

Peer Review File
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Reviewer A

| Original comments of the reviewer | Changes in text | Changes done on page number* |
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| <p>I suggest the order as Introduction, Epidemiology, Pathophysiology, Outcomes, Transfusion vs. Management of Anemia, Pre-operative Anemia Management, Intra-operative Anemia Management, Post-operative Anemia Management, Perioperative Anemia in Special Group of Population, and Future Directions. Please unify the format, whether you use capital letter or small letter for the headings and subheadings.</p> | <p>since the sequence of headings is re-ordered as per suggestion, page number in corrected manuscript has changed</p> | <p>Whole manuscript</p> |
| <p>Line 151: Consider describing the examples of chronic blood loss, such as GI bleeding, by adding a subheading “Acute Hemorrhage and Chronic Blood Loss</p> | <p>A new subheading has been added: “1. Acute hemorrhage and chronic blood loss”. The following text has been added under this subheading: “Preoperative anemia can result from acute hemorrhage in specific emergency surgery settings, e.g. ruptured abdominal aortic aneurysm, traumatic injury. Chronic blood loss may occur with gastrointestinal disorders such as ulcers, polyps, or colorectal cancer; tumors of the kidney or bladder; and heavy menstrual bleeding.” The numbering of subsequent subheadings has been adjusted.</p> | <p>Page 5</p> |
| <p>Lines from 193 to 196: Consider placing a new subheading to separate it from the other pathophysiology</p> | <p>A new subheading has been added before this paragraph: “7. Causes of intraoperative and postoperative anemia”. The first sentence under the subheading was modified slightly by removing the word “Additionally,” from the beginning of the sentence as follows. Original: Additionally, intraoperative and postoperative anemia may result from acute normovolemic hemodilution techniques for blood conservation or from infusion of priming solutions through the cardiopulmonary bypass circuit prior to cardiac surgery. Modified to: Intraoperative and postoperative anemia may result from</p> | <p>Page 7</p> |

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| | acute normovolemic hemodilution techniques for blood conservation or from infusion of priming solutions through the cardiopulmonary bypass circuit prior to cardiac surgery. | |
| Line 198: Consider making flow chart(s) for screening, evaluation, role of pharmacological agents in terms of preoperative anemia management. Please consider reading the article “Need for preoperative anemia management clinics in Japan: initiatives at a university hospital in the USA“ (PMID 34338863) for flow chart examples. | Algorithm 1 added under heading “Pre-Operative Anemia Management: Screening, Evaluation, Role Of Pharmacologic Agents” | Page 14 |
| Lines from 313 to 315: What type of surgery can have the most benefit from hypotensive anesthesia? Please specify. | Line added under heading “Anaesthesia and Role of Surgeon” - Out of all surgeries; head and neck surgeries like FESS, free flap reconstruction, head and neck onco-surgery benefit the most from hypotensive anesthesia. | Page 17 |
| Lines from 315 to 317: How hypotensive anesthesia reduces the rate of DVT and PE? What are the mechanisms? Please consider mentioning them. | By minimizing intra-operative blood loss, disturbances in coagulability decreases. Circulating anticoagulants like anti-thrombin III level decreases intra-operatively due to hemodilution, and there can be post-operative rebound increase in factor VIII which can cause hypercoagulability due to intraoperative blood loss. In this way, hypotensive anaesthesia by decreasing intra-operative blood loss indirectly helps to prevent DVT. Another reason is, if there is excessive fluid resuscitation, hypothermia can occur which triggers Virchow’s triad predisposing to DVT (76,77). Among safety benefits, dexmedetomidine helps in bradycardia, hypotension, pulmonary embolism, DVT | Page 17 |
| Lines from 326 to 331: Consider making a table where readers can easily find the indication, the mechanism of actions, doses, etc., of each hemostatic agent. | Table 1 | Page 18 - 19 |
| Lines from 326 to 331: Consider mentioning recombinant factor VIIa (eptacog alfa), as it is often used in cardiac surgery in the US. Also, although they are not hemostatic agents, please consider mentioning antifibrinolytic agents, such as aminocaproic acid and tranexamic acid, as they are frequently used to reduce perioperative blood loss. | <ol style="list-style-type: none"> 1. In a study conducted on patients with elective orthopaedic surgery who are hemophiliacs with inhibitors, eptacog alfa has been used in initial bolus dose, which helped in overcoming bleeding episodes perioperatively. 2. The off-label use of eptacog alfa has also increased in paediatric cardiac surgery as it acts as effective rescue therapy 3. The hemostatic registry has compiled the data regarding off-label | Page 18 |

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| | <p>use of hemostatic agents in cardiac surgery , traumatic surgery, obstetric surgery and medical bleed over 10 years.</p> <p>4. In UK, tranexamic acid is widely used in cardiac, orthopaedic, liver, gynaecological , neurosurgeries, whereas ε-aminocaproic acid is widely used in USA. Both Tranexamic acid and ε-aminocaproic acid are synthetic lysine analogues that act by blocking plasminogen and prevents activation to plasmin , thereby stops fibrin degradation.</p> | |
| Lines from 339 to 341: Please consider placing citation(s). | Shander A. Preoperative anemia and its management. Transfus Apher Sci. 2014;50:13-5 | Page 20 |
| Lines from 348 to 349: Please consider placing citation(s). | (https://www.who.int/publications/i/item/9789240033733) | Page 20 |
| Lines 360 to 361: Please consider placing citation(s). | <p>Shander A. Preoperative anemia and its management. Transfus Apher Sci. 2014;50:13-5, Am J Obstet Gynecol. 2019 Jul;221(1):19-29.e3. doi: 10.1016/j.ajog.2018.12.016. Epub 2018 Dec 19.</p> <p>Oral vs intravenous iron therapy for postpartum anemia: a systematic review and meta-analysis Pervez Sultan, Sohail Bampoe , Raj Shah, Nan Guo, Jaclyn Estes, Christopher Stave, Lawrence Tim Goodnough, Stephen Halpern, Alex James Butwick PMID: 30578747 PMCID: PMC7060493 DOI: 10.1016/j.ajog.2018.12.016</p> | Page 20 |
| Line 368: Please consider placing citation(s). | (Semin Thromb Hemost. 2005;31(4):426-40. doi: 10.1055/s-2005-916678. Perioperative monitoring of primary and secondary hemostasis in coronary artery bypass grafting Hans-Jörg Hertfelder, Monika Bös, Dagmar Weber, Kai Winkler, Peter Hanfland, Claus J Preusse PMID: 16149021 DOI: 10.1055/s-2005-916678 | Page 20 |
| Line 375: Please consider spelling out PF24. | plasma frozen within 24 hours (PF24) | Page 21 |
| Lines from 394 to 395: Please consider deleting this sentence as this is not directly related to the content of the paragraph. | deleted | Page 21 |
| Lines from 396 to 397: Please consider using either Hct (%) or Hb (g/dL), instead of mixing them over the two sentences. | If the hemoglobin is below 7 g/dL RBC | Page 22 |

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| <p>Lines from 409 to 412: Please consider relocating or deleting the paragraph as the content is not related to pharmacologic agent.</p> | <p>moved paragraph from pharmacologic to post-operative bleeding management.</p> | <p>Page 21-22</p> |
| <p>Lines from 419 to 417: Please consider deleting “Although thorough care of these patient groups is outside the range of this paper,”.</p> | <p>“Although thorough care of these patient groups is outside the range of this paper, there remain a number of vital factors that need to be kept in mind” is modified as “For these special cases, there remain a number of vital factors that need to be kept in mind”</p> | <p>Page 23</p> |
| <p>Lines from 464: Please consider mentioning about the challenge of applying preoperative anemia management to our perioperative practice.</p> <p>Even if we know that the treatment of preoperative anemia brings positive patient outcomes, applying the management to our practice is a different issue. We may need a system where we can detect anemic patients and initiate treatment in a timely manner. Who can order lab tests to make a diagnosis and initiate treating anemic patients (Hb<13) eight weeks prior to surgery? Who is responsible for ensuring that all surgical patients are appropriately managed prior to surgery? Is it the responsibility of a family practitioner, surgeon, or anesthesiologist? Establishing a preoperative anemia clinic for surgical patients is one way to solve the problem. Please consider reading the article “Need for preoperative anemia management clinics in Japan: initiatives at a university hospital in the USA“ (PMID 34338863) for more detail. I hope the authors add discussion regarding this point in the manuscript.</p> | <p>Paragraph added under heading “Future Directions of Perioperative Anemia Management”</p> <p>A key element of optimisation of perioperative anaemia is the establishment of preoperative anaemia clinics. Depending on locally available knowledge and experience of PBM and anaemia management, this can be run by a clinical nurse practitioner, a general medical practitioner or a specialist (e.g. surgeon, anaesthesiologist, haematologist, etc.). Hospitals should be encouraged to make the investment as the likely future savings, coupled with the ethical imperative of improving patient outcomes, should be more than enough compensation for any costs incurred.</p> | <p>Page 26</p> |

Reviewer B

| Original comments of the reviewer | Changes in text | Changes done on page number* |
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| The manuscript would benefit from further proofreading. There are a number of grammatical/syntax errors and missing words which detract from the quality of the manuscript. | Whole manuscript | |
| The manuscript would benefit from a formal conclusion summarising the key points of the paper. | | Page 28 |
| Comments regarding the role of gender or body mass index/body surface area in the incidence of anaemia and its impact on outcomes would be a welcome addition to the paper | The following text has been added in the "Epidemiology – Prevalence of perioperative anemia" section (Line 96 in original version): “Since females generally have a smaller body surface area and lower total blood volume compared to males, an equivalent loss of blood volume during surgery represents a higher proportion of hemoglobin mass lost and a concomitantly higher likelihood of red blood cell transfusion. Therefore, utilizing a criterion of hemoglobin less than 130 g/L for preoperative anemia in females may be more appropriate.” | Page no 4 |