Review Article

Applying principles of patient blood management during COVID-19 pandemic: a literature review

Aditi Khandelwal[1,2,3], Heather Vandermeulen[4], Bryan Tordon[5], Katerina Pavenski[1,3,4,5,6]

[1]Department of Medicine, St. Michael's Hospital, University of Toronto, Toronto, Canada; [2]Canadian Blood Services, Ottawa, Canada; [3]Quality Utilization Efficacy Safety Transfusion (QUEST) Research Program, University of Toronto, Toronto, Canada; [4]Department of Medicine, University of Toronto, Toronto, Canada; [5]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada; [6]Department of Laboratory Medicine, St. Michael's Hospital, Toronto, Canada

Contributions: (I) Conception and design: K Pavenski; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Katerina Pavenski. St. Michael's Hospital, 30 Bond St., Toronto, Ontario M5B 1W8, Canada.
Email: katerina.pavenski@unityhealth.to.

Abstract: As of 15 December 2021, coronavirus disease 2019 (COVID-19) affected approximately 271 million and killed 5.3 million people globally. COVID-19 pandemic had a tremendous impact on world healthcare systems and blood supply. While principles of patient blood management (PBM) may have been previously implemented in many jurisdictions, their widespread adoption has become imperative during the pandemic. This review will discuss the impact of the COVID-19 pandemic on the Canadian blood supply and how the principles of PBM could be applied during a pandemic or other disruptions to healthcare delivery or blood supply. We described the local blood system and how it adapted during the pandemic. We also included a discussion of pandemic-associated local PBM challenges and solutions. We conducted a brief review of English language literature with a specific focus on the application of PBM to reduce unnecessary red blood cell (RBC) transfusions in elective major surgery, hematological malignancies, elective major gynecological surgery and obstetrics between January 2020 and April 2022. The common themes included anemia diagnosis and management, restrictive RBC transfusion strategies and reduction in blood loss. Anemia is common, is frequently caused by iron deficiency and can be treated with oral or intravenous iron. Erythropoiesis stimulating agents are effective in raising hemoglobin and may be indicated in certain perioperative settings. Evidence supports the use of restrictive RBC transfusion thresholds and single unit transfusions in most patient populations. Hemostatic therapy, such as tranexamic acid, is generally safe and effective in reducing bleeding. Diagnostic phlebotomy contributes to anemia and should be restricted to tests that are necessary and likely to change management. In conclusion, PBM interventions are generally effective and safe. Prioritization of PBM during the pandemic or a blood shortage may help sustain the blood supply and lead to improved patient outcomes.

Keywords: Patient blood management (PBM); anemia; iron; erythropoiesis-stimulating agent; transfusion

Received: 01 January 2022; Accepted: 14 October 2022; Published online: 16 November 2022.
doi: 10.21037/aob-22-1
View this article at: https://dx.doi.org/10.21037/aob-22-1

Introduction

As of 15 December 2021, coronavirus disease 2019 (COVID-19) afflicted approximately 271 million and killed 5.3 million people globally (1). This pandemic has had a tremendous impact on every aspect of our lives. As hospitals struggled to keep up while managing those affected with COVID-19, many elective surgeries and treatments were indefinitely postponed. At the same time, widespread lockdowns and restrictions have led to a reduction in trauma. Not surprisingly, many regions experienced a surplus of fresh blood components early in the pandemic. However, as the pandemic continued and donations dwindled, the blood supply started to diminish. The situation worsened, with some countries experiencing severe blood shortages, as long-postponed surgeries proceeded, and trauma numbers started to rise (2). In the wake of a potential blood shortage, patient blood management (PBM) emerged as an important mitigation strategy.

World Health Organization (WHO) defines PBM as patient-focused, evidence-based and systematic approach to improve patient outcomes through safe and rational use of blood and blood products (3). PBM is frequently described as having three pillars: diagnosing and treating anemia, minimizing blood loss and optimizing patient-specific physiological tolerance of anemia (4). A recent systematic review reported that PBM programs were associated with significant reductions in red blood cell (RBC) transfusion rates, number of RBCs transfused per patient, duration of hospitalization, morbidity and mortality (4). Evaluation of multi-modal, regional PBM programs, such as those in Western Australia and in Ontario, Canada have demonstrated a reduction in use of blood and blood products, reduced healthcare costs and improved patient outcomes, including reduced mortality, shorter hospital length of stay and lower post-operative infections (5,6).

Recently published guidelines summarized the evidence for various PBM interventions (7). The first PBM pillar, diagnosis and management of anemia, is established by demonstration of harm associated with anemia. For example, in pre-operative setting, anemia was associated with increased 30-day morbidity and mortality (8,9). Even mild anemia [hemoglobin (Hb) <11g/dL] was associated with adverse outcomes in patients undergoing elective surgery (10). Pre-operative anemia was associated with increased risk of blood transfusions (11) and transfusions were independently associated with patient harm (12,13). Therefore, timely diagnosis and management of anemia is critical in improving patient outcomes and reducing unnecessary transfusions. Commonly used interventions include iron supplementation and erythropoiesis stimulating agents (ESA) (7). This review will address the use of these agents in elective major surgery, hematological cancers, elective major gynecological surgery and obstetrics.

The second pillar, minimizing blood loss, encompasses a multitude of interventions, including promoting hemostasis by administration of anti-fibrinolytics and reducing unnecessary diagnostic phlebotomy. Tranexamic acid (TXA) has been shown to be effective when used prophylactically in elective surgery (14) and therapeutically in managing hemorrhage (15,16). TXA was not associated with increased risk of thromboembolism when used in surgery, trauma or post-partum (14-16). However, thrombosis concerns were recently raised by trials in gastrointestinal bleeding (17) and hematological malignancies (18). Hospital acquired anemia (HAA) occurs in about 40% of patients and diagnostic phlebotomy has been identified as a key contributing factor (19). HAA has been shown to be associated with adverse patient outcomes (19). To prevent this complication, laboratory investigations should be restricted to those that directly impact patient management and routine diagnostic phlebotomy should be curtailed.

The third PBM pillar is optimizing tolerance of anemia through transfusions, while accounting for individual patient's physiological reserve and clinical circumstances. Multiple randomized controlled trials (RCTs) in diverse patient populations have demonstrated that restrictive RBC transfusion strategy is non-inferior to liberal strategy (7). Furthermore, administering single unit transfusions is recommended by the majority of published transfusion guidelines (20). However, each individual transfusion decision should take into account the patient's age, co-morbidities, symptoms, and ability to tolerate anemia. There remains clinical equipoise regarding transfusion triggers in patients with acute cardiac ischemia with a large study underway (NCT02981407). There are also concerns that geriatric patients may not be able to tolerate anemia as well as younger patients, and a study to specifically evaluate this population is in progress (21).

The three pillar PBM programs result in better patient outcomes, cost savings for healthcare systems and reduction in unnecessary transfusions. Reduction in unnecessary transfusions is of particular importance when blood is scarce. To help cope with COVID-19 associated blood

shortages, a few groups issued the urgent plea to implement PBM (22,23). Hospitals without established PBM programs rushed to implement PBM, while their observed positive outcomes have ensured that they would remain the standard of care post-pandemic (24). Which PBM interventions are offered at an individual hospital is dependent on local resources and expertise. In many jurisdictions, PBM interventions may be more cost-effective than transfusions. However, PBM may shift the cost of treatment away from hospitals and healthcare systems onto patients; for example, in Canada the cost of RBC transfusion is borne by the healthcare system, whereas the cost of iron or ESA is usually the patient's responsibility. Moreover, as PBM interventions are not risk free, each PBM plan should be personalized to each patient's clinical context and preferences.

Methods

We provided a brief description of our experience managing challenges with blood supply and optimizing transfusion practice through PBM. For the literature review, we have identified relevant publications through searching OVID Medline and EMBASE from January 1, 2020 to April 12, 2022 for MESH terms "blood preservation", "blood donors", "coronaviridae infections", and "patient blood management". We limited the search to English language. After duplicates were removed, there were a total of 1,611 publications. The citations were manually searched by all authors. We selected original articles on PBM in elective major surgery, hematological malignancies and obstetrics. We recognized that successful PBM initiatives should ensure appropriate utilization of platelets, plasma and other components. However, we decided to limit the scope of this review to strategies aimed at reducing RBC transfusions. We identified 7 reviews/editorials on PBM during COVID-19 pandemic (22,23,25-29). We included 22 original publications (24,28,30-49). We supplemented the literature review with publications that we felt to be highly significant to the PBM field.

Local experience during the COVID-19 pandemic

Adapting donor selection criteria

Having a resilient blood system that can withstand widespread crises, such as pandemics, is an important feature of a sustainable blood supply (50). Pandemics are a sustained disaster with significant impact on the supply of labile components (e.g., RBC, platelets, plasma) and non-labile products (e.g., immune globulins) (51,52). severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for COVID-19 illness, is not transmissible by blood. However, COVID-19 had an impact on donor eligibility, donor availability, and availability of trained personnel to collect and produce blood products (2,53,54).

Similar to other blood operators, the operators in Canada (Canadian Blood Services and Héma-Québec) implemented safety protocols at donor sites during the first COVID-19 wave. Worldwide, blood donation drives were cancelled due to fear, logistical challenges, and the time needed to implement safety protocols (2,52,55,56). Enhanced cleaning, social distancing and wellness checkpoints decreased donor throughput. A decline in collections due to both donor attendance and decreased capacity was observed. At Canadian Blood Services, donor centres that accommodated over 70,000 donors per month pre-pandemic, dropped to 54,738 donors per month by May 2020 and slowly recovered to a robust 72,853 donors by December 2020. This corresponded to an initial drop from 200,000 whole blood collections per quarter to a nadir of approximately 160,000 collections and subsequently a rebound to 190,000 collections by the fourth quarter of 2020 (52,57). During the pandemic, blood collection events shifted from mobile to permanent sites. Permanent sites offer fewer logistical challenges related to clinic flow, transportation, and implementation of enhanced safety protocols

Blood operators worldwide sought to adapt their donor assessment policies (52,58-60) and limited close interactions between donors and frontline collection staff (52,61). In Canada, to mitigate a blood shortage, measures to adapt the donor selection criteria were approved by the regulator, Health Canada. Key changes in donor selection criteria implemented in Canada during the pandemic are described in *Table 1*. Reducing the Hb threshold for donation from 12.5 to 12 g/dL for donors registered as female and from 13 to 12.5 g/dL for donors registered as male has led to decreased deferrals for anemia from 3.4% in January 2020 to 1.7% in August 2020, with a significant decrease in deferrals for donors registered as female from 6.1% in January 2020 to 2.7% in August 2020. This allowed an additional 1,000 donors registered as female to donate per month. In October 2020, the Hb criteria reverted to pre-pandemic criteria as no shortages in labile products were experienced in Canada. Similar to changes by the blood

Table 1 The 2020 major changes in key Canadian Blood Services blood donor criteria

Criteria	Pre-pandemic	Changes during pandemic
Hemoglobin level	12.5 g/dL or higher for women	12 g/dL or higher for women
	13 g/dL or higher for men	12.5 g/dL or higher for men
		Applied from 01 July 2020 to 31 October 2020
Travel	12 months if travel to a malaria endemic area	3 months deferral if travel to a malaria endemic area where chemoprophylaxis is recommended (implemented 30 August 2020)
	No COVID-19 specific guidance	A minimum 14-day deferral if travel outside Canada (due to COVID-19 risk; implemented 29 March 2020)
COVID-19 vaccination	n/a	No deferral required
COVID-19	n/a	Exposure to a case without appropriate precautions (PPE), defer 14 days from date of exposure
		Case of asymptomatic COVID-19, defer for 14-days from positive test
		Case of symptomatic COVID-19, defer for 21 days from full recovery

Adapted from Khandelwal A. Impact of COVID-19 on blood donation in Canada [Internet]. Ottawa: Canadian Blood Services; 2021 [cited 2022 06 09]. Available from: https://professionaleducation.blood.ca/en/transfusion/publications/impact-covid-19-blood-donation-canada. COVID-19, coronavirus disease 2019; n/a, not available; PPE, personal protective equipment.

operators in the United States (60), a shorter deferral after travel to malaria endemic regions where chemoprophylaxis is recommended led to a reduction in donor deferral by 3% (from 6.1% to 3.1%), resulting in a gain of approximately 2,000 donations per month.

In summary, donors demonstrated ongoing commitment to blood donation during the pandemic. Blood centres adapted to the necessary public health measures and maintained safe donation sites.

Adapting local PBM practices

Our hospital is located in downtown Toronto, Canada and is a large academic centre with a robust and effective PBM program. It participates in the provincial pre-operative PBM program Ontario Transfusion Coordinators (ONTraC) (62) and our treatment algorithms are available at ontracprogram.com. Our hospital also has Using Blood Wisely Canada designation for compliance with restrictive RBC transfusion strategies (https://usingbloodwisely.ca/). We universally use intravenous (IV) TXA during cardiovascular surgery and arthroplasty intra-operatively (11). Routine laboratory investigations are discouraged through computerized physician order entry and built-in decision support.

During the initial phases of the COVID-19 pandemic, most elective and non-urgent surgeries were paused, however urgent and emergent surgeries were allowed to proceed. At first, in-person preoperative assessments were restricted and subsequently completely replaced by the virtual visits. Since only urgent cases were proceeding, our PBM team was faced with a number of challenges. Many patients were referred only a few days before surgery, without any lead time to identify or manage preoperative anemia. Due to difficulties in securing outpatient blood work appointments, many patients did not have recent Hb or iron studies.

Implementing virtual assessments was also challenging as significant number of our patients has unstable housing, limited access to technology and is non-English speaking. Previous audit revealed that our patients often had limited financial means and no private drug insurance. COVID-19-associated closures further led to widespread unemployment and unprecedented hardships for patients, adding to the inability to afford IV iron and ESA. Due to overall limited access to ambulatory clinics and primary care, many patients were also presenting with new, yet undiagnosed and untreated medical problems or worsened chronic medical conditions. To facilitate timely PBM access, we collaborated with our surgeons and primary care physicians (PCPs) to obtain referrals as early as possible. Additionally, we proactively checked for laboratory results for all patients scheduled for major surgery and mailed requisitions to patients' homes if no recent results were available. To

improve patients' awareness of PBM and to facilitate virtual consultations, we electronically distributed an animated PBM education video. The PBM team triaged newly identified medical issues, facilitated timely referrals to other specialists and sent letters to PCPs. Appointments for IV iron infusions became scarce. Hence, we prioritized patients based on severity of anemia (Hb <10 g/dL), risk of major surgical blood loss and surgery urgency.

We previously observed that women undergoing major joint arthroplasty or cardiac surgery had lower preoperative, nadir and discharge Hb as compared to men (unpublished ONTraC data). Women also had higher transfusion rates: for example, transfusion rate in coronary artery bypass grafting was 39.6 versus 19.3 percent for women and men respectively (unpublished ONTraC data). Hence, given limited resources, we decided to prioritize female patients for PBM interventions. We also increased post-operative IV iron administration, especially in patients with pre-existent iron deficiency anemia (IDA) and insufficient lead time to surgery. We started to administer ESA on the day of surgery, rather than the recommended 1–2 weeks beforehand. We also tried to perform assessments and treatments on the same day, to minimize visits. Occasionally, the PBM program had to be paused, while our nursing staff were redeployed.

In summary, we modified and adapted our PBM practices in order to maintain PBM service during the pandemic. It is too early to tell what impact these challenges may have had on our transfusion rates.

PBM literature review

Elective major non-gynecological surgery

Anemia: diagnosis and management

Preoperative anemia occurs in 30% of the preoperative patient population (63). Iron deficiency is the leading cause of anemia (64) with over two-thirds of anemic pre-operative patients showing evidence of absolute iron deficiency or iron sequestration (65). The 2018 evidence-based guidelines by the International Consensus Conference on Patient Blood Management (ICC-PBM) strongly recommended for detection and management of preoperative anemia in advance of major elective surgery (7). In many jurisdictions, preoperative patients are usually managed through a PBM program or anemia clinic. Referrals to these clinics may originate from surgeons, anaesthesiologists and PCPs. Engaging PCP is particularly important to facilitate early referrals and to ensure subsequent continuity of care (31). To streamline the process during COVID-19 pandemic, one facility switched from formal referral process to directly triaging patients on the high blood loss surgical list (39).

Preoperative patients with iron deficiency, with or without anemia, benefit from iron replacement. ICC-PBM recommended iron supplementation for adults with IDA and undergoing elective surgery with aim to reduce RBC transfusions (7). Although oral iron is cheap and widely available, it is frequently associated with side effects. Oral iron takes months to replete iron stores and the efficacy is hampered by inflammation (66). Moreover, in our local preoperative cohort, we have found oral iron to be generally ineffective (67). IV iron is more expensive, requires a clinic visit and rarely may be associated with infusion reactions. On the other hand, it rapidly restores iron stores and leads to Hb improvement in patients with IDA (68). In the recently published RCT, use of IV iron alone in anemic patients undergoing major abdominal surgery has not shown a reduction in 30-day RBC transfusion or death (69). However, IV iron administration did improve postoperative Hb and reduced hospital readmission (70). In our recent systematic review, use of IV iron and ESA compared to IV iron alone led to reduction in perioperative RBC transfusions (71). A RCT of IV iron in cardiac surgery is ongoing [Intravenous Iron for Treatment of Anaemia Before Cardiac Surgery (ITACS)] [NCT02632760 (72)]. While we await further evidence, it is reasonable to restrict treatment with IV iron to preoperative patients with evidence of IDA. COVID-19 pandemic has led to widespread clinic closures, making it challenging to administer IV iron prior to surgery. Our literature review revealed that some centres adapted by switching to oral iron (39), while others started to offer IV iron post-operatively with aim to improve Hb recovery (40,49). Of note, the efficacy of post-operative IV iron administration has not been established.

Studies have shown that ESA are effective in significantly reducing perioperative RBC transfusions across several surgical indications (73). However, ESA are expensive and there is a lingering concern about their safety. These concerns resulted in the ICC-PBM issuing a conditional recommendation based on weak evidence against their routine use in anemic adults undergoing elective surgery (7). In contrast, for patients with Hb below 13 g/L and undergoing elective major orthopedic surgery, the ICC-PBM guidelines recommended to consider short-acting erythropoietin combined with iron supplementation (7). Of note, a subsequently published systematic review has

found no evidence of increased thromboembolic events when ESA were used in perioperative setting (73). Although it is preferable to administer ESA at least one week before surgery for maximum benefit, epoetin alpha given as a single dose on the day of surgery has also demonstrated benefit in RCTs (12). When faced with inadequate lead time for PBM interventions, administration of IV iron, ESA, vitamin B12 and folate one day before surgery was associated with a reduction in RBC transfusion up to 90 days post-operatively in a RCT (74).

Reducing blood loss

Blood loss in elective surgical patients can be reduced by utilization of surgical sealants, anti-fibrinolytic agents and reduction of diagnostic phlebotomy. Our review revealed one study where use of surgical sealant was associated with cost savings in vascular surgery, due to lower incidence of bleeding complications (43). Although not captured in our review, utilization of anti-fibrinolytic agents, especially TXA, has been shown to improve surgical hemostasis and reduce RBC transfusions across many surgical indications (14,75). Perioperative use of TXA does not appear to increase the risk of thromboembolic complications (14,76). On the other hand, TXA may be associated with excess thrombotic risk in other settings (e.g., gastrointestinal bleeding) and should only be used after a careful evaluation of risks and benefits. TXA is inexpensive, widely available, and the administration during surgery is logistically facile without a need for additional visits.

Post-operatively, blood loss due to diagnostic phlebotomy should be limited to reduce risk of HAA. Again, our review surprisingly did not find any studies on this topic. According to a large multi-centre European study, less than 20% of patients undergoing major orthopedic surgery were anemic before surgery, but over 80% were anemic after surgery (77). Both surgical bleeding and added burden of diagnostic phlebotomy were thought to contribute to anemia in post-operative patients. Blood loss associated with diagnostic phlebotomy can be reduced by eliminating routine bloodwork and instead ordering tests as needed and when likely to change management, adding tests whenever possible rather than ordering repeat phlebotomy, limiting amount of discarded blood prior to sample collection from indwelling catheters, using point of care testing, switching to smaller volume test tubes and reducing miscollections by performing positive patient identification prior to sampling.

RBC transfusion strategy

The most recent evidence-based guideline on RBC transfusion thresholds was by ICC-PBM and published in 2019 (7). Restrictive transfusion strategy (i.e., transfusing when Hb reaches 7–8 g/dL) was recommended for clinically stable patients admitted to critical care units, hemodynamically stable patients with acute gastrointestinal bleeding, patients undergoing cardiac surgery, and patients with hip fracture and cardiovascular disease or risk factors (7). ICC-PBM did not make any recommendations and urged further studies to establish optimum transfusion thresholds for patients with hematologic and oncologic diseases, coronary heart diseases, noncardiac or non-orthopedic surgery, and brain injury (7). This restrictive approach is further supported by the demonstration that 75% of high to moderate quality systematic reviews reported no statistically significant difference in mortality between restrictive and liberal transfusion groups and 25% reported significantly lower mortality for patients assigned to a restrictive transfusion strategy (78). Moreover, the recently updated Cochrane systematic review demonstrated no difference in 30-day mortality (moderate-quality evidence) or any other outcomes assessed (all high-quality evidence) in patients managed with restrictive (Hgb 7–8 g/dL) *vs.* liberal (Hgb 9–10.9 g/dL) RBC transfusion strategies (79). Restrictive transfusion strategy also supports using the least amount of RBCs to reach a specific Hb target. Transfusing single unit at a time in all non-bleeding patients mitigates the risk of transfusion complications and avoids unnecessary RBC use. Our review revealed that in response to COVID-19 pandemic blood supply challenges, a number of hospitals adopted prospective review of RBC orders to facilitate adherence to restrictive transfusion thresholds and single unit transfusions (32). This prospective review and triage of RBC requests could be successfully carried out by PBM nurses or transfusion medicine laboratory technologists with a physician back-up (47,80). During blood shortage, transfusion thresholds are usually progressively restricted to preserve RBC inventory for patients with critical transfusion need. In one study, adoption of ultra-restrictive transfusion protocol (6.0 g/dL) in surgical intensive care unit appeared safe and effective in preserving RBC during crisis (45).

To promote appropriate utilization and avoid unnecessary hold of RBC for elective surgical patients, many hospitals have established maximum surgical blood

ordering schedules (MSBOS). MSBOS is a prediction tool for intraoperative RBC transfusion requirements, based on the institutional retrospective utilization data. During COVID-19 pandemic, hospitals without established MSBOS proceeded with its implementation to reduce the burden on the blood system during the pandemic (37). A more accurate alternative to MSBOS is predictive modeling, which uses machine learning to analyze patient data in electronic health records and develops predictions on blood usage. This approach was successfully utilized by one hospital during COVID-19 pandemic and in the future may potentially lead to personalized transfusion strategies for patients and improve the hospital's RBC inventory management (35) .

Elective major gynecological surgery

Anemia: diagnosis and management

Globally, women have higher prevalence and severity of anemia throughout adulthood, with iron deficiency being the main driver (64). During the COVID-19 pandemic, hospitals were forced to cancel elective surgical procedures and in-person visits. As a result, many patients with benign causes of gynecologic bleeding were unable to receive timely definitive treatment (e.g., intrauterine device insertion, endometrial ablation, myomectomy, hysterectomy) or had surgeries scheduled on short notice leaving little time for effective preoperative PBM. In these times, especially, PBM can and should begin at first presentation. Patients with abnormal uterine bleeding frequently present to the emergency department, where they are at high risk of being transfused for stable IDA without receiving adequate iron replacement (81,82). This presents a key opportunity for intervention by instituting management pathways involving aggressive iron replacement and rapid referrals to outpatient gynecology (83,84). In times of blood shortage, such interventions are critical.

Once patients are identified as a gynecologic surgery candidate they should be screened for anemia. Patients with a Hb <13 g/dL should be identified as anemic and further tested for iron deficiency (85). This is important to identify because preoperative anemia affects 1 in 5 gynecologic surgery patients and is associated with inferior outcomes including 2.4-fold higher odds of 30-day mortality (86). Waiting for the preoperative assessment to initiate these investigations exposes patients to unnecessary delays in starting targeted therapy. This is especially true when pre-operative assessments are done virtually and may not involve repeating blood tests.

The changed landscape of preoperative care in the pandemic highlights the key role primary care providers have in managing these patients as they await surgical assessment and intervention. Pre-operative optimization of these patients involves both aggressive correction of iron deficiency and mitigation of ongoing blood loss. Supplementation with oral iron therapy should be started if iron deficiency is identified. IV iron should be used if oral therapy is not tolerated, there is inadequate response to oral therapy (<0.5 to 1 g/dL increase in Hb per week), Hb is <10 g/dL or there are less than 4 weeks until surgery. The use of ESAs in addition to iron improves hematologic parameters and reduces transfusions in small RCTs involving gynecologic surgery patients (87,88). During the COVID-19 pandemic, many patients were put on surgical waitlists for benign gynecologic surgeries, resulting in little lead time for Hb optimization. In these situations, IV iron and ESAs are particularly useful to rapidly improve anemia perioperatively.

Ongoing vaginal blood loss must also be addressed to avoid transfusion. Menstrual suppression strategies such as gonadotropin releasing hormone agonists are proven to improve anemia and reduce transfusions in patients undergoing surgical intervention for uterine fibroids (89-91). Adjuvant therapy with TXA at the time of hysterectomy or myomectomy also results in reduced blood loss (92-94). In patients with heavy menstrual bleeding or abnormal uterine bleeding with a normal uterus, hormonal therapies and TXA should be considered (95).

RBC transfusion strategy

We are unaware of any dedicated trials to establish a transfusion threshold in the gynecologic surgery patient. A restrictive threshold (Hb <7 g/dL) remains appropriate in this population (7), however in the presence of stable IDA without hemodynamic instability, we advocate consideration of transfusion-sparing strategies such as IV iron and addressing ongoing blood loss in lieu of transfusion (96).

Hematological malignancies

Anemia: diagnosis and management

Anemia occurs in up to 50% to 70% of patients with hematologic malignancies (97-99). Individuals with anemia report decreased quality of life (QOL) (100,101), experience impaired functional status (102,103), and have reduced overall survival (104-106). Given bone marrow

dysfunction, many patients require chronic transfusion support. Patients with myelodysplastic syndrome (MDS), lymphomas, and leukemia undergoing hematopoietic stem cell transplant (HSCT) are amongst the highest users of RBC transfusions (107,108). In addition to the short term-risks of transfusion, repeated exposure to RBCs promotes the development of iron overload states (109), and alloimmunization with red cell antibodies (110). Patients with hematologic malignancy can have combined bone marrow dysfunction, anemia of chronic inflammation and/or IDA (111). Chronic inflammation contributes to impaired production and response to erythropoietin, as well as alterations in iron metabolism (112-114). Iron deficiency results from inadequate iron intake, malabsorption, and increased bleeding risk due to coagulopathy and concurrent thrombocytopenia (115). Immune-mediated and microangiopathic hemolytic anemias are associated with various hematologic cancers (116) and marrow suppression is a direct consequence of many therapeutics (107). Therefore, the etiology of anemia in this population is often multifactorial, necessitating different treatments. The advent of the COVID-19 pandemic significantly disrupted the delivery of care to patients with hematologic malignancies by decreasing patient access, and also limiting the availability of blood supply in some countries (34,41,117-119). Many institutions began to implement or increase the use of PBM practices into oncologic departments during the pandemic to reduce blood utilization and target underlying causes (33,35,36).

Many patients can achieve a similar benefit from the use of alternatives to transfusion and avoid its associated risks. Iron deficiency may be present in upwards of 40% of patients with a diagnosis of cancer (120,121) and represents a major cause of anemia in hematologic malignancies (112). Most iron-associated anemia in hematologic malignancies results from functional iron deficiency, wherein iron stores are adequate but inaccessible due to sequestration (122,123). Inflammatory states result in an abnormal state of hemostasis and upregulation of hepcidin which may cause functional iron deficiency (124,125). While definitions may vary, absolute iron deficiency is frequently defined as ferritin <30 µg/L, and functional iron deficiency as ferritin >30 µg/L with transferrin saturation (TSAT) <20% (125). Ferritin is an acute phase reactant affected by inflammatory states, therefore in situations with significant inflammation such as hematologic malignancies a higher threshold ferritin >100 µg/L can be applied (122,126).

Oral iron replacement is considered a mainstay for the treatment of iron deficiency in asymptomatic or mildly symptomatic patients without evidence of inflammation. In hematologic malignancies, iron absorption is impaired and underutilized due to dysregulation in iron homeostasis, making oral preparations an unsuitable choice (123). A meta-analysis that included hematologic cancers found significantly reduced response rates to oral iron replacement in comparison to IV preparations (127). In addition, oral iron is often poorly tolerated in these patients due to nausea and gastrointestinal side effects. We therefore use oral replacement only for iron deficiency without evidence of inflammation (122).

IV iron replacement remains a possible option that avoids the stated limitations of oral iron therapy. A 2014 RCT demonstrated that IV iron alone was effective in treating anemia (Hb 8.5–10.5 g/dL) in lymphoid malignancies with functional iron deficiency and was well-tolerated (128). Experience in both inpatients and outpatients found use of IV iron efficacious and reduced the use of RBC transfusion or ESA without differences in in-hospital mortality (129,130). We recognize that IV iron therapy requires adequate treatment space and staffing, though it remains favourable in comparison to RBC transfusion, which carries the same requirements. So far, IV iron does not appear to cause disease progression in hematologic malignancies (131). Higher-dose preparations of IV iron are generally preferable to reduce the number of required visits for centres that have access and funding to multiple IV formulations.

ESA are part of many PBM programs but should only be considered in select patients with hematologic malignancies. Guidelines published by the American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH) recommended ESA use only for non-curative chemotherapy-related anemia (Hb <10 g/dL) (132). Similarly, the National Comprehensive Cancer Network (NCCN) suggests there is insufficient evidence to support their use in those receiving chemotherapy with curative intent (133). The ASCO guidelines recommend consideration of ESAs in patients with multiple myeloma only if chemotherapy alone does not improve Hb (134). Although use of ESA in patients with hematologic malignancies may lead to improved QOL and anemia-related symptoms (135,136), there remain major concerns regarding increased risk of thrombosis, disease progression and mortality (135,137-139). Patients with hematologic malignancies have an elevated risk of thrombosis due to underlying illness and chemotherapy (140,141). Use of prophylactic anticoagulation to prevent

the possible thrombotic complications of ESA has only been demonstrated in the subset of patients with multiple myeloma (142). Anemia of inflammation can improve with remission of the underlying malignancy. Depending on the etiology of anemia, use of ESA may also be inappropriate, such as in autoimmune hemolysis associated with chronic lymphocytic leukemia (143). Patients with low-risk MDS represent a specific population that may routinely benefit from ESA (144). Absolute iron deficiency should be treated before using ESA, and supplemental iron therapy may also be used with ESA to improve the Hb response and avoid iron deficiency (132,145,146). A target Hb <12 g/dL is recommended with ESA to mitigate thrombosis risk (132). ESA should be titrated to the lowest effective dose that avoids RBC transfusion, and discontinued if no Hb response is observed within 6 to 8 weeks (132). Patients with hematologic malignancies may require interventional procedures and PBM improves Hb and overall outcomes in this population (24,40,49,147). Hence, a short pre-operative course of both iron and ESA should be considered in this patient population (132,133). Earlier implementation of PBM strategies prior to surgical procedures may allow for a better Hb response.

Reducing blood loss

As with all surgical patients, intra-operative techniques to minimize blood loss, such as use of minimally invasive surgical techniques should be used where possible (148). Prevention and control of blood loss is also important outside of surgical scenarios. Patients with hematologic malignancies are at an increased risk of bleeding due to coagulopathy, thrombocytopenia, and exposure to anticoagulation (149,150). Although TXA is often used to mitigate bleeding in some patient populations, there remain concerns about an increased risk of thrombosis (151). A recent RCT using prophylactic TXA for patients with hematologic malignancies undergoing chemotherapy or HSCT with platelet count less than 30×10^9/L did not reduce rates of WHO grade 2 or higher bleeding but led to an increase in central line occlusions (18). TXA may still be cautiously considered in situations where bleeding predominates (152). Other factors contributing to bleeding risk including thrombocytopenia, coagulopathy, and anticoagulation should be appropriately managed. Diagnostic phlebotomy and blood loss through flushing and discarding of blood from indwelling venous catheters also leads to development of iatrogenic anemia. Hence, specific efforts should be made to reduce unnecessary testing and discard blood volumes.

RBC transfusion strategy

Despite a paucity of studies on Hb thresholds in patients with hematologic malignancies, transfusion strategies had to be re-evaluated during the pandemic and as a result a few institutions endorsed restrictive transfusion strategies (48). In terms of transfusion thresholds, current guidelines support restrictive (Hb <7 g/dL) compared to liberal (Hb <9 g/dL) transfusion strategies (153,154). However, most studies were conducted in the inpatient population with paucity of evidence regarding impact on outpatient functional and QOL outcomes. A multicentre noninferiority RCT comparing a restrictive (Hb <7 g/dL) to a liberal (<9 g/dL) transfusion strategy in 300 patients with hematologic malignancies undergoing HSCT found no difference in transplant-related mortality, length of stay, or QOL but resulted in fewer total RBC units used (155). A 2015 Cochrane analysis of restrictive versus liberal transfusion thresholds in patients with MDS, aplastic anemia and bone marrow failure syndromes found insufficient evidence to detect differences in all-cause mortality, or anemia-associated complications (156). Recently, a panel of MDS experts suggested that a transfusion threshold should be no higher than 7.5 g/dL for the condition (38). A prospective study of 208 outpatients including hematologic malignancies evaluated changes in a 6-minute walking test and fatigue scores post-transfusion. While no transfusion threshold was specified (median pre-transfusion Hb 7.7 g/dL), a Hb >8 g/dL at 1-week post-transfusion was associated with improved scores (157). A higher transfusion threshold has not demonstrated clinically significant benefit. For these patients, we therefore advise consideration of restrictive transfusion thresholds in the absence of other specific indications.

When RBC transfusion is clinically indicated, current practice recommendations favour provision of a single RBC at a time for management of symptomatic anemia (158). However, real-world practice may differ in the outpatient setting when attempting to avoid clinical decompensation at home, or to reduce frequent clinic visits for patients (159). Following the advent of the COVID-19 pandemic, many clinics shifted to a virtual or telemedicine format with goal of fewer in-person visits. With limited ability to physically assess patients, this may have resulted in a trend towards multiple-dose RBC transfusions. However, clinicians should be reassured that single-unit compared to double-dose RBC transfusion for Hb <7 g/dL was not associated

with more frequent outpatient transfusions in patients with hematologic malignancies receiving intensive chemotherapy or HSCT (160). The symptomatic benefit observed in the 2019 prospective study by St Lezin *et al.* was seen after most patients received single-unit RBC transfusion (157). Therefore, single-unit RBC transfusion for inpatient and outpatients should be considered as it appears safe and effective.

Obstetrics

Anemia: diagnosis and management

Anemia occurs in 38% of pregnancies (161), and the majority is attributable to iron deficiency (162). Low Hb levels in early pregnancy are associated with an increased risk of severe maternal morbidity and mortality (163). When severe anemia (Hb <7 g/dL) ensues, the odds of death are twice that of pregnant individuals without severe anemia (164). Babies born to anemic mothers have higher rates of prematurity, fetal intrauterine growth restriction, developmental delay and perinatal mortality (165,166). In times of blood shortage, maternal anemia and postpartum hemorrhage (PPH) persist (167). For many low-income countries, inadequate blood supply is a chronic reality that directly results in maternal death (168). PBM is therefore critical to mitigate the devastating impacts of blood shortage on maternal and fetal outcomes.

Accessing prenatal care is a barrier experienced by many patients throughout the pandemic, though early detection and treatment of iron deficiency and anemia are key to minimizing maternal transfusion (169). A serum ferritin <30 µg/L is diagnostic of iron deficiency in pregnancy (170). Although screening for anemia with a first trimester CBC is the standard of care, recommendations vary on ferritin testing (171). We believe a CBC in isolation is inadequate to identify those at risk of IDA. For example, a Welsh group used a higher Hb threshold in the first and second trimester Hb (11.5 g/dL from 11 g/dL/10.5 g/dL) to dictate routine iron supplementation in patients scheduled for elective Cesarian sections in an effort to conserve blood during the COVID-19 pandemic (44). This small study of 100 pregnant patients did not see a reduction in term or postnatal anemia, or IV iron requirements in the third trimester and authors speculated that lack of routine first trimester ferritin testing may have limited their ability to identify and treat iron deficiency early, and accurately target therapy to those in need. Given the huge burden of iron deficiency in pregnancy and the strong association with transfusion at delivery (172), we advocate screening all patients with a serum ferritin early in pregnancy, especially in times of potential blood shortage.

In an effort to avoid the contact with the healthcare system required for IV iron and transfusions, a British group published their hospital's strategies to address evidence of iron deficiency early in pregnancy (173). These include universal screening for iron deficiency in pregnancy, oral iron supplementation for those with Hb <12 g/dL or ferritin <30 µg/L and delaying repeat laboratory assessment to 28 weeks unless the index Hb was <10 g/dL. The authors acknowledge that despite the need to minimize hospital visits, early escalation to IV iron is warranted when oral iron is not tolerated, ineffective, IDA is severe (Hb <7 g/dL) or there is insufficient time prior to delivery. We agree with these strategies, however we advocate for more liberal use of oral and IV iron. Since iron deficiency is rampant in pregnancy even in high-resource countries, we believe any pregnant patient with a ferritin <50 µg/L warrants initiation of oral iron supplementation to meet the high iron demands of pregnancy (174). Further, patients with documented iron deficiency or anemia require repeat laboratory assessment with appropriate escalation of therapy if needed. In those with moderate or severe IDA (Hb <9 g/dL and ferritin <30 µg/L), IDA beyond 34 weeks gestation, or intolerance or lack of response to oral iron (<1 g/dL increase in Hb within 2 weeks), IV iron should be considered (72,175). We acknowledge the cost associated with IV iron is significant relative to oral iron; however, it remains less costly than a unit of RBCs (176,177). Unfortunately, the pandemic presented a significant barrier to delivering IV iron due to fewer available infusion spots. Use of more efficient IV iron preparations (e.g., 1,000 mg iron isomaltoside *vs.* 300 mg iron sucrose) in pregnant individuals would maximize infusion availability, and emerging data on high dose IV iron in pregnancy has been reassuring (46,178). Though we agree with Stewart *et al.* that repeated laboratory assessments may present unnecessary patient exposures (173), we still believe it is critical to reassess hematologic and iron indices to ensure adequate response to therapy and allow for timely escalation if needed. Lastly, multiple studies have established the effectiveness of clinical pathways designed to target iron deficiency in pregnancy (174,179). During the COVID-19 pandemic, the implementation of routine ferritin testing at booking, oral and IV iron pathways in pregnancy at one institution increased the mean Hb of patients at term with a non-significant decrease in the rate of anemia at delivery (30). Patient and provider engagement

using phone applications and care pathways may represent an important strategy to minimize blood product use in the era of virtual care.

Reducing blood loss

At the time of delivery, minimizing blood loss is key to reducing our dependence on blood components. While there is likely no role for prophylactic use of TXA in routine vaginal deliveries (180), TXA use should be considered in patients at high risk of PPH (14,181,182). TXA also reduces blood loss in elective Caesarean sections, though larger studies are lacking (183,184). When PPH occurs, early identification and treatment are paramount to minimizing transfusion. The WOMAN trial established TXA as a pillar in the management of PPH, documenting a reduction in deaths due to bleeding in patients, especially when TXA is given early (16). Other important strategies include early replacement of low fibrinogen, uterotonics and surgical strategies (182). Implementation of routine intraoperative cell salvage for all lower segment cesarian sections performed at an institution in Australia during the COVID-19 pandemic successfully decreased postpartum anemia and reduced postpartum IV iron infusions (42), and this may represent an effective augmentation to blood-loss reduction techniques in times of potential shortage.

RBC transfusion strategy

Currently, there are no RCTs to specifically guide transfusion thresholds in pregnancy. In the obstetrical population, the risk of alloimmunization and subsequent hemolytic disease of the fetus and newborn should be specifically considered when weighing the risks and benefits from, transfusion. Transfusion should be considered for fetal concerns or significant maternal symptoms rather than based on a strict Hb threshold (175). In an obstetric patient with bleeding, transfusion can save lives. However, if required in the non-bleeding patient, single unit transfusions are advised (175). The WOMB trial established restrictive transfusion (Hb <4.8 g/dL) as a reasonable strategy for patients with Hb values between 4.8 and 7.9 g/dL, 12 to 24 hours postpartum without severe symptoms or comorbidities (185). In times of blood shortage, this provides comfort that many postpartum patients can tolerate significant anemia without requiring RBC transfusion. In these scenarios, IV iron should be used liberally to optimize postpartum recovery (72).

Conclusions

During the COVID-19 pandemic, many countries experienced shortages in the blood supply. In Canada, although the collections were significantly impacted, the parallel drop in demand and increased recruitment efforts as well as modified donor screening criteria led to maintenance of the labile blood component supply. Previous studies have shown that PBM reduces blood utilization and leads to better patient outcomes. In the times of blood shortage, its implementation becomes imperative to reduce the demand for blood. Although the data are not yet available, adoption of PBM may have contributed to the maintenance of our blood supply. Previous studies have demonstrated that perioperative use of iron, ESA and TXA led to substantial reduction in transfusion rate as well as RBC units transfused. These interventions are generally safe and should be considered where appropriate and after careful review of patients' co-morbidities and preferences. In hematologic malignancies, limited evidence demonstrated elevated thrombosis risk with TXA and ESA; hence, these interventions should be used with caution, after carefully weighing risks and benefits on a case-by-case basis. In pregnancy, importance of early IDA diagnosis and treatment as well as use of TXA for PPH is well established.

Our literature review identified the following practices in response to the pandemic: more wide-spread adoption of PBM, including in patients with hematologic malignancies; changes in PBM referral process; shift to universal screening for IDA in obstetrical patients; type and timing of iron administration in elective surgical patients; increased cell salvage utilization in patients undergoing C-section; and introduction of sealants in vascular surgery. On the other hand, our review did not identify any studies on TXA or restrictive diagnostic phlebotomy. Restrictive RBC transfusion strategy has been previously shown to be non-inferior for many patient populations. Not surprisingly, adherence to restrictive RBC transfusion thresholds was a common theme in our literature review.

COVID-19 has impacted on how we practice PBM locally. We successfully adapted clinical PBM pathways to proactively screen patient laboratory results and facilitate appropriate referrals. We shifted to providing ESA on the day of surgery and adopted more liberal post-operative in-hospital IV iron administration to facilitate Hb recovery in patients with IDA. The pre-pandemic implementation of universal intra-operative TXA in arthroplasty, adoption

of restrictive RBC transfusion strategy and restrictive diagnostic phlebotomy have also likely contributed to a reduction in blood utilization.

Acknowledgments

We gratefully acknowledge Amy Moorehead for assistance with organizing references and Sabine Calleja for assistance with literature search.
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Arwa Z. Al-Riyami) for the series "Blood Transfusion during the COVID-19 Pandemic" published in *Annals of Blood*. The article has undergone external peer review.

Peer Review File: Available at https://aob.amegroups.com/article/view/10.21037/aob-22-1/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://aob.amegroups.com/article/view/10.21037/aob-22-1/coif). The series "Blood Transfusion during the COVID-19 Pandemic" was commissioned by the editorial office without any funding or sponsorship. AK is the employee of the Canadian Blood Services. KP received honoraria for participation in advisory board from Pfizer. BT and HV received the Canadian Blood Services Elianna Saidenberg Transfusion Medicine Traineeship Award. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. WHO. WHO Coronavirus (COVID-19) Dashboard. 2021. Available online: https://covid19.who.int/
2. Al-Riyami AZ, Burnouf T, Wood EM, et al. International Society of Blood Transfusion survey of experiences of blood banks and transfusion services during the COVID-19 pandemic. Vox Sang 2022;117:822-30.
3. WHO. Global Forum for Blood Safety: Patient Blood Management. 14-15 March 2011; United Arab Emirates: WHO; 2011.
4. Althoff FC, Neb H, Herrmann E, et al. Multimodal Patient Blood Management Program Based on a Three-pillar Strategy: A Systematic Review and Meta-analysis. Ann Surg 2019;269:794-804.
5. Leahy MF, Hofmann A, Towler S, et al. Improved outcomes and reduced costs associated with a health-system-wide patient blood management program: a retrospective observational study in four major adult tertiary-care hospitals. Transfusion 2017;57:1347-58.
6. Yanagawa B, Rocha RV, Mazine A, et al. Hemoglobin Optimization for Coronary Bypass: A 10-Year Canadian Multicenter Experience. Ann Thorac Surg 2019;107:711-7.
7. Mueller MM, Van Remoortel H, Meybohm P, et al. Patient Blood Management: Recommendations From the 2018 Frankfurt Consensus Conference. JAMA 2019;321:983-97.
8. Musallam KM, Tamim HM, Richards T, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. Lancet 2011;378:1396-407.
9. Fowler AJ, Ahmad T, Phull MK, et al. Meta-analysis of the association between preoperative anaemia and mortality after surgery. Br J Surg 2015;102:1314-24.
10. Smilowitz NR, Oberweis BS, Nukala S, et al. Association Between Anemia, Bleeding, and Transfusion with Long-term Mortality Following Noncardiac Surgery. Am J Med 2016;129:315-23.e2.
11. LaPar DJ, Hawkins RB, McMurry TL, et al. Preoperative anemia versus blood transfusion: Which is the culprit for worse outcomes in cardiac surgery? J Thorac Cardiovasc Surg 2018;156:66-74.e2.
12. Pavenski K. Update on patient blood management 2019. ISBT Science Series 2020;15:126-30.
13. Wedel C, Møller CM, Budtz-Lilly J, et al. Red blood cell transfusion associated with increased morbidity and mortality in patients undergoing elective open abdominal aortic aneurysm repair. PLoS One 2019;14:e0219263.

14. Ker K, Edwards P, Perel P, et al. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. BMJ 2012;344:e3054.
15. CRASH-2 trial collaborators; Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet 2010;376:23-32.
16. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet 2017;389:2105-16.
17. HALT-IT Trial Collaborators. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial. Lancet 2020;395:1927-36.
18. Gernsheimer TB, Brown SP, Triulzi DJ, et al. Effects of Tranexamic Acid Prophylaxis on Bleeding Outcomes in Hematologic Malignancy: The a-TREAT Trial. Blood 2020;136:1-2.
19. Shander A, Corwin HL. A Narrative Review on Hospital-Acquired Anemia: Keeping Blood where It Belongs. Transfus Med Rev 2020;34:195-9.
20. Shih AW, Liu A, Elsharawi R, et al. Systematic reviews of guidelines and studies for single versus multiple unit transfusion strategies. Transfusion 2018;58:2841-60.
21. Meybohm P, Lindau S, Treskatsch S, et al. Liberal transfusion strategy to prevent mortality and anaemia-associated, ischaemic events in elderly non-cardiac surgical patients - the study design of the LIBERAL-Trial. Trials 2019;20:101.
22. Shander A, Goobie SM, Warner MA, et al. Essential Role of Patient Blood Management in a Pandemic: A Call for Action. Anesth Analg 2020;131:74-85.
23. Schlesinger T, Kranke P, Zacharowski K, et al. Coronavirus Threatens Blood Supply: Patient Blood Management Now! Ann Surg 2020;272:e74.
24. Doukas P, Yfanti M, Doukas E, et al. Bloodless medicine and surgery following PBM principles an internal medicine department's experience in Athens medical center-an update. Anesth Analg 2021;133:52.
25. Baron DM, Franchini M, Goobie SM, et al. Patient blood management during the COVID-19 pandemic: a narrative review. Anaesthesia 2020;75:1105-13.
26. Chegini A. Evaluating the Importance of Patient Blood Management During COVID-19 Pandemic. Anesth Pain Med 2021;11:e112910.
27. Hands K, Taylor C, Kotzé A, et al. Preoperative patient blood management during the SARS-CoV-2 pandemic. Br J Haematol 2021;193:1087-92.
28. Rambiritch V, Verburgh E, Louw VJ. Patient blood management and blood conservation - Complimentary concepts and solutions for blood establishments and clinical services in South Africa and beyond. Transfus Apher Sci 2021;60:103207.
29. Ross B, Clarke L, Freeman P. Patient blood management - a review of accepted practice; with a focus on optimising patient outcomes during the current COVID-19 pandemic. Pathology 2021;53:S14-5.
30. Baban N, Oliver C, James KE, et al. P.78 Tackling antenatal anaemia: a quality improvement project. Int J Obstet Anesth 2021;46:103076.
31. Barrett CL. Primary healthcare practitioners and patient blood management in Africa in the time of coronavirus disease 2019: Safeguarding the blood supply. Afr J Prim Health Care Fam Med 2020;12:e1-3.
32. Gammon R, Counts K, Yordanov B, et al. Patient blood management during a pandemic- the patient wins. Anesthesia and Analgesia 2020;131:43-4.
33. Hofmann A, Aapro M, Fedorova TA, et al. Patient blood management in oncology in the Russian Federation: Resolution to improve oncology care. J Cancer Policy 2022;31:100315.
34. Mastrangelo M, Muir S, Marturano E. Ensuring the Safety of Hospitalized Oncology Patients During a Pandemic. J Adv Pract Oncol 2021;12:535-9.
35. Rivas S, Cox H, Mescher B, et al. Predictive modeling to create a proactive approach to patient blood management in the oncology population. J Clin Oncol 2021;39:abstr 332.
36. Sharafeldin N, Bates B, Vachhani P. How the COVID-19 Pandemic Reshaped the Management of Leukemia and Affected Patient Outcomes. Curr Treat Options Oncol 2022;23:688-702.
37. Tan PP, Abdul Rahman J, Mat Noh S, et al. Implementation of maximum surgical blood ordering schedule in a tertiary hospital in Malaysia during COVID-19 pandemic. Transfus Apher Sci 2021;60:103280.
38. Tanasijevic AM, Revette A, Klepin HD, et al. Consensus minimum hemoglobin level above which patients with myelodysplastic syndromes can safely forgo transfusions. Leuk Lymphoma 2020;61:2900-4.
39. Tolich D, Auron M, McCoy K, et al. Blood management

during the COVID-19 pandemic. Cleve Clin J Med 2020. doi: 10.3949/ccjm.87a.ccc053.
40. Raman VV, Aggarwala R, Dormido C, et al. Using intravenous iron to treat anaemia following major cancer surgery: results from one specialist centre. Anesth Analg 2021;133:1333.
41. Xiao H, Luo Y, Shi J, et al. How Do We Manage Hematopoietic Cell Transplant during the SARS-CoV-2 Pandemic? Acta Haematol 2021;144:500-7.
42. Fox T, Timpani E, Licis A, et al. The impact of routine intraoperative cell salvage use for lower segment cesarean section during the Covid-19 Pandemic. Anesth Analg 2021;193:1052-3.
43. Gresse S, Ramirez M, Martinez N, et al. PCV41 Economic inpact of surgical sealant use verse standard of care in patients undergoing aortic repair and reconstruction: a Brazilian cost-consequence analysis. Value in Health 2020;23:S97-8.
44. Jesty R, Bennetton Z, Morgan E. Service evaluation of the impact of COVID- 19 antenatal haemoglobin threshold on rates of peripartum anaemia in women having elective caesarean sections. Anaesthesia 2022;77:22.
45. Kheirbek T, Martin T, Wakeley M, et al. Safety of ultra-restrictive transfusion protocol as a blood preservation strategy during crisis. Critical Care Medicine 2021;49:206.
46. Parnell L, Barnes C, Marsden P. Efficacy &acceptability of a single dose Monofer infusion to treat antenatal anaemia. BJOG 2021;128:109.
47. Sromovsky MA, Marks M, De Ridder G, et al. Effectiveness of a real-time, nurse driven red blood cell transfusion order review in reducing red blood cell transfusions. Transfusion 2021;61:187A.
48. Massoud M, El Riachy C. MPN-182: Transfusion in Hematology Patients During the COVID19 Pandemic: A Systematic Review. Clinical Lymphoma Myeloma and Leukemia 2020;20:S331.
49. Patel J, Joshi K, Sahni A, et al. Moving into the 'iron age': Perioperative Anaemia service at a tertiary oncology centre. Anesth Analg 2021;133:9-10.
50. Mulcahy AW, Kapinos KA, Briscombe B, et al. Toward a Sustainable Blood Supply in the United States: An Analysis of the Current System and Alternatives for the Future. Santa Monica, CA: RAND Corporation; 2016.
51. Fredrick J, Berger JJ, Menitove JE. Strategic issues currently facing the US blood system. Transfusion 2020;60:1093-6.
52. Prokopchuk-Gauk O, Petraszko T, Nahirniak S, et al. Blood shortages planning in Canada: The National Emergency Blood Management Committee experience during the first 6 months of the COVID-19 pandemic. Transfusion 2021;61:3258-66.
53. Yazer MH, Jackson B, Pagano M, et al. Vox Sanguinis International Forum on transfusion services' response to COVID-19: Summary. Vox Sang 2020;115:536-42.
54. Stanworth SJ, New HV, Apelseth TO, et al. Effects of the COVID-19 pandemic on supply and use of blood for transfusion. Lancet Haematol 2020;7:e756-64.
55. Silva-Malta MCF, Rodrigues DOW, Chaves DG, et al. Impact of COVID-19 in the attendance of blood donors and production on a Brazilian Blood Centres. Transfus Med 2021;31:206-12.
56. Tezcan B. Impact of COVID-19 Pandemic on the Management of Blood Supply and Demand in Turkey. Anestezi Dergisi 2021;29:172-7.
57. Sher G. Open Board Meeting - 2020-2021: Mid-Year Review. Canadian Blood Services, Blood.ca. 2020. Available online: https://www.blood.ca/sites/default/files/CEO_Mid_Year_Review_Q1-Q2_2020-2021_-_OBM_Presentation.pdf
58. Khandelwal A. Impact of COVID-19 on blood donation in Canada. Canadian Blood Services, Ottawa. 2021. Available online: https://professionaleducation.blood.ca/en/transfusion/publications/impact-covid-19-blood-donation-canada. 2022.
59. Vassallo RR, Bravo MD, Kamel H. Pandemic blood donor demographics - Do changes impact blood safety? Transfusion 2021;61:1389-93.
60. Zarpak R, Pina B, Bahara B, et al. Impact of the April 2020 FDA blood donor eligibility changes on a hospital-based donor center. Transfusion 2021;61:49A-50A.
61. Barnes LS, Al-Riyami AZ, Ipe TS, et al. COVID-19 and the impact on blood availability and transfusion practices in low- and middle-income countries. Transfusion 2022;62:336-45.
62. Pavenski K, Howell A, Mazer CD, et al. ONTraC: A 20-Year History of a Successfully Coordinated Provincewide Patient Blood Management Program: Lessons Learned and Goals Achieved. Anesth Analg 2022;135:448-58.
63. Fowler AJ, Ahmad T, Abbott TEF, et al. Association of preoperative anaemia with postoperative morbidity and mortality: an observational cohort study in low-, middle-, and high-income countries. Br J Anaesth 2018;121:1227-35.
64. Kassebaum NJ, Jasrasaria R, Naghavi M, et al. A systematic analysis of global anemia burden from 1990 to 2010. Blood 2014;123:615-24.

65. Muñoz M, Laso-Morales MJ, Gómez-Ramírez S, et al. Pre-operative haemoglobin levels and iron status in a large multicentre cohort of patients undergoing major elective surgery. Anaesthesia 2017;72:826-34.
66. DeLoughery TG. Safety of Oral and Intravenous Iron. Acta Haematol 2019;142:8-12.
67. Lin Y, Howell A, Vernich L, et al. Oral iron versus intravenous iron for preoperative anemia management: the ONTraC experience. Transfusion Medicine Reviews 2020;34:64.
68. Derman R, Roman E, Modiano MR, et al. A randomized trial of iron isomaltoside versus iron sucrose in patients with iron deficiency anemia. Am J Hematol 2017;92:286-91.
69. Litton E, Xiao J, Ho KM. Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomised clinical trials. BMJ 2013;347:f4822.
70. Richards T, Baikady RR, Clevenger B, et al. Preoperative intravenous iron to treat anaemia before major abdominal surgery (PREVENTT): a randomised, double-blind, controlled trial. Lancet 2020;396:1353-61.
71. Kei T, Mistry N, Curley G, et al. Efficacy and safety of erythropoietin and iron therapy to reduce red blood cell transfusion in surgical patients: a systematic review and meta-analysis. Can J Anaesth 2019;66:716-31.
72. Surbek D, Vial Y, Girard T, et al. Patient blood management (PBM) in pregnancy and childbirth: literature review and expert opinion. Arch Gynecol Obstet 2020;301:627-41.
73. Cho BC, Serini J, Zorrilla-Vaca A, et al. Impact of Preoperative Erythropoietin on Allogeneic Blood Transfusions in Surgical Patients: Results From a Systematic Review and Meta-analysis. Anesth Analg 2019;128:981-92.
74. Spahn DR, Schoenrath F, Spahn GH, et al. Effect of ultra-short-term treatment of patients with iron deficiency or anaemia undergoing cardiac surgery: a prospective randomised trial. Lancet 2019;393:2201-12.
75. Gandhi R, Evans HM, Mahomed SR, et al. Tranexamic acid and the reduction of blood loss in total knee and hip arthroplasty: a meta-analysis. BMC Res Notes 2013;6:184.
76. Franchini M, Mengoli C, Marietta M, et al. Safety of intravenous tranexamic acid in patients undergoing majororthopaedic surgery: a meta-analysis of randomised controlled trials. Blood Transfus 2018;16:36-43.
77. Lasocki S, Krauspe R, von Heymann C, et al. PREPARE: the prevalence of perioperative anaemia and need for patient blood management in elective orthopaedic surgery: a multicentre, observational study. Eur J Anaesthesiol 2015;32:160-7.
78. Trentino KM, Farmer SL, Leahy MF, et al. Systematic reviews and meta-analyses comparing mortality in restrictive and liberal haemoglobin thresholds for red cell transfusion: an overview of systematic reviews. BMC Med 2020;18:154.
79. Carson JL, Stanworth SJ, Dennis JA, et al. Transfusion thresholds for guiding red blood cell transfusion. Cochrane Database Syst Rev 2021;12:CD002042.
80. Kron AT, Collins A, Cserti-Gazdewich C, et al. A prospective multi-faceted interventional study of blood bank technologist screening of red blood cell transfusion orders: The START study. Transfusion 2021;61:410-22.
81. Boone S, Peacock WF, Ordonez E, et al. Management of Nonpregnant Women Presenting to the Emergency Department With Iron Deficiency Anemia Caused by Uterine Blood Loss: A Retrospective Cohort Study. J Emerg Med 2020;59:348-56.
82. Spradbrow J, Lin Y, Shelton D, et al. Iron deficiency anemia in the emergency department: over-utilization of red blood cell transfusion and infrequent use of iron supplementation. CJEM 2017;19:167-74.
83. Beverina I, Razionale G, Ranzini M, et al. Early intravenous iron administration in the Emergency Department reduces red blood cell unit transfusion, hospitalisation, re-transfusion, length of stay and costs. Blood Transfus 2020;18:106-16.
84. Khadadah F, Callum J, Shelton D, et al. Improving quality of care for patients with iron deficiency anemia presenting to the emergency department. Transfusion 2018;58:1902-8.
85. Butcher A, Richards T, Stanworth SJ, et al. Diagnostic criteria for pre-operative anaemia-time to end sex discrimination. Anaesthesia 2017;72:811-4.
86. Richards T, Musallam KM, Nassif J, et al. Impact of Preoperative Anaemia and Blood Transfusion on Postoperative Outcomes in Gynaecological Surgery. PLoS One 2015;10:e0130861.
87. Dousias V, Paraskevaidis E, Dalkalitsis N, et al. Recombinant human erythropoietin in mildly anemic women before total hysterectomy. Clin Exp Obstet Gynecol 2003;30:235-8.
88. Larson B, Bremme K, Clyne N, et al. Preoperative treatment of anemic women with epoetin beta. Acta Obstet Gynecol Scand 2001;80:559-62.
89. Lethaby A, Puscasiu L, Vollenhoven B. Preoperative

medical therapy before surgery for uterine fibroids. Cochrane Database Syst Rev 2017;11:CD000547.
90. de Milliano I, Twisk M, Ket JC, et al. Pre-treatment with GnRHa or ulipristal acetate prior to laparoscopic and laparotomic myomectomy: A systematic review and meta-analysis. PLoS One 2017;12:e0186158.
91. Laberge PY, Murji A, Vilos GA, et al. Guideline No. 389-Medical Management of Symptomatic Uterine Leiomyomas - An Addendum. J Obstet Gynaecol Can 2019;41:1521-4.
92. Klebanoff JS, Marfori CQ, Ingraham CF, et al. Applications of Tranexamic acid in benign gynecology. Curr Opin Obstet Gynecol 2019;31:235-9.
93. Topsoee MF, Bergholt T, Ravn P, et al. Anti-hemorrhagic effect of prophylactic tranexamic acid in benign hysterectomy-a double-blinded randomized placebo-controlled trial. Am J Obstet Gynecol 2016;215:72.e1-8.
94. Shaaban MM, Ahmed MR, Farhan RE, et al. Efficacy of Tranexamic Acid on Myomectomy-Associated Blood Loss in Patients With Multiple Myomas: A Randomized Controlled Clinical Trial. Reprod Sci 2016;23:908-12.
95. Bradley LD, Gueye NA. The medical management of abnormal uterine bleeding in reproductive-aged women. Am J Obstet Gynecol 2016;214:31-44.
96. Callum JL, Waters JH, Shaz BH, et al. The AABB recommendations for the Choosing Wisely campaign of the American Board of Internal Medicine. Transfusion 2014;54:2344-52.
97. Schwartz RN. Anemia in patients with cancer: incidence, causes, impact, management, and use of treatment guidelines and protocols. Am J Health Syst Pharm 2007;64:S5-13; quiz S28-30.
98. Ludwig H, Van Belle S, Barrett-Lee P, et al. The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. Eur J Cancer 2004;40:2293-306.
99. Birgegård G, Gascón P, Ludwig H. Evaluation of anaemia in patients with multiple myeloma and lymphoma: findings of the European CANCER ANAEMIA SURVEY. Eur J Haematol 2006;77:378-86.
100. Cella D. Factors influencing quality of life in cancer patients: anemia and fatigue. Semin Oncol 1998;25:43-6.
101. Lind M, Vernon C, Cruickshank D, et al. The level of haemoglobin in anaemic cancer patients correlates positively with quality of life. Br J Cancer 2002;86:1243-9.
102. Ludwig H, Strasser K. Symptomatology of anemia. Semin Oncol 2001;28:7-14.
103. Luciani A, Jacobsen PB, Extermann M, et al. The impact of fatigue and anemia on functional status in older cancer patients treated with chemotherapy. J Geriatr Oncol 2012;3:182-8.
104. Caro JJ, Salas M, Ward A, et al. Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. Cancer 2001;91:2214-21.
105. Shander A, Knight K, Thurer R, et al. Prevalence and outcomes of anemia in surgery: a systematic review of the literature. Am J Med 2004;116 Suppl 7A:58S-69S.
106. Littlewood T, Mandelli F. The effects of anemia in hematologic malignancies: more than a symptom. Semin Oncol 2002;29:40-4.
107. Tas F, Eralp Y, Basaran M, et al. Anemia in oncology practice: relation to diseases and their therapies. Am J Clin Oncol 2002;25:371-9.
108. Zhao J, Rydén J, Wikman A, et al. Blood use in hematologic malignancies: a nationwide overview in Sweden between 2000 and 2010. Transfusion 2018;58:390-401.
109. Gattermann N. Iron overload in myelodysplastic syndromes (MDS). Int J Hematol 2018;107:55-63.
110. Singhal D, Kutyna MM, Chhetri R, et al. Red cell alloimmunization is associated with development of autoantibodies and increased red cell transfusion requirements in myelodysplastic syndrome. Haematologica 2017;102:2021-9.
111. Gaspar BL, Sharma P, Das R. Anemia in malignancies: pathogenetic and diagnostic considerations. Hematology 2015;20:18-25.
112. Adamson JW. The anemia of inflammation/malignancy: mechanisms and management. Hematology Am Soc Hematol Educ Program 2008;159-65.
113. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med 2005;352:1011-23.
114. Fraenkel PG. Understanding anemia of chronic disease. Hematology Am Soc Hematol Educ Program 2015;2015:14-8.
115. Warsch S, Byrnes J. Emerging causes of iron deficiency anemia refractory to oral iron supplementation. World J Gastrointest Pharmacol Ther 2013;4:49-53.
116. Barcellini W, Giannotta JA, Fattizzo B. Autoimmune Complications in Hematologic Neoplasms. Cancers (Basel) 2021;13:1532.
117. Vijenthira A, Gong IY, Fox TA, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. Blood 2020;136:2881-92.

118. Jazieh AR, Akbulut H, Curigliano G, et al. Impact of the COVID-19 Pandemic on Cancer Care: A Global Collaborative Study. JCO Glob Oncol 2020;6:1428-38.
119. Merrell KW, DeWees TA, Osei-Bonsu EB, et al. COVID-19 in Sub-Saharan Africa: A Multi-Institutional Survey of the Impact of the Global Pandemic on Cancer Care Resources. Int J Radiat Oncol Biol Phys 2021;111:e349-50.
120. Ludwig H, Müldür E, Endler G, et al. Prevalence of iron deficiency across different tumors and its association with poor performance status, disease status and anemia. Ann Oncol 2013;24:1886-92.
121. Hedenus M, Birgegård G, Näsman P, et al. Addition of intravenous iron to epoetin beta increases hemoglobin response and decreases epoetin dose requirement in anemic patients with lymphoproliferative malignancies: a randomized multicenter study. Leukemia 2007;21:627-32. Erratum in: Leukemia. 2008 Feb;22(2):462.
122. Aapro M, Beguin Y, Bokemeyer C, et al. Management of anaemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2018;29:iv96-iv110.
123. Wessling-Resnick M. Iron homeostasis and the inflammatory response. Annu Rev Nutr 2010;30:105-22.
124. Naoum FA. Iron deficiency in cancer patients. Rev Bras Hematol Hemoter 2016;38:325-30.
125. Busti F, Marchi G, Ugolini S, et al. Anemia and Iron Deficiency in Cancer Patients: Role of Iron Replacement Therapy. Pharmaceuticals (Basel) 2018;11:94.
126. Ludwig H, Evstatiev R, Kornek G, et al. Iron metabolism and iron supplementation in cancer patients. Wien Klin Wochenschr 2015;127:907-19.
127. Petrelli F, Borgonovo K, Cabiddu M, et al. Addition of iron to erythropoiesis-stimulating agents in cancer patients: a meta-analysis of randomized trials. J Cancer Res Clin Oncol 2012;138:179-87.
128. Hedenus M, Karlsson T, Ludwig H, et al. Intravenous iron alone resolves anemia in patients with functional iron deficiency and lymphoid malignancies undergoing chemotherapy. Med Oncol 2014;31:302.
129. Toledano A, Luporsi E, Morere JF, et al. Clinical use of ferric carboxymaltose in patients with solid tumours or haematological malignancies in France. Support Care Cancer 2016;24:67-75.
130. Gross I, Trentino KM, Andreescu A, et al. Impact of a Patient Blood Management Program and an Outpatient Anemia Management Protocol on Red Cell Transfusions in Oncology Inpatients and Outpatients. Oncologist 2016;21:327-32.
131. Jaspers A, Baron F, Maertens J, et al. Long-term safety follow-up of a randomized trial of darbepoetin alpha and intravenous iron following autologous hematopoietic cell transplantation. Am J Hematol 2015;90:E133-4.
132. Bohlius J, Bohlke K, Castelli R, et al. Management of Cancer-Associated Anemia With Erythropoiesis-Stimulating Agents: ASCO/ASH Clinical Practice Guideline Update. J Clin Oncol 2019;37:1336-51.
133. NCCN. NCCN Guidelines - Hematopoietic Growth Factors. National Comprehensive Cancer Network. 2021. Available online: https://www.nccn.org/guidelines/guidelines-detail?category=3&id=1493
134. Mikhael J, Ismaila N, Cheung MC, et al. Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline. J Clin Oncol 2019;37:1228-63.
135. Tonelli M, Hemmelgarn B, Reiman T, et al. Benefits and harms of erythropoiesis-stimulating agents for anemia related to cancer: a meta-analysis. CMAJ 2009;180:E62-71.
136. Li X, Yan Z, Kong D, et al. Erythropoiesis-stimulating agents in the management of cancer patients with anemia: a meta-analysis. Chin J Cancer Res 2014;26:268-76.
137. Gao S, Ma JJ, Lu C. Venous thromboembolism risk and erythropoiesis-stimulating agents for the treatment of cancer-associated anemia: a meta-analysis. Tumour Biol 2014;35:603-13.
138. Bennett CL, Silver SM, Djulbegovic B, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. JAMA 2008;299:914-24.
139. Tonia T, Mettler A, Robert N, et al. Erythropoietin or darbepoetin for patients with cancer. Cochrane Database Syst Rev 2012;12:CD003407.
140. Blom JW, Vanderschoot JP, Oostindiër MJ, et al. Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study. J Thromb Haemost 2006;4:529-35.
141. Kekre N, Connors JM. Venous thromboembolism incidence in hematologic malignancies. Blood Rev 2019;33:24-32.
142. Anaissie EJ, Coleman EA, Goodwin JA, et al. Prophylactic recombinant erythropoietin therapy and thalidomide are predictors of venous thromboembolism in patients with multiple myeloma: limited effectiveness of thromboprophylaxis. Cancer 2012;118:549-57.
143. Dearden C. Disease-specific complications of chronic

lymphocytic leukemia. Hematology Am Soc Hematol Educ Program 2008;450-6.
144. Giagounidis A. Current treatment algorithm for the management of lower-risk MDS. Hematology Am Soc Hematol Educ Program 2017;2017:453-9.
145. Auerbach M, Ballard H, Trout JR, et al. Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: a multicenter, open-label, randomized trial. J Clin Oncol 2004;22:1301-7.
146. Rodgers GM, Gilreath JA. The Role of Intravenous Iron in the Treatment of Anemia Associated with Cancer and Chemotherapy. Acta Haematol 2019;142:13-20.
147. Keding V, Zacharowski K, Bechstein WO, et al. Patient Blood Management improves outcome in oncologic surgery. World J Surg Oncol 2018;16:159.
148. Shah A, Palmer AJR, Klein AA. Strategies to minimize intraoperative blood loss during major surgery. Br J Surg 2020;107:e26-38.
149. Franchini M, Frattini F, Crestani S, et al. Bleeding complications in patients with hematologic malignancies. Semin Thromb Hemost 2013;39:94-100.
150. Angelini DE, Radivoyevitch T, McCrae KR, et al. Bleeding incidence and risk factors among cancer patients treated with anticoagulation. Am J Hematol 2019;94:780-5.
151. Montroy J, Fergusson NA, Hutton B, et al. The Safety and Efficacy of Lysine Analogues in Cancer Patients: A Systematic Review and Meta-Analysis. Transfus Med Rev 2017;31:141-8.
152. Thachil J, Falanga A, Levi M, et al. Management of cancer-associated disseminated intravascular coagulation: guidance from the SSC of the ISTH. J Thromb Haemost 2015;13:671-5.
153. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999;340:409-17.
154. Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med 2014;371:1381-91.
155. Tay J, Allan DS, Chatelain E, et al. Liberal Versus Restrictive Red Blood Cell Transfusion Thresholds in Hematopoietic Cell Transplantation: A Randomized, Open Label, Phase III, Noninferiority Trial. J Clin Oncol 2020;38:1463-73.
156. Gu Y, Estcourt LJ, Doree C, et al. Comparison of a restrictive versus liberal red cell transfusion policy for patients with myelodysplasia, aplastic anaemia, and other congenital bone marrow failure disorders. Cochrane Database Syst Rev 2015;(10):CD011577.
157. St Lezin E, Karafin MS, Bruhn R, et al. Therapeutic impact of red blood cell transfusion on anemic outpatients: the RETRO study. Transfusion 2019;59:1934-43.
158. Carson JL, Guyatt G, Heddle NM, et al. Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage. JAMA 2016;316:2025-35.
159. Percac-Lima S, Irwin K, Whited E, et al. Implementing a patient navigation program to improve adherence with cancer treatment for community health center patients newly diagnosed with cancer. J Clin Oncol 2021;39:abstr 103.
160. Berger MD, Gerber B, Arn K, et al. Significant reduction of red blood cell transfusion requirements by changing from a double-unit to a single-unit transfusion policy in patients receiving intensive chemotherapy or stem cell transplantation. Haematologica 2012;97:116-22.
161. Stevens GA, Finucane MM, De-Regil LM, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995-2011: a systematic analysis of population-representative data. Lancet Glob Health 2013;1:e16-25.
162. WHO. Guideline: Daily iron and folic acid supplementation in pregnant women. World Health Organization, 2012.
163. Ray JG, Davidson A, Berger H, et al. Haemoglobin levels in early pregnancy and severe maternal morbidity: population-based cohort study. BJOG 2020;127:1154-64.
164. Daru J, Zamora J, Fernández-Félix BM, et al. Risk of maternal mortality in women with severe anaemia during pregnancy and post partum: a multilevel analysis. Lancet Glob Health 2018;6:e548-54.
165. Juul SE, Derman RJ, Auerbach M. Perinatal Iron Deficiency: Implications for Mothers and Infants. Neonatology 2019;115:269-74.
166. Benson CS, Shah A, Frise MC, et al. Iron deficiency anaemia in pregnancy: A contemporary review. Obstet Med 2021;14:67-76.
167. Nieto-Calvache AJ, Quintero-Santacruz M, Macia-Mejía C, et al. Dangerous shortage of blood banks as an indirect effect of SARS-CoV-2: An obstetrics perspective. Int J Gynaecol Obstet 2020;151:424-30.
168. Bates I, Chapotera GK, McKew S, et al. Maternal mortality in sub-Saharan Africa: the contribution of ineffective blood transfusion services. BJOG 2008;115:1331-9.

169. Pant S, Koirala S, Subedi M. Maternal Health Services during COVID-19. Europasian J Med Sci 2020;2:48-52.
170. Hallberg L, Bengtsson C, Lapidus L, et al. Screening for iron deficiency: an analysis based on bone-marrow examinations and serum ferritin determinations in a population sample of women. Br J Haematol 1993;85:787-98.
171. Auerbach M. Commentary: Iron deficiency of pregnancy - a new approach involving intravenous iron. Reprod Health 2018;15:96.
172. VanderMeulen H, Strauss R, Lin Y, et al. The contribution of iron deficiency to the risk of peripartum transfusion: a retrospective case control study. BMC Pregnancy Childbirth 2020;20:196.
173. Stewart T, Lambourne J, Thorp-Jones D, et al. Implementation of early management of iron deficiency in pregnancy during the SARS-CoV-2 pandemic. Eur J Obstet Gynecol Reprod Biol 2021;258:60-2.
174. Abdulrehman J, Lausman A, Tang GH, et al. Development and implementation of a quality improvement toolkit, iron deficiency in pregnancy with maternal iron optimization (IRON MOM): A before-and-after study. PLoS Med 2019;16:e1002867.
175. Muñoz M, Peña-Rosas JP, Robinson S, et al. Patient blood management in obstetrics: management of anaemia and haematinic deficiencies in pregnancy and in the post-partum period: NATA consensus statement. Transfus Med 2018;28:22-39.
176. Hofmann A, Ozawa S, Farrugia A, et al. Economic considerations on transfusion medicine and patient blood management. Best Pract Res Clin Anaesthesiol 2013;27:59-68.
177. D E H O, Hadi F, Stevens V. Health Economic Evaluation Comparing Iv Iron Ferric Carboxymaltose, Iron Sucrose and Blood Transfusion For Treatment of Patients with Iron Deficiency Anemia (Ida) in Singapore. Value Health 2014;17:A784.
178. Wesström J. Safety of intravenous iron isomaltoside for iron deficiency and iron deficiency anemia in pregnancy. Arch Gynecol Obstet 2020;301:1127-31.
179. Flores CJ, Sethna F, Stephens B, et al. Improving patient blood management in obstetrics: snapshots of a practice improvement partnership. BMJ Qual Improv Rep 2017;6:e000009.
180. Sentilhes L, Winer N, Azria E, et al. Tranexamic Acid for the Prevention of Blood Loss after Vaginal Delivery. N Engl J Med 2018;379:731-42.
181. Novikova N, Hofmeyr GJ, Cluver C. Tranexamic acid for preventing postpartum haemorrhage. Cochrane Database Syst Rev 2015;(6):CD007872.
182. Muñoz M, Stensballe J, Ducloy-Bouthors AS, et al. Patient blood management in obstetrics: prevention and treatment of postpartum haemorrhage. A NATA consensus statement. Blood Transfus 2019;17:112-36.
183. Sentilhes L, Daniel V, Deneux-Tharaux C, et al. TRAAP2 - TRAnexamic Acid for Preventing postpartum hemorrhage after cesarean delivery: a multicenter randomized, doubleblind, placebo- controlled trial - a study protocol. BMC Pregnancy Childbirth 2020;20:63.
184. Abdel-Aleem H, Alhusaini TK, Abdel-Aleem MA, et al. Effectiveness of tranexamic acid on blood loss in patients undergoing elective cesarean section: randomized clinical trial. J Matern Fetal Neonatal Med 2013;26:1705-9.
185. Prick BW, Jansen AJ, Steegers EA, et al. Transfusion policy after severe postpartum haemorrhage: a randomised non-inferiority trial. BJOG 2014;121:1005-14.

doi: 10.21037/aob-22-1
Cite this article as: Khandelwal A, Vandermeulen H, Tordon B, Pavenski K. Applying principles of patient blood management during COVID-19 pandemic: a literature review. Ann Blood 2023;8:14.

