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Getting patient blood management Pillar 1 right in the Asia-Pacific: a call for action

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ABSTRACT

Preoperative anaemia is common in the Asia-Pacific. Iron-deficiency anaemia (IDA) is a risk factor that can be addressed under patient blood management (PBM) Pillar 1, leading to reduced morbidity and mortality. We examined PBM implementation under four different healthcare systems, identified challenges and proposed several measures. (a) Test for anaemia once patients are scheduled for surgery. (b) Inform patients about risks of preoperative anaemia and benefits of treatment. (c) Treat IDA and replenish iron stores before surgery, using intravenous iron when oral treatment is ineffective, not tolerated or rapid iron replenishment is needed; transfusion should not be the default management. (d) Harness support from multiple medical disciplines and relevant bodies to promote PBM implementation. (e) Demonstrate better outcomes and cost savings from reduced mortality and morbidity. Although PBM implementation may seem complex and daunting, it is feasible to start small. Implementing PBM Pillar 1, particularly in preoperative patients, is a sensible first step regardless of the healthcare setting.

Keywords: anaemia, Asia Pacific, iron deficiency, patient blood management, Pillar 1

INTRODUCTION

Anaemia is a global health problem, affecting 30% of the world's population in 2015.[1] In 2010, there were 68.4 million years lived with disability from anaemia worldwide, and 56% of these were in Asia-Pacific countries.[2] Anaemia, which is characterised by a decrease in total red blood cell (RBC) mass, is accompanied by reduced haemoglobin (Hb) levels and altered RBC morphology. As its symptoms are nonspecific and develop gradually, it often goes unnoticed and therefore untreated. Iron deficiency (ID) is the most common cause of anaemia (> 50%),[2] manifesting in decreased production of Hb and activity of iron-dependent enzymes.[3] Iron deficiency anaemia (IDA) often presents in young children and pregnant women in developing countries due to malnutrition, multiparity, postpartum haemorrhage and infectious diseases; and in the elderly due to bleeding from gastrointestinal conditions.[4]

Preoperative anaemia represents a significant healthcare problem in Asia-Pacific countries.[5-8] This is compounded by the limited supply of blood products: 19 (23%) out of 82 countries with low donation rates (< 10 donations per 1,000 population) are in the Asia-Pacific.[9] These are typically developing countries with growing populations and a high demand for transfusions.[10] Their blood services also face difficulties in safeguarding blood stocks from risks posed by pathogens in the blood supply.[11] On the other hand, the developed countries, and even some of the less developed countries with ageing populations, have to confront the decreasing numbers of eligible donors. In addition, older persons, who have higher risks of malignancies and chronic diseases, are more likely to require complex surgical interventions.[12]

POORER OUTCOMES FOR PATIENTS WITH PREOPERATIVE ANAEMIA

IDA is an independent risk factor for poor outcomes among patients scheduled for surgery. In a meta-analysis of observational studies, 39.1% of 949,445 patients undergoing surgery were found to be anaemic.[13] This study and others (Table I) found preoperative anaemia to be associated with greater risks of transfusion, morbidity, mortality and increased hospital length of stay (LOS).[5,8,14-19] Despite these risks and the exacerbation of anaemia by surgical blood loss, preoperative anaemia is deemed acceptable by many physicians.[20] Consequently, many patients receive allogeneic RBC transfusions, which have remained the mainstay of perioperative anaemia management in many settings. This may be undesirable, as RBC transfusion is another independent risk factor for adverse outcomes such as infections and lung injury.[21]

Table I. Outcomes in patients with preoperative anaemia.

No.	Study, yr	Description	Results
1	Non-cardiac surgery, 2018[15]	Retrospective analysis of medical records of 24,579 patients aged ≥ 65 years in Singapore (January 2012–October 2016)	Moderate/severe anaemia vs. normal: ↑ 30-day mortality adjusted OR 1.61 (95% CI 1.03–2.52); p = 0.04
2	Cardiac and non-cardiac surgery, 2017[8]	Retrospective review of 97,443 patients in Singapore (January 2012–October 2016) Anaemia prevalence 27.8% (mild anaemia 15.3%, moderate anaemia 12.0%, severe anaemia 0.5%)	Moderate/severe anaemia vs. normal: ↑ 1-year mortality-adjusted HR 2.86 (95% CI 2.56–3.20) Mild anaemia vs. normal: ↑ 1-year mortality-adjusted HR 1.98 (95% CI 1.77–2.21)
3	Primary total knee arthroplasty, 2017[14]	Retrospective study of 2,394 patients in Singapore (January 2013–June 2014) Anaemia prevalence 23.7%: 403 (16.8%) with mild anaemia and 164 (6.8%) with moderate-to-severe anaemia.	Moderate-to-severe anaemia vs. normal: ↑ LOS OR 3.22 (95% CI 2.29–4.53); p < 0.001 Mild anaemia vs. normal: ↑ LOS OR 1.97 (95% CI 1.53–2.53); p = 0.001
4	Orthopaedic surgery, 2015[17]	Observational study of 1,534 patients from 17 centres in 6 European countries Preoperative anaemia prevalence 14.1%, postoperative anaemia prevalence 85.8%	Preoperative anaemia vs. non-anaemic: ↑ Transfusion: 14.8% vs. 2.8% – Units per patient: 2.4 (1.5) vs. 2.2 (1.4) – Median time (min) to first intraoperative transfusion: 130 (range 88–158) vs. 179 (range 135–256); p < 0.001

			↑ Postoperative complications: 36.9% vs. 22.2%; p = 0.009
4	Inpatient surgery, 2014[16]	Retrospective study of 39,309 patients in 28 European nations	Preoperative anaemia vs. normal Hb concentrations: ↑ Mortality for severe (odds ratio 2.82 [95% CI 2.06–3.85]) or moderate (1.99 [95% CI 1.67–2.37]) anaemia higher than those with normal preoperative Hb concentrations ↑ LOS (p < 0.001) ↑ Postoperative admission to intensive care (p < 0.001)
4	Gynaecological surgery, 2013[5]	Retrospective study of 843 women in Western Australia undergoing major gynaecological surgery over a two-year period Preoperative anaemia present in 18.1% of women	Preoperative anaemia vs. without anaemia: ↑ Transfusion: OR 5.74, p < 0.001 No increased complications or LOS
5	Major non-cardiac surgery, 2011[18]	Retrospective study of 227,425 patients undergoing major non-cardiac surgery in United States, of whom 69,229 (30.44%) had preoperative anaemia	Preoperative anaemia vs. without anaemia: ↑ Postoperative mortality at 30 days: OR 1.42 (95% CI 1.31–1.54) Mild anaemia: OR 1.41 (95% CI 1.30–1.53) Moderate-to-severe anaemia: OR 1.44 (95% CI 1.29–1.60) ↑ Composite postoperative morbidity at 30 days: OR 1.35 (95% CI 1.30–1.40) Mild anaemia: OR 1.31 (95% CI 1.26–1.36) Moderate-to-severe anaemia: OR 1.56 (95% CI 1.47–1.66)
6	Hip and knee surgery, 2010[19]	Systematic review of 49 published studies in MEDLINE on anaemia (but not sickle cell) in patients undergoing (1) total hip or knee arthroplasty and (2) hip fracture surgery Preoperative anaemia: 24% (hip/knee arthroplasty) and 44% (hip fracture)	Perioperative anaemia: ↑ Transfusion rate of 45% ± 25% and 44% ± 15% ↑ Postoperative anaemia: 51% and 87% ↑ Postoperative infections, poorer physical functioning and recovery, and increased LOS and mortality

CI: confidence interval; Hb: haemoglobin; HR: hazard ratio; LOS: length of hospital stay; OR: odds ratio; rHuEPO: recombinant human erythropoietin

Patient blood management (PBM) improves patient outcomes by applying evidence-based medical and surgical concepts across its three pillars, namely: Pillar 1 – optimise RBC mass; Pillar 2 – minimise blood loss; and Pillar 3 – optimise anaemia tolerance of the patient to improve outcomes by clinically managing and preserving the patient's own blood.(22) In May 2010, the World Health Organization (WHO) formally recognised the importance of PBM and recommended it to its 193 member states.(23) Under PBM Pillar 1, a key strategy for optimising the total RBC mass of patients undergoing surgery is to identify anaemia and treat its underlying causes preoperatively.(22) For example, the Australian PBM guidelines recommend that doctors perform early evaluation and treatment of preoperative ID/IDA and its underlying causes as part of preparation for elective surgery.(24) In most cases, preoperative IDA can be corrected with iron replacement therapy.(22)

Successful PBM implementation in Western Australia was associated not only with reduced blood use (i.e. RBC units/admission declined by 26% despite a 22% rise in admissions)(25) but also significant reductions in preoperative anaemia, hospital-acquired complications, in-hospital mortality and LOS, with cost savings of > AUD 6 million per year.(26) Such observations give weight to recommendations that elective surgeries be delayed until after anaemia correction.(27) Despite these reasons and the availability of therapeutic strategies and pharmacologic interventions for reducing transfusion in the perioperative setting, PBM implementation has varied widely, even in Europe and Canada where PBM has been practised for many years.(28,29)

CHALLENGES AND PROPOSED SOLUTIONS

We examined PBM implementation in the Asia-Pacific countries of Australia, Malaysia, Republic of Korea and Singapore, discussing specific challenges of implementing PBM in these countries and suggesting potential solutions (Table II).

Table II. Challenges to PBM implementation and proposed solutions.

Challenge	**Reason/perception**	**Recommendation**
Physicians do not want to postpone surgery in order to treat anaemia	They cannot make a patient wait for 2–3 weeks to receive treatment for IDA. There is a fear of complications from delayed surgery.	Elective surgeries are usually scheduled in advance. The referring primary care doctor could exclude anaemia or treat the anaemia appropriately, if present, or the surgeon could check for anaemia and treat as soon as the patient is scheduled for surgery. This allows sufficient time for investigation of the underlying cause and appropriate management.
Physician support	Scepticism about efficacy of PBM, unease with procedural scrutiny and an ingrained belief that transfusion is safe.	• Champions are needed within each discipline to promote PBM from the patient safety perspective. Interdisciplinary collaboration between various stakeholder disciplines, such as the blood transfusion committee working together with clinical departments, is essential to effective implementation. • Focus on efforts to implement PBM to provide the best patient care rather than deliverables. A result-oriented approach may invite resistance from physicians.
Limited time prior to surgery for IDA correction. Hospital administration is concerned about underutilisation of operating theatre resources, as they cannot be re-allocated at short notice.	• Rescheduling a patient for surgery may create a problem that the operating room time slot may not be utilised by another patient due to the short notice. • For patients requiring chemotherapy and surgery, there is a short window period prior to surgery and 2 weeks may not be sufficient.	• Iron studies can be performed at pre-admission assessment and treatment given for underlying causes, if needed, to avoid additional visits or rescheduling. • Intravenous iron can be given on the day before surgery or in operating rooms if time is severely limited. Transfusion alone is insufficient to replenish drained iron stores.
Additional patient visits for iron supplementation result in more costs for patient.	• Patients may be inconvenienced by additional visits for iron studies and iron therapy, e.g. patients who travel out of town for surgery.	• Patients need to be informed about the risks of preoperative anaemia; and that with treatment, he/she can get home sooner after an operation.

Iron studies may add to the cost of treatment	• In some countries, the government bears the cost of iron studies. Hospital administration wants to see cost 'savings'. • Blood is sometimes perceived to be readily available at reasonable costs or even 'free'.	• Help the government and hospital administration see savings in terms of reduction in mortality, morbidity, RBC transfusion and length of stay. • The government or hospital may already be subsidising the cost of blood. The actual cost of providing blood should be made known.
Availability of iron studies	Some iron studies are not readily available at hospitals.	A ferritin assessment (< 100 µg/L) should be sufficiently sensitive to detect most IDA cases. Assess clinical and patient-specific risk factors concurrently, as this also helps to determine the likely cause and guide the management of anaemia, especially in the absence of resources for timely iron status evaluation.
Other clinical considerations	• In cancer patients with IDA (5–7 g/dL), ferritin may be as high as 500 µg/L. • For renal failure patients, it is not recommended to raise Hb above 12 g/dL with erythropoietin-stimulating agents, to reduce risk of conditions such as stroke in non-perioperative settings. • Thalassaemia is prevalent in some parts of Asia and iron supplementation would not help.	There will always be exceptions to the rule. However, the evidence is clear that perioperative iron therapy can improve patient outcomes for patients with IDA.

Hb: haemoglobin; IDA: iron-deficiency anaemia; PBM: patient blood management; RBC: red blood cell

Postponement of surgery due to preoperative anaemia is usually not well received. Hospital administrators are concerned about optimising the utilisation of operating theatres, while physicians are resistant to changes to their clinical practice and concerned that delaying surgery may result in medical complications. Patients do not want to delay treatment, particularly for major illnesses, and are concerned about the cost and time needed for additional visits. Understanding that appropriate changes to current clinical practice can deliver better patient care and educating patients on the potential risks and benefits can help to overcome these challenges. Physicians should initiate anaemia investigations early, while patients should also be informed about the benefits of treating preoperative anaemia. We proposed an algorithm for the diagnosis and treatment of preoperative anaemia (Fig. 1).

Although formal iron studies are needed prior to iron therapy, some tests may not be readily available in resource-limited settings. We suggest that an assessment of ferritin together with clinical and patient-specific risk factors can identify most IDA cases. When IDA is detected early, oral iron supplementation is usually the first-line treatment. Some side effects from the use of oral iron include nausea, constipation and vomiting,[(4)] which may lead to poor compliance to treatment. A systematic review has concluded that patients administered with intravenous (IV) iron experienced fewer gastrointestinal side effects compared to oral iron treatments.[(30)]

When time is limited, IV iron infusions can be used to rapidly and effectively replenish iron stores without compromising outcomes.[(31)] However, in patients who urgently require reliable and rapid iron replacement, IV iron formulations such as iron sucrose, ferric gluconate, iron isomaltoside, low-molecular-weight iron dextran (LMW-ID) or ferric carboxymaltose may be better suited, as they allow the slow release of iron with marginal or no toxicity-related adverse events.[(4,32-34)] Incidence rates of adverse drug events were found to be lower with modern IV iron formulations, including LMW-ID, than with older high-molecular-weight iron dextran preparations.[(35)] Whereas iron sucrose and ferric gluconate infusions need to be administered across several sessions, iron isomaltoside, LMW-ID or ferric carboxymaltose, which bind iron more tightly, can replenish total iron deficit in one or two doses.[(4,32)]

IV iron is applicable in certain instances, including immediately before surgery, post trauma, and in cases of inability to tolerate or absorb oral iron, iron loss exceeding absorption rates, and late pregnancy.[4] When there is insufficient preoperative time (e.g. trauma and emergency surgical cases), postoperative IV iron therapy has also been shown to improve Hb recovery with fewer RBC transfusions, shorter LOS and, importantly, fewer infections.[36] Clinical evidence (Table III) suggests that the use of IV iron increases the total RBC mass of patients undergoing surgery and improves outcomes.[17,37-41] Even in critically ill patients, early IV iron therapy raised discharge Hb levels despite lower transfusion triggers (< 7.5 g/dL) without compromising safety.[42]

Table III. Improvement in patient outcomes from perioperative IV iron therapy.

No.	Study	Description	Results
1	Hip and knee surgery, 2016[37]	Prospective observational, single-centre study; 367 patients (184 before, 183 after)	Before vs. after PBM using EPO and IV iron: ↓ Transfusion: 3% vs. 13%; p = 0.0003 ↓ Severe (Hb < 10 g/dL) anaemia at discharge 14% vs 25%; p = 0.01 TSAT 11.0% vs. 0.1%; p < 0.001
2	Abdominal surgery, 2016[38]	RCT; 72 Australian patients with IDA were randomly assigned to receive either (1) IV iron or (2) usual care	IV iron vs. usual care: ↓ Transfusion: 12.5% vs. 31.3% (60% reduction in RBC transfusion) ↓ LOS: 7.0 days vs 9.7 days; p = 0.026 ↑ Hb: improved by 0.8 g/dL vs. 0.1 g/dL by the day of admission; p = 0.01 ↑ Hb: 1.9 g/dL vs 0.9 g/dL; p = 0.01
3	Colon cancer, 2014[39]	ROS; a total of 266 patients undergoing elective surgery were included: (1) 111 received FCM (median dose 1,000 mg) and (2) 155 were non-IV iron subjects	IV iron (FCM) vs. non-IV iron: ↓ Transfusion: 9.9% vs. 38.7%; OR 5.9; p < 0.001 ↓ LOS: 8.4 ± 6.8 days vs. 10.9 ± 12.4 days; p < 0.001. ↓ % with normalised Hb (30 days post surgery): 40.0% vs. 26.7%; p < 0.05 ↓ Re-interventions and post-surgery complications: 20.7% vs. 26.5%; p = 0.311 ↑ Hb (% of responders):

			48.1% vs. 20.0%; p < 0.0001 at admission 80.0% vs. 48.9%; p < 0.0001 at 30 days post surgery
4	Cardiac surgery, 2015[40]	ROS; 2,662 patients analysed, 387 in the pre-PBM and 2,275 in the PBM epoch	Post-PBM vs. pre-PBM: ↓ Transfusion: 20.8% vs. 39.3%; p < 0.001 ↓ LOS: 10.4 ± 8.0 days vs. 12.2 ± 9.6 days; p < 0.001 Hospital mortality rate and cerebral vascular accident incidence remained unchanged
5	Orthopaedic surgery, 2014[17]	ROS; 1,534 patients undergoing major elective hip, knee or spine surgery from 17 centres in 6 European countries	PBM (n = 7) vs. non-PBM centres: ↓ Preoperative anaemia: 8.0% vs. 18.5%; p < 0.001 ↑ Ferritin: 11.0% vs. 2.6%, TSAT 11.0% vs. 0.1%; p < 0.001
6	Lower-limb arthroplasty, 2014[41]	ROS; 2,547 patients undergoing elective lower-limb arthroplasty (n = 1,186) or hip fracture repair (n = 1,361) were compared; patients received either (1) very-short-term perioperative IV iron (200–600 mg, n = 1,538), with or without recombinant human EPO (40,000 IU), or (2) standard treatment (n = 1,009)	Perioperative IV iron vs. standard treatment: Hip fracture patients ↓ Transfusion: 32.4% vs. 48.8%; p = 0.001) ↓ LOS: 11.9 days vs. 13.4 days; p = 0.001 ↓ PNI: 10.7% vs. 26.9%; p = 0.001 ↓ 30-day mortality: 4.8% vs. 9.4%; p = 0.003 Arthroplasty patients ↓ Transfusion: 8.9% vs. 30.1%; p = 0.001 ↓ LOS: 8.4 days vs. 10.7 days; p = 0.001 No differences in PNI rates and 30-day mortality

EPO: erythropoietin; FCM: ferric carboxymaltose; Hb: haemoglobin; IDA: iron-deficiency anaemia; IV: intravenous; LOS: length of hospital stay; PBM: patient blood management; PNI: postoperative nosocomial infections; RBC: red blood cell; RCT: randomised controlled trial; ROS: retrospective observational study

EXPERIENCE IN THE ASIA-PACIFIC

PBM champions such as national health authorities and/or blood services, professional medical organisations, hospital administrators and, crucially, physicians are pivotal in promoting PBM implementation. They provide the strong leadership needed to sustainably establish effective programmes and create collaborative environments for healthcare professionals from the surgical, medical, transfusion medicine, and nursing departments, laboratory and pharmacy with guidelines, communication tools and education.[43] We herein discuss examples from Australia and Singapore, the Republic of Korea and Malaysia and illustrate how different PBM champions can positively influence the practice of PBM in their respective countries.

National health authorities

In Australia, the National Blood Authority has published comprehensive PBM guidelines since 2012.[24] In addition, the Australian Commission on Safety and Quality in Health Care "*requires that blood and blood product policies, procedures and/or protocols are consistent with national evidence-based guidelines for pre-transfusion practices, prescribing and clinical use of blood and blood products*" (Action 7.1.1).[24] From mid-2010 to mid-2015, the number of RBC units issued saw a 15.8% reduction.[44] A multidisciplinary National Patient Blood Management Collaborative, led by the Department of Health, Australia, was established in 2015 to further promote appropriate care for patients and reduce exposure to transfusion. 12 hospitals were selected and supported with federal funding. They identified and implemented changes in preoperative practice in areas that were at risk for anaemia. Monthly data for 8,758 procedures (May 2015–September 2016) showed that 98% of patients were assessed for preoperative anaemia, an increase from 90%; 71% had their anaemia managed, up from 28%; 90% were assessed for ID, from 25%; and 53% had their ID managed, from 39%.[44]

In Singapore, the Blood Services Group of the Health Sciences Authority, a statutory board of the Ministry of Health, supplies blood nationwide. With an ageing population (11.8% were aged > 65 years) and life expectancy of 82.7 years, blood demand is expected to increase even as eligible donors decrease.[45] To mitigate this, the Ministry of Health and Blood Services Group have actively promoted PBM at public hospitals since 2013. Regular national audits of

PBM-related efforts have been performed since 2017 to promote appropriate clinical indications for RBC transfusion and preoperative anaemia screening for elective surgeries. We herein describe these PBM efforts at two major public hospitals: National University Hospital and Singapore General Hospital, Singapore.

National University Hospital's anaemia clinic was started in 2014 and is integral to its PBM programme. A preliminary survey showed that 23% of patients had preoperative anaemia, with 57% requiring transfusion subsequently, compared to 18% for patients without anaemia. Surgeons were encouraged to refer patients for anaemia management if patients had Hb < 10 g/dL, any degree of anaemia and poor cardiopulmonary reserve; or when the surgery had a potential for high blood loss. IDA management was initiated with oral iron if ferritin < 100 μg/L (< 200 μg/L in non-dialysis-dependent chronic kidney disease) and transferrin saturation < 20%. IV iron was given as soon as was feasible if there was: no response after two weeks, intolerance to oral iron or the surgery was scheduled within four weeks; or after surgery if therapy was not started earlier. EPO was used on an individualised basis, e.g. chronic kidney disease Stage III/V or chemotherapy-induced anaemia in a palliative setting.

At Singapore General Hospital, formal PBM implementation was started in 2013 as part of the national initiative. The hospital had a number of existing measures to support PBM, i.e. a multidisciplinary blood transfusion committee, transfusion guidelines and an early preoperative anaemia assessment clinic. In August 2017, a preoperative anaemia management pathway was instituted in which anaemic patients undergoing surgery were given either oral iron (ferrous fumarate) or single-dose IV iron (ferric carboxymaltose) depending on the severity of anaemia, invasiveness of surgery and time available for optimisation. Mandatory documentation of indications for RBC transfusion was also instituted, while inappropriate indications generated alerts via the computerised physician order entry (CPOE) system. A preliminary one-month audit of the system showed that 21% of CPOEs generated alerts for inappropriate indications and were subsequently cancelled.

Professional medical organisations

The Korean Research Society of Transfusion Alternatives of the Republic of Korea began promoting PBM in 2006. In 2014, the Korean Patient Blood Management (KPBM) Research Group was formed to further promote greater PBM use. Its active participation saw PBM included in the Korean Transfusion Guidelines of 2016 for the first time. In 2016, the KPBM organised a new steering committe comprising > 40 leading physicians from various specialties to promote PBM in their respective clinical fields.

The Korean Society of Blood Transfusion, representing practitioners in blood banking and transfusion medicine, including laboratory physicians, haematologists and anaesthetists, supported PBM with the creation of its PBM committee in 2016. A KPBM survey showed that 70%–80% of practising surgeons supported the use of PBM and had held special PBM symposia within their respective society meetings. A number of Korean hospitals that adopted PBM as part of their clinical practice have already demonstrated its benefits in improved postoperative Hb levels, with reductions in transfusions (Table IV).[46-49]

Table IV. Studies documenting benefits of PBM in Asia-Pacific countries.

Yr	**Country, study**	**Description**	**Results**
2016	Australia, abdominal surgery[38]	RCT; 72 patients with IDA were randomly assigned to receive either (1) IV iron or (2) usual care	IV iron vs. usual care: ↓ Transfusion: 12.5% vs. 31.3% (60% reduction in RBC transfusion) ↓ LOS: 7.0 days vs. 9.7 days; p = 0.026 ↑ Hb: improved by 0.8 g/dL vs. 0.1 g/dL by the day of admission; p = 0.01 ↑ Hb: 1.9 g/dL vs 0.9 g/dL; p = 0.01

2016	Australia, intensive care[42]	RCT; of 140 patients enrolled, (1) 70 were assigned to IV iron and (2) 70 to placebo	IV iron vs. placebo: ↓ Transfusion: 97 vs. 136 red blood cell units yielding an incidence rate ratio of 0.71 (95% CI 0.43–1.18); p = 0.19 ↑ Median Hb at discharge: 107 (IQR 97–115) g/L vs. 100 (IQR 89–111) g/L; p = 0.02 No significant difference between the groups in any safety outcome
2015	Republic of Korea, obstetrics and gynaecology[46]	Retrospective analysis over a 10-year time frame of severely anaemic women (Hb < 50 g/L) with benign conditions who had requested not to receive a blood transfusion and given IV iron and EPO instead. Women were analysed in two groups: (1) a gynaecologic (gyn, n = 12) and (2) an obstetric (ob, n = 7) population.	Mean age 35.8 ± 10.2 yr With IV iron, EPO and no transfusion, ↑ mean Hb concentration 41.3 ± 9.7 g/L (gyn) and 36.0 ± 8.9 g/L (ob) to 67.3 ± 14.3 g/L and 73.1 ± 6.9 g/L, respectively, by the time of hospital discharge No deaths or other serious complications
2014	Republic of Korea, gastric cancer[49]	Case-control study of 2078 gastric cancer patients who underwent surgery between February 2007 and August 2009, 368 patients developed postoperative anaemia (Hb level < 9 g/dL) within the first postoperative week. Patients requiring transfusions were excluded. (1) IV-iron was administered to 63 patients (iron group). (2) 60 patients were observed without treatment (observation group).	IV-iron vs. observation group ↑ Change in Hb level: 0.648 ± 0.054 g/dL vs 0.349 ± 0.038 g/dL; p < 0.001 ↑ Hb Level 1 and 3 mth postoperatively: 10.7 ± 1.3 g/dL to 11.9 ± 1.3 g/dL; p = 0.033 vs. 10.1 ± 1.0 g/dL to 10.8 ± 1.4 g/dL; p < 0.001 ↑ Postoperative LOS: 10.5 ± 6.8 days vs. 7.6 ± 5.5 days; p = 0.011 No significant differences in major and surgical complications between the groups (6.3% vs. 13.3%, p = 0.192; 9.5% vs. 3.3%, p = 0.164)
2011	Republic of Korea, bilateral total knee replacement arthroplasty[47]	RCT; 108 iron-deficient patients were randomly assigned to: (1) Group IE (200 mg of iron sucrose intravenously over 1 hr and 3,000 IU of recombinant human EPO-beta subcutaneously during operation and	IV iron (Group IE) vs. control (Group C): ↓ Transfusion: 20.4% vs. 53.7%; p = 0.011 ↓ Mean number of RBC units transfused: 0.2 ± 0.5 vs. 0.8 ± 0.8; p = 0.005 ↑ Postoperative iron, ferritin, and transferrin saturation levels

		during the postoperative period if the Hb level was 70–80 g/L) or (2) Group C (control)	were significantly higher
2011	Republic of Korea, valvular heart surgery[48]	RCT; 74 patients with preoperative anaemia were randomly allocated to either the (1) EPO group (500 IU/kg EPO and 200 mg iron sucrose intravenously 1 day before the surgery) or (2) control group with equivalent volume of normal saline	IV iron vs. control: ↓ Transfusion: 22 patients (59%) vs. 32 patients (86%); p = 0.009 ↓ Mean no. of units of packed erythrocytes transfused per patient: (3.3 ± 2.2 units/patient vs. 1.0 ± 1.1 units/patient; p = 0.001 ↑ Reticulocyte count was significantly greater on postoperative days 4 (p = 0.001) and 7 (p = 0.001)

CI: confidence interval; EPO: erythropoietin; Hb: haemoglobin; IDA: iron-deficient anaemia; IQR: interquartile ratio; IV: intravenous; LOS: length of hospital stay; PPA: postpartum anaemia; RBC: red blood cell; RCT: randomised controlled trial

Physicians

In Malaysia, PBM is practiced at the local level (e.g. maternal and foetal medicine department at the Sultan Haji Ahmad Shah Hospital, Pahang, Malaysia). Postpartum haemorrhage (PPH) remains one of the main causes of maternal mortality in Malaysia. High parity is common among local women and access to affordable healthcare remains a key challenge. Women at high risk of anaemia are tested for Hb levels and ferritin in early pregnancy. Patients who are found to be iron-deficient are treated with low-dose elemental iron (20–80 mg daily); those with anaemia are given higher-dose elemental iron orally (100–200 mg daily) and their response is monitored. In this resource-constrained setting, IV iron is used when time is limited or when oral iron is ineffective or poorly tolerated. Despite its efficacy, IV iron is used sparingly due to the higher cost of iron sucrose compared to oral iron. Other practical measures to minimise the risk of anaemia included providing dietary advice and advice on increasing the interval period between pregnancies as well as treating comorbidities.

For postpartum haemorrhage, patients who were not actively bleeding were managed in the following ways based on their Hb levels: (a) > 9 g/L – transfusion was deemed inappropriate and discouraged; (b) 7–9 g/L – transfusion was based on the need to relieve clinical signs and symptoms of anaemia, and the availability of anaemia treatment, expected delivery date and risk factors for haemorrhage; and (b) < 7 g/L – transfusion could be used but might not be required for well-compensated patients, or other therapies were available. When indicated, a single RBC unit was given followed by clinical assessment to determine further need.

BENEFITS OF PBM PILLAR 1

Our article has described the practice of PBM in four different healthcare settings. Although these examples are certainly not exhaustive, they illustrate a range of implementation approaches that can be applied in both developed and developing countries. As we and others have noted, there is an urgent need for action.(50) The anaemia burden in the Asia-Pacific region is high, with growing numbers of elderly patients who are more likely to be anaemic.(2) Without PBM, a third to half (30%–54%)(16,18,47) of patients undergoing surgery could require transfusion, increasing the demand for blood and potentially leading to poorer patient outcomes. Shrinking blood donor pools puts a strain on the blood supply system and may result in cancellation or postponement of elective surgery in some countries.

On the other hand, studies in the region have shown that the application of PBM Pillar 1 has led to shorter LOS, improved Hb/ferritin levels and fewer adverse events, besides reduced transfusion rates (Table IV).(38,42,46-49) Implementation of PBM also has a significant positive impact on healthcare costs. A 2012 study of > 100,000 patients in the canton of Zurich, Switzerland, showed a 27% reduction in RBC transfusion in the first year of implementation with direct savings of USD 2.0 million on blood products alone.(43,51) In Australia, the National

Blood Authority estimated that a 5% reduction in RBC use would save AUD 14.6 million nationally.[(51)] Cost savings from the use of IV iron to treat preoperative IDA were reported at USD 730 per patient (Singapore)[(52)] and USD 22,192 per quality-adjusted life-year for patients with chronic heart failure (Republic of Korea)[(53)] in 2014. There is also the intangible cost of RBC transfusion-associated adverse outcomes and prolonged LOS.[(54)]

While each country may face different challenges in implementing PBM, the concept is applicable everywhere. Notwithstanding its urgency, the implementation process should proceed stepwise in a manner that is appropriate to the healthcare setting and acceptable to stakeholders. Post implementation, it is also essential to apply quality assurance measures of good benchmarking, monitoring and feedback,[(54)] and demonstrate improved patient outcomes and safety benefits. Although this review presents PBM Pillar 1 for perioperative settings, the same principles of implementation can be extended to the other two pillars of PBM and to the non-surgical fields of medicine.

CONCLUSION

IDA is common and it is an independent modifiable risk factor for patient outcomes. Physicians and patients need to be aware of the risks of preoperative anaemia and appreciate that early treatment of IDA preoperatively can help to improve patient safety and outcomes. The most feasible way of implementing PBM is to start with small steps and expand efforts over time. Getting PBM Pillar 1 right by using iron replacement therapy to preoperatively optimise red cell mass in patients with IDA is a sensible first step to take when embarking on PBM implementation, regardless of the healthcare setting.

AUTHOR CONTRIBUTIONS

Froessler B and Spahn DR co-chaired the PBM workshop and presented data on current Pillar 1 practice. Froessler B presented data for Australia; Lim KKC for Malaysia; Ang AL, Lee SY and Singh G for Singapore; and Kim YW for the Republic of Korea. All of the authors participated in the workshop discussion, contributed equally to the drafting, reviewed the manuscript and approved its submission.

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FIGURE

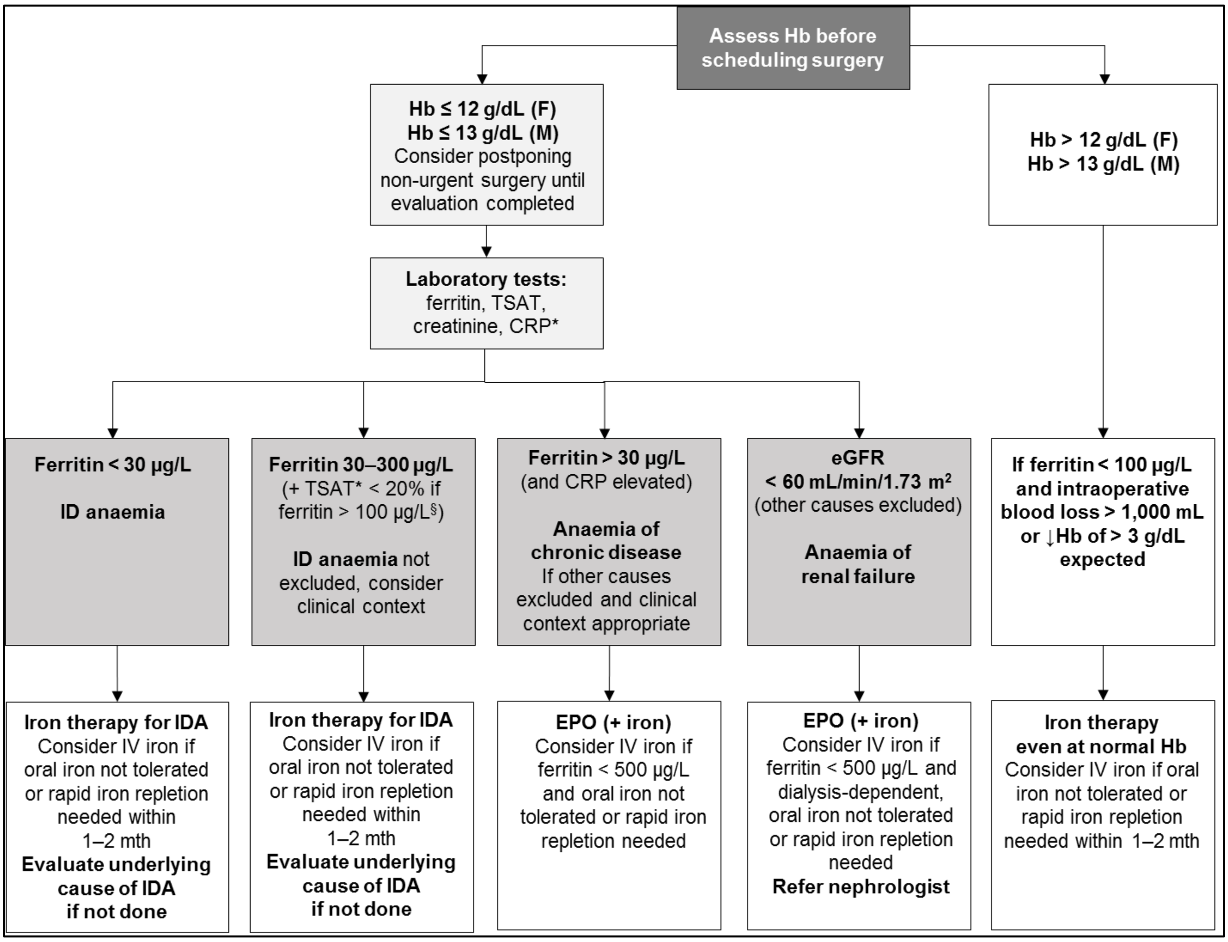

Fig. 1 Proposed algorithm to evaluate and treat perioperative anaemia. *If TSAT is unavailable, assess clinical context for conditions that may falsely elevate ferritin despite ID. §If ferritin is > 100 µg/L, TSAT < 20% is required to support diagnosis of IDA. If anaemia cannot be classified based on these, contact a haematologist. CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; EPO: erythropoietin; F: female; Hb: haemoglobin; ID: iron deficiency; IDA: iron-deficiency anaemia; IV: intravenous; M: male; TSAT: transferrin saturation