducing rebleeding and surgery (RR 0.34 [95 % CI 0.23–0.5]; NNT=5) [6, 8]. Current consensus statements and technology reviews state that epinephrine injection alone is inadequate (unless no other hemostatic modality is available to the endoscopist) for definitive hemostasis and should be used in combination with another modality [6–9].

Sclerosing Agents

Compared to no therapy, the use of sclerosants alone (e.g., absolute alcohol) has been shown to be superior with regard to outcomes of primary hemostasis, need for urgent intervention, surgery, and mortality [6]. A meta-analysis comparing thermal therapy with a sclerosant showed no significant differences in rebleeding rate, surgery, or mortality [8]. Sclerosant injection, however, is rarely used for NVUGIB due to the perceived risk of serious tissue damage.

Thrombin/Fibrin Glue

Thrombin and fibrin glues have been shown to be more effective than no endoscopic therapy in preventing rebleeding. Fibrin glue was only comparable to epinephrine injection for primary hemostasis, and additional studies revealed no significant differences between fibrin glue and polidocanol, or a combination of dilute epinephrine plus fibrin versus dilute epinephrine plus polidocanol [8, 40].

Contact Thermal Therapy

A meta-analysis of 15 trials [8] showed thermal contact therapy with heater probe or bipolar probe to be significantly more effective than no therapy for reducing ulcer rebleeding (RR 0.44 [95 % CI 0.36–0.54]; NNT=4), need for surgery (RR 0.39 [95 % CI 0.27–0.55]; NNT=8), and mortality (RR 0.58 [95 % CI 0.34–0.98]; NNT=33). No difference was observed between the two thermal devices. A benefit of combination therapy with epinephrine plus contact thermal therapy versus thermal coagulation alone was suggested in two trials. A study comparing thrombin injection plus heater probe versus heater probe alone found no superiority for the combination arm [8].

Clips

No studies have evaluated endoscopic clips versus sham therapy. Several studies have compared clips with alternative hemostatic modalities—epinephrine, heater probe, bipolar coagulation plus epinephrine, and sclerosants. Clips were found to be more effective than epinephrine alone in reducing rebleeding and surgery. A summary of the comparative trials against other modalities found no significant differences in rates of rebleeding or surgery [8].

Endoscopic Therapy of High-Risk Versus Low-Risk Lesions

Several well-conducted clinical trials, meta-analyses, and consensus statements have determined that endoscopic hemostasis significantly reduces ulcer rebleeding rates, need for surgery, and mortality in patients with high-risk endoscopic stigmata (i.e., active bleeding, non-bleeding visible vessel, and adherent clot) [7–9]. All methods of endoscopic hemostasis have been shown to be superior to no endoscopic intervention. As previously mentioned, the addition of a second hemostatic modality, such as contact thermal therapy, to injection of dilute epinephrine further reduces the rebleeding rate, need for surgery, and mortality compared with epinephrine injection alone.

Endoscopic therapy for the ulcer with an adherent clot has been advocated, yet remains controversial [6–8, 10, 60–66]. An adherent clot is red, maroon, or black in color, amorphous in texture, and unable to be dislodged from the

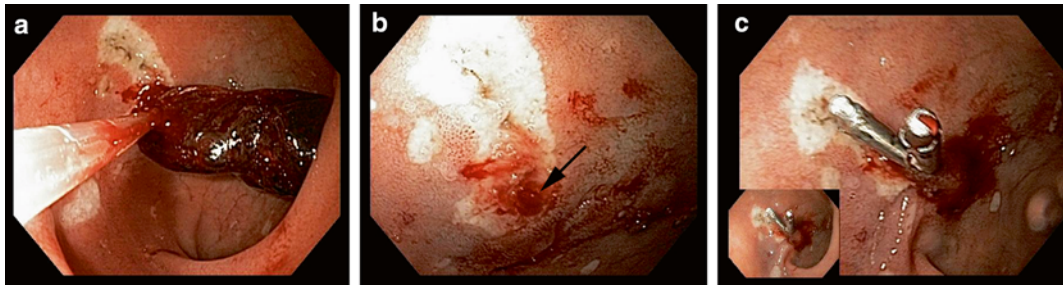

Fig. 11.7 (**a**) Epinephrine injection around duodenal ulcer with adherent clot. (**b**) Clot removal revealed an underlying visible vessel (*arrow*). (**c**) Clip placement performed for definitive hemostasis

ulcer bed by suction or forceful water irrigation. Vigorous irrigation of a clot in an ulcer bed successfully exposes underlying stigmata in 26–43 % of cases and high-risk stigmata in 70 % of those cases [64–66]. The risk for rebleeding with clots that remain adherent after vigorous washing without endoscopic therapy (with or without PPI therapy) has been reported to be as low as 0–8 % in some studies and as high as 25–35 % in others [60–66]. If endoscopic therapy is entertained, the recommended approach is to inject dilute epinephrine (1:10,000 or 1:20,000) around the clot, followed by cold snare guillotine to shave down the clot without disrupting the pedicle of the clot, and finally apply definitive therapy (e.g., bipolar coagulation or clip placement with or without additional epinephrine injection) to any underlying stigmata of hemorrhage (Fig. 11.7 and Video 11.9). A meta-analysis [8] of randomized trials in ulcer patients with an adherent clot did not show a significant benefit for endoscopic therapy over medical treatment (RR 0.31, 95 % CI 0.06–1.77). Similarly, endoscopic therapy did not significantly reduce rebleeding (RR 0.48, 95 % CI 0.18–1.30) compared with medical therapy in another meta-analysis [66]. However, significant heterogeneity was present among the studies, with some trials reporting significant benefit in favor of endoscopic hemostasis [8, 66]. The disparity in the data has led to ongoing controversy regarding the optimal management of adherent clots in peptic ulcers (endoscopic hemostasis vs. high-dose PPI only).

Patients with low-risk stigmata (e.g., ulcer with clean base or flat pigmented spot) have a low likelihood of recurrent bleeding and, therefore, do not benefit from endoscopic therapy [6–9]. Findings from randomized and retrospective trials have shown that, following endoscopy, low-risk patients who are otherwise stable and without significant anemia and comorbidities can be discharged home on the same day [67–71].

Second-Look Endoscopy

Planned second-look endoscopy that is performed within 24 h after initial endoscopic therapy is not recommended [6–9].

A meta-analysis of randomized trials assessing second-look endoscopy reported a small but significant reduction in rebleeding in patients undergoing the procedure (absolute risk reduction 6.2 % [95 % CI 1.3–11.1 %]; NNT=16), with no significant benefit, however, in reducing surgery or mortality rates [72]. A subsequent meta-analysis found no significant benefit when therapy for hemostasis involved epinephrine injection or fibrin glue injection but did identify a significant difference in rebleeding in the two randomized trials employing thermal therapy (RR 0.29, 95 % CI 0.11–0.73) [73]. However, these studies were performed prior to the era of intensive PPI therapy. In a randomized trial of single endoscopy plus high-dose intravenous PPI versus routine second-look endoscopy without PPI, rebleeding rates were similar at 8.2 and 8.7 %, respectively (RR 1.1, 95 % CI 0.4–2.7) [74]. A meta-analysis was published on the effectiveness of routine second-look endoscopy in peptic ulcer bleeding that included four randomized trials encompassing

938 patients [75]. The rebleeding rate was significantly decreased with routine second-look endoscopy (OR 0.55, 95 % CI 0.37–0.81), as was surgery (OR 0.43, 95 % CI 0.19–0.96), but not mortality (OR 0.65, 95 % CI 0.26–1.62). The only trial in which high-dose PPI was used did not show a benefit of second-look endoscopy. When the two trials that included patients at the highest risk of rebleeding were removed, no significant benefit for second-look endoscopy was found (OR 0.65, 95 % CI 0.42–1.00). Also, planned second-look endoscopy may not be cost-effective when medical therapy with intravenous high-dose PPI is used [76].

Repeat upper endoscopy should be considered on a case-by-case basis, particularly when recurrent bleeding is suspected or there is uncertainty regarding the effectiveness of hemostasis during initial endoscopy.

Conclusions

The endoscopic treatment of a patient presenting with acute overt upper GI bleeding is a multi-step process. Following initiation of resuscitative measures with hemodynamic stabilization and clinical risk stratification, most patients should undergo upper endoscopy within 24 h of presentation. In patients who are found to have bleeding due to peptic ulcer, the endoscopic stigmata are critical in directing further management. Patients with high-risk stigmata, such as active bleeding or non-bleeding visible vessel, should receive endoscopic therapy, whereas those with an adherent clot should be considered for endoscopic therapy. Ulcers with flat pigmented spots or clean bases do not require endoscopic therapy. Currently, the best outcomes for endoscopic hemostasis are achieved using a combination of dilute epinephrine injection and a more definitive treatment modality, such as contact thermal therapy or clip placement. Recurrent ulcer bleeding after initial endotherapy should be considered for a second attempt at endoscopic therapy, but if bleeding persists or recurs, referral to interventional radiology or surgery should be undertaken.

In the majority of patients presenting with ulcer- and non-ulcer-related NVUGIB, endoscopic therapy is an effective means of achieving long-term hemostasis. The selection of the most appropriate hemostatic device(s) for a particular lesion, recognition of caveats of endotherapy, and familiarity and proficiency in using the various devices available are important determinants for the safe and effective application of endoscopic hemostasis in NVUGIB.

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Hemostasis of Acute Esophageal Variceal Bleeding

12

Raymond S.Y. Tang and Joseph J.Y. Sung

Introduction

Bleeding from gastroesophageal varices is a life-threatening complication in patients with portal hypertension and cirrhosis. Advances in the management of acute variceal bleeding over the past decade have led to decreased bleeding-related mortality, although the mortality rate remains as high as 20 % [1]. Effective management of acutely bleeding esophageal varices (EV) requires a combination of pharmacological and endoscopic therapy. This chapter aims to review the current management strategy for acute bleeding from EV, with emphasis on endoscopic therapy.

Natural History of Varices

Gastroesophageal varices can be found in approximately 50 % of patients with cirrhosis [2]. The presence of varices correlates with the severity of the underlying liver disease [3]. The prevalence of varices ranges from 40 % in Child's class A cirrhosis to 85 % in Child's class C cirrhosis [3]. In a study of 206 cirrhotic patients either with small EV or without EV, new EV was reported to develop at a rate of 5 % at 1 year and 28 % at 3 years, with EV progression rate up to 31 % at 3 years [4]. Approximately 50 % of patients with cirrhosis develop variceal bleeding during their lifetime [3]. Variceal bleeding was reported to develop in patients with portal hypertension at a yearly rate of 5–15 % [5]. Predictors of variceal bleeding include large variceal size, presence of red wale signs on varices at endoscopy, and decompensated cirrhosis [5, 6].

Variceal Rebleeding and Mortality

Early studies reported that approximately 40 % of patients stop bleeding spontaneously at the time of presentation, but early rebleeding (<6 weeks) occurs in about 30–40 % of patients, resulting in high morbidity and mortality [5, 7]. In patients with early rebleeding, about 40 % of the episodes occur within the first 5 days of the index bleeding [7]. A hepatic venous pressure gradient (HVPG) >20 mmHg measured within 24 h of variceal bleeding, active bleeding at emergency endoscopy, bacterial infections, Child-Pugh score, aminotransferase levels, and presence of portal vein thrombosis have been

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R.S.Y. Tang • J.J.Y. Sung (✉)
Institute of Digestive Disease, The Chinese University of Hong Kong, Prince of Wales Hospital, Room 94020, 7/F, Clinical Science Building, Shatin, New Territories, Hong Kong
e-mail: jjysung@cuhk.edu.hk

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reported to be significant predictors for early rebleeding and 5-day mortality [1, 8–11]. In a more recent study, currently available treatment with vasoactive drugs and endoscopic therapy achieved initial control of bleeding in up to 90 % of cases, with a 5-day failure rate of 13 % [1].

Although data from the 1990s reported a high late rebleeding rate (>6 weeks) of about 60 % in untreated patients within 1–2 years of the index variceal bleed, current therapy with vasoactive drugs and endoscopic therapy in the acute setting and secondary prophylaxis with nonselective beta-blockers and endoscopic treatment have led to a reduction in rebleeding rates in the range of 13–29 % [1, 5, 12–14].

In the last two decades, there has been a decrease in mortality from 42 %, as reported by Graham et al. in 1981, to about 15–20 % in recent studies [1, 7, 13–15]. The reduction in bleeding-related mortality is likely related to the use of vasoactive drugs, antibiotic prophylaxis, more effective endoscopic therapies, and improved general medical/intensive care support [1, 7, 13–17]. Among patients who die after an episode of variceal bleeding, less than 50 % of the cases are directly related to bleeding, while infections, hepatorenal syndrome, and progressive liver failure contribute to most of the other deaths [1, 10–18]. Active bleeding at endoscopy, hypovolemic shock, early rebleeding, Child-Pugh score, renal failure, bacterial infection, and the presence of hepatocellular carcinoma have been reported to be predictors of mortality [1, 7, 10–19].

Management of Acute Esophageal Variceal Bleeding

The patient assessment and medical management of acute variceal bleeding are discussed in detail in a separate chapter. An algorithmic approach to the management of acute esophageal variceal bleeding is shown in Fig. 12.1.

Initial Assessment and Resuscitation

In patients presenting with upper gastrointestinal bleeding, history and physical examination findings suggestive of chronic liver disease, together with laboratory parameters (e.g., thrombocytopenia) and/or imaging features (e.g., splenomegaly, shrunken nodular liver, presences of intra-abdominal varices) suggestive of portal hypertension and cirrhosis, are clues to a potential case of variceal bleeding. In patients with decompensated cirrhosis, other cirrhotic complications, such as hepatic encephalopathy (HE), spontaneous bacterial peritonitis (SBP), or hepatorenal syndrome (HRS), may also accompany an episode of acute EV bleeding [1, 7, 16–18].

The airway should be assessed and secured in patients presenting with hematemesis. This is particularly important in encephalopathic patients who are at high risk for aspiration of blood and gastric contents. Intensive care unit admission should be considered for EV bleeding patients with hemodynamic instability and significant HE requiring intubation before proceeding to endoscopy.

Resuscitation with blood volume and fluid replacement should be implemented promptly with the goals of maintaining hemodynamic stability and a hemoglobin level around 8 g/dL [16, 17]. Caution should be taken not to over-transfuse or over-volume expand as variceal rebleeding may be precipitated based on data from animal studies showing that restitution of all lost blood would lead to an increase in portal pressure, resulting in more rebleeding and mortality [16, 17, 20, 21]. In a recent large randomized trial that compared a restrictive transfusion strategy (transfusion to 7 g/dL) to a liberal transfusion strategy (transfusion to 9 g/dL) in 921 patients with acute upper GI bleeding, a lesser rebleeding rate and higher survival at 6 weeks were observed in the restrictive transfusion group [22]. The difference in survival was mainly noted in patients with Child-Pugh class A and B cirrhosis, providing evidence that a restrictive transfusion approach may be beneficial in patients with variceal bleeding [22].

In patients with significant coagulopathy and thrombocytopenia, transfusion of fresh frozen plasma and platelets, respectively, can be considered [16, 17]. Two randomized controlled studies evaluated the utility of recombinant factor VIIa [23, 24]. Both studies did not find a beneficial

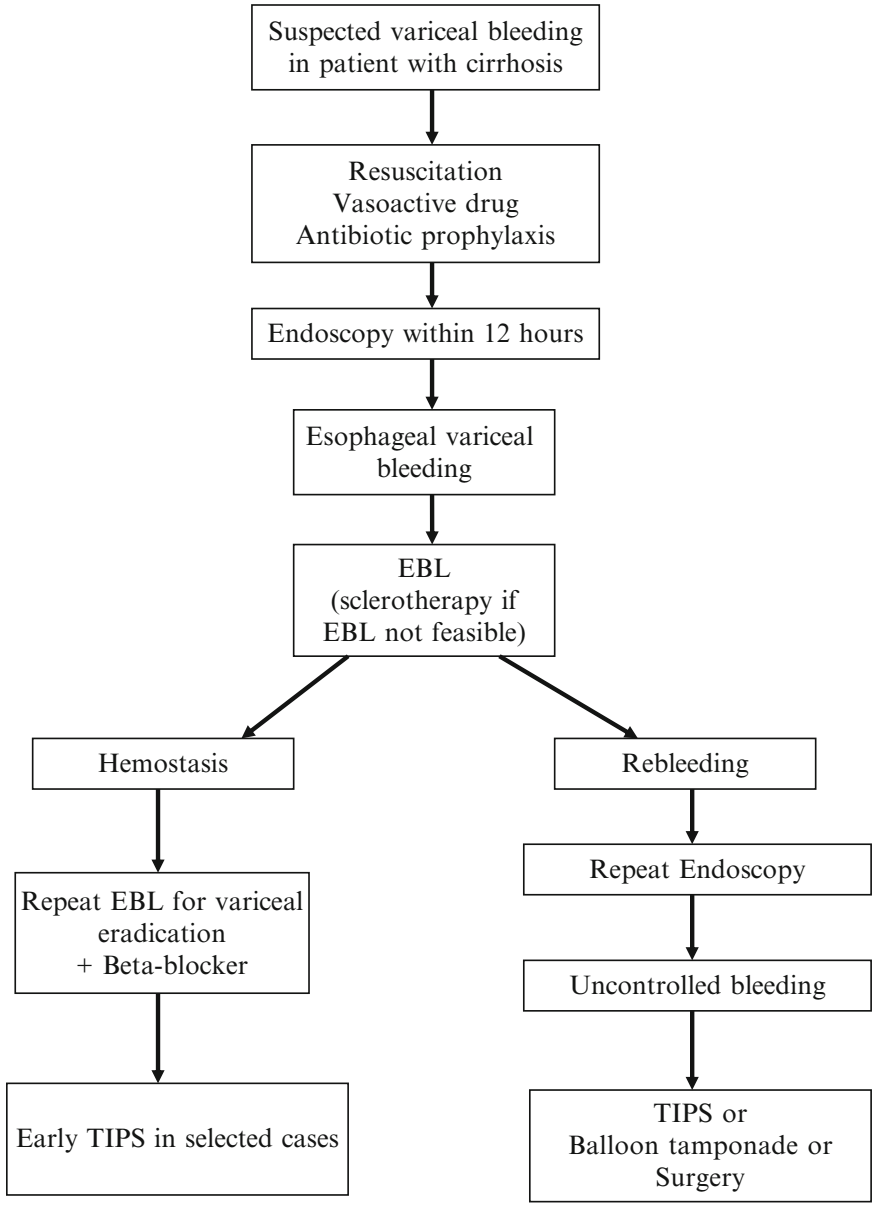

Fig. 12.1 Approach to the management of acute esophageal variceal bleeding (EBL, endoscopic band ligation; TIPS, transjugular intrahepatic portosystemic shunt)

effect of recombinant factor VIIa over standard therapy, although a post hoc subgroup analysis showed a reduced proportion of Child-Pugh class B and C patients with failed control of variceal bleeding [23, 24]. Currently, there is insufficient evidence to support the routine use of recombinant factor VIIa in the management of acute variceal bleeding.

Antibiotic Prophylaxis

Cirrhotic patients who develop upper gastrointestinal bleeding are at high risk for bacterial infections, such as SBP, which in turn put them at greater risk for variceal rebleeding and higher mortality [10, 11]. The use of short-term antibiotic prophylaxis up to 7 days in cirrhotic patients

with variceal bleeding, with or without ascites, has been shown to reduce the risks of bacterial infections, variceal rebleeding, and mortality [25–28]. Quinolones can be used in most patients, while ceftriaxone has been reported to be more effective in patients with Child's class B or C cirrhosis or in centers with high quinolone-resistant organisms [16, 17, 29].

Vasoactive Drugs

When variceal bleeding is suspected, administration of vasoactive drugs should be initiated as soon as possible before endoscopy [16, 17]. Vasopressin, terlipressin, and somatostatin and its analogs (e.g., octreotide or vapreotide) have been investigated in the treatment of acute variceal bleeding [16, 17]. Meta-analyses of more than 15 trials have shown that vasoactive drugs are comparable to emergent endoscopic sclerotherapy as initial therapy for variceal bleeding with regard to outcome measures of rebleeding and mortality but with fewer adverse events [30, 31].

Vasopressin is a potent splanchnic vasoconstrictor and is effective in the control of acute variceal bleeding [32]. However, its clinical utility is often limited by its unfavorable side effect profile, including bowel, cardiac, and peripheral ischemia [33]. The addition of nitrates helps to reduce the side effects of vasopressin monotherapy, but overall side effects are still higher than those associated with terlipressin and somatostatin analogs [16, 17, 32–34]. Hence, the use of vasopressin is generally limited to a maximum of 24 h in order to minimize its side effects [16].

Terlipressin is a synthetic analog of vasopressin with a longer biological activity and significantly fewer side effects. In one randomized study, early administration of terlipressin with glyceryl trinitrate improved bleeding control and mortality [35]. Data from a meta-analysis of 7 studies have demonstrated that terlipressin reduces failure of hemostasis and mortality when compared to placebo [36]. When compared to emergent endoscopic sclerotherapy, terlipressin has been shown to have similar efficacy in terms of bleeding control and mortality [37]. Terlipressin can be initiated at a dose of 2 mg every 4 h. Once bleeding is controlled, it can be titrated down to 1 mg every 4 h for up to 5 days to prevent rebleeding [16, 37]. The efficacy of terlipressin for control of acute variceal bleeding ranges from 75 to 80 % at 48 h and 67 % at 5 days [36, 37]. Severe side effects, such as peripheral and cardiac ischemia, were reported in less than 3 % of treated patients [37].

Somatostatin causes splanchnic vasoconstriction by inhibiting the release of vasodilatory hormones [16]. Somatostatin is given as an initial bolus of 250 μg, followed by intravenous infusion at 250 μg per hour for up to 5 days [38]. Somatostatin has been shown to be as effective as emergent endoscopic sclerotherapy, but with fewer complications [38]. In patients undergoing endoscopic sclerotherapy, early administration of somatostatin was demonstrated to be more effective than placebo in the overall control of acute variceal bleeding [39].

Octreotide is a somatostatin analog with a longer half-life that causes splanchnic vasoconstriction by inhibiting the release of vasodilatory peptides and by local vasoconstrictive property [16]. It is usually administered as an initial bolus of 50 μg, followed by an infusion of 50 μg per hour for up to 5 days [16]. While octreotide was shown to be equally effective in the control of initial bleeding and rebleeding rate when compared to emergent endoscopic sclerotherapy in an early study, there has been some controversy about its efficacy as single therapy [16, 40]. It has been postulated that rapid development of tachyphylaxis may be the reason behind the inconsistent results found in studies using octreotide alone [16, 41]. The benefit of using octreotide as an adjunctive therapy in patients who have undergone endoscopic therapy for EV is more evident [42]. Results from a meta-analysis have shown that octreotide reduces rebleeding in patients treated with endoscopic therapy [43]. Both terlipressin and octreotide are similarly efficacious as adjunctive therapy to endoscopic therapy in patients with variceal bleeding [44]. Octreotide may be the vasoactive drug of choice in countries where terlipressin is not available.

Endoscopic Therapy

Timely endoscopy (within 12 h of presentation) should be performed in patients with suspected EV bleeding [16, 17]. Bleeding from EV is confirmed when active (Fig. 12.2) or definite stigmata of recent hemorrhage, such as fibrin clot/nipple sign (Fig. 12.3), are identified at endoscopy. If definite variceal bleeding stigmata are not seen at endoscopy, upper GI bleeding can be attributed to EV in the absence of other sources of hemorrhage, particularly when the varices are large and demonstrate red signs, such as red wale markings (Fig. 12.4).

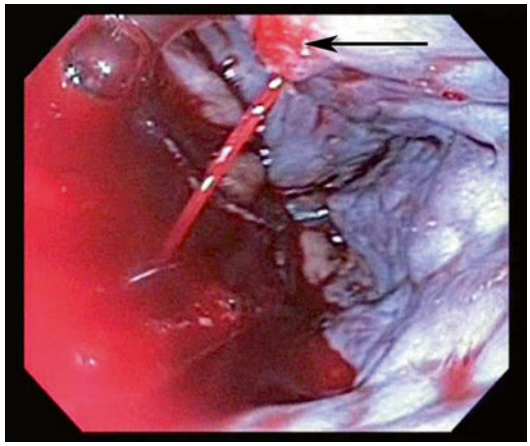

Fig. 12.2 Esophageal varix with active bleeding (*arrow*)

Techniques

Options for endoscopic therapy include endoscopic band ligation (EBL), endoscopic injection sclerotherapy, and endoscopic variceal obturation with a tissue adhesive (e.g., cyanoacrylate).

Endoscopic Band Ligation

Several multiband ligation devices are available that can fit both standard and therapeutic channel gastroscopes. If available, a therapeutic channel gastroscope is recommended due to improved suction capability even with the banding device in place. Placement of up to 6 bands per treatment session is generally sufficient. Placement of >6 bands per treatment session does not improve bleeding or variceal eradication outcomes and is associated with increased overall procedure times and misfired bands.

In a patient who did not undergo endotracheal intubation for airway protection, the procedure is performed with the patient in the left lateral decubitus position and the head of the bed raised about 30° to minimize the risk of aspiration. In the endotracheally intubated patient, the procedure

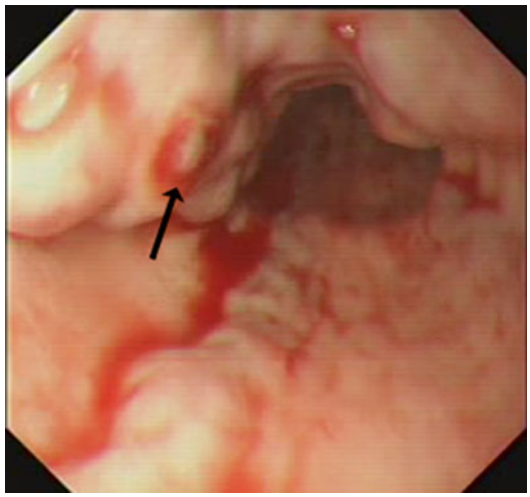

Fig. 12.3 Esophageal varix with fibrin clot/nipple sign (*arrow*)

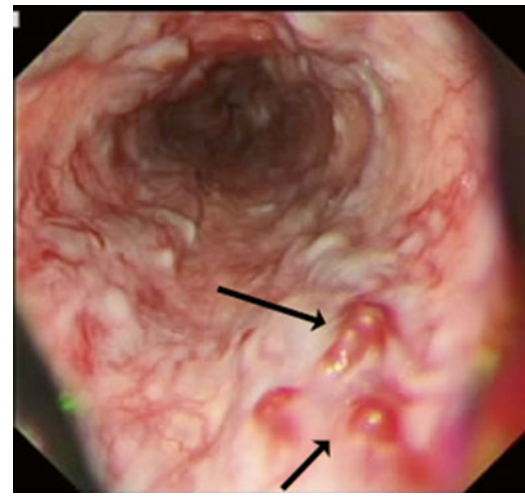

Fig. 12.4 Esophageal varices with *red wale* markings (*arrows*)

can be performed either in the supine or left lateral decubitus position.

Once in the esophagus, the EBL-loaded endoscope is oriented toward the varix and suction is applied. A large varix can be readily suctioned into the cap, whereas a varix that is small or associated with scarring from prior band ligation may require gentle back and forth movement of the shaft of the endoscope or right-left ratchet manipulation with continuous suction to entrap enough of the varix into the cap for effective ligation. Ideally, a "red out" is obtained during suction of the varix into the cap prior to band deployment. If the band is deployed prior to suctioning enough of the varix into the cap, it will most likely slip off and result in a misfire, as well as inciting trauma-induced bleeding. Unless the esophageal lumen is capacious, passage of the endoscope distal to the banded varix should be avoided as this may result in friction and band dislodgement.

In the presence of an actively bleeding varix, the first band should be placed immediately onto the bleeding site (Video 12.1). If the initial ligated varix is located at or near the gastroesophageal junction (GEJ), additional bands can be placed in a cephalad and spiral fashion, targeting the varices in the distal 5–7 cm of the esophagus. If the index bleeding site is in a more proximal location (e.g., proximal or mid-esophagus), it may be preferable to forego placement of further bands distal to the index band since the latter may become dislodged from friction generated by passage of the endoscope, resulting in rebleeding (Video 12.2). If bleeding is torrential, the bleeding varix may be difficult to pinpoint. In this situation, EBL of varices at the cardia or GEJ may be considered, as this often allows decompression of flow so that bleeding from the offending varix can be slowed, identified, and ligated.

The presence of a nipple sign or fibrin plug confirms the site of variceal hemorrhage and should be targeted for EBL (Fig. 12.5). If the target varix with stigmata of recent hemorrhage is more proximally situated, band ligation of varices can start at the GEJ and conclude with the culprit varix.

With regard to follow-up, EBL is typically repeated at 2–4-week intervals until variceal eradication is achieved. EBL at shorter time intervals may be problematic since post-banding ulcers may still be present and interfere with placement of bands.

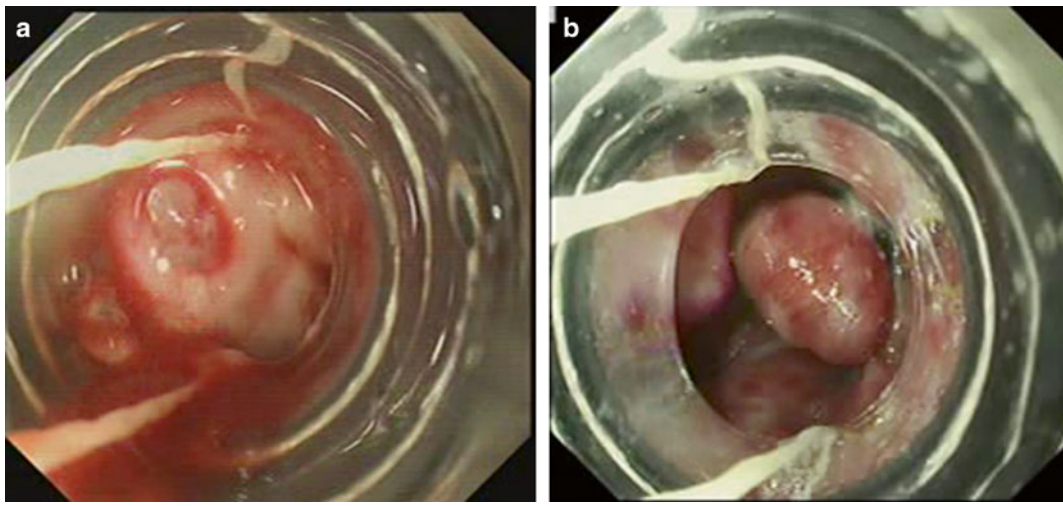

Fig. 12.5 (**a**) Endoscopic band ligation targeting the bleeding point of an esophageal varix indicated by the presence of fibrin clot/nipple sign. (**b**) Banded varix

Endoscopic Injection of Sclerosants and Cyanoacrylates

Several sclerosing agents have been used for variceal sclerotherapy with comparable efficacy (Table 12.1). The injection sites are sealed off due to the local pressure effects of the sclerosants and thrombosis of the varices secondary to inflammation. The selection of a particular sclerosant is largely dependent on operator preference and availability. A freehand injection technique using a 23-gauge injection needle is typically employed for variceal sclerotherapy. Injection of the sclerosant can be performed directly into the varix (intravariceal) or adjacent to the varix (paravariceal), with resultant edema and blanching of the injected area (Fig. 12.6). When feasible, intravariceal injection is preferred since it is associated with fewer complications than the paravariceal approach, although the intended injection technique may not be achieved when the field of view is obscured by blood. In the setting of active variceal bleeding or stigmata of recent hemorrhage, injections are directed in and around the bleeding site (Video 12.3). The injection volume depends on the type of sclerosant utilized and size of the varix (Table 12.1).

Variceal obturation refers to the injection of a tissue adhesive (e.g., cyanoacrylate) directly into the variceal lumen, causing obliteration of the varix. Injection of cyanoacrylate is less commonly performed for bleeding EV compared to bleeding GV, although the injection technique is relatively similar. The technical aspects of cyanoacrylate injection for variceal hemorrhage are described in a separate chapter.

Table 12.1 Sclerosing agents

Agent	Volume per injection site (ml)	Maximum volume per session (ml)	Relative tissue injury
Fatty acid derivatives			
Ethanolamine oleate, 5 %	1.5–5	20	+++
Sodium morrhuate, 5 %	0.5–5	15	+++
Synthetic agents			
Sodium tetradecyl sulfate, 1 % and 3 %	1–2	10	++
Polidocanol, 0.5–3 %	1–2	20	+
Alcohols			
Ethanol, 99.5 %	0.3–0.5	4–5	++++
Phenol, 3 %	3–5	30	+

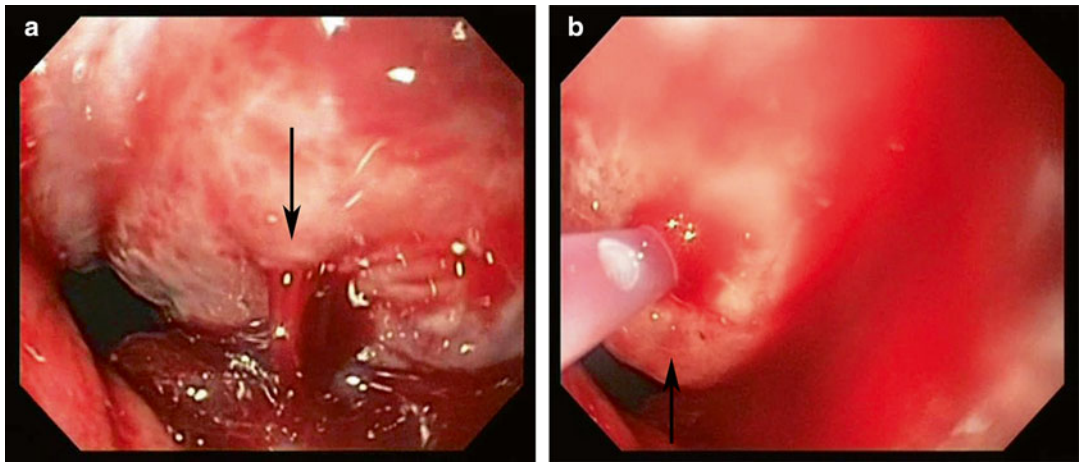

Fig. 12.6 (**a**) Salvage sclerosant injection into a bleeding varix for which banding failed due to surrounding scarring from prior band ligation. (**b**) Swelling and blanching of the bleeding varix during sclerotherapy, resulting in hemostasis

Outcomes

Data from multiple randomized trials support the use of EBL as the preferred endoscopic treatment for acute EV bleeding, with less rebleeding and less complications in the EBL group when compared to the sclerotherapy group [45–52]. Two studies reported a lower mortality rate in the EBL group [45, 52]. In a study of patients with actively bleeding EV at endoscopy, EBL and sclerotherapy were comparable in achieving hemostasis of oozing varices, but EBL was superior to sclerotherapy in the control of spurting varices [50]. Injection sclerotherapy is an alternative in patients in whom EBL is not feasible (e.g., in patients with extensive scarring from prior EBL). Endoscopic ultrasound (EUS) may have a role in monitoring EV eradication and provide prognostic information after index EBL [53]. In patients who underwent EBL for EV bleeding, the presence of large paraesophageal varices at EUS within 4 weeks of index EBL was shown to predict recurrence of EV and rebleeding [53].

While extensive literature is available regarding the use of cyanoacrylate injection for obturation of bleeding gastric varices (GV), data are scant regarding the use of cyanoacrylate injection for bleeding EV [16, 17]. Limited data from one small prospective case series and two small randomized studies reveal conflicting results between EBL and cyanoacrylate injection in terms of acute control of EV bleeding, rebleeding rate, and mortality in patients with cirrhosis [54–56]. Of note, cyanoacrylate injection for bleeding EV is not approved for use in the United States, although it has been utilized on an off-label compassionate basis when standard therapies have failed.

The combination of vasoactive drugs and endoscopic therapy is the current standard of care for acute EV bleeding [16, 17]. Results from a meta-analysis of 8 trials showed that combined pharmacological and endoscopic therapy improved control of initial bleeding and 5-day hemostasis when compared to endoscopic therapy alone (EBL or sclerotherapy) [57]. No difference in severe adverse events or mortality was found between the two groups [57].

Rescue Therapy

Despite the use of pharmacological and/or endoscopic therapy, variceal bleeding may not be controlled in about 10–20 % of cases [16, 17]. Rescue therapies, such as balloon tamponade, transjugular intrahepatic portosystemic shunt (TIPS), shunt surgery, and self-expandable metal stents, are potential options in selected patients, depending on the liver disease status and comorbidities.

Balloon Tamponade

Balloon tamponade is considered a temporary bridge to more definitive therapy for control of variceal bleeding when primary endoscopic hemostasis fails [16, 17]. Several designs of equipment are available: Sengstaken-Blakemore tube, Minnesota tube, and Linton-Nachlas tube. The patient should be admitted to the intensive care unit with intubation for airway protection before insertion of the balloon tamponade system. Initial control of variceal bleeding was reported to be successful in more than 80 % of patients [58]. Because severe complications including aspiration pneumonia, esophageal perforation, tissue necrosis, and acute laryngeal obstruction are not uncommon, balloon inflation generally should not exceed 24 h [16]. Rebleeding rate is high after balloon deflation, and thus, a more definitive therapy (e.g., TIPS) should be planned within 24 h of balloon inflation.

Transjugular Intrahepatic Portosystemic Shunt

TIPS has been accepted as one of the salvage therapies for unsuccessful endoscopic control of variceal bleeding when local expertise is available. The efficacy of TIPS for uncontrolled EV bleeding despite pharmacological and emergent endoscopic therapy has been demonstrated in multiple studies [59–63]. Control of hemorrhage is achieved in more than 90 % of patients [59–63]. In a small study of patients with HVPG >20 mmHg, the early use of TIPS was reported to

improve survival [64]. However, patients with decompensated cirrhosis may not benefit from TIPS. In patients with poor liver reserve and multi-organ failure, the 30-day mortality could reach 100 % [60, 61]. In candidates who are fit for TIPS placement, hepatic encephalopathy and TIPS stenosis over time have been two major concerns following TIPS. Hepatic encephalopathy occurs in 25–35 % of patients after TIPS placement [65]. Patients who develop severe encephalopathy may require either a narrower stent to reduce the size of the shunt or total occlusion of the initial stent. Stent occlusion or stenosis by thrombosis occurs in about half of the patients within 2 years after TIPS creation when bare metal stents are used [66]. Newer polytetrafluoroethylene (PTFE)-covered stents have been reported to increase TIPS patency, with patency rate greater than 70 % at 2 years [67, 68]. In a randomized control trial comparing early TIPS (within 72 h after presentation of variceal bleeding) to continuation of vasoactive therapy and insertion of TIPS as a rescue therapy, the early use of TIPS was associated with a significant reduction in treatment failure and improvement in survival [69]. Therefore, early TIPS should be considered in these patients.

Shunt Surgery

Although shunt surgery is effective in reducing portal hypertension and control of variceal bleeding, the mortality and morbidity of surgery in patients with acute variceal bleeding is high because the majority of the patients are high-risk surgical candidates with decompensated liver disease [16, 17, 70, 71]. A 30-day mortality of 42 % was reported in a large series of 400 patients (89 % were Child's class B and C) [71]. Hepatic encephalopathy is common after shunt surgery [70, 71]. In a randomized trial comparing distal splenorenal shunt to TIPS for variceal bleeding, no difference was reported in rebleeding rate, first encephalopathy event, and survival at 2 years and 5 years [72]. Thrombosis and reintervention rates were higher in the TIPS group [72]. In carefully selected patients with reasonable liver reserve, shunt surgery may be an option for uncontrolled variceal bleeding, especially in those with unfavorable anatomy for TIPS placement.

Self-Expandable Metal Stents

Esophageal self-expandable metal stents (SEMS) have been investigated as an alternative to balloon tamponade in patient with uncontrolled EV bleeding despite pharmacological and endoscopic therapy. In a few case series, placement of a dedicated SEMS for variceal tamponade in the esophagus was successful and effective in controlling variceal bleeding in nearly all patients [73–76]. In some patients, the SEMS were left in place for up to 14 days and were subsequently removed in an atraumatic fashion at endoscopy using a specialized retrieval device [73–76]. SEMS-related adverse events, such as stent migration, esophageal ulceration, and airway compression, have been reported [73–76]. Similar to balloon tamponade, the placement of SEMS is considered a bridge to more definitive therapy. Additional research is needed to assess the long-term outcome and safety of this novel rescue therapy for uncontrolled EV bleeding.

Conclusion

Improvement in medical and intensive care support, routine use of antibiotic prophylaxis, early use of vasoactive drugs, and more effective endoscopic therapy have reduced mortality in patients presenting with acute EV bleeding. The combination of vasoactive drugs and endoscopic therapy (EBL preferably) improves control of initial bleeding and 5-day hemostasis and is currently the standard of care. In patients who fail standard combination therapy, rescue therapies, such as balloon or stent tamponade, TIPS, or shunt surgery, are options in selected patients.

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Hemostasis of Acute Gastric Variceal Bleeding

13

Chris Hamerski, Kenneth F. Binmoeller, and Janak N. Shah

Introduction

Gastric varices are a feared complication of cirrhosis and portal hypertension, with a prevalence of about 20 % in cirrhotic patients [1] and 5–33 % among patients with portal hypertension [2]. Although the risk of bleeding from gastric varices is lower than that of esophageal varices, transfusion requirements, rebleeding, and mortality rates are higher with gastric variceal hemorrhage (GVH) [3]. Approximately 25 % of patients with gastric varices will bleed over a 2-year period. The risk factors for GVH include size of the varices, location of the varices in the fundus, advanced liver disease, and presence of mucosal red spots overlying the varices at endoscopy (Fig. 13.1) [4]. In a study of 117 patients with gastric varices and no prior bleeding, the cumulative rates for the 1st episode of variceal hemorrhage at 1, 3, and 5 years were 16, 36, and 44 %, respectively [4]. Gastric varices may also bleed at a lower portal pressure gradient than that needed for esophageal variceal hemorrhage [5].

The Sarin classification is commonly used to categorize gastric varices on the basis of their location in the stomach and relationship with esophageal varices [1] (Fig. 13.2). Gastroesophageal varices (GOV) are esophageal varices in continuity with gastric varices that extend along the gastric lesser curvature (GOV1) or toward the fundus (GOV2). Isolated gastric varices (IGV) occur in the absence of esophageal varices and are located either in the fundus (IGV1) or elsewhere in the stomach, such as the body, antrum, or pylorus (IGV2). The presence of IGV1 at endoscopy should raise suspicion and evaluation for splenic vein thrombosis (e.g., from pancreatitis) for which the treatment of choice is splenectomy.

Gastric varices are typically secondary to portal hypertension, which is the result of increased portal blood flow and intrahepatic vascular resistance. Blood that normally flows through the portal vein into the liver is now impeded, resulting in diverted flow to alternate venous pathways. Increased pressure into the gastric veins forms fundal varices (IGV1 and GOV2), while increased flow into the gastroepiploic veins forms IGV2 [5]. Gastric varices are typically associated with spontaneous portosystemic shunts, namely, splenorenal or gastrorenal shunts, which drain through the left renal vein. A higher

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C. Hamerski, M.D. • K.F. Binmoeller, M.D.
J.N. Shah, M.D. (✉)
Paul May and Frank Stein Interventional Endoscopy Center, California Pacific Medical Center,
2351 Clay Street; 6th Floor Stanford Building,
Suite 600, San Francisco, CA 94105, USA
e-mail: Janak.shah@gmail.com

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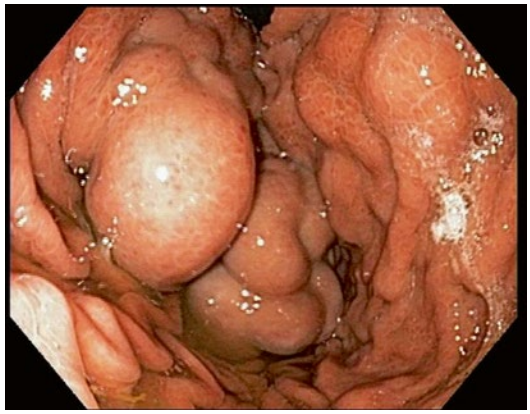

Fig. 13.1 Large fundal varices in cluster of grapes formation

percentage of gastric varices are associated with gastrorenal shunts compared to esophageal varices [6]. These shunts may explain, in part, the lower portal pressures that can be encountered with bleeding gastric varices. The estimated total blood flow through these shunts can be as high as 1.7 l/min, which allows for decompression of the portal system and lowering of the transhepatic pressure gradient [7].

GOV1 are considered an extension of esophageal varices and the management of bleeding GOV1 is, therefore, similar to that of esophageal varices (Video 13.1). Limited data are available regarding the management of IGV2, but its treatment generally mirrors that of GOV2 and IGV1. Herein, the management of GVH from fundal varices (IGV1 and GOV2) will be the focus of this chapter, with emphasis on endoscopic therapy.

Initial Management

The medical management of acute variceal bleeding is detailed in a separate chapter. In brief, initial management of GVH is similar to that of esophageal variceal hemorrhage and consists of hemodynamic stabilization with blood transfusion, as appropriate, prophylactic antibiotics, and administration of a vasoactive drug, such as octreotide or terlipressin. Patients with acute GVH should be managed in an intensive care unit initially, and endotracheal intubation for airway protection is recommended in the setting of active bleeding or other factors that place the patient at risk for aspiration (e.g., encephalopathy). The transfusion strategy should be restrictive in nature, with target hemoglobin of 7–8 g/dl, since transfusions above this level can elevate portal pressure and increase bleeding [8, 9]. Due to the lower venous pressure gradient needed for GVH compared to esophageal variceal hemorrhage, a higher dose of a vasoconstrictor may be required to decrease portal pressure and reduce portal and collateral blood flow [10]. Although there is evidence that octreotide is beneficial for esophageal variceal bleeding, there are no dedicated studies that have examined the role of vasoactive agents in the setting of GVH [11].

Massive bleeding from gastric varices may require initial balloon tamponade as temporary therapy. For this purpose, a variety of balloon devices are available (e.g., Sengstaken-Blakemore, Linton-Nachlas, and Minnesota tubes), although the Linton-Nachlas tube is preferred for GVH due to its larger gastric balloon capacity (600 ml) for more effective tamponade of fundal varices. Although balloon tamponade may provide immediate hemostasis, sustained hemostasis is unlikely, with high rebleeding rates following balloon deflation. The maintenance of balloon tamponade for longer than 24 h may result in ischemic necrosis and perforation [12], and it should only be used as a bridging measure to more definitive therapy.

Endoscopic Therapy

Endoscopic Band Ligation

Although the use of endoscopic band ligation (EBL) for treatment of esophageal varices is well supported in the literature, its application for fundal variceal hemorrhage is limited. Initial case series revealed EBL to be safe and effective for the control of acute GVH [13, 14], but subsequent randomized controlled trials showed rebleeding rates as high as 60–70 % [15]. One prospective study that compared EBL to

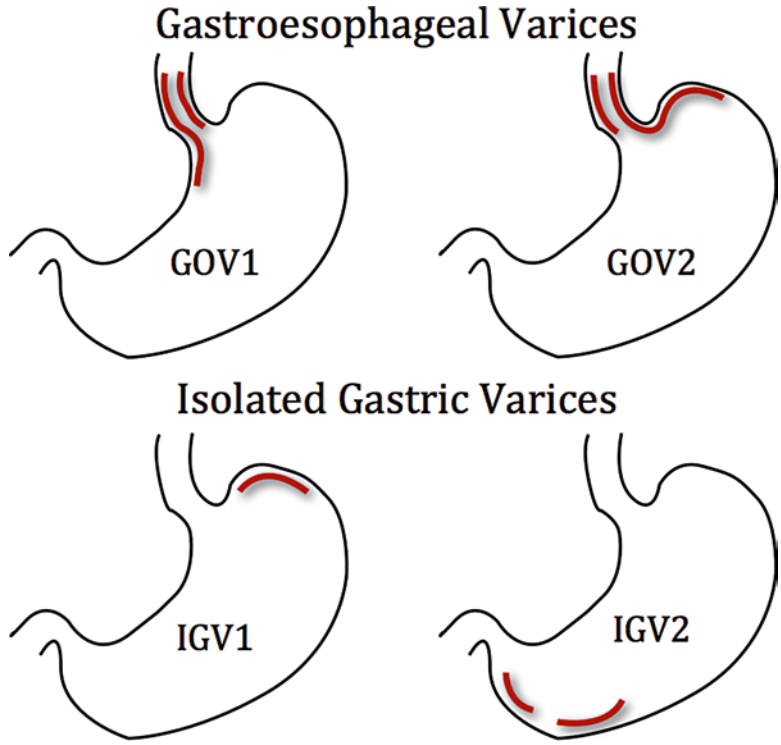

Fig. 13.2 Sarin classification of gastric varices. Gastroesophageal varices (GOV) are esophagogastric varices that extend along the lesser curvature of the stomach (GOV1) or toward the fundus (GOV2). Isolated gastric varices (IGV) occur in the absence of esophageal varices and are located in the fundus (IGV1) or elsewhere in the stomach, such as the body, antrum, or pylorus (IGV2)

cyanoacrylate injection of gastric varices revealed comparable initial hemostasis (100 and 89 %, respectively), but a significantly higher rebleeding rate in the EBL group (72 % vs. 32 %) [16]. EBL is considered an ineffective treatment for sustained hemostasis of fundal variceal hemorrhage due to post-banding ulcers and recurrent hemorrhage after band sloughing (Fig. 13.3), as well as failure to completely ligate the deep aspect of the varix and its feeder vessel(s). Detachable snares or loops have also been used to ligate gastric varices. This technique was associated with low rebleeding rates (0–10 %) in two small studies [17, 18], although the technical challenge in loop placement and risk of torrential bleeding at the site of post-ligation ulcer have restricted the use of these devices in practice. Although EBL or loop ligation is not recommended as primary therapy for fundal variceal bleeding, these techniques can be considered in certain circumstances to temporarily arrest active bleeding from a fundal varix in order to buy time toward preparation for more definitive therapy (e.g., cyanoacrylate injection).

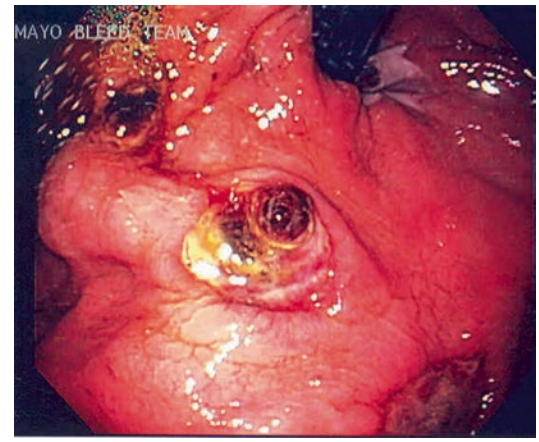

Fig. 13.3 Massive bleeding from post-banding ulcers overlying fundal varices

Sclerotherapy

Endoscopic injection of sclerosants results in endothelial damage and thrombosis, leading to vascular obliteration [19]. Available sclerosing agents include absolute alcohol, fatty acid derivatives (e.g., ethanolamine oleate and sodium

morrhuate), and synthetic chemicals (e.g., sodium tetradecyl sulfate and polidocanol). A sclerotherapy needle is passed through the working channel of the endoscope and the sclerosant is injected either into (intravariceal) or immediately adjacent (paravariceal) to the varix. Intravariceal injection results in direct occlusion of the vessel, while paravariceal injection occludes the vessel by submucosal fibrosis of tissue around the varix, leading to tamponade.

Although sclerotherapy in esophageal variceal hemorrhage is effective, with control of active bleeding in about 90 % of patients [20–23], its use in GVH is less impressive. The rates of initial hemostasis range from 44 to 92 %, with high rebleeding rates of 30–90 % and poor rates of eventual variceal obliteration [24–29]. Adverse events related to sclerotherapy include post-sclerotherapy ulceration with delayed bleeding and bacteremia/sepsis. Sclerotherapy is not recommended as first-line therapy for GVH unless no other options are available.

Cyanoacrylate Injection

Supportive Evidence

The use of cyanoacrylate (glue) injection for the treatment of gastric varices was first described by Soehendra et al. in 1986 [30] and currently constitutes first-line treatment for GVH, where available [2]. There is evidence supporting the use of cyanoacrylate injection, with several large case series (encompassing 121–613 patients per study) reporting >90 % control of bleeding and <15 % rebleeding rates [31]. The most feared complication of glue injection is embolization [32]. However, the rate of clinically relevant glue embolization was only 0.7 % (1 pulmonary, 1 cerebral, and 3 splenic) in the largest case series of cyanoacrylate injection for gastric varices that enrolled over 750 patients [33]. The overall complication-related mortality was 0.53 % and included three deaths from sepsis and one death from rebleeding after early-onset glue cast extrusion. Early-onset (<3 months) rebleeding was 4.4 %.

Sarin et al. showed cyanoacrylate injection to be more effective than alcohol sclerotherapy in achieving gastric variceal obliteration in a small randomized controlled trial of 37 patients [24]. In another prospective nonrandomized trial, cyanoacrylate injection was better than sclerotherapy with regard to acute hemostasis (93 % vs. 67 %), although the rebleeding rates were not different (25 % vs. 30 %) [26].

Two randomized controlled trials have compared EBL with cyanoacrylate injection. A trial of 60 patients showed improved outcomes favoring glue injection over EBL in terms of initial hemostasis (87 % vs. 45 %), rebleeding (31 % vs. 54 %), and mortality (29 % vs. 48 %) [15]. A larger randomized study of 97 patients demonstrated similar rates of initial hemostasis (93 % for both), but a higher rebleeding rate in the EBL group (3-year cumulative rate of 72 % vs. 27 %) [34]. In a retrospective study comparing EBL ($n=18$) to cyanoacrylate injection ($n=19$), the rates of initial hemostasis were similar (89 % vs. 100 %), but the rebleeding rate was significantly less in the cyanoacrylate group (32 % vs. 72 %) [16].

Cyanoacrylate Monomers

Cyanoacrylate monomers differ primarily in the length of their alkyl groups. The two monomers that are currently used for GVH are enbucrilate (N-butyl 2-cyanoacrylate) and ocrylate (2-octyl cyanoacrylate). Enbucrilate polymerizes at a faster rate than ocrylate and is usually mixed with the oily contrast agent, Lipiodol (Guerbet LLC, Bloomington, IN, USA), to slow its polymerization rate and minimize glue solidification within the injection catheter before it reaches the varix. The use of Lipiodol also allows for fluoroscopic visualization of the mixture during injection, if desired. The enbucrilate-to-Lipiodol ratio ranges from 1:1 to 1:6 in published studies [35, 36]. A commercial formulation of enbucrilate adds methacryloxysulfolane to slow the polymerization rate.

Technique for Cyanoacrylate Injection

The technical steps for cyanoacrylate injection are outlined in Table 13.1. After administering

Table 13.1 Technical steps for cyanoacrylate injection

1. Coat the endoscope tip with silicone oil and flush oil through the instrument channel to minimize the risk of glue adherence
2. Prime the injection needle catheter with either sterile water for enbucrilate injection or saline for ocrylate injection
3. Confirm that the initial injection with water or saline is free flowing into the varix and not forming a submucosal bleb
4. Inject the cyanoacrylate into the varix in aliquots of 0.5–1 ml. If used undiluted, enbucrilate must be rapidly injected over a few seconds to avoid premature glue solidification. Due to its longer polymerization rate, ocrylate must be used undiluted and slowly injected over 30–45 s
5. After the glue has been injected, flush out the dead space of the catheter with sterile water or saline
6. Retract the needle from the varix while continuously flushing to keep the needle patent for possible repeat glue injection
7. If there is no bleeding at the puncture site, palpate the varix with a blunt tip catheter or closed forceps. If the varix is still soft, additional glue injections are performed

prophylactic antibiotics, the endoscopic procedure is performed preferably with a therapeutic channel gastroscope coupled to a water irrigation pump. Silicone oil should be used to coat the tip of the endoscope, as well as to flush the instrument channel to minimize the risk of glue adherence that can lead to endoscope damage. The injection needle catheter should be primed with either sterile water for enbucrilate injection or saline for ocrylate injection. Saline should not be used for enbucrilate injection because it accelerates its polymerization rate, which may lead to premature clogging of the catheter.

Once the target varix is punctured, the initial injection of saline or sterile water, depending on the type of cyanoacrylate used, is carefully observed to ensure the solution flows freely into the varix and does not form a submucosal bleb. The varix is then injected with aliquots of 0.5–1 ml of the glue. Injection of more than 1 ml of glue per aliquot may increase the risk of embolization. The injection time will vary depending on the choice of cyanoacrylate and degree of dilution with Lipiodol. If the injection is too slow, the glue may solidify in the needle. If used undiluted, enbucrilate must be rapidly injected over seconds to minimize premature glue solidification. Because of its longer polymerization time, ocrylate must be used undiluted and is slowly injected over 30–45 s (Video 13.2). After the glue has been injected, the catheter's dead space is flushed with sterile water or saline, and the needle is withdrawn from the varix while continuously flushing solution to keep the needle patent for possible repeat glue injection. If there is no bleeding at the punctured site, the varix is palpated with a blunt tip instrument to confirm adequate obturation, as evidenced by a hardened varix. If the varix is still "soft," then additional glue injections are performed (Fig. 13.4). Follow-up endoscopy several weeks later may show retained glue cast at the puncture site(s) (Video 13.3).

Cyanoacrylate Injection for Primary Prophylaxis

The role of primary prophylaxis (prevention of a first bleed) is established in the management algorithm of esophageal varices [2], but no clear guidelines exist with regard to primary prophylaxis of gastric varices. One randomized trial evaluated the role of endoscopic glue injection for primary prophylaxis of gastric varices. A total of 89 patients with fundal varices were randomized to cyanoacrylate injection, beta-blocker therapy, or no treatment. After a mean follow-up of 26 months, the probability of bleeding was 13 % in the cyanoacrylate group, 28 % in the beta-blocker group, and 45 % in the no-treatment group. Survival was higher in the cyanoacrylate group compared to the no-treatment group (90 % vs. 72 %). Predictors of bleeding were variceal size, model for end-stage liver disease (MELD) score, and presence of portal hypertensive gastropathy. Further studies are needed before endorsing endoscopic glue injection for primary prophylaxis of gastric varices, although some centers, including ours, have offered this option on a case-by-case basis, particularly in patients with gastric varices at high risk for bleeding (e.g., large fundal varices with prominent red wale markings or hematocystic spots).

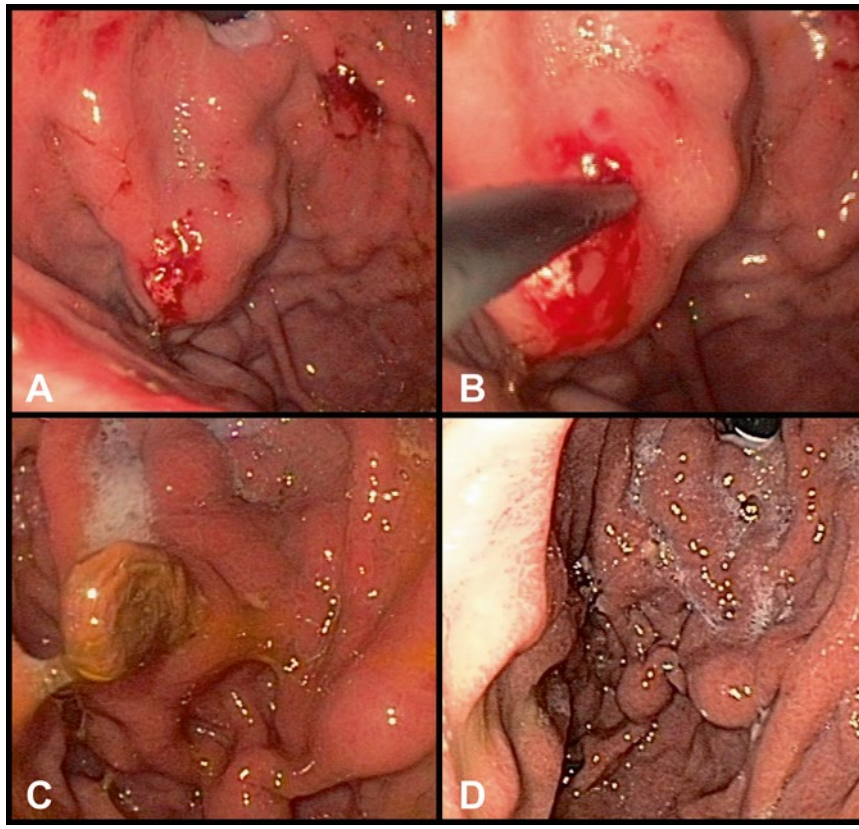

Fig. 13.4 (**a**) Large isolated gastric varix in the fundus (IGV1). (**b**) Endoscopic injection of cyanoacrylate into the varix. (**c**) Follow-up endoscopy at 8 weeks shows partial glue extrusion at the puncture site. (**d**) Obliterated gastric varix on surveillance endoscopy at 6 months

Cyanoacrylate Injection for Secondary Prophylaxis

Despite excellent initial hemostasis following endoscopic therapy, rebleeding occurs at rates of 10–30 % [10]. A randomized trial of 67 patients with prior bleeding from fundal varices compared cyanoacrylate injection with beta-blocker treatment [37]. Rebleeding (15 % vs. 55 %) and mortality (3 % vs. 25 %) were significantly lower in the cyanoacrylate group. If secondary prophylaxis (prevention of recurrent bleeding) is pursued, repeat sessions are often needed to ensure complete eradication. However, a standardized protocol for repeat therapy has not been established. Some centers advocate for retreatment, as appropriate, at intervals of 2–12 weeks to ensure complete gastric variceal obliteration [35, 38].

While the role of combined endoscopic and medical therapies to prevent rebleeding is better established for esophageal varices [39], such combination treatment has not been well studied for gastric varices. In one randomized trial of 95 patients who bled from fundal varices, repeat cyanoacrylate injection every 3–4 weeks until eradication was compared to repeat cyanoacrylate injection plus a nonselective beta blocker [40]. After a mean follow-up of 20.3 months, there was no difference in rebleeding or survival rates between the two groups.

Thrombin Injection

Thrombin assists in hemostasis by converting fibrinogen to a fibrin clot, as well as enhancing local platelet aggregation. Human thrombin is pooled from human plasma donors and is typically injected in aliquots of 1 ml per injection

site, with an average dose of 1500–2000 units [31]. After the initial report of its use in 1947 by Daly [41], numerous small uncontrolled observational studies have shown thrombin to be an effective initial hemostatic agent for the treatment of gastric varices, with successful hemostasis in 70–100 % of patients and relatively low rebleeding rates [42–47]. There are no controlled trials of thrombin injection for gastric varices to date, although one trial that compared ethanolamine injection, with or without thrombin, showed lower rates of bleeding from the injection site in the thrombin group [48]. The cost of thrombin is substantially higher than cyanoacrylate, and further studies are needed before thrombin can be recommended as a primary treatment option for GVH.

EUS-Guided Therapy

EUS-Guided Cyanoacrylate Injection

Most centers perform glue injection under endoscopic guidance, which may result in injection adjacent to rather than within the varix. Data from sclerotherapy suggest that up to 60 % of injections are actually paravariceal in nature [49]. EUS-guided glue injection is attractive as it enables sonographic visualization for precise glue delivery into the variceal lumen. Furthermore, the technique allows for visualization of deeper varices as well as feeder vessels [50], which can be targeted separately. EUS can improve detection and visualization of gastric varices [51], especially in the setting of active bleeding which may obscure the endoscopic field of view. The monitoring of gastric varices with EUS and repeat injections until complete obliteration have been shown to decrease rebleeding rates [52], and color Doppler can be used to confirm complete variceal obliteration with absence of blood flow.

EUS-Guided Coil Injection

A large variety of embolization coils are available for transcatheter vascular use. Many of these fit through EUS fine-needle aspiration (FNA) needles and can be utilized for EUS-guided angiotherapy. The coils used at our institution are made of Inconel, a nickel-based superalloy. The coils contain radially extending, synthetic fibers that help induce clot formation and hemostasis. The coils are MRI conditional and can be used in a static magnetic field of 3 T or less. A variety of coil sizes and lengths are available. A 0.035-in. coil will fit through a 19-gauge FNA needle (Fig. 13.5). Straightened coil lengths range from 2 cm to 15 cm, with coiled diameters of 2 mm to 20 mm and approximate number of loops ranging from 1.9 to 5.6. Smaller 0.018-in. coils are also available and will fit through a 22-gauge FNA needle. Coil selection depends on the size of the varix, but typically a coiled diameter of 10–20 mm is optimal.

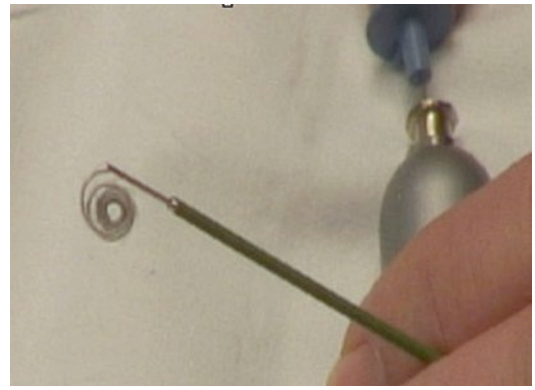

Fig. 13.5 A 0.035-in. embolization coil is advanced through a 19-gauge FNA needle and resumes a coiled configuration as it exits the needle tip

EUS-guided coil injection for acute variceal bleeding was initially reported in 2008 [53]. Embolization was accomplished using microcoils through a 22-gauge FNA needle for variceal obliteration of ectopic varices surrounding a choledochojejunal anastomosis. A retrospective trial of 30 patients comparing EUS-guided coil injection to EUS-guided cyanoacrylate injection revealed similar obliteration rates, but fewer endoscopy sessions were required in the coil group (82 % vs. 53 % obliteration in a single treatment session) [54]. Of note, the intended therapy was for coil injection when feasible, but only 11 of 30 patients underwent such therapy due to technical difficulties hindering the use of coils. The rate of adverse events was significantly

higher in the cyanoacrylate group (58 % vs. 9 %), although 9 of the 11 adverse events in the cyanoacrylate group were asymptomatic pulmonary glue embolisms found on routine post-procedure CT. This indicates that glue embolization is occurring more commonly than appreciated, but that it rarely causes symptoms.

EUS-guided angiotherapy requires additional training and expertise in interventional EUS and performance of the technique appears currently limited to a very small number of tertiary centers. EUS-guided angiotherapy faces several challenges compared to standard endoscopic techniques, including a smaller echoendoscope channel size with limited suction capability and the required ultrasound processor, which makes bedside endoscopy in the intensive care unit difficult. Identification of the feeder vessel can also be challenging and time-consuming. Accidental injection of cyanoacrylate into an efferent vessel would not provide variceal obliteration and could increase the risk of embolization. Lastly, EUS-guided therapy is more suitable for localized gastric varices from a single feeder vessel, whereas a diffuse variceal network may not be amenable to EUS-guided therapy [55].

EUS-Guided Combined Coil and Cyanoacrylate Injection

Our center has developed an EUS-guided approach consisting of coil placement followed immediately by glue injection into the same varix. We theorized that the coil provides a scaffold for glue retention at the site of intravariceal injection. We believe the combination of coil and glue may enhance the rates of hemostasis and variceal obliteration while decreasing the risk of glue embolization.

The procedural protocol at our center for combined EUS-guided coil and glue injection is as follows (Table 13.2 and Fig. 13.6):

1. After administering prophylactic antibiotics, standard upper endoscopy is performed to allow for classification of the varices and assess for active bleeding.
2. EUS with a curvilinear array echoendoscope and intraluminal water filling of the gastric fundus for improved sonographic visualization follows.
3. EUS-guided coil placement is performed. The varix is punctured with a 19- or 22-gauge FNA needle (needle size based on size of coil to be delivered) primed with normal saline. Needle trajectory is often a transesophageal-transcrural path from the distal esophagus. After puncture, intravariceal needle position is confirmed by blood aspiration or saline injection (bubbles visualized endosonographically). The coil is delivered into the varix by using the needle stylet as a pusher and can be sonographically visualized as a curved echogenicity. During this portion, care is taken to ensure that advancement of the coil does not force the needle out of the varix lumen.
4. EUS-guided glue injection follows. Once the coil is deployed, blood is again aspirated to ensure the needle remains within the varix. Then, 1 ml of 2-octyl cyanoacrylate is immediately injected over 30–45 s, followed by normal saline to flush the glue through the dead space of the needle catheter.

Table 13.2 Technique for EUS-guided coil and glue therapy

1. Standard upper endoscopy for classification of varices
2. Perform EUS with curvilinear array echoendoscope with intraluminal water filling
3. Puncture target varix with 19- or 22-gauge FNA needle primed with saline. Verify intravariceal needle position with blood aspiration. Deliver coil into varix with needle stylet as a pusher
4. Re-aspirate blood to ensure needle position is still within the varix. Inject 1 ml of 2-octyl cyanoacrylate over 30–45 s, followed by saline to flush glue through the needle's dead space
5. Reassess varix with EUS and color Doppler to ensure absence of flow. Consider repeating coil and/or glue injection as needed for complete variceal obliteration

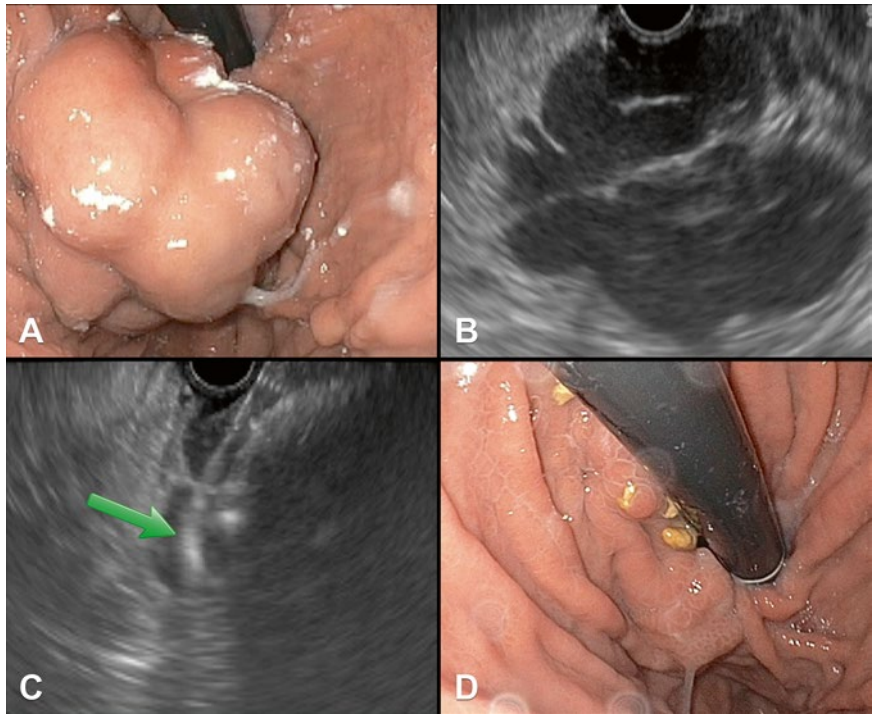

Fig. 13.6 (**a**) Large isolated gastric fundal varix seen at endoscopy. (**b**) Gastric varix seen at EUS. (**c**) Coil (*green arrow*) inserted through a 19-gauge needle under EUS guidance. Cyanoacrylate was then injected (not shown). (**d**) Obliterated gastric varix at a 3-month surveillance endoscopy

5. Post coil/glue injection assessment ensues. After coil and glue injection, the varix is interrogated with EUS, and color Doppler is used to confirm absence of flow. Additionally, the varix can be endoscopically probed with a closed forceps to assess for induration. Further injections of 1 ml of glue or repeat combination of coil and glue are performed, as needed, to achieve complete variceal obliteration. If concomitant esophageal varices are seen, conventional EBL is performed after glue/coil treatment.

In a recent retrospective series published from our center on the use of combined EUS-guided coil and glue injection for gastric varices in 30 patients, technical success was achieved in 100 % of cases and 96 % of varices were obliterated on follow-up endoscopy after a single treatment [56]. No cases of rebleeding (17 %) were attributed to recurrent GVH. There were no procedure-related adverse events and, in particular, no clinically evident glue embolization.

Interventional Radiology Modalities

Transjugular Intrahepatic Portosystemic Shunt

The use of transjugular intrahepatic portosystemic shunts (TIPS) was first reported in humans in the early 1990s [57–59]. This interventional radiology technique creates a fistula between the portal vein and the hepatic vein using a metallic stent, thus decreasing portal pressure. Since intravariceal injection of cyanoacrylate is not a Food and Drug Administration (FDA)-approved procedure, TIPS is the most widely utilized treatment for GVH in the USA. Following TIPS placement for GVH, initial hemostasis rates >90 % can be achieved, although 6- and 12-month rebleeding rates are reported to be 26–29 % and 31 %, respectively [60]. Hepatic encephalopathy occurs at a rate of 15–30 % following TIPS

placement, but can be higher in patients with poor hepatic reserve. A patent TIPS reduces liver perfusion through the portal system and thus may be contraindicated in patients with poor liver function. Interval TIPS occlusion is also a concern, but the use of covered stents has improved shunt patency rates.

Balloon-Occluded Retrograde Transvenous Obliteration

While TIPS manages gastric varices by reduction of portal pressures, balloon-occluded retrograde transvenous obliteration (BRTO) is an interventional radiology technique that enables direct sclerotherapy of gastric varices (Video 13.4). The basic technique was first introduced in the 1970s, and the first contemporary version of the procedure was performed in the early 1990s [61]. In this procedure, the portosystemic gastrorenal shunt is accessed via the left renal vein from a transjugular or transfemoral approach [60–66]. An occlusion balloon catheter is inflated to occlude the shunt and a sclerosant is injected directly into the gastric varices. The balloon catheter is left inflated for a variable period of time, typically 3–24 h, and then deflated and removed. Over 40 studies have reported on the efficacy and safety of BRTO in the treatment of gastric varices. The overall technical success ranges from 79 to 100 %, with acute hemostasis achieved in 91–100 % of cases and with rebleeding rates of 0–20 % [60].

Comparative Studies

TIPS Versus BRTO

A study by Ninoi et al. compared 77 patients who received BRTO with 27 patients who received TIPS. The rebleeding rate at 1 year was higher in the TIPS group (20 % vs. 2 %) and survival rates were improved at 1, 3, and 5 years in the BRTO group (96 %, 83 %, and 76 % vs. 81 %, 64 %, and 40 %) [67]. A more recent comparative study of 50 patients showed no statistical difference with regard to technical success, adverse events, or rebleeding rates, although the encephalopathy rate was 15 % in the TIPS group compared to 0 % in the BRTO group [63].

The data comparing TIPS to BRTO are limited and there are theoretical advantages and disadvantages to each modality. While TIPS decreases portal pressure and bleeding from both esophageal and gastric varices, it can worsen hepatic function and incite or aggravate encephalopathy. In contrast, BRTO preserves hepatic function and may even improve encephalopathy [64]. However, BRTO can increase portal hypertension and worsen esophageal or ectopic varices, resulting in bleeding in 17–24 % of patients [65–68].

TIPS Versus Cyanoacrylate Injection

A retrospective Korean study that compared 43 patients treated with cyanoacrylate injection to 63 patients treated with TIPS found similar rates of initial hemostasis (95 % vs. 92 %), as well as rebleeding and survival [69]. However, adverse events were seen in 51 % of TIPS patients compared with 9 % of patients treated with glue injection. Another retrospective study involving 105 patients in the USA found no significant differences with regard to early or late rebleeding, acute adverse events, or survival. However, the TIPS group had higher morbidity rates, requiring hospitalization (41 % vs. 1.6 %) [70]. A retrospective Chinese study found TIPS to be superior to endoscopic therapy in terms of rebleeding and survival, although 77 % of patients in the endoscopic therapy group were treated with EBL and only a minority received cyanoacrylate injection [71].

Only one prospective randomized trial has compared TIPS with endoscopic cyanoacrylate glue injection. TIPS was found to be more effective in preventing rebleeding (11 % vs. 38 %), but with similar survival and complication rates [72]. However, these results should be interpreted with caution since a lower than expected proportion of patients (51 %) achieved variceal obliteration with cyanoacrylate injection. A retrospective

cost-effectiveness study found that, despite a lower rebleed rate in the TIPS group (15 % vs. 30 %), hospitalization stay was shorter in the cyanoacrylate group with no difference in mortality. The median cost within 6 months of the initial bleed was $4,138 for glue injection versus $11,906 for TIPS [73].

Summary

GVH is one of the most feared endoscopic emergencies. Endoscopic cyanoacrylate injection is currently considered a first-line treatment option, where available. EBL and sclerotherapy are substandard therapies for fundal variceal hemorrhage due to high rebleeding rates. Further research is needed to determine the role of EUS-guided angiotherapy in the management algorithm of bleeding gastric varices. Non-endoscopic treatment options include TIPS and BRTO, and the selection of a particular technique is dependent upon patient factors, local expertise, and consultation among the involved disciplines, including hepatology and interventional radiology. Additional comparative studies regarding the various hemostatic techniques available for GVH are warranted to further define optimal treatment algorithms.

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Hemostasis of Acute Small Intestinal Bleeding

14

Klaus Mönkemüller, C. Mel Wilcox, and Shajan Peter

Introduction

Obscure gastrointestinal bleeding (OGIB) is defined as bleeding of unknown origin that persists or recurs after a negative initial esophagogastroduodenoscopy (EGD) and colonoscopy [1]. Up to 30 % of causes of OGIB are within the reach of an EGD and colonoscopy [2]. The remaining causes for OGIB are within the small bowel [2–6]. Traditionally gastrointestinal bleeding (GIB) has been classified as upper or lower [3]. Upper GIB (UGIB) is defined as hemorrhage originating from the oropharynx to the ligament of Treitz, whereas lower GIB (LGIB) is defined as bleeding distal to the ligament of Treitz [2]. However, this classification is inexact as we currently know that the small bowel represents a significant source of occult and overt GIB [2–7]. Given the importance of the small bowel as a source of bleeding, the term "mid gastrointestinal bleeding" (MGIB) is proposed. MGIB refers to bleeding in the small bowel segment between the ampulla of Vater and the ileocecal valve [8]. The more common causes of MGIB are vascular ectasias and, to a lesser extent, ulcerative diseases and tumors. However, the differential diagnosis of small bowel bleeding remains broad (Table 14.1) (Figs. 14.1, 14.2, 14.3, 14.4, 14.5, and 14.6) [5, 8].

Enteroscopic Diagnosis and Accessories for Small Bowel Bleeding

The preferred endoscopic methods to investigate small bowel bleeding include capsule endoscopy (CE) and device-assisted enteroscopy (DAE) [1, 2, 8]. CE does not allow for therapeutic interventions, but is a useful test to screen for causes of OGIB [8]. DAE includes overtube-assisted enteroscopy, balloon-assisted enteroscopy (BAE), and spiral enteroscopy [5, 7–9]. Whereas traditional push enteroscopy allows for the investigation of the proximal third of the small bowel, DAE enables deeper assessment of the small bowel (deep enteroscopy), including the potential for total examination of the small intestine (complete enteroscopy) [2–9]. Deep enteroscopy has significantly increased our ability to treat and palliate small intestinal bleeding (Table 14.2) [3, 6, 8, 10–23].

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K. Mönkemüller (✉) • C.M. Wilcox • S. Peter
Division of Gastroenterology and Hepatology, Basil Hirschowitz Endoscopic Center of Excellence, University of Alabama at Birmingham, 1720 2nd Ave S, Birmingham, AL 35233, USA
e-mail: klaus1@uab.edu

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Table 14.1 Potential causes of mid GI bleeding

Vascular lesions
Angiodysplasia
Dieulafoy lesion
Ischemic enteritis
Varices
Portal enteropathy
Aortoenteric fistula
Phlebectasia
Telangiectasia (Osler-Rendu-Weber disease, Turner's syndrome, systemic sclerosis)
Hemangioma (blue rubber bleb nevus syndrome, Klippel-Trenaunay-Weber syndrome)
Inflammatory lesions
Nonsteroidal anti-inflammatory drug (NSAID)-induced enteropathy
Crohn's disease
Celiac disease (ulcerative jejunitis)
Vasculitis/ Behcet's disease
Amyloidosis
Radiation enteritis
Eosinophilic enteritis
Anastomotic ulcer
Nonspecific ulcer
Polypoid lesions
Inflammatory polyp
Lipoma
Hamartoma
Adenomyoma
Lymphangioma
Peutz-Jeghers syndrome
Cronkhite-Canada syndrome
Gardner's syndrome
Neoplastic lesions
Gastrointestinal stromal tumor (GIST)
Adenoma
Adenocarcinoma
Leiomyosarcoma
MALT lymphoma
Follicular lymphoma
T-cell lymphoma
Neuroendocrine tumor (carcinoid)
Metastasis (melanoma, breast, renal cell)
Diverticulosis
Meckel's diverticulum
Small bowel diverticulosis
Diverticula retracted by tumors
Diverticula retracted by adhesions
Other lesions
Intestinal intussusception
Whipple's disease
Strongyloidiasis
Cytomegalovirus
Mycobacterium tuberculosis
Mycobacterium avium complex
Blastomycosis

Important differences in endoscopic approach, however, exist when treating small bowel bleeding relative to other parts of the luminal GI tract:

1. The small bowel is long and has many loops, often making it more difficult to obtain a good endoscopic position to target the lesion of interest. Thus, advanced endoscopic skills are needed to maneuver the enteroscope within the tortuous and long small bowel.
2. The small bowel wall is very thin. Therefore, particular attention should be given when applying noncontact or contact thermal therapies, such as argon plasma or bipolar coagulation.
3. The utilization of available hemostatic devices during deep enteroscopy for small bowel bleeding can be challenging, in part due to difficult instrument passage through the long working channel of the enteroscope. The endoscopist should be familiar with the advantages and limitations of particular hemostatic devices, such as clip placement, contact coagulation, and argon plasma coagulation, in the context of deep enteroscopy (Table 14.3).

Technical Details of Enteroscopes and Devices Used for Therapeutic Enteroscopy

Knowledge of the technical details of the deep enteroscopes and accessories available are mandatory when planning endoscopic hemostasis (Tables 14.4 and 14.5) [5, 8, 25]. The spiral overtube is no longer available on a commercial basis and will not be detailed any further. A key difference as

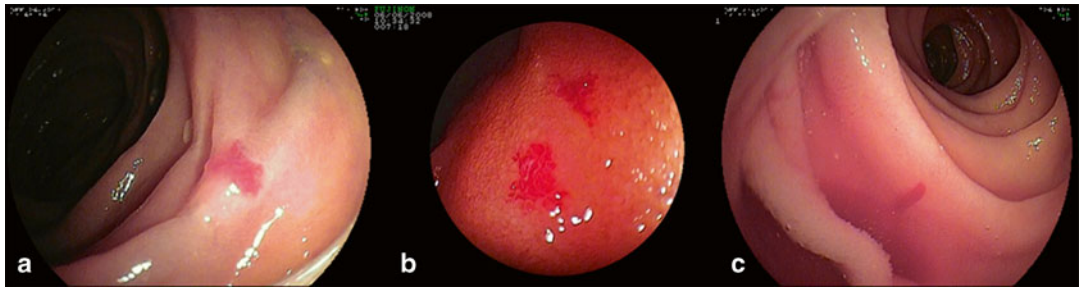

Fig. 14.1 The most common causes of small bowel bleeding are arteriovenous malformations (AVMS). These can be single (**a**) or multiple (**b**). Even small AVMs can result in significant bleeding. Water immersion endoscopy is of particular use to visualize active bleeding, as the blood will spurt into the water (**c**)

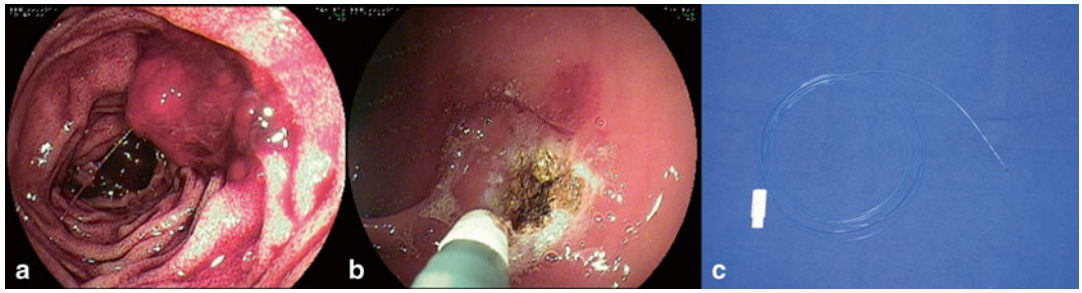

Fig. 14.2 Blood clots and fresh blood may obscure the field of view (**a**). During device-assisted enteroscopy, the lumen can be cleansed using water flushed through the accessory channel of the scope. In this case, argon plasma coagulation is applied to a bleeding AVM (**b**, **c**)

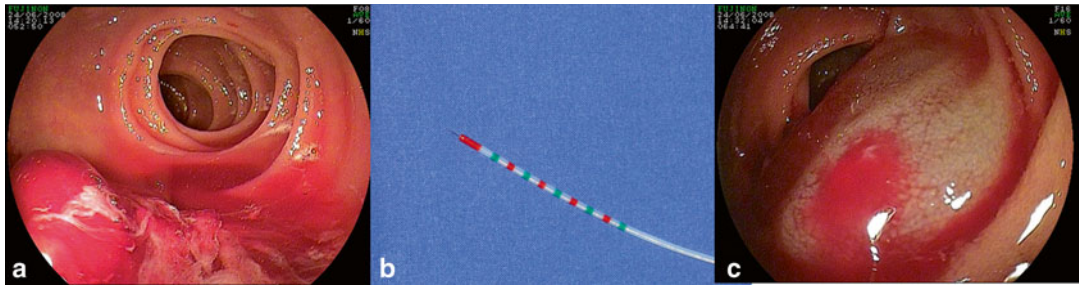

Fig. 14.3 Dieulafoy lesions often cause massive overt obscure GI bleeding. Part A shows large amount of fresh blood clots in a patient with Dieulafoy lesion (**a**). In this case the lesion was treated using combination therapy starting with injection (**b**, **c**). The lesion was first injected with saline-epinephrine mixture (1:20,000) and then cauterized with argon plasma coagulation

regards therapeutic enteroscopy is the need for longer and smaller caliber devices, which can be advanced through the working channel of the enteroscope. The enteroscopes are long and the diameters of their working channels are similar or smaller than that of a diagnostic upper endoscope (Table 14.5). Based on the type of deep enteroscope utilized, proper selection and familiarity with particular hemostatic devices become important. The staff should be well trained in maneuvers related to deep enteroscopy, such as handling of the balloon overtube, as well as devices utilized during the procedure. In addition, the endoscopist treating midgut bleeding should be experienced in small bowel therapeutic endoscopy.

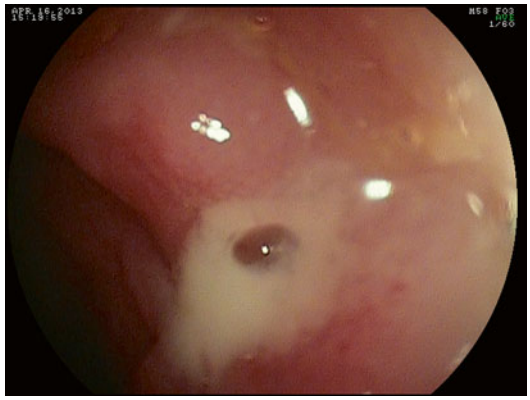

Fig. 14.4 Ulcers with visible vessels are found occasionally in patients with overt or occult OGIB

Determination of the Initial Route of Insertion for Deep Enteroscopy

The choice for either an antegrade (oral) or retrograde (anal) route for BAE depends on the suspected location of the lesion within the small bowel, as assessed by clinical manifestations, laboratory results, radiological studies (e.g., CT enterography), and/or CE examinations [5–11, 19]. For OGIB, CE is currently the main instrument used to determine the preferential route of approach for BAE [23]. However, one may forego CE in a patient with clinically significant and suspected active bleeding, as this approach will only delay the diagnosis [5, 6]. In addition, CE may not be useful in patients with altered upper GI anatomy, such as a Roux-en-Y anastomosis (Figs. 14.7 and 14.8). In a patient with overt OGIB and presumed active bleeding or with surgically altered upper GI anatomy (Fig. 14.9), we thus prefer to proceed directly to BAE. In this setting, the initial route of BAE insertion is dictated by the color of the stool; the antegrade approach is utilized when melena is present, whereas the retrograde approach is selected in the presence of hematochezia [5]. If the initial approach does not yield a diagnosis, the opposite route is used for the subsequent enteroscopic procedure. A tattoo should be placed at the first BAE procedure, so that complete enteroscopy can be confirmed when the tattoo is visualized at the second BAE from the opposite route (Fig. 14.7). Complete enteroscopy can also be confirmed if the cecum is reached during the antegrade approach, although this is a rare event. In general, complete enteroscopy is not required in the majority of patients with overt OGIB, since the definite or potential bleeding source is usually identified during the initial deep enteroscopy without visualization of the entire small bowel. Approximately one third of patients will require two separate BAE procedures to arrive at a diagnosis [5–22].

Approach to Patients with Altered Upper GI Anatomy

Patients with surgically altered upper GI anatomy, such as Roux-en-Y anastomosis and gastric bypass, can also bleed from small bowel sources or the excluded stomach [16–18]. In general, the sources of small bleeding in these patients are similar to those without previous gut surgery. However, consideration should also be given for particular bleeding etiologies in this setting, such as varices and angiodysplastic lesions at the anastomotic sites (Figs. 14.8 and 14.9).

Devices and Techniques for Enteroscopic Hemostasis

The treatment modalities for small bowel hemostasis can be categorized into (a) thermal, (b) injection, and (c) mechanical (Tables 14.3 and 14.4) [5]. There are no comparative studies regarding the use of these modalities for MGIB. The selection of one or a combination of devices is influenced by device availability, operator preference, and characteristics of the targeted lesion, including type, size, location, and access. The concept of dual (or even triple) endoscopic therapy (e.g., injection combined with thermal coagulation and/or clip placement) for small bowel bleeding has not been studied. Nonetheless, we have encountered instances in which a dual approach has been useful (Videos 14.1, 14.2, and 14.3). These lesions have included large anastomotic angiodysplasias or varices, Dieulafoy lesions, and ulcers with spurting vessels.

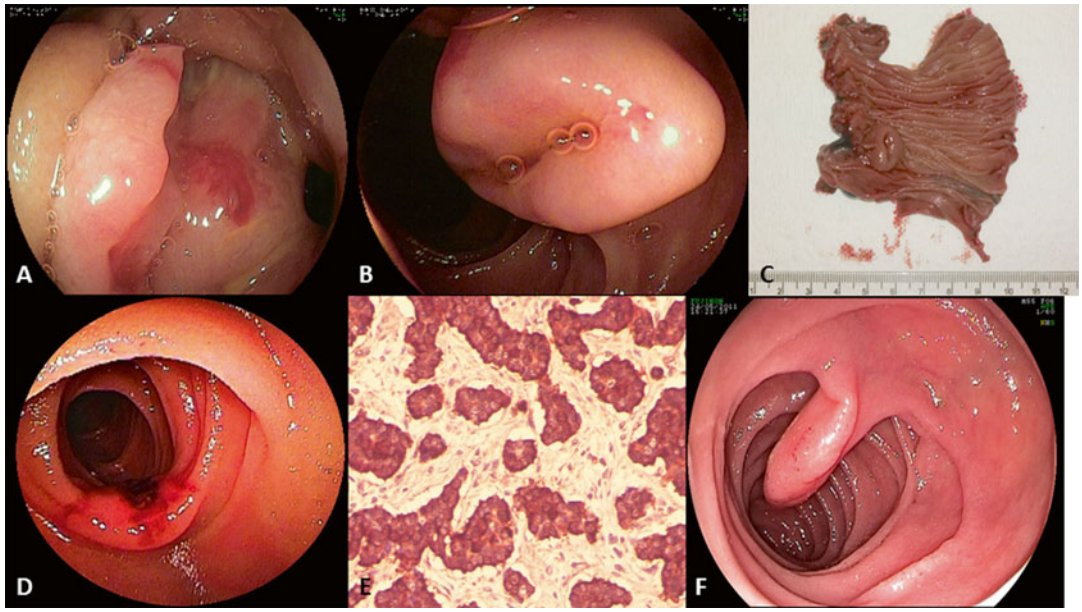

Fig. 14.5 *Small bowel* polyps and tumors are an important cause for both occult and overt OGIB. The tumors include, but are not limited to, carcinoma (**a**), gastrointestinal stromal tumor (GIST) (**b**, **c**), neuroendocrine tumors (NET) (**d**, **e**) and lipomas (**f**). GIST and NET are most commonly submucosal lesions, often missed by capsule endoscopy

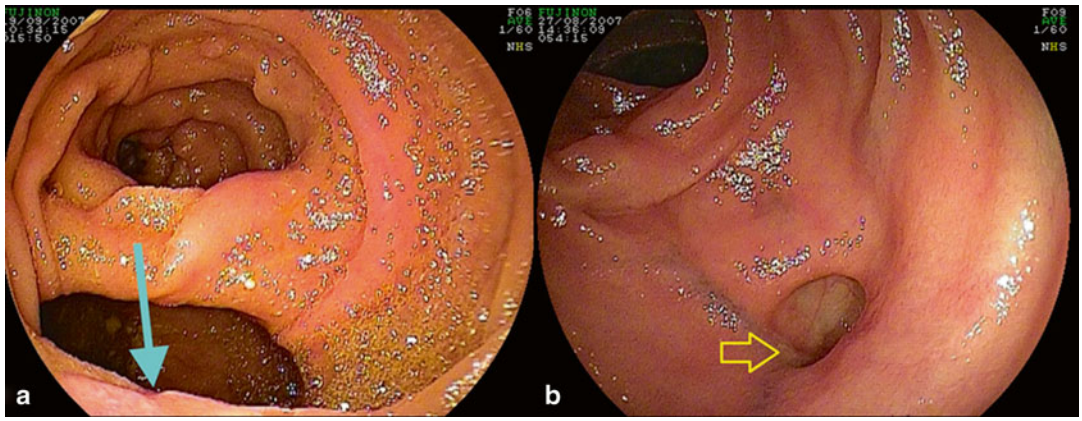

Fig. 14.6 An uncommon but important lesion resulting in OGIB found during retrograde deep enteroscopy is Meckel's diverticulum (**a, b**). The ulcers on the diverticulum's edge are often subtle and can be easily missed (*arrows*)

An algorithm for the endoscopic treatment of small bowel lesions is proposed (Fig. 14.10).

Thermal Therapies

Argon Plasma Coagulation

The primary method used for endoscopic small bowel hemostasis is argon plasma coagulation (APC) (Figs. 14.2 and 14.8). APC application in the small bowel is different than for most other parts of the luminal GI tract for the following reasons:

1. The thin-walled small bowel is at increased risk of perforation. Careful attention should be paid to the selected APC settings for a given electrosurgical generator (ESG). For example, a maximum power of 30–40 W is recommended when using the ERBE ICC 200

Table 14.2 Long-term outcomes of patients with GI bleeding treated using balloon-assisted enteroscopy

Author (reference number)	Year	Number of patients	Diagnostic yield	Patients with AVM	Endoscopic treatment	Follow-up months (range)	Overall re-bleeding rate
Samaha [10]	2012	261	51 %	129	129	22 (1–52)	46 %
May [11]	2011	63	NR	44	44	55	42 %
Fujita [12]	2010	87	46 %	NR	21	41 (2–66)	44.8 %
Shinozaki [13]	2010	200	77 %	29	25	30 (6–78)	39 %
Gerson [14]	2009	85	NR	43 %		30 (19–51)	40 %
Arakawa [15]	2009	162	64 %	26	19	18.5	31 %
Hindryckx [16]	2008	n/a	n/a	18	10	21	38 %
Albert [17]	2008	n/a	n/a	112	36	20.7	31 %
Madisch [18]	2008	124	49 %	n/a	n/a	2 (1–5)	18 %
Ohmiya [20]	2007	479	58 %	63	63	55	42 %
Hsu [21]	2007	20	75 %	n/a	n/a	12 (3–28)	35 %
Sun [22]	2007	152	75 %	n/a	n/a	16	12 %

AVM arteriovenous malformation, *n/a* data not available, *NR* not reported

Table 14.3 Endoscopic hemostatic techniques for small bowel bleeding

Thermal therapy	Argon plasma coagulation
	Electrocoagulation
	Monopolar
	Bipolar/Multipolar
	Heater probe
Injection therapy	Epinephrine
	Fibrin glue/thrombin
	Cyanoacrylate
Mechanical	Endoscopic clips
	Detachable snare (endoloop)

ESG (ERBE Inc., Marietta, GA, USA) as opposed to a maximum of 20–25 W (pulsed) when the newer generation ERBE VIO ESG is used, since the amount of thermal energy delivered by the latter device is larger. The argon flow rate of the APC generator will also influence the amount of thermal energy delivered to the target. We recommend flow rates of 0.6–0.8 l/min in the small bowel. Several APC generators are available on the market, and a good starting point is to follow the manufacturer's recommendations and to be familiar with the technical features of a particular ESG for the safe and effective use of the device during small bowel hemostasis.

2. The small bowel is attached to the mesentery and follows a concentric route. This anatomic configuration makes targeting of specific lesions more difficult, since the bowel tends to slide away from the enteroscope and overtube. Careful coordination with the assistant holding the overtube during APC application is mandatory.
3. Over-insufflation of the small bowel during endotherapy should be avoided as this thins out even further the small bowel wall. Careful, noncontact targeting of the lesion is mandatory and the APC probe should be applied tangentially, if feasible, to minimize the risk of contact and direct delivery of thermal energy, which may spread deeper into the tissue than intended. The treatment objective with APC is to cause superficial ablative injury and induce a fibro-inflammatory reaction, with definitive sealing of the lesion, particularly when targeting vascular ectasias.
4. The deep enteroscopes have "limited" working channels, up to 2.8 mm in diameter (Table 14.5). Unless a thin-caliber probe is used, it is difficult to suction the argon gas during the procedure. The overzealous application of argon gas can result in overdistention and discomfort and increases the potential

Table 14.4 Selected hemostatic tools available for use during deep enteroscopy

Mode of intervention/therapy	Accessories	Company
Argon plasma coagulation	End- and side-firing probes	ERBE
		ConMed
Bipolar probe	7-Fr probe	Olympus
		Boston Scientific
Heater probe	7-Fr probe	Olympus
Injection needle	Carr-Locke injection needle	US Endoscopy
Fibrin glue	Beriplast	CSL Behring
	Tisseel	Baxter
N-butyl-cyanoacrylate	Indermil	Covidien
	Histoacryl	Braun Melsungen
Clips	QuickClip2, QuickClipPro	Olympus
	Resolution	Boston Scientific
	Instinct	Cook Endoscopy
Carbon black (for tattooing)	Spot	GI Supply
Detachable snare	Polyloop	Olympus

Table 14.5 Technical characteristics of balloon-assisted enteroscopes

Device	Company	Scope working length	Scope outer diameter	Working channel	Overtube working length	Overtube outer diameter
DBE EN-450P5	Fujifilm	200 cm	8.5 mm	2.2 mm	135 cm	12.2 mm
DBE EN-450 T5	Fujifilm	200 cm	9.4 mm	2.8 mm	135 cm	13.2 mm
DBE EC-450BI5	Fujifilm	152 cm	9.4 mm	2.8 mm	95 cm	13.2 mm
SBE SIF-Q180	Olympus	200 cm	9.2 mm	2.8 mm	132 cm	14.4 mm

SBE single-balloon enteroscope, *DBE* double balloon enteroscope

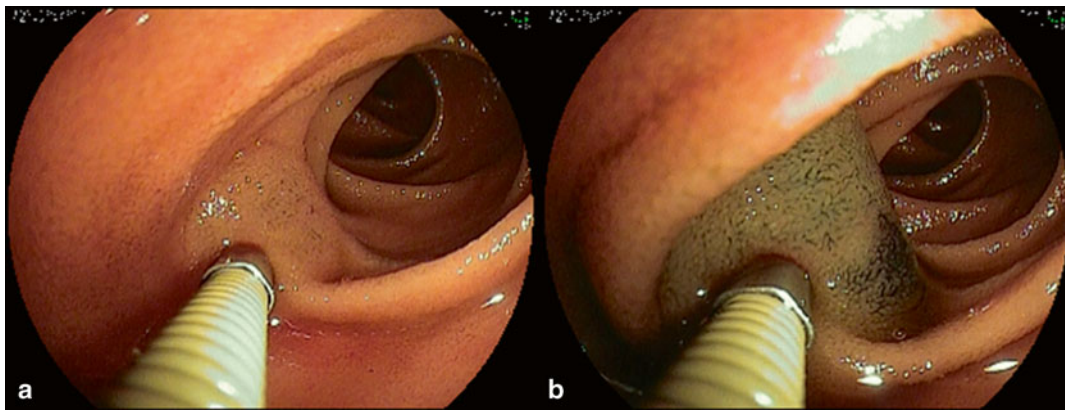

Fig. 14.7 Injection of India ink is of paramount importance to locate tumors or demarcate the depth of insertion. We always inject with saline first (**a**) before injecting the ink (**b**)

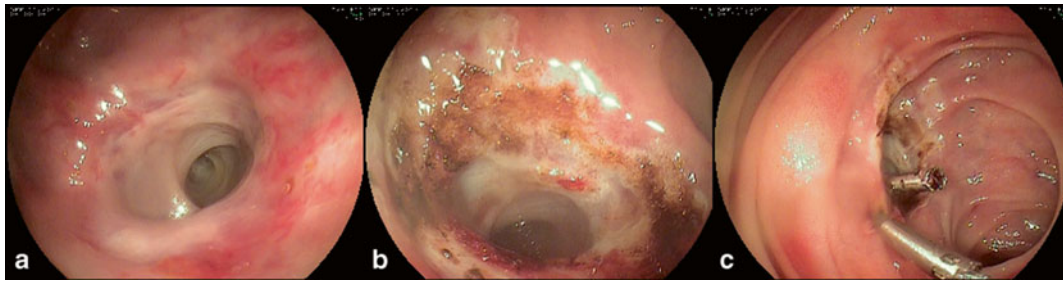

Fig. 14.8 Angiodysplasias at the hepaticojejunostomy are a possible cause of acute and recurrent OGIB in patients with surgically altered upper GI anatomy (**a**). Ablation with APC (**b**) and a combination of APC and hemoclips (**c**) are potential endoscopic therapies for these types of lesions

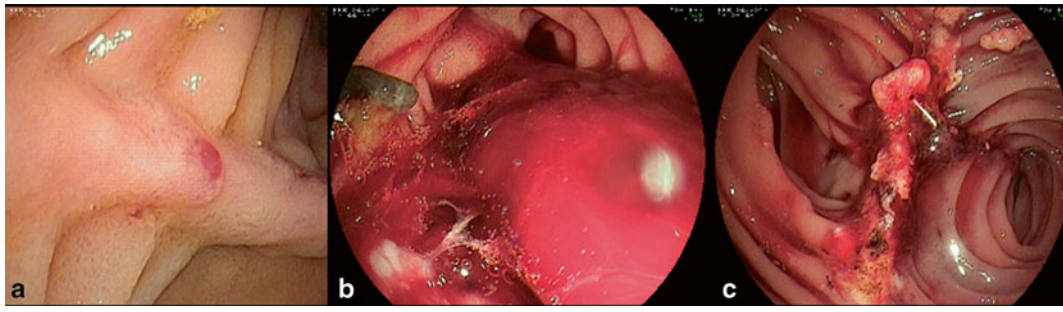

Fig. 14.9 Anastomotic AVMs in a patient with Roux-en-Y anastomosis after gastric bypass surgery (**a**). The AVMs bled massively during the initial application of APC (**b**). The bleeding stopped after application of further APC and four hemoclips (**c**). Do not apply APC on hemoclips in situ as the energy can be transmitted through the clip across the entire GI wall and result in perforation

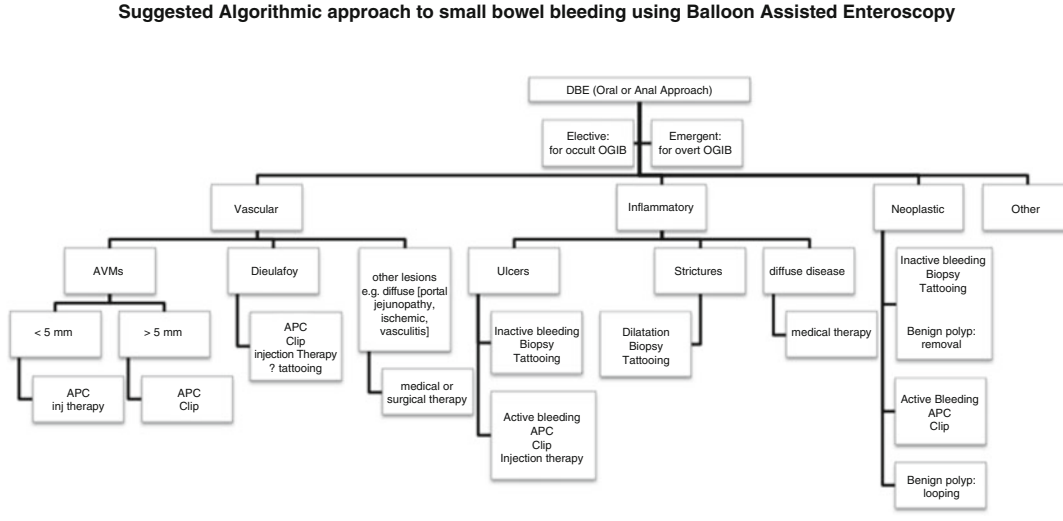

Fig. 14.10 Algorithm for the application of various endoscopic therapies in small bleeding

for small intestinal perforation. Hence, a lower argon flow rate and short bursts of APC application are advised in the small bowel.

Bipolar Electrocoagulation and Heater Probe Coagulation

The application of bipolar electrocoagulation or heater probe coagulation in the setting of small bowel bleeding is not widely used, in part because of the difficulty passing the smaller 7-Fr bipolar or heater probes through the long working channel of the enteroscope and the relative ease of use of APC probes. The recommended settings for the bipolar probe and for the heater probe are 12–15 W and 15 J, respectively. In the small bowel, light probe-tissue contact pressure is advised, with application of energy in short, repetitive bursts until whitening and/or control of bleeding of the treated site occur.

Injection Therapies

The most common injection therapy for small bowel bleeding is saline with epinephrine (Fig. 14.3). Because of the larger surface area of the small bowel, blood circulation may be more easily compromised using constricting agents, such as epinephrine, and small bowel necrosis due to injection of epinephrine solution has been described [26]. We, therefore, recommend diluting epinephrine to 1:20,000, preferably 1:100,000, for small bowel injection. Less commonly used agents for injection into small intestinal bleeding lesions include fibrin glue and cyanoacrylate (e.g., for small bowel varices) [27], although these agents are not approved for this purpose in the United States.

The two main objectives during injection therapy are:

1. To tamponade and vasoconstrict (with epinephrine) the bleeding lesion.
2. To create a submucosal cushion when providing additional therapies, such as APC, or when injecting foreign substances, such as carbon black, for tattooing (Fig. 14.7). This is done with saline or saline-epinephrine solution. By separating the mucosa from the submucosa, endoscopic application of APC on top of the target lesion may be facilitated. In addition, the submucosal fluid provides a safety cushion to minimize damage to the deeper layers of the bowel wall.

When injecting any substance into the small bowel, several steps should be followed:

1. The target lesion or area needs to be in an adequate position for access. Since the accessories exit the enteroscope at the 7 o'clock position, the instrument should be maneuvered so that the area is located at the left lower quadrant of the endoscopic field of view (Figs. 14.2 and 14.7).
2. The injection should occur on the far end of the lesion relative to the tip of the enteroscope, or directly into it. Injection into the proximal aspect of the lesion may result in the lesion lifting away from view, thereby compromising access and further therapy.
3. The needle should penetrate 1–2 mm into the mucosa in a tangential direction, at a 30° angle if possible. If the needle enters the mucosa perpendicularly, the risk of penetrating through the entire small bowel wall is increased and the substance is injected into the peritoneal cavity. Injection of the substance ensues when the needle is retracted slowly. Alternatively, injection commences prior to puncturing the mucosa and needle advancement is stopped as soon as a submucosal bleb is obtained.
4. The injection of any substance should occur slowly, in coordination with the assistant. The amount of injected material will depend on the type of lesion being targeted. In general, 3 to 5 ml of injected solution will result in an adequate "lift" or tamponade, and separate the mucosa from the submucosa or muscularis propria.

Mechanical Hemostasis

Unlike thermal therapies, endoscopic clips provide mechanical hemostasis without extending tissue injury. Through-the-scope (TTS) clips are effective hemostatic tools for a small bleeding vessel or mucosal defect that is visible and accessible (Figs. 14.4, 14.8, and 14.9). Several TTS clips are available for use, with differences in opening width spans, rotation, and/or reopening capability. If the Resolution Clip (Boston Scientific Inc., Marlborough, MA) is utilized, we suggest removing its plastic sheath prior to insertion into the enteroscope to facilitate clip advancement into the working channel and deployment.

Careful attention should be paid while advancing any TTS clip through the enteroscope. Often, the enteroscope has acquired a constrained configuration in the small bowel, and shortening the scope position and/or reducing as many loops as possible will facilitate passage of the TTS delivery catheter through the working channel. Although one study has not found any difference in diagnostic ability of DBE with or without the use of fluoroscopy, data do not exist on the potential utility of fluoroscopy during therapeutic interventions. Fluoroscopy, however, may aid in guiding instrument manipulation in order to obtain better enteroscope configuration for accessory insertion. Another method to facilitate passage of TTS clips and other devices is to use the overtube as an extra "accessory" channel, leaving it anchored in place close to the target lesion, while the enteroscope is pulled back and reinserted through the overtube with the accessory already in the working channel and close to the tip of the scope. This maneuver may salvage the therapeutic procedure when accessories cannot be passed through the working channel of the enteroscope due to constrained positioning. Of note, however, this technique does sacrifice the balloon at the tip of the enteroscope if a DBE instrument is used, and the procedure is converted essentially to single-balloon enteroscopy.

Adverse Events

The adverse events (AE) associated with deep enteroscopy include intestinal perforation, pancreatitis, bleeding, and paralytic ileus. The overall rate of AE for diagnostic DBE appears to be acceptably low and approximates 1 % [28]. The AE rates reported from centers with experience in therapeutic enteroscopy vary from 0.7 to 4.3 %, with the risk of enteroscopic hemostasis within this range. The risk is highest for small bowel polypectomy (overall 3.4 %) [28]. Therefore, adequate training and careful planning of the procedure are mandatory.

Conclusion

Endoscopic therapy for small bowel bleeding is feasible and safe in experienced hands. Therapeutic enteroscopy has become an integral part of interventional endoscopy. In general, all hemostatic modalities, such as APC, injection, and clip placement, can be performed safely and with reasonable efficiency using currently available deep enteroscopy instruments. However, endoscopists performing deep enteroscopy should be well trained and prepared to provide these therapeutic interventions. Thus, patients with MGIB should be evaluated and treated at centers with the capability to offer advanced small bowel therapy.

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Hemostasis of Acute Lower Gastrointestinal Bleeding

15

Linda S. Lee and John R. Saltzman

Introduction

In the management of acute lower gastrointestinal (GI) bleeding, colonoscopy is the test of choice in most patients. Over a decade ago, colonoscopic intervention for diverticular hemorrhage was demonstrated to be effective, with no rebleeding or surgery necessary in patients treated endoscopically [1]. Colonoscopy offers both diagnostic and therapeutic capabilities, with its diagnostic yield ranging from 74 % to 100 % in the setting of lower GI bleeding [2]. This wide range in yield is partially explained by different diagnostic criteria, and often if no definite source is found, bleeding is attributed to a putative lesion (e.g., diverticulosis) if blood is present in the GI lumen. The rates of detecting definite stigmata of hemorrhage (active bleeding, non-bleeding visible vessel, or adherent clot) are lower at 22–42 %. An adult or pediatric colonoscope may be used to perform colonoscopy in lower GI bleeding. The advantages of using a larger channel colonoscope include enhanced suction capability and passage of larger instruments through the working channel. A water-jet pump is essential to allow efficient cleaning of the colon, in addition to precisely pinpointing an actively bleeding site (Video 15.1). In addition, a large caliber endoscope suction device can be coupled directly to the entrance port of the channel of the colonoscope to provide more powerful suction.

Careful examination of the colon must be performed during both insertion and withdrawal because the nature of GI bleeding can be intermittent. Special attention should be given to areas containing fresh blood and/or clots. Vigorous washing must be performed to remove adherent blood, clots, and debris on insertion. Inspection under water may be particularly helpful to allow localization of active bleeding. In areas with multiple diverticula, every effort should be made to irrigate and inspect each diverticulum for stigmata of bleeding and/or active bleeding. Opiates have been reported to reduce visibility of angiodysplasias and naloxone may enhance their visualization, although the latter is not typically done in clinical practice [3]. If no bleeding site has been identified in the colon, the terminal ileum should be intubated to document whether blood is present. If no blood is present in the terminal ileum while blood is visualized in the colon, this implies a colonic source of bleeding.

Visualization of active bleeding, a non-bleeding visible vessel, or an adherent clot

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L.S. Lee • J.R. Saltzman (✉)
Department of Gastroenterology and Hepatology, Brigham & Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA
e-mail: jsaltzman@partners.org

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necessitates treatment to arrest bleeding or prevent rebleeding. All the hemostatic tools used in upper GI bleeding are available for lower GI bleeding, including injection therapy, thermal therapy, clip placement, and band ligation. In contrast to upper GI bleeding where evidence-based data suggest combination therapy to be superior to epinephrine injection alone and the other modalities are effective as monotherapy [4], similar data are lacking for lower GI bleeding.

Hemostatic Devices for Lower GI Bleeding

Injection Therapy

Epinephrine injection therapy is often used to slow the rate of active bleeding and before removal of adherent clots by cold snare guillotine (Video 15.2). The mechanisms of action include tamponade effect on the blood vessel and transient vasoconstriction. Epinephrine injection is typically performed using a dilution of 1:10,000. An injection needle is primed with dilute epinephrine loaded into a syringe that is attached to the needle handle. When the needle is near the target lesion, an assistant advances the needle out of the outer sheath to a preset distance. Similar to bleeding peptic ulcers, injection is performed in a 4-quadrant fashion around the bleeding site in 0.5–2 ml aliquots. Epinephrine should not be injected directly into a non-bleeding visible vessel. Although there are no data to suggest that combination therapy is superior to epinephrine injection alone in lower GI bleeding, the latter is typically used as a precursor to another more definitive treatment modality (as in upper GI bleeding). Most injection catheter needles are 7 Fr in diameter, although 5 Fr and 10 Fr catheters are available. The sheaths and needle lengths vary, as well as the needle gauges, ranging from 19 to 25 G. With regard to adverse events, needle failures have been reported and epinephrine can cause cardiac arrhythmias and hypertension [5].

Thermal Therapy

Thermal therapy is particularly useful for non-bleeding visible vessels, angiodysplasias, radiation proctitis, and postpolypectomy bleeding sites. Both contact and noncontact thermal therapies are available, with one or the other favored in specific situations. Contact thermal therapy is typically performed using devices, such as the heater probe, the bipolar electrocoagulation probe, and the monopolar hemostatic grasper, for coaptation and coagulation of vessels. The heater probe and bipolar probe are equally efficacious and are available in 7 Fr and 10 Fr, with built-in irrigation ports. Irrigation helps visualize the target lesion and allows for a lesser traumatic detachment of the probe from the desiccated tissue. In contrast to the settings for upper GI bleeding, the thermal probe is applied with light to moderate contact pressure for 1–4 s at 10–15 J (heater probe) or 10–15 W (bipolar probe) [6].

The heater probe directly generates heat from an inner heating coil with outer Teflon-coated aluminum cylinder. In contrast, bipolar coagulation probes indirectly generate heat by passing electrical current through the tissue. Because an electrical circuit is completed between 2 closely spaced electrodes in the tip of the probe, no grounding pad is necessary. Adverse events of bleeding and perforation as a result of contact thermal therapy have been reported to occur, with a 2.5 % perforation rate following treatment of colonic angiodysplasias [7].

The hemostatic grasper is similar to a monopolar hot biopsy forceps, except the jaws are flat and the device is rotatable. The technique is to grasp the blood vessel and to gently pull or "tent" the lesion prior to application of current, with suggested settings of 50 W and 1–2 s pulse duration using a soft coagulation mode [5]. This method is often used during endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) when active bleeding occurs or a visible vessel is seen, as this technique allows for rapid sealing of the vessel while keeping the dissected or resected site clean (Video 15.3).

Argon plasma coagulation (APC) is noncontact thermal therapy using electrically ionized argon gas (plasma) that flows from the tip of the probe to nearby tissue. As the tissue desiccates and loses electrical conductivity, the plasma seeks and coagulates adjacent non-desiccated tissue. This protective property minimizes deep tissue injury. Depth of coagulation varies with the generator power setting and flow rate, duration of therapy, and probe distance to lesion. Current generators allow automatic selection of settings by location, which are preprogrammed with the appropriate flow rate. Because the tip of the probe needs to remain about 2–8 mm from the target lesion and touching the mucosa may result in localized pneumatosis and possibly perforation, the endoscopist requires fine control over the endoscope to maintain optimal distance, which is made even more challenging in the setting of vigorous peristalsis [5]. One helpful technique involves gently touching the lesion with the tip of the probe and then backing the probe away slightly before depressing the foot pedal for APC activation. Often, the tip of the probe will need to be removed for cleaning built-up coagulum, which hampers conductivity. Argon gas rapidly accumulates within the GI lumen during APC and should be intermittently suctioned. The colon should not be fully distended during APC therapy to avoid thinning further the colonic wall and increasing the risk of perforation.

APC probes are single-use devices available in various lengths, diameters (5–10 Fr), and firing directions (straight, side, and circumferential). Circumferential firing probes are most versatile and suitable for radiation proctitis. Straight- or side-firing probes are appropriate for targeting single arteriovenous malformations. Perforations have been reported with APC, including colonic explosion in inadequately cleansed colons [8]. Therefore, a full colon preparation with polyethylene glycol or saline-based solution is mandatory prior to APC use. Rare adverse events, such as pneumomediastinum, pneumoperitoneum, and submucosal emphysema, have been described following APC [9].

Mechanical Hemostatic Devices

Mechanical hemostatic devices include clips, bands, and detachable loops. Currently available through-the-scope (TTS) clips are rotatable and/or capable to reopen, with different delivery catheter lengths and jaw widths (Table 15.1). The handling and deployment of a clip typically involves the following steps: advance the clip out of the sheath (if present), open the jaws, position the opened jaws onto the targeted lesion with pressure, close the jaws, and deploy the clip. At this point some clips are fully deployed, while others require further manipulation of the handle to deploy the clip. This final step (if applicable) is important to ensure the clip is detached from the catheter before withdrawing the latter into the endoscope. Otherwise, the clip may be wrenched from the lesion, precipitating bleeding.

Table 15.1 Selected through-the-scope clips

Clip	Width of open jaws (mm)	Rotatable	Reopening capability	MRI[a] conditional
Resolution Clip (Boston Scientific, Inc.)	11	No[b]	Yes	Yes
QuickClip 2 (Olympus Corp.)	9	Yes	No	No
QuickClip 2 Long (Olympus Corp.)	11	Yes	No	No
Instinct clip (Cook Endoscopy, Inc.)	16	Yes	Yes	Yes

[a]*MR* magnetic resonance imaging
[b]Some rotation capability feasible with protective sheath off

Familiarity in the use of a chosen clip device is, therefore, essential. The application of suction before closing the clip helps draw more tissues within the opened jaws, and generally soft pliable tissue is necessary for successful clip closure. Targeted clip placement of a visible vessel within a large fibrotic ulcer base may rupture the vessel and precipitate bleeding since the prongs of the clip may not anchor into fibrotic tissue.

Clip deployment is targeted at the bleeding lesion or visible vessel. Additional clips can then be placed on each side of the clipped lesion to ligate the feeding vessel. If the first clip is placed on one side of the vessel, the second clip is placed on the other side to ensure hemostasis. Thus, two to three clips are typically placed to target a bleeding source (Video 15.2).

Recently, over-the-scope clips (OTSC) have become available for treatment of focal bleeding lesions, typically in cases refractory to standard endoscopic therapies. Although the majority of the OTSC experience to date has been in the management of upper GI bleeding, there are several reports regarding the successful use of OTSC in lower GI bleeding [10].

Endoscopic band ligation (EBL) is typically used for esophageal variceal bleeding, although there are reports of successful banding for diverticular bleeding [11]. The bleeding diverticulum should be marked with a tattoo or clip to aid in subsequent identification, and over-suctioning excess tissue into the banding cap should be avoided to prevent entrapment of the entire colonic wall, which could lead to delayed perforation [12]. EBL requires withdrawal of the colonoscope after site marking for device loading and reinsertion of a gastroscope loaded with the banding apparatus to the bleeding site for band deployment. The logistics of instrument withdrawal and reinsertion may not be feasible in some settings.

Detachable loops or snares for ligation are particularly useful for constricting and tamponading the stalk of large pedunculated polyps before polypectomy. These nylon loops open to a diameter of 3 cm and once lassoed around the stalk, they are tightened to achieve hemostasis or cyanosis of the polyp, followed by loop release. Positioning the loop around the lesion may be difficult because of its floppy nature, and gradually opening the loop over the lesion may help with positioning. If needed, a loop-cutting device can section maldeployed loops. The loop can inadvertently cut through the stalk by constricting the loop too tightly. In contrast, premature loop deployment will result in inefficient tightening of the target lesion, and this can be avoided by slowly tightening and assessing the appearance of the lesion for ischemic change prior to release of the loop. Postpolypectomy loop placement to control active bleeding from a residual stump is feasible as long as enough stalk remains for capture by the loop.

Non-endoscopic Therapy for Lower GI Bleeding

Angiography

Similar to colonoscopy, angiography can be both diagnostic and therapeutic in lower GI bleeding. It is particularly useful in patients with ongoing bleeding whose colons are unprepped and in those with severe bleeding, which would likely limit visualization during colonoscopy. Angiographic vasopressin infusion is not commonly used due to its high bleeding recurrence rate and complications [13]. Super-selective microcatheter embolization is usually performed for hemostasis using small 2.5–3 Fr microcatheters that are advanced through larger catheters and through which various embolic agents can be deployed, including microcoils, microparticles, and glue. Initial clinical success with this technique is achieved in over 95 % of patients, with a rebleeding rate of about 22 %. The major concern with angiographic intervention lies in its potential for serious adverse events in about 17 % of cases, including bowel ischemia and infarction, hematoma, thrombosis, and vascular dissection [14].

Surgery

Surgical resection is the last resort for ongoing lower GI bleeding that is refractory to less invasive endoscopic and angiographic management,

since it carries substantial morbidity and mortality, especially in emergent situations. Blind segmental resection is not recommended due to its high rate of recurrent bleeding, morbidity, and mortality. Segmental resection is preferred with lower rebleeding rates ranging from 0 to 14 %. Subtotal colectomy carries the lowest rebleeding rate (<5 %), but with higher morbidity than targeted segmental resection.

Specific Causes of Lower GI Bleeding

The differential diagnosis of acute lower GI bleeding is broad, although the vast majority of such bleeding is due to diverticulosis, ischemic colitis, angiodysplasias, neoplasia, and hemorrhoids (Table 15.2) [15]. The cause of lower GI bleeding remains uncertain in about 12 % of cases. The use of specific hemostatic tools for the most common lower GI bleeding lesions is highlighted here.

Diverticular Bleeding

Multiple endoscopic options are available for treating a colonic diverticulum with active bleeding or stigmata of recent bleeding, including epinephrine injection, thermal coagulation, mechanical therapy, or a combination thereof [12]. Once a bleeding diverticulum is identified, the location should be marked with a submucosal injection of a tattooing agent to localize the bleeding area if subsequent endoscopic or surgical therapy becomes necessary. Alternatively, a clip can be placed next to the site to mark its location, although the clip is not meant to be served as a permanent endoscopic or fluoroscopic marker.

Epinephrine injection in four quadrants can control bleeding or close the mouth of the diverticulum by tamponade. A bleeding or nonbleeding visible vessel can be identified at the neck or at the dome of the diverticulum. Adherent clots can be removed using the cold snare guillotine technique (similar to the technique for upper GI bleeding), and any underlying lesion should be treated appropriately. TTS clips can be placed directly on the culprit vessel (Video 15.4) or used to close the entire diverticulum (Fig. 15.1) [16]. One study suggests that clip placement targeted at the vessel is more effective than closing the entire diverticulum in a "zipper" fashion [17]. If utilized, contact thermal therapy should be applied carefully, particularly in the dome of the diverticulum. The suggested treatment settings for bipolar coagulation are a power of 10–15 W and short 1–2 s pulse duration, with light to moderate probe-tissue contact pressure (Video 15.5). If clips or thermal therapy are not feasible due to difficult access, particularly in a narrowed, angulated sigmoid colon, EBL can be considered (Fig. 15.2). The band ligation cap is useful in this setting to facilitate access to the bleeding diverticulum. An area adjacent the bleeding diverticulum should be marked with a tattoo or clip to aid visual identification when an upper endoscope loaded with the banding device is subsequently introduced (Video 15.6).

Table 15.2 Etiology of lower gastrointestinal bleeding

Source	Prevalence (%)
Diverticulosis	17–44
Colonic angiodysplasia	2–30
Ischemia	9–21
Malignancy	4–14
Hemorrhoids/anorectal lesions	4–11
Postpolypectomy	6
Unknown	8–12

Angiodysplasias

At colonoscopy, an angiodysplasia has a characteristic appearance of a 2–10 mm, red, fern-like, flat lesion with ectatic vessels radiating from a central vessel. Poor bowel preparation and use of meperidine and other opiates, which transiently decrease mucosal blood flow, could potentially hinder the identification of angiodysplasias. If there is a history of guaiac-positive stool or iron deficiency anemia, angiodysplasias should be treated even if not actively bleeding.

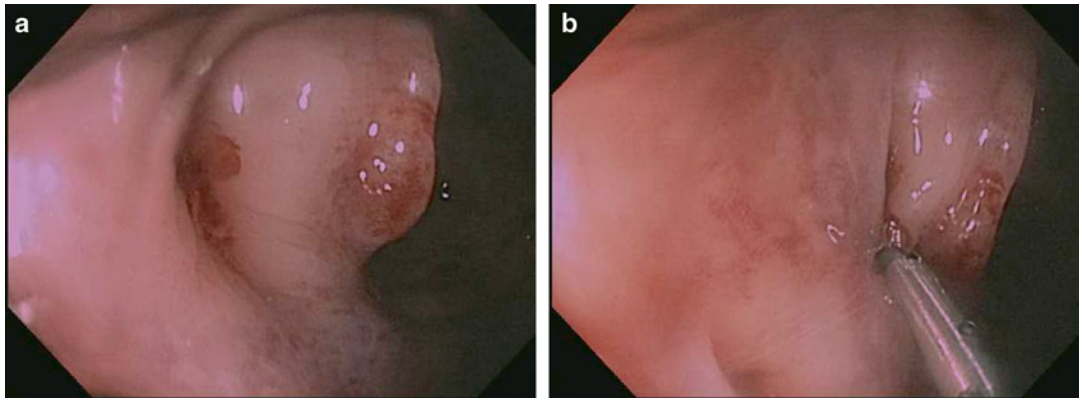

Fig. 15.1 (**a**) Diverticulum with stigmata of recent bleeding. (**b**) Clip placement for closure of diverticulum

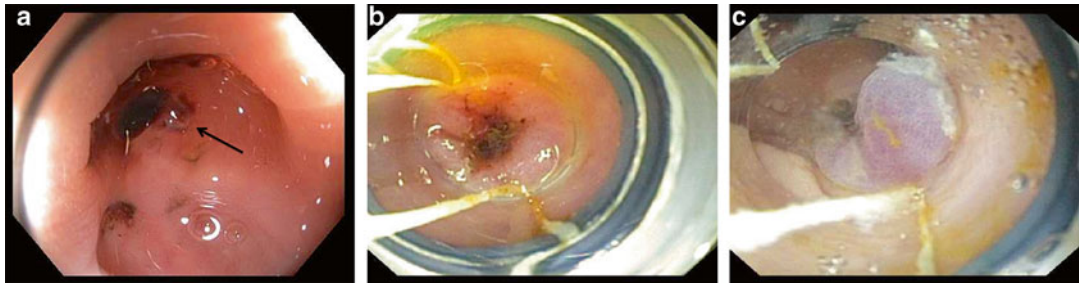

Fig. 15.2 (**a**) Diverticulum with visible vessel in the dome. (**b**) Endoscopic band ligation performed. (**c**) Appearance of post band ligation

Angiodysplasias without evidence of GI bleeding should not be treated.

Bleeding angiodysplasias can be treated with a variety of thermal therapies [12]. Clips may not be effective for angiodysplasias and are not typically used. Contact thermal coagulation begins with the outer feeder vessels and progresses toward the central vessel, although the focus should be on the central vessel. However, APC is more popular than contact thermal methods, with a reported 77–83 % success rate (Fig. 15.3) [18]. Over-insufflation of the colon should be avoided before and during therapy as it can increase the risk of perforation due to thinning of the colon wall. For a very large angiodysplasia, injecting epinephrine near the center vessel can shrink the size of the lesion and decrease the amount of coagulation needed.

There is a potential role for medical treatment of angiodysplasias, particularly when numerous and diffuse, although most of the data are from studies of small bowel angiodysplasias. Octreotide administered subcutaneously in doses ranging from 100 μg to 500 μg two times a day may decrease the need for transfusions [19]. Thalidomide at a dose of 100 mg orally once a day may also decrease the rebleeding rate from angiodysplasias [20]. A randomized trial of estrogen-progesterone treatment for 1 year did not decrease the rebleeding rate from angiodysplasias, with higher morbidity and mortality [21, 22]. Hormone therapy may decrease bleeding from telangiectasias in patients with Osler-Weber-Rendu disease.

Ischemic Colitis

Endoscopic evaluation with sigmoidoscopy or colonoscopy is used to confirm the diagnosis of

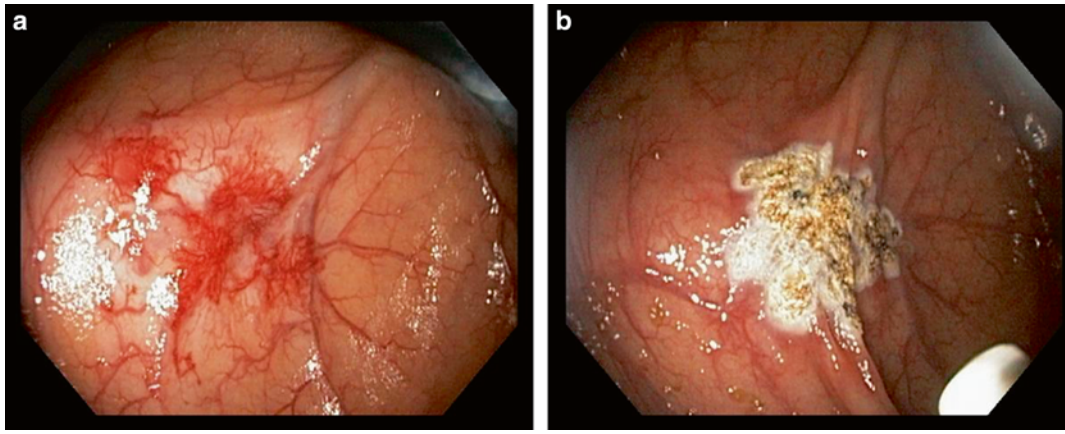

Fig. 15.3 (**a**) Colonic vascular ectasias. (**b**) Ablation with argon plasma coagulation

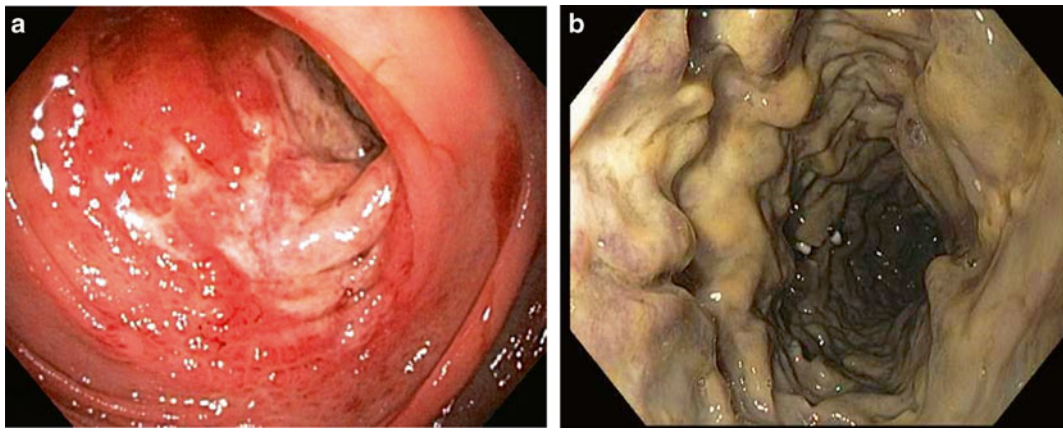

Fig. 15.4 (**a**) Ischemic colitis with ulcerations. (**b**) Severe ischemic colitis with necrotic tissue

suspected ischemic colitis. Care must be taken to minimize endoscopic insufflation and overdistention to prevent worsening ischemic damage. At endoscopy, the ischemic changes usually occur in a segmental distribution and involve the watershed areas (splenic flexure). The endoscopic features vary depending on the degree of injury, ranging from pale mucosa with petechial bleeding to longitudinal ulcers (stripe sign) to cyanotic, necrotic bowel (Fig. 15.4). Endoscopic treatment is usually not indicated or possible in ischemic colitis, except for isolated ulcers with focal active bleeding. Either clip placement or thermal therapy can be performed.

Neoplastic Lesions

In patients over 50 years of age, a colonic neoplasm is the etiology in about 10 % of cases of rectal bleeding (Fig. 15.5). Although tumor bleeding tends to be low grade and occult, bleeding may occasionally be brisk and overt and occurs due to erosion or ulceration of the lesion. Acutely bleeding distal lesions (left-sided colon and rectum) are more likely to present with bright red blood per rectum, whereas more proximal lesions tend to present with maroon stool, melena, or occult blood.

Standard endoscopic therapies for bleeding neoplasms are of limited benefit. Contact thermal

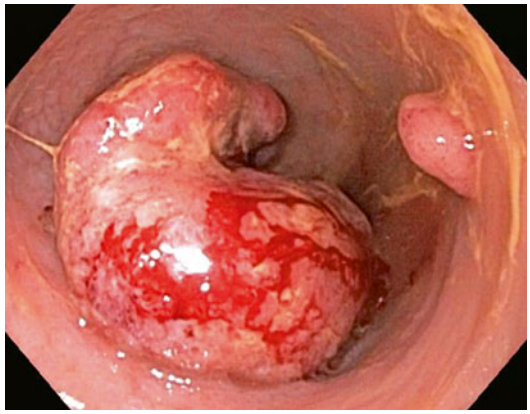

Fig. 15.5 Oozing malignant-appearing rectal mass

therapy, APC, hemostatic spray, or application of fibrin glue may stop bleeding temporarily, but the definitive treatment for most patients with bleeding colonic neoplasms is surgical resection.

Hemorrhoids

Hemorrhoids and other anorectal disorders, such as solitary rectal ulcers (Fig. 15.6) and anal fissures, are an important source of lower GI bleeding. Hemorrhoids are dilated submucosal vessels in the anus, which are considered internal if above the dentate line and external if below. Acute treatment for most patients with bleeding hemorrhoids is not needed since most bleeding episodes are mild in severity and resolve spontaneously. EBL is a reasonable therapeutic option for persistently bleeding internal hemorrhoids (Video 15.7). Surgery is rarely needed for those with persistent or massive bleeding.

Postpolypectomy Bleeding

Postpolypectomy bleeding occurs after 1–6 % of polypectomies and is the leading major adverse event following colonoscopy with polypectomy. Acute hemorrhage occurring at the time of polypectomy accounts for less than 50 % of cases. Therapeutic options include re-snaring the stalk of the polypectomy site (for a pedunculated polyp) to apply pressure, injection with epinephrine, contact or noncontact thermal treatment with bipolar coagulation, coagulation grasping forceps or APC, and clip (Fig. 15.7) or loop (Fig. 15.8) application. Mechanical methods of hemostasis are preferred, when technically feasible, since they do not extend tissue damage and may provide more durable hemostasis (Video 15.2). Delayed postpolypectomy bleeding (Fig. 15.9) usually manifests itself within 7 days, although it can occur up to 30 days following polypectomy when the eschar falls off the site. However, postpolypectomy bleeding is usually self-limited and over 70 % of cases resolve with supportive care only.

Risk factors for postpolypectomy bleeding include removal of large polyps (especially greater than 2 cm in diameter), age over 65 years, cardiovascular or chronic renal disease, platelet dysfunction, and coagulopathy (including the use of antithrombotic medications). The risk of delayed postpolypectomy bleeding may be reduced by prophylactic clip closure of postpolypectomy defects over 2 cm in size [23] and in patients on antithrombotic medications following resection of polyps >1 cm in size. A meta-analysis suggested that use of one or a combination of injection with epinephrine or saline and endoscopic clipping reduces the risk of postpolypectomy bleeding [24].

Radiation Proctitis

Pelvic radiotherapy can cause both acute and chronic radiation proctitis. Acute injury presents within 3 months of radiation therapy with diarrhea, tenesmus, and, rarely, bleeding. Chronic radiation proctitis typically occurs 9–14 months following radiation therapy in up to 20 % of patients, but may occur even years later. Bleeding is a prominent symptom caused by mucosal atrophy and fibrosis, resulting in chronic mucosal ischemia.

There are no standardized recommendations for treatment of bleeding from radiation proctitis. Endoscopic therapy appears superior to medical treatment in reducing severe bleeding, with success rate of nearly 75 % following endoscopic

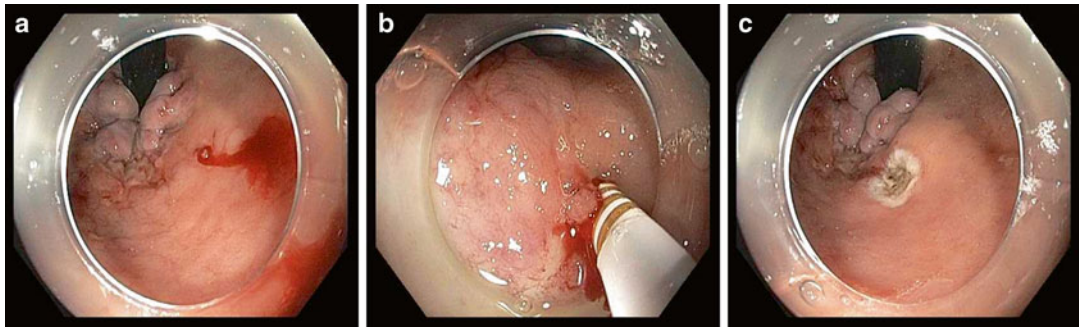

Fig. 15.6 (**a**) Small rectal ulcer with active bleeding. (**b**) Bipolar coagulation of bleeding ulcer. (**c**) Successful hemostasis following thermal therapy

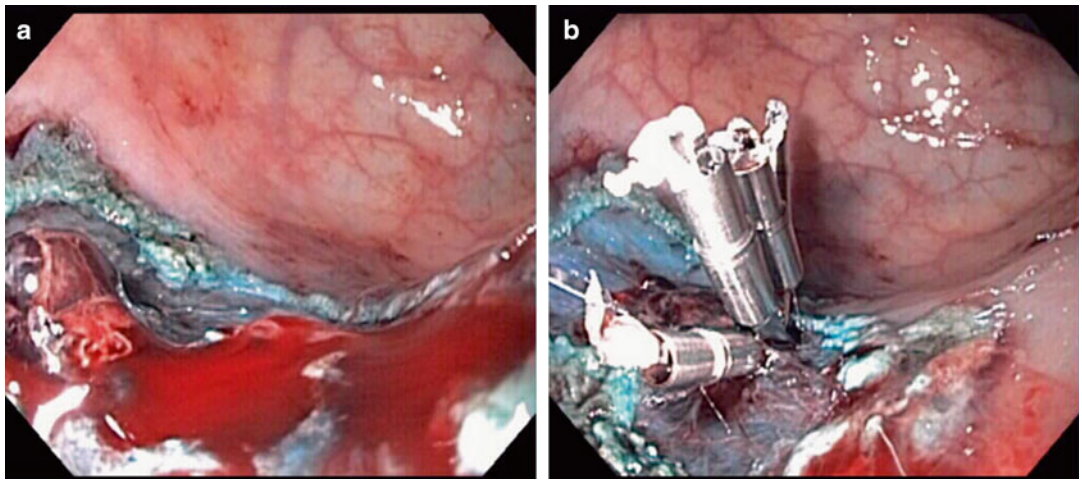

Fig. 15.7 (**a**) Immediate bleeding following endoscopic mucosal resection of a large rectal polyp. (**b**) Hemostasis achieved following clip application

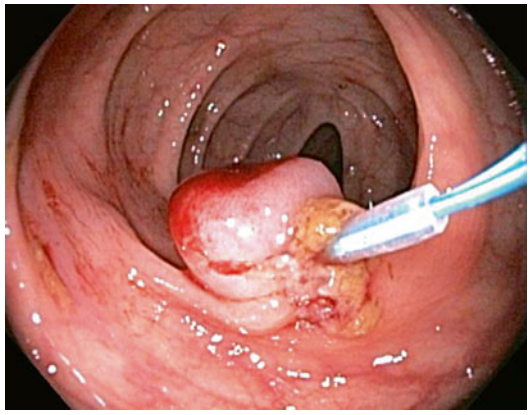

Fig. 15.8 Bleeding postpolypectomy stalk treated with loop placement

treatment compared to 33 % for medical therapy [25]. Heater probe and bipolar coagulation have proven effective in controlling bleeding during a mean of four treatment sessions performed every 4–6 weeks. Due to ease of use, APC is more commonly employed (Video 15.8), with 85–100 % success in reducing or stopping bleeding over a mean of 2–3 treatment sessions every 4–8 weeks (Fig. 15.10). During follow-up of 1–5 years, recurrent bleeding occurred in 0–8 % of patients [26]. The visible telangiectasias are obliterated at each session, although aggressive thermal ablation should be avoided to prevent deep ulcerations, which may not heal readily in the setting of an irradiated field; rectal ulcers from previous

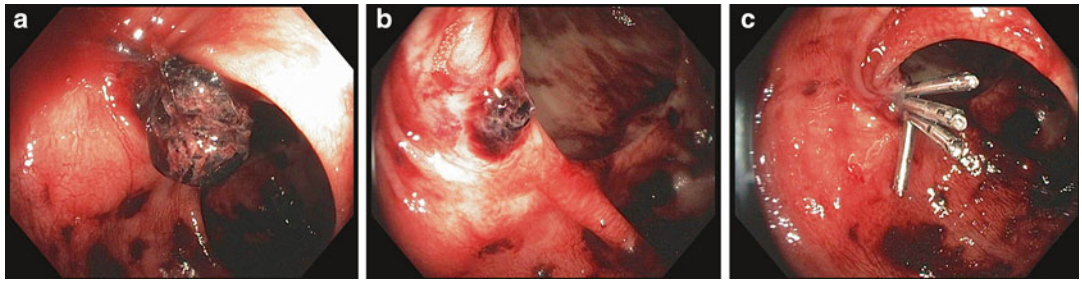

Fig. 15.9 (**a**) Delayed postpolypectomy bleeding with adherent clot. (**b**) Cold snare guillotine of clot, revealing visible vessel. (**c**) Treatment of postpolypectomy bleeding site with clip placement

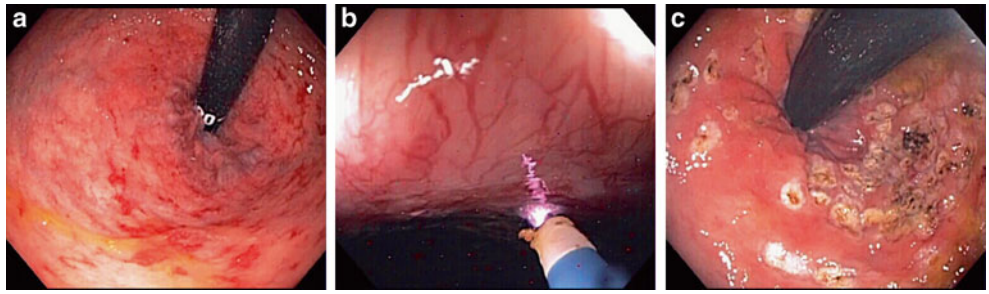

Fig. 15.10 (**a**) Telangiectasias due to radiation proctitis. (**b**) Argon plasma coagulation performed. (**c**) Endoscopic appearance following argon plasma coagulation

treatments should be avoided. Short-term adverse events occur in 7 % of patients and include rectal pain and fever. Rare major adverse events include rectovaginal fistula, anal or rectal stricture, and perforation. A full bowel preparation is required due to reports of colonic gas explosions during APC following enema preparation. A newer endoscopic ablation technique involves radiofrequency ablation, with case reports of successful treatment of radiation proctitis in patients who failed APC [27].

Hyperbaric oxygen is another therapeutic option, which promotes angiogenesis and collagen formation, leading to reepithelialization. A meta-analysis suggests that hyperbaric oxygen therapy is effective in radiation proctitis [28]. However, the treatment regimen is rigorous, requiring that the patient be placed in a hyperbaric chamber at a pressure of 2–2.5 atm with 100 % oxygen for 90 min, 5–7 days per week, for 20–80 sessions [29]. Hyperbaric oxygen therapy may be considered in patients with radiation proctitis who are refractory to standard medical and endoscopic treatments.

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Endoscopic Management of Food Impaction and Foreign Bodies

16

Ian Grimes and Patrick R. Pfau

Introduction

Gastrointestinal foreign bodies (GIFBs) and food impactions are common conditions encountered by gastroenterologists. Next to gastrointestinal bleeding, they are the second most common endoscopic emergency encountered. Prior studies have reported that between 1500 and 2750 deaths occur in the United States secondary to GIFBs [1–3]. More recent studies have suggested the mortality from GIFBs to be significantly lower, with no deaths reported in over 850 adults and only one death in approximately 2200 children [4–10]. However, regardless of imprecise morbidity and mortality rates, serious complications and deaths may occur as a consequence of foreign body ingestions [11–13]. Due to their frequent occurrences and potential for negative consequences, it is, therefore, important to recognize patients who are in need of treatment and employ the best techniques to manage GIFBs, including associated complications.

Flexible endoscopy has become the treatment of choice for food impactions and ingested true foreign bodies because it is safe and highly efficacious. Herein, the indications for endoscopic treatment, patient preparation, and accessory selection for foreign object retrieval are reviewed. The technical aspects to safely and successfully treat food impactions and foreign bodies are outlined.

Pre-endoscopic Considerations

The initial evaluation and non-endoscopic management of ingested foreign bodies and impacted food boluses are described in more detail in a separate chapter.

Initial administration of glucagon, a smooth muscle relaxant, can promote esophageal sphincter relaxation and has been used for alleviating food impaction [14, 15]. Success with glucagon as primary therapy ranges from 12 to 58 % in treating food impactions [16–18]. However, a small randomized study showed no benefit with the administration of glucagon over placebo [19]. Glucagon may facilitate clearance of the food bolus at the time of endoscopy [14].

The use of gas-forming agents, such as carbonated beverages, has been described for treating esophageal food impactions [20]. However, the effectiveness of these agents is doubtful, and

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I. Grimes • P.R. Pfau (✉)
Division of Gastroenterology, University of Wisconsin Medical School, 1685 Highland Avenue, Madison, WI 53711, USA
e-mail: prp@medicine.wisc.edu

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perforations as a result of their use have been reported [21]. Similarly, the meat tenderizer papain is not recommended for the treatment of esophageal meat impaction because of lack of efficacy and risk of perforation and mediastinitis [22].

Radiologic methods have been described for the treatment of esophageal foreign bodies. Several accessories, including Foley catheters, suction catheters, wire baskets, and magnets, have been used to retract objects under fluoroscopic guidance [23, 24]. However, all radiographic methods suffer from lack of control of the object, particularly at the level of the upper esophageal sphincter and hypopharynx. Adverse events may include nosebleeds, laryngospasm, aspiration, perforation, and even death [25]. Radiographic methods have been abandoned in favor of endoscopic modalities for the treatment of ingested foreign bodies and impacted food boluses.

Endoscopic Management

Multiple large series have reported the success rate for endoscopic treatment of GIFBs to be above 95 %, with complication rates of less than 5 % [4, 26–31]. Timing and indication for the treatment of gastrointestinal (GI) foreign bodies should always be planned with the knowledge that 80–90 % of GIFBs will spontaneously pass through the GI tract without complication [4, 7]. Although conservative management may suffice in many cases of GIFBs, it is most appropriate to perform selective endoscopy for treatment based on the location, size, and type of foreign body ingested [28, 32].

Generally, all foreign bodies, including food impactions, lodged in the esophagus require urgent intervention. The risk for an adverse outcome from an esophageal foreign body or food impaction is directly related to how long the object or food dwells in the esophagus [33]. Ideally, no object should be left in the esophagus longer than 24 h. If the patient is in severe distress and unable to handle secretions, the risk for aspiration increases and endoscopy should be performed within 12 h of presentation. It is not unusual to encounter a significant time delay from ingestion to presentation, especially in children and in cognitively impaired adults. Some impacted esophageal foreign bodies, such as disk batteries, represent a medical emergency and should be promptly removed.

Once in the stomach, most ingested objects will pass spontaneously and the risk of complications is much lower, thus making observation acceptable and endoscopic intervention may not be necessary. There are notable exceptions that will almost always require endoscopic intervention due to their increased likelihood of causing a complication or objects not passing beyond the stomach. Sharp and pointed objects are associated with perforation rates as high as 35 % [33] and, thus, should be removed in an urgent fashion due to the risk of complication; removal may also not be possible once the object has passed beyond the ligament of Treitz. Blunt objects longer than 5 cm and/or wider than 2 cm may not pass spontaneously and should be removed from the stomach if they have not progressed in 3–5 days.

With the increasing use of deep enteroscopy, case reports have detailed the use of single- and double-balloon enteroscopes to retrieve foreign bodies from the deep small bowel safely and effectively [34, 35]. Balloon-assisted enteroscopy has been used for removal of entrapped capsule endoscopes [36]. Several accessories, including baskets, hoods, and forceps, have been designed for balloon enteroscopes to enable foreign body retrieval.

The type of sedation selected to facilitate endoscopy for the management of food impactions and ingested foreign objects should be individualized. Conscious sedation is adequate for the treatment of the majority of food impactions and simple foreign bodies in the adult population. Monitored anesthesia care or general anesthesia with endotracheal intubation may be required for uncooperative patients or patients who have swallowed multiple complex objects. This is due to the prolonged time associated with some cases, the necessity to protect the airway, and the need for repetitive esophageal intubation. Anesthesia assistance should be made available even for cases that are initiated with conscious sedation, but which evolve into complex cases due to prolonged procedure, respiratory distress, or inability to safely provide additional moderate sedation. Endoscopy for treatment of foreign bodies in the pediatric

population is performed with the aid of general anesthesia and endotracheal intubation [37].

For management of food or foreign body impactions below the level of the laryngopharynx, flexible endoscopy is almost always preferred [38]. Rigid esophagoscopy and flexible nasal endoscopes can be used for esophageal foreign bodies, but provide no additional benefit and are often available to only a few GI endoscopists [6, 39]. A comparison of rigid versus flexible endoscopes in the treatment of esophageal foreign bodies found significantly less perforations with flexible endoscopes [38]. The use of rigid esophagoscopy and laryngoscopy is usually performed by otolaryngologists. Rigid esophagoscopy will almost always require general anesthesia with endotracheal intubation. Laryngoscopes with the aid of a Kelly or McGill forceps can be useful for very proximal foreign bodies and small sharp objects in the hypopharynx.

The availability of and familiarity with multiple endoscopic retrieval devices for the removal of foreign bodies and food impactions are critical (Table 16.1). An endoscopy suite or an endoscopy travel cart should be equipped with at least the following equipment to allow successful treatment of a variety of GI foreign bodies: a rat-tooth or alligator grasping forceps, polypectomy snares, Dormia basket, and retrieval nets (Fig. 16.1) [40]. Removal of foreign bodies with standard biopsy forceps is rarely successful and not recommended. A transparent vacuum cap, similar to that used for esophageal banding or endoscopic mucosal resection, can be useful in challenging food impactions. Overtubes that are 45 cm (esophageal) and 60 cm (gastric) in length should be available to the endoscopist (Fig. 16.2). An overtube allows protection of the airway, multiple passes of the endoscope, and mucosal protection from sharp objects [41]. The longer 60 cm overtube bypasses the lower esophageal sphincter and enables retrieval of sharp and complex objects from the stomach. Due to the size of the overtubes and potential trauma upon insertion, their use is limited in the pediatric population. An alternative adjunct for the safe extraction of sharp objects is a latex protection hood, which fits onto the tip of the endoscope [42, 43].

Table 16.1 Equipment for management of gastrointestinal foreign bodies and food impactions

Endoscopes	Overtubes	Accessories
Flexible endoscope	45–60-cm-long overtubes	Retrieval net
Rigid endoscope		Grasping forceps
Laryngoscope		Dormia basket
		Polypectomy snares
		Transparent vacuum cap
		Latex protector hood
		Kelly or McGill forceps

When planning for extraction of complex objects, a valuable exercise is to go through an ex vivo simulation on a similar object to identify optimal retrieval devices and extraction techniques [4]. Success and speed of retrieval of a foreign body have been shown to be directly related to endoscopist experience [44]. When personnel or facilities are not available to accomplish safe and effective endoscopic retrieval, consideration should be given to transfer the patient to a more experienced center.

Prior to endoscopic intervention, assessment of the patient's airway, ventilatory status, and risk for aspiration is crucial. A neck and chest examination that identifies crepitus, erythema, and swelling suggests a proximal perforation. Lung examination should be performed to detect the presence of aspiration or wheezing. An abdominal examination should be performed to evaluate for signs of perforation or obstruction. If there is evidence of potential aspiration or perforation on physical examination, chest and/or abdominal radiographs should be performed.

Food Impaction

Given that food boluses may pass spontaneously, the need for endoscopic intervention is based on the persistence of symptoms. Patients with signs of complete or near-complete obstruction with drooling or excessive salivation should undergo urgent endoscopy. Endoscopic intervention should be achieved at the latest within 24 h of

Fig. 16.1 Endoscopic retrieval devices for management of food impactions and foreign bodies (from *left to right*: basket, retrieval net, snare, rat-tooth forceps)

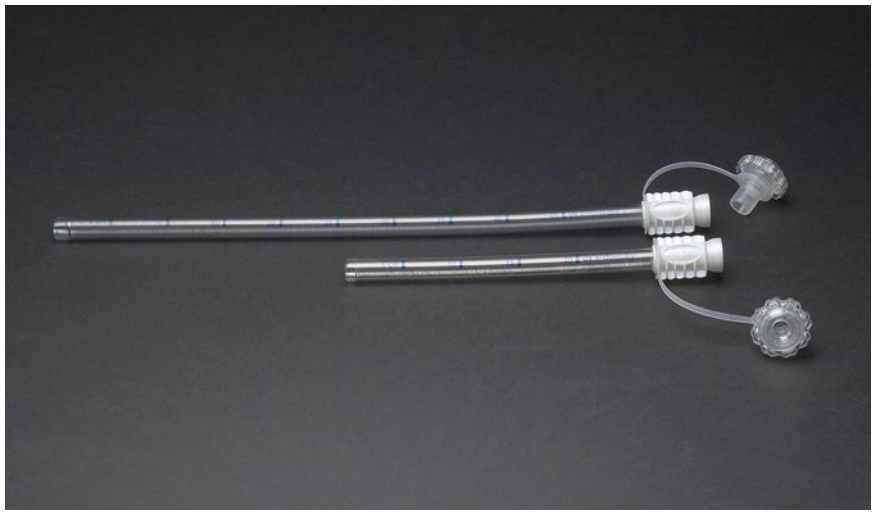

Fig. 16.2 Esophageal (45 cm) and gastric (60 cm) length overtubes

onset of symptoms and ideally within the first 12 h. The performance of endoscopy within hours of presentation may allow removal of the food bolus in one piece before it has a chance to soften, making extraction more challenging and time-consuming [45]. The increased risk for complications is proportional to the duration of esophageal food impaction [46–48].

The primary method to treat food impaction is the push technique, with success rates over 90 % and with minimal complications (Video 16.1) [49]. Before the food bolus is pushed into the stomach, steering the endoscope around the bolus into the stomach should be attempted. If the endoscope can be passed around the food bolus into the stomach, the latter can be safely pushed

into the stomach without difficulty. This also allows assessment of any obstructive esophageal pathology beyond the food impaction. If the endoscope cannot steer around the food impaction, gentle pushing pressure with the tip of the endoscope can be attempted. If significant resistance is encountered, pushing should not continue. In a patient with a known hiatal hernia, the gastroesophageal junction may take a left turn, and thus, pushing the food bolus from the right side may allow easier and safer passage of the obstructing bolus into the stomach. Larger boluses of impacted meat can be broken apart with the endoscope or an accessory prior to pushing the smaller pieces into the stomach safely. When the food bolus cannot be dislodged with the push technique, a method has been described in which a Savary wire is passed into the stomach and the food is subsequently pushed into the stomach via the use of Savary-Gillard dilators [50]. Although this method has been shown to be successful, it should be used with extreme caution because of the lack of visualization and risk of perforation.

Eosinophilic esophagitis has increasingly been associated with esophageal food impactions. Reports indicate that food impaction in patients with eosinophilic esophagitis can be treated effectively and safely with the push method (Fig. 16.3) [51]. However, care should be taken to minimize the risk of dilation-induced mucosal tears [52]. Caution is advised when using rigid endoscopes in the setting of suspected eosinophilic esophagitis since perforation rates with rigid instruments in this patient population have been reported to be as high as 20 % [53]. If eosinophilic esophagitis is suspected, mucosal biopsies should be obtained after removal of the food bolus.

Food impactions that cannot be pushed into the stomach must be extracted via the mouth (Video 16.2). Removal can be achieved using various retrieval devices, including snares, baskets, nets, and alligator or rat-tooth forceps. When grasping the food bolus with a snare, basket, or forceps, the bolus should be pulled tight against the tip of the endoscope and then the retrieval accessory, endoscope, and food bolus should be withdrawn simultaneously. The use of a net may reduce the risk of a food bolus being dislodged in the hypopharynx during withdrawal and has been shown to result in fewer endoscope passes and to shorten overall procedure duration [54]. A dedicated food bolus retrieval net can be useful for removing large pieces of food without the use of an overtube because the food can be satisfactorily secured within the net, thus reducing the risk of aspiration [54]. For complicated food boluses, an esophageal overtube is useful because it protects the airway and allows for multiple passage of the endoscope for piecemeal extraction.

Transparent plastic hoods or caps, such as those used to perform variceal band ligation and endoscopic mucosal resection, have been used successfully for the removal of large, tightly impacted meat boluses. With the cap secured to the tip of the endoscope, the device can be used to suction the food into the vacuum chamber and to withdraw the bolus per os [55, 56]. The use of a

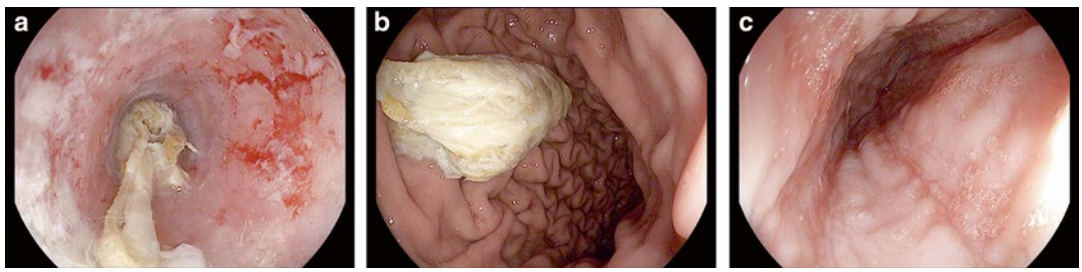

Fig. 16.3 (**a**) Esophageal food impaction. (**b**) Meat bolus dislodged in the stomach using the push technique. (**c**) Esophageal rings and furrows noted, with biopsies confirming eosinophilic esophagitis

Dormia basket within a transparent cap has also been used successfully in the extraction of difficult food impactions [57]. Two large Asian studies have demonstrated that sharp food impactions, usually fish or chicken bones, are best retrieved with a rat-tooth forceps [58, 59].

More than 75 % of patients with food impactions have associated esophageal pathology [4, 60]. In addition, approximately half of patients with food bolus impactions have abnormal 24-h pH studies and/or esophageal manometry. If an esophageal stricture or Schatzki's ring is present after the food bolus is cleared, it can be safely and effectively dilated concurrently if circumstances allow. More often, mucosal abrasions, edema, and erythema exist from the food dwelling in the esophagus for an extended period, and dilation is preferably delayed for 2–4 weeks during which time patients should be prescribed proton pump inhibitor therapy. When multiple esophageal rings and other findings suggestive of eosinophilic esophagitis are present, biopsies should be obtained. Lack of appropriate follow-up, particularly in patients with strictures or rings, has been shown to be a predictor for recurrent food impaction [61].

True Foreign Bodies

True foreign bodies (nonfood objects) can occur from either intentional or unintentional ingestion. Children between the ages of 6 months and 6 years are the most common cohort to intentionally ingest foreign bodies [4, 62]. In adults, true foreign body ingestion is more common in patients who are acutely intoxicated from alcohol and in those who have a psychiatric disorder, are developmentally delayed, are seeking secondary gains, or are edentulous [4, 63]. Following one episode, a higher rate for recurrent ingestion of foreign bodies is found in male prisoners with psychiatric disorders [64].

Sharp and Pointed Objects

The ingestion of sharp and pointed objects carries a significant risk of complications, including perforation, which can occur in up to 35 % of patients [65]. Sharp and pointed objects retained in the esophagus are considered a medical emergency and should be removed without delay. Objects lodged at the cricopharyngeus may be best visualized and removed with a laryngoscope. Due to risk of complications, any sharp or pointed object within reach of the endoscope should be removed urgently if this can be done safely. Chevalier Jackson's axiom should be remembered during removal of sharp objects: "advancing points puncture, trailing points do not" [66]. Thus, the sharp foreign body should be grasped and oriented so that the pointed end of the object trails upon withdrawal to reduce the risk of mucosal laceration or perforation (Fig. 16.4) [66]. This sometimes entails pushing the object in an esophageal location into the stomach and then orientating the sharp edge of the object to be the trailing point upon withdrawal.

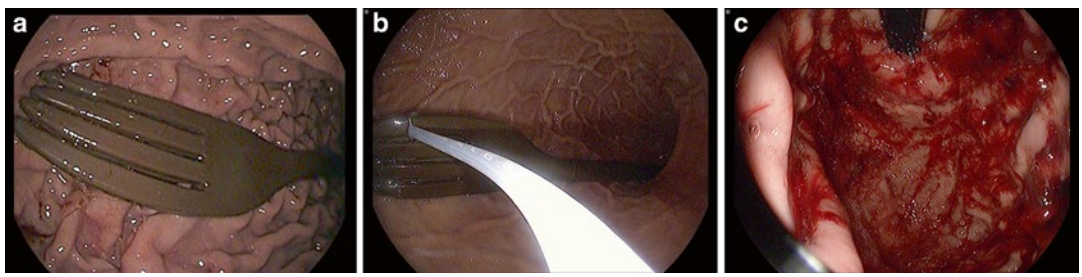

Fig. 16.4 (**a**) Large plastic fork in the stomach swallowed by a patient with psychiatric illness. (**b**) Incorrect snare capture of the sharper and wider end of the fork instead of its blunt end. (**c**) Extensive mucosal damage of the proximal stomach noted during repeated attempts to pull the pointed end of the fork through the lower esophageal sphincter. The fork was subsequently rotated in the stomach, grasped at its blunt end, and pulled for retrieval

For sharp and pointed objects, retrieval is best achieved using a grasping forceps, such as a rat-tooth or alligator forceps, a tripod forceps, a polypectomy snare, or a biliary stone retrieval basket [44]. Retrieval nets tend to shear during removal of sharp objects and may compromise visualization.

The use of an overtube should be considered to protect the esophagus and oropharynx (Video 16.3). Long pointed objects in the esophagus or stomach can be grasped and directed into the overtube; the entire assembly, including the sharp object, the endoscope, and the overtube, can then be removed in unison. An alternative to the overtube for the extraction of sharp and pointed objects is a retractable, bell-shaped, latex hood attached to the tip of the endoscope (Fig. 16.5). When the endoscope is pulled back through the lower esophageal sphincter, the hood flips over the grasped object and protects the esophageal mucosa during withdrawal (Video 16.4) [42, 67].

Despite the increased risk of perforation, most sharp or pointed objects that are beyond the reach of the endoscope will pass unimpeded and be eliminated through the GI tract without complication. However, serial daily radiographs should be obtained to ensure progression of these objects. If a sharp or pointed object fails to progress over 3 days or if there is evidence of a complication, such as abdominal pain, fever, bleeding, or overt signs of perforation, surgical evaluation is warranted.

Long Objects

Ingested objects longer than 5 cm (2 in.), and especially those longer than 10 cm (4 in.), such as toothbrushes and spoons, have difficulty passing through the pylorus and duodenal sweep. This can lead to obstruction or perforation at these locations. Removal is best attempted while the object remains in the stomach, as duodenal removal is more difficult. The most commonly ingested long objects are pens, pencils, toothbrushes, and eating utensils. Removal of these objects is challenging and caution to avoid mucosal injury or perforation should be taken. Grasping forceps and polypectomy snares are commonly used to secure and remove long objects. The use of snares can be problematic if the object orients horizontally rather than vertically. Horizontal orientation can make removal of the object difficult, particularly across the gastroesophageal junction, resulting in mucosal tearing. Long objects should be grasped at one end and oriented longitudinally to permit removal. For extraction of long objects, the use of a gastric length overtube can be beneficial. The object can be grasped at one end with a retrieval device and then brought into the overtube to align it along the axis of the esophagus.

Blunt Objects: Coins, Batteries, and Magnets

Small blunt objects, such as pieces of toys and coins, are the most commonly ingested objects in children. Disk (button) battery and magnet

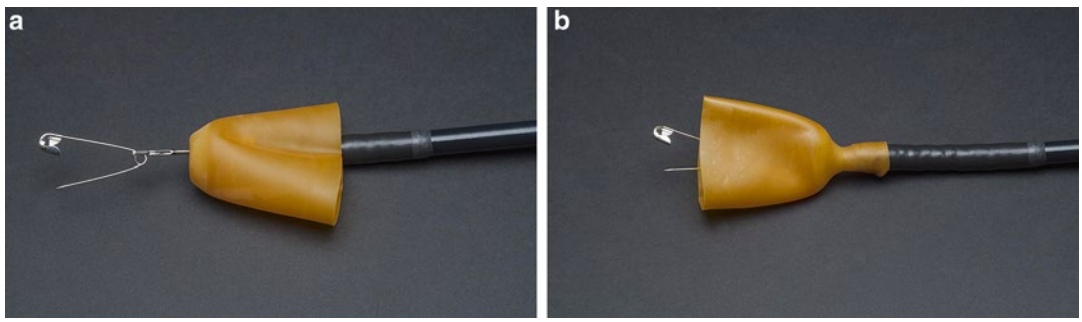

Fig. 16.5 (**a**) Latex protector hood placed in an inverted fashion during insertion of the endoscope into the GI tract. (**b**) When the protector hood is pulled through the lower esophageal sphincter, it flips forward covering the sharp object and protecting the mucosa during instrument withdrawal

ingestions are uncommon but pose unique potential dangers. Blunt objects in the esophagus should be removed promptly with the use of a grasping forceps, snare, retrieval basket, or net. Coins impacted in the esophagus can result in pressure necrosis of the esophageal wall and lead to perforation or fistulization. A coin of any size can become lodged in the esophagus of children, but ingested coins, in particular dimes and pennies measuring 17 and 18 mm, will usually pass through the adult esophagus. Coins located in the distal esophagus on imaging are more likely to pass spontaneously than coins in the proximal esophagus [68].

Retrieval nets are the preferred retrieval devices as they allow capture and secure removal of coins and most small blunt objects (Video 16.5) [44]. The net also allows for airway protection as the object is pulled through the cricopharyngeus. Grasping forceps and biliary stone retrieval baskets are also effective but with lesser control of the object. Standard biopsy forceps and snares are not recommended because they fail to secure coins reliably during extraction and can lead to airway compromise. If it is difficult to capture a blunt object in the esophagus, it is best to push it in the stomach where there is more room to facilitate its manipulation and removal. If there is concern regarding airway compromise, particularly for removal of coins in the esophagus, endotracheal intubation should be considered. Alternatively, an overtube can be used for airway protection.

Once a small blunt object enters the stomach, conservative outpatient management is appropriate in most patients [69]. Exceptions to this include patients with surgically altered digestive tract anatomy, those with symptoms, and those who have ingested large blunt objects. In adults, the pylorus will allow passage of most blunt objects up to 25 mm in diameter, which include all coins except half-dollars (30 mm) and silver dollars (38 mm). If conservative management is deemed appropriate, a regular diet can be resumed with radiographic monitoring every 1–2 weeks to confirm progression or elimination of the object. If after 3–4 weeks, the blunt object has not passed the stomach, endoscopic removal should be performed [70].

Disk batteries are of special concern because they may contain an alkaline solution that can rapidly cause liquefaction necrosis of esophageal tissue, resulting in perforation or fistula formation. Disk batteries are present in many small toys and electronic devices that are accessible to young children. Disk battery ingestion occurs most commonly in younger children with approximately 10 % becoming symptomatic [71]. Therefore, any clinical suspicion of a disk battery in the esophagus should prompt emergent endoscopy. Grasping forceps and snares are generally ineffective for disk battery removal, but the use of a retrieval net permits successful removal in almost 100 % of cases [72]. Protection of the airway with an overtube or endotracheal intubation in pediatric patients is crucial in retrieval of disk batteries. Once in the stomach or small intestine, disk batteries rarely cause clinical problems and can be monitored radiographically. Once in the duodenum, 85 % will pass through the GI tract within 72 h. Batteries located in the stomach require endoscopy if the patient develops symptoms or the battery remains in the stomach for 48 h on repeat radiograph [23].

Cylindrical batteries appear to cause symptoms less frequently, with no reports of major life-threatening injuries and only approximately 20 % of patients having minor symptoms after ingestion [23]. Cylindrical batteries should be removed from the esophagus. If in the stomach, batteries larger than 20 mm or those that have not progressed in 48 h should be removed by endoscopy.

Small coupling magnets have become popular as children's toys. Ingested magnets within the reach of the endoscope should be removed on an urgent basis. Although a single magnet will rarely be a cause of symptoms, concern exists if multiple magnets are ingested or if magnets were ingested with other metal objects. This can result in magnetic attraction between the objects and coupling between interposed loops of bowel with subsequent pressure necrosis, fistula formation, and bowel perforation [73, 74]. Removal should be performed urgently when the magnets are more likely to be within reach of an endoscope and accessories such as grasping forceps, retrieval net, or basket can be used. Magnetic attraction to

metallic retrieval devices may ease the task of removal [75, 76]. If multiple magnets have been ingested, a post-procedure x-ray can be performed to ensure that all magnets have been retrieved. If more than one magnet is not within endoscopic reach, surgical removal should be contemplated.

Narcotic Packets

Endoscopic removal is contraindicated because of the high risk for package perforation with resultant drug overdose [46]. Observation on a clear liquid diet is recommended with serial radiographs. Operative intervention is indicated when bowel obstruction, failure of the packets to progress, or drug leakage/toxicity is suspected. Up to 45 % of patients may require surgery, with gastrotomy, enterotomy, or colotomy performed based upon the location of the packets [77].

Colorectal Foreign Bodies

Ingested objects infrequently become lodged in the colorectum (Fig. 16.6). More commonly, colorectal foreign bodies are inserted into the rectum intentionally or unintentionally. Males are much more likely than females to present with a rectal foreign body. Radiographs should be obtained prior to attempting removal of colorectal foreign bodies for visualization of the location, orientation, and configuration of the object. To avoid health-care provider injury, attempts at manual removal or digital rectal examination should be deferred until the presence of a sharp or pointed object has been excluded.

The majority of objects (76 %) can be removed nonsurgically [78]. Manual digital extraction may be successful for the removal of small blunt objects in the distal rectum that are palpable on rectal examination.

Non-palpable and sharp or pointed objects should be removed under direct visualization with the use of a rigid proctoscope or flexible sigmoidoscope [79]. Standard retrieval devices can be used, as described earlier for the upper digestive tract. The use of obstetric tools has also been reported [80]. A latex hood or overtube can be particularly useful in removing long, sharp-pointed objects to protect the rectal mucosa from laceration and to overcome the tendency of the anal sphincter to contract on attempted removal of objects. Although conscious sedation may suffice, general anesthesia allows maximum dilation of the anal sphincter during removal of larger and more complex objects [81].

Operative intervention is indicated when endoscopic intervention fails and for any suspected complication secondary to the colorectal foreign body, including perforation, abscess, and obstruction. Complications are more common when the object is situated proximal to the rectum [82].

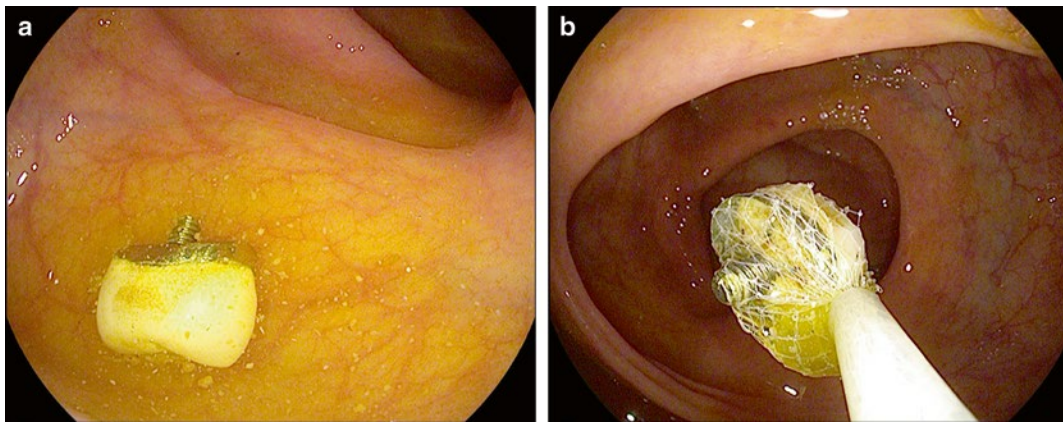

Fig. 16.6 (**a**) Dental tooth implant found in colon during routine screening colonoscopy. (**b**) Successful removal of dental implant with a retrieval net

Adverse Events

Although the reported adverse event (AE) rates associated with endoscopic removal of GI foreign bodies and food impactions are low (0–1.8 %), their occurrences are thought to be higher in clinical practice [4, 8, 26, 27, 49]. Perforation is the most feared AE. Other AEs include bleeding, aspiration, and sedation-related cardiopulmonary complications. Factors that increase the risk for AEs include the removal of sharp and pointed objects, an uncooperative patient, multiple and/or deliberate ingestion of GIFBs, and extended time interval from food impaction or foreign body ingestion to intervention [11].

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Endoscopic Management of Acute Colonic Obstruction and Pseudo-obstruction

17

Thomas C. Queen and Douglas G. Adler

Introduction

Acute colonic pseudo-obstruction (ACPO) and acute colonic obstruction (ACO) from mechanical causes are serious conditions that can lead to complications, such as perforation, bowel ischemia, and sepsis, if not properly managed. Endoscopic therapy is widely employed in the management of ACPO and ACO. Patients with ACPO refractory to supportive and medical therapy can be treated with endoscopic decompression. For more than a decade, patients with ACO have been treated with endoscopic placement of self-expanding metal stents (SEMS) for treatment of colonic obstruction. Herein, the management of ACPO and ACO is discussed with emphasis on endoscopic therapy.

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T.C. Queen, MD • D.G. Adler, MD, FACG, AGAF, FASGE (✉)
Division of Gastroenterology and Hepatology, Department of Internal Medicine, Huntsman Cancer Center, University of Utah School of Medicine, 30N 1900E 4R118, Salt Lake City, UT 84132, USA
e-mail: douglas.adler@hsc.utah.edu

Acute Colonic Pseudo-obstruction

ACPO or Ogilvie's syndrome was first reported in 1948 by Sir William Ogilvie [1]. This entity and the medical management are described in a separate chapter. If medical therapy fails, the next step in the management of ACPO consists of endoscopic decompression of the colon, with or without placement of a decompression tube. Endoscopic colonic decompression remains the preferred nonsurgical management for patients with colonic distension after failure of supportive management, those with a cecal diameter >10 cm for more than 3 days and those who have failed and/or have contraindications to medical management (e.g., neostigmine therapy) [2, 3].

First described by Kukora and Dent in 1977, colonoscopic decompression has an overall success rate of approximately 79 % [4–9]. Successful resolution of ACPO with the first attempt at endoscopic decompression occurs in approximately 68 % of patients; as many as 20 % of patients require more than one decompression [4–8]. Adverse events (AEs) following endoscopic decompression occur in approximately 3 % of patients, including a reported perforation rate of 2 % [6, 8, 10]. It is uncertain whether ischemia is an absolute contraindication to endoscopic decompression [2]. Fiorito et al. reported successful endoscopic colonic decompression with tube placement in 3 patients with ACPO and

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right-sided colonic ischemia [11, 12]. Nonetheless, if significant ischemia is present, surgical intervention is often necessary, although this presents something of a "catch-22" situation since ischemia is often not detected definitively until endoscopy is performed [13]. Perforation and overt peritonitis are absolute contraindications to colonic decompression and, when present, require surgical management [12].

Unlike typical non-emergent colonoscopies, bowel preparations and oral laxatives usually cannot be administered prior to colonoscopy [14]. Although enemas can be used, their ability to facilitate colonoscopy is limited in ACPO. The use of a colonoscope with a dual-channel or large-diameter accessory channel is generally preferred due to better suction capability and lesser chance of loop formation in a distended colon.

As the colonoscope is advanced in the colon, insufflation should be minimized since the bowel is already significantly distended [14]. Carbon dioxide, which is now widely available, is preferred to air for insufflation. Advancement of the colonoscope to the cecum is not necessary; in general the colonoscope should be advanced as far as considered reasonable and safe in light of the individual patient's overall clinical situation. There is disagreement in the literature as to exactly how far the endoscope should be advanced into the colon [8, 14].

Colonic Decompression Tube Placement

In 1982, Bernton et al. first demonstrated the possibility of using a decompression tube for the management of ACPO [15, 16]. Decompression tube insertion in the context of colonoscopic decompression is frequently performed [12]. Prior to tube placement, a guidewire is advanced through the instrument channel of the endoscope as far proximally as possible [12, 14]. The endoscope is removed leaving the wire in place. As the colonoscope is removed, gas and stool are aspirated as much as possible. Fluoroscopy is typically used to ensure that guidewire position is maintained in the colon and excessive looping does not occur (Fig. 17.1) [14].

Once the colonoscope is removed, a decompression tube is passed over the guidewire under fluoroscopic guidance. Fluoroscopy ensures proper placement of the tube and minimizes guidewire and tube loop formation during advancement [14]. Once the tube is in position, the guidewire is removed [14]. Alternatively, a through-the-scope (TTS) decompression tube can be deployed through the channel of a large-diameter colonoscope, negating the requirement for guidewire placement and fluoroscopic assistance [12].

Once placed, the decompression tube is connected to gravity drainage and/or low intermittent suction. It is recommended that the tube be flushed with saline intermittently to reduce the risk of clogging [12, 14].

Despite the lack of controlled studies, placement of a decompression tube after endoscopic decompression is thought to improve the overall clinical success rate [3]. In a study of 29 patients with ACPO, 1 in 15 patients who underwent colonic decompression with tube placement had recurrent colonic dilation compared to 6 of 14 patients who underwent colonic decompression alone [17]. In another study, the clinical success rates were 80 % and 25 % in patients who underwent colonoscopic decompression with and without tube placement, respectively [8].

Percutaneous Endoscopic Colostomy

Percutaneous endoscopic colostomy (PEC) is another endoscopic technique that is used in ACPO patients who are nonresponsive to medical or endoscopic decompression therapy [18]. It is a minimally invasive procedure in which a plastic tube is endoscopically placed into the cecum (percutaneous endoscopic cecostomy) or left colon, allowing irrigation and/or decompression. PEC is similar to placement of a percutaneous endoscopic gastrostomy (PEG) tube for venting, and a standard PEG kit and pull-through technique are utilized. In one retrospective study, the efficacy of PEC placement in ACPO,

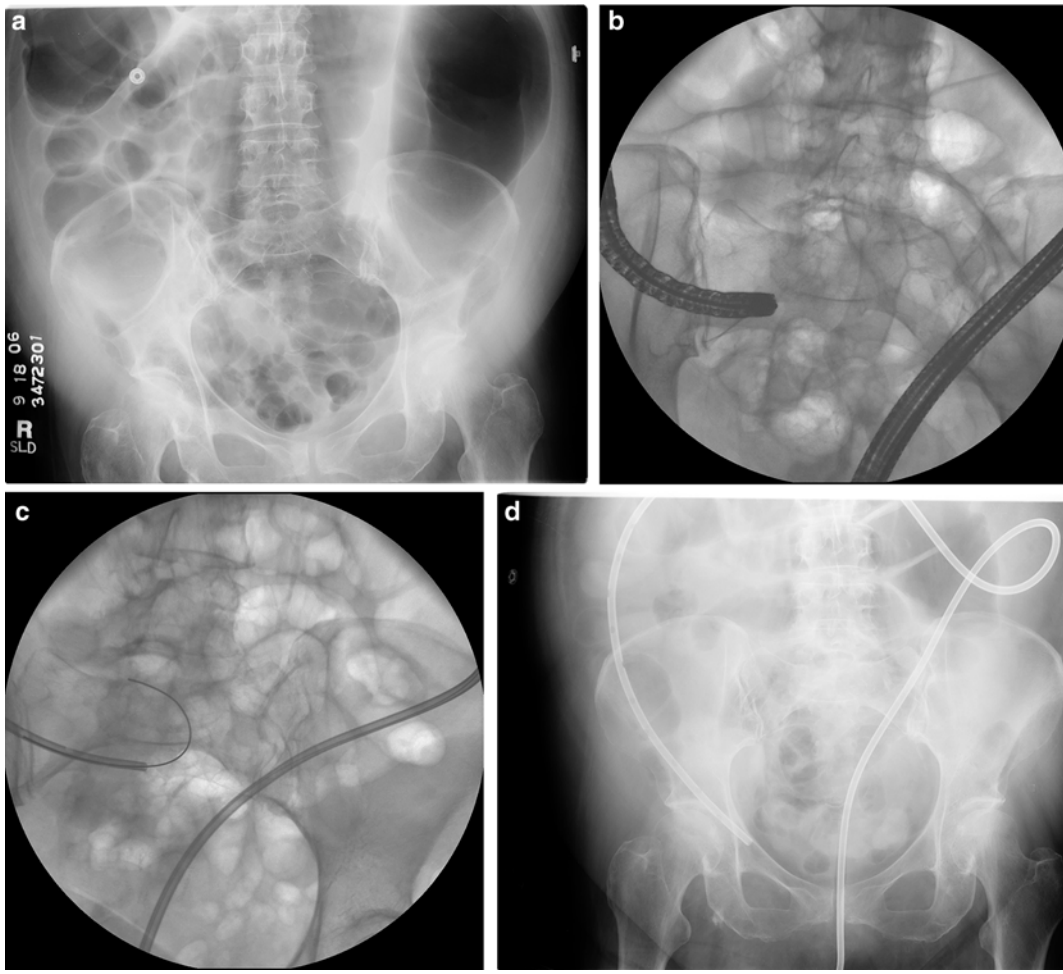

Fig. 17.1 (**a**) Acute colonic pseudo-obstruction with significantly dilated colon throughout. (**b**) Colonoscope advancement as far as technically safe and feasible to the right colon. (**c**) Fluoroscopic placement of colonic decompression tube over a guidewire following endoscopic decompression and placement of guidewire. (**d**) Final position of the tip of the decompression tube in the right colon

neurologic constipation, functional constipation, and recurrent sigmoid volvulus was examined [18]. Eighty-one percent of the patients had marked symptomatic improvement after insertion, although the study's mortality rate was 26 % [18]. In a separate study of 60 patients, PEC was associated with a 42 % complication rate [19]. Complications included granulomas, bleeding, hematoma formation, wound infection, perforation leading to peritonitis, retraction of PEC, and buried PEC bumper [19]. PEC should be considered in patients who are poor surgical candidates and who have failed to respond to pharmaceutical or endoscopic management [20, 21].

Surgical Decompression

Surgical options, including colectomy and surgically placed cecostomy tubes, are rarely needed in ACPO patients [13, 20]. Surgical decompression has been associated with high morbidity and mortality rates. In one study of 179 patients, the success rate of surgery was 90 %, but the morbidity and mortality rates in ACPO patients undergoing surgical intervention were 6 % and 30 %, respectively [15]. Surgical intervention should be considered when there is an imminent risk for perforation and peritonitis and for patients in whom nonsurgical options have been exhausted [12, 13, 20].

Acute Colonic Obstruction

Overview

Colorectal cancer is the third most common cancer in the United States and one of the most common cancers worldwide [22]. In the United States, it is estimated that more than 100,000 new cases are diagnosed each year with approximately 50,000 annual deaths [22]. Despite aggressive screening for colorectal cancer, subtotal or complete colonic obstruction is still a common presentation [23]. Approximately 20–25 % of patients with colorectal cancer present with acute colonic obstruction (ACO) [24, 25]. The majority of the malignancies causing colonic obstruction are primary colon cancers, most commonly located in the left side of the colon (Fig. 17.2) [12, 23]. Metastatic disease to the colon is relatively uncommon, but on occasion invades the large bowel and causes obstruction [12, 23]. Additionally, metastatic genitourinary tumors can extrinsically compress the large bowel and lead to colonic obstruction [23]. Failure to treat ACO can lead to metabolic abnormalities, intestinal ischemia, perforation, sepsis, and death [26].

Historically, a surgical approach has primarily been utilized in the management of ACO. Patients often required a two-stage resection or Hartmann's procedure, involving a diverting colostomy with resection of the primary tumor [27]. Typically, patients need to wait at least 8 weeks before the colostomy can safely be reversed [27]. A one-stage resection and primary anastomosis is performed by some surgeons. However, ACO patients are generally considered poor surgical candidates and emergent surgery is associated with a mortality rate as high as 30 % [27–29].

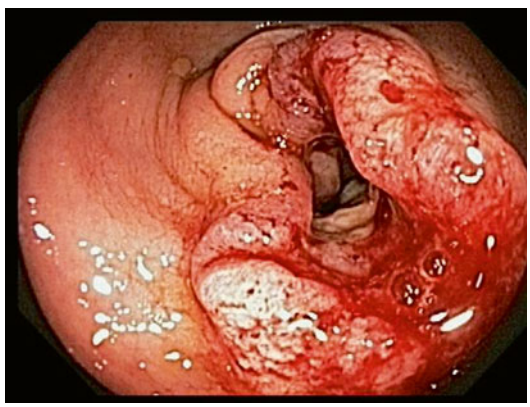

Fig. 17.2 Patient with left colon cancer and obstructive symptoms despite a residual lumen

The use of self-expanding metal stents (SEMS) has emerged as a mainstay in the therapy for ACO (Video 17.1) [23]. Currently, SEMS placement is indicated for either palliative therapy in patients with unresectable malignant large bowel obstruction or as a preoperative bridge until definitive surgery is possible [23, 27]. The use of SEMS as a bridge to surgery for ACO allows the correction of metabolic imbalances, optimization of comorbid conditions, full colonic preparation, and assessment for synchronous lesions [27, 30].

This section will focus primarily on the use of SEMS as a bridge to surgery and as palliative therapy for ACO patients. The use of decompression tubes and tumor debulking therapy for ACO, as well as stent placement for benign causes of obstruction, are discussed briefly.

Stent Placement

Equipment and Technique

Several colonic SEMS of varying lengths and diameters are commercially available for the management of ACO. Stents also differ by coating (uncovered vs. covered) and mechanism of delivery (through the scope (TTS) vs. non-TTS). Uncovered stents have a small risk of migration, but are susceptible to occlusion by tumor ingrowth and/or tissue hyperplasia. Conversely, covered stents help prevent tumor ingrowth but have a higher incidence of stent migration [31, 32]. Currently, only uncovered stents are available in the United States.

The colonic TTS WallFlex stent (Boston Scientific Inc., Natick, MA), the Ultraflex Precision stent (Boston Scientific Inc., Natick, MA), the colonic Z-Stent (Cook Endoscopy, Winston-Salem, NC), and the colonic Evolution

stent (Cook Endoscopy, Winston-Salem, NC) are the most commonly used stents in North America [33]. Several other colonic SEMS are available worldwide, many of which are not available on the US market for clinical use.

In most patients, prior cross-sectional imaging study (e.g., CT) is available before endoscopy. If not, it is generally recommended to obtain such a study to assess the etiology, location, and severity of obstruction, as well as determining whether or not perforation has occurred. Most patients with malignant colonic obstruction have left-sided disease, although right-sided obstruction can be treated via stent placement with similar efficacy and safety [34, 35]. There are few absolute contraindications to colonic stent placement, although patients with perforation, hemodynamic instability, and inability to undergo endoscopy are generally treated surgically.

In general, passage of the endoscope through the site of obstruction is not feasible, but this is not required for successful stent placement (Fig. 17.3). If the endoscope cannot pass through the stricture, a guidewire (passed through a biliary occlusion balloon catheter) is advanced across the stricture under combined endoscopic and fluoroscopic guidance to allow access to the large bowel proximal to the obstruction (Video 17.2). Balloon dilation of the stricture is discouraged due to the increased risk of tumor

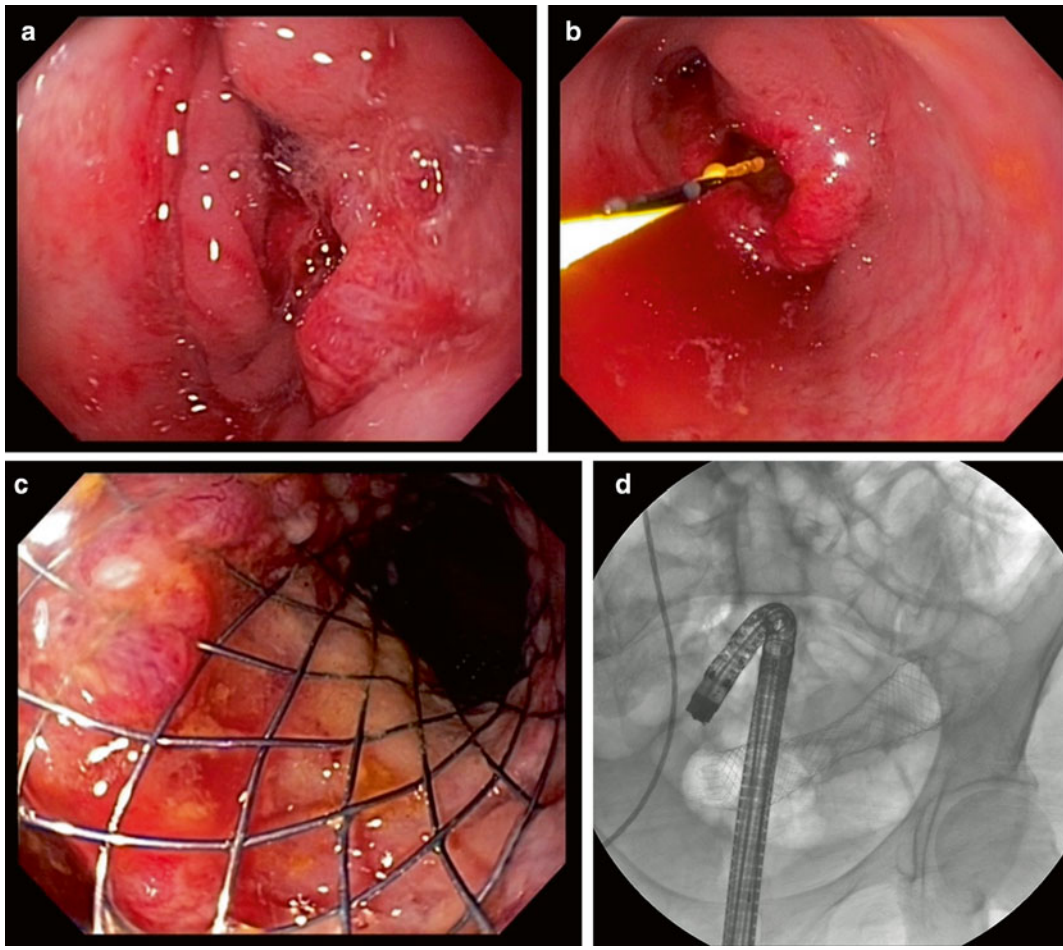

Fig. 17.3 (**a**) Acute obstruction from sigmoid colon cancer with near-complete luminal obliteration. (**b**) Guidewire placement across the obstruction. (**c**) Deployment of an uncovered self-expanding metal stent across the obstruction. (**d**) Fluoroscopic image of deployed colonic stent in satisfactory position

perforation [36]. Once guidewire access across the obstruction is obtained, the catheter is advanced over the wire and used to inject contrast. Injection of contrast allows confirmation of access to the proximal colon, evaluation for any extravasation that would suggest perforation, and assessment of the configuration, length, and severity of the stricture. Fluoroscopic markers can be placed at the proximal and distal ends of the obstruction as an aid to deployment, although in practice these are rarely required. After contrast injection has been performed and guidewire positioning is adequate, a stent of proper dimensions is selected. The stent should generally exceed the length of the obstruction by 2–3 cm on either side of the tumor, and a long stenosis can be treated via multiple stents placed in an overlapping (stent-within-stent) manner. If a TTS stent is selected, the catheter is removed over the wire and exchanged for the stent through the therapeutic working channel of the endoscope. If a non-TTS stent is selected, the catheter and endoscope are removed, leaving the guidewire in place for stent insertion. TTS stents are deployed under combined endoscopic and fluoroscopic guidance (Fig. 17.3). Non-TTS stents may be deployed under fluoroscopic guidance alone or an endoscope can be advanced next to the stent's delivery catheter to provide endoscopic guidance as well. After deployment, the patient should be evaluated for AEs and to assess adequacy of colonic decompression and satisfactory stent positioning. Most patients experience prompt relief with passage of gas and stool material through the stent.

Stent Placement as Palliative Therapy

Since Dohmoto et al. first described the use of colonic metallic stents in 1991, SEMS have been used frequently as palliative therapy in patients who are nonsurgical candidates with advanced colon cancer [37, 38]. Colonic stent placement allows for rapid decompression of the bowel, as well as time for medical stabilization and complete oncologic staging [23]. SEMS have been shown to significantly reduce medical complications, need for stoma formation, length of hospital stay, and mortality [39, 40].

SEMS placement has a high success rate in relieving obstructive symptoms in patients receiving palliative therapy. In one retrospective study, stent placement was technically successful in 94 % of the patients [41]. The duration of stent patency ranged from 2 to 64 weeks, with a mean of 17.3 weeks. The overall clinical effectiveness of SEMS for relief of obstruction in patients on palliative therapy was 82 % [41].

In a retrospective study of 144 patients, the long-term outcome of palliative stent placement vs. surgery was examined [42]. There was no statistical difference in the early success rates between the stent and surgery groups (95.8 % vs. 100 %, $p=0.12$). In the first 30 days after stent placement, SEMS patients had less complications than surgical patients (15.5 % vs. 32.9 %, $p=0.015$). The duration of initial stent patency was shorter than the luminal patency in the surgical group (average 137 days vs. 268 days, $p<0.001$). However, the duration of overall luminal patency in the SEMS group was similar to the surgical group when a second stent was placed (average 229 days vs. 268 days, $p=0.239$). The SEMS group was found to have a higher rate of AEs than the surgical group at 30 days after stent placement (33.8 % vs. 17.8 %, $p=0.028$). However, the rates of major AEs did not significantly differ between the 2 groups (18.3 % vs. 8.2 %, $p=0.074$). American Society of Anesthesiologists Physical Status (ASA PS) classification, stent diameter, and palliative chemotherapy were independent risk factors for the development of late events. Overall long-term efficacy and complications of SEMS were comparable to surgery [42].

Stent Placement as a Bridge to Surgery

ACO patients often present with a number of medical comorbidities, such as metabolic disturbances and dehydration, rendering them suboptimal surgical candidates. Accordingly, emergent surgery for ACO is associated with a mortality rate as high as 30 % [28]. One-stage surgical resection with primary anastomosis is sometimes performed in ACO patients. However, due to concern for anastomotic dehiscence, surgeons often perform a two-stage Hartmann's procedure,

which involves surgical decompression by formation of a diverting colostomy plus tumor resection with creation of a distal stump [27]. These patients often have to wait at least 8 weeks before reanastomosis can be safely attempted [27, 43, 44].

Colonic stent placement as a bridge to surgery allows for decompression, staging, bowel preparation, and optimization of the patient's medical status prior to surgery [27, 41, 45]. The colonic malignancy can then be surgically resected electively, decreasing the risk of morbidity and mortality [27, 46]. Additionally, bowel preparation and decompression increase the likelihood of primary anastomosis, minimizing the need for colostomy and stoma formation [27].

In the largest review to date, 88 studies were examined assessing the safety and efficacy of SEMS placement vs. surgical intervention in malignant colonic obstruction [47]. The overall technical and clinical success rates for SEMS placement were 96 % and 92 %, respectively. There were no differences in the technical and clinical success rates between the stent and surgery groups. The average time from colonic stent placement to subsequent elective surgery in the bridge to surgery group was 7 days (range 2–12 days). Primary colonic anastomosis rates in the bridge to surgery group were at least twice those of the emergency surgery group. Moreover, the length of hospital stay was greater in those who underwent emergency surgery when compared to those who underwent stent placement. The 3- and 5-year prognosis (overall survival) did not differ between the two groups [47]. Colonic stent placement was, thus, deemed to be safe and effective for the relief of acute malignant colonic obstruction.

Stent Placement for Extracolonic Malignancy

Stent placement is not limited to patients who have primary colorectal cancer. Patients may also present with colonic obstruction that arises from invasion or extrinsic compression of the bowel due to an extracolonic malignancy (ECM) [12]. ECM that causes colonic obstruction includes metastatic gynecologic, bladder, pancreatic, gastric, and small bowel malignancies [48, 49]. Several retrospective studies have showed variable technical success (20–87 %) in this setting [48–50]. In addition, higher AE rates (33–65 %) from SEMS placement for management of obstruction due to ECM have been reported, most notably increased migration [48–50]. Still, colonic SEMS are widely employed in this setting since many of these patients are poor surgical candidates and/or would undergo ostomy construction.

Adverse Events

The data on AEs related to colonic SEMS are conflicting [51]. When all major and minor AEs are taken into account, SEMS placement carries an AE rate up to 25 %, although the rate is usually far lower in tertiary referral centers [51, 52]. Several factors have been linked to a higher incidence of AEs following SEMS placement, including the type of stent, etiology of stricture, operator experience, and whether the patient has received chemotherapy or radiation therapy [51, 53].

Colonic perforation is the most concerning AE following SEMS placement. In a review encompassing 82 studies, the median colonic stent perforation rate was 4.9 %, with an associated mortality rate of 16 % [54]. Perforation can be immediate as a result of the procedure itself or delayed due pressure necrosis or trauma related to stent pressure in the tumor area or adjacent uninvolved bowel wall [51]. Patients receiving chemotherapy have a higher risk of perforation, often in a delayed manner [54]. In particular, the chemotherapy agent bevacizumab administered to patients with colonic stents significantly increases the risk of perforation. Bevacizumab is not absolutely contraindicated, but recognition of its potential to increase the perforation risk is warranted [53, 55]. Other factors shown to increase the risk of perforation include anatomical factors, corticosteroids, and radiotherapy [53, 54]. Stent location may play a factor in the AE rate. In one study, stents placed in the left colon had a higher rate of AEs than those placed in the right colon (27.2 % vs. 12.5 %, $p = 0.06$) [53].

Another AE of colonic SEMS placement is stent migration. The median rate of stent migration

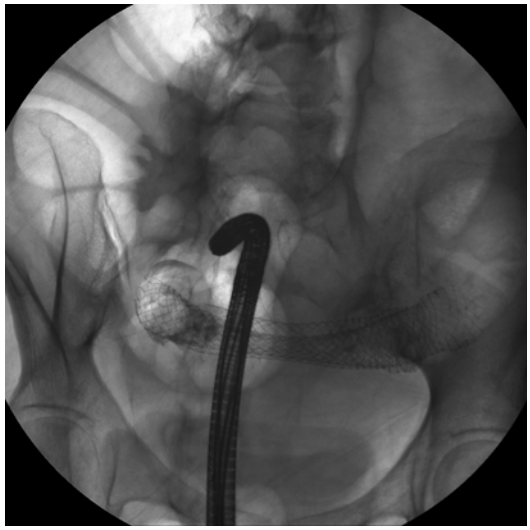

Fig. 17.4 Fluoroscopic image of stent-within-stent deployment to treat tumor ingrowth in a previously placed colonic stent

after colonic SEMS placement is 11 % (range 0–50 %) [47]. Factors that predispose to stent migration include extrinsic lesions, stricture dilation, benign strictures, small stent caliber, post-stent radiotherapy, and the use of covered stents [56].

Tumor overgrowth and/or ingrowth can be seen in the long term following colonic stent placement and result in re-obstruction. This is often treated via placement of another stent inside the first stent (Fig. 17.4). Stent fracture, tenesmus, incontinence, fecal impaction, infection, post-procedure bleeding, and abdominal and rectal pain can also occur [51, 57].

Benefit of Stent Placement Versus Surgery

Several studies have examined the cost-effectiveness of colonic SEMS placement for palliative therapy and as a bridge to surgery. In one study, a decision analysis was used to calculate the cost-effectiveness of SEMS placement with elective surgery vs. emergency surgery in a hypothetical patient presenting with ACO [27]. The SEMS group had a lower mean cost per patient in comparison to the emergency surgery group ($45,709 vs. $49,941). The SEMS group had an 83 % reduction in stoma requirement, 23 % fewer operative procedures per patient, and a lower procedure-related mortality rate.

In another study, the costs related to hospitalization, intensive care unit utilization, stent placement, and surgery were compared between patients receiving SEMS placement (either as a bridge to surgery or palliation) and those undergoing surgery alone [58]. An overall 19.7 % cost reduction was noted in the SEMS group as a result of shorter hospitalization stay and lower complication rates. In the bridge to surgery group, the cost reduction was more significant at 28.8 % in comparison to the surgery-only group.

In a European study, the safety, efficacy, and cost of palliative treatment with SEMS placement were compared to that of stoma creation in patients with inoperable ACO [40]. Although stoma creation was less expensive, the difference in the total health-care cost between the 2 groups was only €132 or 6.9 % of the total cost. SEMS placement also seemed to provide a better quality of life for the patient than stoma creation.

Decompression Tubes and Tumor Debulking Therapy

Prior to the advent of colonic SEMS, decompression tube placement was the nonsurgical modality available for malignant ACO [23]. The tubes are placed endoscopically as a temporizing measure to relieve obstructive symptoms. Decompression tubes are relatively inexpensive, are widely available, and allow stabilization of the patient, potentially avoiding the need for emergent surgical decompression [23]. However, placement of a decompression tube can be time-consuming and only temporizing. Decompression tubes are not helpful in patients who require decompression indefinitely for palliation. Other disadvantages include tube expulsion, patient discomfort, and the risk of bleeding and perforation during placement [23, 24].

Endoscopic laser therapy may enable recanalization of intrinsic bulky tumors in patients with colonic obstruction [23]. Although it allows treatment of bulky, intrinsic tumors under direct vision, laser therapy is technically difficult in the proximal colon and is rarely used to treat tumors above the sigmoid colon [23]. Furthermore, the

availability of laser therapy is limited to only a few centers given its cost, high maintenance requirement, and restricted portability and usage for GI indications. Although argon plasma coagulation (APC) has been used to debulk colonic tumors, its efficacy and safety have only been examined in small case series [24, 59, 60]. The risk of colonic explosion also hinders its use in an unprepped colon.

Stent Placement for Benign Colonic Obstruction

SEMS placement has been performed in patients with benign obstructive diseases, such as diverticulitis with an associated diverticular stricture, anastomotic strictures, radiation-induced strictures, and inflammatory bowel disease (IBD) [51]. In these situations, stent placement can be considered a method for temporary decompression when emergent surgical treatment is contraindicated [51].

In one retrospective study, 23 patients with benign obstructive disease underwent endoscopic stent placement [61]. Stent placement was technically successful in all patients and colonic obstruction was relieved in 22 of 23 patients (95 %). Major AEs occurred in 38 % of patients, including re-obstruction ($n=4$), migration ($n=2$), and perforation ($n=2$). Most of these AEs (87 %) occurred at an average of 7 days after stent deployment. Despite the AEs, 16 of 19 patients who underwent planned surgical resection were successfully decompressed and converted from an emergent to an elective surgery. The median time to surgical intervention was 12 days (range 2 days to 18 months), and 42 % (8/19) of patients who underwent colectomy did not need a stoma after stent deployment. Thus, SEMS can effectively decompress benign colonic obstruction as a bridge to surgery, although it is associated with a high rate of delayed AEs. If elective surgery is planned, it preferably should be performed within 7 days of SEMS deployment. It should be noted that colonic stent placement for benign strictures may have a higher migration rate than stents placed for malignant stenosis.

Colonic Volvulus

Colonic volvulus is occasionally encountered as a mechanical cause of ACO. Endoscopic detorsion is an effective means of treating sigmoid volvulus in the acute setting (Fig. 17.5). At endoscopy, a twist or rosette formation is identified at the point of obstruction. The latter can generally be untwisted by gentle push of the endoscope with air (preferably carbon dioxide) or water insufflation, aided by torquing the tip of the endoscope in the direction opposite the orientation of the twisted folds (Video 17.3). Once the obstruction is relieved, the endoscope should readily advance into a proximally dilated colon. In general, a decompression tube is left in place to minimize the risk of recurrence. Definitive surgical therapy on a semi-elective or elective basis should be considered since the recurrence rate for sigmoid volvulus is high.

Summary

In the setting of ACPO, colonoscopic decompression with decompression tube placement provides reliable relief of distension in patients who are not candidates for or do not respond to medical therapy (i.e., neostigmine). Advanced techniques, such as percutaneous endoscopic cecostomy or colostomy, are potential alternatives to tube decompression, although additional studies are needed to assess their safety and efficacy.

SEMS placement for malignant ACO is indicated as palliative therapy in patients with unresectable disease or as a preoperative bridge to definitive surgery. Decompression tubes and laser therapy for tumor debulking are no longer the first-line treatment of choice for malignant ACO, but can still be used in selected patients. Endoscopic detorsion is an effective means for managing sigmoid volvulus in the acute setting. Recent advances in endoscopic management for ACPO and ACO have reduced the need for emergent surgery, with high technical and clinical success rates.

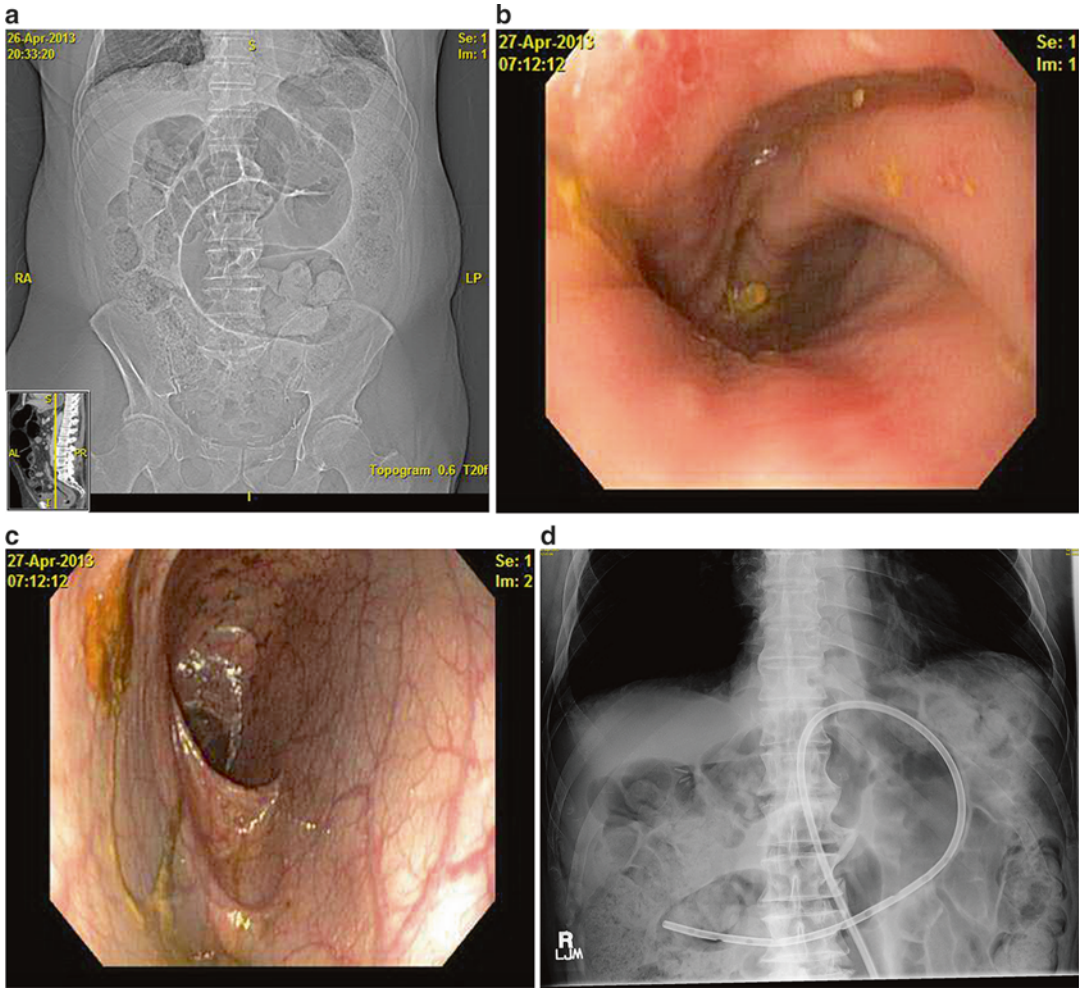

Fig. 17.5 (**a**) CT topogram showing sigmoid volvulus. (**b**) Endoscopic view of point of torsion. (**c**) Advancement of the endoscope into a significantly dilated sigmoid colon following detorsion maneuvers. (**d**) Placement of a colonic decompression tube to minimize the risk of prompt recurrent volvulus

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Endoscopic Management of Pancreaticobiliary Emergencies

18

James H. Tabibian and Todd H. Baron

Introduction

Disorders of the pancreaticobiliary system are estimated to account for hundreds of thousands of hospitalizations and billions of dollars of healthcare expenditures annually [1, 2]. Indeed, the two most common digestive disease-related principal hospital discharge diagnoses in the United States are acute pancreatitis and cholelithiasis [1]. While the management of these disorders depends on the specific diagnosis, underlying etiology, severity, and other factors, many of them incorporate pancreaticobiliary endoscopy in their diagnostic and therapeutic approach. This is particularly the case with several urgent or emergent disorders and complications of the pancreaticobiliary system, wherein endoscopic intervention has the potential to provide the most favorable combination of expediency, efficacy, and minimal invasiveness.

In this chapter, our objective is to highlight the current state of endoscopic management of potential pancreaticobiliary emergencies (Table 18.1) and to identify areas in need of further research in this clinical context. For the purpose of organization, each of the pancreaticobiliary emergencies reviewed herein is addressed as a separate subsection under the heading of "pancreas" or "biliary."

J.H. Tabibian
Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN 55902, USA

T.H. Baron (✉)
Division of Gastroenterology and Hepatology, University of North Carolina, 41041 Bioinformatics Blvd, CB 7080, Chapel Hill, NC 27599-0001, USA
e-mail: todd_baron@med.unc.edu

Pancreas

In this section, we address acute gallstone pancreatitis, infected pancreatic pseudocysts, infected pancreatic necrosis, and occluded pancreatic stents. Of note, these entities are generally considered endoscopic "emergencies" to the extent that there is at least clinical suspicion or evidence of sepsis or similar decompensation, which can be alleviated endoscopically.

Acute Gallstone Pancreatitis

Gallstones represent the most common cause of acute pancreatitis, accounting for approximately 35–45 % of cases worldwide [3]. The mechanism by which gallstones induce acute pancreatitis is uncertain, but it may be related to reflux of bile or to pancreatic ductal hypertension from obstruction at the ampulla (due to the presence of a stone or to ampullary edema consequent to recent passage of a stone) [4]. Although a majority of patients will have a brief and conservatively manageable disease course, up to 25 % will

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Table 18.1 Potential pancreaticobiliary emergencies managed endoscopically

Pancreatic
Gallstone pancreatitis
Infected pancreatic pseudocyst
Infected pancreatic necrosis
Occluded pancreatic stent
Biliary
Acute cholangitis
Acute cholecystitis
Bile leak
Hepatic abscess

develop local and/or systemic complications requiring more intensive management; this risk is higher among those with necrotizing pancreatitis as compared to acute interstitial edematous pancreatitis.

The role and timing of endoscopic intervention in the management of acute gallstone pancreatitis has been a subject of debate for several decades. Randomized clinical trials, systematic reviews, and meta-analyses have, over the years, provided conflicting results [5–9]; this is likely related to heterogeneity in patient samples, study methodology, definitions (e.g., of what constitutes "early"), and endpoints. As a result, large prospective studies continue to be performed to settle controversies and perhaps more carefully identify subgroups which may particularly benefit (or not) from endoscopic intervention.

In a recent Cochrane review and meta-analysis, it was determined that early endoscopic retrograde cholangiopancreatography (ERCP) did not significantly affect mortality and local or systemic complications of pancreatitis, regardless of predicted severity [10]. Only in the subgroup of patients with acute cholangitis or biliary obstruction were improved outcomes seen with ERCP. These findings are congruent with the most recent societal guidelines, which provide relatively clear recommendations in this regard [11]. Per consensus, urgent ERCP is not needed in most patients with gallstone pancreatitis in the absence of laboratory or clinical evidence of ongoing biliary sepsis or obstruction [5]. In cases where the index of suspicion is high for choledocholithiasis despite the absence of findings suggestive of biliary obstruction or sepsis, magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) should be pursued in lieu of ERCP. For the minority of patients in whom ERCP is indicated (i.e., those with acute pancreatitis and concurrent acute cholangitis), ERCP is recommended within 24 h of presentation. Moreover, among this subset of patients, measures should be taken to prevent further exacerbation of pancreatitis post-ERCP (e.g., guidewire cannulation, pancreatic duct stents, and/or post-procedure rectal nonsteroidal anti-inflammatory drug suppositories) in high-risk patients even though they are not well studied in the context of acute gallstone pancreatitis [11–13]. Until more data become available, the role of endoscopic management in acute gallstone pancreatitis thus appears to be limited to those with suspected concomitant acute cholangitis or biliary obstruction.

Infected Pancreatic Pseudocysts

Pancreatic pseudocysts develop in 10–20 % of patients following acute interstitial pancreatitis. Unlike acute fluid collections, pseudocysts are more mature collections (typically developing at least 4 weeks after acute pancreatitis) with generally homogeneous liquid components contained within a well-defined wall [14]. The management of pseudocysts depends primarily on the presence of symptoms and complications (e.g., infection) and to a lesser extent on the characteristics and location of the fluid collections. Asymptomatic pseudocysts, regardless of size or location, do not typically warrant intervention. For symptomatic (e.g., abdominal pain, fever, early satiety, jaundice) pseudocysts, drainage is critical, and while historically it was only a surgical option, the latter has been largely replaced by endoscopic and/or percutaneous (interventional radiologic) drainage. Each approach has its own advantages and disadvantages, and there is a paucity of comparative trials to determine the superiority of one technique over another. Therefore, the choice of drainage procedure is largely determined based on local expertise and the

anatomical features of the fluid collection. In our experience, however, a majority of pseudocysts that abut the stomach or duodenum can be successfully drained endoscopically, and this has been demonstrated in numerous published reports.

Drainage, together with antibiotic therapy, becomes an urgent procedure in patients with signs of clinical deterioration due to suspected infection. The endoscopic approaches for drainage of pseudocysts are transpapillary, transmural, or a combination thereof [15]. The choice of approach is based upon the anatomic relationship of the pseudocyst to the stomach or duodenum, the presence of pancreatic ductal communication with the pseudocyst, and the size of the pseudocyst [15]. With respect to transmural drainage, this is achieved by large-bore stenting (plastic or metal) through the gastric or the duodenal wall [15–17]. Pre-drainage imaging with EUS has been advocated to limit complications, but lack of EUS availability need not preclude transmural drainage if pre-procedural computed tomography (CT) imaging is available. The main advantages of EUS-guided drainage are the ability to detect unsuspected perigastric varices or other vascular structures and to facilitate transmural drainage in the absence of an endoscopically visible bulge, particularly for lesions near the pancreatic tail [18]. EUS-guided drainage should thus be employed in select circumstances, such as a small "window" of entry based on pre-procedural CT findings, unusual pseudocyst location, or documented major intervening vasculature.

Infected Pancreatic Necrosis

Approximately 10 % of patients with acute pancreatitis develop necrosis of the pancreatic parenchyma, the peripancreatic tissue, or both [14]. The most common manifestation of necrotizing pancreatitis is necrosis involving both the pancreas and peripancreatic tissues. The natural history of necrotizing pancreatitis is variable as the necrotic collection(s) may remain solid or liquefy, be localized or extend into the pelvis and elsewhere in the abdomen, and/or become infected, persist, or spontaneously disappear over time.

Infected pancreatic necrosis, in itself, is not an indication for emergent endoscopic intervention. Indeed, in stable patients with infected necrosis, initial treatment is expectant (including antibiotics), as surgical, radiologic, and/or endoscopic drainage should be delayed to allow for (semi) liquefaction of the contents and development of a fibrous wall around the necrotic material (i.e., walled-off pancreatic necrosis [WOPN]); this process generally takes at least 4 weeks, and in some cases, as with pseudocysts, necrotic collections can spontaneously resolve. By this point in time, if a drainage procedure is still needed, it is generally planned via a multimodality (endoscopic, radiologic and/or surgical) approach and on an elective basis. However, drainage may be considered on a more urgent basis in the uncommon circumstance wherein conservative management for 4 weeks is not deemed feasible because of ongoing symptoms and/or clinical decompensation related to infection (Fig. 18.1). Intervention in these settings carries greater risk (e.g., perforation, leakage) in part due to the lack of maturity of the acute necrotic collection as well as the generally higher level of patient morbidity. Whenever possible, an aspirate of the collection should be obtained and sent for microbiological studies to guide antibiotic therapy.

As with pseudocysts, endoscopic drainage for immature necrotic collections or for WOPN can be performed through the stomach or duodenum, depending on the location of the necrotic collection. Because necrotic tissue is of variable texture and frequently includes a gelatinous, heterogeneous, and semisolid component, standard drainage with stenting (as employed for pseudocysts) is often inadequate, and direct endoscopic necrosectomy is generally needed [19]. Even necrosectomy, however, may require repeated endoscopy for lavage, additional tract dilation, stenting, debridement, and other interventions. At the end of endoscopic treatment, outcomes of necrosectomy in centers with expertise are favorable, reaching success rates of approximately 90 % [20]; nevertheless, it is important to discuss with the patient and care team, prior to the first endo-

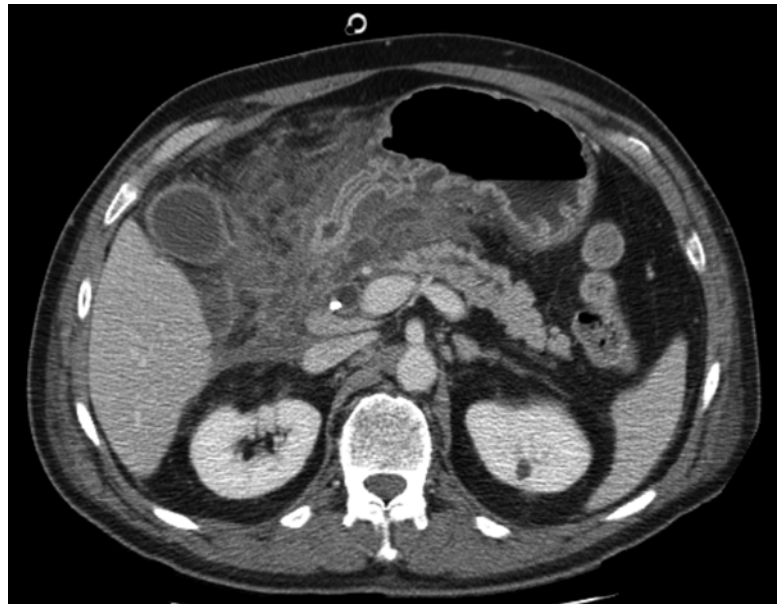

Fig. 18.1 Infected pancreatic necrosis with symptomatic mass effect including biliary and gastric outlet obstruction on CT. Endoscopic necrosectomy at 3 weeks post-pancreatitis resulted in clearance of infection and improvement of mass effect

scopic procedure, the potential requirement for multiple endoscopy sessions to achieve therapeutic success.

Occluded Pancreatic Stents

Pancreatic duct stent placement has been increasingly used for the treatment of a variety of disorders including chronic pancreatitis, pancreatic duct leaks or disruptions, drainage of pseudocysts, and the prevention of post-ERCP pancreatitis. Pancreatic duct stent occlusion is a potential late complication, which occurs at rates similar to those described for biliary stents of the same caliber. Most (small caliber) pancreatic stents occlude within 2 months [21]. Stent occlusion, similar to the biliary tree, is related to adherence of protein matrices to the inner surface of the stent, with or without interspersed mixed bacterial flora and calcium carbonate precipitates (Fig. 18.2) [22, 23]. Stent occlusion may be silent or may lead to increased pain, acute pancreatitis, or other acute and potentially lethal complications [24, 25]. In these circumstances, endoscopic removal or replacement of the pancreatic stent may be urgent or even emergent.

To avoid complications related to pancreatic duct occlusion, pancreatic stents should be removed or exchanged electively at predetermined intervals. Although the duration of this interval has not been determined (and may well depend on the initial indication for stent placement), an indwelling period of 2–6 weeks appears reasonable; covered metal stents may be left in situ for longer periods [26].

Biliary

In this section, the topics of acute cholangitis, acute cholecystitis, bile leaks, and liver abscesses are addressed. As with the previously discussed pancreatic disorders, not all of these biliary disorders require emergent endoscopic intervention, and indeed some may have alternative management options, be it medical (e.g., antibiotics) or procedural (e.g., interventional radiology).

Acute Cholangitis

Acute cholangitis is a state of biliary infection associated with partial or complete obstruction of the biliary tree caused by any of various etiologies

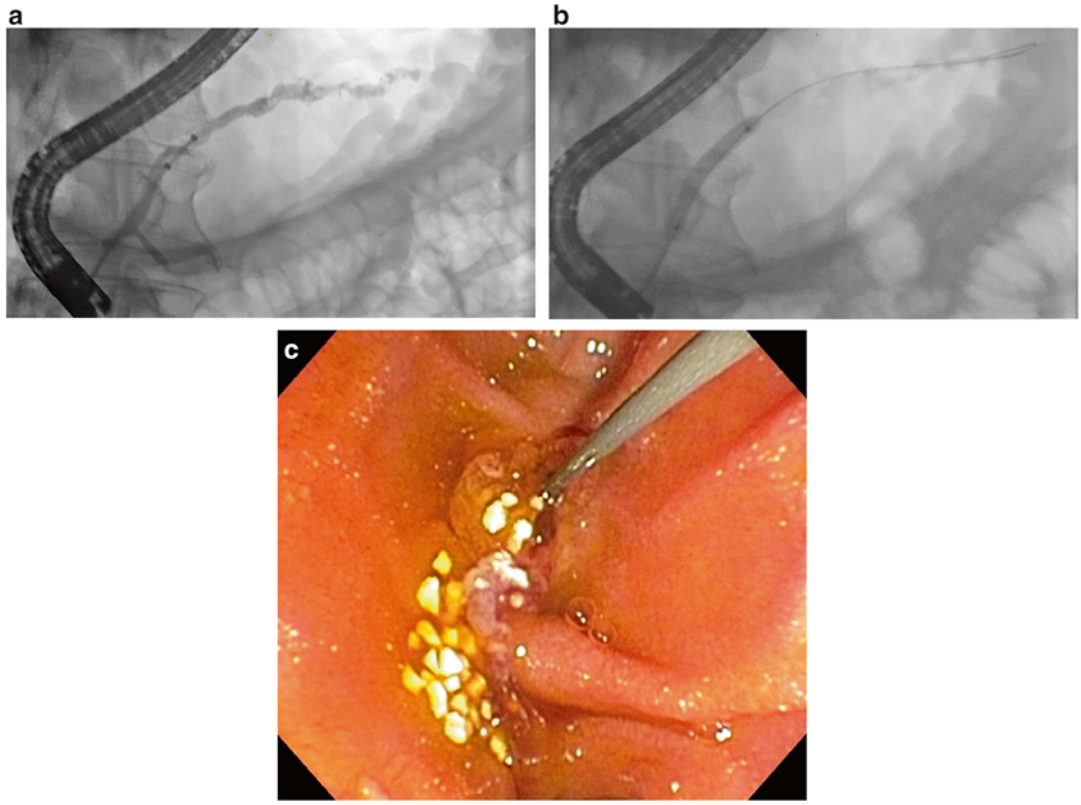

Fig. 18.2 Pancreatic duct obstruction. The patient had undergone balloon dilation of a pancreatic duct stricture with plastic stent placement; within 1 week, the patient developed acute pancreatitis. ERCP was performed, and the pancreatic duct stent was removed. (**a**) Pancreatogram revealed ductal irregularity, filling defects, and proximal side branch dilatation. (**b**) Balloon dilation performed. (**c**) Ductal sweeping revealed numerous calcium carbonate pancreatoliths

[27, 28], including choledocholithiasis (most common), benign and malignant strictures or masses, and indwelling biliary stent malfunction, among others. From a pathophysiological perspective, biliary infection alone is not believed to cause clinical cholangitis unless biliary obstruction raises the intraductal pressure sufficiently to cause cholangiovenous or cholangiolymphatic reflux [29]. The diagnosis of acute cholangitis is made on the basis of clinical findings such as Charcot's triad, first described in 1877 [30], or Reynold's pentad, first described in 1959 [31], in combination with serum biochemical data and imaging findings. A variety of different criteria for acute cholangitis have been historically used in the published literature, each with varying (but generally low) sensitivity and specificity; however, consensus definitions have been established [32] and recently revised [33].

Rapid and precise determination of the cause and severity of acute cholangitis is critical for appropriate management. Consensus criteria have been proposed for defining the severity of acute cholangitis and consist of three grades [28]. In brief, these consist of:

1. *Severe*, which is characterized by the onset of dysfunction or failure of at least one organ system despite supportive care with intravenous antibiotics and fluid resuscitation
2. *Moderate*, which entails at least two risk factors for progression to organ dysfunction (e.g., temperature ≥39 °C and serum bilirubin ≥5 mg/dL)

3. *Mild*, which does not meet criteria for either of the other two grades

The timing of biliary drainage is based on the severity grade [34]; urgent or emergent drainage is indicated in severe disease, while "early" drainage (generally defined as <72 h) is recommended for moderate disease [34–36].

Endoscopic drainage with ERCP, whenever feasible, is generally advocated over surgical and percutaneous drainage [37]. The endoscopic approach to drainage, once selected as the modality of choice in a given case, can vary depending on the underlying etiology of acute cholangitis. Considerations for a few of the common etiologies of acute cholangitis are described below.

Choledocholithiasis

The standard approach to choledocholithiasis is endoscopic sphincterotomy followed by stone extraction with an occlusion balloon or basket. This allows for successful extraction of >95 % of stones <1.5 cm when performed by experienced endoscopists and in the absence of underlying strictures or altered bilioenteric anatomy [38]. Larger stones may require more advanced techniques, which are discussed later. The requisite length of sphincterotomy depends on papillary anatomy and stone size, and in some instances (e.g., when stone size is small and/or the papilla is patulous), it may not be necessary. There are also select clinical scenarios where sphincterotomy alone is insufficient to allow extraction of choledocholithiasis, in which case combined endoscopic papillary balloon dilation may be preferable [39, 40]. The use of prophylactic pancreatic duct stents and/or nonsteroidal anti-inflammatory drugs should be considered in these patients to decrease the risk of associated post-ERCP pancreatitis [11–13].

When a stone is anticipated but not visualized during cholangiography, the potential advantages of empiric endoscopic sphincterotomy (e.g., for facilitating bile duct sweeping and increase detection of small stones) [41] should be weighed against the potential short- and long-term complications of an unnecessary sphincterotomy. Ultimately, the decision to perform or forego sphincterotomy is at the discretion of the endoscopist and influenced by the pretest probability for choledocholithiasis, quality of fluoroscopy, and availability of potentially helpful ancillary techniques (e.g., EUS). Of note, when incomplete stone extraction is known or suspected, a biliary stent should be placed to aid in biliary drainage [42].

Extraction of impacted and large bile duct stones may require additional techniques for successful removal and biliary drainage [43]. Stones impacting the ampulla make traditional biliary cannulation and sphincterotomy difficult or unfeasible; in these cases, needle-knife sphincterotomy is generally effective in disimpacting the stone, and the underlying stone may in fact help protect the pancreatic sphincter from inadvertent thermal injury from the needle knife (Fig. 18.3) [44, 45]. Thereafter, lithotripsy may be required for extraction of residual large stones. One form of lithotripsy is *mechanical* lithotripsy, in which a stone is captured in a specialized large basket and crushed (Fig. 18.4) [46]; fragments are then extracted using standard techniques. Another form of lithotripsy is *intraductal* lithotripsy, in which laser or electrohydraulic lithotripsy catheters are passed into the bile duct and used to fragment stones under direct endoscopic visualization via choledochoscopy [47]. Direct visualization is essential (unless a "centering" balloon is used [48]) to ensure that the lithotripsy catheter is directed at the stone and not the bile duct wall so as to prevent choledochal injury. An ancillary technique for large stone management is the combination of endoscopic biliary sphincterotomy and large-diameter (>12 mm and up to 20 mm) papillary balloon dilation; since the initial description of this technique in 2003 [49], several studies have found this approach to be safe, to facilitate large stone extraction, and to decrease the need for mechanical lithotripsy [35]. Although beyond the scope of this chapter, extracorporeal shock wave lithotripsy represents another adjunctive modality in the management of endoscopically challenging choledocholithiasis [35].

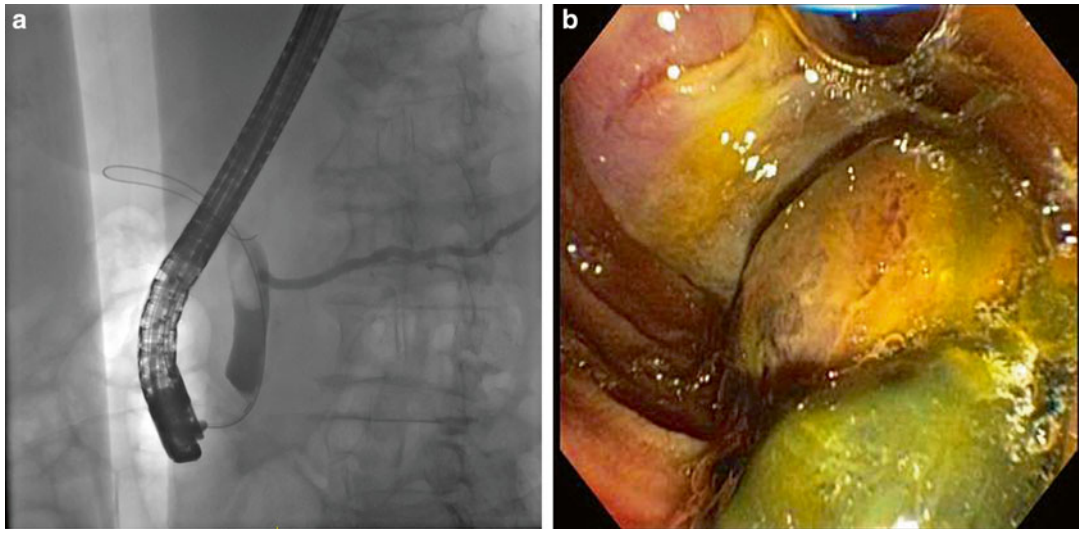

Fig. 18.3 Common bile duct stone-associated acute cholangitis. (**a**) A radiolucent, partially obstructing choledocholith was seen during ERCP. (**b**) Biliary sphincterotomy was performed, and balloon sweeping successfully removed a single, large choledocholith

Biliary Strictures

Biliary strictures can occur due to a variety of benign and malignant causes, but in nearly all instances, endoscopic management in the context of acute cholangitis consists of expeditious biliary drainage with balloon dilation (Fig. 18.5) and, if indicated, stenting of the stricture. As with management of biliary strictures in the absence of acute cholangitis, the type and number of stents placed (as well as the need for sphincterotomy) depend on a variety of factors, including the etiology of the stricture, location within the biliary tree (e.g., distal versus hilar), nature of prior endoscopic or non-endoscopic biliary therapies, and local expertise, among others [43]. In the presence of acute cholangitis, however, a distinction (as compared to elective biliary drainage of hilar obstruction) that should be made is that complete bilateral drainage should be performed; this is particularly the case if both sides of the biliary tree have been previously instrumented (and thus potentially contaminated) or if multifocal strictures (e.g., posttransplant nonanastomotic strictures [50], primary sclerosing cholangitis) are present. It is worth noting that while drainage is critical, the need for stent deployment (as compared to biliary balloon dilation and sweeping only) is less clear and may depend on the etiology of the underlying stricture and response to balloon dilation [51–54].

Stent Dysfunction

Biliary stent dysfunction (occlusion or migration) can predispose to the development of acute cholangitis and may require prompt intervention depending on the severity of cholangitis, as mentioned above. In patients with mild acute cholangitis, abdominal imaging should be performed to assess stent position as compared to images obtained during prior ERCP; if the stent appeared to be in satisfactory position, was placed recently, and believed to have provided complete drainage, continued medical management is reasonable [34, 55]. Otherwise, or in moderate or severe cholangitis, ERCP should be performed to ensure stent position and adequate biliary drainage and perform stent replacement as needed. Contrast injection should be minimized while doing so since debris and pus may be retained in the bile ducts, and increasing intraductal pressure at endoscopy with contrast injection may augment cholangiovenous or cholangiolymphatic flow

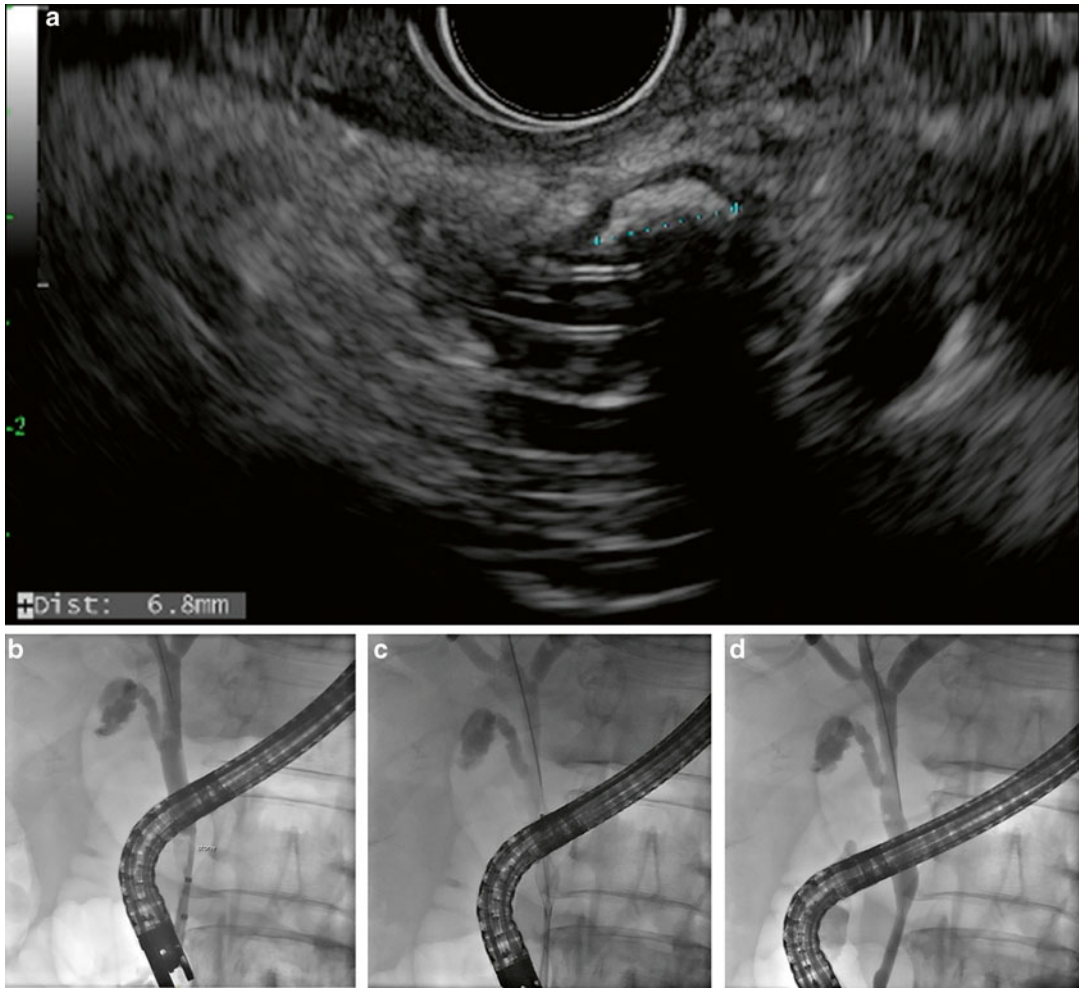

Fig. 18.4 Distal common bile duct stone. (**a**) EUS image of a 6.8 mm echogenic, obstructive choledocholith. (**b**) The same stone is seen during ERCP. (**c**) Mechanical lithotripsy is performed with a flower basket. (**d**) Cholangiogram following lithotripsy and balloon sweeping

and precipitate or exacerbate biliary sepsis. Further details regarding the management of stent dysfunction are provided elsewhere [55].

Acute Cholecystitis

As with acute cholangitis, consensus guidelines exist for grading the severity of acute cholecystitis [33] and provide some guidance for its management [34]. For patients with moderate or severe disease, urgent biliary drainage (i.e., gallbladder decompression) is indicated in addition to antibiotic therapy; unlike in acute cholangitis, endoscopic intervention is rarely used and is reserved for patients with comorbidities that preclude surgical cholecystectomy and contraindications to percutaneous tube cholecystostomy (e.g., large-volume ascites, coagulopathy, or the presence of an interposed loop of bowel) [55]. In cases where endoscopic management is selected, the two main options are nasocystic catheter or stent placement during ERCP (i.e., transpapillary drainage) and EUS-guided drainage via a transluminal approach [56]. In patients who require only temporary gallbladder decompression as a bridge to elective surgery, transpapillary drainage can be effective [57]. Nasocystic catheter placement is

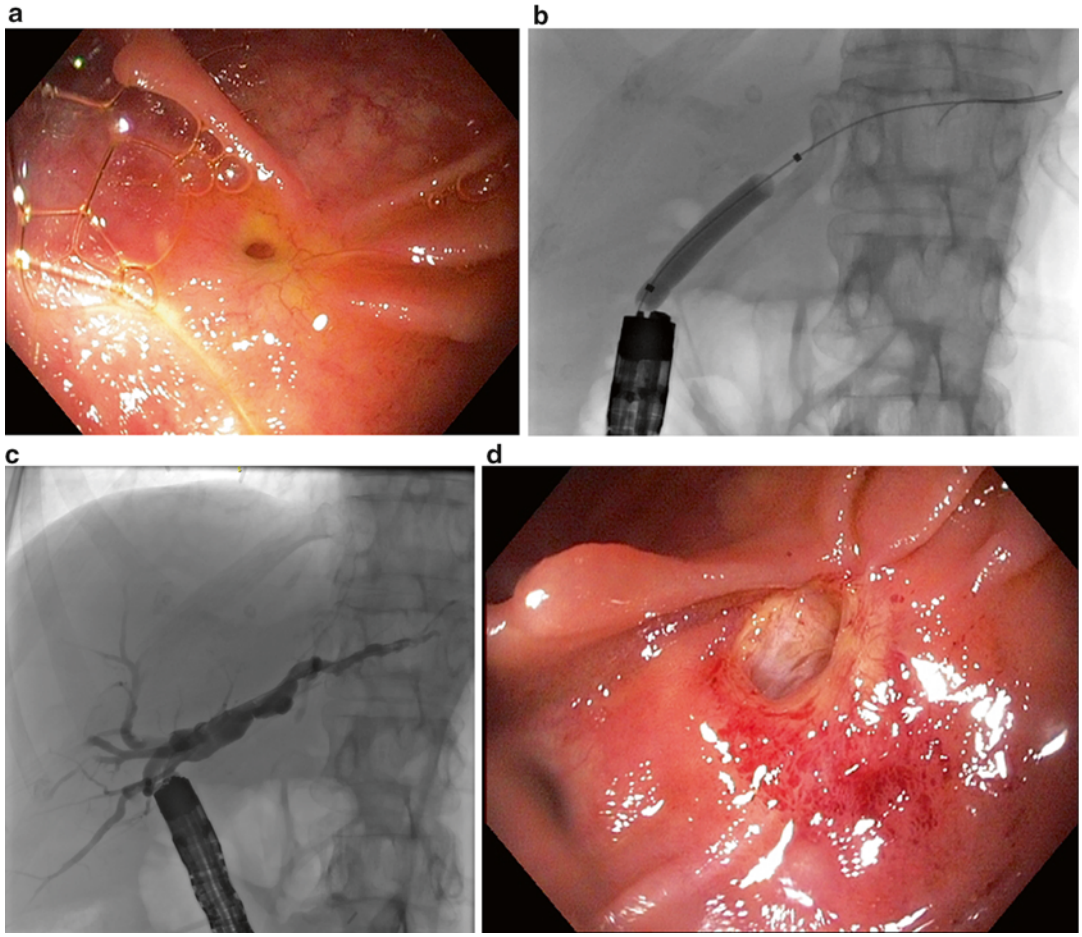

Fig. 18.5 Acute cholangitis secondary to hepaticojejunostomy site biliary obstruction. (**a**) Endoscopic image of strictured hepaticojejunal anastomosis. (**b**) ERCP with balloon dilation of the hepaticojejunal stricture. (**c**) Cholangiogram following successful balloon dilation. (**d**) Endoscopic view of the hepaticojejunostomy post-dilation

now rarely performed in the United States due to the availability of alternative treatment modalities. EUS-guided transluminal drainage has not gained traction into mainstream clinical practice due to the complexity of the procedure and risk of bile leaks.

Bile Leak

Bile leaks can occur following hepatobiliary surgeries, such as open or laparoscopic cholecystectomy, hepatic resection, and liver transplantation, as well as after other procedures (e.g., ERCP, percutaneous transhepatic cholangiography). The location (e.g., cystic duct, accessory or anomalous duct, biliary anastomosis), cause (e.g., slipped ligature, inadvertent trauma, transection), and severity of the bile leak are largely determined by the nature of the preceding hepatobiliary intervention [58]. Bile leaks can be divided into (1) low grade, where the leak is only identified after complete opacification of the intrahepatic biliary tree, and (2) high grade, where the leak can be observed before intrahepatic opacification [58]. In either case, endoscopic management represents the preferred therapeutic modality, although the grade and other features of the leak may influence which endoscopic interventions are performed [59, 60]. Endoscopic

management can also be effective for blunt or penetrating trauma-induced bile leaks based on a recent report [61].

The overarching goal of endoscopic management for bile leaks is to decrease the transpapillary pressure gradient to facilitate preferential bile flow through the papilla as opposed to the leak site, thereby providing time for the biliary defect to seal. This therapeutic diversion of bile is most commonly achieved by placing a transpapillary stent, with or without sphincterotomy [62]; the stent, traditionally and most often plastic but in some instances metal [63, 64], is generally left in place for approximately 4–6 weeks. Others have suggested that performance of endoscopic sphincterotomy alone is sufficient and has the advantage of eliminating a subsequent endoscopy for stent removal (although at the expense of the potential short- and long-term sequelae of sphincterotomy) [58]. A more recent study found that success of endoscopic management was predicted by location of the leak and placement of a stent and not by performance of sphincterotomy [65]. Ultimately, a variety of options exist, all of which have high success rates, and thus, the choice should be tailored to the particular leak and patient characteristics [59, 60].

An alternative endoscopic approach for management of bile leaks is placement of a nasobiliary catheter. This offers the advantage of permitting repeat cholangiography without requiring another ERCP. Although this method still has a role in select cases of bile leak, its use has declined due to poor patient tolerance, inadvertent catheter displacement, and need for hospitalization until the catheter is removed [58]. Similarly, its use in duodenal perforations has decreased due to the abovementioned reasons, as well as the advent of endoscopic closure techniques [66].

Liver Abscess

Although consensus guidelines do not exist regarding the management of liver abscesses, those that are of sufficient size or not responding to antibiotic therapy should be drained urgently. Liver abscesses have been traditionally treated surgically or percutaneously. More recently, endoscopic management via EUS-guided drainage has been reported [67]. The left lobe of the liver can be readily accessed by EUS guidance through the stomach, and the use of Doppler during EUS facilitates avoidance of blood vessels. The theoretical advantages of EUS-guided drainage include avoidance of an external drain and of external fistulae. In some instances, EUS-guided drainage can even be performed for abscesses that are not amenable to percutaneous drainage (e.g., abscesses involving the caudate lobe or gastrohepatic space) [68]. EUS-guided liver abscess drainage, however, remains in the realm of clinical trials and is not routinely performed in clinical practice.

Conclusions

Endoscopic intervention is indicated and critical in the management of a variety of pancreaticobiliary urgencies and emergencies. Advances in ERCP and EUS, coupled with a growing body of literature from prospective trials and outcomes studies, continue to provide insight as to how and when to best apply endoscopic techniques to achieve optimal patient outcomes in these scenarios. Given the morbidity and potential mortality of patients requiring urgent or emergent endoscopic management, we advocate for a multidisciplinary, evidence-based, and patient-tailored approach.

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Endoscopic Management of Procedure-Related Bleeding and Perforation

19

Alessandro Repici, Angelo Zullo, Andrea Anderloni, and Cesare Hassan

Introduction

The performance of endoscopic procedures is increasing worldwide. In addition to commonly performed therapeutic procedures, such as simple snare polypectomy and dilation, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), which were pioneered in Asia, are now increasingly being performed in Western countries [1]. The criteria for endoscopic removal of various GI lesions continue to evolve. The diameter of lesions suitable for endoscopic resection has increased substantially over the past few years [2–4], and deeper lesions, such as small stromal tumors arising from the muscularis propria in the upper GI tract, are now being resected endoscopically [5–7]. Furthermore, advanced resection procedures, such as EMR and ESD, are performed even in selected patients with significant comorbidities, such as cirrhosis, coagulopathy, and cardiovascular issues, who are not optimal candidates for surgery [8, 9]. On the basis of these practice trends, intra- and post-procedural adverse events, such as bleeding and perforation, are expected to increase. In the past, endoscopy-related perforation and some iatrogenic bleeding cases required surgical intervention. The recent development of more robust endoscopic devices for hemostasis and defect closure has enabled successful conservative management of these adverse events in a significant proportion of cases [10]. However, the decision to intervene endoscopically should be individualized, taking into account patient factors, lesion characteristics, availability of endoscopic devices, and local expertise, among others [11].

Procedure-Related Bleeding

Bleeding is the most common adverse event associated with endoscopic resections. The burden of post-procedural bleeding is relevant. In the setting of colorectal cancer screening, it is

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A. Repici (✉)
Digestive Endoscopy Unit, Department of Gastroenterology, Instituto Clinico Humanitas, Milan, Italy

Gastroenterology and Digestive Endoscopy, Nuovo Regina Margherita Hospital, Via Manzoni 56, Rozzano, Rome, Italy
e-mail: alessandro.repici@humanitas.it

A. Zullo
Digestive Endoscopy Unit, Department of Gastroenterology, Instituto Clinico Humanitas, Milan, Italy

A. Anderloni • C. Hassan
Gastroenterology and Digestive Endoscopy, Nuovo Regina Margherita Hospital, Via Manzoni 56, Rozzano, Rome, Italy

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estimated that post-biopsy or post-polypectomy hemorrhage leading to hospitalization occurs in 4.8 per 1000 colonoscopies [12]. Bleeding-related hospitalization generates substantial costs that impact the cost-effectiveness profile of preventative endoscopic procedures [12, 13].

Procedure-related bleeding can be immediate (intra-procedural) or delayed (post-procedural). Measures to minimize the risk of procedure-related bleeding include adherence to guidelines regarding the periprocedural management of antithrombotic therapy [14, 15], as well as prophylactic application of endoscopic clips or loops to decrease the risk of delayed bleeding post-resection [16–19]. The application of effective hemostatic techniques intra-procedurally, such as clips [20, 21], argon plasma coagulation (APC) [21, 22], and monopolar coagulation forceps [23], has substantially reduced the incidence of delayed bleeding, even following the resection of large lesions [24, 25].

Procedure-Related Perforation

Perforation can occur in the midst of a diagnostic procedure, such as during retroflexion of the colonoscope in a small rectum; during difficult instrument traversal through a narrowed diverticular-filled sigmoid colon fixed by adhesions (Fig. 19.1) [26], following challenging deep enteroscopy maneuvers [27]; and during difficult endoscopic ultrasound (EUS) instrument passage through a narrowed and tortuous esophagus or duodenum [28]. Diagnostic-related perforations are mainly due to blunt force trauma or torque from the endoscope and tend to be larger in size (and more difficult to fix endoscopically) than therapeutic-related perforations, such as following EMR or ESD [26]. Although an iatrogenic perforation may be evident during the endoscopic procedure, it should be suspected in some cases where either the patient condition or technical complexity predisposes to a complication. The key determinant to successful closure and outcome is immediate recognition of the perforation, since the latter results in prompt intervention before egress of intraluminal contents occurs, leading to mediastinitis or peritonitis [11]. However, signs and symptoms of a perforation may be masked in certain circumstances, such as in the deeply sedated and elderly patient with multiple comorbidities, making a prompt diagnosis difficult [11].

As described below, several endoscopic devices are currently available that can be used either alone or in combination for closure of defects and perforations. These devices include through-the-scope (TTS) (Fig. 19.2) and over-the-scope (OTS) clips (Fig. 19.3), endoscopic suturing

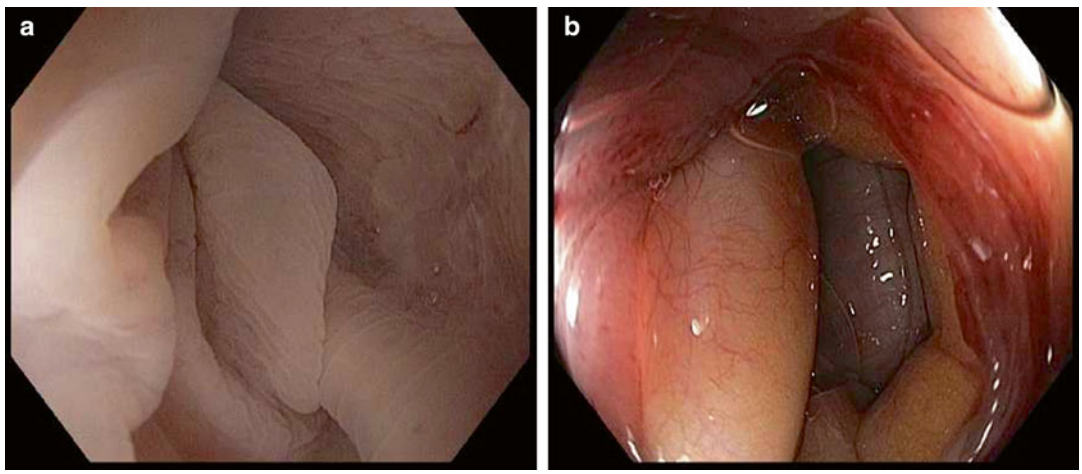

Fig. 19.1 Colonoscope insertion through a narrowed, angulated, and fixated sigmoid colon (**a**) resulting in a large perforation with visualization of intra-abdominal organs (**b**)

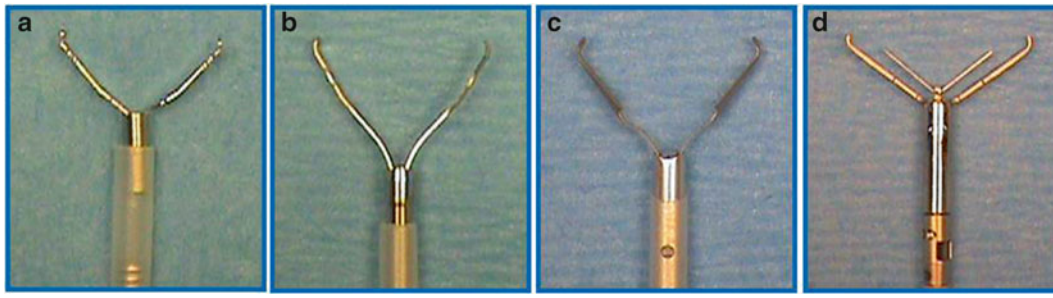

Fig. 19.2 Through-the-scope clips. (**a**) QuickClip2. (**b**) QuickClip Pro. (**c**) Resolution clip. (**d**) Instinct clip

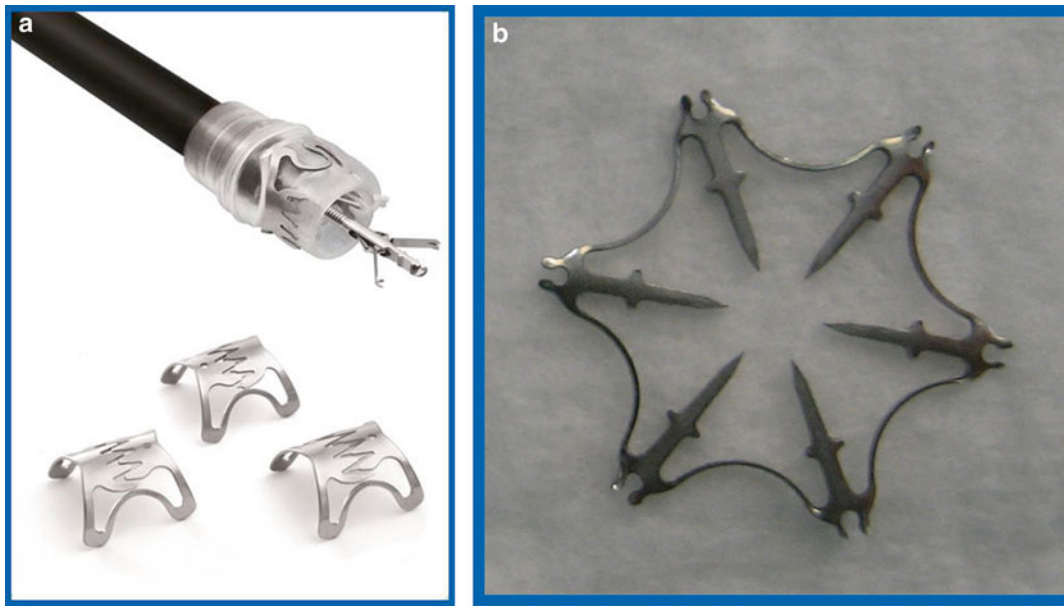

Fig. 19.3 Over-the-scope clipping devices. (**a**) Over-the-scope clip (OTSC™) system with a through-the-scope twin grasper device for lesion retraction (picture courtesy of Ovesco Endoscopy AG, Tubingen, Germany). (**b**) Padlock clip

(Fig. 19.4), and covered stents (Fig. 19.5) [29–32]. Some of these devices are a result of technical innovations in the field of natural orifice transluminal endoscopic surgery (NOTES). A working knowledge and appropriate use of these instruments, based in part on lesion location and features, are critical for the successful application of these devices. In some cases, needle decompression of tension pneumoperitoneum must be performed before endoscopic closure [33].

In addition to endoscopic repair, supportive measures, including nothing by mouth, intravenous fluids, tube feeding/parenteral nutrition, intravenous antibiotics, and continuous monitoring of the patient's status to determine the need for operative intervention, are essential.

Devices and Technical Considerations

Several endoscopic devices are available for the management of procedure-related bleeding and perforation. A good working knowledge of these devices is important for their safe and effective use.

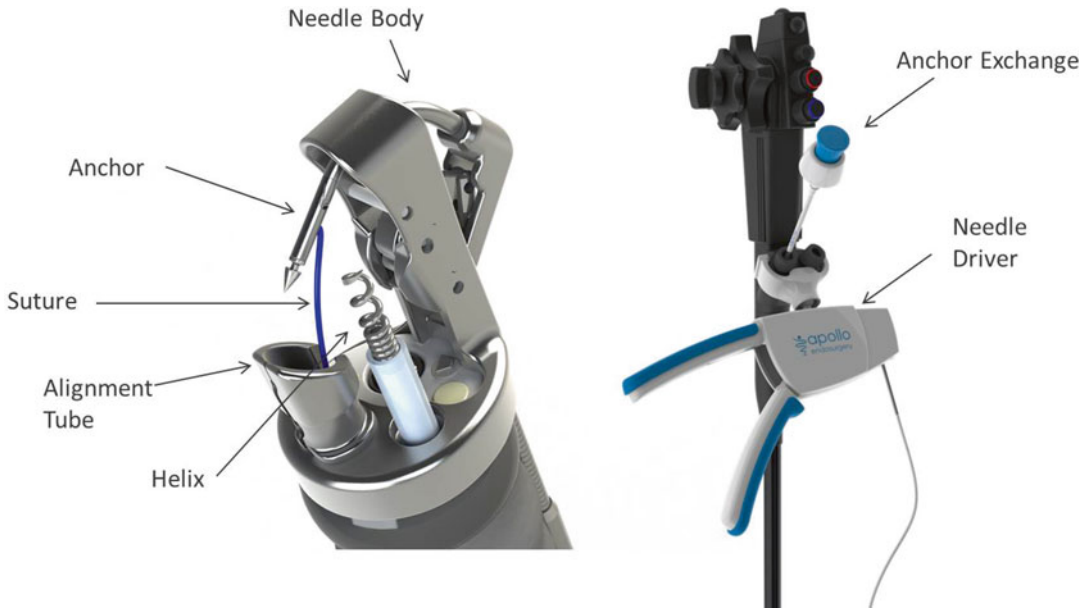

Fig. 19.4 OverStitch™ endoscopic suturing system (picture courtesy of Apollo Endosurgery, Austin, TX, USA)

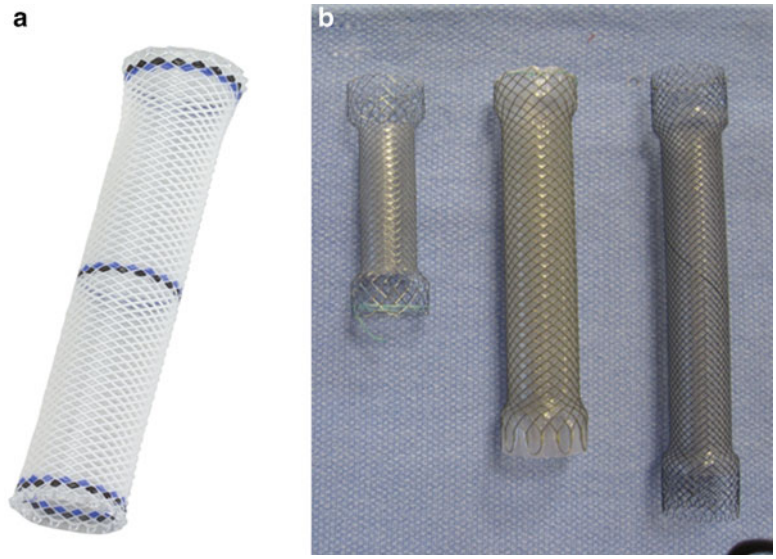

Fig. 19.5 (**a**) Covered self-expandable plastic stent. (**b**) Covered self-expandable metal stents

Procedure-Related Bleeding

Procedure-related bleeding that may require intervention more commonly follows endoscopic resection techniques, such as EMR and ESD. Biopsy and cold snare resection of small mucosal lesions is rarely associated with persistent intra-procedural (Fig. 19.6) or delayed bleeding that requires endoscopic therapy. An endoscope that is equipped with water-jet irrigation is very helpful for precise identification and therapy of the bleeding point.

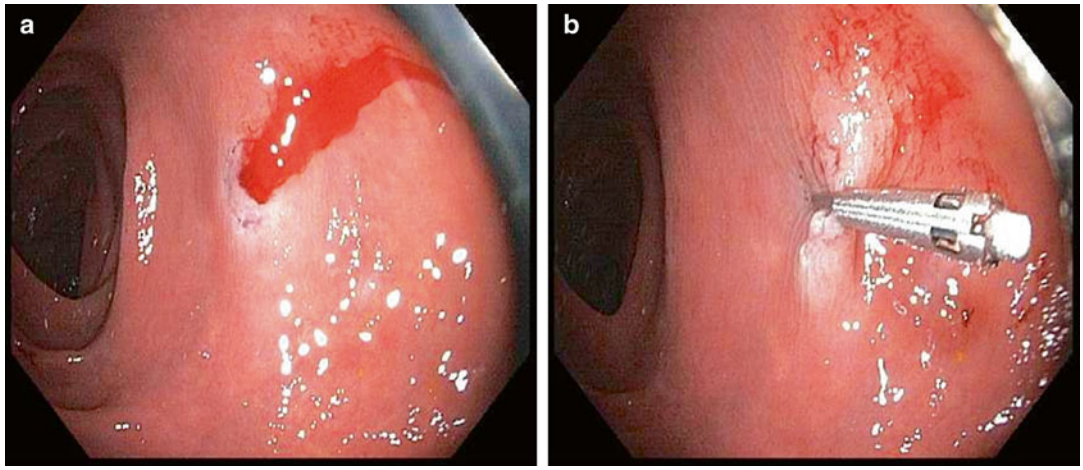

Fig. 19.6 (**a**) Intra-procedural persistent post-biopsy bleeding. (**b**) Hemostasis achieved with clip placement

Immediate Bleeding

Intra-procedural bleeding as a result of EMR or ESD can be managed by a variety of hemostatic techniques. Epinephrine injection in 1:10,000 dilution (or higher) can be injected in 1–2 ml aliquots to stop active bleeding, although it does not prevent delayed hemorrhage. If active bleeding occurs immediately after completion of lesion resection, placement of clips targeting the bleeding point is preferable to contact thermal coagulation (e.g., bipolar coagulation) since the former does not extend tissue injury. However, clip placement should be avoided if the EMR, for example, is not complete since the clips may interfere with subsequent resection of residual lesion and serve as a current conductor to deeper tissue layers during inadvertent snare wire contact with the clips. The selection of a particular TTS clip for hemostasis is primarily dependent upon device availability and operator preference since there are no prospective comparative trials demonstrating the superiority of one clip over another in the setting of intra-procedural iatrogenic bleeding. The use of a dedicated hemostatic forceps (Coagrasper, Olympus Corp., Tokyo, Japan) is ideal for hemorrhage that occurs in the midst of an EMR or ESD procedure. The technique involves grasping, tenting, and applying coagulation current for sealing of the vessel (Fig. 19.7). The suggested settings for the Coagrasper are a power of 50 W and 1–2 s pulse duration using a soft coagulation mode (Video 19.1).

Snare resection of a pedunculated polyp with a thick stalk can result in active bleeding, which can immediately be controlled by recapturing and constricting the stump with the snare for several minutes. If bleeding resumes upon loosening the snare, epinephrine can be injected within the stump to slow or stop bleeding, followed by definitive therapy. If feasible, mechanical hemostasis is preferable to avoid extending thermal injury. Clips can be used to close the end of the stump. A detachable snare is also an option if the length and location of the residual stump is suitable for loop placement. Occasionally, access to the stump is difficult for either clip or loop placement, and a contact thermal probe is used with light–moderate contact pressure of 3–5 s to achieve hemostasis, with suggested settings of 15 J for the heater probe and 12–15 W for the bipolar probe.

Delayed Bleeding

In patients who require endoscopic intervention for delayed post-polypectomy bleeding, assessment of the post-polypectomy ulcer site partly dictates the need for therapy, although the significance and rebleeding rates of stigmata of recent

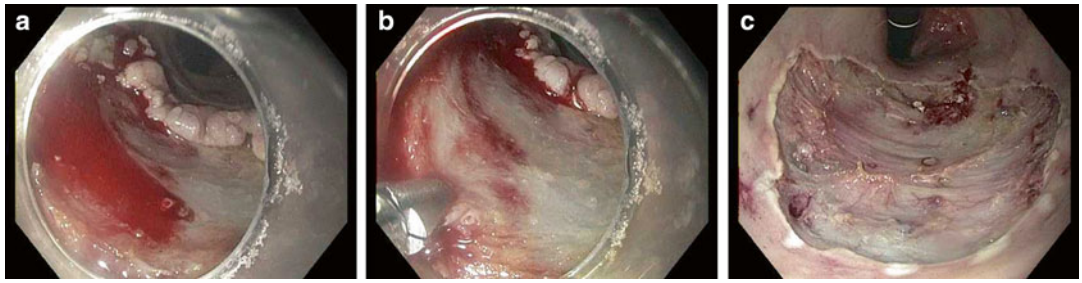

Fig. 19.7 (**a**) Active arterial bleeding during endoscopic resection of a large rectal lesion. (**b**) Visible vessel targeted using the monopolar coagulation grasping forceps (Coagrasper, Olympus Corp., Tokyo, Japan). (**c**) Hemostasis secured within the resection bed

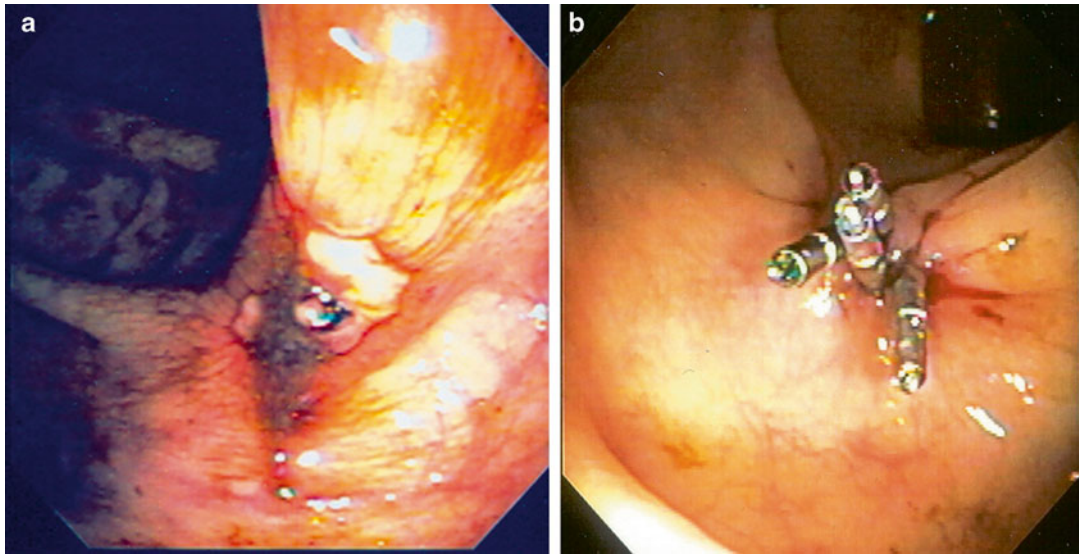

Fig. 19.8 (**a**) Delayed bleeding from post-polypectomy ulcer with visible vessel. (**b**) Hemostasis secured with clip placement

hemorrhage (SRH) within post-resection ulcers are not as well studied as SRH associated with bleeding peptic ulcers. Post-polypectomy ulcers with clean bases or flat pigmented spots are not generally treated, whereas endoscopic therapy is performed for post-polypectomy ulcers with non-bleeding visible vessels (Fig. 19.8), adherent clots, or active bleeding. Clip placement and contact (coaptive) coagulation, with or without epinephrine injection, are commonly used modalities for delayed post-polypectomy hemorrhage. However, TTS clips may be ineffective if the ulcer base is quite indurated due to insufficient clip closure force. Also, a bleeding vessel entrenched in a fibrotic ulcer base may not be amenable to Coagrasper coagulation. The indurated base, however, provides a safety cushion for the use of coaptive coagulation, such as a bipolar probe, which may be more suitable in this setting (Fig. 19.9). The over-the-scope clip (OTSC®, Ovesco Endoscopy AG, Tübingen, Germany) provides greater compression force and tissue capture than TTS clips (Video 19.2), although the use of this device requires endoscope removal to fit the OTSC, which may not be practical in some actively bleeding cases.

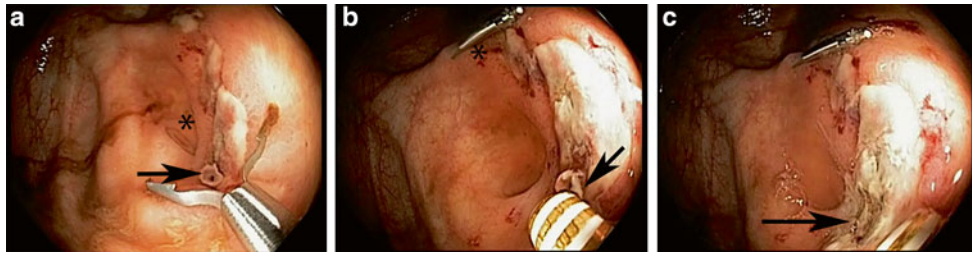

Fig. 19.9 (**a**) Delayed bleeding from post-polypectomy cecal ulcer with visible vessel (*arrow*) next to appendiceal orifice (*asterisk*). (**b**) Bipolar coagulation of visible vessel following failed attempt at clip placement (*asterisk*) due to indurated ulcer base. (**c**) Obliteration of visible vessel following bipolar coagulation (*arrow*)

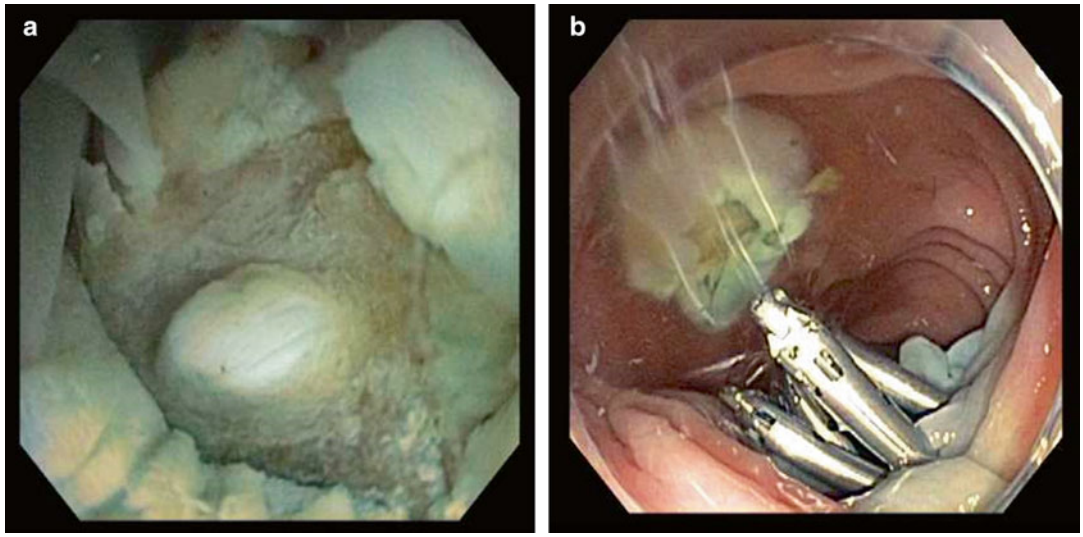

Fig. 19.10 (**a**) Target sign following endoscopic mucosal resection (EMR). (**b**) Clip closure of) EMR defect

The use of a hemostatic spray (Hemospray, Cook Medical Inc., Bloomington, Indiana, US) requires active bleeding, and its role in the management of delayed post-polypectomy bleeding is currently being defined.

Procedure-Related Perforation

A key determinant for a successful endoscopic outcome is intra-procedural recognition and attempted closure of the perforation, if technically feasible. If the perforation site is quite small and passes unrecognized, continuation of the procedure with liberal air insufflation may result in air under tension (e.g., tension pneumoperitoneum) requiring percutaneous needle decompression to relieve cardiorespiratory compromise. Once a perforation is recognized, CO_2 insufflation should be employed instead of air and its use should be minimized to curtail egress of gas and enteric contents outside the gut lumen.

After dye-assisted EMR, the target sign should be sought, which is characterized by concentric rings with an outer white ring (cauterization), a blue-stained submucosal connective tissue ring (due to submucosal injection of methylene blue or indigo carmine), and a central white-gray circular disk, which corresponds to injury to the muscularis propria and potential perforation (Fig. 19.10). A mirror target sign can also be seen on the cut surface of the resected

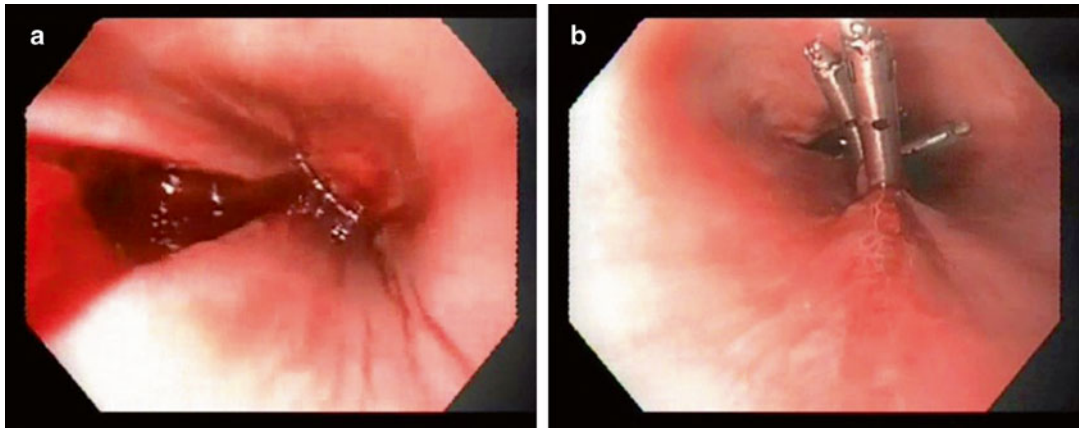

Fig. 19.11 (**a**) Iatrogenic linear esophageal perforation recognized intra-procedurally. (**b**) TTS clip closure of perforation in a zipper fashion

specimen. The target sign should be closed with placement of clips.

For obvious colonic perforations due to EMR or ESD, the decision between endoscopic versus operative repair is influenced by several factors, including size and location of the perforation, status of colon prep, the presence or absence of extraluminal egress of colonic contents, unresected pathology (i.e., incomplete EMR/ESD), clinical stability of the patient, available devices, and operator expertise. Surgical intervention is indicated in the setting of a large perforation, gross extraluminal spillage, residual lesion, and clinical deterioration on conservative management. Endoscopic closure can be considered for readily accessible perforations <1–2 cm in size.

TTS clips are the most commonly used devices for closure of EMR and ESD perforations and are generally successful at closing linear perforations <2 cm in size (Fig. 19.11). The clips are placed in a zipper fashion and controlled suction helps in capturing the margins of the perforation between the opened prongs of the clip prior to closure and deployment. Successful TTS clip application requires familiarity with the chosen device and coordination between the endoscopist and assistant handling the clip. In some cases where the perforation is large, the omental patch method may be effective, if technically feasible. This involves pulling omental fat through the defect into the lumen, followed by clip anchoring of the fat pad to the mucosa.

TTS clips may not provide secure sealing of large, gaping perforations, and in this regard the OTSC may be a better alternative as it is capable of grasping more tissue and applying greater compression force for full-thickness closure (Fig. 19.12). Furthermore, dedicated TTS grasping devices, such as the twin grasper, can be used to grasp and pull the opposite margins of the perforated defect into the OTSC cap prior to clip deployment (Video 19.3). Controlled suction during OTSC placement is advised to minimize the risk of extraluminal tissue or organ entrapment into the OTSC cap. Although the setup and deployment are similar to that of a variceal band ligator, limitations of the OTSC include the need to withdraw the endoscope for device loading, as well as the potential difficulty in maneuvering the device through a narrowed and angulated lumen (e.g., sigmoid colon), and failure to reidentify the perforation site. The latter can be avoided by placing a tattoo or TTS clip on the opposite wall of the perforation prior to scope withdrawal.

Endoscopic suturing of certain luminal perforations is feasible, with one endoscopic suturing device (OverStitch™, Apollo Endosurgery, Austin, Texas, USA) currently available on the market. This particular suturing system requires a specific double-channel upper endoscope (GIF

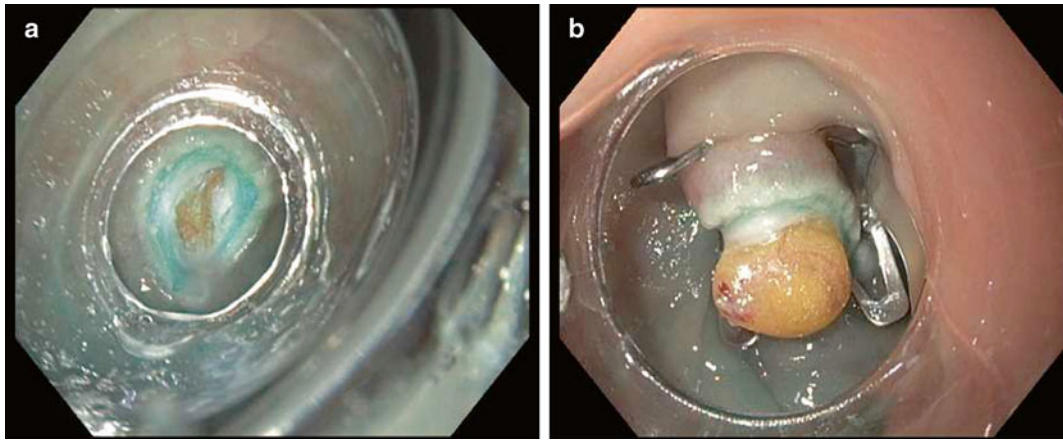

Fig. 19.12 (**a**) Perforation following cap-assisted EMR in the rectum. (**b**) Over-the-scope clip closure of the perforated site

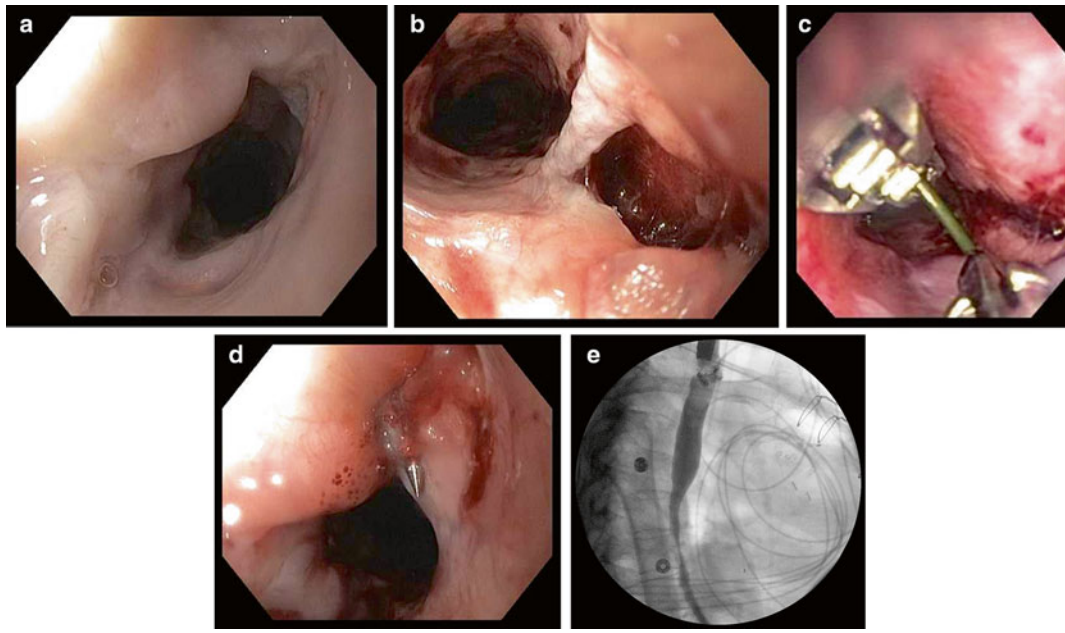

Fig. 19.13 (**a**) Esophageal stricture. (**b**) Dilation-induced perforation. (**c**) OverStitch™ suturing system in the esophagus for perforation closure. (**d**) Appearance following suture closure of perforation. (**e**) The absence of fluoroscopic contrast extravasation at the site of endoscopic repair of perforation

2 T160 or GIF2TH-180, Olympus Corp., Tokyo, Japan) and allows placement of interrupted or running stitches for full-thickness closure (Fig. 19.13). Device limitations include the inability to treat lesions beyond the reach of the upper endoscope and accessibility issues. Locations that are relatively accessible for endoscopic suturing include the esophagus, distal stomach, and rectum. Experience with regard to this system is accumulating.

With regard to esophageal perforation, endoscopic management is limited when the perforation is situated in a hypopharyngeal or high cervical esophageal location. Conservative management in

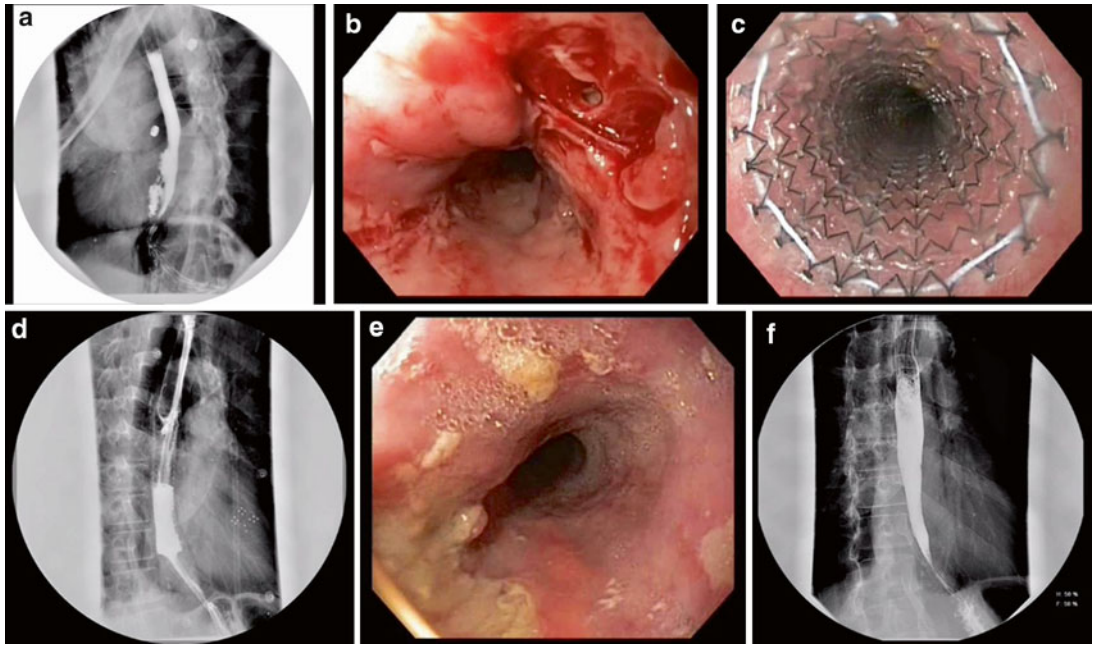

Fig. 19.14 (**a**) Dilation of esophageal stricture resulting in perforation with fluoroscopic contrast extravasation. (**b**) Disrupted esophageal wall with visualization of perforation site. (**c**) Placement of a fully covered self-expandable metal stent. (**d**) Successful sealing of perforation site without contrast extravasation and nasogastric tube placement. (**e**) Stent removal at 4 weeks with healing of perforation site. (**f**) Contrast esophagram confirming healed perforation site

this setting is generally sufficient, though ongoing cervical leaks can be managed by neck incision and drainage, with primary surgical repair as appropriate. Thoracoabdominal esophageal perforations that are recognized intra-procedurally or within hours post-procedure may be amenable to endoscopic closure and/or diversion. Endoscopic clips can effectively close fresh esophageal perforations that are <2 cm in size, whereas larger perforations can be sealed by temporary placement of covered self-expandable plastic (SEPS) or metal stents (SEMS), with or without defect approximation with endoscopic suturing. Stents are also preferable for sealing iatrogenic perforations and palliation of dysphagia in patients with non-operable malignant esophageal obstruction. Stents are not appropriate for very large gaping perforations (>6 cm), for perforations in a high cervical esophageal location, and in the setting of near-complete anastomotic dehiscence or necrosis of the gastric conduit. Also, a dilated esophageal lumen (>3 cm luminal diameter), as can be seen in achalasia, for example, will not allow adequate sealing of the stent against the esophageal wall.

If stent placement is entertained, the selected stent should be of sufficient diameter and length to provide adequate sealing between the stent and esophageal wall and bridge the perforation for at least 2–3 cm above and below the site (Fig. 19.14 and Video 19.4). Smaller diameter stents are generally used for proximal esophageal perforations due to a narrower esophageal lumen and to minimize the risk of stent-induced tracheoesophageal fistula. Larger diameter stents are used in the mid and distal esophagus, especially if there is no shelf or stricture to anchor the stent. Although fully covered stents are preferred, stent migration is problematic when the device is placed across the gastroesophageal junction, though stent fixation techniques, such as endoscopic suturing, have reduced the risk of migration in this setting (Video 19.5). The alternative is to place a partially covered SEMS so that the uncovered flanges of the stent embed into tissue to minimize its migration. The partially covered SEMS can be

removed using the stent-in-stent technique by placing a fully covered SEMS through the indwelling stent to cause pressure necrosis of tissue ingrowth at the uncovered flanges of the partially covered SEMS. This technique facilitates removal of both stents in one procedure 1–2 weeks later.

Once the stent is placed, the ideal dwell time is unknown and ranges from 4 to 12 weeks. Partially covered SEMS should be removed within 4–6 weeks and may necessitate the stent-in-stent technique, whereas plastic and fully covered stents can be left in place for a longer time period.

Site-Specific Adverse Events and Outcomes

Esophagus

Perforation

Esophageal perforation is associated with significant morbidity and mortality, especially when management is delayed for >24 h [34, 35]. In one systematic review, esophageal perforation occurred in 56/3071 (1.8 %) patients with achalasia who underwent pneumatic balloon dilation, with an incidence rate ranging from 0 % to 5.4 % [36]. Recent data suggest that dilation is effective and relatively safe for the treatment of strictures associated with eosinophilic esophagitis. A meta-analysis involving 525 patients and a total of 992 dilations showed that perforation occurred in 3 patients only (0.3 %; 95 % CI: 0–0.9 %) [37].

Endoscopic clips are generally successful at closing esophageal perforations [38], particularly when the perforation size is <1 cm [30]. Unlike chronic fistulas, acute esophageal perforations generally heal with clip closure alone within 1 week. For larger perforations, SEMS is a potential option. In general, larger diameter (23–28 mm) covered SEMS are employed particularly when there is not a stricture of shelf to anchor the stent [39]. As previously mentioned, achalasia patients with a dilated esophagus (diameter >3 cm) may not benefit from stent placement due to the lack of adequate sealing between the stent and the esophageal wall [40]. In one retrospective study, esophageal leaks and perforations were closed in 77.6 % of cases using SEMS [39]. A partially covered SEMS may be placed to seal an esophageal perforation, especially when the stent crosses the gastroesophageal junction, to minimize the risk of stent migration. However, utilization of a partially covered SEMS may be hampered by tissue ingrowth and embedment at the uncovered flanges of the stent, requiring the stent-in-stent technique for its eventual removal [39]. As discussed above, a more attractive alternative is to place a fully covered SEMS with endoscopic suture fixation of the stent to the esophageal wall to prevent its migration (Fig. 19.15). One prospective study of 33 patients with esophageal perforation, including 19 iatrogenic perforations, found that temporary placement of SEMS of different types was successful in as many as 97 % of cases [41]. Of note, stent extraction was uneventful in all cases when performed within 6 weeks of insertion, whereas stent extraction was complicated in 50 % of cases when it was performed after 6 weeks [41]. It is suggested, therefore, that the stent dwell time should be less than 6 weeks. Stent migration ranges from 11.1 % to 33 % among various studies and, therefore, ongoing patient monitoring is required for signs of stent migration following placement [39–42].

In addition to EMR or ESD, endoscopic submucosal tunnel dissection (ESTD) has been pioneered for en bloc excision of larger lesions (>5 cm) [4, 43]. These advanced resection techniques may result in esophageal perforation, although such a complication can be managed successfully in the hands of a skilled endoscopist without resorting to surgery. It has been suggested that perforation is to be expected (or even sometimes intended) with these enhanced resection techniques, and it should not simply be considered as an adverse event in a controlled setting [30]. In one study of 306 ESD and 171 EMR performed to remove esophageal neoplasms in 368 patients, esophageal perforations occurred in 7 (1.9 %) cases. All perforated patients were male and had undergone ESD, while no perforation occurred in the EMR group [44]. Perforations

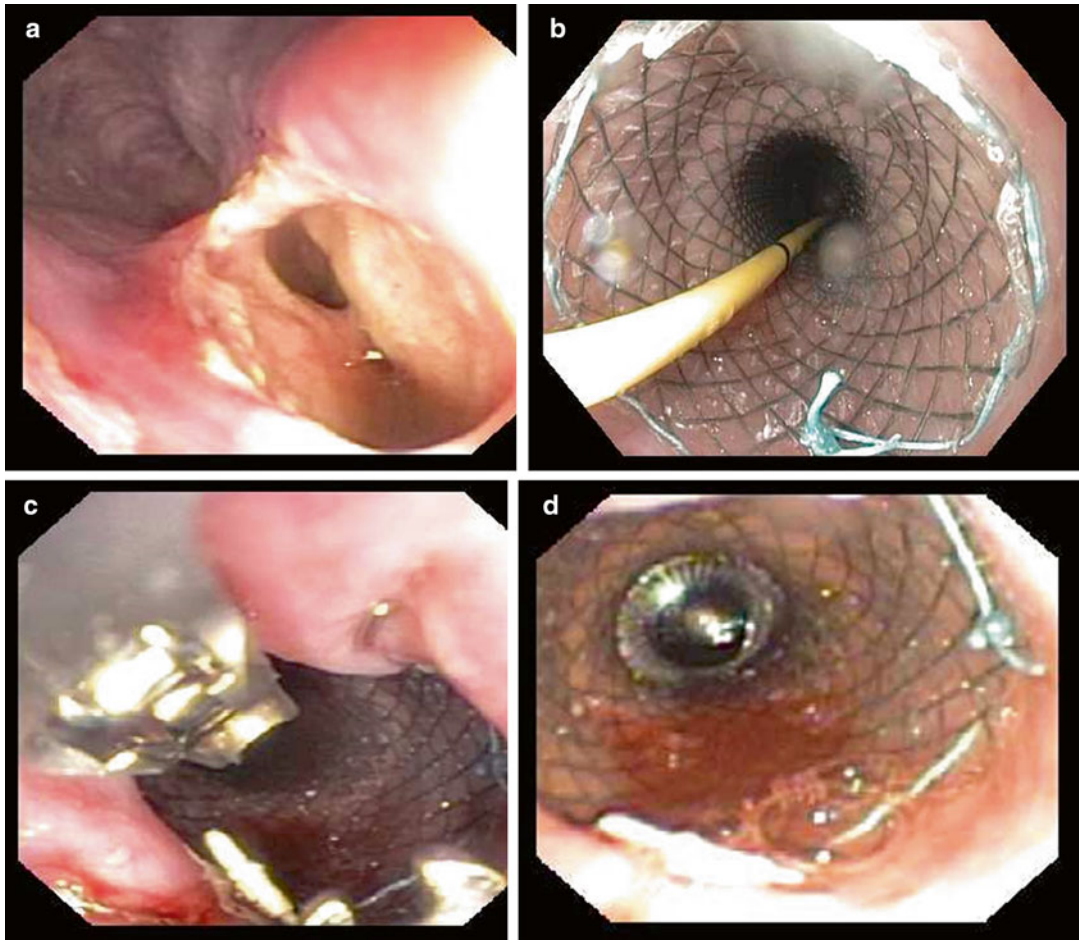

Fig. 19.15 (**a**) Dilation-induced esophageal perforation. (**b**) Fully covered self-expandable stent placement. (**c**) Stent fixation using the OverStitch™ suturing system. (**d**) Anchored stent to the esophageal wall

occurred intra-procedurally in 3 cases, after stricture dilatation in another 3, and due to food bolus impaction in the remaining patient [44]. In another study, perforations occurred in 4/58 (6.9 %) patients during ESD and was successfully managed conservatively following perforation closure with endoscopic clips [38, 45].

The incidence of perforation was higher following ESD for Barrett's-associated adenocarcinoma (20 %; $n=25$) compared to either esophagogastric junction (2.9 %; $n=103$) or non-junction squamous cancers (2.7 %; $n=1335$) [46]. In contrast, two studies found no perforations following EMR performed in 102 patients [47] and following 2513 EMR procedures in 681 patients with neoplastic appearing lesions in Barrett's esophagus [48]. In another study, perforations occurred in only 3/185 (1.6 %) patients, which were successfully managed with clips [45].

Pneumomediastinum without overt perforation may occur after esophageal EMR and ESD, with an incidence of 6 % and 10 %, respectively [47, 49]. In a study where systematic radiographic imaging was performed in 58 patients who underwent esophageal ESD, mediastinal emphysema was detected in 18 (31 %) patients by chest CT as opposed to only 1 (1.7 %) patient by chest x-ray. The ESD-induced exposure of the muscularis propria ($n=32$) was the only significant risk factor [50]. In all the reported cases, pneumomediastinum promptly regressed with conservative treatment alone [47, 49, 50].

Bleeding

Although post-procedural bleeding in the esophagus is mainly attributed to endoscopic resection of Barrett's esophagus or squamous cell dysplasia/early carcinoma, the risk appears to be small without an overall significant impact on patient outcome or procedural safety [51–53]. In an early series of 216 EMR for dysplastic Barrett's esophagus [53], the risk of post-EMR bleeding occurred in 1 % of patients, which was successfully managed endoscopically in all cases. In a larger series encompassing 1060 resections in Barrett's patients, the overall risk of delayed bleeding was 2.1 %, which was also effectively managed endoscopically. The same risk has been observed during the learning curve of this procedure with less experienced endoscopists [54]. EMR of squamous dysplasia or early carcinoma appears to carry a lesser risk of bleeding than Barrett's lesions [55, 56]. ESD is extensively used for the treatment of squamous cell carcinoma, especially in Asia. ESD does not appear to result in a greater risk of post-procedural bleeding relative to EMR [49, 57–59]. The same appears to be true with regard to ESD for Barrett's esophagus based on a small series [60].

Stomach

Perforation

Endoscopic TTS or OTS clip approximation and closure of small gastric perforations (<2 cm) secondary to EMR or ESD are generally effective. For large perforations, the omental patch method should be considered [29]. Alternatively, endoscopic suturing may be an option if the device is available and the defect readily accessible.

In a large single-center Japanese series, perforation occurred in 121/2460 (4.9 %) cases who underwent gastric EMR [61]. The first 4 patients were treated with emergent surgery and the subsequent 117 patients were treated with endoscopic clips. The latter treatment was successful in 115 (98.3 %) patients, and salvage surgery was required in 2 patients due to failed endoscopic closure [61]. In another study [29], a gastric perforation was encountered in 7/789 (0.88 %) patients following EMR, with the defect diameter ranging from 4 to 25 mm. These cases were successfully managed with clips (range 3 to 11), with the addition of an omental patch in the patient with the largest perforation.

A systematic review encompassing12 studies and 3806 gastric lesions evaluated the safety of ESD compared with EMR for the resection of early gastric cancers [62]. A significantly higher perforation rate occurred in the ESD group (4.54 %) compared with the EMR group (1.03 %), with an estimated increased risk of 3.58 (95 % CI: 1.95–6.55). The perforation rate did not significantly differ according to the type of ESD knife used. In those who perforated, surgical intervention was required more frequently in the ESD group (11.7 %) than in the EMR group (6.2 %), although the difference was not statistically significant [62].

Risk factors for ESD-related perforation were assessed in a large single-center study involving 1123 lesions [63]. Perforation occurred during ESD of 27 (2.4 %) lesions, and resection of lesions in the proximal stomach was the only significant risk factor (OR 4.88, 95 % CI: 2.21–10.75) on multivariate analysis. Surgical intervention was needed in one patient 5 days after an ESD-associated perforation due to dehiscence of the defect despite initial successful closure with endoscopic clips [64].

Both EMR and ESD procedures have been found to be relatively safe even in cirrhotic and elderly patients [8, 9]. In one systematic study, perforation occurred in only 1 (1.6 %) of 68 cirrhotic patients with gastric neoplastic lesions removed by ESD, which was successfully treated with endoscopic clips [8]. A comparative study found that post-ESD perforation rate was not increased in the elderly (14/372; 3.8 %) relative to non-elderly patients (4/143; 2.8 %) patients [9]. However, in those who perforated, emergency surgery was required in 14.3 % of elderly patients as opposed to none in the non-elderly group.

Bleeding

Similar to the esophagus, EMR and ESD of gastric lesions are the most frequent causes of

post-procedural bleeding. A systematic review of 12 studies involving 3806 early gastric cancers compared the efficacy and safety of ESD ($n=1734$) to EMR ($n=2072$) [62]. The overall bleeding rate was 7 % for both procedures, though the rate of immediate bleeding was over twofold higher in the ESD group compared to the EMR group. On the other hand, the delayed bleeding risk was slightly lower in the ESD group, but the difference was not statistically significant. None of the patients in the ESD group underwent surgery due to delayed bleeding. A similar risk profile for post-procedural bleeding was noted in another meta-analysis study [65]. In cirrhotic patients, post-ESD bleeding occurred in 8/61 (13.1 %) patients, with successful endoscopic treatment in all cases [8]. This data support similar previous findings with regard to ESD for early gastric cancer in the setting of liver disease [66–68].

In one retrospective analysis of 1123 ESD procedures for early gastric neoplasms, the only predictors for increased risk of delayed bleeding were age ≥80 years and long procedure times. Gender, comorbidities, lesion location and characteristics, and operator experience were not found to be risk factors. Of note, the rate of residual disease or recurrence after ESD appears to be higher in resected lesions with delayed bleeding than in those without [63]. In contrast to the above study, two studies involving 478 and 1000 ESD procedures revealed that lesion size was a strong predictor of delayed bleeding [69, 70]. Although prophylactic coagulation of submucosal visible vessels within the ESD defect reduces the risk of delayed bleeding by twofold, post-ESD bleeding risk does not appear to be increased by the concomitant use of antiplatelet drugs [71] or decreased by the pre-procedural administration of proton pump inhibitors [72].

With regard to predictive factors for post-EMR bleeding in the stomach, age, size of the lesion, experience of the endoscopist [73], and intra-procedural bleeding [74] were associated with the risk of delayed bleeding.

Although there are no studies that specifically assess the comparative efficacy and safety of various hemostatic procedures after EMR/ESD of gastric lesions, most reported studies describe a similar approach to prevent post-procedural bleeding [75]. As previously mentioned, the use of clips during ongoing ESD is not recommended since the clips may interfere with subsequent dissection. On the other hand, clips may be useful to prevent delayed bleeding from visible vessels within the post-ESD defect. More often, the monopolar coagulation forceps (Coagrasper) is used during and immediately after the ESD procedure to prophylactically seal non-bleeding visible vessels or treat actively bleeding vessels.

Colon

Perforation

Colonic perforation may occur following either diagnostic or therapeutic colonoscopy, such as balloon dilation, simple polypectomy, EMR, and ESD. The incidence of colon perforation during diagnostic colonoscopy ranges from 0.03 % to 0.8 %. The incidence is higher (0.1–1.1 %) following therapeutic maneuvers, such as large polyp resections [10, 26, 76]. Perforations that occur as a result of diagnostic maneuvers tend to be large (>2 cm) and are mainly localized in the rectosigmoid colon. In contrast, perforations due to therapeutic procedures, such as argon plasma coagulation and hot snare electrosurgery, tend to be smaller in size (~0.9 cm) and depend on both the type and duration of electrosurgical current employed [26, 76]. The depth and extent of tissue injury during polypectomy increases the risk of perforation [77].

In a pooled study of 4 trials, perforation following standard snare resection occurred in 53/31,516 (0.17 %) polypectomies [78]. Perforation is more likely to develop following resection of polyps >1 cm in size in the right colon or >2 cm in size in the left colon or when multiple polyps are removed [76, 79].

Perforation occurs more frequently with EMR and ESD procedures relative to standard snare polypectomy [79]. The perforation rate ranges from 0 % to 5 % for colonic EMR [80]. A systematic review on colonic ESD performed in Japan

between 2007 and 2011 showed that perforations occurred in 127/2719 (4.7 %) patients, with an incidence rate ranging from 1.8 % to 8.2 % [81]. The rates for immediate and delayed perforations were 3.3–14.0 % and 0.4–0.7 %, respectively, in 11,512 procedures in which learning curve data were included [81].

Balloon dilation of strictures related to Crohn's disease may result in perforation, particularly at the site of prior anastomoses. In one systematic review, dilation-related perforation occurred in 13/347 (2 %) patients [82].

Immediately recognized colonic perforations <1–2 cm in size may be managed successfully at endoscopy using clips, with or without loop placement [30, 83]. In one study, the target sign occurred in 10/425 (2 %) patients after EMR, which was successfully managed with placement of TTS clips [84]. When accessible, the OTS clip is another useful device to repair colonic perforations [31]. A study of 14 patients showed that colonic perforations up to 30 mm in diameter can be successfully managed with OTS clip placement [85]. If the OTS clip is not suitable or available, placement of closely stacked TTS clips in a zipper fashion may be an option in select cases for closure of large defects, as evidenced by closure of a large 3 cm colonic perforation [86]. Endoscopic closure of promptly recognized colonic perforations significantly reduces the hospitalization length relative to surgery (3.5 vs. 12.2 days) [87].

Bleeding

Post-polypectomy bleeding represents by far the most frequent adverse event in countries with well-established screening colonoscopy programs. A retrospective analysis of hospital admissions within 30 days of colonoscopy estimated a post-polypectomy bleeding risk of 4.8 per 1000 colonoscopies [12]. This is in line with reports from previous clinical series [88–91] and a recent epidemiological survey [92]. In the Munich Polypectomy Study, the risk of major bleeding was 1.6 % in more than 4000 colonoscopies with snare polypectomies.

The risk of delayed post-polypectomy hemorrhage correlates with polyp size [93] [94]. In another study, polyp size and location were independent risk factors for delayed bleeding. The risk increased by 13 % for every 1 mm increase in polyp diameter, and polyps located in the right colon had an odds ratio (OR) of 4.7 for this event [95]. These findings were confirmed by another similar case–control study [96]. When the analysis was limited to polyps >10 mm, polyp size ≥14 mm and the presence of villous architecture or high-grade dysplasia emerged as the main predictors of post-polypectomy bleeding in a multivariate analysis involving 1894 patients [97]. In a series of 302 EMR of large lateral spreading tumors (LST), age, right colon location, and the use of aspirin were independent predictors of post-procedural bleeding [98]. A prospective analysis of 1172 patients undergoing EMR of sessile polyps >20 mm revealed that immediate bleeding is associated with larger lesions, lesion histology, and Paris classification of type 0-IIa + Is, while delayed bleeding is associated with occurrence of immediate bleeding and lesion location in the proximal colon [99].

The relation between post-polypectomy bleeding and the use of antiplatelet drugs has also been evaluated. A case–control study excluded aspirin in increasing the bleeding risk [89]. A retrospective cohort study on 1174 polypectomies also showed a lack of association between post-polypectomy bleeding and nonsteroidal anti-inflammatory agents (NSAIDs) [100], as did another retrospective series [101]. However, concomitant therapy with clopidogrel and aspirin or other NSAIDs has been associated with a small but significant increase in the risk of post-polypectomy bleeding [102].

The use of prophylactic clip placement for prevention of delayed post-polypectomy bleeding is controversial. In a randomized controlled trial, clip closure of polypectomy sites was not associated with a reduced risk of bleeding when compared with a no-clip strategy, although the mean size of the resected polyps was relatively small in both groups [103]. In contrast, a larger historical cohort study that included 524 colorectal lesions

≥2 cm in size showed that the no-clipping strategy was strongly associated with delayed bleeding on multivariate analysis [16]. In a randomized study that included 561 polyps >10 mm in size, prophylactic submucosal injection of dilute epinephrine did not provide any additional advantage over saline injection alone for the prevention of post-polypectomy bleeding [104]. However, a randomized trial involving large pedunculated polyps showed that either epinephrine injection in the polyp stalk or placement of a detachable snare significantly reduced the risk of post-polypectomy bleeding [19]. Similarly, in a randomized trial involving 159 patients, the combination of detachable snare and epinephrine significantly reduced the risk of post-polypectomy bleeding [18]. The efficacy of such combination therapy was further confirmed in a small randomized trial encompassing 64 patients [17]. Prophylactic coagulation of non-bleeding visible vessels in post-resection defects did not decrease delayed post-polypectomy bleeding, however [105].

Endoscopic hemostasis of delayed post-polypectomy bleeding can be achieved with a variety of modalities, including epinephrine injection, thermal coagulation, clip placement, or a combination thereof [106, 107]. When feasible, clip or loop placement is preferred since these devices do not extend tissue injury [20]. In a study of 196 patients undergoing EMR for lesions >20 mm, the safety and efficacy of the snare tip soft coagulation (STSC) technique to control bleeding were tested. STSC achieved effective hemostasis in 40/44 (91 %) cases of bleeding, while no STSC-related adverse events occurred [108].

Summary

The endoscopist will inevitably face procedure-related adverse events, namely, bleeding and perforation, in his or her practice. A variety of endoscopic tools are currently available for the safe and effective management of procedure-related bleeding, as well as perforation, in most cases. These devices primarily include TTS and OTS clips, endoscopic suturing, and self-expandable covered stents. Early recognition of the adverse event, particularly perforation, is essential for a good clinical outcome. Device availability, operator familiarity with particular technique(s), identification of lesions suitable for endoscopic intervention, excellent supportive care, and provision of care in the context of a multidisciplinary approach are key determinants for a successful outcome.

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Index

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