Perioperative allogenic red blood cell transfusion: available guidance and audit of appropriateness in liver resection

Laura Baker, MDCM, BSc (Honors), MSc Candidate

Supervisors: Guillaume Martel & Dean Fergusson

uOttawa

The University of Ottawa

Abstract

Red blood cells are commonly administered during the perioperative period, however our understanding of available guidance informing transfusion decisions as well as appropriateness of current practice is not well understood. Blood transfusions are associated with post-operative morbidity and possibly worse long-term outcomes. Furthermore, they are a costly and limited resource. They should therefore be used sparingly. The objective of this thesis was to further our understanding of guidance available for administration of intraoperative red blood blood cell transfusion, as well as conduct an audit of the appropriateness of transfusions administered during the perioperative period. This thesis is composed of both a systematic review as well as a retrospective review of a prospectively maintained database. The systematic review of identified 10 guidelines published between 1992-2018 that included indications for intraoperative transfusions. Six provided objective clearly defined criteria for transfusion based on hemoglobin triggers (range 60-100g/L) or hematocrit (<30%); one stated a specific clinical situation for which transfusion would be appropriate (ST changes). The evidence supporting intraoperative recommendations was extrapolated primarily from the non-operative setting. Retrospective review of a single centre revealed 19% of patients underging liver resection were transfused a mean of 2.6 units during the perioperative period. A total of 22% to 63% of transfusions administered during the intraoperative period were considered inappropriate based on the application of three different instruments. In contrast, 38% to 67% of transfusions administered during the postoperative period were considered inappropriate. Patients considered to have been inappropriately transfused during the intraoperative period were at increased risk of developing a major postoperative adverse event (Clavien-Dindo≥grade 3) compared to those who did not receive a transfusion (OR 4.2; 95% CI 1.1-15.6). In conclusion, this thesis demonstrates evidence-based, practitioner oriented, intraoperative transfusion guidance for clinicians is lacking. Furthermore, a significant proportion of patients continue to be exposed to unnecessary transfusion. Further work in this area is warranted to clarify indications for intraoperative transfusion and subsequently minimize the administration of unnecessary transfusion.

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1. INTRODUCTION & THESIS OUTLINE

Red blood cells are commonly administered during the perioperative period, however our understanding of available guidance informing transfusion decisions as well as appropriateness of current practice is not well understood. Blood transfusions are associated with post-operative morbidity and possibly worse long-term outcomes. Furthermore, they are a costly and limited resource. They should therefore be used sparingly.

This thesis examines the available guidance for intraoperative red blood cell transfusions. It also includes an audit and evaluation of appropriateness of perioperative red blood cell transfusion in patients undergoing liver surgery, a patient population at increased risk of transfusion.

This thesis consists of three manuscripts-either published or in preparation for submission to peer-reviewed journals:

1. Guidelines on the intraoperative transfusion of red blood cells: a protocol for systematic review (published)
2. Guidelines on the intraoperative transfusion of red blood cells: a systematic review (published)
3. An audit and evaluation of appropriateness of blood transfusion in liver surgery: application of three decision rules (in preparation)

2. GUIDELINES ON THE INTRAOPERATIVE TRANSFUSION OF RED BLOOD CELLS: A PROTOCOL FOR SYSTEMATIC REVIEW

Laura Baker[1,2,3,4], Lily Park[4], Richard Gilbert[1,4], Andre Martel[1,4], Hilalion Ahn[4], Alexandra Davies[5], Daniel McIsaac[2,3,6] Elianna Saidenberg[2,7], Alan Tinmouth[2,3,7], Dean Fergusson[2,3], Guillaume Martel[1,2,3]

Liver and Pancreas Unit, Department of Surgery, The Ottawa Hospital[1]

Ottawa Hospital Research Institute[2]

School of Epidemiology and Public Health, Faculty of Medicine, The University of Ottawa[3]

Faculty of Medicine, The University of Ottawa[4]

Learning Services, The Ottawa Hospital[5]

Departments of Anesthesiology & Pain Medicine, University of Ottawa and The Ottawa Hospital[6]

Division of Hematology, Department of Medicine, The Ottawa Hospital[7]

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2.1 Abstract

Introduction A significant proportion of red blood cell transfusions are administered intraoperatively; yet there is limited evidence to guide transfusion decisions in this setting. The objective of this systematic review is to explore the availability, quality and content of clinical practice guidelines (CPG) reporting on the indication for allogenic RBC transfusion during surgery.

Methods Major electronic databases (MEDLINE, EMBASE and CINAHL), guideline clearinghouses and Google Scholar, will be systematically searched from inception to January 2019 for CPGs pertaining to indications for intraoperative allogenic RBC transfusion. Characteristics of eligible guidelines will be reported in a summary table. The AGREE II instrument will be used to appraise the quality of identified guidelines. Recommendations advising on indications for intraoperative RBC transfusion will be manually extracted and presented to allow for comparison of similarities and/or discrepancies in the literature. .

Ethics and dissemination The results of this systematic review will be disseminated through relevant conferences and peer-reviewed journals.

Protocol registration number PROSPERO CRD42018111487

2.2 Introduction

Red blood cell (RBC) transfusions although potentially lifesaving, are a costly and limited resource, associated with possible harm. Potential adverse outcomes range in severity, from minor to life-threatening. Relatively mild reactions include febrile non-hemolytic transfusion reactions, minor allergic reactions, or development of RBC alloantibodies. RBC alloantibodies can usually be managed with the provision of antigen negative products (1)(2). However, in the case of rare antibodies, development of alloantibodies can complicate administration of future blood products (1). Life-threatening transfusion reactions include anaphylaxis, transfusion related acute lung injury, bacterial contamination of blood products resulting in sepsis, acute hemolytic transfusion reactions, and transfusion associated circulatory overload (1)(2). While the risk of transfusion transmitted viral infections has dropped drastically in recent years and the risk of this occurring is extremely low, it remains a concern when deciding to transfuse patients (2). RBC transfusions may also cause immunosuppression in the recipient, a process called “transfusion-related immunomodulation (TRIM) (3). TRIM provides rationale for the negative association observed between RBC transfusion and post-operative adverse events as well as cancer recurrence in patients undergoing oncology surgery (4) (5) (6) (7) (8) (9) (10). There is mounting evidence demonstrating patients who receive perioperative blood transfusions suffer from early oncologic recurrence and worse long-term survival. A recently published retrospective review on patients with oral squamous cell carcinoma undergoing surgical resection with curative intent reported a significant reduction in 5 year overall survival in those transfused (41% versus 70%; $p<0.001$). This difference was persisted when controlling for demograhic, clinical and hisopathologic features (11). Furthermore, this relationship was demonstrated to be dose-dependent. Patients with increasing numbers of transfusions were demonstrated to have worse overall and recurrence free survival, on multivariate analysis. Another retrospective review of 287 patients undergoing pancreatic resection identified intraoperative blood transfusion as independent predictor of reduction in disease free survival (12). There are several systematic reviews reporting on the deleterious oncologic effects of transfusion

admistered during the perioperative period at the time of surgical management of colon, hepatobiliary and prostate cancers (12) (13) (14). At an estimated price tag of 102-761 USD per unit, RBC transfusions are costly (15) (16) (17) (18). They are also in short supply, relying on altruistic blood donors to ensure inventory stability (19) (20). Given their associated risk, expense and scarcity, it is critical they are administered wisely.

There has been significant evolution in our understanding of humans' ability to tolerate anemia; resulting in a shift in approach to RBC transfusion prescribing practices from the "10/30" rule (i.e. transfusion indicated below a hemoglobin of 10g/L or hematocrit <30%) to the widely accepted transfusion trigger of 70g/L in the asymptomatic patient without significant cardiac comorbidity. This change came into effect following reporting of the TRICC trial and others that have shown the safety of a restrictive transfusion threshold **(21, 22) (23) (24)**. Importantly, the findings of these studies, which have impacted transfusion practices across a broad spectrum of clinical scenarios, are not necessarily applicable in the operative setting.

The operative setting presents a unique situation in which the indications for transfusion commonly reported in the non-operative patient have limited transferability. As blood loss, and consequently hemoglobin concentration can be unpredictable during surgery, hemoglobin concentrations may drop suddenly, making previous measurements of hemoglobin concentration invalid. This limits the feasibility of utilizing specific hemoglobin levels to guide RBC transfusion administration in surgical patients **(25)**. There is some literature to suggest estimated surgical blood loss can be utilized to guide transfusion decisions **(26) (27)**. However, there is good evidence to support the inability of clinicians to accurately predict blood loss **(28)**. It is also important to appreciate that not all intraoperative bleeding is the same, varying from a persistent, slow ooze, to massive, rapid blood loss from a major vessel. Additionally, reliance on hemodynamics is complex as in addition to blood loss, it is a reflection of multiple variables, including but not limited to: anesthetic agents, patient positioning, presence of pneumoperitoneum and neurologic stimulation **(29)**. In the non-operative setting, acute blood loss of approximately 20% results in a compensatory tachycardia **(30)**. However, because of the other variables at play in the anesthetized patient,

tachycardia is not a reliable marker of blood loss. Another common recommendation is to monitor for the presence of inadequate perfusion and oxygenation of vital organs **(27)**. The ability to monitor for symptoms of decreased end-organ perfusion such as decreased level of consciousness, chest pain, or abdominal pain, are not possible in the unconscious patient under general anesthesia. Incorporation of decision rules specific to surgical patient, such as monitoring for ST changes, are fundamental to guiding appropriate RBC transfusion for a patient under general anesthesia for surgery**(31)**. Another aspect unique to the unconscious patient under general anesthesia, subject to dynamic changes in hemodynamics for a number of reasons, is our limited ability to identify transfusion reactions. Although literature in this area is lacking, it would be reasonable to hypothesize that transfusion reactions in the intraoperative setting are underreported. This, in combination with the evidence that patients who receive intraoperative transfusions suffer increased short and long term morbidity, advocates for careful consideration of transfusion administration **(32)** (7).

The uncertainty of transfusion indications in this patient population is demonstrated by the abundance of literature reporting on the wide variability in transfusion practices but largely reporting over-transfusion of surgical patients **(33) (34) (35) (36) (37)**. A 2007 audit of 1112 RBC transfusions reported a high incidence of overtransfusion **(33)**. Patient's hemoglobin concentration in the recovery room was evaluated to determine appropriateness of intraoperative transfusions. Based on the 1996 American Society of Anesthesiology (ASA) Guidelines, which specifies that transfusion is rarely indicated when hemoglobin is >100g/L, a significant proportional of patients were considered to have been overtransfused (38). Five percent of patients transfused has post-operative hemoglobin concentrations greater than or equal to 140g/L and forty-nine percent creater than or equal to 100g/L. Another audit of intr-operative transfusion practices in elective non-cardiac surgery reported 19% of transfusions were in appropriate. Similarly to the previously mentioned study, transfusion for a hemoglobin concentration >110g/dL was considered inappropriated based off the ASA guidelines (35). A recent survey of Canadian liver surgeons and anesthesiologists highlights the lack of consensus between practitioners regarding indications for transfusion. In response to the

question “what is the most important information you use to decide on intraoperative transfusion,” the majority of anesthesiologist selected hemoglobin value (47.2% vs 19% of surgeons; $p<0.05$), whereas surgeons selected hemodynamics (33.4% vs 14% of anesthesiologist; $p>0.05$) (39). A prospective observational study of intraoperative transfusion practices in Europe reported “physiologic trigger irrespective of hemoglobin” as the most common indication for transfusion in a cohort of 5803 patients (40). Despite a global shift to a more restrictive transfusion strategy, wide variability in practice patterns in the intraoperative setting exists, and therefore warrants a review of the recommendations.

A preliminary search reveals guidance pertaining to RBC transfusion in the intraoperative patient population is lacking. Recently published guidelines from AABB, a worldwide leader in producing clinical practice guidelines for utilization of blood components, neglected to provide recommendations on indications for RBC transfusion in the intraoperative setting likely due to a lack of evidence on which to base recommendations **(41)**. Guidelines endorsed by surgical and anesthesia societies offer vague recommendations with limited directives for when to transfuse, for example, to monitor for blood loss, check hemoglobin or hematocrit prior to transfusion, adopt a restrictive transfusion strategy or assess for adequate perfusion and oxygenation **(42) (43) (38) (44) (45)**. As alluded to previously, reliance on these variables is limited in the intraoperative period. A formal review of the literature to understand available guidance for intraoperative RBC decisions is necessary.

In summary, blood transfusions are associated with possible harm and over-transfusion in the intraoperative setting is common. Although there is an abundance of guidance pertaining to indications for RBC transfusion, a review of guidance dedicated to the intraoperative patient does not currently exist.

2.3 Objective

The objective of this systematic review is to explore the availability, quality and consistency of published guidelines reporting on the indication for allogenic red blood cell

transfusion in the intraoperative setting. We also aim to summarize the existing recommendations and associated level of evidence.

2.4 Methods

The Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) checklist guidelines were referenced for development of this protocol (46) (47). A PRISMA-P checklist is available as a supplementary document. The protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews on October 16, 2018 (CRD42018111487).

Any amendments made to the current protocol will be published using a protocol addendum, accompanied by the date of and rationale for the reported amendment, with the final manuscript.

Eligibility criteria:

Guidelines reporting on indications for allogenic red blood cell transfusion in the intraoperative setting will be considered for inclusion. Our definition of clinical practice guidelines is adopted from the Institute of Medicine and National Guideline Clearinghouse which define them as recommendations, derived from systematic review of evidence, from collective opinions of an expert panel, aimed at health care providers intended to improve patient care (48, 49). An article will be included if it: (1) is presented as a clinical practice guideline; (2) is based on a systematic review of evidence; (3) is produced by a medical association, professional society, public or private organization or government agency and not by an individual(s) not sponsored or supported by the above groups; (4) includes recommendations for indications for allogenic red blood cell transfusion in patients undergoing general anesthesia in an operating room; (5) in any language; (6) full-text available.

We plan on excluding: (1) documents that do not meet the definition of a guideline as stated above; (2) guidelines pertaining to the perioperative period that do not make specific recommendations on the intraoperative setting (3) previous documents replaced by updated versions from the same organization.

Information sources and search strategy

MEDLINE (OVID interface, including In-Process and Epub Ahead of Print) and EMBASE (OVID interface) and CINHAL will be systematically searched from inception to January 2019, through application of a search strategy developed by a health science librarian with expertise in systematic reviews. Search terms will include 'allogenic red blood cell transfusion', 'guideline' and 'operative'. The search will not be restricted by date, language or patient population (ie. adult versus pediatric). A Peer Review of Electronic Search Strategies (PRESS) will be performed by a second information specialist who is not associated with the project. A draft search strategy for Medline can be found in Appendix 1. The following guideline-specific databases will also be searched: National Institute for Health and Care Excellence (NICE) (UK), the Canadian Medical Association Infobase (Canada), the G-I-N International Guideline Library, the New Zealand Guidelines (NZG) Group, The World Health Organization and the Scottish Intercollegiate Guidelines Network (SIGN) (50-55). Google Scholar will be searched with '(intraoperative OR perioperative) AND (guideline OR consensus OR recommendation OR statement)' and the first 200 records will be screened. References of identified articles will be reviewed for relevant guidelines.

Study Records

Articles identified through the electronic databases (MEDLINE and EMBASE) will be imported into Covidence, an online citation manager (56). All titles and abstracts identified will be independently screened by two reviewers for relevance and categorized as relevant, possibly relevant, or irrelevant. Articles categorized as relevant or possibly relevant will be retrieved for further evaluation. Full texts will also reviewed in duplicate for eligibility. Google translate will be used to translate non-English, non-French articles, with the exception of those written in Chinese (57). Any disagreement regarding relevancy will be resolved by a senior author, independent from the reviewers. Reason for study exclusion will be documented and presented in the PRISMA flow diagram for study screening (Figure 1).

Guidelines identified from the guideline repositories will be recorded in an Excel spread sheet.

Data Items

Data pertaining to the publication details (authors, year of publication, journal, etc) will be identified. All relevant recommendations will be extracted from the guidelines to aid in the determination of population(s) in which the intraoperative transfusion guidelines pertain to (type of surgery), patient variables taken into consideration in determining appropriateness for transfusion, and grading of recommendation if assigned will be extracted. We will identify whether or not the following variables are accounted for in identified decision rules or recommendations: patient comorbidities-specifically a history of coronary artery disease, hemodynamics (hypotension, tachycardia, or presence of vasopressor support), estimated blood loss, evidence of cardiac ischemia, and evidence of end organ ischemia in addition to cardiac. Data extraction forms (DEF) will be developed and piloted independently by two reviewers on a set of 5 randomly selected guidelines. Modifications will be made to the DEF as necessary. Data will be extracted independently by two reviewers, in duplicate.

Outcomes & Prioritization

The objectives are to (1) characterize the clinical practice guidelines advising on intraoperative RBC utilization (2) appraise their quality and (3) provide a descriptive summary of the included guidelines.

Characterization of identified guidelines

A descriptive table of identified guidelines will be presented. This table will include information publication information as well as the target patient population of the guideline.

Guideline quality assessment: AGREE II

The Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument will be used to assess the quality of included guidelines (58). The AGREE II instrument is a validated questionnaire aimed at assessing the methodologic quality of clinical practice guidelines and has been widely adopted in the scientific literature (58) (59) (60). It is comprised of 23 questions scored on a seven-point Likert scale (whereby 7 indicates the highest quality), covering 6 domains, inclusive of scope and purpose of the guidelines, stakeholder involvement, rigour of development, clarity of presentation and editorial independent. There

are two additional questions. The first assesses the overall quality of the guideline, rated on a seven-point Likert scale. The final question asks the evaluator whether they would recommend using this guideline, to which the assessor responds “yes,” “yes, with modifications,” or “no.”

It is recommended that four assessors complete the AGREE II to achieve an intra-class correlation coefficient ≥0.7. Four appraisers will therefore be selected to complete the online training and independently evaluate the included guidelines. Once complete, the evaluators will meet and discuss any scores differing by more than 1 point. At that point, evaluators can amend or keep their original score. Inter-rater reliability will be calculated using the intraclass correlation coefficient (ICC) using SAS.

Domain scores will be reported separately using both the median and scaled domain scores, as is recommended by the AGREE II consortium. The scaled domain score will be calculated as follows: (obtained score-minimal possible score)/(maximal possible score-minimal possible score)=__%. The minimum possible score is calculated as: (number of questions) x (number of reviewers) x 1. The maximum possible score is calculated as: (number of questions) x (number of reviewers) x 7.

Recommendation synthesis

A descriptive table of included studies will be presented displaying all recommendations pertaining to indications for RBC transfusion in the intraoperative period. Recommendations will be compared for consistency and/or repetition.

Analysis of subgroups or subsets

Guidelines pertaining to indications for blood transfusion in cardiac versus non-cardiac surgery patients will be grouped and considered separately. In addition, guidelines published following publication of the TRICC trial in May 1997 will be considered separately in our descriptive analysis (22). The rationale for this being that the prevailing theme of current practice is a result of this trial.

Dissemination

The results of this review will be submitted for presentation at national and international meetings and publication in a peer-reviewed journal.

Reporting of review

The findings of this systematic review will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. The completed checklist will be provided as supplementary material.

Confidence in cumulative evidence

The quality of recommendations will be evaluated by using the systematic and comprehensive approach known as Grading of Recommendations, Assessment, Development and Evaluations (GRADE) (61). The quality of evidence will be assessed across the domains of risk of bias, consistency, directness, precision and publication bias.

Patient and public involvement

This investigation is aligned with research priorities established by The Canadian Blood Services (CBS), a not-for-profit charitable organization, responsible for managing the Canadian blood supply (with the exception of Quebec) (62). Specifically, they have identified: (1) promoting appropriate blood product utilization and (2) ensuring an adequate blood product supply, as two of five research priorities. CBS invites public participation in their bi-annual board meetings, where a number of issues are addressed, inclusive of priority research agendas. Patients or the public were not involved in the development of our specific research question or outcome measures of interests.

2.5 Discussion

A significant number of patients receive intraoperative transfusion. However, there is substantial variation in transfusion practice and a paucity of guidance available. Despite the fact that a plea for intraoperative blood transfusion guidelines was made over 20 years ago, widely adopted recommendations have yet to be developed. (63) A systematic review of transfusion guidelines in the intraoperative setting has not previously been performed. Although a quality appraisal of RBC and plasma guidelines was published in 2018, it did not

identify intraoperative recommendations (42). Additionally, their search strategy did not include guideline clearinghouses or the grey literature.

There are several methodologic strengths of our review, these include multidisciplinary input, a PRESS reviewed search strategy, review of the grey literature and application of the AGREE II tool to assess the quality of identified guidelines by four independent reviewers.

This systematic review will allow for identification, appraisal and summary of literature devoted to the guidance of intraoperative allogenic RBC transfusion. The Perioperative Anesthesia Clinical Trials Group (PACT) identified transfusion as 1 of 7 themes that has a significant impact on mortality, reinforcing the importance of this review (64). The results of this review will provide rationale and justification for development of guidance, or the need for prospective evaluation of various intraoperative transfusion strategies. If evidence-informed recommendations for the use of intraoperative transfusion can be developed and disseminated the incidence of over-transfusion may be reduced, ensuring responsible use of this limited resource, and minimizing patient exposure to the risks of transfusion.

To achieve this goal will require collaboration between surgeons, anesthetists, and transfusion specialists. Given the paucity of high quality data on which to base guidelines, this collaboration must first identifies areas where only expert opinion exists and propose methods for further examination. The input of patients who have had intraoperative transfusion should be sought to determine where patient preference may supersede rigorous adherence to guidelines. Following well planned knowledge translation phase, auditing to monitor compliance with the guidelines will need to be done. Additionally, following guideline implementation quality assurance initiatives with patient centred outcomes will also be necessary to ensure that the safety and tolerability of developed guidelines. Thus, it is unlikely that final guideline recommendations regarding intraoperative transfusion will be forthcoming in the near future. However, this review reinforces the urgent need to begin the undertaking.

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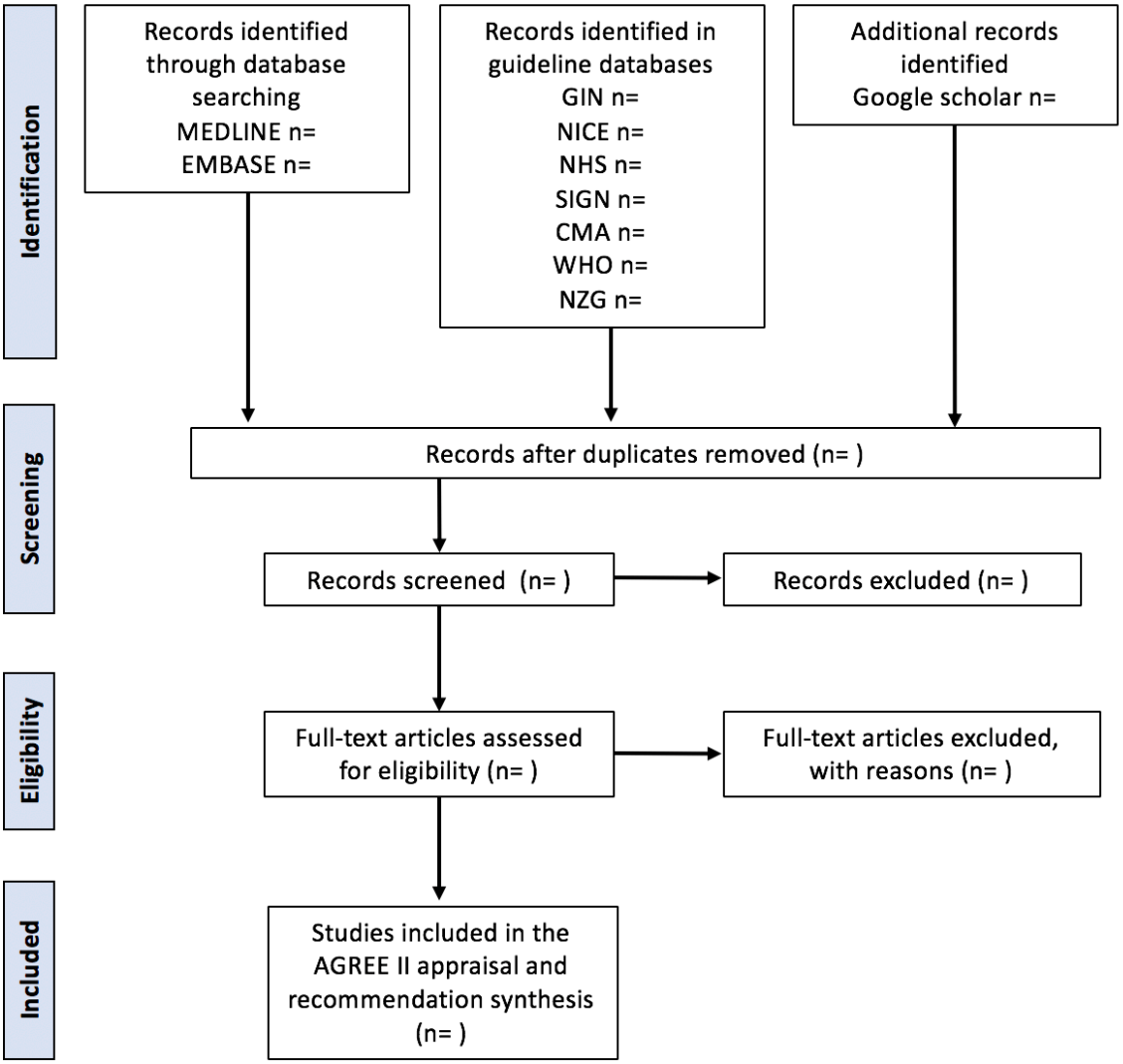

Figure 1. Flow diagram of study selection process.

3. GUIDELINES FOR THE INTRAOPERATIVE TRANSFUSION OF RED BLOOD CELLS: A SYSTEMATIC REVIEW

Laura Baker[1,2], Lily Park[1], Richard, Gilbert[1], Hilalion Ahn[1], Andre Martel[1], Alexandra Davis[3], Elianna Saidenberg[2,4], Daniel I McIsaac[2,5], Alan Tinmouth[2,4], Dean Fergusson[2,6], Guillaume Martel[1,2]

Department of Surgery, Liver and Pancreas Unit, The Ottawa Hospital[1]

Clinical Epidemiology Program, Ottawa Hospital Research Institute[2]

Learning Services, The Ottawa Hospital[3]

Department of Medicine, Division of Hematology, The Ottawa Hospital[4]

Departments of Anesthesiology & Pain Medicine, The Ottawa Hospital and University of Ottawa[5]

Department of Medicine, University of Ottawa[6]

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3.1 Abstract

Introduction: Red blood cell (RBC) transfusions are common during surgery, yet there is limited evidence guiding indications for their administration in this setting. The objective of this systematic review is to explore the availability, content and quality of published clinical practice guidelines (CPG) reporting on the indications for allogenic RBC transfusion in the intraoperative setting.

Methods: Major electronic databases (MEDLINE, EMBASE and CINAHL), guideline clearinghouses and Google Scholar were systematically searched from inception to January 2019 for CPGs pertaining to indications for intraoperative allogenic RBC transfusion. Identified guidelines meeting our eligibility criteria were reported and their quality assessed using the AGREE II instrument. Relevant recommendations were abstracted and synthesized to allow for a comparison of similarities and/or discrepancies between guidelines.

Results: No guideline exclusively dedicated to intraoperative transfusion decision making was identified. Ten guidelines published between 1992-2018 included indications for intraoperative transfusions. Six provided objective clearly defined criteria for transfusion based on hemoglobin triggers (range 60-100g/L) or hematocrit (<30%); one stated a specific clinical situation for which transfusion would be appropriate (ST changes). CPGs recommended considering blood loss (n=7), signs of end organ ischemia (n=5) and hemodynamics (n=3) in the absence of clear directives for transfusion. The evidence supporting intraoperative recommendations was extrapolated primarily from the non-operative setting. There was wide variability in the quality of included guidelines based on AGREE II scores.

Conclusion: Evidence-based intraoperative transfusion guidance for clinicians is lacking. Given the magnitude and importance of transfusion events in surgery, this represents a major evidence gap.

Protocol registration number PROSPERO CRD42018111487

Keywords: transfusion; blood; surgery; anesthesiology; clinical practice guideline; decision-making

Summary Boxes

Section 1: What is already known on this topic

- Although potentially life-saving, intraoperative red blood cell (RBC) transfusions are associated with a dose-dependent increased risk of post-operative morbidity and mortality.
- Intraoperative RBC transfusion practices highly variable amongst medical providers.
- In contrast to the non-operative setting, a universally agreed upon transfusion strategy does not exist, therefore a review of clinical practice guidelines reporting on indications for intraoperative RBC transfusion was preformed.

Section 2: What this study adds

- This study demonstrates that high quality, user friendly, evidence-based recommendations guiding intraoperative red blood cell utilization are lacking.
- Further investigation to determine optimal approach to guide RBC transfusion in the operating room is necessary.

3.2 Background

Red blood cell (RBC) transfusions are potentially life-saving, but they can also at times be inappropriate and potentially harmful interventions. RBC transfusions carry specific risks that range from mild to life threatening **(65) (66)**. Intraoperative transfusions have been identified to be associated with a dose-dependent increased risk of post-operative morbidity and mortality **(4, 5, 8, 9, 65-67)**. Transfusion associated immunomodulation "TRIM" is hypothesized to attribute to the increased infectious complications, delayed recovery and possibly worse cancer-specific survival observed with intraoperative RBC transfusion (4, 5, 9). In addition to being associated with possible harm, RBCs are a costly and limited resource **(17, 19, 20)**. The decision to administer an RBC transfusion must therefore be considered carefully.

Despite the fact that almost one quarter of the 15 million units of packed RBCs administered annually in the United States are used in surgical patients, guidance pertaining to their administration in this setting is limited (68). A high degree of variability in intraoperative RBC transfusion practice supports the lack of clarity surrounding the management of this unique patient population (69, 70). Guidelines exist to help clinicians make evidence-based decisions about transfusion and avoid unnecessary transfusions (41, 71). These have traditionally been limited to care provided in emergency units, as well as to medical and surgical wards, and are thus likely to have limited generalizability to the surgical patient under general anesthesia. A recent systematic review reported on the quality of evidence-based RBC and plasma transfusion guidelines. It identified 26 guidelines reporting on RBC transfusions, of which only 4 were targeted to anesthesiologists or surgeons **(27, 42-45)**. Furthermore, a summary of recommendations guiding RBC administration in the intraoperative setting does not appear to exist.

A surgical patient is at risk of acute and rapid blood loss. Therefore, transfusion triggers or hemoglobin concentrations at which a transfusion is indicated do not always apply **(25)**. In the non-surgical patient, hemodynamic instability can be a reflection of anemia and is utilized to guide the need for transfusion following acute blood loss. However, in surgical patients, variations in hemodynamic changes may result from potent pharmacologic agents, patient positioning, mechanical ventilation, surgical manipulation, abdominal insufflation with gas, as well as surgical blood loss **(29)**. Transfusion guidelines commonly recommend transfusing for clinical evidence of end-organ ischemia, however in the anesthetized patient, clinical symptoms which would normally prompt investigation cannot be assessed **(27)**.

Given the potential harm of inappropriate transfusion, as well as the significant expense and scarcity of RBCs, it is clear that evidence-based recommendations are needed to guide transfusion decision-making. The unique and dynamic features of surgical patients necessitate that such recommendations be specifically targeted to intraoperative management.

3.3 Objective

To address this high priority knowledge gap, the objective of this work was to carry out a systematic review of published guidelines reporting on the indication for allogenic red blood cell transfusion in the intraoperative setting. Specifically, we sought to determine whether such guidelines were available, to examine their quality, and to synthesize their recommendations.

3.4 Methods

A systematic review of Clinical Practice Guidelines (CPGs) reporting on indications for intraoperative RBC transfusion was performed using the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement (46) (47). The PRISMA-P checklist is presented in Appendix 1. The protocol for this systematic review was registered with PROSPERO (CRD42018111487) and published (72).

Eligibility criteria

All CPGs providing recommendations on the use of allogenic RBCs in the intraoperative setting were considered for inclusion. We defined a CPG as recommendations aimed at health care providers intended to improve patient care, based on the following criteria: 1) systematic review of the evidence; 2) produced by a medical association, professional society, public or private organization, or government agency, and not by an individual(s) not sponsored or supported by one of the above groups (48, 49).

Guidelines that failed to explicitly state that recommendations were indicated for the surgical patient in the intraoperative setting were excluded. If multiple editions from the same guideline were identified, the most recent CPG was included.

Information sources and search strategy

A Peer Reviewed Electronic Search Strategy (PRESS) was devised by medical librarians with expertise in systematic review. The following databases were systematically searched from inception to January 18, 2019: MEDLINE (OVID interface, including In-Process and Epub Ahead of Print), EMBASE (OVID interface) and CINHAL. The search

strategy included a combination of MeSH terms and search terms such as ‘red blood cell transfusion’, ‘guideline’ and ‘operative’. The search strategy for MEDLINE is presented in Appendix 2. There were no date or language restrictions. Additionally, the following guideline databases were manually searched in duplicate: the National Institute for Health and Care Excellence (NICE), the Canadian Medical Association Infobase, the G-I-N International Guideline Library, the New Zealand Guidelines (NZG) Group, The World Health Organization, and the Scottish Intercollegiate Guidelines Network (SIGN). A manual search of the first 200 hits on Google Scholar was performed on January 10, 2019, using the following search terms: “intraoperative,” “guidelines,” and “red blood cell transfusions.” Finally, the references of eligible guidelines were manually reviewed for any relevant missing citations.

Study records

Covidence (Melbourne, Australia) was used as an online citation manager to screen articles identified from electronic databases (56). Guidelines identified from guideline databases were recorded separately in an Excel (Microsoft Corporation, Redmond, WA) spread sheet. Titles and abstracts screening was performed in duplicate by two independent reviewers (LB and LP). Articles advanced to full-text screening were reviewed in duplicate for eligibility (LB and LP). Any disagreement regarding relevancy were resolved by the senior authors (GM and DF). Reasons for study exclusion were documented and presented in the PRISMA flow diagram (Figure 1).

Data items

The following characteristics were extracted by two reviewers independently: publication details (authors, year of publication, journal, etc), surgical population that is targeted by the intraoperative transfusion guidelines, patient variables taken into consideration in determining the appropriateness of transfusion (eg. hemodynamics, blood loss, evidence of cardiac ischemia, etc.), and grading of recommendations. Data extraction forms (DEF) were developed and piloted independently by two reviewers (LB and LP) on a set of 5 randomly

selected guidelines. Modifications were made to the DEF as necessary. Discrepancies were discussed until a consensus was reached on data items of interest.

Data synthesis

A descriptive summary of identified guidelines and their associated recommendations was synthesized and tabulated.

The Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument was applied independently by four reviewers to assess the quality of included guidelines (58-60). AGREE II consists of 25 items pertaining to key quality and reported domains for CPGs. These are graded using a 7-point Likert scale. For a given item, any scores differing more than two points were discussed amongst all four reviewers. Following discussion, evaluators were given the opportunity to amend or keep their original score.

Domain scores were reported separately using both the median and scaled domain scores, as is recommended by the AGREE II consortium. The scaled domain scores were calculated as follows:

$$\frac{obtained\ score - minimum\ possible\ score}{maximum\ possible\ score - minimum\ possible\ score} * 100\%$$

The minimum possible score is calculated as: (number of questions) x (number of reviewers) x 1. The maximum possible score is calculated as: (number of questions) x (number of reviewers) x 7.

Finally, a subgroup analysis of guidelines targeted towards indications for RBC transfusion in patients undergoing cardiac surgery was conducted. This analysis had been defined *a priori* in the study protocol (73).

Patient and public involvement

Neither patients or the general public were involved in the design or conduct of this study.

3.5 Results

Selected guidelines

The search identified 974 de-duplicated records (Figure 1). Following screening, 10 guidelines met our eligibility criteria (31, 45, 74-81). The majority of included guidelines were produced by speciality societies (n=7); the remainder from government affiliated organizations (n=2) and academic experts (n=1) (Table 1). Of the guidelines created by speciality societies, the majority were produced by one organization (n=5), with two created by collaborative efforts by two speciality societies. Five guidelines were produced with representatives from a single country (United States n=3, France n=1, Scotland n=1), one with North American representation and four with greater than two continents represented.

Medical specialists involved in guideline development

Anesthesiologists contributed at least in part to the development of 60% (n=6) of included guidelines, whereas the remainder were created under the provision of a single medical subspecialty (internists, pediatricians and obstetrician and gynecologists) (Table 1). Forty percent (n=4) of guidelines included medical professionals from both surgery and anesthesia in their guideline development group.

Recommendations: target population

Intraoperative recommendations are included under the following subheadings: “intraoperative” (n=5), “intraoperative during active bleeding” (n=1), “under general anesthesia” (n=2), “intraoperative and postoperative” (n=1), and “during cardio-pulmonary bypass” (n=1). None of the included guidelines were dedicated exclusively to the intraoperative period.

Two guidelines were directed towards patients undergoing elective surgery. Two guidelines did make recommendations regarding patients undergoing surgical procedures, but do not further specify a specific patient population. The remainder of guidelines advised on the management of either specific patient populations or intraoperative procedures, including patients undergoing hepatectomy, pediatric patients with congenital or acquired

heart defects undergoing cardiac surgery, patients with severe perioperative bleeding, patients with placenta accreta undergoing caesarean section, patients undergoing abdominal aortic aneurysm repair, and patients undergoing cardiothoracic surgery on cardio-pulmonary bypass.

Recommendations: clinician targeted transfusion rules

Sixty percent of guidelines provided objective practitioner-friendly directives for indications on intraoperative RBC transfusion (Table 2). All of these recommendations were based on hemoglobin or hematocrit transfusion triggers or targets. Transfusion hemoglobin triggers ranged between 60-100 g/L (n=4 guidelines), while hematocrit <30% was recommended in one guideline. Recommended target hemoglobin of 70-90 g/L was reported in one guideline. Two guidelines provided specific recommendations for selected patient populations. Lienhart et al. recommend using a transfusion trigger of 100 g/L in patients with coronary artery disease, heart failure or patients on beta-blockers. In the absence of these risk factors, a trigger of 70 g/L was recommended (77). Ferraris et al. recommend a transfusion trigger of 70 g/L in patients at risk of critical end-organ ischemia, compared to 60 g/L in patients without such risk (78). The guideline by Bennett et al. was the only guideline that provided a specific objective indication for transfusion using factors other than hemoglobin concentration (31). The authors stated that transfusion is appropriate in the context of cardiac ischemia demonstrated on ECG.

Consideration of hemoglobin and blood loss

Eight of the ten guidelines made reference to utilizing hemoglobin concentration to guide transfusion in some capacity (Table 2) (79, 81). As stated above, six provided specific triggers or thresholds at which a transfusion is indicated. Two guidelines recommend “considering hemoglobin,” or adhering to “a restrictive transfusion strategy” without providing further definition of the term (74, 76). None of the included guidelines provided recommendations on the most appropriate tool to monitor hemoglobin, discussed the

acceptability of point of care testing, or recommended a particular timing of pre- and post-transfusion hemoglobin testing.

Seventy percent of guidelines recommended considering blood loss when deciding whether or not to transfuse a patient in the operating room. Two of the guidelines instructed the clinician to “monitor” or “pay attention” to blood loss (75, 79). One guideline recommended “conduct(ing) a visual assessment” of the operative field to determine if a transfusion is indicated (76). Of note, there was no further recommendations specifying how to quantify blood loss or at what volume a transfusion should be indicated. One guideline stated that “significant blood loss” would be an appropriate indication for transfusion, quantifying significant as ≥1500 mL within the body of the manuscript. This volume was not included in the summary recommendation statement (31). Another guideline recommended transfusion in the event of “massive” blood loss, without reference to quantity (78, 81).

Consideration of hemodynamics and end-organ perfusion in deciding whether to transfuse

Three guidelines refenced patient hemodynamics in their recommendations. Two guidelines recommended “monitoring” or “considering” vital signs when deciding if blood transfusion is appropriate (74, 76). One guideline provided the directive to transfuse patients with “vital sign instability” at risk of cerebral ischemia, without defining vital sign instability (81).

Six guidelines referenced end-organ perfusion in some capacity, either via physical examination, laboratory values (eg. lactate), or other diagnostic modalities such as intraoperative echocardiogram. As noted previously, only one guideline gave clear instructions to transfuse when ST changes are seen on cardiac monitoring as an indication of cardiac ischemia (31).

How much to transfuse

Three guidelines recommended transfusing on a unit-by-unit basis. (76, 80, 81). The remainder did not provide an indication of how to dose transfusions.

Subgroup analysis

Two guidelines targeted towards patients undergoing cardiac surgery were identified: one in pediatric patients with congenital cardiac abnormalities; the other in adult patients undergoing cardiac surgery with cardiopulmonary bypass (78) (82). Due to the heterogeneity of these patient populations, the planned subgroup analysis was not carried out.

Evaluation of quality with AGREE II

Table 3 displays the median and scaled scores of each of the six domains. Median scores ranged from 1-7 and scaled scores ranged from 2-96%. The overall guideline assessment was scored a median independent score of 5 (range: 2-7). For eight of the publications, 100% of reviewers indicated they would either recommend the guideline or recommend the guideline with modifications. Seventy-five percent of assessors indicated they would not recommend the guideline by Belfort et al. for use (79).

Clarity of presentation was the highest scoring domain, with an average median score of 6.1 (range 6-7) and scaled score of 83±9%. The domain “clarity of presentation” is comprised of 3 independent questions, assessing a guideline on the specificity of recommendations, presentation of options for management, and identifiability of recommendations within the body of the manuscript. Recommendations included in all guidelines were distinguishable from the remainder of the text through the use of different font or a summary box.

The domain “applicability” was poorly executed across all guidelines. The average median score was 2 (range 1-5.5) and scaled score was 23±23%.This domain assesses the guideline for the following: description of facilitators and barriers to application, advice on implementation of the guideline, resource implications associated with applying the guideline, and inclusion of advice for monitoring or auditing implementation of the guideline.

Evaluation of evidence supporting intraoperative recommendations

Evidence supporting indications for intraoperative RBC transfusion was derived from a combination of interventional studies (n=5 guidelines) and observational data (n=7 guidelines) (Supplement Table 1). Two guidelines did not provide any accompanying

references to support the recommended intraoperative transfusion strategy (45) (79). Interventional studies comparing liberal and restrictive transfusion strategies in both medical and surgical patient populations were referenced. Non-surgical trials compared transfusion triggers in critical care (n=2), upper gastrointestinal bleeding (n=1) and patients undergoing cardiac catheterization (n=1) (83) (84) (85) (86). With the exception of three referenced studies, all supporting interventional studies in perioperative patients randomized patients to liberal or transfusion triggers following surgery (87) (88) (89). Two systematic reviews of interventional studies comparing transfusion triggers were referenced (90, 91). Although both reviews preformed subgroup analysis by "patient type" (eg. cardiac, critical care, orthopedic, etc.), identification of studies which applied triggers in the intraoperative phase was not preformed. Review of all included articles identified a total of 5 trials which evaluated transfusion strategies in the intraoperative period; 3 in orthopedic surgery, 1 in cardiac surgery, and 1 in vascular surgery (87, 88, 92-94) (Supplement Table 2).

3.6 Discussion

Clinical practice guidelines exclusively dedicated to the transfusion of allogenic red cells in the intraoperative phase of care do not exist. Systematic review of the literature identified a total of ten guidelines containing recommendations pertaining to the indications for RBC transfusion in the intraoperative setting. Only six CPGs provided specific triggers or transfusion rules, five of which were exclusively based on hemoglobin values. With the exception of one guideline that formulated recommendations based on the RAND/UCLA methodology, the other guidelines recommended hemoglobin triggers or targets on the basis of data extrapolated largely from postoperative and non-surgical settings (31). Recommended hemoglobin thresholds prompting transfusion varied between studies, ranging from 60-100 g/L. The majority of guidelines made reference to considering intraoperative blood loss and/or end-organ perfusion, with only one indicating the specific context in which transfusion is warranted (ST changes) (31). The remainder of the

recommendations were vague or undefined. Less than a third of guidelines included recommendations on how transfusions should be dosed. Those were all in agreement that blood should be transfused on a unit-by-unit basis. Lastly, the quality of guidelines, as appraised by the AGREE II tool, varied considerably.

Strengths of this review include its adherence to methodologic rigour. The study was designed and conducted by a team with content expertise in anesthesia, transfusion medicine, surgery, and systematic review methodology. The protocol was registered prospectively on PROSPERO and published in a peer-reviewed journal (73). The search strategy was reviewed by a second information specialist as per PRESS recommendations (95). A grey literature search of both Google Scholar and guideline clearinghouses was undertaken. No restriction was placed on language or dates, allowing for a comprehensive review of all available literature on the subject. Appraisal of guidelines using AGREE II was preformed independently by 4 assessors. The current review presents a narrative synthesis of available guidelines, representing a limitation of this study. Another limitation is that local guidelines not available in the guideline clearinghouses searched may not have been captured.

To our knowledge, this is the only review of guidance pertaining to RBC transfusion recommendations specific to the intraoperative setting. As previously highlighted, a recent systematic review of guidelines on RBC and plasma transfusion was preformed (42). However, that publication was intended to appraise the quality of such guidelines and was intended for consumption by the transfusion medicine community, and as such eligibility criteria were very different from that of the current review. Only three of the twenty-six guidelines identified in their review were included in the current study (75) (45) (76).

It has been over 20 years since Sudhindran called upon the medical community with “a plea for perioperative blood transfusion guidelines” (63). Since that time, there has been significant evolution in our understanding of humans’ tolerance to anemia. Landmark trials such as TRICC, supporting the use of a restrictive transfusion strategy in critical care,

inspired subsequent investigation of transfusion triggers in other patient populations. Synthesis of the evidence supporting the included recommendations in this review highlights a paucity of trials evaluating transfusion strategies in the operative setting (22). The majority of the interventional studies referenced herein investigated transfusion strategies in the nonoperative setting, either in non-surgical or postoperative surgical patients (83-86, 96-98) (93, 99) (23, 92, 100) .

Although surgical patients are being recognized as a patient population requiring special consideration, it is critical to acknowledge that the surgical patient requires distinct considerations as they transition through the pre-, intra- and postoperative periods (101) (102) (103). Alarmingly, policy makers do not appear to appreciate this distinction. The American Association of Blood Banks (AABB), a global leader in transfusion medicine, and The Frankfurt Consensus Committee, an international consortium of organizations with expertise in blood transfusion, recommend a transfusion trigger of 80g/L in patients "undergoing orthopedic surgery" or "with a hip fracture and cardiovascular disease," respectively (41, 104). Although one may interpret the above recommendations as encompassing the intraoperative setting, no further information pertaining to blood loss, hemodynamics or evidence of end organ ischemia are provided. This recommendation limits the surgeon or anesthesiologist's ability to make informed decisions regarding transfusion in the operating room. Furthermore, the evidence supporting these recommendations is drawn largely from the postoperative period (23, 100, 105-107). Of the four trials identified investigating transfusion triggers in the intraoperative period, one reported increased mortality in the restrictive group (transfuse if hemoglobin <80g/L) (8% vs 0%, p=0.02) (92, 94, 108, 109). Critical appraisal of the evidence supporting these recommendations calls into question whether the intraoperative phase was taken into consideration when reviewing the literature and formulating the recommendations.

Although major strides have been made over the past two decades, this review has identified a lack of objective practitioner-friendly guidelines with indications for transfusion in the intraoperative period. Given the frequency with which blood is transfused in the operating

room, as well as the morbidity and costs associated with unnecessary blood transfusions, this review has highlighted a major gap in the literature. Transfusion decision-making in the operating room appears to be taught to practitioners using a traditional apprenticeship model rather than using evidence-based practice guidelines. These findings support further clinical trials focusing on the intraoperative period, as well as making the production and dissemination of evidence-based recommendations in this field a priority agenda.

At this point, further trials evaluating intraoperative transfusion decision rules are needed to determine indications for transfusion. Review of the evidence supporting the included guidelines has identified 5 trials investigating intraoperative transfusion strategies (Table S1 & S2). All of the above studies based decisions on hemoglobin thresholds. Importantly, the same threshold was applied to the entire perioperative period. Based on the intraoperative period being distinct from other phases of care, we believe that the exploration of other physiologic and intraoperative factors, such as blood loss and hemodynamics, would be valuable to incorporate into a decision tool. As a matter of example, a recent randomized trial in neurocritical care patients demonstrated that the utilization of transcranial oxygen saturation to guide RBC transfusion was association with a reduction in transfusion compared to the control arm which was targeting a hemoglobin of 85-100 g/L (110). The application of transcranial oxygen saturation in guiding intraoperative transfusions has been examined in cardiac surgery (111). We therefore advocate for investigating transfusion strategies that encompass more than just hemoglobin transfusion triggers.

At this point, a systematic review and meta-analysis of trials comparing intraoperative transfusion strategies is an important next step (PROSPERO CRD42019138397). This exercise will allow for development of targeted guidelines, as well as identification of areas requiring further investigation.

3.7 Conclusion

This review has identified a lack of high-quality practice guidelines to inform clinical decision-making surrounding red blood cell transfusion in the operating room setting. This represents a major knowledge gap in the literature, given the high prevalence of intraoperative transfusions.

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3.9 Tables & Figures

Table 1. Characteristics of included guidelines.

Guideline	Language	Journal (IF)	Location (number of countries)	Development group (type of organization)	Medical specialities involved	Target population: patient/procedure	Number of individuals	Number of academic institutions represented
Benne t, 2018	English	Annals of Surgery (9.203)	North America (2)	N/A (I)	Anesthesiology, critical care, hematology, surgery	Hepatectomy	11	6
Cholet te, 2018	English	Pediatric Critical Care Medicine (3.092)	International (8)	SCCM, WFPICCS (S)	Pediatrics	Pediatric acquired and congenital heart disease undergoing cardiac surgery	38	29
Kozek -Langenecker, 2017	English	European Journal of Anaesthesi ology (3.634)	International (14)	ESA (S)	Anesthesiology, surgery	Severe peri-op bleeding	25	23
Apfelb aum, 2015	English	Anesthesiol ogy (5.163)	United States	ASA (S)	Anesthesiology, pathology	NR	10	10
Lienha rt, 2014	French	NA	France	HAS (G)	Anesthesiology, geriatrics, gastroenterology, hematology, medical genetics, neonatology, pediatrics	NR	26	NR
Ferrari s, 2011	English	The Annals of Thoracic Surgery (3.849)	International (3)	STS, SCA (S)	Anesthesiology, pathology, surgery	Cardiovascular surgery	19	17
Moll, 2011	English	Eur J Vasc Endovasc Surg (3.877)	International (6)	ESVS (S)	Surgery	AAA	13	

Belfort, 2010	English	American Journal of Obstetrics and Gynecology (5.732)	United States	SMFM (S)	Obstetrician-gynecology	Placenta accreta	13	NR
Tansey, 2001	English	NA	Scotland	SIGN (G)	Anesthesiology, general practitioner, hematology, surgery	Elective surgery	18	NR
Audet, 1992	English	Annals of Internal Medicine (19.384)	United States	ACP (S)	Cardiology, general medicine	Elective surgery	6	NR

Abbreviations - NA: not applicable, IF: Impact factor, I: independent experts, S: speciality society, G: government, SCCM: Society of Critical Care Medicine, WFPICCS: World Federation of Pediatric Intensive and Critical Care Society, ESA: European Society of Anesthesiologists, ASA: American Society of Anesthesiologists, SCA: Society of Cardiovascular Anesthesia, SOAP: Society for Obstetric Anesthesia and Perinatology, SCC: Society of Critical Care Anesthesia, HAS: Haute Autorité de Santé or French National Authority for Health, STS: The society of thoracic surgeons, ICEBP: The International Consortium for Evidence Based Perfusion, ESVS: European Society for Vascular Surgery, SMFM: Society for Maternal-Fetal Medicine, SIGN: Scottish Intercollegiate Guidelines Network, ACP: American College of Physicians

Table 2. Variables referred to in recommendations pertaining to indications for intraoperative allogenic RBC transfusion.

Guideline	Hemoglobin (g/L)	Blood loss	Hemodynamics	End-organ perfusion	Number of units
Bennet, 2018	Y-Tr. ≤75	Y-≥1500	-	Y-ST changes	-
Cholette, 2018	Y	-	Y	Y	-
Kozek-Langenecker, 2017	Y-Ta. 70-90	Y	-	Y	-
Apfelbaum, 2015	Y	Y	Y	Y	Y-One at a time
Lienhart, 2014	Y-Tr. <70*	-	-	Y	-
Ferraris, 2011	Y-Tr. <60**	Y	-	Y	-
Moll, 2011	Y-Tr. Hct. <30%	Y	-	-	-
Belfort, 2010	-	Y	-	-	-
Tansey, 2001	Y-Tr. Hb<70	Y	-	-	Y-One at a time
Audet, 1992	-	-	Y	-	Y-One at a time

*<100 if pt has CAD, HF or beta-blocked

**<70 for pts at risk of critical end-organ ischemia

Table 3. Appraisal of guideline quality by the AGREE II tool.

	Domain scores						Scaled domain scores (%)						
First author, year	Scope and purpose	Stakeholder involvement	Rigor of development	Clarity of presentation	Applicability	Editorial independence	Scope and purpose	Stakeholder involvement	Rigor of development	Clarity of presentation	Applicability	Editorial independence	Yes (%)
Bennet, 2018	4.5	3	3	6	1	3	68	42	45	81	3	46	100
Cholette, 2018	5.5	4	5	7	1	5.5	74	44	55	89	4	73	100
Kozek-Langenecker, 2017	6	5	6	7	2	4.5	83	53	74	94	29	58	100
Apfelbaum, 2015	7	4	6	6	1	4	96	47	65	83	10	50	100
Lienhart, 2014	7	6	5	6	1	2.5	96	76	61	81	10	33	100
Ferraris, 2011	5	5.5	4	6	2	2.5	69	60	57	90	17	27	100
Moll, 2011	5	4	5	5	4	5	61	53	55	68	47	67	100
Belfort, 2010	5	1.5	2.5	5	1	2	69	11	31	71	2	10	25
Tansey, 2001	7	6.5	7	7	5.5	2	93	75	85	93	73	21	100
Audet, 1992	5	3	2	6	1.5	2	63	25	23	79	15	25	75

Supplementary tables

Table S1. Evidence supporting intraoperative transfusion indication recommendations.

Guideline	Supporting evidence-interventional studies	Supporting evidence-observational studies	Notes
Bennet, 2018	**Non-op:** critical care (83) **Post-op:** Orthopedic sx (96), oncology sx (97)	**Peri-op:** (112)	Recommendations adopted from non-op setting
Cholette, 2018	NR	**Non-op:** UGIB(84) **Peri-op:** cardiac sx (113)	Cholette et al. report insufficient evidence to provide tx rules, recommend need for intra-op tx guideline.
Kozek-Langenecker, 2017	**Non-op:** UGIB(84) **Post-op:** oncology sx(97), cardiac sx(98) **Non-op and op setting:** SR of trials comparing tx triggers (90, 91)	NR	Studies referenced in SR that compared intra-op triggers identified NS difference between R and L tx strategies. All trials were in orthopedic patients. (88, 92, 94)
Apfelbaum, 2015	**Non-op:** cardiac cath (85) **Peri-op:** vascular sx (87), ortho sx (88) **Post-op:** cardiac sx (93, 99), ortho sx (23, 92, 100)	**Peri-op:** ortho sx (114) **Post-op:** cardiac sx (115)	"Restrictive" tx strategy highly variable in interventional intra-op studies (defined as Hb<90 in Bush et al. and as low as 64 in So-Osman et al.)
Lienhart, 2014	**Non-op:** critical care(86) **Post-op:** Orthopedic sx (23) **Non-op and op setting:** SR of trials comparing tx triggers (91), SR of trials evaluating treatment of anemia (116)	**Non-op:** critical care(117), MI (118) **Peri-op:** ortho sx(119-121), non-cardiac sx(26, 122, 123), vascular sx (124) **Post-op:** cardiac sx (125)	Recommendations adopted from non-op and post-op setting
Ferraris, 2011	NR	**Intra-op:** CPB(126-132)	Referenced observational studies conflicting. Recommending a Tx trigger of 60 not supported by included ref. 53 (128) (129)
Moll, 2011	NR	NR	-
Belfort, 2010	NR	NR	-
Tansey, 2001	NR	**Intra-op:** CPB(126, 127)	Recommendation adopted from observational studies in cardiac surgery.
Audet, 1992	**Peri-op:** cardiac sx (89)	**Non-op:** UGIB (133) **Peri-op:** cardiac sx (134)	Studies on human tolerance of anemia presented. Audet et al. recommend utilizing hemodynamics to determine need for tx.

Abbreviations-hb: hemoglobin, op: operative, sx: surgery, SR: systematic review, tx: allogenic red blood cell transfusion

Table S2. Randomized controlled trials involving intraoperative transfusion triggers identified in systematic reviews referenced in included guidelines (90) (91)

Author, year	Sample size (n)	Primary outcome	Surgical patient population	Restrictive intervention (R)	Liberal intervention (L)	Conclusion
Grover, 2006 (92)[1,2]	260	MI	Orthopedics	<80g/L in peri-op period	<100g/L in peri-op period	• MI: NS
Hajjar, 2010 (93)[1]	502	30-day mortality and severe AE	Cardiac	hematocrit <24% from the start of surgery until discharge from ICU	hematocrit <30% from the start of surgery until discharge from ICU	• Mortality: NS • Severe AE: NS
Foss, 2009 (94)[1,2]	102	Post-op functional mobility	Orthopedics	<80g/L in peri-op period	<100g/L in peri-op period	• Mobility: NS
So-Osman, 2009 (88)[1,2]	603	RBC utilization	Orthopedics	Dependent on patient comorbidities- for healthy patients, <50 years old, transfusion indicated if Hb <64g/L	Dependent on hospital, various liberal transfusion policies in place	• Utilization: NS • AE: NS
Bush, 1997 (87)[1]	99	AE	Vascular	90g/L	100g/L	• NS

Abbreviations-AE: adverse event, MI: myocardial infarction, NS: not significant, ICU: intensive care unit, op: operative, RBC: red blood cell

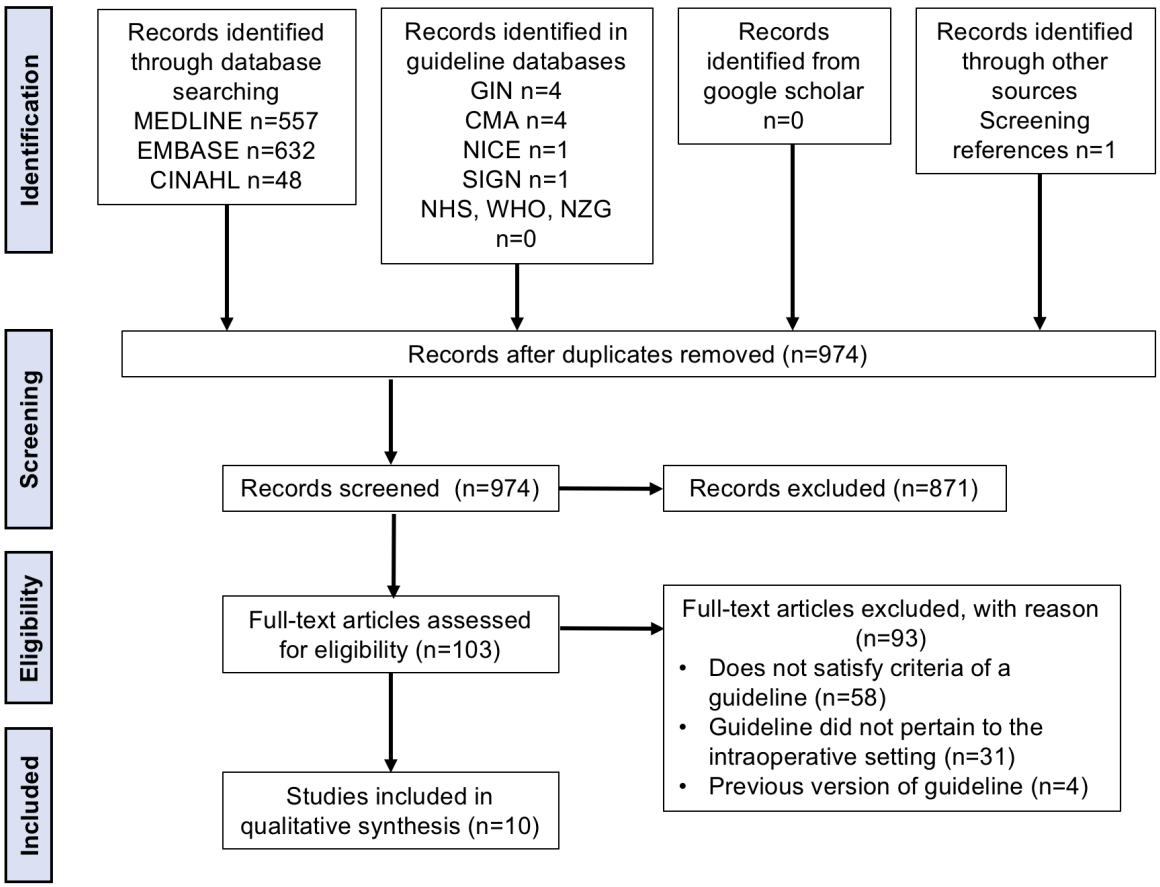

Figure 1. PRISMA flow diagram of included guidelines.

Appendix 1. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4,5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6 Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12, Table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

Appendix 2. Search Strategy

Database: Ovid MEDLINE(R) ALL <1946 to January 18, 2019>
Search Strategy:
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1 *blood transfusion/ or blood component transfusion/ or erythrocyte transfusion/ (36558)
2 ((red blood cell$ or rbc or erythrocyte$ or red cell$) adj3 (transfus$ or infus* or retransfus*)).tw. (10752)
3 (blood adj4 transfus*).tw. (55497)
4 RBCT.tw,kw. (98)
5 (RBC transfusion or red blood cell transfusion).kw. (119)
6 (hemotransfus$ or haemotransfus$).tw,kw. (235)
7 or/1-6 (79262)
8 INTRAOPERATIVE COMPLICATIONS/ or INTRAOPERATIVE CARE/ or INTRAOPERATIVE PERIOD/ or Perioperative Care/ (70692)
9 (intraoperat* or intra-operat* or perioperat* or peri-operat*).tw,kw. (211023)
10 (surg* or operat*).ti. (719593)
11 (transfus* adj5 (operat* or surg*)).tw. (8809)
12 ((undergoing or during) adj4 (surg* or operat*)).tw. (184619)
13 or/8-12 (984957)
14 7 and 13 (18727)
15 exp clinical pathway/ (6144)
16 clinical protocol/ (26321)
17 exp consensus/ (9848)
18 exp consensus development conference/ (11219)
19 exp consensus development conferences as topic/ (2650)
20 guidelines as topic/ (37447)
21 exp practice guideline/ (24669)
22 practice guidelines as topic/ (107723)
23 health planning guidelines/ (4020)
24 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt. (40219)
25 (standards or guideline or guidelines).ti,kf,kw. (98974)
26 ((practice or treatment* or clinical) adj guideline*).ab. (34823)
27 (CPG or CPGs).ti. (5373)
28 consensus*.ti,kf,kw. (22761)
29 ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw. (17868)
30 recommendat*.ti,kf,kw. (36530)
31 or/15-30 (340961)
32 14 and 31 (560)
33 (rbc transfusion* or red blood cell* transfusion*).ti. (1089)
34 (transfus* and (intraoperat* or intra-operat* or perioperat* or peri-operat*)).ti. (1042)
35 33 or 34 (2059)
36 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt. (40219)
37 (standards or guideline or guidelines).ti,kf,kw. (98974)
38 36 or 37 (124845)
39 35 and 38 (64)
40 32 or 39 (590)
41 animals/ not humans/ (4505965)
42 40 not 41 (589)
43 (exp infants/ or child/) not adult/ (1532610)
44 42 not 43 (557)

4. AN AUDIT AND EVALUATION OF APPROPRIATENESS OF BLOOD TRANSFUSION IN LIVER SURGERY: APPLICATION OF THREE DECISION TOOLS

Laura Baker, Tori Lenet, Michael Vered, Aklile Workneh, Amin Zahrai, Jad Abou-Khalil, Fady Balaa, Kimberly Bertens, Daniel McIsaac, Alan Tinmouth, Dean Fergusson & Guillaume Martel

4.1 Abstract

Red blood cell (RBC) transfusion in liver surgery is common and is associated with postoperative morbidity. Evaluation of appropriateness of administered transfusions in patients undergoing liver surgery is lacking. The objective of this study is to (1) evaluate the appropriateness of perioperative transfusions, (2) identify prescriber-associated characteristics associated with inappropriate transfusions, and (3) determine if patients deemed inappropriately transfused are at increased risk of postoperative adverse events in comparison to patients not transfused.

A retrospective review of patients undergoing hepatectomy at a tertiary care liver surgery unit from March 2011 to April 2018 was performed. Patient demographics, operative details, clinical variables surrounding transfusion events, and data pertaining to patients' postoperative course were collected. Appropriateness of RBC transfusions was determined via the application of three independent tools, independently, in duplicate.

A cohort of 489 patients underwent liver resection was identified during the study period. Among those, 19% (n=91) of patients were transfused a total of 241 units of RBC in the perioperative period. Ten percent of patients were transfused a total of 124 units intraoperative and twelve percent of patients were transfused a total of 112 units postoperative. Forty-one percent of patients underwent a major liver resection. Ninety percent of cases were performed open. The primary indication for hepatectomy was colorectal liver metastases (52%); 22% of patients underwent resection for primary liver malignancy. Median preoperative hemoglobin was 132g/L; 19% of patients were anemic at the time of surgery. A total of 22% to 63% of transfusions administered during the intraoperative period were considered inappropriate based on the application of three different instruments. In contrast, 38% to 67% of transfusions administered during the postoperative period were considered inappropriate. Patients were at increased risk of being inappropriately transfused in the immediate postoperative period while in the postoperative recovery unit while their care was being overseen by an anesthesiologist, compared to later in the postoperative period (OR 7.5 95% CI 1.9, 29.0). Prescriber experience (junior versus senior resident versus attending physician), time of transfusion (evenings and

weekends versus business hours) and method through which transfusion order was delivered (written versus verbal order) did not influence appropriateness of the transfusion. Patients considered to have been inappropriately transfused during the intraoperative period were at increased risk of developing a major postoperative adverse event (Clavien-Dindo≥grade 3) compared to those who did not receive a transfusion (OR 4.2; 95% CI 1.1-15.6).

Despite trends towards reductions in perioperative transfusions in patients undergoing hepatectomy, a significant proportion of patients continue to be exposed to unnecessary transfusion. A substantial variability in the estimates of inappropriate RBC transfusion was identified. The immediate postoperative period was noted as a particularly vulnerable period for patients being transfused unnecessarily. Finally, an association between major postoperative adverse events was identified in patients that were inappropriately transfused,further supporting the previously described potentially deleterious effects of blood transfusions in surgical patients. Further work in this area is warranted to minimize the administration of unnecessary transfusion.

4.2 Introduction

Despite improvements in perioperative complications and mortality, major blood loss and red blood cell transfusion (RBC) remain significant concerns for surgeons, anaesthesiologists and patients. Among high surgical volume institutions, the incidence of RBC transfusion in elective liver surgery ranges from 17-41% (135-139). Population-based analysis from the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) demonstrated an RBC transfusion rate of 22% in liver surgery in 2013 (139). Similarly, a recent Canadian multicentre cohort of liver resections documented a RBC transfusion rate of 26.5% among 1,287 patients (140). Among those patients that do require a RBC transfusion, a median of two units is given (141).

Inappropriate Blood transfusions in liver surgery may lead to poor patient outcomes:

Although RBC transfusions can be life-saving, they can also lead to significant harm (142-144). It is estimated that between 2009 and 2013, 3,368 Canadians suffered from severe adverse events from RBC transfusions (145). These include transfusion-associated circulatory overload (TACO) occurring in 1-5% of transfusion events, and less commonly fever, chills, allergic reactions (occurring in 0.5-1% of transfusions events) and transmission of infectious diseases (occurring in less than 1 in 1 million transfusions) (142-144). Most importantly, transfusions have been shown to have significant immunomodulatory effects that are associated with increased perioperative infectious complications, delayed recovery, as well as worsened long-term cancer-specific survival (5). Our group has recently published a systematic review examining the effects of transfusion in liver surgery, confirming the relationship with worsened perioperative outcomes in 83% of included papers, and decreased cancer-specific survival in 63% of papers (146).

Blood transfusions are limited and costly recourses:

In Canada, Canadian Blood Services, a not-for-profit organization primarily funded by provincial governments, manages the national blood supply (with the exception of Quebec) (147). Blood shortages are fairly common and are highly visible in the media (Appendix A, Figure 1) (148). In this context, it is essential that mechanisms be implemented to reduce inappropriate blood transfusions. Additionally, RBC transfusions are estimated to cost $1,200 per unit (19), an estimate that does not account for expenses incurred by hospitals from adverse reactions or poor outcomes. With over 1 million units collected in Canada on an annual basis, transfusions are associated with a significant economic burden.

Reduction of perioperative blood transfusions:

Strategies to reduce intraoperative and postoperative RBC transfusion are collectively referred to as Perioperative Blood Management (Appendix A, Figure 2). Although all components of this paradigm are important, the area of highest potential impact is the reduction and elimination of RBC transfusions deemed inappropriate, as per evidence-based guidelines. Red blood cell transfusions can be considered 1) appropriate (clinically-indicated)

or 2) inappropriate (not indicated based on the best evidence) (Appendix A, Figure 3) (149). Using this simple framework, interventions can be devised to decrease transfusions by decreasing the risk of requiring an appropriate transfusions and minimizing/eliminating inappropriate transfusions.

Despite evidence and practice guidelines supporting restrictive transfusion thresholds in surgery, there remains substantial provider-level variation in transfusion practice in liver surgery (41, 150). Inappropriate transfusions that are generally not clinically-indicated and could thus be reduced using targeted knowledge translation and behaviour-modification interventions. The Ottawa Criteria for Appropriate Transfusion in Hepatectomy (OCATH), a recently developed set of criteria using the RAND/UCLA appropriateness process, represents a useful framework from which to minimize inappropriate transfusions in liver surgery (Appendix B, Figure 1) (151). This tool addresses liver-specific transfusion scenarios, and it is anticipated that the broad application of OCATH could decrease inappropriate transfusions. In addition to OCATH, other methods of evaluating appropriateness exist. Spradbrow et al. have reported on a set of criteria derived from guidelines published by the American Association of Blood Banks (Figure 5); and Frank et al. have proposed that a patients' hemoglobin at the time of discharge can be utilized to determine if a patient was unnecessarily or over-transfused (149) (152). Of note, in contrast to OCATH, neither of these tools provide specific recommendations for the intraoperative setting.

Why study institutional blood transfusion prescribing practices in patients undergoing liver surgery?

Approximately one quarter of patients undergoing liver surgery receive RBC transfusions. At present, it is poorly understood what proportion of these are clinically appropriate. Fortunately, we now have a tool to assess appropriateness of RBC transfusions administered to patients undergoing liver surgery in the perioperative period. Application of this tool to a retrospective cohort of liver surgery patients is expected to provide important information on the incidence and clinical context of overuse of RBC transfusions in the perioperative period. This information, even if retrospective, is critical to the future development of targeted

knowledge translation initiatives aimed at reducing clinically unnecessary and potentially harmful RBC transfusions.

Objective

The objective of our retropsepective audit and evaluation is to define the epidemiology of perioperative allogenic RBC transfusions in patients undergoing liver resection, as well as to define the burden of inappropriate transfusions. Additionally, this work seeks to determine if there are any clinical settings or prescriber variables associated with increased risk of exposure to clinically unnecessary transfusions. Finally, this work seeks to evaluate a possible association between inappropriately administered RBCs and postoperative morbidity.

4.3 Methods

A retrospective audit of patients undergoing liver resection between January 1, 2011 and May 31, 2018 was performed at a one tertiary academic center. Six fellowship-trained liver surgeons were involved over the duration of this cohort. Ethics approval was obtained from the Ottawa Health Science Network Research Ethics Board.

Selection criteria

The audit period was selected based on the availability of anesthesia electronic medical records. Prior to January 1, 2011, anesthesia records were handwritten, and detailed information pertaining to intraoperative events was not reliably available.

Inclusion criteria for this study were: 1) patients undergoing liver resection for any indication (including synchronous extrahepatic resection), and 2) ≥18 years of age. Patients who underwent unroofing of hepatic cysts only, and did not require hepatic parenchymal transection were excluded.

Data sources

The Ottawa Hospital HepatoPancreatoBiliary (HPB) service maintains a prospective dataset of all liver procedures for research purposes (153). It includes information pertaining to patient demographics, perioperative course as well as postoperative outcome. This list was used to identify relevant cases within the study period. This list was provided to analysts from

The Ottawa Hospital (TOH) Data Warehouse. The TOH Data Warehouse is a database that contains clinical data (labs, pharmacy, radiology and clinical notes) on all patients registered at TOH dating back from 1996 to present. From there, data pertaining to patient demographics, intraoperative details, medication, laboratory values, and course in hospital were extracted. This data was supplemented with information from the HPB dataset, as well as manual review of individual electronic medical records, where appropriate.

Assessment of appropriateness using three tools

The following tools were utilized to assess appropriateness:

1. The Ottawa Criteria for Appropriate Transfusion in Hepatectomy (OCATH) (Bennett et al. 2018) (Appendix B, Figure 1) (31)
2. Adjudication criteria developed by Spradbrow et al. 2016 (Appendix C, Figure 1) (149)
3. Analysis of hemoglobin triggers and targets (Frank et al. 2013) (152)

The Ottawa Criteria for Appropriateness in Hepatectomy (OCATH)

OCATH was developed utilizing the UCLA/RAND criteria for evaluation of appropriateness, following systematic review of transfusion and outcomes in liver surgery (Appendix B). It is a tool that relies on real-time, clinical information. It states whether a transfusion is “appropriate” or “inappropriate.” It is unable to distinguish whether the dose or quantity of blood given was appropriate. We therefore utilized it to determine if the decision to initiation allogenic RBC transfusion was appropriate, independent of the dose administered. As per OCATH, the decision to initiate transfusion was considered appropriate in the event of “significant bleeding,” “ST segment changes,” or “hemoglobin $\leq$ 75g/L” in the intraoperative setting. The determination of ST changes using intraoperative ECG leads can be challenging in clinical practice and requires interpretation. As a result, this is difficult to adjudicate retrospectively. The presence of cardiac enzyme measurement at the end of surgery (CK, TNI), was thus utilized a clinically-appropriate surrogate for ST segment changes was utilized instead. After discussion with content experts, these tests were felt to be an appropriate indicator of patients who had demonstrated intraoperative evidence of cardiac ischemia on ECG monitoring. As OCATH is a tool that is meant to be used prospectively, with the

information the clinician has at hand, concern, without objective proof, was determined to be an appropriate indication for transfusion. “Significant bleeding” was defined as ≥ 1500mL in OCATH. The decision to transfuse was deemed inappropriate if the lowest intraoperative hemoglobin remained ≥85g/L, without concern of cardiac ischemia or major bleeding. Patients who were given an intraoperative transfusion that neither satisfied the criteria of clearly appropriate or inappropriate were categorized as “indeterminate.” The algorithm applied to determine appropriateness of intraoperative transfusions can be found in Appendix B, Figure 2.

In the postoperative setting, transfusion triggers of 80g/L and 70g/L are recommended in stable, asymptomatic patients with and without coronary artery disease, respectively (18). Transfusion was considered appropriate in patients with a hemoglobin ≤75g/L in the immediate postoperative period, which was defined as the first 6 postoperative hours. Additionally, a threshold of 75g/L was considered appropriate in patients with a hemoglobin drop of 15g/L. The algorithm applied to determine appropriateness of intraoperative transfusions can be found in Appendix B, Figure 3.

Adjudication by Spradbrow et al.

Each transfusion event was deemed either appropriate or inappropriate through application of Spradbrow’s criteria (Appendix C) (149). In the event of insufficient information to adjudicate appropriateness, it was reported that insufficient information was now available.

Analysis of hemoglobin triggers and targets by Frank et al.

Three separate analyses were preformed to determine the appropriateness of perioperative transfusions by Frank et al.’s method(152). Frank’s method is based on the concept that each unit of PRBCs increases hemoglobin concentration by 10g/L. By utilizing transfusion triggers of 70g/L in patients without coronary artery disease and 80g/L in those with coronary artery disease, you can estimate whether or not an individual was transfused unnecessarily, as well as by how many units.

First, the appropriateness of intraoperative transfusions was determined by utilizing the hemoglobin concentration on postoperative day 3 in patients that were transfused intraoperatively but did not receive any additional units in the first 3 postoperative days. The postoperative day 3 hemoglobin was selected as it takes approximately 72 hours for intraoperative fluid shifts to equilibrate following surgical trauma and the administration of large volumes of intravenous fluids (102). As a result, postoperative day 0, day 1, and day 2 hemoglobins are commonly falsely elevated and will tend to even out by day 3. Second, the appropriateness of postoperative transfusions was evaluated by utilizing the hemoglobin concentration at discharge in patients transfused exclusively during the postoperative period. Third, the appropriateness of all perioperative transfusion was evaluated based on the hemoglobin concentration at discharge.

Adjudication of appropriateness

Adjudication of appropriateness by application of both OCATH and Spradbrow et al.'s tools were applied by two authors independently (LB and AZ). Any discrepancy in adjudication was discussed with a senior author (GM).

Risk factors and implications of inappropriate transfusions

Information pertaining to timing of transfusion, method via which transfusion was ordered (written versus verbal order), prescriber demographics (attending versus trainee; specialty) and setting of transfusion (operating room, postoperative recovery unit, intensive care unit, or ward), was obtained.

Additionally, the association between inappropriate transfusions and morbidity was explored by comparing the incidence of postoperative adverse events in patients transfused inappropriately intraoperatively to those not exposed to intraoperative RBC transfusion.

Data analysis

Baseline demographics as well as details pertaining to the intraoperative and postoperative course of included patients were summarized. Categorical variables were reported as frequencies and percentages. Continues variables were expressed as means with standard deviations (SD) or medians with interquartile ranges (IQR), as appropriate. Baseline

demographics, intraoperative and postoperative details of patients transfused intraoperatively were compared to those not transfused using mean or median differences for continuous outcomes, and odds ratios with 95% confidence intervals for dichotomous outcomes. Appropriateness of perioperative transfusion was reported using counts and percentages. Details pertaining to the timing, location and prescriber (level of training, speciality) responsible for ordering RBCs were reported using counts and percentages. Odds ratios with 95% confidence intervals were generated to evaluate the association between inappropriate transfusions and prescriber/setting variables. Finally, the frequency of adverse events in patients inappropriately transfused was compared to patients not transfused using odds ratios to determine if an association between inappropriate transfusions and morbidity exists. All analysis was conducted using Statistical Analysis Software (SAS version 9.3; SAS Institute, Inc.).

4.4 Results

Patients

489 patients underwent liver resection during the study period (Figure 1). Two-hundred and two (41%) underwent major hepatic resection: 68 (14%) patients had a left hepatectomy, 13 (3%) extended left, 76 (16%) right lobectomy, 26 (5%) extended right; the remaining 12 (2%) had some other combination of 4 or more segments resected (Table 1). Two hundred and eighty-seven (59%) patients underwent a minor hepatectomy, the majority of which had a single segment resected (21%). One hundred and one (21%) patients underwent synchronous resection of extrahepatic disease. The majority of cases were performed open (90%).

Mean age at the time of surgery was 61±13 years old. Median ASA was 3 (IQR: 3,3). Seven percent (n=34) of patients had coronary artery disease. The most common indication for liver resection was colorectal liver metastases (52%). Twenty-two percent (n=110) of the cohort underwent hepatic resection for a primary liver malignancy (12% cholangiocarcinoma and gallbladder cancer, 10% hepatocellular carcinoma). Ninety four (19%) patients underwent resection for benign entities.

Intraoperative information

Median operative time was 285 minutes (IQR: 209, 384). Tranexamic acid was administered to 28% of patients, an epidural was placed in 89% of patients and hypovolemic phlebotomy was performed in 17% of patients. For intraoperative blood product utilization, 11% of patients received 5% albumin, 10% received packed red blood cells, 3% received fresh frozen plasma and 1% received platelets. The median estimated blood loss was 500mL (IQR 300mL, 966mL).

Postoperative information

Median length of stay was 6 days (IQR 5, 9). Twenty (4%) patients were admitted to the ICU for a median of 4 days (IQR 5, 9). Nineteen percent of patients presented back to the emergency department within the first 30 days following surgery, half of which required readmission to hospital (n=45 patients).

Forty-eight percent (n=236) of patients experienced some deviation from routine postoperative course (Clavien Dindo Grade I-V). Eleven percent of patients experienced a major postoperative adverse event (Clavien Dindo Grade ≥III). Twelve percent of patients received a postoperative allogenic RBC transfusion. There were 3 deaths (1%) within the first 30 postoperative days.

Perioperative allogenic red blood cell transfusion administration

Nineteen percent (n=91) of patients were transfused a total of 241 units of PRBCs during the perioperative period. Forty-nine (10%) patients were transfused a median of 2 units (IQR 1,3) during the intraoperative period. Sixty (12%) patients were transfused a median of 2 units (IQR 1,3) during the postoperative period. Four percent (n=18) of patients were transfused during both the intra and postoperative periods.

Risk factors for perioperative allogenic red blood cell transfusion

Patients that received an intraoperative RBC transfusion were more likely to be anemic preoperatively (OR 8.4, 95% CI 3.2, 11.8) with a median difference in hemoglobin concentration of 15g/L (MD -15, 95% CI -20, -11) (Table 2). Patients with intraoperative transfusion had a higher transfusion risk score, signifying increased risk of perioperative

transfusion (MD 1 ; 95% CI 1, 1). Patients that received a transfusion had a median OR time of 119 minutes longer than those that were not transfused (95% CI 82, 157). Median blood loss was significantly higher in those transfused compared to those that did not receive an intraoperative transfusion (MD 1092mL; 95% CI 919mL, 1264mL). Blood loss of ≥1000mL, 1500mL was associated with 9.3 (95%CI 4.9, 17.9) and 20.0 (95%CI 9.9, 40.3) increased odds of being transfused intraoperatively, respectively. Patients that were transfused intraoperatively had an increased length of stay (MD 8 days; CI 5,11), risk of admission to ICU (OR 13.9; 95%CI 5.4, 35.5), development of postoperative adverse event (OR 2.7; 95%CI 1.4, 5.0) and development of major postoperative adverse event (OR 4.1; 95%CI 1.9, 8.8).

Appropriateness of intraoperative transfusions

Application of OCATH demonstrated that 22% of patients were transfused inappropriately (Table 4a). The most common indication was due to a pre-transfusion hemoglobin concentration of ≥95g/L in the absence of a major indication for transfusion (blood loss ≥1500mL or ST changes) (64%). The decision to initiate transfusion was considered appropriate in 69% of patients. The most commonly satisfied criteria was major blood loss (76%), followed by hemoglobin nadir ≤75g/L (38%) and concern of cardiac ischemia (29%). Of note, multiple patients satisfied more than one criteria. In the remaining 9% of patients, the appropriateness of initiating transfusion was considered “indeterminate.”

Evaluation of appropriateness by Spradbrow et al.’s criteria adjudicated 45% of intraoperative transfusion events as inappropriate and 39% as appropriate (Table 4b). The remaining 16% could not be evaluated due to sequential transfusions events occurring without a hemoglobin value being measured in between.

Determination of appropriateness of intraoperative transfusions based on postoperative day 3 hemoglobin in patients that did not receive any additional transfusions in the first 3 days after surgery (n=38) classified 63% of patients as inappropriately transfused (Table 4c). Thirteen percent were considered to have been appropriately transfused the correct quantity; whereas the remaining 87% were over-transfused a total of 51 units.

Agreement of appropriateness across tools

Review of agreement between appropriateness adjudication reveals that in all 11 patients considered to have been transfused inappropriately by OCATH, a minimum of one other tool was in agreement that the transfusion was considered inappropriate (Figure 3).

Appropriateness of postoperative transfusions

Thirty-six (38%) of the 96 postoperative transfusion events were considered inappropriate by OCATH (Table 4a). There were an additional 4 transfusion events that were categorized as “indeterminate-likely inappropriate” (Appendix). Forty-three (45%) transfusion events were considered appropriate by application of OCATH. An additional 8% were considered “indeterminate-likely appropriate” upon further review of patients’ chart.

The majority of postoperative transfusion events were considered appropriate by Spradbrow et al.’s criteria (57%) (Table 4b). The most common indication for appropriately administered RBCs was for a hemoglobin less than or equal to 90g/L in a patient experiencing symptoms of anemia. Forty percent of transfusion events were considered inappropriate. Transfusions were most commonly inappropriately transfused in patients without coronary artery disease with pre-transfusion hemoglobin values above 70g/L who were not considered to be bleeding, without documented evidence of symptomatic anemia. Appropriateness of 3% of transfusion events could not be determined due to missing hemoglobin values between transfusion events.

Review of hemoglobin concentrations at discharge in patients transfused exclusively postoperatively suggests that 79% of patients were overtransfused and 67% were unnecessarily transfused.

Appropriateness of peri-operative transfusion

Evaluation of appropriateness of perioperative transfusion based on hemoglobin concentration at discharge (Frank et al’s criteria) suggests that 57% of the 91 patients that were transfused in the perioperative period were inappropriately exposed to RBCs. Additionally, 84% of patients were considered to have been over transfused. The total number

of units which patients were overtransfused is estimated at 98 or an average of 1 unit per patient transfused.

Association between prescriber characteristics and clinical setting on appropriateness of postoperative allogenic RBC transfusions

A total of 96 unique transfusion events occurred during the postoperative period, the majority of which were administered to patients on the surgical ward (55%, versus 29% in the intensive care unit and 15% in the post anesthesia recovery unit) (Table 6). Red blood cell transfusion orders were most often prescribed by residents (69 transfusion events, 72%). Eleven percent were ordered by the attending physician. In the remaining 17% of transfusion events we were unable to identify the position of the prescriber. Fifty-one (53%) transfusions events were administered after-hours, which was defined as evenings (5pm-6am) or weekends. Eighty-two (85%) transfusions events were prescribed via a written order, the remainder of which were verbal orders.

Patients were at increased risk of being inappropriately transfused in the immediate postoperative period while in the post anesthesia recovery unit (11 of 14 units administered considered inappropriate, OR 7.5; 95% CI 1.9, 29.0). Administration by anesthesiology was also associated with an increased risk of inappropriate transfusion (10 of 12 units administered considered inappropriate, OR 11.2; 95% CI 2.3, 54.5). A non-statistically significant increased incidence of inappropriate transfusions were observed in transfusions prescribed by attendings (64% versus 36% by junior and 52% by senior residents), in the evening between 5pm-11pm (57% versus 34% during the day between 6am-5pm) and via verbal order (50% versus 35% of written orders).

Association between inappropriate transfusions and postoperative adverse events

Patients transfused inappropriately as adjudicated by OCATH in the early perioperative period (intraoperative to 72 hours postoperative) were at increased risk of developing a postoperative adverse event compared to patients that were not (OR 7.7; 95% CI 2.6, 22.6). Patients considered to have been inappropriately transfused intraoperatively by

OCATH were at 4.2 fold increased odds (95%CI 1.1, 15.7) of developing a major adverse event compared to patients that were not transfused intraoperatively.

4.5 Discussion

This single-centre, retrospective audit of appropriateness of perioperative allogenic RBC transfusion suggests that liver surgery patients are being exposed to clinically unnecessary transfusions. The extent of over-transfusion varies based on the tool being used to evaluate appropriateness. Differences are also observed in the intraoperative period compared to the postoperative period. Importantly, this work demonstrated an association between inappropriate transfusions and major postoperative adverse events, suggesting a link between transfusions and harm. Together, these findings support the importance of further guidance on perioperative transfusion and audit and evaluation of current perioperative transfusion practices, ultimately leading to a reduction in unnecessary transfusions.

To our knowledge, this is one of the first studies dedicated to evaluating the issue of over-transfusion in the perioperative period. This is an important topic given the potential negative repercussion of red cell transfusions on patient outcomes, associated cost and the limited supply. The perioperative period is unique in that there are numerous dynamic and competing factors that influence the complexity of the decision to transfuse. Intraoperatively, acute blood loss limits reliance on hemoglobin concentration. General anesthesia, patient positioning and surgical maneuvers influence patient hemodynamics making them unreliable indicators of anemia. Lastly, an unconscious patient is unable to raise alarms of potentially symptomatic anemia, for example, chest pain, shortness of breath or light headedness. The postoperative period is also unique due to the physiologic and pathologic fluid shifts that occur around the time of surgery, which have both hemodilutional as well as hemoconcetrating effects (103). Fluid shifts typically equilibrate after 72 hours (102). In contrast, in the non-operative patient, hemoglobin concentration alone is a reliable marker of anemia.

There is a large body of evidence describing the incidence of overtransfusion in the non-operative setting. In the majority of identified studies, adjudication of appropriateness is based entirely on pre-transfusion hemoglobin concentration (154).

Despite mounting evidence to support the harmful association between RBC transfusions and postoperative outcomes, evaluation of appropriateness of transfusion administered during the perioperative period is limited. Literature describing the appropriateness of intraoperative RBC transfusion is limited to hospital wide audits that include surgical patients. The general consensus from these reviews is that surgical patients are at increased risk of inappropriate perioperative transfusions in comparison to non-surgical patients (155, 156). In regards to quantifying the scope of the problem, the results of these reviews should be interpreted with caution as the tools used to adjudicate appropriateness may not be sensitive enough to establish appropriateness in the intraoperative setting. Application of the 2016 AABB RBC transfusion guidelines via a retrospective audit of all transfusions administered at a single centre over a 3-month period demonstrated that surgical patients were at the highest risk of inappropriate transfusion (41, 155). Of all transfusion deemed inappropriate, 29% were administered to asymptomatic anemic patients either pre- or intraoperatively and 10% were given for intraoperative blood loss without associated hemodynamic instability or hemoglobin below transfusion trigger. When interpreting these results, it is important to note that the AABB does not provide guidance on indications for transfusion of intraoperative patient with hemodynamic instability, which in the operative patient, may not be secondary to anemia. Furthermore, their recommendations are largely based on hemoglobin concentration, which in the acutely bleeding patient may not be an accurate reflection of anemia. These recommendations, which include: a transfusion trigger of (1) 70g/L in hemodynamically stable, hospitalized patients and (2) 80g/L in patients undergoing orthopedic surgery, cardiac surgery and those with preexisting cardiovascular disease are largely based on evidence from either non-surgical patients or patients in the postoperative period (100, 157, 158). A 2005 review of almost 1500 transfusions administered in hospitalized patients in Northern Ireland reported that surgical patients were at a 3-fold increased risk of inappropriate transfusion compared to medical patients; 34% of “surgical patient(s) with bleeding” were transfused inappropriately (156). This adjudication was based on a patient having either a pre-transfusion hemoglobin concentration above 100g/L or posttransfusion concentration above 120g/L. Importantly,

these criteria do not quantify the amount of bleeding that needs to have occurred to satisfy the definition of “surgical patient with bleeding.” Their transfusion trigger of 100g/L and target of 120g/L are far more liberal than what is recommended in other RBC transfusion guidelines. Therefore 34% is likely an underestimation of overtransfusion (27). Lastly, application of Spradbrow et al.’s criteria to 498 RBC units at 10 hospitals adjudicated 22% as inappropriate (149). Although their review included transfusions given in the OR (9%), the majority of transfusions were given on the ward (59%). Their audit revealed that “bleeding patients with no history of cardiac disease” was the second most common indication for inappropriate transfusion. Upon review of their indication for transfusion, they categorize a patient as “bleeding” if the transfusion is given intraoperatively to the first 48 hours postoperatively. If a patient is “bleeding,” a transfusion is considered appropriate if the pre-transfusion hemoglobin is ≤70g/L or the post-transfusion hemoglobin is ≤90g/L in the context of no known cardiac disease. These recommendations suggest that an intraoperative or early postoperative patient that is not experiencing acute blood loss should be considered similarly to one that is bleeding. Furthermore, a target of 90g/L is considered high for a patient that is not experiencing acute blood loss. Review of the literature supports our finding that patients are being transfused unnecessarily during the perioperative period. Furthermore, it suggests that patients are at increased susceptibility to inappropriate transfusion during this period in comparison to non-surgical patients. The lack of consistency of transfusion rules highlights a potential area of improvement for aiding in defining the problem and guiding perioperative transfusions.

The Ottawa Criteria for Appropriate Transfusion in Hepatectomy provides evidence based, expert-consensus derived guidance regarding perioperative RBC transfusion in patient undergoing liver surgery. In contrast to other tools described above, it was developed specifically for patients in the perioperative period, and takes into account the following clinical parameters: hemoglobin, cardiac ischemia, blood loss and hemodynamics. Application of OCATH to our retrospective cohort demonstrated that up to 22% of patients were transfused unnecessarily intraoperatively and up to 38% of transfusion events were classified as inappropriate during the postoperative period. Of the 19% of patients exposed to allogenic

RBC transfusion in this cohort, 46% of them were exposed to a minimum of 1 inappropriate transfusion. Considering that the reported incidence of transfusion in our cohort is on the lower end of the published range of 18-57%, this number may be an underestimation of the burden over transfusion (9, 159-161).

In addition to quantifying the incidence of over-transfusion in hepatectomy, this review was able to identify an association between inappropriate transfusions and harm. There is mounting evidence to support the association between transfusion and worse postoperative and oncologic outcomes, however a causal link has yet to be established(112, 160) (9, 162). Many of the characteristics associated with increased morbidity are also associated with increased risk of transfusion. To control for this, we compared the incidence of postoperative morbidity in patients that were transfused inappropriately intraoperatively to those who were not transfused. Patients considered to have been inappropriately transfused during the intraoperative period were at increased risk of developing a major postoperative adverse event (Clavien-Dindo≥grade 3) compared to those who did not receive a transfusion (OR 4.2; 95% CI 1.1-15.6) (163).

This study had several limitations. The ability to adjudicate appropriateness is reliant on several factors which may not have been captured due to the retrospective nature. Although we are confident that we were able to capture the majority of the transfusion events, patient variables surrounding the event which contribute to our ability to determine appropriateness may not have been documented. Both OCATH and Spradbrow's criteria consider hemodynamic instability or symptomatic anemia justification for transfusion. Reliance on documentation by medical personal limits reliance of capturing this information. The retrospective nature also limits our ability to capture other outcomes, including postoperative adverse events. Another limitation is that this study is based on an audit of a single-centre, and may therefore not be representative of other centres. It is worth noting that our centre practices a restrictive transfusion policy and is actively investigating transfusion-reduction strategies in liver surgery (141, 153). Our centre may therefore be an underrepresentation of the scope of the problem. Lastly, although our series include almost 500 patients, due to the

limited number of patients transfused, our ability to make associations between inappropriate transfusions and adverse events is likely underpowered.

As this is the first study dedicated to evaluating the burden of inappropriate transfusion in the perioperative period, it was largely exploratory in nature. Future directions include larger, retrospective analysis of appropriateness of perioperative transfusions in various surgical patient populations, across centres. In addition, prospective application of perioperative transfusion guidelines, such as OCATH, should be performed. An extension of this would be to develop additional guidance for perioperative RBC administration in a variety of surgical patient populations.

4.6 Conclusion

In conclusion, our retrospective audit of appropriateness of perioperative allogenic RBC transfusion highlights that a significant proportion of patients transfused are transfused without strong clinical justification or in excess. Given the potential harmful implications and associated economic burden associated with administration of unnecessary PRBCs, further work is needed to be done to eliminate unnecessary transfusion.

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4.8 Tables

Table 1. Characteristics of included cohort (n=489).

Patient demographics	
Sex, M	249 (51%)
Age, mean±SD, years (range)	61±13 (21-86)
BMI, mean±SD, kg/m^2 (range)	28±6 (15-68)
ASA, median (IQR)	3 (3,3)
I	4 (<1%)
II	53 (11%)
III	386 (79%)
IV	46 (9%)
Coronary artery disease	34 (7%)
Pre-operative characteristics	
Preop Hbg, g/L, median (IQR) (n=487)	132 (122,143)
Preop Hbg <125g/L, incidence	148 (30%)
Preop anemia <125g/L male or <115g/L, incidence	91 (19%)
Previous liver resection	39 (8%)
Neoadjuvant chemotherapy	163 (33%)
Indication	
Primary liver malignancy	110 (22%)
Chonagio/GB Ca	58 (12%)
HCC	50 (10%)
EHE	1 (<1%)
Sarcoma	1 (<1%)
Malignancy-other	
Colorectal liver metastasis	253 (52%)
Metastatic disease-other	32 (7%)
Benign	94 (19%)
Intraoperative details	
Length of surgery, min, median (IQR)	285 (209,384)
Surgical approach	
Open	438 (90%)
Laparoscopic + laparoscopic converted to open	51 (10%)
No. resected segments, median (IQR)	3 (2,4)
Major hepatic resection (≥4 segments)	202 (41%)
Left lobe	68 (14%)
Extended left lobe	13 (3%)
Right lobe	76 (16%)
Extended right lobe	26 (5%)
Left lateral +right posterior	7 (1%)
Other	12 (2%)
Minor (<4 segments)	287 (59%)
Central (any combination 4a,4b,5,8)	11 (2%)
Left lateral	55 (11%)
Right posterior	49 (10%)
Multiple segments-other	48 (10%)
Single segment	104 (21%)
Wedge	18 (4%)
Other	2 (<1%)
Synchronous extrahepatic resection	101 (21%)

Bowel	48 (10%)
Anterior resection	20 (4%)
Abdominalperineal resection	4 (<1%)
Left hemicolectomy	3 (<1%)
Right hemicolectomy	16 (3%)
Small bowel	5 (1%)
Abdominal wall	6 (1%)
Adrenal gland	4 (1%)
Diaphragm	14 (3%)
Gastric	3 (1%)
Gynecologic structures	5 (1%)
Hepaticojejunostomy	19 (4%)
Other[1]	12 (3%)
Anesthesia information	
TXA administered	139 (28%)
5% albumin administered	55 (11%)
FFP administered	13 (3%)
Platelets administered	4 (1%)
Epidural placed preoperatively	434 (89%)
Hypovolemic phlebotomy preformed	82 (17%)
Estimated blood loss, mL, median (IQR) (n=479)	500 (300, 966)
Intraoperative allogenic RBC Transfusions	
Patients	49 (10%)
RBC Units (range of number of units per patient)	124 (1-10)
Units per patient amongst those transfused, median (IQR)	2 (1,3)
Transfusion events	76
1 unit prescribed/event	44 (58%)
2 units prescribed/event	25 (33%)
3 or more units prescribed/event	7 (9%)
Perioperative Hb value in patients transfused intraoperatively	
Pre-op hemoglobin, median (IQR)	122 (109, 130)
POD 0 Hb in PACU, median (IQR) (n=46 patients)	105 (97, 116)
POD 1 Hb, median (IQR) (n=45 patients)	99 (93, 109)
POD 2 Hb, median (IQR) (n=42 patients)	95 (87, 103)
POD 3 Hb, median (IQR) (n=38 patients)	95 (89, 100)
Postoperative allogenic RBC Transfusions	
Patients	60 (12%)
RBC Units (range of number of units per patient)	117 (1-15)
Transfusion events	96
1 unit prescribed/episode	75
2 units prescribed/episode	21
Perioperative allogenic RBC Transfusions	
Patients that received RBC transfusion perioperative	91 (19%)
Patients transfused both intra- and postoperative	18 (4%)
RBC Units total	241
Units per patient amongst those transfused, median (IQR)	2 (1,3)
Postoperative outcomes/resource utilization	
Length of stay, days, median (IQR)	6 (5,9)
ICU admission, incidence	20 (4%)
ICU length of stay, days, median (IQR)	4 (3,5)
Representation to ED within 30 days post-op, incidence	95 (19%)
Readmission within 30 days post-op, incidence	45 (9%)

Postoperative complications* **	
Overall	236 (48%)
Major (Clavien Dindo Score ≥III)	52 (11%)
30 day mortality	3 (1%)

[1]Other extra-hepatic resection: distal pancreatectomy and spleenectomy (n=1), iliac artery (n=1), inferior vena cava (n=2), mesentery (n=3), nephrectomy (n=1), omentum (n=2), pulmonary (n=2)

***Highest AE reported. Also, postoperative RBC transfusion considered Grade II AE.

Table 2. Intraoperative RBC transfusion data

	Transfused intraoperatively (n=49)	Not transfused intraoperatively (n=440)	Effect size (95% CI)*
Age, years, mean ± sd	64±13	61±13	3 (-1, 7)
Sex, male	29 (59%)	220 (50%)	1.5 (0.8, 2.6)
BMI, kg/m^2, mean ± sd	27±5	28±7	-1 (-3,1)
ASA, median (IQR)	3 (3,4)	3 (3,3)	0 (0, 0)
Liver disease	24 (49%)	195 (44%)	1.2 (0.7, 2.2)
Cirrhosis	3 (6%)	20 (5%)	1.4 (0.4, 4.8)
Previous liver resection	5 (10%)	34 (8%)	1.4 (0.5, 3.6)
Preoperative chemotherapy	14 (29%)	149 (34%)	0.8 (0.4, 1.5)
Transfusion risk score, median (IQR)**	2 (1,2)	1 (0,1)	**1 (1,1)**
Pre-operative hemoglobin, g/L, mean±SD	118±18 (n=48)	133±15 (n=439)	**-15 (-20, -11)**
Pre-operative hemoglobin <125g/L	33 (69%) (n=48)	115 (26%) (n=439)	**6.2 (3.2, 11.8)**
Pre-operative anemia	28 (58%) (n=48)	63 (14%) (n=439)	**8.4 (4.4, 15.7)**
No. resected segments, median (IQR)	4 (2,4)	3 (2,4)	1 (-0.2, 2.2)
Extra-hepatic resection	11 (22%)	90 (20%)	1.1 (0.6, 2.3)
Resection for primary hepatic malignancy	15 (31%)	95 (22%)	1.6 (0.8, 3.1)
OR time, min, mean ± SD	412± 138	292±124	**119 (82, 157)**
Epidural	47 (96%)	387 (88%)	3.2 (0.7, 13.6)
Hypovolemic phlebotomy	3 (6%)	79 (18%)	**0.3 (0.1, 0.9)**
EBL, mL, mean ± SD	1676±1179	584±470 (n=430)	**1092 (919,1264)**
Blood loss ≥500mL	44 (90%)	215 (50%) (n=430)	**8.8 (3.4, 22.6)**
Blood loss ≥750mL	37 (76%)	125 29%) (n=430)	**7.5 (3.8, 14.9)**
Blood loss ≥1000mL	34 (69%)	84 (20%) (n=430)	**9.3 (4.9, 17.9)**
Blood loss ≥1200mL	30 (61%)	37 (9%) (n=430)	**16.8 (8.6-32.7)**
Blood loss ≥1500mL	26 (53%)	23 (5%) (n=430)	**20.0 (9.9, 40.3)**
Blood loss ≥1750mL	20 (41%)	15 (3%) (n=430)	**19.1 (8.9, 41.1)**
Blood loss ≥2000mL	17 (35%)	12 (3%) (n=430)	**18.5 (8.1, 42.1)**
Blood loss ≥2250mL	9 (18%)	3 (<1%) (n=430)	**32.0 (8.3, 123.0)**

Blood loss ≥2500mL	9 (18%)	3 (<1%) (n=430)	**32.0 (8.3, 123.0)**
Blood loss ≥2750mL	7 (14%)	1 (<1%) (n=430)	**71.5 (8.6, 595.1)**
Length of stay, days, mean± SD	16± 20	8± 8	**8 (5,11)**
ICU admission, incidence	11 (23%)	9 (2%)	**13.9 (5.4, 35.5)**
ICU length of stay, days, mean± SD (n=20)	10±14	9±19	0.3 (-15.5, 16.1)
Representation to ED within 30 days post-op	10 (20%)	85 (19%)	1.1 (0.5, 2.2)
Readmission within 30 days post-op, incidence (n=7 missing)	7 (14%)	38 (9%)	1.7 (0.7, 4.1)
Post-operative AE, any	34 (69%)	202 (46%)	**2.7 (1.4, 5.0)**
Major AE	16 (47%)	36 (18%)	**4.099 (1.910, 8.798)**

*Effect sizes are mean or median differences for continuous outcomes, and odds ratios for dichotomous outcomes.

**Three point transfusion risk score predicts risk of perioperative red blood cell transfusion. Points are allocated for hemoglobin <125g/L, resection for primary hepatic malignancy and major hepatic resection (≥ 4 segments)

Table 3. Appropriateness of intraoperative transfusions. **A.** appropriateness of decision to initiate transfusion by OCATH (n=49 patients transfused intraoperatively) **B.** appropriateness of transfusion event by Spradbrow (n=76 transfusion events) **C.** appropriateness of decision to initiate transfusion and quantity transfused utilizing POD3 hemoglobin in patients not transfused within the first 3 days post-operative (n=38 patients)

a.

	n=49	
Appropriate	**34**	**69%**
Hb nadir ≤75g/L	13	27%
Concern of cardiac ischemia	10	20%
EBL ≥1500mL	26	53%
Hb nadir ≤75g/L + concern of cardiac ischemia	4	8%
Hb nadir ≤75g/L+ EBL ≥1500mL	7	14%
Concern of cardiac ischemia + EBL ≥1500	7	8%
All 3	3	6%
EBL, mL, mean±SD	2033±1239	
Indeterminate (Hemoglobin >75 and <85)	**4**	**9%**
EBL ≤1000mL	3	6%
EBL <1500mL, >1000mL	1	2%
EBL, mL, mean±SD	651±451	
Inappropriate	**11**	**22%**
Hemoglobin ≥95, no major indication*	7	14%
Hemoglobin >=85 <95 without strong justification**	4	8%
EBL, mL, mean±SD	946±330	

EBL: estimated blood loss, Hb: hemoglobin
*****Major indication includes concern of cardiac ischemia, demonstrated by performance of post-operative TNI and ECG and major blood loss (≥1500mL)
**Strong justification includes major indications in addition to documentation in the anesthesia record specifying indication for RBCs

b.

	N=76 transfusion events	
Appropriate	**30**	**39%**
Hb ≤70g/L pre-tx OR ≤90g/L post-tx, no CAD	17	22%
Hb ≤80g/L pre-tx OR ≤100g/L post-tx, CAD	5	7%
≤100g/L pre-tx AND ≤100g/L post-tx, marked ongoing blood loss*	8	11%
Inappropriate	**34**	**45%**
>70 pre-tx AND >90 post-tx, no CAD	31	41%
>80 pre-tx AND >100 post-tx, CAD	3	4%
>100 pre-tx OR >100 post-tx, marked ongoing blood loss	0	0%
Unable to determine	**12**	**16%**
No Hb available between transfusions	12	16%

CAD: coronary artery disease, Hb: hemoglobin, tx: transfusion

*Marked ongoing blood loss was defined by Spradbrow et al. as loss of >4 units of packed red blood cells in 24 hours

c.

	Patients transfused intraoperatively without additional postoperative transfusion prior to POD3 (n=38)	POD3 Hb (g/L) in patient without CAD (n=32)	POD3 Hb (g/L) in patients with CAD (n=6)
Decision to initiate transfusion			
Yes	14 (37%)	83±9 (n=11)	98±7 (n=3)
No	24 (63%)	103±16 (n=21)	103±15 (n=3)
Quantity transfused appropriate			
Yes	5 (13%)	73±4 (n=5)	-
No	33 (87%)	99±15 (n=27)	99±8 (n=6)
Number of units overtransfused, median (IQR)	2 (2,3)	2 (2,3)	2(2,3)

IQR: interquartile range, POD: post-operative day

Table 4. Appropriateness of post-operative transfusions. **A.** appropriateness of post-operative transfusion events by OCATH (n=96 post-operative transfusion events) **B.** appropriateness of transfusion events by Spradbrow (n=96 transfusion events) **C.** appropriateness of decision to initiate transfusion and quantity transfused utilizing hemoglobin at discharge in patients transfused exclusively in the post-operative period (n=42)

a)

Appropriate	**43**	**45%**
Hb ≤70g/L, no CAD	34	35%
Hb ≤80g/L with CAD	6	6%
Hb ≤75g/L, no CAD, immediate post-operative period*	0	0
Hb ≤75, no CAD, with drop in hb ≥15g/L	3	3%
Indeterminate-likely appropriate	**8**	**8%**
ST changes	1	1%
HD instability, tachycardia ≥110bpm	4	4%
Hypotension	3	3%
Inappropriate	**36**	**38%**
HD stable, asymptomatic, Hb >70g/L, no CAD	33	34%
HD stable, asymptomatic, Hb >80g/L, CAD	3	3%
Indeterminate-likely inappropriate	**4**	**4%**
HD instability, tachycardia ≥110bpm	4	4%
Unable to assess appropriateness	**5**	**5%**
Unable to access chart	2	2%
Hb not preformed following last transfusion, prior to transfusion being evaluated	3	3%

BPM, beats per minute, Hb: hemoglobin, HD: hemodynamic
*The immediate post-operative period was defined as the first 6 hours post-operative

b)

Appropriate	**55**	**57%**
Hb ≤70g/L, no CAD, asymptomatic, not bleeding*	16	17%
Hb ≤80g/L, CAD, asymptomatic**, not bleeding	3	3%
Hb ≤90g/L, symptomatic, not bleeding	19	20%
Pre-Tx <=70 OR post-Tx <=90, no CAD, bleeding,	16	17%
Pre-Tx Hb ≤ 80g/L OR post-Tx Hb ≤ 100g/L, CAD, bleeding	1	1%
Inappropriate	**38**	**40%**
Pre-tx Hb >70g/L, no CAD, not symptomatic, not bleeding	19	20%
Pre-tx Hb >70g/L AND post-tx Hb>90g/L, no CAD, bleeding	16	17%
Pre-tx Hb >80g/L AND post-tx Hb>100g/L, CAD, bleeding	3	3%
Unable to determine	3	
No Hb available between transfusions	3	3%

Hb: hemoglobin, Tx: transfusion

* “A patient was considered to be actively bleeding if any of the following were observed: intraoperative to <48 hours postoperative transfusions; need for inotropes for hypotension secondary to bleeding; systolic blood pressure <90mmHg from bleeding; need for immediate

intervention for bleeding (e.g. surgery, interventional radiology, interventional endoscopy); drop in hemoglobin in last 36 hours of 20g/L or more; blood loss >1000mL; hemoglobin posttransfusion<pretransfusion hemoglobin; >4 RBC units in 24 hours" (149)

**"Symptomatic refers to the presence of any of the following symptoms within 24 hours of the transfusion: heart rate >100, systolic blood pressure <90mmHg, presyncope, syncope, dizzy upon walking/standing, chest pain, dyspnea, ST changes on electrocardiogram, positive troponin (asymptomatic referes to patients without any of these symptoms)" (149)

c.

	Patients transfused exclusively postoperatively (n=42)	Hb at discharge in patients without CAD, g/L, mean±SD	Hb at discharge in patients with CAD, g/L, mean±SD
Decision to initiate transfusion appropriate			
Yes	14 (33%)	80±7 (n=11)	80±7 (n=3)
No	28 (67%)	98±10 (n=28)	-
Quantity transfused appropriate			
Yes	9 (21%)	74±4 (n=6)	80±7 (n=3)
No	33 (79%)	98±11 (n=33)	-
Number of units overtransfused, median (IQR)	2 (1,3)	2 (1,3)	-

Table 5 Evaluation of appropriate peri-operative RBC transfusions by Frank et al. based on patients hemoglobin at discharge

	Patients transfused perioperatively (n=91)	Hb at discharge in patients without CAD, g/L, mean±SD	Hb at discharge in patients with CAD, g/L, mean±SD
Decision to initiate transfusion appropriate			
Yes	39 (43%)	85±11 (n=33)	89±11 (n=6)
No	52 (57%)	101±13 (n=49)	104±11 (n=3)
Quantity transfused appropriate			
Yes	15 (16%)	75±3 (n=12)	80±7 (n=3)
No	76 (84%)	100 ±12(n=70)	88±11(n=6)

Number of units overtransfused, median (IQR)	1 (1,2)	1 (1, 2)	1 (0,2)

CAD: coronary artery disease, Hb: hemoglobin, IQR: interquartile range, SD: standard deviation

Table 6. Location, timing and prescriber level details associated with post-operative transfusion events

Parameter	Total number of transfusion events (%)	Inappropriate by OCATH (% of transfusion events by considered inappropriate)	Odds ratio (95% Confidence interval)
Physician specialty*			
Surgery	52 (54%)	17 (33%)	0.639 (0.278, 1.468)
Anesthesia	12 (13%)	10 (83%)	**11.154 (2.281, 54.535)**
Critical care	30 (31%)	9 (30%)	0.619 (0.246, 1.577)
Location			
Ward	53 (55%)	16 (30%)	0.497 (0.215, 1.150)
ICU	29 (30%)	9 (31%)	0.667 (0.264, 1.683)
PACU	14 (15%)	11 (79%)	7.469 (1.923, 29.018)
Level of trainee/staff			
Junior resident	42 (44%)	15 (36%)	0.873 (0.379, 2.013)
Senior resident	27 (28%)	10 (52%)	0.973 (0.388, 2.442)
Attending	11 (11%)	7 (64%)	3.378 (0.914, 12.492)
Timing of transfusion			
M-F 6:00-16:59	45 (47%)	15 (33%)	0.714 (0.310, 1.644)
Evenings and weekends	51 (53%)	21 (41%)	1.400 (0.608, 3.223)
6:00-16:59	68 (71%)	23 (34%)	0.602 (0.247, 1.468)
17:00-22:59	21 (22%)	12 (57%)	1.369 (0.516, 3.633)
23:00-5:59	7 (7%)	1 (14%)	0.136 (0.016, 1.177)
Type or order			
Written	82 (85%)	29 (35%)	0.547 (0.175, 1.713)
Verbal	14 (15%)	7 (50%)	1.828 (0.584, 6.722)

ICU: intensive care unit, junior resident: trainee in their first 2 years of residency, PACU: post anesthesia care unit, senior resident: trainee in their 3rd year or above of residency

*Unable to decipher physician specialty in 2 transfusion events

**Unable to decipher prescriber position (trainee versus staff) in 16 transfusion events

Table 7. Comparison of adverse events in patients transfused inappropriately intraoperatively and the early post-operative period compared to patients non-transfused.

a) Adverse event-any

Decision tool	AE patients inappropriately transfused (%)	AE in patients not transfused (%)	Odds Ratio (95% CI)*
OCATH: intraop tx	7 (64%)	202 (46%)	2.062 (0.595-7.144)
OCATH: intraop + 72 hours post-op tx	22 (85%)*	171 (42%)	**7.655 (2.591-22.616)**
Spradbrow: intraop tx	15 (65%)	202 (46%)	2.209 (0.918-5.317)
Spradbrow: intraop + 72 hours post-op tx	31 (80%)**	171 (42%)	**5.393 (2.419-12.023)**
Frank: intraop	6 (50%)	202 (46%)	1.178 (0.374-3.710)

b) Major adverse event (Clavien Dindo Grade 3 or higher)

Decision tool	Major AE in patients inappropriately transfused (%)	Major AE in patients not transfused (%)	Odds Ratio (95% CI)*
OCATH: intraop tx	3 (27%)	36 (8%)	**4.209 (1.070-15.564)**
OCATH: intraop + 72 hours post-op tx	7 (27%)*	30 (7%)	**4.654 (1.813-11.950)**
Spradbrow: intraop tx	5 (22%)	36 (8%)	**3.117 (1.093-8.889)**
Spradbrow: intraop + 72 hours post-op tx	9 (23%)**	30 (7%)	**3.790 (1.648-8.713)**
Frank: intraop	3 (25%)	36 (8%)	3.741 (0.970-14.436)

* There were 27 patients transfused intraoperatively and within the first 3 days postoperative in which all transfusion events that occurred were considered inappropriate by OCATH

**The denominator is comprised of 23 patients in which all intraoperative transfusion events considered inappropriate, and an additional 16 patients in which all transfusion events given within the first 3 days post-operative were considered inappropriate (n=39).

4.9 Figures

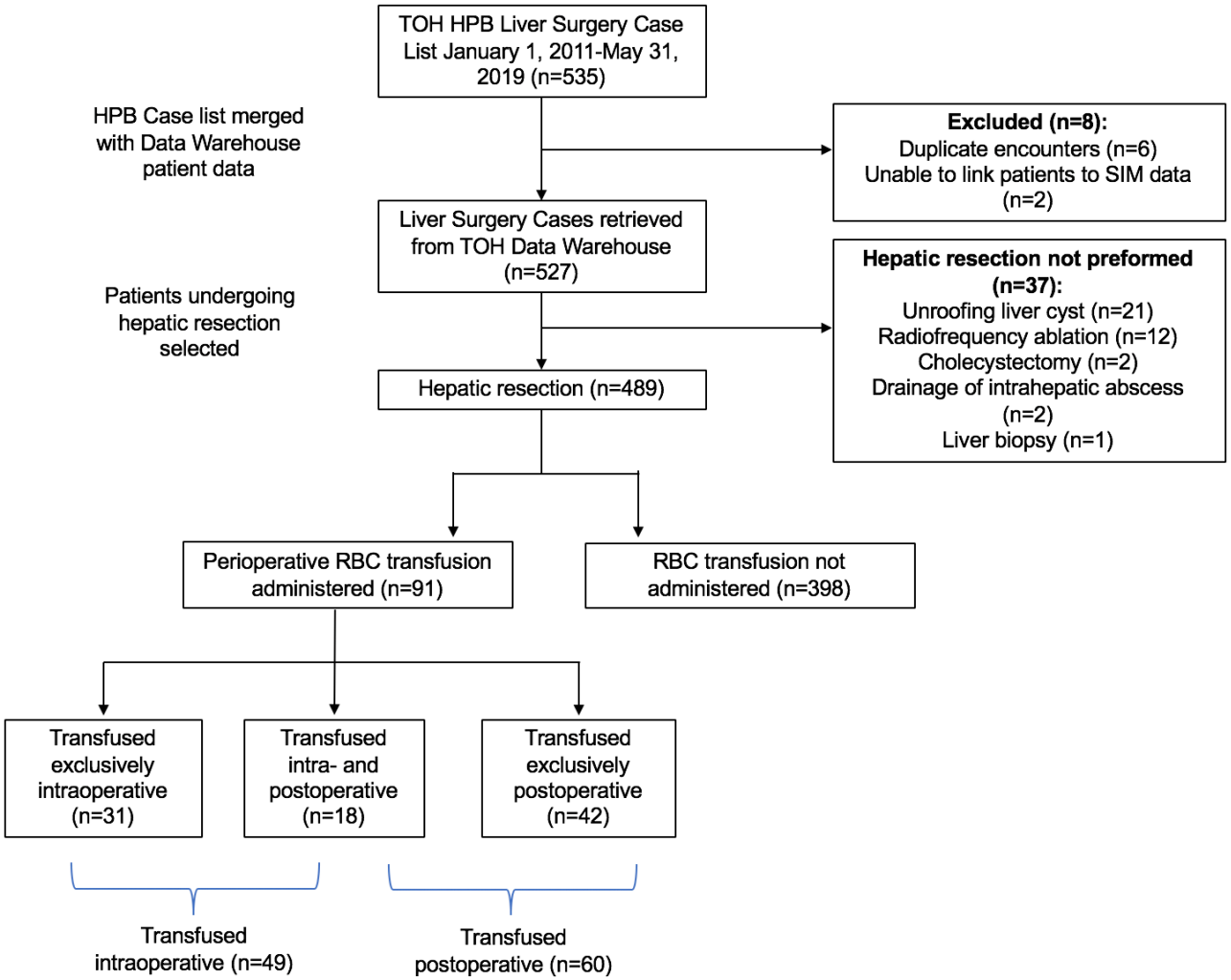


Figure 1. Identification of eligible cases.

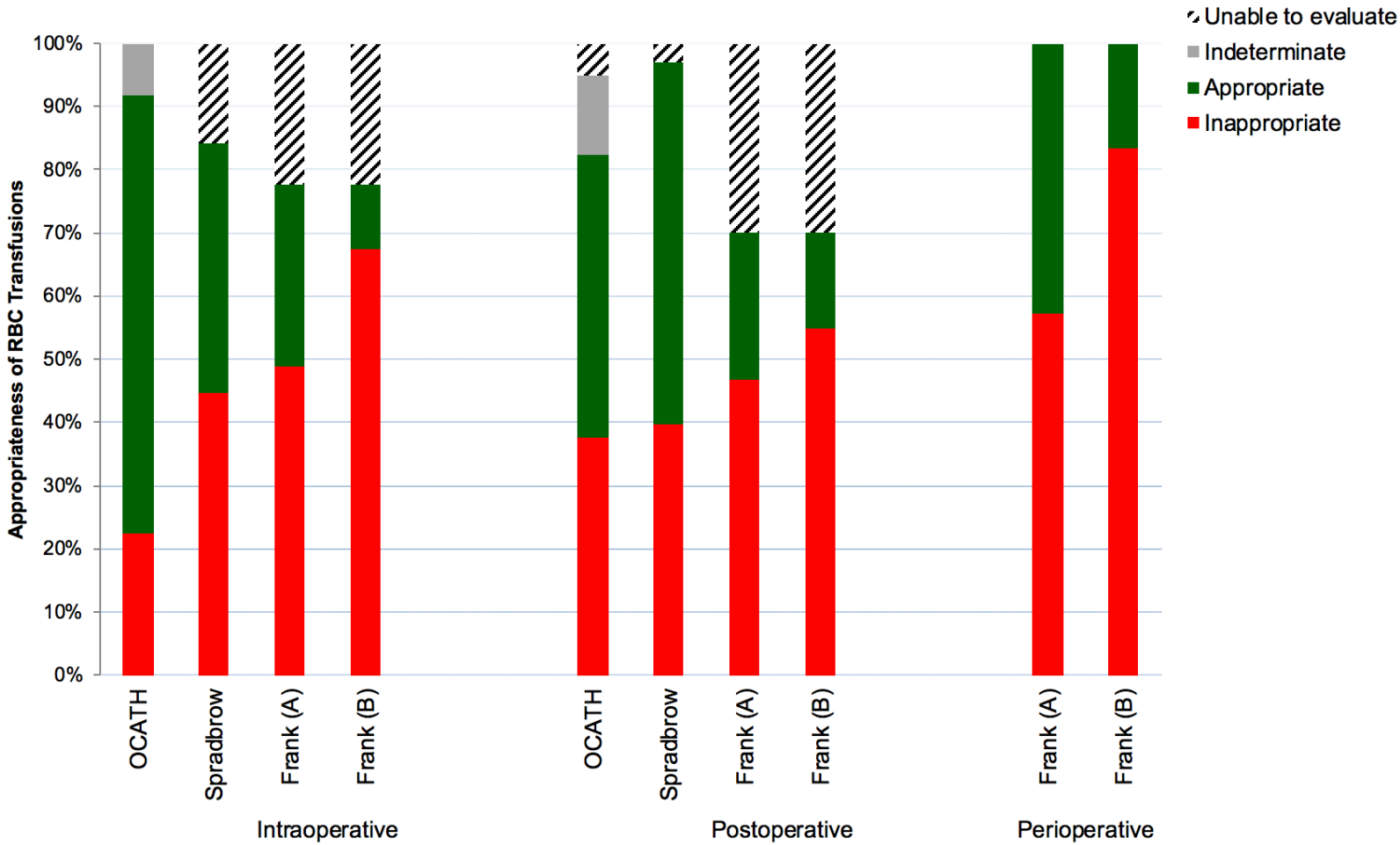
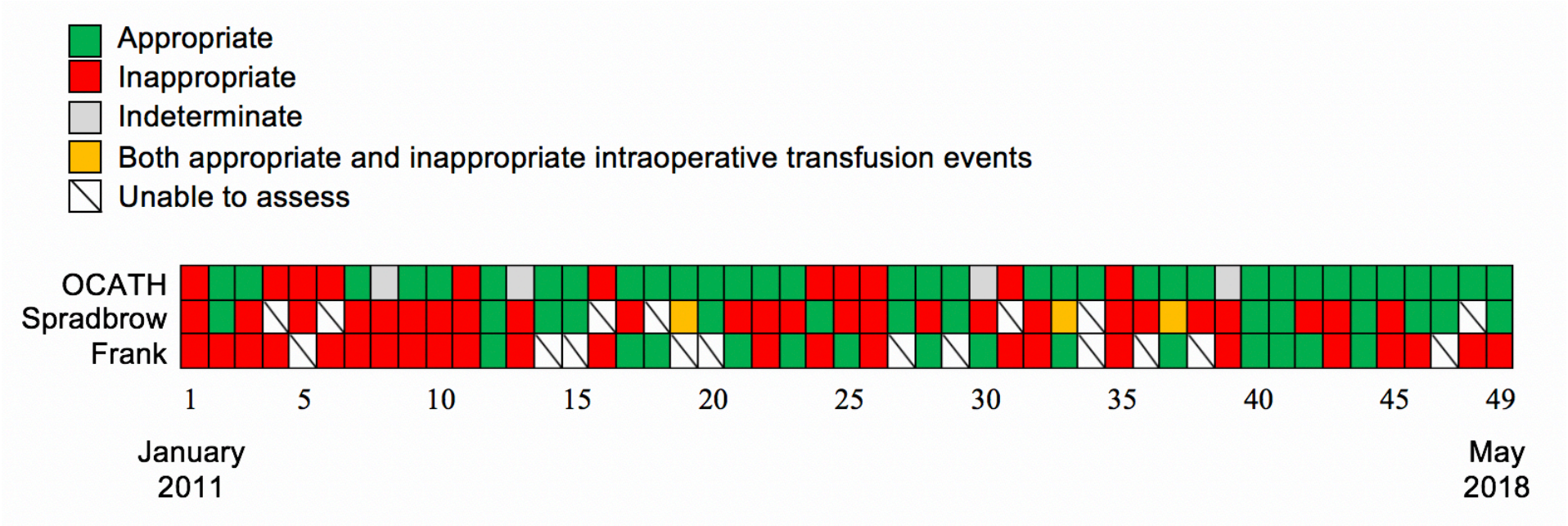


Figure 2. Appropriateness of intraoperative, postoperative and perioperative transfusions. Frank (A) represents whether the decision to initiate RBC transfusion was appropriate (for example, a minimum of one units of PRBC was appropriate). Frank (B) represents whether the quantity transfused was considered appropriate.



	Appropriate	Inappropriate	Indeterminate	Unable to evaluate
Decision to initiate transfusion by OCATH	34 (69%)	11 (22%)	4 (8%)	-
Transfusion event (Spradbrow et al)	30 (39%)	34 (45%)	-	12 (16%)*
Transfusion warranted based on POD3 hemoglobin Frank	14 (37%)	24 (63%)	-	11 (22%)**

*Unable to assess due to missing information-either pre-transfusion or post-transfusion hemoglobin missing.
**These patients received a post-operative transfusion prior to post-operative day 3 routine morning bloodwork, therefore unable to assess influence of intraoperative transfusions administered on POD3 hemoglobin. These patients have been removed from the denominator.

Figure 3. Appropriateness of intraoperative transfusions by three tools.

4.10 Appendix A

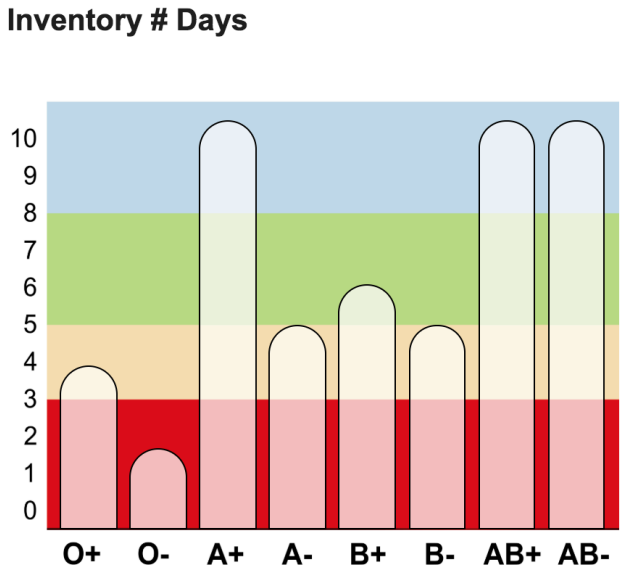


Figure 1. The national inventory of blood, reported by Canadian Blood Services on June 26, 2018 (13)

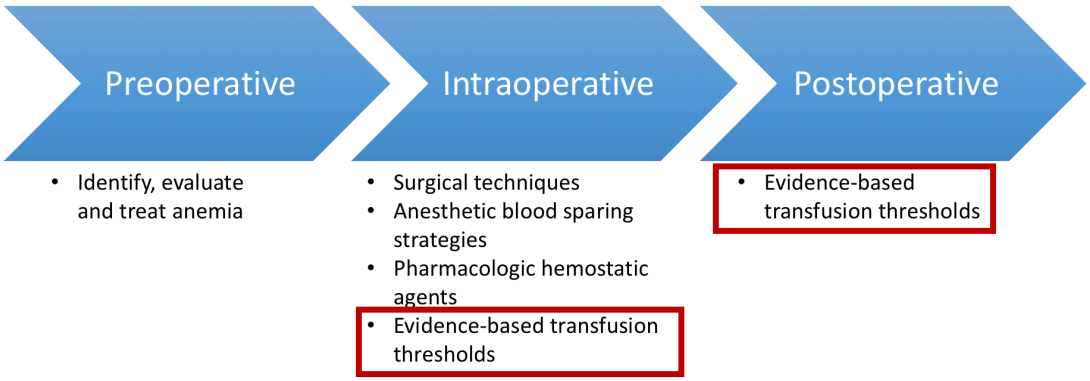


Figure 2. Perioperative blood management: strategies to reduce perioperative red blood cell transfusion (15).

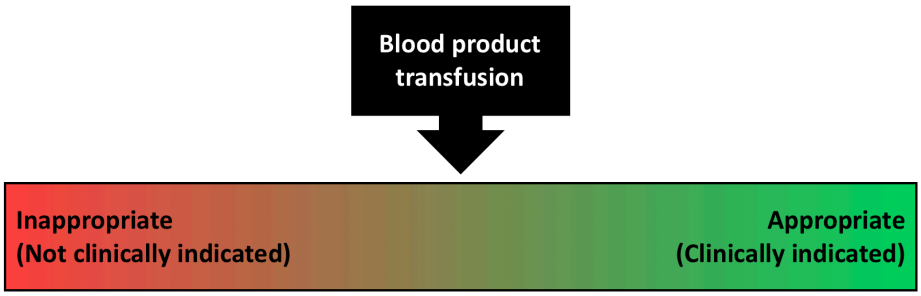


Figure 3. Spectrum of appropriateness of red blood cell transfusions.

4.11 Appendix B

Intraoperative:

1. Significant bleeding and ST segment changes trump other factors. It is never inappropriate to transfuse for these reasons.
2. It is never inappropriate to transfuse for an intraoperative hemoglobin value ≤ 75 g/L.
3. Without major indications (significant bleeding, ST segment changes) transfusion for a hemoglobin of ≥ 95 g/L is inappropriate, and transfusion for a hemoglobin of ≥ 85 g/L requires strong justification.

Post-operative:

1. In a stable, asymptomatic patient, appropriate transfusion triggers are 70 g/L (without CAD) and 80 g/L (with CAD).
2. In the immediate post-operative setting, or with a hemoglobin drop of more than 15 g/L later in the post-operative period, it is appropriate to transfuse for a hemoglobin of 75 g/L or less.

Figure 1. The Ottawa Criteria for Appropriate transfusion in hepatectomy (18).

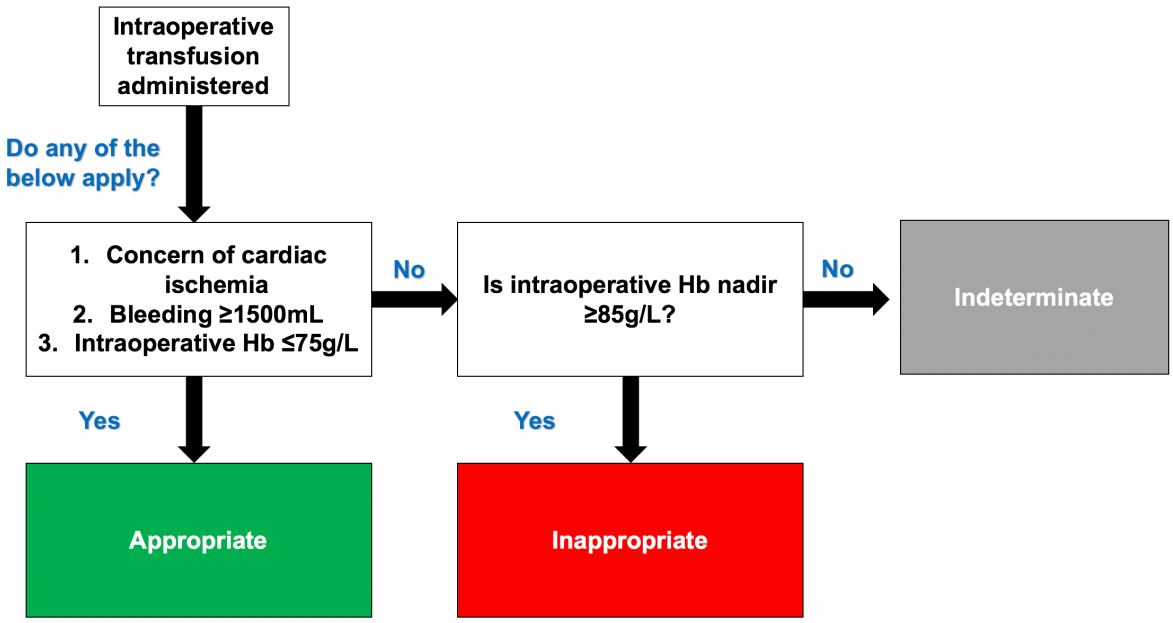


Figure 5. Algorithm for adjudicating appropriateness of decision to initiate intraoperative transfusion. Adopted from OCATH for retrospective review of intraoperative transfusions(18)..

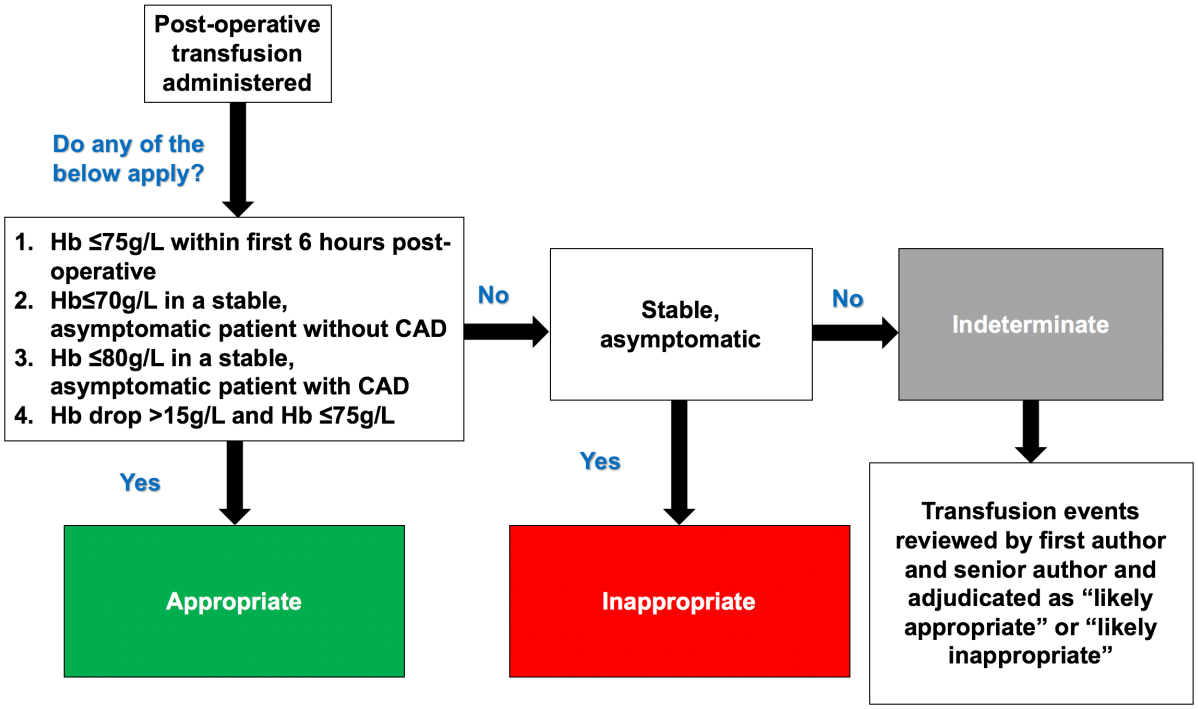


Figure 6. Algorithm for adjudicating appropriateness of post-operative transfusion event. Adopted from OCATH for retrospective review of intraoperative transfusions(18)..

4.12 Appendix C

TABLE 1. Criteria used to adjudicate RBC transfusions

Hb pre-Tx	Hb post-Tx	Symptomatic?*	Bleeding?†	Details	Appropriate?	Category
≤50	—	No	No	Iron deficiency (MCV <75 fL and previously normal or ferritin <30 μg/L) and age ≤50 years	Yes	A1[4,24,25]
≤70	—	No	No	No known cardiac disease	Yes	A2[22,26-30]
≤80	—	No	No	Known cardiac disease	Yes	A3[22]
≤70	—	Yes	No	Iron deficiency (MCV <75 fL and previously normal or ferritin <30 μg/L) and age ≤50 years	Yes	A4[4,24,25]
≤90	—	Yes	No	Symptomatic anemia*	Yes	A5[22]
≤70	≤90	—	Yes	No known cardiac disease	Yes‡	A6[22,26]
≤80	≤100	—	Yes	Known cardiac disease	Yes‡	A7[22,26]
≤100	≤100	—	Yes	Marked ongoing blood loss (>4 units over 24 hours)	Yes‡	A8
>50	—	No	No	Iron deficiency (MCV <75 fL or ferritin <30 μg/L) and age ≤50 years	No	I1
>70	—	No	No	No known cardiac disease	No	I2
>80	—	No	No	Known cardiac disease	No	I3
>70	>70	Yes	No	Iron deficiency (MCV <80 fL or ferritin <30 μg/L) and age ≤50 years	No	I4
>90	>90	Yes	No	Symptomatic anemia*	No	I5
>70	>90	—	Yes	No known cardiac disease	No§	I6
>80	>100	—	Yes	Known cardiac disease	No§	I7
>100	>100	—	Yes	Marked ongoing blood loss (>4 units over 24 hours)	No§	I8

* Symptomatic refers to the presence of any of the following symptoms within 24 hours of the transfusion: heart rate >100, systolic blood pressure <90 mmHg, presyncope, syncope, dizzy upon walking/standing, chest pain, dyspnea, ST changes on electrocardiogram, positive troponin (asymptomatic refers to patients without any of these symptoms).

† A patient was considered to be actively bleeding if any of the following were observed: intraoperative to <48 hours postoperative transfusions; need for inotropes for hypotension secondary to bleeding; systolic blood pressure <90 mmHg from bleeding; need for immediate intervention for bleeding (e.g., surgery, interventional radiology, interventional endoscopy); drop in hemoglobin in last 36 hours of 20 g/L or more; blood loss >1000 mL; hemoglobin posttransfusion < pretransfusion hemoglobin; >4 RBC units in 24 hours.

‡ Either pre or post must be appropriate.

§ Both pre and post must be inappropriate.

Hb = hemoglobin (g/L); MCV = mean corpuscular volume; Tx = transfusion.

Figure 1. Criteria used to determine appropriateness of transfusion in audit by Spradbrow et al. (149)

4.13 Appendix D

Explaination of transfusion events categorized as "likely inappropriate" (n=4)

They did not fully satisfy "inappropriate" criteria due to the patient exhibiting hemodynamic instability, more specifically, tachycardia ≥110 beats per minute, prior to the transfusion. However, review of their clinical scenario provides alternative explanation for their tachycardia. In all of the following cases, the patient did not have a history of coronary artery disease and was documented as normotensive prior to transfusion. One patient went into rapid atrial fibrillation (HR 130-150) post-operative following combined case with thoracics. In addition, they were having issues with pain control post-operative. Their pre-transfusion hemoglobin was 86g/L and their post-transfusion hemoglobin was 96g/L. One patient was tachycardic (HR 110), however their pre-transfusion hemoglobin concentration was 90g/L and their post-transfusion hemoglobin was 110g/L. Another patient was tachycardic secondary to presumed sepsis with a pre-transfusion hemoglobin of 75g/L. In the last case, the patient was tachycardic in atrial fibrillation (HR 130), however pre-transfusion hemoglobin was 100g/L.

Explaination of transfusion events categorized as "likely appropriate" (n=8)

One patient had evidence of ST changes on ECG, with a pre-transfusion hemoglobin of 78g/L, in the context of no known coronary artery disease. Four patients were tachycardic with pre-transfusion hemoglobin <80g/L. There were three distinct events which occurred in the same patient where there were issues with ongoing hypotension requiring vasopressor support. The pre-transfusion hemoglobin concentrations were 72, 74 and 83g/L. One patient was transfused two units in the context of tachycardic (HR 132), with suspicion of ongoing bleeding secondary to a rectovesicular fistula in the context of gross hematuria. Their pre-transfusion hemoglobin hemoglobin was 75g/L and post-transfusion hemoglobin was 95g/L. Given the suspicion of bleeding, the authors felt that first of the two units was appropriate.

5. CONCLUSION

Summary of findings

This work focused on perioperative red blood cell transfusions. More specifically, it (1) sought to identify available guidance to aid clinicians in determining whether or not RBC transfusions are indicated in the intraoperative setting and (2) attempted to quantify the indicidence of inappropriate transfusion in liver surgery.

Our systematic review of guidelines reporting on intraoperative red blood cell transfusion practices identified a major gap in the literature. It identified a limited number of guidelines (n=10), none of which were exclusively dedicated to intraoperative transfusion practices. Furthermore, four of the guidelines did not include objective, clearly defined indications for when transfusion would be indicated. The remaining guidelines provided discrete transfusion triggers or targets based on hemoglobin or hematocrit. One provided additional directives to transfuse based on evidence of end-organ ischemia, specifically ST changes on ECG. It was also noted that the evidence supporting these recommendations was lacking. Supporting recommendations were largely derivced from studies conducted in the non-operative setting. Lastly, the quality of the included guidelines varied considerably through application of the AGREE II tool.

Our institutional audit of perioperative transfusion practices during hepatectomy indentified high rates of overtransfusions during the perioperative period. Application of three different criteria demonstrated between 22% to 63% and 38% to 67% of transfusions were considered inappropriate in the intraoperative and postoperative period, respectively. The immediate post-operative period was a time of increased susceptibility of inappropriate transfusion. We also demonstrated inappropriate tranfusions may be associated with increased risk of major post-operative complications.

Discussion of collective significance

Avoidance of unnecesarry transfusions has been identified has having the highest potential impact on reducing perioperative transfusions. In order to avoid unnecessary

transfusions, clear guidance regarding indications for transfusions are necessary. Absence of this makes it challenging to fulfill this objective. This project is a natural evolution of Dr. Sean Bennett's Master's Thesis Project, under the supervision of Dr. Martel's guidance, which aimed to establish appropriateness criteria for transfusion in liver surgery.

The first part of this thesis project aimed to identify and summarize available guidance. In addition to identifying Dr. Bennett's recommendations, an additional 9 practice guidelines satisfied our inclusion criteria. As eluded to above, the compilation of recommendations left the prescribing physician with several unanswered questions. General themes of limitations include that the recommendations were too focused towards a specific patient population. For example, Dr. Benentt's criteria are intended for patient's undergoing hepatectomy. Other guidelines are focused on the management of specific conditions, for example abdominal aortic aneurysm, or placenta accrete, with minimal content devoted to intraoperative transfusion recommendations. Another question that remains is which hemoglobin or hematocrit concentration should prompt transfusion, and what pre-existing medical comorbidities require more liberal transfusion thresholds. The recommended hemoglobin transfusion triggers range from 60g/L to 100g/L. Some guidelines indicate more liberal threshoulds for patients "at risk of end organ ischemia," whereas others state patients with "heart block, angina or beta-blocked," should be considered differently. Ideally, there would be some consistency amongst guidelines in regards to which patient populations have lower tolerance to anemia. Another major limitation was the absence of discussion surrounding modality and timing of hemoglobin measurements. As eluded to previously, there are several different instruments available to test hemoglobin concentration. None of the guidelines advise on the role of point of care testing versus labarotomy testing. Further guidance pertaining to their roles in determining need for intraoperative transfusions is critical. Lastly, with the exception of one guideline specifying that ST changes are an indication for transfusion, no other guideline provided objective indications for transfusion. Although the majority of guidelines recommended monitoring for end organ ischemia, lack of values which trigger transfusion make it difficult to adhere to guidelines.

The second half of this thesis was dedicated to quantifying the incidence of inappropriate transfusion in the perioperative period, identify patient, practicioner and clinical settings associated with increased risk of transfusion; and lastly determine if there was an association between inappropriate transfusions and adverse events. Prior to conducting our systematic review of intraoperative transfusions guidelines, we decided we were going to apply Bennett et al.'s criteria, as well as two additional tools we had identified to determine appropriateness. Bennett's criteria was the only one of the three included in the systematic review of intraoperative guidelines. The remaining tools were described as criteria that could be applied to determine appropriateness of transfusion based on retrospective analysis. Frank et al. utilized hemoglobin concentration at discharge to esablishe approrpriateness. Spradbrow et al. considered a combination of clinical parameters to establish appropriateness. These included pre- and post-transfusion hemoglobin concentration, history of cardiac disease, presence of "active bleeding," whether they were symptomatic of anemia, and more. The exercise of applying these three tools identified 22% to 84% of transfusions were considered inappropriate. Although these estimates are limited by their retrospective nature, it identifies that overtransfuse is a problem. The exact extent of the problem is challenging to quantify. The potential harm of unnecessary transfusion is supported by the finding that there was a higher inciednece of major adverse events in patients unnecessarily transfused compared to those that were not transfused.

Unanswered questions and future directions

A question that remains is determining what rate of overtransfusion would be considered appropriate. Undertransfusion has the potentional for adverse consequences, therefore complete elimination of overtransfusion introduces the risk of harm. This is a very challenging question to answer given the dynamic nature of patients clinical status and all of the factors being taken into consideration when determining whether a transfusion is necessary. One of the most objective ways of understanding whether we are overtransfusing, given the limitations of retrospective review, is to apply Frank's method and determine if a patient was overtransfed based on their hemoglobin concentration at discharge. Based on

their tool, 84% of patients were considered to have been overtransfused at our institution. Furthermore, 22% of patients had hemoglobin concentrations above 100g/L. At this point, striving to eliminate transfused patients having discharge hemoglobins >90g/L without CAD with >100g/L with CAD would be a good first step. Given the care taken to devise Bennett's tool, it would be reasonable to predict that adherance to the recommendations would not result in adverse events. In the intraoperative setting, continuous cardiac monitoring allows for early identification of concern of end organ ischemia, which is an indication for transfusion. In the post-operative setting, a combination of hemoglobin concentration and clinical status are used to determine if transfusion is indicated. Spradbrow's criteria takes into consideration similar parameters.

The next step going forward would be to apply Bennett's tool prospectively and determine the feasibility of doing so. Monitoring for adverse events secondary to anemia would be useful in determining if strict adherance to these rules was associated with harm. Once feasibility has been established, an interventional study comparing the application of this tool to usual practice is warranted. This would determine whether prospective application of a transfusion tool was assocatied with a reduction in transfusion as well as both short term and long term adverse events.

Lastly, creation of more widely applicable transfusion rules, for all perioperative patients is warrented. Although patients undergoing liver resection are at increased risk of blood transfusion relative to the average surgical patient, they represent only a small proportion of patients undergoing surgery. Development of intraoperative transfusion for all surgical patients rules may have the potential to reduce the economic and clinical burden associated with inappropriate transfusions.

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