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Changing epidemiology and etiology of upper and lower gastrointestinal bleeding

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ABSTRACT

Upper gastrointestinal bleeding (UGIB) develops in the oesophagus, stomach or duodenum and has an incidence of 47/100,000. Lower GIB (LGIB) develops in the small bowel, colon or anorectum and has an incidence of 33/100,000. Where the incidence of UGIB has fallen, driven by helicobacter pylori eradication and the use of proton pump inhibitors, the incidence of LGIB may be increasing. Interventions such as early endoscopy, risk assessment and national guidelines have improved clinical outcomes but have had limited impact on the economic burden of GIB. Previously LGIB was thought to be less severe than UGIB, but contemporary data suggest that patients with LGIB tend to have a longer length of hospital stay and may be at higher risk of death or re-bleeding.

Introduction

Traditionally upper and lower gastrointestinal bleeding (UGIB and LGIB, respectively) have been distinguished by the origin of bleeding in relation to the ligament of Treitz. UGIB corresponds to bleeding in the oesophagus, stomach and duodenum, whereas LGIB encompasses bleeding in the small bowel, colon and anorectum. UGIB tends to be subdivided into variceal bleeding (VUGIB) and non-variceal UGIB (NVUGIB). Developments in options for investigating bleeding from the small bowel have led to the emergence of a the term 'mid-GI' bleeding, corresponding to bleeding originating in the jejunum and ileum [1]. At presentation UGIB can cause haematemesis, coffee ground vomiting or melena. LGIB can cause bright rectal bleeding, clots, blood mixed in with stool as well as melena, although the latter may indicate an upper- or mid-GI source. Additionally, a brisk UGIB can present with clots or fresh blood per rectum.

Global incidence UGIB

Across the last two decades several population-based studies have demonstrated a reduction in incidence of UGIB. In Spain the incidence of upper GI complications fell from 87/100,000 to 47/100,000 between 1996 and 2005 [2]. Similar trends have been seen in studies from the United States of America (US) [3,4] and Europe [5]. When stratifying by variceal and non-variceal causes, the trends are similar. In the Netherlands hospitalisations due to peptic ulcer bleeding halved between 1980 and 2003 [6]. In the Spain the hospitalisation rate has also halved [7] and in US the hospitalisation rate has fallen by 20% [8]. This trend is attributed to helicobacter pylori (HP) eradication, the increased use of proton pump inhibitors (PPIs), increased access to endoscopy and improved endoscopic therapy. In populations with varying access to endoscopy such as those with high proportions of 'remote and rural' facilities, trends in hospitalisation have remained constant [9,10]. Studies from the US demonstrate that the incidence of VUGIB has also fallen [11,12]. A study reporting findings from the National Impatient Sample in the US between 2002 and 2012 found that oesophageal variceal bleeding rates fell despite an increase in hospitalisations due to cirrhosis [13]. These findings are likely due to improvements in primary prophylaxis in the form of non-selective beta blockade and endoscopic band ligation.

Global incidence LGIB

Although LGIB is common condition, there are limited studies documenting its incidence. A population based study in ten hospitals in Spain compared patients discharged with hospital codes consistent with GI complications over ten years. In comparison to the upper GI tract, where the incidence of complications has fallen, the incidence of complications in the lower GI tract increased from 20/100,000 to 33/100,000 [2]. The same group estimate that bleeding from diverticular disease and angiodysplasia has

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increased from 3.3 to 0.9 per 100,000 person years respectively, to 8 and 2.6 [7]. The results of the aforementioned study are limited by its sample size; results were extrapolated from ten hospitals to calculate a national incidence. Additionally cases were captured using discharge codes that included GI complications not related to bleeding. A group in Iceland calculated an incidence of 87/100,000 for LGIB by multiplying the number of endoscopy referrals for the investigation of rectal bleeding or melaena to a single hospital in 2010 [14]. This method also comprised a small number of patients and may be inaccurate as endoscopy is not the sole mode of investigation of LGIB. Historical studies estimate the incidence of LGIB as 20.5/100,000 but again this is based on data from a single centre [15].

Patient demographics and Co-morbidity in GIB

Peptic ulcer bleeding is more common in men [6,9], and the mean age of patients is approximately 63 years [7]. VUGIB is also more common in men, but patients tend to be younger, with a mean age of 54 [11]. Approximately 37% of patients with peptic ulcers take aspirin and a further 18% take NSAIDs [16]. In the US the majority of VUGIB is related to alcoholic liver disease [11] and a similar picture is seen in low and middle income countries [17].

Two recent prospective national audits of GIB in the UK allow comparison of the demographics of upper and lower GI bleeders; the national audit of UGIB was undertaken in 2007 [16] and the national audit of LGIB in 2015 [18]. Patients presenting with LGIB tended to be older (median 74 years for LGIB and 68 years for UGIB) with a higher burden of co-morbidity although a similar frequency of antiplatelet use (aspirin and or clopidogrel use found in 28% and 5.3% patients with UGIB, respectively, and 23.1% and 9.3% patients with LGIB, respectively) [16,18]. Frequency of oral anticoagulation was also similar (warfarin use 7.0% in UGIB and 10.7% in LGIB) [16,18]. Studies of hospital registries have shown that patients that develop LGIB tend to be elderly, with a mean age of 63–69 years [19,20]. Co-morbid illness is common, 78% admitted patients have >1 co-morbid conditions and 3% have $\geq$2 [21]. Aspirin for secondary prevention is used in 20–33%, clopidogrel in 3–9% and warfarin in 6–10% patients [18,22]. The national audit of UGIB was conducted before the widespread use of direct oral anticoagulants (DOACs), but 5.2% patients in the audit of LGIB were receiving apixaban, rivaroxaban or dabigatran [18].

Helicobacter pylori (HP)

The discovery of HP in 1984 as the principle cause of peptic ulcer disease has revolutionised the treatment of NVUGIB. HP is extremely common; prevalence ranges from 34 to 36% in Western Europe and the US, to 69–70% in South America and Africa [23]. Risk factors for HP infection include male gender, increasing age, increasing body mass index and socioeconomic status [24]. Eradication therapy in the form of combination antibiotic and PPI therapy is extremely effective and has led to a decline in the prevalence of HP infection in Western countries [25]. In the last two decades population based studies in Asia also demonstrate a successful reduction in HP infection rates with eradication therapy [26,27]. In countries with widespread adoption of HP eradication therapy the frequency of peptic ulcer disease and its complications has reduced [28], however other causes such as drugs that affect the gastric mucosa or promote bleeding still play a key role in the aetiology of GIB.

Drugs and risk factors for GIB

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs irreversibly inhibit cyclo-oxygenase 1 which is associated with reduced levels of protective mucosal prostaglandins [29] which induces gastric and intestinal ulceration [30]. Reported rates of GIB in patients receiving NSAIDs range from 2.4% to 12% [31,32] although the risk may be higher if patients also consume alcohol [33]. In the upper GI tract the effects of NSAIDs are mitigated by the concomitant use of PPIs [34]. However in the lower GI tract PPIs may not be effective [35] and some studies suggest that they promote in bleeding. [36,37]

Antiplatelets

The incidence of GIB in patients who are taking low dose aspirin is approximately 0.97/1000 person years for UGIB and 1.68 for LGIB [38]. A systematic review of 11 randomised controlled trials (RCTs) comparing patients receiving low-dose aspirin with controls found that aspirin increased the risk of GIB by around 60% [39]. Aspirin disrupts the production of prostaglandins, which renders the gastric mucosa more susceptible to injury by inhibiting mucus secretion and reducing bicarbonate production [40]. Aspirin can also cause mucosal inflammation and ulceration in the small bowel [41], and population-based database studies suggest it increases the risk of developing colonic bleeding [14]. Understanding the effects of antiplatelets in the colon is important as a recent database study of 199,079 patients receiving low dose aspirin reported that patients who developed GIB were more likely to bleed from the lower GI tract than the upper. However bleeding may be less severe in the colon as patients were less likely to be hospitalised [38]. Pooled randomised data from RCTS found that UGIB was less likely to be fatal in patients receiving low-dose aspirin compared with controls [39]. Data reporting LGIB that develops in patients receiving aspirin are few, but cohort studies report that although aspirin is associated with higher rates of in-hospital and longer term re-bleeding, it is associated with lower rates of death compared to patients that stopped their aspirin following the development of bleeding [42,43].

Clopidogrel is also associated with the development of GIB [44], although the risk may be lower than that of aspirin [45]. Dual antiplatelet therapy (DAPT) increases the risk of GIB further [46]. There is conflicting evidence that co-therapy with PPIs in patients at risk of UGIB may lead to an increase in adverse cardiovascular outcomes [47]. There are few data describing the incidence of LGIB in patients receiving DAPT, but patients that do develop it tend to have higher rates of re-bleeding [42].

Anticoagulants

The risk of developing UGIB is approximately 11 per 1000 person years for warfarin and 14, 12 and 7 per 10,000 person years for rivaroxaban, dabigatran and apixaban, respectively [48]. Vitamin K antagonists are also associated with developing of LGIB [49,50].

Unlike NSAIDs and aspirin, the effects of oral anticoagulants are most likely limited to disruption of coagulation as opposed to local effects on the GI tract, although there is evidence that PPI co-therapy may reduce the risk of developing UGIB suggesting there may be some local causative factors [48]. DOACs are used as alternatives to warfarin due to their more predictable pharmacodynamics and improved side effect profiles. DOAC-based anticoagulation is increasingly used in secondary prevention of cardiovascular events, often in combination with antiplatelet therapy, which is likely to lead to an increased incidence of GIB,

particularly in the elderly population. Pooled analyses from randomised controlled trials indicate that in comparison to conventional anticoagulation, patients receiving dabigatran or rivaroxaban may have an increased risk of severe GIB [51].

Selective serotonin reuptake inhibitors (SSRIs)

Selective serotonin reuptake inhibitors (SSRIs) are associated with the development of UGIB. Unlike NSAIDs, which directly damage the gastric mucosa, studies suggest that SSRIs cause bleeding by inhibiting platelet serotonin mediated platelet aggregation. A systematic review of observational studies that pooled data from over 1,000,000 patients reported that SSRI use was associated with odds of developing UGIB of 1.55 [52]. A smaller systematic review of 400,000 patients found that if an SSRI was co-prescribed with NSAIDs the odds of developing UGIB increased four fold [53]. SSRIs may also promote the development of LGIB, and an observational study of 9753 patients taking SSRIs found that the risk of developing LGIB was actually higher than that of UGIB [54].

Other risk factors for GIB

A retrospective database study has suggested links between bisphosphonates and an increased risk of GIB [55], but whether this risk is clinically significant remains unclear. A national study in Scotland demonstrated that socio-economic deprivation was also a risk factor for hospitalisations with UGIB [10].

Etiology of UGIB

National observational and database studies from the US and the UK demonstrate that the most common cause of UGIB remains peptic ulcer disease, representing approximately 32–36% of all hospitalised patients [16,56]. The next most frequent diagnoses are oesophagitis (24%), gastritis or gastric erosions (18–22%) and duodenitis (13%) [16,56]. Variceal bleeding accounts for approximately 11% of hospitalisations with UGIB [16]. Other causes such as malignancy, dieulafoy lesions and isolated Mallory Weiss tears individually account for less than 4% [16]. In US national databases studies suggest an increase in the frequency of UGIB caused by malignancy or dieulafoy lesions [8]. As many as 17% patients have no identifiable cause at endoscopy [16,56].

Etiology of LGIB

Multicentre database studies in the US and Europe suggest that the most common sources of bleeding are diverticular disease (26–33%), haemorrhoids (10.0–20.0%), colonic polyps (3–13%) and colitis (11–13%) [18,20]. Although diverticular disease is the most common cause of LGIB, two longitudinal studies in the US suggest that between the years 2000 and 2010 overall hospitalisations due to diverticular bleeding decreased [57,58]. In contrast, a multicentre study in Spain suggested that the frequency of diverticular bleeding increased between 1996 and 2005 [2]. The authors from the US based study did not provide a hypothesis for this reduction in incidence [58], although they did suggest that the difference in findings compared to the Spanish study was the use of different methods for classifying unspecified cases of GIB [58]. Lanas et al. suggested that an increase in diverticular bleeding may be due to the increased use of anticoagulants, antiplatelets and NSAIDs, as seen in an ageing population [7]. Longitudinal studies suggest that the incidence of angiodysplasia [7], colonic polyps [59] and colorectal cancer is also increasing. This trend is likely due to the introduction of bowel screening and adenoma surveillance programmes leading to increased rates of diagnosis [60]. Any effect on polyp and cancer related LGIB is unknown.

Determining the source of LGIB can be difficult and 23–50% patients are discharged without a diagnosis [18,20]. This reduces to 9.2% in cohorts where all patients receive colonoscopy [14].

Outcomes of GIB

The mortality rate for UGIB ranges from 8 to 10% in de novo hospitalisations for bleeding, to 26% in patients who are already hospitalised for another reason [9,16]. Mortality rates for NVUGIB tend to be lower than that of VUGIB [16]. In the 1990s and early 2000s database studies suggested that although the incidence of NVUGIB was declining, there was no equivalent reduction in case fatality rates [61,62]. However, more recently several large population-based studies have demonstrated a reduction in mortality. A database study of peptic ulcer bleeding from the US conducted between 1989 and 2009 found that the mortality rate had halved, falling from 4.5 to 2.1% [3]. In the UK a similar trend is seen, although the effect is less marked; deaths due to NVUGIB fell from 11.3% in 1999 to 9.3% in 2007 [63]. Most deaths occur in patients with pre-existing medical co-morbidity such as heart failure, stroke and malignancy [16].

The reduction in mortality rates is thought to be due early risk stratification, improvements in access to and quality of endoscopic therapy, improved processes of care and the adoption of best practice clinical guidelines. Improvements in the quality of endoscopic therapy has resulted in a reduction in rates of re-bleeding and reduced use of more invasive modes of haemostatic therapy, such as surgery. In Greece rates of re-bleeding have fallen from 12 to 6%, matched by a reduction in the proportion of patients receiving surgical haemostasis [5]. In the US as fatality rates have fallen, the frequency of endoscopic haemostasis has increased [3]. Rates of minimally invasive therapy such as interventional radiology remain low, at between 0.6 and 1.2% however [9,16]. Unlike NVUGIB, rates of variceal-bleeding related deaths have remained constant [8].

For LGIB, database studies estimate in-hospital mortality of 3.4–8.8% [2,18], and most deaths are due to medical morbidity, such as sepsis and cardiac events [18]. Deaths due to severe haemorrhage occur in as less than 1% of cases [14,18]. Observational studies suggest that re-bleeding occurs in 13% cases during admission, 12.4% at 3 months and 9% at one year [15]. The highest rates of re-bleeding are reported in patients diagnosed with diverticular bleeding or angiodysplasia. [18,64,65] The frequency of endoscopic haemostasis is lower than that of UGIB, at 2.1–4.6% demonstrated in multicentre studies from the US and UK [18,66]. The use of interventional radiology is also rare, as is the need for colonic surgery to achieve haemostasis [18].

In comparison to UGIB, LGIB is thought have a more benign course, however several observational studies challenge this view. A multicentre study in Spain compared the outcomes of patients admitted with GIB, finding that patients with LGIB had a higher frequency of death (8.8% versus 5.5%) and a longer length of hospital stay (11.6 versus 7.8 days) [2]. A study from Korea found no difference in mortality rates between lower and upper GIB (5.0% versus 4.5%) but LGIB was associated with higher rates of re-bleeding (16.8% versus 9.9%) [67]. In the US a similar study demonstrated no difference in rates of death or 30-day re-admissions [68]. This difference between UGIB and LGIB in perceived risk of adverse outcomes and reality may have been accurate historically, but the increased availability of upper endoscopy and endoscopic haemostasis, the adoption of national guidelines on optimal management and the development of risk assessment tools may have improved outcomes in UGIB, whereas similar advances in LGIB are lagging behind. Additionally patients

with LGIB tend to be older, with a higher frequency of co-morbidities, factors that may contribute to adverse outcomes and increased length of hospital stay.

Health economics

Key cost drivers in the management are inpatient bed days, endoscopy and colonoscopy and the use of red blood cell transfusion [69]. VUGIB tends to be associated with a higher cost burden than NVUGIB [70]. Between 1989 and 2009 the length of stay for NVUGIB has reduced in the US from 4.5 to 2.8 days, but despite this the economic burden has increased, with median costs of hospitalisation rising from $9249 to $20,370 [3]. Reasons for this are likely to be due to general increases in healthcare costs seen across many healthcare systems as opposed to specific costs related to UGIB.

There are few data describing the total economic burden of LGIB, but data from a national database in the US in 2010 suggested that hospitalisation costs between $22,142 and $28,749 [71]. LGIB may utilise more resources than UGIB [2]. A retrospective analysis in the US found that 40% costs related to GIB were incurred following discharge [72], suggesting significant on-going resource utilisation beyond the initial hospital stay. For both UGIB and LGIB early endoscopy or colonoscopy has been shown to reduce hospitalisation costs, although is predominantly due to the associated reduction in total length of stay as opposed to improved clinical outcomes [71,73]. In LGIB as many as 60% hospitalised patients undergo no inpatient investigation and experience no adverse outcomes [74]. Identifying and triaging these patients to outpatient management may reduce the economic burden of inpatient treatment. In UGIB using the Glasgow-Blatchford score to identify low risk patients may reduce hospital admission by 20% [75].

Outstanding questions in GIB

In GIB and particularly LGIB there are a global lack of high quality epidemiological data that can be used to track trends in diagnoses, management and outcomes. This has implications for the critical appraisal of new interventions and processes of care as there are limited baseline data to use for comparison. There is conflicting evidence that the incidence of LGIB is increasing but without robust detailed data collection on time trends and incidence determining the cause of this is extremely difficult. The increased use of drugs that promote bleeding may be driving this, but there are little data that support that this disproportionately affects LGIB. Diagnostic uncertainty may be key component of this trend, and may also contribute to variation in the frequency of causes of bleeding between studies. In the national audit of LGIB in the UK 48% hospitalised patients were discharged with no inpatient investigation meaning that many diagnoses were presumed or based on the results of historical imaging [18]. This was particularly evident in patients diagnosed with diverticular bleeding or angiodysplasia. Quality of data capture can also affect outcomes such as re-bleeding as its definition varies between studies.

The description of outcomes of patients with LGIB are currently limited to a single multicentre prospective study from the UK [18] and national database studies from the US and Europe [2,7,71]. The use of databases populated by hospital insurance claims limits the granularity of the study of clinical outcomes. Additionally many of these studies capture GIB patients using administrative codes, which may be applied differently between healthcare systems and study periods. Improved epidemiological studies that standardise patient capture and the reporting of outcomes are urgently needed to allow temporal comparison of trends in incidence and adverse events.

The impact of DOACs and the increasing use of antiplatelet therapy in the context of GIB remain uncertain. There are few studies describing the optimum management of these drugs, particularly in terms of balancing the risk of severe bleeding with adverse cardiovascular events. Similarly the effects of NSAIDs on the small bowel and colon are less well understood than on the gastroduodenal mucosa. This is particularly important, as PPIs may not be effective in the lower GI tract.

Epidemiological studies demonstrate that although treatment advances have not initially lead to a reduction in mortality rates in NVUGIB, the risk of death has now started to fall. There remain key subgroups of patients who are at risk of adverse outcomes, such as the elderly or those with a high burden of medical co-morbidity. Strategies to mitigate the risk in these groups are not straightforward as initiatives that have been effective in other groups, such as early endoscopy may pose additional risks related to the intervention itself. There are few studies describing trends in mortality in LGIB and those that have studies interventions such as early colonoscopy have reported conflicting effects on clinical outcomes [76].

Health economic data suggest that costs associated with GIB are increasing and this may be despite a reduction in length of hospital stay. Patient triage using risk scoring is established in UGIB but tends to focus on the identification of patients at risk of adverse outcomes. Focussing research into the identification of patients at low risk of harm may have greater utility. Limited capture of cost data on interventions for the diagnosis and treatment of GIB restricts detailed analysis of cost-effectiveness of management strategies across populations.

Summary

In summary epidemiological studies from Western populations suggest that the incidence of UGIB has reduced and was likely driven by HP eradication and the widespread use of PPI therapy. Rates of variceal bleeding have also fallen, attributed to increased use of primary prophylaxis. Historical studies showed that LGIB was less common, but its incidence may be increasing and one day may overtake that of UGIB. Interventions such as early endoscopy, improved efficacy of endoscopic haemostasis and robust risk assessment have led to reduction in length of hospital stay in UGIB, but the economic burden of care has increased. There are few high quality studies describing patient outcomes and healthcare costs in LGIB, but it may be associated with higher healthcare resource utilisation than UGIB and be associated with poorer outcomes. Where UGIB has seen many advances in care, improvements in the prevention, diagnosis and management of LGIB are yet to be established. Key questions regarding trends in incidence of certain aetiologies and the impact of preventative strategies and management remain for both upper and lower GIB.

Practice points

- In several national longitudinal studies the incidence of NVUGIB and VUGIB has fallen
- The identification and eradication of HP has been a key driver in the reduction in incidence seen in UGIB due to peptic ulcer disease
- Despite a reduction in length of hospital stay and improvements in access to care the economic burden of GIB is increasing

Research agenda

- Strategies that balance the risk of developing severe GIB in patients receiving drugs that promote bleeding, with the risks of adverse cardiovascular outcomes are urgently needed
- Improved epidemiological studies that standardise patient capture and the reporting of clinical outcomes are needed to allow accurate description of global trends in incidence and efficacy of interventions
- Innovations that specifically target patients with LGIB are needed to allow the improvements in patients outcomes that have been seen with UGIB

Conflicts of interest

None.

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