The patient with anemia

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Purpose of review
Anemia remains a global health issue. This review addresses the recent findings on anemia in surgical patients and its significance in perioperative setting.

Recent findings
The prevalence of anemia in surgical populations is high, ranging from one-third of population to nearly 100%. Anemia is an independent, modifiable risk factor for a growing list of unfavorable events, complications and diminished functional outcomes (lasting for months following discharge), as well as a major predisposing factor for allogeneic blood transfusions. Therefore, timely screening and diagnosis of anemia prior to elective surgeries is of great importance. Nonetheless, studies suggest that many opportunities to properly manage anemia in perioperative setting are lost. Patient blood management provides a framework of evidence-based strategies to effectively reduce the risk of occurrence of anemia and treat it with the ultimate goal of improving patient outcomes. Studies on the clinical impact of patient blood management strategies are emerging.

Summary
Active screening for anemia and proper management of it in perioperative setting is essential. Several strategies to prevent anemia – including elimination of unnecessary diagnostic blood draws – are effective and reasonable approaches.

Keywords
anemia, iron, patient blood management, surgery, transfusion

INTRODUCTION

Anemia remains a global health issue. It is estimated that one out of every three to four human beings across the world meets the WHO definition of anemia (hemoglobin <13 g/dl in adult men and 12 g/dl in adult nonpregnant women) [1,2]. Anemia is often multifactorial and various causes including nutritional deficiencies (iron, vitamin B_{12} and folic acid), inflammatory processes and blood loss (acute or chronic) usually play a role to some degree. Iron deficiency – absolute or functional – is common in anemia and it can be easily treated using supplemental iron [3,4].

The overall prevalence of anemia in surgical patients is believed to be higher than general population [5]. Anemia is particularly important in patients undergoing surgery for a number of reasons. In general, some patients undergo surgery due to chronic conditions that also increase the risk of anemia (e.g. chronic cardiac disease or malignancies). Other surgeries such as certain orthopedic procedures are typically performed more commonly in elderly populations who face increased prevalence of anemia. Not only procedures associated with high blood loss may cause or exacerbate anemia, but hospital stay on its own is increasingly being recognized as a risk factor for anemia. On the contrary, presence of anemia in surgical patients is a risk factor for allogeneic blood transfusion – a major independent contributor to unfavorable outcomes – and a growing list of other complications. This review addresses the recent findings on anemia in surgical patients and its significance in perioperative setting.

REVIEW

Prevalence and significance of anemia in surgery

Anemia is a common, independent and modifiable risk factor for various unfavorable outcomes in a

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KEY POINTS

- The prevalence of anemia is high in general population and even higher in surgical patients. The prevalence often continues to rise throughout the hospital stay and it persists beyond discharge, even for months and years.
- A growing body of evidence implicates anemia with worsening of outcomes in various surgical patient populations.
- Anemia is a major risk factor for allogeneic blood transfusion in perioperative setting, and the evidence on the independent link between transfusion and worse outcomes continues to grow as well, giving more reasons to take anemia more seriously.
- Surgical patients often face high risk of blood loss, during and following surgery. For example, repeated and unwarranted diagnostic blood draws can lead to significant blood loss, and they should be avoided unless when likely to affect the care of the patients.
- PBM focuses on maintaining hemoglobin level, optimizing hemostasis and minimizing blood loss using evidence-based strategies to improve the outcomes of patients. These measures effectively reduce the risk of occurrence of anemia, and reduce its severity and negative impact when present.

wide range of patient populations including surgical patients. Recent studies continue to demonstrate the negative impacts of anemia in various surgical populations. In addition, the presence of 'unexplained' anemia in the preoperative setting should alert the clinicians to rule out the possibility of underlying conditions such as kidney disease or malignancy. Iron-deficiency anemia without overt bleeding can be a sign of gastrointestinal cancers and other conditions such as atrophic gastritis, celiac disease or gastrointestinal ulcers [6].

Table 1 summarizes the findings of a number of recent publications on the prevalence of anemia and its impact on outcomes in surgical patients [7▪,8–17]. In a systematic review of studies in patients with fractured hips, preoperative anemia was independently associated with increased risk of death in half of the studies [18]. A recent meta-analysis focused on the association between preoperative anemia and outcomes in surgical patients (excluding pediatric and obstetric populations as well as trauma, burn and transplant surgeries) [19]. Main outcomes included 30-day or in-hospital mortality, acute kidney injury, stroke and myocardial infarction, with subgroup analyses on cardiac and noncardiac surgery patients. The investigators identified 24 studies encompassing a total of nearly 950 000 surgical patients, of which 39.1% had preoperative anemia. Anemia was independently associated with increased risk of mortality [odds ratio (OR) 2.90, 95% confidence interval (CI) 2.30–3.68], acute kidney injury (OR 3.75, 95% CI 2.95–4.76) and infection (OR 1.93, 95% CI 1.17–3.18) across the populations, and increased risk of stroke (OR 1.28, 95% CI 1.06–1.55) in patients undergoing cardiac surgery. Significant heterogeneity was noted between the studies, and it could not be determined whether anemia was an independent risk factor of unfavorable outcomes or a marker of underlying diseases [19].

Considering the totality of evidence on the link between anemia and worse outcomes, it is not unreasonable to conclude that anemia can often act as a marker of underlying diseases. Indeed, as the term 'anemia of chronic disease/inflammation' might suggest, the presence of anemia can be a result of underlying inflammatory processes. Another common example is iron deficiency, which has been independently linked to worse outcomes regardless of anemia. Again, in this context, anemia can be viewed as a 'marker' of underlying conditions. Nonetheless, and as demonstrated by numerous other studies, there is little doubt on the independent link between anemia and worse outcomes. It is important to note that this role does not necessarily contradict the role of anemia as a marker of underlying illness, and the two roles can coexist in the same patient more often than not.

Anemia and the risks of transfusion

Across various populations, anemia dramatically increases the risk of red blood cell transfusions by as much as five-fold or more [19]. In a study of over 4000 patients who underwent elective hepatectomy, preoperative anemia was diagnosed in 22.7% of the patients. Anemia was independently associated with 2.8-fold increased risk of blood transfusion and significantly longer duration of hospital stay (10.0 vs. 7.4 days), which translates to substantial resource utilization [20▪▪]. In a recent multicenter study in patients undergoing major orthopedic surgery in Europe, anemia was associated with more than five-fold increased risk of being transfused during surgery [11]. In another study in 288 elderly patients undergoing cardiac surgery, preoperative anemia (alongside postoperative bleeding volume) was among the main risk factors of transfusion [21].

The link between transfusion and worse outcome has been supported by countless studies. The bulk of evidence on the outcomes of

Table 1. Recent findings on prevalence and significance of anemia in surgery

Study	Population	Prevalence of anemia	Impact of anemia on outcomes
DeLarochelliere *et al.* [7▪]	438 patients undergoing TAVR in a single center	64.4% before the procedure 62% at 6-month follow-up	Anemia independently associated with worsening of various functional and quality-of-life measures
Ebner *et al.* [8]	331 out-patients with stable chronic HF	At baseline, 30% with anemia, 45% with ID and 19% with ID anemia	Exercise capacity significantly lower in patients with anemia and ID After adjusting for other factors, anemia was an independent predictor of mortality
Gierth *et al.* [9]	A multicenter study of 684 patients undergoing radical cystectomy for transitional cell carcinoma of bladder	39.3% in preoperative period	Anemia was an independent predictor of cancer recurrence and mortality (cancer specific and all-cause)
Landes *et al.* [10]	Over 11 000 patients who underwent PCI		Previous history of anemia was independently associated with mortality or myocardial infarction
Lasocki *et al.* [11]	1500 patients who underwent major elective knee, hip or spine surgery at 17 hospitals across six European countries	14.1% in the preoperatively period 85.8% in the postoperative period Patients with preoperative anemia had a mean Hb drop of 1.9 g/dl in the postoperative period, vs. 3 g/dl drop in Hb of patients who were not anemic at baseline	Anemia was associated with increase rate of postoperative complications
Menendez *et al.* [12]	A nationwide study of over 3 million total joint arthroplasty surgeries		Anemia identified among the risk factors of in-hospital, postoperative myocardial infarction
Seicean *et al.* [13]	668 patients undergoing open surgery for intracranial aneurysms (60% ruptured)	29.6% in preoperative period	Preoperative anemia independently associated with preoperative complications, need for reoperation and longer hospital stay
Shacham *et al.* [14]	1248 patients admitted with STEMI who underwent PCI	Anemia at admission detected in 27% of patients who developed AKI and 12% of those without AKI	Anemia at admission was independently associated with the risk of AKI
Spiegelstein *et al.* [15]	Over 2300 patients undergoing nonemergent-isolated CABG	Mean preoperative Hct was 38.9 ± 4.8%	Lower preoperative Hct was independently associated with increased risk of perioperative major morbidity in higher risk patients
Uchilda *et al.* [16]	337 patients admitted for PCI	17.5% at admission	Anemia was an independent significant risk factor for adverse outcomes and worse prognosis during the median follow-up period of 4.5 years
Viola *et al.* [17]	13 500 patients undergoing total joint arthroplasty in a single center	19% in the preoperative period	Anemia independently associated with increased risk of complications, particularly cardiac and genitourinary complications

AKI, acute kidney injury; CABG, coronary artery bypass grafting; Hb, hemoglobin; Hct, hematocrit; HF, heart failure; ID, iron deficiency; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction; TAVR, trans-catheter aortic valve replacement.

transfusions comes from uncontrolled observational studies that are prone to the risk of bias and confounders. The link has been shown in almost every type of patient population and procedure. In a multicenter study of 765 patients undergoing resection of gastric adenocarcinoma with curative intent, 22% of the patients received allogeneic blood transfusion in the perioperative period. Transfusion was

an independent risk factor for decreased recurrence-free and overall survival (hazard ratio 1.64, 95% CI 1.13–2.37 and hazard ratio 1.79, 95% CI 1.21–2.67, respectively) [22]. In a study of nearly 3000 patients who underwent major vascular surgeries, 25% of patients were transfused at a median hemoglobin level of 7.7 g/dl. Preoperative anemia was an independent and strong predictor of perioperative transfusion (OR 4.2, 95% CI 3.3–5.1), whereas perioperative transfusion was independently associated with increased risk of death (OR 6.9, 95% CI 3.2–15), myocardial infarction (OR 8, 95% CI 3.7–17) and pneumonia (OR 7.4, 95% CI 3.3–17) [23].

In a study of 1444 patients who underwent cardiac surgery with cardiopulmonary bypass in 16 hospitals in Canada, 37% had preoperative anemia, 35% developed intraoperative anemia and 43% of the patients received blood transfusions. After adjusting for other confounders, patients with a combination of having anemia and receiving transfusion had the highest risk of developing acute kidney injury [24]. The interaction between anemia, transfusion and comorbidities such as cardiac or kidney disease has been long recognized and highlights the importance of aggressive treatment (and prevention) of anemia and more judicious use of blood transfusions [25].

Clinical trials on transfusion practices have also provided some valuable evidence, but one has to remember that no clinical trial to date has compared transfusion with no transfusion (or other alternative treatments, with exception of a few ill-fated trials on artificial blood substitutes), and these trials at best can compare the impact of less vs. more transfusions. In addition, clinical trials are no guarantee against low quality of evidence and persistent risk of bias [26].

Several studies including large clinical trials over the past few years have supported the notion that more liberal use of blood transfusion is associated with worse or comparable outcomes compared with more judicious use of red blood cells. More recently, few studies have questioned this notion. In a randomized controlled trial on 198 cancer patients undergoing major abdominal surgery, the use of a liberal transfusion strategy (hemoglobin threshold <9 g/dl) was associated with 16% lower risk of occurrence of the primary composite outcome of mortality or major morbidity compared with restrictive transfusion strategy (hemoglobin threshold <7 g/dl) [27▪]. Of note, the study arms had some differences in baseline characteristics and surgical procedures that might affect the outcomes favoring the liberal transfusion strategy arm.

A recent meta-analysis looked at six trials comparing liberal transfusion strategies (usually based on a target hemoglobin threshold of 10 g/dl) vs. restrictive transfusion strategies (usually based on an 8 g/dl hemoglobin threshold), involving 2722 patients undergoing surgery for hip fracture [26]. Of note, almost 75% of the patients came from just one trial, and over 60% of these cases had a history of cardiovascular disease. There was no significant difference in postoperative mortality between the liberal and restrictive transfusion strategies (risk ratio 0.92, 95% CI 0.67–1.26 for 30-day mortality and risk ratio 1.08, 95% CI 0.80–1.44 for 60-day postoperative mortality). Overall, trends toward lower risk of postoperative morbidity (including thromboembolic events, stroke, wound infection and pneumonia) were observed in patients randomized to more restrictive transfusion strategies, whereas a trend toward lower risk of heart failure and myocardial infarction was observed among patients managed with more liberal transfusion strategies. In addition, more liberal use of blood transfusions did not have any significant impact on functional recovery (risk ratio 1.00, 95% CI 0.87–1.15) [26]. This finding is of particular interest, as 'accelerating recovery' has been one of the common anecdotal and inappropriate 'indications' for use of allogeneic blood. This is further supported in a recent clinical trial in 284 anemic elderly hip fracture patients who were randomized to a restrictive (hemoglobin <9.7 g/dl) or liberal (hemoglobin <11.3 g/dl) transfusion strategy during the first 30-day postoperative period. There was no significant difference in recovery in daily living activities or 90-day mortality between the patients managed with liberal and restrictive transfusion strategies [28].

On the contrary, long-term follow-up of 1016 patients enrolled in a large trial of liberal vs. restrictive transfusion strategy (FOCUS trial) indicated that the long-term mortality did not differ between the patients randomized to liberal vs. restrictive strategies [29]. The interpretation of this finding depends on the viewpoint of the interpreter: For some, this is an evidence that liberal transfusion poses no additional long-term risk to this high-risk, elderly population [29], while it can also be argued that this study shows the futility of a high-risk and costly treatment. The ongoing debate over various transfusion strategies highlights the importance of management of anemia in perioperative setting: if anemia is properly managed and prevented in surgical patients, the patients will be less likely to reach a threshold for transfusion (even the liberal ones). Simply put, why should we preoccupy ourselves with the debate between two options, when we can effectively avoid both by planning ahead of time [30]?

Toward better management of anemia

It is often stated that prevention is better than treatment, and anemia in the surgical setting is among the best examples. Left untreated, anemia will expose the patients to risks of its own, and the risks of transfusion. Effort to control and minimize bleeding (surgical and iatrogenic such as phlebotomies for tests) is key in preventing and reducing the severity of anemia and avoiding many of its consequences. Interestingly, the presence of preoperative anemia (alongside a number of other factors including older age, comorbidities, prolonged length of surgery and the use of anticoagulants) was among the main risk factors associated with increased surgical blood loss in a study in orthopedic surgeries [31]. Similarly, anemia was found to be independently associated with increased risk of bleeding following primary percutaneous coronary intervention in a study of 770 patients with ST-elevation myocardial infarction [32]. The increased blood loss in anemic patients is expected to exacerbate the anemia, creating a positive feedback loop with serious negative consequences.

In a recent systematic review of 49 studies performed in patients undergoing hip and knee arthroplasty, intraoperative use of tranexamic acid was found to be associated with decreased surgical blood loss, increased hemoglobin level, reduced risk of transfusion and shorter hospital stay. The use of topical hemostatic agents was also found to be effective [33].

The clinical team should remain vigilant and continue the efforts to minimize blood loss in the postoperative period as well. Diagnostic blood draws are gaining more attention as one of the factors contributing to development of hospital-acquired anemia (or exacerbation of pre-existing anemia). In a study on 248 critically ill patients, the use of small-volume phlebotomy tubes for blood draws was associated with significantly lower volume of blood draw compared with conventional phlebotomy tubes (mean $\pm$ standard deviation 174 ± 182 vs. 299 ± 355 mL, $P = 0.001$) [34]. Although in this study no difference in the amount of blood transfusions was noted, this study indicates that patients can lose around 5% of their total blood volume to diagnostic blood tests alone during their hospital stay. The use of small-volume (e.g. pediatric) tubes is a simple strategy. Also, standing orders of tests without specific indication and orders for diagnostic tests that are not likely to affect the course of clinical management of the patients should be avoided. Implementing an educational programme for internists at a hospital – highlighting the notion that daily blood tests should be ordered only if the results are likely to change the patient care – was associated with a reduction of complete blood counts from 1.46 to 1.37 per patient per day [35▪]. With the advancements of technology, the ability to run complete tests in much smaller specimens – as low as 50 μl blood in one example [36] – will soon become a reality.

New advancements in medical technologies come with the hope of more accurate and less invasive diagnostic tests. Continuous noninvasive hemoglobin monitoring is of special interest, as not only does it allow for noninvasive measurement of hemoglobin level without drawing any bloods, but it also provides continuous, real-time data that can aid clinicians in making better-informed clinical decisions (e.g. in face of rapidly declining hemoglobin level that might otherwise go undetected for long until a blood test is performed). However, the accuracy and precision of these devices have been a matter of contention [37]. Evidence generally suggests low bias despite wide variations compared with conventional methods of measurement of hemoglobin, and hence, currently available noninvasive hemoglobin monitoring devices should be used to supplement more accurate blood tests rather than substitute them [37,38].

Patient blood management (PBM) provides a road map to address anemia and other modifiable risk factors in patients – particularly surgical patients – to improve clinical outcomes. PBM relies on multidisciplinary, evidence-based medical and surgical approaches to maintain hemoglobin level, optimize hemostasis and minimize blood loss [39]. Emerging studies continue to support the effectiveness of these approaches individually and in concert under PBM programmes in reducing the risk of anemia and achieving better outcomes for patients [40▪▪]. Among all the strategies, timely detection and management of anemia remains one of the simplest and most effective approaches, which is still being frequently ignored [41]. The call for early detection and management of anemia during the preoperative period – a golden opportunity in patients scheduled for elective surgery – is growing stronger. Neither us the clinicians nor our patients can afford missing this opportunity. Algorithms to guide the detection and management of anemia in preoperative setting are available [6,41,42▪]. In a study across 17 hospitals in Europe, the prevalence of preoperative anemia was reduced to 8%, whereas the prevalence in other centers was more than twice higher, around 18.5%. Tests used to assess iron status were performed significantly more frequently in the centers implementing PBM strategies [11]. It is regrettable that a substantial number of hospitals still continue to fail to properly diagnose and manage anemia in their patients, exposing them to avoidable significant risks [11].

Once anemia diagnosis is made, treatment should be guided by the results of the diagnostic work-ups, and it includes iron and erythropoiesis-stimulating agents [43,44]. As indicated earlier, functional iron deficiency is common in surgical patients, necessitating iron therapy. However, management of anemia in surgical patients is often a race against time and given the limited absorption of iron from gastrointestinal tract, intravenous iron formulae are preferred for faster and better results [5,44]. As a highly bioactive element, iron plays roles in many pathways, and just as its deficiency can lead to a multitude of problems, the consequences of its administration to the body may also be far-reaching. Some studies have linked iron administration with oxidative stress and immunomodulatory effects [45]. Increased risk of infections is also a known risk [46]. Hypersensitivity reactions have also been reported, but more recent parenteral iron preparations are generally safer in this regard and preferred over the older preparations (namely high molecular weight iron dextran) [47]. Recently, it has been shown in the Ferric CarboxymaltOse evaluatioN on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure (CONFIRM-HF) trial that treatment of iron-deficient heart failure patients with intravenous iron is associated with improved functional capacity and quality of life, in addition to reducing the risk of subsequent hospital admissions [48]. This makes a strong case for using intravenous iron in iron-deficient heart failure patients. A number of randomized controlled trials in other populations have compared intravenous iron with oral iron or placebo, and some have provided evidence in support of efficacy of intravenous iron in correcting anemia, reducing transfusions and (to less extent) improving clinical outcomes [46,49].

Although the use of intravenous iron in anemic surgical patients appears to be reasonable and based on sound theoretical grounds, the evidence from the studies in perioperative setting is limited, with no report of large randomized trials published recently. A recent systematic review could identify only four studies that focused on the impact of perioperative intravenous iron on outcomes in anemic patients. In one small study, concomitant use of intravenous iron and ESAs in preoperative setting was associated with reduced blood transfusion, shorter hospital stay and reduced mortality. However, in the three other studies, postoperative use of intravenous iron (with or without ESAs) was not associated with reduced transfusion utilization [50]. Clearly, more studies are needed to better characterize the clinical impact of intravenous iron treatment in perioperative setting. A number of trials including the Prevention of Recurrent Venous Thromboembolism (PREVENT) trial are underway, and they are hoped to provide the needed evidence on the use of iron in the surgical patients [51].

Novel strategies to diagnose and manage anemia are under investigation. Hepcidin, the master regulator of iron metabolism in the body and a key player in anemia of inflammation and functional iron deficiency – continues to receive significant interest. Briefly, under normal circumstances and when adequate iron is available to support erythropoiesis, hepcidin acts to maintain iron hemostasis, by inhibiting iron absorption from the gastrointestinal tract, and iron mobilization from its stores (liver and reticuloendothelial system). Conversely, when iron deficiency is sensed, hepcidin is downregulated, allowing more iron absorbed by the enterocytes and mobilized from iron stores in the body. On the contrary, hepcidin is upregulated under inflammatory conditions, leading to reduced bioavailability of iron and contributing to anemia of inflammation and functional iron deficiency. Given its central role in iron regulation, hepcidin remains promising as a biomarker for diagnostic tests, as well as a potential therapeutic target for anemia [52]. In a study of 165 patients undergoing cardiac surgery, plasma hepcidin was the only hematological parameter that was reliably associated with the outcomes [53].

CONCLUSION

Anemia continues to pose a significant risk to patients undergoing surgery. The prevalence ranges from that of general population (1/3–1/4) to nearly 100%, depending on the population, risk factors and timing of assessment. Anemia is an independent risk factor for worsening of outcomes and a major predisposing factor for allogeneic blood transfusion – a costly and high-risk treatment with dubious effectiveness. Timely screening and diagnosis of anemia prior to elective surgeries can greatly reduce the risk by providing the clinicians with a golden opportunity to properly manage anemia and optimize the patients for the upcoming surgery. This screening is most appropriate for patients scheduled to undergo surgeries with potential for sizeable blood loss. One practical strategy is to consider anemia screening for any patients scheduled for procedures that are routinely subject to blood type and screen or crossmatch. The presence of comorbidities that increase the risk of anemia (e.g. cardiovascular diseases) or are known to be associated with higher prevalence of anemia and/or iron deficiency (e.g. heart failure) can also be considered in making the decision to screen for anemia ahead of the surgery.

Although surgery acts as a contributing factor to development or exacerbation of anemia, the evolution of anemia continues in the postoperative period and beyond discharge into years. Therefore, clinicians should remain vigilant and actively screen for anemia in the postoperative period and as part of subsequent surveillance of their patients.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. World Health Organization. Worldwide prevalence of anaemia 1993–2005: WHO global database on anaemia. de Benoist B, McLean E, Egli I, Cogwell MEDS, editors. Geneva, Switzerland: World Health Organization; 2008.
2. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva, Switzerland: World Health Organization; 2011.
3. Spahn DR, Zacharowski K. Nontreatment of preoperative anaemia is substandard clinical practice. Br J Anaesth 2015; 115:1–3.
4. Maccio A, Madeddu C, Gramignano G, *et al.* The role of inflammation, iron, and nutritional status in cancer-related anemia: results of a large, prospective, observational study. Haematologica 2015; 100:124–132.
5. Clevenger B, Richards T. Preoperative anaemia. Anaesthesia 2015; 70 (Suppl 1):20–28.
6. Dahlerup JF, Eivindson M, Jacobsen BA, *et al.* Diagnosis and treatment of unexplained anemia with iron deficiency without overt bleeding. Dan Med J 2015; 62:C5072.
7. ■ DeLarochelliere H, Urena M, mat-Santos IJ, *et al.* Effect on outcomes and exercise performance of anemia in patients with aortic stenosis who underwent transcatheter aortic valve replacement. Am J Cardiol 2015; 115:472–479.

A large study across several hospitals in the Europe that reported six-fold increase in prevalence of anemia in orthopedic surgery patients throughout the course of hospitalization, while providing an accurate snapshot of the current status of anemia in Europe.

8. Ebner N, Jankowska EA, Ponikowski P, *et al.* The impact of iron deficiency and anaemia on exercise capacity and outcomes in patients with chronic heart failure. Results from the studies investigating co-morbidities aggravating heart failure. Int J Cardiol 2016; 205:6–12.
9. Gierth M, Mayr R, Aziz A, *et al.* Preoperative anemia is associated with adverse outcome in patients with urothelial carcinoma of the bladder following radical cystectomy. J Cancer Res Clin Oncol 2015; 141:1819–1826.
10. Landes U, Kornowski R, Assali A, *et al.* Predictors of long term outcomes in 11 441 consecutive patients following percutaneous coronary interventions. Am J Cardiol 2015; 115:855–859.
11. Lasocki S, Krauspe R, von HC, *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; 32:160–167.
12. Menendez ME, Memtsoudis SG, Opperer M, *et al.* A nationwide analysis of risk factors for in-hospital myocardial infarction after total joint arthroplasty. Int Orthop 2015; 39:777–786.
13. Seicean A, Alan N, Seicean S, *et al.* Risks associated with preoperative anemia and perioperative blood transfusion in open surgery for intracranial aneurysms. J Neurosurg 2015; 123:91–100.
14. Shacham Y, Gal-Oz A, Leshem-Rubinow E, *et al.* Association of admission hemoglobin levels and acute kidney injury among myocardial infarction patients treated with primary percutaneous intervention. Can J Cardiol 2015; 31:50–55.
15. Spiegelstein D, Holmes SD, Pritchard G, *et al.* Preoperative hematocrit as a predictor of perioperative morbidities following nonemergent coronary artery bypass surgery. J Card Surg 2015; 30:20–26.
16. Uchida Y, Ichimiya S, Ishii H, *et al.* Impact of admission anemia on coronary microcirculation and clinical outcomes in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Int Heart J 2015; 56:381–388.
17. Viola J, Gomez MM, Restrepo C, *et al.* Preoperative anemia increases postoperative complications and mortality following total joint arthroplasty. J Arthroplasty 2015; 30:846–848.
18. Potter LJ, Doleman B, Moppett IK. A systematic review of preoperative anaemia and blood transfusion in patients with fractured hips. Anaesthesia 2015; 70:483–500.
19. Fowler AJ, Ahmad T, Phull MK, *et al.* Meta-analysis of the association between preoperative anaemia and mortality after surgery. Br J Surg 2015; 102:1314–1324.
20. ■■ Tee MC, Shubert CR, Ubl DS, *et al.* Preoperative anemia is associated with increased use of hospital resources in patients undergoing elective hepatectomy. Surgery 2015; 158:1027–1036.

A comprehensive review and meta-analysis of the studies on the significance of anemia in surgical patients.

21. Isil CT, Yazici P, Bakir I. Risk factors and outcome of increased red blood cell transfusion in cardiac surgical patients aged 65 years and older. Thorac Cardiovasc Surg 2015; 63:39–44.
22. Squires MH III, Kooby DA, Poultsides GA, *et al.* Effect of perioperative transfusion on recurrence and survival after gastric cancer resection: a 7-institution analysis of 765 patients from the US Gastric Cancer Collaborative. J Am Coll Surg 2015; 221:767–777.
23. Obi AT, Park YJ, Bove P, *et al.* The association of perioperative transfusion with 30-day morbidity and mortality in patients undergoing major vascular surgery. J Vasc Surg 2015; 61:1000–1009.
24. Karkouti K, Grocott HP, Hall R, *et al.* Interrelationship of preoperative anemia, intraoperative anemia, and red blood cell transfusion as potentially modifiable risk factors for acute kidney injury in cardiac surgery: a historical multicentre cohort study. Can J Anaesth 2015; 62:377–384.
25. Shander A, Javidroozi M, Ozawa S, Hare GM. What is really dangerous: anaemia or transfusion? Br J Anaesth 2011; 107 (Suppl 1):i41–i59.
26. Brunskill SJ, Millette SL, Shokoohi A, *et al.* Red blood cell transfusion for people undergoing hip fracture surgery. Cochrane Database Syst Rev 2015; 4:CD009699.
27. ■ de Almeida JP, Vincent JL, Galas FR, *et al.* Transfusion requirements in surgical oncology patients: a prospective, randomized controlled trial. Anesthesiology 2015; 122:29–38.

As the number of transfusion trials grows, the need for secondary studies to pool the data from various studies grows. This is one of the latest meta-analyses of transfusion studies in patients undergoing orthopedic surgery.

28. Gregersen M, Borris LC, Damsgaard EM. Postoperative blood transfusion strategy in frail, anemic elderly patients with hip fracture: the TRIFE randomized controlled trial. Acta Orthop 2015; 86:363–372.
29. Carson JL, Sieber F, Cook DR, *et al.* Liberal versus restrictive blood transfusion strategy: 3-year survival and cause of death results from the FOCUS randomised controlled trial. Lancet 2015; 385:1183–1189.
30. von HC, Rosenthal C, Sander M, *et al.* Liberal transfusion practice or perioperative treatment of anemia to avoid transfusion? Anesthesiology 2015; 123:971–973.
31. Sizer SC, Cherian JJ, Elmallah RD, *et al.* Predicting blood loss in total knee and hip arthroplasty. Orthop Clin North Am 2015; 46:445–459.
32. Matic DM, Asanin MR, Stankovic SD, *et al.* Incidence, predictors and prognostic implications of bleeding complicating primary percutaneous coronary intervention. Vojnosanit Pregl 2015; 72:589–595.
33. Khan N, Troelsen A, Husted H. Prevention of postoperative anaemia in hip and knee arthroplasty: a systematic review. Dan Med J 2015; 62:pii:A5170.
34. Dolman HS, Evans K, Zimmerman LH, *et al.* Impact of minimizing diagnostic blood loss in the critically ill. Surgery 2015; 158:1083–1087.
35. ■ Thakkar RN, Kim D, Knight AM, *et al.* Impact of an educational intervention on the frequency of daily blood test orders for hospitalized patients. Am J Clin Pathol 2015; 143:393–397.

The negative impact of unwarranted diagnostic blood draws is being increasingly recognized as an easily avoidable cause for blood loss.

36. Punter-Villagrasa J, Cid J, Colomer-Farrarons J, *et al.* Toward an anemia early detection device based on 50-muL whole blood sample. IEEE Trans Biomed Eng 2015; 62:708–716.

37. Suehiro K, Joosten A, Alexander B, Cannesson M. Continuous noninvasive hemoglobin monitoring: ready for prime time? Curr Opin Crit Care 2015; 21:265–270.

38. Phillips MR, Khoury AL, Bortsov AV, *et al.* A noninvasive hemoglobin monitor in the pediatric intensive care unit. J Surg Res 2015; 195:257–262.

39. Shander A, Javidroozi M. Blood conservation strategies and the management of perioperative anaemia. Curr Opin Anaesthesiol 2015; 28:356–363.

40. ■■ Clevenger B, Mallett SV, Klein AA, Richards T. Patient blood management to reduce surgical risk. Br J Surg 2015; 102:1325–1337.
Review of current status of PBM and its application in surgical patient to prevent and manage anemia.

41. Munoz M, Gomez-Ramirez S, Kozek-Langeneker S, *et al.* 'Fit to fly': overcoming barriers to preoperative haemoglobin optimization in surgical patients. Br J Anaesth 2015; 115:15–24.

42. ■ Shander A, Goodnough LT, Javidroozi M, *et al.* Iron deficiency anemia: bridging the knowledge and practice gap. Transfus Med Rev 2014; 28:156–166.
Despite readily available strategies to prevent and manage anemia, opportunities to address anemia in perioperative settings are often easily lost. Some common barriers against effective management of anemia are discussed here.

43. Weltert L, Rondinelli B, Bello R, *et al.* A single dose of erythropoietin reduces perioperative transfusions in cardiac surgery: results of a prospective single-blind randomized controlled trial. Transfusion 2015; 55:1644–1654.

44. Auerbach M, Adamson J, Bircher A, *et al.* On the safety of intravenous iron, evidence trumps conjecture. Haematologica 2015; 100:e214–e215.

45. Koskenkorva-Frank TS, Weiss G, Koppenol WH, Burckhardt S. The complex interplay of iron metabolism, reactive oxygen species, and reactive nitrogen species: insights into the potential of various iron therapies to induce oxidative and nitrosative stress. Free Radic Biol Med 2013; 65:1174–1194.

46. 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.

47. Wang C, Graham DJ, Kane RC, *et al.* Comparative risk of anaphylactic reactions associated with intravenous iron products. JAMA 2015; 314:2062–2068.

48. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, *et al.* Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency dagger. Eur Heart J 2015; 36:657–668.

49. Onken JE, Bregman DB, Harrington RA, *et al.* A multicenter, randomized, active-controlled study to investigate the efficacy and safety of intravenous ferric carboxymaltose in patients with iron deficiency anemia. Transfusion 2014; 54:306–315.

50. Hogan M, Klein AA, Richards T. The impact of anaemia and intravenous iron replacement therapy on outcomes in cardiac surgery. Eur J Cardiothorac Surg 2015; 47:218–226.

51. Richards T, Clevenger B, Keidan J, *et al.* PREVENTT: preoperative intravenous iron to treat anaemia in major surgery – study protocol for a randomised controlled trial. Trials 2015; 16:254.

52. Blanchette NL, Manz DH, Torti FM, Torti SV. Modulation of hepcidin to treat iron deregulation: potential clinical applications. Expert Rev Hematol 2016; 9:169–186.

53. Hung M, Ortmann E, Besser M, *et al.* A prospective observational cohort study to identify the causes of anaemia and association with outcome in cardiac surgical patients. Heart 2015; 101:107–112.