

# Implementation of a Patient Blood Management Program in a Large, Diverse Multi-Hospital System

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## ABSTRACT

**Background:** There is limited literature relating to patient blood management (PBM) programs in large multi-hospital systems or addressing challenges of implementation across diverse systems comprised of community and academic hospitals.

**Objective:** To establish a PBM program to improve utilization of blood transfusion units at a multi-hospital system in the Midwest (BJC HealthCare).

**Methods:** High-impact strategies in establishing the PBM program included formation of Clinical Expert Councils (CECs) of providers, establishment of consensus utilization guidelines, and development of a robust reporting tool. CECs enabled collaboration and facilitated standardization across a complex system of academic, private practice, and tertiary facilities with a diverse community of medical providers. Consensus guidelines and the PBM reporting tool were key to creating meaningful reports to drive provider practice change.

**Results:** Over the 5 years following implementation of the PBM program, there has been a steady decrease in red blood cell (RBC) utilization. Noticeable changes have taken place at individual hospitals in the system, including reductions in transfusions falling outside guideline parameters from 300 per quarter to less than 8 per quarter at 1 of our community hospitals. No negative impact on patient care has been identified.

**Conclusion:** In response to current transfusion guidelines and the need for optimizing stewardship of blood product resources, this hospital system successfully implemented a robust PBM program that engaged academic and non-academic community providers and decreased utilization of blood transfusion resources in line with consensus guidelines.

**Keywords:** quality improvement; RBC transfusion; transfusion practices; provider practice change; utilization trends.

Evidence from clinical trials and published clinical guidelines support the adoption of a restrictive blood transfusion approach in hospitalized, stable patients as best practice.<sup>1-5</sup> As such, the development and implementation of patient blood management (PBM) programs has become an increasingly important process improvement for reducing variability in transfusion practices and clinical outcomes.

As recently as 2013, BJC HealthCare, a multi-hospital system in the Midwest, had no standardized, system-wide blood management program, and transfusion practices varied widely across providers and between individual hospitals based on size, patient population, and resources. The system consisted of 13 hospitals, ranging from large tertiary to smaller commu-

nity and academic hospitals. Although adults constituted the vast majority of the patient population, the hospital system also included a pediatric specialty hospital, St. Louis Children's Hospital. In addition, some sites were staffed by private practice providers and others by university-based providers, including blood bank medical directors. Due to the diversity of settings and populations, efforts to align transfusion and other practices often faced multiple challenges. However, improving the management of blood transfusions was identified as a key resource stewardship priority in 2013, and implementation of a system-wide program began after extensive discussions and consensus approval by senior

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hospital system and medical leadership. The primary aim of the program was to optimize overall blood product resource stewardship. Specifically, we sought to control or reduce costs per patient-care episode using strategies that would not negatively impact patient care and could potentially even improve patient outcomes (eg, by avoiding unnecessary transfusions and their attendant risks).

There is a plethora of literature related to the implementation of PBM programs in individual hospitals,<sup>6-18</sup> but few reports specifically relate to large multi-hospital health systems,<sup>19-21</sup> or directly address the unique challenges of implementation across a diverse system of community and academic hospitals and providers.<sup>19</sup> Here, we discuss our experience with establishing a PBM program in a large, diverse, multi-hospital health system, provide examples of innovative strategies, and address challenges faced and lessons learned. Future endeavors of the PBM program at BJC HealthCare are also described.

### Setting

BJC HealthCare is one of the largest nonprofit health care organizations in the United States, delivering services to the greater St. Louis, southern Illinois, and mid-Missouri regions, and addressing the health care needs of urban, suburban, and rural communities. As of 2018, the system included 15 hospitals and multiple community health locations comprising more than 3400 staffed beds, 31,500 employees, and 4300 physicians with privileges. The system annually has more than 151,000 hospital admissions, 81,000 outpatient surgery visits, and 537,000 emergency department visits. In addition to inpatient and outpatient care, services include primary care, community health and wellness, workplace health, home health, community mental health, rehabilitation, long-term care, and hospice. As a nonprofit system, BJC is the largest provider of charity care, unreimbursed care, and community benefit in Missouri, highlighting the fact that resource stewardship is a critical issue across the entire system and the communities served.<sup>22</sup>

### PBM Project

Preparation for large-scale change across several hospitals began with creating a framework for the initiative, which consisted of a “burning platform,” a guiding

vision, and a coalition. The burning platform identifies the importance and urgency of a change and helps to establish commitment. Between 2012 and 2014, the American Association of Blood Banks (AABB) released new evidence-based guidelines and recommendations calling for more restrictive transfusion practices pertaining to red blood cells (RBCs; ie, a hemoglobin threshold of 7 to 8 g/dL) in both inpatient and outpatient care.<sup>2</sup> In addition, use of single-unit transfusions was recognized as best practice by the AABB in the Choosing Wisely campaign.<sup>23</sup> Historically, adult patients requiring transfusions were given 2 units in succession. The new recommendations provided a strong basis for changing transfusion practices at BJC. It was believed that aligning transfusion practices with the new guidelines was consistent with the mission and vision of the work: that these changes could lead to optimization of resources, cost control, reductions in unnecessary blood transfusions, and potentially improved care (eg, fewer transfusion-related complications). We used the national guidelines to initiate discussions and to identify clinical conditions and associated laboratory parameters for transfusion therapy.

Once this burning platform was established, a team comprised of physicians, blood bank experts, quality consultants, data analysts, and supply managers, referred to as the Outcomes Team, was formed to lead the change efforts across the system. Initial projects for the team included developing system-wide consensus-based transfusion guidelines, providing education to providers on the new evidence in transfusion practice, and sharing BJC-specific historical utilization data. The guiding principle for the group was that “blood is a valuable resource, but not without risk, and less is more.” In order to disseminate the vision of the initiative across the system, campaign signs with the slogans “7 is the new 10” (referring to the g/dL transfusion threshold) and “1 is the new 2” (referring to the new practice of the preferential transfusion of single units rather than 2 at a time) were displayed in system hospitals.

Last, a guiding coalition of system leaders was needed to help push the initiative forward and sustain the program once fully implemented. Thus, a multidisciplinary PBM Clinical Expert Council (CEC) was formed to assist with implementation and maintenance of the program.

**Role of PBM Clinical Expert Council**

The PBM CEC was designed to improve overall physician and expert engagement and provide a forum where stakeholders from across the system could participate to voice their expert opinion. CECs (which BJC formed in other clinical areas as well) are multidisciplinary teams consisting of clinical, administrative, and technical staff. The open, multidisciplinary structure of the councils allows for collaboration that promotes change across a complex multi-hospital system. Each hospital is represented by key physicians and technical leaders, opening opportunity for both horizontal and vertical partnership.

As part of the overall physician engagement strategy, the PBM CEC was launched across BJC in November 2013 as a decision-making body for gaining system consensus on matters relating to blood management. The initial goals for the PBM CEC were to share information and educate providers and others on the latest evidence, to subsequently debate and develop consensus for guidelines to be applied across BJC, and to identify and adopt gold standard practices to drive and sustain compliance across the system. More specifically, we wanted to focus on how to avoid unnecessary blood transfusions known to be associated with increased risk for adverse reactions, other morbidity, mortality, and longer length of stay. Council members met quarterly to address 6 key drivers: patient safety, informatics and data, quality improvement, efficiencies and workflows, education and competency, and communication and engagement. Members then voted to approve guidelines, policies, and procedures. The group continues to assist in updating and standardizing guidelines and providing input on improving the functionality of the PBM reporting tool.

**Development of the PBM Reporting Tool**

Providing and sharing data on blood utilization and practices with the CEC and hospital leaders was imperative to driving change. The Outcomes Team deliberated on how best to generate and provide such information, conducting comparisons between selected vendor-based tools and potential internal BJC solutions. After investigation, BJC leadership approved the development of an in-house PBM dashboard tool using Tableau Desktop

(Tableau Software, Inc.). The tool consists of an executive page with 5 additional tabs for navigating to the appropriate information (**Figure 1** and **Figure 2**); data within the tool are organized by facility, service, provider, ICD diagnosis, transfusion indication, and the Clinical Classifications Software category, as defined by the Agency for Healthcare Research and Quality.

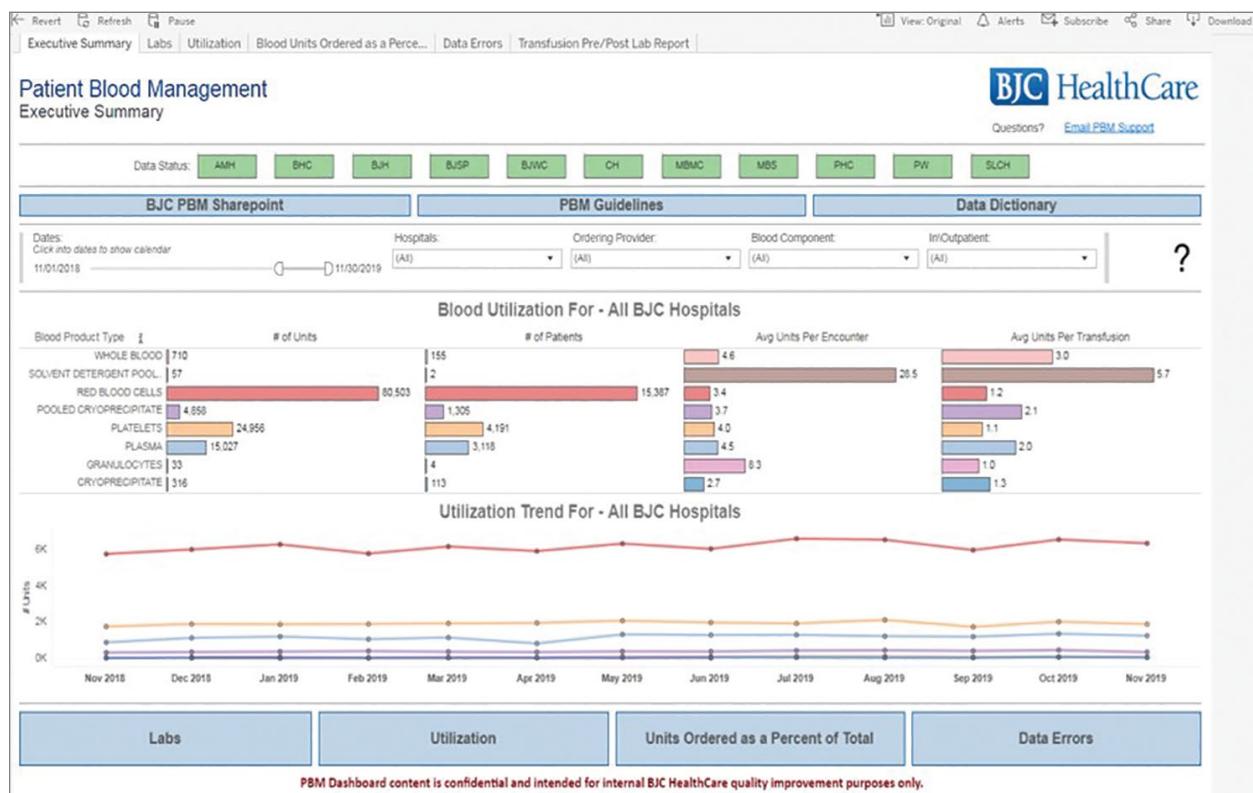
The PBM reporting tool was launched on December 31, 2014. The next priority after the launch was to validate the tool's blood utilization data and implement enhancements to make the tool more effective for users. A super-user group consisting of blood bank supervisors and managers was established. The goals of the user group were to preview any enhancements before presenting the tool to the larger CEC, test and validate data once new information was added, and share and prioritize future enhancements. User group meetings were held monthly to share best practices and discuss individual facilities' blood utilization data. In addition, each facility's representative(s) shared how they were driving changes in provider practice and discussed challenges specific to their facility. Enhancements suggested through the user group included: incorporation of additional lab values into the tool to correspond with other blood products (eg, fibrinogen, hematocrit, international normalized ratio, and platelet count), addition of the specific location where the blood product was administered, and standard naming conventions of locations to allow comparisons across facilities (eg, Emergency Department instead of ED, ER, or EU).

All hospital users were given access to a test version of the reporting tool where they could review enhancements, identify what worked well and what could be done better, and suggest corrections. As changes were made to the hospital lab systems, a sample of data was reviewed and validated with affected facilities to confirm the continued accuracy of the data. To ensure its practicality to users, the tool continues to be improved upon with input from council stakeholders and subject-matter experts.

**Measurements**

To monitor blood utilization across the health system, we tracked the total RBC units administered by hospital, service, and provider and also tracked pre- and post-transfusion hemoglobin values.

# Patient Blood Management



**Figure 1.** Executive page of the Patient Blood Management dashboard (November 2018 to November 2019).

## Results

Overall, the system has seen a steady decrease in RBC utilization over the 5 years since the PBM program was implemented (**Table**), with an absolute decrease of 3998 RBC units utilized per year from 2013 to 2018. From this assessment, focus efforts are being identified and future work will incorporate targeted metrics for those areas with higher utilization of RBCs. More importantly, from 2014 through 2017, there was a consistent decreasing trend in the number of transfusion-related safety events (302 to 185, respectively). However, there was a slight increase in reported events from 2018 to 2019 (188 and 266, respectively).

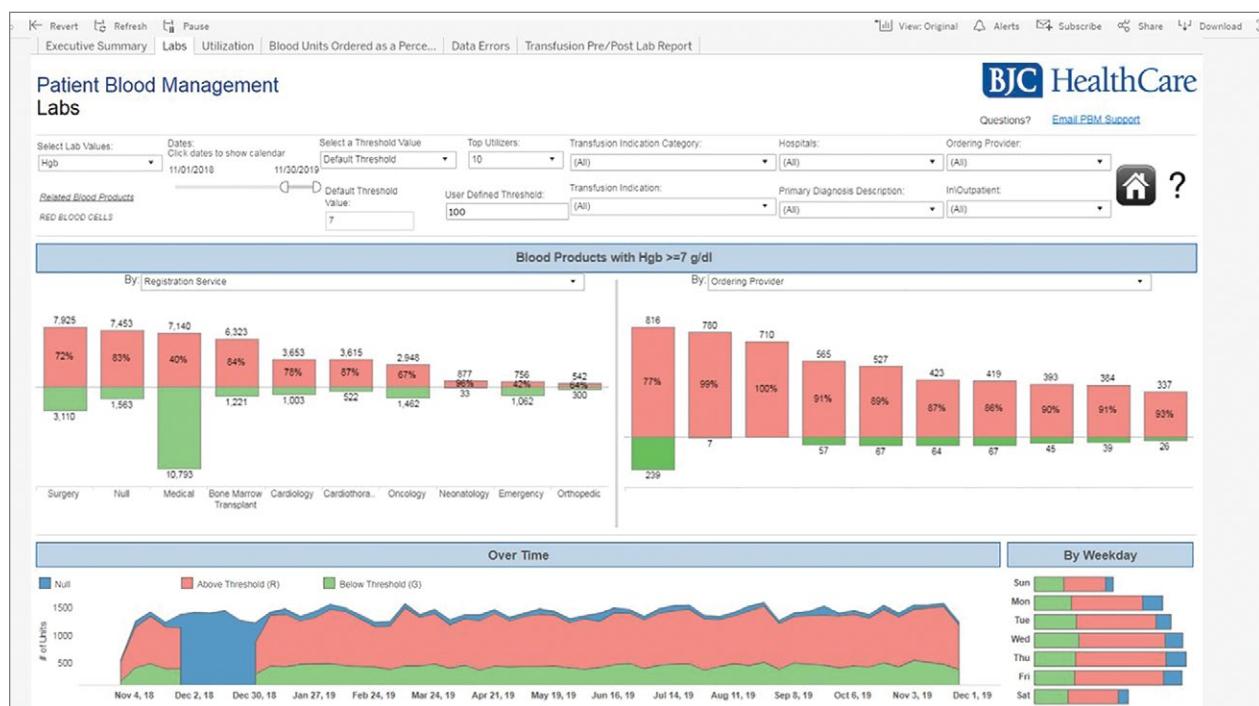
In addition to system-wide improvement, noticeable changes have taken place at individual hospitals in the BJC system. For example, Boone Hospital Center in Columbia, Missouri, began critically reviewing all RBC transfusions starting in 2015 and, to raise awareness, communicating with any provider who transfused a patient outside of transfusion guidelines. Since then, Boone Hospital has seen a dramatic reduction in transfusions considered noncom-

pliant (ie, falling outside guideline parameters), from 300 transfusions per quarter, down to less than 8 per quarter. St. Louis Children's Hospital also began reviewing blood products utilized by providers that fell outside of the standardized guidelines. At this hospital, physician champions discuss any outliers with the providers involved and use multiple methods for disseminating information to providers, including grand rounds, faculty meetings, and new resident orientations.

Another success has been the partnership between Barnes Jewish St. Peters and Progress West Hospitals in providing PBM education. Their joint effort resulted in implementation of education modules in BJC's internal learning system, and has provided PBM-related education to more than 367 nurses, blood bank staff, and physicians.

## Challenges and Lessons Learned

Implementation of the PBM program was generally successful, but it was not without challenges. One of the biggest challenges was addressing the variation in care and



**Figure 2.** Labs tab of Patient Blood Management dashboard—transfusions with hemoglobin < 7 g/dL.

practices across the hospital enterprise. Due to the varying sizes and service goals of individual hospitals, lack of standardization was a significant barrier to change. Gaining trust and buy-in was imperative to increasing compliance with new transfusion policies. The primary concern was finding a balance between respecting physician autonomy and emphasizing and aligning practices with new evidence in the literature. Thus, understanding and applying principles of thoughtful change management was imperative to advancing the framework of the PBM program. The CEC venue enabled collaboration among hospitals and staff and was ultimately used to facilitate the necessary standardization process. To gain the trust of hospital and medical staff, the Outcomes Team conducted several site visits, enabling face-to-face interaction with frontline staff and operational leaders. Moreover, the team's emphasis on the use of the latest evidence-based guidelines in discussions with hospital and medical staff underscored the need for change.

Frank et al<sup>19</sup> describes using an approach similar to our Outcomes Team at the Johns Hopkins Health System. A designated multidisciplinary quality improvement team,

referred to as the “clinical community,” worked on implementing best practices for blood management across a system of 5 hospitals. The authors reported similar results, with an overall decrease in number of units transfused, as well as substantial cost savings.<sup>19</sup> Our project, along with the project implemented by Frank et al, shows how a “consensus-community” approach, involving stakeholders and various experts across the system, can be used to align practices among multiple hospitals.

Development of a robust PBM reporting tool was key to creating meaningful monthly reports and driving provider practice change. However, this did require several training sessions, site visits, and computer-based training. Members of the Outcomes Team engaged in one-on-one sessions with tool users as a way of addressing specific areas of concern raised by staff at individual blood banks, and also took part in system-wide initiatives. The team also attended blood bank staff meetings and hospital transfusion committee meetings to educate staff on the evidence and initiative, provide demos of the reporting tool, and allow for a more robust discussion of how the data could be used and shared with other

Table. Red Blood Cell Units Dispensed From BJC Blood Banks

Year	Total RBC Units	Average RBC Units per Transfusion	RBC Units per 1000 CMI APD*
2013	77,229	No data	3101
2014	75,914	1.3	2875
2015	73,003	1.3	2578
2016	73,667	1.3	2409
2017	73,909	1.3	2316
2018	73,231	1.2	2241
2019 annualized	75,178	1.2	2249

APD, adjusted patient days; CMI, case mix index; RBC, red blood cell.

\*Adjusted by volume (adjusted patient days) and patient acuity (case mix index).

departments. These sessions provided opportunities to identify and prioritize future enhancements, as well as opportunities for continued education and discussion at hospitals, which were critical to ongoing improvement of the reporting tool.

## Conclusion and Future Directions

Blood products remain extremely valuable and scarce resources, and all health care professionals must work to prevent unnecessary transfusions and improve clinical outcomes by adhering to the latest evidence-based guidelines. In response to current transfusion guidelines and the need to optimize blood product resources, our system successfully implemented a robust PBM program that engaged both academic and non-academic providers and communities. Several elements of the program helped us overcome the challenges relating to standardization of transfusion practices: consensus-based development of guidelines using the latest scientific evidence; formation and utilization of the CEC venue to gain system-wide consensus around both guidelines and approaches to change; development of a trustworthy and accessible PBM reporting tool (as well as continuing education sessions to improve adoption and utilization of the tool); and ongoing multidisciplinary discussions and support of thoughtful change and sustaining activities. We have seen a system-wide decrease in the number of RBC units transfused (absolute and per case mix-adjusted patient day) since implementing the PBM program, and in the following years have noted a trending

decrease in transfusion-related safety events. Although there was a slight increase in reported safety events from 2018 to 2019, this was likely due to the systematic implementation of a new electronic medical record system and improved reporting infrastructure.

Upcoming phases of our system-wide PBM program will include looking at opportunities to improve blood utilization in other specific clinical areas. For example, we have begun discussions with hematology and oncology experts across the system to expand their patient population data within the PBM reporting tool, and to identify areas of opportunity for provider practice change within their specialty. We are also reviewing cardiothoracic surgery transfusion data to identify opportunities for reducing blood utilization in specific clinical scenarios. In addition, we are working to incorporate our 2 newest hospital system members (Memorial Hospital East and Memorial Hospital Belleville) into the PBM program. In collaboration with perioperative leaders across the system, the surgical blood ordering process is being reviewed. The goal of this effort is to reduce blood products ordered in preparation for surgical procedures. We are also currently investigating whether an impact on safety events (ie, reduction in transfusion reactions) can yet be detected. Last, our health care system recently launched a system-wide electronic medical record, and we are eager to see how this will provide us with new methods to monitor and analyze blood administration and utilization data. We look forward to reporting on the expansion of our program and on any clinical outcome

improvements gained through avoidance of unnecessary transfusions.

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## HOW DO I OBTAIN MEANINGFUL METRICS?

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Patient Blood Management (PBM) metrics are crucial to demonstrate program outcomes, opportunities, evaluate initiatives and monitor practice patterns. The guidance document for the AABB PBM Standards includes suggestions for metrics and program elements that can be measured.<sup>1</sup> Meaningful metrics develop from applying SMART principles: specific, measurable, achievable, relevant and time-specific.<sup>2</sup> Other considerations include the purpose, audience and resulting actions. A metric can be used for trending, monitoring, improving or correcting. It may be reported to hospital leadership, transfusion service leaders, physicians, licensed independent practitioners (LIP) or nurses. A calculated metric is derived from an aggregate data set whereby more detail will be needed to understand sources and contributing factors. W. Edwards Deming sums up the value of meaningful metrics:

“Scientific data are not taken for museum purposes; they are taken as a basis for doing something. If nothing is to be done with the data, then there is no use in collecting any. The ultimate purpose of taking data is to provide a basis for action or a recommendation for action. The step intermediate between the collection of data and the action is prediction.”<sup>3</sup>

Once a metric has been determined, there are additional considerations to assess in order for it to become meaningful. Visualization management is important to augment and aid in interpretation. The ease in which the metric is made accessible and the ability of the consumer to translate the information into action are steps on the path to meaningful metrics.

### METRICS THAT MATTER

The decisions surrounding what to measure should include consideration of data sources, ease of extraction, the amount of refining involved and limitations of the data. Metrics will change over time based upon the focus and initiatives of a PBM program. Three or four key metrics will serve the needs of a PBM program (Table 1.0) without being overwhelming. The presence of complicated dashboards or multiple reports may obscure the ability to synthesize data into actionable information. Therefore, not only minimizing the number of metrics, but also ensuring that each metric is clear, concise and comprising well-defined action steps, is important.

A multi-hospital health system may be challenged to compare facilities that differ in size, services and the complexity of patients. Metcalf et al.<sup>4</sup> found that red blood cell (RBC) utilization moderately to strongly correlated to all-patient-refined (APR) diagnosis-related groups (DRG). Furthermore, the work of Stonemetz<sup>5</sup> et al. reaffirms findings of a direct correlation between case mix index (CMI)

and transfusion requirements for red blood cells, plasma and platelets in surgical patients. Creating a metric using both DRG-based CMI and acute patient days or length of stay (LOS) adjusts for both patient volume and severity of illness. Chart 1.0 demonstrates the variation of RBC utilization within a multi-hospital health system.

It is important to create an atmosphere of transparency by showing key stakeholders and leadership how a hospital compares with others in a system. Translating a high-level aggregate metric into action occurs through exploring more deeply the drivers of a trend or outliers. Chart 1.0 generates questions about the driving variables at hospitals with the highest adjusted utilization. Hospitals with the lowest adjusted utilization may have developed best practices that can be replicated throughout the health system. Further investigation may include probing into clinical practices such as transfusion thresholds, ordering patterns, indications and dosing.

The “Choosing Wisely” campaign promoted the use of single-unit RBCs in stable non-bleeding patients.<sup>6</sup> A metric evolving from this practice is the percentage of one-unit RBC orders. To drive the practice, decision support may be added to the electronic medical record blood ordering process or a simple ordering default to one unit. Chart 2.0 represents a comparison of hospitals within a health system. A target can be set at 60% or greater for one-unit transfusions. The PBM program staff would review the data in more detail to gain insight into the ordering practices at hospitals below target. A review of services and providers routinely ordering two units of RBCs may identify opportunities for improvement or justify some deviations. The PBM program may engage in a targeted campaign to remind ordering providers of the benefits of single-unit ordering practices as the basis for “right dosing.” The intervention can be built upon by providing individual feedback to providers ordering two units without an interim hemoglobin evaluation.

Initiative-directed metrics are of value to PBM programs, since they are created from the prospect of improvement. There are countless opportunities for metrics within this space involving the dosing of blood products, preoperative anemia and utilization of a specific PBM method or strategy. The 3<sup>rd</sup> edition of the AABB Standards for PBM<sup>7</sup> has added the categories of obstetrics, pediatrics, medical patients and outpatient transfusions. Examples of metrics for these categories include the percentage of non-oncology outpatient RBC transfusions with a nutritional deficiency assessment or the percentage of anemic pregnant patients treated for iron deficiency.

## VISUALIZATION MANAGEMENT

How metrics are displayed is paramount to viewer interpretation. Whether as an online dashboard or in another form, the primary aim is to minimize the intellectual load on the end-user.<sup>8</sup> Easy access, display flexibility, consistency in design, as well as spatial layout, contribute to decreased cognitive load. Therefore, it is important to limit extraneous or distracting information by questioning the value of each element. The display should include definitions, how to interpret the data elements, limitations and any recommended actions without clouding the display. Titles of metrics should be clear and concise, stating if the metric is a percentage, average or another measure. A good investment into a metric display involves taking time to obtain feedback in order to gauge the effectiveness of a visual format as well as to evaluate potential barriers in interpretation.

Frank et al.<sup>9</sup> described the manner and methods of visualization for the measures of transfusion thresholds and targets. The displayed metric was in a format that was easy for the end-user to determine whether or not their practice was outside the recommended range. Printed tables were posted in areas that provided passive access meaning the physician did not have to find the data; the data found the physician. It is important to give consideration to the ease at which the metric will be available. Displaying metrics in an online dashboard or shared file may be a good choice if the desired audience is already going to this area for other metrics or information. Emailing metrics should include a read receipt to monitor if the message was opened. When presenting metrics at meetings, the presenter should have a firm understanding of the metric as well as the associated actions needed to achieve target goals and be able to answer questions. There are many potential unknowns, including who may be viewing, how the information is interpreted and the ability to translate the data into action.

## **DATA TO ACTION**

Meaningful metrics serve a purpose; it cannot be assumed that providers will know clinical practices associated with a specific metric or what the expectation is on their part. The Knowledge to Data (K2D) framework is a five-step process of transforming data into information which is translated into action. The framework uses a rapid feedback cycle that includes clear intent for each data collection initiative, collecting “good enough” data for the purpose, presenting a brief results report, a result debrief, and decisions regarding the data.<sup>10</sup> Steering the PBM team and a small group of key stakeholders through the K2D process provides opportunity to critique and identify potential barriers. It also positions the PBM team to lead metric consumers through the process of interpretation, information, knowledge and action.

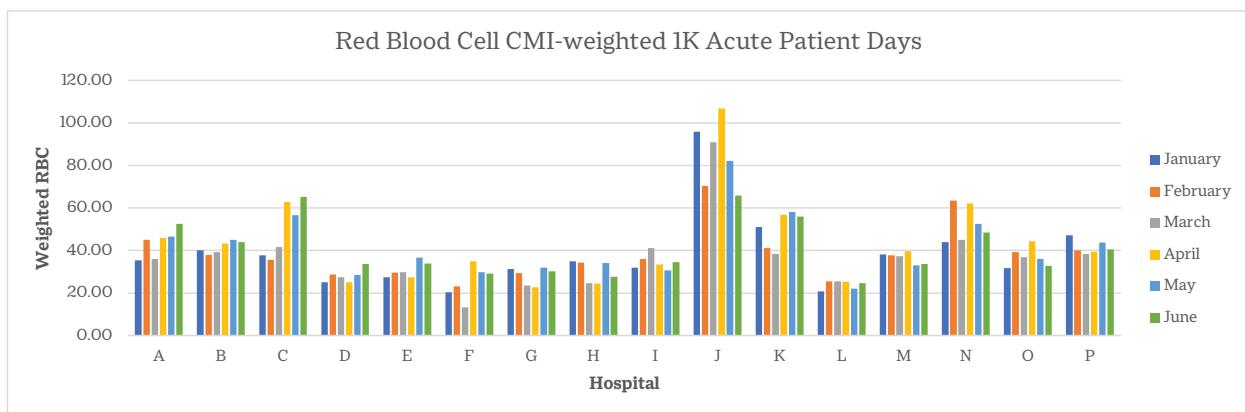
## **CONCLUSION**

Metrics often generate more questions than answers. A good metric will aid a PBM program in achieving its goals. Developing meaningful metrics is a process and one that, if done well, creates a framework for effective execution. The actual metric is just the starting gate to becoming a measure that holds value. The areas of display, access, dissemination and action require a methodical approach. Taking time to obtain constructive feedback and to present a metric based upon those who are expected to take action, will greatly improve its value.

Table 1.0

Metric or Measure	Definition
Blood product utilization	Number of transfused blood products
Blood product adjusted by patient days or discharges	Numerator: number of units transfused Denominator: total patients days or discharges
Blood product case mix index (CMI) weighted by patient days or discharges	Numerator: total blood product Denominator: CMI x( total patient days/1000)
Transfusion rate	Percentage of patients transfused
Single-unit RBC orders	Percentage of RBC orders quantity = 1 unit
Average RBC dose	Numerator: number of RBC units transfused Denominator: number of patients transfused
Average nadir hemoglobin or platelet count	Lowest hemoglobin or platelet count. Surrogate for transfusion threshold
Average final hemoglobin or platelet count	Last hemoglobin or platelet count prior to discharge. Surrogate for transfusion threshold.
Average highest INR	Highest INR used as surrogate for transfusion threshold.
Final INR	Last INR prior to discharge. Surrogate for transfusion target.

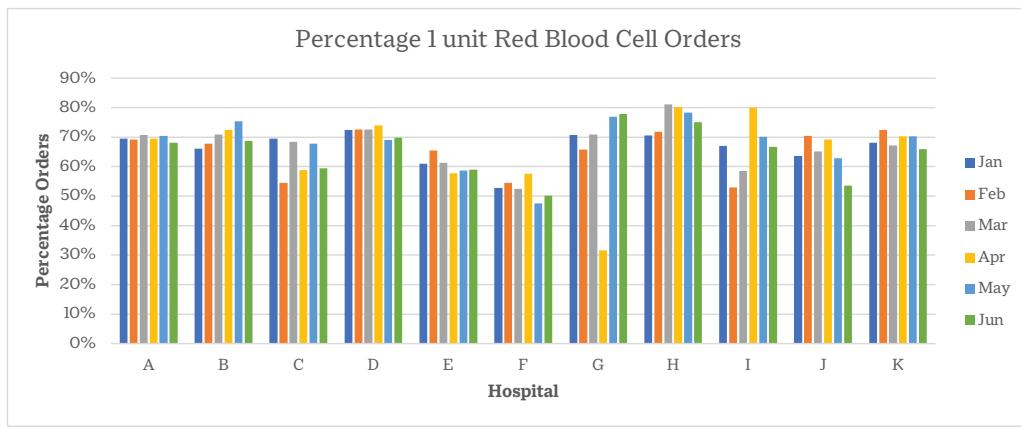
Chart 1.0



Y axis = monthly red blood cell utilization after adjustment

X axis = each letter represents a hospital

Chart 2.0



Y axis = percentage of red blood cell orders with quantity 1 unit

X axis = each letter represents a hospital

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## Transfusion guidelines: when to transfuse

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**Transfusion of blood and blood components has been a routine practice for more than half a century. The rationale supporting this practice is that replacement of blood loss should be beneficial for the patient. This assumption has constituted the underpinning of transfusion medicine for many decades. Only over the past 20 years, we have seen a more concerted effort to answer very basic questions regarding the value of transfusion therapy. An assessment of the value of transfusion based on well-designed and appropriately powered randomized, controlled trials is the first step in optimizing transfusion practices. Systematic reviews provide the second step by building the knowledge base necessary to assess the impact of transfusion practice on patient outcomes. The third step is the development of clinical practice guidelines, and this occurs when systematic reviews are interpreted by individuals with expertise in transfusion medicine. Such guidelines are typically supported by professional organizations and/or health authorities. Implementation of clinical practice guidelines can be challenging, especially in an area as heterogeneous as transfusion medicine. However, clinical practice guidelines are necessary for the practice of evidence-based medicine, which optimizes patient care and improves patient outcomes. This review focuses on clinical practice guidelines for transfusion of three blood components: RBCs, platelets and plasma. In addition, we provide the approach used to implement clinical practice guidelines at our own institution.**

### Introduction

Transfusion of blood and blood components (ie, RBCs, platelets, plasma, and cryoprecipitate) is one of the most common medical procedures performed in the developed world. However, the decision to transfuse or not to transfuse is one of the more complex decisions made by medical practitioners. Clearly no medical intervention is without risks, but in principle, these risks should be offset or justified by immediate or long-term benefits.

A better understanding of the risks of transfusion has transformed transfusion medicine through the accelerated development of more sophisticated donor testing (eg, ever-improving infectious disease tests), pretransfusion testing, recipient identification, and multiple improvements in blood component characteristics and quality (eg, leukoreduction, irradiation, pathogen inactivation). These developments have resulted in improved safety profiles for transfused components and a perception of minimal risk. At the same time, the introduction of patient blood management (PBM), defined as an evidence-based approach to optimizing the care of patients who might need transfusion, shows that the need for transfusion can be minimized in many patients by implementation of thoughtful processes often beginning days or even weeks before the actual decision to transfuse or not is being made.

In this context, the focus has now shifted to the benefit side of the equation. Are the assumed benefits of transfusion universal or are they limited to only a well-defined population of patients? What triggers should be used to administer blood components and when should transfusions occur? What component dose is sufficient and/or necessary to confer clinical benefit? The answers to these questions have been sought in multiple randomized clinical trials. The next step of this process is to translate this information into widely adopted and consistent practice through the development of

clinical practice guidelines that can become a part of comprehensive PBM.

Clinical practice guidelines are defined as systematically developed statements to assist with practitioner and patient decisions about appropriate health care for specific clinical circumstances.<sup>1-3</sup> There is a growing body of literature on the best approaches to develop clinical practice guidelines. One system that is used more frequently than others is the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.<sup>4</sup> This process-oriented approach provides for significant uniformity in arriving at recommendations and making them clinically relevant. After clinical practice guidelines are developed, their adoption by individual physicians, clinical practices, and healthcare systems is accomplished in different ways. Initial broad-based education efforts are strengthened by the development of critical pathways, hospital policies, and systems to support adherence.

Although the development of clinical practice guidelines is time consuming and expensive, several professional societies and health authorities have participated in the development of transfusion-specific clinical practice guidelines to support evidence-based transfusion practice. These clinical practice guidelines support optimization of patient outcomes and appropriate utilization of limited and costly resources and allow for transfusion medicine physicians to become an integral part of the treatment team.<sup>5</sup> Successful implementation of clinical practice guidelines in transfusion medicine can often be supported by computerized physician order entry systems and order auditing.

In this short review, we highlight current clinical practice guidelines regarding transfusion of RBCs, platelets, and plasma and illustrate how these guidelines are integrated into clinical practice at our own institution with support from our electronic medical record system.

This can be also considered as the first step to implementation of comprehensive PBM.

## Guidelines for RBC transfusion

The development of clinical practice guidelines for RBC transfusion has been challenged by a limited availability of high-quality evidence to support practice recommendations. There is general agreement that RBC transfusion is typically not indicated for hemoglobin (Hb) levels of  $> 10$  g/dL and that transfusion of RBCs should be considered when Hb is  $< 7$  to  $8$  g/dL depending on patient characteristics.<sup>6,7</sup> The decision to transfuse RBCs should be based on a clinical assessment of the patient that weighs the risks associated with transfusion against the anticipated benefit. As more studies addressing RBC transfusion become available, it becomes increasingly clear that liberal transfusion strategies are not necessarily associated with superior outcomes and may expose patients to unnecessary risks.

The most recently published guidelines from the AABB (formerly the American Association of Blood Banks) are based on a systematic review of randomized, controlled trials evaluating transfusion thresholds.<sup>8</sup> (selected trials are presented in Table 1) These guidelines recommend adhering to a restrictive transfusion strategy and consider transfusion when Hb is 7 to 8 g/dL in hospitalized, stable patients. This strong recommendation is based on high-quality evidence from clinical trials comparing outcomes in liberal versus restrictive transfusion strategies in this patient population.<sup>9-11</sup> A restrictive transfusion strategy is also recommended for patients with preexisting cardiovascular disease. In this population, transfusion should be considered when Hb levels are  $< 8$  g/dL or for symptoms such as chest pain, orthostatic hypotension, tachycardia unresponsive to fluid resuscitation, or congestive heart failure.<sup>8</sup> This weak recommendation is based on moderate-quality evidence due to limited clinical trial data directly addressing this population of patients. Additional clinical practice guidelines exist that specify Hb targets for critical care patients with conditions including sepsis, ischemic stroke, and acute coronary syndrome.<sup>12,13</sup>

RBC transfusion is indicated in patients who are actively bleeding and should be based on clinical assessment of the patient in addition to laboratory testing. Much remains to be learned about the optimal resuscitation of the bleeding patient, and this topic is outside of the scope of this review. However, a recent study examining transfusion in patients with active upper gastrointestinal bleeding showed superior outcomes in patients treated with a restrictive transfusion strategy ( $< 7$  g/dL).<sup>14</sup>

At our institution, patients with active and clinically significant bleeding are transfused with RBCs as needed to meet the clinical needs of the patient and to optimize laboratory values. Laboratory monitoring of the Hb level is performed to assess the response to transfusion and the need for ongoing blood component support. Transfusion Medicine Service (TMS) physicians are available on call at all times to assist with the appropriate transfusion support of patients requiring massive transfusion.

Our guidelines for RBC transfusion in stable nonbleeding patients were developed by the transfusion committee in collaboration with medical and surgical providers based on a synthesis of existing clinical evidence, practice guidelines, and institutional preferences (Table 2). Stable, nonbleeding medical and surgical inpatients patients are considered candidates for RBC transfusion when the Hb level is  $\leq 7$  g/dL.<sup>9</sup> Transfusion should be considered for inpatients with active acute coronary syndromes with an Hb level  $\leq 8$  g/dL.<sup>13</sup>

**Table 1. Selected recent multicenter randomized, controlled trials informing RBC guidelines**

Design (N)	Population	Transfusion threshold	Primary outcome(s)	Secondary outcome(s)	General conclusions
Hebert et al <sup>9</sup> (TRICC) RCT (838)	Stable, critically ill patients $> 16$ y of age with Hb $< 9$ g/dL	Restrictive (Hb $< 7$ g/dL) vs liberal (Hb $< 10$ g/dL)	Death within 30 d of randomization	Death at 60 d, assessment of organ dysfunction	Restrictive transfusion strategy is at least as effective and possibly superior to a liberal transfusion strategy with the possible exception of patients with acute myocardial infarction or unstable angina
Lacroix et al <sup>10</sup> (TRIPICU) RCT (637)	Stable, critically ill children with Hb $< 9.5$ g/dL	Restrictive (Hb $< 7$ g/dL) vs liberal (Hb $< 9.5$ g/dL)	Death within 28 d of randomization, development or progression of MODS	Daily assessment of organ dysfunction, sepsis, transfusion reactions, infections, adverse events, length of stay, overall mortality	Restrictive transfusion strategy decreases transfusion requirements without increasing adverse events
Carson et al <sup>11</sup> (FOCUS) RCT (2016)	Adults $> 50$ y of age with history or risk factors for cardiovascular disease with Hb $< 10$ g/dL after hip fracture surgery	Restrictive (Hb $< 8$ g/dL) vs liberal (Hb $< 10$ g/dL)	Death or inability to walk across room at 60 d follow-up	In-hospital myocardial infarction, unstable angina, or death	Liberal transfusion strategy did not reduce rate of death or inability to walk at 60 d follow-up
Villanueva et al <sup>14</sup> RCT (921)	Adult patients with severe upper gastrointestinal bleeding	Restrictive (Hb $< 7$ g/dL) vs liberal (Hb $< 9$ g/dL)	Death within 45 d of randomization	Rates of further bleeding or hospital complications	Restrictive transfusion strategy was associated with improved outcomes

MODS indicates multiple-organ dysfunction syndrome; FOCUS, Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical hip Fracture Repair; RCT, randomized, controlled trial; TRICC, Transfusion Requirements in Critical Care; and TRIPICU, Transfusion Requirements in Pediatric Intensive Care Unit.

**Table 2. Triggers for transfusion of RBCs at our institution**

Hemoglobin level	Patient population
< 7 g/dL	Nonbleeding medical and surgical inpatients
< 8 g/dL	Inpatients with active acute coronary syndrome
< 10 g/dL	Inpatients being treated for sepsis during the first 6 hours of resuscitation

Adult critical care medical and surgical inpatients being treated for sepsis during the first 6 hours of resuscitation may be transfused with an Hb level  $\leq 10$  g/dL.<sup>15</sup> All RBC transfusions in nonbleeding inpatients should be ordered as single units. If transfusion is indicated based on Hb level, posttransfusion Hb must be obtained before ordering additional units.

Our computerized physician order entry system is configured to automatically query the most recent Hb value when an order for inpatient RBC transfusion is placed. If the most recent Hb is  $> 7$  g/dL or has not been measured in the past 24 hours, the physician receives a best practice alert prompting them to select from a limited menu of appropriate indications or cancel the transfusion order. In addition, all orders are retrospectively audited to ensure compliance and to provide education to providers practicing outside of these guidelines.

### Guidelines for platelet transfusions

It has been shown that patients with severe thrombocytopenia are at increased risk of bleeding. Platelet transfusions can be administered either as a prophylactic to minimize the risk of bleeding or as a therapeutic to control bleeding. It has been assumed for many years that transfusion of platelets should decrease the bleeding risk in the patients with hypoproliferative thrombocytopenia (eg, post myelosuppressive chemotherapy). Early guidelines for platelet transfusion developed in 1980s and 1990s relied primarily on systematic reviews of the literature available at the time, which primarily consisted of small trials.<sup>16</sup> The initial guidelines recommended transfusion of nonbleeding patients at the level of 20 000/ $\mu$ L. This value was extrapolated from the observation that there is significantly increased risk of bleeding when the platelet count is  $< 5000/\mu$ L and the risk of bleeding does not seem to change between 10 000/ $\mu$ L and 100 000/ $\mu$ L.<sup>16</sup> Several studies in different patient populations have shown that there is no difference in bleeding risk between a platelet count of 10 000/ $\mu$ L and a count of 20 000/ $\mu$ L.<sup>17,18</sup> It has been also observed that  $\sim 7100/\mu$ L/d is necessary for interaction with the endothelium.<sup>16,19</sup>

Recently, several important randomized trials and systematic reviews were completed that have further clarified platelet transfusion triggers<sup>17</sup>; these include: platelet dosing (Prophylactic Platelet Dose Trial [PLADO] and subsequent analysis);<sup>20,21</sup> Strategies for Transfusion of Platelets [SToP];<sup>22</sup> type of platelet component (eg, apheresis vs whole blood-derived platelets; leukoreduction; HLA matching; pathogen inactivation); and therapeutic versus prophylactic platelet transfusion (Trial of Prophylactic Platelets [TOPPS];<sup>23</sup> Study Alliance Leukemia<sup>24</sup>; Cochrane review<sup>25</sup>). A summary of the randomized, controlled trials is presented in Table 3. These studies have also shown that bleeding in hypoproliferative thrombocytopenia is common and decreases with age (starting at 86% in the 0 to 5 years of age group and decreases to 50% in adults).<sup>20,21,23</sup> Interestingly, bleeding occurs at any platelet range and prophylactic transfusions have only limited impact on bleeding frequency. However, patients receiving prophylactic transfusions do have a delayed onset of bleeding.<sup>23,25</sup> It has also been established that a

lower dose of platelets is noninferior to a larger dose when measured by incidence of World Health Organization (WHO) Grade 2 or above bleeding.<sup>21,22</sup> It has also become apparent, however, that there remain challenges in how the bleeding is measured and reported. The Biomedical Excellence for Safer Transfusion (BEST) Collaborative ([www.bestcollaborative.org](http://www.bestcollaborative.org)) analyzed the heterogeneity in reporting of the amount and type of documented bleeding in 13 clinical trials of platelet transfusions.<sup>26</sup> They concluded that consensus bleeding definitions, a standardized approach to record and grade bleeding, and guidance notes to educate and train bleeding assessors are necessary to be able to attribute observed bleeding differences to studied interventions.

The most recent clinical practice guidelines on platelet transfusions were developed by the American Society of Clinical Oncology for cancer patients in 2001 and by the British Committee for Standards in Haematology in 2003.<sup>27,28</sup> We are aware of ongoing preparation of 2 new clinical practice guidelines for platelet transfusion. The first is being prepared by the International Collaboration for Guideline Development, Implementation, and Evaluation for Transfusion Therapies (ICTMG) and should be finalized and available this year. The second is being prepared by the AABB and is likely to be available in 2014. Because the methodologies for the development of these guidelines are not identical, there is a possibility that they may differ in their final recommendations.

At our institution (Table 4), inpatients not actively bleeding are only transfused when the platelet count is  $< 5000/\mu$ L. This threshold was introduced in our institution and approved by the providers 18 years ago based on the publication by Gmür et al.<sup>29</sup> Patients with a temperature  $\geq 38^\circ\text{C}$  or with recent hemorrhage can receive platelets with platelet count  $< 10 000/\mu$ L. If the patient is on heparin, has coagulopathy, or has an anatomic lesion that is likely to bleed or is an outpatient, the trigger is placed at 20 000/ $\mu$ L. Patients who are bleeding or have scheduled an invasive procedure within the next 4 hours can be transfused for platelet count  $< 50 000/\mu$ L. Finally, the trigger for the patients with CNS bleeding is 100 000/ $\mu$ L. The last 2 thresholds have no data to support or refute their benefit. There is no trigger for patients with dysfunctional platelets due to underlying platelet function disease or medication affecting platelet function. However, in both situations, the TMS physician is involved in helping to establish the dose and frequency of transfusion if multiple transfusions are required. For the common bedside procedures such as central line placement, lumbar puncture, and BM biopsy, the threshold is provider and service dependent and falls between 20 000 and 50 000/ $\mu$ L. This is an area where we see an opportunity to further standardize our institutional approach.

The criteria for administration of platelets at our institution have not changed since 1995. Platelet concentrates (exclusively apheresis platelets) are ordered using an electronic order entry system in which the ordering physician is prompted to select the appropriate indication from a limited menu of options. If the patient does not meet the established criteria (Table 4) or the most recent platelet value is inconsistent with the selected indication, the request is referred to a TMS physician (ie, resident, fellow, or attending) for further investigation.<sup>5</sup> This conversation between the ordering physician and TMS physician may lead to the release of platelets or denial based on the clinical circumstances. This system, which has been in place for almost 20 years and is supported by real-time education provided by the TMS physicians to ordering providers, has led to significantly improved compliance with our platelet transfusion guidelines.

**Table 3. Selected recent multicenter randomized controlled trials informing plt guidelines**

Study	Design (N)	Population	Study groups	Primary outcome(s)	Secondary outcome(s)	General conclusions
Heddle et al <sup>22</sup> (SToP)	RCT (118)	Inpatients with HT and weight 40-100 kg; plt transfusion if < 10 000/ $\mu$ L or higher if appropriate circumstances	Low-dose arm (1.5-3.0 $\times$ 10 $^{11}$ plt) vs high-dose arm (3.0-6.0 $\times$ 10 $^{11}$ plt)	Occurrence of grade 2 or higher bleeding (grade 1-4); time to first bleed; number of bleeding days per 100 patients; duration of thrombocytopenia; plt and RBC transfusion requirements; interval between transfusions; modeling of bleeding risk over the next 24 h	Frequency of bleeding (grade 1-4); time to first bleed; number of bleeding days per 100 patients; duration of thrombocytopenia; plt and RBC transfusion requirements; interval between transfusions; modeling of bleeding risk over the next 24 h	Study stopped prematurely due to reaching prespecified difference in grade 4 bleeding. Primary outcome was met by 49.2% in the low-dose group vs 51.7% in the high-dose group (RR = 1.052; 95% CI, 0.74-1.5). It is unclear if the higher rate of grade 4 bleeding in the low-dose arm (5.2% vs 0%) was due to chance or represented a real difference
Slichter et al <sup>21</sup> (PLADO)	RCT (1272)	Inpatients with HT due to HSCT or chemotherapy and weight 10-135 kg; no age limitations; plt transfusion if plt < 10 000/ $\mu$ L	Low-dose arm (1.1 $\times$ 10 $^{11}$ plt/m $^2$ ) vs medium-dose arm (2.2 $\times$ 10 $^{11}$ plt/m $^2$ ) vs high-dose arm (4.4 $\times$ 10 $^{11}$ plt/m $^2$ )	Occurrence of grade 2 or higher bleeding	The highest grade of bleeding; total number of plt transfused; number of plt transfusions	There was no difference in grade 2 or higher bleeding at doses between 1.1 $\times$ 10 $^{11}$ and 4.4 $\times$ 10 $^{11}$ plt/m $^2$ . Low-dose arm resulted in decreased number of plt transfused but increased number of transfusions
Josephson et al <sup>20</sup> (PLADO pediatric)	RCT; pediatric (198), adult (1044)	Inpatients with HT due to HSCT or chemotherapy and weight 10-135 kg; no age limitations; plt transfusion if plt < 10 000/ $\mu$ L; age group analysis of PLADO data (children < 18 y)	As above; 4 age groups (0-5 y; 6-12 y, 13-18 y and adults)	Occurrence of grade 2 or higher bleeding	The highest grade of bleeding; total number of plt transfused; number of plt transfusions	Plt dose did not predict bleeding for any age group. Children had a significantly higher risk of grade 2 or higher bleeding than adults and more days with grade 2 or higher bleeding. Pediatric subjects were at higher risk of bleeding over a wide range of plt counts

Table 3. Continued

Study	Design (N)	Population	Study groups	Primary outcome(s)	Secondary outcome(s)	General conclusions
<b>Prophylactic vs therapeutic plt transfusion</b> Wandt et al <sup>24</sup>	RCT (391)	AML or auto HSCT patients; age 16-80 y	Therapeutic strategy (either bleeding or plt count < 10 000/ $\mu$ L) vs prophylactic strategy (plt count < 10 000/ $\mu$ L)	The number of plt transfusions over 14 d observation period	Clinically relevant bleeding	Therapeutic strategy reduced number of transfusions by 33.5% in all patients. No increased risk of bleeding in auto HSCT recipients but increase nonfatal grade 4 in AML recipients
Stanworth et al <sup>23</sup> (TOPPS)	RCT/NI (600)	HSCT or chemotherapy receiving patients > 16 y	No-prophylaxis group (not receiving plt for plt count < 10 000/ $\mu$ L) vs prophylaxis group (receiving plt for plt count < 10 000/ $\mu$ L)	Bleeding grade 2, 3, or 4 up to 30 d after randomization	Number of days with bleeding grade 2 or higher; time from randomization to bleeding grade 2 or higher; bleeding event of grade 3 or 4; numbers of plt and RBC transfusions; days with plt count < 20 000/ $\mu$ L; time to recovery from thrombocytopenia; time in the hospital	The results support the need for prophylactic transfusions with the shown benefit in reducing bleeding. Overall bleeding risk in these groups is high. Primary outcome was met by 50% in the no-prophylaxis group vs 43% in the prophylaxis group ( $P = .06$ ). More days with bleeding and a shorter time to first bleeding in the no-prophylaxis group. Reduced use of plt in no-prophylaxis group.

Grades of bleeding refer to the WHO bleeding grades.  
 AML indicates acute myeloid leukemia; HSCT, hematopoietic stem cell transplantation; plt, platelet; HT, hypoproliferative thrombocytopenia; NI, noninferiority; and RCT, randomized, controlled trial.

**Table 4. Triggers for transfusion of platelets at our institution**

Platelet concentration	Patient population
< 5000/ $\mu$ L	All inpatients who are not bleeding and clinically stable
< 10 000/ $\mu$ L	Patients with fever
< 20 000/ $\mu$ L	Patients receiving heparin; all outpatients or those who are to be discharged
< 50 000/ $\mu$ L	Patients who are actively bleeding or who will undergo invasive procedure within the next 4 hours
< 100 000/ $\mu$ L	Neurosurgical patients
Any	Patients with dysfunctional platelet count (eg, medication, disease-related, after bypass)

### Guidelines for plasma transfusions

Plasma for transfusion is produced from volunteer donation of either whole blood or apheresis plasma and is labeled as fresh frozen plasma when frozen within 8 hours of collection or plasma frozen within 24 hours (FP24). Both products are considered clinically equivalent and are typically transfused using a weight-based dosing of 10 to 20 mL/kg of recipient weight. Once thawed, either product must be transfused within 24 hours or be relabeled as “thawed plasma” to allow for refrigerated storage for up to 5 days.<sup>30</sup> Although degradation of the labile clotting factors V and VIII is observed during refrigerated storage, there is an overall maintenance of coagulation factors at sufficient levels for therapeutic use.<sup>30</sup> Risks associated with plasma transfusion include allergic reactions, transfusion-related circulatory overload, transfusion-related acute lung injury, and transfusion-transmitted infections.<sup>31</sup> Several pathogen-reduced plasma products are currently available for use outside of the United States and one has been recently approved for use in the United States.<sup>30</sup>

Currently, randomized, controlled clinical trial evidence to guide plasma transfusion practice is lacking. Published guidelines based on “expert opinion” support the transfusion of plasma for the following clinical indications: active bleeding in the setting of multiple coagulation factor deficiencies (massive transfusion, disseminated intravascular coagulation); emergency reversal of warfarin in a patient with active bleeding in settings where prothrombin complex concentrate with adequate levels of factor VII is not available; and for use as replacement fluid when performing plasma exchange, particularly in the treatment of thrombotic thrombocytopenic purpura.<sup>32-36</sup>

However, in addition to these accepted indications, a significant amount of plasma is currently used in settings where there is a lack of evidence demonstrating clinical benefit.<sup>37</sup> One common reason that plasma is requested is to normalize an elevated international normalized ratio (INR) before a planned surgery or invasive procedure.<sup>38</sup> The faulty assumptions in this situation are that the elevated INR correlates with a risk for bleeding and that plasma transfusion will normalize the INR and reduce this risk.<sup>39</sup>

However, an analysis of available studies demonstrated that a mildly elevated INR is not predictive of an elevated risk for bleeding.<sup>40</sup> Further, for mild prolongation of the INR (1.1-1.85), transfusion of plasma has not been shown to significantly improve the INR value.<sup>41</sup> The INR calculation was developed to standardize variations in clotting times between institutions using different testing reagents for the sole purpose of monitoring patients on warfarin. Use of the INR has never been validated in other patient populations. In patients with liver disease, analysis of factor levels over an INR range of 1.3 to 1.9 demonstrated mean factor levels that were adequate to support hemostasis (> 30%).<sup>42</sup>

**Table 5. Triggers for transfusion of fresh frozen plasma at our institution**

INR results	Patient population
> 1.5	Neurosurgical patients
> 2.0	Patients who will undergo invasive procedure
Undefined	Trauma patients who are receiving trauma-associated transfusion algorithm

At our institution (Table 5), patients with evidence of hemorrhagic shock or active bleeding leading to hemodynamic instability are transfused with plasma as needed to optimize laboratory values. Laboratory testing must be performed to assess the response to transfusion and the need for ongoing blood component support. If plasma transfusion is indicated to correct an elevated INR, a posttransfusion INR must be obtained before ordering additional plasma. Patients with an INR  $\geq$  2.0 ( $\geq$  1.5 for neurosurgical patients) are considered appropriate candidates for plasma transfusion. Plasma is ordered using patient-weight-based dosing and all orders that are not consistent with weight-based dosing are investigated before plasma is dispensed.

As described above for platelets, all orders for plasma at our institution are prospectively reviewed to ensure both appropriate indications and dosing. Potentially inappropriate orders are referred to a TMS physician (ie, resident, fellow, or attending) for further investigation.

### Conclusions

There are an increasing number of high-quality clinical practice guidelines addressing transfusion of blood components. These guidelines are based on increasing numbers of high-quality randomized clinical trials that have been completed over the past 15 years. The implementation of clinical practice guidelines into the routine practice of medicine can be supported through the use of electronic health records and physician order auditing.

### Disclosures

Conflict-of-interest disclosure: Z.M.S. is on the board of directors or an advisory committee for AABB, National Marrow Donor Program, Fenwal/Fresenius Kabi and Grifols Inc and is employed by Dartmouth-Hitchcock Medical Center. N.M.D. declares no competing financial interests. Off-label drug use: None disclosed.

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# Guidelines on transfusion for fetuses, neonates and older children

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The guideline is a revision of the 2004 British Committee for Standards in Haematology (BCSH) guideline on transfusion in neonates and older children (BCSH, 2004). Although there has been little evidence on which to base paediatric clinical transfusion decisions in the past, there have been a number of studies and national audits published over recent years that contribute to decision-making in this area. In addition there have been changes to other guidance, including the management of neonatal jaundice National Institute for Health and Clinical Excellence (NICE, 2010) and the requirement for cytomegalovirus (CMV) seronegative components.

The clinical section focuses largely on aspects relating to transfusion indications and administration, whereas the laboratory section contains most of the information relating to pre-transfusion testing and component selection. Details relating to blood component specification and typical transfusion volumes and rates may be found in Appendix 1.

## Methods

The guideline writing group was selected to be representative of UK-based medical experts including specialists from fetal medicine, neonatology, paediatric intensive care, cardiac anaesthesia, paediatric haematology, clinical and laboratory transfusion medicine. The guideline is based on a systematic literature search subsequent to the 2004 guideline up to November 2014 together with other relevant papers identified. The search strategy is presented in Appendix 2. Information from other relevant international guidelines has also been considered. The writing group produced a draft guideline,

which was subsequently revised by consensus following comment by members of the Transfusion Task Force of the BCSH and by a sounding board including UK haematologists, paediatricians/neonatologists. The 'GRADE' system was used to quote levels and grades of evidence ([http://www.bcsghguidelines.com/BCSH\\_PROCESS/EVIDENCE\\_LEVELS\\_AND\\_GRADES\\_OF\\_RECOMMENDATION/43\\_GRADE.html](http://www.bcsghguidelines.com/BCSH_PROCESS/EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION/43_GRADE.html)). Recommendations entirely extrapolated from evidence from adult studies have been given a lower grade for children.

The objective of this guideline is to provide healthcare professionals with clear guidance on the management of transfusion in fetuses, neonates and older children. The guidelines represent recommended UK practice. The guidance may not be appropriate for patients with certain rare disorders and does not cover unusual procedures, such as extracorporeal membrane oxygenation (ECMO). In all cases, individual patient circumstances may dictate an alternative approach.

## Clinical transfusion

### Introduction

Appropriate transfusion of fetal and paediatric patients of all ages is vital in order to balance transfusion benefits against risks. These risks include transfusion of an incorrect blood component due to errors, such as mistaken patient identity, or unpredictable acute transfusion reactions (Stansby *et al*, 2008). Recent studies suggest that a significant percentage of paediatric transfusion recipients receive only one transfusion during their admission (Slonim *et al*, 2008; New *et al*, 2014), raising the possibility that some may be avoidable.

Specialized components are available for transfusion to different paediatric patient groups and for different clinical indications. Plasma components have been imported for all patients born on or after 1 January 1996 in order to reduce the risk of transfusion transmission of variant

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Creutzfeldt–Jakob disease (vCJD; see Section 7). Additional component safety measures are applied for fetal and neonatal patients, who are particularly vulnerable recipients because of their small size and developmental immaturity and who also have the longest potential lifespan. Information on components and their transfusion volumes is included in Section 7 and Appendix 1, with additional detail in the text where relevant.

Standard definitions of neonates (up to 28 d of postnatal age) and infants (>28 d to <1 year) are used. The definition of a child is <18 years, but in many cases children are admitted to adult wards from 16 years of age, and for these patients local blood transfusion administration transfusion policies for adults may be followed. Thresholds for transfusion are typically based on the haemoglobin concentration (Hb), platelet count and/or coagulation screen results (Venkatesh *et al*, 2013). These are surrogates for clinical transfusion need (and coagulation ranges in neonates are particularly difficult to interpret) but in most cases are the most pragmatic solution until there is evidence for better clinical measures.

The term ‘clinically significant bleeding’ has been used for some of the recommendations in the guideline. The most widely recognized approach to standardizing bleeding events in transfusion is the system is based on the World Health Organization (WHO) bleeding scale, which assigns different types and severities of bleeds to different grades between 1 and 4. Significant bleeding is typically considered at grades 2–4 (for example Stanworth *et al*, 2013; NICE, 2015). Although the WHO bleeding scale is more commonly used for clinical research in adults, we suggest that a pragmatic modification may be used to help guide transfusion decisions based on bleeding risk, taking into account the types of bleeding and changes in haemodynamic parameters appropriate for neonatal and paediatric patients in different clinical situations (see Section 4 for cardiac surgery).

## 1 Intrauterine transfusions

### 1.1 Principles

Intrauterine transfusions (IUTs) are invasive procedures with a risk of fetal death of 1–3% per procedure and up to 20% for hydropic fetuses, depending on the underlying aetiology of the anaemia (Lee & Kaufman, 2011). IUTs are only undertaken in specialized fetal medicine units with the requisite interventional skills and expertise. The National Clinical Reference Group has recommended that such centres are defined as those performing at least 15 procedures per year, with a minimum of two specialists. Although technically challenging, fetal blood sampling (FBS) and IUTs can be performed as early as 16 weeks gestation. IUTs can be performed as late as 34–35 weeks gestation, however the increased risk/benefit ratio must be considered with very late interventions. Complications of FBS/IUT include

miscarriage/preterm labour, fetal bradycardia, cord haematoma, vessel spasm, bleeding from the puncture site and fetal death. The procedure is carried out under continuous ultrasound guidance with facilities for immediate analysis of the fetal blood Hb and haematocrit (Hct) or platelet count, allowing any decision to transfuse the fetus to be made concurrently.

Good multidisciplinary communication is essential between fetal medicine units undertaking the IUTs, the hospital transfusion laboratory and their counterparts in the hospital where the baby will be delivered.

### 1.2 Red cell IUT

Red cell IUTs are performed for the treatment of fetal anaemia, most commonly due to haemolytic disease of the fetus and newborn (HDN) caused by anti-D, -c or -K (Royal College of Obstetricians and Gynaecologists, 2014; BCSH, 2016a), or fetal parvovirus infection. Ultrasound monitoring using middle cerebral artery peak systolic velocities (MCA PSV) is generally done on a weekly basis for pregnancies at risk. MCA PSV monitoring is the standard technique for non-invasive diagnosis of fetal anaemia (Pretlove *et al*, 2009) and can predict moderate or severe fetal anaemia with 88% sensitivity and a false positive rate of 18% (Oepkes *et al*, 2006). If MCA monitoring suggests anaemia (MCA PSV >1.5 multiples of the median), FBS and possibly IUT are indicated. MCA PSV monitoring should be used with caution after 36 weeks as its sensitivity for the detection of fetal anaemia decreases. If there are concerns beyond this gestation because of raised MCA PSV, further advice should be sought from a fetal medicine specialist experienced in managing fetal anaemia.

IUT procedures may be required every 2–3 weeks, the frequency minimized by transfusing red cells of high Hct and the maximum volume. The aim of each transfusion is to raise the Hct to 0.45. In general, for red cell antibodies that could cause fetal anaemia but which have been stable throughout pregnancy and where the MCA PSV is normal, delivery should take place between 37 and 38 weeks of gestation. If an IUT has not been required but antibody levels are rising and there is evidence of fetal anaemia, then consideration of earlier delivery may be necessary. If an IUT has been required, the timing of delivery will depend on the degree of fetal anaemia, time from IUT, rate of fall in fetal Hb/Hct and gestation. It is important to ensure that antigen-negative blood is available at delivery for known pregnancies with HDN if it is anticipated that the baby will be anaemic.

After delivery, neonates with HDN following IUTs may become anaemic due to haemolysis or bone marrow suppression (Millard *et al*, 1990) and require monitoring for several weeks post-delivery (see 2.2.1). Anaemia persisting for a few weeks after birth is usually the result of passively acquired maternal antibodies causing continued haemolysis, in which case the baby will be jaundiced and the blood film will show

## Guideline

evidence of haemolysis. Late anaemia may develop due to a transient suppression of neonatal erythropoiesis by transfusion. Babies who have required several IUTs are at particular risk. All babies who have had an IUT require admission to a neonatal unit for early phototherapy and investigation for on-going haemolysis or anaemia.

### 1.2.1 Red cell transfusion and component type

- Red cells for IUT are irradiated to prevent transfusion-associated graft-versus-host disease (TA-GvHD) and have specific features (Appendix 1, Tables a and b). They have only a 24-h shelf life following irradiation and the supplying Blood Service ideally requires a minimum of 24 h notice. If an IUT is required urgently for an anaemic fetus then this should be discussed with medical staff from the Blood Services who can expedite preparation of a suitable pack or suggest a rapidly available alternative (see below). As with neonatal exchange transfusion, if maternal antibodies other than anti-D, -c, -C, -E or -K are present, additional notice is required, where possible, to ensure that suitable blood negative for all relevant antigens is available.
- Blood for IUT should not be transfused straight from 4°C storage due to risks of fetal bradycardia but there are no specifically designed warming systems for the small blood volume required and the component should not be exposed to radiant heaters or sunlight as the temperature is unmonitored and there is a risk of haemolysis.
- Transfusion volume required may be calculated based on donor and fetal Hcts and the estimated fetoplacental blood volume (Rodeck & Deans, 2008). The fetoplacental volume depends on gestation and fetal weight.
- In urgent situations, if IUT units are unavailable, acceptable alternatives are irradiated neonatal red cell exchange units or irradiated paedipacks (small-volume splits of single-donor units, Appendix 1, Table b). These are available at all times from the Blood Services, so use of non-irradiated blood for IUTs should be extremely rare. In emergency situations where requesting irradiated red cells from the Blood Services would cause life-threatening delay, it may be necessary to use a non-irradiated alternative, ideally a fresh neonatal paedipack (before the end of Day 5 following donation, see 7.1.5) or an exchange transfusion unit (see Appendix 3). The risk of TA-GvHD using these alternatives, although not eliminated, is acceptable in an emergency because these components have been leucodepleted and in most cases there will be no shared haplotype between donor and recipient. Maternal blood should not be used for IUTs because of the significant risk of TA-GvHD (Bolton-Maggs *et al*, 2013).

### 1.3 Platelet IUT

Intrauterine platelet transfusions are usually given to correct fetal thrombocytopenia caused by platelet alloimmunization:

'neonatal alloimmune thrombocytopenia' (NAIT). Alloantibodies to human platelet antigens (HPA)-1a, HPA-5b and HPA-3a account for almost all cases of NAIT, the commonest being anti-HPA-1a (80–90% of cases). In most cases fetal transfusion can be avoided by treating the mother with intravenous immunoglobulin (IVIg) and/or corticosteroids (Peterson *et al*, 2013). Compatible platelets should be available at the time of diagnostic fetal sampling for NAIT, in order to prevent fetal haemorrhage if severe thrombocytopenia is detected, the risk of which increases substantially with platelet counts  $<50 \times 10^9/l$ .

### 1.3.1 Platelet component and transfusion

- Platelets provided for IUT are HPA compatible with maternal antibody and irradiated
- The volume transfused is calculated based on the fetal and concentrate platelet count
- Platelets should be transfused more slowly than red cells for IUT because of increased risk of fetal circulatory stasis and stroke.

#### Key practice points

- Fetal blood counts should be rapidly available using near patient analysers and a blood film should subsequently be made to confirm the count and underlying diagnosis.*
- There must be good communication between the Blood Services, hospital transfusion laboratories and clinical staff to ensure timely provision of correct blood components for red cell and platelet IUTs. It is essential to communicate with the hospital where the baby is subsequently delivered so that appropriate (irradiated) components can be ordered.*

## Recommendations

- Red cells specific for intrauterine transfusion (IUT) should be used whenever possible. Fetal Medicine Units in conjunction with Hospital Transfusion teams should develop local written protocols and provide education regarding the hierarchy of possible alternatives for emergency IUT (Appendix 3) (1C).**
- Maternal blood should NOT be used for IUT due to the risk of transfusion-associated graft-versus-host disease (TA-GvHD) (1B).**

## 2 Transfusions to neonates

### 2.1 Principles

Transfusion triggers for neonates will vary depending on the clinical context, including the gestational age at birth. Neonatal transfusion guidelines have generally been developed as a result of neonatal studies predominantly of very low birth weight (VLBW;  $<1.5$  kg) babies. In neonatal

intensive care units (NICUs) most transfusions are given to preterm neonates (mostly <32 weeks gestational age; National Comparative Audit of Blood Transfusion, 2010), some of whom will require transfusion beyond 28 d of life. In general, babies of all gestational and postnatal ages on NICUs will tend to be transfused using the same guidelines although there is little evidence specifically related to term babies.

## 2.2 Red cell transfusions

The majority of extremely preterm neonates (<28 weeks gestation) receive at least one red cell transfusion as they frequently become anaemic, partly caused by phlebotomy losses (note: a 0.5 ml blood sample in a 500 g infant (1 ml/kg), is roughly equivalent to a 70 ml sample in a 70 kg adult), sometimes with sample volumes larger than required (Lin *et al*, 2000). Use of cord blood for initial blood tests for VLBW neonates has been advocated in order to reduce the need for transfusion (Baer *et al*, 2013), but results should be interpreted with caution if there are sampling difficulties. Neonatal transfusions are usually given as small-volume 'top-up' transfusions, to maintain the Hb above a particular threshold or because of the presence of surrogate markers of anaemia, such as poor growth, lethargy or increased episodes of apnoea.

Potential benefits of transfusion in this group include improved tissue oxygenation and a lower cardiac output to maintain the same level of oxygenation (Fredrickson *et al*, 2011). These benefits need to be weighed against possible adverse outcomes (Christensen & Ilstrup, 2013). In addition to the standard risks associated with transfusion, necrotizing enterocolitis (NEC) may follow neonatal transfusion, although a causal link has not been demonstrated (Christensen, 2011; Paul *et al*, 2011; Mohamed & Shah, 2012). The use of paedipacks reduces donor exposure for these multiply transfused preterm infants (Wood *et al*, 1995; Fernandes da Cunha *et al*, 2005; Strauss, 2010a). Although sequential use of paedipacks may result in the use of older blood, the Age of Red Blood Cells in Premature Infants (ARIPI) trial reported no effects on clinical outcomes for preterm neonates using red cells of different storage ages (Fergusson *et al*, 2012).

### Key practice points

- 1 Hospitals should develop policies that help to minimize exposure of infants to multiple donors (see 7.1.4).
- 2 Minimize phlebotomy where possible: agree a local policy on the frequency and types of regular blood tests required, collecting small samples, and using small-volume laboratory analysers and near-patient testing.
- 3 Hospital policies should ensure that paedipacks are available for emergency use by maternity and neonatal units (Appendix 1, Table b; see 7.2). The laboratory should be notified once they have been used.

### 2.2.1 Exchange transfusion

#### Indications and aims

Exchange blood transfusion (EBT) is performed to manage a high or rapidly rising bilirubin not responsive to intensive phototherapy or IVIg (NICE, 2010), or for severe anaemia. EBT is mainly used in the treatment of HDN to prevent bilirubin encephalopathy by removing the antibody-coated red cells and excess bilirubin. It may also be required for neonatal hyperbilirubinaemia due to other causes, such glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Exchange blood transfusion is a specialist procedure with associated risks (Ip *et al*, 2004; Smits-Wintjens *et al*, 2008) and is now infrequently performed in most neonatal units mainly as a result of the reduction in HDN following routine antenatal anti-D prophylaxis for D-negative women (BCSH, 2014a) and the ready availability of intensive phototherapy. EBT must take place in an intensive care setting with intensive physiological and biochemical monitoring, carried out by staff trained in the procedure, following written informed parental consent ([www.bapm.org/publications/documents/guidelines/procedures.pdf](http://www.bapm.org/publications/documents/guidelines/procedures.pdf)).

A single blood volume EBT will remove 75% of the neonatal red cells, and a double volume (160–200 ml/kg depending on gestational age) up to 85–90% red cells (Lathe, 1955; Sproul & Smith, 1964), and up to 50% of circulating bilirubin (Forfar *et al*, 1958). A double-volume exchange transfusion should be more successful in removing antibody-sensitized neonatal red cells and reduce the need for a subsequent EBT, but there is little direct evidence (Thayyil & Milligan, 2006).

#### Key practice point

*Prior to and following discharge, babies who received EBT (and/or IUT) should have on-going close monitoring, both clinically and haematologically (with full blood count, reticulocytes, blood film and, if necessary, serum bilirubin), until the haemolysis resolves and the Hb starts to rise (see also 1.2). While these babies still have evidence of haemolysis they should receive folic acid supplementation.*

#### Component and procedure specifications

- A specific red cell component for neonatal exchange transfusion is provided by the UK Blood Services, usually group O, and should also be compatible with any maternal antibody. Red cell units for neonatal exchange transfusion are rarely available immediately from the hospital transfusion laboratory and need to be requested with sufficient notice to allow for irradiation and transportation to the hospital. When HDN is caused by an unusual antibody, it may take longer for red cell units to be provided by the Blood Services, and at least 24 h notice should be given if possible. In emergency situations, it is occasionally necessary to use antigen-negative red cells in saline, adenine, glucose and mannitol

## Guideline

- (SAGM) if red cells specific for exchange transfusion cannot be provided in time. The baby will require careful biochemical monitoring e.g. for possible rebound hypoglycaemia.
- Red cells suitable for neonatal exchange are irradiated and 'fresh' (before the end of Day 5 following donation, see 7.1.5), with a 24-h shelf-life post-irradiation in order to reduce the risk of recipient hyperkalaemia. They have a controlled Hct 0.5–0.6 (NHS Blood and Transplant [NHSBT] 0.5–0.55), in order to reduce the risk of both post-exchange anaemia and polycythaemia (see Appendix 1, Table b). They are negative for high-titre anti-A and anti-B antibodies (HT negative).
  - EBT should not be undertaken with red cells straight from 4°C storage, and an approved/CE-marked blood-warming device can be used to avoid hypothermia (AABB 2012). However, use of a blood warmer is only appropriate if the infusion is given at a constant rate (warming is not suited to the intermittent bolus nature of a single vessel EBT where the 'push-pull' cycle method is used). Blood warming during EBT should not be uncontrolled, e.g. infusion lines exposed to a radiant heater (AABB, 2012), because of the risk of red cell haemolysis.

## Recommendations

- 1 **Neonatal intensive care units (NICUs) should have local protocols for exchange blood transfusion (EBT) procedures. There should be early contact with the local hospital transfusion laboratory, which will contact the Blood Services to request specific red cells suitable for neonatal exchange transfusion (1C).**
- 2 **If an exchange blood transfusion is required, a double volume procedure should be undertaken (1C).**

### *Haemodilution for polycythaemia ('partial exchange transfusion')*

Polycythaemia and hyperviscosity can occur in situations of chronic fetal hypoxia, e.g. growth restricted infants, and following twin-to-twin transfusion. Although neonatal hyperviscosity has been implicated as a cause of long-term neurodevelopmental delay (Delaney-Black *et al*, 1989; Drew *et al*, 1997), the use of haemodilution (described by neonatologists as 'partial exchange transfusion') for the treatment of polycythaemia is controversial. There is no evidence of long-term benefit and the procedure has been associated with up to an 11-fold increase in risk of NEC (Dempsey & Barrington, 2006; Özek *et al*, 2010), although the confidence intervals are wide. For the haemodilution procedure there is minimal difference in the effectiveness of plasma, 5% albumin or crystalloid in reducing haematocrit and no difference in viscosity or symptom relief (de Waal *et al*, 2006). Therefore to minimize risks associated with use of blood products, normal saline should be used if haemodilution is undertaken.

## Recommendation

**The use of haemodilution (partial exchange transfusion) for treatment of polycythaemia is not supported by evidence, and not recommended in the asymptomatic patient (1A). Its use in the symptomatic patient requires clinical judgement to assess the risks and benefits (2C).**

### *2.2.2 Small volume transfusion*

The majority of red cell transfusions to neonates are top-up transfusions of small volumes (traditionally 10–20 ml/kg, typically 15 ml/kg over 4 h) given to replace phlebotomy losses in the context of anaemia of prematurity, particularly for preterm VLBW neonates. There is very limited evidence to define optimal volumes for neonatal red cell transfusions, particularly relating to long-term outcomes. Volumes greater than 20 ml/kg may increase the risk of volume overload in non-bleeding patients. Therefore, in the context of data supporting restrictive transfusion thresholds from patients of all age groups including neonates, and the recommendations for older children (see 3.1), it seems prudent to use top-up transfusion volumes of 15 ml/kg for non-bleeding neonates in most cases.

There is evidence that having a blood transfusion policy and a method of ensuring its implementation has an impact in reducing the number of red cell transfusions (Baer *et al*, 2011). Hb levels are widely used as a marker of need for transfusion despite the limitations (Banerjee & Aladangady, 2014). Specific thresholds of Hb at which neonates are transfused vary according to the cardiorespiratory status and postnatal age of the infant, partly following the normal physiological reduction in Hb over the first few weeks of life (National Comparative Audit of Blood Transfusion, 2010; Whyte & Kirpalani, 2011).

Since publication of the previous BCSH guidelines (BCSH, 2004), three randomized studies addressing 'restrictive' versus 'liberal' transfusion thresholds for neonatal red cell transfusion in VLBW babies have been published (Iowa study, Bell *et al*, 2005; Premature Infants in Need of Transfusion (PINT), Kirpalani *et al*, 2006; Chen *et al*, 2009), and these are included in updated systematic reviews (Whyte & Kirpalani, 2011; Venkatesh *et al*, 2012). Liberal transfusion thresholds were those more typically applied in the past, by comparison to policies describing more restricted use of red cells (at lower 'restrictive' thresholds by Hb or Hct). The trials in neonates reported a small and variable reduction in the number of transfusions with restrictive regimens. For the restrictive group (transfused at lower Hbs), at short-term follow-up the Iowa study (Bell *et al*, 2005) reported an increase in episodes of apnoea, and at 18–21 month follow-up the PINT study found a statistically significant cognitive delay in a *post-hoc* analysis (Whyte *et al*, 2009). For the liberally transfused group, the Iowa study patients had significantly poorer learning outcomes (McCoy *et al*, 2011) and reduced brain volume on magnetic resonance imaging (Nopoulos

*et al*, 2011). However, information on long term outcomes is limited and contradictory and overall there is no evidence that restrictive transfusion policies have a significant impact on mortality or major morbidity (Whyte & Kirpalani, 2011). It should be noted that safety of Hb thresholds below those used in the trials is unknown.

Suggested red cell transfusion thresholds for very preterm neonates are given in Table I. They have been developed from the restrictive thresholds of the recent randomized controlled trials of VLBW babies (gestational ages mostly <31 weeks gestation) and are consistent with the neonatal transfusion data from the National Comparative Audit of Blood Transfusion (2010). The precise thresholds used will depend on the clinical situation. Further evidence based on short-term and long-term outcomes should become available from the multicentre randomized controlled trial (RCT) ETTNO (Effects of Transfusion Thresholds on Neurocognitive Outcome of extremely low birth weight infants; ETTNO Investigators, 2012), and the TOP-trial (Transfusion of Prematures trial; Clinicaltrials.gov NCT01702805).

There is no specific evidence relating to transfusion of infants with chronic lung disease (CLD; defined as oxygen dependency beyond 28 d of age). Ex-preterm infants with CLD should be transfused as suggested in Table I, taking into account their clinical status. Some clinicians may accept Hbs as low as 80 g/l with adequate reticulocytes. There is no justification for top-up transfusion simply because the baby is about to be discharged.

Table I does not include suggested thresholds for moderate to late preterm ( $\geq 32$  weeks gestational age at birth) or term neonates, as there is little evidence regarding the appropriate thresholds for these groups. Clinicians may consider similar thresholds to those used for preterm babies off oxygen.

### Erythropoietin (EPO)

There are several systematic reviews and over 30 trials of EPO use in neonates (Aher & Ohlsson, 2012, 2014; Ohlsson

Table I. Suggested transfusion thresholds for preterm neonates.\*

Postnatal age	Suggested transfusion threshold Hb (g/l)		
	Ventilated	On oxygen/ NIPPV†	Off oxygen
First 24 h	<120	<120	<100
$\leq$ week 1 (d 1–7)	<120	<100	<100
week 2 (d 8–14)	<100	<95	<75†
$\geq$ week 3 (d 15 onwards)	<100	<85	<75†

\*Standard definition of preterm is <37 weeks gestational age at birth but table applies to very preterm neonates (<32 weeks).

†It is accepted that clinicians may use up to 85 g/l depending on clinical situation.

‡NIPPV, non-invasive positive pressure ventilation.

& Aher, 2014). EPO may reduce red cell transfusion requirements in neonates but its effect appears to be relatively modest whether given early or late. EPO has been suggested to have broader neuroprotection roles, but risks include the development of retinopathy of prematurity (ROP) related to pathological neovascularization (Aher & Ohlsson, 2014). Although underpowered for ROP, a recent RCT of EPO and darbepoetin alfa (a novel erythropoiesis stimulating agent) in 102 preterm infants reported a significant reduction in transfusion requirements and donor exposures in both the EPO and darbepoetin alfa groups compared with placebo (Ohls *et al*, 2013). EPO may be considered for preterm babies of parents who object to transfusion, e.g. Jehovah's Witnesses, but may not prevent the need for transfusion.

### Placental transfusion including delayed cord clamping

Delayed cord clamping (DCC) of at least 1 min is recommended for the term and preterm neonate not requiring resuscitation (Wyllie *et al*, 2015). Systematic reviews of DCC in term neonates have shown significantly increased Hb after birth and decreased iron deficiency at 2–6 months of age (Hutton & Hassan, 2007; McDonald *et al*, 2013). There was a significant increase in asymptomatic polycythaemia (Hct >65%) and a tendency to increased blood viscosity following DCC (Hutton & Hassan, 2007). In preterm neonates with DCC, the Hb is higher after birth, together with higher blood pressure and reduced red cell transfusion requirement (Rabe *et al*, 2012; Ghavam *et al*, 2014). However, although Rabe *et al* (2012) found reduction in intraventricular haemorrhage (IVH) (all grades together) the numbers were too small to comment on the clinically significant IVHs (grade 3 or 4), and there is paucity of evidence about the long-term neurodevelopmental outcomes. Further RCT evidence is needed for DCC in the very preterm neonate and those in need of resuscitation at birth, e.g. Australian Placental Transfusion Study (APTS); (<https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=335752>).

### Recommendations

- 1 Studies to date support restrictive transfusion thresholds (2B) and suggested Hb thresholds for top-up transfusions are given in Table I.
- 2 Transfusion volumes of 15 ml/kg are generally recommended for non-bleeding neonates (2C).
- 3 The routine use of EPO or darbepoetin alfa is not recommended in preterm infants to reduce transfusion (1B).
- 4 Where the term neonate (1B) or preterm neonate (2C) does not require resuscitation, undertake delayed cord clamping.

## Guideline

### **2.2.3 Surgery and large volume neonatal transfusion (non-cardiac)**

For surgery in neonates, the thresholds given in Table I may be used, as there is no evidence that higher perioperative Hbs are required (for neonates on cardiopulmonary bypass see Section 4). Large volume transfusion, defined as at least equivalent to a single circulating blood volume (approximately 80 ml/kg for neonates) over 24 h or 50% of the circulating volume within 3 h, may be needed for specific types of neonatal surgery, e.g. craniofacial or liver surgery. If major blood loss ( $>40$  ml/kg) is anticipated, consideration should be given to the use of antifibrinolytic agents, such as tranexamic acid, although there is little published evidence in neonates undergoing non-cardiac surgery. Cell salvage for neonates with large volume blood loss is technically feasible and could be used to reduce allogeneic transfusion as in older children (Section 3.2.4). For situations of massive haemorrhage in neonates, it seems reasonable to apply the principles of the management of major bleeding in children (Section 5) although there is little evidence for this age group (Diab *et al*, 2013).

There is a risk of hyperkalaemia following large volume transfusions, particularly if infused rapidly (Strauss, 2010b; Vraets *et al*, 2011; Lee *et al*, 2014), so it is recommended that red cells for large volume neonatal and infant transfusions (Appendix 1, Table b) are used before the end of Day 5 following donation (and within 24 h of irradiation) in order to reduce this risk in the recipient (see Sections 4.1 and 7.1.5). Rapid transfusion via a central line may represent a particular risk, and the alternative use of large bore (greater than 23 g) peripheral lines in small babies may not always be technically feasible. Serum electrolyte concentrations should be monitored frequently, including calcium (to prevent hypocalcaemia secondary to citrate overload) and potassium. All large volume transfusions should be given via a blood warmer to avoid the development of hypothermia and the core temperature should be monitored, as recommended for adults (NICE, 2008).

## Recommendation

**Transfuse red cells for large volume neonatal and infant transfusion before the end of Day 5 following donation (1C).**

### **2.3 Neonatal platelet transfusions**

The use of platelet transfusions for neonates with thrombocytopenia and active bleeding is considered appropriate, but there is uncertainty and practice variation in the wider use of platelet transfusions for prophylaxis in the absence of bleeding. In an evidence-based review of the use of platelets, Lieberman *et al* (2014a) noted that most studies explored the relationships between thrombocytopenia and clinical outcomes rather than the direct effects of platelet transfusions.

In a multicentre prospective observational study of 169 neonates with platelet counts of less than  $60 \times 10^9/l$ , most transfusions were prophylactic and given to pre-term neonates, and many were given after the period when major bleeding, including IVH, occurs most frequently. Most infants received platelet transfusions within a range of pre-transfusion platelet counts between 25 and  $50 \times 10^9/l$  (Stanworth *et al*, 2009). There has been only one RCT in neonates to assess a threshold level for the effectiveness of prophylactic platelet transfusions (to compare prophylactic platelet thresholds of  $50$  vs.  $150 \times 10^9/l$ ) (Andrew *et al*, 1993), and the recruited patient population in that trial, conducted over 20 years ago, may be of limited relevance to current neonatal practice. A randomized trial of prophylactic platelet thresholds is on going in the UK, Ireland and the Netherlands (International Standard Randomized Controlled Trial Number [ISRCTN] 87736839; www.planet-2.com; Curley A. *et al*, 2014). Other studies are required to address gestational age- and postnatal age-specific effects on neonatal platelet function (Ferrer-Marin *et al*, 2013).

In the absence of results from RCTs in this patient group, recommendations for prophylactic platelet transfusion are made on the basis of clinical experience. Suggested thresholds for pre-term infants and those with NAIT are summarized in Table II. While these may also apply to term neonates (e.g. those admitted to paediatric intensive care units (PICUs)), many paediatricians might consider more liberal use of platelets in unstable preterm neonates and more restrictive use in stable term infants. In the absence of specific evidence on platelet thresholds for prophylaxis before invasive procedures, recommendations for older children may be followed (see Table III). Information on neonates undergoing cardiac surgery is described later (Section 4.4).

### **Neonatal alloimmune thrombocytopenia (NAIT)**

NAIT results most commonly from maternally derived anti-HPA-1a or 5b platelet antibodies. All neonates with NAIT (or

**Table II.** Suggested thresholds of platelet count for neonatal platelet transfusion.

Platelet count ( $\times 10^9/l$ )	Indication for platelet transfusion
<25	Neonates with no bleeding (including neonates with NAIT if no bleeding and no family history of ICH)
<50	Neonates with bleeding, current coagulopathy, before surgery, or infants with NAIT if previously affected sibling with ICH
<100	Neonates with major bleeding or requiring major surgery (e.g. neurosurgery)

NAIT, neonatal alloimmune thrombocytopenia; ICH, intracranial haemorrhage.

suspected NAIT) and thrombocytopenia after birth should be discussed with a haematologist. Severely thrombocytopenic neonates with suspected NAIT should receive platelet transfusions at thresholds depending on bleeding symptoms or family history (see Table II). The suggested threshold of  $25 \times 10^9/l$  in the absence of bleeding is the same as that for neonates without NAIT, but it is acknowledged that this is not evidence-based. Results of diagnostic serological tests may not be available immediately, but the UK Blood Services stock platelets that are negative for HPA-1a/5b antigens, antibodies to which are responsible for over 90% of cases. A post-transfusion platelet count should be measured to check the increment. The baby should be monitored for intracranial haemorrhage (ICH) by cranial ultrasound and, if there is evidence of ICH, platelet transfusions should be given to maintain platelet counts between  $50$  and  $100 \times 10^9/l$  for the period that the baby is felt to be at highest risk of on going haemorrhage.

If HPA-1a/5b-negative platelets are unavailable or ineffective in producing a platelet rise (Department of Health, 2008), random donor platelets and/or IVIg may be used, which may reduce the need for platelet transfusions until spontaneous recovery in platelet count occurs 1–6 weeks after birth (see also Section 7.2).

## Recommendations

- 1 For preterm neonates with very severe thrombocytopenia (platelet count below  $25 \times 10^9/l$ ) platelet transfusions should be administered in addition to treating the underlying cause of the thrombocytopenia (Grade 2C). Suggested threshold counts for platelet transfusions in different situations are given in Table II (2C).
- 2 Consider intravenous immunoglobulin in NAIT refractory to platelets negative for HPA-1a/5b antigens or if antigen-matched platelets are unavailable (1C).

## 2.4 Neonatal fresh frozen plasma (FFP) and cryoprecipitate

### 2.4.1 FFP

There is considerable uncertainty about appropriate use of FFP in neonates, which reflects the lack of evidence in this area. National audits have shown high proportions of FFP transfusions are given for prophylaxis: 42% of infant FFP transfusions in a UK audit (Stanworth *et al*, 2011) and 63% in a similar Italian audit (Motta *et al*, 2014). Prophylactic use of FFP, including prior to surgery, is of unproven benefit and uncertainty is compounded by the difficulty in defining a significant coagulopathy in this age group. A large RCT reported by the Northern Neonatal Nursing Initiative (NNNI Trial Group, 1996) reported no benefit from prophylactic FFP given to neonates to prevent ICH, although the study did not assess coagulopathy and the gestational age

distribution of enrolled babies would not reflect current neonatal practice. More recent non-randomized studies in preterm infants (Dani *et al*, 2009; Tran *et al*, 2012) have shown inconsistent benefits from coagulopathy screening and early plasma use for prevention of IVH.

Neonates have a different balance of procoagulant and anti-coagulant proteins compared to older children, although overall haemostasis may be functionally adequate when defined by global measures of haemostasis (Tripodi *et al*, 2008). This results in different postnatal and gestational age-related coagulation ranges in the first months of life, particularly for the activated partial thromboplastin time (APTT) (Andrew *et al*, 1987, 1988; Monagle *et al*, 2006). Most laboratories rely on previously published neonatal ranges due to difficulties in obtaining locally-derived ranges in this age group but variation in reagents and analysers can make interpretation of results difficult, and the widely quoted work is now dated. Polycythaemia with a raised Hct may further contribute to apparent prolongation of coagulation times, in particular the prothrombin time (PT). In older children and adults, coagulopathy is often defined as a PT or APTT greater than 1.5 times the mid-point of normal range, but this is more difficult to apply in neonates, especially in very preterm neonates, given that the ranges may be uncertain and broad. Moreover disseminated intravascular coagulation (DIC) is a poorly defined entity in neonates.

Routine coagulation screening of babies admitted to NICUs may lead to increased transfusion and it is unclear, from retrospective studies, whether mild/moderate abnormalities are predictive of bleeding (Catford *et al*, 2014; Christensen *et al*, 2014). Coagulation screening should therefore only be undertaken for selected neonates with evidence of bleeding or at high risk of DIC, such as those with NEC or severe sepsis. Although most neonatal coagulopathies will be secondary to acquired bleeding disorders, undiagnosed congenital bleeding disorders should also be considered (see Section 3.4.8). For transfusion management of DIC see Section 3.4.3.

### Key practice points

- 1 A policy of routine coagulation screening is inappropriate as results are difficult to interpret in neonates and routine testing may lead to increased transfusion of FFP without benefit.
- 2 Wherever possible, a sample for testing should be taken prior to transfusion. Although correction of abnormal coagulation screens by FFP is unpredictable it is good practice to recheck tests following transfusion.

## Recommendations

- 1 There is no evidence to support the routine use of fresh frozen plasma (FFP) to try to correct abnormalities of the coagulation screen alone in non-bleeding neonates (1C).
- 2 FFP may be of benefit in neonates with clinically significant bleeding (including massive blood loss) or prior to invasive procedures with a risk of significant bleeding, and who have an abnormal coagulation profile, defined

## Guideline

- as a PT or APTT significantly above the normal gestational and postnatal age-related reference range (taking into account local reference ranges where available) (2C).
- 3 FFP should not be used for simple volume replacement or routinely for prevention of IVH (1B).**

### 2.4.2 *Purpura fulminans secondary to severe homozygous deficiency of protein C or protein S*

Neonatal purpura fulminans (PF) may be the presenting feature of a severe deficiency of either protein C (PC) or, less commonly, protein S (PS) (Chalmers *et al*, 2011; Price *et al*, 2011). These deficiencies are due to pathological mutations in the *PROC* and *PROS1* genes respectively. Neonatal PF is a haematological emergency characterized by skin necrosis and DIC that may progress rapidly to multi-organ failure. Early recognition is crucial to reduce morbidity and mortality. While PC concentrate has better efficacy in the management of PC deficiency, early empiric FFP (15–20 ml/kg given 8–12 hourly) is likely to be required until the diagnosis is confirmed and PC concentrate is made available (Dreyfus *et al*, 1995). FFP is the only available treatment for severe PS deficiency (Mahasandana *et al*, 1996).

#### Recommendations

- 1 FFP is appropriate for the early management of severe hereditary protein C deficiency but should not be used in preference to protein C concentrate if this is available (2B).**
- 2 FFP should be used for the management of severe hereditary protein S deficiency (2C).**

### 2.4.3 *Neonatal cryoprecipitate*

Overall, the management of low fibrinogen is the same in neonates as in children. Severe congenital hypofibrinogenaemia (see Section 3.4.8) may present in the neonatal period but neonatal hypofibrinogenaemia is most likely to be acquired, secondary to DIC (see Section 3.4.3) or liver dysfunction (see Section 3.4.4). Cryoprecipitate may also be indicated in neonatal cardiac surgery and major haemorrhage (see Sections 4 and 5).

### 2.4.4 *Vitamin K deficiency bleeding*

Vitamin K deficiency bleeding (VKDB) may occur and require urgent treatment if major bleeding occurs in neonates or children. Four factor prothrombin complex concentrate (PCC) is preferable to FFP, although there is little published data on this indication. Vitamin K is recommended for every newborn infant, and bleeding may occur after missed prophylaxis (Clarke & Shearer, 2007).

### 2.5 *Neonatal granulocyte transfusions*

A recent Cochrane review identified 4 RCTs which addressed the effect of granulocyte or buffy coat transfusions as adjuncts to antibiotics after confirmed or suspected sepsis in neutropenic neonates (Pammi & Brocklehurst, 2011). The authors concluded that the evidence from RCTs was insufficient to support or refute the routine use of granulocyte transfusions in septic neutropenic neonates.

#### Recommendation

**There is insufficient evidence to recommend the routine use of granulocyte transfusions for neonates (Grade 2C).**

### 2.6 *T-activation*

T-activation occurs when sialic acid residues are stripped from the red cell surface by neuraminidase producing organisms, exposing the T-cryptantigen. It can occur in infants with NEC and children with *S. pneumoniae* infection, including pneumococcus-associated haemolytic uraemic syndrome (pHUS) (Crookston *et al*, 2000). T-activation can be detected using a lectin panel. Anti-T antibodies are naturally occurring IgM antibodies in adult plasma, developing during infancy and absent in neonates. A causal role for anti-T antibodies in post-transfusion haemolysis of T-activated red cells or in the pathogenesis of pHUS has not been established (Crookston *et al*, 2000; Eder & Manno, 2001; Ramasethu & Luban, 2001; Johnson & Waters, 2012). Investigation for T-activation in infants with NEC in whom haemolysis has occurred following transfusion and in children with suspected pHUS should include a lectin test for T-activation (for further information see Massey, 2011).

If transfusion is required for neonates with T-activation (usually in the context of NEC) and haemolysis following previous transfusion, red cells in SAGM are suitable as these contain little plasma. If platelets or FFP are clinically indicated (see Sections 2.3 and 2.4.1), ‘washed’ platelets in platelet suspension medium, or low-titre anti-T FFP (Appendix 1, Table d) may be used. There is no consensus as to the need for routine provision of these platelet and FFP components for children with pHUS (who are usually old enough to have developed anti-T) or for neonates with T-activation but no transfusion-related haemolysis.

#### Key practice point

*The provision of special blood products for neonates with suspected T-activation and transfusion-related haemolysis requires close liaison between neonatologists and haematologists, including with the Blood Services. The time taken to provide special rather than standard components should be balanced against the urgency of transfusion. The causes of haemolysis should be investigated and other measures to treat*

coagulopathy, such as use of vitamin K, employed where appropriate.

### 3 Transfusions to infants and children

This section relates to infants and children, excluding neonates.

#### 3.1 Principles of red cell transfusion

The National Comparative Audit of Blood Transfusion of paediatric red cell transfusions reported that more than half of paediatric transfusions on non-neonatal wards were given to haematology/oncology patients (New *et al*, 2014). Other frequently transfused groups include those on PICU or undergoing cardiac surgery or ECMO. A significant proportion of children are transfused on general rather than specialist paediatric wards. Transfused children often have only a single transfusion during their admission (Slonim *et al*, 2008; New *et al*, 2014), and indications for transfusions should be followed carefully to ensure that they are not given unnecessarily. RCTs of different red cell transfusion policies have mostly been conducted in adults and systematic reviews indicate that liberal transfusion thresholds are not associated with benefit and may be associated with harm (Carson *et al*, 2012; Hébert & Carson, 2014; Rohde *et al*, 2014).

Most recent research has related to transfusion thresholds rather than optimal volumes for transfusion. Nonetheless, in the context of the evidence favouring restrictive thresholds, transfusions of single red cell units have been recommended for non-bleeding adults (BCSH, 2012a; NICE, 2015). In the absence of evidence to the contrary, this guideline recommends that the volume of red cells transfused should also be minimized for infants and children, taking into account the likelihood of requiring subsequent transfusions.

All children starting regular transfusions should be vaccinated against hepatitis B as early as possible (Sickle Cell Society, 2008). Those on chronic transfusion regimens should have an extended red cell phenotype/genotype (Section 8.4), particularly those with haemoglobinopathies, but also those with congenital dyserythropoietic anaemia, aplastic anaemia and other bone marrow failure syndromes. This should be performed prior to, or as soon as possible after, commencing regular transfusions. For chronically transfused paediatric patients, monitoring growth and development are important outcome measures of efficacy.

#### **Key practice point**

*Transfusion volumes for non-bleeding infants and children, excluding those on chronic transfusion programmes, should generally be calculated to take the post-transfusion Hb to no more than 20 g/l above the transfusion threshold (see Section 6.1.2 for calculation), usually a maximum of one unit. Where arterial or central venous access is available (e.g. in theatres) use*

*regular Hb estimation to ensure the smallest necessary volume is transfused.*

#### 3.2 Red cell transfusion

##### 3.2.1 Paediatric intensive care

Transfusion indications in children are largely extrapolated from adult studies. However, the Transfusion Requirements in the Pediatric Intensive Care Unit (TRIPICU) study of red cell transfusions in stable critically ill children on PICU (Lacroix *et al*, 2007) compared a restrictive Hb transfusion threshold (70 g/l) vs. a liberal (95 g/l). The more restrictive transfusion practice (mean Hb 87 g/l vs. 108 g/l in the liberal group) was associated with reduced blood use and no significant increase in adverse outcomes. The findings were similar by subgroup analysis of patients including those with sepsis, non-cardiac surgery, and respiratory dysfunction (Lacroix *et al*, 2012). A transfusion threshold of 70 g/l in stable, non-cyanotic, patients on PICU is therefore considered reasonable based on current evidence in children. This threshold also concurs with the recommended threshold for most adult red cell transfusions following systematic reviews and an increasing evidence base (Carson *et al*, 2012; BCSH, 2013a; Hébert & Carson, 2014; NICE, 2015). For cyanotic patients see Section 4.

As on NICU, phlebotomy losses on PICU may contribute to anaemia, are associated with increased transfusion requirements (Fowler & Berenson, 2003; Bateman *et al*, 2008) and may be partially avoidable (Valentine & Bateman, 2012).

#### **Key practice point**

*In order to reduce the requirement for red cell transfusions in paediatric intensive care, minimize blood sampling and use near patient testing where possible as for neonates.*

#### **Recommendation**

**Use an Hb threshold of 70 g/l pre-transfusion in stable non-cyanotic patients (1B). If the child is unstable or has symptomatic anaemia a higher threshold may be considered (2C).**

##### 3.2.2 Stem cell transplant/oncology

For paediatric haemopoietic stem cell transplant (HSCT) and oncology patients, there is no specific evidence to guide the optimum Hb transfusion threshold although current practice would suggest that a threshold between 70–80 g/l may be reasonable. In the acute setting, the TRIPICU study supports a threshold of 70 g/l. This threshold has been reported (Lightdale *et al*, 2012; Bercovitz & Quinones, 2013), and is also implied by the median pre-transfusion Hb of 74 g/l for oncology patients in the UK National Comparative Audit of Blood Transfusion (New *et al*, 2014) and of 72 g/l at a Canadian oncology centre (Lieberman *et al*, 2014b). A Canadian multicentre RCT in paediatric HSCT randomized between Hb triggers of 120 g/l and 70 g/l but was

## Guideline

closed after enrolling only six patients: those in the higher Hb arm developed veno-occlusive disease but those in the lower Hb arm did not (Robitaille *et al*, 2013). The authors recommend a threshold of 70 g/l as the standard of care. The results of a restrictive *versus* liberal transfusion RCT in adults undergoing HSCT are awaited (Tay *et al*, 2011).

For children undergoing HSCT for thalassaemia, some centres use hypertransfusion (for example keeping the Hb >130 g/l) during the peri-transplant period to try to reduce the incidence of donor chimerism (Amrolia *et al*, 2001), with the rationale that bone marrow hyperplasia may be associated with a decreased chance of successful transplant (Shen *et al*, 2008). However, there is insufficient evidence to make a specific recommendation.

There is little evidence to guide best practice for red cell transfusion in the setting of chronic anaemia other than in haemoglobinopathy patients (BCSH, 2016b,c; Yardumian *et al*, 2016). A threshold of 70 g/l may be insufficient in the long-term to support normal growth and development in non-haemoglobinopathy children with chronic anaemia. Practice is consensus-based, and for patients with Diamond–Blackfan anaemia, transfusion to keep the Hb above 80 g/l has been recommended (Vlachos *et al*, 2008). The management of iron overload and chelation is beyond the scope of this guideline.

## Recommendations

- 1 There is insufficient evidence to make recommendations for pre-transfusion Hb thresholds in paediatric haematology/oncology patients and those undergoing stem cell transplantation (2C).
- 2 Patients with chronic anaemia due to red cell aplasia may require an Hb threshold of 80 g/l (2C).

### 3.2.3 Haemoglobinopathies

For children with sickle cell disease (SCD) or thalassaemia, the new BCSH SCD transfusion guidelines and the UK Thalassaemia Society clinical standards bring together guidance for both adults and children and should be referred to for these groups of patients (BCSH, 2016b,c; Yardumian *et al*, 2016; see also Section 8.4 and Appendix 1, Table b).

### 3.2.4 Surgery (non-cardiac)

Major blood loss in paediatric surgery mostly occurs in craniofacial, scoliosis and cardiac surgery (see Section 4, and also Section 2.2.3 for infant large volume transfusion). Prior to elective surgery, the preoperative Hb should be optimised by treating iron deficiency anaemia, which is common in children (Brotanek *et al*, 2008). With the exception of children with sickle cell disease (Howard *et al*, 2013), there is no evidence to suggest that children undergoing elective non-cardiac surgery require a higher Hb transfusion

threshold than those on PICU (70 g/l; for cyanotic children see Section 4.1). Evidence from a subgroup analysis of 124 paediatric general surgery patients in the TRIPICU study (Rouette *et al*, 2010) supported a threshold of 70 g/l for stable postoperative patients, and this threshold has been also reported in paediatric scoliosis surgery (van Popla *et al*, 2014).

There is evidence that antifibrinolytics, such as tranexamic acid, reduce blood loss (Neilipovitz *et al*, 2001; Sethna *et al*, 2005; Tzortzopoulou *et al*, 2008; Verma *et al*, 2014), the amount of blood transfused (Song *et al*, 2013), or both (Goobie *et al*, 2011) in children undergoing craniosynostosis and scoliosis surgery. This is broadly consistent with evidence from adult surgery (Henry *et al*, 2011; Ker *et al*, 2013). However the appropriate dose is unclear (Royal College of Paediatrics and Child Health, 2012; Goobie, 2013), as is the incidence of serious side effects. Large well-designed RCTs are required to address these issues.

Cell salvage can significantly reduce allogeneic blood transfusion in adults (Carless *et al*, 2010) and with the development of small bowls, is feasible in infants as well as older children (Seyfried *et al*, 2014). Contraindications include sickle cell disease and other conditions characterized by red cell fragility. A careful risk assessment is essential in malignancy and abdominal injury when the salvaged blood may contain a high concentration of malignant cells or bacteria (Association of Anaesthetists of Great Britain and Ireland [AAGBI] Safety Guideline, 2009).

### Key practice point

*Cell salvage should be supported by a programme of staff training, accreditation and audit in order to ensure a product of a consistently high quality (AAGBI Safety Guideline 2009).*

## Recommendations

- 1 The preoperative Hb should be optimised by treating iron deficiency anaemia (1C).
- 2 A perioperative Hb transfusion threshold of 70 g/l should be used in stable patients without major comorbidity or bleeding (1C).
- 3 Tranexamic acid should be considered in all children undergoing surgery where there is risk of significant bleeding (1B).
- 4 Red cell salvage should be considered in all children at risk of significant bleeding undergoing surgery and where transfusion may be required, providing there are appropriately trained staff (2C).

### 3.3 Platelet transfusion

Most platelet transfusions are given to critically ill children in PICU, haematology-oncology patients and those undergoing cardiac surgery. Children may also bleed during recovery

from HSCT and frequently receive prophylactic platelet transfusions. A recent systematic review summarized the effect of platelet transfusions on platelet count increment, bleeding and mortality and aimed to formulate recommendations for the use of platelet transfusions for non-bleeding critically ill children with severe thrombocytopenia (platelet count  $<50 \times 10^9/l$ ; Lieberman *et al*, 2014a). Only one study relevant to critically ill children was identified (prospective cohort,  $n = 138$ ) which reported no difference in mortality between transfused and non-transfused children in adjusted analyses (Agrawal *et al*, 2008).

There are very few descriptive data on patterns of bleeding and use of platelet transfusions in children with haematological malignancies. In a (*post-hoc*) subgroup analysis of a RCT of different platelet doses in patients with haematological malignancies (PLADO), higher rates of bleeding were noted in children, although the reasons for this difference compared to adults was not clear (Josephson *et al*, 2012). The optimal safe platelet count for routine lumbar punctures (LPs) for children on treatment for leukaemia is also uncertain. One of the few (and largest) case series to report on outcomes of children treated for acute lymphoblastic leukaemia undergoing LP reported no haemorrhagic complications in 941 procedures performed in children with platelet counts  $<50 \times 10^9/l$  who had not received a prophylactic platelet transfusion (Howard *et al*, 2000; Astwood & Vora, 2011). A recent survey of UK paediatric oncology centres showed that prior to LP, there was variation in accepted platelet transfusion threshold between 10 and  $70\text{--}80 \times 10^9/l$  (E. Chalmers unpublished observation). For insertion of central venous catheters in patients with thrombocytopenia, a retrospective study in adults with acute leukaemia by Zeidler *et al* (2011) showed an increased risk of non-severe bleeding only in patients with platelet counts  $<20 \times 10^9/l$ .

Overall, there is insufficient evidence in children to significantly change recommendations made in the previous BCSH guidelines (BCSH, 2004). Suggested thresholds are shown in Table III. The precise platelet threshold used for individual patients or patient groups will depend on the presence of other clinical risk factors. Indications for platelet transfusion in children are consensus-based; in general, a platelet count of  $10 \times 10^9/l$  can be used as a transfusion trigger in non-infected well children, but higher thresholds are used for children who are unstable and/or bleeding. Patients with aplastic anaemia may be best managed without routine prophylactic platelet transfusions in order to reduce the risk of alloimmunization, apart from situations of increased risk of bleeding.

Platelet transfusions are not given on the basis of a low count alone in immune thrombocytopenias, such as immune thrombocytopenia (ITP), or in the thrombotic disorders heparin-induced thrombocytopenia (HIT) and thrombotic thrombocytopenic purpura/hæmolytic uraemic syndrome (TTP/HUS). Platelets should only be used where there is life-

threatening bleeding in HIT and TTP/HUS as there is a risk of exacerbating thrombosis (BCSH, 2012b,c; George & Al-Nouri, 2012; Balestracci *et al*, 2013; Goel *et al*, 2015).

## Recommendations

- Given a lack of studies in paediatrics, recommendations for platelet transfusions in critically ill children or those with haematological/oncological malignancies who develop severe thrombocytopenia are drawn from the wider adult literature and recommendations (2C) (BCSH, 2016d; see Table III for suggested thresholds).
- As pragmatic guidance, it is suggested that for most stable children prophylactic platelet transfusions should be administered when the platelet count is below  $10 \times 10^9/l$ , excluding patients with immune

Table III. Suggested thresholds of platelet counts for platelet transfusion in children.

Platelet count ( $\times 10^9/l$ )	Clinical situation to trigger platelet transfusion
<10	Irrespective of signs of haemorrhage (excluding ITP, TTP/HUS, HIT)
<20	Severe mucositis Sepsis Laboratory evidence of DIC in the absence of bleeding* Anticoagulant therapy Risk of bleeding due to a local tumour infiltration Insertion of a non-tunneled central venous line
<40	Prior to lumbar puncture†
<50	Moderate haemorrhage (e.g. gastrointestinal bleeding) including bleeding in association with DIC Surgery, unless minor (except at critical sites) • including tunneled central venous line insertion
<75–100	Major haemorrhage or significant post-operative bleeding (e.g. post cardiac surgery) Surgery at critical sites: central nervous system including eyes

ALL, acute lymphoblastic leukaemia; DIC, disseminated intravascular coagulation; HIT, heparin-induced thrombocytopenia; HUS, hæmolytic uraemic syndrome; ITP, immune thrombocytopenia; LP, lumbar puncture; TTP, thrombotic thrombocytopenic purpura.

\*Note: routine screening by standard coagulation tests not advocated without clinical indication; for laboratory evidence of DIC see Section 3.4.3.

†It is accepted that prior to lumbar puncture some clinicians will transfuse platelets at higher counts (e.g.  $50 \times 10^9/l$ ) in clinically unstable children, non ALL patients, or for the first LP in newly-diagnosed ALL patients to avoid haemorrhage and cerebrospinal fluid contamination with blasts, or at lower counts ( $\leq 20 \times 10^9/l$ ) in stable patients with ALL, depending on the clinical situation. These practices emphasise the importance of considering the clinical setting and patient factors.

## Guideline

thrombocytopenia, thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome and heparin-induced thrombocytopenia who should only be transfused with platelets for life-threatening bleeding (2B).

### 3.4 FFP and cryoprecipitate

#### 3.4.1 Principles

Fresh frozen plasma and cryoprecipitate may be administered either therapeutically for the management of bleeding or prophylactically. There is very little evidence of benefit from FFP administration in many settings where it is currently used (Stanworth *et al*, 2004; Yang *et al*, 2012) and significant variation in practice is seen. As a result it appears there is frequent inappropriate use of FFP (Stanworth *et al*, 2011). Although there is little direct evidence in children relating to the appropriate FFP transfusion volume, for example in patients with significant bleeding, higher doses are likely to have a greater effect on reducing the abnormality of coagulation tests.

In the UK, the main source of concentrated fibrinogen is cryoprecipitate, although FFP also contains fibrinogen. Fibrinogen concentrate is only licensed in the UK for treatment of congenital deficiency although it is sometimes used for acquired deficiency on an individual patient basis. There is no evidence of a benefit from prophylactic use of cryoprecipitate. The major indications for cryoprecipitate transfusion in infants and children are DIC with bleeding, bleeding following cardiac surgery and major haemorrhage. There remains controversy over the fibrinogen transfusion threshold for cryoprecipitate transfusion. There is no evidence to alter the previously recommended fibrinogen threshold of 1·0 g/l outside the setting of major bleeding. Fibrinogen threshold levels of 1·0 g/l are recommended for inherited hypofibrinogenaemia (BCSH, 2014b) but where there is rapid consumption e.g. in DIC or major haemorrhage, higher target thresholds for therapy may be recommended (Sections 3.4.3, 4.4 and 5).

There is increasing interest in point-of-care testing results, such as thromboelastography/thromboelastometry, but there is limited evidence as to how/whether these should guide transfusion in children in the absence of bleeding (see also Section 4.4.1).

#### Key practice points

- 1 Transfuse FFP volumes of 15–20 ml/kg, using the higher volumes particularly in bleeding patients, and ensure monitoring of clinical outcome. However, care should be taken to avoid volume overload, particularly in vulnerable patients.
- 2 Transfuse cryoprecipitate volumes of 5–10 ml/kg, using the higher volumes particularly in bleeding patients, and ensure monitoring of clinical outcome and fibrinogen levels.

#### 3.4.2 Correction of minor acquired coagulation abnormalities in non-bleeding patients (excluding DIC)

One of the commonest reasons for the administration of FFP in both children and adults is for the correction of minor/moderate abnormalities of the PT/International Normalized Ratio (INR) in non-bleeding patients (Stanworth *et al*, 2011), often done prior to surgery or other invasive procedures. There is accumulating evidence that this approach is incorrect and that much of this FFP use is likely to be inappropriate and exposes patients to unnecessary risk. Minor abnormalities of the PT or INR are poorly predictive of surgical bleeding (Segal & Dzik, 2005; BCSH, 2008) and the effect of FFP in normalizing the PT/INR is poor. Two studies in adults and children assessing the effect of FFP in patients with INRs 1·1–1·6 and 1·1–1·85 found that FFP failed to significantly improve the INR in the majority of cases and also noted no relationship with bleeding (Abdel-Wahab *et al*, 2006; Holland & Brooks, 2006). Abnormalities of the PT or APTT should however be appropriately investigated.

Cryoprecipitate similarly should not be given to correct mild degrees of hypofibrinogenaemia in non-bleeding patients.

#### Recommendations

- 1 Prophylactic FFP should not be administered to non-bleeding children with minor prolongation of the prothrombin time (PT) (2B)/activated partial thromboplastin time (APTT) including prior to surgery, although it may be considered for surgery to critical sites (2C).
- 2 Prophylactic cryoprecipitate should not be routinely administered to non-bleeding children with decreased fibrinogen including prior to surgery. It may be considered for fibrinogen <1 g/l for surgery at risk of significant bleeding or to critical sites (2C).

#### 3.4.3 Disseminated intravascular coagulation

Data on blood product support in children with DIC are limited and there are no guidelines for paediatric practice. Recommendations are therefore largely extrapolated from adult practice. The primary aim should be reversal of the underlying cause. Recent guidance published by the Scientific and Standardization Committee on DIC of the International Society on Thrombosis and Haemostasis harmonizes guidelines published from the UK, Italy and Japan (Wada *et al*, 2013). These guidelines state that FFP may be useful in patients who are actively bleeding and who have either a prolonged PT/APTT (>1·5 times midpoint of normal range) or a decreased fibrinogen (<1·5 g/l) and that FFP should also be considered in patients with similar laboratory abnormalities prior to invasive procedures. The evidence for these recommendations is of low quality. Similar recommendations can be applied to children with

DIC. For children, evidence for a fibrinogen level of 1·0 vs. 1·5 g/l as a threshold for transfusion remains unclear. In practice, it is necessary to take into account clinical factors including the rate of fall of fibrinogen and severity of bleeding. FFP contains all the coagulation factors and fibrinogen, so is used in the first instance for DIC with bleeding, reserving cryoprecipitate for persistent hypofibrinogenaemia despite FFP. However, consideration may be given to giving cryoprecipitate as the initial treatment prior to FFP when the fibrinogen is very low (e.g. 0·5 g/l), dropping rapidly, or if there is major haemorrhage.

Fresh frozen plasma and cryoprecipitate should not be administered on the basis of laboratory tests alone but should be restricted to those with signs of bleeding or where invasive procedures are planned. A possible exception in clinical practice is children presenting with acute promyelocytic leukaemia, who may be at particularly high risk of developing bleeding problems and may require more aggressive initial support as part of their leukaemia management protocol (Breen *et al*, 2012). Patients should also be treated with vitamin K if deficiency is suspected.

#### *Purpura fulminans (PF)*

Purpura fulminans in children may occur in both inherited (see Section 2.4.2) and acquired deficiencies of protein C and S (Chalmers *et al*, 2011; Price *et al*, 2011) and requires urgent investigation to determine the most likely cause. Where inherited PC or PS deficiency is suspected (sometimes in combination with sepsis), initial treatment is usually with FFP as for neonates. Protein C concentrate is the treatment of choice for on-going management of severe homozygous protein C deficiency (see Section 2.4.2). In acquired PF, management of the underlying cause is crucial. There is much less evidence to support the use of PC and PS supplementation in PF due to sepsis although FFP is frequently used for this indication. PC concentrate has been reported to be of benefit in some studies (Veldman *et al*, 2010), but is not currently licensed for this indication.

#### **Key practice points**

- 1 Make sure that patients are vitamin K replete; this may mean giving it routinely to sick children.
- 2 FFP (15–20 ml/kg given 8–12 hourly) may be used as first line therapy to treat acquired PF in association with PC or PS deficiency while the underlying cause is being investigated. The underlying cause should be treated, and it may be helpful to monitor PC/PS levels.

#### **Recommendation**

FFP may be beneficial in children with DIC who have a significant coagulopathy (PT/APTT >1·5 times midpoint of normal range or fibrinogen <1·0 g/l) associated with clinically significant bleeding or prior to invasive procedures

(2C). Cryoprecipitate may be given if the fibrinogen is <1·0 g/l despite FFP, or in conjunction with FFP for very low or rapidly falling fibrinogen (2C).

#### **3.4.4 Liver disease**

Liver disease may be associated with a variable degree of coagulopathy. Severe liver failure is usually accompanied by profound coagulation derangement, including hypofibrinogenaemia. Lesser degrees of liver dysfunction may also be associated with abnormal coagulation but recent evidence shows that the haemostatic system is reset, with an accompanying reduction in the natural anticoagulants associated with an increased risk of thrombosis (Weeder *et al*, 2014). No RCTs have addressed the use of FFP or cryoprecipitate in this setting although the use of blood product support may have a role in patients with bleeding and prior to interventions with clinically significant bleeding risk.

#### **Key practice point**

*In liver disease the standard coagulation tests may be misleading and do not reflect bleeding risk. They should generally not be used alone to trigger transfusion with FFP or cryoprecipitate.*

#### **3.4.5 Warfarin anticoagulation reversal**

Most children on long-term warfarin therapy have underlying congenital heart disease. Emergency reversal of over-anticoagulation is occasionally required to treat major bleeding, or bleeding in critical sites. High quality evidence from adult studies shows that FFP produces suboptimal correction of coagulation defects compared with PCCs (Makris *et al*, 1997; Goldstein *et al*, 2015). A dose of 25–50 iu/kg of a four factor PCC (containing factors II, VII, IX and X) together with vitamin K administration is now the treatment of choice (BCSH, 2011a). FFP should only be used if four factor PCC is not available. Treatment options for bleeding in association with use of new oral anti-coagulants are beyond the scope of this guideline.

#### **Recommendation**

FFP should not be used for urgent warfarin reversal unless four factor prothrombin complex concentrate is unavailable (1B).

#### **3.4.6 Vitamin K deficiency bleeding**

See Section 2.4.4.

#### **3.4.7 Thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome**

TTP, with pathological features caused by microangiopathic thrombosis, results from a deficiency of the ADAMTS13

## Guideline

enzyme. This may be secondary to anti-ADAMTS13 antibodies, or due to an inherited deficiency in congenital TTP (Loirat *et al*, 2013).

### *Acquired TTP*

TTP should be considered in the differential diagnosis in children presenting with microangiopathic haemolytic anaemia (MAHA) and thrombocytopenia. It is a serious disease with a high mortality if not treated promptly (BCSH, 2012b). Urgent (within 6 h) plasma exchange (PEX) using solvent detergent (SD) treated FFP is mandatory and is superior to plasma infusion alone. Methylene blue (MB) FFP has been associated with a need for increased numbers of PEX and with a longer hospital stay in TTP (de la Rubia *et al*, 2001; del Río-Garma *et al*, 2008). Urgent PEX is also recommended for some forms of atypical HUS although not routinely for diarrhoea-associated HUS (Schwartz *et al*, 2016) or pHUS (Spinale *et al*, 2013; Schwartz *et al*, 2016;). It may be considered for HUS with cerebral symptoms. Note that platelet transfusions are generally avoided in TTP or HUS unless there is life-threatening bleeding due to concerns that they may worsen the clinical situation (see Section 3.3).

### *Congenital TTP*

Congenital TTP is a rare disorder that can present at any age (e.g. triggered by pregnancy), with more severe forms usually presenting early in life. Congenital TTP is managed with either SD FFP or with intermediate purity FVIII concentrate, which contains ADAMTS13 (e.g. BPL 8Y) and which may also be used for prophylaxis. For further information see BCSH guidelines (BCSH, 2012b).

## Recommendations

- 1 **Urgent plasma exchange with SD FFP is indicated for TTP (1B) and some forms of atypical HUS (2C).**
- 2 **SD FFP infusion (in the acute phase) and intermediate purity Factor VIII (e.g. BPL 8Y) should be used to treat congenital TTP (1C).**

### **3.4.8 Inherited bleeding disorders**

Where specific coagulation factor concentrates are available, these are the treatment of choice for patients with inherited bleeding disorders. FFP and cryoprecipitate should not be used (United Kingdom Haemophilia Centre Doctors' Organization [UKHCD], 2008; BCSH, 2014b). Factor (F) V deficiency is the only single factor deficiency where a factor concentrate does not currently exist; in this situation, pathogen-inactivated plasma, e.g. SD FFP is recommended. This can also be used together with FVIII concentrate in

the management of combined FV & FVIII deficiency. In FXI deficiency, pathogen-inactivated plasma FFP may be preferred in certain situations due to prothrombotic risks associated with FXI concentrate (Pike & Bolton-Maggs, 2015). This is less likely to be an issue in children where the overall risk of thrombosis is low but SD FFP may be used if replacement therapy is required urgently and FXI concentrate is not immediately available.

In certain situations, while awaiting confirmation of a suspected inherited factor deficiency, FFP may be used for acute management. In suspected haemophilia, doses of 20 ml/kg are often recommended but will only result in a relatively small increase in the FVIII or FIX and should not be used once a specific factor deficiency is confirmed.

## Recommendations

- 1 **FFP should not be used in the management of inherited factor deficiencies other than in a few exceptional circumstances where specific factor concentrates are not available (1B).**
- 2 **Cryoprecipitate should not be used for congenital hypofibrinogenaemia unless fibrinogen concentrate is unavailable (1C).**

### **3.5 Granulocytes**

In the UK, granulocytes for transfusion are produced using one of two means: by apheresis or as a component derived from whole blood donations (Bashir *et al*, 2008). Granulocyte transfusions may be requested for use in neutropenic haematology/oncology/immunology patients with refractory infection or at high risk of developing severe infection (Strauss, 2012). Most patients prescribed granulocyte transfusions are those with cancer-related neutropenia, who are receiving myeloablative chemotherapy with or without haemopoietic stem cell rescue. Recent studies with variable or promising, but overall inconclusive, results have been reported both in adults (Oza *et al*, 2006; Seidel *et al*, 2008) and children (Sachs *et al*, 2006). The exact role of granulocyte transfusions (whether derived from whole blood or collected by apheresis) therefore remains unclear. In the UK, a recent study reported on the safety of the use of a component derived from whole blood donations, and recruitment included 13 children (Massey *et al*, 2012). The reaction profile was similar to that with other granulocyte components and all the children recovered.

## Recommendation

- Granulocyte transfusions may be considered for treatment of refractory infections in children with severe neutropenia (2C).**

## 4 Cardiac surgery

Approximately 13% of red cell transfusions to children in the UK are to support cardiac surgery (New *et al*, 2014). The factors contributing to this high blood use include the nature of the surgery and the coagulopathy associated with cardiopulmonary bypass (CPB). Clinically significant bleeding associated with paediatric cardiac surgery may be defined as WHO grade 3–4. Certain congenital cardiac conditions are associated with T-cell immunodeficiency (including Di George syndrome) and, if suspected, irradiated cellular blood components should be provided until the syndrome is excluded by diagnostic testing (BCSH, 2011b).

### 4.1 Red blood cells

Red blood cells (RBCs) are required during cardiac surgery with CPB, both as part of the priming solution for the bypass circuit to counter the effects of haemodilution and following CPB to replace losses. The primary transfusion threshold for red cells in paediatric cardiac surgery remains the Hb. The optimum Hb thresholds are not clear and there is variation in practice (Mazine *et al*, 2015).

A recent Cochrane review of children requiring surgery for congenital disorders (Wilkinson *et al*, 2014) including 862 patients in 11 RCTs found insufficient evidence to assess the impact of different red cell transfusion strategies due to the small size and heterogeneity of the trials. It is argued that oxygen delivery in cyanotic heart disease is reduced and to compensate for this such children require a higher Hb than children with non-cyanotic heart disease. The evidence to support this is limited and does not take into account the multiple compensatory physiological mechanisms that help support adequate oxygen delivery in progressive anaemia and desaturation (Wang & Klein, 2010). However current practice is that children with cyanotic heart disease are treated differently to those with non-cyanotic disease (Du Pont-Thibodeau *et al*, 2014).

It is recommended that red cells for neonates and infants receiving large volume red cell transfusions for cardiac surgery should be used before the end of Day 5 (see Sections 2.2.3 and 7.1.5), although there is not strong evidence to support this strategy. Electrolyte changes, such as hypocalcaemia, must be closely monitored and corrected and there is concern that older or irradiated blood might be associated with cardiac arrest at the start of CPB in small children due to high serum potassium concentrations. It is also possible that some rare units might have particularly high levels of potassium if the donor has a mutation for familial pseudohyperkalaemia, resulting in red cells that leak potassium more rapidly at the low temperatures of red cell storage (Bawazir *et al*, 2014). If the concentration of potassium in a unit of red cells is high, it is possible to wash the red cells in a cell saver prior to addition to the circuit (Hall *et al*, 1993; Lee *et al*, 2014).

### Cardiopulmonary bypass

The volume of red cells required in the priming solution depends upon the mismatch between the volume of the circuit and the weight of the child, together with the pre-bypass and target Hb. Although experience with miniaturized circuits is reported, reducing the need for red cells, (Redlin *et al*, 2012) their use is uncommon and currently red cells are usually required for priming standard circuits for neonates.

For non-cyanotic children during CPB, an RCT reported by de Gast-Bakker *et al* (2013) showed that a transfusion threshold of 80 g/l was safe both on bypass and in the postoperative period for low risk non-neonatal patients. During CPB in children with cyanotic heart disease, better outcomes were shown in three small randomized trials including neurodevelopmental outcome at 1 year when the haematocrit on bypass was maintained above 0.25 (Hb approximately 85 g/l) (Jonas *et al*, 2003; Newburger *et al*, 2008; Wypij *et al*, 2008). Adult evidence (Curley G. *et al*, 2014) may also be used to guide red cell usage in low risk patients. However, the current level of evidence in children precludes making firm recommendations.

There is no evidence to guide appropriate transfusion thresholds in neonates during CPB; current practice generally follows the guidance for cyanotic non-neonatal patients.

### Post-cardiopulmonary bypass

Data derived from cardiac patients in the TRIPICU study showed that in 125 stable non-neonatal, non-cyanotic patients, a restrictive red-cell transfusion strategy with a threshold of 70 g/l in the postoperative period was not associated with a statistically significant change in rates of organ dysfunction when compared with a more liberal threshold of 95 g/l (Willems *et al*, 2010). de Gast-Bakker *et al* (2013) compared a restrictive (80 g/l) and liberal (108 g/l) transfusion strategy in non-neonatal, non-cyanotic children undergoing cardiac surgery and found that the restrictive group had a shorter length of hospital stay, suggesting that a threshold of 80 g/l throughout the perioperative course was safe. It remains unclear whether a higher threshold for transfusion is required for unstable non-cyanotic patients (Lacroix *et al*, 2012).

In a small postoperative study of 60 children with single ventricle (cyanotic) physiology, 30 were randomized to a restrictive strategy (threshold 90 g/l) and 30 to a liberal strategy (130 g/l) (Cholette *et al*, 2011). The two groups showed no difference in outcomes including lactate concentration, arteriovenous and arteriocerebral oxygen content and length of hospital stay. This suggests that a transfusion threshold of 90 g/l may be safe for stable cyanotic children following cardiac surgery but the study was small and insufficient to support a recommendation.

In unstable or actively bleeding cyanotic or non-cyanotic patients in the post-CPB period, in addition to Hb, overt

## Guideline

signs of inadequate oxygen delivery, such as tachycardia, hypotension, a rising lactate concentration or decreasing mixed venous or cerebral regional oxygen saturation, may provide additional information to support transfusion (Guzzetta, 2011).

### Recommendations

- 1 There is insufficient evidence to make a recommendation regarding an appropriate transfusion threshold during cardiopulmonary bypass (CPB) for non-cyanotic or cyanotic patients (2C).
- 2 For stable children with non-cyanotic heart disease, a restrictive transfusion threshold of 70 g/l following CPB is recommended (2B). There is insufficient evidence to make a recommendation for children with cyanotic heart disease (2C).
- 3 In neonates (both cyanotic and non-cyanotic) or actively bleeding or unstable children following CPB, a higher Hb threshold may be appropriate (see Table I for general neonatal guidance), and signs of inadequate oxygen delivery can provide additional information to support transfusion (2C).
- 4 Blood used for cardiac surgery in neonates and infants should be used before the end of Day 5 (see Section 2.2.3) (1C)
- 5 Potassium concentrations should be checked in the bypass fluid before connecting to the patient to ensure that they are within the normal range. Individual paediatric cardiac surgery units should have their own internal guidance on the maximum acceptable potassium concentration in the circuit prior to commencing CPB, and measures to adjust the level if necessary, such as washing or ultrafiltration of the prime. If the bypass circuit potassium levels are noted to be unusually high such that they cannot be adjusted by normal procedures, an alternative red cell unit should be requested (with appropriate specification dependent on availability if the situation is urgent) (1C).

### 4.2 Cell salvage

Cell salvage including collection and washing of the residual bypass circuit contents is commonly used during cardiac surgery in both neonates and children. In addition to reducing allogeneic transfusion in the first 48 h following surgery (Cholette *et al*, 2013), cell salvage is associated with a lower incidence of postoperative renal failure, a higher postoperative haematocrit and no increase in chest tube drainage (Ye *et al*, 2013). The transfusion thresholds described in the previous section apply to allogeneic blood; cell salvage is frequently reinfused in theatre at Hbs above these thresholds in order to reduce subsequent allogeneic transfusion.

### Key practice point

*It is reasonable to re-infuse salvaged cells even if the patient's Hb is above the recommended transfusion threshold as this may reduce subsequent allogeneic transfusion and additional donor exposure. The risks are low, but adequately trained staff are essential.*

### Recommendation

Red cell salvage is recommended for all neonates and children undergoing cardiac surgery with CPB (1B).

### 4.3 Antifibrinolytics and other strategies to reduce blood loss

Tranexamic acid significantly reduces bleeding and blood transfusion following paediatric cardiac surgery (Zonis *et al*, 1996; Chauhan *et al*, 2003; Faraoni *et al*, 2012), with most evidence from patients with cyanotic heart disease. However, although several studies are reported, most are small and poorly designed with a marked variation in dosing (from 10–100 mg/kg as a bolus dose, 0–200 mg/kg during CPB and 0–15 mg/kg/h). A systematic review found that due to the heterogeneity of the studies, the benefit to risk ratio of tranexamic acid for paediatric cardiac surgery could not be adequately defined, and therefore current evidence to support its routine use in these patients is weak (Faraoni *et al*, 2012). The optimum dose of tranexamic acid for different age groups remains unclear, but recent pharmacokinetic analysis (Wesley *et al*, 2015) suggests that a bolus dose should be followed by an infusion. In view of increasing evidence to support the use of tranexamic acid in non-cardiac surgery, there is an urgent need for large well-designed randomized trials to also clarify its possible role in cardiac surgery.

Aprotinin, an alternative antifibrinolytic agent, also reduces bleeding and blood transfusion following paediatric cardiac surgery (Arnold *et al*, 2006; Breuer *et al*, 2009; Guzzetta *et al*, 2009). The adverse outcomes reported in some adults, including acute kidney injury, have not been reported in children. A recent multicentre comparative analysis of aprotinin and other antifibrinolytics in 22 258 children reported that aprotinin vs no drug was associated with a reduction in bleeding, reoperation and mortality without an increase in the need for dialysis (Pasquali *et al*, 2012). There was, however, no observed benefit of aprotinin in neonates. Conversely, tranexamic acid vs aprotinin showed improved benefits for tranexamic acid in all ages including in neonates, apart from a re-do sternotomy subgroup. This large but observational study was limited by the lack of data on comparative dosing. Overall, UK paediatric cardiac surgery practice in the use of antifibrinolytics is variable due to a persisting lack of clarity on appropriate dosing (Arnold, 2014).

Modified ultrafiltration immediately following separation from CPB has been shown to reduce dilutional coagulopathy, increase Hb, and decrease postoperative bleeding and transfusion (Friesen *et al*, 1997).

Fibrin sealants are increasingly used in paediatric cardiac surgery. There is some evidence from adult studies and a limited number of small randomized controlled trials in children to suggest that these may have some additional benefits in reducing bleeding and blood transfusion following cardiac surgery (Codispoti & Mankad, 2002; Carless *et al*, 2003).

## Recommendation

**Consider using antifibrinolytic therapy in neonates and children undergoing cardiac surgery at high risk of significant bleeding (1B).**

## 4.4 Haemostasis

Pre-operative haemostasis should be optimised, e.g. by ensuring adequate vitamin K replacement. In addition, children may have been prescribed oral anticoagulants or anti-platelet agents following previous cardiac surgery; these must be discontinued and, if necessary, bridged with unfractionated or low molecular weight heparin (Jain & Vaidyanathan, 2010; Mohanty & Vaidyanathan, 2013). Pre-operative prophylactic transfusion of FFP or cryoprecipitate is not indicated for minor coagulation abnormalities, particularly as the patients will be anticoagulated with heparin prior to CPB. If there is post-operative bleeding and the APTT is prolonged it is important to ensure that heparin has been adequately reversed. The recommendations below refer to transfusion for clinically significant bleeding post-CPB.

Cardiopulmonary bypass results in reduced platelet numbers and impairs platelet function, predisposing to increased postoperative bleeding. If the patient is bleeding and a surgical source cannot be identified platelet transfusions are frequently prescribed when the platelet count is less than  $100 \times 10^9/l$  (Table III). CPB in neonates and children may result in marked reduction of coagulation factors including fibrinogen, due to haemodilution, loss from the circuit and consumption. In a patient with significant bleeding following cardiac surgery, FFP may be of benefit when the PT is greater than 1.5 times normal. A number of recent studies have correlated fibrinogen levels with blood loss following adult (Kindo *et al*, 2014) and paediatric cardiac surgery (Moganasundram *et al*, 2010; Faraoni *et al*, 2014). A fibrinogen level of 1.5 g/l is commonly used as the transfusion threshold for cryoprecipitate in line with major haemorrhage guidelines (BCSH, 2015). There has been increasing interest in the role of fibrinogen concentrate, but a recent systematic review by Lunde *et al* (2014) concluded the quality of the currently available evidence was insufficient to support this. This guidance may change in the

light of future high quality RCTs. Fibrinogen concentrate is not licensed for this use in the UK.

## Recommendation

**For clinically significant bleeding following CPB and platelet count  $<100 \times 10^9/l$ , PT or APTT  $>1.5$  times midpoint of normal range, fibrinogen  $<1.5$  g/l specific component replacement may be warranted (2C).**

### 4.4.1 The role of point of care testing

Thrombelastometry and thromboelastography may support early appropriate treatment of the coagulopathy associated with CPB and haemorrhage in paediatric cardiac surgery (Moganasundram *et al*, 2010). It remains unclear whether the correlation between thromboelastography and postoperative bleeding is better than with conventional laboratory testing (Pekelharing *et al*, 2014), but results may be available more quickly, allowing earlier intervention. Several small randomized controlled trials have suggested that the development of algorithms based on this technology may reduce blood loss and transfusion, however the predictive value has still not been fully validated, and large scale studies are required (Romlin *et al*, 2011; Nakayama *et al*, 2015). In addition, there are few data on reference ranges for point of care testing in neonates (Chan *et al*, 2007).

### Key practice point

*Point-of-care testing in paediatric cardiac surgery may support a rational approach to coagulopathy following CPB. Further developments in this area must be supported by a critical evaluation of developing evidence and an on-going programme of audit and quality assurance.*

## 5 Major haemorrhage

### 5.1 Massive blood loss in infants and children

Massive blood loss (MBL) related to trauma is uncommon in children. Major bleeding is more common in the surgical setting. The total blood volume in children ranges from 90 ml/kg in term infants down to 70–80 ml/kg in later childhood/adolescence. For simplicity, a figure of 80 ml/kg could reasonably be applied for all children. Massive blood loss may be defined as either 80 ml/kg in 24 h, 40 ml/kg in 3 h or 2–3 ml/kg/min. In clinical practice, haemodynamic changes compatible with hypovolaemia accompanying evidence or suspicion of serious haemorrhage are the usual triggers.

The principles of management of massive blood loss in adults should be broadly applied to the care of children (Spahn *et al*, 2013; BCSH, 2015). There is little evidence available to guide paediatric care (Diab *et al*, 2013).

## Guideline

Key principles in MBL are:

- 1 Early recognition of children at risk of MBL using clinical parameters
- 2 Education of staff to understand when to activate/trigger the local major haemorrhage protocol and to seek specialist assistance as appropriate
- 3 Active resuscitation and control of bleeding
- 4 Seek specialist assistance (with paediatric expertise)
- 5 Rapid provision of O D-negative or group-specific red cells
- 6 Prescribe all transfused components in ml/kg bodyweight (for children <50 kg) and not as units
- 7 Anticipate and treat coagulopathy and thrombocytopenia in trauma with early use of FFP and consideration of platelets and cryoprecipitate in on-going bleeding
- 8 Use tranexamic acid in trauma (see below)
- 9 Avoid hypothermia, hypocalcaemia, acidosis and hyperkalaemia

Good communication with the hospital transfusion laboratory is essential and should be clearly defined in a massive haemorrhage protocol (MHP), which should include a section adapted for children. Education about the core principles of MHP activation and management in children should be targeted at paediatric trainees and staff in Emergency Departments and theatres. Audit and review of management of all cases of massive blood loss/activation of protocols in children should be planned.

### 5.2 Component use

Transfuse age-appropriate components where possible (Section 7). If a child has life-threatening haemorrhage and no suitable paediatric component is available, then the next best adult component should be provided until the situation is stabilized or the laboratory receives age-appropriate components.

Because unit sizes vary for children, the recommended component ratios should be pragmatically given on a volume basis rather than as units. Initial immediate transfusion of 20 ml/kg RBCs should be given (up to four adult units), O D-negative or ABO and D-specific. The recent Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) RCT (Holcomb *et al*, 2015) in adults reported that there was no difference in overall survival between early administration of plasma, platelets and RBCs in a 1:1:1 ratio and in a 1:1:2 ratio. However fewer patients in the 1:1:1 group died due to exsanguination by 24 h. Therefore, early use of FFP and platelets should be considered prior to the results of coagulation tests where bleeding is on-going.

A ratio of at least 1 FFP:2 RBC is recommended in early resuscitation of major haemorrhage (in major trauma clinicians may consider aiming for a ratio of 1 FFP:1 RBC). Platelets and cryoprecipitate must be considered if active bleeding persists after initial resuscitation. Appropriate aliquots to be transfused are as follows:

- RBCs 20 ml/kg aliquots (maximum four adult units), O D-negative or ABO and D-specific (ideally, cross-matched)
- FFP in 20 ml/kg aliquots (maximum four adult units)
- Platelets in 15–20 ml/kg aliquots (maximum one adult therapeutic dose) to be considered after every 40 ml/kg RBCs
- Cryoprecipitate 10 ml/kg (maximum two pools)

These aliquots should be repeated in recommended ratios as necessary until bleeding is controlled. Ratios should be modified accordingly once laboratory parameters are available. The therapeutic aims should be Hb 80 g/l, fibrinogen >1.5 g/l, PT ratio <1.5, platelet count >75 × 10<sup>9</sup>/l. Careful monitoring for adequacy of resuscitation and for circulatory overload is essential. See Appendix 4 for an example of a major blood loss algorithm.

### Key practice points

- 1 Each hospital that may encounter children with massive blood loss should agree and operate a dedicated children's massive blood loss guideline and algorithm including transfusion and clinical guidance. Surgical and trauma teams should have immediate access to emergency RBCs and transfusion laboratories should have plans in place to ensure rapid provision of components for children.
- 2 Early use of FFP, platelets and cryoprecipitate is recommended in order to reduce coagulopathy and thrombocytopenia.

Early use of tranexamic acid has been shown to reduce mortality in adult trauma (CRASH-2 trial collaborators, 2010) and this beneficial effect may also apply in children. An initial dose of 15 mg/kg (maximum 1000 mg) intravenously over 10 min given as soon as possible and within 3 h of trauma, followed by 2 mg/kg/h for at least 8 h or until the bleeding stops has been recommended by the RCPCH and the Neonatal and Paediatric Pharmacists Group (RCPCH, 2012).

### Recommendation

**Tranexamic acid should be used where massive blood loss is anticipated in children presenting with major traumatic injuries, according to the timing and dosage recommended by the Royal College of Paiatrics and Child Health (2012) (Grade 2C).**

### 6 Prescription and administration

The recommendations of the BCSH Guideline on the administration of blood components (BCSH, 2009) should be followed. However, there are a number of circumstances that may place infants and children at particular risk and where particular care is required. The Serious Hazards of Transfusion reporting scheme has shown that there were a disproportionate number of transfusion errors in the paediatric age group (Stansby *et al*, 2008) and the paediatric red cell

National Comparative Audit of Blood Transfusion reported a significant proportion of transfusions prescribed as units, and with volumes transfused >20 ml/kg (New *et al*, 2014). Education should be targeted at all clinical staff on all paediatric wards.

## 6.1 Key areas for caution in paediatric administration and prescribing

### 6.1.1 Patient identification

There may be confusion over maternal and baby samples, multiple births (especially using consecutive identification numbers), babies without first names, failure to apply wristbands, removal of wristbands by children and/or parents or during procedures and failure to make wristbands accessible during surgery (note alternatives may be used (National Comparative Audit of Blood Transfusion, 2011)). For these reasons, the practice of requiring a second sample collected at a different time for confirmation of the ABO group of a first time patient prior to crossmatching is advocated (BCSH, 2013b; see also Section 8.2.3) unless secure electronic patient identification systems are in place, as long as this does not delay urgent transfusion. In order to reduce neonatal blood testing it is acceptable to use a cord sample as the first grouping sample.

### 6.1.2 Transfusion volumes

In order to prevent over-transfusion of blood components all prescriptions should be ordered and prescribed in millilitres rather than units although some hospitals may have local protocols allowing transfusion in units for larger, older children. The maximum prescribed volume should not be greater than the volume for equivalent adult transfusions. See Appendix 1 for further details including transfusion rates.

#### *Calculation of red cell transfusion volume in non-bleeding patients*

In a non-bleeding infant or child it is important to take into account the pre-transfusion Hb in relation to the transfusion threshold, and it is recommended that a post-transfusion Hb no more than 20 g/l above the threshold be aimed for.

*Volume to transfuse (ml) =*

$$\frac{\text{Desired Hb (g/l)} - \text{Actual Hb (g/l)} \times \text{Weight (kg)} \times \text{Factor}}{10}$$

This transfusion formula does not provide a precise prediction of the rise in Hb for a given transfused volume due to variation in the clinical situation and Hct of transfused red cells. Factors between 3 and 5 have been recommended (see New *et al*, 2014). It is reasonable to use a factor of 4 in order to avoid over-transfusion but this should be assessed on an

individual patient basis. 4 ml/kg approximates to a one unit transfusion for a 70–80 kg adult, typically giving an Hb increment of 10 g/l (BCSH, 2012a)

*Note: the formula has been adapted to the harmonized units for Hb in g/l (previously usually quoted as Hb in g/dl), which requires that the calculation includes a step of division by 10. As this is a change from previous practice, in order to prevent over-transfusion it is recommended that clinicians double-check that the final volume calculated is not more than 20 ml/kg for top-up transfusions.*

Blood components will be provided by hospital transfusion laboratories as units, and it is good practice to liaise with the laboratory in order to ensure that donor exposure is minimized and that the volume ordered and prescribed is not above the maximum normally prescribed for an adult in a similar situation e.g.

- Platelets – 1 pack (approx. 200 ml for apheresis platelets)
- Red cells – 1 unit (approx. 280 ml) for a paediatric top-up transfusion

*Note: this is particularly relevant for children >50 kg in weight.*

Consideration should be given to a dedicated prescription chart for blood components in neonatal units and paediatric wards, allowing for the inclusion of prompts for correct prescribing and space for recording multiple units of blood for a single transfusion episode.

#### *Key practice points*

- 1 Hospitals should have clear guidelines on transfusion thresholds for different paediatric patient groups.
- 2 Hospitals are recommended to develop paediatric prescription charts to aid correct prescribing of blood components.
- 3 Monitoring during the transfusion process is essential, especially as neonates and younger children may be less able to communicate symptoms of a transfusion reaction.

#### **Recommendations**

- 1 Prescription of blood components for paediatric transfusion should be in millilitres unless there are local risk-assessed protocols for prescribing in units for older children, and the maximum volume should not be greater than prescribed for adults (1C). Prescribers must take particular care in calculating paediatric transfusion volumes using a transfusion formula, noting particularly the recent changes to reporting Hb (1C).
- 2 As for recommendations in adults (BCSH, 2013b), a second sample collected at a different time should be tested for confirmation of the ABO group of a first time patient prior to transfusion unless secure electronic patient identification systems are in place, as long as this does not delay urgent transfusion (1C).

## Guideline

### 6.1.3 Consent

Formal signed consent by the patient (or parent/carer) is not required for blood transfusion (SaBTO [Advisory Committee on the Safety of Blood, Tissues and Organs], 2011), but the issues surrounding transfusion must be discussed with the parent/carer and patient (where age-appropriate) and valid consent taken and documented prior to transfusion wherever possible (Akinkugbe *et al*, 2016). Parent/child information leaflets are published by NHSBT (<http://hospital.blood.co.uk/patient-services/patient-blood-management/patient-information-leaflets>). The British Association of Perinatal Medicine recommends formal written consent for neonatal exchange transfusion (Section 2.2.1).

For children whose parents refuse to consent to transfusion, for example Jehovah's witnesses, a full and timely discussion between the consultant and the family is crucial. The discussion should include optimising any cardiovascular or respiratory disease, investigation and correction of anaemia, and nutritional advice including information on ensuring adequate iron in the diet. Other measures are use of erythropoietin and iron therapy where appropriate to maximize the Hb, stopping non-steroidal anti-inflammatory drugs between 10 d and 2 weeks prior to surgery, and making a perioperative management plan for children who are on warfarin. Blood components have been administered in order to save life, despite parental refusal or refusal of the child, and individual cases should always be discussed with the Trust/Health Board legal department where possible. For further details see BSCH (2009) and the UK Handbook of Transfusion Medicine (Norfolk, 2013).

## Blood components and pre-transfusion testing

### 7 Blood components and specifications

In the UK, blood components and their specifications are described in the UK 'Guidelines for the Blood Transfusion Services' (<http://www.transfusionguidelines.org.uk/red-book>) and the NHSBT components portfolio (<http://hospital.blood.co.uk/products>). In order to reduce the risk of transfusion transmission of vCJD, it is recommended that non-UK plasma from countries with a low risk of vCJD is used for all patients born on or after 1 January 1996 (thus including all children) ([http://hospital.blood.co.uk/media/26824/plasma\\_components\\_paed.pdf](http://hospital.blood.co.uk/media/26824/plasma_components_paed.pdf); SaBTO, 2012a) and that apheresis platelets should be provided for this age group whenever possible. MB FFP, MB cryoprecipitate and SD FFP (commercially available) are non-UK sourced and have additional pathogen inactivation steps to reduce the risk of viral transmission due to differences in baseline viral infectivity levels between countries.

### 7.1 Fetal/neonatal/infant components

Blood components provided for the fetal/neonatal/infant age group in the UK have a particular specification with additional safety features, as these recipients are a vulnerable group due to factors including immunological and neurodevelopmental immaturity and small circulating blood volumes.

Blood components with fetal/neonatal/infant specification are suitable for all recipients under 1 year of age. Individual component types have additional special features, which are described in more detail in Appendix 1. For example, red cells for intrauterine and neonatal exchange transfusion are suspended in citrate-phosphate dextrose to reduce the theoretical risk of toxicity of adenine and mannitol to this age group. Red cells for neonatal exchange transfusion and other large volume neonatal and infant red cell transfusions need to be 'fresh' (used before midnight of Day 5; see Section 7.1.5 and Appendix 1, Table b) in order to reduce the risk of hyperkalaemia.

Fetal/neonatal/infant specification components include the following, details of which can be found in Appendix 1, Tables a–c:

- Intra-uterine transfusion (IUT) red cells and platelets
- Neonatal small volume red cells ('paedipacks')
- Neonatal large volume red cells ('LVT's')
- Neonatal exchange red cells
- Neonatal platelets

*Note: MB FFP and MB cryoprecipitate, SD FFP, granulocytes and low titre anti-T fresh frozen plasma may be used for neonates and infants but are not of specific fetal/neonatal/infant specification.*

#### 7.1.1 Donor microbiological testing

Components with fetal/neonatal/infant specification are prepared from blood donated by donors who have given at least one previous donation within the previous 2 years, which was negative for all mandatory microbiological markers (unless the components have been treated with a validated pathogen inactivation process). SaBTO <https://www.gov.uk/government/groups/advisory-committee-on-the-safety-of-blood-tissues-and-organs> recommended in 2013 that components for infants under 1 year old should continue to be manufactured from donors who have donated at least once previously.

Hepatitis E virus (HEV) transfusion transmission has been reported in the UK and other countries (Hewitt *et al*, 2014). Although transfusion-transmitted HEV infection rarely causes acute morbidity, in some immunosuppressed recipients hepatitis E infection can become persistent. As a result, the introduction of HEV RNA testing of blood components for solid organ and stem cell transplant recipients has been recommended (SaBTO, 2015), and some

Blood Services may also provide these component for infants under 1 year old.

### 7.1.2 CMV seronegativity

SaBTO (2012b) recommended that CMV seronegative components are required for IUTs and neonates up to 28 d post-expected date of delivery (i.e. 44 weeks corrected gestational age). Once an infant is greater than 4 weeks after their expected date of delivery, they no longer require CMV-negative components. Due to the difficulty in communicating the corrected gestational age for every neonate, issuing CMV-negative components up to 6 months post-delivery irrespective of gestational age would provide a safety net to comply with the SaBTO recommendations. However, all cellular blood components of fetal/neonatal/infant specification for use up to 1 year of age are currently CMV negative, so are compliant with the SaBTO recommendation.

Granulocytes should be CMV negative for neonates up to 28 d post-expected date of delivery or recipients who otherwise require CMV-negative components (see Section 9.3).

### 7.1.3 Additional antibody screening

Red cell and platelet components with fetal/neonatal/infant specification have been tested by the UK Blood Services and found to be negative for high titre (HT) anti-A and anti-B antibodies. This is in order to minimize risk of haemolysis due to transfusion of ABO non-identical plasma. However, the selection of HT negative platelet components does not totally eliminate the risk of haemolysis. Note that MB FFP and MB cryoprecipitate are not tested for HT antibodies, therefore appropriate group selection of components within the laboratory must also be undertaken (Table IV).

An additional indirect antiglobulin test is performed to screen donor blood for clinically significant red cell antibodies. This is sometimes known as PANTS ('paediatric antibody test') testing.

### 7.1.4 Minimizing donor exposure

Hospital transfusion laboratories should liaise with neonatal units to develop policies and procedures that help to reduce exposure of recipients to components from multiple donors by using paedipacks (see Section 2.2). For neonatal top-up transfusions paedipacks can be transfused until the expiry date (end of Day 35); ideally, the first paedipack allocation should have a long expiry date so that the multiple packs from the same donor can be used for the neonate as required (see Appendix 5). These measures further reduce the risk of transmission of infectious agents via the blood supply.

### 7.1.5 Minimizing risk of hyperkalaemia

For some neonatal/infant transfusions 'fresh' blood is recommended in order to reduce the risk of hyperkalaemia: red cell IUTs, neonatal exchange transfusion and neonatal/infant

Table IV. Group selection of plasma-based components.

Patient's ABO Group	ABO group of plasma components to be transfused		
	Platelets	MB FFP & SD FFP <sup>†</sup>	MB Cryoprecipitate <sup>‡</sup>
O			
1st choice	O	O <sup>†</sup>	O <sup>†</sup>
2nd choice	A, B or AB	A or B or AB	A or B or AB
A			
1st choice	A	A	A
2nd choice	AB	AB	AB
3rd choice	B*	B <sup>‡</sup>	B <sup>‡</sup>
4th choice	O*	—	—
B			
1st choice	B	B	B
2nd choice	AB	AB	AB
3rd choice	A*	A <sup>‡</sup>	A <sup>‡</sup>
4th choice	O*	—	—
AB			
1st choice	AB	AB	AB
2nd choice	A*	A <sup>‡</sup>	A <sup>‡</sup>
3rd choice	B*	B <sup>‡</sup>	B <sup>‡</sup>
4th choice	O*	—	—
Unknown			
1st choice	AB	AB	AB
2nd choice	A*	A <sup>‡</sup>	A <sup>‡</sup>
3rd choice	B*	B <sup>‡</sup>	B <sup>‡</sup>
4th choice	O*	—	—

FFP, fresh frozen plasma; HLA, Human leucocyte antigen; HT, high titre MB, methylene blue; SD, solvent detergent.

*Notes: Platelets*

\*Tested and negative for HT antibodies: where denoted on the component label this indicates that the component has been tested and contains a low titre of anti-A or anti-B in the plasma.

- Group B or AB platelets may not be available. However, the use of group O platelets for non-O patients should be avoided as much as possible. Platelets should be compatible for D.
- If a patient requires HLA matched platelets, HLA match usually takes precedence over ABO group

*Notes: MB FFP, SD FFP and MB cryoprecipitate*

†Group O FFP and cryoprecipitate should **only** be given to group O patients.

‡Group compatible plasma should be used wherever possible. MB FFP, SD FFP and MB cryoprecipitate are not tested for HT antibodies. Non-compatible groups should only be used in emergencies when compatible groups are not available.

- AB plasma, though haemolysin free and suitable for patients of any ABO group, should be conserved for group AB patients or emergency transfusions where the patient's group is unknown. Group AB MB cryoprecipitate has limited availability

## Guideline

large volume transfusions. The red cells should be less than 5 d old at the time of transfusion. This means if the collection date is Day 0, the component must be transfused before midnight of Day 5.

Irradiation of red cell units affects the expiry date of the unit due to increases in potassium levels, which occur rapidly following irradiation, reaching levels normally seen at end of storage within a few days post irradiation (Serrano *et al*, 2014). For IUT, exchange transfusions and neonatal/infant large volume transfusions, irradiated red cells must be given within 24 h of irradiation. Red cells for top-up transfusions given at standard flow rates may be used up to 14 d following irradiation (BSCH, 2011b).

Emergency paedipacks intended for neonatal resuscitation (up to 20 ml/kg) should ideally be less than 14 d old to reduce the risk of hyperkalaemia although this is not evidence-based. It is considered good practice for hospitals to have a robust stock rotation mechanism to ensure that the freshest paedipack units are available for resuscitation, especially if they are irradiated.

### 7.2 Emergency situations

Emergency blood should be available for maternity and specialist neonatal units. Group O D-negative paedipacks should be available for emergency neonatal use. However, O D-negative red cells are incompatible with anti-c/cE and relevant antigen-negative red cells should be used for babies with these maternal antibodies. Two paedipacks should provide a sufficient volume for neonatal resuscitation (up to 20 ml/kg). Standard ‘adult’ units are not suitable as a standby for neonatal resuscitation except in an extreme emergency as they lack the additional safety specification of neonatal components, including HT negative status.

If maternal and neonatal blood units are stored in the same refrigerator, they should be separated and clearly labelled to prevent accidental selection of the wrong component.

#### *Alternative components in emergency*

In emergency situations it may not be possible to meet all the standard neonatal/paediatric specifications and the risks of delays in transfusion have to be balanced against the risk of using components of alternative specification. This includes the use of D-negative units for babies of mothers with non-D antibodies (e.g. anti-c/cE). There should be a locally agreed concessionary release policy for acceptable alternatives for emergency use including a process for communication between the clinical area, the laboratory and the Blood Services (see also BSCH, 2015).

Alternatives are dependent upon the reason for transfusion, availability of components routinely held in stock, timescales for delivery from the Blood Centre and proximity of the local blood storage to the clinical area. A hierarchy for consideration is:

- 1 ABO compatibility with mother and infant
- 2 Antigen-negative for maternal antibodies
- 3 Age of unit
- 4 Irradiation status
- 5 CMV negativity: there is acceptance that, in an emergency situation, leucodepleted components may be provided for recipients who would normally receive CMV-negative components
- 6 A component that satisfies the neonatal specification e.g. multi-satellite packs, MB FFP, HT negative red cells.

It should be noted that in the situation of emergency large volume transfusion for a neonate or infant < 1 year with no neonatal/infant specification red cells available in the hospital, if a non-group O neonate/infant was given an adult group O unit with unknown HT antibody status there is a very low risk of haemolysis from HT antibodies given the small volume of plasma in SAGM units.

Recommended alternatives for emergency intrauterine red cell transfusion can be found in Appendix 3.

#### *Use of D-positive platelets for D-negative female recipients in an emergency*

If it is necessary to transfuse a D-negative female recipient with D-positive platelets in an emergency where the appropriate component is unavailable, the recipient should be given anti-D prophylaxis following BCSH recommendations (BCSH, 2014a). This is particularly likely if HPA-1a/5b negative platelets are transfused in suspected NAIT, as HPA antigen negativity would have higher priority than D-type.

#### **Key practice points**

- 1 Allocate a set of paedipacks when the first neonatal top-up transfusion is requested. They can be used up to 35 d after donation (see Appendix 5).
- 2 Hospital transfusion laboratories should ensure that maternity and neonatal units have access to emergency O D-negative paedipacks (see Section 2.2).
- 3 Hospitals should agree a protocol outlining the hierarchy for acceptable alternatives if specific components are not available in an emergency, and the communication pathway between the clinical area, the hospital transfusion laboratory and the Blood Services.

#### **Recommendations**

- 1 It is recommended that recipients under 1 year of age be transfused with components with neonatal/infant specification (1C).
- 2 In order to avoid delays in blood provision, if specific components are not available in an emergency, use pre-agreed hierarchies of alternative components and communication pathways (1C).

## 8 Key principles for pre-transfusion testing and selection of red cells for neonates and infants less than 4 months of age

### 8.1 Principles

Fetal and neonatal ABO grouping differs from adult ABO grouping because:

- Fetal/neonatal ABO red cell antigens may be poorly expressed (Klein & Anstee, 2005)
- Due to the naivety of the fetal/neonatal immune system, the corresponding ABO red cell antibodies are not usually well-developed
- Maternal IgG ABO antibodies may be detectable in the fetal/neonatal plasma (Roseff, 2011; Shaikh & Sloan, 2011).

The in-built laboratory double-check for ABO blood grouping cannot be used for fetal/neonatal samples because the red cell antigen (forward) group cannot be confirmed by the plasma antibody (reverse) group.

Fetal/neonatal antibody screening differs from adult antibody grouping because:

- Red cell antibodies are not usually produced within the first 4 months of life even after multiple transfusions (Floss *et al*, 1986; Ludvigsen *et al*, 1987; Klein & Anstee, 2005).
- Maternal IgG antibodies are actively transported across the placenta during the second trimester onwards (Saji *et al*, 1999) providing acquired immunity to the fetus and neonate. These can include clinically significant red cell antibodies and prophylactic anti-D if administered during pregnancy.

Due to these factors, antibody screening of a fetus/neonate represents the maternal antibody status rather than the fetal/neonatal antibody status.

### 8.2 Pre-transfusion testing for neonates and infants less than 4 months of age

#### 8.2.1 Why use the maternal sample?

Within the first 4 months, wherever possible, samples from both mother and infant should be obtained for initial ABO and D group determination. The antibody screen should be undertaken on the maternal sample when available. A maternal sample is preferred for antibody testing for the following reasons:

- If maternal antibody has bound to fetal cells *in vivo*, the resulting lower concentration of antibody in neonatal plasma could lead to a false negative antibody screen result.
- It is easier to obtain a sufficiently large sample from the mother to allow for screening and antibody identification if required.

- Sample collection from the infant exacerbates the anaemia of prematurity.

The maternal sample should be collected within 3 d pre-delivery or collected post-delivery.

#### 8.2.2 Determining the maternal transfusion history

If the maternal sample is unavailable or the baby was born in another hospital, the maternal group and antibody status and the transfusion history of both mother and baby should be sought from the referring hospital transfusion laboratory. It is vital to remember that sick neonates may be transferred between multiple hospitals: a full transfusion and testing history should be obtained. All information regardless of source should be relayed to the hospital transfusion laboratory, particularly if an IUT has been given, when the infant would require irradiated cellular blood components until 6 months after the expected date of delivery (BSCH, 2011b). Hospitals should use agreed procedures for obtaining clinical information (see Appendix 6 for example proforma), and for management of compatibility testing if the mother remains at a separate hospital following an ex-uterio transfer.

#### 8.2.3 Sample testing

All reagents and sample testing processes should be in accordance with BCSH guidelines for Pre-Transfusion Compatibility Testing (BSCH, 2013b).

Investigations on the maternal sample:

- 1 ABO and D groups (BSCH, 2013b)
- 2 Screen for the presence of atypical red cell antibodies
- 3 Identification of the antibody/antibodies if the antibody screen is positive

Investigations on the infant sample:

- 1 ABO and D forward group: if transfusion is required or likely to be required the infant's blood group should be verified on two samples (unless a secure electronic patient identification system is in place) collected at different times, where this does not impede the delivery of urgent red cells or other components (BSCH, 2013b). One of these samples can be a cord blood sample. Prior transfusion can affect blood group interpretation so any transfusion history needs to be taken into account.
- 2 Direct antiglobulin test (DAT) should be performed when haemolysis/HDN is suspected or where the mother has had clinically significant red cell antibodies. DATs should not be routinely performed in other situations, including on cord samples sent from neonates of D-negative mothers (BCSH, 2016).
- 3 In the absence of maternal plasma, screen the infant's plasma for atypical antibodies.

### **8.2.4 Interpretation of test results and further investigations**

Caution when interpreting neonatal ABO grouping is required because fetal or neonatal transfusion prior to sample collection may lead to mixed field results, or misinterpretation of the blood group due to presence of transfused cells. Ensure that the neonate's transfusion history is considered when interpreting and reporting ABO and D grouping.

If the DAT (if indicated) and antibody screen are negative and the confirmation ABO and D groups are not anomalous, then no further pre-transfusion testing is required for 4 months.

If there is an atypical red cell antibody in the maternal or neonatal plasma and/or a positive DAT on the neonate's red cells further investigations should be undertaken to identify the following:

- 1 Has the maternal antibody the potential to cause HDN?
- 2 Is the neonate antigen-positive for the maternal antibody?
- 3 Is there ABO incompatibility between mother and infant?
- 4 Has the mother received prophylactic anti-D?

When the neonatal DAT is positive an elution may be performed if there is haemolysis and diagnostic uncertainty but is otherwise not generally required. A flowchart for a summary algorithm of testing decisions is shown in Appendix 7. The likelihood of HDN based on the clinical significance of the implicated antibody should be reported and appropriate blood selected for transfusion (see Section 8.3.2).

*Note: care must be taken when interpreting a DAT result. It can sometimes be negative during acute haemolysis or be positive for no obvious clinical or serological reason. It may be positive due to anti-D given to D-negative mothers as part of routine antenatal prophylaxis.*

### **8.2.5 Clinical special requirements**

Special requirements may be due to clinical factors not known to the laboratory e.g. IUT, immunodeficiency, transplantation. There should be local and shared care procedures for communicating this information to the laboratory (see Appendix 6). The laboratory should have a procedure for recording and managing this information in the form of rules for selection of suitable blood components, e.g. in the Laboratory Information Management System (LIMS).

### **8.2.6 Neonatal name change**

There should be a local policy in place regarding the management of temporary names for neonates e.g. 'Baby' to 'Clare'. The local policy should identify whether a repeat sample is required when the baby's name is changed in the hospital patient administration system.

### **8.3 Red cell selection for neonates and infants less than 4 months of age**

It is important to take the following into consideration:

- Red cells for IUT or neonatal transfusion must be ABO and D compatible with both maternal and neonatal groups, and must be IAT crossmatch-compatible with clinically significant red cell antibodies present in maternal or neonatal plasma.
- If mother and infant are not ABO identical and maternal anti-A or anti-B is present in the infant's plasma, transfused blood that is ABO identical to the infant might haemolyse due to stronger ABO antigen expression on adult donor cells. This is why units that are ABO compatible with both mother and baby must be selected even if the pre-transfusion DAT is negative.
- In general, group O D-negative red cells are used for most neonatal top-up and exchange transfusions. If hospitals use group-specific red cells, most commonly for elective large volume transfusions, they must be ABO and D compatible with both maternal and neonatal groups. It is good practice to use group identical units for elective large volume transfusions in infants in order to minimize use of group O D-negative red cells where possible.
- It is important to minimize donor exposure. Hospital transfusion laboratories may use algorithms that include information about the likelihood of transfusion and age of red cells to guide allocation of paedipacks for top-up transfusion, see Appendix 5 for an example.

#### **8.3.1 Red cell selection: no maternal antibodies present**

Select appropriate group and correct neonatal specification red cells. Group O D-negative red cells may be issued electronically without serological crossmatch. If the laboratory does not universally select group O D-negative red cells for neonatal transfusions, group selection should either be controlled by the LIMS to prevent issue of an incorrect ABO group of red cells, or an IAT crossmatch should be performed using maternal or neonatal plasma to serologically confirm ABO compatibility.

#### **8.3.2 Red cell selection: maternal antibodies present**

Select appropriate group red cells, compatible with maternal alloantibody/ies. An IAT crossmatch should be performed using the maternal plasma. If it is not possible to obtain a maternal sample it is acceptable to crossmatch antigen-negative units against the infant's plasma.

In cases where paedipacks are being issued from one donor unit it is only necessary to crossmatch the first split as the crossmatch result will be representative of all the satellite units from that donor unit. Subsequent packs from this

multi-satellite unit can be automatically issued without further crossmatch until the unit expires or the infant is older than 4 months. If packs from a different donor are required, an IAT crossmatch should be performed.

Blood that is compatible with maternal antibodies should be provided until the maternal antibody is undetectable in the neonate. However, it is not always practical to repeatedly collect neonatal samples to perform antibody screening so antigen-negative blood crossmatched against maternal plasma is usually provided for up to 4 months. If there is no maternal plasma sample left, repeat testing can either be performed against a fresh maternal or a neonatal sample. If the neonate's antibody screen and DAT become negative, no further crossmatching is required.

Transfusion laboratories should consider how electronic rules for red cell selection and issue are controlled given that the presence of maternal antibody in the neonatal circulation is transient and not neonatal in origin.

#### **Key practice point**

*It is vital to communicate the need for special transfusion requirements (e.g. irradiated components post IUT) to the laboratory, with shared care hospitals, or internally with other wards.*

#### **Recommendations**

- 1 Obtain the neonatal and maternal transfusion history (including fetal transfusions) for all new neonatal admissions. Obtain a maternal sample for initial testing when possible and use this for crossmatching if required (1C).**
- 2 Laboratory control measures are required, ideally controlled by the LIMS, to ensure that units are ABO, D compatible with both mother and baby, and antigen-negative for clinically-significant maternal antibodies (1C).**

#### **8.4 Pre-transfusion testing and red cell selection for infants and children from 4 months of age**

For infants and children from 4 months of age, pre-transfusion testing and compatibility procedures should be performed as recommended for adults (BSCH, 2013b). This includes the recommendation that children with sickle cell disease should have extended red cell phenotyping or genotyping (D, C, c, E, e, K, Fy<sup>a</sup>, Fy<sup>b</sup>, Jk<sup>a</sup>, Jk<sup>b</sup>, M, N, S and s) prior to transfusion and, as a minimum, red cells should be matched for Rh (D, C, c, E, e) and K antigens. It is considered good practice for these same recommendations to apply to children on chronic transfusion programmes, such as those with thalassaemia and bone marrow failure syndromes.

Recipients of allogeneic haemopoietic stem cell transplants present blood grouping complexities with associated red cell selection problems. Blood component group selection

for these patients should be performed as recommended for adults (BSCH, 2013b).

### **9 Selection of other blood components**

For further details see Table IV.

#### **9.1 Selection of platelets**

Platelets should match the recipient ABO blood group wherever possible, but it may be necessary to use alternative groups as in Table IV. D-negative paediatric recipients should not receive D-positive platelets because of the risk of allo-immunization to the D antigen. If D-positive platelets must be given in emergency (see Section 7.2), prophylactic anti-D should be considered if the recipient is female.

When NAIT is suspected and results of diagnostic tests are not available, order platelets negative for HPA-1a/5b antigens from the Blood Services until the tests either confirm or exclude the presence of NAIT.

#### **9.2 Selection of plasma**

Plasma components should be ABO compatible with the recipient's blood group. In emergencies it may be necessary to use alternative groups, but note that MB FFP and MB cryoprecipitate components are not tested for HT antibodies. Information on HT antibodies is unavailable for SD FFP and ABO compatible SD FFP is recommended ([www.octapharma.co.uk](http://www.octapharma.co.uk)).

D compatibility is irrelevant for FFP and cryoprecipitate due to negligible residual red cells. Rules for group and specification of suitable plasma components should be managed by the LIMS (BCSH, 2014c).

#### **9.3 Selection of granulocytes**

CMV-negative granulocytes should be selected for CMV seronegative recipients. Granulocytes are irradiated to prevent TA-GvHD. Granulocyte pools are contaminated with RBCs (Hct <0.20) and, as such, should be selected by blood group, crossmatched if necessary or electronically issued based on the same rules as for red cells (for further information see Appendix 1, Table e and Elebute *et al*, 2016).

#### **Disclaimer**

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

## Guideline

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### Author contributions and declarations of interest

HN chaired the writing group and assembled the final draft. All authors took an active role in drafting and

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### Competing interests

The authors have no competing interests.

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## Appendix 1

### Component specifications and transfusion volumes

**Table a.** Fetal/neonatal/infant specification components (general principles).

Suitable for neonates and infants less than 1 year of age. Information is given on those tests that are in addition to those for standard 'adult' components (see <http://www.transfusionguidelines.org.uk/red-book>).

Component type	Specification	Comments
All	<p><b>Donors:</b> Previously tested donors who have given at least one donation in the previous 2 years, negative for mandatory microbiology markers for the current donation. Some Blood Services are introducing Hepatitis E RNA testing for these recipients in addition to solid organ and stem cell recipients</p> <p><b>Processing and selection:</b> Components should be tested and shown to be free of clinically significant, irregular blood group antibodies including HT anti-A and anti-B. For this group of recipients an additional indirect antiglobulin test (IAT) is used to screen for clinically significant antibodies, sometimes known as 'PANTS' (paediatric antibody test) tested</p> <p><i>Where specified to be used within a certain time frame, e.g. 'before the end of Day 5', the collection date = Day 0 and the component must be used by midnight on the specified Day</i></p>	<p>Reduces risk of infection <i>Note: imported FFP and cryoprecipitate are not currently from second time donors but they are pathogen inactivated</i></p> <p>Aims to reduce risk of recipient red cell haemolysis, although the risk of haemolysis is low for red cell concentrates in SAGM due to the low volume of plasma <i>Note: imported FFP and cryoprecipitate are not currently HT or PANTS tested</i></p>
Red cells	<p>Red cell components for IUTs, neonatal exchange transfusion, and neonatal/infant large volume transfusion are made from blood donations that are processed on Day 0 (not stored at ambient temperature for up to 24 h before processing as for other red cells by some of the UK blood services)</p> <p>Haemoglobin S (sickle screen) negative (unless the Blood Centre recommends that screening is unnecessary)</p> <p>K-negative (unless maternal anti-k (cellano) is present, then k-negative must be provided)</p>	<p>2,3 DPG levels are significantly higher in red cells processed on the day of collection (Wilsher <i>et al</i>, 2008), of possible clinical benefit for fetal/neonatal recipients of large volume transfusions</p> <p>Geographical variation – requirement for provision of haemoglobin S-negative red cells is dependent on prevalence in the population Considered best practice to provide K-negative red cells for all recipients in this age group, although the only recommendation is that females of child bearing potential should receive K-negative red cells (BCSH, 2013b)</p>
Red cells and platelets	<p>CMV seronegative</p> <p>Irradiated cellular components are supplied for fetal transfusions and specific neonatal recipient groups (BCSH 2011b)</p>	<p>Although all fetal/neonatal/infant red cells and platelets are provided as CMV negative, this is not required for infants &gt;28 d post the expected date of delivery (SaBTO, 2012b) Some Blood Services may provide Hepatitis E RNA tested components for these recipients.</p> <p>Irradiated to prevent transfusion-associated graft-vs-host disease</p>

*Note:* see Appendix 1, Tables c and d for general principles of platelet and plasma components for all paediatric age groups. Pathogen-inactivated imported FFP does not currently have a specific neonatal/infant specification.

**Table b.** Red cell components for fetal/neonatal/infant/paediatric transfusion.

Component type	Component details and administration	Comments
All red cells	<p><i>Group and phenotype:</i></p> <p><i>Less than 4 months of age:</i></p> <p>Compatible with maternal and neonatal ABO and D group (usually supplied as group O) and clinically-significant maternal antibodies.</p> <p><i>From 4 months of age:</i></p> <p>Compatible with recipient's ABO and D group and any red cell alloantibodies.</p>	<p>D-negative red cells should be selected for all D-negative patients less than 18 years old and all females of childbearing age.</p> <p>Fetal/neonatal/infant specification red cells are currently K-negative (Appendix 1, Table a)</p> <p>All females of child-bearing potential should receive K-negative red cells unless unavailable in an emergency (BSCH, 2013b)</p>
IUT	Red cells up to the end of Day 5	Not stocked in the hospital BT laboratory, special order from the Blood Services
Approx unit volume 240 ml	<p>Hct 0.70–0.85</p> <p>Irradiated</p> <ul style="list-style-type: none"> <li>• shelf-life 24 h post-irradiation</li> </ul> <p>In CPD</p> <p>See Section 1.2.1 for administration details</p>	<ul style="list-style-type: none"> <li>• 'fresh' blood, within 24 h of irradiation to reduce the risk of hyperkalaemia</li> <li>• high Hct to minimize number of IUT procedures required</li> <li>• irradiated cellular components are recommended for infants up to 6 months of age post-IUT (BSCH, 2011b)</li> </ul> <p>For urgent and emergency situations refer to Appendix 3 for options when specific IUT red cells are not readily available</p>
Neonatal exchange transfusion	Red cells up to the end of Day 5	Not stocked in the hospital BT laboratory, special order from the Blood Services
Approx unit volume 355 ml	<p>Hct 0.5–0.6 (NHSBT provide 0.5–0.55)</p> <p>Irradiated</p> <ul style="list-style-type: none"> <li>• shelf-life 24 h post-irradiation.</li> </ul> <p>In CPD</p> <p>Transfusion volume: typically 160 ml/kg (double volume exchange)</p> <p>Transfusion rate: depends on clinical status of baby, discuss with NICU consultant</p>	<ul style="list-style-type: none"> <li>• tight Hct range provided to reduce the chance of post-exchange transfusion anaemia or polycythaemia</li> <li>• irradiation recommended for all exchanges post- IUT, and for all others unless would cause undue delay (BSCH, 2011b)</li> <li>• 'fresh' blood, within 24 h of irradiation, to reduce the risk of hyperkalaemia</li> <li>• CPD instead of SAGM reduces theoretical risk of toxicity from mannitol and adenine additives (Luban <i>et al</i>, 1991)</li> <li>• exchange units contain 100–120 ml plasma with significant coagulation factor activity</li> </ul> <p>It is recommended that this component is used only for exchange transfusion of neonates <math>\leq 28</math> d of age, to reduce exposure of older infants to UK plasma and to reduce the theoretical risk of haemolysis from the (usually) group O plasma.</p> <p>If not used, may be reissued for patients born before 1 January 1996</p>
Neonatal/infant small volume transfusions ('Paedipacks')	<p>Red cells up to the end of Day 35</p> <p>Hct approx 0.5–0.7</p> <p>In SAGM additive solution</p> <ul style="list-style-type: none"> <li>• if irradiated, shelf-life for top-up transfusion 14 d post irradiation</li> </ul> <p>Transfusion volume: typically 15 ml/kg (for non-bleeding patients) or use transfusion formula (see Section 6.1.2)</p> <p>Transfusion rate: 5 ml/kg/h</p>	<p>Generally available from hospital BT laboratory stock</p> <p><i>Note: specification is the same as for 'LVT' but units are split, and may have been stored at ambient temperature for up to 24 h before processing</i></p> <ul style="list-style-type: none"> <li>• there is no requirement to use red cells before the end of Day 5 for neonatal top-up transfusions but caution should be exercised at high flow rates (Strauss, 2010b). To minimize donor exposure, consider age of red cells when allocating a set of paedipacks to a neonate requiring repeat transfusions</li> <li>• paedipacks are usually transfused on neonatal units; may be used for small infants on other wards</li> <li>• for maternity and specialist neonatal units group O D-negative paedipacks should be available for emergency use. Two paedipacks should provide sufficient volume for resuscitation (up to 20 ml/kg), ideally less than Day 14 to reduce the risk of hyperkalaemia (see Section 7.1.5)</li> <li>• group O D-negative adult emergency units are NOT suitable for neonatal resuscitation: they lack the additional neonatal component safety specification</li> <li>• if maternal and neonatal blood are stored in the same refrigerator they must be separated and clearly labelled</li> </ul>
Approx unit volume 45 ml (Six split paedipack from single-donor unit)		

## Guideline

Table b. (Continued)

Component type	Component details and administration	Comments
Neonatal/infant 'LVT' units	Red cells up to the end of Day 5 if used for large volume transfusion for neonates and infants less than 1 year of age	Not stocked in the hospital BT laboratory, special order from the Blood Services
Approx unit volume 295 ml	If irradiated, use within 24 h of irradiation for large volume transfusion Hct approx 0.5–0.7 In SAGM additive solution  For transfusion volumes and rates in surgery (e.g. cardiac) consult local guidelines	Component appropriate for large volume neonatal/infant transfusion e.g. cardiac surgery (BCSH, 2005) <ul style="list-style-type: none"><li>• 'Large volume transfusion': typically equivalent to at least a single circulating blood volume (approx 80 ml/kg for neonates) over 24 h or 50% of the circulating volume within 3 h</li><li>• only contains a small volume of plasma, approx 20 ml (see BCSH, 2005)</li><li>• if used for small volume top-up transfusion for larger infants, may be used up to end of 35-d shelf-life (14 d post-irradiation)</li></ul>
Red cells for children from 1 year of age (standard 'adult' component)	These are standard red cells in SAGM as provided for adult transfusion (BCSH, 2009)  Transfusion volume (see Sections 3.1 and 6.1.2): <ul style="list-style-type: none"><li>• generally calculate to take post-transfusion Hb to no more than 20 g/l above the transfusion threshold</li></ul>	For patients with sickle cell disease, red cells should be Haemoglobin S negative. They should be less than 10 d old, or less than 7 d old for sickle red cell exchange transfusion, although this may not be possible where the patient has multiple alloantibodies. In such situations the freshest available suitable units may be transfused (BCSH, 2016b)
Approx unit volume 280 ml	Transfusion rate 5 ml/kg/h (usual maximum rate: 150 ml/h)	For patients with thalassaemia, red cells less than 14 days old are preferred to try to reduce transfusion frequency (Yardumian <i>et al.</i> , 2016)

**Table c.** Platelets for fetal/neonatal/infant/paediatric transfusion.

Component type	Component details and administration	Comments
IUT platelets Approx unit volume 75 ml	Group A, D-negative (if ABO D group unknown) or group specific/compatible with maternal antibody HPA compatible with maternal antibody for NAIT (HPA-1a,5b-negative/as required) Obtained by apheresis from a single donor Hyperconcentrated to a platelet count of at least $2000 \times 10^9/l$ , shelf-life 24 h Irradiated  See Section 1.3.1 for administration details	Special order from Blood Services, requiring several days notice <ul style="list-style-type: none"> <li>group O platelets should not normally be selected for non-O or unknown group recipients, however the availability of HPA antigen-negative platelets may override ABO group selection considerations</li> <li>for HPA matched platelets, donors are negative for clinically significant HLA and HPA antibodies</li> <li>hyperconcentrated to optimise platelet count and minimize volume load</li> </ul> Irradiated cellular components are recommended for infants up to 6 months of age post- IUT (BSCH, 2011b)
Neonatal platelets Approx unit volume 45 ml	ABO and D identical or compatible with recipient (see Table IV) HPA compatible with maternal platelet antibody for neonates with NAIT (as for IUT platelets) Obtained by apheresis from a single donor, split into four smaller units  Typical transfusion volume: 10–20 ml/kg Transfusion rate: 10–20 ml/kg/h	HPA matched platelets require special order from Blood Services, but HPA-1a/5b-negative usually available 'off the shelf' depending on the geographical location Suitable for neonatal and infant transfusion
Platelets for children from 1 year of age (standard 'adult' apheresis platelets) Approx unit volume 200 ml	ABO and D identical or compatible with recipient (see Table IV) Obtained by apheresis from a single donor where possible  Typical transfusion volume: <ul style="list-style-type: none"> <li>10–20 ml/kg for children &lt;15 kg, or a single pack for children <math>\geq 15</math> kg</li> <li>maximum volume 1 pack</li> </ul> Transfusion rate: 10–20 ml/kg/h	These differ from 'neonatal' platelets by not having fetal/neonatal/infant specification. <ul style="list-style-type: none"> <li>recipients born on or after 1 January 1996 should be provided with apheresis platelets when possible, as a vCJD risk reduction measure</li> </ul>

## Guideline

**Table d.** FFP and cryoprecipitate for neonatal/infant/paediatric transfusion.

Component type	Component details and administration	Comments
All (apart from low titre anti-T FFP)	Imported from overseas, subject to pathogen inactivation  FFP is available either from the Blood Services (single donor, MB treated), or commercially available (pooled, SD treated). Cryoprecipitate is only available from the Blood Services (single donor units, MB treated)  ABO compatible plasma should be selected as far as possible (see Table IV). Group O plasma must only be given to O recipients	Plasma (FFP and cryoprecipitate) for use in the UK for those born on or after 1 January 1996 is currently imported from a country with low risk of vCJD in order to reduce the risk of transfusion transmission of vCJD • imported plasma is pathogen inactivated due to different baseline viral infectivity rates in overseas source countries Group AB FFP, though haemolysin-free and suitable for patients of any ABO group, is often in short supply. The D group of plasma components is not relevant
Methylene blue-treated FFP for neonates/paediatrics	Single donor non-UK FFP, MB treated then exposed to visible light to inactivate enveloped and some non-enveloped viruses (Prowse, 2009)  Approx unit volumes: 55 and 230 ml	Available from UK Blood Services • 90% of MB is removed following treatment • MB treatment results in 25–30% reduced factors VIII XI, and fibrinogen, and decreased thrombin generation. However, these are not associated with a reduction in the rate of clot formation or in clot firmness; the clinical significance of the differences is uncertain (Cardigan <i>et al</i> , 2009) • MB-treated components are not tested for HT anti-A and anti-B antibodies There is no evidence to guide FFP transfusion volumes for neonates
Solvent detergent FFP	Pooled FFP from multiple non-UK donors, SD treated, inactivating enveloped viruses.  Unit volume 200 ml	Commercially available as 'Octaplas' (Octapharma, Lachen, Switzerland) • the Octaplas LG (ligand gel) product utilizes prion removal technology and is licensed and supplied in the UK • SD plasma has reduced protein S, antitrypsin and antiplasmin and its use has been associated with thrombosis (Prowse, 2009) • a minimum of 0.5 iu/ml of each of the measured factors V, VIII and XI is present;* as it is a pooled product there is less variability than for single donor FFP • administration of Octaplas must be based on ABO-blood group compatibility
Methylene blue-treated cryoprecipitate for neonates/paediatrics	This is the cryoglobulin fraction manufactured from imported plasma which has already undergone MB treatment and removal  Approx unit volume 50 ml, pool volume 280 ml.	Available from UK Blood Services as single units or pools • mean fibrinogen approximately 250 mg/unit, 1273 mg/pool • used mainly for fibrinogen replacement: measure plasma fibrinogen levels following transfusion to confirm the outcome • infusion must be completed as soon as possible and within 4 h of thawing • MB-treated components are not tested for HT anti-A and anti-B antibodies Note: group AB MB treated cryoprecipitate has only limited availability (Table IV)
Low titre anti-T FFP	UK sourced FFP, MB treated Group selection, transfusion volumes and rates as for MB and SD FFP above	Available from UK Blood Services, limited supply, requires special order Indicated ONLY for transfusion of neonates with haemolysis following blood component transfusion in whom classical T activation has been demonstrated (Massey, 2011)

\*See [http://www.octapharma.co.uk/fileadmin/user\\_upload/Octapharma\\_UK\\_New/OPL1202.pdf](http://www.octapharma.co.uk/fileadmin/user_upload/Octapharma_UK_New/OPL1202.pdf)

**Table e.** Granulocytes for neonatal/infant/paediatric transfusion.

Component type	Component details and administration	Comments
Pooled buffy coat derived granulocytes.	ABO and D identical and crossmatch-compatible with clinically-significant maternal antibodies as for red cells If ABO compatible but not identical, should be HT negative Irradiated CMV negative for neonates up to 28 d post expected date of delivery or recipients who otherwise require CMV negative	Limited availability (Tues–Sat) requiring at least 24 h notice and Blood Service consultant authorization. Shelf life until midnight on Day 1 Granulocytes derived from buffy coat layer of centrifuged whole blood. 10 donations pooled; each pack contains approximately $1 \times 10^{10}$ granulocytes ( <i>note: some Blood Services may provide single buffy coat packs</i> ) Buffy coats contain large numbers of both red cells and platelets: <ul style="list-style-type: none"><li>• Hct &lt;0.20 so venesection unlikely to be required</li><li>• Each pack has equivalent of 2.5 adult packs of platelets</li></ul> Irradiated to prevent transfusion-associated graft-vs-host disease due to lymphocyte numbers Not neonatal specification; same component as used for adult transfusion Further information available from the NHSBT Clinical guideline (Elebute <i>et al</i> , 2016)
Approx volume of pool 205 ml	Typical transfusion volume: 10–20 ml/kg to a maximum of 2 pools Transfusion rate: suggested 10–20 ml/kg/h	

BT, blood transfusion; CMV, cytomegalovirus; CPD, citrate-phosphate-dextrose; FFP, fresh frozen plasma; Hct, haematocrit; HLA, Human leucocyte antigen; HPA, human platelet antibody; HT, high titre; IUT, Intrauterine transfusion; LVT, large volume transfusion; MB, methylene blue; NAIT, neonatal alloimmune thrombocytopenia; NICU, neonatal intensive care unit; PANTS, paediatric antibody test; SAGM, saline, adenine, glucose, mannitol; SD, solvent detergent; vCJD, variant Creutzfeldt–Jakob disease.

*Note:* Approximate component volumes from NHSBT components portfolio (<http://hospital.blood.co.uk/products>). The volumes for components supplied by other UK blood services may vary.

Typical transfusion volumes and rates are given, but may be modified according to individual clinical situations.

## Appendix 2

### Guideline literature search terms

((Blood Transfusion[mh:exp]) OR (transfus\*[TI] OR pretransfus\*[TI] OR retransfus\*[TI] OR red cell\*[TI] OR red blood cell\*[TI] OR RBC\*[TI] OR PRBC\*[TI] OR FFP[TI] OR fresh plasma[TI] OR frozen plasma[TI] OR maternal plasma[TI] OR platelets[TI] OR platelet concentrate\*[TI] OR granulocytes[TI] OR cryoprecipitate[TI] OR blood component\*[TI] OR blood product\*[TI] OR cell salvage[TI] OR blood salvage[TI] OR cell saver\*[TI] OR TRALI[TI])) OR ((exchange transfusion\*[Title/Abstract] OR plasma exchange[Title/Abstract] OR plasmapheresis[Title/Abstract] OR in utero transfusion\*[Title/Abstract] OR intrauterine transfusion\*[Title/Abstract] OR maternal transfusion\*[Title/Abstract] OR placental transfusion\*[Title/Abstract] OR partial exchange[Title/Abstract] OR neonatal exchange[Title/Abstract] OR disseminated intravascular coagulation[Title/Abstract] OR DIC[Title] OR T-activation[Title/Abstract] OR coagulopathy\*[Title/Abstract] OR ((transfus\*[Title/Abstract] OR retransfus\*[Title/Abstract] OR red cell\*[Title/Abstract] OR red blood cell\*[Title/Abstract] OR RBC\*[Title/Abstract] OR PRBC\*[Title/Abstract] OR FFP[Title/Abstract] OR plasma[Title/Abstract] OR platelet\*[Title/Abstract]) AND (trigger\*[Title/Abstract] OR threshold\*[Title/Abstract]))) AND ((Child[mh:exp]) OR (Pediatrics[mh:exp]) OR (Infant[mh:exp]) OR (Adolescent[mh]) OR (low birth weight\*[Title/Abstract]) OR (child[Title/Abstract] OR children[Title/Abstract] OR paediatric[Title/Abstract] OR pediatric\*[Title/Abstract] OR infant\*[Title/Abstract] OR infancy[Title/Abstract] OR neonat\*[Title/Abstract] OR newborn\*[Title/Abstract] OR babies[Title/Abstract] OR adolescen\*[Title/Abstract] OR teen\*[Title/Abstract]))) AND (random\* OR blind\* OR control group OR groups OR placebo\* OR controlled trial OR controlled study OR guideline\* OR trials OR systematic review OR meta-analysis OR metaanalysis OR literature search OR medline OR cochrane OR embase)

### Appendix 3

#### Suggested alternatives to IUT red cells for emergency fetal transfusion

##### 1. 'Urgent' situations

Where there is unexpected anaemia requiring an IUT within a few hours, but not an immediate life-threatening emergency	
Option (in order of preference)	Notes
1. Irradiated IUT red cells	Generally available from Blood Services in urgent situations within 3-4 h (6 h if out of hours) for fetal medicine units, including transport time, unless there is a maternal antibody that requires sourcing of antigen-negative blood.
2. Irradiated neonatal exchange red cells	If IUT red cells unavailable/take longer than clinically acceptable and neonatal exchange units more readily available <i>NB</i> <ul style="list-style-type: none"> <li>• Hct is lower than standard IUT red cells so post transfusion Hb may be lower</li> <li>• still in CPD like IUT red cells</li> </ul>

N.B. If neonatal exchange red cells are unavailable (rarely) or take longer than clinically acceptable it is reasonable to request an urgent irradiated paedipack. Blood Services clinicians are available for discussion.

##### 2. 'Emergency' transfusions

Requiring immediate IUT in order to prevent fetal death	
Option (in order)	Notes
1. Irradiated paedipacks	Very few hospitals in the UK are able to irradiate blood components on site, therefore consider ordering irradiated paedipacks on standby near FMU/Labour Ward for suspected high risk cases. <i>NB</i> <ul style="list-style-type: none"> <li>• Hct is lower than standard IUT red cells so post transfusion Hb may be lower.</li> <li>• use within 24 h from the time of irradiation</li> <li>• should be before the end of Day 5 at the time of irradiation, in line with the large volume neonatal transfusion recommendations.</li> <li>• suspended in SAGM, not CPD.</li> </ul>
2. Non irradiated paedipacks	As above. Not irradiated, therefore has theoretical risk of TA-GvHD.
3. Adult 'flying squad' blood	Not irradiated, as above Not neonatal/infant specified blood, might not be CMV negative Not necessarily before the end of Day 5 following donation – therefore increased risk of hyperkalaemia

CMV, cytomegalovirus; CPD, citrate-phosphate-dextrose; FMU, Fetal medicine unit; Hb, haemoglobin; Hct, haematocrit; IUT, intrauterine transfusion; SAGM, saline, adenine, glucose, mannitol; TA-GvHD, transfusion-associated graft-versus-host disease.

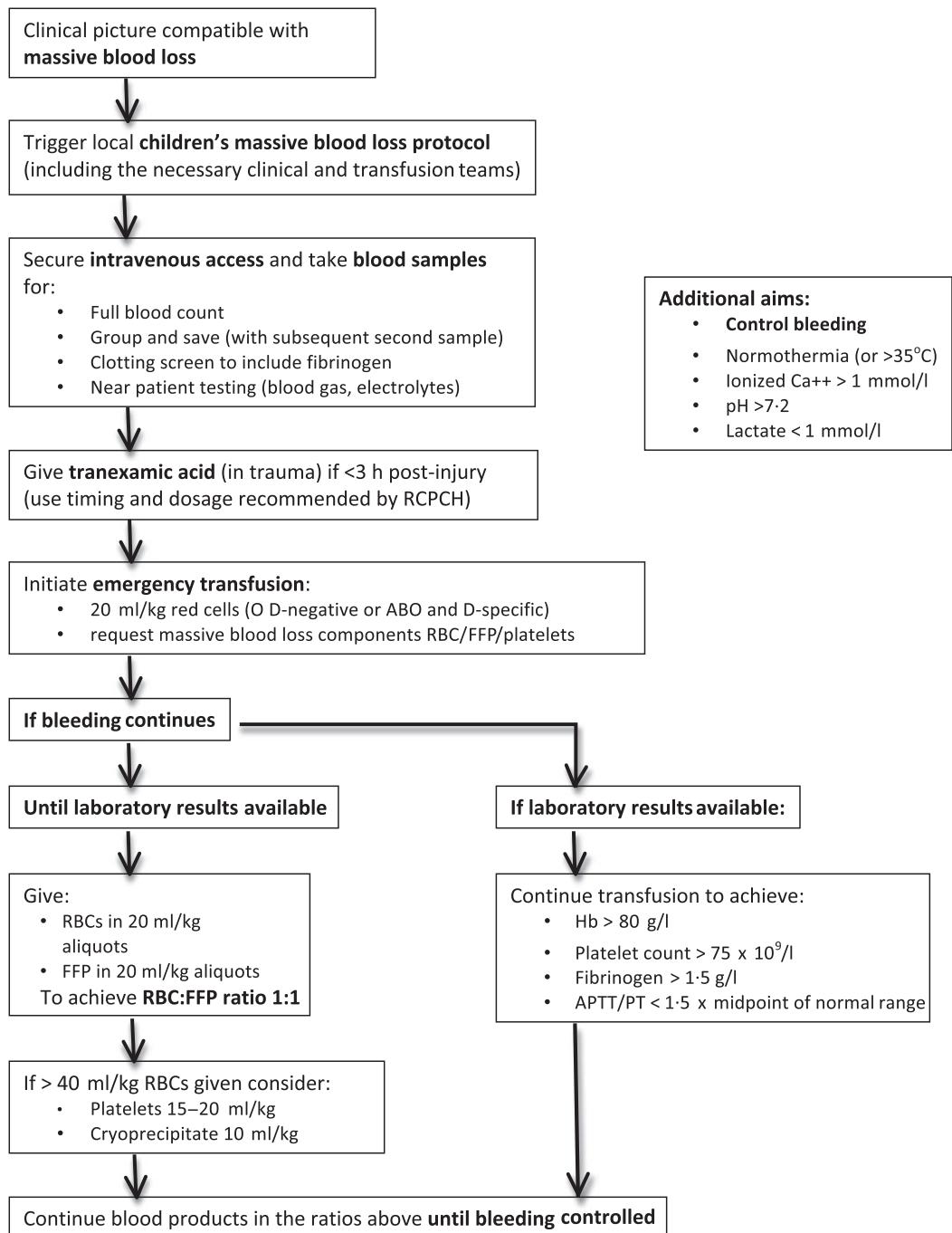
Hospitals should develop local protocols to clarify the options for IUT components.

***NB Maternal blood should not be used for IUT due to the risk of TA-GvHD (as it is not leucodepleted, not irradiated and it is closely related to the recipient)***

## Appendix 4

### Example massive blood loss algorithm

#### Transfusion management for children (<50 kg) with massive blood loss\*



\*This is an example algorithm of transfusion-related management of massive blood loss. Local guidelines will need to be developed to take into account current national and local resuscitation standards and surgical and trauma standards.

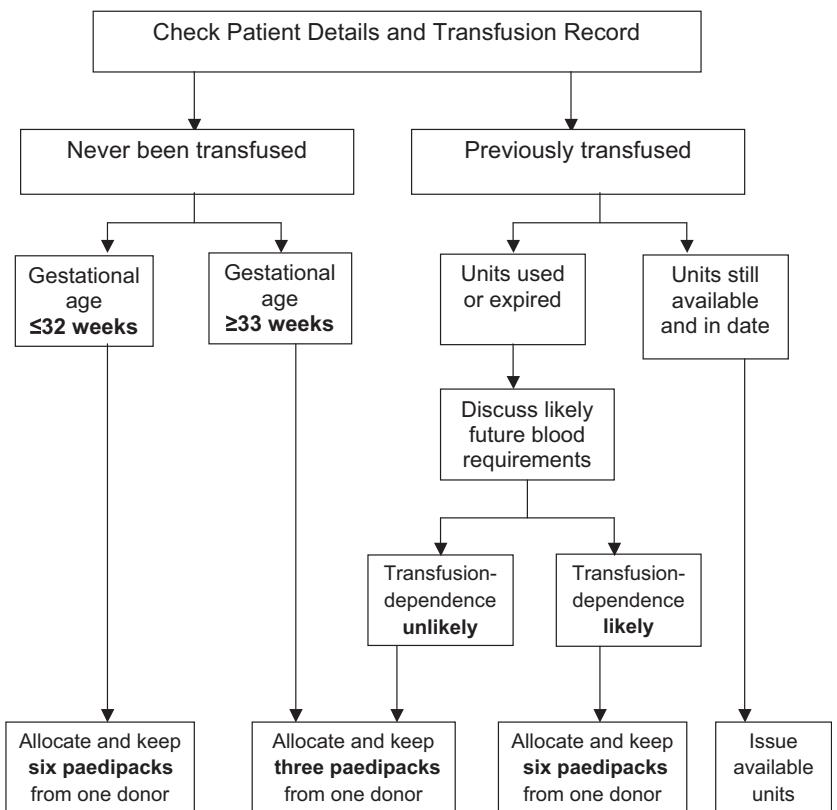
Algorithm may be adapted for neonatal use. Children  $>50 \text{ kg}$  should be managed according to adult guidelines.

APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; PT, prothrombin time; RBC, red blood cell; RCPCH, Royal College of Paediatrics and Child Health.

## Appendix 5

### Example neonatal paedipack allocation algorithm

This is an example of an algorithm used to allocate paedipacks in order to help reduce donor exposure. It is based on the likelihood of an infant needing repeat transfusion dependent upon gestational age. Gestational age refers to gestational age at birth. When a new paedipack is allocated it should be as fresh as possible in order to maximize the available shelf-life. Local data should be used to help develop the algorithm. Audits should be undertaken periodically to assess its effectiveness in minimizing donor exposure.



## Appendix 6

### Record of neonate transfusion history enquiry

#### Part A. Hospital transfusion laboratory to clinical area

Information required from clinical staff to guide safe and appropriate transfusion:

**BABY:**

Full Name: \_\_\_\_\_ D.O.B. \_\_\_\_\_

Current Hospital No: \_\_\_\_\_ NHS No: \_\_\_\_\_

**Birth/Referring Hospital(s):** \_\_\_\_\_ Hospital No: \_\_\_\_\_

Transfused? YES/NO If yes, details: \_\_\_\_\_

IUT red cells/platelets? YES/NO If yes, details: \_\_\_\_\_

Any additional Special Requirements e.g. Irradiated, HPA matched platelets? YES/NO

If yes, details: \_\_\_\_\_

Gestational age: \_\_\_\_\_ to assist paedipack allocation (Appendix 5)

**MOTHER:**

Full Name: \_\_\_\_\_ D.O.B. \_\_\_\_\_

NHS No: \_\_\_\_\_

**Birth/Referring Hospital(s):** \_\_\_\_\_ Hospital No: \_\_\_\_\_

Any known antibody results from other hospital \_\_\_\_\_

Details completed by (BMS): \_\_\_\_\_

Information provided by (clinician's name): \_\_\_\_\_

Time: \_\_\_\_\_ Date: \_\_\_\_\_

#### Part B. Hospital transfusion laboratory to hospital transfusion laboratory

**BABY:**

Full Name: \_\_\_\_\_ D.O.B. \_\_\_\_\_

Current Hospital No: \_\_\_\_\_ NHS No: \_\_\_\_\_

**Birth/Referring Hospital:** \_\_\_\_\_ Originating Hospital No: \_\_\_\_\_

Group: \_\_\_\_\_ DAT Result: \_\_\_\_\_

Transfused YES/NO If yes, no. of units given \_\_\_\_\_ Group of units \_\_\_\_\_

IUT given YES\*/NO

\*Use IRRADIATED must be added to the baby record in the LIMS IMMEDIATELY.

Special Requirements: YES/NO If yes, details: \_\_\_\_\_

**MOTHER:**

Full Name: \_\_\_\_\_ D.O.B. \_\_\_\_\_

NHS No: \_\_\_\_\_

**Referring Hospital(s):** \_\_\_\_\_

Original Hospital no. (if known) \_\_\_\_\_

Group: \_\_\_\_\_ Antibody history: \_\_\_\_\_

Transfusion History: \_\_\_\_\_

Special Requirements: YES/NO If yes, details: \_\_\_\_\_

Name of BMS in BT at Referring Hospital: \_\_\_\_\_

**Details recorded by (BMS):** \_\_\_\_\_ Time: \_\_\_\_\_ Date: \_\_\_\_\_

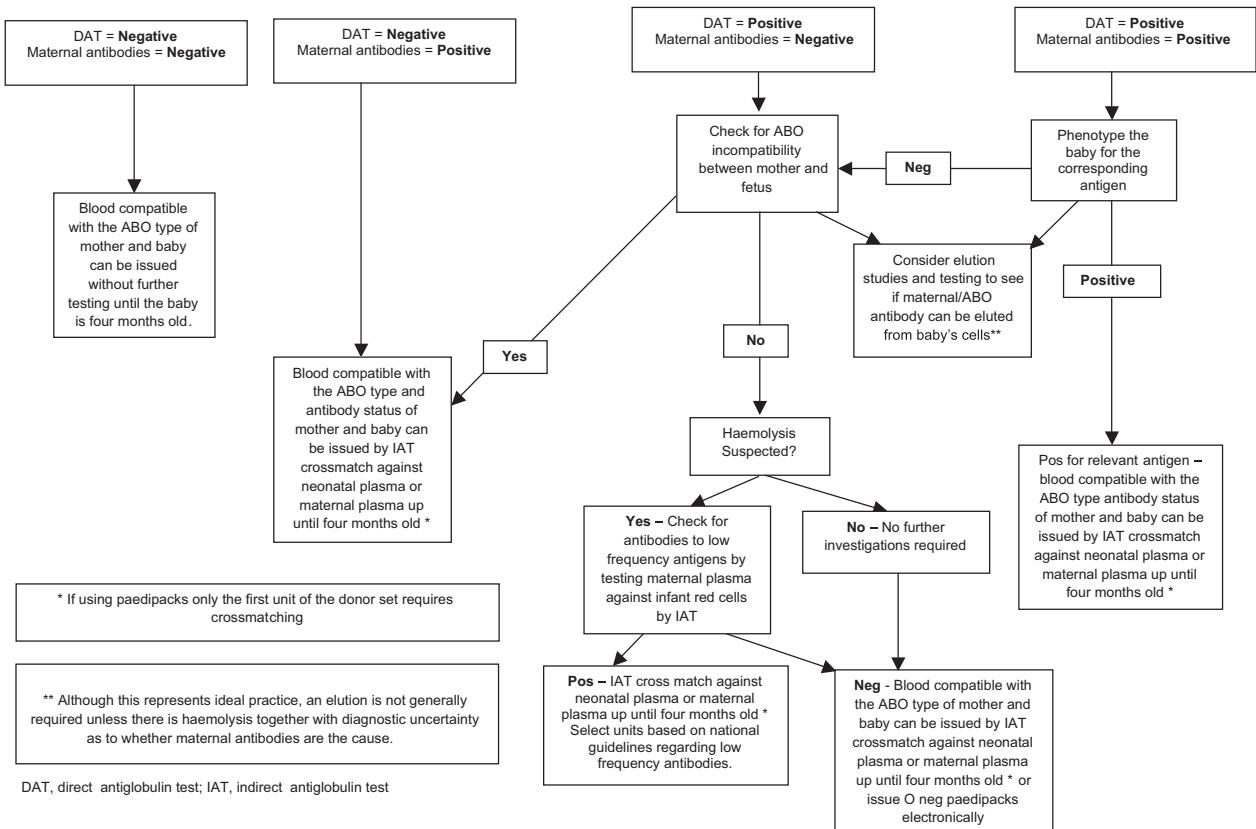
**Note:** If IUT or post-delivery transfusion might have occurred at more than one hospital, each hospital transfusion laboratory will need to be contacted in order to obtain full transfusion history.

BMS, Biomedical Scientist; BT, blood transfusion laboratory; DAT, direct antiglobulin test; HPA, human platelet antibody; IUT Intrauterine transfusion.

## Guideline

## Appendix 7

### Algorithm for compatibility testing for a neonate



# Guidelines on the use of irradiated blood components

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## Methodology

This guideline was compiled according to the British Society for Haematology (BSH) process at <https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf>.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at <http://www.gradeworkinggroup.org>.

## Literature review details

The last guideline covering this topic was published in 2012.

Publications were searched systematically in English between 2008 and August 2019 covering the period since the last publication (Appendices 2 and 3).

## Review of the manuscript

Review of the manuscript was performed by the BSH Guidelines Committee Transfusion Task Force, the BSH Guidelines Committee and the Transfusion and Malignant Haematology sounding board of BSH, and relevant specialists including paediatric cardiac anaesthetists and haematologists specialising in

malignant diseases. It was also on the members section of the BSH website for comment.

## Purpose

To provide healthcare professionals with clear guidance on situations when the use of irradiated blood components is indicated. The term 'blood component' means the therapeutic constituents of human blood (red cells, white cells, platelets and plasma) that can be prepared by various methods (JPAC <https://www.transfusionguidelines.org/red-book/definitions>). The multidisciplinary writing group developed evidence-based clarification and practical guidance in clinical areas of ambiguity. Publications relating to patients of all age groups have been assessed. The guidance may not be appropriate in all patient situations and assessment of individual circumstances with the appropriate risk assessments and patient involvement may lead to alternative decisions.

## Introduction

Transfusion-associated graft-*versus*-host disease (TA-GvHD) is a rare, usually fatal, complication of transfusion of blood components containing lymphocytes. There are no published clinical trials, and evidence for the prevention mostly relies on case reports, haemovigilance data and laboratory methods aiming to inactivate or eliminate lymphocytes in the transfused components. Attempts have been made in the literature to understand recipient susceptibility based on retrospective epidemiological data and information about the level of immunosuppression, not specific for the pathophysiology of TA-GvHD.

The clinical and laboratory features of TA-GvHD and the relative contribution of recipient and component factors remain poorly understood.

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[Following technical errors at the editorial office and publisher's office, this Guideline has been updated on 8 October 2020 after its first online publication. If you downloaded a version of this Guideline before this date, we ask you to refer to this updated version]

The condition was first recognised in immunocompromised recipients transfused with cellular blood components containing viable lymphocytes.<sup>1,2,3</sup> Subsequently it was evident that non-immunosuppressed patients could also develop the condition, particularly if the blood components transfused derived from a human leucocyte antigen (HLA)-haploididentical unrelated donor or family member.<sup>4,5,6,7</sup>

The current hypothesis is that the risk associated with an individual transfusion depends on the number and viability of contaminating lymphocytes, susceptibility of the recipient's immune system to their engraftment and degree of immunological (HLA) disparity between donor and patient. The minimum number of transfused lymphocytes necessary to provoke a GvHD reaction is unknown and may vary by clinical setting.

A systematic review<sup>8</sup> of the world literature relating to TA-GvHD examined some of the features of TA-GvHD. The sharing of HLA antigens between donor and recipient was the strongest risk factor for development of the condition (71% of reported cases with available HLA data) among recipients without other typical indications for component irradiation. The review included 348 cases and suggested that the incidence in recipients is very much in keeping with transfusion rates rather than with patient characteristics. The authors concluded that immune incompetence as a risk for TA-GvHD is less significant than previously thought.

Components were typically whole blood and red cells. Component storage time was reported in the same review in 158 cases (45.4%) reviewed. In these, the implicated component was either described as fresh or as ≤10 days old in 148 cases (93.7%). Ten cases (6.3%) reported a storage time of 11–14 days, with no cases implicating components stored for >2 weeks. Similar findings were reported by the Japanese Red Cross in two series of TA-GvHD with no case reported with components stored for >14 days.<sup>9,10</sup>

Leucocyte depletion has been considered as a protective intervention.<sup>11</sup> However, TA-GvHD continues to be reported within the era of leucocyte depletion, with 66 out of the 348 (18.9%) cases being reported between 2000 and 2013.<sup>8</sup> In some instances patients were transfused with leucocyte-depleted (LD) blood components with no full details available for the quality of leucocyte depletion.

Features of TA-GvHD noted in the Kopolovic *et al.*<sup>8</sup> review include: rash (80.2%), fever (67.5%), elevated liver enzymes (66.4%), pancytopenia (65.2%), diarrhoea (43.1%), bone marrow aplasia (22.7%) or hypocellularity (17.2%) and hepatomegaly (13.5%). Relevant abnormalities occur 1–6 weeks after transfusion, with the median time from transfusion to first symptom being 11 days. The majority of reported cases (61.6%) occurred in men. Overall survival rate is reported to be 8.4%.<sup>12</sup>

As part of the literature search for this guideline, the authors reviewed all cases of TA-GvHD reported in the literature from 2008 to 2018 and these are summarised in Table I. Although the information and exact specification are

limited, note that three cases occurred in patients despite use of LD components.

## Diagnosis

Diagnosis is usually made by biopsy of skin, gut or liver. The presence of donor cells can be demonstrated by DNA amplification in peripheral blood<sup>35</sup> or short tandem repeat analysis using peripheral blood and skin biopsies from affected and non-affected sites in the patient, and peripheral blood samples from the implicated donors.<sup>36</sup> Fluorescence *in situ* hybridisation (FISH) can be used for the diagnosis of TA-GvHD in sex mis-matched cases with rapid turnaround of results.<sup>37</sup>

## Serious Hazards of Transfusion (SHOT) incidents relevant to the irradiation guidelines

The SHOT scheme collects data on adverse events related to transfusion of all labile blood components. A retrospective analysis of 21 years of SHOT reporting (April 1996 to December 2019) found 14 cases of TA-GvHD, 12 prior to the introduction of pre-storage LD that was achieved by November 1999, none of which have been reported in the literature other than in the annual SHOT Reports. These data are included in the Kopolovic *et al.*<sup>8</sup> review. Only two cases have been reported since then, one of which received non-LD blood. One of the cases reported during the period of introduction of universal LD did receive LD red cells; however, it is not clear if the LD was undertaken pre-storage. Symptoms generally occurred rapidly following the transfusion, reported in most cases to be between 5 and 20 days.

### Summary of cases reported to SHOT

Apart from the case of intrauterine transfusion (IUT), none of the cases occurred in patients considered at high risk of TA-GvHD at the time of transfusion, and so these individuals would not normally have received irradiated components, although two may have been immunodeficient.

In the 21 years following the introduction of LD, only two cases of TA-GvHD were reported to SHOT: the first was a patient with B-cell acute lymphoblastic leukaemia (B-ALL) in 2000 and the second was in a baby following an emergency IUT of non-irradiated maternal blood in 2012.<sup>25</sup> This is despite reported omission of irradiation in 1478 patients identified as being at risk.<sup>38</sup> It is important to recognise that many of these patients are exposed to non-irradiated blood components on more than one occasion.

A detailed retrospective analysis was undertaken to review SHOT cases where the specific requirement for irradiation was not met between 2010 and 2016,<sup>39</sup> updated by P.H.B. Bolton-Maggs to include 2017 data. This included 637 reports. The three largest cohorts of patients were those having received purine analogue chemotherapy ( $n = 290$ , 46%),

those with a history of Hodgkin lymphoma (HL;  $n = 132$ , 21%) and those treated with alemtuzumab ( $n = 53$ , 8%). For 43 patients the indication for irradiation was haematopoietic stem cell transplantation (HSCT). The number of components received by an individual was variable (not reported in 66, 10%) and ranged from 1 to 486. Overall, 477 (84%) patients received between 1 and 4 components. Where the patient received 486 non-irradiated blood components this was due to a failure to identify a historical diagnosis of HL.

Overall, from the SHOT data, given the dramatic reduction of reported cases in the UK since the introduction of universal LD, compared with 12 cases reported in immunocompetent recipients in the prior 3 years (1996–1999), it appears that standardised pre-storage LD is sufficient to prevent or markedly reduce TA-GvHD at least in the immune-competent non-HLA-matched recipients (Table II).

In the recent 'Recommendations For the Use of Irradiated Blood Components in Canada' by the National Advisory Committee on Blood and Blood Products ([https://nacblood.ca/resources/guidelines/downloads/Recommendations\\_Irradiated\\_Blood\\_Components.pdf](https://nacblood.ca/resources/guidelines/downloads/Recommendations_Irradiated_Blood_Components.pdf)), storage time of cellular blood components was recognised as a significant factor, with no cases of TA-GvHD reported in the literature involving components stored for >14 days.<sup>8,9,10</sup>

**Recommendations.** In an emergency the provision of red cells or platelets must not be delayed by sourcing irradiated components for patients with the appropriate indication; LD blood or platelets must be sourced rapidly from the blood bank; where non-irradiated components are used in this setting because of urgency this should be recorded and clinical observation made for any evidence of TA-GvHD over the next 6 weeks (1/C).

In emergency situations where irradiated components are unavailable, blood banks should consider preferentially issuing older red cells where possible (>14 days) (2/C). For neonates and infants, see BSH guidelines for transfusion of fetuses, neonates and older children<sup>40</sup> for a suggested hierarchy of blood component characteristics to use in emergency.

## Prevention of TA-GvHD

Prevention of TA-GvHD requires a strategy to address risk factors for the development of the condition. It involves selection of an effective method for inactivation of lymphocytes in the transfused components, management of transfusions where HLA haplotypes are likely to be shared between donor and recipient, and identification of susceptible individuals where the intervention is necessary. It is likely that different interventions work in synergy to provide the best protection. Identification of susceptible individuals might vary in different countries, as it can be influenced by the overall characteristics of the population in terms of HLA typing. Specifications of cellular blood components and more

specifically implementation and effectiveness of universal leucodepletion should be taken into consideration.

TA-GvHD is a rare condition with significant mortality and no randomised control trials available. It should be noted that the literature is scant and levels of evidence are low. In addition, local practices and processes for the development of blood components vary among countries. For these reasons there is considerable variation in recommendations between different national guidelines.

The writing group aims to offer guidance on selection of the effective method for inactivation of lymphocytes on the transfused component, identification of components requiring irradiation (either universally or selectively for susceptible individuals) and identification of susceptible individual. The guideline is based on information from the literature, data from the UK (where universal LD is standard practice since 1999) and cases reported to SHOT.

The authors aim to offer guidance for reduction rather than elimination of the risk of TA-GvHD acknowledging that exceptionally rarely the condition might be a complication of blood transfusion that cannot be predicted when there are no identifiable risk factors.

### *Inactivation or elimination of lymphocytes in the transfused components*

Irradiation remains the main method of inactivating lymphocytes in the transfused component. Washing red cells using standard methods employed in the UK does not appreciably reduce the leucocyte content<sup>41</sup> and therefore these need to be irradiated for susceptible patients. The authors, as part of the literature review, assessed LD and pathogen inactivation as alternative strategies to prevent TA-GvHD.

**Irradiation.** The major technology for preventing TA-GvHD is irradiation of blood components to inactivate residual lymphocytes. Gamma rays and X-rays are similar in their ability to inactivate T lymphocytes in blood components at a given absorbed dose. There is international interest in moving away from using radioactive sources for gamma irradiation due to concerns with respect to biosecurity. Dedicated X-ray blood irradiators are now available, have been widely used in North America and are also used within the UK Transfusion Services. Published data indicate that the small differences in red cell permeability found between X- and gamma-irradiated components are not clinically significant.<sup>42</sup> Further work, commissioned by the Joint United Kingdom Blood Transfusion Services Professional Advisory Committee (JPAC) on blood components irradiated using the Radsource irradiator, concluded that gamma- and X-irradiation can be regarded as equivalent and both are suitable and safe for clinical use (JPAC Guidelines for the Blood Transfusion Services in the UK <https://www.transfusionguidelines.org/document-library/position-statements>).

Table I. Summary of cases of TA-GvHD reported since 2008

Year	Case summary and reference	Component	LD	Irr	HLA*	Immunosuppression	Preventable by previous UK guidelines and practice
2008	4-year-old child with SCID <sup>13</sup>	Red cells	NR	N	Y	Y	Y
2009	Family-directed transfusion during CABG <sup>14</sup>	Red cells	NR	Y	N	Y	Y
2010	Goodpasture's syndrome <sup>15</sup>	Red cells	Y	N	Y	Y	Y
2010	Whole blood transfusion <sup>16</sup>	Red cells	NR	NR	NR	N	Y
2010	2 cases of TA-GvHD following non-irradiated blood given to SCID patients <sup>17</sup>	Red cells	NR	NR	NR	Y	Y
2010	7-month-old admitted to Paediatric Intensive Care Unit with infective complications of what was later confirmed to be combined immunodeficiency <sup>18</sup>	Red cells	Y	N	Y	U†	
2010	Patient who received transfusion abroad, presumed family directed <sup>19</sup>	Red cells	NR	NR	Y	N	Y
2010	56-year-old man given non-irradiated granulocyte transfusion <sup>20</sup>	Granulocytes	N	N	N	Y	Y
2012	Family-directed transfusion <sup>21</sup>	Red cells	NR	NR	NR	N	Y
2012	Afghanistan trauma resuscitation <sup>22</sup>	Red cells and whole blood	N	N	Y	N	Y
2012	Family-directed transfusion for anaemia due to malaria <sup>23</sup>	Red cells	NR	N	Y	N	Y
2012	52-year-old man given blood during CABG 11 years after treatment for HI <sup>24</sup>	Red cells	NR	N	N	Y	Y
2013	IUT <sup>25</sup>	Whole blood	N	N	Y	Y	Y
2013	59-year-old following family-directed transfusion <sup>26</sup>	Red cells	NR	N	Y	N	Y
2013	Family-directed transfusion for post-operative bleeding <sup>27</sup>	Red cells	NR	N	Y	N	Y
2013	Delayed TA-GvHD in patient who received blood prior to liver transplant, and treated with anakinra <sup>28</sup>	Red cells	N	N	Y	Y	Y
2013	66-year-old given family-directed transfusion post-CABG <sup>29</sup>	Red cells	NR	N	Y	N	Y
2013	70-year-old male post liver transplant – convincing evidence of TA-GvHD responded to IL2 blockade <sup>30</sup>	Red cells	NR	N	N	Y	U†
2013	55-year-old male patient with acute lymphoblastic leukaemia previously treated with purine analogue (fludarabine) <sup>31</sup>	Red cells	Y	N	NR	Y	Y
2016	5-year old with unexplained pancytopenia – TA-GvHD diagnosis not confirmed <sup>32</sup>	Red cells	N	N	Not done	Y	Y
2016	45-year-old post hysterectomy received red cells from a sibling donor. A week later developed classical TA-GvHD and died 3 weeks after onset <sup>33</sup>	Red cells	NR	Y	N	Y	Y
2017†	Neonate with haemophagocytic lymphohistiocytosis; TA-GVHD diagnosis based on skin biopsy <sup>34</sup>	Red cells	NR	N	Not done	Y	U

CABG, coronary artery bypass graft; IL2, interleukin 2; Irr, irradiated; LD, leucocyte depleted; N, no; NR, not reported; SCID, severe combined immunodeficiency; U, unclear; Y, yes.

\*Evidence of HLA relatedness, either by genotyping or for family-directed transfusion where the mechanism is presumed to be HLA mediated.

†It is not clear from the publications whether immunodeficiency could have been suspected prior to transfusion.

Table II. All SHOT cases 1996–2017

Year	Diagnoses	Shared haplotype
1996–97	No risk factors – woman in her 80s transfused for epistaxis	NR
	Premature neonate, born at 32 weeks and multiply transfused prior to diagnosis of severe combined immunodeficiency	NR
	Two middle aged men with NHL	NR NR
1997–98	Coronary artery bypass surgery followed by transfusion of red cells <5-days-old	Yes
	Autoimmune thrombocytopenia treated only with oral steroids, transfused red cells and platelets	NR
	B-cell NHL in remission, transfused for GI bleeding	NR
1998–99	Waldenström's macroglobulinaemia	Yes
	Myeloma; woman in her 60s, 6 units of red cells 5–7-days-old. These were LD but unclear if pre-storage or at bedside	NR
	Uncharacterised immunodeficiency; 51-year-old man presented with pneumocystis pneumonia, transfused for GI bleeding	NR
1999–2000	Cardiac surgery, a man in his 60s exposed to 32 donors	NR
	Cardiac surgery, a man in his 60s, 2 units of red cells	Yes
	No cases reported	
2000–01	B-ALL, a teenager in the UKALL R2 trial (no fludarabine). Components irradiated in hospital. At relapse she received non-irradiated red cells and platelets (2 units of each)	NR
2001–11	No cases reported	
2012	IUT with maternal blood, therefore fresh, not LD, not irradiated, fully HLA matched with the fetus. <sup>19</sup>	Yes
2013–19	No cases reported	

ALL, acute lymphoblastic leukaemia; GI, gastrointestinal; NHL, non-Hodgkin lymphoma; NR, not recorded

**Recommendation.** Gamma- or X-irradiation of blood components, by validated systems, is the recommended procedure to prevent TA-GvHD (1/B).

**Effective dose**—Studies indicate that a dose of 25 Gy, measured at the mid-plane of a component, completely abolishes mixed lymphocyte responses.<sup>43</sup> The American Association of Blood Banks (AABB) *Standards for Blood Banks and Transfusion Services*, 32nd Edition,<sup>44</sup> recommends a dose of 25 Gy to the central area of the component with no portion receiving <15 Gy, but sets no upper limit. The Japanese Society of Blood Transfusion's Guidelines recommend a similar dose.<sup>45</sup> In the UK, a minimum of 25 Gy is recommended, but with the dose to any bag in the container not exceeding 50 Gy. To ensure this dose distribution is achieved, consultation with supporting physicists is mandatory, as is validation and regular monitoring of dosimetry in accordance with relevant standards.<sup>46,47</sup> JPAC Guidelines for the Blood Transfusion Services in the UK are available at: <https://www.transfusionguidelines.org/red-book/chapter-7-specifications-for-blood-components>. Data substantiating the effect of irradiation in excess of 50 Gy on cell quality are lacking.

**Recommendation.** The minimum dose achieved in the irradiation volume should be 25 Gy, with no part receiving >50 Gy (1/B). The irradiation procedure must be validated and there must be regular monitoring of dosimetry.

**Leucocyte depletion.** In the UK all cellular components except granulocytes are LD. This raises the question of whether irradiation, in addition to LD, is necessary to prevent TA-GvHD. It is not possible to sample and test all blood components for residual leucocytes, and therefore the specification for LD is based on statistical confidence from testing a sample of those produced, typically 1%. The current specification is that >99% of components should contain  $<5 \times 10^6$  leucocytes per unit and >90%  $<1 \times 10^6$  per unit with 95% confidence. The process of LD fails occasionally and the UK calculate figures for the residual risk of issuing a unit above these specified levels. At the time of writing, the likelihood of a unit of red cells containing more than  $1 \times 10^6$  leucocytes is 1:230, and  $>5 \times 10^6$  leucocytes is 1:1881. For apheresis platelets these values are 1:321 and 1:8154 respectively, and for pooled platelets 1:75 and 1:3205 (personal communication, Simon Procter Head of Quality Monitoring NHS Blood and Transplant, June 2020).

Therefore, in considering the effectiveness of LD alone in preventing TA-GvHD, one must consider the risk of issuing a non-LD component and its potential clinical consequences, that is, that TA-GvHD is usually fatal when it does occur. In a recent international systematic review of 348 cases of TA-GvHD,<sup>8</sup> LD components were implicated in 17% of cases where LD status was reported (6.6% overall cases). However, in about half of these cases the level of leucocyte depletion achieved was below current standards in the UK. We are not

aware of any country that relies on leucocyte depletion alone for effective prevention of TA-GvHD.

**Recommendation.** There is insufficient evidence to recommend leucocyte depletion alone to prevent TA-GvHD in susceptible patients (1/C).

**Pathogen inactivation.** Systems to pathogen inactivate platelets are now licensed in Europe. Due to their mechanism of action, as well as inactivating bacteria and viruses, they also inactivate lymphocytes.<sup>48,49</sup> The manufacturers therefore claim that these systems can be used as an alternative to irradiation for the prevention of TA-GvHD, and many centres that have implemented this technology have stopped irradiating platelets.<sup>50</sup> Although these systems are considered by some authors as potential future solutions for prevention of TA-GvHD,<sup>51,52</sup> they are not yet used in the UK, and similar systems in development for red cells are not yet licensed with limited data available.<sup>53,54</sup>

## Manufacturing aspects for irradiated components

Irradiation of blood components constitutes a manufacturing process. The responsible institution is therefore expected to comply with relevant aspects of the European Commission Guide to Good Manufacturing Practice<sup>55</sup> and hold the appropriate licence as a Blood Establishment according to the Blood Safety and Quality Regulations 2005.<sup>56</sup>

### Red cells

Irradiation of red cells results in significant changes in some markers of red cell quality, most notably increased haemolysis and potassium leakage. Irradiation has no clinically significant effect on red cell pH, glucose consumption, ATP or 2,3-diphosphoglycerate (DPG) levels,<sup>57</sup> but can increase levels of microparticles<sup>58</sup> with no adverse effects reported. The magnitude of this effect of irradiation on red cells is dependent upon the age of red cells prior to irradiation, dose of irradiation and length of storage once irradiated. Irradiation of red cells in the last few weeks of their normal shelf life, currently permitted by AABB standards (*Standards for Blood Banks and Transfusion Services*, 32nd Edition),<sup>44</sup> and Council of Europe guide (*Guide to the Preparation, Use and Quality Assurance of Blood Components*, 20th Edition, 2020)<sup>59</sup>, results in increased haemolysis of red cells<sup>60,61</sup> and reduced post-transfusion red cell recovery, although recovery is still above the minimum defined as acceptable by the United States Food and Drug Administration (75%).<sup>62,63</sup> As red cells can be irradiated up to 14 days after collection and stored for a maximum of a further 14 days without significant loss of viability<sup>64</sup> or haemolysis,<sup>61</sup> and there is little operational gain in enabling irradiation later in shelf life in the UK, it is recommended

that red cells are irradiated within 14 days from collection, and stored for a maximum of 14 days after irradiation.

Both gamma- and X-irradiation of red cells result in significantly accelerated leakage of potassium and an increase in the level of extracellular potassium.<sup>42,65,66</sup> Small volume 'top-up' transfusions given at standard flow rates do not constitute a risk of hyperkalaemia, even when given to premature neonates.<sup>67</sup> Potassium load may be clinically important in rapid large-volume transfusions, such as neonatal exchange blood transfusion (EBT) or IUT,<sup>68,69</sup> and therefore the shelf life of the latter components is restricted to 24 h following irradiation and by the end of Day 5 from collection to reduce the risk of hyperkalaemia.<sup>40</sup> These restrictions are also recommended for infants receiving other large volume transfusions such as for cardiac bypass or extracorporeal membrane oxygenation (ECMO): small infants are particularly susceptible to risks of hyperkalaemia due to their small size compared to extracorporeal circuits and the potential for high transfusion rates relative to weight. Routine removal of supernatant plasma and washing of irradiated red cells is not considered necessary. Rapid infusion of irradiated red cells for patients with massive haemorrhage could potentially contribute to the development of hyperkalaemia. With only limited data available,<sup>70</sup> it is probably safer to avoid transfusion of irradiated blood for patients with massive haemorrhage, unless irradiated blood is otherwise indicated.

For patients requiring washed and irradiated red cells, red cells can be irradiated at any time up to 14 days after collection. Due to the effect of the combination of washing and irradiation on red cell quality, the shelf life of these red cells is shorter than standard red cells (JPAC Guidelines for the Blood Transfusion Services in the UK <https://www.transfusionguidelines.org/>).

In a recently published retrospective study,<sup>71</sup> prolonged storage of irradiated red cells was associated with a significant increase in non-allergic transfusion reactions. Overall, the irradiated red cells appeared to cause more non-allergic reactions compared with non-irradiated red cells with the leading type of reaction being febrile non-haemolytic transfusion reaction. Red cells units included in this study could be irradiated at any time before the expiry date and subsequently could be stored for up to 28 days or up to expiry date (whichever comes first). This finding has not been recorded in the UK haemovigilance system, where manufacturing practice is different with <15% of the reported febrile non-haemolytic transfusion reactions involving irradiated components (Bolton-Maggs, P, personal communication from SHOT data).

**Recommendations.** Red cells may be irradiated at any time up to 14 days after collection, and thereafter stored for a further 14 days from irradiation. Where the patient is at risk from hyperkalaemia, e.g. IUT or neonatal EBT, or other large-volume transfusion of neonates and infants, it

**is recommended that red cells are transfused within 24 h of irradiation (1/C).**

**If washed red cells are irradiated, they should be transfused as soon as possible and according to UK Blood Transfusion Services Guidelines (1/B).**

**Irradiated components not used for the intended recipient can be returned to stock to be used for recipients who do not require irradiated components (1/C).**

### *Platelets*

Although recent laboratory studies suggest that irradiation may result in proteomic/metabolomic changes in platelets, irradiation <50 Gy has not been shown to produce significant clinical changes in platelet function.<sup>58,72,73,74</sup>

**Recommendation.** Platelets can be irradiated at any stage during storage and can thereafter be stored up to their normal shelf life after collection (1/A).

### *Granulocytes*

The evidence for irradiation damage to granulocyte function is conflicting, but in any case, granulocytes should be transfused as soon as possible after production and irradiation, as granulocyte function declines rapidly with time.<sup>75,76</sup>

**Recommendation.** All granulocytes should be irradiated before issue. They should be transfused with minimum delay (1/C).

### *Labelling and documentation requirements*

Irradiated components must be identified by the applied labelling and include any reduction in shelf life.

Labels that are sensitive to irradiation and undergo a visual change to indicate their irradiated status are available and are considered a useful indicator of exposure to irradiation. The dose at which the label changes to indicate irradiated status must be marked on the label. It must be remembered that such labels simply reflect that the unit has been exposed to radiation and their use does not replace the need for regular and precise dosimetry nor for carefully controlled working procedures.

**Recommendation.** All irradiated units should be labelled as such, using an approved bar code label. Each unit should be monitored using a radiation-sensitive device, and the result should be permanently recorded, manually or by computer (1/C).

### *Blood components that should be irradiated*

TA-GvHD has been reported after transfusion of whole blood, red cells, platelets and granulocytes.<sup>77</sup> Scotland, Wales

and Northern Ireland use universal irradiation of platelets, whereas England irradiates blood components on request. Internationally there is also variation. In the USA, a survey of irradiation practices at College of American Pathologists member institutions (>2000) showed considerable variation in practice for different conditions. Some institutions irradiated by specialty or service, and 75 institutions used universal irradiation.<sup>78</sup>

Japan uses universal irradiation of all labile blood components,<sup>45</sup> as a higher rate of TA-GvHD has been reported due to common HLA tissue types.<sup>79</sup>

### *Blood components that do not require irradiation*

TA-GvHD has not been described following transfusion of frozen deglycerolised red cells, which are thoroughly washed free of leucocytes after thawing.<sup>80</sup>

TA-GvHD has not been described following transfusion of cryoprecipitate, fresh frozen plasma or fractionated plasma products, such as clotting factor concentrates, albumin and intravenous immunoglobulin. Liquid (never frozen) plasma is not currently produced in the UK. In contrast to frozen plasma components, any contaminating lymphocytes can remain viable in the component during storage and the component has been implicated in cases of TA-GvHD.<sup>81</sup> Therefore, this component, where produced, should be irradiated.

Pathogen inactivation systems for platelets may obviate the need for irradiation based on the capability of these systems to inactivate lymphocytes. Data and claims from the manufacturers of these systems should be reviewed to determine the effectiveness of lymphocyte inactivation and prevention of TA-GvHD.

**Recommendation.** For all at-risk patients, all red cell, platelet and granulocyte components should be irradiated, except cryopreserved red cells after deglycerolisation. It is not necessary to irradiate fresh frozen plasma, cryoprecipitate or fractionated plasma (1/B).

### *Donations from family members and HLA-selected donors*

Because of the sharing of HLA haplotypes, donations from family members pose a risk of TA-GvHD. Red cells, granulocytes, platelets and fresh plasma (not previously frozen) have all been implicated in TA-GvHD after transfusion from family members,<sup>4</sup> and there is an increased risk with donations from both first- and second-degree relatives.

Several cases of TA-GvHD have been reported from Japan, where limited diversity of HLA haplotypes in the population increases the chance of a transfusion recipient receiving blood from a HLA-haploidentical or HLA-identical donor.<sup>82</sup>

These observations are of relevance for patients receiving HLA-selected platelet concentrates from non-family members because of alloimmune refractoriness to random donor

platelets. This would be expected to increase the risk of TA-GvHD, especially if the platelet donor is homozygous for one of the recipient HLA haplotypes (analogous to donations within families or within racial groups of limited genetic diversity).

Transfusion of donor lymphocytes whose HLA antigens are all shared by the recipient was recognised as the strongest risk factor for the development of TA-GvHD in the recent review<sup>8</sup> of the world literature.

There are no reports of TA-GvHD following transfusion of HLA-matched red cells. However, it is likely for the risk to be similar to the transfusion of HLA-matched platelets.

**Recommendations.** All transfusions of cellular components and fresh plasma from first- or second-degree relatives should be irradiated, even if the patient is immunocompetent. All HLA-selected components should be irradiated even if the patient is immunocompetent (1/B).

## Clinical indications for use of irradiated components

### Paediatric practice

The risk of TA-GvHD in the fetus and neonate, especially if preterm, is thought to be higher than in older recipients. Contributing factors are the immunological immaturity,<sup>83</sup> the use of fresher blood<sup>8</sup> and transfusion of relatively large volumes in situations such as neonatal EBT. Donor lymphocytes have been found in the neonatal circulation up to 6–8 weeks after EBT,<sup>84</sup> and cases of TA-GvHD have been described in neonates and young infants.<sup>82,85,86</sup> These cases were almost exclusively in the presence of additional risk factors: EBT with or without preceding IUT, congenital immunodeficiency syndromes, and transfusion from blood relatives. Moreover, many publications on TA-GvHD in neonates were prior to the introduction of pre-storage LD, known to have had a major impact on TA-GvHD reduction.<sup>8,11</sup>

International practice for irradiation of components for neonates and children varies,<sup>87</sup> although in the UK the same irradiation recommendations for the perinatal period have been in place since 1996.<sup>88</sup> In some countries and institutions, irradiation is undertaken for blood for older children because of concerns over unrecognised immunodeficiency.<sup>89</sup> However, potential benefits of universal irradiation need to be balanced against the ability to use multiple ‘paedipacks’ for neonatal top-up transfusions to reduce donor exposure (not practical in the UK if universally irradiated by blood centres) and the potential risk of hyperkalaemia following rapid transfusion of older irradiated blood to a neonate.<sup>40</sup> The combination of irradiation for high-risk patients together with pre-storage LD for all others is considered to be sufficient to prevent virtually all TA-GvHD in the UK.<sup>11</sup>

Nonetheless, it is important for neonatologists and paediatricians to retain a high index of suspicion of undiagnosed immunodeficiency in infants and older children (see section on congenital immunodeficiencies in infants and children). It should also be noted that signs of TA-GvHD may present later in neonates than in adults.<sup>82</sup>

*Intrauterine and neonatal exchange red cell transfusions.* A fatal case of TA-GvHD occurred following IUT of non-irradiated maternal blood in an emergency.<sup>25</sup> BSH guidelines recommended that maternal blood should not be used for IUT to avoid this risk.<sup>40</sup>

*Intrauterine transfusion (IUT)*—Red cells for IUT are used by the end of Day 5 of storage. Despite current practice of LD and the few reported cases of TA-GvHD following IUT from unrelated donors,<sup>90</sup> irradiation is recommended given the setting of large-volume transfusion of fresh blood to a very immature recipient. Specific, irradiated, red cells for IUT should be used where possible, and local written protocols should be in place regarding alternatives for use in emergency.<sup>40</sup>

Previous BSH irradiation guidelines<sup>88,91</sup> have recommended that irradiated components continue to be provided for routine ‘top-up’ neonatal transfusions following IUT, in line with recommendations for EBT following IUT. This recommendation was based on the presumption of transfusion-induced tolerance or immune suppression following IUT and the knowledge of cases of TA-GvHD in the situation of IUT followed by EBT, rather than on specific evidence, and was originally made prior to universal pre-storage LD in the UK. Missed irradiation following IUT appears to be relatively common, in part due to miscommunication between fetal medicine and obstetric delivery centres. Although there have been 18 reports to SHOT from 2007 to 2017 where red cell irradiation was missed for transfusion following IUT (e.g. Bolton-Maggs *et al.*<sup>25</sup>), none resulted in TA-GvHD. However, there is still previous evidence to suggest a degree of adaptive immune paresis following red cell IUT, although the clinical significance is uncertain (e.g. Radder *et al.*<sup>92</sup>). Therefore, although the risk of TA-GvHD is likely to be very low, the recommendation to irradiate transfusions of cellular blood components to infants following IUT remains.

*Neonatal exchange blood transfusion (EBT)*—Given that there were cases of TA-GvHD in the past reported following EBT, both with and without prior IUT,<sup>85,86</sup> it seems reasonable to continue with previous guidance to irradiate blood for this large-volume indication despite the introduction of LD. Blood issued routinely for EBT by the UK Blood Services is currently universally irradiated.

**Recommendations.** Red cells for IUT should be irradiated (1/C).

Red cells for neonatal EBT should be irradiated (1/C).

**As recommended above (Manufacturing), red cells for IUT and EBT should be transfused within 24 h of irradiation.**

**Intrauterine platelet transfusions**—As platelet concentrates may contain small numbers of residual lymphocytes, the relevant recommendations for red cell transfusion should also apply to platelets.

**Recommendation.** Platelets for IUT should be irradiated (1/C).

**Neonatal top-up transfusions.** Preterm infants are often multiply transfused yet there are few reports of TA-GvHD.<sup>85</sup> With increasing gestational age, the neonatal immune system becomes progressively more mature.<sup>83</sup> Even in the setting of multiple transfusions associated with ECMO there has been only one reported case of TA-GvHD,<sup>93</sup> which could have been associated with a primary immunodeficiency. It is not considered necessary to irradiate components for neonatal/infant top-up transfusions unless a congenital T-cell immunodeficiency is suspected, or if the infant has had a previous IUT.

**Recommendations.** Routine irradiation of red cells for transfusion to preterm or term infants (other than for EBT) is not required unless there has been a previous IUT, in which case irradiated components should be administered until 6 months after the expected delivery date (40 weeks gestation) (2/C).

Routine irradiation of platelet transfusions for preterm or term infants is not required unless there has been a previous IUT, in which case irradiated components should be administered until 6 months after the expected delivery date (40-weeks gestation) (2/C).

**Congenital immunodeficiencies in infants and children.** TA-GvHD has been reported in children with severe primary T-lymphocyte immunodeficiencies characterised by an absence of T lymphocytes or a severe defect of T-cell function.<sup>18,94</sup> In the newborn infant the presenting features of immunodeficiency syndromes (e.g. cardiac disease, hypocalcaemia, thrombocytopenia, eczema) may be unrelated to the immune defect and a high index of suspicion is required, particularly in infants aged <6 months with recurrent or persistent respiratory or gastrointestinal infections. In view of the recent case of possible TA-GvHD in an infant with congenital familial haemophagocytic lymphohistiocytosis (HLH),<sup>34</sup> it is reasonable to give irradiated cellular blood components for patients with suspected congenital HLH and lymphopenia, until T-cell immunodeficiency has been excluded. To date, there have been no reports of TA-GvHD occurring in patients with isolated defects of humoral immunity.

**Recommendation.** All severe congenital T-lymphocyte immunodeficiency syndromes with significant qualitative

or quantitative T-lymphocyte deficiency should be considered as indications for irradiation of cellular blood components (1/B).

Once a diagnosis of severe T-lymphocyte immunodeficiency has been suspected, irradiated components should be given while further diagnostic tests are being undertaken. A clinical immunologist should be consulted for advice in cases where there is uncertainty (1/C).

**Cardiac surgery in neonates and infants (and older patients).** There have been occasional published reports of TA-GvHD in apparently immunocompetent neonates and older patients undergoing cardio-pulmonary bypass surgery.<sup>9,11,95</sup> There should be a high index of suspicion concerning co-existing cardiac defects and immunodeficiency. If in doubt, blood should be irradiated until a definitive diagnosis is made. Irradiated components are essential if an immunodeficiency syndrome increasing the risk of TA-GvHD is diagnosed, such as the severe T-lymphocyte immunodeficiency syndrome that may be associated with DiGeorge syndrome or CHARGE syndrome (rare complex genetic disorders).

Only around 0.5–1% of infants with suspected DiGeorge or CHARGE syndrome will have a severe co-existing immunodeficiency,<sup>96,97</sup> and most of the severe immunodeficiencies will be diagnosed within the first year of life. Genetic testing (FISH) detects the majority of patients with DiGeorge syndrome, but the presence or absence of a 22q11 chromosomal deletion by FISH does not predict an associated immunodeficiency. Ideally, immunological assessment comprising T-lymphophenotype enumeration, including naïve (CD45<sup>+</sup> (+/− CD27<sup>+</sup> or CD31<sup>+</sup>) CD4<sup>+</sup>) T lymphocytes, and T-lymphocyte proliferation measurement will be performed prior to cardiac surgery for all infants with the suspected syndromes.

For those infants where this is not possible prior to urgent cardiac surgery, irradiated cellular blood components should be given. For infants with a T-lymphocyte count of >400 cells/μl of which ≥30% are naïve T lymphocytes, and no other evidence of immune deficiency, administration of non-irradiated blood is considered safe.<sup>98</sup> For children aged 1 to <2 years without a significant history of infection the risk of TA-GvHD will be extremely low, but for this age group it is reasonable to follow the recommendations for neonates and infants regarding immunological testing and use of irradiated cellular blood components. From 2 years of age without a significant history of infection, it is reasonable to follow the recommendations for adults below, even in the absence of immunological testing.

Sometimes it is discovered during infant cardiac surgery that the patient has no thymus, indicating probable immunodeficiency. In this situation where there is no specific evidence to guide practice it is reasonable to wait for irradiated blood to arrive if this is practical, but not to delay surgery if this would cause a significant detrimental clinical impact given that all blood in the UK is LD.

**Recommendations.** Neonates and infants with suspected immunodeficiency syndromes should undergo T-lymphocyte enumeration prior to cardiac surgery wherever possible. If the T-lymphocyte count is >400 cells/ $\mu$ l, of which 30% are naive T lymphocytes, there is no need to irradiate red cells or platelets. If it is not possible to undertake T-cell investigations prior to surgery, irradiated cellular blood components should be given until immunological investigations have been undertaken (1/C).

Adults, and children aged > 2 years without a significant history of infections, referred for elective cardiac surgery for problems associated with DiGeorge syndrome, such as aortic arch anomalies and pulmonary artery stenosis, or in whom DiGeorge anomaly is suspected, do not need to receive irradiated cellular blood components, unless there is a significant history consistent with severe T-lymphocyte-associated immunodeficiency, as the risk of TA-GvHD is extremely low (2/C).

*Acquired immunodeficiency states in childhood.* Transient defects of T-lymphocyte function can occur following common childhood viral infections and in the setting of tuberculosis, leprosy, autoimmune disorders, malnutrition and burns. TA-GvHD has not been reported in these situations and irradiation of blood components is not recommended. Despite the profound T-lymphocyte defect in human immunodeficiency virus (HIV) infection, no cases of TA-GvHD have been described in children or adults.

**Recommendation.** There is no indication for irradiation of cellular blood components for infants or children with temporary defects of T-lymphocyte function as the result of a viral infection. There is also no indication for irradiation of cellular blood components for adults or children who are HIV antibody positive or who have acquired immune deficiency syndrome (AIDS) (1/B).

#### *Allogeneic haematopoietic stem cell transplantation (HSCT)*

Use of irradiated components for patients undergoing allogeneic HSCT is common and widely accepted practice.

Our literature search did not identify any cases of TA-GvHD related to allogeneic HSCT. Furthermore, it is unclear if irradiation of cellular blood components is required for reduced intensity conditioned (RIC) stem cell transplantation and this practice has been questioned in the literature. Jaime-Pérez *et al.* (2015) describe their experience of giving non-irradiated blood components to patients undergoing RIC allogeneic HSCT; 156 patients were exposed to non-irradiated blood with no cases of TA-GvHD, offering some indication that the risk of TA-GvHD is not high in recipients of RIC transplants.<sup>8,99</sup>

Given the severity of TA-GvHD, and the complexity of recognising the diagnosis in this patient population, there is no convincing evidence that the current guidance should be changed.

**Recommendations.** All recipients (adult and paediatric) of allogeneic HSCT should receive irradiated blood components from the time of initiation of conditioning chemo/radiotherapy. The recommendation applies for all conditions where HSCT is indicated regardless of the underlying diagnosis (1/B).

Irradiated components should be continued until all of the following criteria are met:

1. >6 months have elapsed since the transplant date
2. The lymphocyte count is  $>1.0 \times 10^9/l$
3. The patient is free of active chronic GvHD
4. The patient is off all immunosuppression

If chronic GvHD is present or continued immunosuppressive treatment is required, irradiated blood components should be given indefinitely (2/C).

Treatment with irradiated blood components should continue indefinitely if this is required based on transplant conditioning, underlying disease or previous treatment, e.g. previous diagnosis of HL or previous purine analogue treatment (1/C).

Allogeneic cellular blood components transfused to bone marrow and peripheral blood stem cell donors of all ages within 7 days prior to or during the harvest should also be irradiated (2/C).

#### *Autologous stem cell transplantation (ASCT)*

Despite reports of immune defects persisting for many years following successful ASCT, no cases of TA-GvHD following ASCT were found in our literature review and analysis of reported cases and therefore current recommendations remain unchanged.

**Recommendations.** Patients (adult and paediatric) undergoing bone marrow or peripheral blood stem cell collections for future autologous re-infusion should receive irradiated cellular blood components for 7 days prior to and during the bone marrow/stem cell harvest to prevent the collection of viable allogeneic T lymphocytes, which can potentially withstand cryopreservation (1/C).

All patients undergoing ASCT irrespective of underlying diagnosis or indication for this treatment should receive irradiated cellular blood components from initiation of conditioning chemo/radiotherapy until 3 months post-transplant (6 months if total body irradiation was used in conditioning) unless conditioning, disease or previous treatment determine indefinite duration, for example previous diagnosis of HL or previous purine analogue treatment (1/C).

### *Hodgkin lymphoma (HL)*

Patients with HL are known to be at risk for TA-GvHD unrelated to treatment modality or disease stage or histology.<sup>100,101</sup>

Current recommendations for adults and children with HL are to receive irradiated blood components for life. This guidance is often difficult to follow and many reports of failure to offer irradiated components to patients with history of HL have been reported to SHOT with no adverse effects.

The guideline authors attempted to identify evidence from literature to guide optimal duration of the use of irradiated components, acknowledging the challenges and compliance issues with the lifelong recommendations. Literature review and conclusions are summarised as follows:

TA-GvHD has been reported rarely in patients with HL many years after the induction of remission. As patients who are in long-term remission from HL may only rarely need blood component transfusion the relative risk for TA-GvHD in such patients is impossible to determine. In the literature search, one case of TA-GvHD occurred 11 years after successful treatment of HL.<sup>24</sup> However, it should be noted this was in the context of coronary artery bypass surgery; TA-GvHD has been reported in immune-competent patients undergoing such surgery in the past, so that it is not possible to ascertain whether the history of HL was relevant or not.

Individuals with HL exhibit defects in the immune system, including defects in T-cell mediated immunity.<sup>102–111</sup> However, all these studies of immune function in this condition were published up to the 1990s, and the methods used were not as specific as those available today. These included basic enumeration of lymphocyte phenotypes, lymphocyte mitogen responses, mixed lymphocyte responses, and *in vivo* assessment of delayed hypersensitivity. It is quite relevant that allogeneic skin graft rejection was documented to be impaired in patients with HL, indicating that responses to major histocompatibility complex (MHC) antigens were impaired.<sup>112–114</sup>

Humoral responses to bacterial antigens, especially polysaccharide antigens such as the pneumococcal capsular polysaccharides, may be impaired, especially in those treated by splenectomy or lymphoid irradiation.<sup>105,108</sup>

Susceptibility to infections with common opportunistic organisms is a surrogate marker of impaired immunity. Most infections documented in patients with HL are invasive bacterial infections, characteristic of those with antibody deficiency, with the pneumococcus dominating. Splenectomy is often a contributory factor.

Although SHOT surveillance indicates that a considerable number of patients with a history of HL have received non-irradiated blood components with no adverse effects, without detailed analysis of the clinical details of each patient, including the type of HL, staging of disease, therapy received, and time from completion of therapy, it is difficult to provide guidance about risk-assessment for individual patients.

In view of the seriousness of TA-GvHD the recommendation remains unchanged and patients with HL should receive irradiated blood components indefinitely.

**Recommendation.** All adults and children with HL at any stage of the disease should have irradiated red cells and platelets indefinitely (2/C).

### *Other patient groups*

*Patients treated with purine analogues (regardless of the underlying condition).* The purine analogues fludarabine, cladribine and pentostatin induce profound lymphopenia with low CD4 counts that may persist for several years after treatment.<sup>115</sup> There are case reports of TA-GvHD following treatment of low-grade B-cell malignancies with fludarabine<sup>116,117</sup> and cladribine.<sup>118</sup>

Although no cases of TA-GvHD secondary to purine analogues have been reported in the UK since the introduction of universal LD, there is no adequate evidence in the literature to support modification of current recommendations. It remains a recommendation that cellular blood components should be irradiated for patients receiving purine analogues.

*Haematology patients and patients with rare types of immune dysfunction treated with alemtuzumab (campath 1H-anti-CD 52) or anti-thymocyte globulin (ATG).* Use of alemtuzumab (campath 1H; anti-CD 52) has been considered as an indication for irradiation of blood components. This recommendation was based on a reported non-infection-related fatality in a Cancer and Leukaemia Group B (CALGB010101) study, a Phase II study of fludarabine and rituximab induction followed by alemtuzumab in chronic lymphocytic leukaemia (CLL).<sup>119</sup> Treatment schedule varies in different series, with the most common treatment dose to be up to 30 mg three-times a week for 12 weeks.<sup>120</sup>

The risk for development of TA-GvHD for aplastic anaemia patients treated with alemtuzumab remains unclear.

Currently, there is no evidence to discontinue irradiation for patients receiving alemtuzumab for treatment of haematological malignancies or bone marrow failure. It is not possible, based on existing evidence, to make a firm recommendation on how long irradiated blood components should be used for this group of patients.

The risk of development of TA-GvHD for patients with aplastic anaemia following treatment with anti-thymocytic globulin (ATG) is considered to be low. However, it remains unclear if the absence of reported cases is due to the low risk or whether the current guidance for using irradiated blood components is highly effective. In view of the seriousness of TA-GvHD, and unless new evidence emerges, current guidance remains unchanged and irradiated blood components are recommended for bone marrow failure patients receiving ATG (see also solid organ transplant section). This is in line

with the BSH guidelines<sup>121</sup> and European Group for Blood and Marrow Transplantation (EBMT) recommendations.<sup>122,123</sup> It is not known how long the use of irradiated blood components following ATG treatment should be continued, but it is considered reasonable to continue while patients are still taking ciclosporin following ATG therapy.

Rarely, potent immunosuppressive (T-cell depleting) agents are used for treatment of immunology patients. An example is the use of ATG for treatment of familial haemophagocytic lymphohistiocytosis.<sup>124</sup> Most centres treating these rare patients utilise irradiated components. Although there is no evidence from the literature, the authors consider this as a prudent practice. For patients receiving potent T-cell depleting serotherapy (e.g. ATG) for inherited immune dysfunction, irradiation will continue until there is evidence of immune reconstitution (will require immunological review).

**Recommendations.** All patients treated with purine analogue drugs (fludarabine, cladribine, bendamustine and pentostatin) should receive irradiated blood components indefinitely (2/C).

**Patients with CLL or other haematological diagnosis treated with alemtuzumab should receive irradiated components (2/C).**

**Patients with aplastic anaemia undergoing treatment with ATG or alemtuzumab should receive irradiated blood components (2/C).**

**Patients receiving ATG or other T-lymphocyte-depleting serotherapy for rare types of immune dysfunction conditions should receive irradiated blood components (2/C).**

**Chimeric antigen receptor T-cell (CAR-T) therapy.** CAR-T therapy is a complex and innovative treatment and it is currently approved in the UK for the treatment of some cases of lymphoma and acute leukaemia. A patient's own T cells are collected and genetically altered to recognise target antigens expressed on the cell surface of specific neoplastic cells.<sup>125</sup> CAR-T therapy can lead to significant immunosuppression.

In addition to the immunosuppression associated with CAR-T administration, the process of development of CAR-T therapy involves autologous lymphocyte collection by apheresis; the apheresis product could theoretically contain viable lymphocytes, which could contaminate the final product and lead to TA-GvHD. Therefore, it is recommended that the guidance for autologous stem cells also be followed for CAR-T cells. It has to be noted that no cases of TA-GvHD secondary to CAR-T cells administration have been reported to SHOT, nor were any cases found in the literature review; it is expected that patients receiving CAR-T therapy will already have other indications for blood component irradiation.

**Recommendations.** Patients (adult and paediatric) undergoing peripheral blood lymphocyte collections for future

CAR-T cell re-infusion should receive irradiated cellular blood components for 7 days prior to and during the harvest, to prevent the collection of viable allogeneic T lymphocytes. Irradiated blood components should continue to be used until 3 months following CAR-T cell infusion unless conditioning, disease or previous treatment determine indefinite duration, e.g. previous diagnosis of HL or previous purine analogue treatment (1/C).

**Aplastic anaemia.** Adult and paediatric patients following the diagnosis of aplastic anaemia are not known to have increased susceptibility for TA-GvHD and no cases have been identified by the literature search or reported to SHOT.

**Recommendation.** For patients with aplastic anaemia, transfusion of irradiated cellular components is not routinely recommended, except for HLA-selected platelets, transfusion of granulocytes, donations from first- or second-degree relatives, or planned relevant treatment (e.g. ATG, alemtuzumab, HSCT) (1/B).

**Acute leukaemia and non-Hodgkin lymphoma (NHL).** Use of irradiated blood components is not routinely recommended for adults or children receiving treatment for acute leukaemia or NHL, except for HLA-selected platelets, granulocytes, donations from first- or second-degree relatives or if patients receive treatment with purine analogues, alemtuzumab or HSCT (1/B).<sup>91</sup> This is consistent with adult and paediatric practice in the UK, with no cases of TA-GvHD reported since 2012. For intermediate forms of lymphoma that show some features of HL, such as grey zone lymphoma, there is no current evidence to suggest that irradiation is required.

**Recommendation.** Use of irradiated components for adult patients or children treated for acute leukaemia or NHL (including CLL unless treated with alemtuzumab) is not routinely recommended except for HLA-selected platelets, transfusion of granulocytes, donations from first- or second-degree relatives, or due to current or previous treatment (2/C).

**Use of irradiated cellular blood components for patients receiving immunosuppressive agents (ATG or alemtuzumab) for non-haematological indication: multiple sclerosis (MS), vasculitis and solid organ transplantation.** Potent immunosuppressive agents are used with increasing frequency for patients with autoimmune conditions or in the context of solid organ transplantation. The writing group reviewed the evidence for irradiation when alemtuzumab is used for treatment of patients with MS, vasculitides and solid organ transplantation with the following conclusions and recommendations.

**Multiple sclerosis (MS)—**Alemtuzumab was licensed as a treatment for active MS in 2013 (EU) and 2014 (USA). Evidence in relation to the level of immunosuppression is based

on the results of Phase III clinical trials<sup>126–128</sup> and subsequent publications<sup>129,130</sup> assessing the incidence of opportunistic and other infections in relation to treatment. Vaccinations are effective at  $\geq 1$  month after each treatment cycle.<sup>131</sup> Overall patients are immunocompetent following alemtuzumab treatment when given according to the published regimes and current protocols for MS (alemtuzumab [12 mg/day], infused intravenously on 5 days at baseline and 3 days at 12 months) and therefore they should not be considered at risk of TA-GvHD.

There are currently no reported cases of TA-GvHD following treatment with alemtuzumab for MS. The summary of product characteristics (SPC) for alemtuzumab (now marketed as Lemtrada® for MS) does not include a recommendation for irradiation of cellular blood components.

**Vasculitis**—Alemtuzumab has been used ‘off label’ for refractory vasculitides and Behçet’s syndrome since 1989 in approximately 250 patients. It is mentioned as a treatment option in the NHS England Behçet’s syndrome treatment pathway. No data are available from randomised controlled trials. Mortality, side-effects, development of opportunistic and other infections as well as autoimmune complications have been published.<sup>132–135</sup> A range of opportunistic infections has been observed after alemtuzumab, but these have not differed in type or frequency from those seen with other immunosuppressive treatments. There has been no obvious increased risk of late infection or increased risk of malignancy and no cases of TA-GvHD have been reported.

**Solid organ transplantation**—GvHD is a rare complication of solid organ transplantation. Most reported cases have been in liver and intestinal transplant recipients, likely reflecting the large lymphoid load within the transplanted organ.

Since 2001 the majority of solid organ transplant recipients have received induction immunosuppression, with either interleukin 2 (IL2) receptor-blocking antibody (basiliximab) or T-cell depleting antibody (ATG or alemtuzumab). The induction dose of ATG is typically 6mg/kg, and a single dose of 30mg of alemtuzumab.

Although the existing recommendation is that alemtuzumab-treated patients should receive irradiated cellular blood components, practice in UK solid organ transplant units is variable. A retrospective review of  $>600$  transfused patients treated with alemtuzumab conditioning for renal transplantation in one centre did not identify any risk of TA-GvHD,<sup>136</sup> despite receiving non-irradiated cellular blood components according to the local practice. Similarly, most USA blood banks do not routinely irradiate blood following treatment with alemtuzumab for solid organ transplantation.<sup>79</sup>

Use of irradiated cellular blood components for solid organ transplanted recipients treated with ATG (either as a pre-transplant conditioning or for treatment of graft rejection) has not been recommended in previous guidelines<sup>91</sup>

and it is not included at the licence indications for Atgam®<sup>137</sup> (commonly used preparation of ATG).

There have been no confirmed cases of TA-GvHD in the UK since routine LD of blood components became standard practice in 1999, while  $>50\,000$  patients have received an organ transplant since then. Accordingly, there is no indication for irradiation of cellular blood components administered to alemtuzumab or ATG-treated solid organ transplant recipients.

**Recommendations.** Use of irradiated cellular blood components is not indicated following treatment with alemtuzumab using the schedule currently recommended for MS or vasculitis (1/B).

Use of irradiated cellular blood components is not indicated for patients undergoing solid organ transplantation who have received alemtuzumab or ATG as induction therapy or for treatment of graft rejection (1/B).

#### Rituximab (anti-CD20)

Use of irradiated components following treatment with rituximab is not recommended<sup>91</sup> and no case of TA-GvHD has been reported in the literature or to SHOT following this treatment (regardless of the patient’s underlying diagnosis).

**Recommendation.** Treatment of patients with rituximab is not an indication for use of irradiated cellular blood components unless this is indicated for a different reason (underlying diagnosis, type of component or previous treatment) (1/B).

#### New immunosuppressive agents

Despite the development and wide usage of new potent immunosuppressive agents, no cases of TA-GvHD have been reported in the literature. The authors are unable to make any recommendation for those agents and advise that manufacturers’ recommendations should be followed.

#### Blood prescription/authorisation and administration issues

It is the responsibility of the clinical team involved with the patient’s care to identify patients at risk of TA-GvHD, to inform the transfusion laboratory, and to request and prescribe/authorise cellular blood components as irradiated. This will facilitate appropriate bedside checks and ensure patients’ specific requirements are met.<sup>138,139</sup>

Laboratory information management systems (LIMS) should be able to hold information regarding patients’ specific requirements and prevent selection of non-irradiated cellular components unless appropriate overrides have been authorised.

For patients under shared care, clinical areas and transfusion laboratories must ensure adequate communication about the requirement for irradiated components.

Patients requiring irradiated components should be informed of the need and the reasons for this.<sup>140</sup> Where possible patients should carry cards to facilitate provision of appropriate components.

**Recommendations.** Where patients require irradiated cellular blood components, components must be requested and clearly prescribed as irradiated (1/C).

Specific requirements, including need for irradiated blood components, must be part of the bedside check prior to administration of all blood components with documentation of checks (1/C).

Clinical areas and transfusion laboratories should agree and implement communication processes to ensure specific requirements and provision of irradiated cellular blood components are met for patients under shared care (1/C).

Patients requiring irradiated cellular blood components should receive appropriate information. Where possible patients should carry cards to facilitate provision of appropriate components (1/C).

## Recommendations for further research

- Is it necessary to provide lifelong irradiated cellular blood components for all patients treated with purine analogues?
- Is it necessary to provide lifelong irradiated cellular blood components for all patients with a history of HL regardless of stage or therapy?
- Further research should be undertaken on the immunological status of neonates and infants following IUT to investigate whether it is necessary to provide irradiated cellular blood components to these recipients.
- Research should continue into methods of pathogen inactivation, which may also reduce the risk of TA-GvHD. These technologies will need validation by blood establishments and wider consultation

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All authors have made a declaration of interests to the BSH and Task Force Chairs which may be viewed on request. Ania Manson has undertaken advisory boards with CSL and Pharming, received speakers' fees from CSL and had educational grants from CSL, Pharming, Takeda and Shire. Dinakantha Kumararatne has received educational grants from CSL Behring and Shire (now Takeda).

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## Review process

Members of the writing group will inform the writing group Chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant Task Force and the literature search will be re-run every 3 years to search systematically for any new evidence that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website ([www.b-s-h.org.uk/guidelines/](http://www.b-s-h.org.uk/guidelines/)).

## Disclaimer

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## Appendix 1

### Major changes since the last guideline

1. In an emergency the provision of red cells or platelets must not be delayed by sourcing irradiated components for patients with the appropriate indication; LD blood or platelets must be sourced rapidly from the blood bank; where non-irradiated components are used in this setting because of urgency this should be recorded and clinical observation made for any (unlikely) evidence of TA-GvHD over the next few weeks. Where possible, older blood should be used (>14 days) unless there are specific indications for using fresher red cells. For neonates and infants, see BSH guidelines for transfusion of fetuses, neonates and older children<sup>40</sup> for a suggested hierarchy of blood component characteristics to use in emergency.
2. Neonates and infants with suspected immunodeficiency syndromes should undergo T-lymphocyte enumeration prior to cardiac surgery wherever possible. If the T-lymphocyte count is >400 cells/ $\mu$ l, of which  $\geq 30\%$  are naive T lymphocytes, there is no need to irradiate red cells or platelets. If it is not possible to undertake T-cell investigations prior to surgery, irradiated cellular blood components should be given until immunological investigations have been undertaken.

3. Adults, and children aged > 2 years without a significant history of infection, referred for elective cardiac surgery for problems associated with DiGeorge syndrome, such as aortic arch anomalies and pulmonary artery stenosis, or in whom DiGeorge anomaly is suspected, do not need to receive irradiated cellular blood components, unless there is a significant history consistent with severe T-lymphocyte-associated immunodeficiency as the risk of TA-GvHD is extremely low.
4. Patients (adult and paediatric) undergoing peripheral blood lymphocyte collections for future CAR-T cell reinfusion should receive irradiated cellular blood components for 7 days prior to and during the harvest, to prevent the collection of viable allogeneic T lymphocytes. Irradiated blood components should continue to be used until 3 months following CAR-T cell infusion unless conditioning, disease or previous treatment determine indefinite duration, e.g. previous diagnosis of HL or previous purine analogue treatment (1/C).
5. Use of irradiated cellular blood component is not indicated following treatment with alemtuzumab at the schedule recommended for multiple sclerosis or vasculitis.
6. Use of irradiated cellular blood components is not indicated for patients undergoing solid organ transplantation who have received alemtuzumab or ATG as induction therapy or for treatment of graft rejection.

## Appendix 2

### Search strategy and results November 2016

#### A. The search strategy requested for this guideline:

##### 1. Transfusion associated graft-versus-host disease (TA-GvHD)

AND

Contributory factors

Prevention

campath-1h or alemtuzumab

Bendamustine

Anti-thymocytic globulin (ATG)

Brentuximab (or anti-CD30)

solid organ (kidney/ pancreas/ liver/ heart/ lung) transplant

transplantation and Induction/ antibody induction/ T cell depletion/ lymphocyte depletion/ thymoglobulin/ Anti-thymocytic globulin (ATG)/ ATGAM/antilymphocytic globulin (ALG)/campath1H/ alemtuzumab/ muromonab-CD3/Orthoclone OKT3  
multiple sclerosis (MS)/ vasculitis/ aplastic anaemia/ DiGeorge/ congenital/primary immunodeficiency

idelalisib/ ibrutinib/ Rituximab/ purine analogues(fludarabine, pentostatin and cladribine)

bone marrow/ peripheral stem cell/allogeneic transplantation/ autologous bone marrow transplantation/ Hodgkin disease, Hodgkin lymphoma

## 2. T-cell depletion

AND

1. Campath 1H or alemtuzumab
2. Brentuximab
3. Bendamustine
4. Anti-thymocytic globulin (ATG)/ ATGAM/ anti-lymphocytic globulin(ALG)
5. Idelalisib, ibrutinib, rituximab
6. Purine analogues (fludarabine, pentostatin and cladribine)
7. Transplantation and combine immunosuppression
  
3. Immune reconstitution post-Hodgkin lymphoma/Hodgkin disease

### B. Details of the searches

#### 1. Search overview for transfusion-associated graft-versus-host disease

##### *Records generated*

Database searched	Date searched	Results
CENTRAL (The Cochrane Library)	21/11/16	6
Issue 10 of 12 2016		0
CDSR (The Cochrane Library)		0
Issue 11 of 12 2016		
DARE (THE Cochrane Library)		
Issue 2 of 4 2015		
(All searched from 2008–)		
MEDLINE (OVID) 2008 to 18/11/16	21/11/16	78
EMBASE (OVID) 2008 to 18/11/16	21/11/16	210
CINAHL (Ebsco) 2008 to Nov 2016	21/11/16	20
Web of Science (SCI-exp & CPCI-S)	21/11/16	91
2008 to Nov 2016		
<b>Total</b>		<b>405</b>
<b>After de-duplication</b>		<b>239</b>
<b>Further duplicates removed during review (9)</b>		<b>230</b>
<b>Exclusions (78)</b>		
Not relevant to clinical question (74)		
No abstract and, from title, not likely to be useful (4)		

##### *Breakdown of remaining results*

Articles included	115
Alternative methods (40)	
Background/diagnosis (8)	
Clinical indications (8)	
Irradiation techniques/effects (29)	
Practice audit (8)	
Reported cases (22)	
Possible articles	37
Possibly of interest (10)	
Possibly relevant based on title only (27)	

*Search terms used.* TA-GvHD or TAGvHD or transfusion-associated graft-versus-host or transfusion-associated graft vs host disease

Searches restricted to English language where available.

#### 2. Search overview for immune reconstitution in Hodgkin disease

##### *Records generated*

Database searched	Date searched	Results
CENTRAL (The Cochrane Library)	28/11/16	2
Issue 10 of 12 2016		0
CDSR (The Cochrane Library)		0
Issue 11 of 12 2016		
DARE (THE Cochrane Library)		
Issue 2 of 4 2015		
(All searched from 2008–)		
MEDLINE (OVID) 2008 to 25/11/16	28/11/16	18
EMBASE (OVID) 2008 to 23/11/16	28/11/16	118
CINAHL (Ebsco) 2008 to Nov 2016	28/11/16	1
Web of Science (SCI-exp & CPCI-S)	28/11/16	24
2008 to 25 Nov 2016		
<b>Total</b>		<b>163</b>
<b>After de-duplication</b>		<b>129</b>
<b>Further duplicates removed during review (2)</b>		<b>127</b>
<b>Exclusions (85)</b>		
Not relevant to clinical question (83)		
No abstract (2)		

##### *Breakdown of remaining results*

Articles included	10
Most relevant (9)	
Rituximab therapy (1)	
Possible articles	32
Allo transplant (23)	
Possibly of interest (9)	

Searches restricted to English language where available.

### Search terms used

1. Hodgkin Disease/
2. (hodgkin\* not non-hodgkin\*).tw.
3. 1 or 2
4. Radiotherapy/
5. radiotherapy.tw.
6. drug therapy/ or chemotherapy, adjuvant/
7. chemotherapy.tw.
8. exp Adrenal Cortex Hormones/
9. (Corticosteroid\* or Prednisolone or Methylprednisolone or Dexamethasone).tw.
10. Bone Marrow Transplantation/
11. transplant\*.tw.
12. exp Biological Therapy/
13. exp Stem Cell Transplantation/
14. ("biologic\* therap\*" or therapy or treatment\*).tw.
15. or/4-14
16. -3 and 15
17. ((recovery or reconstitution or regeneration) adj5 immun\*).tw.
18. -16 and 17
19. limit 18 to (english language and yr="2008 -Current")

### 3. Search overview for T-cell depletion

#### Records generated

Database searched	Date searched	Results
CENTRAL (The Cochrane Library)	22/11/16	45
Issue 10 of 12 2016		0
CDSR (The Cochrane Library)		2
Issue 11 of 12 2016		
DARE (THE Cochrane Library)		
Issue 2 of 4 2015		
(All searched from 2008–)		
MEDLINE (OVID) 2008 to 21/11/16	22/11/16	664
EMBASE (OVID) 2008 to 21/11/16	22/11/16	1823
CINAHL (Ebsco) 2008 to Nov 2016	22/11/16	14
Web of Science (SCI-exp & CPCI-S) 2008 to 22 Nov 2016	22/11/16	384
<b>Total</b>		<b>2932</b>
<b>After de-duplication</b>		<b>2138</b>
<b>Further duplicates removed during review (34)</b>		<b>2104</b>
<b>Exclusions (1980)</b>		
Not relevant to clinical question (1807)		
No abstract (173)		

#### Breakdown of remaining results

Articles included	54
Most relevant (31)	
Allo transplant (23)	
Possible articles	70
Possibly of interest (67)	
Possibly relevant based on title only (3)	

Searches restricted to English language where available

#### Search terms used

- MeSH descriptor: [Lymphocyte Depletion] this term only
- (T-lymphocytes near/2 deplet\*):ti,ab,kw (Word variations have been searched)
- (T-cell near/2 deplet\*):ti,ab,kw (Word variations have been searched)
- #1 or #2 or #3
- alemtuzumab:ti,ab,kw (Word variations have been searched)
- Campath 1H":ti,ab,kw (Word variations have been searched)
- Brentuximab:ti,ab,kw (Word variations have been searched)
- MeSH descriptor: [Bendamustine Hydrochloride] this term only
- Bendamustine:ti,ab,kw (Word variations have been searched)
- MeSH descriptor: [Antilymphocyte Serum] this term only
- (Antithymocytic globulin or antithymocytic serum):ti,ab,kw (Word variations have been searched)
- (antilymphocytic globulin or antilymphocytic serum):ti,ab,kw (Word variations have been searched)
- (Antilymphocyte near/2 (globulin or serum)):ti,ab,kw (Word variations have been searched)
- (ATG or ATGAM or ALG):ti,ab,kw (Word variations have been searched)
- Idelalisib:ti,ab,kw (Word variations have been searched)
- ibrutinib:ti,ab,kw (Word variations have been searched)
- MeSH descriptor: [Rituximab] this term only

- Rituximab:ti,ab,kw (Word variations have been searched)
- (purine analogue\* or purine analog):ti,ab,kw (Word variations have been searched)
- fludarabine:ti,ab,kw (Word variations have been searched)
- MeSH descriptor: [Pentostatin] explode all trees
- pentostatin:ti,ab,kw (Word variations have been searched)
- MeSH descriptor: [Cladribine] explode all trees
- cladribine:ti,ab,kw (Word variations have been searched)
- #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
- MeSH descriptor: [Bone Marrow Transplantation] explode all trees
- transplant\*:ti,ab,kw (Word variations have been searched)
- #26 or #27
- combined immunosuppression:ti,ab,kw (Word variations have been searched)
- #28 and #29
- #25 or #30
- #4 and #31 Publication Year from 2008 to 2016

#### Appendix 3

#### Search updates 2019 for irradiated blood components guideline

#### Overview for transfusion-associated graft-versus-host disease

#### Records generated

Database searched	Date searched	Results
CENTRAL (The Cochrane Library)	30/08/19	11
Issue 8 of 12 2019		4
CDSR (The Cochrane Library)		
Issue 8 of 12 2019		
(Both searched from 2016–)		
MEDLINE (OVID) Nov 2016 to 29/08/19	30/08/19	24
EMBASE (OVID) Nov 2016 to 2019 week 34	30/08/19	67
CINAHL (Ebsco) Nov 2016 to Aug 2019	30/08/19	16
<b>Total</b>		<b>122</b>
<b>After de-duplication</b>		<b>102</b>
<b>Further duplicates removed during review (4)</b>		<b>98</b>
<b>Exclusions (70)</b>		
Not relevant to clinical question (65)		
Too early (4)		
No abstract and, from title, not likely to be useful (1)		

#### Breakdown of remaining results

Articles included	28
Alternative methods (10)	
Irradiation techniques/effects (4)	
Practice audit (5)	
Reported cases (9)	

## Overview for immune reconstitution in Hodgkin disease

### Records generated

Database searched	Date searched	Results
CENTRAL (The Cochrane Library)	30/08/19	3
Issue 8 of 12 2019		0
CDSR (The Cochrane Library)		
Issue 8 of 12 2019		
(Both searched from Nov 2016–)		
MEDLINE (OVID) Nov 2016 to 29/08/19	30/08/19	4
EMBASE (OVID) Nov 2016 to 2019 week 34	30/08/19	21
CINAHL (Ebsco) Nov 2016 to Aug 2019	30/08/19	5
<b>Total</b>		<b>33</b>
<b>After de-duplication</b>		<b>30</b>
<b>Exclusions (25)</b>		<b>5</b>
Not relevant to clinical question (22)		
Too early (3)		

### Breakdown of remaining results

Articles included	5
Most relevant (5)	

## Overview for T-cell depletion

### Records generated

Database searched	Date searched	Results
CENTRAL (The Cochrane Library)	30/08/19	33
Issue 8 of 12 2019		0
CDSR (The Cochrane Library)		
Issue 8 of 12 2019		
(Both searched from Nov 2016–)		
MEDLINE (OVID) Nov 2016 to 29/08/19	30/08/19	137
EMBASE (OVID) Nov 2016 to 2019 week 34	30/08/19	332
CINAHL (Ebsco) Nov 2016 to Aug 2019	30/08/19	9
<b>Total</b>		<b>511</b>
<b>After de-duplication</b>		<b>465</b>
<b>Further duplicates removed during review (2)</b>		<b>463</b>
<b>Exclusions (437)</b>		<b>26</b>
Not relevant to clinical question (412)		
Too early (8)		
No abstract (17)		

### Breakdown of remaining results

Articles included	26
Non-transplant treatments (7)	
HSCT (19)	

**GUIDELINE**

# Haematological management of major haemorrhage: a British Society for Haematology Guideline

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## METHODOLOGY

This updated guideline<sup>1</sup> was compiled by a writing group selected to be representative of UK haematology/transfusion experts, according to the British Society for Haematology (BSH) process at [<https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf>].<sup>2</sup> An updated search (PubMed and Embase) for articles (in English, only human studies) published from July 2014 up to March 2020 was undertaken by the BSH information specialist using the terms 'bleeding' and 'haemorrhage' combined with 'management' and 'trials'. Systematic reviews were identified<sup>3</sup> and cross-checked by searching the National Health Service Blood and Transplant Systematic Review Initiative Transfusion Evidence Library. A total of 530 citations were screened (L.G., S.J.S.) of which, 365 citations were excluded as they were narrative reviews, case-reports, case series

(without comparator groups), and studies of anticoagulation reversal; 65 citations were trial protocols; and four citations were duplicates. A total of 96 citations were included and reviewed by the members of the writing group. We reviewed a recent clinical practice guideline from the European Society of Intensive Care Medicine,<sup>4</sup> and recent UK Serious Hazards of Transfusion (SHOT) haemovigilance reports.<sup>5</sup> The writing group focused on systematic reviews and randomised controlled trials (RCTs) to formulate recommendations, although recognising that the literature underpinning laboratory and organisational aspects would likely be based on observational studies and descriptions of practice, rather than interventional trials. In areas where the evidence base was limited, the writing group presented pragmatic guidance. The following areas were considered beyond the scope of this guideline: techniques for resuscitation, surgical, radiological and endoscopic interventions to control

and monitor bleeding, the use of crystalloids and colloids for fluid resuscitation. Recommendations on thromboprophylaxis were also not considered in this guideline, but the authors recognised the importance of this topic, noting that trauma patients have high rate of hospital-acquired venous thromboembolism. The scope of this guideline included the emerging practice of pre-hospital transfusion and emergency transfusion in the context of mass casualty events (MCEs).

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations (<http://www.gradeworkinggroup.org>).<sup>6</sup> The guideline was reviewed by the BSH Guidelines Committee Transfusion Task Force, and Thrombosis & Haemostasis Task Force, and placed on the members section of the BSH website for comments. Readers are referred to linked BSH guidelines on transfusion support in children and the use of viscoelastic haemostatic assays (VHAs).<sup>7,8</sup>

## Background

Major haemorrhage is a clinical emergency that results in morbidity and mortality: practice guidance is important to reduce these risks. Delayed recognition of bleeding continues to be one factor for adverse outcomes in the management of major haemorrhage, as described in a recent SHOT report.<sup>5</sup> This guideline mandates a multidisciplinary approach involving the close working between laboratories, and clinical departments enabling a timely, targeted approach to transfusion support. The following sections consider the evidence for practice by components, major haemorrhage protocols (MHPs) and specific clinical settings.

## Definitions

There is a spectrum of severity and presentation of major haemorrhage, which at one extreme is seen as acute major blood loss associated with haemodynamic instability and risk of shock, but also those in whom the bleeding appears controlled but still require 'massive' transfusion. Variable definitions of major haemorrhage continue to be used in the literature based on volumes of blood loss, or volume of blood transfused over a period.<sup>9</sup> These are retrospective definitions, arguably arbitrary, and difficult to apply in the acute situation. The current trend is towards the use of a more anticipatory or dynamic definition for major haemorrhage, based on the clinical status of the patients, their physiology and response to resuscitation therapy,<sup>10</sup> e.g., heart rate >110 beats/min and/or systolic blood pressure <90 mm Hg. It is important to emphasise that these physiological changes may be masked in some patient groups, e.g., the elderly or pregnancy,<sup>11–13</sup> potentially delaying diagnosis. The overall clinical and organisational context determines the transfusion thresholds, targets and testing. Further details of the organisational aspects are in the Supplement.

## A. Use of blood components

### Red blood cells (RBCs)

Haemoglobin concentration (Hb) is a surrogate measure of oxygen transfer to tissues. It is unlikely that a single universal target can be defined for all patients even with similar causes of major haemorrhage. This guideline makes general recommendations for RBC transfusion in patients with major haemorrhage, at a level to provide critical life-saving support, based on clinical judgement of the severity of bleeding, and informed by the findings of RCTs as discussed later.<sup>14–16</sup> Although RBC transfusion is a potential lifesaving treatment, there are risks,<sup>5</sup> and unnecessary exposure to excessive RBC transfusion should be minimised.

Repeated measurement of Hb through a central laboratory in a patient receiving crystalloids and fluids may not provide sufficiently timely or valid measures of RBC requirements in the face of major bleeding. RBC transfusion is usually required when 30%–40% of blood volume is lost (1500 ml in a 70 kg male). More than 40% blood volume loss (1500–2000 ml) is life threatening and requires immediate transfusion.<sup>17</sup> The rates of RBC (and plasma) transfusion is guided by the rate of blood loss and the degree of haemodynamic compromise, aiming at maintain critical perfusion and tissue oxygenation.<sup>18</sup> Haematologically, the purpose of using RBCs is to maintain Hb at a level high enough to support adequate oxygen delivery to the tissues (pragmatic target range 60–100 g/l in the face of major bleeding<sup>19,20</sup>). Blood should be transfused through a warming device to minimise the development of hypothermia. Rapid infusion over 5–10 min may be required, which may be facilitated using appropriate infusion devices designed for the purpose. Once bleeding is controlled, there is no indication to restore Hb to physiological levels.

### Fresh Frozen Plasma (FFP)

Plasma provides a balanced source of all coagulant factors and volume expansion. In vitro data show it may have additional actions, including a protective effect on the endothelium.<sup>21</sup> FFP has been used as the component of choice to manage the coagulopathy of bleeding, although it is not the optimal therapy for low fibrinogen. While data support the role of early empirical use of plasma in major traumatic bleeding, in non-trauma settings the effect of high transfusion ratios of RBC and FFP on mortality is uncertain due to lack of clinical trials to assess its utility. Differential effects on mortality have been reported by ratio of RBC and FFP depending on clinical setting.<sup>22,23</sup> In the absence of any tests of coagulation, low ratios of empirical RBC to FFP (defined pragmatically as >2:1), with a marked excess of RBC units, should be avoided in major bleeding. After initial empirical transfusion of FFP, further plasma transfusion should be guided by serial results of coagulation tests and/or near-patient tests, which may include VHAs (for information on thresholds see BSH guideline<sup>8</sup>).

We suggest a general weight-adjusted recommended dose of FFP of 15–20 ml/kg, although recognising that attempting to correct coagulopathy in the face of major bleeding is challenging, and that large-volume transfusions of FFP would be required for above average body weights.<sup>24</sup>

## Fibrinogen replacement

Hypofibrinogenaemia is common in major haemorrhage,<sup>25,26</sup> but there is very limited evidence to define critical levels of fibrinogen on which to base decisions to administer fibrinogen, or the role of early empirical supplementation. In patients with critical hypofibrinogenaemia (<1 g/l). FFP contains insufficient fibrinogen to achieve the rapid rise in levels required to support haemostasis, and supplementation in the form of cryoprecipitate or fibrinogen concentrate should be offered.<sup>27</sup>

A number of RCTs of fibrinogen supplementation have been reported in bleeding after cardiac surgery, with inconsistent results.<sup>28,29</sup> Clinical data do not support one form of concentrated fibrinogen replacement over the other (i.e. cryoprecipitate or fibrinogen concentrate) and there is a paucity of cost-effectiveness comparative research between fibrinogen concentrate and cryoprecipitate.<sup>30,31</sup> A RCT comparing the efficacy of fibrinogen concentrate with cryoprecipitate in patients undergoing cardiac surgery who developed clinically significant bleeding and hypofibrinogenaemia reported that fibrinogen concentrate was non-inferior (but not superior) to cryoprecipitate with regard to number of blood components transfused in a 24-h period post-bypass.<sup>32</sup>

Cryoprecipitate is the standard concentrated source of fibrinogen in the UK. Two five-donor pools may increase fibrinogen in an adult by ~1 g/l, although recognising the limitation of a non-weight adjusted dose and that the (sustained) increase in fibrinogen in patients with bleeding may be less.<sup>33,34</sup> Fibrinogen concentrate may also be considered as an alternative for management of bleeding in patients: 4–5 g of fibrinogen concentrate may increase fibrinogen in an adult by ~1 g/l.<sup>32,35,36</sup>

## Platelets

A measure of platelet count does not provide an assessment of platelet dysfunction seen in patients with shock and hypotension. Significant thrombocytopenia is considered a late event in major haemorrhage, typically seen after a loss of at least 1.5 blood volumes.<sup>37</sup> As a pragmatic approach in cases of major bleeding, it is suggested that platelet transfusion should be given to maintain the platelet count at  $>50 \times 10^9/l$ , although higher thresholds may be indicated in patients with intracranial/spinal bleeding, or in actively bleeding patients with falling platelet counts.

Patients presenting with major bleeding may be on antiplatelet medications. Platelet transfusions have been considered a safe and potentially effective intervention in major haemorrhage in these patients. The results of the PATCH trial demonstrated that platelet transfusion increased the risk of

death in patients receiving antiplatelet therapy (mainly aspirin) and presenting with acute spontaneous intracerebral haemorrhage (stroke),<sup>38</sup> although methodological limitations have been described.<sup>39</sup> It is unclear how these trial results should be applied to patients taking other types of antiplatelet agents, or those presenting with traumatic intracerebral haemorrhage or other types of major haemorrhage. Some data also support the cautious use of platelet transfusions in patients on antiplatelet therapy with gastrointestinal bleeding.<sup>40</sup>

## B. Major haemorrhage protocols and transfusion testing

Establishment of MHPs form the basis of standardising transfusion support for bleeding patients. A MHP is a site-specific protocol that outlines the processes, people and blood components required to treat a patient who is bleeding. The MHP is a treatment algorithm that pre-specifies the order and ratios of how different blood components (or products) can be delivered to treat the bleeding in different clinical contexts, and are widely available in NHS hospitals.<sup>5,41</sup> MHPs enable rapid provision of blood components to a bleeding patient through agreed communication channels between clinical staff and the transfusion laboratory without escalation for approval.<sup>1,42</sup> The local MHP must identify the location of emergency blood components (RBCs, plasma and platelets) and provide clear instructions on how to access these during a major bleeding event.

While it seems intuitive that rapid and early transfusion of blood components in bleeding patients will improve survival, the impact of protocolised management (through use of MHP) on outcomes of bleeding patients and healthcare resources, has not been fully established, although there may be some evidence of clinical benefit.<sup>42</sup> Irrespective of the levels of evidence for transfusion support, the management principles of major haemorrhage are those of any medical emergency, where communication and co-ordination are key to optimising the delivery of a safe and effective transfusion response and enabling better use of resources.

The MHP should state the details required to activate the transfusion emergency response by providing appropriate contact numbers (through the switchboard) including the terminology for alerts that should be distinct and easily identifiable. Communication with the laboratory should be timely and targeted. A structured approach to communication between the clinical and laboratory areas is recommended (see Table S1).

Red blood cells should be readily available for life-threatening bleeding, including prompt access to group O RBCs as emergency stock. Where appropriate, NHS organisations and laboratories should risk assess the need for having pre-thawed plasma available to speed up plasma provision during major haemorrhage, particularly for trauma patients. Blood may be provided remotely to clinical areas through remote blood fridges or validated blood-boxes, to facilitate timely delivery of RBCs, which should be supported by a quality management system and governance

framework. Accurate documentation of blood components transfused is necessary to comply with the legal requirement for full traceability.<sup>43</sup> Laboratories should be informed when patients are moved rapidly between departments and hospitals (e.g. theatre, radiology, or transfer to another hospital). Deactivation of the MHP is also important, as delays in standing down the MHP will lead to blood wastage and prevent resumption of other laboratory services.

Baseline blood samples for an ABO group and antibody screen should be taken as early as possible, and ideally before the start of the first transfusion. Accurate patient and sample identification are fundamental to providing safe transfusion, to avoid the accidental administration of ABO incompatible RBCs. Wrong blood in tube continues to be the commonest near miss events reported to SHOT, occurring more frequently in the emergency setting.<sup>44,45</sup> All patients receiving a blood transfusion must wear a patient identification wristband. Further details on laboratory aspects are provided in supplementary pages.

## C. Tranexamic Acid (TXA)

A meta-analysis of 216 trials (125 550 patients) found no evidence to support an overall increased risk of thromboembolic complications with use of TXA, supporting the general safety of this drug.<sup>46</sup> Large, pragmatic RCTs have compared TXA with placebo for the management of bleeding, establishing the benefits of TXA, with reductions in mortality in trauma and postpartum haemorrhage (PPH).<sup>47-49</sup> A meta-analysis of two trials showed that immediate treatment improved survival by >70% and thereafter, the survival benefit decreased by 10% for every 15 min of treatment delay until 3 h, after which there was no benefit.<sup>50</sup> In an effort to give TXA as early as possible, pre-hospital use is now supported by ambulance services in the UK. Current research is evaluating alternative doses and formulations including intramuscular TXA,<sup>51,52</sup> which appears more feasible for timely administration in emergencies.

## D. Other haemostatic agents

Different haemostatic agents have been evaluated for benefit in major haemorrhage, including prothrombin complex concentrate (PCC), aprotinin and recombinant activated factor VII (rVIIa). Calcium levels should be monitored and supplemented as appropriate.

### Prothrombin complex concentrate

Systematic reviews have identified few RCTs on the use of PCC versus FFP in adult patients with major bleeding.<sup>31,53</sup> While the use of PCC is safe and recommended for urgent reversal of the effect of vitamin K antagonists,<sup>54</sup> there is currently limited evidence to support its use in the management of major haemorrhage not related to vitamin K antagonists.

Two pilot RCTs in cardiac surgery have recently been published; both were underpowered for clinical outcomes, but no safety concerns were observed.<sup>55,56</sup>

### Aprotinin

Aprotinin is a serine protease inhibitor with multiple effects, including antithrombotic, antifibrinolytic and anti-inflammatory actions. Although efficacious in reducing bleeding in cardiac surgery, its license was suspended in 2007 following concerns about its safety, but it was later reinstated following a re-evaluation,<sup>57</sup> with a revised indication applies for the prevention of bleeding in adult patients at high risk of major blood loss undergoing isolated cardiopulmonary bypass graft surgery. Aprotinin is a bovine protein and there is a risk of allergy.

### Desmopressin

Randomised controlled trials have assessed the role of desmopressin outside inherited bleeding disorders, including the perioperative setting and cardiac surgery.<sup>58,59</sup> Desmopressin increases the release of high molecular weight von Willebrand factor from the endothelium and has been considered as an alternative to platelet transfusions. Desmopressin has a good safety profile, although further data continue to be required including in older patients or those with cardiovascular risk factors.<sup>60,61</sup> Robust evidence of the clinical effectiveness of desmopressin (and/or with TXA) is not available and further studies in major bleeding are required.

### Recombinant activated factor VII

Recombinant activated factor VII has been used widely 'off label' in bleeding after major surgery or trauma, but reviews of trial data have shown only modest reductions in total blood loss or transfusion requirements, with no consistent clinical benefit including mortality,<sup>62</sup> but an increased risk of arterial thromboembolism.<sup>63</sup>

## E. Coagulation testing and cell salvage

### Haemostatic testing and monitoring

The coagulopathy of bleeding is related to blood loss, consumption of coagulation factors, activation of fibrinolysis and haemodilution when resuscitation fluids are used.<sup>64</sup> Hypothermia, acidosis and hypocalcaemia will further worsen coagulation. Coagulopathy is associated with worse outcomes, and it is important to attempt its correction as part of the initial haemostatic resuscitation. We recommend performing coagulation tests and platelet counts every 30–60 min, depending on the severity of blood loss, until bleeding ceases. There is a need

to regularly undertake and improve rapid turnaround times for coagulation results in a major haemorrhage setting and we suggest these times should be regularly audited.<sup>65</sup>

It is important to establish early in the course of bleeding whether a patient has taken anticoagulant or antiplatelet agents, as these medications will further exacerbate bleeding. Mortality rates are high in patients with major bleeding on oral anticoagulants. Detection of oral anticoagulants or antiplatelet agents are challenging by routine testing, although types of rapid tests may be applied.<sup>66,67</sup> A reliable medication history remains key.

The method of assessing coagulation varies between institutions, some relying on standard coagulation screens others on near patient VHAs, including thromboelastography or rotational thromboelastometry (for thresholds for VHA, please refer to guidelines<sup>8</sup>). Repeated testing, with comparisons made between longitudinal tests, provides more information than a stand-alone VHA tests to aid the decision for plasma and other component transfusion.<sup>65</sup> Point-of-care whole blood coagulation tests for the prothrombin time are available, but they may be dependent on the haematocrit and thus not provide an accurate assessment in a bleeding patient. The Clauss fibrinogen assay should be used in preference to a fibrinogen estimated from the optical change in the prothrombin time (PT-derived fibrinogen), as some of these methods give falsely high functional levels.<sup>68</sup>

Data to evaluate the impact of the use of VHAs on clinical outcomes in the bleeding patient<sup>8,69–71</sup> remain limited outside cardiac surgery and trauma.<sup>35,72</sup> VHA testing is less sensitive to measuring fibrinolytic activation in trauma and should not be used to withhold the use of TXA.<sup>73</sup>

## Cell salvage

Cell salvage can produce a rapid re-supply of RBCs, with 250 ml of washed salvaged RBCs considered to be equivalent to 1 RBC unit, but requires a 24-h service to cover all emergencies.<sup>74–76</sup> In a RCT of >3000 women at risk of PPH, the use of cell salvage did not reduce the rate of blood transfusion, and was reported not to be cost-effective (in this context, cell salvage may also be associated with risks of increased maternal exposure to fetal blood in RhD-negative mothers).<sup>77</sup> Further studies continue to be needed in other clinical setting to demonstrate the (cost-) effectiveness of cell salvage in the management of major bleeding. Cell salvage in emergency trauma surgery may reduce overall transfusion needs, but without an impact on overall mortality and costs.<sup>78</sup>

## F. Specific clinical settings including emergency planning

### Obstetric haemorrhage

A PPH is usually defined as an estimated blood loss of >1000 ml during a Caesarean section, or >500 ml after a vaginal birth.<sup>13</sup>

Severe PPH of >1500 ml remains a leading cause of early maternal death and morbidity, and obstetric management should consider prevention and management including uterotronics for uterine atony and surgery.<sup>13,79,80</sup> There are limited RCT data on optimal strategies for RBC transfusion in obstetric bleeding,<sup>16,81</sup> and we suggest following general recommendations.

Overall, a coagulopathy develops only in a minority of women with PPH,<sup>82</sup> but is difficult to predict, and needs urgent identification and management to prevent bleeding becoming overwhelming. There is evidence that patterns of haemostatic responses differ by cause of bleeding in PPH.<sup>83</sup> The cut-off thresholds for defining an abnormal PT/activated partial thromboplastin time (APTT) are typically based on non-pregnant individuals and do not take into consideration the rise in clotting factors seen during pregnancy and therefore a mildly elevated PT or APTT, should it develop, can represent a more significant haemostatic deficit during PPH. Serial monitoring of coagulation tests is recommended. The evidence on the optimal ratios of RBCs to plasma in PPH remains unknown, and further studies are needed.

Fibrinogen levels increase during pregnancy (range of 4–6 g/l at delivery vs. 2–4 g/l when non-pregnant). A low fibrinogen level during PPH is an important predictor of the severity of PPH and poor clinical outcome.<sup>84,85</sup> RCTs do not support the early unselected use of fibrinogen concentrate replacement therapy,<sup>86,87</sup> and administering fibrinogen supplementation to women with PPH who have fibrinogen levels of >2 g/l is unlikely to have added benefit.<sup>88</sup> A recent pilot cluster RCT in severe PPH highlighted practical challenges around the early delivery of cryoprecipitate in PPH, and further trials are required to evaluate clinical outcomes.<sup>89</sup>

A quality improvement programme has described the role of a 'bundle of care' in PPH management (measurements of blood loss after delivery, escalated care to senior staff, timely VHA point-of-care guided fibrinogen concentration, and risk assessments) to successfully reduce transfusion requirements.<sup>90</sup>

The WOMAN trial showed that TXA reduces bleeding deaths and need for surgery in women with PPH.<sup>91</sup> However, prophylactic use of TXA did not show any benefit in a large study of women delivering vaginally who were randomised to 1 g TXA versus placebo in addition to oxytocin after delivery.<sup>92</sup> In both studies there were no increased rates of thrombosis.

### Gastrointestinal haemorrhage

A common indication for transfusion is acute gastrointestinal bleeding.<sup>93</sup> The initial management of gastrointestinal bleeding involves fluid and transfusion resuscitation with pharmacological therapies and timely access to endoscopy or definitive interventional procedures.

Red blood cell transfusion policies in the haemodynamically stable patient with acute gastrointestinal bleeding have been defined by RCTs including a trial that reported a higher 6-week survival and lower re-bleeding rate in patients allocated to a restrictive threshold for RBC transfusion at Hb of 70 g/l (patients

with exsanguinating bleeding were not eligible).<sup>14,16,94</sup> Portal pressures were reported to be increased significantly in patients with acute variceal bleeding allocated to the liberal transfusion group. A meta-analysis across all trials reported a significant reduction in all-cause mortality and re-bleeding with restrictive transfusion practices, with no increase in ischaemic events.<sup>6,15</sup>

There are limited prospective studies characterising changes in coagulopathy or thrombocytopenia in gastrointestinal bleeding. In this patient population, especially those with liver disease and cirrhosis, rapid changes to vascular pressures are not desired, and there are concerns about the use of excessive plasma transfusions to achieve arbitrary reductions in PT.<sup>95</sup> Recent retrospective studies have described an association between use of FFP with adverse clinical outcomes, and with use of platelets in patients with gastrointestinal bleeding taking antiplatelet agents.<sup>40,96</sup> The results of a pragmatic trial of TXA in patients with acute gastrointestinal bleeding reported an increased risk of venous thrombosis and seizures.<sup>97</sup> Reasons for this result could be due to the dose and schedule for TXA (given over 24 h), and that hospital presentation in these patients may occur many hours after the onset of bleeding, missing the period where there is excess fibrinolytic activation. Patients with gastrointestinal bleeding are typically older than trauma patients and have different comorbidities including liver disease.

## Trauma including pre-hospital management

The mortality rate after major haemorrhage in trauma is high unless actively managed. Transfusion support, as part of 'Damage Control Resuscitation' (DCR), is now closely integrated with all other aspects of resuscitation including haemorrhage control and surgery. Early and pre-hospital use of TXA has been discussed earlier. Time to initial transfusion is critical in trauma.<sup>98</sup> Early pre-hospital transfusion, before patients arrive to hospital, may improve survival, although the evidence is inconclusive and patterns of blood component use are variable.<sup>99–101</sup> More recently, the RePHILL trial did not show that pre-hospital RBC–LyoPlas resuscitation was superior to saline (0.9% sodium chloride) for adult patients with trauma-related haemorrhagic shock.<sup>102</sup> The trial had limitations including the composite primary outcome and wide confidence intervals for results. Two other RCTs reported on the effect of pre-hospital plasma transfusion on patient outcomes, including mortality, with contrasting results, one cluster trial reporting that pre-hospital plasma use led to 30-day mortality that was 10% lower compared to the standard-care group,<sup>103</sup> while the other individual patient randomised trial found no difference.<sup>104</sup> The differing results may be explained by factors including different transport times and type of injury.<sup>105,106</sup>

The use of RBCs in trauma follows the general principles of shock mitigation and support of Hb. The updated European Guidelines<sup>4,17</sup> recommend a target Hb of 70–90 g/l based on data extrapolated from the TRICC study, which retrospectively analysed a subgroup of trauma patients.<sup>107,108</sup> The RePHILL study showed that despite significant injury

few patients (6%) receiving saline had a Hb of <80 g/l on arrival at hospital.<sup>99</sup> The average age of patients with traumatic major bleeding is increasing,<sup>109</sup> and more patients aged >60 years are being seen alongside younger patients. Some older patients have comorbidities including cardiac disease, which may affect the selection of Hb thresholds for RBC transfusion in major bleeding due to trauma.<sup>16,110</sup>

A significant proportion of trauma patients with major bleeding present early with coagulopathy, typically defined by abnormalities of PT,<sup>111</sup> which is associated with increased mortality. Early empirical plasma transfusion has been advocated to manage coagulopathy and prevent deterioration of coagulation, although methodological limitations, including survivorship bias, have been recognised in many earlier studies.<sup>3,112</sup> The PROPPR trial<sup>113</sup> reported no difference in overall survival between early administration of plasma, platelets and RBCs in a 1:1:1 ratio compared to 1:1:2 ratio; however, more patients in the 1:1:1 group achieved 'anatomic' haemostasis and fewer experienced death due to exsanguination by 24 h, although the results of the post hoc analyses has been challenged.<sup>3,114</sup> A smaller trial compared fixed high-dose ratios (including platelets) against laboratory testing in trauma, and established feasibility but demonstrated wastage of blood.<sup>115</sup> Overall, we recommend that plasma and RBCs are given initially in a 1:1 ratio (and not less than 1:2) in major traumatic bleeding, until bleeding is under control and the results of coagulation tests are available to guide further transfusion. The iTACTIC RCT in trauma bleeding patients tested whether augmenting MHPs with VHA versus Conventional Coagulation Tests, would reduce mortality or massive transfusion at 24 h; results showed no difference in overall outcomes between the two groups.<sup>116</sup> The thresholds for the VHA parameters used for viscoelastic tests in this trial in trauma are reproduced in a supplementary table.

Many patients with trauma have levels of fibrinogen at hospital admission around 1 g/l, which may rapidly fall further in the event of on-going blood loss.<sup>117</sup> The CRYOSTAT-2 trial is evaluating the effects of early empirical high-dose cryoprecipitate in adult patients with major trauma haemorrhage requiring MHP activation versus standard of care.<sup>118</sup>

The management of patients with traumatic brain injury (TBI) is distinct from general trauma, that may include (small volume) bleeding or re-bleeding occurring in a critical site. However, many patients with TBI have co-existing general injuries and may present with major bleeding. Optimal transfusion support in TBI is poorly defined. A factorial RCT in TBI reported that neither erythropoietin nor transfusions to maintain Hb concentration above 100 g/l resulted in improved long-term functional outcomes, and liberal transfusion threshold were associated with more adverse events.<sup>119</sup> By contrast a pilot trial that randomised patients with TBI to a restrictive (Hb threshold 70 g/l) versus liberal (Hb 90 g/l) transfusion strategy, reported higher hospital mortality in the restrictive group.<sup>16,120</sup> The presence of coagulopathy in TBI is associated with more severe injuries and increased morbidity and mortality<sup>121</sup> and early coagulation testing is advised.

The utility of antifibrinolytics in trauma is defined by the CRASH-2 trial,<sup>47</sup> and trauma induces a massive fibrinolytic

activation, the extent of which relates to the degree of injury; crucially, the benefits of TXA are not restricted to patients with only the more severe injuries, and TXA is effective in minor bleeding across all ages (patients with low baseline risk of death).<sup>122</sup> Strategies for TXA use need to recognise that women may be less likely to be treated with TXA.<sup>123</sup> The CRASH-3 trial (subgroup analyses) in adults with TBI (intracranial bleeding on computed tomography [CT] scan, and no major extracranial bleeding), reported that treatment with TXA reduced head injury-related death in patients with mild-to-moderate head injury.<sup>49</sup> A further RCT evaluated different dosing regimens for pre-hospital TXA in TBI, reporting no overall benefits for functional neurological outcomes at 6 months.<sup>124</sup> The role of TXA in other contexts, such as sub-arachnoid haemorrhage and non-traumatic intracranial bleeding is not clearly established by randomised trials.<sup>125,126</sup>

Different blood products continue to undergo evaluation in clinical studies, particularly in trauma. Lyophilised plasma offers logistic advantages but requires reconstitution. There may be human factor advantages of administering whole blood over separated blood components, but this remains an area of active research to establish effectiveness.<sup>127-129</sup> Cold-stored low-titre type O whole blood is under investigation in the UK and has a shorter shelf life (14–21 days) than RBCs in optimal additive solutions.<sup>130</sup> Finally, extending the use of blood for major traumatic haemorrhage into the pre-hospital environment may seem clinically intuitive,<sup>131</sup> but has significant implications for transfusion laboratory services at a local and national level.<sup>131</sup> Such challenges include the demand for use of 'universal' blood group components, the potential for wastage, and the need for regulatory compliance and associated workload.<sup>132</sup> Further information on the selection of blood for pre-hospital transfusion and transferring of blood between hospitals is provided in the Supplement.

## Surgery

Major bleeding in the setting of surgery is generally managed in theatres rather than emergency departments, with support staff on-site including surgeons and radiology, and timely access to laboratory coagulation monitoring, which would inform the need for further blood components in addition to RBCs. In the absence of coagulation testing, an ideal ratio of RBCs to FFP, has not been defined due to lack of RCTs.<sup>23</sup> A large observational study in cardiac surgery patients assessed the impact of different FFP to RBC ratios in patients who had received massive transfusion (defined as ≥8 RBC units): patients with a high FFP:RBC ratio (>1:1) had improved 30-day survival when compared with those with a low ratio (<1:2), and high transfusion ratios appeared to be associated with fewer complications.<sup>133</sup>

Evidence that TXA reduces blood transfusion needs in surgery has been available for many years,<sup>134</sup> including the recent POISE-3 trial, which reported a significantly lower incidence of a composite bleeding outcome in non-cardiac surgery patients receiving TXA.<sup>135</sup> Information on doses of TXA as prophylaxis prior to surgery with anticipated moderate blood loss

is also provided in the National Institute for Health and Care Excellence transfusion guidelines; higher doses have no greater haemostatic effect and may be associated with seizures.<sup>136,137</sup>

## Emergency planning and mass casualty events

National emergency planning requires healthcare organisations to assess that they can deal with incidents while maintaining critical services. Organisational preparation aims to ensure an overall co-ordinated approach together that includes a good transfusion response. Many events can challenge transfusion services, including MCEs, and pandemics.<sup>138</sup> As part of contingency planning for any national blood shortage, every hospital should have access to the national guidance and triage tool for cellular components.<sup>139</sup> Hospital should also have established emergency blood management arrangements, or equivalent arrangements such as an independent multidisciplinary clinical triage team to provide further support in the context of severe blood shortage.<sup>140,141</sup> This should include a mechanism for making decisions on an individual basis, considering factors such as comorbidity, potential for control of bleeding, reversal of the underlying cause and competing demands for available blood components. In mass casualty events, all injured patients should receive tranexamic acid as soon as possible, which might be provided more feasibly as an IM injection as part of triage.

The aim of transfusion support during MCEs is to supply sufficient prompt blood components and diagnostic services, whilst maintaining support to other patients not involved in the event.<sup>142</sup> Identification of patients in need of emergency blood transfusion is a key priority of triage. Typically, the number of patients requiring massive transfusion following MCEs is low, but this cannot be predicted.<sup>140</sup> Evidence suggests an estimate of 2–4 RBC units per patient for all hospitalised casualties admitted with bleeding,<sup>143,144</sup> although the total may be increased with additional haemostatic components for those severely injured admitted to Major Trauma Centres. Consideration should be given to transfusion triage to identify those needing activation of MHPs, so that pre-agreed numbers of RBCs and plasma can be issued to patients during MCE so that overall blood supply can be controlled optimally in this setting. Most blood components are initially ordered and used within the first 6 h, although some patients may have an ongoing demand for blood over days, especially where repeat surgery may be necessary.<sup>145-147</sup> The main risk during MCEs is assumed to be the accidental use of ABO incompatible blood, and policies described earlier should be followed.

## G. Audit and Quality Management Education (refer to Supplement)

Review and audit of major haemorrhage management is essential to assess timeliness of providing blood to bleeding patients, patient outcome and overall blood component use and wastage, e.g., comparing practices to guidelines and

outcomes.<sup>20</sup> Where adverse incidents occur, they should be investigated locally, and reported externally to SHOT haemovigilance scheme as required. Staffing levels have been recognised as a risk factor for adverse events, and laboratory managers should consider the acceptable staffing resources required for MHP provision and have a clear staffing capacity plan in place, with escalation routes to management of potential risks associated with staff shortages.<sup>148,149</sup> Training and competency assessment, and annual drills of MHP systems including mechanisms for communication to laboratories and responses by laboratories provide an important means of review. Following MHP events, the teams should hold a de-brief, to address learning points from the event, including emotional support for staff, as required.<sup>150,151</sup>

## H. Conclusions and future research

The major risks in emergency settings of bleeding remain delays in identification of the bleed, activation of MHP and timely provision of blood components. The evidence and practice recommendations in this guideline emphasise the need for protocols that are increasingly targeted for different clinical contexts of major bleeding. A single universal or common approach to the management of all types of bleeding patients is not optimal. There is a need to conduct research on transfusion strategies for bleeding patients other than due to trauma (obstetrics, gastrointestinal, surgery), as well as to better understand the efficacy, safety and cost effectiveness of different haemostatic agents and cell salvage to manage major bleeding.

Organisational oversight by the Hospital Transfusion Committee and Patient Blood Management teams is integral for audit, governance, and growth of effective and safe transfusion support in emergencies, and implementation of a MHP.<sup>152</sup> An integrated electronic pathway from the Blood Service operator to the hospitals will further enhance the transfusion response during emergencies making it simpler, safer, and more resilient. The design and ongoing development of the MHP should be considered a dynamic process to allow for future evidence and developments in components/products, policy, and practice.<sup>153,154</sup>

## RECOMMENDATIONS

### General recommendations

- Hospitals must have local MHPs in relevant clinical areas that includes a clear mechanism for contacting all relevant team members and support staff. (2C)
- Clinical staff involved in frontline care must be trained to recognise major blood loss early, be familiar with the contents of MHPs and know when to activate and deactivate the local MHP. (2B)
- Hospitals must have a strategy to ensure that emergency 'universal' RBCs are readily available for treatment of

life-threatening bleeding, including prompt access to group O RBC as emergency stock. Group O RhD- and K-negative RBCs should be prioritised for females of childbearing potential (aged <50 years) and in patients whose sex is unknown. (2B)

- We recommend a standard threshold and target Hb range for RBC transfusion to provide critical life-saving support in major bleeding alongside clinical judgement on the severity of bleeding (threshold Hb 70 g/l, target range for the post-transfusion HB level of 70–90 g/l). (1B)
- If major bleeding is on-going and results of standard coagulation tests or near-patient tests are not available, we suggest that units of FFP be transfused in at least a 1:2 ratio with units of RBCs. (2B)
- If major bleeding is on-going, and laboratory results are available, we suggest further FFP be administered aiming to maintain the PT ratio at <1.5-times mean normal (or equivalent). (2C)
- We suggest that serial haemostatic tests should be checked regularly, every 30–60 min depending on the severity of the haemorrhage, to guide and ensure the appropriate use of haemostatic blood components. (1B)
- We suggest fibrinogen supplementation should be given if fibrinogen concentrations fall below 1.5 g/l (non-pregnant women). (2B)
- If major bleeding is on-going, we suggest using platelet transfusions to maintain platelet counts at  $>50 \times 10^9/l$ . (2C)
- We suggest that VHAs are used to guide transfusion therapy in cardiac surgery, although for other clinical settings of major bleeding (e.g. trauma and PPH), hospitals should evaluate the costs and benefits of running these assays and ensure policies are in place to maintain these devices on a daily basis. (1B)

### Recommendations—alternatives to transfusion

- Tranexamic acid is recommended for patients with presentations of major bleeding due to trauma and PPH, but not gastrointestinal bleeding. (1A)
- Current evidence does not support the universal policy of 24-h cell salvage for patients with major bleeding and hospitals should evaluate the costs and benefits of running the cell salvage service. (1B)
- The use of cell salvage should be considered for patients who refuse to have blood transfusion. (1B)
- The use of desmopressin, rVIIa or aprotinin is not recommended in the management of major haemorrhage unless as part of a clinical trial. (1B)

### Recommendations—specific settings

#### Postpartum haemorrhage

- In patients with PPH, general recommendations for RBC and plasma transfusion should apply. (2A)
- Special attention should be paid to identifying women with PPH who develop a coagulopathy and/or low

- fibrinogen levels. Use of fibrinogen supplementation is recommended in PPH, especially when there is ongoing bleeding and if fibrinogen levels are <2.0 g/l. (2B)
- We recommend that an initial dose of TXA (1 g intravenously) is given to women with PPH within 3 h of bleed onset. If bleeding continues after 30 min, or it stopped and restarted within 24 h of the first TXA dose, a second dose of 1 g should be given. (1A)

#### Gastrointestinal bleeding

- In patients with gastrointestinal haemorrhage, general recommendations for RBC transfusion should apply. (1A)
- Special attention should be paid to heightened risks of raising vascular pressures with excessive plasma transfusions and the limitations of standard coagulation tests to monitor coagulation status in patients with liver disease. (2B)
- Tranexamic acid is not recommended for patients with acute gastrointestinal bleeding. (1A)

#### Trauma

- There are insufficient clinical data to support a role for pre-hospital transfusion resuscitation with RBCs and plasma, but if considered, it should not unduly add to transport delays to hospital. (2C)
- We recommend plasma should be given early as part of initial resuscitation in major haemorrhage due to trauma, and in a 1:1 (not >1:2 ratio) with RBCs, until results from coagulation monitoring are available. (1B)
- Fibrinogen supplementation should be given to patients with traumatic injury if fibrinogen levels fall to <1.5 g/l. (1B)
- Patients with traumatic injury (including mild–moderate TBI) should be given TXA as soon as possible after injury (and no later than 3 h); a suitable regimen includes 1 g bolus dose intravenously over 10 min, followed by a maintenance infusion of 1 g over 8 h should be used. (1A)

#### Surgical bleeding

- In major bleeding during/after surgery, general recommendations should apply, for RBC transfusion and other blood components. (2C)
- Timely and repeated access to laboratory coagulation monitoring should be available and inform the need for blood components including plasma. (2C)
- It is recommended that all patients having in-patient surgery should receive 1 gram of tranexamic acid prior to skin incision to reduce major surgical bleeding and reduce the need for blood transfusion. (1A).

### Recommendations—mass casualty events

- The laboratory should have systems in place to identify and prioritise the testing of group and screen samples from major haemorrhage cases, patients receiving pre-hospital

transfusion and severely injured patients during MCEs). (2C)

- Hospital Transfusion Teams should be engaged with local MCEs planning, scenario training, skills and drills, which include effective policies for extended use of TXA. (2C)
- Effective systems should be in place for major haemorrhage management in the context of blood shortage and/or MCEs. Modified MHPs or tailored transfusion should be considered together with triage during blood shortage or MCEs to optimise the use of blood and support blood stocks management. (2C)
- Transfusion Teams should be aware of their hospital's predetermined casualty load and their regional incident response plan to aid with stock and staff planning. (2C)

### GOOD PRACTICE STATEMENTS FOR LABORATORY/ ORGANISATIONAL SUPPORT

- Major haemorrhage protocols should be reviewed at least annually, or whenever there are changes in guidance, or new evidence becomes available to suggest change of practice. Where MHPs are not used frequently through 'live' events, they should be tested periodically, at least annually, with regular drills, especially in areas known to be at greatest risk due to location or clinical speciality. (2C)
- The most significant adverse transfusion-associated event in emergencies is ABO mismatched transfusion. Robust patient and sample identification systems for unknown patients are essential to avoid errors in emergency and multiple casualty situations. All patients receiving a blood transfusion must wear a patient identification wristband containing the unique identifier. (2C)
- Hospitals must have clear policies on changing patient's Unique Identifier from 'Emergency' or 'Major Incident' identifiers to 'Routine' hospital Identifiers. (2C)
- Group and screen samples should be taken wherever possible before administration of the first unit of RBCs and samples must be labelled correctly. For hospitals supporting pre-hospital care with blood components, there should be a clear policy for how pre-transfusion samples are collected and labelled. (2C)
- The use of pre-hospital transfusion should follow the regulatory framework with special attention to cold chain monitoring and traceability (2C)
- The laboratory should have a clear protocol for when it is appropriate to convert to group-specific blood, including consideration of potential mixed field reactions caused by group O RBC transfusion. (2C)
- If a patient's blood group is unknown or unsure, universal components or appropriate substitutes should be used to avoid delays in issuing blood during major bleeding. (2C)
- Hospital transfusion laboratories should have a formal training and competency process evaluation,

covering all aspects of blood component provision for major haemorrhage cases and emergency stock management. (2C)

## AUTHOR CONTRIBUTION

Simon J. Stanworth chaired the Guidelines Group, with Kerry Dowling for the laboratory aspects. Laura Green was the BSH Blood Transfusion Taskforce representative. All authors were involved in formulation, writing, and all authors approved the final version of the manuscript.

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## CONFLICT OF INTEREST

All authors have made a declaration of interests to the BSH and Task Force Chairs that may be viewed on request. Simon J. Stanworth and Laura Green are employees of NHSBT and report obtaining research funds for multiple clinical studies; both report no direct relevant financial disclosures. Nikki Curry reports research led study support from CSL Behring, is an educational consultant for LFB and Bayer and has received support for conference attendance from Sobi and NovoNordisk.

## DISCLAIMER

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the BSH, nor the publishers accept any legal responsibility for the content of these guidelines.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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**GUIDELINE**

# Guideline on the investigation and management of acute transfusion reactions

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## METHODOLOGY

This guideline was compiled according to the British Society for Haematology (BSH) process at <https://b-s-h.org.uk/media/19922/bsh-guidance-development-process-july-2021.pdf>. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations.<sup>1</sup> The GRADE criteria can be found in Appendix S3 of the above BSH document.

## LITERATURE REVIEW

The literature search was performed in January 2021 and updated in January 2022. With the assistance of the Oxford Systematic Reviews Initiative (SRI), the following databases were searched for relevant publications in English: MEDLINE (from 1950), EMBASE (from 1980), CINAHL (from 1982), The Cochrane Library, DARE (CRD website) and SRI hand search databases. The initial search and filtering produced 1693 systematic reviews, randomised controlled trials and observational studies from which relevant publications were extracted by the members of the Writing Group. Search terms include Transfusion AND ('TACO' OR 'TRALI' OR 'TAD' OR 'pulmonary complication' OR 'lung'

OR 'pulmonary oedema' OR 'respiratory' OR 'ARDS' OR 'reaction' OR 'anaphylaxis' OR 'febrile reaction' OR 'allergic reaction' OR 'non haemolytic reaction' OR 'haemolytic reaction'), wrong blood to wrong person, incompatible transfusion reaction, ABO-related incompatible transfusions.

## PURPOSE AND OBJECTIVES

The purpose of this document is to provide clear guidance on the recognition, investigation and management of acute adverse reactions to blood components. It is clinically focused and recognised that the precise nature of reactions may not be apparent at presentation. The emphasis is on the immediate management of potentially life-threatening reactions, but it also makes recommendations around appropriate investigation and prophylactic strategies. The key objectives are to:

1. Provide a flow diagram to aid recognition of acute transfusion reactions (ATRs) and their immediate clinical management;
2. Advise on further management of the patient during the reaction;
3. Provide advice on investigations;
4. Discuss management of subsequent transfusions;

5. Present recommendations for reporting adverse reactions to UK haemovigilance organisations, to blood services and within the hospital.

The guideline does not cover the detailed medical management of ATRs such as treatment of cardiac/respiratory failure or bacterial sepsis. Measures that might be employed for primary prevention of ATRs are outside the scope of the guideline. Readers may also find it useful to cross reference to other related British Society for Haematology guidelines such as The Administration of Blood Components and Pre-Transfusion Compatibility Procedures in Blood Transfusion

Laboratories; all are available at <https://b-s-h.org.uk/guidelines>.

The full guideline with appendices providing detailed information on symptoms and signs, laboratory investigations, the International Society for Blood Transfusion (ISBT)/International Haemovigilance Network (IHN) classification of ATRs, a table describing differences between transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO) and an algorithm for investigating and categorising pulmonary complications of transfusion can also be found on the BSH guidelines website.

Summary of key recommendations	Strength	Quality of evidence
<b>Recognition of ATRs</b>		
Initial treatment of ATR should be directed by symptoms and signs. Treatment of severe reactions should not be delayed while waiting for the results of investigations.	1	C
All patients should be transfused in clinical areas where they can be directly observed and where staff are trained in the administration of blood components and the management of transfused patients, including the emergency treatment of anaphylaxis.	1	C
The recognition and immediate management of ATR should be incorporated into local transfusion policies and there should be mandatory transfusion training requirements for all clinical and laboratory staff involved in the transfusion process.	1	C
Patients should be asked to report symptoms which develop following completion of the transfusion.	1	C
<b>Immediate management of ATR</b>		
If a patient develops new symptoms or signs during a transfusion, this should be stopped temporarily but venous access should be maintained. Identification details should be checked between the patient, their identity band and the compatibility label of the blood component. The component should be inspected visually and the patient should be assessed with standard observations.	1	C
For patients with mild reactions, such as a temperature rise of 1–2°C leading to pyrexia $\geq 38^\circ\text{C}$ but $< 39^\circ\text{C}$ , <b>and/or</b> pruritus or rash but <b>without</b> other features, the transfusion may be continued with appropriate treatment and direct observation.	2	B
Patients with mild isolated febrile reactions may be treated with oral paracetamol (500–1000 mg in adults). Patients with mild allergic reactions may be managed by slowing the transfusion and treatment with an antihistamine. Corticosteroids should not be used routinely.	2	C
Anaphylaxis should be treated with intramuscular adrenaline (epinephrine). Patients who are thrombocytopenic or who have deranged coagulation should also receive intramuscular adrenaline if they have an anaphylactic reaction.	1	A
If a patient being transfused for haemorrhage develops hypotension, careful clinical risk assessment is required. If the hypotension is caused by haemorrhage, continuation of the transfusion may be life-saving. In contrast, if the blood component is considered the most likely cause of hypotension, the transfusion must be stopped or switched to an alternative component and appropriate management and investigation commenced.	1	C
If a patient develops <u>sustained</u> febrile symptoms or signs of moderate severity (temperature $\geq 39^\circ\text{C}$ <b>or a</b> rise of $\geq 2^\circ\text{C}$ <b>and/or</b> systemic symptoms such as chills, rigors, myalgia, nausea or vomiting), bacterial contamination or a haemolytic reaction should be considered.	1	C
<b>Diagnostic investigations</b>		
In all moderate and severe transfusion reactions, standard investigations including full blood count, renal and liver enzymes should be performed. Patients with respiratory symptoms not due to allergy should also have a chest X-ray.	1	C
If febrile symptoms of moderate severity are sustained, implicated units should be returned to the laboratory for further investigation and the blood service contacted immediately so that associated components from the implicated donation can be withdrawn if appropriate. Samples should be taken for repeat compatibility testing and culture and urine assessed for haemoglobin.	1	C
Patients who have experienced anaphylactic reactions or recurrent severe febrile/inflammatory reactions within the first 15 min should have IgA levels measured. Patients with IgA deficiency diagnosed after an ATR should be discussed with an expert in transfusion medicine regarding future management.	2	C

Summary of key recommendations	Strength	Quality of evidence
In an ATR with only allergic features, repeat compatibility testing is not required.	1	B
In the absence of platelet transfusion refractoriness or acute post-transfusion thrombocytopenia or leucopenia, investigation of the patient with ATR for leucocyte, platelet or neutrophil-specific antibodies is not indicated.	1	B
Patients with respiratory symptoms not caused by anaphylaxis or allergy should have investigations for left atrial hypertension (e.g. echocardiography and pre- and post-transfusion NT-Pro BNP) to help distinguish the type of pulmonary complication to assist diagnosis and haemovigilance reporting.	2	B
<b>Subsequent management of the patient</b>		
Patients who have experienced an anaphylactic reaction should be discussed with an allergist or immunologist if there is uncertainty about the causative agent (e.g. if other drugs were administered at the same time as the transfusion).	2	C
For patients with recurrent febrile reactions, we recommend a trial of premedication with oral paracetamol given 1 h before the reaction is anticipated (or non-steroidal anti-inflammatory drugs in patients with predominant chills or rigors—but an assessment of the risks of medication against the severity of reaction should be made in each case). Patients who continue to have recurrent moderate or severe febrile reactions despite premedication should have a trial of washed blood components (i.e. red cells and platelets). There is no role for prophylactic antihistamine or corticosteroids in the absence of allergic symptoms.	2	C
For recurrent mild allergic reactions, there is no evidence to support routine prophylaxis with antihistamines or corticosteroids. Alternative causes such as allergy to drugs or latex gloves should be excluded.	2	C
For patients with recurrent moderate or severe allergic reactions, options for further transfusion include:		
• If prior reactions were to apheresis platelets, consider pooled platelets (suspended in platelet additive solution).	2	B
• Consider antihistamine prophylaxis (although the evidence for efficacy is low, the risks are also low).	2	B
• Routine prophylaxis with corticosteroids is <u>not</u> recommended.	2	C
• Transfusion of washed red cells or platelets	2	C
• The use of pooled solvent-detergent-treated fresh frozen plasma (FFP) when there are recurrent allergic reactions to FFP in patients undergoing plasma exchange.	2	B
• If further transfusion is urgent and withholding blood is a greater risk, transfuse standard components under direct monitoring in a clinical area with resuscitation facilities.	2	C
<b>Patients with confirmed IgA deficiency (IgA &lt;0.07 g/L):</b>		
• with a history of reaction to blood components should receive washed components for elective transfusion but life-saving transfusion should not be delayed if these are not immediately available. The patient must be monitored closely for an acute reaction.	1	C
• with no history of blood transfusion reactions should receive standard components with a higher frequency of monitoring. Those with a history of allergy/anaphylaxis in other settings should be discussed with a transfusion medicine or clinical immunology or allergy specialist if time allows.	2	C
<b>Reporting of ATR</b>		
All transfusion reactions except mild febrile and/or allergic reactions must be reported to appropriate regulatory and haemovigilance organisations and should also be reviewed within the hospital.	1	C

## INTRODUCTION

Acute transfusion reactions (ATRs) are defined as those occurring within 24 h of the administration of blood or blood components.<sup>2</sup>

ATRs vary in severity from minor febrile reactions to life-threatening allergic, haemolytic or hypotensive events. Allergic and febrile non-haemolytic transfusion reactions (FNHTR) are those most commonly reported, but the true incidence of ATR is uncertain as most haemovigilance systems only collect information on the more serious reactions, there are wide variations in institutional reporting rates and the introduction of new processes may differentially alter reaction rates over time (e.g. prestorage leucodepletion reduces the rate of FNHTR but not allergic reactions).<sup>3,4</sup> ATR rates of 0.5–3% of transfusions are commonly quoted.<sup>5</sup> The 2020

Serious Hazard of Transfusion (SHOT) report reviewed 10 years of reporting data and calculated the risk of a febrile, allergic or hypotensive reaction as 1:7704 and the risk of a haemolytic reaction as 1:57425. Pulmonary complications were the foremost cause of morbidity and mortality accounting for 65% of reported transfusion-related deaths. Platelets are the components with the highest number of reported reactions per 10 000 transfusions.<sup>6</sup>

There is uncertainty about the cause of ATRs. There is good evidence, supported by the impact of leucodepletion, that many febrile reactions are caused by reactions to donor white cells or accumulation of biological response modifiers during component storage.<sup>7</sup> Except in rare cases, a specific allergen will not be identified in patients with allergic transfusion reactions,<sup>8</sup> although plasma reduction may lower their frequency.<sup>9</sup> It is increasingly recognised that

recipient factors, particularly underlying diagnosis and allergic predisposition, may be paramount in predicting allergic transfusion reactions.<sup>10–13</sup> It is possible that genetic polymorphisms play a role.<sup>14,15</sup> Patients' age, physical characteristics and baseline observations may be significant risk factors for development of febrile reactions.<sup>16–18</sup> Preventative strategies should be directed at the minority of patients who have a propensity to severe reactions.

Although it is useful to categorise ATR for reporting and research purposes and for international comparison,<sup>19</sup> patients with severe ATR often present with an overlapping complex of symptoms and signs, the differential diagnosis of which includes potentially life-threatening allergy or anaphylaxis, acute haemolytic transfusion reactions, bacterial transfusion-transmitted infection, transfusion-associated acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO). Transfusion-associated dyspnoea (TAD) may be suspected when respiratory distress has a temporal association with transfusion and does not meet the criteria for allergic reaction, TRALI or TACO. The initial clinical picture is also often obscured by factors related to the patient's underlying medical conditions, such as febrile septic episodes in neutropenic patients who also happen to be receiving a blood component transfusion. For this reason, this guideline will consider all causes of a possible reaction during blood transfusion and focus on initial recognition and general management of the *clinical* problem, guided in the main by symptoms and clinical signs and assessment of the *severity* of the problem. This allows appropriate investigation, specific treatment and, where possible, prevention of future episodes.

## RECOGNITION AND INITIAL MANAGEMENT OF ATR

To minimise the risk of harm, early identification of transfusion reactions and rapid clinical assessment are essential.

## RECOMMENDATIONS

- All patients should be transfused in clinical areas where they can be directly observed and where staff are trained in the administration of blood components and the management of transfused patients, including the emergency treatment of anaphylaxis. (1C)
- The recognition and immediate management of ATR should be incorporated into local transfusion policies and there should be mandatory transfusion training requirements for all clinical and laboratory staff involved in the transfusion process. (1C)

If transfusions are administered at a patient's home, these should only be conducted in accordance with well-developed policies in patients deemed to be at low risk of ATR while otherwise abiding by the above recommendations.

Although anaphylactic and haemolytic reactions can present after only a small volume of blood has been transfused,<sup>20</sup> reactions can present much later, on occasion several hours after completion of the transfusion.<sup>21</sup> Delayed haemolytic reactions can present after days to weeks. Therefore, observation and monitoring are required throughout the transfusion episode and patients should be asked to report symptoms which develop after transfusion, particularly fever, dark urine, jaundice or symptoms suggestive of anaemia.<sup>22</sup> Unconscious patients, or those unable to report symptoms, require direct monitoring. The evidence on the use of early warning scores (EWS) to aid recognition of reactions is limited; however, when changes from the baseline are seen in EWS during or post-transfusion, consideration should be given to a possible transfusion reaction. Retrospective analysis has shown that in cases of patient deterioration the link to the transfusion is not always recognised and in particular pulmonary complications may not be identified.<sup>23</sup>

## RECOMMENDATION

Patients should be asked to report symptoms which develop following completion of the transfusion. (1C)

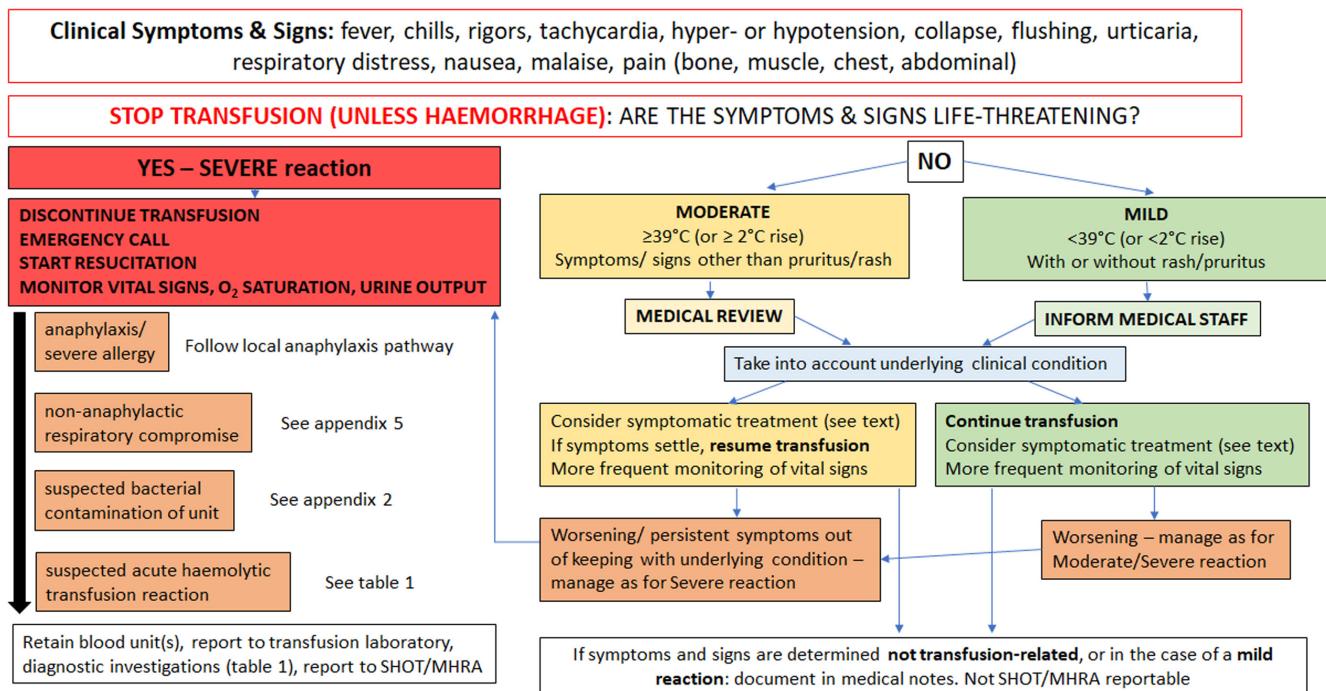
## INITIAL CLINICAL ASSESSMENT

Initial clinical assessment seeks to quickly identify those patients with serious or life-threatening reactions so that immediate treatment/resuscitation can be initiated. Figure 1 provides a practical guide to recognition and initial management of suspected ATR.

In *all* cases, the transfusion must be stopped temporarily and venous access should be maintained with physiological saline. The patient's airway, breathing and circulation ('ABC') must be assessed.<sup>24</sup> Their core identification details must be checked to ensure that they correspond with those on the blood component compatibility label—is the reaction due to transfusion of a component intended for another patient?<sup>22</sup> The component must be examined for unusual clumps or particulate matter, or discolouration suggestive of bacterial contamination. Provided that the reaction is not severe or life-threatening, as defined in the flow diagram (Figure 1), standard observations on the patient are then performed.

## RECOMMENDATION

- If a patient develops new symptoms or signs during a transfusion, this should be stopped temporarily, but venous access should be maintained. Identification details should be checked between the patient, their identity band and the compatibility label of the blood component. The component should be inspected visually and the patient should be assessed with standard observations. (1C)



**FIGURE 1** Flow diagram for recognition, initial management and subsequent management and investigations.

## Severe reactions

If the presumed ATR is *severe or life-threatening*, a doctor should be called immediately and the blood transfusion should be discontinued. Caution is required in bleeding patients where hypotension may be associated with haemorrhage and continuing the transfusion may be life-saving.

## RECOMMENDATIONS

- If a patient being transfused for haemorrhage develops hypotension, careful clinical risk assessment is required. If the hypotension is caused by haemorrhage, continuation of the transfusion may be life-saving. In contrast, if the blood component is considered the most likely cause of hypotension, the transfusion must be stopped or switched to an alternative component and appropriate management and investigation should be commenced. (1C)

## Mild or moderate reactions

If the reaction is *mild*, for example an isolated rise in temperature without chills, rigors or other change in observations, medical staff should be informed but the transfusion may be restarted under direct supervision. In the case of reactions considered *moderate*, urgent medical advice should usually be sought before the transfusion is restarted. Exceptions to this would include reactions where there is an obvious alternative explanation for the symptoms/signs or the patient

has a history of similar, previously investigated, non-serious transfusion reactions.

## RECOMMENDATION

- For patients with mild reactions, such as a temperature rise of 1–2°C leading to pyrexia  $\geq 38^\circ\text{C}$  but  $<39^\circ\text{C}$ , and/or pruritus or rash but WITHOUT other features, the transfusion may be continued with appropriate treatment and direct observation. (2B)

## STANDARD OBSERVATIONS

The patient's pulse rate, blood pressure, temperature and respiratory rate should be monitored,<sup>22</sup> and abnormal clinical features such as fever, rashes or angioedema should be frequently assessed. A patient who has experienced a transfusion reaction should be observed directly until the clinical picture has improved.

## SYMPTOMS AND SIGNS OF ATR

ATRs can present with a range of symptoms and signs of varying severity. These include the following:

- Fever and related inflammatory symptoms or signs such as chills, rigors, myalgia, nausea or vomiting
- Cutaneous symptoms and signs including urticaria (hives), other skin rashes and pruritus

- Angioedema (localised oedema of the subcutaneous or submucosal tissues), which may be preceded by tingling
- Respiratory symptoms and signs including dyspnoea, stridor, wheeze and hypoxia
- Hypotension
- Pain
- Severe anxiety or ‘feeling of impending doom’
- Bleeding diathesis with acute onset

Rapidly developing features of ABC problems, usually associated with skin and mucosal change would suggest anaphylaxis.<sup>25</sup>

The symptoms and signs of reactions are discussed in more detail in Appendix S1. A table incorporating both the ISBT/IHN and SHOT classifications and gradations of severity can be found in Appendix S3. Both these appendices can be found on the BSH website.

## MANAGEMENT OF ATRS

Management is guided by rapid assessment of symptoms, clinical signs and severity of the reaction rather than laboratory investigations.

## RECOMMENDATION

- Initial treatment of ATR should be directed by symptoms and signs. Treatment of severe reactions should not be delayed until the results of investigations are available. (1C)

### Severe reactions

Medical support should be given as appropriate for an acutely ill patient.<sup>26</sup> In all cases, disconnect the component and giving set from the patient and retain for further investigation, maintaining venous access with intravenous physiological saline. If the patient is *severely dyspnoeic*, ensure the airway is patent and give high flow oxygen through a mask with a reservoir. If wheeze is present without upper airways obstruction, consider nebulising a short-acting, inhaled, beta-2 agonists such as salbutamol.<sup>27</sup> Position *hypotensive* patients flat with leg elevation, or in the recovery position if unconscious or nauseated and at risk of vomiting. Further management is dependent on expert medical assessment and appropriate specialist support, such as the *resuscitation team* or *critical care outreach team*, who should be alerted according to local policies. Prompt treatment may be life-saving, and it may not be appropriate to wait for the results of investigation. A rational outline of management is provided below.

### Shock/severe hypotension associated with wheeze or stridor

This is strongly suggestive of ***anaphylaxis*** with airways obstruction, especially if examination reveals angioedema and/or urticaria. This requires immediate intervention to ensure the airway is patent and the administration of adrenaline (epinephrine) is according to the UK Resuscitation Council (UKRC) guidelines.<sup>25</sup> Intramuscular (IM) adrenaline is rapidly effective and prevents delay in attempting to get venous access in a patient with peripheral venous shutdown. It should not be prohibited in patients with thrombocytopenia or coagulopathy. Intravenous adrenaline should only be given by expert practitioners such as intensive care specialists or anaesthetists.

For adults and children over 12 years, administer IM adrenaline: 0.5 mL of 1:1000 adrenaline (500 µg) into the anterolateral aspect of the middle third of the thigh.

For children between 6 and 12 years, give 0.3 mL of 1:1000 IM adrenaline (300 µg).

For children less than 6 years, give 0.15 mL of 1:1000 IM adrenaline (150 µg).

Adrenaline is repeated, if necessary, at 5-minute intervals according to blood pressure, pulse and respiratory function under the direction of appropriately trained clinicians.

Supportive care of anaphylaxis includes the following:

- Rapid fluid challenge of 500–1000 mL crystalloid
- Administration of 10 mg of chlorphenamine IM or by slow intravenous (IV) injection *following initial resuscitation* if there are also skin symptoms
- If the patient has continuing symptoms of asthma or wheeze, inhaled or intravenous bronchodilator therapy should be considered

Patients who have had an anaphylactic reaction should be discussed with an allergist or immunologist regarding further assessment and investigation if there is uncertainty about the cause (e.g. if other drugs had been administered at the same time as transfusion). A policy for future blood component therapy must be formulated (see section *Subsequent Management*).

## RECOMMENDATION

- Anaphylaxis should be treated with intramuscular adrenaline (epinephrine). Patients who are thrombocytopenic or who have deranged coagulation should also receive intramuscular adrenaline if they have an anaphylactic reaction. (1A)

### Shock/severe hypotension without clinical signs of anaphylaxis or fluid overload

Consider ABO blood group incompatibility or bacterial contamination. Both require supportive care with fluid

resuscitation, expert evaluation for inotropic, renal and/or respiratory support and blood component therapy for disseminated intravascular coagulation with bleeding. Isolated hypotension can occur in anaphylaxis and severe hypotension can occur in TRALI. In the latter, the clinical picture is usually dominated by dyspnoea.

If the identity check suggests ABO incompatibility due to transfusion of a unit intended for another patient, contact the transfusion laboratory immediately.

If bacterial contamination is suspected, take blood cultures from the patient (peripheral vein and through central line, if present) and then start broad spectrum intravenous (IV) antibiotics (the local regimen for patients with neutropenic sepsis would be appropriate). Immediately notify the transfusion laboratory staff and haematologist. The blood transfusion service should be contacted to arrange the recall of the implicated unit and for this to be cultured. They will also arrange recall and quarantine of all other components manufactured from the implicated donation.

### Severe dyspnoea without shock

Consider TACO, TRALI or TAD where allergic reaction has been excluded as a cause for dyspnoea. Ensure the airway is patent and high-flow oxygen therapy started while urgent expert medical assessment is obtained. Initial investigation should include chest X-ray and oxygen saturation. Detailed investigation and treatment of TRALI (non-cardiogenic pulmonary oedema) and TACO (left atrial hypertension due to fluid overload) are beyond the scope of this guideline. The distinction is clinically important as the primary treatment of TRALI is ventilatory support and mortality/morbidity may be increased by loop diuretic therapy in patients who already have depleted intravascular volume.<sup>28</sup> Appropriate medical management should be initiated promptly. Cases where TRALI is strongly suspected should be discussed with a haematologist at the national blood service as investigation of donors may be required. It should be noted that TACO and TRALI may coexist<sup>29</sup> and pathology may be similar.<sup>30</sup> Appendix S4 provides a comparison of the pulmonary complications of transfusion<sup>31</sup> and Appendix S5 provides guidance on differentiating TACO, TRALI and TAD.

### Moderate reactions

The differential diagnosis and investigation are similar to severe ATR. Unless there is an obvious alternative explanation for the symptoms/signs or the patient has a history of comparable, previously investigated, non-serious transfusion reactions, transfusion of the implicated unit should only be resumed after full clinical evaluation.

### Moderate febrile symptoms

Symptoms and signs are defined as a temperature  $\geq 39^{\circ}\text{C}$  or a rise of  $\geq 2^{\circ}\text{C}$  from baseline and/or systemic symptoms such as chills, rigors, myalgia, nausea or vomiting in keeping with ISBT/IHN criteria. Bacterial contamination or a haemolytic reaction is very unlikely if the reaction is transient and the patient recovers with only symptomatic intervention. If the reaction is sustained, however, these possibilities should be considered. Management of bacterial contamination and haemolysis due to ABO incompatibility (also occasionally due to non-ABO antibodies, e.g. Wr<sup>a</sup>) are described above under severe reactions and symptomatic treatment of febrile reactions is included in section Mild reactions.

### RECOMMENDATION

If a patient develops sustained febrile symptoms or signs of moderate severity (temperature  $\geq 39^{\circ}\text{C}$  OR a rise of  $\geq 2^{\circ}\text{C}$  from baseline AND/OR systemic symptoms such as chills, rigors, myalgia, nausea or vomiting), bacterial contamination or a haemolytic reaction should be considered. (1C)

### Moderate allergic symptoms

Signs and symptoms may include angioedema and dyspnoea, but not sufficiently severe to be life-threatening. Antihistamines such as chlorphenamine orally or IV may be effective and in addition oxygen therapy and a short-acting inhaled beta-2 agonists such as salbutamol may be useful for respiratory symptoms.<sup>27</sup> Corticosteroids act only to down-regulate the late-phase inflammatory response and have no role in managing acute symptoms.

### Moderate respiratory symptoms

The decision to continue transfusion will depend on the clinical assessment of the probable cause of the symptoms, response to initial therapy and the urgency of transfusion.

### Mild reactions

These are defined as having no or limited change in observations, for example an isolated fever  $\geq 38^{\circ}\text{C}$  but  $< 39^{\circ}\text{C}$  and rise of  $\geq 1^{\circ}\text{C}$  but  $< 2^{\circ}\text{C}$  from baseline and/or pruritus or rash but without other features (Figure 1). In these cases, it is reasonable to restart the transfusion under direct observation.

There are no randomised controlled trials (RCTs) which consider the symptomatic treatment of febrile symptoms associated with transfusion. Experience with paracetamol suggests that it is a useful antipyretic agent but less effective for

the management of symptoms such as chills or rigors. A systematic review of the use of non-steroidal anti-inflammatory drugs (NSAIDs) in fever unrelated to transfusion suggests that they may be more effective for this purpose.<sup>32</sup> An assessment of the risks of medication against the severity of the reaction should be made in each case. Caution would be required in the use of NSAIDs in patients with thrombocytopenia, reduced platelet function or renal impairment.

There are no reported trials of treatment of skin symptoms but clinical experience suggests that patients with skin reactions such as itch or rash with no other features may continue to receive the transfusion. Reducing the rate of transfusion and the use of a systemic antihistamine may be helpful.

## RECOMMENDATION

- Patients with mild isolated febrile reactions may be treated with oral paracetamol (500–1000 mg in adults). Patients with mild allergic reactions may be managed by slowing the transfusion and treatment with an antihistamine. Corticosteroids should not be used routinely. (2C)

## LABORATORY INVESTIGATION OF ATR

(See Appendix S2 for detailed discussion).

This is largely determined by the pattern of symptoms and clinical signs and the severity of the reaction. We recommend that all reactions considered to be a result of the transfusion, except minor allergic or febrile reactions, and without a history of comparable, non-serious reactions, be investigated with a standard battery of tests together with additional investigations based on the symptom complex (Table 1). The urgency of investigations and clinical details must be communicated to the laboratory. If febrile symptoms of moderate severity are sustained, bacterial contamination or a haemolytic reaction should be considered. Implicated units should be returned to the laboratory for further investigation and the blood service contacted immediately so that any associated components from the implicated donation can be withdrawn. If however, febrile symptoms are transient and the patient recovers with only symptomatic treatment, further investigation to exclude these possibilities is unlikely to be required.

## Standard investigations

Standard investigations provide a baseline in case of subsequent clinical deterioration and may give an early indication of whether haemolysis has occurred.

## RECOMMENDATION

- In all moderate and severe transfusion reactions, standard investigations, including full blood count, renal and liver

enzymes should be performed. Patients with respiratory symptoms not due to allergy should also have a chest X-ray. (2C)

## Investigations dependent on symptom complex

Further investigations should be guided by the clinical symptoms and signs, rather than the presumed category of reaction.

## RECOMMENDATIONS

- If febrile symptoms of moderate severity are sustained, implicated units should be returned to the laboratory for further investigation and the blood service contacted immediately so that associated components from the implicated donation can be withdrawn if appropriate. Samples should be taken for repeat compatibility and culture and urine assessed for haemoglobin. (1C)
- In an ATR with only allergic features, repeat compatibility testing is not required. (1C)

## Testing the patient for human leucocyte antibodies (HLA), human platelet antibodies (HPA) or human neutrophil-specific antibodies (HNA)

These are usually an incidental finding in patients with ATR and routine screening is not recommended (see Appendix S2 for detailed discussion and references).

## RECOMMENDATION

- In the absence of platelet transfusion refractoriness or acute post-transfusion thrombocytopenia or leucopenia, investigation of the patient with ATR for leucocyte, platelet or neutrophil-specific antibodies is not indicated. (1B)

## MANAGEMENT OF PATIENTS WITH REPEATED REACTIONS

This section focuses on the management of recurrent febrile and allergic reactions. In the small number of patients with repeated reactions, premedication and/or component manipulation by washing or plasma removal is usually considered, although the evidence base is weak<sup>33</sup>

## Febrile non-haemolytic transfusion reactions

Reports on prevention of FNHTRs using premedication with paracetamol (acetaminophen), usually in a dose of 500–650 mg, are of inadequate quality, include both primary and secondary prevention, and report contradictory results. Studies suggesting a reduced incidence of febrile reactions in

**TABLE 1** Investigation of Moderate or Severe Acute Transfusion Reactions (for detailed guidance and references, see Appendix S2).

Symptoms	Investigations
Fever ( $\geq 2^{\circ}\text{C}$ rise or $\geq 39^{\circ}\text{C}$ ), and/or chills, rigors, myalgia, nausea or vomiting and/or loin pain	Standard investigations <sup>a</sup> If febrile reaction sustained: Return unit to laboratory Take samples for repeat compatibility testing and DAT on both the pre- and post-transfusion samples. If the DAT is positive or stronger on the post-transfusion sample, elution studies should be performed <sup>b</sup> Haptoglobin, LDH <sup>b</sup> Coagulation screen Assessment of urine for haemoglobin <sup>b</sup> Blood cultures from patient
Dyspnoea, wheeze, or features of anaphylaxis	Standard investigations <sup>a</sup> Check oxygen saturation or blood gases. Chest X-ray (mandatory if symptoms are severe) If severe allergy/anaphylaxis suspected, consider measurement of serial mast cell tryptase (plain tube) (immediate, 1–2 h and 24 h) Patients with respiratory symptoms not caused by anaphylaxis or allergy should have investigations for left atrial hypertension (e.g. echocardiography and pre- and post-transfusion NT-Pro BNP) to help distinguish the type of pulmonary complication to assist diagnosis and haemovigilance reporting
Hypotension (isolated fall systolic of $\geq 30\text{ mm Hg}$ resulting in level $\leq 80\text{ mm Hg}$ )	Investigate as for fever If severe allergy/anaphylaxis, consider measurement of serial mast cell tryptase, as above

Abbreviations: DAT, direct antiglobulin test; LDH, lactate dehydrogenase; NT-Pro BNP, N-terminal-pro hormone B-type natriuretic peptide.

<sup>a</sup>Standard investigations: full blood count, renal and liver enzymes.

<sup>b</sup>Note that in adults, platelets and plasma components are unlikely to cause significant haemolysis and so haemolysis screen is of limited value.

patients premedicated with paracetamol<sup>34–37</sup> are counterbalanced by studies with negative results.<sup>38–42</sup> Studies on patients with a previous febrile reaction showed no difference in reaction rates compared to those with no previous reaction.<sup>39,40</sup> There is little information on the timing of administration of paracetamol (peak activity is 30–60 min after oral administration). Several studies show that paracetamol does not prevent inflammatory symptoms such as chills and rigors.<sup>35,37–40</sup> Plasma removal was reported to reduce the incidence of FNHTR before the introduction of prestorage leucodepletion,<sup>43,44</sup> but there are no recent publications to support this practice.

In the absence of clear evidence, if recurrent reactions occur, options include premedication with oral paracetamol given 1 h before the reaction is anticipated (first option) or the use of washed blood components. NSAIDs may be useful in patients with chills or rigors associated with red cell transfusions but must be used with caution in patients with thrombocytopenia or renal impairment. An assessment of the risks of medication against the severity of reaction should be made in each case.

## RECOMMENDATION

- For patients with recurrent febrile reactions, we recommend a trial of premedication with oral paracetamol given 1 h before the reaction is anticipated (or NSAIDs in patients with predominant chills or rigors—but an assessment of the risks of medication against the severity of reaction should be made in each case). Patients who continue to have moderate or severe febrile reactions despite

premedication should have a trial of washed blood components (i.e. red cells and platelets). There is no role for prophylactic antihistamine or corticosteroids in the absence of allergic symptoms. (2C)

## Allergic reactions

There are several studies of prevention/prophylaxis, including one large RCT.<sup>37–40,42</sup> None showed that premedication with an antihistamine (diphenhydramine), as widely used in the United States, was effective whether or not patients had experienced a previous reaction. There are no studies which assess the use of corticosteroids. The use of plasma-reduced (washed) components was shown to reduce the incidence of allergic complications in two before and after cohort studies<sup>45,46</sup> and in a post hoc analysis of a RCT investigating transfusion reactions to platelets (compared with prestorage leucodepletion).<sup>35</sup>

## Mild allergic reactions

In the absence of evidence that prophylaxis is beneficial, patients who have experienced a mild allergic reaction may receive further transfusions without prior intervention and any subsequent mild reaction can be managed by reducing the rate of transfusion and by the use of a systemic antihistamine such as chlorphenamine orally or IV, which is effective in some patients with mild reactions.<sup>2</sup>

Alternatively, intervention as described for more severe reactions, detailed below in recommendation, may be used.

## Moderate and severe allergic reactions

In patients with previous severe reactions who need urgent transfusion, infusion of standard components with or without antihistamine premedication with direct monitoring is justified.<sup>47</sup> Pooled platelets (suspended in platelet additive solution) are associated with fewer allergic reactions than apheresis platelets, which have a higher plasma content.<sup>48–51</sup> Recurrent allergic transfusion reactions to fresh frozen plasma (FFP) in patients treated with plasma exchange for conditions such as thrombotic thrombocytopenia purpura are reduced by the use of pooled solvent–detergent-treated FFP.<sup>47,52–55</sup>

## RECOMMENDATIONS

For recurrent mild allergic reactions, there is no evidence to support routine prophylaxis with antihistamines or corticosteroids. Alternative causes such as allergy to drugs or latex gloves should be excluded. (2C)

For patients with recurrent moderate or severe allergic reactions, options for further transfusion include the following:

1. If prior reactions were to apheresis platelets, pooled platelets should be considered (suspended in platelet additive solution). (2B)
2. Consider antihistamine prophylaxis (although the evidence for efficacy is low, the risks are also low). (2B)
3. Routine prophylaxis with corticosteroids is not recommended. (2C)
4. Transfusion of washed red cells or platelets. (2C)
5. The use of pooled solvent–detergent-treated plasma when there are recurrent allergic reactions to FFP in patients undergoing plasma exchange. (2B)
6. If further transfusion is urgent and withholding blood is a greater risk, transfuse standard components under direct monitoring in a clinical area with resuscitation facilities. (2C)
- Patients who have experienced an anaphylactic reaction should be discussed with an allergist or immunologist if there is uncertainty about the causative agent (e.g. if other drugs were administered at the same time as the transfusion). (2C)

## Patients with IGA deficiency

Anaphylactic transfusion reactions have rarely been described in patients with severe congenital IgA deficiency, sometimes in association with anti-IgA antibodies. However, there is a lack of evidence for a causative role and the link remains unclear. Haemovigilance data do not support an increased incidence of IgA deficiency in patients experiencing anaphylaxis, and reported reactions in IgA-deficient patients more often

involve inflammatory features (fever, rigors, myalgia), with rapid onset (in the first 15 min of transfusion).<sup>56</sup>

Low IgA levels found on screening, in the absence of generalised hypogammaglobulinaemia, should be confirmed by a more sensitive method and IgA antibodies should be checked (assays done by the national blood services). Patients with confirmed IgA deficiency ( $<0.07\text{ g/L}$ ) and a history of transfusion reactions should be transfused with washed red cells and washed platelets resuspended in platelet additive solution in elective situations. If FFP is required, the UK blood services keep a small stock of IgA-deficient plasma available on a national basis. If reactions persist in spite of washed components, the case should be discussed with a transfusion medicine specialist from the national blood service. If urgent, life-saving transfusion is needed, standard blood components should be transfused with direct observation in a clinical area with the skill and facilities to manage severe acute reactions.<sup>57</sup>

There is no high-level evidence to guide the management of patients with IgA deficiency and no prior transfusion. Serious reactions to standard components are very rare in this group<sup>58</sup> and patients with no history of allergic reactions may be transfused with standard components. Occasionally, the balance of clinical risks in a patient with a history of significant allergic reactions in other settings might warrant washed components. Discussion of the case with a transfusion medicine specialist or clinical immunologist may be helpful. Urgent transfusion must not be denied because washed components are not immediately available.

## RECOMMENDATIONS

- Patients experiencing anaphylactic reactions to blood transfusion, or recurrent severe febrile/ inflammatory reactions within the first 15 min should have IgA levels measured. Patients with IgA deficiency diagnosed after an ATR should be discussed with a specialist in transfusion medicine regarding future management. (2C)
- Patients with confirmed IgA deficiency and a history of reaction to blood should receive washed components for elective transfusion but life-saving transfusion should not be delayed if these are not immediately available. The patient must be monitored closely for an acute reaction. (1C)
- Patients with known IgA deficiency ( $\text{IgA} <0.07\text{ g/L}$ ) and no history of reactions to blood should receive standard components with a higher frequency of monitoring. Those with a history of allergy/anaphylaxis in other settings should be discussed with a transfusion medicine or clinical immunology or allergy specialist if time allows. (2C)

## Patients with antibodies to HLA, HPA or HNA

There is little evidence that the use of HLA-, HNA- or HPA-matched components is of benefit in reducing the incidence

of transfusion reactions and these are not required unless there is evidence of platelet refractoriness (See Appendix S2).

## Hypotensive reactions

Patients with otherwise unexplained hypotensive reactions should be given a trial of washed red cells or platelets resuspended in platelet additive solution.

In rare cases, it is thought to be due to bradykinin release, ACE inhibitors should be stopped before transfusion if clinically safe to do so.

## ATR IN CHILDREN AND NEONATES

Symptoms and signs of ATR may be less easily recognised in children or neonates,<sup>59</sup> although they may have a higher prevalence than in adult transfusion recipients.<sup>60</sup> A high degree of vigilance by treating clinicians is needed. Protocols for drug management should be written in close collaboration with paediatric specialists. In the case of anaphylaxis, UKRC guidelines should be followed.<sup>25</sup> Appropriate paediatric doses of adrenaline are given above.

## REPORTING ATR

### Reporting to national haemovigilance schemes

Moderate and severe ATRs, as defined in this guideline, meet the criteria for serious adverse reactions and there is a legal requirement to report them to the Medicines and Healthcare Products Regulatory Agency (MHRA) (the UK Responsible Body under the Blood Safety and Quality Regulations, 2005).<sup>61</sup>

They should also be reported to the UK SHOT haemovigilance scheme to contribute to analysis of transfusion hazards and recommendations for improved safety. The latter is not a legal requirement but is mandated by laboratory accreditation and hospital quality assurance schemes and should therefore be considered a professional requirement. Reporters may wish to classify the reaction, as set out in Appendices S3 and S4. However, as classification can be difficult, the SHOT organisation will aid in classification into the appropriate category and provide a tool 'definitions of current SHOT reporting categories and what to report' (available on SHOT website).

### Reporting to the blood transfusion service

This is essential when bacterial contamination of transfused components may have occurred, when TRALI is suspected or there is severe neutropenia or thrombocytopenia associated with an ATR, as associated components from the implicated donation must be removed from the blood supply.<sup>62</sup> A transfusion medicine specialist will also be available to

give advice on the choice of components for future transfusion and the need for investigation of donors. Hospitals should have clear mechanisms in place to ensure prompt and effective communication with the blood service.

## Reporting within the hospital

All healthcare organisations should have clear and effective systems in place for reporting transfusion incidents through local risk management and clinical governance structures and review by the Hospital Transfusion Committee. Patients with moderate or severe ATR should be reviewed by the Hospital Transfusion Team to:

1. Assess the appropriateness of management and investigations;
2. Plan management of future transfusions for the patient;
3. Ensure the suspected reaction has been reported to the MHRA, SHOT and blood service as appropriate;
4. Review the appropriateness of the transfusion;
5. Identify practice concerns, lessons to be learnt and any training requirements;
6. Identify and monitor trends.

## RECOMMENDATION

- All transfusion reactions except mild febrile and/or allergic reactions must be reported to appropriate regulatory and haemovigilance organisations (MHRA and SHOT) and should also be reviewed within the hospital. (1C)

SHOT provides resources to support reporting and structured review of reaction incidents. See "Current Resources" section of the SHOT website, [www.shotuk.org](http://www.shotuk.org)

## TOPICS FOR AUDIT

Audit of acute transfusion reactions within a hospital, including documentation, management, internal and external reporting and planning of subsequent transfusions.

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## CONFLICT OF INTEREST STATEMENT

The BSH paid the expenses incurred during the writing of this guidance. All authors have made a full declaration of interests to the BSH and Task Force Chairs which may be viewed on request. None of the authors have any relevant conflicts of interest to declare.

## REVIEW PROCESS

Members of the writing group will inform the writing group Chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant Task Force and the literature search will be re-run every 3 years to search systematically for any new evidence that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made, an addendum will be published on the BSH guidelines website ([www.b-s-h.org.uk/guidelines](http://www.b-s-h.org.uk/guidelines)).

## DISCLAIMER

While the advice and information in this guidance is believed to be true and accurate at the time of going to press, neither the authors, the BSH nor the publishers accept any legal responsibility for the content of this guidance.

## AUDIT TOOL

Blank Audit template can be found on the [www.b-s-h.org.uk](http://www.b-s-h.org.uk)

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

[Corrections made on 5 October 2023, after first online publication: The Supporting Information was corrected in this version.]

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# Red Blood Cell Transfusion

## 2023 AABB International Guidelines

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**IMPORTANCE** Red blood cell transfusion is a common medical intervention with benefits and harms.

**OBJECTIVE** To provide recommendations for use of red blood cell transfusion in adults and children.

**EVIDENCE REVIEW** Standards for trustworthy guidelines were followed, including using Grading of Recommendations Assessment, Development and Evaluation methods, managing conflicts of interest, and making values and preferences explicit. Evidence from systematic reviews of randomized controlled trials was reviewed.

**FINDINGS** For adults, 45 randomized controlled trials with 20 599 participants compared restrictive hemoglobin-based transfusion thresholds, typically 7 to 8 g/dL, with liberal transfusion thresholds of 9 to 10 g/dL. For pediatric patients, 7 randomized controlled trials with 2730 participants compared a variety of restrictive and liberal transfusion thresholds. For most patient populations, results provided moderate quality evidence that restrictive transfusion thresholds did not adversely affect patient-important outcomes.

Recommendation 1: for hospitalized adult patients who are hemodynamically stable, the international panel recommends a restrictive transfusion strategy considering transfusion when the hemoglobin concentration is less than 7 g/dL (strong recommendation, moderate certainty evidence). In accordance with the restrictive strategy threshold used in most trials, clinicians may choose a threshold of 7.5 g/dL for patients undergoing cardiac surgery and 8 g/dL for those undergoing orthopedic surgery or those with preexisting cardiovascular disease. Recommendation 2: for hospitalized adult patients with hematologic and oncologic disorders, the panel suggests a restrictive transfusion strategy considering transfusion when the hemoglobin concentration is less than 7 g/dL (conditional recommendations, low certainty evidence). Recommendation 3: for critically ill children and those at risk of critical illness who are hemodynamically stable and without a hemoglobinopathy, cyanotic cardiac condition, or severe hypoxemia, the international panel recommends a restrictive transfusion strategy considering transfusion when the hemoglobin concentration is less than 7 g/dL (strong recommendation, moderate certainty evidence). Recommendation 4: for hemodynamically stable children with congenital heart disease, the international panel suggests a transfusion threshold that is based on the cardiac abnormality and stage of surgical repair: 7 g/dL (biventricular repair), 9 g/dL (single-ventricle palliation), or 7 to 9 g/dL (uncorrected congenital heart disease) (conditional recommendation, low certainty evidence).

**CONCLUSIONS AND RELEVANCE** It is good practice to consider overall clinical context and alternative therapies to transfusion when making transfusion decisions about an individual patient.

+ Viewpoint

+ Supplemental content

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**R**ed blood cell (RBC) transfusion is a common and costly treatment; approximately 118 million units of blood are collected worldwide each year.<sup>1,2</sup> Clinicians should offer RBC transfusion to patients only when benefits outweigh harms. Harms include infectious and noninfectious complications; although serious reactions are infrequent, there remains potential for substantial harm (Table 1).<sup>3,4</sup> Patient advocacy groups support minimizing harms by avoiding transfusions without clear benefit.<sup>5</sup>

Although the average acquisition cost of a unit of RBCs is \$215 in the United States,<sup>6,7</sup> it varies by country and region. Acquisition costs do not typically cover expenses of distribution, storage, processing, administration, and monitoring for complications.<sup>7,8</sup> Many blood transfusion providers face challenges, exacerbated by the COVID-19 pandemic, in maintaining adequate stocks of RBCs.<sup>9</sup>

Randomized controlled trials (RCTs) assessing outcomes of different transfusion thresholds typically compare higher hemoglobin thresholds (liberal transfusion strategy) with lower ones (restrictive transfusion strategy) for RBC transfusions. The numbers of these trials continue to increase. AABB guidelines in 2012 included 19 RCTs; in 2016, 31 RCTs.<sup>10,11</sup> In 2018, the Transfusion and Anemia Expertise Initiative published guidelines based on 5 RCTs for RBC transfusion in critically ill children.<sup>12</sup> In 2021, an updated Cochrane systematic review included 48 trials.<sup>13</sup> Given the expanded evidence base and the prior absence of AABB guidelines specific to children, we reexamined the transfusion threshold evidence and provide updated guidance.

## Guideline Development Process

The AABB commissioned and funded updated guidelines through the AABB Clinical Transfusion Medicine Committee. To encourage wide implementation of the recommendations, the board of directors supported recruiting experts in RBC transfusion from international professional organizations (eAppendix in the *Supplement*). These recommendations were developed in collaboration with and are endorsed by the International Society of Blood Transfusion, International Collaboration for Transfusion Medicine Guidelines, the Society of Critical Care Medicine, the European Blood Alliance, and the Society for the Advancement of Patient Blood Management.

These guidelines follow existing standards of trustworthiness,<sup>14</sup> including use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for summarizing evidence and moving from evidence to recommendations<sup>15</sup> to provide credible recommendations for clinicians caring for adults and children considered for RBC transfusions. These guidelines do not address transfusion in preterm neonates.

## Perspective

The panel chose individual patients as the primary perspective but also considered public health considerations; for example, supply of blood.

## Panel Composition and Conflicts

The international panel included members with expertise in transfusion medicine, supported by a GRADE methodologist (G.G.) and a patient partner (A.D.) (eAppendix in the *Supplement*). In accordance with

**Table 1. Approximate Per-Unit Risk for Red Blood Cell (RBC) Transfusion in the US<sup>a</sup>**

Adverse event	Approximate risk per RBC transfusion
Febrile reaction	1:161 <sup>3</sup>
Allergic reaction	1:345 <sup>3</sup>
Transfusion-associated circulatory overload	1:125 <sup>3</sup>
Transfusion-related acute lung injury	1:1250 <sup>3</sup>
Anaphylactic reactions	1:5000 <sup>3</sup>
Hepatitis B virus	1:1 100 000 <sup>4</sup>
Hepatitis C virus	1:1 200 000 <sup>4</sup>
HIV	1:1 600 000 <sup>4</sup>

<sup>a</sup> The incidence of noninfectious complications of transfusion reactions is based on active surveillance from 4 institutions. These rates will vary according to patient population (national databases vs hospital experience) and reporting practices and criteria (active, passive, severity, case definition, and others). The estimated incidence of infectious complications is derived from the Transfusion-Transmissible Infections Monitoring System.

AABB policy, individual members disclosed all potential financial, professional, or personal conflicts of interest; none had substantive conflicts.<sup>16</sup> Five members were authors of trials included in a systematic review on transfusion thresholds (J.L.C., S.J.S., Y.L., C.S.-O., and E.M.W.) and did not vote on corresponding recommendations.

## Population, Intervention, Comparator, and Outcomes Questions

We provide recommendations for 2 questions:

- For hospitalized, hemodynamically stable adult patients, should clinicians transfuse with a restrictive strategy (typical hemoglobin level <7.8 g/dL) vs a liberal strategy (typical hemoglobin level <9.10 g/dL)?
- For hospitalized, hemodynamically stable pediatric patients (a) without congenital heart disease (infancy to 16 years), should clinicians transfuse with a restrictive strategy (hemoglobin level <7.8 g/dL) vs a liberal strategy (hemoglobin level <9.10 g/dL); and (b) with congenital heart disease, should clinicians transfuse with a restrictive vs liberal strategy based on the cardiac lesion?

We provide recommendations for patients with acute or prolonged need of transfusions, but not for those who are transfusion dependent (eg, hemoglobinopathies). For adults, we examined subgroups in which the harm and benefit of a particular transfusion threshold might differ from that of overall populations: preexisting coronary artery disease, cardiac surgery, orthopedic surgery, and oncologic or hematologic conditions.

We examined subgroups of children in whom the risk and benefit of transfusion threshold might differ from that of the overall populations of patients: those with heart disease (congenital or acquired) or surgery and hematologic or oncologic conditions. We excluded trials of preterm neonates, which have been reviewed elsewhere.<sup>17</sup>

## Values and Preferences

Recommendations are based on the following values and preferences:

- Avoid the adverse effects after RBC transfusion (high value).
- Conserve resources related to RBC transfusions (high value) to ensure blood is available for individuals who need it most.
- Prefer the demonstrated benefits of a restrictive transfusion policy despite the remaining possibility of a small increase in mortality.

## Comments and Modification

J.L.C., S.J.S., G.G., S.V., and M.B.P. prepared the draft guideline document that was modified and approved by all panel members and the AABB Clinical Transfusion Medicine Committee. Subsequently, the AABB board of directors and international partner organizations also reviewed the guidelines.

## Evidence Review and Grading

### Systematic Review

We developed recommendations based on recently published systematic reviews of transfusion thresholds in adults (Cochrane review conducted in 2021)<sup>13</sup> and children (Transfusion and Anemia Expertise Initiative, 2018),<sup>12</sup> supported by literature searches up to February 2021. We reviewed evidence from 45 RCTs with 20 599 adults, 5 RCTs identified within the Transfusion and Anemia Expertise Initiative in 2018, and 2 additional pediatric trials (the 5 RCTs and 2 pediatric trials had a total of 2730 participants).<sup>18–20</sup> The systematic reviews included RCTs in which the transfusion groups were assigned based on a clear transfusion threshold, described as the hemoglobin concentration or hematocrit level required before RBC transfusion. Outcomes in adults included 30-day mortality, nonfatal myocardial infarction, pulmonary edema or congestive heart failure, stroke, thromboembolism, acute kidney injury, infection, hemorrhage, mental confusion, proportion of patients with an allogeneic or autologous RBC transfusion, hemoglobin concentration (postoperative or discharge), number of RBC units transfused, and quality of life. An updated search conducted in January 2023 identified 3 trials with 151 patients.<sup>21–23</sup> For children, outcomes included mortality, thromboembolism, infection, and transfusion requirements.

### Analysis

We assessed risk of bias in each RCT as recommended by Cochrane,<sup>24</sup> assessed statistical heterogeneity by both  $I^2$  and  $\chi^2$  tests,<sup>25</sup> and used the Instrument to Assess the Credibility of Effect Modification Analyses criteria for making inferences regarding subgroup effects.<sup>26</sup> All analyses were performed with Review Manager version 5.4 (Cochrane Collaboration).<sup>27</sup> Relative risks and the corresponding 95% CIs were calculated for each outcome with random-effects models<sup>28</sup> unless counterintuitive results mandated use of a fixed-effect model. We calculated absolute risks by applying the relative effect to the median of control group risks. When events were anticipated to be rare (eg, for thromboembolism), the Peto odds ratio informed relative effect estimates.

### Rating Quality of Evidence and Making Recommendations

We used GRADE methodology to develop these guidelines (see the Supplement).<sup>15,29</sup> The panel came to consensus for quality of evidence ratings that were included in summary of findings tables that served as the bases for panel judgments.<sup>30</sup> In moving from evidence to recommendations, the panel considered criteria in GRADE's evidence to decision framework.<sup>31</sup> The panel came to consensus for all recommendations except for using different restrictive strategy thresholds by clinical subgroup in which a vote was required.

## Good Practice Statement

In deciding when a particular patient should undergo transfusion, the panel considers it good clinical practice to consider not only the hemoglobin concentration but also symptoms, signs, other laboratory data, patients' values and preferences, and the overall clinical context. Relevant variables include the rate of hemoglobin level decline, intravascular volume status, dyspnea, decreased exercise tolerance, lightheadedness, chest pain thought to be cardiac in origin, and hypotension or tachycardia unresponsive to fluid challenge. Clinicians should consider alternatives to transfusion, including medical treatment of anemia and blood conservation strategies.

## Disclaimer

This practice guideline will not apply to all individual RBC transfusion decisions.

## Recommendations for Adults

### Recommendation 1

For hospitalized adult patients who are hemodynamically stable, the international panel recommends a restrictive RBC transfusion strategy in which the transfusion is considered when the hemoglobin concentration is less than 7 g/dL (strong recommendation, moderate certainty evidence).

Remark: in accordance with the restrictive strategy threshold used in most of the trials for subgroups of patients, clinicians may choose a threshold of 7.5 g/dL for patients undergoing cardiac surgery and 8 g/dL for patients undergoing orthopedic surgery or those with preexisting cardiovascular disease.

### Recommendation 2

For hospitalized adult patients, the panel suggests a restrictive RBC transfusion strategy in which transfusion is considered when the hemoglobin concentration is less than 7 g/dL in those with hematologic and oncologic disorders (conditional recommendation, low certainty evidence).

## Evidence Summary for Adults

The 45 RCTs with adult participants were conducted across a range of settings, including orthopedic surgery ( $n = 11$ ), cardiac surgery ( $n = 8$ ), hematologic and oncologic conditions ( $n = 7$ ), critical care ( $n = 8$ ), acute blood loss ( $n = 6$ ), acute myocardial infarction ( $n = 3$ ), and vascular surgery ( $n = 2$ ). The most common liberal transfusion threshold was 9 to 10 g/dL and the most common restrictive threshold was 7 to 8 g/dL.

Table 2 presents the summary of findings comparing restrictive with liberal transfusion strategies for 30-day mortality, multiple morbidities, and transfusion requirements. Thirty trials including data from 16 092 participants evaluated 30-day mortality, with a pooled relative risk of 1.00 (95% CI, 0.86-1.16). The baseline mortality rate was 8.3%, and an absolute difference between transfusion strategies was 0% (95% CI, 1.2% fewer to 1.3% more deaths) (high certainty). The restrictive strategy resulted in a 32.4% absolute reduction (95% CI, 37.3%-27.5% fewer deaths) in receiving a transfusion.

Chance may explain differences in mortality estimates among the clinical conditions (test for subgroup differences,  $P = .34$ ). Given limited trial data in hematologic malignancies (2 trials,  $N = 149$  participants) and an upper CI limit consistent with substantial harm

**Table 2.** Summary of Findings in Trials Comparing Liberal vs Restrictive Transfusion Strategies on Mortality, Morbidity, and Blood Transfusion in Adults

Outcome, No. of participants (No. of RCTs)	Relative effect (95% CI)	Absolute effects, %			Certainty	Plain language summary
		Restrictive	Liberal	Difference (95% CI)		
30-d Mortality, N = 16 092 (30)	RR, 1.00 (0.86-1.16)	8.3	8.3	0.0 Fewer (1.2 fewer to 1.3 more)	High	Transfusion threshold likely has little or no effect on mortality
MI, N = 14 370 (23)	RR, 1.04 (0.87-1.24)	3.3	3.2	0.1 More (0.4 fewer to 0.8 more)	High	Transfusion threshold has little or no effect on MI
CHF, N = 6610 (15)	RR, 0.86 (0.56-1.33)	3.2	3.7	0.5 Fewer (1.6 fewer to 1.2 more)	Low <sup>a,b</sup>	Transfusion threshold likely has little or no effect on CHF
CVA, N = 13 985 (19)	RR, 0.84 (0.64-1.09)	1.4	1.7	0.3 Fewer (0.6 fewer to 0.2 more)	High	Transfusion threshold likely has little or no effect on CVA
Rebleeding, N = 3412 (8)	RR, 0.80 (0.59-1.09)	12.6	15.8	3.2 Fewer (6.5 fewer to 1.4 to more)	Moderate <sup>a</sup>	Transfusion threshold likely has little or no effect on rebleeding
Infection, N = 16 466 (24)	RR, 0.98 (0.89-1.09)	13.6	13.9	0.3 Fewer (1.5 fewer to 1.2 more)	High	Transfusion threshold likely has little or no effect on infection
Thromboembolism, N = 4201 (13)	OR, 1.11 (0.65-1.88)	1.7	1.5	0.2 More (0.5 fewer to 1.3 more)	Moderate <sup>b</sup>	Transfusion threshold likely has little or no effect on thromboembolism
Delirium, N = 6442 (9)	RR, 1.11 (0.88-1.40)	11.9	10.7	1.2 More (1.3 fewer to 4.3 more)	Moderate <sup>b</sup>	Transfusion threshold likely has little or no effect on delirium
Transfusion, N = 19 419 (41)	RR, 0.60 (0.54-0.66)	48.6	81.0	32.4 Fewer (37.3 to 27.5 fewer)	High	Restrictive transfusion threshold results in large reduction in transfusion

Abbreviations: CHF, congestive heart failure; CVA, cerebrovascular accident; MI, myocardial infarction; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

<sup>a</sup> Downgraded for inconsistency. 95% CIs were calculated with Review Manager version 5.4 (Cochrane).<sup>27</sup> See eFigures 1 through 9 in the Supplement for details.

<sup>b</sup> Downgraded for imprecision.

**Table 3.** Summary of Findings in Trials of Patients With Hematologic Malignancies and Myocardial Infarction Comparing Liberal vs Restrictive Transfusion Strategies on 30-Day Mortality

Patient group (No. of RCTs)	30-d Mortality relative effect (95% CI)	Absolute effects, %			Certainty
		Restrictive	Liberal	Difference (95% CI)	
Hematologic malignancies, N = 149 (2)	RR, 0.37 (0.07-1.95)	2.4	6.6	4.1 fewer (6.1 fewer to 6.2 more)	Low <sup>a</sup>
Myocardial infarction, N = 820 (3)	RR, 0.99 (0.59-1.65) <sup>b</sup>	6.7	6.8	0.1 fewer (2.8 fewer to 4.4 more)	Low <sup>c,d</sup>

Abbreviations: RCT, randomized controlled trial; RR, relative risk.

<sup>a</sup> Two downgrades for very serious imprecision.

<sup>b</sup> Note that in consultation with a methodologist (GG), a fixed effect model has been presented for this outcome due to low event rate. Random effects model

absolute difference = 4.1% more (4.2 fewer and 39.7 more).

<sup>c</sup> Imprecision.

<sup>d</sup> Inconsistency. 95% CIs calculated with Review Manager version 5.4 (Cochrane Collaboration).<sup>27</sup>

(6.2% rate of increased deaths in the restrictive transfusion strategy), certainty of the evidence for mortality in this population was rated low (Table 3). Given heterogeneity in results and an upper CI limit consistent with substantial harm (4.4% rate of increased deaths in the restrictive transfusion strategy), the certainty of the evidence was rated low for mortality in acute myocardial infarction (Table 3).

There were no apparent differences between transfusion strategies for the morbidity outcomes (Table 2). Data from 3 RCTs that enrolled 448 participants suggested the risk of bleeding in hematology and oncology patients was uninfluenced by transfusion strategy (relative risk, 1.03; 95% CI, 0.87 to 1.23; absolute difference, 0.6%; 2.7% fewer to 4.8% more bleeding events).<sup>32-34</sup>

The most common restrictive transfusion strategy applied in the trials was 7 or 8 g/dL (Figure), although variations included critical care and cardiac surgery trials that used a transfusion strategy of 7 to 7.5 g/dL and orthopedic and acute myocardial infarction trials that used a restrictive strategy of 8 g/dL.<sup>35-64</sup>

#### Rationale for Recommendations for Adults

The panel recommends that RBC transfusion be administered using a restrictive transfusion strategy of 7 g/dL for most hemody-

namically stable adults (strong recommendation, high certainty evidence).

The panel was divided (by vote) on whether to recommend different restrictive transfusion strategy thresholds by clinical subgroup. The rationale for recommending a universal threshold of 7 g/dL is that many trials used this threshold, and there is no strong clinical or biological basis for expecting different effects between 7 and 8 g/dL (with the possible exception of cardiovascular disease and hematology or oncology; see later). Furthermore, the effects on mortality were consistent across all subgroups, and there were no apparent differences in outcomes between trials that used a threshold of 7 and 8 g/dL (see earlier) (Figure). Recommending a hemoglobin threshold of 7 g/dL would conserve more blood.

An alternative view is that the recommendations should closely follow the clinical trial evidence and avoid extrapolating trial results when a threshold of 7 g/dL has not been explicitly tested. Most of the trials in orthopedic surgery used a threshold of 8 g/dL, and the largest trial conducted in cardiac surgery used a threshold of 7.5 g/dL. Some members of the panel thought that higher hemoglobin thresholds might improve outcomes other than mortality, including improved function and recovery after surgery or acute illness.

Figure. Comparison of Randomized Trials in Adults Using Different Restrictive Transfusions for the Outcome of Mortality at 30 Days

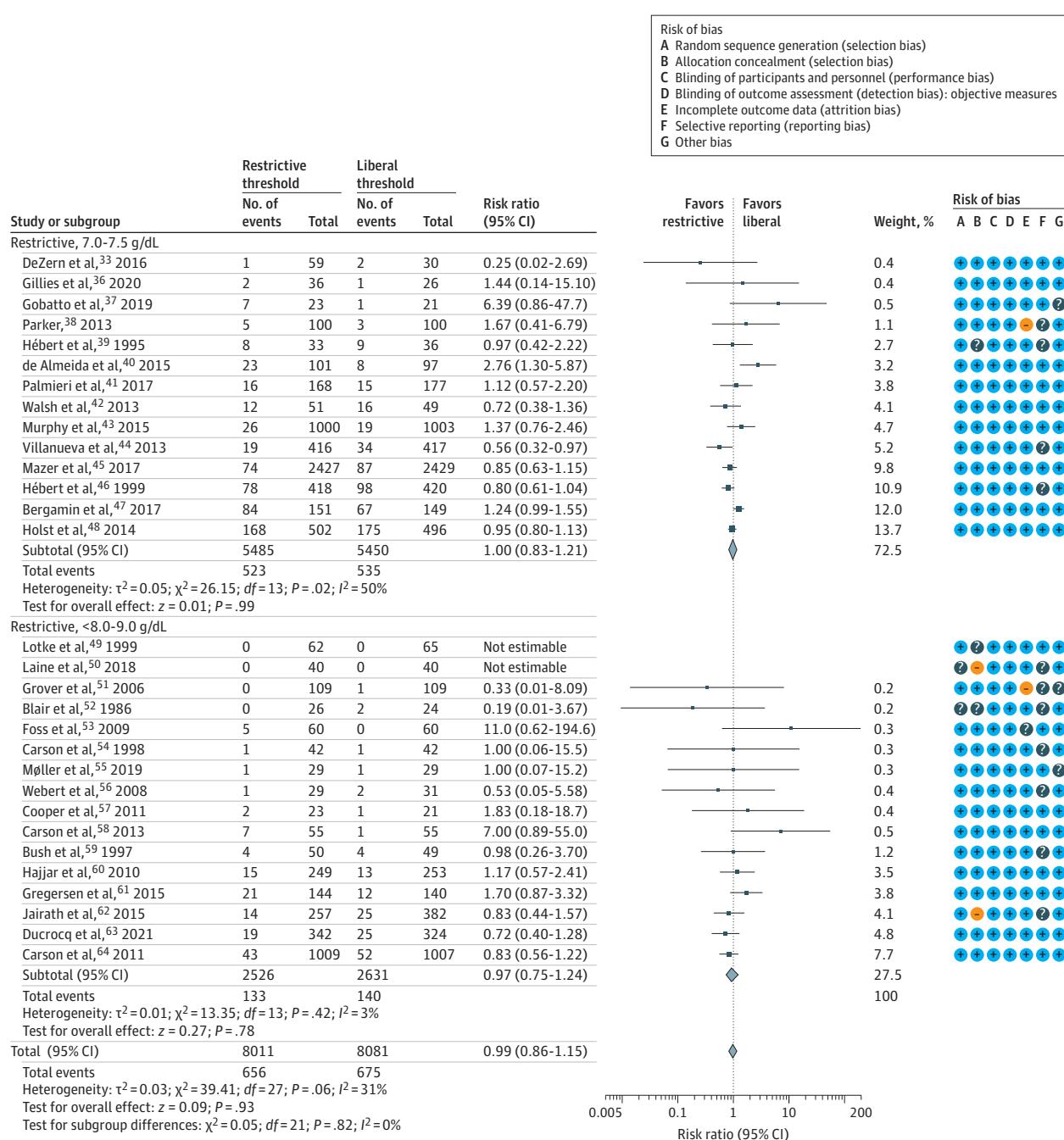


Figure modified from the Cochrane review<sup>13</sup> by removing 1 trial performed with pediatric patients (Lacroix et al<sup>35</sup>) and placing a second trial (Laine et al<sup>50</sup>) in the correct subgroup. Relative risks and the corresponding 95% CIs were calculated

for each outcome with random-effects models unless counterintuitive results mandated use of a fixed-effect model. The blue pluses indicate low risk of bias; gray question marks, unclear risk of bias; and orange minuses, high risk of bias.

For patients with acute and chronic ischemic cardiac disease, there remains substantial uncertainty regarding the safety of restrictive thresholds. As in the AABB's previous guidelines,<sup>10,11</sup> the panel chose not to recommend for or against a liberal or restrictive transfusion threshold for patients with acute myocardial infarction. Although the pooled estimates of effects on mortality with acute myocardial infarction were almost identical to the overall effects, the

absolute and relative risk estimates were imprecise, with wide CIs. The panel noted that the MINT trial (including 3500 participants with acute myocardial infarction) is nearing completion. MINT compares a liberal transfusion at 10 g/dL with a restrictive transfusion strategy of 7 to 8 g/dL.<sup>65</sup>

In the setting of hematology and oncology inpatients, the panel suggests transfusion at 7 g/dL (conditional, low certainty evidence).

**Table 4.** Summary of Findings in Trials Comparing Liberal vs Restrictive Transfusion Strategies on Mortality, Morbidity, and Blood Transfusion in Children

Outcome, No. of participants (No. of RCTs)	Relative effect (95% CI)	Anticipated absolute effects (95% CI), %			Certainty	Plain language summary
		Restrictive	Liberal	Difference (95% CI)		
Participants exposed to blood transfusion, 799 (2)	RR, 0.51 (0.41-0.65)	48.0	94.2	46.2 Fewer (55.6 to 33 fewer)	High	Restrictive transfusion threshold has a large effect on reduction of transfusion
30-d Mortality (follow-up range, 28-30 d), 972 (5)	RR, 0.44 (0.04-4.45)	1.7	3.9	2.2 Fewer (3.8 fewer to 13.5 more)	Moderate <sup>a,b</sup>	Transfusion threshold likely has little effect on mortality
Pneumonia, 744 (2)	RR, 1.14 (0.58-2.23)	4.6	4.0	0.6 More (1.7 fewer to 5 more)	Moderate <sup>a</sup>	Transfusion threshold likely has little or no effect on pneumonia
Thrombosis (follow-up, 28 d), 799 (2)	OR, 1.78 (0.61-5.22)	2.3	1.3	1.0 More (0.5 fewer to 5.4 more)	Low <sup>c</sup>	Transfusion threshold may have little or no effect on thrombosis
30-d Mortality subgroup analysis by clinical specialties (cardiac surgery), 454 (4)	RR, 0.62 (0.12-3.13)	1.1	1.8	0.7 Fewer (1.6 to 3.8 more)	Low <sup>a,b,d</sup>	Transfusion threshold may have little effect on mortality

Abbreviations: OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

<sup>a</sup> One downgrade for imprecision; even the largest included study was not adequately powered for the outcome of mortality. Smaller studies were not always informative because they included low-risk populations only, terminated early, or reported no or few events.

<sup>b</sup> For 1 study reporting mortality data only within the scope of its study period, we obtained supplementary data for 30 days.

<sup>c</sup> Two downgrades for serious imprecision (rare event).

<sup>d</sup> Downgraded for imprecision. 95% CIs were calculated with Review Manager version 5.4 (Cochrane Collaboration).<sup>27</sup> See eFigures 10 through 14 in the Supplement for details.

Although the number of patients enrolled in these trials was smaller than that in many other clinical subgroups, because new RCTs have suggested neither harm nor increased bleeding when using a restrictive threshold, this recommendation differs from the 2016 guidelines.<sup>11</sup> There were insufficient trial data to inform recommendations in outpatient transfusion management.

### Recommendations for Children

#### Recommendation 3

For critically ill children and hospitalized children at risk of critical illness who are hemodynamically stable and without a transfusion-dependent hemoglobinopathy, cyanotic cardiac condition, or severe hypoxemia, the international panel recommends a restrictive transfusion strategy in which a transfusion is considered when the hemoglobin level is less than 7 g/dL compared with one of less than 9.5 g/dL (strong recommendation, moderate certainty evidence).

#### Recommendation 4

The international panel suggests considering a transfusion threshold for hemodynamically stable children with congenital heart disease that is based on the cardiac abnormality and stage of surgical repair: 7 g/dL (biventricular repair), 9 g/dL (single-ventricle palliation), or 7 to 9 g/dL (uncorrected congenital heart disease) (conditional recommendation, low certainty evidence).

### Evidence Summary for Children

The populations of children included in the RCTs were critically ill patients ( $n = 2$ ),<sup>20,35</sup> those with hematologic conditions ( $n = 1$ ),<sup>66</sup> those with acquired and congenital heart disease ( $n = 3$ ),<sup>67-69</sup> and those with severe (malarial) anemia ( $n = 1$ )<sup>18,19</sup> (Table 4). The largest single intensive care unit RCT reported a 51.8% absolute reduction in transfusions in the restrictive strategy group compared with the liberal strategy group,<sup>35</sup> with no significant difference reported for 30-day mortality within a meta-analysis of 5 RCTs (relative risk, 0.44; 95% CI, 0.04-4.45). In the latter analysis, the baseline mortality rate was 3.9%, with an absolute difference of 1.7% (95% CI,

0.2% fewer to 17.5% more deaths) (moderate certainty). There were no clear differences in the morbidity outcomes (Table 4). We evaluated the transfusion strategies on 30-day mortality in subgroups of heart disease (acquired and congenital) (eFigure 12 in the Supplement). Chance may explain differences in mortality among the clinical populations. The certainty of the evidence was rated as low because of small sample size and various surgical settings and clinical conditions.

### Rationale for Recommendations for Children

It is likely that mortality is similar for restrictive strategies compared with liberal ones (moderate certainty, rated down because of inconsistency and the remaining possibility of an increase in 30-day mortality after application of a restrictive strategy of up to 3%).

Although the direct evidence was dominated by a single trial,<sup>35</sup> a large well-conducted RCT of transfusion volumes and timing in anemic children (hemoglobin level <6 g/dL) with malaria also supported the safety of a restrictive transfusion threshold. The panel concluded this evidence supported a strong recommendation.<sup>18,19</sup>

Children with acquired or congenital heart disease form a subgroup in which there remains uncertainty regarding the pathophysiological safety of restrictive thresholds, and the RCTs had recruited different populations of children undergoing surgery.

### Discussion

The expanding number of RCTs of RBC transfusion thresholds informs best practice in adults and children. Many of the RCTs tested different protocols including thresholds for RBC transfusion that varied by clinical setting. The panel debated whether to recommend a threshold of 7 g/dL for all hemodynamically stable adults or adopt a higher threshold in select clinical subgroups (cardiac surgery, 7.5 g/dL; orthopedic surgery and chronic cardiovascular disease, 8 g/dL), ultimately concluding that each approach has its merits. Our guideline also now incorporates specific guidance

for hemodynamically stable children, and the findings support recommendations for a restrictive strategy (threshold <7 g/dL for children, excluding those with congenital heart disease). Minimizing unnecessary complications of transfusion and responding to the ongoing global challenges of having a safe and secure blood supply will require effective strategies, including blood management programs, for implementation of these guidelines.

Good transfusion practice should rely not only on hemoglobin concentration thresholds but also incorporation of patients' symptoms, signs, comorbid conditions, rate of bleeding, values, and preferences. This guidance is particularly important because clinicians commonly use only hemoglobin concentration to decide when to transfuse.<sup>70</sup> Blood management programs that audit blood should attend to these broader considerations in their policies and decisions. Given that RCTs demonstrated no effect on mortality,<sup>71,72</sup> the storage age of transfused RBCs need not be considered in transfusion decisions.

Similar to older guidelines,<sup>73-78</sup> this guideline and other guidelines published after 2016 continue to recommend restrictive transfusion strategies<sup>79-83</sup> (Box).

### Research Recommendations

Ongoing trials for patients with acute myocardial infarction, vascular disease, and neurologic disorders will inform transfusion practice.<sup>17</sup> Further analyses of subgroups of trials using individual patient data from existing trials are needed by age, sex, preexisting cardiovascular disease, pregnancy status, and other clinical factors. There are gaps in the evidence regarding the needs of individuals with myelodysplastic syndromes who are transfusion dependent. To modify symptoms of anemia, such people may require higher thresholds for transfusions. Given the findings indicating the safety of restrictive thresholds, new trial designs should focus on the safety of lower transfusion thresholds (eg, 5-6 g/dL), incorporation of physiologic parameters, and the conduct of health economic analyses.

## Conclusion

Our panel recommends restrictive transfusion strategies, typically with a threshold of 7 g/dL for both adult and pediatric patients. The

### Box. Red Blood Cell Transfusion Guidelines Since 2016

#### Society and Recommendation

UK National Clinical Guidelines Centre (2016)<sup>79</sup>

Restrictive threshold (7 g/dL) for patients who do not have major hemorrhage or acute coronary syndrome or need long-term transfusion. In acute coronary syndrome, transfusion should be considered at a threshold of 8 g/dL. Clinicians should consider setting individual targets for patients with chronic anemia.

European Society of Anaesthesiology (2017)<sup>80</sup>

Target hemoglobin level of 7.9 g/dL in patients with active bleeding

Frankfurt Germany Consensus conference (2018)<sup>81</sup>

Varied depending on clinical setting: 7 g/dL for critically ill patients, 7.5 g/dL in cardiac surgery, 8 g/dL in hip fracture and cardiovascular disease, and 7-8 g/dL in acute gastrointestinal bleeding

Pediatric Critical Care Transfusion and Anemia Expertise Initiative (2018)<sup>12</sup>

Varied depending on clinical setting: 7 g/dL for hemodynamically stable critically ill children; for hemodynamically stable children with congenital heart disease, varied based on cardiac abnormality and stage of repair; 7 g/dL biventricular repair, 9 g/dL stage 1 and stage 2 palliation

Society of Cardiovascular Anesthesiologists (2019)<sup>82</sup>

Transfusion threshold of 7.5 g/dL is reasonable in cardiac surgery

The Society of Thoracic Surgeons and affiliated groups (2021)<sup>83</sup>

Restrictive transfusion strategy, although a specific hemoglobin level was not provided

panel recognizes important additional considerations, including signs, symptoms, comorbid conditions, and patient values and preferences, that will differ between patients. The recommendation is strong, based on moderate certainty evidence for most patients, but conditional, based on lower certainty evidence subgroups that include hematologic and oncologic disorders in adults and cyanotic cardiac condition in infants.

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**Conflict of Interest Disclosures:** Dr Carson reported serving as chair of the data and safety monitoring board for Cerrus for a clinical trial on a treatment system to pathogen-reduce human blood products outside the submitted work; being the principal investigator of a National Heart, Lung, and Blood Institute-supported trial called Myocardial Ischemia and Transfusion, which is evaluating transfusion thresholds in patients with acute myocardial infarction; and receiving financial support paid to his institution. Dr Stanworth reported receiving grants for multiple clinical trials of red blood cell transfusion to his institution, but no direct financial benefits outside the submitted work; receiving grants for red blood cell transfusion trials through his institutions; and being employed by NHSBT, who processes and manufactures red blood cells for transfusion in England. Dr Cohn reported being a paid staff member (chief medical officer) of the AABB during the conduct of the study. Dr Kaplan reported receiving a stipend from the Society of Critical Care Medicine for serving as president from 2020 to 2021 outside the submitted

work. Dr Lin reported receiving grants from Canadian Blood Services, consulting for Choosing Wisely Canada, and receiving grants from Octapharma outside the submitted work.

Dr Metcalf reported receiving speakers honoraria from Cerus Corporation outside the submitted work. Dr Pavenski reported serving as vice chair of the International Collaboration for Transfusion Medicine Guidelines and as director for North Americas, as well as serving on the board of directors for the International Society of Blood Transfusion. Dr Prochaska reported receiving fees for medicolegal consulting outside the submitted work. Dr Raval reported receiving consultancy fees from Sanofi Genzyme outside the submitted work. Dr Saifee reported nonfinancial support from AABB for travel during the conduct of the study.

Dr Zantek reported receiving fees from the Association for the Advancement of Blood and Biotherapies for travel to a meeting for guideline development during the conduct of the study; that her spouse is an employee of Boston Scientific and has financial interest in the company and in ENDO International outside the submitted work; and serving on the board of directors for the American Society for Apheresis, BloodNet, External Quality Assurance in Thrombosis and Hemostasis, and the North American Specialized Coagulation Laboratory Association. No other disclosures were reported.

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