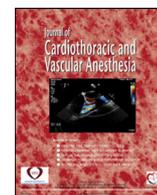


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## Editorial

## Preoperative Anemia Treatment in Cardiac Surgery: Past Due and Time to Act

FOR DECADES, the mainstay role of preoperative clinics was to identify comorbid medical conditions, evaluate their severity, and convey an opinion on fitness for surgery. Anesthesiologists who staffed preoperative clinics frequently consulted with primary care physicians and/or subspecialty consultants to obtain the coveted “surgical clearance” so that a proposed surgery could move forward. The “raison d’être” of preoperative clinics was to avoid day of surgery cancellations, which justified funding for years. Fortunately, we have entered a renaissance in perioperative medicine, where we now aim to improve patient outcomes through comprehensive health optimization before surgery. Increasingly, preoperative clinics do not simply diagnose comorbidities, but prescribe treatment, and monitor for therapeutic effectiveness. Preoperative clinics have become hubs of patient and caregiver education, where expectations are set and patients’ goals are outlined. This evolution has the potential to enormously enhance quality of care, reduce cost, and improve the perioperative experience.

In this issue of *Journal of Cardiothoracic and Vascular Anesthesia*, Kloeser et al. systematically reviewed preoperative anemia treatment before cardiac surgery.<sup>1</sup> The authors summarized randomized controlled trials and put forth practical algorithms for diagnosing anemia’s etiology and effectively treating it before surgery. The authors’ review was timely, as anemia increasingly is recognized as a modifiable risk factor. Several key trials have been published in recent years, demonstrating that preoperative anemia treatment can impact meaningful patient outcomes.<sup>2,3</sup> Additionally, recent expert consensus statements and practice guidelines have endorsed preoperative anemia treatment as a key element of holistic patient blood management (PBM).<sup>4,5</sup>

Anemia is one of the most common health problems, affecting up to 25% to 30% of the world’s population.<sup>6</sup> In recent years, the United Nations, World Health Organization (WHO), and numerous medical societies have highlighted its importance in public health. In the United States, anemia has garnered mainstream media attention, with a recent article published in *Scientific American* describing its impact.<sup>7</sup> The

WHO has described holistic PBM as being supported by 3 pillars (Fig 1). The first is appropriate diagnosis and treatment of anemia before surgery with optimization of red blood cell (RBC) mass. The second and third pillars are intraoperative blood conservation and optimization of anemia tolerance.

Comprehensive PBM can improve perioperative hemoglobin levels and reduce allogeneic transfusion.<sup>8,9</sup> It also may reduce complications (eg, thrombosis, infection, and acute kidney injury),<sup>10</sup> but larger studies are needed to adequately study these potential benefits. In the last decade, PBM has gained tremendous momentum. The Joint Commission now offers formal PBM certification for hospitals in the United States. In Canada and Australia, entire provinces/territories have designated PBM programs, which has reduced allogeneic blood transfusion significantly.<sup>11,12</sup> The most effective PBM programs incorporate all pillars, but simultaneous implementation can be politically challenging, costly, and resource-intensive.

In their article, Kloeser et al. provided a blueprint for building the first pillar of PBM. The authors’ work built upon that of prior innovators in the field.<sup>10,13,14</sup> The first step is to effectively identify all cardiac surgical patients (both inpatients and outpatients) who are anemic and may benefit from treatment. For outpatients, this can be achieved through comprehensive anemia screening using point-of-care hemoglobin measurement devices. After an anemia diagnosis is made, the focus shifts to determining etiology. As Kloeser et al. pointed out, this starts by taking a careful social, nutritional, medical, and surgical history. Obtaining a pertinent medical history cannot be emphasized enough because it is often the cheapest and most enlightening piece of the diagnostic puzzle. Likewise, understanding a patient’s medical history helps to identify which treatments are most effective. As the authors mention, the diagnostic evaluation of preoperative anemia should ideally occur several weeks before surgery to allow adequate time for treatment. One approach that has been used is reflex (automatic add-on) diagnostic testing with iron studies (eg, ferritin, transferrin saturation, etc.) when a patient is found to be anemic. This eliminates the need for an additional preoperative visit before treatment occurs.

Although there are congenital anemias, such as the thalassemia, sickle cell disease, and congenital spherocytosis, most

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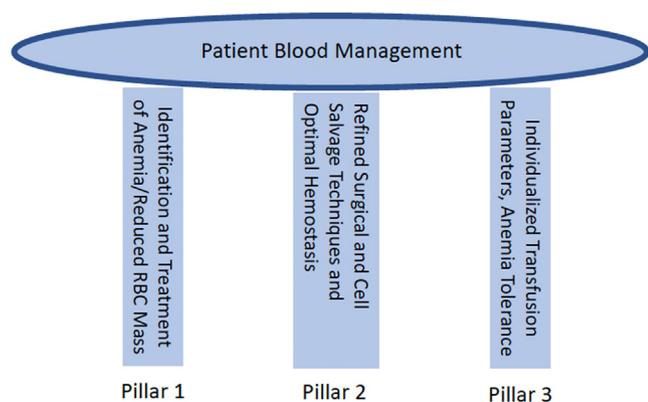


Fig 1. The 3 foundational pillars of comprehensive patient blood management.

anemias in adult cardiac surgical patients are acquired. As the authors pointed out, the etiology of anemia in precardiac surgical patients may not be as simple as isolated iron deficiency. Chronic inflammation, renal disease, intrinsic bone marrow pathology, hepatic dysfunction, and gastrointestinal malabsorption can all contribute to insufficient RBC substrate (ie, iron, folate, and B12) or an insufficient production stimulus (ie, erythropoietin). Hemolysis also can contribute to anemia in select adult cardiac surgical patients (eg, paravalvular leak, stenotic mechanical valve, etc.). In cases of suspected malignancy or myelodysplastic syndrome, referral to a hematologist/oncologist should occur before surgery.

Preoperative anemia treatment has unique challenges. In their article, Kloeser et al. highlighted pretreatment insurance authorization and high cost as barriers to more widespread treatment in Switzerland. In the United States, there are similar issues. Health and socioeconomic disparities, access to insurance, and lack of adequate transportation and home-care resources are all potential barriers. Some payers limit access to newer intravenous iron formulations, which are easier to administer, which further complicates the ability to effectively treat all patients. The downstream effects are that physicians, nurses, and administrative staff often have to dedicate significant time to navigate both requesting and obtaining insurance authorization—a process that differs by insurer. These burdens complicate providers' ability to complete treatment in a timely manner.

More expensive intravenous iron formulations (which require less-frequent dosing) may not be covered fully by insurers, and, hence, rapid-release formulations (which require more frequent dosing) may be the only treatment option. In the United States, patients sometimes travel hours for specialty care, or alternatively may live in urban areas where they are unable to access high-level care because of inadequate resources. Because preoperative anemia treatment frequently occurs in the ambulatory environment, patients may refuse therapy altogether because of time, cost, and/or transportation issues. It is important to address these factors early in the process, as anemia itself is a disease exacerbated by food insecurity and lower socioeconomic status. Partnering with either a social worker or care coordinator helps to address these issues.

In the United States, insurance authorization can be so limiting that some “high-yield” therapies are not possible. For example, erythropoiesis-stimulating agents (ESAs) can be so costly that some institutions forego them, particularly in the absence of insurance coverage or in states with global hospital budgets, where hospitals must reduce cost to increase their financial margin. If deemed absolutely necessary for an outpatient with limited resources, one strategy is to administer ESAs on the day of surgery, which effectively bundles the medication's cost into the hospitalization. Unfortunately, this may lead to less-efficacious treatment compared with giving ESAs several weeks before surgery.

Many potential benefits of preoperative anemia treatment (eg, reductions in complications and transfusions) are difficult to quantify for hospital administrators and payers because they are based on cost avoidance. This makes business planning and strategizing for an anemia treatment program challenging. Having PBM allies at the highest possible levels in hospital administration and insurance organizations is key to the long-term success of anemia treatment programs. Advocacy from organizations such as the American Society of Anesthesiologists, American College of Surgeons, and American Medical Association also will help.

Studies investigating the lowest efficacious dose of ESAs and optimal timing of treatment have not yet been completed in cardiac surgical patients. Kloeser et al. suggested that ESAs may require administration several days to weeks before surgery, but most published studies have evaluated treatment closer to the time of surgery. In Canada, where there is nationalized healthcare, efficacious ESA doses were found to be double of what typically is administered for PBM purposes in the United States, bringing into question whether ESAs can become more cost-effective in the United States. Thrombotic and hypertensive events associated with ESAs also may limit their inclusion in optimization pathways until more studies demonstrate their safety in surgical patients, particularly those with cancer or other risk factors for hypercoagulability.

The authors briefly discuss the potential use of preoperative RBC transfusion as a treatment for anemia, avoiding the so-called “double hit” of simultaneous surgery and allogeneic transfusion. During the COVID-19 pandemic, blood supplies became dangerously low. The American Red Cross experienced a significant decline in donations because of staffing vacancies and blood drive cancellations, compounding existing reductions in blood donations over time. This, combined with that fact that stored RBCs have a limited shelf-life and allogeneic transfusion is associated with numerous adverse outcomes, further underscores the importance of preoperative anemia treatment with iron and ESAs whenever possible.

After decades of neglect, preoperative anemia treatment in cardiac surgical patients finally is getting the attention that it deserves. The limitations of and potential complications associated with allogeneic RBC transfusion also are better-understood. Kloeser et al. appropriately highlighted that high-quality randomized controlled trials are still needed to evaluate optimal timing of treatment, ESA, and iron dosing, and how anemia treatment impacts longer-term patient-centered

outcomes. As preoperative anemia treatment programs continue to develop, medical providers should advocate for equity and inclusivity, as many anemic patients throughout the world have limited resources. Maximal patient benefit and optimal cost-effectiveness will be obtained through development of standardized treatment pathways, appropriate use of technology to make treatment more available, development of social support structures for anemic patients, and advocacy with hospital, pharmaceutical, and insurance leaders. Continuing to aim high in our efforts to reduce allogeneic transfusion and improve outcomes in cardiac surgical patients is worth our time, energy, and resources. Preoperative anemia treatment is certain to have a critical role in these efforts moving forward, and will continue to be a “hot topic” for years to come.

### Conflict of Interest

M.M. has previously received consulting fees from Hemosonics and Octapharma.

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