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Closing the evidence to practice gap in neonatal transfusion medicine

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ABSTRACT

Significant resources are directed towards world-class research projects, but the findings are not necessarily translated into better healthcare outcomes, either at all or in a sustained way. There is a clear need to dedicate further resources to understanding how to promote the uptake of evidence and effectively change neonatal transfusion practice to improve outcomes. Approaching blood transfusion behaviour change more systematically, and working across disciplines and involving families, holds the potential to increase the rate of uptake of emerging evidence in clinical practice. This approach holds the potential to save costs, conserve resources, and improve clinical outcomes. Our paper focuses on the use of quality improvement to bridge the gap between evidence-based knowledge and transfusion practice in neonatal units around the world.

1. Introduction

Transfusion is no different to the many other areas in neonatal care that an evidence to practice gap exists [1]. Getting evidence into practice is a priority for the families of vulnerable infants born preterm or critically ill and for the healthcare professionals who care for them. Transfusion of blood products is common in neonatal units, with preterm infants remaining the most heavily transfused patient population with the longest life span [2]. Despite this, the use of blood products outside of evidence-based clinical guidelines, primarily over transfusion, and significant variation in practice continues to occur in neonatal units around the world [3]. These practices persist despite improvements in the evidence base for transfusion, the existence of clinical guidelines, and numerous initiatives, including patient blood management, to reduce the inappropriate use of blood products [1]. It remains a complex endeavour to change clinicians' practice to align with best practice by getting them to stop using various interventions that are not supported by evidence, free from harm and truly necessary [4]. This equally applies to neonatal transfusion practice as much as it does in other areas of healthcare.

As a result of persistent evidence to practice gaps, patients fail to benefit optimally from advances in healthcare and are exposed to unnecessary risks, and healthcare systems are exposed to unnecessary expenditure resulting in significant opportunity costs [5]. This continued inability to get research evidence into everyday clinical practice remains, despite decades of attempts to improve this situation [6]. Millions of funds are directed towards world-class research projects, but the findings are not necessarily translated into better healthcare outcomes, either at all or in a sustained way. There is a clear need to dedicate further resources to understanding how to promote the uptake of evidence and effectively change neonatal transfusion practice [7]. This paper focuses on the use of quality improvement to bridge the gap between evidence-based knowledge and everyday transfusion practice in neonatal units.

1.1. A hopeful era

Neonatal transfusion practice is entering an exciting time with a new and rapid evolving high quality evidence-base for transfusion practices [8–10] and international collaborative research between neonatologists, paediatric intensivists, transfusion practitioners, haematologists, and nursing staff [11]. These developments offer an excellent opportunity to examine the ways to best implement evidence into everyday neonatal transfusion practice through the combined efforts of transfusion and neonatal healthcare professionals.

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2. Neonatal transfusion practice

Over the last 100 years, whilst significant developments in neonatal transfusion practice have occurred, the effects of blood transfusion on many important neonatal outcomes remain unknown [12]. The first report of a neonatal transfusion dates back to 1908 and describes the direct transfusion from a father's radial artery to his child's popliteal vein [13]. Transfusion of blood products in neonates continue to be a key component of care in those born preterm or critically ill. To help guide potential projects in quality improvement, we provide a brief overview of the current evidence base and consensus opinion in neonatal transfusion.

2.1. Current practice – red cells

In neonatal units today, red cells transfusions are most frequently undertaken to manage anaemia of prematurity [14]. A national audit in the United Kingdom [14] found the median (interquartile range) gestational age at birth was 27 (26–30) weeks, n = 1194, for the first red cell transfusion, with the majority (81%; 971) of first transfusions given to infants born at < 32 weeks' gestational age. Most first red cell transfusions were given for anaemia, with (60%) or without (21%) any associated symptoms. The majority of infants (75%) were either invasively ventilated or on continuous positive airway pressure at the time of their first red cell transfusion. A retrospective cohort study of preterm neonates born at <30 weeks' gestational age and cared for in neonatal units participating in the Canadian Neonatal Network (CNN) (2004–2012) was undertaken to evaluate blood product usage [2]. Of 14 868 eligible neonates admitted to during the study period, 8252 (56%) received at least one red cell transfusion.

An overview of the evidence base for red cell transfusion is provided in Table 1. Of note, the two long-awaited studies comparing liberal and restrictive red cell thresholds recently were published [15,16]. The ETTNO Randomised Clinical Trial [15] compared liberal and restrictive red cells thresholds among infants (birthweight <1000 g). The primary outcome (death or any of cognitive deficit, cerebral palsy, or severe visual or hearing impairment) occurred in 200/450 (44.4%) versus 205/478 (42.9%), with a difference of 1.6% (95% CI, −4.8%–7.9%; $P = 0.72$) [15]. The Transfusion of Prematures (TOP) trial examined whether a higher haemoglobin threshold for red cell transfusions compared with a lower threshold would reduce the risk of death or neurodevelopmental impairment at 22–26 months corrected age [16]. Of the 845 infants in the liberal group, 423 (50.1%) died or survived with neurodevelopmental impairment compared to 422 of 847 infants (49.8%) in the restrictive group (relative risk 1.00; 95% confidence interval [CI], 0.92 to 1.10; P = 0.93). At 2 years corrected age, the liberal and restrictive groups had similar incidences of death (16.2% and 15.0%, respectively) and neurodevelopmental impairment (39.6% and 40.3%, respectively).

2.2. Current practice – platelets

Platelet use remains prevalent in neonatal units, with 2151 (15%) of the 14 868 eligible neonates receiving at least one platelet transfusion in the previously discussed CNN study [2]. Until recently, information was lacking from randomised studies to compare clinically relevant outcomes associated with the commonly used platelet count thresholds in preterm infants with thrombocytopenia. However, the recent Platelets for Neonatal Thrombocytopenia (PlaNeT-2) study found an overall benefit of a prophylactic platelet transfusion threshold of 25×10^9 per litre compared with 50×10^9 per litre for major haemorrhage and/or death in preterm neonates (7% absolute-risk reduction) [10]. Additional analysis found that these harmful effects occurred in neonates who had both high and low baseline risks of death or haemorrhage [9]. This analysis was performed, as the PlaNeT-2 study was criticised for including too few neonates with early onset thrombocytopenia, with some clinicians hesitant to use the 25×10^9/L threshold for early onset thrombocytopenia. However, the secondary analysis provides proof of harm in the overall PlaNeT-2 population [9] and there remains no evidence that this effect is different in subgroups in the PlaNeT-2 study or any other studies [17]. A systematic review protocol examining the evidence for platelet transfusion thresholds and effect on death and major morbidity in neonates with thrombocytopenia has been recently published [18] and the completed review is highly anticipated.

An overview of the evidence base for platelet transfusion thresholds is provided in Table 1. Of note, a recent addendum to the British Society for Haematology (BSH) Guidelines on transfusion for fetuses, neonates, and older children [19] was made. The BSH now recommends that for preterm neonates with thrombocytopenia (platelet count below 25×10^9 per litre), platelet transfusions should be administered. For non-bleeding neonates, platelet transfusions should not be routinely administered if platelet count is $\geq 25 \times 10^9$ per litre.

2.3. Current practice – plasma

Plasma use is relatively common in neonatal units with 1556 (11%) of 14 868 eligible neonates receiving at least one plasma transfusion In the previously outlined CNN study [2]. Again, there remains limited evidence to guide the use of plasma in the neonatal unit. A recent review of the evidence-base found that transfusion of plasma to correct coagulation tests without active bleeding or before invasive procedures exposes neonates to infectious and non-infectious risks associated with transfusion, without providing any measurable clinical benefit [20]. A significant proportion of plasma transfusions in neonates are given to non-bleeding neonates with minor abnormalities in coagulation parameters of unclear significance. The evidence base is again summarised in Table 1. We remain in need of better diagnostic testing to identify which neonates would benefit most from plasma transfusion [21]. Our recommendation is to use plasma when active bleeding is present or before invasive procedures in those neonates with a risk of significant bleeding and who have an abnormal coagulation profile (defined as a prothrombin time or an activated partial thromboplastin time significantly above the normal gestational and postnatal age-related reference range) [20,21].

2.4. Current practice – other blood products

Other products used in the CNN database study included albumin at 915 (6%) and cryoprecipitate at 302 (2%) of 14 868 eligible neonates receiving at least one transfusion [2]. Additional blood products include intravenous immunoglobulin and recombinant factor VIIa. Intravenous immunoglobulin is used to reduce haemolysis in those born with alloimmune haemolytic disease (haemolytic disease of the fetus and newborn). The Cochrane review examining the use of immunoglobulin for alloimmune haemolytic disease found that although overall results show a significant reduction in the need for exchange transfusion in neonates treated with IVIg, the applicability of the results is limited because of low to very low quality of evidence [22]. We recommend reviewing and adapting the most relevant clinical practice guidelines, which include expert consensus opinion as necessary (Table 1), to guide practice.

2.5. Current practice – additional strategies

A number of evidence-based strategies to reduce the numbers of transfusions, generally red cell transfusions, exist. They include (1) deferred cord clamping [8] and (2) minimising blood sampling. Iatrogenic blood loss resulting from the intensive clinical monitoring for critically ill neonates in first weeks after birth is one of the key contributors to neonatal anaemia and the need for RBC transfusion [23]. A recent study found blood sampling resulted in a 58% depletion of the endogenous blood volume across postnatal days 1–14 (median 40.4 mL/kg,

Table 1
Overview of the evidence-base to guide neonatal transfusion practice.

Intervention	Citation	Study design	Level of Evidence[a]	Methodology/Number of participants/Population	Objective/Main outcome	Findings
Red Blood Cells	Whyte & Kirpalani 2011 [55]	Systematic review & meta-analysis	I	Four RCTs with total of 614 preterm neonates with birth weight <1500 g were included	Comparison of liberal versus restrictive red blood cell transfusion strategies on composite outcome of death or serious morbidity at initial hospital admission discharge[b]	No difference in liberal compared with restrictive haemoglobin thresholds in outcomes of death or serious morbidity Modest reduction in exposure to red cell transfusion and haemoglobin levels in restrictive compared to liberal threshold
	Franz et al., 2020 [15]	RCT	II	Multicentre RCT included 1013 neonates with a birth weight of <1000 g	Comparison of liberal versus restrictive red blood cell transfusion strategies on outcome of death or disability at 24 months corrected age	No difference in liberal compared with restrictive haemoglobin thresholds on likelihood of death or disability at 24 months of corrected age
	Kirpalani et al.[16]		II	Multicentre RCT included 1824 neonates between 22[c]0 and 28[c]6 weeks' GA	Comparison of liberal versus restrictive red blood cell transfusion strategies on outcome of death or neurodevelopmental impairment at 22–26 months corrected age	No difference in liberal compared with restrictive haemoglobin thresholds on likelihood of death or neurodevelopmental impairment at 22–26 months of corrected age Modest reduction in exposure to red cell transfusion and haemoglobin levels in restrictive compared to liberal threshold groups
Platelets	Fustolo-Gunnink et al. [56]	Systematic review & meta-analysis	I	Six studies, with total of 1580 neonates born <37 weeks' GA, were included (4 case control studies, total [n = 456],1 RCT [n = 152],1 cohort study [n = 972])	To investigate 1) If platelet count is associated with major bleeding; 2) Whether prophylactic platelet transfusions decrease risk of major bleeding in preterm infants; 3) If an association between various platelet indices (ie platelet mass or mean platelet volume) and major bleeding exist	Insufficient evidence to assess whether platelet counts are causally related to major haemorrhage Insufficient evidence to assess whether mean platelet volume or mass are implicated in major haemorrhage Possible association of increased risk of bleeding with platelet transfusion. This prompted further RCT [10] (see below)
	Curley et al., 2019 [10]	RCT	II	Multicentre RCT included 660 neonates born < 34 weeks' GA	Comparison of low vs high thresholds[d] for prophylactic platelet transfusion on composite outcome of death or major bleeding	Overall benefit of a low compared with high prophylactic platelet transfusion threshold on major bleeding and/or death in preterm neonates (ARR 7%)
	Fustolo-Gunnink et al., 2019 [9]		II	Additional analysis of above RCT (Curley et al. [10]) using a multivariate logistic regression model	Exploration of heterogeneity of treatment effect in original RCT and to examine effect of platelet transfusion thresholds on neonates with varying baseline outcome risk	Harmful effect of prophylactic platelet transfusion at high thresholds hold true for neonates with high baseline risk of death or major bleeding; appropriate to adopt low threshold in all preterm neonates despite baseline outcome risk
	Stanworth et al., 2009 [57]	Prospective observational study	III2	Cross-sectional, observational study included 169 neonates with platelet counts of $<60 \times 10^9$ platelets per litre	Frequency and timing of haemorrhage and utilisation of platelet transfusions	Despite 34% enrolled neonates developing platelet counts $< 20 \times 10^9$ per litre, only 9% developed major haemorrhage Most platelet transfusions were given to neonates with thrombocytopenia with no bleeding or minor bleeding only
Plasma	Osborn & Evans 2004 [58]	Systematic review & meta-analysis	I	Systematic review examined role of early volume expansion using various solutions in neonates <32 weeks GA and/or with a birth weight of <1500 g • Three RCTs with a total of 654 neonates compared FFP versus no treatment on death • Two RCTs with a total of 120 neonates compared FFP versus no treatment on periventricular/intraventricular haemorrhage		No significant difference in death or rates of periventricular/ intraventricular haemorrhage
	Stanworth et al. [59] Yang et al. [60] (Updated Version)	Systematic review	I	12 RCTs with a total of 1502 neonates across different clinical settings: Five compared FFP to alternatives or colloid, seven compared plasma compared with no transfusion. Updated version [60]; Two additional RCTs with a	Assess clinical effectiveness of prophylactic FFP on numerous outcomes	Original and updated version found no difference in clinical outcomes with prophylactic plasma use compared with colloid or no transfusion; importantly four RCTs assessing prophylactic use of FFP for prevention of intraventricular haemorrhage in

(*continued on next page*)

Table 1 (*continued*)

Intervention	Citation	Study design	Level of Evidence[a]	Methodology/Number of participants/Population	Objective/Main outcome	Findings
				further 23 neonates (all in cardiothoracic surgical setting)		preterm neonates showed no clear benefit
Other Products						
Intravenous immunoglobulin (IVIg)	Zwiers [61]	Systematic review & meta-analysis	I	Nine RCTs with total of 658 neonates (term and preterm)	Effect of IVIg administration on number of exchange transfusions for the treatment of alloimmune Haemolytic Disease of the Newborn	Significant decrease in use of exchange transfusion in group receiving IVIg (RR 0.35)[e]
	Ohlsson [62]	Systematic review & meta-analysis	I	Nine studies with a total of 3973 neonates were included in this review (seven RCTs, two quasi-RCTs)	Assess effects of IVIg on death and serious disability caused by infection (suspected or proven) in neonates	No reduction in death during admission, or death or major disability at two years of age
Cryoprecipitate	Limited evidence available; inadequate quality of evidence for decision making therefore rely on consensus opinion [63] [f]					
	National Blood Authority (NBA) Australia [63]			No level I, II or III evidence found to inform NBA guideline		Expert opinion [63]: Cryoprecipitate may be used to treat active bleeding in the setting of hypofibrinogenemia. Aim for a fibrinogen level >2 g per litre in neonates
	Motta et al. [64]	Review article	IV	Review article	Role of FFP and cryoprecipitate in neonatal intensive care	Cryoprecipitate is indicated in patients with congenital disorder of haemostasis and to control bleeding in congenital fibrinogen deficiency [64] (only if fibrinogen concentrate is not available [19, 64])
	Poterjoy et al. [65]	Review article	IV	Review article Eight studies with total of 20 patients (Five case reviews, two case studies, one case control trial)		• Cryoprecipitate use should be considered for congenital bleeding disorders if specific factors not available • Whilst use of cryoprecipitate has been extrapolated from the adult literature, it has become standard to neonates with acquired hypofibrinogenemia in setting of DIC/liver failure
	New et al. [19]	National Guideline (United Kingdom)				In context of DIC consider cryoprecipitate [19]: • If the fibrinogen is < 1.0 g/L despite FFP • Giving with FFP for very low or rapidly falling fibrinogen Cryoprecipitate should not be given to correct "mild degrees of hypofibrinogenaemia in non-bleeding patients" [19]
Fibrinogen/ Prothrombin complex concentrate	Zeng et al. [66]	Systematic review & meta-analysis	I	Three RCTs with total of 330 neonates Three observational (non-randomised) studies with total of 238 neonates In the above six studies, all patients were neonates but heterogeneous[c] population and clinical condition noted Two additional observational cohort studies (for effectiveness evaluation only) with total of 125 (NB: Patients in above 2 studies included infants and not exclusively neonates)	Effect of PCC on death and intracranial haemorrhage	Insufficient evidence to recommend use of PCC in neonates and infants
Albumin	Jardine et al. [67]	Systematic review & meta-analysis	I	Two RCTs with a total of 64 preterm neonates (born <37 weeks' GA) with hypoalbuminemia	Effect of albumin infusions on death and major morbidity	Insufficient evidence to support routine infusion of albumin to correct low serum albumin levels Insufficient evidence to asses safety of albumin infusions
	Roberts et al. [68]	Systematic review & meta-analysis	I	12 RCTs with total of 757 patients looked at role of albumin infusion inf hypalbuminaemia (only 7 studies involved neonates, no subgroup analysis performed) Effect of infusion of albumin in critically ill patients on death assessed		No evidence that albumin infusion reduced death

Abbreviations: ARR: absolute risk reduction; DIC: disseminated intravascular coagulopathy; GA: gestational age; RCT: randomised controlled trial; PCC: Fibrinogen/prothrombin complex concentrate.

Key.

[a] NHMRC levels of evidence and grades for recommendations for developers of guidelines. In: National Health and Medical Research Council; 2009 [69].

[b] Retinopathy of prematurity ≥ grade3; grades 3–4 intraventricular haemorrhage, hydrocephalus, cortical atrophy or periventricular leukomalacia; bronchopulmonary dysplasia; cerebral palsy (by physician assessment; developmental delay; blindness (visual acuity <20/200 in best eye) or hearing loss requiring amplification of cochlear implantation.

[c] Neonates <34 weeks GA/1500 g; neonates <37 weeks' GA with respiratory distress, neonates with hypoxic ischemic encephalopathy; preterm neonates with gastrointestinal bleeding; infants with vitamin K deficiency bleeding.

[d] Low threshold platelet level 25 × 10^9 per litre, high threshold platelet level 50 × 10^9 per litre.

[e] Applicability due to low/very low evidence quality.

[f] A case-control trial was published in 2018 exploring prophylactic vs rescue solvent-detergent plasma and cryoprecipitate transfusions and rates of IVH in neonates born <28 weeks' GA. Whilst result indicate a reduction in all grade intraventricular haemorrhage, a lack of robust methodology makes it difficult to interpret relevance of the findings.

interquartile range 23.9–53.3 mL/kg) in one neonatal unit [24]. Blood conversation strategies in the neonatal setting require further attention and may include a standardised approach to blood sampling, removal of the concept of 'routine bloods', use of microcontainers, obtaining admission laboratory tests from the placenta [23], and early removal (or non-placement) of arterial catheters. Erythropoietin previously was used to reduce the numbers of RBC transfusions, however, since the mid 2000s, it has not been routinely recommended for this purpose due to a potential association with increased rates of retinopathy of prematurity [25,26].

We strongly recommend the use and effective implementation of clinical guidelines – evidence-based and/or consensus based as required – in neonatal transfusion practice [27]. These guidelines are best viewed as living documents and require frequent review and updating as more evidence is made available (Table 2). It is key that we effectively implement the evidence base for neonatal transfusion we do have to ensure appropriate and rational use of blood products in this vulnerable group of patients.

3. Closing the evidence to practice gap in neonatal transfusion

Closing the evidence to practice gap is a complex, time consuming, and challenging task. Healthcare professionals are often on the receiving end of many approaches that aim to close this gap, including clinical guidelines, audit, and quality improvement, all which have been used in transfusion practice, with varying levels of success [7,28–30]. Computerised (physician) order entry systems with integrated clinical decision support system software, supported by education and clinician feedback, reduces unnecessary transfusions (over transfusion) in some clinical settings [31]. Patient blood management (PBM), as further described in more detail later in this article, is an additional approach specific to transfusion; however, it is much more developed in adult care settings, and currently in limited use in neonatal care [32]. A recent systematic review assessed the impact of behaviour modification interventions to promote restrictive red cell transfusion practices [33]. Eighty-four studies were identified, primarily non-randomised studies of low to moderate quality, examining the impact of a behaviour modification intervention, compared with no intervention, on red transfusion practices. The majority of studies used a combination of interventions, including education, computerised physician order entry, guidelines, audit, and feedback. The primary outcome for the review, the proportion of patients transfused, was reported in 33 studies with use of an intervention associated with reduced odds of transfusion (OR 0.63 (95% CI 0.56 to 0.71)). Use of a protocol/algorithm and a combination of interventions were associated with the greatest decreases in the proportion of patients transfused [33]. We will further review a number of these approaches are relevant to neonatal transfusion practice.

Table 2
Examples of currently available neonatal transfusion guidelines[a].

Australia	**National Blood Authority, Australia – Patient Blood Management Guidelines:** Module 6 – Neonatal and Paediatrics https://www.blood.gov.au/pbm-module-6 Published in 2016 and currently under review
Canada	**Canadian Paediatric Society Red blood cell transfusions in newborn infants:** Revised Guidelines https://professionaleducation.blood.ca/en/transfusion/guide-clinique/neonatal-and-pediatric-transfusion Published in 2014
Italy	**Italian Society of Transfusion Medicine and Immunohaematology (SIMTI) and Italian Society of Neonatology (SIN):** Recommendations for transfusion therapy in neonatology [70] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4607607/Published in 2015
United Kingdom	**British Society of Haematology (BSH):** Guidelines on transfusion for foetuses, neonates and older children [19] https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.14233 Published in 2016 with an addendum in August 2020

[a] None of the included guidelines incorporate findings of the ETNNO study [15] and only the BSH guidelines have updated their recommendations to include the PlaNet-2 study [10] findings.

4. Clinical guidelines

The explosion of clinical guidelines has not necessarily been accompanied by the same level of improvement in clinical outcomes. Clinical guidelines are an excellent resource for quality improvement in neonatal transfusion practice, but their existence alone is not usually enough to change practice [28]. A number of barriers to clinical guideline adherence are reported, including lack of awareness, lack of familiarity, lack of agreement, lack of self-efficacy, lack of outcome expectancy, the inertia of previous practice, and numerous external barriers [34]. Clinical guidelines are not necessarily able to rapidly translate new results found in multicentre randomised clinical trials, as is evidenced in Table 2, where a number of the clinical guidelines are out of date in some respects.

A systematic review of transfusion guidelines for red cells and plasma [35] found the most common limitation to the actual guidelines was lack of implementation tools for them. The authors suggested coordinated international effort for guideline development with a particular focus on implementation tools may be one way of addressing this [35]. As the evidence base for neonatal transfusion medicine continues to evolve, there is a need to dedicate further resources to understanding how to promote the uptake of evidence and effectively change transfusion clinical practice [7].

5. Audit & feedback

Audit and feedback are a well described strategy for changing clinical practice. It is one, if not the commonest, quality improvement strategy used to try and improve patient care and outcomes. Audit has been incorporated and applied at every level of health care, and ranges from small local audits within individual healthcare departments or organisations to national or indeed international clinical audits. It is

very widely used in transfusion medicine [30]. Yet, findings from audits continue to highlight variability in transfusion practice and ongoing discrepancies with clinical guidelines [30]. This raises questions about the effectiveness of current audit strategies to change neonatal transfusion practice [7]. Audit tends to only make modest effects on healthcare; however, these changes can make a significant difference at a healthcare system level, if improvements accumulate over time with repeated audit cycles [30]. This is where using quality improvement approaches, including audit and feedback as an implementation strategy, is likely to be useful. The impact of audits could be increased by applying implementation science, considering the needs of clinicians and families, and emphasising action over measurement [36].

The AFFINITIE (Development and Evaluation of Audit and Feedback INterventions to Increase evidence-base Transfusion practice) program [37] follows the United Kingdom Medical Research Council (MRC) Framework [38] for the design and evaluation of complex interventions and comprises four work streams with the following objectives:

- To develop, pilot and refine two feedback interventions, either *enhanced content* or *enhanced follow-on support*
- To evaluate effectiveness and cost-effectiveness of the two enhanced feedback interventions compared with current standard feedback practice
- To investigate the intervention fidelity, including mechanisms of change, for the evaluated interventions
- To develop general implementation recommendations and tools for relevant audit and feedback programs in the wider healthcare system [37].

Initial results from this program found that healthcare teams involved with transfusion could be better supported with more systematic dissemination of feedback documents throughout the hospital and practical tools to support strategic decision making, for example, for action planning and identify key measures and goals for improving practice [39].

6. Patient blood management

The past decade has seen an increased emphasis on optimising blood utilisation through a variety of modalities that include (1) anaemia management, (2) perioperative blood conservation, and (3) appropriate blood use through the successful implementation of evidence-based transfusion guidelines [40]. This evidence-based 'package of care' is termed patient blood management (PBM) and is well developed in adult transfusion practice [32]. The definition and implementation of PBM in neonates is less developed with adult PBM programs not necessarily directly transferable to neonatal care.

A suggested PBM approach in neonatal transfusion practice was recently published by Crighton and colleagues [32]. These PBM principles are well aligned with the goals of quality improvement, namely that the decision to transfuse a neonate should be evidence-based where evidence is available; otherwise, it should be based on consensus-based guidance. Elements of PBM proposed by the authors include: (1) assessment and management of anaemia, and anaemia of prematurity; (2) blood conservation strategies; (3) optimising coagulation and haemostasis; (4) surgical and anaesthetic techniques; (5) patient and family-centred decision making; (6) multi-disciplinary clinician engagement, clinical leadership and staff education; (7) audit and review [32]. All the aspects of this PBM approach in neonates are potential targets for quality improvement. At present, PBM programs in neonatal care are limited [29], however, it appears to represents a key opportunity to promote evidence-based practices.

7. Quality improvement in neonatal transfusion practice

It is widely recognised that in complex systems such as a healthcare system, there is no universal way of implementing change, necessitating adaptive and flexible approaches. We will ultimately learn more about how interventions work to change transfusion practice if they are based on relevant evidence and theory [7]. Evidence-based practice ideally would be consistently complemented by evidence-based implementation. We are currently in a situation where there are many approaches to improving the use of evidence-based practices, all of which have some value and may be useful and effective, depending on the changes aimed at, the target group, the clinical setting, and the barriers and facilitators relevant to the local context [41].

7.1. *Why use quality improvement to close the evidence to practice gap?*

Quality improvement in healthcare is about involving all relevant people, including consumers and families, at all levels in the making of and sustaining of efforts resulting in positive change. Quality improvement approaches are well recognised as an important tool for facilitating research translation. However, in the healthcare setting they are often poorly implemented and not necessarily sustained. Further, quality improvement programs may be driven by middle management with a focus on patient safety and performance indicators necessary for hospital accreditation, rather than quality care across the full spectrum of clinical practice. Unfortunately, there has been limited research focus on how best to implement evidence-based practices. Instead existing initiatives aimed at improving healthcare quality often focus on compliance, very few are truly embedded programs, and most involve external individuals, groups or regulatory bodies. Significant resources are often expended on system-wide strategies, evidence-based guidelines and policies, with limited attention to actual implementation or evaluation of these approaches.

8. Implementation science

There are valuable lessons to be learned, from the knowledge, experience, and tools from implementation science, which greatly overlaps with quality improvement. A systematic approach is likely to facilitate the cumulative building of a body of knowledge about precisely "what works" in changing transfusion practice [7]. Implementing changes involves a considered stepwise process, including a combination of interventions, linked to identified barriers to change [41]. Two systematic reviews, specific to transfusion practice, examine the range of intervention strategies that have been applied with the goal of changing practice, and range from educational interventions to audit and feedback [42,43]. The conclusions from these reviews are consistent with there being many interventions effective in changing transfusion practice. Unfortunately, due to limitations and variations in the included studies, the authors were unable to draw any specific conclusions about which intervention strategy was more effective than another [42,43]. This may indicate that the studies were not well designed or that a mix of implementation strategies, tailored to the local context, are necessary to effect change in transfusion practice. What works in one clinical setting may not work in another, and it seems unlikely that a single intervention to change practice would be effective in the long term.

The increasing recognition of the challenges of implementing evidence-based practices into complex healthcare systems has led to calls for more collaborative, iterative, and adaptive approaches to implementation and its evaluation [44]. Factors that increase receptivity of healthcare professionals to adaptive change include when the benefits of change are presented by respected peers and opinion leaders; when the change is compatible with professional values and self-efficacy; when an evidence-based rationale underpins the change; and when all involved in the process are given the opportunity to develop, observe, refine and lead the change [45]. Behavioural interventions, including simple interventions, appear to be effective in changing clinical transfusion practices and reducing blood utilisation. However, appropriately designed studies are still needed to evaluate the

relative effectiveness of different interventions to change transfusion practices [42]. Using quality improvement to close the evidence to practice gap in neonatal transfusion is likely to be successful when multiple implementation strategies are used. Implementing changes rarely entails a single action; it demands good planning and a combination of different interventions [41], ideally with an evidence-based implementation approach.

9. Where to now?

Despite the rapid growth of implementation science, designing implementation research is like to represent a complex and daunting task for healthcare professionals [46]. Fortunately, there are easily accessible guides developed for healthcare professionals wanting to design implementation research in a robust manner [46]. An example of a guide is the Implementation Science Research Development (ImpRes) guide [46]. Table 3 displays examples of the various implementation strategies available to improve update of evidence-based practice in neonatal transfusion. The full guide and tool are freely available elsewhere [46].

10. Pulling it all together - examples

Healthcare professionals attempting to determine, for example, the effectiveness of interventions to change inappropriate transfusion rates are confronted with many methodologic challenges [43]. Fortunately, quality improvement approaches are able to deal with the majority of these challenges, when designed in a robust and considered manner. We provide some examples of work underway in this area.

10.1. Australia

The Australian Red Cross Lifeblood led a program designed with practice-based evidence for clinical practice improvement (PBD-CPI) [47] methodology. This program was limited by having only one improvement cycle performed and involved multiple interventions with a relatively short follow-up. The resources used in this program, including a combination of neonatal-specific quality improvement tools, clinician education, and parent information aligned with Australian Patient Blood Management Guidelines and national safety and quality standards, are freely available (https://transfusion.com.au/neonates_paediatrics). They are likely to be of use to neonatal units in Australia and elsewhere undertaking quality improvement in neonatal transfusion practice.

10.2. United Kingdom

The AFFINITIE (Development and Evaluation of Audit and Feedback INterventions to Increase evidence-base Transfusion practice) used a multidisciplinary approach that applied behavioural theory and evidence to optimise the design and delivery of feedback on transfusion practice. It provides a framework for implementation research aimed at addressing the often limited translation of research into neonatal transfusion practice [30].

Table 3
Potential implementation strategies based on the Implementation Science Research Development (ImpRes) guide and tool [46].

Implementation strategy category	Examples
Use of evaluative and iterative strategies	Audit and feedback, local needs assessment, conduct small cyclical tests of change
Provide interactive assistance	Facilitation
Adapt and tailor to the local context	Tailor strategies to the local setting
Support clinicians	Facilitate provision of clinical data to providers
Engage patients/service users	Involve patients/consumers and family members
Develop stakeholder relationships	Identify and prepare local champions, identify early adopters, conduct local consensus discussions

10.3. Other examples

Intermountain Healthcare in the USA uses electronic ordering for neonatal blood products to support compliance with local transfusion guidelines [27]. The program found that all four neonatal units within the network had an increase in compliance with guidelines from 65% to 90% with concurrent reduction use of blood products after the program was introduced.

11. Getting started in quality improvement in neonatal transfusion practice

There is no agreed best approach to quality improvement and there are many different methods and tools available to use. We suggest reviewing Table 1 to identify areas in neonatal transfusion practice that may benefit from a quality improvement approach. For those starting out in quality improvement, there are numerous resources freely available, including from King's Improvement Science (www.kingsimprovementscience.org/about-kis) to guide you and your team.

12. Evaluation

Without robust evaluation, patients may be deprived of benefit, resources, and energy may be wasted on ineffective quality improvement interventions. The study of improvement has an important role in developing an evidence-base and in exploring questions beyond effectiveness alone, and in particular showing the need to establish improvement as a collective activity [48]. Consequently, it is vital to formally evaluate the effectiveness of any quality improvement intervention.

Both qualitative and quantitative data are necessary for evaluating and guiding improvement. A number of measures, including outcome, process, and balancing measures, ideally are used to track improvement work. A time series analysis, using small amounts of data collected and displayed frequently, is the gold standard for using data for improvement [49]. Statistical process control (SPC) is a set of statistical methods based on the theory of variation that can be used to make sense of any process or outcome measured over time, usually with the intention of detecting improvement or maintaining a high level of performance. This methodology combines a time series analysis with graphical presentation of data, and provides early insights in to data in a manner understandable to a wide range of audiences [50]. There are many resources available to guide healthcare professionals in this useful methodology and it is highly recommeded [51–53].

Consideration of an economic evaluation of quality improvement projects or programs may provide insight on whether specific implementation efforts are likely to be a cost-effective use of limited healthcare resources [46]. This is an important aspect for quality improvement in neonatal transfusion practice.

13. The importance of dissemination

Standardised reporting guidelines for reporting quality improvement in healthcare are available [54] and are highly recommended. Sharing and disseminating quality improvement work is vital, whether it is through local presentations, conferences or publication in a peer-reviewed journal. Quality improvement is a collective activity that benefits from leadership and sharing of findings [48] as well as resources broadly, so as not to 'reinvent the wheel'. Harnessing the enthusiasm of the neonatal transfusion community to build a quality improvement

collaborative is an additional option.

14. Conclusions

Approaching blood transfusion behaviour change more systematically, and working across disciplines, holds the potential to increase the rate of uptake of emerging evidence in clinical practice. This process holds the potential to save costs, conserve resources, and improve clinical outcomes [7]. Regarding the evidence-base in neonatal transfusion, and at times the lack of one, our advice is to remain conservative. In the majority of situations, the baby's own blood will be better than transfused blood, so maximise what you can to keep it in the baby. Where you can, implement evidence-based guidelines around transfusion practices and have a consistent approach for those situations where evidence is lacking.

14.1. Practice points

- Use of evidence-based guidelines minimises the adverse effects of transfusion and wastage of products, which are donated by volunteers, costly, and sometimes in short supply
- Children transfused in fetal or neonatal life have the longest potential lifespan in which to develop late adverse effects of transfusion
- Potential risks and benefits must always be considered when making the decision to transfuse children but there is a lack of high-quality research evidence on which to base guidelines

15. Research directions

- Establishment of a quality improvement collaborative in neonatal transfusion practice
- Further resources to better understand how to promote the uptake of evidence and effectively change neonatal transfusion practice

Declaration of competing interest

The authors have no conflict of interests to declare.

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