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Survey of transfusion practices in preterm infants in Europe

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ABSTRACT

Background Preterm infants commonly receive red blood cell (RBC), platelet and fresh frozen plasma (FFP) transfusions. The aim of this Neonatal Transfusion Network survey was to describe current transfusion practices in Europe and to compare our findings to three recent randomised controlled trials to understand how clinical practice relates to the trial data.

Methods From October to December 2020, we performed an online survey among 597 neonatal intensive care units (NICUs) caring for infants with a gestational age (GA) of <32 weeks in 18 European countries.

Results Responses from 343 NICUs (response rate: 57%) are presented and showed substantial variation in clinical practice. For RBC transfusions, 70% of NICUs transfused at thresholds above the restrictive thresholds tested in the recent trials and 22% below the restrictive thresholds. For platelet transfusions, 57% of NICUs transfused at platelet count thresholds above 25×10^9/L in non-bleeding infants of GA of <28 weeks, while the 25×10^9/L threshold was associated with a lower risk of harm in a recent trial. FFP transfusions were administered for coagulopathy without active bleeding in 39% and for hypotension in 25% of NICUs. Transfusion volume, duration and rate varied by factors up to several folds between NICUs.

Conclusions Transfusion thresholds and aspects of administration vary widely across European NICUs. In general, transfusion thresholds used tend to be more liberal compared with data from recent trials supporting the use of more restrictive thresholds. Further research is needed to identify the barriers and enablers to incorporation of recent trial findings into neonatal transfusion practice.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Neonates frequently receive red blood cell (RBC), platelet or fresh frozen plasma (FFP) transfusions.
⇒ Two recent trials showed no difference in death or neurodevelopmental delay at 2 years' corrected age between liberal and restrictive RBC transfusion thresholds.
⇒ One recent trial showed a reduction in the combined risk of mortality and major bleeding in the restrictive versus the liberal platelet transfusion threshold.

WHAT THIS STUDY ADDS

⇒ RBC transfusion practices across Europe vary widely.
⇒ Over 50% of European neonatal intensive care units use platelet count thresholds above 25×10^9/L for non-bleeding neonates, potentially exposing neonates to increased risk of mortality and bleeding.
⇒ There is substantial variation in transfusion volume and duration, particularly for platelets and FFP, reflecting lack of evidence to support practice.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Researchers might use these data to investigate the impact of different transfusion practices on regional differences in short-term and long-term clinical outcomes.
⇒ Our survey data will help align regional, national and international practice guidelines with the currently best available evidence.
⇒ Policy makers might use our data to better understand regional differences in healthcare uses and costs and to assist in planning future healthcare strategies.

INTRODUCTION

Blood component transfusions of red blood cells (RBCs), platelets and fresh frozen plasma (FFP) are commonly administered to preterm infants, but the evidence base for these transfusions, particularly for platelets, has thus far been limited.[1] Since 2019, three large randomised controlled trials (RCTs) were published. The Effects of Transfusion Thresholds on Neurocognitive Outcomes of Extremely Low-Birth-Weight Infants (ETTNO) and

Transfusion of Prematures (TOP) trials reported no difference between the effects of liberal versus restrictive RBC thresholds on death or neurocognitive deficit at 2 years' corrected age.[2–4] The Platelets for Neonatal Transfusion 2/Management of Thrombocytopenia in Special Subgroup: Neonates (PlaNeT-2/MATISSE) trial compared liberal (50×10^9/L) versus restrictive (25×10^9/L) platelet count thresholds, reporting a higher rate of death and major bleeding in the liberal platelet transfusion threshold group (26% vs 19%).[5] This effect was shown to be present irrespective of varying baseline risk of outcome.[6] The extent to which findings of the aforementioned trials correspond with clinical practice in Europe is unknown. The aims of the study were to describe current transfusion practices and to compare these to the recently generated evidence from clinical trials.

METHODS

This survey was performed by the Neonatal Transfusion Network (NTN) (www.neonataltransfusionnetwork.com), an international research group which aims to generate evidence to improve clinical practice in neonatal transfusion medicine. An NTN panel of four neonatologists (EL, ED, CD and CCR), one trainee neonatologist (AS), three haematologists (SJS, HN and KF) with paediatric transfusion expertise, and one clinical epidemiologist (SFFG) developed a preliminary list of questions. Topics included RBC, platelet and FFP transfusion practices in premature neonates of less than 32 weeks' gestational age (GA) at birth, addressing transfusion thresholds or indications, durations and volumes, concomitant use of diuretics, withholding enteral feeding and parental consent. We used a ranking procedure to obtain a final set of 31 questions, which we entered into LimeSurvey (LimeSurvey GmbH, Hamburg, Germany) (online supplemental materials) Neonatologists from 18 European countries volunteered to disseminate the survey. These national coordinators received a password protected link to the questionnaire, which they disseminated between October and December 2020 to neonatal intensive care unit (NICUs) providing care for infants born at <32 weeks of GA. In the United Kingdom only larger regional NICUs were approached for participation, as these are known to dictate local transfusion practices. We limited responses to one per NICU. National coordinators were free to use their own contacts or use an existing neonatal network (online supplemental materials).

We extracted the LimeSurvey data to SPSS V.27, for data cleaning and analysis, by two authors working independently. We used GraphPad Prism V.9.0.1 for Windows (GraphPad Software, San Diego, California USA) for graphs. We excluded confirmed double entries, ineligible responses and responses that were>75% blank, and converted haematocrit to haemoglobin using this formula: haemoglobin (g/L)=haematocrit(%)×300.

The TOP and ETTNO trial had only recently been published at the moment of survey dissemination.[2 3] Therefore, we did not aim to assess implementation of their results but instead to assess how current clinical practice compared with the thresholds tested in these trials. To make the comparison, we combined the two trials to select one liberal and one restrictive 'ETTNO/TOP threshold' for each of our 15 survey clinical scenarios: 'air', 'low flow', 'high flow </>30% FiO_2' and 'intubated' for three postnatal age groups. Where ETTNO and TOP thresholds differed, we selected the higher liberal value and the lower restrictive. The low flow and high flow' clinical scenarios could not be assigned to either the 'critical' or the 'non-critical' strategies in the ETTNO and TOP trials because of overlapping definitions. Therefore, some clinical scenarios were classified as both critical and non-critical in one or both trials, leading to relatively wide ETTNO/TOP threshold ranges (online supplemental tables S1 and S2). We calculated the proportion of reported thresholds in our survey that were at or above the liberal ETTNO/TOP threshold, between the liberal and restrictive ETTNO/TOP threshold or at or below the restrictive ETTNO/TOP threshold, for all clinical scenarios for both RBC and platelet transfusion thresholds.

We performed two sensitivity analyses. To estimate the effect of non-responder bias, we compared early versus late responders. This is an established method to estimate if responders answered survey questions differently from non-responders, where late responders are considered a proxy for non-responders. We combined the first and last 20% of entries in each country to form the early-responder and late-responder groups. We also assessed the effect of varying response rates between countries in a weighted sensitivity analysis, where entries received a weight equal to one divided by the response rate in their respective country.

RESULTS

Response rate

After removal of seven duplicate responses, 10 ineligible responses and 168 responses which were >75% blank, responses from 343 NICUs were included, yielding an overall response rate of 57% (343/597). The response rate per country varied between 21% and 100% (median 81%). We included NICUs in Austria (7 of a total of 7 units), Belgium (16/19), Finland (5/5), Germany (112/160), Hungary (21/21), Italy (49/105), Malta (1/1), the Netherlands (9/9), Norway (6/6), Poland (18/36), Portugal (10/11), Romania (4/19), Slovakia (10/13), Slovenia (3/4), Spain (41/111), Sweden (8/8), Switzerland (6/8) and the United Kingdom (17/55).UK

RBC transfusion thresholds

A violin plot of haemoglobin thresholds for RBC transfusions is shown in figure 1A. A total of 104 NICUs used haematocrit thresholds, which were converted into haemoglobin. Higher haemoglobin thresholds were adopted as the degree of respiratory support intensified. On average, over all 15 clinical scenarios, 22% of reported thresholds were below, and 8% at the restrictive ETTNO/TOP threshold, 68% were in between the restrictive and liberal ETTNO/TOP threshold, <1% at the liberal threshold and 2% above the liberal ETTNO/TOP threshold (figure 1B).

Platelet transfusion thresholds

A violin plot of platelet count thresholds for platelet transfusions is shown in figure 2. Platelet transfusion thresholds above 25×10^9/L were used in 57% (188/332) and 47% (158/333) of NICUs for a non-bleeding infant of <28 weeks' GA or 28–32 weeks' GA, respectively. For infants treated with ibuprofen, platelet transfusion thresholds above 25×10^9/L were used in 84% (249/297 and 248/297) of NICUs for infants of <28 weeks' GA and infants of 28–32 weeks' GA. Thresholds of 20×10^9/L or less were used in 27% (91/332) for infants with GA of <28 weeks without bleeding, 34% (114/333) for infants with GA of 28–32 weeks without bleeding, 8% (25/297) for infants with GA of <28 weeks and ibuprofen and 9% (26/297) of infants with GA of 28–32 weeks with ibuprofen. Infants with lumbar puncture, surgery or active bleeding could not be compared with the trial results as they were allowed additional transfusions at the

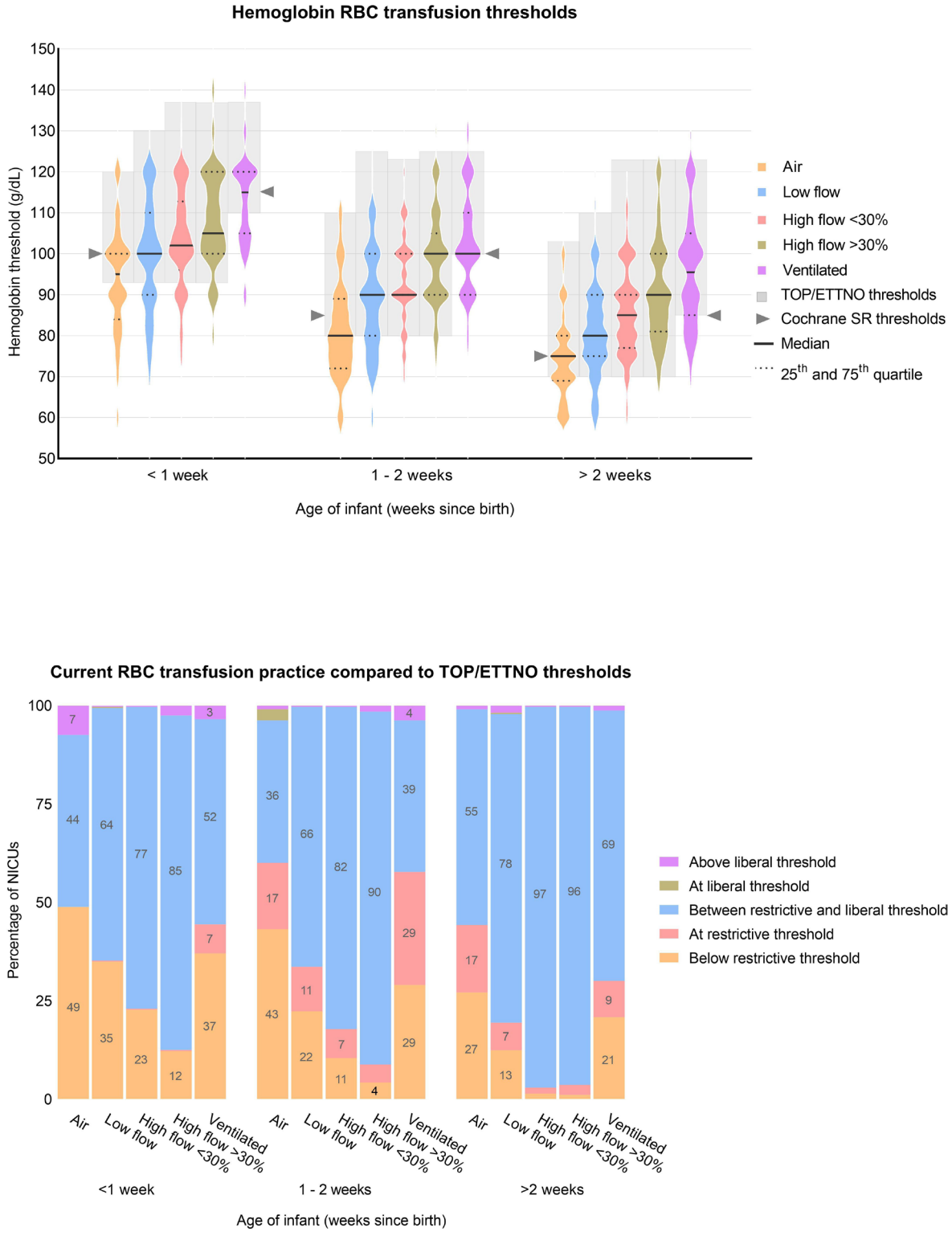

Figure 1 (A) Violin plots of haemoglobin-based RBC transfusion thresholds for different postnatal age and respiratory support levels in infants born at 30%=infants on 30% oxygen by non-invasive respiratory support (including continuous positive airway pressure, biphasic intermittent positive airway pressure (synchronised or unsynchronised) and nasal high flow). Ventilated=infants who are intubated and ventilated. The grey boxes highlight the values between the restrictive and liberal ETTNO/TOP thresholds (online supplemental table S1). Cochrane SR refers to the restrictive thresholds of previous trials, summarised in a Cochrane systematic review by Whyte *et al*. Number of datapoints per violin plot: 325, 323, 324, 324, 326, 327, 326, 325, 324, 327, 327, 327, 324, 325 and 326 (from left to right). Violin plots are a combination of a boxplot (showing median and IQRs) with a kernel density plot (showing the distribution of the data). The wider the plot, the more NICUs selected this threshold. (B) 100% stacked bar chart showing for each clinical scenario the proportion of the reported transfusion thresholds (from top to bottom) that were above the liberal ETTNO/TOP threshold, at the liberal ETTNO/TOP threshold, between the liberal and restrictive ETTNO/TOP threshold, at the restrictive ETTNO/TOP threshold or below the restrictive ETTNO/TOP threshold. ETTNO, Effects of Transfusion Thresholds on Neurocognitive Outcomes of Extremely Low-Birth-Weight Infants; NICU, neonatal intensive care unit; RBC, red blood cell; TOP, Transfusion of Prematures.

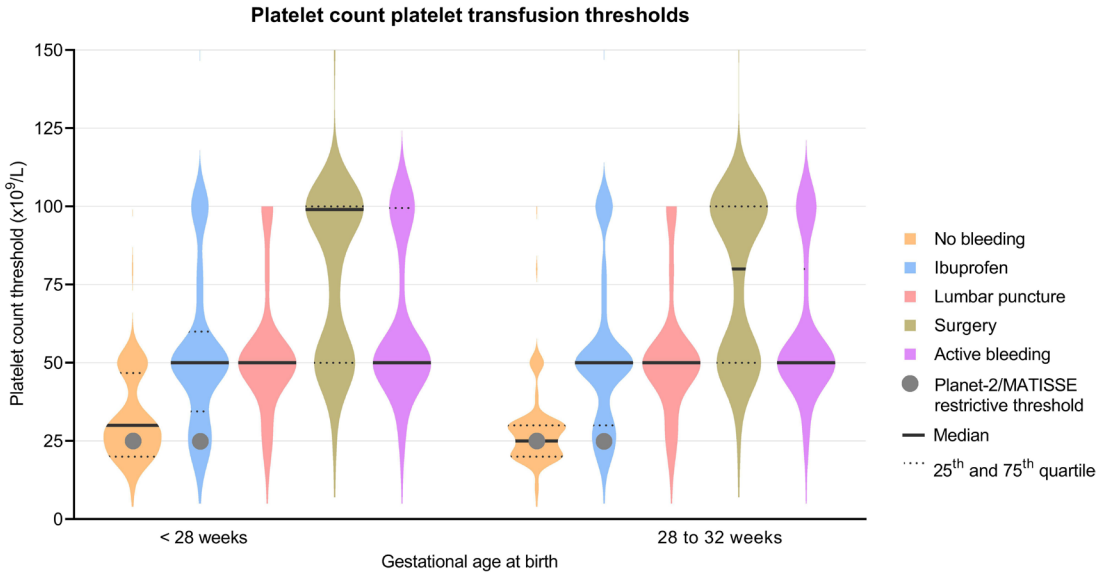

Figure 2 Violin plots of platelet count transfusion thresholds for different clinical scenarios. Datapoints per violin plot: 332, 297, 316, 311, 329, 333, 297, 317, 311 and 331, from left to right. Violin plots are a combination of a boxplot (showing median and IQRs) with a kernel density plot (showing the distribution of the data). The wider the plot, the more NICUs selected this threshold. MATISSE, Management of Thrombocytopenia in Special Subgroup.

discretion of the treating neonatologist according to the RCT protocol in the PlaNeT-2/MATISSE trial.

Fresh frozen plasma

Eleven percent of NICUs (38/332) performed routine coagulation tests on infants born at <32 weeks' GA. FFP was used for the following indications: coagulopathy with active bleeding, 93% (320/343); active bleeding without coagulopathy, 46% (158/343); coagulopathy without active bleeding, 39% (133/343); sepsis, 26.5% (91/343); and hypotension, 25% (85/343).

Duration, volume and rates of transfusion

Transfusion volume and duration are depicted in figure 3. We calculated transfusion rates in millilitre per kilogram per hour by dividing volume (mL/kg) by duration (hours). Volumes ranged between 10 mL/kg and 20 mL/kg in 99% of transfusions. The median volume was 15 mL/kg for RBC (IQR 15–20), platelet transfusions (IQR 15–15) and FFP (IQR 15–20). Duration ranged between 1 hour and 7 hours for RBC transfusions (median 4, IQR 3–4), 15 min and 4 hours for platelets (median 1, IQR 0.5–2.0), and 30 min and 4 hours for FFP (median 2, IQR 1–3). Transfusion rates varied between 3.3 mL/kg/hour and 15.0 mL/kg/hour for RBCs (median 4.0, IQR 3.8–5.0), 3.3 mL/kg/hour and 60.0 mL/kg/hour for platelets (excluding two outliers at 120 and 80 mL/kg/hour) (median 15.0, IQR 7.5–20.0) and 2.5 mL/kg/hour and 50.0 mL/kg/hour for FFP (median 10.0, IQR 5–15).

Diuretics, enteral feeding and parental consent

Diuretics were 'always' or 'sometimes' prescribed in conjunction with RBC, platelet and FFP transfusions in 47% (154/329), 18% (57/322) and 28% (92/323) of NICUs, respectively. Enteral feeding was always or sometimes withheld during RBC transfusion in 28% (94/337) and 9% (31/337) of NICUs, respectively. Parental consenting for non-emergency transfusion practices varied, with 8% of NICUs (28/335) requiring no consent, 9% (31/335) requiring verbal consent only, 6% (20/335) requiring verbal consent documented by a clinician, 70% (241/335) requiring verbal and written consent and 4% (15/335) used other forms of consent, not otherwise specified.

Sensitivity analyses

Our weighted analysis showed no substantial changes compared with our primary analysis, suggesting that bias because of varying response rates between countries was likely limited (online supplemental tables S3–S6). The results of our non-responder analysis indicated that non-response bias may have resulted in an underestimation of platelet transfusion thresholds and the proportion of NICUs giving FFP for indications other than active bleeding, as these were higher in the late responders (online supplemental table S7)

DISCUSSION

Despite recent evidence from clinical trials, we demonstrated substantial variation in transfusion practices for RBC, platelets and FFP, regarding thresholds, volume and rate of transfusion across European NICUs. To our knowledge, this is the first survey to assess neonatal transfusion practices across Europe. Other surveys included only selected countries or included mostly non-European NICUs.[7 8] A retrospective cohort study of North American NICU blood component transfusion thresholds for all infants between 2013 and 2016 by Patel *et al* also found wide variation in practice with regard to transfusion thresholds.[9]

Comparison with RBC trials

The large variation in RBC transfusion thresholds probably reflects the lack of international and European consensus in transfusion criteria, and the lack of evidence until recently. Prior to 2020, clinical practice was partly based on two RCTs (the Premature Infants in Need of Transfusion and Iowa trials), which have been summarised in systematic reviews and national guidelines supporting the use of restrictive thresholds.[2–4 10–15] These thresholds were roughly similar to those tested in the TOP and ETTNO trials (online supplemental table S2). In our survey, reported use of thresholds similar to or above the previously tested liberal thresholds was rather rare. However the majority

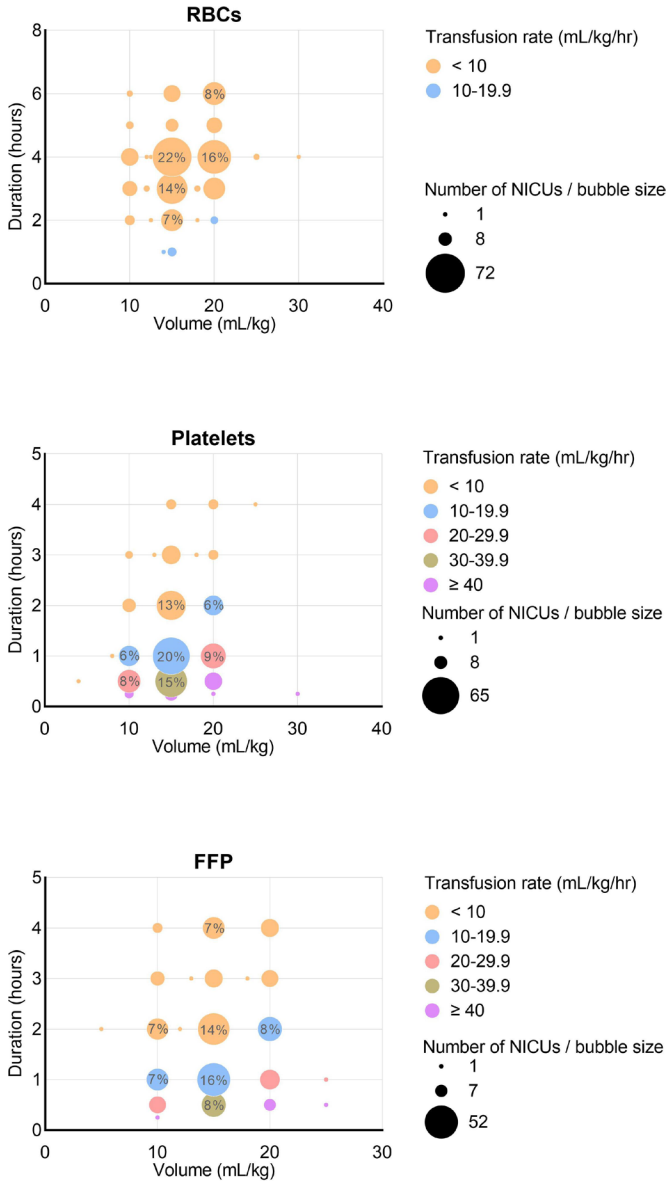

Figure 3 Transfusion volume, duration and rates for RBC, platelet and plasma transfusions. Bubble size and values within larger bubbles represent the number and percentage of NICUs. Platelet transfusion volume outlier at 4 mL/kg represents one NICU providing hyperconcentrated platelet transfusions. Datapoints for RBC, platelet and FFP volumes: 335, 335 and 336. Datapoints for RBC, platelet and FFP durations: 333, 330 and 335. FFP, fresh frozen plasma; NICU, neonatal intensive care unit; RBC, red blood cell.

(70%) of thresholds reported were above the TOP/ETTNO restrictive thresholds, while surprisingly, 22% reported thresholds below the restrictive thresholds. These results could be due to implementation of evidence from earlier trials but could also indicate that neonatologists are uncertain regarding restrictive thresholds. Arguments against restrictive thresholds include the possibility of minor neurodevelopmental abnormalities or impairments that become apparent at a later age, which have not been assessed in existing trials. Arguments against a liberal threshold include the lack of clinical benefit of liberal thresholds in clinical trials, and observational studies suggesting potential transfusion-related harm.[16–20] The reasons for the use of such low haemoglobin thresholds in 22% of units are unclear but may represent an underestimation of transfusion threshold, as we had to use wide ranges for several clinical scenarios as described previously (online supplemental table S1). Without further clinical trials, it is not known whether these low haemoglobin thresholds are safe for neonates, as various preclinical studies have suggested adverse outcomes following prolonged severe anaemia.[21–23]

Comparison with platelet transfusion trials

In our survey, 47%–57% of NICUs indicated using platelet count thresholds above 25×10^9/L for stable non-bleeding infants. Given the strong and concerning evidence for platelet transfusion-mediated harm, the use of platelet transfusion thresholds above 25×10^9/L for non-bleeding neonates should be discouraged while we await results from long-term neurodevelopmental analyses. Our study also showed that 27%–34% of NICUs use thresholds equal to or lower than 20×10^9/L for non-bleeding infants. The use of thresholds lower than those tested in trials may be an acceptable practice for platelet transfusions, given the evidence in favour of the restrictive versus liberal threshold, but again this needs to be tested in a clinical trial. Possible explanations for platelet transfusion-mediated adverse effects include the role of platelets in inflammatory and immunoregulatory responses,[24] a developmental mismatch between adult donor platelets and neonatal platelets[25 26] and volume-mediated effects, since platelet transfusions are given at relatively high volumes and rates compared with adult transfusions.[27]

Fresh frozen plasma

There are no recent trials investigating FFP transfusion indications, but based on observational and adult data, most guidelines recommend that FFP should not be administered to non-bleeding infants to correct abnormalities of the coagulation screen alone.[15 28–30] Minor coagulation abnormalities are poor predictors of bleeding risk and FFP administration often will not correct these abnormalities.[30 31] In addition, they can be difficult to interpret, particularly for very preterm babies. We found that 39% of NICUs in our survey administered FFP in case of coagulopathy without bleeding. Furthermore, 25% of NICUs transfused FFP to treat hypotension, for which there is no robust evidence, yet there are potential risks such as transfusion-related acute long injury and severe allergic reactions.[32] These findings indicate an urgent need for clinical trials in this area.

Volume, duration and rate of transfusion

Transfusion duration and rate were marked in their variation. The cause for this variation is unclear, but evidence to guide practice is lacking. On average, volumes were comparable to those used in the recent trials (15 mL/kg for PlaNeT-2/MATISSE and TOP, 20 mL/kg for ETTNO). Only a few small studies have assessed neonatal transfusion volume and suggested that these volumes are tolerated, though there is also evidence for harm.[14 33–38] Duration or rates of transfusions were not reported in the ETTNO and TOP trials. High-volume or high-rate transfusions may increase the risk of transfusion associated circulatory overload (TACO), a leading cause of transfusion-associated morbidity and mortality in adults.[39] Neonatal TACO is poorly defined and the true incidence of this and other transfusion-related lung injuries in neonates is not known; observational studies have shown variable outcomes.[37 40–42] However, it should be noted that weight-related volumes transfused to non-bleeding neonates (usually 10–20 mL/kg) are commonly higher than those for adults (typically, 350 mL for packed red cells and 200–300 mL for platelets,

which equates to <5 mL/kg for an 80 kg adult).[27 43 44] Moreover, the vulnerability of the cerebral vasculature and increased risk of intraventricular haemorrhage in preterm infants should also be considered. Further high-quality research is urgently needed to optimise transfusion rates and volumes.

Limitations and strengths

There are some limitations to our survey. First, we requested one response per neonatal unit, which may mask intraunit variation. Second, we did not ask for detailed transfusion product information because we anticipated that these data were not always available to neonatologists. Third, our eligibility criteria were broad; we only defined that NICUs should care for neonates born at <32 weeks' GA. We chose this pragmatic approach to be able to paint a picture of current transfusion practices across Europe and because NICU level definitions differ per country. Lastly, combining the ETTNO and TOP trials was not always possible due to varying clinical definitions, highlighting the need for uniform transfusion indications in future trials. Strengths of our survey include the relatively high response rate despite the ongoing pandemic, use of sensitivity analyses and the wide range of countries included. This is, to our knowledge, the first study to map European neonatal transfusion practices, and given the recently published trials, our data are timely and provide a valuable starting point for further studies and highlight the need for guideline development.

CONCLUSIONS

In Europe, transfusion practices for preterm infants vary widely. Transfusion thresholds tend to be more liberal compared with data from recent trials supporting the use of more restrictive thresholds. Transfusion indications, volume, duration, concomitant use of diuretics, withholding enteral feeds and parental consent requirements differ considerably. These areas, including factors affecting the implementation of research findings, deserve further attention and clinical research.

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Contributors The study was planned and executed by the members of the Neonatal Transfusion Network steering committee (CCR, CD, ED, EL, HVN, JvbB, KF, SS, SFG, AS, HS, LH, NH and NJR) with significant input from MAC, KB, FSC, FC, RF, SGh, JL, KM, TM, US, HS, MS, TS and GZ, who also facilitated region-specific data collection. S F-G is guarantor.

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Competing interests None declared.

Patient consent for publication Not applicable.

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Survey of Transfusion Practices in European Preterm Infants – supplementary materials.

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Content

Scrivens A, *et al. Arch Dis Child Fetal Neonatal Ed* 2023;0:1–7. doi: 10.1136/archdischild-2022-324619

COMPARISON OF TRIAL THRESHOLDS AND ALLOCATION OF SURVEY CLINICAL SCENARIOS TO TOP AND ETTNO TREATMENT CATEGORIES AND OVERVIEW OF RESTRICTIVE AND LIBERAL TRANSFUSION THRESHOLDS IN THE LARGEST RBC TRIALS.

Table S1. Comparison of ETTNO and TOP trial thresholds and selection of restrictive and liberal ETTNO/TOP threshold for each of 15 clinical scenarios.

Clinical scenario	Critical or non-critical in ETTNO trial[1]	Critical or non-critical in TOP trial[2]	Selected ETTNO/TOP threshold in g/dL for < 1 week		Selected ETTNO/TOP threshold in g/dL for 1-2 weeks		Selected ETTNO/TOP threshold in g/dL for >2 weeks	
Mechanically ventilated	Critical	Critical	Restrictive: Liberal:	11.0 13.7	Restrictive: Liberal:	10.0 12.5	Restrictive: Liberal:	8.5 12.3
CPAP with FiO2 >0.30	Critical or non-critical *Trial cut off 12 hrs*	Critical or non-critical *Trial cut off 0.35*	Restrictive: Liberal:	9.3 13.7	Restrictive: Liberal:	8.0 12.5	Restrictive: Liberal:	7.0 12.3
CPAP with FiO2 < 0.30	Critical or non-critical *Trial cut off 0.25 for 12 hrs*	Non-critical	Restrictive: Liberal:	9.3 13.7	Restrictive: Liberal:	8.0 12.3	Restrictive: Liberal:	7.0 12.3
Low flow (<2 L/min)	Non-critical	Critical or non-critical *Trial cut off 1 L/min*	Restrictive: Liberal:	9.3 13.0	Restrictive: Liberal:	8.0 12.5	Restrictive: Liberal:	7.0 11.0
No respiratory support	Non-critical	Non-critical	Restrictive: Liberal:	9.3 12.0	Restrictive: Liberal:	8.0 11.0	Restrictive: Liberal:	7.0 10.3

Critical = critical health state (ETTNO definition) or respiratory support (TOP definition). Non-critical = non-critical health state (ETTNO definition) or no respiratory support (TOP definition). Hb = hemoglobin. After categorization as critical or non-critical for in both trials, the highest threshold tested in either one of the trials was selected as liberal threshold and the lowest in either one as restrictive threshold.

Example of comparison in more detail

Infants on CPAP with FiO2 >0.30 would meet the 'critical' criteria for ETTNO only if the respiratory requirements persisted for at least 12 hours, but we did not specify a timeframe in our survey. For TOP, these infants would meet the criteria for 'critical' only if FIO2>0.35. This clinical scenario could therefore be classified as both 'critical' and 'non-critical' in both trials, leading to a relatively wide *ETTNO/TOP threshold* range of, for example for children more than two weeks old, 7.0 (restrictive) to 12.3 g/dL (liberal)

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Table S2. Overview of restrictive and liberal transfusion thresholds in the four largest RBC RCTs.

Restrictive study arms in RBC trials.

	TOP[2]		ETTNO[#][1]		PINT[##][3]		IOWA[4]		
	Respiratory support*	No support	Critical**	Non-critical	Respiratory support***	No support	Phase 1[$]	Phase 2[$$]	Phase 3[$$$]
Randomization to 7 days after birth	11.0	10.0	11.3	9.3	11.5	10.0	11.3	9.3	7.3
Day of life 8-14	10.0	8.5	10.0	8.0	10.0	8.5	11.3	9.3	7.3
Day of life 15-21	8.5	7.0	10.0	8.0	8.5	7.5	11.3	9.3	7.3
Older than 21 days	8.5	7.0	9.0	7.0	8.5	7.5	11.3	9.3	7.3

Liberal study arms in RBC trials.

	TOP		ETTNO[#]		PINT[##]		IOWA		
	Respiratory support*	No support	Critical**	Non-critical	Respiratory support***	No support	Phase 1[$]	Phase 2[$$]	Phase 3[$$$]
Randomization to 7 days after birth	13.0	12.0	13.7	11.7	13.5	12.0	15.3	12.7	10.0
Day of life 8-14	12.5	11.0	12.3	10.3	12.0	10.0	15.3	12.7	10.0
Day of life 15-21	11.0	10.0	12.3	10.3	10.0	8.5	15.3	12.7	10.0
Older than 21 days	11.0	10.0	11.3	9.3	10.0	8.5	15.3	12.7	10.0

*mechanical ventilation, continuous positive airway pressure, FiO2 >0.35, or nasal cannula ≥1 liter per min (room air nasal cannula ≥1 liter per min was considered respiratory support).

** at least 1 of the following criteria: invasive mechanical ventilation, continuous positive airway pressure with fraction of inspired oxygen >0.25 for >12 hours per 24 hours, treatment for patent ductus arteriosus, acute sepsis or necrotizing enterocolitis with circulatory failure requiring inotropic/vasopressor support, >6 nurse-documented apneas requiring intervention per 24 hours, or >4 intermittent hypoxemic episodes with pulse oximetry oxygen saturation <60%.

*** assisted ventilation, continuous positive airway pressure, or supplemental oxygen.

[#]a conversation factor of 3.0 was used to convert IOWA and ETTNO thresholds.

[##] different thresholds were specified for capillary and central blood sampling strategies, capillary thresholds are reported here.

[$] tracheally intubated for assisted ventilation

[$$] nasal continuous positive airway pressure or supplemental oxygen

[$$$] neither positive pressure nor oxygen

The Cochrane systematic review by Whyte et al [5] summarized the restrictive thresholds evaluated in their review as reported below. These thresholds are identical to the PINT thresholds.

Postnatal Age	Respiratory Support	No Respiratory Support
	Haemoglobin g/l (Haematocrit %)	
Week 1	115 (35%)	100 (30%)
Week 2	100 (30%)	85 (25%)
Week 3	85 (25%)	75 (23%)

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RESULTS OF WEIGHTED ANALYSIS

Tables S3 and S4 show the median and interquartile ranges for hemoglobin and platelet count threshold for transfusion in a weighted analysis, where each center was assigned a weight equal to the number of NICU's included in their country divided by the total number of eligible NICUs in their country. This is a way to correct for biased outcomes as a result of variable response rates. Table S5 shows the weighted analysis of transfusion duration, volume and rate. Table S6 shows the weighted FFP indications. As can be seen, few changes occur as a result of weighting (highlighted), suggesting limited impact of variable response rates on our findings.

Table S3. Weighted and unweighted median and interquartile ranges for hemoglobin transfusion thresholds

	Unweighted median (IQR)		Weighted median (IQR)	
<1 week				
Air	95	(84-100)	90	(84-100)
Low flow	100	(90-110)	100	(90-105)
High flow <30%	102	(96-113)	102	(99-110)
High flow >30%	105	(100-120)	105	(100-120)
Intubated	115	(105-120)	115	(105-120)
1-2 weeks				
Air	80	(72-89)	80	(72-85)
Low flow	90	(80-100)	90	(80-95)
High flow <30%	90	(90-100)	90	(90-100)
High flow >30%	100	(90-105)	100	(90-105)
Intubated	100	(90-110)	100	(90-110)
<2 weeks				
Air	75	(69-80)	75	(69-80)
Low flow	80	(75-90)	80	(75-85)
High flow <30%	85	(77-90)	85	(77-90)
High flow >30%	90	(81-100)	90	(81-100)
Intubated	96	(85-105)	100	(85-105)

Table S4. Weighted and unweighted median and interquartile ranges for platelet count transfusion thresholds

	Unweighted median (IQR)		Weighted median (IQR)	
<28 weeks GA				
No bleeding	30	(20-45)	30	(20-40)
Ibuprofen	50	(39-60)	50	(40-60)
Lumbar puncture	50	(50-50)	50	(50-50)
Surgery	99	(50-100)	100	(50-100)
Active bleeding	50	(50-99)	50	(50-100)
28-32 weeks GA				
No bleeding	25	(20-30)	25	(20-30)
Ibuprofen	50	(30-50)	50	(35-60)
Lumbar puncture	50	(50-50)	50	(50-50)
Surgery	80	(50-100)	100	(50-100)
Active bleeding	50	(50-80)	50	(50-80)

Table S5. Weighted and unweighted median and interquartile ranges for transfusion volume, duration and rate.

	Unweighted median (IQR)		Weighted median (IQR)	
RBC				
Volume	15.0	(15.0-20.0)	15.0	(15.0-20.0)
Duration	4.0	(3.0-4.0)	4.0	(3.0-4.0)
Rate	4.0	(3.8-5.0)	5.0	(3.8-5.0)
Platelet transfusion				
Volume	15.0	(15.0-15.0)	15.0	(15.0-15.0)
Duration	1.0	(0.5-2.0)	1.0	(0.5-2.0)
Rate	15.0	(7.5-20.0)	15.0	(10.0-30.0)
FFP				
Volume	15.0	(15.0-20.0)	15.0	(15.0-18.0)
Duration	2.0	(1.0-3.0)	2.0	(1.0-2.0)
Rate	10.0	(5.0-15.0)	10.0	(5.0-15.0)

Table S6. Weighted and unweighted proportions for FFP indications

	Unweighted proportion (95% CI)		Weighted proportion (95% CI)	
Coagulopathy with active bleeding	93.3	(90.3-95.6)	93.8	(91.7-95.5)
Active bleeding without coagulopathy	46.1	(40.8-51.4)	45.0	(40.9-48.9)
Coagulopathy without active bleeding	38.8	(33.7-44.0)	39.8	(36.0-43.8)
Sepsis	26.5	(22.1-31.4)	25.8	(22.4-29.4)
Hypotension	24.8	(20.4-29.5)	23.8	(20.5-27.3)

RESULTS OF NON-RESPONDER ANALYSIS

The table below shows the comparison of responses by early responders (first 20%) and late responders (last 20%), where late responders are considered a proxy for non-responders, with differences highlighted.

Table S7. Results of non-responder analysis.

		Early responders		Late responders	
		Median	Count	Median	Count
Threshold_Hb_no_oxygen_first_day		100		100	
Threshold_Hb_no_oxygen_first_week		100		100	
Threshold_Hb_no_oxygen_2weeks		80		80	
Threshold_Hb_no_oxygen_3weeks		75		75	
Threshold_Hb_low_flow_first_day		111		110	
Threshold_Hb_low_flow_first_week		100		100	
Threshold_Hb_low_flow_2weeks		90		90	
Threshold_Hb_low_flow_3weeks		80		80	
Threshold_Hb_high_flow_oxygen_until_30_first_day		115		115	
Threshold_Hb_high_flow_oxygen_until_30_first_week		105		105	
Threshold_Hb_high_flow_oxygen_until_30_2weeks		100		100	
Threshold_Hb_high_flow_oxygen_until_30_3weeks		85		85	
Threshold_Hb_high_flow_oxygen_over_30_first_day		120		120	
Threshold_Hb_high_flow_oxygen_over_30_first_week		115		110	
Threshold_Hb_high_flow_oxygen_over_30_2weeks		100		100	
Threshold_Hb_high_flow_oxygen_over_30_3weeks		90		89	
Threshold_Hb_intubated_ventilated_first_day		120		120	
Threshold_Hb_intubated_ventilated_first_week		116		120	
Threshold_Hb_intubated_ventilated_2weeks		100		100	
Threshold_Hb_intubated_ventilated_3weeks		94		95	
Threshold_Hct_no_oxygen_first_day		34		30	
Threshold_Hct_no_oxygen_first_week		28		30	
Threshold_Hct_no_oxygen_2weeks		24		25	
Threshold_Hct_no_oxygen_3weeks		21		23	
Threshold_Hct_low_flow_first_day		32		30	
Threshold_Hct_low_flow_first_week		28		30	
Threshold_Hct_low_flow_2weeks		25		28	
Threshold_Hct_low_flow_oxygen_3weeks		25		25	
Threshold_Hct_high_flow_oxygen_until_30_first_day		35		35	
Threshold_Hct_high_flow_oxygen_until_30_first_week		30		32	
Threshold_Hct_high_flow_oxygen_until_30_2weeks		30		30	
Threshold_Hct_high_flow_oxygen_until_30_3weeks		25		30	
Threshold_Hct_high_flow_oxygen_over_30_first_day		38		35	
Threshold_Hct_high_flow_oxygen_over_30_first_week		34		35	
Threshold_Hct_high_flow_oxygen_over_30_2weeks		30		30	
Threshold_Hct_high_flow_oxygen_over_30_3weeks		30		30	
Threshold_Hct_intubated_ventilated_first_day		38		36	
Threshold_Hct_intubated_ventilated_first_week		35		35	
Threshold_Hct_intubated_ventilated_2weeks		30		30	
Threshold_Hct_intubated_ventilated_3weeks		30		30	
Volume_RBC_per_kilo		15,0		15,0	
Duration_RBC_transfusion	1 hour		2		1
	2 hours		10		5
	3 hours		11		17

	4 hours		29		31
	5 hours		2		3
	6 hours		10		9
	Other		1		1
Withhold_enteral_feeding	no		37		46
	yes		24		16
	other		6		5
Threshold_platelets_below_28_weeks_no_bleeding		30		30	
Threshold_platelets_below_28_weeks_active_bleeding		50		50	
Threshold_platelets_below_28_weeks_ibuprofen		50		50	
Threshold_platelets_below_28_weeks_lp		50		50	
Threshold_platelets_below_28_weeks_major_surgery		90		100	
Threshold_platelets_28_to_32_weeks_no_bleeding		30		25	
Threshold_platelets_28_to_32_weeks_active_bleeding		50		50	
Threshold_platelets_28_to_32_weeks_ibuprofen		50		50	
Threshold_platelets_28_to_32_weeks_lp		50		50	
Threshold_platelets_28_to_32_weeks_major_surgery		80		100	
Volume_platelets_per_kilo		15		15	
Duration_platelet_transfusion	15 minutes		0		2
	30 minutes		21		14
	1 hour		22		26
	2 hours		13		17
	3 hours		5		4
	4 hours		3		3
	other		2		2
Indication_FFP_volume_replacement_hypotension			9		23
Indication_FFP_active_bleeding_without_coagulopathy			26		32
Indication_FFP_coagulopathy_no_active_bleeding			20		28
Indication_FFP_coagulopathy_active_bleeding			67		62
Indication_FFP_sepsis			17		21
Volume_FFP_per_kilo		15		15	
Duration_FFP_transfusion	15 minutes		0		0
	30 minutes		8		10
	1 hour		25		19
	2 hours		19		19
	3 hours		7		5
	4 hours		7		13
	other		1		2
Routine_diuretics_RBC	never		35		38
	always		1		4
	sometimes		30		24
Routine_diuretics_platelets	never		58		51
	always		1		2
	sometimes		7		12
Routine_diuretics_FFP	never		54		45
	always		1		3
	sometimes		9		18
Consent_non_emergency transfusion	No consent		4		4
	Verbal consent only		2		10
	Verbal consent documenten by clinician		10		2
	Verbal and written consent from parents		46		50
	Other		4		1

QUESTIONNAIRE

This document contains all the survey questions that were analyzed in this manuscript. Two questions were not analyzed, see specifications below.

How many babies are born at <32 weeks gestation at your unit each year? Due to a Limesurvey error, data entry for this question was inaccurate and could therefore not be analyzed.

Which form of platelets does your unit use for neonatal transfusions? One of the answer options was 'Platelet hyperconcentrate', which is a product that is used very sparsely, but would be given at a dose of only 3-5 ml/kg, depending on exact product specifications. On further analyses we observed that many entries that selected 'platelet hyperconcentrate' subsequently reported giving this at a dose of 15 ml/kg. It is likely that these centers use regular platelet transfusion products, not hyperconcentrate, but we were not able to obtain this information. Therefore we have not analyzed these data.

Do you use any of the following on your neonatal unit? (if yes, please indicate when you would use them): Antithrombin III, Tranexamic acid, Another agent which promotes clotting/coagulation, Another agent which prevents clotting/coagulation. The specifications that were given for 'another agent' often contained indications that were unlikely to be correct. For example, .. Therefore, these data were considered unreliable and not analyzed or presented.

We did not report RBC thresholds for babies <24 hours of age, because…

The survey also contained questions about treatment with recombinant human erythropoietin and supplementation of iron, which will be analyzed separately and have not been presented here.

Neonatal blood components survey

Hello,

You have been contacted as a representative clinician for your neonatal unit. As part of an international survey on blood products, we are contacting representatives from neontal units who regularly care for infants born at <32 weeks' gestation.

We would be very grateful if you could spare a few minutes to help us to better understand the variations in neonatal blood product transfusion practices, which exist across Europe, by answering the following questions on behalf of your neonatal unit.

If practice varies between attending clinicians at your unit, please indicate the response you feel best represents the general consensus amongst senior clinicians in your hospital: we only want one response for each neonatal unit. Please also note that there are no right or wrong answers!

We are looking to develop a network of interested neonatologists, health care professionals, and transfusion specialists aimed at advancing the practice of neonatal transfusion medicine and designing new clinical studies. Please let us know at the end of the survey if you are interested in taking part.

Participation in this survey is voluntary.

No individual, hospital or neonatal unit will be identifiable from any reports or publications from this survey. Location information is collected to allow us to track who has responded and ensure that we have a good representative sample from each country.

If you have any questions or concerns about this survey, please contact the representative for your country (the person who sent you the survey invitation) or alexandra.scrivens@ouh.nhs.uk

There are 30 questions in this survey.

General Questions

Does your neonatal unit/hospital routinely look after babies born at less than 32 weeks of completed gestation?

Please choose **only one** of the following:

- Yes
- No

How many babies are born at <32 weeks gestation at your unit each year?

Choose one of the following answers
Please choose **only one** of the following:

- <50
- 50-100
- 100-200
- >200

Please indicate on the map the location of your hospital.

Your responses and your hospital will not be identifiable from any report or publication from this survey. Tracking location in this way allows us to track which hospitals have responded to our survey. This information will be used for this purpose only.

Please write your answer here:

Red Blood Cells

Please answer the following questions relating to how your unit routinely cares for infants born under 32 weeks of gestational age.

The next questions will ask about the threshhold(s) which you use for red cell/blood transfusion in preterm babies. Please select which units your hospital uses to decide whether a blood transfusion is necessary.

Choose one of the following answers. Please choose **only one** of the following:
Haemoglobin level in g/L or g/dL / Haematocrit

What haemoglobin level would use you as a threshold to transfuse the following babies born at <32 weeks' GA?

Please give answers in g/L where 1.0 g/dL = 10 g/L

Only answer this question if the following conditions are met:
Answer was 'Haemoglobin level in g/L or g/dL' at question '5 [RBC3]' (The next questions will ask about the threshhold(s) which you use for red cell/blood transfusion in preterm babies. Please select which units your hospital uses to decide whether a blood transfusion is necessary)

	less than 24 hours of age	24 hours to 7 days of age	2 weeks of age	3 weeks of age
Infant on no added oxygen or respiratory support (g/L)				
Infant on <2L/min added oxygen by low flow nasal cannula (g/L)				
Infant on 21-30% oxygen by non-invasive respiratory support (Including continuous positive airway pressure (CPAP), Biphasic intermittent positive airway pressure (BiPAP; synchronised or unsynchronised), nasal high flow) (g/L)				
Infant on >30% oxygen by non-invasive respiratory support (g/L)				
Infant who is intubated and ventilated (g/L)				

What haematocrit would use you as a threshold to transfuse the following babies born at <32 weeks' GA?

Please give answers as haematocrit percentage. e.g. haematocrit 0.1 = 10% = answer 10

Only answer this question if the following conditions are met: Answer was 'Haematocrit' at question '5 [RBC3]' (The next questions will ask about the threshhold(s) which you use for red cell/blood transfusion in preterm babies. Please select which units your hospital uses to decide whether a blood transfusion is necessary)

	less than 24 hours of age	24 hours to 7 days of age	2 weeks of age	3 weeks of age
Infant on no added oxygen or respiratory				

	less than 24 hours of age	24 hours to 7 days of age	2 weeks of age	3 weeks of age
support				
Infant on <2L/min added oxygen by low flow nasal cannula				
Infant on 21-30% oxygen by non-invasive respiratory support (Including continuous positive airway pressure (CPAP), Biphasic intermittent positive airway pressure (BiPAP; synchronised or unsynchronised), nasal high flow)				
Infant on >30% oxygen by non-invasive respiratory support				
Infant who is intubated and ventilated				

What volume of red cells would you typically transfuse to a haemodynamically stable baby on your neonatal unit?
Please give your answer in **ml/kg**. Only numbers may be entered in this field.
Please write your answer here: …

Over what duration would you normally give an RBC transfusion in a haemodynamically stable baby born at <32 weeks?
Choose one of the following answers. Please choose **only one** of the following:
6 hours / 5 hours / 4 hours / 3 hours / 2 hours / 1 hour / 30 minutes / 15 minutes / Other

Do you withhold enteral feeds during red blood cell transfusions for babies born <32 weeks gestational age? (if you choose 'sometimes', please specify when you would withhold feeds)
Choose one of the following answers. Please choose **only one** of the following:
Yes / No / Sometimes

Platelets

please answer the following questions

At which platelet count threshold would you usually transfuse the following babies in the first week since birth? (answers given as x10^9/L or micromol/L)

	Stable, no bleeding	Active bleeding e.g. new intraventricular haemorrhage	Undergoing ibuprofen treatment for PDA	Before a lumbar puncture	Before major surgery (e.g. laparotomy)
An infant born at <28 weeks' gestation					
An infant born at 28-32 weeks' gestation					

Which form of platelets does your unit use for neonatal transfusions?

Choose one of the following answers. Please choose **only one** of the following:

- Standard/Normal concentration platelets
- Platelet hyperconcentrate
- I do not know
- Other

What volume of platelets would you typically transfuse to a haemodynamically stable baby on your NNU?

Please give your answer in **ml/kg**. e.g. '15' = 15ml/kg. Only numbers may be entered in this field.
Please write your answer here: …

Over what duration would you normally transfuse platelets in a haemodynamically stable baby on your NNU?

Choose one of the following answers. Please choose **only one** of the following:

4 hours / 3 hours / 2 hours / 1 hour / 30 mins / 15 mins / Other

Plasma/Fresh Frozen Plasma

For which main indication(s) would you prescribe fresh frozen plasma (FFP) to babies in your hospital?
Check all that apply. Please choose **all** that apply:

- Volume replacement/hypotension
- Active bleeding without coagulopathy
- Coagulopathy with no active bleeding
- Coagulopathy with active bleeding
- Sepsis
- Other:

Do you routinely perform coagulation/clotting tests in babies born <32weeks who are not bleeding?
Choose one of the following answers. Please choose **only one** of the following:

Yes / No

What volume of plasma/FFP would you usually administer to a haemodynamically stable baby born at <32 weeks on your NNU?

Please give your answer in **ml/kg**. e.g. '15' = 15ml/kg**.** Only numbers may be entered in this field.
Please write your answer here: …

Over what duration would you usually give a plasma/FFP transfusion in a haemodynamically stable baby on your NNU?
Choose one of the following answers. Please choose **only one** of the following:

4 hours / 3 hours / 2 hours / 1 hour / 30 mins / 15 mins / Other

Do you use any of the following on your neonatal unit? (if yes, please indicate when you would use them)

Comment only when you choose an answer. Please choose all that apply and provide a comment:

- Antithrombin III
- Tranexamic acid
- Another agent which promotes clotting/coagulation
- Another agent which prevents clotting/coagulation
- No

Transfusion management

Do you routinely prescribe diuretics alongside blood component transfusions?

Please choose the appropriate response for each item:

	No, never	Yes, always	Yes, sometimes
Red blood cells			
Platelets			
Plasma/FFP			

In common practice on your unit, what consent do you obtain from parents for a non-emergency blood component transfusion?

Choose one of the following answers. Please choose **only one** of the following:

- No consent
- Verbal consent only
- Verbal consent documented in the notes by clinician
- Verbal and written consent from parents (parents have to sign a form)
- Other

Would you be interested in participating in a national / international network to address further research questions in neonatal transfusion practice?
Over the coming year, you may be invited to taking part in a short point prevalence study on neonatal blood transfusions. This would involve collecting data on all neonatal transfusions on your unit for a short period of time.
Choose one of the following answers. Please choose **only one** of the following:

No thank you / Yes

Thank you very much for your time in answering our survey.

Submit your survey.
Thank you for completing this survey.

LIST OF PARTICIPATING NEONATAL (RESEARCH) NETWORKS

To be added after review by national coordinators.