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DE MEDICINĂ ŞI FARMACIE
„VICTOR BABEŞ“ DIN TIMIŞOARA

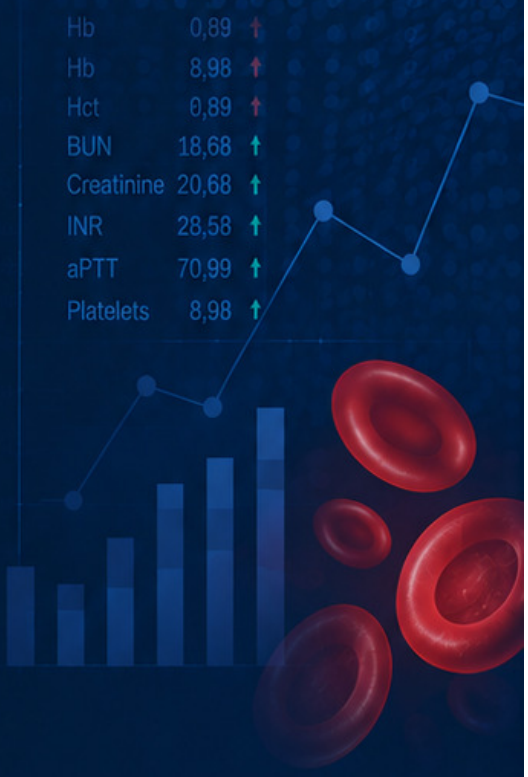
Clinical and Biochemical Differences in Patients with Non-Variceal Upper Gastrointestinal Bleeding

Associated with NSAIDs, Oral Anticoagulants, and Antiplatelet Therapy

NSAIDs

ORAL ANTICOAGULANTS

ANTIPLATELET THERAPY



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Preface

Upper gastrointestinal bleeding remains one of the most urgent and challenging conditions encountered in clinical practice, requiring rapid assessment, precise diagnosis and coordinated multidisciplinary management. Among its various etiologies, non-variceal upper gastrointestinal bleeding continues to represent a substantial proportion of cases, with significant implications for patient morbidity, mortality, and healthcare resource utilization.

In recent decades, the widespread use of nonsteroidal anti-inflammatory drugs, oral anticoagulants, and antiplatelet agents has transformed the therapeutic landscape for many chronic conditions, including cardiovascular disease, inflammatory disorders, and thromboembolic prevention. While these medications have undoubtedly improved patient outcomes in their respective domains, they have also introduced new complexities in the pathogenesis, presentation, and management of gastrointestinal bleeding.

This book aims to explore the clinical and biochemical differences observed in patients with non-variceal upper gastrointestinal bleeding associated with these commonly prescribed drug classes. By examining variations in patient profiles, laboratory findings, endoscopic characteristics, and outcomes, we seek to provide a deeper understanding of how pharmacological factors influence disease expression and progression. Such insights are essential for improving risk stratification, guiding therapeutic decisions, and ultimately enhancing patient care.

The content presented herein is grounded in current clinical evidence and supported by biochemical analysis, offering a comprehensive perspective that bridges bedside observation with laboratory investigation. Particular attention is given to the interplay between drug mechanisms—such as platelet inhibition, anticoagulation pathways, and mucosal injury—and their clinical consequences.

This work is intended for clinicians, researchers, and students in gastroenterology, internal medicine, emergency medicine, and related fields. It is our hope that the material will not only inform but also stimulate further research and discussion in this evolving area of medicine.

As the use of these medications continues to expand, understanding their impact on gastrointestinal pathology becomes increasingly critical. Through this book, we aspire to contribute meaningfully to that understanding and to support the ongoing effort to balance therapeutic benefit with patient safety.

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Chapter 1: Foundations of Upper Gastrointestinal Bleeding

Roxana Buzaş, Nilima Rajpal Kundnani, Vlad-Sabin Ivan, Daniel Lighezan

1.1. Definition of Upper Gastrointestinal Bleeding (UGIB)

Upper gastrointestinal bleeding (UGIB) is classically defined as hemorrhage originating from a source proximal to the ligament of Treitz that represents the anatomical landmark of separation between duodenum and jejunum and demarcates the upper from the lower gastrointestinal tract (1). This anatomical definition remains clinically relevant because it guides the diagnostic approach, including the use of esophagogastroduodenoscopy as the first-line investigation in suspected cases (2). From a clinical perspective, UGIB encompasses a broad spectrum of presentations, from occult bleeding that can be detected only through laboratory abnormalities to overt and massive hemorrhage associated with hemodynamic instability (3). Hematemesis, melena, or both, are the thypical manifestation of UGIB whereas occult bleeding may present with iron deficiency anemia or positive fecal occult blood tests in the absence of visible bleeding (4). The variability in presentation reflects differences in bleeding rate, location, and duration, as well as patient-specific factors such as comorbidities and physiological reserve (5).

UGIB is not a single disease entity but rather a syndrome resulting from diverse pathological processes affecting the upper gastrointestinal tract (6). The most common etiologies include erosive gastritis, peptic ulcer disease, esophagitis, vascular malformations such as angiodysplasia, and mucosal tears such as Mallory–Weiss syndrome (7). Causes that are less frequent include neoplasms, Dieulafoy lesions, and iatrogenic injury secondary to endoscopic or surgical procedures (8). Of all these causes, peptic ulcer disease remains the leading cause of UGIB globally, accounting for a substantial proportion of cases despite a declining incidence in regions with widespread eradication of *Helicobacter pylori* (9).

Over time, the definition of UGIB has evolved in order to incorporate anatomical and also functional considerations. While the anatomical definition remains the cornerstone, modern clinical practice increasingly emphasizes pathophysiological and clinical severity-based definitions, particularly in the context of risk stratification and management (10). For example, UGIB may be categorized based on severity into minor, moderate, and severe bleeding depending on parameters such as hemoglobin drop, transfusion requirements, and

hemodynamic status (11). This functional approach is essential for guiding clinical decision-making and prioritizing resource allocation in acute care settings (12).

UGIB can manifest in two different ways: as an overt or obscure bleeding. Overt bleeding is characterized by signs that are visible such as hematemesis or melena, whereas obscure bleeding refers to a bleeding that can be recurrent or persistent without an identifiable source after initial endoscopic evaluation (13). Although obscure bleeding is less common, it presents a real diagnostic challenge and may require advanced imaging techniques or capsule endoscopy for localization (14).

The clinical manifestations of UGIB are closely linked to the underlying pathophysiology of bleeding and the rate of blood loss. Hematemesis, defined as the vomiting of fresh red blood or coffee-ground material, indicates bleeding proximal to the ligament of Treitz and often reflects active or recent hemorrhage (15). Melena is characterized by black, tarry stools, results from the digestion of blood as it passes through the gastrointestinal tract and typically indicates bleeding that has slowed (16). In cases of massive and rapid bleeding, hematochezia may occur, although this is more commonly associated with lower gastrointestinal bleeding.

Hemodynamic instability is a critical aspect of UGIB and reflects the severity of blood loss. Patients may present with tachycardia, hypotension, orthostatic changes, and signs of hypovolemic shock in severe cases (2). The presence of hemodynamic compromise is associated with increased mortality and necessitates urgent resuscitation and intervention (17). Laboratory findings such as decreased hemoglobin levels and elevated blood urea nitrogen may provide additional clues to the severity and chronicity of bleeding (18).

At the molecular and physiological level, UGIB results from disruption of the balance between mucosal protective mechanisms and injurious factors within the gastrointestinal tract (19). A complex system that includes mucus and bicarbonate secretion but also epithelial integrity, adequate mucosal blood flow and prostaglandin-mediated defense mechanisms has the role of protecting the gastric mucosa (20). Disruption of these protective factors, whether due to endogenous processes such as acid-peptic activity or exogenous influences such as medications, can lead to mucosal injury and subsequent bleeding (21).

The concept of UGIB as a dynamic process rather than a static event is increasingly recognized in contemporary literature. Bleeding may be intermittent, recurrent, or continuous, and its clinical course can be influenced by factors such as clot stability, local hemostatic mechanisms, and systemic coagulation status (22). This dynamic nature underscores the importance of continuous monitoring and reassessment in patients with UGIB (10).

In recent decades, the epidemiology and clinical characteristics of UGIB have been significantly influenced by the widespread use of medications that alter mucosal integrity and hemostasis. Non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants, and antiplatelet agents are now recognized as major contributors to UGIB, either independently or in combination (23). These agents exert their effects through distinct mechanisms, including inhibition of prostaglandin synthesis, interference with the coagulation cascade, and impairment of platelet aggregation (24). As a result, the definition of UGIB in modern clinical practice increasingly incorporates drug-related etiologies and risk stratification, reflecting the changing landscape of gastrointestinal bleeding (25).

Furthermore, advances in diagnostic and therapeutic modalities have expanded the clinical framework of UGIB. Endoscopic techniques allow for direct visualization and also for localization of bleeding sources but can also be used as therapeutic interventions such as when using thermal coagulation, injection therapy, and mechanical hemostasis (26). Consequently, the definition of UGIB is now closely linked to endoscopic findings and classifications, which provide valuable information regarding bleeding activity and risk of rebleeding (27).

In summary, UGIB is a multifaceted clinical syndrome defined anatomically as bleeding proximal to the ligament of Treitz but encompassing a wide range of clinical presentations, etiologies, and pathophysiological mechanisms. Its definition has evolved to integrate anatomical, clinical, and functional perspectives, reflecting advances in understanding and management. For accurate diagnosis, effective treatment, and improved of patient outcomes, all this diverse manifestations and underlying mechanisms of UGIB must be understood and recognized particularly in the context of increasing exposure to medications that can predispose to bleeding.

1.2. Classification of Upper Gastrointestinal Bleeding: Variceal vs Non-variceal

Upper gastrointestinal bleeding (UGIB) is broadly classified into **variceal and non-variceal bleeding**, a distinction that is fundamental to clinical practice because it directly influences diagnostic strategies, therapeutic interventions, and prognosis (2). This classification reflects differences in underlying pathophysiology, hemodynamic consequences, and response to treatment (3).

1.2.1 Variceal Upper Gastrointestinal Bleeding

Variceal bleeding arises as a direct consequence of portal hypertension, most commonly associated with liver cirrhosis, although it may also occur in conditions such as portal vein thrombosis or schistosomiasis, massive fatty change, diseases affecting portal microcirculation, such as nodular regenerative hyperplasia and diffuse fibrosing granulomatous disease, such as sarcoidosis (28). Other rare causes of portal hypertension include Wilson disease, alpha-1 antitrypsin deficiency, primary biliary cirrhosis or constrictive pericarditis. The increase of portal venous pressure leads to the formation of collateral vessels, particularly in the distal esophagus and proximal stomach, which become dilated and tortuous (29).

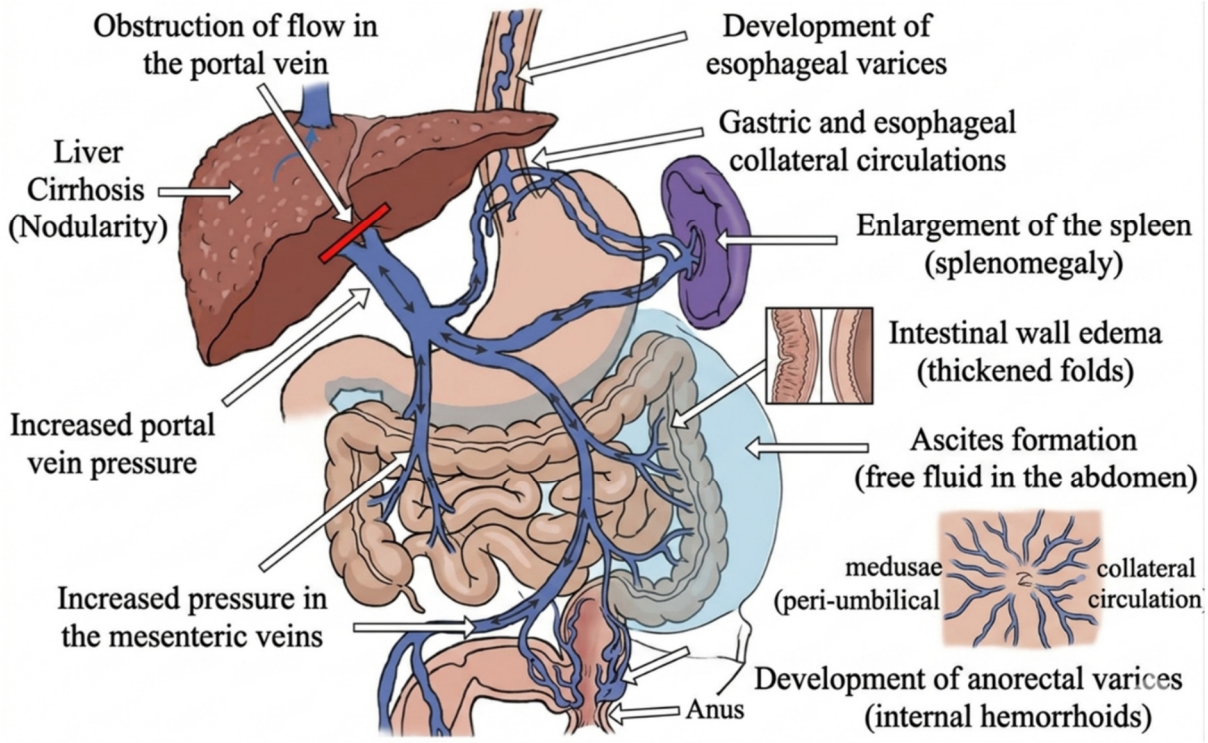

Fig. 1. Effects of portal hypertension on the abdominal organs

(Adapted from: Deep Neural Network Regression to Assist Non-Invasive Diagnosis of Portal Hypertension, Healthcare, September 2023; 11(18))

These varices structure is fragile and prone to rupture due to increased wall tension, as described by Laplace's law, where tension is proportional to vessel radius and intraluminal pressure (39). Once rupture occurs, bleeding is often rapid and severe, frequently resulting in significant hemodynamic compromise (31).

Variceal bleeding is associated with a high mortality rate, particularly in patients with advanced liver disease (32). Variceal bleeding has a 6-week mortality rate of 10%–20%, sometimes reaching up to 30% according to APASL guidelines. Despite advances in therapy, it remains a leading cause of death in cirrhotic patients**,** often recurring within the first few days to weeks after the initial bleeding episode. The severity of bleeding is compounded by coexisting factors such as coagulopathy, thrombocytopenia, and impaired hepatic synthesis of clotting factors (33). In addition, portal hypertensive gastropathy may contribute to chronic or acute bleeding in these patients (34).

Clinically, variceal bleeding typically presents with massive hematemesis and it is often accompanied by signs of hypovolemic shock (35). The presence of underlying liver disease, including jaundice, ascites, or encephalopathy, may provide important diagnostic clues (36). Management of variceal bleeding differs significantly from non-variceal bleeding and includes: vasoactive agents (e.g., octreotide, terlipressin), endoscopic band ligation, antibiotic prophylaxis and transjugular intrahepatic portosystemic shunt (TIPS) in refractory cases (32).

1.2.2 Non-variceal Upper Gastrointestinal Bleeding (NVUGIB)

Non-variceal upper gastrointestinal bleeding accounts for approximately 80–90% of all UGIB cases, making it the most common category encountered in clinical practice (19). Unlike variceal bleeding, NVUGIB is primarily caused by local mucosal injury and erosion of submucosal vessels rather than systemic hemodynamic alterations (7).

The most frequent causes include:

- Peptic ulcer disease (gastric and duodenal ulcers)
- Erosive gastritis and duodenitis
- Esophagitis
- Mallory–Weiss syndrome
- Vascular lesions such as angiodysplasia and Dieulafoy lesions
- Malignancies (14).

Peptic ulcer disease remains the leading cause of NVUGIB worldwide, accounting for a significant proportion of cases despite declining incidence in some regions (21). This trend is largely related to increased use of proton pump inhibitors, effective *Helicobacter pylori* eradication strategies, and reduced prevalence of infection in developed countries. The pathogenesis involves an imbalance between aggressive factors such as gastric acid and pepsin and protective mechanisms of the mucosa (33).

Drug-related mucosal injury, particularly from NSAIDs and antiplatelet agents, has become an increasingly important contributor to NVUGIB (38). In addition, infection with Helicobacter pylori plays a critical role in ulcer formation and bleeding risk (15).

Clinically, NVUGIB often presents with melena or less severe hematemesis compared to variceal bleeding, although severe cases can still occur (17). Hemodynamic instability may be present depending on the extent of blood loss.

1.2.3 Endoscopic Classification Systems in NVUGIB

Endoscopy plays a central role in the classification and management of NVUGIB by allowing direct visualization of the bleeding source and assessment of bleeding activity (27). One of the most widely used systems is the **Forrest classification**, which stratifies peptic ulcers based on their bleeding characteristics and risk of rebleeding (2).

Forrest Classification

- **Forrest Ia**: Active spurting bleeding
- **Forrest Ib**: Active oozing bleeding
- **Forrest IIa**: Non-bleeding visible vessel
- **Forrest IIb**: Adherent clot
- **Forrest IIc**: Flat pigmented haematin on ulcer base
- **Forrest III**: Clean ulcer base (32).

This classification has significant prognostic value, as lesions with active bleeding or visible vessels (Forrest Ia–IIa) are associated with a high risk of rebleeding and typically require endoscopic intervention. In contrast, lesions with a clean base (Forrest III) have a low risk of recurrence and may be managed conservatively (27).

1.2.4 Pathophysiological Differences between Variceal and Non-variceal Bleeding

The difference between variceal and non-variceal upper gastrointestinal bleeding is fundamentally based on their underlying pathophysiological mechanisms. While variceal bleeding arises is related to portal hypertension as consequence of systemic hemodynamic disturbances, non-variceal upper gastrointestinal bleeding (NVUGIB) is predominantly driven by disruption mucosal integrity disruption and subsequent vascular injury (2).

Variceal bleeding represents a direct complication of portal hypertension, most commonly associated with advanced liver disease. Increased resistance to portal blood flow leads to elevated portal venous pressure, which in turn promotes the development of

portosystemic collateral circulation. Among these collaterals, esophageal and gastric varices are particularly prone to rupture due to their superficial location and structural fragility. The progressive dilation of these vessels cause am increase of wall tension making them highly susceptible to rupture even in the absence of overt mucosal injury. Coagulopathy, thrombocytopenia and platelet dysfunction are frequent findings in patient with portal hypertension, all of witch contribute to impaired hemostasis and exacerbate the severity of bleeding once vascular rupture occurs (29).

In contrast, non-variceal upper gastrointestinal bleeding is primarily a consequence of mucosal injury and the breakdown of protective mechanisms that normally preserve gastrointestinal integrity. Both gastric and duodenal mucosa are exposed to potentially harmful factors such is the action of gastric acid, pepsin, bile salts, and also to external factors like medications and infectious agents. Under physiological conditions, a complex system of defense—comprising the mucus-bicarbonate barrier, epithelial cell integrity, mucosal blood flow, and prostaglandin-mediated regulation—maintains mucosal homeostasis. Disruption of these defenses, whether through Helicobacter pylori infection, non-steroidal anti-inflammatory drug use, or ischemic injury, leads to increased vulnerability of the mucosa to acid-peptic damage.

As mucosal injury progresses, it may progress to an extension deeper into the submucosa, where it can erode underlying blood vessels and result in clinically significant hemorrhage. Unlike variceal bleeding, which is primarily pressure-driven, NVUGIB is therefore characterized by structural damage to the mucosal and submucosal layers. This process often involves ulcer formation, erosive gastritis, or vascular lesions such as angiodysplasia, each of which can serve as a source of bleeding (19).

These fundamental pathophysiological differences explain for the distinct clinical profiles observed between variceal and non-variceal bleeding. Variceal bleeding is usually abrupt, severe, and associated with hemodynamic instability, reflecting the high-pressure nature of the underlying vascular system. In contrast, NVUGIB may present with a broader spectrum of severity, ranging from occult bleeding to overt hemorrhage, depending on the extent of mucosal damage and the size of the involved vessel. Furthermore, these differences have important therapeutic implications, as variceal bleeding requires interventions aimed at reducing portal pressure, whereas NVUGIB management focuses on acid suppression, mucosal healing, and endoscopic control of localized bleeding sources (22).

1.2.5 Clinical Implications of Classification

Accurate classification of upper gastrointestinal bleeding (UGIB) into variceal and non-variceal etiologies is a fundamental step in clinical decision-making and has direct implications for both immediate management and long-term outcomes (39). Although initial assessment and resuscitation strategies are broadly similar—focusing on hemodynamic stabilization, volume replacement, and correction of coagulopathy—the subsequent diagnostic and therapeutic approaches diverge significantly depending on the underlying source of bleeding (28).

In the setting of variceal bleeding, management is primarily directed toward reducing portal hypertension and controlling hemorrhage from dilated portosystemic collateral vessels. Early pharmacological therapy with vasoactive agents, such as somatostatin analogues or vasopressin derivatives, plays a central role in decreasing portal venous pressure and variceal blood flow. These agents are usually initiated as soon as variceal bleeding is suspected, even prior to endoscopic confirmation. Endoscopic intervention, especially endoscopic variceal ligation, is then performed urgently to achieve definitive hemostasis. In cases of refractory or recurrent bleeding, more advanced interventions, such as transjugular intrahepatic portosystemic shunt (TIPS), may be required to decompress the portal circulation and prevent further hemorrhagic episodes (29).

In contrast, the management of non-variceal upper gastrointestinal bleeding focuses on controlling mucosal bleeding and treating the underlying pathological processes. Proton pomp inhibitors (PPIs) are the cornerstone of the therapy because they reduce gastric acid secretion, promote clot stability, and facilitate mucosal healing. Early endoscopic evaluation is essential for both diagnostic and treatment allowing targeted hemostatic interventions such as injectable therapy, thermal coagulation, or mechanical clipping. In addition, identification and eradication of causative factors-particularly Helicobacter pylori infection-are critical components of long-term management, significantly reducing the risk of recurrence (19).

The distinction between variceal and non-variceal bleeding is not merely academic but has profound clinical consequences. Misclassification may lead to inappropriate therapeutic strategies, such as the use of PPIs alone in variceal bleeding or delayed initiation of vasoactive therapy, both of which may lead to uncontrolled hemorrhage and adverse outcomes. Conversely, unnecessary use of vasoactive agents in non-variceal bleeding may expose patients to avoidable side effects without clinical benefit. Such errors can increase morbidity, prolong hospitalization, and contribute to higher mortality rates (19).

For all of these reasons, early diagnostic clarification is essential. Endoscopy remains the gold standard for differentiating between variceal and non-variceal sources of bleeding and should be performed promptly in all patients presenting with UGIB, ideally within the first 24 hours after stabilization. Beyond its diagnostic value, endoscopy also provides an opportunity for immediate therapeutic intervention, thereby playing a pivotal role in the overall management strategy (22).

1.3. Epidemiology and Global Burden of Upper Gastrointestinal Bleeding

Upper gastrointestinal bleeding (UGIB) remains a significant global health concern, and it still represents one of the most common gastrointestinal emergencies requiring hospitalization (3). Despite advances in diagnostic modalities and therapeutic interventions, UGIB continues to impose a considerable burden on healthcare systems worldwide, both in terms of morbidity and economic cost (2).

The incidence of UGIB varies across geographic regions but is generally estimated to range between 50 and 150 cases per 100,000 population annually (9). In Western countries, recent epidemiological studies suggest a slight decline in incidence, largely attributed to improved management of *Helicobacter pylori* infection and the widespread use of proton pump inhibitors (PPIs) (40). However, this decline has been partially offset by the increasing use of medications such as non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants, and antiplatelet agents, particularly in aging populations (23).

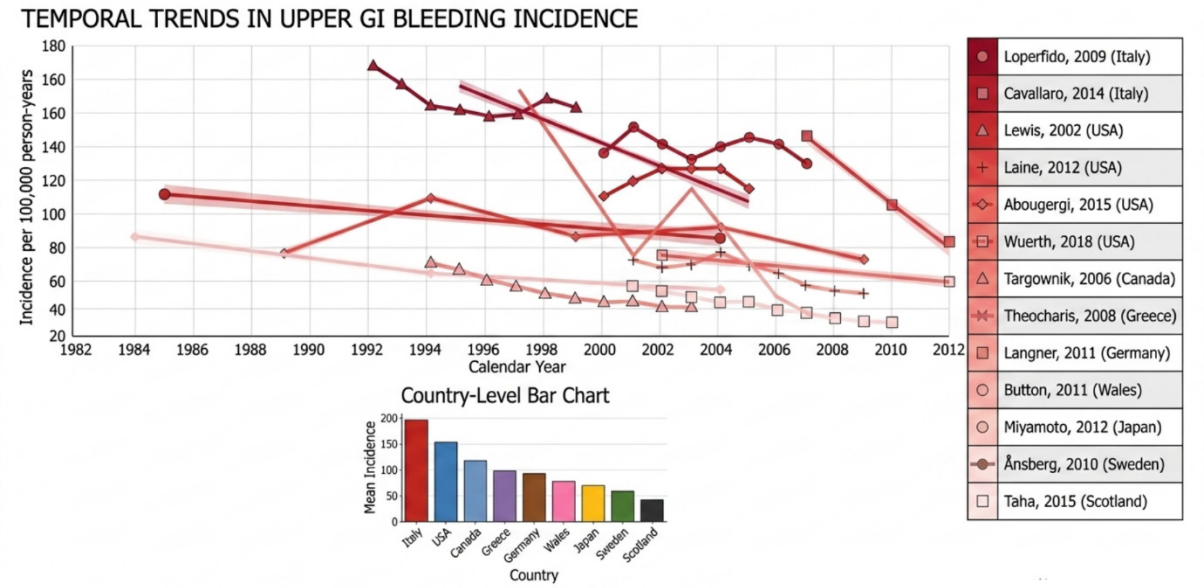

Fig. 2. Temporal trends of upper gastrointestinal bleeding incidence
(Adapted from: Şiir Su Saydam, Megan Molnar, Pareen Vora, The global epidemiology of upper and lower gastrointestinal bleeding in general population: A systematic review, World J Gastrointest Surg 2023 April 27; 15(4): 723-739)

UGIB related mortality is declining as seen over the past decades but yet remains significantly a matter of concern, typically ranging between 5% - 10% (8). Higher mortality rates are observed in elderly patients, with multiple comorbidities, and those presenting with severe bleeding or delayed treatment (17). More important, mortality is often related not only to the bleeding event itself but also to underlying comorbid conditions associated such as cardiovascular disease, liver disease, and chronic kidney disease (35).

1.3.1 Temporal Trends and Changing Epidemiology

Over the past several decades, the epidemiology of UGIB has undergone notable changes. Historically, peptic ulcer disease secondary to *Helicobacter pylori* infection was the predominant cause of bleeding (7). With the advent of effective eradication therapies and improved sanitation, the prevalence of *H. pylori*-associated ulcers has declined in many regions (38).

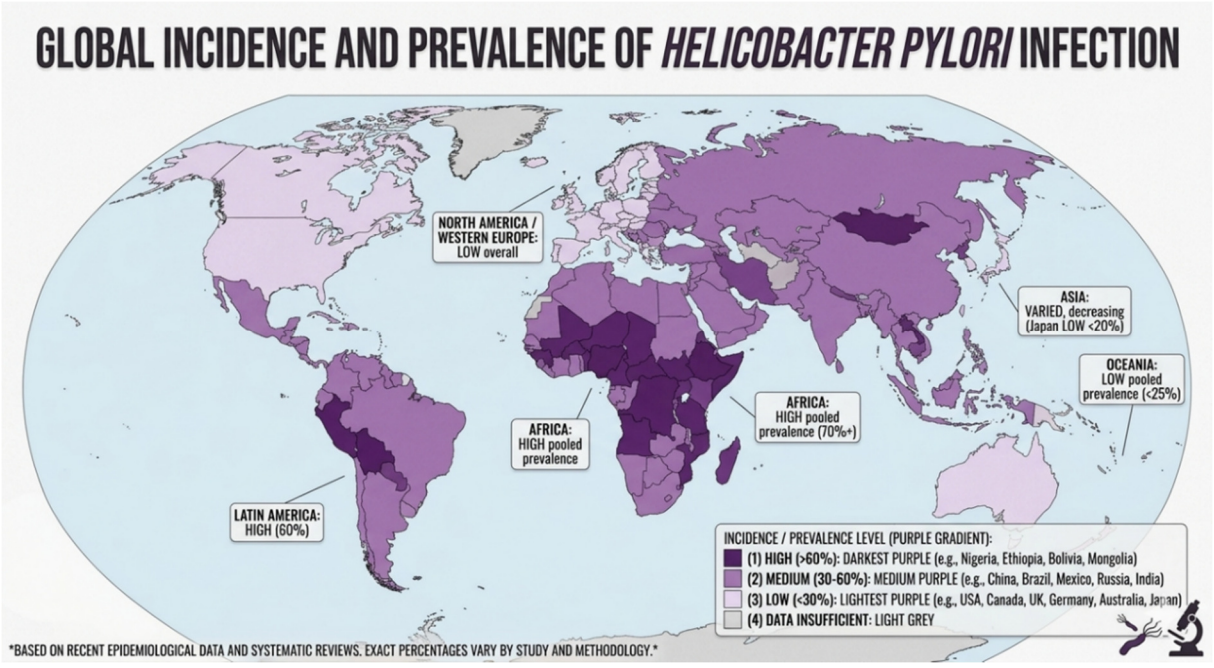

Fig. 3. Global prevalence of Helicobacter pylori infection
(Adapted from: Hooi JKY, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, Malfertheiner P, Graham DY, Wong VWS, Wu JCY, Chan FKL, Sung JJY, Kaplan GG, Ng SC. Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-Analysis. Gastroenterology. 2017 Aug;153(2):420-429. doi: 10.1053/j.gastro.2017.04.022)

Conversely, there has been a marked increase in drug-related UGIB, particularly associated with NSAIDs, anticoagulants, and antiplatelet agents (24). This shift reflects demographic changes, including increased life expectancy and the growing prevalence of

cardiovascular diseases requiring long-term pharmacological therapy (25). As a result, medication-related mucosal injury and impaired hemostasis have become central contributors to the modern epidemiology of UGIB (21).

1.3.2 Age and Gender Distribution

Age is one of the most important determinants of UGIB incidence and outcome. The risk of UGIB increases substantially with advancing age, with the highest incidence observed in individuals over 65 years (9). This increased risk is multifactorial, reflecting age-related changes in mucosal defense, higher prevalence of comorbidities, and greater exposure to medications that predispose to bleeding (19).

Elderly patients are also more likely to experience severe bleeding and adverse outcomes, including higher rates of rebleeding and mortality due to a higher burden of comorbidities, increased use of antithrombotic medications, impaired mucosal healing, and altered pharmacokinetics (8). In addition, physiological reserve is often reduced in this population, making them more susceptible to the consequences of acute blood loss (2).

Gender differences have also been observed, with UGIB generally more common in males than females, although this gap narrows with increasing age (35). The higher incidence in males has been attributed to greater exposure to risk factors such as NSAID use, alcohol consumption, and smoking (34).

1.3.3 Regional Variations

Significant geographic variation exists in the incidence and etiology of UGIB. In developed countries, the declining prevalence of *H. pylori* infection has led to a reduction in ulcer-related bleeding, whereas in developing regions, *H. pylori* remains a major etiological factor (38).

Additionally, access to healthcare resources, availability of endoscopic services, and differences in prescribing practices influence both incidence and outcomes (3). For example, regions with limited access to endoscopy may experience higher mortality due to delayed diagnosis and treatment (41).

1.3.4 Drug-Related Epidemiology

One of the most significant developments in UGIB epidemiology is the increasing role of pharmacological agents. NSAIDs are associated with a fourfold increase in the risk of UGIB, particularly in elderly patients and those with a history of peptic ulcer disease (23). The risk is dose-dependent and increases with prolonged use (42).

Oral anticoagulants, including both vitamin K antagonists and direct oral anticoagulants (DOACs), have also been implicated in UGIB (43). These agents increase bleeding risk by interfering with the coagulation cascade, and their use has expanded significantly in recent years due to indications such as atrial fibrillation and venous thromboembolism (44).

Antiplatelet agents, particularly aspirin and P2Y12 inhibitors, are widely used for cardiovascular prevention and are associated with an increased risk of gastrointestinal bleeding (25). The risk is further amplified when these agents are used in combination, such as dual antiplatelet therapy used in coronary syndromes or concurrent use with anticoagulants.

The interaction between these drug classes is of particular clinical importance, as combination therapy is increasingly common in patients with complex cardiovascular conditions (23). Such combinations significantly increase both the incidence and severity of UGIB, posing challenges for management and prevention (10).

1.3.5 Economic and Healthcare Burden

There is a substantial economic burden on healthcare systems worldwide caused bu UGIB due to frequent hospitalization and because many patients suffering from this disease necessitate intensive care, blood transfusions, and endoscopic or surgical interventions (45). The cost of managing UGIB includes not only direct medical expenses but also indirect costs in terms of socio-economical aspects related to lost productivity and long-term complications (22).

Length of hospital stay varies depending on severity but is typically longer in patients with comorbidities or complications such as rebleeding (8). Readmission rates are also significant, particularly among high-risk populations (46).

1.3.6 Prognostic Factors and Outcomes

Several factors influence the prognosis of UGIB, including age, comorbidities, hemodynamic status at presentation, and the underlying cause of bleeding (35).] Glasgow-Blatchford score and Rockall score are risk stratification tools widely used to predict outcomes and guide management (11).

Among comorbid conditions, chronic kidney disease (CKD) represents a particularly important determinant of adverse outcomes in patients with UGIB. Patients with CKD exhibit a complex hemostatic imbalance characterized by platelet dysfunction, impaired platelet adhesion and aggregation, and alterations in the coagulation cascade. Uremia is known to disrupt platelet–vessel wall interactions, leading to a bleeding diathesis even in the absence of overt coagulopathy. In addition, the anemia frequently observed in CKD further compromises

hemostatis by reduction blood viscosity and platelet margination, thereby impairing primary hemostatic responses.

CKD is also associated with significant alterations in vascular integrity and mucosal defense mechanisms. The increased prevalence of angiodysplasia, particulary in the gastrointestinal tract, has been well documented in patients with advanced renal disease and is a recognized source of recurrent bleeding. In addition, impaired mucosal healing and reduced regenerative capacity contribute to the persistence of bleeding lesions and increase the likelihood of rebleeding episodes.

The pharmacological management of CKD patients further complicates the clinical picture. Many patients require anticoagulant or antiplatelet therapy due to coexisting cardiovascular disease, which substantially supplementary increases the risk of both initial bleeding and recurrent hemorrhage. In addition, altered drug clearance in CKD leads to accumulation of certain medications, including direct oral anticoagulants, thereby enhancing bleeding risk and complicating therapeutic decision-making.

Rebleeding occurs in approximately 10–20% of cases and is associated with increased mortality (1). In patients with CKD, this risk is further amplified due to the persistence of underlying hemostatic abnormalities and the frequent presence of multiple bleeding sources. Recurrent bleeding episodes in this population are often more difficult to control and may necessitate repeated endoscopic interventions, transfusions, or escalation to more invasive therapies.

Recent advances in endoscopic therapy and pharmacological treatments have led to improved clinical outcomes, however patient at high-risk still face considerable morbidity (10). Patients with CKD are especially vulnerable, experiencing longer hospital stays, need for intensive care, and overall increased mortality. As a result, renal function has become an increasingly important component of risk assessment models, helping clinicians to achieve more accurate prognostic evaluations and tailor management strategies to individual patient needs.

1.4. Clinical Importance of Upper Gastrointestinal Bleeding

Upper gastrointestinal bleeding (UGIB) represents a major medical emergency with significant implications for patient outcomes, a burden for healthcare system affecting patients long-term prognosis (2). Despite advances in diagnostic and therapeutic modalities, UGIB continues to

be associated with substantial morbidity and mortality, particularly among elderly patients and those with multiple comorbidities (3).

The clinical importance of UGIB extends beyond immediate risk of hemorrhage. It often reflects the presence of a severe underlying disease and increase overall patient vulnerability (6). Many individuals presenting with UGIB have chronic illnesses such as cardiovascular disease, liver disease, or renal impairment, which can complicate treatment and negatively influence outcomes (18).

1.4.1 Acute Clinical Impact and Hemodynamic Consequences

The immediate clinical significance of UGIB is related to the severity and rate of blood loss, which determine the degree of hemodynamic compromise (37). Rapid or massive bleeding can lead to hypovolemic shock, characterized by hypotension, tachycardia, decreased tissue perfusion, and organ dysfunction (5). The physiological response to acute blood loss involves activation of compensatory mechanisms, including sympathetic nervous system stimulation and vasoconstriction, aimed at maintaining perfusion to vital organs (47). However, these compensatory responses may be insufficient in severe cases, particularly in elderly patients or those with limited cardiovascular reserve (17).

Laboratory findings often reflect the systemic effects of bleeding, including:

- Decreased hemoglobin and hematocrit levels
- Elevated blood urea nitrogen due to increased protein absorption from digested blood
- Electrolyte imbalances secondary to volume depletion (18).

These biochemical changes provide important diagnostic and prognostic information and are integral to the assessment of UGIB severity.

1.4.2 Risk Stratification and Prognostic Assessment

Accurate risk stratification is essential in the management of UGIB, as it allows clinicians to identify patients at high risk of complications and allocate resources appropriately (11). Several validated scoring systems have been developed to predict outcomes, including the Glasgow-Blatchford score and the Rockall score (12).

For the initial assessment of patients, Glasgow-Blatchford score is particularly useful, as it relies not just on clinical but also and laboratory parameters such as blood urea, hemoglobin, blood pressure, and heart rate (11). Patients with low scores may be safely managed as outpatients, whereas those with higher scores require hospitalization and urgent intervention (12).

The Rockall score incorporates both clinical and endoscopic findings and is primarily used to predict mortality and risk of rebleeding.

Key prognostic factors include:

- Advanced age
- Presence of comorbidities
- Hemodynamic instability
- Endoscopic stigmata of recent hemorrhage (5).

These scoring systems highlight the multifactorial nature of UGIB outcomes and emphasize the importance of integrating clinical, biochemical, and endoscopic data in patient assessment (10).

1.4.3 Rebleeding and Long-Term Outcomes

One of the most significant complications of UGIB is rebleeding. It occurs in approximately 10–20% of cases, depending on the underlying cause and initial management. A particularly elevated risk of rebleeding is observed in patients with high-risk endoscopic stigmata, such as active bleeding, non-bleeding visible vessels, or adherent clots, as defined by the Forrest classification. An initial hemostasis that is inadequate, delayed endoscopic intervention, and suboptimal pharmacological therapy contribute to a further increase of the likelihood of recurrent hemorrhage (2).

There are also several patient-related factors that also contribute to rebleeding risk, including advanced age, comorbid conditions such as we mention the chronic kidney disease and also the cardiovascular disease, and the use of anticoagulant or antiplatelet medications. In addition, persistent or untreated etiological factors—most notably Helicobacter pylori infection or continued exposure to non-steroidal anti-inflammatory drugs—can predispose to recurrent mucosal injury and bleeding.

Rebleeding is associated with substantial clinical consequences, including increased transfusion requirements, prolonged hospitalization, need for repeat endoscopic or interventional procedures, and significantly higher mortality rates. Early risk stratification and appropriate post-endoscopic management, including high-dose proton pump inhibitor therapy and close clinical monitoring, are therefore essential to reduce the risk of recurrence and improve overall patient outcomes.

Identifying patient that are at high risk of rebleeding is essential using endoscopic classification systems, such as the Forrest classification, for guiding therapeutic decisions to follow (27).

Long-term outcomes are also affected by the underlying etiology of bleeding and the presence of comorbid conditions (3). Patients with cardiovascular disease, for example, may require continued antithrombotic therapy, which complicates management and increases the risk of recurrent bleeding (24).

1.4.4 Impact of Comorbidities

Comorbid conditions play a critical role in determining the clinical course and prognosis of UGIB. Patients with liver cirrhosis, chronic kidney disease, or cardiovascular disease are at increased risk of severe bleeding and poor outcomes.

In liver disease, impaired synthesis of clotting factors and thrombocytopenia contribute to coagulopathy, exacerbating bleeding (32). In patients with renal impairment, platelet dysfunction and uremia further increase bleeding risk (19).

Cardiovascular comorbidities are particularly important, as they often necessitate the use of extended antiplatelet or anticoagulant therapy, which increases the likelihood of both initial bleeding and recurrence (25). Balancing the risks of thrombosis and bleeding in these patients represents a major clinical challenge.

1.4.5 Healthcare Burden and Resource Utilization

UGIB imposes a significant burden on healthcare systems worldwide, accounting for a large number of emergency admissions and hospitalizations (3). Management often requires:

- Intensive monitoring
- Blood transfusions
- Endoscopic interventions
- Pharmacological therapy (2).

The economic impact of UGIB is substantial, with costs driven by hospitalization, procedural interventions, and complications such as rebleeding (22). Length of hospital stay varies but is typically longer in patients with severe bleeding or comorbid conditions.

Readmission rates are also significant, particularly among high-risk patients, further contributing to healthcare costs and resource utilization (17).

1.4.6 Clinical Relevance in the Context of Drug-Induced Bleeding

The clinical importance of UGIB has increased in parallel with the widespread use of medications that affect gastrointestinal integrity and hemostasis (23). NSAIDs, oral anticoagulants, and antiplatelet agents are now major contributors to UGIB, particularly in elderly populations (24).

Drug-induced bleeding is often more severe and may present atypically, making diagnosis and management more challenging (21). In addition, the need to balance bleeding risk with the therapeutic benefits of these medications complicates clinical decision-making (25).

Preventive strategies, including the use of proton pump inhibitors and careful patient selection, are essential for reducing the incidence of drug-related UGIB (7).

For an effective management and prevention strategies it is essential to completely understand the clinical importance of UGIB. Early diagnosis, appropriate risk stratification, and timely intervention are key factors in improving patient outcomes.

The integration of all clinical, biochemical, and pharmacological factors is particularly important, in a modern clinical context as it allows for personalized management approaches tailored to individual patient risk profiles.

1.5. Pathophysiology of Non-Variceal Upper Gastrointestinal Bleeding

Non-variceal upper gastrointestinal bleeding (NVUGIB) arises from a complex interplay between mucosal injury, impaired protective mechanisms, and disruption of hemostatic processes, ultimately leading to exposure and rupture of submucosal blood vessels (6). The integrity of the upper gastrointestinal mucosa depends on a finely regulated balance between aggressive luminal factors, such as gastric acid and pepsin, and defensive mechanisms, including mucus secretion, epithelial regeneration, and mucosal blood flow (19).

Disruption of this balance—whether by endogenous factors such as acid hypersecretion or exogenous influences such as medications and infection—results in mucosal damage and bleeding (23). Understanding these mechanisms is essential for interpreting the clinical and biochemical differences observed in patients exposed to NSAIDs, anticoagulants, and antiplatelet agents (10).

1.5.1 Gastric Mucosal Defense

The gastric mucosa is protected by a complex defense system that helps maintain tissue integrity despite the continuous exposure to gastric acid and digestive enzymes (20). The protective mechanism relies on the coordinated action of several factors, including the mucus-bicarbonate layer covering the mucosal surface, the integrity and regenerative capacity of the epithelial cell, adequate mucosal perfusion, and the regulatory effects of prostaglandins. Together, these components work to preserve mucosa and prevent injury under normal physiological conditions (19).

1.5.2 Mucus-Bicarbonate Barrier

The first line of defense is the mucus gel layer, secreted by surface epithelial cells, which forms a physical barrier between the luminal contents and the mucosa (20). Embedded within this layer is bicarbonate, which neutralizes hydrogen ions and maintains a near-neutral pH at the epithelial surface despite the highly acidic gastric environment (48).

Disruption of this barrier increases mucosal permeability, allowing acid and pepsin to penetrate and damage epithelial cells (19). This process is particularly relevant in NSAID-induced injury, where prostaglandin inhibition reduces mucus and bicarbonate secretion (23).

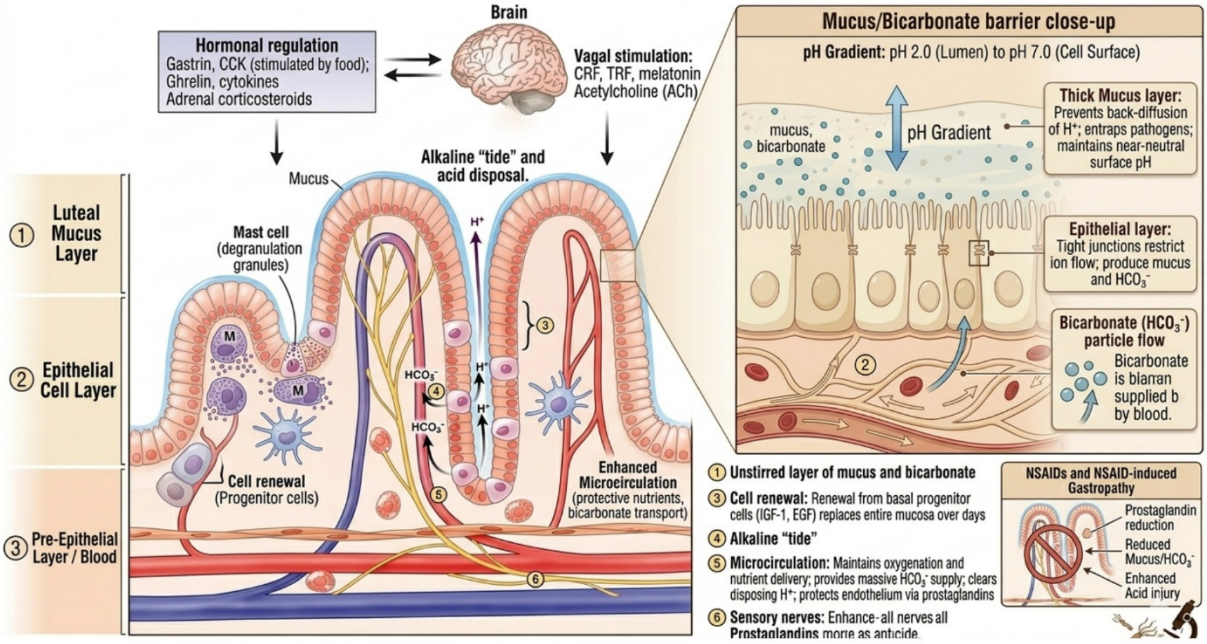

Fig. 4. Gastric mucosal barrier

(Adapted from: Harathi Yandrapu, Jerzy Sarosiek Curr Gastroenterol Rep (2015) 17: 24, STOMACH AND DUODENUM (J PISEGNA, SECTION EDITOR). Protective Factors of the Gastric and Duodenal Mucosa: An Overview, DOI 10.1007/s11894-015-0452-2)

1.5.3 Epithelial Integrity and Cellular Repair

Gastric epithelial cells are tightly connected by tight junctions, which prevent back-diffusion of hydrogen ions into the mucosa (49). Rapid epithelial restitution and regeneration can restore mucosal integrity when injury occurs. (50).

These tight junctions, composed of specialized transmembrane proteins such as claudins, occluding, and junctional adhesion molecules, play a critical role in maintaining epithelial barrier function. By regulating paracellular permeability, they limit the penetration of luminal acid, pepsin, and other potentially harmful substances into the deeper layers of the gastric mucosa. Whether it is caused by chemical injury, ischemia, or inflammatory processes, the

disruption of these junctions result in increased mucosal permeability and facilitates acid back-diffusion, leading to cellular injury and necrosis.

Epithelial restitution represents a rapid, energy-dependent process in which viable epithelial cells migrate to cover superficial defects without requiring cell proliferation. It is a process that occurs within minutes to hours following the injury and is regulated by a complex interplay of growth factors, including epidermal growth factor (EGF) and transforming growth factor-α (TGF-α), as well as intracellular signaling pathways that modulate cytoskeletal reorganization. An adequate mucosal blood flow is essential for this process, as it ensures the delivery of oxygen and nutrients necessary for cellular migration and repair. In the meantime, epithelial regeneration involves cellular proliferation and differentiation to replace lost cells and restore normal mucosal architecture. This is a process that occurs over a longer timeframe and is essential for sustained healing and maintenance of mucosal integrity. The inbalance between restitution or regeneration—such as in the presence of ongoing acid exposure, NSAID use, or Helicobacter pylori infection—can impair mucosal healing and increase susceptibility to ulcer formation and bleeding (19).

Thus, the integrity of tight junctions and the efficiency of epithelial repair mechanisms are fundamental components of gastric mucosal defense, and their impairment plays a central role in the pathogenesis of non-variceal upper gastrointestinal bleeding.

This repair process is dependent on:

- Cellular migration
- Growth factor signaling
- Adequate blood supply (19).

Impairment of these mechanisms, as seen in elderly patients or those with chronic disease, delays healing and increases susceptibility to bleeding (8).

1.5.4 Mucosal Blood Flow

Adequate mucosal blood flow is essential for maintaining tissue viability and supporting repair processes. It facilitates:

- Delivery of oxygen and nutrients
- Removal of toxic metabolites
- Maintenance of pH balance.

Mucosal perfusion, in addition to these fundamental functions, plays a critical role in sustaining epithelial integrity and also coordinating the complex processes involved in mucosal defense. The secretion of mucus and bicarbonate is supported by a continuous blood flow.

Both of mucus and bicarbonate secretion contribute to the formation of a protective barrier against luminal acid and digestive enzymes. It also enables the rapid distribution of locally produced mediators, including prostaglandins and nitric oxide, which regulate vasodilation, epithelial restitution, and inflammatory responses within the gastric mucosa.

Moreover, adequate perfusion is essential for maintaining microvascular integrity and preventing endothelial dysfunction. The gastric microcirculation acts as a dynamic interface between systemic hemodynamics and local tissue requirements, adapting to both physiological and pathological stimuli. Disruption of this finely regulated system can result in capillary stasis, increased vascular permeability, and localized hypoxia, all of which contribute to mucosal vulnerability.

Shock or systemic illness by reducing the blood flow, can compromise mucosal defense and predispose to ischemic injury and bleeding (2). Under such conditions, diminished oxygen delivery leads to impaired cellular metabolism, accumulation of lactic acid, and disruption of epithelial tight junctions. These changes facilitate back-diffusion of hydrogen ions into the mucosa, exacerbating tissue injury and promoting ulcer formation. In severe cases, prolonged ischemia may result in necrosis of the mucosal and submucosal layers, further increasing the risk of clinically significant gastrointestinal hemorrhage.

1.5.5 Role of Prostaglandins

Prostaglandins, particularly those derived from cyclooxygenase-1 (COX-1), play a central role in maintaining gastric mucosal integrity by regulating multiple protective mechanisms within the gastrointestinal tract (18). These bioactive lipid mediators are synthesized locally in the gastric mucosa and act in a paracrine and autocrine manner to preserve the balance between mucosal defense and luminal aggressors (21).

The synthesis of prostaglandins originates from the arachidonic acid cascade**,** a fundamental biochemical pathway involved in inflammation and cellular homeostasis (51). Arachidonic acid is a polyunsaturated fatty acid released from membrane phospholipids through the action of phospholipase A□ (PLA□) in response to mechanical, chemical, or inflammatory stimuli (52). Once released, arachidonic acid is metabolized via two principal enzymatic pathways:

- The cyclooxygenase (COX) pathway**,** leading to prostaglandin and thromboxane synthesis
- The lipoxygenase (LOX) pathway**,** producing leukotrienes.

In the context of gastric physiology, the COX pathway is of primary importance, as it generates prostaglandins that exert protective effects on the mucosa (7).

There are two main isoform for cyclooxygenase:

- COX-1 (constitutive enzyme)
- COX-2 (inducible enzyme) (54).

COX-1 is constitutively expressed in most tissues, including the gastric mucosa, and is responsible for the continuous production of prostaglandins involved in physiological homeostasis (21). In the stomach, COX-1-derived prostaglandins—primarily PGE□ and PGI□ (prostacyclin)—are essential for maintaining mucosal integrity (54).

COX-2, in contrast, is primarily produces during inflammatory states and contributes to the production of prostaglandins involved in pain and inflammation (19). Although COX-2 also plays a role in mucosal healing, its contribution to baseline gastric protection is less significant than that of COX-1 (23).

Prostaglandins have multiple protective effect on gastric mucosa, acting through specific receptors on epithelial and endothelial cells (54).

Prostaglandins enhance the secretion of mucus and bicarbonate by surface epithelial cells, reinforcing the mucus-bicarbonate barrier that protects the mucosa from acid and pepsin (30). This barrier is involved in maintaining a neutral pH at the epithelial surface despite the acidic gastric lumen. Prostaglandins also promote vasodilation of the gastric microcirculation, thereby increasing mucosal blood flow (55). This effect supports: oxygen and nutrient delivery, removal of toxic metabolites and also the maintenance of cellular homeostasis (50).

Prostaglandins inhibit gastric acid secretion by parietal cells through modulation of intracellular signaling pathways, including reduction of cyclic AMP levels (49). This inhibitory effect helps limit mucosal exposure to aggressive luminal factors (22).

Prostaglandins facilitate epithelial restitution by promoting cell migration, proliferation, and differentiation following injury (7). They also stimulate the release of growth factors that contribute to mucosal healing (24). At the cellular level, prostaglandins regulate epithelial cell turnover and modulate intracellular signaling pathways involved in cytoskeletal reorganization, which is essential for effective cell migration during restitution. They also exert anti-apoptotic effects, preserving epithelial cell viability under conditions of stress or injury. Furthermore, prostaglandins interact with immune and inflammatory pathways, limiting excessive inflammatory responses that could otherwise exacerbate mucosal damage. The release of growth factors, including epidermal growth factor (EGF) and transforming growth factor-α (TGF-α), is closely linked to prostaglandin activity and contributes to both rapid restitution and

longer-term regenerative processes. These factors promote epithelial proliferation, angiogenesis, and restoration of normal mucosal architecture, thereby enhancing the overall healing response (7).

Affecting the prostaglandin synthesis, most notably through the use of non-steroidal anti-inflammatory drugs (NSAIDs), impairs these protective and reparative mechanisms. This causes a reduced mucosal blood flow, and also diminished secretion of mucus and bicarbonate and delays epithelial healing, ultimately increasing susceptibility to ulcer formation and gastrointestinal bleeding.

By preserving tight junction integrity and preventing back-diffusion of hydrogen ions, prostaglandins play a crucial role in maintaining epithelial barrier function (2).

Prostaglandins clinical importance is most evident in the context of NSAID-induced gastrointestinal injury**.** NSAIDs exert their therapeutic effects by inhibiting COX enzymes, but this inhibition also reduces prostaglandin synthesis, particularly through COX-1 blockade (26).

This leads to:

- Decreased mucus and bicarbonate secretion
- Reduced mucosal blood flow
- Increased acid secretion
- Impaired epithelial repair (19).

The combined effect is a marked reduction in mucosal defense, making the gastric lining highly susceptible to injury and ulcer formation (21).

Selective COX-2 inhibitors were developed to minimize gastrointestinal toxicity by sparing COX-1 activity; however, they are not entirely devoid of GI risk, particularly with long-term use or in high-risk patients (23).

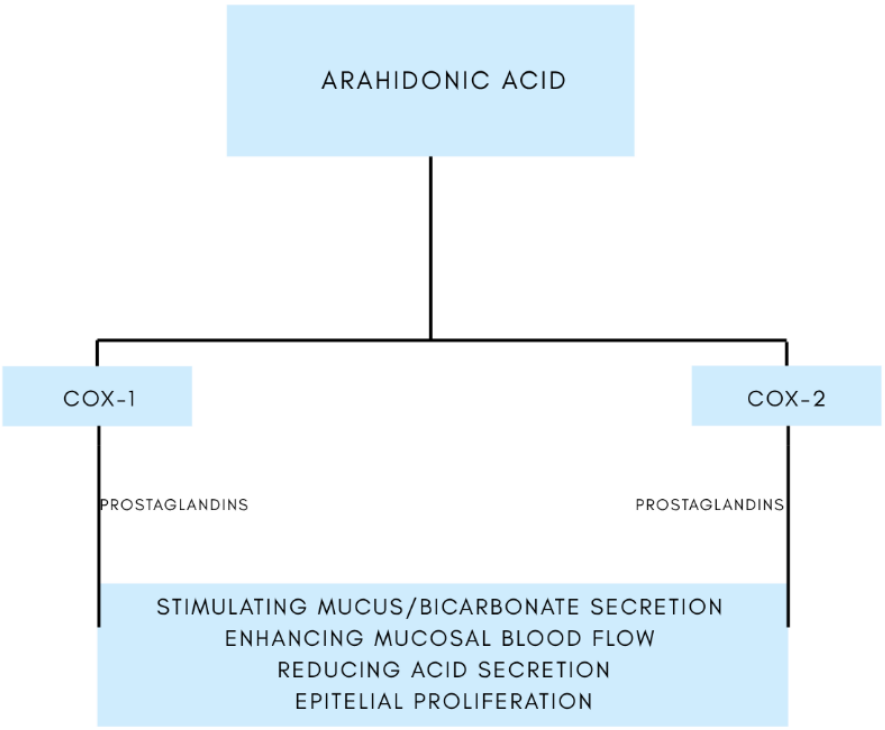

Fig. 5- Different Chemical Structures and Physiological/Pathological Roles of Cyclooxygenases, *(Adapted from: Faki Y, Er A. Different Chemical Structures and Physiological/Pathological Roles of Cyclooxygenases. Rambam Maimonides Med J. 2021 Jan 19;12(1):e0003. doi: 10.5041/RMMJ.10426)*

Gastric acid and pepsin are essential for digestion but also represent potent aggressive factors capable of damaging the mucosa when protective mechanisms are impaired (21). Acid-peptic injury is central to the pathogenesis of peptic ulcer disease, the most common cause of NVUGIB (22). Gastric acid, secreted by parietal cells via the H^+ /K^+ -ATPase pump, contributes to mucosal injury by:

- Disrupting epithelial cells
- Activating pepsinogen to pepsin
- Promoting inflammation (23).

High levels of acid secretion, especially when buffering mechanism are impaired, can lead to damage of the mucosal lining and promote ulcer formation (24).

Pepsin, a proteolytic enzyme, degrades mucosal proteins and exacerbates tissue injury once the epithelial barrier is compromised (25). Its activity is highly dependent on acidic pH, creating a synergistic effect with gastric acid in promoting mucosal damage (26).

Persistent mucosal injury leads to ulcer formation, characterized by full-thickness loss of the mucosal layer (27). As the ulcer deepens, it may erode into submucosal or even larger vessels, resulting in bleeding (28).

The severity of bleeding depends on the size and location of the affected vessel, the degree of local inflammation and also of the effectiveness of hemostatic mechanisms (29).

The severity of acid-peptic damage may be increase by the use of NSAIDs and antiplatelet agents, both of which compromise mucosal protection and elevate bleeding risk (30). By reducing gastric acid secretion and stabilizing clots, proton pomp inhibitors remain a key component of effective management strategies. (31).

1.5.6 Role of Helicobacter Pylori

Infection with Helicobacter pylori is a major etiological factor in NVUGIB and plays a critical role in the development of peptic ulcer disease (38). This Gram-negative bacterium colonizes the gastric mucosa and induces chronic inflammation, leading to mucosal damage and increased susceptibility to bleeding (56).

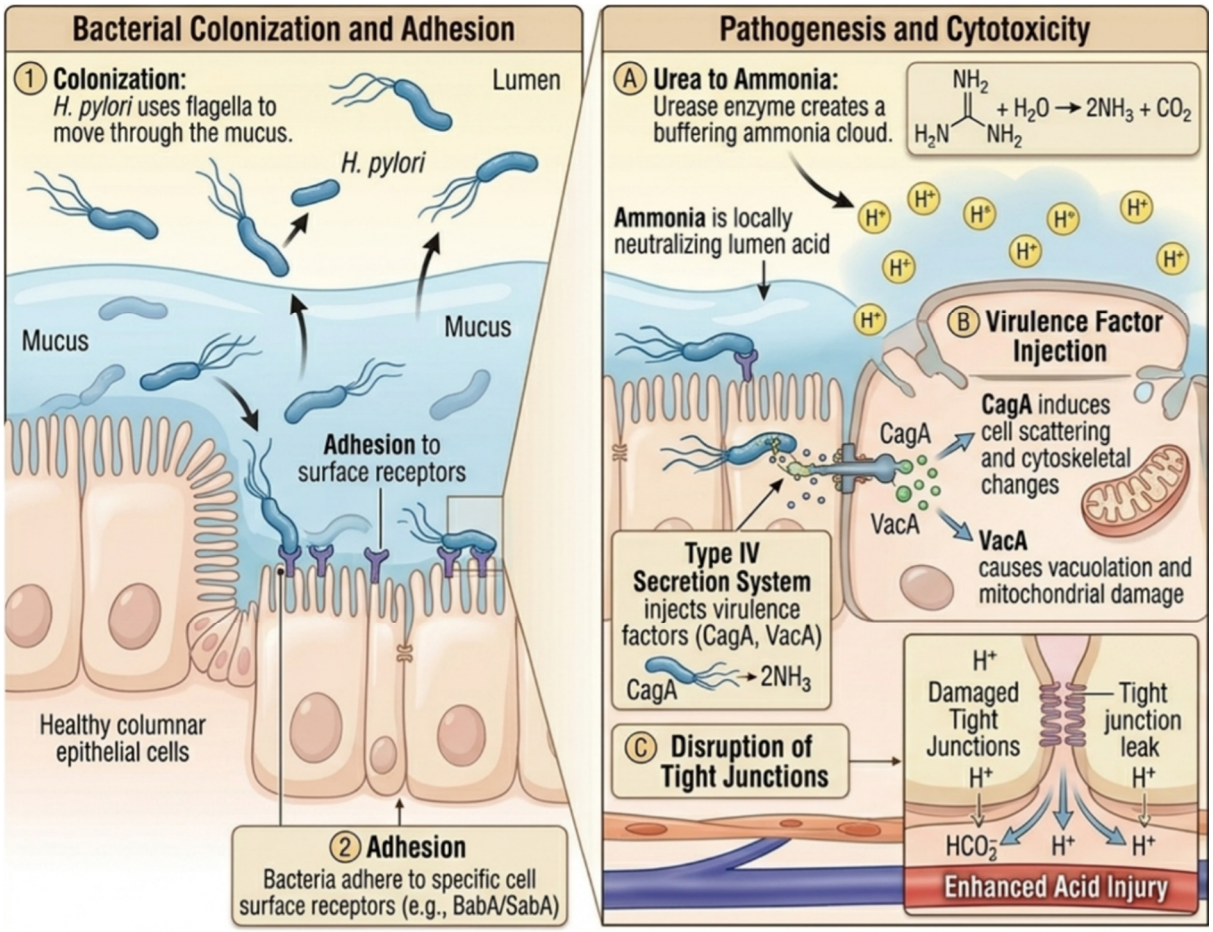

Fig. 6- Helicobacter pylori bacteria urease-mediated alkalinization of the gastric environment *(Adapted from: Eman Marzouk, Adil Abalkhail, Unraveling Helicobacter pylori: Insights into Pathogenesis, Immune Evasion, and Progress Toward Effective Vaccination ,* Vaccines ***2025***, 13*(7), 725)*

The pathogenic effects of *Helicobacter pylori* on the gastric mucosa arise from a combination of bacterial virulence mechanism and host inflammatory responses. These include the production of urease, which hydrolyzes urea to ammonia and carbon dioxide, thereby buffering the acidic gastric environment and facilitating bacterial survival through a more favorable local pH. In the same time, the organism secretes virulence factors, such as cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA), which directly disrupt epithelial cell integrity and contribute directly to cellular injury. Parsistent *H. pylori* infection triggers a robust inflammatory response characterized by the release of pro-inflammatory cytokines and activation of immune pathways, resulting in chronic inflammation and progressive mucosal damage (56).These processes result in chronic gastritis, disruption of epithelial integrity, and increased vulnerability to acid-peptic injury (7).

The impact of *Helicobacter pylori* infection on gastric acid secretion is influenced by the distribution of gastritis within the stomach (57). In cases of antral-predominant gastritis, increased gastrin release leads to enhanced gastric acid secretion, which is commonly associated with the development of duodenal ulcers. In contrast, corpus-predominant gastritis is characterized by inflammation of the acid-secreting mucosa, resulting in reduced acid production and a higher propensity for gastric ulcer formation. This variation influences the location and severity of ulceration and bleeding (22).

The combination of *H. pylori* infection and NSAID use significantly increases the risk of UGIB, with a synergistic effect on mucosal damage (23). Both factors independently impair mucosal defense, and their coexistence dramatically increases the likelihood of ulcer formation and bleeding (7). The combined presence of these factors results in a marked reduction in mucosal resilience and an increased susceptibility to injury from gastric acid and pepsin. In particular, NSAID-induced suppression of prostaglandins exacerbates the inflammatory and cytotoxic effects of *H. pylori*, while the infection itself may impair healing responses and prolong mucosal damage. This creates a permissive environment for the development of deeper and more clinically significant ulcers.

Clinical studies have consistently demonstrated that patients with concurrent *H. pylori* infection and NSAID exposure have a substantially higher risk of both initial ulcer formation and complicated bleeding compared with those exposed to either factor alone. This synergistic effect is especially pronounced in elderly patients and those with additional risk factors, such as prior ulcer disease or concomitant use of anticoagulants or antiplatelet agents. (58).

Importantly, eradication of *H. pylori* has been shown to reduce the risk of ulcer recurrence and bleeding in patients requiring long-term NSAID therapy. Therefore, current clinical

guidelines recommend testing for and treating *H. pylori* infection in patients at risk before initiating chronic NSAID use. This approach represents a key preventive strategy in reducing the burden of non-variceal upper gastrointestinal bleeding.(38).

Eradication of *H. pylori* has been shown to reduce the risk of recurrent bleeding in patients with peptic ulcer disease (6). Therefore, testing and treatment for infection are essential components of UGIB management (2).

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Chapter 2: Drug-Related Gastrointestinal Bleeding

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2.1. Non-steroidal Anti-inflammatory Drugs and Gastrointestinal Injury

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed and widely used medications worldwide because of their effectiveness in relieving pain, reducing inflammation, managing musculoskeletal conditions. Despite their therapeutic benefits, their clinical utility is significantly limited by gastrointestinal toxicity, particularly their well-established association with non-variceal upper gastrointestinal bleeding (NVUGIB). This complication remains a major contributor to drug-related morbidity and hospital admissions, especially in elderly populations and in patients with multiple comorbidities (1,2).

The mechanism underlying NSAID-induced gastrointestinal injury are complex and involve both systemic and local effects on the gastric mucosa. Central to this process is the inhibition of cyclooxygenase enzymes, which reduces in prostaglandin production and weakens the protective mechanism that maintain mucosal integrity. However, this classical explanation alone is insufficient to fully account for the clinical variability observed in NSAID-related injury, and additional mechanisms—including microvascular dysfunction, mitochondrial injury, and immune-mediated effects—must also be considered (3,4).

At the molecular level, NSAIDs exert their effects through inhibition of cyclooxygenase (COX) enzymes, which catalyze the conversion of arachidonic acid into prostaglandin H□, a precursor of multiple biologically active prostanoids. The distinction between COX-1 and COX-2 isoforms is central to understanding both therapeutic efficacy and toxicity.

COX-1 is constitutively expressed within the gastric mucosa and plays a fundamental role in preserving mucosal integrity through the continuous production of protective prostaglandins. These include prostaglandin E□ (PGE□) and prostacyclin (PGI□), which stimulate mucus and bicarbonate secretion, support adequate mucosal blood flow, and help regulate gastric acid secretion. Consequently, inhibition of COX-1 compromise these protective therefore results in mechanisms, increasing the vulnerability of the gastric epithelium to acid related injury (5, 6).

COX-2, although primarily induced during inflammatory processes, it also contributes to the maintenance and also repair of the gastrointestinal mucosa. It promotes angiogenesis,

epithelial cell proliferation, and tissue regeneration following injury. Inhibition of COX-2 may impair mucosal healing, delay ulcer healing and extend the duration of tissue damage, particularly in patients with pre-existing mucosal lesions (7, 8).

Beyond systemic enzyme inhibition, NSAIDs exert direct cytotoxic effects on the gastric epithelium. Due to their weakly acidic nature, NSAIDs can penetrate epithelial cells in their non-ionized form. Once inside the neutral intracellular environment, they become ionized and accumulate, leading to cellular injury.

NSAID-induced cellular injury is closely linked to mitochondrial dysfunction, characterized by uncoupling of oxidative phosphorylation, leading to reduced ATP generation, and increased production of reactive oxygen species. These changes compromise cellular energy metabolism and lead to disruption of tight junctions, increasing mucosal permeability and facilitating back-diffusion of hydrogen ions (9, 10).

The resulting epithelial damage is further intensified by inflammatory processes. Activation of neutrophils and the release of pro-inflammatory cytokines contribute to tissue injury, promote mucal inflammation, and facilitates ulcer formation (11).

Alteration in the gastric microcirculation also represents a critical but often overlooked aspect of NSAID-induced injury. Under normal conditions, prostaglandins play a key role in maintaining mucosal blood flow through vasodilation. When prostaglandin synthesis is inhibited, blood flow to the gastric mucosa decrease, increasing the risk of tissue hypoxia and impairing mucosal defense.

Experimental studies have shown that NSAID exposure reduce mucosal blood flow and dimmish the capacity of the microvasculature to respond effectively to injury, while the clearance of harmful metabolic b-products become less efficient, further aggravation mucosal damage. In addition, endothelial dysfunction and reduced nitric oxide bioavailability may also contribute to microvascular impairment, highlighting the complex interplay between prostaglandin pathways and vascular regulation.

The clinical relevance of NSAID-induced gastrointestinal injury has been extensively evaluated in several randomized controlled trials, which have provided important insights into the relative risks associated with different NSAIDs and therapeutic strategies.

One of the most influential studies is the VIGOR Trial, which compared the COX-2 selective inhibitor rofecoxib with naproxen in patients with rheumatoid arthritis. The investigators reported a significantly lower rate of gastrointestinal complications, including bleeding events in the rofecoxib group. However, this benefit was accompanied by an increased incidence of cardiovascular events, drawing attention to the balance that must be achieved

between gastrointestinal protection and cardiovascular safety when selecting anti-inflammatory therapy. (13).

The CLASS Trial similarly evaluated the safety of celecoxib compared with non-selective NSAIDs. Although celecoxib demonstrated a reduction in symptomatic ulcers and gastrointestinal complications in several analyses, the overall benefit was less pronounced when patients receiving concomitant aspirin were included, underscoring the importance of patient selection and co-therapy (14).

Additional insight was provided by the CONDOR Trial, witch further explored this issue by comparing celecoxib monotherapy with diclofenac plus omeprazole in high gastrointestinal risk patients. The study found that celecoxib alone was associated with fewer clinically significant gastrointestinal events, suggesting that COX-2 inhibition may offer advantages even when proton pump inhibitors are used (15).

These trials collectively illustrate the complexity of NSAID-related gastrointestinal risk and highlight the importance of tailoring treatment decisions to individual patient risk factors.

A comprehensive meta-analysis published in 2025 by Tawfik AG et al., demonstrated marked variability in the risk of upper gastrointestinal bleeding among individual NSAIDs, with selective COX-2 inhibitors such as celecoxib exhibiting the lowest risk profile, while agents such as ketorolac were associated with dramatically increased bleeding risk, exceeding a 20-fold elevation in odds. These findings challenge the traditional perception of NSAIDs as a relatively uniform drug class and support a more nuanced approach to risk assessment and prescribing practices. In parallel, large pharmacovigilance analyses based on real-world datasets, including the FDA Adverse Event Reporting System, has likewise demonstrated distinct patterns of gastrointestinal toxicity across different NSAIDs, highlighting the importance of drug-specific safety profiles. In addition, observational cohort studies such as the EVIDENCE study have shown that serious gastrointestinal complications often develop in the absence of preceding symptoms and that adherence to gastroprotective strategies remains suboptimal in routine clinical practice. Collectively, these contemporary data strengthen the case for personalized therapeutic decision-making and reinforce the importance of integrating both randomized trial evidence and real-world data in the assessment of NSAID-related gastrointestinal risk.

The risk of NSAID-induced gastrointestinal bleeding is not uniform and is influenced by multiple patient-specific and treatment-related factors. Age remains one of the most important determinants, with elderly patients exhibiting a significantly higher risk due to reduced mucosal resilience, impaired healing capacity, and increased prevalence of comorbidities (16).

Dose and duration of NSAID therapy also play a critical role, with higher doses and prolonged exposure associated with increased risk. This relationship is likely mediated by cumulative prostaglandin depletion and progressive mucosal injury (17).

A history of peptic ulcer disease or prior gastrointestinal bleeding represents a strong predictor of recurrence, reflecting the presence of underlying mucosal vulnerability. In such patients, even short-term NSAID use may precipitate significant bleeding (18).

Concomitant use of other medications further amplifies risk. Anticoagulants and antiplatelet agents impair hemostasis, while corticosteroids and selective serotonin reuptake inhibitors may exacerbate mucosal injury. The combined use of these agents with NSAIDs results in a synergistic increase in bleeding risk (19).

Infection with Helicobacter pylori is another important factor that interacts with NSAID use.

NSAID-induced gastrointestinal injury represents a multifactorial process involving disruption of mucosal defense, impairment of microcirculation, and alterations in hemostasis. Insights from large clinical trials have improved understanding of risk stratification and therapeutic strategies, but the optimal management of these patients remains a challenge requiring individualized assessment.

2.2. Oral Anticoagulants and Bleeding Risk

Oral anticoagulants play a fundamental role in the prevention and treatment of thromboembolic disorders, particularly atrial fibrillation and venous thromboembolism. Over the past decades, anticoagulation therapy has undergone substantial evolution, from traditional vitamin K antagonists (VKAs), such as warfarin and acenocoumarol, to direct oral anticoagulants (DOACs), which provide more predictable pharmacological profiles and reduced monitoring requirements. Despite these therapeutic advances, gastrointestinal bleeding remains one of the most common and clinically relevant adverse event associated with anticoagulant therapy (1–3).

The gastrointestinal tract is especially susceptible to bleeding due to its rich vascularization and the frequent presence of underlying pathological conditions, such as peptic ulcers, angiodysplasia, or malignancies. Unlike NSAIDs, which exert direct damaging effects on the mucosal barrier, oral anticoagulants primarily increase bleeding risk by impairing normal hemostatic mechanism. As a result, pre-existing lesions that might otherwise remain clinically silent can become significant sources of hemorrhage (3). This distinction is of

particular importance when interpreting clinical presentations, as bleeding often reflects the unmasking of latent pathology rather than primary drug-induced injury.

The growing use of anticoagulants in aging populations has led to a parallel rise in anticoagulant-associated gastrointestinal bleeding, making it a substantial cause of hospital admissions and healthcare burden worldwide. The coexistence of multiple comorbidities, including cardiovascular disease, renal impairment, and polypharmacy, further complicates clinical management and risk stratification.

2.2.1 Historical Evolution of Oral Anticoagulants

The development of oral anticoagulants originated from observations of hemorrhagic disease in cattle consuming spoiled sweet clover, leading to the identification of dicoumarol. This discovery ultimately resulted in the synthesis of warfarin in the mid-20th century, initially used as a rodenticide and subsequently adopted into clinical practice and became one of the most widely used oral anticoagulants worldwide (4).

Acenocoumarol was later introduced as an alternative vitamin K antagonist characterized by a shorter half-life and more rapid pharmacodynamic response. It became widely adopted in European countries due to its flexibility in dose adjustment, although it is associated with greater variability in anticoagulation levels (5). Over time, both agents became essential tools in long-term anticoagulation, despite their limitations.

The well-recognized limitations of VKAs—including a narrow therapeutic window, delayed onset of action, and numerous dietary and pharmacological interactions—prompted the search for more predictable anticoagulant options. This led to the introduction of DOACs in the early 21st century, marking a major paradigm shift in anticoagulant therapy. By selectively inhibiting key components of the coagulation cascade, these agents provide effective thromboembolic protection while offering greater convenience and a more predictable therapeutic response than tradition VKAs (6).

2.2.2 The Coagulation Cascade: Functional Overview

The coagulation cascade is a highly coordinated enzymatic system that culminates in the formation of a stable fibrin clot. It begins with vascular injury, which exposes tissue factor and activates the extrinsic pathway. This leads to activation of factor VII and subsequently factor X. The intrinsic pathway amplifies this process through activation of factors VIII and IX.

Factor Xa represents a critical convergence point, catalyzing the conversion of prothrombin into thrombin. Thrombin is the central effector enzyme, converting fibrinogen

into fibrin, activating platelets, and amplifying the cascade. The clot is ultimately stabilized by factor XIII-mediated cross-linking (7).

In modern understanding, the coagulation process is better described using a cell-based model, in which coagulation occurs on the surface of activated platelets and endothelial cells. This model emphasizes the dynamic and localized nature of clot formation and highlights the importance of thrombin generation as the key determinant of effective hemostasis.

Pharmacological anticoagulants interfere with this cascade at distinct points, resulting in impaired clot formation and increased bleeding risk. The specific target within the cascade determines both the efficacy and safety profile of each anticoagulant.

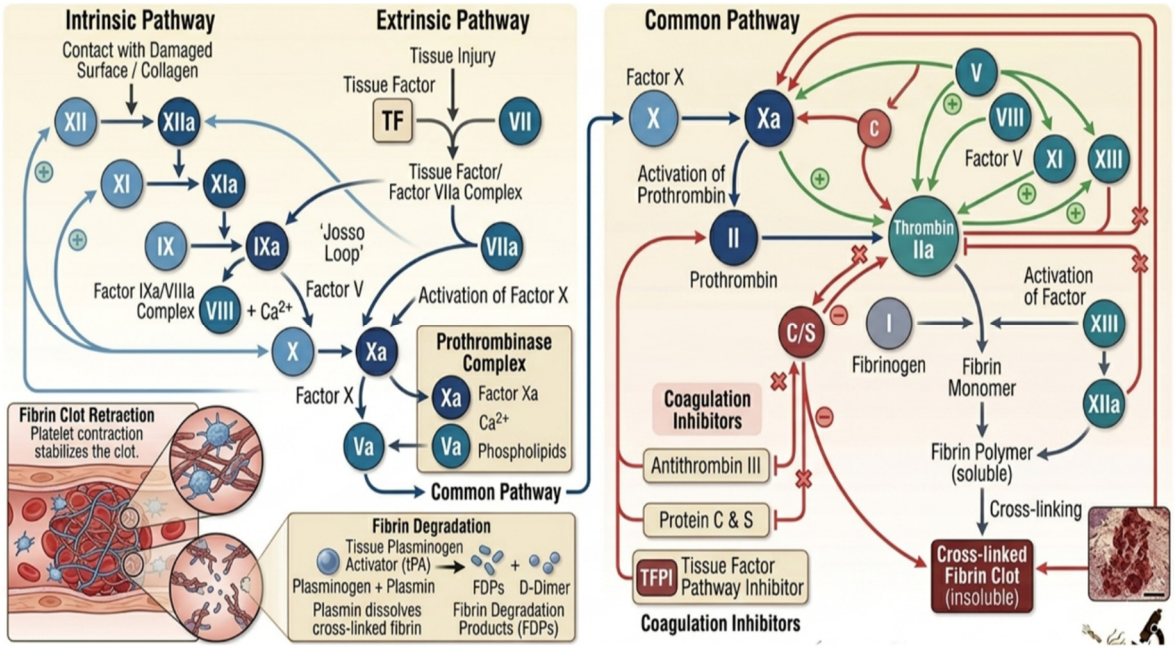

Fig. 1. Coagulation Cascade

(Adapted from: Torsten G. Loof, Christin Deicke and Eva Medina, The role of coagulation/fibrinolysis during Streptococcus pyogenes infection, Frontiers in Cellular and Infection Microbiology, September 2014, Volume 4, Article 128)

2.2.3 Vitamin K Antagonists: Warfarin and Acenocoumarol

Vitamin K antagonists exert their anticoagulant effect by inhibiting vitamin K epoxide reductase (VKORC1), thereby preventing regeneration of reduced vitamin K required for activation of clotting factors II, VII, IX, and X. This leads to the synthesis of dysfunctional clotting factors and reduced thrombin generation (8).

Warfarin is characterized by a long half-life and relatively stable anticoagulant effect once steady state is achieved. However, it is influenced by dietary vitamin K intake, genetic

polymorphisms, and drug interactions, necessitating regular INR monitoring. The variability in patient response and the need for frequent dose adjustment remain significant limitations of therapy.

Acenocoumarol, in contrast, has a shorter half-life and more rapid pharmacodynamic response, resulting in greater variability and potential instability in anticoagulation. This may lead to fluctuations in INR values and increased risk of both bleeding and thrombotic events if not carefully managed (5).

Gastrointestinal bleeding associated with VKAs is strongly correlated with supratherapeutic INR levels and often reflects bleeding from pre-existing mucosal lesions. The relationship between INR and bleeding risk is well established, with exponential increases in bleeding risk observed at higher INR values (9).

2.2.4 Direct Oral Anticoagulants: Mechanisms of Action and Clinical Implications

The development of DOACs represents a fundamental shift in anticoagulation therapy, moving from indirect modulation of clotting factor synthesis to selective inhibition of specific enzymes within the coagulation cascade. This targeted approach allows for more predictable pharmacological effects while maintaining effective antithrombotic activity.

Dabigatran etexilate is a prodrug converted into dabigatran, a direct inhibitor of thrombin (factor IIa). By binding to thrombin, it prevents the conversion of fibrinogen into fibrin and inhibits thrombin-mediated platelet activation and amplification of coagulation (10).

Due to incomplete gastrointestinal absorption, dabigatran may exert local mucosal effects, potentially contributing to gastrointestinal symptoms and increasing propensity for bleeding. Renal clearance is the primary route of elimination, making kidney function a major determinant of both drug exposure and bleeding risk (11).

Dabigatran’s pharmacokinetic profile is characterized by rapid onset of action and relatively short half-life compared with VKAs, facilitating peri-procedural management and reducing the need for prolonged interruption before invasive interventions.. However, its reliance on renal elimination necessitates careful patient selection, particularly in elderly individuals and those with chronic kidney disease. Impaired drug elimination may result in accumulation, leading to excessive anticoagulation and increased bleeding risk.

Another important aspect of dabigatran therapy is its interaction with P-glycoprotein transporters, which influence drug absorption and elimination. Agents such as amiodarone or verapamil, also P-glycoprotein inhibitors, increase circulating dabigatran concentrations, thereby enhancing anticoagulant effects and elevating bleeding risk. These pharmacological

considerations underscore the importance of individualized dosing and careful review of concomitant medications.

In contrast to dabigatran, factor Xa inhibitors exert their anticoagulant effect at an earlier stage of the coagulation cascade by preventing thrombin generation. Factor Xa occupies a pivotal position within the coagulation cascade, serving as the convergence point of the intrinsic and extrinsic pathways. Through the conversion of prothrombin (factor II) to thrombin (factor IIa), it drives the amplification phase of coagulation of factor Xa therefore results in a marked reduction in thrombin generation, limiting fibrin formation and clot stabilization. Unlike direct thrombin inhibitors, which act on circulating thromb. Consequently, inhibition of factor Xa leads to a substantial reduction in thrombin production, limiting fibrin generation and impairing clot stabilization. Edoxaban demonstrates dose-dependent effects, with higher doses associated with increased bleeding (12–14). Factor Xa inhibition interrupts the coagulation cascade at a critical amplification step, reducing thrombin generation without directly inhibiting circulating thrombin. This mechanism preserves some physiological hemostatic activity, which may partly explain differences in bleeding patterns compared with direct thrombin inhibitors.

Edoxaban demonstrates predictable pharmacokinetics and a linear dose–response relationship, allowing for simplified dosing strategies. However, its anticoagulant effect is strongly influenced by renal function, as a significant proportion of the drug is eliminated unchanged by the kidneys. Higher-dose regimens have been associated with increased bleeding risk, whereas reduced doses provide improved safety at the potential cost of reduced efficacy in preventing thromboembolic events. Achieving an appropriate balance between efficacy and safety therefore remains essential, particularly in patients with impaired renal function, low body weight, or concomitant medication that alter drug exposure. Careful dose adjustment based on individual patient characteristics is critical to maximizing therapeutic benefit while minimizing the risk of bleeding.

Rivaroxaban is characterized by rapid oral absorption and high bioavailability, which is notably enhanced when administered with food. As a once-daily agent, it produces considerable to fluctuations in plasma concentration, with peak levels that may transiently elevated bleeding risk. Elimination occurs through hepatic metabolism, primarily via cytochrome P450 enzymes alongside renal excretion-rendering the drug susceptible to clinically significant drug–drug interactions and vulnerable to the effects of hepatic or renal impairment.

Apixaban offers a more favorable pharmacokinetic profile by virtue of its twice-daily dosing schedule, which yields lower peak plasma concentrations and reduced intra-

dayvariability. This dosing regimen provides more stable anticoagulation and is associated with lower gastrointestinal bleeding risk. Its multi-pathway elimination, including hepatic metabolism and renal clearance, contributes to greater tolerability in patients with varying degrees of renal impairment. This pharmacological profile is thought to underlie its consistently lower rates of gastrointestinal bleeding observed in both clinical trials and real-world studies.

Edoxaban exhibits predictable pharmacokinetics with once-daily dosing and a relatively linear dose-response relationship. Its anticoagulant effect is influenced by renal function, and dose adjustments are required in patients with impaired clearance. Clinical evidence suggest that reduced-dose regimens are associated with favorable bleeding profile; however, this benefit must be carefully weighed against the potential for diminished thromboembolic protection, underscoring the importance of individualized dosing decision in clinical practice.

2.2.5 Mechanistic Implications for Gastrointestinal Bleeding

Differences in pharmacokinetics and pharmacodynamics contribute to variability in bleeding risk. Dabigatran's luminal exposure and rivaroxaban's peak concentrations may predispose to bleeding, whereas apixaban's stable profile offers improved safety (11, 14).

Local drug effects within the gastrointestinal tract, particularly in the case of dabigatran, may impair mucosal integrity or interfere with healing processes. Dabigatran etexilate is administered as a prodrug that requires an acidic environment for optimal absorption, and its formulation contains tartaric acid to facilitate this process. This acidic component may exert a direct topical effect on the gastrointestinal mucosa, contributing to irritation and promoting mucosal vulnerability (20, 21). In addition, incomplete absorption of dabigatran in the proximal small intestine results in the presence of active drug within the intestinal lumen, where it may come into direct contact with the mucosal surface (22).

This luminal exposure may exacerbate existing mucosal lesions, such as erosions or ulcers, by impairing local hemostasis and delaying epithelial restitution. Unlike vitamin K antagonists, which act systemically, dabigatran's local presence within the gastrointestinal tract introduces an additional mechanism by which bleeding risk may be increased (23). Furthermore, the inhibition of thrombin at the mucosal level may interfere with physiological processes involved in tissue repair, including fibrin formation and stabilization of the extracellular matrix, both of which are essential for effective mucosal healing (24).

The combination of these local and systemic effects creates a permissive environment for bleeding, particularly in regions of pre-existing injury. This phenomenon may partly explain the higher incidence of gastrointestinal bleeding observed with dabigatran in certain clinical

studies, especially at higher doses and in vulnerable patient populations such as the elderly or those with underlying gastrointestinal pathology (25).

2.2.6 Comparative Risk of Gastrointestinal Bleeding

DOACs reduce intracranial hemorrhage compared with VKAs but show variable gastrointestinal bleeding risk. Dabigatran and rivaroxaban increase risk, whereas apixaban demonstrates a more favorable profile (15).

These differences are clinically relevant and should guide anticoagulant selection, particularly in patients with a history of gastrointestinal bleeding or other risk factors.

The heterogeneity in gastrointestinal bleeding risk among anticoagulants arise from a combination of pharmacodynamic and pharmacokinetic factors, as well as variations in study populations and clinical contexts. Although randomized controlled trials established the initial comparative framework, subsequent meta-analyses and real-world observational studies have provided a more nuanced understanding of these safety profiles. Notably, pooled analyses have consistently demonstrated that factor Xa inhibitors as a class exhibit variable gastrointestinal safety profiles, with a non-uniform gastrointestinal bleeding risk, with apixaban emerging as the agent associated with the lowest relative risk.

Dabigatran, particularly at higher doses, has been associated with a higher incidence of gastrointestinal bleeding in comparison to warfarin. This increased risk appears to reflect not only its systemic anticoagulant effect but also to its potential local action within the gastrointestinal tract. The presence of active drug in the intestinal lumen may contribute to mucosal irritation and exacerbate bleeding from pre-existing lesions. Evidence from clinical trails indicate that lower-dose regimens are associated with improved safety outcomes highlighting the importance of individualized dose selection.

Rivaroxaban has likewise been linked to an increased risk of gastrointestinal bleeding, especially among older adults. Its once-daily dosing schedule produce relatively high peak plasm concentrations, which may transiently amplify anticoagulant activity and increase susceptibility to hemorrhagic events. Additionally, variability in absorption and metabolism may further influence individual patient risk.

Apixaban consistently demonstrates a more favorable gastrointestinal safety profile in both randomized trials and observational studies. Its twice-daily dosing regimen results in more stable plasma concentrations and reduce fluctuations in anticoagulant activity, thereby minimizing peak-related bleeding risk. Furthermore, its balanced elimination through renal and

hepatic pathways contributes to a more predictable pharmacokinetic profile, particularly in patients with moderate renal impairment.

Edoxaban presents an intermediate profile, with bleeding risk largely influenced by dose selection related to dose and individual patient characteristics. Clinical trials have shown that lower-dose regimens can substantially decrease bleeding risk while preserving acceptable antithrombotic efficacy, underscoring the importance of individualized dosing strategies.

Comparative studies have also highlighted the influence of patient-related factors on bleeding risk. Advanced age, impaired renal function, and a history of gastrointestinal disease are among the most important predictors for hemorrhagic complications and can significantly influence the relative safety of different anticoagulants. In particular, elderly patients appear to derive greater benefit from agents with more stable pharmacokinetic profiles, such as apixaban, while those with impaired renal function require careful dose adjustment, especially when treated with dabigatran.

Evidence from real-world has further emphasized that the relative risk of gastrointestinal bleeding is influenced not only by the anticoagulant itself but also by the clinical circumstances in which it is prescribed. Concomitant use of antiplatelet agents or NSAIDs significantly increases bleeding risk across all anticoagulant classes, although the magnitude of this effect varies. These findings underscore the importance of comprehensive medication review and careful risk stratification when selecting anticoagulant therapy.

Another important consideration is the anatomical location and clinical severity of gastrointestinal bleeding. Some studies suggest that DOAC-associated bleeding may more frequently involve the lower gastrointestinal tract compared with VKA-associated bleeding, although findings are not entirely consistent. The clinical implications of this observation remain an area of ongoing research. From a practical standpoint, anticoagulant selection should be individualized, guided by a careful assessment of both thrombotic and bleeding risks. In patients considered to be at high risk of gastrointestinal bleeding, agents with more favorable safety profiles, such as apixaban, may be preferred. Conversely, in patients with lower bleeding risk but higher thrombotic risk, other agents may represent appropriate therapeutic options depending on clinical context.

Recent real-world and meta-analytic data have further reinforced these differences, consistently demonstrating that apixaban is associated with a lower risk of gastrointestinal bleeding compared with rivaroxaban and dabigatran, particularly in elderly populations and those with multiple comorbidities (15-19).

Accumulating evidence from observational studies suggest that the gastrointestinal safety profile of DOACs is influenced not only by the pharmacological properties of the agents but also by patient-specific factors and concomitant therapies, highlighting the importance of individualized anticoagulant selection (20-21).

More recent nationwide cohort studies and real-world analyses have confirmed that these patterns persist across different healthcare systems, with consistent findings supporting the favorable gastrointestinal safety profile of apixaban and the higher bleeding risk associated with rivaroxaban in routine clinical practice (16, 18, 19).

Additionally, large observational datasets continue to emphasize the critical role of polypharmacy and comorbidities in modulating bleeding risk, reinforcing the importance of individualized risk assessment in anticoagulant therapy (19, 20).

2.2.7 Clinical Evidence

Landmark randomized controlled trials, including RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF–TIMI 48, have established the efficacy and safety profile of direct oral anticoagulants (DOACs) in comparison with vitamin K antagonists. These studies consistently demonstrated that DOACs are at least non-inferior to warfarin in the prevention of stroke or systemic embolism in patients with atrial fibrillation, while also showing important differences in bleeding outcomes, particularly with respect to gastrointestinal hemorrhage (1–4, 14). These trials form the foundation of current clinical practice, although their findings must be interpreted alongside real-world data to fully appreciate their applicability in broader patient populations.

The RE-LY trial (Randomized Evaluation of Long-Term Anticoagulation Therapy) evaluated more than 18,000 patients with atrial fibrillation and compared two fixed doses of dabigatran (110 mg and 150 mg twice daily) with warfarin (25). Dabigatran 150 mg twice daily significantly reduced the annual rate of stroke or systemic embolism to 1.11%, compared with 1.69% per year in the warfarin group, representing a relative risk reduction of approximately 34%. The lower dose (110 mg) demonstrated non-inferiority, with an annual event rate of 1.53%. Major bleeding rates were 3.36% per year with warfarin, compared with 3.11% for dabigatran 150 mg and 2.71% for dabigatran 110 mg. However, gastrointestinal bleeding was more frequent with the higher dabigatran dose, reaching approximately 1.5% per year versus 1.0% per year with warfarin, highlighting a dose-dependent increase in gastrointestinal risk.

The ROCKET-AF trial evaluated rivaroxaban in over 14,000 high-risk patients with atrial fibrillation (26). Rivaroxaban proved non-inferiority to warfarin for the prevention of stroke

and systemic embolism with annual events rates of 2.1% per year and 2.4% respectively. Major and non-major clinically relevant bleeding occurred at similar overall rates between the two groups (14.9% vs 14.5% per year), but rivaroxaban was associated with a higher incidence of gastrointestinal bleeding (3.2% vs 2.2% per year). This observation has been linked, at least in part, to higher peak plasma concentrations resulting from once-daily dosing and its pharmacokinetic profile.

A different safety profile emerged from the ARISTOTLE trial which demonstrated a more favorable bleeding profile for apixaban (27). In this study of over 18,000 patients, apixaban reduced the annual rate of stroke or systemic embolism to 1.27%, compared with 1.60% with warfarin. Major bleeding was significantly reduced with apixaban (2.13% vs 3.09% per year), corresponding to a relative risk reduction of approximately 31%. Notably, rates of gastrointestinal bleeding with apixaban were comparable to or slightly lower than those observed with warfarin, distinguishing it from other DOACs and contributing to its favorable safety profile in patients at increased bleeding risk.

The ENGAGE AF–TIMI 48 trial evaluated the efficacy and safety of edoxaban in more than 21,000 patients with atrial fibrillation and demonstrated non-inferiority to warfarin across both high-dose and low-dose regimens (28). The high-dose edoxaban strategy (60 mg daily) demonstrated stroke or systemic embolism rates of 1.18% per year, compared with 1.50% with warfarin. Major bleeding occurred at rates of 2.75% per year with high-dose edoxaban and 3.43% with warfarin. However, gastrointestinal bleeding was increased with the high-dose regimen (approximately 1.5% vs 1.2% per year), whereas the lower-dose regimen was associated with reduced risk of bleeding but slightly higher thromboembolic risk, emphasizing the need to balance efficacy and safety when selecting the appropriate dose.

A notable finding shared across the pivotal trails was the substantial reduction in intracranial bleeding with DOAC therapy compared with warfarin, relative risk reduction generally ranging from 30% to 70% (25-28). This consistent benefit represents one of the principal advantages of DOACs and has played a major role in its widespread incorporation in clinical practice. However, the variability in gastrointestinal bleeding risk remains a key limitation, particularly for dabigatran and rivaroxaban.

Evidence from pooled analyses has largely confirmed these observation demonstrating that while DOACs reduce intracranial bleeding by approximately 50%, they may increase gastrointestinal bleeding by 20–30% overall, with important differences between individual agents (29). Apixaban has consistently demonstrated the most favorable gastrointestinal safety

profile with the lowest gastrointestinal bleeding risk, whereas rivaroxaban and higher-dose dabigatran are associated with higher rates, especially in elderly patients.

It is important to recognize that the populations included in randomized trials are often highly selected, with exclusion of patients at extreme risk of bleeding or with multiple comorbidities. As a result, real-world studies have provided valuable complementary insights, often confirming trial findings but also highlighting the influence of age, renal function, and polypharmacy on bleeding risk. These factors are particularly relevant in clinical practice, where individualized anticoagulant selection is essential.

In summary, the available clinical evidence demonstrates that DOACs provide effective anticoagulation with a more favorable overall safety profile compared with vitamin K antagonists, particularly in terms of intracranial hemorrhage. However, gastrointestinal bleeding risk varies significantly among agents, and this variability must be carefully considered when selecting therapy, especially in patients with pre-existing gastrointestinal disease or additional risk factors.

In recent years, registry-based and real-world evidence has assumed a central role in elucidating the safety profile of oral anticoagulants in routine clinical practice. Unlike randomized controlled trials, which often involve highly selected patient populations under controlled conditions, registry studies encompass a broader and more representative spectrum of patients, including elderly individuals and those with multiple comorbidities and complex therapeutic regimens.

European registry-based research, particularly from Scandinavian countries such as Denmark and Sweden, has provided robust population-level data through linkage of prescription databases, hospital admissions, and mortality records. These studies have been instrumental in characterizing anticoagulant-associated gastrointestinal bleeding and have consistently demonstrated variability in bleeding risk among different agents. Notably, apixaban has been associated with lower rates of gastrointestinal bleeding compared with rivaroxaban and dabigatran, findings that are concordant with results from randomized clinical trials (27, 29).

Similarly, large observational datasets from the United Kingdom, including the analyses from the Clinical Practice Research Datalink and Hospital Episode Statistics, have further underscored the importance of individual patient characteristics in determining bleeding risk. These analyses have shown the critical role of advanced age, impaired renal function, and a history of gastrointestinal disease. In addition, concomitant medication use has emerged as a key contributor to hemorrhagic risk. In particular, polypharmacy—especially the combined use

of anticoagulants with non-steroidal anti-inflammatory drugs or antiplatelet agents—has emerged as a major determinant of bleeding risk in real-world settings.

Additional insights have been provided by large international registries such as GARFIELD-AF which encompass broad and diverse patient populations across multiple healthcare systems, including Europe. Data from these registries consistently demonstrate that major bleeding, including gastrointestinal hemorrhage, remains a significant complication of anticoagulant therapy and is strongly associated with increased mortality, prolonged hospitalization, and higher healthcare utilization.

2.2.8 Risk Factors and Clinical Considerations

The risk of gastrointestinal bleeding during anticoagulant therapy is influenced by a complex interplay of patient-related and treatment related factors. Among the most important are advanced age, impaired renal function, prior gastrointestinal disease, and use of concomitant medications. Renal impairment significantly increases DOAC exposure and bleeding risk, while polypharmacy further compounds this risk (18).

Advanced age represents one of the most consistently recognized risk factors for anticoagulant-associated gastrointestinal bleeding. Elderly patients frequently present multiple comorbidities, including reduced physiological reserve, increased prevalence of comorbidities, and higher likelihood of polypharmacy. Age-related changes in drug metabolism and renal function further contribute to increased anticoagulant exposure, thereby amplifying bleeding risk.

Renal function plays a particularly important role in patients receiving DOAC therapy. Since several DOACs, especially dabigatran, rely heavily on renal elimination, reduced renal clearance leads to drug accumulation and prolonged anticoagulant activity. Even moderate renal impairment can significantly alter drug pharmacokinetics, necessitating dose adjustment and careful monitoring. In contrast, vitamin K antagonists are less dependent on renal excretion but remain susceptible to fluctuations due to other systemic factors.

Pre-existing gastrointestinal pathology, including peptic ulcer disease, gastrointestinal bleeding, or inflammatory mucosal conditions, is a strong predictor of recurrent bleeding. The presence of Helicobacter pylori infection may further increase the risk of disrupting mucosal defenses and promoting ulcer formation. In such patients, anticoagulant therapy may unmask or exacerbate pre-existing lesions, leading to clinically significant hemorrhage.

Concomitant medication use also has a substantial impact on hemorrhagic risk.. The combined use of anticoagulants with non-steroidal anti-inflammatory drugs or antiplatelet

agents significantly increases the likelihood of gastrointestinal bleeding through complementary mechanisms involving the impaired mucosal protection and hemostasis. Additional medications, such as corticosteroids and selective serotonin reuptake inhibitors, have been associated with an increased risk of gastrointestinal bleeding, potentially through their effects on mucosal integrity and platelet function.

The presence of significant comorbidities, including liver disease, malignancy, and cardiovascular disease, further influence bleeding risk. Hepatic dysfunction may alter the both the synthesis of coagulation factors and drug metabolism, while malignancy may predispose to both bleeding and thrombosis. Moreover, patients with cardiovascular disease frequently require combination antithrombotic therapy, further increasing bleeding risk.

Finally, the intensity and appropriateness of anticoagulation therapy are critical determinants of bleeding risk. Among patients receiving VKAs, inadequate control of the international normalized ratio, particularly supratherapeutic values, is strongly associated with major bleeding events. In patients receiving DOACs, inappropriate dosing may likewise compromise safety, as excessive doses increase bleeding risk whereas insufficient doses may reduce protection against thromboembolic complications, highlighting the importance of individualized therapy based on patient-specific characteristics.

2.2.9 Management and Reversal of Anticoagulant-Associated Gastrointestinal Bleeding

The management of gastrointestinal bleeding in anticoagulated patients requires rapid stabilization, identification of the bleeding source, and appropriate reversal of anticoagulation. Initial management includes hemodynamic assessment and resuscitation, with a restrictive transfusion strategy generally recommended (30). Anticoagulants should be withheld immediately.

For VKAs, reversal is achieved with vitamin K and prothrombin complex concentrates, allowing rapid normalization of INR (31). For DOACs, idarucizumab reverses dabigatran, while andexanet alfa reverses factor Xa inhibitors. In the absence of these agents, PCCs may be used (32, 33).

Endoscopy is essential for diagnosis and treatment, and proton pump inhibitors reduce rebleeding risk. Anticoagulation should generally be resumed within 3–7 days once hemostasis is achieved, balancing thrombotic and bleeding risks (32).

The initial stabilization phase requires continuous monitoring of vital signs and laboratory parameters, including hemoglobin, hematocrit, platelet count, renal function, and coagulation indices. Early risk stratification is essential in determining the level of care,

including the need for intensive monitoring or admission to a high-dependency unit. Clinical scoring systems, such as the Glasgow-Blatchford score, may assist in identifying patients at high risk of adverse outcomes and guiding early management decisions.

In patients presenting with severe or ongoing hemorrhage, prompt multidisciplinary collaboration is essential. Coordination between gastroenterologists, hematologists, cardiologists, and intensivists allows for individualized management strategies, particularly in patients with high thrombotic risk or complex comorbid conditions. The decision to reverse anticoagulation must always consider the underlying indication for therapy, as abrupt cessation may increase the risk of thromboembolic events.

For patients receiving vitamin K antagonists, the choice of reversal strategy depends on the severity of bleeding and the INR level. Intravenous vitamin K provides sustained reversal by restoring endogenous clotting factor synthesis, although its onset of action is delayed. Prothrombin complex concentrates offer rapid correction and are preferred in life-threatening bleeding. Fresh frozen plasma may be used when PCC is unavailable, although its use is limited by slower onset and risk of volume overload.

In patients treated with DOACs, additional considerations include the timing of the last dose, renal function, and the pharmacokinetic profile of the specific agent. Activated charcoal may be considered in cases of recent ingestion to reduce further drug absorption. Hemodialysis may be effective in removing dabigatran due to its low protein binding, whereas it is ineffective for factor Xa inhibitors.

Endoscopic management plays a central role in achieving definitive hemostasis. Early endoscopy, ideally within 24 hours of presentation, is associated with improved outcomes and reduced rebleeding rates. The choice of endoscopic therapy depends on the underlying lesion and may include injection therapy, thermal coagulation, or mechanical clipping. In high-risk lesions, combination therapy is often employed to maximize hemostatic efficacy.

Adjunctive pharmacological therapy with proton pump inhibitors constitutes a cornerstone of management in patient with suspected peptic ulcer bleeding and contributes to clot stabilization by maintaining an intragastric pH conducive to platelet aggregation and fibrin formation. In cases where bleeding persists despite endoscopic and pharmacological therapy, additional interventions such as transcatheter arterial embolization or surgical management may be required to achieve definitive control of hemorrhage.

An important component of management is the optimal timing for resumption of anticoagulant therapy. Current evidence suggests that restarting early the anticoagulation is associated with reduced thromboembolic events and improved survival, although it must be

balanced against the risk of rebleeding. Factors influencing this decision include the severity of the initial bleeding episode, the stability of hemostasis, and the patient's underlying thrombotic risk.

Long-term management should focus on secondary prevention strategies. These include eradication of Helicobacter pylori infection when present, long-term proton pump inhibitor therapy in high-risk patients, and careful review of concomitant medications. Whenever possible, the selection of anticoagulant therapy should be optimized to minimize bleeding risk, with consideration given to agents associated with more favorable gastrointestinal safety profiles.

Recent systematic reviews and real-world studies has provided additional support for the use of targeted reversal agents in the management of anticoagulant-associated bleeding. In particular, andexanet alfa has demonstrated effectiveness in rapidly reversing the anticoagulant activity of factor Xa inhibitors and facilitating hemostatic control in patient with major bleeding events, although concerns regarding cost and thrombotic complications remain (33, 34)

In addition, recent studies have reinforced the safety of early resumption of anticoagulation following successful management of gastrointestinal bleeding, demonstrating improved survival and a lower incidence of thromboembolic events when therapy is reintroduced in appropriately selected patients (35, 36).

2.3. Antiplatelet Therapy and Gastrointestinal Bleeding

Antiplatelet therapy remains a cornerstone in the prevention and management of atherothrombotic disease, particularly in patients with acute coronary syndromes and those undergoing percutaneous coronary intervention. Over the past decade, advances in pharmacology and clinical trial evidence have led to the widespread adoption of more potent P2Y12 inhibitors and evolving strategies for dual antiplatelet therapy (DAPT). However, these therapeutic advances have been accompanied by an increased risk of bleeding, with the gastro-intestinal tract representing the most common site of hemorrhagic complications (37, 38).

Recent evidence suggests that gastrointestinal bleeding risk has become even more clinically relevant with the use of newer-generation antiplatelet agents, particularly ticagrelor and prasugrel, which provide more potent platelet inhibition but at the cost of increased bleeding (38,40). This evolving balance between ischemic protection and bleeding risk has become a central theme in modern antiplatelet therapy.

2.3.1 Platelet Physiology and Primary Hemostasis

Platelets play a fundamental role in primary hemostasis through adhesion, activation, and aggregation. Following endothelial injury, exposure of subendothelial structures such as collagen and von Willebrand factor facilitates platelet adhesion via glycoprotein receptors, including glycoprotein Ib and glycoprotein VI. Subsequent activation leads to intracellular signaling cascades, cytoskeletal rearrangement, and release of pro-aggregatory mediators, including adenosine diphosphate (ADP) and thromboxane A□, which amplify platelet recruitment and aggregation (1,2).

Activated platelets undergo conformational changes that enable the activation of glycoprotein IIb/IIIa (integrin αIIbβ3), allowing fibrinogen binding and cross-linking of adjacent platelets. This process results in the formation of a platelet plug, which is further stabilized by fibrin generated through activation of the coagulation cascade. Thrombin plays a central role in this interaction, serving as a potent platelet activator and bridging primary and secondary hemostasis (3).

In physiological conditions, platelet activation is tightly regulated by endogenous inhibitory mechanisms, including nitric oxide and prostacyclin released by intact endothelium. These mediators prevent inappropriate platelet aggregation and maintain vascular homeostasis. Disruption of this balance, either by endothelial injury or pharmacological intervention, can lead to altered hemostatic responses and increased bleeding risk.

2.3.2 Aspirin and Cyclooxygenase Inhibition

Aspirin exerts its antiplatelet effect through the irreversible inhibition of cyclooxygenase-1 (COX-1) by acetylating a serine residue within the enzyme, thereby preventing the conversion of arachidonic acid to prostaglandin H□ and ultimately thromboxane A□ (4). Because platelets are unable to generate new COX-1 mediator due to the absence of a nucleus, this inhibitory effect persists throughout their lifespan, which is approximately 7–10 days. This leads to increased susceptibility to mucosal injury and ulcer formation (7). In addition, aspirin can exert a direct topical iritative effect on the gastric epithelium. These mechanisms explain why aspirin remains one of the most significant pharmacological contributors to upper gastrointestinal bleeding worldwide. By inhibiting prostaglandin synthesis in the gastric mucosa, aspirin reduces mucosal defense mechanisms, including mucus and bicarbonate secretion, mucosal blood flow, and epithelial regeneration.

While this mechanism is highly effective in reducing platelet aggregation and preventing arterial thrombosis, it also has important consequences for gastrointestinal physiology. Prostaglandins derived from COX-1 play a crucial role in maintaining mucosal integrity by stimulating mucus and bicarbonate secretion, promoting mucosal blood flow, and supporting epithelial repair. Inhibition of these protective mechanisms contributes directly to mucosal injury and increases susceptibility to ulcer formation and bleeding (5).

2.3.3 P2Y12 Receptor Inhibitors

P2Y12 inhibitors, including clopidogrel, prasugrel, and ticagrelor, block ADP-mediated platelet activation by inhibiting the P2Y12 receptor on the platelet surface. This prevents activation of the glycoprotein IIb/IIIa receptor complex and reduces platelet aggregation (6). Clopidogrel and prasugrel are prodrugs that require hepatic activation via cytochrome P450 enzymes, leading to variability in antiplatelet response due to genetic polymorphisms and drug interactions. Ticagrelor, in contrast, is a direct-acting agent with reversible receptor binding and more rapid onset of action, resulting in more consistent platelet inhibition.

The degree of platelet inhibition achieved with these agents correlates with both antithrombotic efficacy and bleeding risk. More potent inhibition, as seen with prasugrel and ticagrelor, is associated with improved prevention of ischemic events but also an increased risk of major bleeding, including gastrointestinal hemorrhage (7).

Clopidogrel remains one of the most frequently prescribed P2Y12 receptor inhibitors, largely used due to its well-established efficacy, favorable safety profile, particularly in patients at high bleeding risk. Following hepatic bioactivation, it irreversibly inhibits the P2Y12 receptor, thereby reducing ADP-mediated platelet activation and aggregation. Compared with newer-generation P2Y12 inhibitors, clopidogrel is generally associated with a lower risk of gastrointestinal bleeding, making it a attractive option for patients with underlying gastrointestinal pathology.

Recent meta-analyses suggest that newer-generation P2Y12 inhibitors, particularly ticagrelor and prasugrel, are associated with significantly increased gastrointestinal bleeding risk compared with clopidogrel. A large meta-analysis published in 2025 which included approximately 60,000 patients reported that these agents increase the risk of gastrointestinal bleeding by approximately 30% (RR ≈ 1.31), with prasugrel exhibiting the highest risk within the class (42).

These findings align with the results of earlier clinical trials such as PLATO and TRITON-TIMI 38, which showed improved cardiovascular outcomes but with higher rates of non-procedural bleeding, including clinically significant gastrointestinal hemorrhage.

The increased bleeding risk is primarily attributable to more potent and consistent inhibition of platelet activity, which can impair formation and maintenance of effective hemostatic plugs at sites of mucosal bleeding.

2.3.4 Dual Antiplatelet Therapy and Clinical Implications

The combination of aspirin and a P2Y12 inhibitor constitutes dual antiplatelet therapy (DAPT), which is a cornerstone in the management of acute coronary syndromes and after percutaneous coronary intervention. By targeting two distinct pathways of platelet activation, DAPT provides synergistic inhibition of platelet aggregation and significantly reduces the risk of thrombotic events (42).

Both clinical trials and guideline-based recommendations have demonstrated that DAPT reduces the incidence of myocardial infarction, stent thrombosis, and cardiovascular death. However, this enhanced antithrombotic efficacy is accompanied by a proportional increase in bleeding risk. Gastrointestinal bleeding is one of the most common and clinically relevant complications associated with DAPT, particularly in patients with established risk factors such as advanced age, prior ulcer disease, or concomitant use of anticoagulants (9).

However, recent guidelines and studies have shifted toward shorter DAPT durations and individualized treatment strategies.

Reflecting this shift, updated guidelines (2023–2025) recommend:

- Use of ticagrelor or prasugrel over clopidogrel in patients with low bleeding risk
- Consideration of shortened DAPT (1–3 months) followed by P2Y12 monotherapy in high bleeding risk patients (38, 43).

Recent trials such as TWILIGHT have shown that discontinuation of aspirin after a short course of DAPT reduced bleeding events without a corresponding reduction of ischemic outcomes.

Importantly, DAPT has been associated with a up to 7-fold increase in the risk of gastrointestinal compared with antiplatelet monotherapy, highlighting the importance of careful patient selection and preventive measures. The optimal duration of DAPT remains an area of ongoing investigation as shorter treatment may reduce bleeding risk, whereas prolonged therapy provides additional protection against thrombotic events. Current clinical practice guidelines recommend individualized decision-making based on a careful assessment of ischemic versus bleeding risk.

2.3.5 Pathophysiology of Gastrointestinal Injury with Antiplatelet Therapy

The risk of gastrointestinal bleeding among patients receiving antiplatelet therapy is influenced by a complex interplay of individual patient characteristics, underlying medical conditions, and treatment-related factors. Advanced age remains one of the most robust predictors of bleeding, reflecting not only an increased burden of comorbidities but also age-associated changes in mucosal protection mechanisms, reduced regenerative tissue capacity, and altered pharmaco-kinetics. In addition, a prior history of peptic ulcer disease or previous gastrointestinal bleeding markedly increases the risk of recurrent hemorrhagic events, underscoring the need for rigorous risk assessment in this high risk population (1, 43, 44).

Concomitant pharmacotherapy represents a critical and often modifiable determinant of bleeding risk. The combined use of antiplatelet agents with non-steroidal anti-inflammatory drugs, corticosteroids, or anticoagulants results in synergistic impairment of mucosal integrity and hemostatic function (3, 45). In parallel, *Helicobacter pylori* infection represents a key pathogenic factor by disrupting mucosal defense mechanism and promoting ulcerogenesis. When antiplatelet therapy is administered in the presence of *H. pylori* infection, the risk of gastrointestinal bleeding significantly amplifies, thereby supporting guideline-recommended strategies for screening and eradication in high-risk individuals (46).

Underlying systemic diseases exert profound effects on bleeding susceptibility through multifactorial mechanisms. Chronic kidney disease is characterized by uremic platelet dysfunction, characterize by impaired adhesion, activation, and aggregation, which predisposes patients to bleeding even in the absence of antithrombotic therapy, a risk that is further amplified by platelet inhibition (47). Similarly, chronic liver disease contributes to a fragile hemostatic balance through reduced synthesis of coagulation factors, thrombocytopenia secondary to hypersplenism, and the hemodynamic consequences of portal hypertension, including the development of varices and portal hypertensive gastropathy (48). Malignancy is also recognized as an additional high-risk condition for gastrointestinal bleeding. Several mechanism as tumor-related mucosal disruption, neoangiogenesis, and treatment-induced cytopenias collectively increase the propensity for gastrointestinal hemorrhage (44).

At the mucosal level, the pathogenesis of bleeding reflects disruption of the finely regulated balance between aggressive luminal factors and protective mechanisms. Gastric mucosal integrity is maintained through coordinated processes involving mucus and bicarbonate secretion, epithelial restitution, and adequate mucosal perfusion. Although antiplatelet agents do not directly induce mucosal injury, they critically impair primary

hemostasis at sites of microscopic damage, thereby facilitating progression from subclinical lesions to clinically significant bleeding (3). This mechanism is particularly relevant in patients with pre-existing mucosal vulnerability.

The pharmacodynamic properties of antiplatelet agents further modulate bleeding risk. Aspirin produce irreversible inhibition of cyclooxygenase-1, resulting in persistent suppression of thromboxane A□ synthesis and prolonged impairment of platelet aggregation (3). P2Y12 receptor inhibitors acts through a distinct but complementary mechanism by blocking ADP-mediated platelet activation pathways, thereby enhancing antithrombotic efficacy but also increasing the likelihood of bleeding complications, particularly when multiple antiplatelet agents are used concurrently as part of combination therapy (39, 49). The intensity and duration of platelet inhibition are therefore key determinants of bleeding risk.

Polypharmacy constitutes an important and frequently underappreciated contributor to gastrointestinal bleeding. Selective serotonin reuptake inhibitors, for example, impair platelet aggregation by depleting intraplatelet serotonin stores, thereby potentiating bleeding risk when combined with antiplatelet agents (50). Moreover, the concomitant use of dual antiplatelet therapy and oral anticoagulation, a strategy frequently required in patients with atrial fibrillation undergoing percutaneous coronary intervention, is associated with a markedly increased risk of major bleeding events, reflecting cumulative inhibition of both primary and secondary hemostatic pathways (45, 38).

Treatment-related variables, including dose and duration of therapy, play also an important role. Even low-dose aspirin is associated with a measurable increase in gastrointestinal bleeding risk, while higher doses further enhance mucosal injury and hemorrhagic complications (3, 45). Extend exposure to dual antiplatelet therapy is associated with a progressive accumulation of bleeding risk, particularly among patients with additional predisposing factors, necessitating careful consideration of treatment duration in clinical practice (38).

Emerging evidence suggests that systemic inflammatory states and endothelial dysfunction may further influence bleeding risk by altering vascular integrity and impairing adaptive hemostatic responses. These processes may be particularly relevant in patients with complex comorbid conditions, where multiple pathophysiological pathways converge to increase susceptibility to bleeding.

Lifestyle-related factors provide an additional dimension of risk modulation. Alcohol consumption adversely affects platelet function, compromise mucosal integrity, and exacerbates underlying liver disease, thereby increasing the susceptibility to gastrointestinal

hemorrhage. Smoking, although primarly recognized as a prothromboticrik factor may also be implicated in impaired mucosal repair and contribute to ulcer formation through mechanisms involving oxidative stress and microvascular dysfunction (1, 3).

Collectively, these findings highlight that the management of patients receiving antiplatelet therapy must be individualized, integrating patient characteristics, comorbid conditions, and treatment-specific variables. A comprehensive and nuanced assessment of bleeding and thrombotic risk is essential to optimize clinical outcomes while minimizing adverse events.

2.3.6 Risk Factors for Antiplatelet-Associated Gastrointestinal Bleeding

The likelihood of gastrointestinal bleeding in patients receiving antiplatelet therapy is determined by multiple factors. Advanced age is consistently recognized as one of the strongest predictors, reflecting both increased comorbidity burden and reduced physiological reserve. A history of peptic ulcer disease or prior gastrointestinal bleeding is also strongly associated with recurrence (1, 44, 51)**.**

The bleeding risk is further amplified by the concomitant use of NSAIDs, corticosteroids, or anticoagulants through complementary mechanisms (52, 53). *Helicobacter pylori* infection plays a critical role by compromising mucosal integrity and promoting ulcer formation. The coexistence of *H. pylori* infection and antiplatelet therapy has been shown to significantly increase the risk of bleeding, underscoring the importance of screening and eradication strategies in high-risk patients (46).

Renal dysfunction, liver disease, and malignancy also contribute to increased bleeding risk through complex interactions involving impaired hemostasis, altered drug metabolism, and mucosal vulnerability (44, 48, 54). These factors must be carefully considered when selecting and managing antiplatelet therapy.

In addition to these established risk factors, both age-related physiological changes and treatment-related characteristics further modulate bleeding risk. Older individuals are particularly vulnerable because aging is associate with progressive impairment of gastrointestinal protective mechanism, including reduced prostaglandin synthesis, diminished mucosal blood flow, and impaired epithelial regeneration capacity, increase susceptibility to injury (44, 52). In addition, pharmacokinetic changes such as reduced renal clearance and altered hepatic metabolism may lead to increased drug exposure, thereby amplifying the antiplatelet effect and associated bleeding risk.

Polypharmacy represents a major and often underrecognized contributor to gastrointestinal bleeding. The concomitant use of multiple medications, particularly those affecting hemostasis or mucosal integrity, results in additive or even synergistic effects (44, 53). Selective serotonin reuptake inhibitors, for example, have been associated with impaired platelet aggregation due to inhibition of serotonin uptake in platelets, thereby further increasing bleeding risk when combined with antiplatelet agents (37, 39, 49)**.** Likewise, the concomitent use of dual antiplatelet therapy with oral anticoagulation—commonly required in patients with atrial fibrillation undergoing percutaneous coronary intervention—substantially increases the incidence of major gastrointestinal (38, 53).

Both, antiplatelet dose and the duration of therapy, play a critical role. Aspirin-associated gastrointestinal toxicity is dose dependent, with higher doses linked to a greater incidence of mucosal injury and bleeding risk. Neverthelss, even low-dose aspirin (75–100 mg daily) prescribed for cardiovascular prevention, significantly elevates bleeding risk when compared with no therapy (52, 53). Prolonged duration of dual antiplatelet therapy further compounds this risk, particularly in patients with additional predisposing factors (38). Importantly, the intensity of platelet inhibition achieved with more potent P2Y12 inhibitors, such as prasugrel and ticagrelor, is associated with higher bleeding rates compared with clopidogrel, especially in vulnerable populations (39, 49).

Comorbid conditions exert multifactorial effects on bleeding risk. Chronic kidney disease is associated with uremic platelet dysfunction, characterized by impaired platelet adhesion and aggregation, as well as altered endothelial function (54). These abnormalities contribute to an increased baseline bleeding tendency, which is further exacerbated by antiplatelet therapy. In patients with liver disease, reduced synthesis of coagulation factors, thrombocytopenia due to hypersplenism, and increased portal pressure collectively predispose to gastrointestinal hemorrhage (48). Additionally, portal hypertensive gastropathy and varices may coexist, further increasing the risk of bleeding.

Malignancy represents another important risk factor, as tumors may directly invade the gastrointestinal mucosa or induce angiogenesis and fragile neovascularization, predisposing to bleeding (44). Furthermore, cancer-associated treatments, including chemotherapy and radiotherapy, may compromise mucosal integrity and induce thrombocytopenia, effects that can potentiate the hemorrhagic risk associated with antiplatelet agents.

Lifestyle-related factors may also influence bleeding susceptibility. Excessive alcohol consumption has been shown to impair platelet function, disrupt mucosal integrity, and aggravate undelying liver disease, thereby increasing susceptibility to gastrointestinal bleeding (44, 52).

Importantly, several validated risk stratification tools have been developed to assist clinicians in balancing thrombotic and bleeding risks in patients receiving antiplatelet therapy. The PRECISE-DAPT score is specifically designed to estimate bleeding risk during dual antiplatelet therapy and incorporates clinical and laboratory variables such as age, hemoglobin level, renal function, white blood cell count, and prior bleeding history. A score ≥25 identifies patients at high bleeding risk, in whom shorter durations of therapy or modified antithrombotic strategies may be considered (55).

Although the HAS-BLED score was originally developed to assess bleeding risk in patients receiving oral anticoagulant therapy, it is widely used also in patients receiving combination antithrombotic therapy and provides a practical framework for identifying modifiable bleeding risk factors, including uncontrolled hypertension, renal or hepatic dysfunction, a history of prior bleeding, and concomitant use of medication known to affect hemostasis (56).

In addition, the DAPT score offers a complementary approach by integrating both ischemic and bleeding risks to guide decisions regarding the duration of dual antiplatelet therapy. Higher risk scores generally indicate a net clinical benefit from extended therapy, whereas lower scores favor shorter treatment durations to reduce the likelihood of bleeding complications (57).

In the acute setting of gastrointestinal bleeding, the Glasgow-Blatchford score remains a valuable tool for assessing severity and predicting the need for intervention (58). Although not specific to antiplatelet therapy, it provides important prognostic information and can guide early clinical management.

The incorporation of these risk assessment tools into clinical practice emphasizes the importance of individualized treatment strategies. Rather than applying a uniform therapeutic regimen, clinicians must carefully evaluate each patient's bleeding and thrombotic risk profile, select tailored treatment strategies in order to optimize outcomes and reduce complications.

2.3.7 Prevention Strategies

Preventive strategies are essential in reducing the incidence of gastrointestinal bleeding associated with antiplatelet therapy. Proton pump inhibitors (PPIs) are widely recommended for patients at increased risk, as they reduce gastric acid secretion, promote mucosal healing, and stabilize clot formation.

Eradication of Helicobacter pylori infection is another key intervention, particularly in patients with a history of ulcer disease. Evidence suggests that H. pylori eradication significantly reduces the risk of recurrent bleeding in patients receiving antiplatelet therapy.

In addition, careful selection of antiplatelet agents and dosing regimens can help mitigate bleeding risk. In some cases, monotherapy may be preferred over dual therapy, particularly in patients with high bleeding risk and lower thrombotic risk. Regular reassessment of therapy is essential to balance efficacy and safety over time (38).

Gastrointestinal bleeding associated with antiplatelet therapy is associated with significant morbidity and mortality. Patients often require hospitalization, endoscopic intervention, and blood transfusion, resulting in increased healthcare utilization. Rebleeding occurs in a substantial proportion of patients and is associated with worse outcomes.

Importantly, interruption of antiplatelet therapy following bleeding episodes may increase the risk of thrombotic complications, including myocardial infarction and stent thrombosis. Therefore, the management of such patients requires a careful balance between bleeding and thrombotic risks, often necessitating multidisciplinary collaboration.

2.4. Combined Drug Effects in Non-Variceal Upper Gastrointestinal Bleeding

The concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants (OACs), and antiplatelet agents is recognized as one of the most clinically significant and increasingly prevalent contributors to non-variceal upper gastrointestinal bleeding (NVUGIB). In contemporary medical practice, the coexistence of cardiovascular disease, chronic pain syndromes, and thromboembolic conditions frequently necessitates the use of multiple pharmacological agents. While each of these therapies offers well-established clinical benefits, their combined use is associated with a substantially increase in the risk of gastrointestinal complications. This concern is particularly relevant in older adults, among whom polypharmacy, multiple comorbid conditions, and altered physiological reserve collectively heighten vulnerability to adverse events (1, 48, 44).

The effects of combined antithrombotic and anti-inflammatory therapy extend beyond a simple additive increase in risk. These medications interact at multiple levels of gastrointestinal physiology and hemostasis, simultaneously weakening mucosal defenses and impairing clot formation. NSAIDs induce structural mucosal injury, antiplatelet agents disrupt primary

hemostasis, and anticoagulants impair fibrin stabilization. The convergence of these effects creates a pathophysiological setting in which even minimal mucosal defects may rapidly evolve into clinically significant hemorrhage. Moreover, impaired healing responses and continued exposure to injurious luminal factors further increase the risk of recurrent bleeding episodes (3, 43, 59).

2.4.1 NSAIDs and Antiplatelet Agents: A Common but Potent Combination

Among the various drug combinations associated with gastrointestinal bleeding, the concomitant use of NSAIDs and antiplatelet agents remains one of the most frequently encountered in clinical practice. This pattern is particularly evident in patients with cardiovascular disease who require long-term antiplatelet therapy and who also use NSAIDs for chronic musculoskeletal conditions.

The interaction between these agents is mechanistically complementary and clinically significant. NSAIDs compromise mucosal protection through inhibition of cyclooxygenase-dependent prostaglandin synthesis, leading to reduced mucus and bicarbonate secretion, decreased mucosal perfusion, and impaired epithelial restitution. This results in a structurally compromised mucosa prone to erosion and ulceration. At the same time, antiplatelet agents impair primary hemostasis and interfere with thromboxane A□-mediated platelet activation, thereby limiting the formation of a primary hemostatic plug.

The coexistence of these mechanism, create a high risk environment for gastrointestinal bleeding. Lesions that might otherwise remain asymptomatic are more likely to bleed and to do so in a clinically significant manner. Large observational studies have demonstrated that the concomitant use of NSAIDs with low-dose aspirin increases the risk of upper gastrointestinal bleeding by approximately 3- to 6-fold compared with non-use, with even higher risks observed in older patients and those with a history of ulcer (1, 45).

Selective COX-2 inhibitors were introduced with the aim of reducing gastrointestinal adverse effects. However, this benefit is substantially attenuated when this agents are used with aspirin. The systemic inhibition of platelet function by aspirin negates much of the mucosal advantage conferred by COX-2 selectivity, resulting in a residual bleeding risk that remains clinically relevant (1, 45).

2.4.2 NSAIDs and Oral Anticoagulants: The Intersection of Injury and Coagulation Failure

The combination of NSAIDs and oral anticoagulants is regarded as a particularly hazardous interaction, as it simultaneously promotes mucosal injury and disrupts secondary hemostasis. NSAID-induced epithelial damage provides the substrate for bleeding, while anticoagulants impair thrombin generation and fibrin clot formation, thereby preventing effective stabilization of the hemostatic plug.

This interaction is particularly important in patients receiving direct oral anticoagulants (DOACs), where the balance between thromboembolic protection and bleeding risk is intrinsically narrow. Evidence from real-world studies and meta-analyses consistently demonstrated that concomitant NSAID use increases the risk of gastrointestinal bleeding by approximately two- to threefold in anticoagulated patients, with consistent findings across different healthcare settings (60, 61).

The degree of risk may vary according to the specific anticoagulant presibed. Agents such as rivaroxaban and dabigatran have been associated with higher rates of gastrointestinal bleeding, potentially due to higher peak plasma concentrations or local luminal effects, whereas apixaban appears to confer a comparatively lower risk. Despite these differences, the pathophysiological mechanism remains unchanged: the coexistence of mucosal injury and impaired coagulation markedly increases the likelihood of clinically significant hemorrhage (27. 60, 61).

2.4.3 Antiplatelet Agents and Oral Anticoagulants: Dual Disruption of Hemostasis

The concomitant use of antiplatelet agents and oral anticoagulants is often required in patients with overlapping indications, such as atrial fibrillation and coronary artery disease. While this strategy provides significant protection against thrombotic events, it is accompanied by a considerable increase in bleeding risk.

From a pathophysiological standpoint, this combination disrupts both primary and secondary hemostasis. Platelet inhibition reduce their ability to form an initial platelet plug, while anticoagulation impairs thrombin generation and fibrin deposition required for clot stabilization. This dual impairment results in a hemostatic system that is highly vulnerable to failure even in response to minor vascular injury.

Evidence from both clinical trials and large observational cohorts have consistently shown a significant increase in major bleeding, including gastrointestinal hemorrhage, in patients receiving combined therapy. The risk is further amplified when dual antiplatelet

therapy is combined with anticoagulation, highlighting the importance of minimizing treatment intensity whenever possible (62, 63).

2.4.4 Triple Therapy: Clinical Necessity and Therapeutic Challenge

Triple therapy, defined as the combination of an oral anticoagulant with dual antiplatelet therapy, represents the highest level of antithrombotic intensity and carries a particularly high risk of bleeding. Although sometimes unavoidable in high-risk patients, particularly following percutaneous coronary intervention, this approach is associated with a substantial increase in bleeding complications.

Observational studies and randomized trials have demonstrated that triple therapy significantly increases the incidence of major gastrointestinal bleeding, particularly during the early phase of treatment. This has led to a paradigm shift in clinical practice, with current guidelines recommending the shortest possible duration of triple therapy and early transition to dual therapy regimens (62, 63).

The clinical challenge lies in balancing thrombotic protection against bleeding risk. This requires individualized assessment, careful selection of antithrombotic agents, and ongoing reassessment of therapy based on evolving patient risk profiles.

2.4.5 Insights from Real-World Clinical Practice

Real-world evidence provide important insights into the impact of combined pharmacotherapy in routine clinical settings. Observational studies consistently demonstrate that the risk of gastrointestinal bleeding increases with the number of antithrombotic agents prescribed, reflecting a cumulative and clinically meaningful effect (48, 61).

Beyond confirming findings from randomized trials, real-world evidence highlights several nuances that are often underrepresented in controlled study populations. First, registry-based and administrative database analyses consistently show that patients encountered in daily practice are older, more comorbid, and more frequently exposed to polypharmacy than those enrolled in clinical trials. These characteristics substantially modify bleeding risk and often result in higher absolute rates of gastrointestinal hemorrhage than those reported in randomized studies (44, 61).

Large population-based cohorts from Europe and North America have shown that the addition of even a single interacting drug—such as an NSAID or a second antithrombotic agent—can substantially increase bleeding risk, particularly among elderly individuals. In some cohorts, the incidence of major gastrointestinal bleeding in patients receiving

combination therapy approaches 3–5% per year, with the highest rates observed in patients receiving triple antithrombotic therapy or those with prior gastrointestinal disease (48, 60).

Real-world analyses have also revealed differences between individual agents within the same pharmacological class. For example, comparative effectiveness studies suggest that apixaban is associated with a lower risk of gastrointestinal bleeding compared with rivaroxaban or dabigatran in routine clinical use, a finding that has influenced prescribing patterns in high-risk patients. Similarly, more potent P2Y12 inhibitors have been associated higher bleeding rates compared with clopidogrel, particularly when used in combination regimens (61, 63).

Another important contributor of real-world evidence is the identification of modifiable risk factors. Inappropriate NSAID use, lack of gastroprotective therapy, excessive duration of combination antithrombotic treatment, and suboptimal dose adjustment in renal impairment have all been consistently associated with increased bleeding risk. These findings suggest that a considerable proportion of gastrointestinal bleeding events may be preventable through careful prescribing practices and adherence to guideline recommendations (1, 48, 64).

Real-world studies also underscore the clinical consequences of bleeding events. Patients who experience gastrointestinal hemorrhage while receiving combined antithrombotic therapy have higher rates of hospitalization, longer lengths of stay, and increased healthcare costs. Moreover, bleeding events frequently lead to interruption or discontinuation of antithrombotic therapy, which may in turn increase the risk of thromboembolic complications. This bidirectional relationship between bleeding and thrombosis represents a central challenge in clinical management (62, 63).

Finally, registry data have highlighted the importance of individualized risk stratification. Instead of applying uniform treatment strategies, clinicians are increasingly encouraged to individualize therapy based on patient-specific factors, as age, preexisting medical conditions, prior bleeding events, and concomitant medications.

2.4.6 Prevention and Risk Mitigation

Given the substantial risks associated with combined drug therapy, preventive strategies are essential. Proton pump inhibitors (PPIs) have been shown to significantly reduce the incidence of upper gastrointestinal bleeding and are recommended in patients receiving combination antithrombotic therapy, particularly those with additional risk factors (1, 64).

Eradication of *Helicobacter pylori* infection represents another key preventive measure, particularly in patients with a history of ulcer disease. In addition, careful selection of antithrombotic regimens, minimization of treatment duration, and avoidance of unnecessary NSAID use are critical components of risk reduction.

2.4.7 Conclusion

The combined use of NSAIDs, antiplatelet agents, and oral anticoagulants represents a major determinant of non-variceal upper gastrointestinal bleeding. These agents interact through complementary mechanisms that disrupt both mucosal integrity and hemostatic function, creating a high-risk environment for gastrointestinal hemorrhage.

A comprehensive understanding of these interactions, combined with individualized risk assessment and targeted preventive strategies, is essential to minimize bleeding complications while preserving the therapeutic benefits of antithrombotic therapy in modern clinical practice.

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Chapter 3: Clinical and Biochemical Differences of NVUGIB in patients receiving NSAID vs Anticoagulation vs Antiplatelet Agents-Associated Gastrointestinal Injury

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3.1. Clinical Presentation of NSAID vs Anticoagulation vs Antiplatelet Agents-Associated Gastrointestinal Injury

3.1.1 Clinical Presentation of NSAID-Associated Gastrointestinal Injury

The gastrointestinal injury associated with nonsteroidal anti-inflammatory drugs (NSAIDs) clinically presents itself as being very heterogeneous. In this case there are frequent inconsistencies and sometimes paradoxes when it comes to the correlation between its symptoms and the degree of the underlying mucosal damage. The injury induced by NSAID stays unnoticed because there are no clinical symptoms, thus differentiating itself from a lot of other gastrointestinal conditions with a progression of symptoms that indicate the evolution of the disease. Unfortunately, this lack of symptomatology triggers a deceptive and insidious course (1).

The NSAID-related gastrointestinal injury is characterized by the absence of symptoms despite the fact that a lot of patients have many mucosal lesions, erosions or peptic ulcers, without any obvious discomfort. On the one hand, such cases are represented mainly by elderly people who overlook or do not perceive the signs because of coexisting comorbidities, polypharmacy or change in pain perception. On the other hand, there are the patients undergoing chronic NSAID therapy who develop tolerance and do not respond to nociceptive stimuli. As a consequence, the first clinical manifestation of disease may not be a prodromal symptom complex but rather a major complication, most commonly upper gastrointestinal bleeding, or, less frequently, perforation. This 'silent' evolution underscores the inherent unpredictability of NSAID-associated injury (2).

When present, symptoms most commonly manifest as a nonspecific dyspeptic syndrome. Patients complain from epigastric discomfort, in terms of burning, aching, pressure, with varying intensity and in absence of clear connection to food intake. In addition, people also mention early satiety, postprandial fullness, nausea and abdominal bloating all indicating functional gastrointestinal disorders. There may be encountered severe ulcerative lesions

without any symptoms but, at the same time, there are patients with strong dyspeptic symptoms but otherwise minimal or no structural abnormalities. Consequently, dyspepsia ought to be regarded with precaution as a marker of the severity of the disease for users of NSAID who mention the above symptoms (3).

One of the early presentations of the NSAID-induced injury is the acute gastrointestinal hemorrhage which starts suddenly, sometimes at patients who have not had gastrointestinal antecedents, thus confirming the silent characteristic of this disease. Patients present with hematemesis, that is bleeding varying from fresh red blood to coffee-ground material. In addition, another manifestation of this disease is melena, that are tarry stools with a distinctive odor, indicating the digestion of blood within the upper gastrointestinal tract. There are times when hematochezia, abrupt or large quantity hemorrhage, occurs especially in cases of accelerated intestinal transit. Due to such unexpected episodes, it is crucial to stay vigilant even in asymptomatic individuals as they may be indicators for the severity of NSAID-associated injury (4).

NSAID-induced gastrointestinal injury does not occur only through overt bleeding but also through chronic, occult blood loss, a presentation which is frequently underrecognized because of subtle systemic symptoms. As the symptoms like progressive fatigue, diminished exercise tolerance or generalized weakness are nonspecific, they may be attributed to aging or other medical conditions and lead to a delay in diagnosing the gastrointestinal disease. Such instances occur with individuals who are under the protocol of long-term NSAID therapy, but also with those with involvement of the small intestine, where mucosal injury may exist in the long term without symptoms.

In some less frequent cases, life-threatening emergencies take place, when gastro-intestinal perforation outbursts with sharp and diffuse abdominal pain evolving to signs of peritoneal irritation. However, event in this context, the clinical picture may deviate from traditional expectations. Again, elderly patients may suffer a diminishing manifestation of symptoms, less pain and a later inflammatory response so the presentation is delayed. The silent nature of NSAID-induced gastrointestinal injury is represented by the fact that perforation may happen without prior dyspeptic symptoms (2).

Moreover, the focus nowadays is directed towards NSAID-induced injury of the small intestine as well, because of its frequency. The patients accuse intermittent abdominal discomfort, bloating or unexplained fatigue, but the NSAID enteropathy is predominantly asymptomatic and is discovered indirectly through chronic blood loss. In conclusion, individuals with a long NSAID exposure should be observed with heightened clinical awareness.

More attention ought to be given to individuals with comorbid conditions and concomitant therapies as those intaking corticosteroids, anticoagulants or antiplatelet agents register a larger risk of bleeding with minimal symptomatology. Atypical or diminished manifestations occur in patients suffering from cardiovascular disease, chronic kidney disease or patients with advanced age who may experience systemic signs like, functional decline, syncope, decompensation of underlying disease, adding thus to the clinical spectrum of presentation.

To sum it up, the symptoms of the NSAID-associated gastrointestinal injury are varied, subtle and unreliable. While the symptoms may lack, the condition may be present and mild dyspeptic problems do not offer sufficient data about the mucosal damage. Unexpected hemorrhage and perforation are complications which indicate pathology. This distinctive clinical profile necessitates a high index of suspicion in all patients exposed to NSAIDs, particularly those with additional risk factors, and underscores the limitations of relying solely on symptomatology in the assessment of gastrointestinal risk (5).

3.1.2 Clinical Presentation of Gastrointestinal Injury in Patients Receiving Oral Anticoagulant Therapy

The clinical presentation of gastrointestinal bleeding in patients receiving oral anticoagulant therapy is shaped by a distinct and fundamentally different paradigm compared to NSAID-associated injury, in which the principal abnormality resides not in the initiation of mucosal damage, but in the amplification and persistence of hemorrhage once mucosal integrity has been compromised. Impaired secondary hemostasis may cause minor lesions to lead to considerable bleeding. For example, anticoagulated patients are not able to benefit from stable clot formation and effective hemostatic control and undergo a severe lesion manifestation (6).

In contrast to other etiological categories of gastrointestinal injury, patients receiving oral anticoagulants often lack preceding gastrointestinal symptoms prior to the onset of bleeding. If the patient meets the normal hemostatic parameters, the lesions, which are usually small erosions, angiodysplasias or asymptomatic ulcers, do not have manifestations. The condition will manifest itself through open gastrointestinal bleeding with no prior prodromal dyspepsia or warning signs. Such an occurrence makes the anticoagulation a precipitating and not a causative factor, but the subclinical mucosal abnormalities become a clinically significant hemorrhagic episode (7).

In most cases acute gastrointestinal hemorrhage in the upper gastrointestinal tract is accompanied by hematemesis or melena. Hematemesis ranges from fresh red blood to coffee-

ground material which is indicative of the frequency and the length of the bleeding. At the same time, melena is representative for the digestion of blood in the gastrointestinal lumen. Hematochezia sometimes occurs when the hemorrhage is sudden and in large quantity. Anticoagulated patients suffer from surprisingly large bleedings although the endoscopic findings are not very alarming, pointing to the fact that impaired coagulation plays a central role in the clinical expression of the disease (4).

Anticoagulant-associated bleeding experienced by anticoagulated patients is characterized by a tendency to persist and happen recurrently, thus being distinctive from self-limited bleeding episodes in people having intact hemostasis. Sometimes, patients have frequent episodes of melena or recurrent hematemesis. These events are proof of incomplete or unstable clot formation and they are a met at individuals intaking direct oral anticoagulants (DOACs), which inhibit thrombin or factor Xa, but at the same time produces bleeding although the lesions are neither large nor actively progressing. In such cases, it is important to remain vigilant and constantly reassess the patients because their clinical course fluctuates (6).

Not only does the anticoagulant-associated gastrointestinal bleeding manifests through overt bleeding, but, unfortunately, also through chronic, low-grade blood loss. Elderly patients complain of tiredness, reduced exercise endurance or generalized weakness as their physiological reserve is diminished and they do not perceive the symptoms as accurately. The absence of visible bleeding frequently delays clinical recognition, and the underlying gastrointestinal source may remain undetected for extended periods. This presentation emphasizes the importance of considering occult gastrointestinal bleeding in anticoagulated patients presenting with otherwise unexplained functional decline (7).

Another important dimension of the clinical presentation is the often-imperfect correlation between reported symptoms and the degree of hemodynamic compromise. When the hemorrhage outbursts, some patients may seem clinically stable, but seniors or those with cardiovascular comorbidities may experience rapid clinical deterioration despite very few symptoms. At the beginning of clinical assessment and risk stratification in any individual, it is essential to consider the interplay between bleeding dynamics, patient physiological reserve and pharmacological effects of anticoagulation (4).

The oral anticoagulant class determines the clinical phenotype. For example, vitamin K antagonists like warfarin determine fluctuations in anticoagulation intensity and therapeutic control and lead to an unstable clinical course, which manifests in surprising bleeding patterns, both mild and severe. Despite the fact that direct oral anticoagulants help with a more stable pharmacokinetic profile, they pose the risk of gastrointestinal bleeding especially among

elderly patients and people with pre-existing mucosal lesions. Most patients undergoing DOACs therapy, present a pattern in the case of gastrointestinal bleeding, like abrupt onset, absence of prodromal symptoms and persistence (6, 8).

Unrecognized gastrointestinal pathology, such as neoplasia, vascular malformations or ulcer disease may be discovered due to gastrointestinal bleeding in anticoagulated patients, with the anticoagulation serving as a 'tool test' for mucosal integrity and revealing hidden lesions. Therefore, gastrointestinal hemorrhage in these patients should not be interpreted solely as a pharmacological complication, but rather as a potential marker of underlying disease requiring comprehensive diagnostic evaluation (9).

An additional layer of complexity is introduced by the frequent coexistence of multimorbidity and polypharmacy in anticoagulated patients. Concomitant use of antiplatelet agents, NSAIDs, or corticosteroids may further amplify bleeding risk and modify the clinical presentation, often result in in more severe or prolonged hemorrhagic episodes.

In conclusion, patients that undergo oral anticoagulant therapy may face gastrointestinal injury characterized by abrupt onset, lack of preceding symptoms and inclination towards persistence or recurrence. Sometimes the hemorrhage is overt and massive while other times there is chronic blood loss with nonspecific systemic features. In addition, the disproportionate relation between lesion severity and clinical manifestation mixed with potential rapid and unforeseen deterioration highlights the need for meticulous clinical evaluation in all anticoagulated patients coming with minimal or ambiguous symptoms.

3.1.3 Clinical Presentation of Gastrointestinal Injury in Patients Receiving Antiplatelet Therapy

Besides the individuals with NSAID-related injury and those with anticoagulant therapy, a distinctive place is occupied by patients with antiplatelet treatment. Antiplatelet agents, especially aspirin inhibit cyclooxygenase-1 and trigger mucosal vulnerability and impair primary hemostasis, facilitating bleeding form silent lesions. The resulting clinical picture is therefore shaped by a dual mechanism, in which modest structural injury and defective platelet aggregation interact to produce a pattern of bleeding that is often subtle in onset yet potentially serious in clinical consequences (3, 5).

Antiplatelet- associated gastrointestinal injury is frequently characterized by the lack of meaningful prodromal symptoms. Most patients ingesting low-dose aspirin remain asymptomatic before the bleeding begins and only a small number pf individuals complain of dyspepsia. The clinical manifestation resembles the one with anticoagulant treatment, that is

overt gastrointestinal hemorrhage without any signs, especially in elderly individuals, in patients with long-term treatment and people with pre-existing mucosal lesions. Accordingly, the absence of dyspepsia should not be interpreted as evidence of low gastrointestinal risk in patients exposed to antiplatelet agents (2).

There are instances when the symptoms appear, but they are mild, and unspecific, miming a dyspeptic syndrome, with episodes of epigastric discomfort, burning sensation, upper abdominal unease, nausea, early satiety or postprandial fullness. Unfortunately, these signs do not indicate severe mucosal damage or significant bleeding, just like it happens in NSAID-related injury as well. This discordance between symptoms and bleeding risk substantially reduces the clinical utility of symptom-based stratification and contributes to delayed recognition in ambulatory practice (3, 5).

The most clinically relevant presentation in patients receiving antiplatelet therapy is gastrointestinal bleeding, which may occur anywhere along the gastrointestinal tract but often presents as upper gastrointestinal hemorrhage with hematemesis or melena, is not as violent as in anticoagulant-associated bleeding and its may evolution may last several hours or days. During discussions with medical personnel, individuals mention having had darkening of stools, intermittent melena, dizziness, decreased stamina or ability to support long-term effort. Nevertheless, severe and abrupt presentations do occur, particularly in patients with established peptic ulcer disease, prior gastrointestinal bleeding, advanced age or dual antiplatelet therapy, the latter one being identified as substantially riskier for determining a lot of blood loss compared to aspirin monotherapy (1, 4).

The bleeding in patients with antiplatelet therapy is persistent and not explosive, being of prolonged low- to moderate- intensity, thus showing impaired platelet plug formation instead of a serious disruption of the coagulation cascade. Individuals may experience ongoing melena, repeated dark stools, slow symptomatic decline or various small bleeding episodes and not a singular critical hemorrhagic event. Nevertheless, high-risk patients may suffer from large-volume hemorrhage. This pattern becomes particularly evident in patients receiving dual anti-platelet therapy, in whom inhibition of multiple pathways of platelet activation further compromises primary hemostasis and increases both the likelihood and duration of bleeding (10, 11).

In addition to overt bleeding, antiplatelet therapy is frequently associated with chronic, occult gastrointestinal blood loss. Such patients may present not with obvious digestive symptoms, but with fatigue, generalized weakness, reduced functional reserve, or progressive exercise intolerance. In long-term aspirin users, repeated microbleeding events combined with chronic mucosal vulnerability may generate a clinically significant but initially unrecognized

syndrome of slow blood loss. This presentation is particularly relevant in older adults, who often have limited physiological reserve and in whom subtle decline may be attributed to age or comorbidity rather than gastrointestinal pathology. Studies in elderly populations demonstrate an association between antiplatelet therapy and occult bleeding, frailty, and anemia, highlighting the insidious clinical nature of this presentation (5, 11).

The clinical phenotype also varies according to the specific antiplatelet regimen.

It is acknowledged that low-dose aspirin monotherapy does not trigger major bleedings compared to combined regimens. However, clinically significant gastrointestinal events may happen so it is important to stay vigilant.

By contrast, patients on dual antiplatelet therapy, most often aspirin combined with a P2Y12 inhibitor such as clopidogrel, ticagrelor, or prasugrel, demonstrate a distinctly higher risk of both upper and lower gastrointestinal bleeding. In such cases, bleeding may occur earlier, persist longer, and recur more readily, reflecting more profound impairment of platelet-mediated hemostasis. Recent analyses further suggest increased bleeding risk with newer P2Y12 inhibitors such as ticagrelor compared with clopidogrel (10, 12, 13).

An additional consideration is the capacity of antiplatelet therapy to unmask previously silent gastrointestinal pathology. As with anticoagulants, impairment of hemostasis may reveal lesions that would otherwise have remained clinically unapparent, including ulcers, angio-dysplasias, erosive disease, and neoplastic lesions. In this context, gastrointestinal bleeding should not be regarded solely as an adverse pharmacological effect but rather as a potential clinical signal of underlying structural disease that merits thorough investigation (11, 12).

Another clinically important dimension is the modifying effect of multimorbidity and polypharmacy. Many patients receiving antiplatelet therapy are elderly and have extensive cardiovascular disease, diabetes, renal dysfunction, or concomitant exposure to NSAIDs, corticosteroids, or anticoagulants. These factors may attenuate early symptoms while simultaneously increasing the likelihood of more serious bleeding. As a result, patients come with a diverse symptomatology, such as syncope, exertional intolerance, strength loss or even decompensation of pre-existing cardiac disease. The above aspects represent a syndrome which is very relevant in real practice as it often occurs for gastrointestinal bleeding to appear through systemic, not only digestive manifestations (3, 12).

In conclusion, patients administering antiplatelet treatment experience mucosal vulnerability and impaired primary hemostasis with episodes of persistent and pernicious bleeding with no prior symptoms. Although dyspeptic complaints may occur, they are unreliable indicators of clinically significant pathology. **Bleeding**, whether overt or occult,

remains the dominant mode of presentation and often serves as the first clue to underlying disease. This clinical profile requires a high degree of **vigilance**, particularly in patients receiving dual antiplatelet therapy, in the elderly, and in those with additional risk factors for gastrointestinal complications (1, 3, 11, 13).

3.1.4 Comparative Clinical Presentation of Gastrointestinal Injury: NSAIDs vs Oral Anticoagulants vs Antiplatelet Therapy

The three types of therapies influence differently the mucosal integrity and the hemostasis. Consequently, the gastrointestinal injury has multiple manifestations, specific patterns of early symptoms and of the evolution in time of the hemorrhage exposed in distinct phenotype progression (1, 4, 14).

In the case of NSAID therapy, the gastrointestinal injury is marked by direct and indirect mucosal damage, most time in the absence of clinically meaningful symptoms. Sadly, there may be minimal correspondence between dyspeptic symptoms and the seriousness of the mucosal lesions to that extent that patients cand be asymptomatic while having advanced ulcerative disease. In these circumstances, the condition starts clinically with bleeding or perforation, but having progressed silently over an extended period of time, especially in elderly patients and those with chronic therapy, thus hindering early recognition (2, 14, 15).

In contrast, the clinical presentation in patients receiving oral anticoagulant therapy is dominated by impaired secondary hemostasis rather than primary mucosal injury. Substantially overt hemorrhage may occur suddenly in cases of minor or clinically silent lesions accompanied by hematemesis or melena. The discrepancy between the bleeding and the lesion reflects impaired clot formation and stabilization. Moreover, the bleeding is constant and repetitive, with a more unstable and aggressive clinical course (16, 17).

The individuals under antiplatelet therapy experience both mucosal vulnerability and impaired primary hemostasis without symptoms until the beginning of the bleeding, which, in turn, is more prolonged and in the form of melena or chronic occult blood loss, but less abrupt. The risk and clinical severity increase significantly in patients receiving dual antiplatelet therapy, in whom platelet inhibition is more profound and sustained (18, 19, 20).

A key point of differentiation across these therapeutic classes lies in the relationship between symptoms and clinical outcomes. NSAID users may report dyspeptic symptoms, although these correlate poorly with disease severity. In contrast, patients receiving anticoagulants or antiplatelet agents frequently lack prodromal symptoms, with bleeding serving as the first indication of pathology. The tempo of bleeding further distinguishes these

groups: it is typically abrupt and potentially severe in anticoagulated patients, more insidious and persistent in antiplatelet therapy, and variable in NSAID users, depending on the extent and nature of mucosal injury (1, 16).

There are clear distinctions regarding the connection between underlying lesions and pharmacological effects. On the one hand, patients with NSAID-associated injury do not sense the mucosal damage until complications arise. On the other hand, anticoagulant patients suffer from impaired coagulation and minor lesions may have clinical significance. In patients receiving antiplatelet therapy, both mechanisms coexist, producing a subtle, yet progressive, with a tendency toward delayed recognition. Across all groups, gastrointestinal bleeding may also represent the first manifestation of previously undiagnosed pathology, including ulcer disease, vascular lesions, or malignancy, particularly in the context of anticoagulant or antiplatelet therapy (15, 19).

An additional layer of complexity arises from the frequent coexistence of advanced age, multimorbidity, and polypharmacy in these patient populations. The concomitant use of NSAIDs, anticoagulants, and antiplatelet agents markedly amplifies bleeding risk and may further obscure the clinical presentation (5, 17).

Table 1. Comparative overview of clinical presentation in NVUGIB

Synthesis

Feature	**NSAIDs**	**Oral Anticoagulants**	**Antiplatelet Therapy**
Primary mechanism influencing presentation	Mucosal injury	Impaired coagulation	Mucosal injury + impaired platelet aggregation
Prodromal symptoms	Often present (dyspepsia), but unreliable	Typically absent	Often absent or mild
Silent disease	Very common	Common (lesions silent, bleeding reveals them)	Common
Typical initial presentation	Dyspepsia or complication (bleeding/perforation)	Overt bleeding	Overt or occult bleeding
Onset of bleeding	Variable	Abrupt	Often insidious
Bleeding severity	Variable	Often disproportionate/severe	Moderate, persistent
Bleeding pattern	Episodic or complication-driven	Persistent/recurrent	Persistent, often chronic
Occult bleeding	Possible	Common	Common
Perforation risk	Present	Rare (indirect)	Rare
Correlation symptoms–lesion	Poor	Very poor	Poor

In conclusion, individuals under NSAID therapy, who experience gastrointestinal injury, suffer from silent mucosal damage and unreliable dyspeptic symptoms, whereas patients ingesting oral anticoagulant treatment face abrupt, severe bleeding determined by impaired hemostasis but with no prior manifestation. The phenotype of patients receiving antiplatelet treatment represents a combination of subclinical mucosal injury with defective platelet aggregation and it does not have a clear manifestation, being unnoticed, gradual, but persistent. It is of utmost importance to recognize the patterns for the patients undergoing these widely used therapies in order to establish risk stratification, to diagnose in good time and to manage the complications.

3.2. Hemodynamic and Laboratory Differences in Gastrointestinal Bleeding: NSAIDs vs Oral Anticoagulants vs Antiplatelet Therapy

3.2.1 Hemodynamic Differences in Gastrointestinal Bleeding

Patients following therapy with nonsteroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants and antiplatelet agents have different hemodynamic presentations of gastrointestinal bleeding, also involving clot stability and physiological compensatory capacity. Although hypovolemia and circulatory compromise represent the final common pathway in all three groups, the tempo of blood loss, predictability of progression, and ability to maintain hemodynamic stability differ in clinically meaningful ways, giving rise to distinct hemodynamic phenotypes (1, 3 ,4).

When it comes to NSAID-associated gastrointestinal bleeding, the anatomical severity of the underlying lesion, that is the peptic ulcer disease, determines the hemodynamic status, with the bleeding resulting from erosion into submucosal or arterial vessels. The size, depth and vascular involvement of the lesion caused by the erosion correlates directly with the degree of circulatory compromise. The NSAID-associated bleeding is temporary permitting transient hemostasis and partial physiological compensation. Hence, preserved blood pressure, mild tachycardia and a compensated state are initial manifestations in these patients which may turn into hypovolemia should the bleeding persist or recur. However, because NSAID-induced injury is frequently clinically silent prior to complication, patients may also present abruptly with moderate or severe hemodynamic compromise without preceding warning signs (1, 15).

As opposed to manifestation in NSAID- associated bleeding, patients under oral anticoagulant therapy have a different hemodynamic profile, dominated by defective secondary hemostasis leading to impaired clot formation and reduced stability of hemostatic plugs. Such is the case that even superficial mucosal lesions can result in sustained and progressive hemorrhage and a fluctuating hemodynamic pattern with a limited capacity for spontaneous stabilization. The anticoagulant-associated hemorrhage is woefully unable to stop through intrinsic hemostatic mechanisms, but predisposed to continuous intravascular volume depletion. Despite a stable appearance in the beginning, the patients may face rapid and unforeseen deterioration, indicative of blood loss that exceed compensatory capacity (4, 16).

In the case of anticoagulant-associated bleeding, there is a constant dissociation between visible bleeding and hemodynamic compromise. Despite modest external manifestations, patients may experience a lot of intravascular volume loss, especially in the beginning. By contrast, senior patients and those with limited cardiovascular reserve may suddenly

decompensate. In this context, a persistent hemorrhage is going to increase the risk of early and severe hemodynamic instability, when close monitoring and immediate intervention is necessary (1, 3, 4).

Patients receiving antiplatelet therapy exhibit a hemodynamic profile that is generally intermediate between NSAID- and anticoagulant-associated bleeding, reflecting impairment of primary hemostasis with preservation of the coagulation cascade. Bleeding in this group tends to be less explosive than in anticoagulated patients but more persistent than in NSAID-related injury. From a hemodynamic perspective, hypovolemia is installing and the patients who initially present a compensated state, with mild tachycardia, preserved blood pressure and subtle signs of volume depletion gradually shift to circulatory compromise because of continued low- to moderate-intensity blood loss. Individuals under dual antiplatelet therapy are more prone to endure hypovolemia as the platelet inhibition is more profound (3, 18).

Antiplatelet-associated bleeding usually has a subacute hemodynamic trajectory; it lasts hours even days so there is not an event of abrupt collapse. The patient may go through orthostatic hypotension, mild tachycardia, diminished strength before progressing to clear instability should the bleeding persist. Unlike anticoagulant-associated hemorrhage, rapid catastrophic decompensation does not take place, but the constant bleeding may lead to hypovolemia for old or weak patients (15, 18).

The interdependence between bleeding dynamics and compensatory physiology represents the distinctive characteristic of these therapeutic groups. The bleeding in patients with NSAID treatment is episodic, depends on the lesion and may stop naturally while in patients with anticoagulant treatment, the blood loss is incessant and recurrent, making the patients susceptible to decompensation. The antiplatelet patients undergo a gradual but constant hemodynamic decline caused by ongoing low-intensity hemorrhage.

Another important difference concerns the predictability of hemodynamic evolution. It is easier to identify the injury at patients with NSAID therapy because the clinical deterioration offers indications for the injury, whereas anticoagulated patients are unpredictable due to the lack of obvious initial manifestations although there may be rapid deterioration. Patients with antiplatelet treatment evolve progressively and are simpler to trace, but the risk of cumulative blood loss requires careful monitoring. An additional clinical dimension is the influence of age, comorbidities, and polypharmacy on hemodynamic presentation. Senior patients and those with cardiovascular disease from all the therapies under scrutiny, may decompensate very fast. Individuals receiving anticoagulant and antiplatelet treatment are in danger of severe blood loss and rapid hemodynamic decline (18, 19, 20).

Table 2. Comparative Overview of Hemodynamic Profiles

Synthesis

Feature	**NSAIDs**	**Oral Anticoagulants**	**Antiplatelet Therapy**
Primary determinant of bleeding severity	Lesion size/depth	Impaired coagulation	Impaired platelet aggregation
Onset of hemodynamic compromise	Variable	Often early, may be abrupt	Gradual
Bleeding course	Episodic or self-limited	Persistent, ongoing	Persistent, low–moderate intensity
Initial hemodynamic state	Often compensated initially	May appear stable but deteriorates	Usually compensated
Progression to shock	Depends on lesion severity	Faster, less predictable	Gradual, progressive
Compensatory capacity	Relatively preserved	Often impaired	Partially preserved
Risk of recurrent instability	Moderate	High	Moderate

Briefly, the structural severity of mucosal injury determines the hemodynamic profile in the NSAID-associated gastrointestinal bleeding with the possibility of partial compensation and a variable course. On the contrary, oral anticoagulant therapy determines swift hemodynamic instability with constant hemorrhage. Between these two points, there is the hemodynamic of the patients with antiplatelet medication who experience steady but sustained blood loss triggering circulatory compromise in time. Recognition of these distinct hemodynamic phenotypes is essential for accurate risk stratification, early clinical recognition, and timely therapeutic intervention in patients presenting with gastrointestinal bleeding.

3.2.2. Laboratory Differences in Gastrointestinal Bleeding

3.2.2.1. Laboratory Differences in Hemoglobin and Hematocrit: NSAIDs vs Oral Anticoagulants vs Antiplatelet Therapy

The context of the pharmacological background of the NSAID ingestion, oral anticoagulation or antiplatelet medication must be taken into consideration for the interpretation of hemoglobin and hematocrit values in the case of gastrointestinal bleeding. These substances determine the bleeding peril, the evolution over time and its persistence, thus leading to different laboratory paths. So, the way the hemoglobin and hematocrit are not static data, but help understand the pattern and the continuity of blood loss (1, 3).

The laboratory findings in the case of NSAID-associated gastrointestinal bleeding reveal the structural nature of mucosal injury usually caused by peptic ulceration. In the beginning, hemoglobin and hematocrit levels may be regular, although the blood loss is considerable, due to the fact that the plasma is not immediately redistributed. After the acute stage, the changes in the intravascular volume determines hemodilution and a postponed decline the concentration of the hemoglobin, which may stabilize if the bleeding stops naturally. On the other hand, chronic NSAID therapy produces a steady decline in hemoglobin and hematocrit because of progressive and low levels of blood loss. In conclusion, laboratory findings for patients with NSAID therapy will indicate acute dilutional anemia up to chronic iron-deficiency anemia affected by the duration and bleeding characteristic (1,4).

Anticoagulant therapy exposes the patients to a laboratory profile showing continuous and uncontrolled bleeding instead of low-level blood loss episodes. The second hemostasis is affected by anticoagulants and in the case of mucosal lesions the blood loss will be unrestrained, hence the hemoglobin and hematocrit levels will drop. The fact that the persistent bleeding does not allow the hemoglobin to stabilize, even after initial fluid resuscitation is an important laboratory trait of patients under anticoagulants medication. The difference in the hemoglobin levels in the two conditions is a clear indication towards NSAID-associated injury or anticoagulant gastrointestinal bleeding. Moreover, the disproportion between the anemia level and the endoscopic findings underscores the role of impaired clot formation rather than the lesion severity alone. There should be made several measurements because only one hemoglobin value does not show the consequence of the hemorrhage (3, 4, 16).

Anticoagulated patients experience hemoglobin level fluctuation, when there is intermittent or recurrent bleeding, with momentary stabilization succeeded by decline, setting trend analysis as compulsory (3).

Patients under antiplatelet therapy do not face abrupt bleeding like those under NSAID medication but the platelet inhibition influences primary hemostasis, resulting in the gradual decrease of the hemoglobin and the hematocrit, especially with chronic or subacute bleeding. Individuals following dual antiplatelet therapy may witness acute hemoglobin and hematocrit drops. Nevertheless, they are not as striking as with anticoagulant-associated hemorrhage.

The laboratory pattern is characterized by chronic mild-to-moderate anemia, with recurrent blood loss events, obvious in long-term users who can suffer from sustained bleeding because of cumulative mucosal injury and impaired platelet aggregation. While the magnitude of hemoglobin decline is often less dramatic than in anticoagulated patients, the chronicity of blood loss may result in significant cumulative anemia over time (1, 3, 4, 21).

The hemoglobin and hematocrit values change in case of gastrointestinal bleeding in all three conditions, but they differ from one disease to another and according to the time they are measured and the physiological response. Time plays a crucial role in the evolution of the patients, while NSAID- patients experience bleeding which is delayed or possibly self-limited, anticoagulant patients are exposed to constant decreases and antiplatelet patients bleed gradually but persistently leading to reduction in hemoglobin and hematocrit. These distinct laboratory trajectories provide valuable diagnostic and prognostic information and may aid in differentiating the underlying etiology of gastrointestinal bleeding.

Table 3. Comparative Overview of Hemoglobin and Hematocrit Patterns

Synthesis

Feature	**NSAIDs**	**Oral Anticoagulants**	**Antiplatelet Therapy**
Initial hemoglobin	Often normal in early phase	Often near normal initially	Usually near normal
Pattern of decline	Delayed, may stabilize	Progressive, sustained decline	Gradual, persistent decline
Severity of anemia	Variable	Often severe, disproportionate	Moderate
Temporal evolution	Episodic or transient	Continuous or recurrent	Subacute/chronic
Stabilization pattern	Often stabilizes after bleeding stops	Frequently continues to decline	Slow stabilization
Chronic anemia	Common (iron deficiency)	Possible (recurrent bleeding)	Common

To sum it up, patients registering gastrointestinal bleeding associated with NSAIDs, oral anticoagulants and antiplatelet therapy suffer different changes in the hemoglobin and hematocrit values. Individuals under NSAID medication will experience a postponed deterioration, with the blood loss frequently stopping naturally. People who intake oral anticoagulants face constant decrease in hemoglobin, which demonstrates continuous hemorrhage and impaired clot stability. Patients under antiplatelet therapy have long but low-intensity bleeding, thus enduring gradual and steady hemoglobin reductions. In conclusion, it is utterly important to recognize the different laboratory patterns so as to interpret the clinical symptoms accurately, to diagnose in good time and to monitor appropriately.

3.2.2.2. Laboratory Differences in BUN/Creatinine and Coagulation Parameters: NSAIDs vs Oral Anticoagulants vs Antiplatelet Therapy

The interpretation of biochemical and coagulation parameters in patients presenting with gastrointestinal bleeding provides critical insight into both the source and dynamics of hemorrhage, as well as the underlying pharmacological context. A key factor to decide upon diagnostic stratification, to determine how severe and persistent the bleeding is and to establish its pathophysiological mechanism is the blood urea nitrogen (BUN)/creatinine ratio and the coagulation indices. The interaction between mucosal injury and hemostatic dysfunction reflect differently in the laboratory markers for patients under NSAID therapy, oral anticoagulants and antiplatelet medication (1, 4).

When individuals digest and absorb hemoglobin-derived proteins within the gastro-intestinal tract, the BUN level increases thus showing biochemically a gastrointestinal bleeding. The BUN elevation is followed by hepatic urea synthesis. Therefore, there will be registered a superfluous increase in BUN relative to creatinine, exceeding 20:1. Despite it being characteristic of upper gastrointestinal bleeding, the blood loss volume, the time it lasts and its evolution in time fluctuate according to the bleeding dynamics of each pharmacological group (1, 3).

Small mucosal lesions in peptic ulcers may cause episodic hemorrhage, exhibited in the BUN/creatine ratio at patients with NSAID therapy. When there is only one episode of intraluminal blood digestion, the BUN levels augment temporarily and at the end of the bleeding, the ratio stabilizes or steadily normalizes. The increase in the BUN level will continue if the patients experience lasting or recurrent bleeding and if they have large or complicated ulcerative lesions. It is paramount to observe the correlation between the degree of BUN and the volume of blood exposed to the gastrointestinal lumen as structurally important lesions are

related to NSAID medication. Once effective hemostasis is achieved, the biochemical profile generally normalizes in parallel with clinical stabilization (2, 4).

On the other hand, in the case of patients under anticoagulant therapy, the constant or recurrent bleeding is traced in the sustained and progressive elevation in BUN. The patients may face continuous protein digestion and urea production because of intraluminal blood loss determined by minor mucosal lesions, a situation which in turn was caused by impaired secondary hemostasis. Moreover, in anticoagulated patients, the dissociation between clinical findings and laboratory abnormalities may be particularly pronounced, with significant biochemical derangements occurring despite relatively modest external signs of bleeding (16, 17).

Patients receiving antiplatelet therapy typically exhibit an intermediate biochemical profile. In this case the blood loss is chronic or subacute because it is less intense but more prolonged, leading to moderate but sustained BUN elevation. Unlike the levels of BUN in severe anticoagulant-associated bleeding, the patients under antiplatelet therapy have a BUN/creatinine less amplified. Nevertheless, the ratio increase persists over a longer period exhibiting an ongoing low-grade intraluminal blood digestion. This is the case of patients under long-term aspirin or dual antiplatelet therapy, in whom biochemical abnormalities are determined by cumulative blood loss (18, 21).

The mechanism and clinical significance of bleeding is shown both through biochemical markers and coagulation parameters, in particular in patients under oral anticoagulant therapy. Individuals facing NSAID-associated bleeding primarily suffer from abnormalities in the mucosal integrity but not in their systemic coagulation so their coagulation profiles, prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (aPTT) are within normal boundaries. Similarly, in patients receiving antiplatelet therapy, conventional coagulation tests are generally normal, reflecting the inability of these assays to capture platelet dysfunction. Accordingly, the routine coagulation testing emphasizes the limited diagnostic sensitivity because there is clinically significant bleeding despite normal coagulation parameters (1, 4).

In contrast, patients receiving oral anticoagulants demonstrate distinct and clinically meaningful alterations in coagulation parameters, depending on the class of agent used.

Patients with vitamin K antagonists treatment register a prolonged PT and elevated INR which lead to bleeding risk and severity. If the INR values are very high there is the risk of severe or uncontrolled hemorrhage, which necessitates urgent correction. In the case of direct oral anticoagulants (DOACs) PT and aPTT are sensitive to variation determined by specific agents so routine coagulation tests are not to be completely trusted. Due to small observable

prolongations, specific assays-such as anti-factor Xa levels or diluted thrombin time- will assess more accurately the activity of the anticoagulant and the bleeding risk (16).

It is crucial to remember that normal level coagulation tests may exist despite significant bleeding risk in NSAIDs patients or antiplatelet treatment. Contrary to this fact, anticoagulation patients exhibit abnormal coagulation parameters, them being a pivotal factor in bleeding severity. While in anticoagulant-associated hemorrhage, the correction of coagulopathy is the priority of the therapy, in NSAID- and antiplatelet-associated bleeding, the focus goes towards the underlying lesion and to offer care and support (1, 4).

The changes shown over a period of time, in the laboratory parameters represent another discrepancy. Patients with NSAID-associated bleeding tend to have normal levels of BUN and coagulation parameters when the blood loss ceases. In anticoagulated patients, however, abnormalities in both BUN and coagulation indices may persist until effective reversal or clearance of the anticoagulant is achieved. In patients receiving antiplatelet therapy, coagulation parameters remain normal throughout, while BUN elevation reflects the chronicity and persistence of bleeding rather than its intensity (3, 16).

Table 4. Comparative Overview regarding BUN/Creatinine and Coagulation Parameters Synthesis

Feature	**NSAIDs**	**Oral Anticoagulants**	**Antiplatelet Therapy**
BUN/Creatinine ratio	Elevated (transient/episodic)	Persistently elevated, progressive	Mild–moderate, sustained
Correlation with bleeding	Reflects acute blood digestion	Reflects ongoing hemorrhage	Reflects chronic/subacute bleeding
Normalization pattern	Stabilizes after bleeding stops	Persists until hemostasis achieved	Gradual normalization
PT/INR	Normal	Prolonged (especially VKA)	Normal
aPTT	Normal	May be prolonged (agent-dependent)	Normal
Platelet function	Normal	Normal	Impaired
Utility of coagulation tests	Limited	High clinical relevance	Limited

In brief, BUN/creatinine and coagulation parameters offer additional information about the cause and dynamics of gastrointestinal bleeding in diverse pharmacological contexts. The temporary biochemical variations and normal coagulation profiles in NSAID-associated bleeding reflect the episodic nature of the mucosal injury. The unremitting BUN elevation and deviant coagulation parameters in patients under oral anticoagulant therapy indicate the continuous hemorrhage and impaired clot stability. Normal coagulation tests but consistent moderate BUN elevation typically exhibit antiplatelet treatment, low-grade bleeding because of impaired primary hemostasis. When patients present with gastrointestinal bleeding, it is crucial to distinguish among these laboratory profiles so as to diagnose accurately, facilitate early risk stratification and support adapted clinical management.

3.2.2.3. Comparative Interpretation of Liver Enzymes in Gastrointestinal Bleeding: NSAIDs vs Oral Anticoagulants vs Antiplatelet Therapy

The evaluation of liver enzymes in people with gastrointestinal bleeding helps the identification of underlying hepatic pathology and facilitates an insight into the severity and systemic impact of hemorrhage. Despite the fact that the agents used in these conditions are not primarily hepatoxic, when it comes to acute, severe and prolonged gastrointestinal bleeding or blood loss associated to underlying liver disease, their associated clinical scenarios may trigger abnormalities in the liver enzymes.

Gastrointestinal mucosa is the primary pathology in the context of NSAID-associated gastrointestinal bleeding with the liver enzymes having normal levels. There may be moderate transient elevations in transaminases at the beginning of the drug administration with induced hepatotoxicity or systemic hypoperfusion in the case of high-volume hemorrhage. Substantial deviation in AST, ALT or cholestatic markers in NSAID patients indicate that alternative or concomitant pathology ought to be taken into consideration (15).

There are several mechanisms through which the levels of the liver enzymes rise in the case of patients with oral anticoagulant therapy. First, anticoagulants reveal chronic liver disease, specifically in patients with cirrhosis or portal hypertension and a more severe gastrointestinal bleeding. Secondly, in the context of a heavy or long lasting hemorrhage, hepatic hypoperfusion could lead to a pattern of ischemic hepatitis, with more than ten times higher levels of AST and ALT compared to the upper limit of normality. Such contexts arise in association with significant hemodynamic compromise and as a consequence of hepatocellular injury secondary to reduced oxygen delivery (4, 16).

The situation of individuals following antiplatelet medication is similar to that in the NSAID patients in the case of liver enzyme profiles, having normal or minimally altered transaminase levels without systemic complications. There are similitudes with anticoagulant patients as well, that is the unmasking of underlying hepatic pathology, especially in chronic liver disease, where platelet dysfunction and portal hypertension can overlap. In such cases, liver enzyme abnormalities are more reflective of the underlying disease process than of the pharmacological agent itself (18).

The occurrence of shock liver (ischemic hepatitis) represents a perilous clinical scenario in all three conditions should severe gastrointestinal hemorrhage happen. In this case there would be abrupt and striking elevation in transaminases, regularly with risen lactate and signs of systemic hypoperfusion. This scenario is not attributed to any pharmacological class, but it is more often encountered in anticoagulant-related bleeding because of the potentiality of high-volume, severe hemorrhage. It is crucial to recognize this pattern due to the fact that it denotes systemic compromise and supports major prognostic implications (4).

Table 5. Algorithm for Interpretation of Liver Enzymes in Gastrointestinal Bleeding

Step 1: Assess Magnitude of Transaminase Elevation
Normal or mildly elevated AST/ALT (<2–3× ULN) → Likely **no hepatic involvement** → Consider:
▪ NSAID-associated bleeding
▪ Antiplatelet-associated bleeding
▪ Early or mild anticoagulant-associated bleeding
Moderate elevation (3–10× ULN) → Consider:
▪ Underlying liver disease
▪ Drug-related hepatotoxicity
▪ Early hypoperfusion
Marked elevation (>10× ULN) → Suggests:
Ischemic hepatitis (shock liver) → Strongly associated with:
▪ Severe or prolonged bleeding
▪ More common in anticoagulant-associated hemorrhage

Step 2: Evaluate Pattern of Liver Injury
Hepatocellular pattern (↑AST, ↑ALT predominance) → Consider:
▪ Ischemic injury (severe bleeding)
▪ Drug-induced liver injury (rare)
▪ Underlying viral or chronic liver disease
Cholestatic pattern (↑ALP, ↑bilirubin) → Suggests:
▪ Pre-existing hepatobiliary disease
▪ Not directly related to bleeding mechanism
Step 3: Correlate with Clinical Context
Stable hemodynamics + normal liver enzymes → Most consistent with:
▪ NSAID or antiplatelet-related bleeding
Progressive hemodynamic instability + rising AST/ALT → Suggests:
▪ Ongoing hemorrhage
▪ Possible ischemic hepatitis
→ More typical of:
▪ Anticoagulant-associated bleeding
Known liver disease + bleeding → Consider:
▪ Portal hypertension-related bleeding
▪ Coagulopathy secondary to liver dysfunction
Step 4: Integrate with Other Laboratory Findings
Elevated **BUN/creatinine ratio** + normal liver enzymes → Supports upper GI bleeding without hepatic involvement
Elevated **transaminases + lactate** → Suggests systemic hypoperfusion
Abnormal **INR independent of anticoagulation** → Indicates underlying hepatic dysfunction

Table 6. Comparative overview of liver function tests

Synthesis

Feature	**NSAIDs**	**Oral Anticoagulants**	**Antiplatelet Therapy**
Baseline liver enzymes	Normal	Normal or variable	Normal
Mild elevations	Rare, nonspecific	Possible	Rare
Severe elevation (ischemic hepatitis)	Uncommon	More frequent	Uncommon
Mechanism of enzyme elevation	Hypoperfusion (rare)	Hypoperfusion, drug effect	Usually none
Association with severity	Weak	Strong	Moderate
Diagnostic value	Limited	High (severity marker)	Limited

In short, the severity and systemic consequences of hemorrhage primarily produce change in the lever enzymes in gastrointestinal bleeding and not the pharmacological agent itself. Most often there are normal or minimally modified liver enzymes in bleeding in patients with NSAID and antiplatelet therapy, but in the case of anticoagulant patients the hemorrhage determines significant rise in transaminases, particularly if there is hemodynamic instability. If hepatocellular injury is identified, ischemic hepatitis must be urgently taken into consideration as it is a pivotal sign of severe systemic compromise. Hence, the seriousness of bleeding and the underlying pathophysiological context are reflected both in the liver enzyme interpretation and the clinical and laboratory data.

3.3. Endoscopic Findings in Non-Variceal Upper Gastrointestinal Bleeding (NVUGIB)

3.3.1. Introduction

Non-variceal upper gastrointestinal bleeding (NVUGIB) is a clinically heterogeneous condition in which the bleeding occurs next to the ligament of Treitz but without portal hypertension. Although there have been made advances in pharmacologic therapy and supportive care, the most important step for diagnosis, risk stratification and definitive management is

endoscopy which provides direct visualization of the bleeding source, accelerates classification of hemorrhagic stigmata, eases immediate hemostatic intervention and gives crucial prognostic information about the risk of recurrent bleeding and mortality (1, 3).

The spectrum of endoscopic findings in NVUGIB is broad and reflects multiple underlying pathophysiological mechanisms. Considerable bleeding can be driven by structural mucosal injury, vascular abnormalities, mucosal tears, inflammatory lesions and malignant processes. The bleeding severity, the recurrence risk and the response to endoscopic therapy are closely linked to the morphology of these lesions. In conclusion, the endoscopic examination in NVUGIB is not just a descriptive procedure but a diagnostic and prognostic assessment (4, 22). Peptic ulcer disease, erosive gastritis and duodenitis, Mallory-Weiss tears, Dieulafoy lesions, angiodysplasia and malignancy-associated bleeding are the typical endoscopic etiologies of NVUGIB, each having particular morphological patterns and clinical implications.

3.3.2. Peptic Ulcer Disease

Nowadays, peptic ulcer disease is the most frequent cause of NVUGIB, ranging from one-third to one-half of all cases. Endoscopically, in a peptic ulcer there can be seen mucosal defect extending through the muscularis mucosae, frequently enclosed by inflammatory changes like edema, erythema and fibrin deposition. In tight correlation with the stage of the bleeding, the ulcer base could hold fresh blood, adherent clot, hematin or exposed vascular structures (1, 3).

Gastric ulcers usually appear along the lesser curvature, in the antrum, or at the incisura angularis, while duodenal ulcers generally manifest at the duodenal bulb. Posterior duodenal ulcers are particularly important, as erosion into branches of the gastroduodenal artery may result in brisk arterial hemorrhage and hemodynamic instability (4).

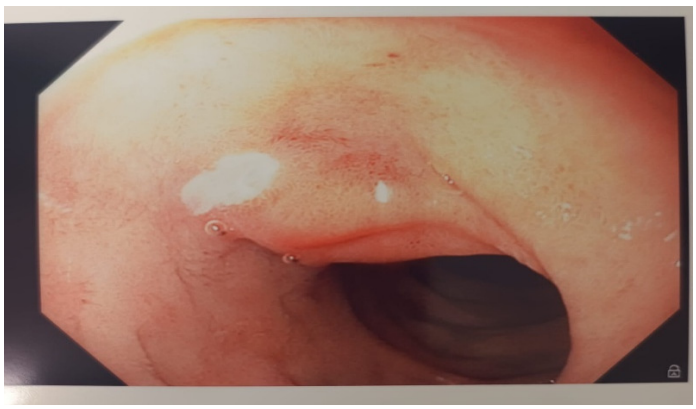

Fig. 1- Gastric ulcer Forrest III (34)

The Forrest classification is the most widely acknowledged system for categorizing the endoscopic seriousness of peptic ulcer bleeding and for stratifying rebleeding risk. Active spurting hemorrhage (Forrest Ia) stands as the most severe form, with pulsatile arterial bleeding coming from the ulcer. Active oozing hemorrhage (Forrest Ib) has diffuse bleeding without pulsatility but with a high risk of constant hemorrhage. A non-bleeding visible vessel (Forrest IIa) can be seen as a protruding or pigmented vascular structure in the ulcer crater and is very much related to recurrent bleeding if not treated. Adherent clots (Forrest IIb) could mask an underlying vessel, whereas flat pigmented spots (Forrest IIc) and clean-based ulcers (Forrest III) usually point ou lower risk lesions (1, 3, 27, 28, 29, 34).

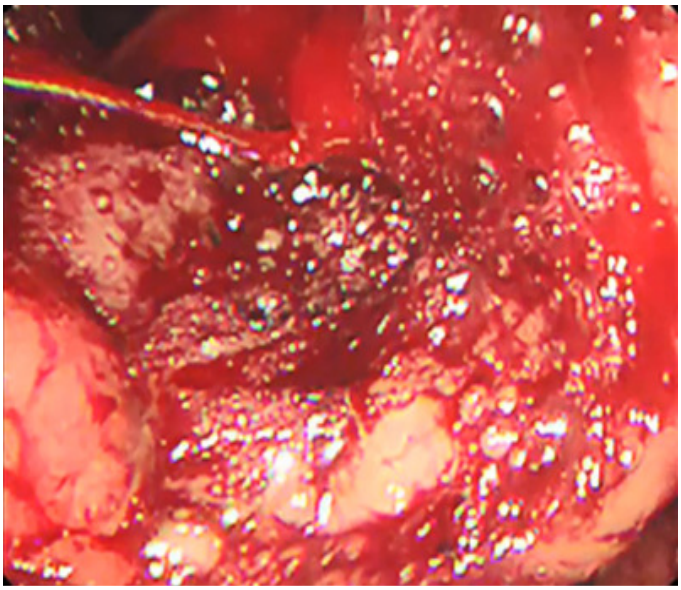

Fig. 2 -Gastric ulcer Forrest Ia (27)

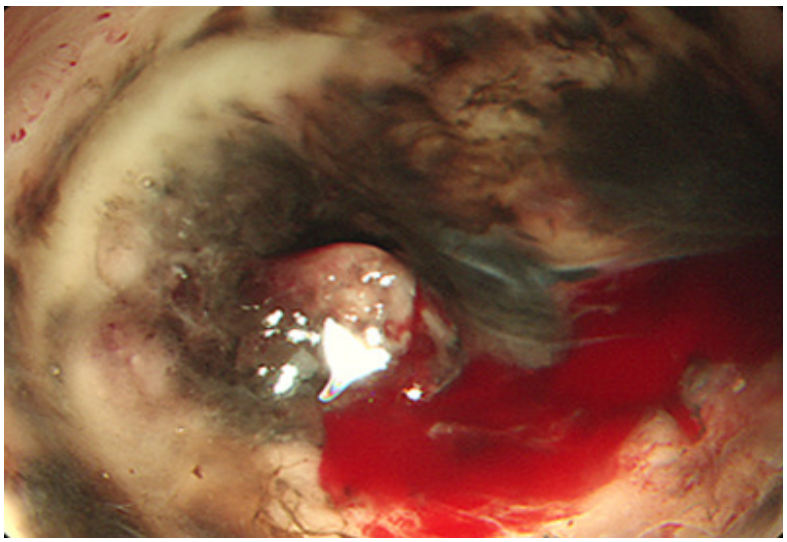

Fig. 3- Gastric ulcer Forrest IIa- visible vessel (28)

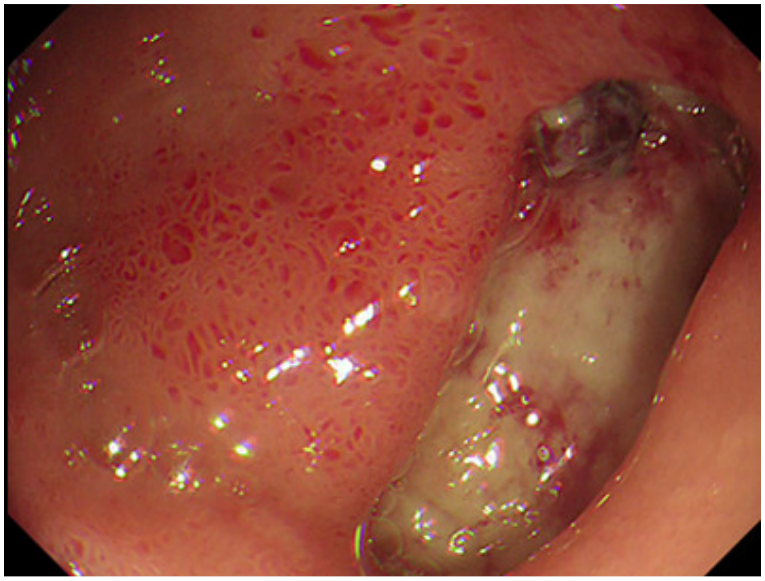

Fig. 4- Gastric ulcer Forrest IIa- visibile vessel (29)

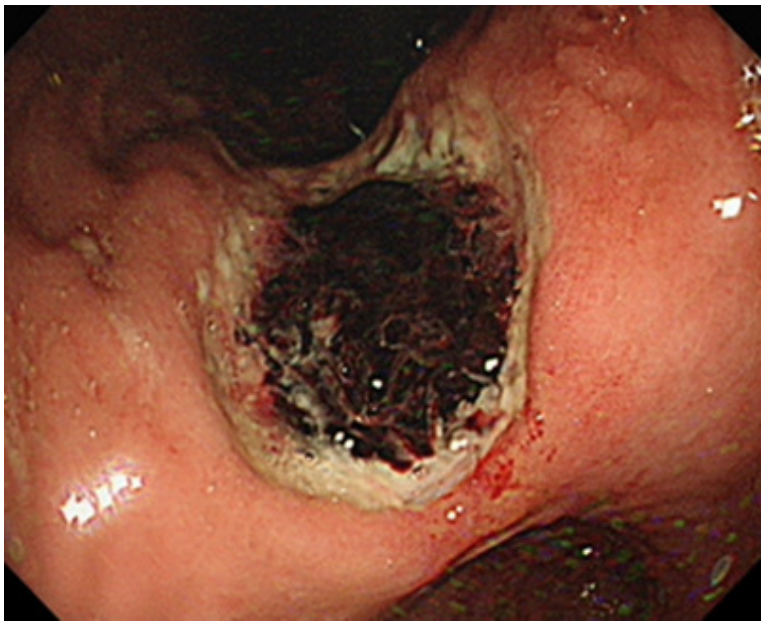

Fig. 5- Gastric ulcer Forrest IIb- clot (28, 29)

Fig. 6- Gastric Ulcer Forrest III (34)

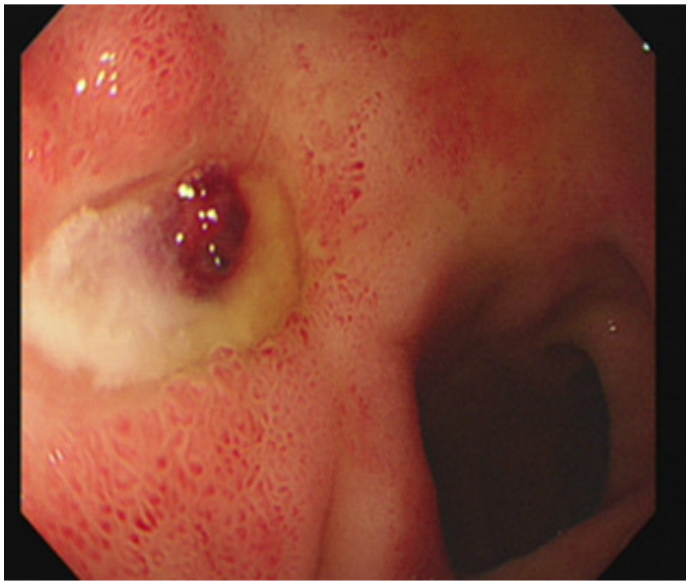

Fig. 7- Gastric ulcer Forrest IIa- visible vessel (28)

Peptic ulcers have various morphological appearances. Large ulcers could display deep excavated craters with irregular margins and encircling mucosal inflammation, while smaller ulcers have a benign appearance even though there has been a recent major hemorrhage. Thus, it is necessary to carefully inspect the ulcer base and surrounding mucosa. If there is active bleeding, visible vessels or adherent clots, then it is imperative to administer endoscopy hemostatic therapy (22).

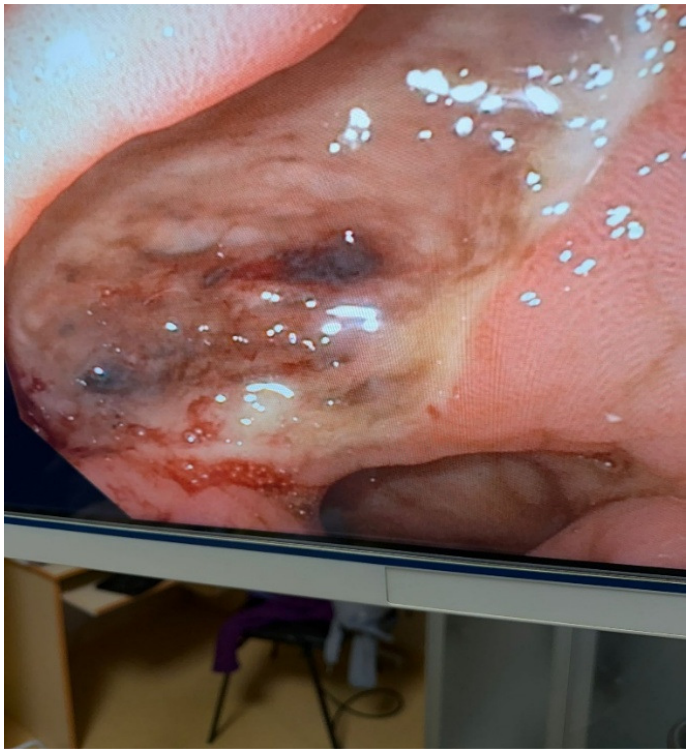

Fig. 8- Giant gastric ulcer Forrest IIc- Neoplasia? (34)

3.3.3. Erosive Gastritis and Duodenitis

Erosive gastroduodenal disease represents another important source of NVUGIB, particularly in patients exposed to NSAIDs, antiplatelet therapy, anticoagulants, or physiological stress. Unlike peptic ulcers, erosions are superficial mucosal defects that typically involve only the mucosal layer and do not extend deeply into the submucosa (3, 30, 34).

Endoscopically, erosive gastritis is characterized by diffuse or patchy mucosal erythema, multiple superficial erosions, and mucosal friability. The mucosa may appear edematous and congested, with punctate hemorrhages or shallow mucosal breaks scattered throughout the gastric body or antrum. It is frequent to find contact bleeding and low-grade dripping from various sites and in severe cases, the mucosal surface looks diffusely hemorrhagic, exemplifying widespread superficial vascular injury (4).

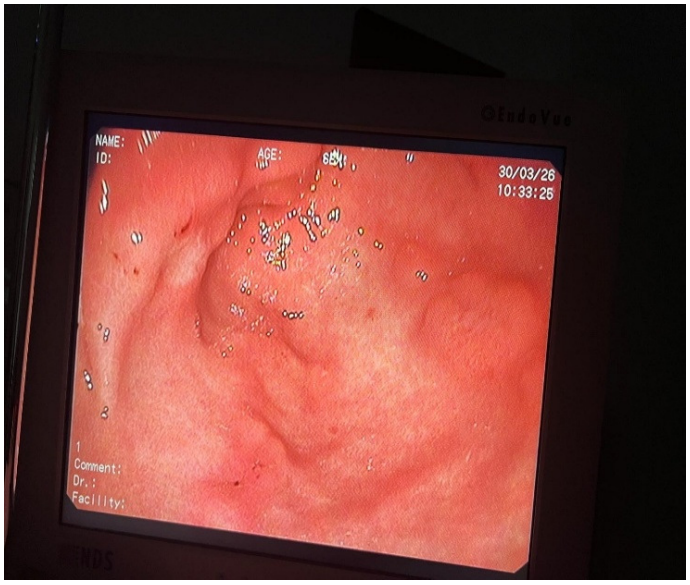

Fig. 9-Erosive gastritis (34)

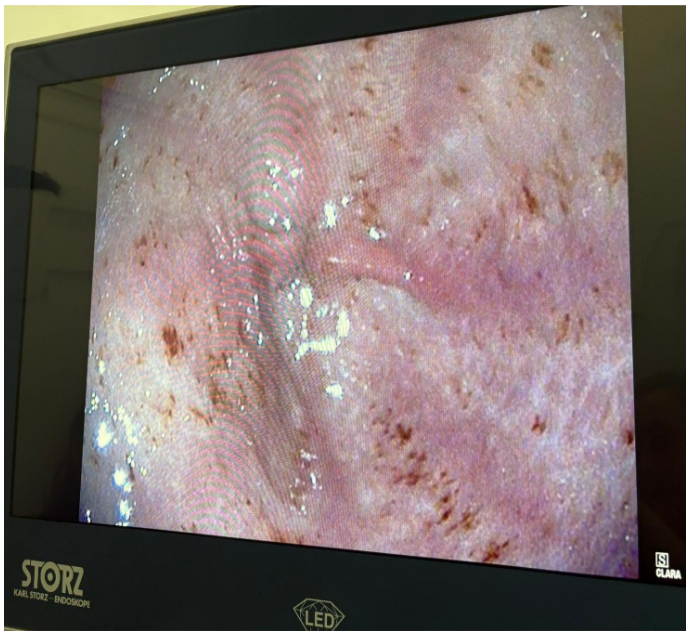

Fig. 10- Antral, erosive gastritis (34)

Erosive duodenitis presents similarities both in the duodenal bulb and the proximal descending duodenum, with the mucosa showing sporadic superficial erosions, erythema and petechial hemorrhage. These lesions do not usually manifest with surprising bleeding as in the case of arterial peptic ulcers, unless the patients are old or have antithrombotic medication. The diffuse nature of erosive disease distinguishes it from focal ulcer bleeding and may complicate endoscopic identification of a single dominant bleeding source (1).

3.3.4. Mallory-Weiss Tears

In the Mallory-Weiss syndrome there are encountered longitudinal mucosal lacerations at the gastroesophageal junction, as a result of forceful retching, vomiting, coughing or unexpected increases in intra-abdominal pressure. During the endoscopic evaluation, there are noticed linear tears at the gastroesophageal junction or just below it, often on the gastric side of the cardia (23, 31).

The tears appear solitary and are limited to the mucosa or superficial submucosa. The lesion may appear erythematous and fresh, covered by fibrin, or partially obscured by clot. Active bleeding is observable sometimes, and the blood is tracked along the laceration. The lesion is usually a non-bleeding tear with evidence of recent hemorrhage while the enclosing mucosa is typically normal, thus differentiating Mallory-Weiss tears from inflammatory or ulcerative lesions (4).

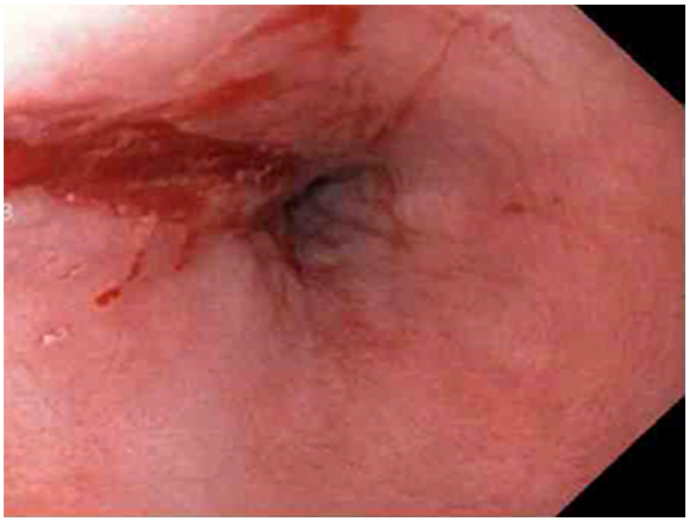

Fig .10- Mallory- Weiss "tear" gastroesophageal junction (31)

Most Mallory-Weiss tears stop bleeding spontaneously, and the overall prognosis is favorable. However, in cases of persistent hemorrhage, endoscopic therapy may be required. It is important to identify this lesion because it highlights that there have been vomiting episodes prior to acute hematemesis.

3.3.5. Dieulafoy Lesions

Dieulafoy lesions are a special vascular cause of NVUGIB with a large-caliber submucosal artery protruding through a small mucosal defect. Even though the mucosal injury of the surrounding area is minimal, these lesions could generate severe and sudden hemorrhage (24,

32). Dieulafoy lesions are notice endoscopically because they are vessels extending from regular mucosa. In the absence of a visible ulcer crater, active spurting or oozing are detected. Alternatively, the lesion may present as a small adherent clot overlying a pinpoint mucosal defect. The most common location is the proximal stomach along the lesser curvature, although Dieulafoy lesions may occur throughout the upper gastrointestinal tract (1).

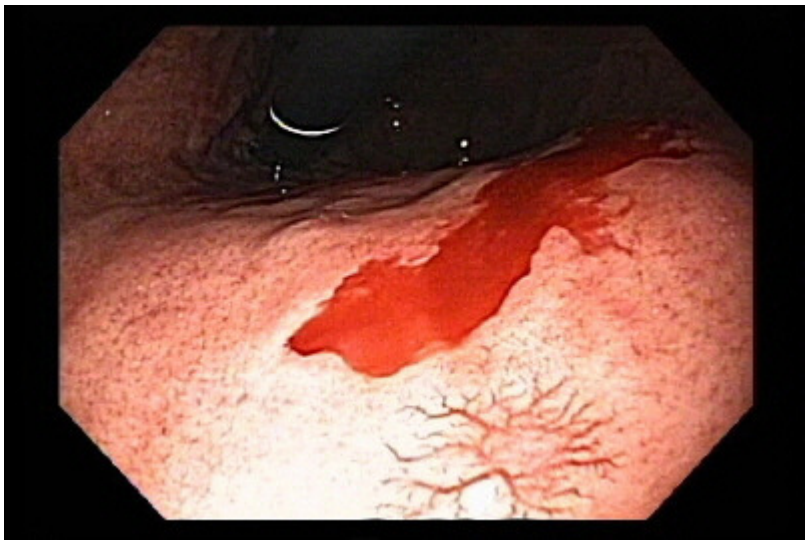

Fig. 11- Fundic Dieulafoy lesion (32)

The hallmark of Dieulafoy lesions is the disproportion between minimal mucosal injury and severe bleeding. Because bleeding may be intermittent, careful irrigation and repeated examination are often required to identify the lesion.

3.3.6. Angiodysplasia and Vascular Lesions

Angiodysplasia is a vascular abnormality with a higher incidence among elderly patients and individuals with kidney or cardiovascular disease (25, 33) having dilated mucosal and submucosal vessels. During endoscopic assessment, there can be noticed flat or marginally raised red lesions with arborizing or spider-like vascular patterns, but the mucosa around the lesion stayed intact. The blood loss does not look like an arterial hemorrhage as it is intermittent and barely observable, in the form of oozing. These lesions may be solitary or multiple and can occur anywhere in the stomach or duodenum (1).

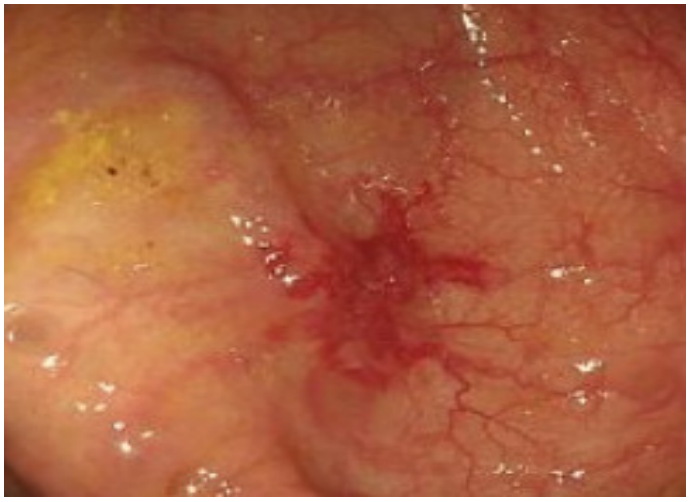

Fig. 12- Gastric angiodysplasia (33)

3.3.7. Malignancy-Associated Bleeding

NVUGIB may be associated with upper gastrointestinal malignancies, especially gastric cancer. Upon endoscopic examination, there can be observed irregular malignant lesions, which are also friable and ulcerated, having raised, nodular or infiltrative margins. If the endoscope touches the mucosa, it will bleed immediately.

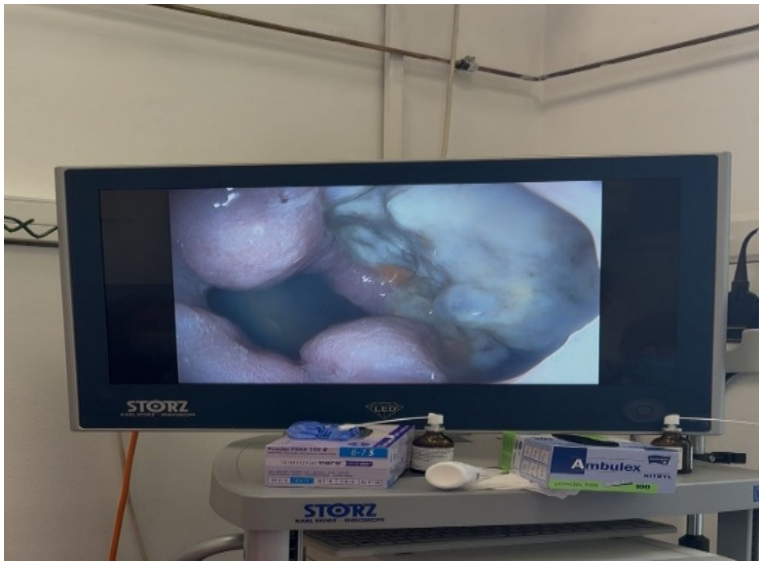

Fig. 13- Gastric neoplasia- posterior face (34)

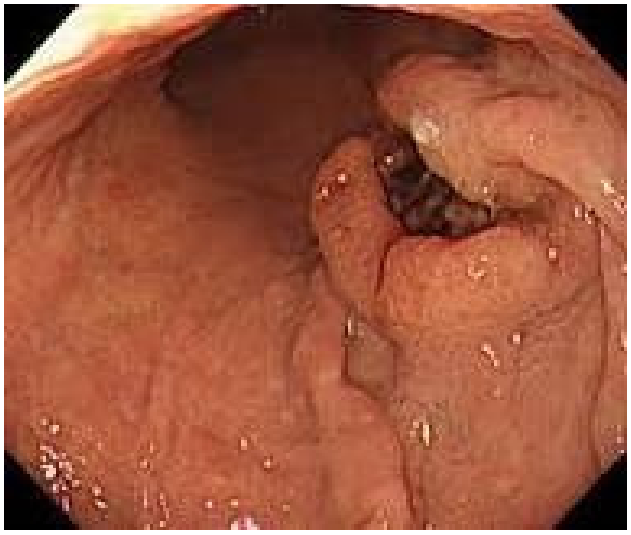

Fig. 14- Gastric, body neoplasia (26)

The origin of a tumor bleeding is represented by a broad surface and not a separate vessel, encountering necrotic debris, spontaneous oozing and mucosal distortion. The tumor vascularity and the tissue fragility make the hemostasis challenging.

3.3.8. Stigmata of Recent Hemorrhage

Not only does the endoscopy assesses the specific lesions, but it also showcases the signs of recent bleeding, like fresh blood, hematin, adherent clot or visible vessels. These findings correlate strongly with rebleeding risk and guide therapeutic decisions (1, 3).

Good diagnostic and prognostic information in the case of NVUGIB can be obtained through endoscopic data. It will also reveal underlying mechanisms, but the peptic ulcers, erosive disease, vascular lesions, mucosal tears, and malignancy stand as causes for NVUGIB. It is crucial how the lesion morphology and the hemorrhagic stigmata are understood so as to make the best decision and to enhance the results in NVUGIB.

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Chapter 4. Clinical Implications of NVUGIB

Melania Veronica Ardelean, Ovidiu Florin Ardelean

4.1. Risk Stratification in Non-Variceal Upper Gastrointestinal Bleeding: An Integrated Clinical and Laboratory Approach

4.1.1. Introduction

One of the emergencies in gastroenterology and acute care medicine is represented by non-variceal upper gastrointestinal bleeding (NVUGIB). Mortality linked to NVUGIB ranges from 5% up to 10%, being constant over the last decades, although there have been registered advances in endoscopic evaluation, pharmacologic management and supportive care. The rise in the number of elders, in comorbid disease and the extensive use of antithrombotic medication, among which anticoagulants and antiplatelet agents determine the progressing epidemiology of the condition (1, 2, 3). As a result, clinicians know how important it is to establish the risk stratification as quickly as possible in order to prioritize urgent intervention, identify patients with a high risk of adverse outcomes and enhance allocation of healthcare resources (1, 4, 5).

One takes into account the multiple dimensions of NVUGIB and its evolution when establishing risk stratification. This process starts when the patient comes to hospital, is carried out all the time the patient is hospitalized and it includes the clinical traits, hemodynamic parameters, laboratory data, comorbid conditions, medication intake and endoscopic aspects. Thus, there is obtained a complex evaluation regarding the severity of the bleeding, the physiological compromise and the patient's vulnerability. It has been proved that all the clinical and laboratory data should be considered within the broader clinical spectrum when acknowledging risk stratification (2, 3, 5).

4.1.2. Clinical Determinants of Risk in NVUGIB

The bleeding severity in NVUGIB and its potential outcomes are usually quite clear from the clinical presentation. An adverse prognosis can be determined through analysis of the hemodynamic instability. Patients, especially elders or those with cardiovascular comorbidities, coming with hypotension, tachycardia, orthostatic changes or affected mental status, usually suffer from important intravascular volume depletion, impaired compensatory mechanisms and risk continuous bleeding, re-bleeding and mortality, (1, 2, 6).

The ration between the heart rate and the systolic blood pressure in regarded as a shock index and is a useful tool to immediately evaluate risk stratification. It is utterly important to intervene when the value passes 1 because it is a clear indication of severe bleeding and bigger values are linked to escalated mortality. The clinical utility of this parameter lies in its rapid availability and its ability to identify patients who may appear deceptively stable but are physiologically compromised (5, 6, 7, 8).

Beyond hemodynamic parameters, the mode of presentation also provides prognostic information. Hematemesis shows active bleeding and high-risk endoscopic lesions, even peptic ulcers in which the vessels are visible or the spurting hemorrhage is active. Accordingly, the patients need urgent endoscopic intervention and blood transfusion. On the other hand, melena demonstrates mild bleeding and may pose a lower immediate risk, but should the patient suffer from melena and hemodynamic instability then the differences diminish. If at the start of NVUGIB, there is also hematochezia, then the bleeding is extensive, the intestinal transit is rapid and the mortality rate is high calling for urgent intervention (1, 5, 9).

Age plays a major role in these cases as old patients run a higher mortality risk, register higher transfusion requirements and longer hospitalization. Such things happen because of lower physiological reserve, higher prevalence of cardiovascular disease and anticoagulant or antiplatelet treatment. Frailty, which is increasingly recognized as a determinant of outcome independent of chronological age, further contributes to adverse prognosis (2, 4, 10).

NVUGIB is very much impacted by comorbid conditions, meaning that cardiovascular disease, chronic kidney disease, liver disease chronic disease and malignancy augment the mortality risk. It is important to mention that decompensation of underlying comorbid conditions determined by blood loss and hemodynamic compromise is associated with mortality in NVUGIB and not the bleeding directly. Consequently, a patient ought to be assessed globally, avoiding focusing solely on the bleeding lesion (1, 2, 3, 10, 11).

Risk stratification is also determined by the patients' treatments. There is change in the epidemiology of NVUGIB in the case of antiplatelets, anticoagulants and nonsteroidal anti-inflammatory drugs. If the patients undergo a combination therapy, like dual antiplatelet medication or anticoagulant-antiplatelet associations, they have higher bleeding severity, re-bleeding risk and increased mortality. These patients should therefore be considered high-risk even when presenting with relatively mild clinical features (1, 3, 12, 13).

4.1.3. Laboratory Markers in Risk Stratification

Laboratory parameters provide essential complementary information in the evaluation of NVUGIB. These markers reflect the physiological consequences of bleeding, underlying comorbidities, and coagulation status. Their interpretation, however, must always occur within the clinical context, as isolated laboratory abnormalities may be misleading (1, 2, 3).

Despite it being one of the most widely used indicators of bleeding severity, hemoglobin concentration may underestimate the volume of the blood loss in the beginning as the hemodilution appears several hours after acute hemorrhage. Repeated hemoglobin measurements are necessary and if constant decline is noticed, then it is a clear indication of continuous bleeding and the intervention is imminent. In the case of severe anemia, transfusion requirements, hemodynamic instability and mortality raise the stakes (1, 2, 4).

Blood urea nitrogen (BUN) findings are also helpful in NVUGIB as high levels show that the patient has digested and absorbed blood proteins in the gastrointestinal tract and that he suffers from hypovolemia and reduced renal perfusion. The ration BUN-to-creatinine demonstrates upper gastrointestinal bleeding if it is high thus aiding the clinicians to distinguish between upper and lower gastrointestinal sources. Furthermore, elevated BUN indicates the possibility of bleeding severity, transfusion requirements and mortality and it is the more important as it is incorporated into validated risk scores such as the Glasgow-Blatchford score (2, 14, 15).

Serum creatinine offers an overview for renal perfusion and comorbidity burden since high levels prove chronic kidney disease or acute kidney injury secondary to hypovolemia. Heightened mortality, long hospitalization and intensive care are correlated with renal dysfunction (16).

Coagulation parameters also play an important role in risk stratification. Elevated international normalized ratio (INR) and thrombocytopenia increase bleeding severity and re-bleeding risk. These abnormalities are particularly relevant in patients receiving anticoagulant therapy or those with liver disease. Correction of coagulopathy may be necessary prior to endoscopic intervention (1, 2, 16).

Serum lactate has emerged as an important marker of tissue hypoperfusion and severity of illness as hemodynamic instability, increased mortality and demand of intensive care are linked to a high level in lactate. Lactate is particularly useful in identifying high-risk patients who may appear clinically stable but demonstrate underlying physiological compromise (3,17).

The patient vulnerability plays a crucial role in the outcome of risk stratification because chronic illness, malnutrition and frailty are reflected in hypoalbuminemia, which is may trigger increased mortality and prolonged hospitalization (2, 14).

4.1.4. Integration of Clinical and Laboratory Findings and the Role of Risk Scores in NVUGIB

One of the pillars of modern risk stratification in non-variceal upper gastrointestinal bleeding (NVUGIB) is represented by the integration of clinical and laboratory data. Nowadays it is emphasized that the sooner the increased risk for inimical outcomes such as requirement of urgent intervention, re-bleeding, prolonged hospitalization and mortality is identified the more complex is the assessment framework. From the moment the patient presents, the evaluation begins and continues throughout the hospitalizing time, integrating hemodynamic parameters, laboratory abnormalities, comorbidities and endoscopic discovery as well (1, 2, 3, 5).

Urgent resuscitation and immediate endoscopic examination are mandatory in the case of patients arriving with hemodynamic instability, severe anemia, elevated blood urea nitrogen (BUN), renal dysfunction or coagulopathy. Patients have a higher risk of mortality and necessitate intervention if they present with hypotension, tachycardia, modified mental status and symptoms of hypoperfusion as all these aspects signify intravascular volume depletion. Likewise, bleeding severity and primary physiological vulnerability are also seen from laboratory data like elevated BUN, low hemoglobin concentration, prolonged coagulation parameters and hypoalbuminemia (2, 4, 5, 10).

On the other side, there are patients that run a low risk and they are those who come with stable vital signs, register minimal laboratory abnormalities and absence of serious comorbidities. They can be examined endoscopically and, sometimes, they might be managed at home, thus reducing unnecessary hospitalization and usage of healthcare resources but preserving the patient's safety (3, 5).

The integrative management infers the use of various validated risk stratification scores which merge clinical and laboratory elements into predictive models that appraise risk of intervention, re-bleeding and mortality. The systems which are most widely validated and effective from a clinical point of view encompass:

- Glasgow-Blatchford Score (GBS)
- Rockall Score
- AIMS65 Score
- PNED Score

Not only does modern NVUGIB management rely on these tools, but they are also endorsed by international guideline (1, 2, 5).

4.1.5. Glasgow-Blatchford Score in Non-Variceal Upper Gastrointestinal Bleeding

Concept and Clinical Rationale

An utterly important instrument for early risk stratification is the Glasgow-Blatchford Score (GBS) which is used during initial emergency assessment and identifies patients in need of clinical intervention before endoscopy. Unlike other scoring systems, the GBS does not require endoscopic data, allowing rapid risk stratification at the time of presentation (3, 14). This score pinpoints low-risk patients who can be safely taken care of outside the hospital, hence reducing resource usage. Several large cohort studies have demonstrated that patients with GBS scores of 0–1 have extremely low rates of adverse outcomes, including need for transfusion, endoscopic intervention, or surgery (3, 14).

Components of the Glasgow-Blatchford Score

The Glasgow-Blatchford score incorporates a combination of clinical and laboratory parameters:

- Hemoglobin level
- Blood urea nitrogen
- Systolic blood pressure
- Heart rate
- Presence of melena
- Presence of syncope
- Liver disease
- Heart failure

All of these components mirror crucial physiological aspects regarding the severity of the bleeding and the individual's vulnerability. Hemoglobin concentration is indicative of cumulative blood loss and estimates indirectly the duration of the bleeding and its severity. The digestion of blood proteins in the gastrointestinal tract is seen in the elevated blood urea nitrogen which also shows powerful upper gastrointestinal bleeding. Hypotension and tachycardia are signs of hemodynamic compromise and continual blood loss. Comorbidities such as liver disease and heart failure increase mortality risk by reducing physiological reserve (14, 16).

Clinical Interpretation and Predictive Value

The Glasgow-Blatchford score demonstrates strong predictive accuracy for:

- Need for transfusion
- Need for endoscopic therapy
- Need for surgical intervention
- Re-bleeding risk
- Mortality

A score of 0-1 reflects that the patients have a low risk and can be discharged, but the higher the score the more the patients are at risk of intervention. For example, a score ≥7 urges hospitalization and early endoscopic evaluation.

The Glasgow-Blatchford score surpasses other risk scoring systems in anticipating intervention and establishing low-risk patients as shown in comparative studies. Comparative studies demonstrate that the Glasgow-Blatchford score highlights other risk scoring systems in predicting the need for intervention and identifies low-risk patients suitable for outhospital management (3, 14, 18).

4.1.6. Rockall Score in Non-Variceal Upper Gastrointestinal Bleeding

Concept and Clinical Role

One of the most secure prognostic instruments for the evaluation of patients with upper gastrointestinal bleeding, including non-variceal upper gastrointestinal bleeding (NVUGIB) is the Rockall score. It was designed to foretell mortality as a consequence of acute gastrointestinal hemorrhage, but it has become a comprehensive risk stratification system that can rank mortality and re-bleeding risk. Despite newer systems, it is nevertheless relevant in post-endoscopic risk evaluation and as an aftermath indicator (1, 3, 5).

This score analyses clinical and endoscopic variables and this association showcases the progressive nature of NVUGIB. The immediate prognostic information is postulated during the initial clinical presentation and the endoscopic evaluation clarifies risk stratification. Therefore, the Rockall score eases decision making in the post-endoscopic stage that involves monitoring level, necessity of endoscopy repetition and plan of discharging (10, 18).

Two versions of the Rockall score are commonly utilized:

- Pre-endoscopic Rockall score
- Complete Rockall score (post-endoscopic)

Before endoscopy, the score offers early risk stratification when the patients arrives, while the complete score takes into account endoscopic report as well and predicts more accurately the clinical outcomes.

Pre-Endoscopic Rockall Score

The pre-endoscopic Rockall score incorporates three clinical variables:

- Age
- Hemodynamic status
- Comorbidities

These variables reflect baseline patient vulnerability and severity of bleeding.

Age

Age represents one of the strongest predictors of mortality in NVUGIB. Elderly patients often present with reduced physiological reserve, increased prevalence of cardiovascular and renal disease, and higher rates of antithrombotic therapy which all favor decompensation and escalate sensitivity to unfortunate outcomes.

Studies have demonstrated that mortality increases consistently in patients older than 65 years, with further increases observed in those older than 80 years. Older patients also present higher rates of re-bleeding, prolonged hospitalization, and need for intensive care admission (3, 10).

Hemodynamic Status

Hemodynamic instability is a critical determinant of prognosis in NVUGIB. Intravascular volume depletion and continuous hemorrhage are displayed through hypotension and tachycardia. Patients presenting with signs of shock run the risk demonstrate increased risk of:

- Re-bleeding
- Blood transfusion
- Surgical intervention
- Mortality

Early risk evaluation focuses on the hemodynamic instability that reveal the bleeding seriousness and the diminished physiological reservoir. (1, 5).

Comorbidities

Comorbid conditions importantly influence evolution in NVUGIB. The Rockall score reveales severe comorbidities, including:

- Cardiovascular disease
- Renal failure
- Liver disease
- Malignancy

Such contexts negatively affect physiological resources and deter hemostatic mechanisms. Individuals suffering from liver diseases exhibit coagulopathy and thrombo-cytopenia, patients facing renal problems have platelet dysfunction while those with malignant conditions are the most susceptible to mortality because of repetitive bleeding and underlying illness burden (16, 18).

Complete Rockall Score: Endoscopic Variables

The complete Rockall score iincludes two additional endoscopic parameters:

- Endoscopic diagnosis
- Stigmata of recent hemorrhage

These variables allow more precise risk stratification following endoscopic evaluation.

Endoscopic Diagnosis

The basic bleeding source is pivotal for the prognosis as some lesions are linked with higher risk of re-bleeding and mortality, like:

- Peptic ulcers
- Malignancy-associated bleeding
- Large gastric ulcers
- Posterior duodenal ulcers

On the other hand, Mallory-Weiss lesions and erosive gastritis register lower risk and have a favorable outcome. Unlikely, malignant-related lesions do not have an optimistic prognosis due to periodic blood loss and limited therapeutic options (1).

Stigmata of Recent Hemorrhage

Endoscopic stigmata of recent bleeding represent one of the most important predictors of recurrent hemorrhage. High-risk stigmata include:

- Active bleeding

- Oozing hemorrhage
- Non-bleeding visible vessel
- Adherent clot

These findings are associated with increased re-bleeding risk and mortality, but clean-based ulcers and flat pigmentation are correlated with low risk and good results. It is crucial to look for these traits so as to steer endoscopic therapy and to monitor the patient after the procedure (1, 5).

Clinical Interpretation

Table. 1 Graded risk stratification provided by the Rockall score

Low Rockall score (0–2) Associated with low mortality and low re-bleeding risk. These patients may be suitable for early discharge following stabilization.
Intermediate Rockall score (3–4) Associated with moderate risk. These patients are inpatients and close monitoring.
High Rockall score (≥5) Associated with high mortality, higher re-bleeding risk, and prolonged hospitalization. These patients require intensive care monitoring and multidisciplinary management.
Several studies have demonstrated that increasing Rockall scores correlate with worsening outcomes, including need for repeat endoscopy, transfusion requirements, and mortality (3, 10).

Clinical Utility and Limitations

The Rockall score is considered particularly useful for:

- Predicting mortality
- Predicting re-bleeding
- Guiding level of care
- Determining monitoring intensity

However, compared with the Glasgow-Blatchford score, the Rockall score is less effective for predicting need for intervention. Additionally, because the complete Rockall score needs endoscopic findings, it is less useful for early triage decisions (3, 4). Though, the Rockall score remains an important tool for post-endoscopic risk stratification and outcome prediction.

Role in Integrated Risk Stratification

Modern guidelines recommend sequential use of risk stratification tools:

Initial evaluation

→ Glasgow-Blatchford score

Post-stabilization

→ AIMS65 score

Post-endoscopy

→ Rockall score

This integrated approach improves clinical decision-making and optimizes patient outcomes (1).

Conclusion

The Rockall score remains an important component of risk stratification in NVUGIB due to the fact that it integrates clinical and endoscopic data, bringing prognostic information about mortality and re-bleeding risk. Besides the latest scoring systems in the early stages of risk stratification, the Rockall score is pivotal in post-endoscopic assessment and when clinicians have to make a decision. It can be easily use alongside other tools for better patient management.

4.1.7. AIMS65 Score in Non-Variceal Upper Gastrointestinal Bleeding

Concept and Clinical Role

Patients with upper gastrointestinal bleeding, including NVUGIB can also benefit from the AIMS65 score which is an additional simple and extensively used tool for foreseeing in-hospital mortality. It is utilized at the time of admission for fast evaluation operating with clinical and laboratory parameters and it proves very useful in emergency contexts, so high-risk patients may be identified immediately and there may be established the monitoring intensity (1, 3, 9).

Not only does it predict mortality risks, as it was created, but it also coordinates with further clinical evolution like hospitalization length, urge for intensive care admission and global bleeding seriousness. Consequently, AIMS65 has become an important component of integrated risk stratification strategies in NVUGIB (16, 18).

Components of the AIMS65 Score

The AIMS65 score includes five variables:

- Albumin <3.0 g/dL
- INR >1.5
- Altered mental status
- Systolic blood pressure <90 mmHg
- Age >65 years

Each parameter reflects either acute bleeding severity or underlying physiological vulnerability. The score ranges from 0 to 5, with increasing scores indicating higher mortality risk.

Physiological Significance of Variables

Hypoalbuminemia reflects chronic illness, malnutrition, or liver disease and is associated with reduced physiological reserve and increased mortality. Anticoagulant medication and hepatic dysfunction may cause coagulopathy and persistent bleeding and faulty hemostasis reflected in elevated INR. Another sign of blood loss is the worsened mental status, implying cerebral hypoperfusion and severe hemodynamic compromise.

Hypotension represents one of the most important indicators of severe hemorrhage and is associated with increased mortality, need for urgent intervention, and intensive care admission. Advanced age contributes to more adverse outcomes due to a reduced physiological reserve, multiple comorbidities, and increased susceptibility to complications (1, 5, 16).

Clinical Interpretation

Table 2. Graded mortality risk stratification provided by the AIMS65 score

Score 0–1
Low mortality risk
Score 2
Moderate risk requiring close monitoring
Score ≥3
High mortality risk requiring intensive management

Higher AIMS65 scores correlate with increased mortality, prolonged hospitalization, and need for ICU admission. Patients with scores ≥2 generally require close monitoring, while those with scores ≥3 represent a high-risk population requiring aggressive management (17).

Clinical Utility

The AIMS65 score is particularly useful for:

- Mortality prediction
- ICU triage
- Monitoring intensity decisions
- Early risk stratification

Unlike the Glasgow-Blatchford score, which predicts need for intervention, the AIMS65 score is focused on mortality prediction. Therefore, it is best used in combination with other risk stratification tools.

Role in Integrated Risk Stratification

Modern management strategies recommend sequential risk assessment:

Initial evaluation

→ Glasgow-Blatchford score

Early hospitalization

→ AIMS65 score

Post-endoscopy

→ Rockall score

This integrated approach improves risk stratification and patient outcomes.

Conclusion

The AIMS65 score represents a simple, practical, and effective tool for mortality prediction in NVUGIB. By incorporating markers of physiological vulnerability and bleeding severity, the AIMS65 score provides valuable prognostic information and helps guide clinical decision-making. When used in combination with other scoring systems, AIMS65 contributes to comprehensive risk stratification and optimized patient management

4.1.8. PNED Score in Non-Variceal Upper Gastrointestinal Bleeding

Concept and Clinical Role

Patients undergoing endoscopic assessment may receive an exhaustive prognostic through the PNED score (Progetto Nazionale Emorragia Digestiva) which can predict mortality and unfortunate outcomes. Confronting the scores previously mentioned, the PNED offers a wider variety of clinical, laboratory and endoscopic data, more detailed risk stratification ensuing the endoscopy (1, 5, 19).

Although it is applied only after endoscopic evaluation, the PNED score is highly accurate when it comes to predicting mortality, re-bleeding and clinical complications (16, 20).

Components of the PNED Score

The PNED score integrates multiple clinical domains reflecting both bleeding severity and baseline patient vulnerability:

- Age
- Comorbidities
- Hemodynamic instability
- Laboratory parameters
- Endoscopic findings
- Re-bleeding during hospitalization
- American Society of Anesthesiologists (ASA) score

This multidimensional structure enhances prognostic accuracy by combining acute clinical severity with underlying patient condition.

Clinical Significance of Variables

Higher age and important comorbidities, including cardiovascular disease, renal failure, liver disease, and malignancy, are associated with increased mortality in NVUGIB. These factors low down physiological reserve and impair compensatory responses to acute hemorrhage.

Hemodynamic instability, including hypotension and tachycardia, reflects significant blood loss and is associated with increased transfusion needs, re-bleeding risk, and mortality. Laboratory parameters such as low hemoglobin, renal dysfunction, and coagulopathy further contribute to risk stratification by reflecting both bleeding severity and physiological vulnerability (1, 3).

Endoscopic findings play an important role in the PNED score. High-risk lesions such as active bleeding, visible vessels, large ulcers, and malignancy-related bleeding are related with increased risk of re-bleeding and adverse outcomes. Additionally, the inclusion of the ASA classification provides an overall assessment of patient condition and comorbidity burden, further improving predictive accuracy.

Clinical Interpretation

Table 3. **Graded risk stratification provided by the PNED score**

Low PNED score

→ Low mortality risk and favorable clinical course

Intermediate PNED score

→ Moderate risk requiring hospitalization and monitoring

High PNED score

→ High mortality risk requiring intensive monitoring and aggressive management

Higher PNED scores correlate with increased mortality, re-bleeding risk, prolonged hospitalization, and need for intervention.

Clinical Utility

The PNED score is particularly useful for:

- Mortality prediction
- Post-endoscopic risk stratification
- Identification of high-risk patients
- Comprehensive prognostic assessment

However, due to its complexity, the PNED score is generally used alongside other scoring systems rather than for early triage.

Role in Integrated Risk Stratification

Sequential risk assessment in NVUGIB may include:

Initial evaluation

→ Glasgow-Blatchford score

Early hospitalization

→ AIMS65 score

Post-endoscopy

→ Rockall score

Comprehensive prognosis

→ PNED score

This integrated approach improves clinical decision-making and patient outcomes.

Conclusion

The PNED score represents a comprehensive and accurate prognostic tool in NVUGIB. It analyses clinical, laboratory and endoscopic data, details the risk assessment, especially in the case of mortality and adverse events.

4.1.9. Algorithmic Comparison of Risk Scores in NVUGIB

Risk stratification in NVUGIB is an organized layered process which incorporates both clinical resolution and certified prognostic scoring systems. Because each score evaluates different aspects of disease severity and predicts distinct clinical outcomes, no single tool is sufficient when used in isolation. That is why contemporary practice applies various scores at certain stages of patient evaluation, thus making the prognostic assessment clearer and instructing the case administration (1, 3, 5).

This procedure starts when the patient arrives, lasts all along the hospitalization and post-endoscopic evaluation and helps the clinicians constantly reevaluate risk and tailor management.

Initial Presentation: Early Risk Stratification

When the patient presents, the focus is to quickly decide whether it is a low-risk individual who may not even need hospitalization or a high-risk patient who depends upon urgent intervention. The best instrument during emergency assessment is the Glasgow-Blatchford score since it comprises clinical and laboratory data obtained before endoscopy. This score was designed to search for those situations which may call for clinical intervention, including blood transfusion. Low scores, for example values like 0-1, prove very unlikely to have adverse outcomes and can be discharged, while higher scores point to increasing bleeding severity, obligation of hospitalization, immediate endoscopy and thorough monitoring.

Early Hospital Assessment: Mortality Risk and Clinical Vulnerability

The moment the patient is stabilized, it is crucial to use the AIMS65 score in order to identify individuals with a high mortality risk and clinical deterioration.

This score assesses physiological vulnerability by applying five parameters which are available, hypoalbuminemia, coagulopathy, hypotension, altered mental status and old age, and which indicate acute bleeding severity and underlying patient frailty.

It the score is low, the clinical course is favorable but if it is high, then there are worries regarding increased mortality, prolonged hospitalization and need for intensive monitoring.

Should the score equal 2 or exceed it, the case needs closer observation and those with scores of 3 or greater are a high-risk population that may be monitored under intensive care.

Post-Endoscopic Assessment: Re-Bleeding and Outcome Prediction

Following endoscopic evaluation, additional prognostic information becomes available. At this stage, the **Rockall score** plays an important role in predicting re-bleeding and overall clinical outcomes.

It takes into account clinical information, endoscopic data, underlying cause of bleeding and signs of the recent blood loss, facilitating more precise risk stratification after endoscopic therapy.

Low scores are indicative of minor mortality and re-bleeding risk and, after they are stabilized, they can be discharged. On the other hand, higher Rockall scores relate to more re-bleeding, extended hospitalization and close intensive monitoring.

Comprehensive Prognostic Assessment

An overall assessment is obtained through PNED that observes clinical, laboratory and endoscopic information, but also comorbidities, with the clear purpose of separating individuals with higher risk of mortality and aggravation.

The PNED is very sophisticated and it is applied in complex cases because it contributes to the management of the cases from a multidisciplinary perspective by bringing valuable prognostic knowledge.

Integrated Sequential Algorithm

Table 4. The sequential application of risk scores

Patient Presentation

↓

Glasgow-Blatchford score

(Need for intervention and admission decision)

↓

Early Hospitalization

↓

AIMS65 score

(Mortality risk and monitoring intensity)

Post-Endoscopy

↓

Rockall score

(Re-bleeding and outcome prediction)

Comprehensive Assessment

↓

PNED score

(Global prognosis and complication risk)

Comparative Clinical Roles of Risk Scores

Each scoring system therefore contributes distinct and complementary information:

- **Glasgow-Blatchford score** — best for early triage and predicting need for intervention
- **AIMS65 score** — best for mortality prediction and ICU triage
- **Rockall score** — best for post-endoscopic re-bleeding and outcome prediction
- **PNED score** — best for comprehensive prognostic evaluation

Together, these tools offer the physician a structured and multidimensional approach to risk stratification.

Conclusion: Integrated Risk Stratification in NVUGIB

Risk stratification in NVUGIB fluctuates, requesting constant evaluation from the clinicians and the use of various risk scoring systems in order to obtain more details regarding the risks the patient faces and personalized treatment.

When the patient arrives, it is applied the Glasgow-Blatchford score which highlights the individuals that necessitate intervention. Next the AIMS65 score checks the physiological vulnerability and mortality risk and then, after the endoscopic prognosis, the Rockall score is used. Finally, the PNED score offers a global prognostication.

This multilayered perspective enhances early triage, improves monitoring strategies, establishes the moment for endoscopy and reinforces safe discharge planning, making a difference in the management of NVUGIB (1, 3, 5).

4.2. Management Strategies in Non-Variceal Upper Gastrointestinal Bleeding (NVUGIB)

4.2.1. Introduction

Gastroenterology and acute care medicine regards non-variceal upper gastrointestinal bleeding (NVUGIB) as a medical emergency because mortality rates stay between 5-10% or even higher for patients with various comorbidities, and those with antithrombotic medication. Unfortunate results often happen because of chronic conditions or postponed or inadequate management (1, 2).

Supervision of NVUGIB targets patient stabilization, bleeding control, re-bleeding prevention and reduced mortality so, to achieve this there has been developed a structured, multidisciplinary and time-sensitive approach. It covers early risk stratification, prompt resuscitation, pharmacologic therapy, timely endoscopy, endoscopic hemostasis and post-endoscopic management.

4.2.2. Initial Assessment and Resuscitation

4.2.2.1. Clinical Assessment

Right after the patient presents with an episode of NVUGIB, there must be run a clinical assessment to protect the airway, to get information about the hemodynamic status and the bleeding severity. It is crucial to notice the hemodynamic instability since a large percentage in mortality and necessity of urgent intervention is connected to symptoms like hypotension and tachycardia.

Patients presenting with:

- Hypotension
- Tachycardia
- Syncope
- Altered mental status
- Ongoing hematemesis

should be considered high risk and require immediate resuscitation and early endoscopy.

It is vital to protect the airway due to the fact that aspiration risk is substantial, especially in patients that have an aggravated mental status or continuous hematemesis (1).

4.2.2.2. Hemodynamic Resuscitation

In the early management stage, there is administered intravenous fluid as isotonic crystalloid solutions are provided to bring back intravascular volume and stabilize blood pressure. However, excessive fluid administration should be avoided, particularly in elderly patients and those with cardiac1 disease.

Blood transfusion strategies have changed toward a **restrictive transfusion approach**. Current guidelines recommend transfusion when hemoglobin falls below **7 g/dL** in most patients, although a higher threshold (8 g/dL) may be appropriate in patients with cardiovascular disease. Restrictive transfusion strategies have been considered to improve outcomes and reduce re-bleeding (2, 4).

4.2.3 Pharmacologic Management

Proton Pump Inhibitor Therapy

Proton pump inhibitors (PPIs) represent the cornerstone of pharmacologic management in NVUGIB because the acid suppression endorses clot stability and diminishes the re-bleeding risk.

High-dose intravenous PPI therapy is typically administered as:

- Bolus dose
- Continuous infusion for 72 hours

This approach has been shown to reduce re-bleeding, need for surgery, and mortality in high-risk patients (1).

Following endoscopic therapy, PPI treatment is continued IV, typically then transitioning to oral therapy after 72 hours.

Prokinetic Agents

The administration of prokinetic agents takes place before endoscopy because it facilitates gastric excretion, weakens the blood and clot burden and enhances diagnostic accuracy.

Pre-endoscopic IV erythromycin administration has been associated with:

- Improved visualization
- Reduced need for repeat endoscopy
- Shorter hospital stay

However, routine use remains optional and is generally reserved for patients with suspected large amounts of blood or clot in the stomach (2).

4.2.4. Endoscopic Management of Non-Variceal Upper Gastrointestinal Bleeding

4.2.4.1. Introduction

Endoscopy is essential in the management of NVUGIB and there have been registered advances in endoscopic hemostatic techniques for the last thirty years. This stage in the administration of NVUGIB had greatly diminished the requirement for surgical intervention because it focuses on achieving prompt hemostasis, reducing the risk of re-bleeding, minimizing transfusion requirements and cut down mortality. As a consequence, it has enhanced patient outcome.

There are elements like, precise identification of the bleeding source, understanding of high-risk problems, decision upon appropriate hemostatic modalities and use of ancillary pharmacologic therapy that contribute to the success of endoscopic therapy. There is a lot of emphasis on adopting an organized approach to this method by analyzing the peculiarities of the lesion, observing the bleeding severity, including mechanical, thermal and injection techniques (1, 2).

4.2.4.2. Timing of Endoscopic Intervention

When a patient presents with NVUGIB, it is recommended to apply endoscopic therapy in the first 24 hours after initial resuscitation and stabilization as it provides exact diagnosis, risk stratification and capacitates efficient hemostatic therapy.

In the case of patients with high-risk clinical traits such as hemodynamic instability, continuous hematemesis or dangerous bleeding, it is advisable to perform an endoscopy in the first 12 hours since the patient's arrival. This immediate therapy has proved beneficial as there have been registered improved outcomes, abridged hospitalization and lower need for surgery.

Adequate resuscitation prior to endoscopy remains essential. Endoscopy should not be delayed unnecessarily, but stabilization of airway, breathing, and circulation is critical to ensure procedural safety (1).

4.2.4.3. Endoscopic Identification of High-Risk Lesions

If high-risk stigmata of recent hemorrhage are discovered, then the patient undergoes endoscopic therapy, using the Forrest classification as it is the system most widely employed.

High-risk lesions include:

- Active spurting bleeding (Forrest Ia)
- Active oozing bleeding (Forrest Ib)
- Non-bleeding visible vessel (Forrest IIa)
- Adherent clot (Forrest IIb)

While these lesions have a high risk of re-bleeding and need endoscopic intervention, flat pigmented spots or clean-based ulcers are regarded as low-risk and do not call for hemostasis.

Endoscopic therapy should therefore be directed primarily at patients with high-risk stigmata, as treatment of low-risk lesions does not improve outcomes and may increase procedural risks unnecessarily (2).

4.2.4.4. Injection Therapy

The first worldwide implemented endoscopic hemostatic technique is the injection therapy which consists of diluted epinephrine and which is still an important part in the case management.

Epinephrine injection achieves hemostasis through several mechanisms:

- Local vasoconstriction
- Tissue edema producing tamponade
- Platelet aggregation

Injection is typically performed in a circumferential pattern around the bleeding vessel, followed by injection directly into the bleeding site when appropriate.

Despite driving temporary hemostasis, it has been demonstrated that the injection alone runs the risk of re-bleeding. As a consequence, it is recommended to administer it alongside mechanical or thermal therapy (2, 5).

Other injection agents, including sclerosants and thrombin, have been studied but are used less commonly in now-a-day practice.

4.2.4.5. Thermal Hemostatic Therapy

One of the most efficient ways for achieving long-lasting hemostasis is thermal therapy when heat is applied to coagulate bleeding vessels and promote tissue coagulation.

Common thermal modalities include:

- Heater probe
- Bipolar electrocoagulation
- Argon plasma coagulation (APC)

Contact thermal devices such as heater probe and bipolar electrocoagulation are particularly effective for peptic ulcer bleeding. These devices permit direct compression of the bleeding vessel combined with thermal coagulation, increasing hemostatic efficacy.

Argon plasma coagulation is a non-contact thermal modality frequently used for diffuse bleeding lesions, including vascular ectasia and superficial mucosal bleeding. APC is particularly useful in lesions such as gastric antral vascular ectasia or angiodysplasia.

Thermal therapy has demonstrated high success rates in achieving primary hemostasis and reducing re-bleeding risk (1).

4.2.4.6. Mechanical Hemostatic Therapy

Mechanical hemostasis has become increasingly favored in modern endoscopic practice due to its high efficacy and safety profile. Mechanical devices provide immediate closure of bleeding vessels without tissue injury associated with thermal therapy.

Hemoclips

Through-the-scope hemoclips are largely used for peptic ulcer bleeding, Dieulafoy lesions, and Mallory-Weiss tears. Hemoclips function by mechanically approach to the bleeding vessel and surrounding tissue, achieving immediate hemostasis.

Advantages of hemoclips include:

- High efficacy
- Minimal tissue injury
- Low re-bleeding rates

Hemoclips are particularly effective when applied directly to visible vessels or actively bleeding lesions.

Over-the-Scope Clips

Over-the-scope clips (OTSC) are a newer generation of endoscopic devices that provide stronger tissue compression. These clips are particularly useful in:

- Large ulcers
- Refractory bleeding
- Fibrotic lesions

OTSC devices have demonstrated high success rates in patients with recurrent or difficult-to-control bleeding.

Combination Therapy

Combination therapy has become the standard of care for high-risk lesions. This typically involves:

- Epinephrine injection
- Followed by thermal or mechanical therapy

Combination therapy improves outcomes by:

- Obtaining immediate hemostasis
- Reducing re-bleeding risk
- Improving long-term evolution

Multiple studies from the literature have demonstrated superiority of combination therapy over injection therapy alone (2).

4.2.4.7. Emerging Endoscopic Therapies

Hemostatic Powders

Topical hemostatic powders proved to be an emerging therapeutic option. These agents form a mechanical barrier over the bleeding site and promote clot formation.

Hemostatic powders are particularly useful in:

- Diffuse bleeding
- Malignant bleeding
- Difficult-to-access lesions

However, these agents are typically considered **intermediate therapy** rather than definitive treatment.

Endoscopic Suturing

Endoscopic suturing techniques have been explored in refractory bleeding but remain limited to specialized centers.

4.2.5. Re-Bleeding and Post-Endoscopic Management in Non-Variceal Upper Gastrointestinal Bleeding

4.2.5.1. Clinical Significance of Re-Bleeding in NVUGIB

One of the most decisive complications in NUVGIB is re-bleeding being a serious cause for morbidity, mortality and healthcare employment. In spite of the progress in endoscopic hemostatic techniques and pharmacologic therapy and despite improvement in hemostasis rates, around 10-20% of patients still suffer from recurrent bleeding. It is correlated with extreme transfusion requirements, longer hospitalization and necessity for rerunning of endoscopic and radiologic intervention and considerable higher mortality rates (1, 2, 3).

Besides the initial hemorrhage event, the re-bleeding has more serious implications as it happens under the auspices of physiological vulnerability in patients with recurrent instances of hypotension and anemia which may trigger cardiovascular complications, renal dysfunctions and multi-organ failure. Old-age people and individuals with cardiovascular disease are the most vulnerable to complications so there should be implemented a delicate post-endoscopic case management.

Predictors of Re-Bleeding

4.2.5.2. Endoscopic Predictors

Endoscopic lesions remain the most important factors of re-bleeding risk. The Forrest classification continues to represent the most largely used classification for stratifying risk following endoscopic evaluation. High-risk stigmata of recent hemorrhage are associated with significantly increased risk of recurrent bleeding and therefore require aggressive management and close monitoring.

High-risk lesions include:

- Active spurting bleeding (Forrest Ia)
- Active oozing bleeding (Forrest Ib)
- Non-bleeding visible vessel (Forrest IIa)
- Adherent clot (Forrest IIb)

Without endoscopic therapy, these lesions may carry re-bleeding rates as high as 40–50%. The rate drops with successful hemostasis, but in the case of patients with chronic conditions, it is important to stay alert as there is the chance of recurrent bleeding, especially in the first 72 hours. Flat pigmented spots (Forrest IIc) which are intermediate-risk lesions have

reduced re-bleeding risk and clean-based ulcers (Forrest III) register minimal risk and optimistic outcomes. It is clinically important to distinguish among these aspects as they play a valuable part in the monitoring intensity and duration of hospitalization (2).

4.2.5.3. Clinical Predictors of Re-Bleeding

Endoscopic findings, advanced age, hemodynamic instability at presentation, serious comorbidities and continual use of anticoagulant or antiplatelet medication are factors that determine the probability of re-bleeding. Patients with large ulcers, particularly those greater than 2 cm, and those with posterior duodenal ulcers are also at increased risk of recurrent bleeding due to involvement of larger arterial vessels.

Renal failure and liver disease further increase re-bleeding risk by impairing coagulation and platelet function. Similarly, patients with cardiovascular disease may experience hemodynamic compromise more readily during recurrent bleeding episodes. The presence of multiple risk factors significantly increases the probability of recurrent hemorrhage and should prompt more intensive monitoring (1, 3).

4.2.5.4. Post-Endoscopic Pharmacologic Management

Proton Pump Inhibitor Therapy

Proton pump inhibitor therapy represents the cornerstone of post-endoscopic management in NVUGIB. In order to stabilize the clot overlying the bleeding, there is administered acid suppression to reduce gastric acidity and prevent clot dissolution. Maintenance of intragastric pH above 6 has been shown to promote platelet aggregation and enhance clot stability.

Fortunate endoscopic hemostasis is usually succeeded by a high-dose of intravenous PPI therapy, during which clinicians administer an initial bolus and then the infusion continues for 72 hours as long as it is the highest risk of re-bleeding exists.

It has been proved that a high-dose of PPI therapy reduces re-bleeding rates, diminishes the need for surgical intervention and enhance overall outcomes. The treatment is gradually transitioned to oral PPI medication to support ulcer healing and avoid recurrent bleeding (1, 2).

4.2.5.5. Monitoring After Endoscopic Hemostasis

Vigilant clinical monitoring subsequent to successful endoscopic therapy is crucial during the first 72 hours because it is the most vulnerable period, when recurrent bleeding may happen since the clot stability is under development and the base lesions under healing.

Following typically includes:

- Frequent assessment of vital signs
- Serial hemoglobin measurements
- Evaluation for recurrent hematemesis or melena
- Assessment of urine output and hemodynamic status

It is pivotal to notice recurrent bleeding in good time since punctual intervention determines enhanced outcomes and reduces complications. If the patients have stable clinical parameters and no sign of recurrent bleeding, they can be transferred to subjacent care following the critical period.

Second-Look Endoscopy

It is disputed whether a routine second-look endoscopy is necessary, but it may be taken into account in patients with large ulcers, incomplete hemostasis or recurrent bleeding. Although it may be useful in finding recurrent bleeding, high-risk stigmata or it may help in the administration of further hemostatic therapy, it is advisable to do it after close scrutiny as the outcomes have not consistently improved after it.

Repeat endoscopy may identify signs of recurrent bleeding or high-risk stigmata and initiate additional hemostatic therapy. However, routine second-look endoscopy didn't demonstrate improved outcomes and that is why is reserved only for selected cases (2).

Management of Re-Bleeding

Constant hematemesis, melena, hemodynamic instability and deterioration in hemoglobin levels are indications of recurrent bleeding and in this case the first stage in the management strategy.

Repeat endoscopic therapy is successful in a substantial proportion of patients and allows reassessment of the bleeding source. Combination therapy is not strongly advised, thus being particularly advised in patients with persistent high-risk lesions.

If repeat endoscopy fails to achieve hemostasis, angiographic embolization performed by interventional radiology is recommended. This minimally, radiologically approach has widely replaced surgery as the preferred second-line intervention in many centers, particularly for high-risk patients.

Surgical intervention is reserved for patients with persistent bleeding despite endoscopic and radiologic therapy, or in cases complicated by perforation or malignancy.

Resumption of Antithrombotic Therapy

Management of antithrombotic therapy following bleeding represents an important component of post-bleeding care. Premature resumption may increase bleeding risk, whereas delayed resumption increases thrombotic risk. Current recommendations generally favor early resumption of antiplatelet or anticoagulant therapy once hemostasis has been achieved, particularly in patients with high cardiovascular risk.

These decisions should be made by a multidisciplinary collaboration between gastroenterology, cardiology, and hematology units (1).

Conclusion

One important factor in the evolution of a patient with non-variceal upper gastrointestinal bleeding is re-bleeding. It is essential to carefully manage the case after the endoscopy, pay attention to the therapy with the high-dose proton pump inhibitor, closely monitor the patient and immediately recognize recurrent hemorrhage. Should re-bleeding occur, the primary therapy is repeated endoscopy and in very difficult cases, clinicians resort to interventional radiology and surgery. Early resumption of antithrombotic therapy and multidisciplinary management further optimizes outcomes. This structured and proactive approach becomes a fundamental component of modern NVUGIB management.

4.2.6. Multidisciplinary Management in Non-Variceal Upper Gastrointestinal Bleeding

4.2.6.1. Introduction

A case of NVUGIB requires a multidisciplinary management, which ought to be well coordinated and time-dependent. Endoscopic hemostasis represents the pillar for definitive therapy, but favorable outcomes can be achieved by corroborating multiple medical and surgical specialties. Multidisciplinary is decidedly necessary in complex cases with abundant hemorrhage, old age, serious comorbidities, or anticoagulant or antiplatelet medication where the focus has to go beyond the bleeding. Itself (1, 2, 3).

Nowadays, management of NVUGIB starts with the stabilization in the emergency department, guides the post-endoscopic monitoring and designs strategies for prolonged prevention. The team of clinicians may engage emergency physicians, gastroenterologists, intensivists, anesthesiologists, interventional radiologists, surgeons and specialists in cardiology or hematology. Prompt cooperation among the above mentioned branches has proved successful in rapidly finding a definitive therapy, stabilizing the patient hemodynamically, reducing re-bleeding rates and enhancing patient survival (1, 2, 3, 4).

4.2.6.2. Role of the Emergency and Acute Care Team

The NVUGIB management starts with a multidisciplinary perspective in the emergency room, where clinicians recognize the problem, assess quickly and stabilize the patient. The first intervention physicians diagnosticate the individuals at high risk and perform the maneuvers preceding the endoscopic assessment (1, 2).

Initial responsibilities of the emergency and acute care team include:

- Early recognition of gastrointestinal bleeding
- Assessment of hemodynamic stability
- Initiation of intravenous access and fluid resuscitation
- Blood transfusion decisions
- Early initiation of proton pump inhibitor therapy
- Risk stratification using validated scoring systems
- Coordination of urgent endoscopic evaluation

It is fundamental to acknowledge hemodynamic instability, like hypotension, tachycardia, modified mental status or continuous hematemesis. Such aspects demonstrate abundant bleeding and entail rapid resuscitation and quick endoscopy. The emergency teams decide if there is exigency for airway protection if the patients arrived with weakened consciousness or active hematemesis (1, 5). In order to reduce postponement for endoscopy, the emergency physicians rely on gastroenterologists, which has been evidenced to improve outcomes and shorten hospitalization (1, 3).

4.2.6.3. Gastroenterology and Endoscopy Team

The management of a NVUGIB case is carried out by an entire team of gastroenterologists that runs the endoscopic evaluation, identifies the bleeding source, decides upon the risk tiers after the endoscopy and implements the therapeutic interventions (1, 2).

Key responsibilities of the gastroenterology team include:

- Diagnostic endoscopy
- Endoscopic hemostasis
- Risk stratification based on endoscopic findings
- Post-endoscopic management
- Management of recurrent bleeding

Although endoscopy has scaled down surgery necessity and has tremendously helped recovery rates in NVUGIB, it is a therapy that requires cooperation from teams of anesthesiologists to run it safely and effectively, most importantly for unstable patients or with

serious comorbidities. Procedural risks can be decreased with the implication of a multidisciplinary physicians to manage the sedation, to protect the airway to hemodynamically monitor the patient (1, 2, 16).

4.2.6.4. Intensive Care and Anesthesiology

Intensive care unit (ICU) charge is usually obligatory if the patients face abundant bleeding, hemodynamic instability or considerable comorbidities.

The intensive care unit contributes to:

- Continuous hemodynamic monitoring
- Airway protection and ventilatory support
- Vasopressor therapy when required
- Management of multi-organ dysfunction
- Optimization of fluid balance

This level of care is particularly important in elderly patients or those with cardiovascular disease, in whom recurrent bleeding or anemia may precipitate myocardial ischemia, renal dysfunction, or respiratory compromise. Early ICU involvement demonstrated in high-risk patients improved outcomes and reduced complications (3, 14).

4.2.6.5. Interventional Radiology

If the bleeding does not cease or the endoscopic procedure is not successful, interventional radiology will be applied; it consists of an angiographic embolization which is a minimally invasive alternative to surgery resulting in lower morbidity even in elders or high-risk individuals (1, 2, 21).

Indications for interventional radiology include:

- Failed endoscopic hemostasis
- Recurrent bleeding after endoscopic therapy
- Inaccessible bleeding source
- High surgical risk patients

Angiographic embolization allows targeted occlusion of bleeding vessels while avoiding the risks associated with surgical intervention. Widely spread, interventional radiology is considered more and more a second-line therapy following failed endoscopic management (2, 21).

4.2.6.6. Surgical Team

Surgery continues to be a crucial part of integrative case administration in difficult patients that face high risks or unmanageable blood loss in spite of the fact that the intervention rate has decreased due to progresses in endoscopic and radiologic medicine (1, 2).

Indications for surgical intervention include:

- Persistent bleeding despite endoscopic and radiologic therapy
- Hemodynamic instability
- Suspected perforation
- Malignancy-related bleeding

When the unit of surgeons is involved from the beginning, they deal with ulcer oversewing, gastroduodenal artery ligation or broader procedures should chronic pathology require (2, 21).

4.2.6.7. Hematology and Cardiology Collaboration

Patients receiving anticoagulant or antiplatelet therapy represent a particularly challenging group in NVUGIB management. Decisions regarding temporary discontinuation and timing of resumption of antithrombotic therapy require careful balancing of bleeding and thrombotic risks. (1, 13).

Multidisciplinary collaboration with hematology and cardiology specialists is particularly important in patients with:

- Mechanical heart valves
- Recent coronary stenting
- Atrial fibrillation with high thrombotic risk
- Recent thromboembolic events

Integrative choice of action is crucial to obtain positive results. The clinicians need to personalize the risk a patient is exposed to, for instance immediate reopening of antithrombotic therapy can diminish thrombotic complications. Nevertheless, precipitated resumption might escalate re-bleeding risk (13).

Multidisciplinary Coordination in Clinical Practice

Effective multidisciplinary management requires structured communication between teams. This coordination includes:

- Early notification of gastroenterology teams
- ICU consultation for high-risk patients

- Early involvement of interventional radiology
- Surgical consultation in refractory cases
- Cardiology and hematology input for anticoagulated patients

Such coordinated care pathways have been shown to reduce delays in treatment, improve hemostasis rates, and decrease mortality (1, 2, 3, 4).

Conclusion

Multidisciplinary management is regarded as a one of the pillars of contemporary patient supervision in non-variceal gastrointestinal bleeding. Emergency physicians, gastro-enterologists, intensivists, anesthesiologists, interventional radiologists, surgeons and further specialists cooperate to obtain a holistic patient evaluation and to act in good time. Complex, high-risk cases require such means of action to enhance clinical results, overcome complications and curtail mortality in NVUGIB (1, 2, 3, 4, 13).

4.3. Prognosis and Outcomes in NVUGIB Associated With NSAIDs, Oral Anticoagulants, and Antiplatelet Therapy

Despite medical advances like, endoscopic hemostasis, acid suppression and ancillary effort, NVUGIB is still a clinically compelling emergency, associated with important morbidity rates, constant bleeding and sudden mortality. The prognosis is determined by multiple factors, besides the endoscopic lesion, senectitude, chronic disease, hemodynamic instability, renal dysfunction and antithrombotic treatment ingestion (1, 2, 3). Consequently, NSAID-associated bleeding, anticoagulant-associated bleeding and antiplatelet-associated bleeding are separate clinical complications, showing various pathophysiologic balance between mucosal injury and flawed hemostasis (1, 2, 5).

Recovery in NSAID-related NVUGIB is additionally influenced by ulcer size, location, depth and the proof of recent hemorrhage not only by the structural mucosal injury in peptic ulceration. On the other hand, the bleeding in the case of oral anticoagulant therapy is not relevant to the lesion dimension because impaired secondary hemostasis intensifies and stretches the blood loss. Patients under antiplatelet medication, specifically aspirin, and suffering from gastrointestinal bleeding, present a minor modification in the mucosal vulnerability, notable deficiency of primary hemostasis. Even though the bleeding does not look dangerous in the beginning, old age patients and those with comorbidities have uncertain prospects (1, 10, 12).

4.3.1. NSAID-Associated NVUGIB

In the case of NSAID-associated NVUGIB, the prospect depends on the chronic mucosal damage as in gastric and duodenal ulceration, erosive gastroduodenitis, ulcer complication which may be active bleeding, visible vessels and adherent clot. The lesion acts as the trigger for unfavorable outcomes, with large gastric ulcers, posterior duodenal ulcers and ulcers with noticeable scars of previous hemorrhage necessitating transfusion, having a higher re-bleeding risk and urgency for endoscopic hemostasis. The prospect is optimistic after performing the endoscopy, halting NSAID ingestion and the treatment for ulcer is begun because the pathogenic mechanism is primarily mucosal injury.

Not in all cases the NSAID bleeding is benign. Ulcer bleeding could call for lengthy hospitalization, transfusion and constant hemorrhage. Old patients represent a special category so in 2023, there was carried out a study which correlated individuals with anti-thrombotic therapy and those with NSAID medication and it proved that, for them, NSAID-triggered bleeding represents an urgent event (2, 3).

Generally speaking, the prospect of NSAID-related NVUGIB is closely linked to the ulcer biology and endoscopic risk peculiarities. Nevertheless, recurrent bleeding risk remains relevant when NSAIDs are continued, when ulcers are large or anatomically unfavorable, or when NSAID use coexists with aspirin or anticoagulants.

4.3.2. Oral Anticoagulant-Associated NVUGIB

Oral anticoagulant-associated NVUGIB usually presents a different prognostic profile. In these patients, the lesion responsible for hemorrhage may be relatively small, but the degree of bleeding may be amplified by impaired coagulation. Consequently, there is registered serious anemia, more abundant bleeding, more distress about hemodynamic instability and more problematic aspects to consider, like reversal therapy and the correct moment to have the endoscopy. In spite of the above-mentioned features, anticoagulant ought not to hinder immediate endoscopy, but the peri-endoscopic stage and the post-bleeding prognosis have to be taken into account with the utmost seriousness.

In prognostic terms, anticoagulated patients frequently appear more vulnerable because they are older and have greater comorbidity burden, including atrial fibrillation, heart failure, chronic kidney disease, prior thromboembolism, or valvular disease. This means that poor outcomes in this group are not explained solely by the pharmacologic effect of anticoagulation, but by the conjunction of bleeding, frailty, and competing thrombotic risk. During a study run on patients with acute NVUGIB who were under anticoagulant medication, it was observed

that prompt endoscopy implied higher rates of endoscopic treatment and fewer days of hospitalization, but the moment it was done did not influence re-bleeding or 30-day mortality. Thus, the prospects depend almost equally on the patient weakness, the lesion seriousness and the moment of the endoscopy (22, 23).

From a clinical perspective, BVIGIB in patients under anticoagulant medication makes the case more complicated in the cute stage since hemorrhagic control must be in equilibrium with the peril of thrombosis when the anticoagulation therapy is suspended. Hemostatic status can ameliorate with reversal strategies, specifically in vitamin K antagonist patients or in blood loss connected to serious DOAC. It is crucial to mention that by going back to anticoagulation treatment for stroke or thromboembolism prevention, the prediction outcome differs from the blood loss connected to NSAID. Thus, outcomes in this group should be assessed not only in terms of transfusion, re-bleeding, or mortality, but also in terms of thrombotic events, prolonged hospitalization, and the safety of antithrombotic resumption.

In general, NVUGIB in individuals under anticoagulant medication is more complicated than the same event related to NSAID. The hemorrhage is cause by the hemostasis than the lesion and immediate results are decided by the interrelation between bleeding severity, renal function, reversal efficiency and the cardiovascular urgency to reinstate anticoagulant medication.

4.3.3. Antiplatelet-Associated NVUGIB

In the case of antiplatelet users, an episode of NVUGIB has a central place compared to NSAID and anticoagulants. However, it carries a pivotal prognostic position. Persistent usage of aspirin determines mucosal vulnerability because it impedes cyclooxygenase-1 and diminishes the synthesis of protective prostaglandin. On the other hand, antiplatelet substances worsen primary hemostasis. Therefore, the bleeding phenotype is abundant compared to the mucosal lesions but, the quantity does not parallel the hemorrhage in patients with anticoagulation therapy. Basically, in such contexts, particularly geriatric or concomitant comorbidity individuals, have peptic ulcer disease, erosive lesions or lose blood from prior unmanifested pathology.

The prognostic challenge in antiplatelet-associated NVUGIB lies in the tension between recurrent bleeding risk and cardiovascular protection, notably in patients ingestion aspirin for secondary prevention, patients with coronary stents or people under dual antiplatelet medication. Antiplatelet-associated NVUGIB constitutes an intermediate clinical profile defined by minor mucosal lesions mixed with defective platelet plug formation. Aspirin

conduces to compromised mucosal barrier through cyclooxygenase-suppression and diminished prostaglandin synthesis as opposed to antiplatelet agents which inhibit platelet aggregation enhancing the chance of bleeding from injuries that might, under different circumstances, continue to be asymptomatic. In spite of the fact that bleeding in these patients may initially manifest more insidiously than in anticoagulated ones, prognostic stratification remains a critical determinant of management, especially in elderly people and in those under dual antiplatelet treatment. A vital characteristic of this group is represented by the necessity to reconcile recurrent bleeding with cardiovascular safety profile.

This is more evident in patients taking aspirin for secondary prevention, those with recent coronary stents, or those receiving dual antiplatelet therapy. Guidelines consistently stress that interruption of aspirin used for secondary cardiovascular prevention should be minimized, and if temporarily held, it should generally be resumed early once hemostasis has been achieved. This recommendation reflects the fact that mortality in such patients may be driven not only by bleeding itself but also by cardiovascular events precipitated by prolonged antiplatelet interruption (1, 13, 24).

In outcome terms, antiplatelet-associated bleeding may involve lower immediate coagulopathic burden than anticoagulant-associated bleeding, but it is far from trivial. Older cohort data and contemporary reviews indicate that antiplatelet users remain at increased risk for transfusion, prolonged hospitalization, and recurrent bleeding, especially when aspirin is combined with other antithrombotics or when pre-existing ulcer disease is present. The prognosis therefore depends heavily on whether antiplatelet therapy is single or dual, whether there is concomitant NSAID exposure, and whether the patient has high cardiovascular risk necessitating early resumption.

4.3.4. Comparative Analysis of Non-Variceal Upper Gastrointestinal Bleeding Across NSAIDs, Oral Anticoagulants, and Antiplatelet Therapy

Non-variceal upper gastrointestinal bleeding (NVUGIB) represents a common, yet heterogeneous clinical pathology in which pharmacologic involvement plays a pivotal role in shaping disease phenotype, severity, therapeutic response, and clinical outcomes. Among the most clinically relevant drug-associated etiologies, bleeding related to **nonsteroidal anti-inflammatory drugs (NSAIDs)**, **oral anticoagulants**, and **antiplatelet therapy** proves distinct pathophysiological mechanisms and clinically differences in presentation and outcomes. Following these differences is essential for risk stratification, individualized management, and prognostic optimization. (1, 2, 3).

From a pathophysiological point of view, NSAID-associated bleeding is first caused by **structural mucosal injury**, resulting from both topical epithelial damage and systemic prostaglandin inhibition. The reduction in mucosal gastric, protective mechanisms tend to form the ulcers, typically involving the gastric antrum or duodenal bulb, and bleeding comes following erosion into submucosal vessels. Importantly, NSAID-associated NVUGIB largely presents with **well-defined, focal lesions**, often large ulcers with high-risk stigmata such as visible vessels, adherent clots, or active arterial bleeding. This structural nature of injury explains the frequent effectiveness of endoscopic hemostatic therapy in this group (1, 5, 12).

In contrast, oral anticoagulant-associated NVUGIB is characterized first by **hemostatic dysfunction rather than mucosal injury**. Anticoagulants affect fibrin clot formation and stabilization, permitting even minor mucosal abnormalities—such as erosions, gastritis, or angiodysplasia—to produce clinically significant hemorrhage. This notable difference results in a clinical pattern in which the **severity of bleeding may be disproportionate to the endoscopic lesion**. Patients receiving anticoagulants present with severe anemia, increased transfusion requirements, and higher rates of hemodynamic instability. Additionally, the impaired coagulation cascade contributes to **persistent or recurrent bleeding**, even following apparently successful endoscopic therapy (2, 3, 13).

Antiplatelet-associated bleeding comes as an intermediate type, predominantly characterized by **impaired primary hemostasis**. Platelet inhibition interferes with initial clot formation, resulting in diffuse mucosal oozing, multiple erosions, and small superficial ulcers. These lesions are often multiple and are associated with chronic or intermittent bleeding patterns. Although antiplatelet-related bleeding is typically less dramatic compared to anticoagulant-associated hemorrhage, the risk of **rebleeding remains clinically significant**, particularly in patients receiving dual antiplatelet therapy. Thus, management of this pathology is often hard to manage by the need to balance bleeding control with prevention of thrombotic complications, particularly in patients with recent cardiovascular events or coronary stent placement. (1, 5, 13).

These etiological differences mean distinct clinical presentations. NSAID-associated NVUGIB often manifests as **acute, overt hemorrhage**, including hematemesis or melena, accompanied by moderate hemodynamic compromise. Oral anticoagulant-associated bleeding presents with **more severe anemia and hemodynamic instability**, reflecting persistent hemorrhage and impaired clot stabilization. In contrast, antiplatelet-associated bleeding more commonly demonstrates **subacute or chronic presentation**, with melena, iron-deficiency anemia, or intermittent bleeding episodes (2, 3).

Laboratory findings further sustain these distinctions. NSAID-associated bleeding usually present with acute anemia with preserved coagulation parameters. Oral anticoagulant-associated bleeding largely comes with **modifications of coagulation indices**, depending on the specific agent. In antiplatelet-associated bleeding, routine coagulation tests are generally normal, despite clinically significant platelet dysfunction, highlighting the limitations of conventional laboratory evaluation in this population (1, 5).

Endoscopic findings also differ among the three groups. NSAID-associated bleeding commonly presents with **large peptic ulcers with high-risk stigmata**, whereas anticoagulant-associated bleeding enlights **diffuse mucosal oozing, small erosions, or vascular lesions**. Antiplatelet-associated bleeding typically comes with **multiple superficial erosions or small ulcers**, often involving the gastric mucosa (2, 23).

Thus, management strategies have to be individualized. Proton pump inhibitor therapy remains a first and important line of treatment among all groups; however, anticoagulant-associated bleeding frequently needs **interruption of anticoagulation**, while antiplatelet therapy is often continued or briefly interrupted, depending on cardiovascular risk. Endoscopic hemostatic therapy remains essential, although rebleeding rates are highest in anticoagulated patients (1, 2, 3).

Prognostically, oral anticoagulant-associated NVUGIB is generally associated with **the highest risk of outcomes: mortality, transfusion requirement, and rebleeding**, reflecting both patient comorbidity and hemostasis. NSAID-associated bleeding proves an **intermediate risk**, dependent on ulcer size and patient comorbidity. Antiplatelet-associated bleeding typically carries **lower immediate mortality but with substantial rebleeding risk**, particularly in patients requiring continued antiplatelet therapy (3, 5, 13).

Taken together, NVUGIB associated with NSAIDs, oral anticoagulants, and antiplatelet agents represents **three distinct clinical phenotypes**:

- NSAIDs — structural ulcer bleeding
- Oral anticoagulants — hemostatic failure bleeding
- Antiplatelets — platelet dysfunction bleeding

Knowing and expectation of these differences is crucial for accurate risk stratification, appropriate therapeutic decision-making, and improved clinical outcomes. Future management strategies come to emphasize **multidisciplinary care**, individualized pharmacologic treatment, and early endoscopic intervention, reflecting the complexity of NVUGIB in modern clinical practice (1, 2, 3).

Table 5. Comparative Summary of the NVUGIB

Feature	NSAIDs	Anticoagulants	Antiplatelets
Lesion type	Structural ulcer	Small lesions	Diffuse erosions
Bleeding severity	Moderate–severe	Severe	Mild–moderate
Rebleeding	Moderate	High	High
Mortality	Moderate	Highest	Moderate
Endoscopic therapy	Often	Frequently	Sometimes

4.4. Future Perspectives in Non-Variceal Upper Gastrointestinal Bleeding (NVUGIB): Expanding Toward Predictive, Intelligent, and Precision-Guided Care

4.4.1. Introduction

Non-variceal upper gastrointestinal bleeding is a multifaceted and diverse clinical entity in which pharmacologic exposures have a central role in outlining disease phenotype, the level of gravity, therapeutic reaction and clinical results. The most widespread clinically relevant drug-associated etiologies such as bleeding, caused by nonsteroidal anti-inflammatory drugs, oral anticoagulants and antiplatelet therapy substantiates different pathophysiological processes and clinically meaningful discrepancies in presentation and prognosis. Comprehending these variations is pivotal for risk stratification, personalized management and outcome improvement.

The prospective expectations in NVUGIB are becoming more and more focused on AI integration, precision risk stratification, latest endoscopic technologies, pharmacologic advancement, biomarker-based management and pluridisciplinary care directions. These changes are supposed to remodel NVUGIB management from a reactive emergency-based pattern into a predictive and individualized care system elevating short-term and long-term consequences altogether (1, 3).

4.4.2. Artificial Intelligence and Predictive Risk Stratification

What seems to be most promising in NVUGIB management is Artificial Intelligence. Even if traditional clinical scoring systems such as the Glasgow-Blatchford score, Rockall score and AIMS65 continue to be used to a great extent, their predictive accuracy is finite, especially in present-day populations defined by increased anticoagulant use, polypharmacy and complex

comorbidity profiles. These scoring systems rely on relatively limited clinical variables and do not account for dynamic clinical changes during hospitalization (4).

Artificial intelligence models, in particular machine learning algorithms permit the assimilation of multidimensional datasets, among which clinical, laboratory, endoscopic and demographic variables. They assist in the identification of erratic connections and sophisticated patterns that are difficult to detect only by using standard statistical techniques. Thus, AI-based predictive models have shown increased achievements in establishing clinically pertinent results such as rebleeding, mortality, transfusion requirements and the necessity for prompt intervention (3, 25).

There is a high chance that future AI-based systems be incorporated into electronic medical records so that automatic risk stratification is enabled as soon as hospital admission is required. For instance, shortly after a patient shows signs of NVUGIB, AI-based systems might instantly be able to analyze:

- Hemodynamic parameters
- Laboratory values
- Medication exposure
- Comorbidity burden
- Previous bleeding history

Having all this information, AI systems can go on and create differentiated risk profiles and also suggest appropriate clinical actions such as:

- Timing of endoscopy
- Need for ICU admission
- Transfusion strategy
- Monitoring intensity

Such automated decision-making props can lead towards important decreases in delays as far as patient care is concerned and to improved clinical outcomes. In addition to that, AI-based patterns might periodically update predictions throughout hospitalization, enhancing the possibility of reevaluation of patient risk and informing clinical decision-making during the clinical path.

4.4.2.1. Artificial Intelligence in Endoscopic Evaluation

Artificial intelligence is bound to assist doctors a great deal in endoscopic evaluation of NVUGIB. Computer vision systems which have been fed on large endoscopic datasets will aid in identifying bleeding origins, in finding high-risk lesions and in foreseeing clinical outcomes.

Moreover, these computer-assisted systems will be vital in emergency contexts when detecting the cause of the lesion is limited by active bleeding, poor preparation or hemodynamic instability. AI-based endoscopy might increase identification of inconspicuous lesions like small ulcers, diffuse erosions and vascular anomalies. These lesions mostly appear in patients under treatment with anticoagulants where bleeding may be the effect of minor mucosal abnormalities. Advanced detecting may perfect diagnostic accuracy and decrease the danger of overlooked lesions.

AI-assisted endoscopy may improve detection of subtle lesions such as small ulcers, diffuse erosions, and vascular abnormalities. These lesions are particularly relevant in patients receiving anticoagulants, where bleeding may originate from minimal mucosal abnormalities. Improved detection may enhance diagnostic accuracy and reduce the risk of missed lesions.

In addition to all the above, AI may help in computerized categorization of bleeding lesions by employing systems such as the Forest classification. An important limitation of standard endoscopic evaluation remains interobserver variability, especially among inexperienced endoscopists. Automated classification systems may lead to customized analysis and level up prediction of recurring bleeding risks (26).

In the future, AI-based endoscopy may inform specialists about what procedural paths to follow in real time. To illustrate this idea, rooted in lesion morphology and bleeding phenotype, AI systems may propose certain hemostatic methods, among which mechanical clipping, thermal coagulation or mixed therapy. This strategy may attain a higher rate of success in hemostatic endeavors and diminish rebleeding risk.

Advances in Endoscopic Hemostatic Technologies

Technological advancement in endoscopic hemostasis is presumed to extend NVUGIB management even further. Traditional endoscopic techniques such as injection therapy, thermal coagulation and mechanical clipping continue to be successful, still, up to date technologies are arising with the capability of accelerating hemostatic effectiveness.

One of the most promising advances in this region of activity is represented by hemostatic powders. The agents within promise a swift, non-contact hemostasis and are of vital use in diffuse mucosal bleeding, anticoagulant-based bleeding and malignant hemorrhage as well. Hemostatic powders hold the capacity of becoming bridge therapy in patients with unstable conditions and who require other interventions. Great steps forward are expected also when it comes to better adhesion, prolonged duration of action and desired delivery systems (5).

Over-the-scope clips (OTSC) are another crucial breakthrough. These mechanisms grant successful treatment of major ulcers, refractory bleeding and recurrent bleeding situations. As opposed to standard clips, OTSC devices offer higher mechanical compression and optimized hemostasis. Upcoming refinement in device layout may systematically extend their feasibility and simplicity in utilizing them (27).

Forthcoming endoscopic suturing systems will undoubtedly improve therapeutic possibilities. They will be able to provide patients with a closure of their high-risk ulcers and will deter further bleeding. Preventive endoscopic closure represents a potential paradigm shift from reactive hemostasis toward proactive bleeding prevention.

Pharmacologic Innovations and Precision Therapy

Pharmacologic advancement remains an active factor in NVUGIB handling. Potassiun-competitive acid blockers (P-CABs) among which vonoprazan furnishes accelerated and constant acid suppression in contrast to traditional proton pump inhibitors. Enhanced acid suppression could increase the chance of clot stability and diminish rebleeding dangers. Early studies suggest that P-CABs may represent an important future alternative in high-risk bleeding patients (28).

Moreover, the growing use of direct oral anticoagulants has underscored the urge for elevated reversal techniques. Innovative reversal agents characterized by immediate-release and refined security profiles are being engineered. The above-mentioned agents could considerably improve results in bleeding caused by anticoagulants (29).

Future pharmacologic strategies may also incorporate pharmacogenomic approaches. Genetic variability in drug metabolism may influence response to acid suppression therapy. Personalized pharmacologic strategies may optimize therapy and improve outcomes.

Biomarkers and Precision Medicine

Biomarker-based approaches represent another emerging future direction in NVUGIB management. Detecting biomarkers that can foresee rebleeding, mortality and severity could fine-tune preliminary risk stratification.

Potential biomarkers include:

- Lactate
- Inflammatory markers
- Coagulation markers
- Platelet function markers

Integration of biomarker data into predictive models may improve accuracy of risk stratification and guide management decisions (3).

Precision medicine approaches may also allow individualized preventive strategies, particularly in patients receiving antithrombotic therapy.

Multidisciplinary Care and Integrated Pathways

Future NVUGIB management is expected to increasingly involve multidisciplinary care models. It is essential for patients receiving anticoagulants or antiplatelet therapy to benefit from the collaboration of various specialists such as gastroenterologists, cardiologists, hematologists and intensivists. Multidisciplinary decision-making is particularly important in determining timing of antithrombotic therapy resumption and balancing bleeding and thrombotic risks (1).

Blended treatment strategies based on AI risk stratification and preset endoscopic procedures may favorably influence patient outcomes and standardize care delivery.

4.4.2.2. Preventive Strategies

Prophylactic measures are due to hold an ever-growing part in NVUGIB management. Among these worthwhile mentioning are, risk-based gastroprotection, H. pylori screening and also antithrombotic therapy. Preventive methods will be optimized through the use of AI by detecting highly vulnerable patients long before hemorrhage manifests.

Conclusion closing remarks

The future of NVUGIB management is heading towards a pattern which will consist of the integration of artificial intelligence, accuracy in risk stratification, latest endoscopic technologies and patient centric pharmacologic remedy. These breakthroughs are supposed to elevate early patient evaluation, improve hemostasis and decrease rebleeding and mortality. Due to patient population becoming substantially intricate, management strategies that are both predictive and individualized will be of outmost importance.

4.5. General Conclusions: NVUGIB in NSAIDs, Oral Anticoagulants and Antiplatelet Therapy

Non-variceal upper gastrointestinal bleeding (NVUGIB) resulted from anti-inflammatory medication (NSAIDs), oral anticoagulants and antiplatelet treatment presents three different but intersecting clinical manifestations, each of them described through distinct pathophysiological mechanisms, clinical profile, endoscopic attributes and prognostic relevance. Even though these categories overlap in their clinical trajectories, including both mucosal lesions and impaired hemostasis, the input they offer varies greatly and influences short-term management as well as long-term results.

NSAID-related NVUGIB is fundamentally rooted in structural mucosal lesions. NSAIDs weaken mucosal barrier via cyclooxygenase inhibition, mitigation of prostaglandin synthesis and damage of mucosal microcirculation conducting to ulceration and erosive injury. Hence, illness severity is mainly connected to lesion features, namely ulcer size, ulcer site and depth. Related to increased transfusion demands, greater recurrent bleeding risk and extended length of stay in hospital are the following: large gastric ulcers, posterior duodenal ulcers and injuries with high-risk indicators of recent hemorrhage. Nonetheless, as endoscopic hemostasis is met and NSAID contact is limited, outcomes are generally promising, predominantly in patients with insignificant comorbidities. Yet, bleeding connected to NSAID retains clinical relevance in geriatric populations and in those undergoing concurrent antithrombotic treatment which often results in the amplification of hemorrhagic intensity and poorer clinical outlook (1, 2, 12, 24).

By comparison, oral anticoagulant-associated NVUGIB is chiefly defined by coagulopathy as opposed to severe mucosal lesion. In these patients, minor mucosal injuries may generate disproportionate bleeding because of increased clot friability and defective hemostasis. Consequently, anticoagulated patients suffer from more profound anemia, extended bleeding and transfusion dependency. In addition to that, this kind of patients generally manifest higher clinical intricacy given the advanced age, cardiovascular illness, renal impairment and overlapping thrombophilic tendencies. Treatment thus calls for meticulous calibration between hemorrhagic control and appropriate scheduling of anticoagulant resumption, principally in patients with atrial fibrillation, mechanical valves or recent thromboembolic incidents. Prognosis in anticoagulant-related NVUGIB is established by several factors: hemorrhage intensity, co-existing disease load and the risks driven by cessation of anticoagulant therapy (3, 5, 11).

Antiplatelet-associated NVUGIB constitutes an intermediate clinical profile defined by minor mucosal lesions mixed with defective platelet plug formation. Aspirin conduces to compromised mucosal barrier through cyclooxygenase-supression and diminished prostaglandin synthesis as opposed to antiplatelet agents which inhibit platelet aggregation enhancing the chance of bleeding from injuries that might, under different circumstances, continue to be asymptomatic. In spite of the fact that bleeding in these patients may initially manifest more insidiously than in anticoagulated ones, prognostic stratification remains a critical determinant of management, especially in elderly people and in those under dual antiplatelet treatment. A vital characteristic of this group is represented by the necessity to reconcile recurrent bleeding with cardiovascular safety profile 1, 2, 13, 24, 30).

The three aforementioned categories share however several prognostic factors: hemodynamic compromise at admission, older age, renal insufficiency, major comorbidities and endoscopic predictors of rebleeding rank first in determining unfavorable outcomes like recurrent hemorrhage, necessity for clinical management and mortality. Risk assessment instruments such as the Glasgow-Blatchford score, Rockall score, AIMS65 score and PNED score offer significant clinical utility in detecting high-risk patients and informing treatment selection. Nevertheless caution and clinical acumen should play a primordial part when making decisions even though scores like the ones above are used, especially in patients under antithrombotic treatment in which case clinical courses of action transcend hemostasis (4, 9, 10, 14).

The modern management of NVUGIB associated with NSAIDs, oral anticoagulants, and antiplatelet therapy therefore requires a structured and multidisciplinary approach. Immediate fluid resuscitation, timely endoscopic assessment, suitable pharmacologic treatment and minutious post-endoscopic examination are vital care factors. Furthermore, tailored decisions concerning interruption and reinitiation of antithrombotic therapy are paramount in improving outcomes and reducing both bleeding and thromboembolic events to a minimum.

Lastly, NSAID-associated NVUGIB can be regarded as primarily lesion-specific, anticoagulant-induced hemorrhage as mainly hemostasis-dependent and antiplatelet-related bleeding as a multifactorial entity encompassing both mucosal fragility and platelet dysfunction. Identification of these different clinical phenotypes establish a theoretical paradigm for understanding variations in clinical manifestation, prognosis and therapeutic approaches.

Finally, NVUGIB associated with NSAIDs, oral anticoagulants and antiplatelet therapy comprise a diverse clinical landscape wherein clinical trajectories are governed by

multifactorial processes where end results depend on the conflation of mucosal damage, coagulopathy, patient health status and management strategies. A holistic, multidisciplinary and individualized clinical pathway to risk categorization and therapeutic modality is crucial in order to improve patient-centered results, minimize blood loss and curtail mortality within this expanding intricate patient cohort.

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Abbreviations:

ADP	Adenosine diphosphate
AI	Artificial intelligence
AIMS65	Albumin level, International Normalized Ratio, Mental status alteration, Systolic blood pressure, Age >65 years
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMP	Adenosine Monophosphate
APASL	Asian Pacific Association for the Study of the Liver
APC	Argon plasma coagulation
aPTT	Activated Partial Thromboplastin Time
ARISTOTLE	Apixaban for Reduction in Stroke and Other ThromboembоLic Events in Atrial Fibrillation
ASA	American Society of Anesthesiologists
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CagA	Cytotoxin-associated gene A
CKD	Chronic Kidney Disease
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
DAPT	Dual Antiplatelet Therapy
DOACs	Direct Oral Anticoagulants
EGF	Epidermal Growth Factor
ENGAGE AF-TIMI 48	Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48
g/dL	grams per deciliter
GARFIELD-AF	Global Anticoagulant Registry in the FIELD–Atrial Fibrillation
GBS	Glasgow-Blatchford Score
H. pylori	Helicobacter pylori
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs/alcohol
ICU	Intensive Care Unit
INR	International Normalized Ratio
LOX	Lipoxygenase
mmHg	millimeters of mercury
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NVUGIB	Non-Variceal Upper Gastrointestinal Bleeding
OTSC	Over-the-scope clips
P2Y12	Purinergic Receptor P2Y12
P-CABs	Potassium-competitive acid blockers
PCCs	Prothrombin Complex Concentrates
PGE_2	Prostaglandin E_2
PGI_2	Prostacyclin
pH	potential of Hydrogen
PLA_2	Phospholipase A_2
PLATO	PLATelet inhibition and patient Outcomes
PNED	Progetto Nazionale Emorragia Digestiva
PPIs	Proton Pump Inhibitors

PRECISE-DAPT	Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy
PT	Prothrombin Time
RE-LY	Randomized Evaluation of Long-term anticoagulation Therapy
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
ROCKET-AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
RR	Relative Risk
TGF-α	Transforming Growth Factor-α
TIMI	Thrombolysis In Myocardial Infarction
TIPS	Transjugular Intrahepatic Portosystemic Shunt
TRITON	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition
TWILIGHT	Ticagrelor With Aspirin or Alone In High-Risk Patients After Coronary Intervention
UGIB	Upper Gastrointestinal Bleeding
ULN l	Upper Limit of Norma
VacA	Vacuolating cytotoxin A
VKAs	Vitamin K Antagonists
VKORC1	Vitamin K Epoxide Reductase