Joint recommendations on management of anaemia in patients with gastrointestinal bleeding in Hong Kong

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ABSTRACT

The demand for blood products continues to grow in an unsustainable manner in Hong Kong. While anaemia associated with gastrointestinal bleeding (GIB) is the leading indication for transfusion, there is no local recommendation regarding best practices for transfusion. We aimed to provide evidence-based recommendations regarding management of anaemia in patients with acute and chronic GIB. We reviewed all original papers, meta-analyses, systematic reviews, or guidelines that were available in PubMed. For acute GIB, a restrictive transfusion strategy, targeting a haemoglobin threshold of 7 to 8 g/dL, should be adopted because overtransfusion is associated with significantly higher all-cause mortality and re-bleeding. A liberal transfusion strategy should only be considered in patients with co-existing symptomatic coronary artery disease, targeting a haemoglobin threshold of 9 to 10 g/dL. When acute GIB settles, patients should be prescribed iron supplements if iron deficiency is present. For chronic GIB, iron stores should be replenished aggressively via iron supplementation before consideration of blood transfusion, except in patients with symptoms of severe anaemia. Oral iron replacement is the preferred first-line therapy, while intravenous iron is indicated for patients with inflammatory bowel disease, poor response or poor tolerability to oral iron, and in whom a rapid correction of iron deficit is preferred. Intravenous iron is underutilised and the risk of anaphylactic reaction to current preparations is extremely low. These recommendations are provided to local clinicians to facilitate judicious and appropriate use of red cell products and iron replacement therapy in patients with GIB.

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Introduction

Gastrointestinal bleeding (GIB) is a leading indication for blood transfusion in Hong Kong. In a recent report issued by The Hong Kong Red Cross Blood Transfusion Service, 242 379 units of red cells (RBCs) were issued in 2016, an increase of 34% from 2006. More than 90% of blood products were used by patients in public hospitals; more than 70% of RBCs were utilised in medical/geriatric and surgery departments.[1] Blood demand is expected to continue rising because of the ageing population, in whom the highest amount of blood was used, compared with younger age-groups. The respective units of blood use per 1000 person-years were: 0 to 14 years (8.0), 15 to 64 years (17.5), 65 to 74 years (58.4), 75 to 84 years (117.7) and ≥85 years (209.3).[1] Importantly, compared with many western countries, Hong Kong is using more RBCs per population. In 2016, Hong Kong used 33.0 units of RBCs per 1000 population, compared with 20.7 in Singapore, 25.3 in Japan, 19.0 in Western Australia, 23.5 in New Zealand, 28.5 in England and North Wales, and 20.8 in Canada (unpublished data from Hong Kong Red Cross Blood Transfusion Service). Possible explanations for lower usages in other nations include the adoption of restrictive transfusion practices and more frequent utilisation of iron replacement therapy. With the continuously rising demand for blood products in Hong Kong, unmatched by a corresponding increase in blood donors, there is a pressing need to institute sustainable transfusion practices, such that blood products can be used appropriately.

In addition to the inadequate supply of blood products, transfusion is not without risks. Approximate risks per unit of RBC transfusion are 1:60 for febrile reaction, 1:100 for transfusion-associated circulatory overload, 1:250 for allergic reaction, and 1:12 000 for transfusion-related acute lung injury. In Hong Kong, the most recent estimated risks for transmission of hepatitis B virus (1:58 000), hepatitis C virus (1:8 000 000), and human immunodeficiency virus (1:2 400 000) are not negligible.[2-10] There are additional risks of overtransfusion. Hence, blood transfusion should be instituted appropriately with good indications which should outweigh the potential risks.

Because of these issues and the lack of standardisation of local clinical practices for blood transfusion, the aim of this joint recommendation paper by the Hong Kong Society of Gastroenterology, the Hong Kong IBD Society, the Hong Kong Society of Digestive Endoscopy, and the Hong Kong Red Cross Blood Transfusion Service was to provide evidence-based recommendations for the management of anaemia in patients with acute and chronic GIB; this will facilitate more judicious and appropriate use of RBC products, as well as other alternative measures to control anaemia resulting from GIB.

消化道出血致貧血的治療：聯合建議

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本港的輸血需求日益劇增，而因消化道出血致貧血屬於供應紅血球最常見的病因。有見及此，本文希望為照顧此類患者的醫護人員提供適合而有醫學實證為基礎的治療建議。透過搜索PubMed內研究文章、元分析、系統性文獻回顧和準則得出的分析，在急性消化道出血的情況下，醫護人員應採取限制性輸血策略（即血紅素目標為7-8 g/dL），因過度輸血有機會增加併發症風險，包括死亡或再度出血。相比之下，開放性輸血策略（即血紅素目標為9-10 g/dL）只適用於同時有冠心病患者。當急性消化道出血穩定下來，醫護人員應為帶缺鐵性貧血的患者提供鐵質補充。在慢性消化道出血的大部份情況下，醫護人員應先考慮積極補充鐵質以治理缺鐵性貧血，而輸血治療應只預留給帶有嚴重貧血的患者。口服鐵質補充劑是第一線治療；但在發炎性腸炎疾病、對口服鐵質補充劑起副作用，或須快速補充鐵質的情況下應給予靜脈注射鐵質補充劑。現有的靜脈注射鐵質補充劑都非常安全有效，卻甚少被善用，而醫護人員最擔心出現的全身性過敏反應副作用，其實非常罕見。以上建議旨在促進本地醫護人員對消化道出血患者善用和適當使用紅血球製品和的鐵質補充劑療法。

Types of gastrointestinal bleeding

Gastrointestinal bleeding can be classified on the basis of the speed of blood loss, site of bleeding (upper or lower GIB), or aetiology of bleeding. For the purpose of this recommendation paper, only the speed of blood loss (ie, acute or chronic) is considered. Acute GIB, also known as overt GIB, is defined as frank bleeding from the gastrointestinal tract, with or without iron deficiency. Clinically visible bleeding typically presents as haematemesis, coffee-ground vomiting, melena or haematochezia. Conversely, chronic GIB, also known as occult bleeding, is defined as guaiac positive stool accompanying iron deficiency.[11-13] In this group of patients, blood is not visible macroscopically; they are typically managed in an out-patient setting. Iron deficiency is inevitable in this context of blood loss, because every 1 mL of blood contains 0.5 mg of elemental iron; a decrease of 1 g/dL haemoglobin results in approximately 200 mg elemental iron loss.

Some patients present with acute massive exsanguinating GIB, where life-saving blood transfusion is essential. There are no universally accepted definitions for massive exsanguinating GIB. Some trials have defined it as the need for transfusion of at least 4 units of blood during a period of 24 hours in-hospital, or hypotension with systolic blood pressure <90 mm Hg.[14] In the acute care setting, massive bleeding is defined as 50% blood volume loss within 3 hours, or a rate of 150 mL per minute. In patients with haemodynamic instability, initial resuscitation is the primary goal and blood transfusion is often dictated by haemodynamic status, including the degree of depletion of intravascular volume and clinical signs of organ hypoperfusion. Thus, these patients are excluded from clinical trials of transfusion strategies, as discussed in the following sections, and should be managed accordingly.

Acute gastrointestinal bleeding

Transfusion strategies

The haemoglobin threshold below which RBC transfusion should be given has been controversial. Older observational studies and smaller controlled trials suggested that transfusion may be harmful for patients with hypovolemic anaemia due to GIB.[15-19] Recently, increasing evidence from randomised controlled trials has suggested that a restrictive transfusion strategy is preferred in patients with acute GIB.[2,3,20] In most trials, a restrictive transfusion strategy has referred to a haemoglobin threshold of 7 to 8 g/dL, whereas a threshold of 9 to 10 g/dL is used in liberal transfusion strategy. A restrictive transfusion strategy has been associated with significantly lower short-term mortality. In a study by Villanueva et al,[3] the hazard ratio (HR) for death at 6 weeks was lower in the restrictive strategy group than in the liberal strategy group (HR=0.55; 95% confidence interval [CI]=0.33-0.92; P=0.002). Moreover, re-bleeding risk was significantly lower for the restrictive transfusion

group than the liberal transfusion group (10% vs 16%, respectively; P=0.01; HR=0.68; 95% CI=0.47-0.98).[3] In a subgroup of patients with cirrhosis, the survival advantage conferred by a restrictive transfusion strategy remained for those with Child-Pugh class A or B disease (HR=0.30; 95% CI=0.11-0.85). Additionally, a restrictive transfusion strategy is not associated with harm in terms of risks of myocardial infarction, pulmonary oedema, stroke, pneumonia, or thromboembolism. In a meta-analysis of four randomised controlled trials that examined this issue, restrictive transfusion was associated with a lower risk of all-cause mortality (relative risk [RR]=0.65, 95% CI=0.44-0.97; P=0.03) and a lower overall re-bleeding rate (RR=0.58, 95% CI=0.40-0.80; P=0.004).[21] It has become clear that a restrictive transfusion strategy should be adopted for acute GIB; this is currently recommended in many international guidelines.[22-25]

The above recommendation includes exceptions where a more liberal transfusion strategy should be adopted. This is particularly true for patients with concurrent symptomatic coronary artery disease. It is estimated that up to 14% of patients with acute upper GIB exhibit coexisting coronary artery disease.[26] In a prior analysis, these patients showed greater risk of death, myocardial infarction or unscheduled revascularisation at 30 days if a restrictive transfusion strategy (haemoglobin threshold of 8 g/dL) was adopted, compared with a liberal transfusion strategy (haemoglobin threshold of 10 g/dL) [25.5% vs 10.9%, respectively, risk difference=15%, 95% CI=0.7-29.3%; P=0.054].[27]

Haemostasis

Ongoing bleeding should be controlled whenever possible, including endoscopic, radiographic or surgical interventions to reduce the blood loss and hence, transfusion requirement.[22,23] Correction of coagulopathy and use of antifibrinolytic agents should be considered in appropriate cases. For patients who are using antithrombotic or anticoagulant therapies, specific reversal agents can be considered. Ideally, a multidisciplinary team including a haematologist, cardiologist, neurologist, and gastroenterologist or surgeon should be involved to ensure the best decision regarding discontinuation of medications or the use of reversal agents after balancing risk of bleeding versus risk of thromboembolic events.[22]

Iron therapy after initial haemostasis

Patients with acute GIB typically exhibit iron-deficiency anaemia. Although haemoglobin <10 g/dL was associated with doubling of short-term mortality,[28] iron replacement therapy should be considered in stable patients with borderline low haemoglobin, rather than blood transfusion. In a randomised controlled trial, oral or intravenous iron supplementation significantly reduced the proportion of patients with anaemia at 3 months after acute GIB.[29] Unfortunately, this was often underutilised and only 16% of patients with acute GIB were prescribed with iron supplements upon discharge.[30]

Chronic gastrointestinal bleeding

Replenishing the iron store

Iron deficiency should always be corrected by iron replacement before consideration of blood transfusion in the context of chronic GIB. Adults typically have approximately 50 mg/kg of total bodily elemental iron; two thirds is stored in haem and one third is stored in the form of ferritin or haemosiderin. Approximately 20 mg of iron is recycled daily in the bone marrow and spleen to maintain haem synthesis, and approximately 1 to 2 mg/day of additional dietary iron is needed to balance losses in urine, sweat, and stool. Assuming absorption of 10% of iron in the medicinal form, the daily elemental iron requirement is approximately 10 mg; this requirement is higher for menstruating women and pregnant mothers.[31,32] Dietary iron is present in two main forms. Haem iron is found in meat-based foods and fish. Absorption of haem iron is independent of body iron status. Non-haem iron is found in plant-based foods, cereals, or egg yolks. Absorption of non-haem iron, in contrast to haem iron, is enhanced if the body's iron store declines. It is absorbed in its ferrous form in the duodenum and proximal jejunum; therefore, an acidic environment favours iron absorption. Another important molecular mechanism of iron absorption involves hepcidin, which regulates ferroportin-mediated release of iron from enterocytes and macrophages. In a chronic inflammatory state, hepcidin is increased and negatively regulates iron homeostasis.[33]

In patients with iron-deficiency anaemia, the daily recommended iron requirement substantially increases to 150 to 200 mg elemental iron per day to replenish the deficit; approximately 4 weeks are needed to fully correct the iron deficit.[32] Iron replacement therapy is indicated in these patients, because dietary iron intake alone is unlikely to replace this deficit. The Ganzoni equation is used in some studies to estimate the iron deficit as follows: iron deficit (mg) = body weight (kg) × [target haemoglobin (g/dL) – actual haemoglobin (g/dL)] × 2.4 + 500 mg.[34] However, many clinicians view this formula as inconvenient and may underestimate iron deficit[35]; therefore, it is not widely used in clinical practice. A simplified fixed-dose regimen, as used for treatment of patients with inflammatory bowel disease (IBD), may be considered for iron replacement (Table 1).[36]

TABLE 1. Simplified scheme for estimation of total iron requirements based on body weight and haemoglobin level[36]

Degree of iron deficiency	Haemoglobin level (g/dL)	Iron deficit (mg)	
		Body weight <70 kg	Body weight ≥70 kg
Moderate	10-12 (women)	1000	1500
	10-13 (men)		
Severe	7-10	1500	2000
Critical	<7	2000	2500

Route and dosing of iron replacement therapy

Iron replacement can be administered in either oral or intravenous form. In most cases, the oral route remains first-line treatment because of its convenience, low cost and avoidance of hospitalisation, as well as the potential risks of anaphylactic reaction with intravenous iron. However, gastrointestinal upset, such as nausea and constipation, is very common with oral iron replacement, which decreases patient compliance. Additionally, this method requires a few weeks or months to replenish depleted iron stores in the body. To further complicate treatment, oral iron therapy is ineffective in a few clinical situations. First, in patients with chronic inflammation, hepcidin is upregulated and exerts a negative effect on intestinal iron absorption. Second, in patients with achlorhydria (eg, those undergoing long-term treatment with proton pump inhibitors), or a history of vagotomy or gastric bypass, the acidic gastric environment that maintains the ferrous state of iron is lost; thus, absorption is largely impaired. Other causes of poor response to oral iron replacement include small bowel malabsorption (eg, IBD, prior small bowel resection, or celiac disease) and co-administration of iron with coffee or tea. In particular, IBD patients with iron-deficiency anaemia are recommended to receive intravenous iron as first-line therapy, because of its greater effectiveness than oral iron.[37] The "Day-14 haemoglobin", ie, increase in haemoglobin by ≥1 g/dL on day 14 after oral iron therapy, is a useful tool to determine whether and when to transit from oral to intravenous iron.

Because of the above caveats related to oral iron replacement, intravenous iron replacement can be considered as an alternative. Intravenous iron may also be considered in accordance with patient preference, as some patients cannot tolerate the adverse effects of oral iron or prefer rapid correction of iron deficiency. An older preparation of intravenous iron, in the form of high-molecular-weight iron dextran, was underutilised in the past because of potential anaphylactic reactions. However, this preparation has been removed from the US and Europe. In recent years, the safety of intravenous iron has been vastly improved by newer well-tolerated preparations, such as iron sucrose and iron isomaltoside. According to the US Food and Drug Administration, the cumulative rate of serious adverse reactions is <1:200 000 with different intravenous compounds (iron sucrose, ferric gluconate and low-molecular-weight iron dextran).[38,39] Intravenous iron is now generally considered safe and more effective than oral preparations.[40-42]

Table 2 shows the recommended dosing of commonly used preparations of oral and intravenous iron replacement available in Hong Kong.[43] A 300-mg iron sulphate tablet contains 20% to 30% elemental iron. Typical dosing of an oral iron sulphate tablet would be 300 mg administered twice daily, which would supply approximately 120 to 180 mg of elemental iron to the patient. However, the recommended dosing for patients with IBD might be lower. According to the European Crohn's and Colitis Organisation Consensus, no more than 100 mg elemental iron per day should be administered to patients with IBD, as a result of a few preclinical or early reports of the adverse effects of oral iron on

TABLE 2. Recommended dosing of oral and intravenous iron replacement therapies commonly used in Hong Kong

Oral formulation	Preparation	Commonly used dose
Iron sulphate ($FeSO_4$)	Tablet	300 mg twice daily (consider alternate daily)
Iron hydroxide polymaltose complex (Ferrum Hausmann®, Vifor Pharma, Switzerland)	Drops/syrup	50 mg/mL (1 mL = 20 drops), taken at 5-10 mL twice daily
Intravenous formulation[43]	**Dose per infusion**	
	Standard	**Maximum per single infusion**
Iron sucrose (Venofer®, American Regent, Inc, New York, US)	200 mg	200 mg over 60 minutes
Iron isomaltoside (Monofer®, Pharmacosmos, Denmark)	20 mg/kg of body weight	20 mg/kg of body weight over >15 minutes; not to exceed 1000 mg per infusion
Iron carboxymaltose (Ferinject®, Vifor Pharma, Switzerland)	15 mg/kg of body weight	1000 mg over 15 minutes

exacerbation of disease activity, carcinogenesis, and alteration of intestinal microbiota.[37] The benefits of lower iron dosing are not limited to IBD patients. A recent randomised unblinded trial showed that alternate daily dosing of iron is superior to daily dosing of iron in terms of efficacy (specifically related to hepcidin regulation) and tolerability.[44] Most oral preparations of iron replacement therapy are equally effective, as long as compliance is ensured. Liquid preparations may minimise gastrointestinal upset and avoid the risk of iron tablet–induced gastric erosion.[45,46] Co-administration of oral iron with ascorbic acid is advocated by some experts because of the theoretical enhancement of iron absorption by reduction of ferric iron to the ferrous form.[47] Indeed, oral ascorbic acid administration was associated with a dose-dependent increase of oral iron absorption in healthy volunteers.[48] Although large-scale studies of patients with iron-deficiency anaemia are lacking, oral ascorbic acid is well tolerated and may be considered for concomitant administration with oral iron.

Intravenous iron can be considered as first choice in patients with a high probability of non-compliance, small bowel malabsorption, severe anaemia, or multiple co-morbidities that affect hepcidin-regulated iron absorption. There are two preparations of intravenous iron commonly available in Hong Kong: iron sucrose (Venofer®, American Regent, Inc, New York, US) and iron isomaltoside (Monofer®, Pharmacosmos, Denmark). Monofer® can be administered at a maximum of 20 mg/kg or 1000 mg per single dose weekly. Premedication to prevent anaphylaxis is not routinely needed, but patients should be monitored for at least 30 minutes after drug administration.

Blood transfusions should not be routinely used in chronic GIB and are reserved for patients with severe anaemic symptoms, where blood transfusion would provide rapid relief of the symptoms. Typically, 1 unit of RBC provides approximately 200 mg elemental iron, which would increase haemoglobin by 1 g/dL.

Further management

Whenever possible, the source of bleeding should be identified, with haemostasis secured to prevent continuous blood loss. It may remain difficult in some cases of obscure bleeding, or with multiple sites of bleeding (eg, multiple small bowel angiodysplasia). Clinicians should always maintain awareness of other potential causes of anaemia in these patients, including malabsorption, chronic inflammation, erythropoietin deficiency and other concurrent nutritional deficiencies, such as vitamin B_{12} and folate; these must be corrected to optimise the haemoglobin level.

Recommendations

1. In massive exsanguinating GIB, blood transfusion for life-saving purposes should be administered on the basis of haemodynamic status and response to fluid resuscitation.
2. In acute GIB:
   - A restrictive transfusion strategy should be adopted, which involves a haemoglobin threshold of 7 to 8 g/dL; below this threshold, RBC transfusion should be administered.
   - Overtransfusion is associated with higher all-cause mortality and re-bleeding.
   - A less restrictive transfusion strategy, targeting a haemoglobin level of 9 to 10 g/dL, is only preferred in patients with coexisting symptomatic coronary artery disease.
   - After acute GIB settles, patients should be prescribed iron supplements. The duration of this supplementation is not yet defined, but should be titrated in accordance with haemoglobin and iron status.
3. In chronic GIB:
   - Iron stores should be replenished aggressively via iron supplementation.
   - Blood transfusion should not be routinely used and is reserved for patients with severe anaemic symptoms.
   - Oral iron replacement is the first-line therapy, whereas intravenous iron is indicated in patients with IBD, poor response or poor tolerability to oral iron, and in whom a rapid correction of iron deficit is preferred.
   - Oral iron can be given at alternate daily dosing to improve effectiveness and tolerability.
   - Co-administration of ascorbic acid with oral iron may be considered.
   - Intravenous iron is underutilised. The risk of anaphylactic reaction to current preparations of intravenous iron is extremely low.

Author contributions

This is a Joint Position Statement issued by the three professional gastrointestinal societies (Hong Kong Society of Gastroenterology, Hong Kong Society of Digestive Endoscopy, Hong Kong IBD Society) and the Hong Kong Red Cross Blood Transfusion Service. All authors were involved in the preparation, drafting, and critical review of this article.

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