How 217 pediatric intensivists manage anemia at PICU discharge: online responses to an international survey

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How 217 Pediatric Intensivists Manage Anemia at PICU Discharge: Online Responses to an International Survey*

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Objective: To describe the management of anemia at PICU discharge by pediatric intensivists.

Design: Self-administered, online, scenario-based survey.

Setting: PICUs in Australia/New Zealand, Europe, and North America.

Subjects: Pediatric intensivists.

Interventions: None.

Measurements and Main Results: Respondents were asked to report their decisions regarding RBC transfusions, iron, and erythropoietin prescription to children ready to be discharged from PICU, who had been admitted for hemorrhagic shock, cardiac surgery, craniofacial surgery, and polytrauma. Clinical and biological variables were altered separately in order to assess their effect on the management of anemia. Two-hundred seventeen responses were analyzed. They reported that the mean (± SEM) transfusion threshold was a hemoglobin level of 6.9 ± 0.09 g/dL after hemorrhagic shock, 7.6 ± 0.10 g/dL after cardiac surgery, 7.0 ± 0.10 g/dL after craniofacial surgery, and 7.0 ± 0.10 g/dL after polytrauma ($p < 0.001$). The most important increase in transfusion threshold was observed in the presence of a cyanotic heart disease (mean increase ranging from 1.80 to 2.30 g/dL when compared with baseline scenario) or left ventricular dysfunction (mean increase, 1.41–2.15 g/dL). One third of respondents stated that they would not prescribe iron at PICU discharge, regardless of the hemoglobin level or the baseline scenario. Most respondents (69.4–75.0%, depending on the scenario) did not prescribe erythropoietin.

Conclusions: Pediatric intensivists state that they use restrictive transfusion strategies at PICU discharge similar to those they use during the acute phase of critical illness. Supplemental iron is less frequently prescribed than RBCs, and prescription of erythropoietin is uncommon. Optimal management of post-PICU anemia is currently unknown. Further studies are required to highlight the consequences of this anemia and to determine appropriate management. (*Pediatr Crit Care Med* 2020; 21:e342–e353)

*See also p. 597.

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Anemia is highly prevalent worldwide and is associated with a high disability burden, especially in children (1). Critically ill patients are particularly at risk: up to 90% of critically ill adults are anemic by ICU day 3, and approximately 75% of critically ill children are anemic at admission or become anemic during their stay in PICU (2, 3).

Based on data published in the last decades, it is now recommended that most critically ill patients should be transfused RBCs according to a restrictive strategy (4, 5). This recommendation, combined with the high prevalence and occurrence rate of anemia during critical illness, raises the question of anemia after critical illness. Scarce data suggest that about 85% of adults are anemic when leaving the ICU, whereas more recent pediatric data show that the prevalence of anemia at PICU discharge could be as high as 60% (6–8). Anemia has been found to be associated with bad outcomes in several noncritical settings: reduced health-related quality of life in patients with renal transplant or cancer, infection in patients with ischemic stroke, or higher likelihood of unfavorable neurologic outcome following cardiac arrest (9–13). It is, thus, plausible that anemia is associated with worse outcomes after critical illness, which makes it an important issue to explore for critical care physicians.

To date, available evidence to guide critical care physicians in the management of anemia stems from studies that have enrolled patients during the acute phase of their critical illness and have not reported outcomes related to the morbidity after PICU discharge (4, 5, 14, 15). No data are available that describe current practice on the management of anemia in the patient about to be discharged from PICU, nor is there any evidence to guide practitioners on how to best manage anemia at PICU discharge.

Assessment of current practices is of key importance to understand and interpret observational data and to generate or refine hypotheses for future research (16, 17). We designed a survey to explore how pediatric intensivists manage anemia at PICU discharge. We aimed to assess three therapeutic modalities commonly used to treat anemia: RBC transfusion, erythropoietin administration, and iron supplementation.

MATERIALS AND METHODS

Study Design

Self-administered, web-based survey consisting of four clinical scenarios.

Study Outcomes

Study outcomes were stated hemoglobin thresholds used to prescribe RBC transfusions (primary outcome), erythropoietin, and iron supplementation (secondary outcomes).

Study Population

This survey targeted pediatric intensivists working in North America, Europe, and Australia/New Zealand. The questionnaire was electronically distributed to members of the Pediatric Acute Lung Injury and Sepsis Investigators Network and the Australian and New Zealand Intensive Care Society, to the heads of all PICUs in Canada and in the United Kingdom (via the Paediatric Intensive Care Society), and to members of national pediatric critical care societies in several European countries (Belgium, France, Italy, the Netherlands, Spain, and Switzerland). Eligible participants were excluded if they were retired; worked outside Europe, North America, Australia, or New Zealand; worked exclusively in a neonatal or adult ICU; were still in training; and/or were not a physician.

Development and Distribution of the Questionnaire

The survey instrument was developed in English and formatted using a website (http://www.surveymonkey.com).

The variables assessed in our questionnaire were selected by consulting five pediatric intensivists with an expertise in the field of anemia and transfusion medicine in critically ill children, who were asked to list all the diagnoses, clinical and biological variables that they thought could influence the prescription of RBCs/erythropoietin/iron in anemic children at PICU discharge (item generation [16]). Four diagnoses (for four scenarios, see **Table 1**) and 11 clinical/biological variables were then selected by eight pediatric intensivists who were asked to rank each variable according to their possible influence on the management of anemia (item reduction [16]). A 12th clinical variable (chronic kidney disease [CKD]) was added to the questionnaire during testing, based on respondent request (Table 1).

The questionnaire was piloted using semistructured interviews administered to two pediatric intensivists with an aim to identify redundant, irrelevant, or poorly worded questions (16). Clinical sensibility testing of the questionnaire, aiming to assess its comprehensiveness, clarity, and face validity, was conducted by administering questions to be answered with a seven-point Likert scale to six other pediatric intensivists. Finally, the reliability of the questionnaire was assessed with a test-retest: the questionnaire was administered to the same six pediatric intensivists twice with an 8-week interval and the reproducibility of their answers was assessed (78% of the answers were reproducible; Pearson coefficient, 0.7; $p < 0.001$).

Within each scenario, respondents were asked to indicate the hemoglobin threshold that would trigger a prescription for RBCs, erythropoietin, or iron supplementation. For each of these three treatments, the "baseline" threshold was collected for each scenario ("what is the hemoglobin value below which you would prescribe RBCs/iron/erythropoietin to this child, all other laboratory values being within normal range?"). The influence of the 12 clinical/biological variables (determinants) on this baseline threshold was estimated by systematically altering each of these variables one at a time ("what is the hemoglobin value below which you would prescribe RBCs/iron/erythropoietin to this child if each of the following characteristics was

TABLE 1. Description of the Four Scenarios and of the Variables Assessed Within Each Scenario

1 Scenarios
Scenario 1
A 3-yr-old child is going to be transferred from the PICU to the ward. He was admitted to the PICU 5 d ago for a "hemorrhagic shock" due to a traumatic splenic rupture with no other injuries. The massive transfusion protocol was initiated when the child arrived at the emergency department, and it was continued after PICU admission. Approximately 300% of the total blood volume was replaced with transfusions during the first 24 hr of his hospital stay. A splenectomy was finally required to control the bleeding. The child was mechanically ventilated for 3 d. He was on a noradrenaline/norepinephrine infusion for 2 d. At PICU day 5, the child is ready to be discharged to the ward. He is doing well, playing and eating appropriately. He does not require oxygen supplementation. He has normal vital signs. His clinical examination is normal. He has no other health-related concerns.
Scenario 2
A 5-mo-old child is going to be transferred from the PICU to the ward. He was admitted to the PICU 5 d ago after "surgical repair of a complete atrioventricular canal." The postoperative echocardiogram showed good biventricular contractility with no significant residual lesion. His postoperative course was excellent. The child was extubated 2 hr after PICU admission, inotropic support (milrinone) was discontinued at PICU day 1, and chest tubes were removed at PICU day 4. No organ dysfunction occurred. On PICU day 5, the child is ready to be discharged to the pediatric cardiology ward. He is doing well, playing and eating appropriately. He does not require oxygen supplementation. He has normal vital signs. His clinical examination is normal. He has no other health-related concerns.
Scenario 3
An 8-mo-old child is going to be transferred from the PICU to the ward. He was admitted to the PICU 5 d ago after a "complex craniofacial surgery with a high risk of bleeding." No complications occurred during the surgery, and blood loss was estimated to be < 10% of the total blood volume (= 8 mL/kg). The PICU course was unremarkable, no hemorrhagic complications occurred, and pain was well controlled with usual medications. On PICU day 5, the child is ready to be discharged to the ward. He is doing well, playing and eating appropriately. He does not require oxygen supplementation. He has normal vital signs. His clinical examination is normal. He has no other health-related concerns.
Scenario 4
A 3-yr-old child is going to be transferred from the PICU to the ward. He was admitted to the PICU 5 d ago after a "motor vehicle accident." The child suffered a femoral fracture, a grade II hepatic injury (intraparenchymal hematoma < 2 cm diameter), a pulmonary contusion, and a fracture of the body of the fifth and the sixth thoracic vertebra, all of which did not require surgery. The PICU course was unremarkable, no hemorrhagic complications occurred, and pain was well controlled with usual medications. The child is now ready to be discharged to the ward. He is doing well, playing and eating appropriately. He does not require oxygen supplementation. He has normal vital signs. His clinical examination is normal. He has no other health-related concerns.

2 Biological and Clinical Variables Assessed in Each Scenario	
Low mean corpuscular volume	Low ferritin level
Low reticulocytosis	Asthenia
Tachycardia	Sickle cell disease
Upcoming surgery with a high risk of bleeding	Oxygen therapy
Cyanotic congenital heart disease	Left ventricular dysfunction with reduced ejection fraction
Chronic kidney disease	Lengthy PICU stay (30 d)

modified while other factors remained unchanged?") (see the survey, available as **supplemental data file 1**, Supplemental Digital Content 1, http://links.lww.com/PCC/B295). No questions were mandatory: each participant could advance in the survey after skipping a question.

The survey was distributed by e-mail, with a cover letter stating the objectives of the survey and providing an estimate of the completion time (16).

Approval for survey distribution, data collection, and analysis was obtained from the ethics committee of the French Pediatric Society (CER_SFP 2017_056).

Statistical Analysis

Respondents' characteristics (all categoric variables) were described as number (percentage), whereas hemoglobin levels triggering RBC transfusion (threshold concentration) were described as mean ± SE (we analyzed hemoglobin level as a continuous variable considering the high number of discrete values).

First, we compared the threshold hemoglobin concentration between the four baseline scenarios using a linear mixed model by including a random respondent effect to account for correlation between the four scenarios. Second, after pooling

together the four scenarios and after adjusting for scenario effect, we investigated the association of respondents' characteristics with the threshold hemoglobin concentration for baseline conditions by using a linear mixed model; in these models, respondents' characteristics and scenario were considered fixed effects. Third, we calculated the difference between threshold hemoglobin concentration from each determinant and baseline conditions and compared these differences between the four scenarios using a linear mixed model in which scenarios, determinants, and determinants × scenarios were fixed effects. Hemoglobin was analyzed as a continuous variable considering the high number of discrete values (18). As a high number of respondents did not prescribe iron and erythropoietin, these variables were categorized as a binary variable (prescription vs no prescription). We assessed the influence of scenario and determinants on iron and erythropoietin prescription using a generalized linear mixed model (distribution binomial, logit link function) with scenarios, determinants (including baseline), and determinants × scenarios as fixed effects, and respondent as random effect.

Statistical testing was performed at the two-tailed αlevel of 0.05. Data were analyzed using SAS software (version 9.4; SAS Institute, Cary, NC).

RESULTS

Demographic and Baseline Data Analyses

The survey was completed between September 2018 and January 2019. The response rate was 20.4% (276/1,354). Fifty-nine respondents were excluded because of the a priori defined exclusion criteria. The analyzed sample included thus 217 respondents whose characteristics are described in **Table 2**.

Geographic location was available for 162 participants with a majority working in Europe (115, 71%). However, the proportion of North American pediatric intensivists who answered the survey (40 respondents out of 168 invited to participate, 23.4%) was higher than the proportion in Europe (115/1,106, 10.4%) or of Australia (7/80, 8.8%). Most of the respondents worked in a multidisciplinary PICU with (41.4%) or without (42%) cardiac surgery, and half of the participants (52.8%) worked in a 10- to 20-bed PICU. Approximately half of the participants (45.1%) stated that an RBC transfusion protocol was available in their PICU, whereas a protocol to guide iron supplementation and erythropoietin prescription was rarely available (4.3%).

The proportion of missing values was 18.5% for RBC transfusions, 24.3% for erythropoietin, and 22.9% for iron.

RBC Transfusions

The hemoglobin level triggering an RBC transfusion at PICU discharge varied slightly according to the baseline scenarios: the mean ± SEM was 6.9 ± 0.09 g/dL after hemorrhagic shock, 7.6 ± 0.10 g/dL after cardiac surgery, 7.0 ± 0.10 g/dL after surgery with a high risk of bleeding, and 7.0 ± 0.10 g/dL after polytrauma ($p < 0.001$) (**Table 3** and **Fig. 1**). The proportion of respondents choosing a transfusion threshold less than or equal to 7 g/dL was 87% after hemorrhagic shock, 60% after cardiac surgery, 81% after surgery with a high risk of bleeding, and 83% after polytrauma. The baseline hemoglobin triggers varied according to some respondents' characteristics (Table 2). European respondents used a higher hemoglobin level to prescribe RBCs: their mean hemoglobin trigger for the four baseline scenarios was 7.6 ± 0.09 g/dL, whereas it was 6.7 ± 0.1 g/dL for North American respondents and 6.7 ± 0.19 g/dL for Australian respondents ($p < 0.001$) (Table 2). A larger PICU size or patient volume was associated with a reduced hemoglobin trigger: it was 6.6 ± 0.10 g/dL for PICU with greater than or equal to 20 beds (vs 7.3 ± 0.09 g/dL if 10–20 beds and 7.5 ± 0.10 g/dL if < 10 beds; $p < 0.001$) and 6.7 ± 0.10 g/dL for PICU with greater than or equal to 1,000 admissions per year (vs 7.2 ± 0.09 g/dL if 500–1,000 admissions and 7.5 ± 0.09 g/dL if < 500 admissions; $p < 0.001$). Furthermore, experienced physicians used lower transfusion thresholds when compared with young physicians: the mean pretransfusion hemoglobin ranged from 6.9 ± 0.19 g/dL for respondents with greater than or equal to 30 years of experience to 7.4 ± 0.11 g/dL for respondents with less than 5 years of experience ($p = 0.027$).

Some biological and clinical variables did not influence the transfusion strategy: a low mean corpuscular volume (MCV), a low ferritin level, a low reticulocyte count, and a longer PICU stay were not associated with a significant change in the hemoglobin level triggering an RBC transfusion (Table 3). Other variables were associated with a slight (< 1 g/dL) but statistically significant increase of the hemoglobin threshold: asthenia, tachycardia, sickle cell disease (SCD), upcoming surgery with a high risk of bleeding, oxygen requirement, and CKD. Finally, two variables induced an important increase of the pretransfusion hemoglobin: presence of a cyanotic congenital heart disease (mean increase ranging from 1.80 to 2.3 g/dL when compared with the baseline scenario) or left ventricular dysfunction (mean increase ranging from 1.41 to 2.15 g/dL). The effect of those clinical or biological variables was the same from one scenario to another, with the following exceptions: the increase in threshold hemoglobin induced by tachycardia was more pronounced after cardiac surgery ($p = 0.016$), and the effect of cyanotic congenital heart disease and left ventricular dysfunction was more important after hemorrhagic shock ($p < 0.001$) (Table 3).

Iron

One third of the respondents stated that they would not prescribe iron at PICU discharge for any of the four baseline scenarios, regardless of the hemoglobin level (proportion ranging from 32.3% to 34.8%, not influenced by the baseline scenario [$p = 0.964$]) (**Table 4**; and **supplemental data file 2**, Supplemental Digital Content 2, http://links.lww.com/PCC/B296). The proportion of participants prescribing iron was significantly higher in case of microcytosis (82–86% prescribing iron) or if the ferritin level was low (86.4–87% prescribing iron); this increase was not related to the baseline scenario ($p = 0.687$ and 0.993, respectively). On the other hand, fewer physicians prescribed iron in the presence of tachycardia (42–48% of the

TABLE 2. Characteristics of the Respondents and Their Association With the Hemoglobin Level Triggering an RBC Transfusion

Characteristics	Respondents, *n* (%)	Baseline Hemoglobin Level (g/dL) Triggering RBC Transfusion (mean ± SE of the Four Scenarios)[a]	*p*[a]
Place of work	162 (100)		< 0.001
Australia/New Zealand	7 (4.3)	6.7 ± 0.19	
Europe	115 (71)	7.6 ± 0.09	
North America	40 (24.7)	6.7 ± 0.1	
Type of hospital[b]	162 (100)		
Free-standing children's hospital	58 (35.8)	7.2 ± 0.09 vs 7.1 ± 0.09[c]	0.42
Children's hospital in an adult hospital	46 (28.4)	7.2 ± 0.07 vs 7.0 ± 0.10[c]	0.017
Academic center	87 (53.7)	7.1 ± 0.08 vs 7.2 ± 0.10[c]	0.46
Community hospital	5 (3.1)	–	–
Other	1 (0.6)	–	–
No. of in-house pediatric beds	162 (100)		< 0.001
0–50	15 (9.3)	7.4 ± 0.14	
51–100	44 (27.2)	6.9 ± 0.09	
101–150	18 (11.1)	7.1 ± 0.13	
151–200	30 (18.5)	6.9 ± 0.11	
201–300	19 (11.7)	6.7 ± 0.12	
301–400	14 (8.6)	7.5 ± 0.16	
> 400	22 (13.6)	7.5 ± 0.12	
Kind of PICU	162 (100)		
Cardiac only	3 (1.9)	–	
Medical and surgical with cardiac surgery	67 (41.4)	7.0 ± 0.09 vs 7.2 ± 0.08[c]	0.002
Medical and surgical without cardiac surgery	68 (42)	7.1 ± 0.09 vs 7.2 ± 0.09[c]	0.23
Mixed NICU and PICU with cardiac surgery	8 (4.9)	–	
Mixed NICU and PICU without cardiac surgery	14 (8.6)	–	
Other	2 (1.2)	–	
No. of PICU beds	161 (100)		< 0.001
< 10	36 (22.4)	7.5 ± 0.10	
10–20	85 (52.8)	7.3 ± 0.09	
≥ 20	40 (18.4)	6.6 ± 0.10	
No. of patients admitted annually in the PICU	158 (100)		< 0.001
< 500	51 (32.5)	7.5 ± 0.09	
500–1,000	61 (38.9)	7.2 ± 0.09	
≥ 1,000	45 (28.7)	6.7 ± 0.10	
Years in practice as a senior PICU physician	162 (100)		0.027
< 5	37 (22.8)	7.4 ± 0.11	
5–9	35 (21.6)	7.1 ± 0.11	
10–19	49 (30.3)	7.1 ± 0.10	
20–29	31 (19.1)	7.1 ± 0.11	
≥ 30	10 (6.2)	6.9 ± 0.19	

(*Continued*)

TABLE 2. (*Continued*). Characteristics of the Respondents and Their Association With the Hemoglobin Level Triggering an RBC Transfusion

Characteristics	Respondents, *n* (%)	Baseline Hemoglobin Level (g/dL) Triggering RBC Transfusion (mean ± SE of the Four Scenarios)[a]	*p*[a]
Protocol available in the PICU for	162 (100)		
RBC transfusion	73 (45.1)	7.1 ± 0.09 vs 7.2 ± 0.08[c]	0.40
Iron	7 (4.3)	–	–
Erythropoietin	7 (4.3)	–	–

NICU = neonatal ICU.

[a]Mean ± SE calculated using linear mixed model including respondents' characteristic and scenario as fixed effects and respondent as a random effect to account for the correlation between the four scenarios within respondents.

[b]More than one answer could be chosen.

[c]Comparison of respondents with the condition versus those without the condition.

Dashes indicate no analysis considering the small number of respondents with the condition.

TABLE 3. Hemoglobin Level That Would Trigger RBC Transfusion at Baseline, and Difference With Baseline Transfusion Threshold Hemoglobin Induced by Each Determinant

Determinant	Scenario 1: Hemorrhagic Shock	Scenario 2: Postcardiac Surgery (Biventricular Physiology)	Scenario 3: Postsurgery With a High Risk of Bleeding	Scenario 4: Polytrauma	*p*
1/Baseline scenario: mean hemoglobin ± SE (g/dL)					
	6.9 ± 0.09	7.6 ± 0.10	7.0 ± 0.10	7.0 ± 0.10	< 0.001[a]
2/Difference with baseline transfusion threshold hemoglobin: Δ g/dL (95% CI)					
Low mean corpuscular volume	−0.07 (−0.21 to 0.06)	0.04 (−0.10 to 0.19)	−0.08 (−0.23 to 0.07)	−0.10 (−0.26 to 0.05)	0.49[b]
Low ferritin level	−0.07 (−0.21 to 0.06)	0.06 (−0.09 to 0.20)	−0.08 (−0.23 to 0.07)	−0.11 (−0.27 to 0.04)	0.38[b]
Low reticulocytosis	0.09 (−0.04 to 0.22)	0.08 (−0.06 to 0.23)	−0.04 (−0.19 to 0.11)	−0.06 (−0.21 to 0.09)	0.32[b]
Asthenia	0.84 (0.71–0.97)[c]	0.90 (0.75–1.04)[c]	0.70 (0.55–0.85)[c]	0.65 (0.50–0.80)[c]	0.054[b]
Tachycardia	0.83 (0.70–0.96)[c]	1.01 (0.87–1.16)[c]	0.76 (0.61–0.90)[c]	0.71 (0.56–0.86)[c]	0.016[b]
Sickle cell disease	0.66 (0.53–0.79)[c]	0.53 (0.39–0.68)[c]	0.45 (0.31–0.60)[c]	0.49 (0.34–0.65)[c]	0.15[b]
Upcoming surgery with a high risk of bleeding	0.24 (0.10–0.37)[c]	0.26 (0.12–0.41)[c]	0.20 (0.05–0.35)[c]	0.23 (0.07–0.38)[c]	0.94[b]
Oxygen therapy	0.72 (0.59–0.85)[c]	0.77 (0.62–0.91)[c]	0.61 (0.46–0.75)[c]	0.58 (0.43–0.73)[c]	0.21[b]
Cyanotic congenital heart disease	2.30 (2.17–2.43)[c]	1.80 (1.66–1.95)[c]	1.94 (1.79–2.09)[c]	1.93 (1.78–2.08)[c]	<0.001[b]
Left ventricular dysfunction with reduced ejection fraction	2.15 (2.02–2.28)[c]	1.41 (1.27–1.56)[c]	1.75 (1.60–1.89)[c]	1.66 (1.51–1.81)[c]	<0.001[b]
Chronic kidney disease	0.41 (0.28–0.54)[c]	0.37 (0.22–0.51)[c]	0.37 (1.22–0.51)[c]	0.31 (0.16–0.46)[c]	0.80[b]
Lengthy PICU stay (30 d)	0.02 (−0.11 to 0.16)	0.25 (0.10–0.40)[c]	0.08 (−0.07 to 0.24)	0.04 (−0.11 to 0.20)	0.12[b]

[a]Calculated using linear mixed model with scenarios as fixed effect and respondent as random effect to account for the correlation between the four scenarios within respondents.

[b]Calculated from the difference between determinant and baseline values by using a linear mixed model with scenarios, determinants and determinants × scenarios as fixed effects, and respondent as random effect to account for the correlation between the four scenarios within respondents. Mean difference (95% CI) between each determinant and baseline values and *p* values for comparison of those differences between the four scenarios were derived from this linear mixed model using linear contrasts.

[c]$p < 0.05$ (for the change in threshold hemoglobin when compared with the hemoglobin level chosen at baseline).

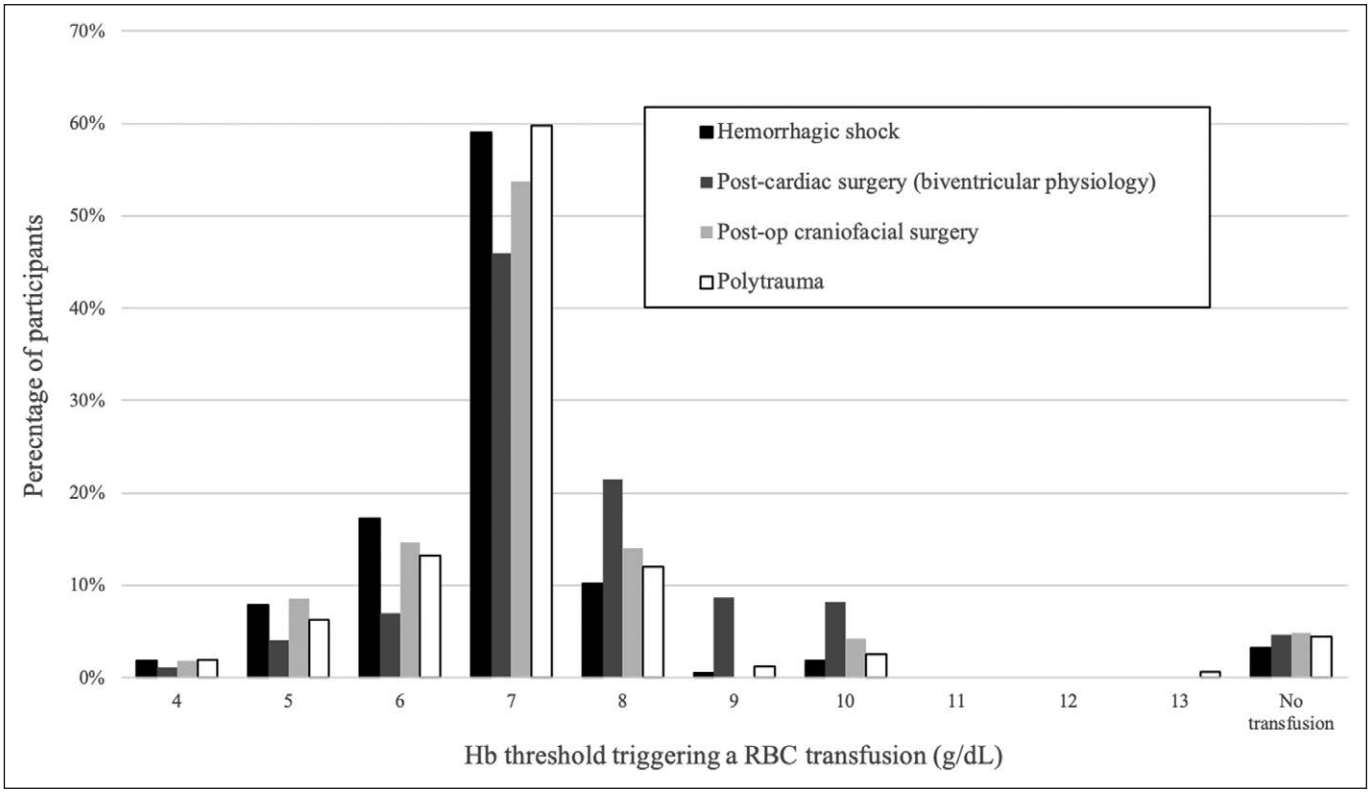

Figure 1. Distribution of hemoglobin (Hb) thresholds triggering an RBC transfusion, according to the baseline scenarios.

respondents stating that they would not prescribe iron), SCD (53–61%), or oxygen therapy (41–47%), independently of the baseline scenario ($p = 0.662$, 0.740, and 0.698, respectively) (Table 4).

Erythropoietin

Most of the respondents stated that they would not prescribe erythropoietin at PICU discharge for the four baseline scenarios, regardless of the hemoglobin level (proportion ranging from 69% to 75%, not influenced by the baseline scenario [$p = 0.611$]) (**Table 5**; and **supplemental data file 3**, Supplemental Digital Content 3, http://links.lww.com/PCC/B297). More physicians prescribed erythropoietin in case of low reticulocyte count (34–39% prescribing erythropoietin), of upcoming surgery with a high risk of bleeding (40–46%), or of CKD (70–77%), with no influence of the baseline scenario (Table 5).

Perception of Anemia at PICU Discharge

When asked to estimate prevalence of anemia at PICU discharge, 39.5% of respondents answered that it was less than 30%, 36% estimated that it ranged between 30% and 50%, 19.1% between 50% and 70%, and 5% stated the prevalence was greater than 70% (**Fig. 2**). The monitoring of the hemoglobin level at PICU discharge was done rarely to very rarely for 25% of the respondents, sometimes for 18%, often for 17%, frequently for 24%, and very frequently for 15%. Finally, the clinical importance of anemia on post-PICU outcomes was considered low for 27% of the respondents (scores 1–2 on a six-point Likert scale), intermediate for 60% (scores 3–4), and high for 14% (scores 5–6).

DISCUSSION

This international survey of 217 pediatric intensivists shows that they use restrictive transfusion strategies to treat anemia at the time of PICU discharge. We also observed that iron prescription at PICU discharge was less common than RBC transfusion and was positively influenced by microcytosis and low ferritin levels but negatively influenced by some clinical conditions (tachycardia, SCD, and oxygen requirements). In addition, erythropoietin prescription was infrequent even though more commonly used in patients with CKD and, to a lesser extent, low reticulocyte count and SCD. Finally, anemia at PICU discharge may be underestimated: most of the respondents stated that they do not frequently monitor the hemoglobin level at PICU discharge, and 75% estimated that anemia is encountered in less than 50% of children discharged alive from PICU (while recent data indicate post-PICU anemia prevalence could be as high as 60% [7, 8]).

RBC Transfusion: Same Strategy for Acute and Recovery Phases?

Anemia triggers a series of compensatory responses to maintain homeostasis. These responses include an increase in cardiac output, a redistribution of flow to critical organs (e.g., heart and brain), and an increase in oxygen extraction from the capillary blood to meet the metabolic need (19). Critically ill patients suffer from a multitude of physiologic derangements that may affect oxygen kinetics and impair their ability to compensate for anemia. Furthermore, according to the two-hit model, the risk of transfusion-related complications is

TABLE 4. Number and Proportion of Respondents Who Would Not Prescribe Iron (Regardless of the Hemoglobin Level) According to the Baseline Scenario and to Each Determinant

Determinant	Scenario 1: Hemorrhagic Shock	Scenario 2: Postcardiac Surgery (Biventricular Physiology)	Scenario 3: Postsurgery With a High Risk of Bleeding	Scenario 4: Polytrauma	*p*
1/Baseline scenario: respondents who would "not" prescribe iron (*n*/*n*tot [%])					
	71/204 (34.8)	54/163 (33.1)	54/160 (33.8)	50/155 (32.3)	0.96[a]
2/Effect of the determinants: respondents who would "not" prescribe iron (*n*/*n*tot [%])					
Low mean corpuscular volume	31/206 (15.1)[b]	22/162 (13.6)[b]	27/156 (17.3)[b]	27/150 (18.0)[b]	0.69[a]
Low ferritin level	26/206 (12.6)[b]	22/162 (13.6)[b]	20/156 (12.8)[b]	19/150 (12.7)[b]	0.99[a]
Low reticulocytosis	54/206 (26.2)	41/162 (25.3)	44/156 (28.2)	37/150 (24.7)	0.90[a]
Asthenia	85/204 (41.7)	66/161 (41.0)	62/155 (40.0)	61/149 (40.9)	0.99[a]
Tachycardia	98/203 (48.3)[b]	72/160 (45.0)[b]	65/155 (41.9)	64/147 (43.5)[b]	0.66[a]
Sickle cell disease	123/202 (60.9)[b]	88/159 (55.4)[b]	84/153 (54.9)[b]	78/147 (53.1)[b]	0.47[a]
Upcoming surgery with a high risk of bleeding	62/205 (30.2)	51/160 (31.9)	52/155 (33.6)	46/149 (30.9)	0.92[a]
Oxygen therapy	96/203 (47.3)[b]	69/160 (43.1)	64/155 (41.3)	64/148 (43.2)[b]	0.70[a]
Cyanotic congenital heart disease	87/204 (42.7)	62/160 (38.8)	60/155 (38.7)	55/149 (36.9)	0.72[a]
Left ventricular dysfunction with reduced ejection fraction	94/204 (46.1)[b]	64/160 (40.0)	59/155 (38.1)	56/149 (37.6)	0.32[a]
Chronic kidney disease	79/204 (38.7)	63/161 (39.1)	60/154 (39.0)	50/148 (33.8)	0.73[a]
Lengthy PICU stay (30 d)	90/203 (44.3)[b]	67/161 (41.6)	64/154 (41.6)	62/147 (42.2)	0.94[a]

*n*tot = number of participants who answered the question.

[a]Calculated using generalized linear mixed model (GLMM, binomial distribution, logit link function) with scenarios, determinants (including baseline) and determinants × scenarios as fixed effects and respondents as random effect to account for the correlation between the four scenarios within respondents. Comparison of the proportions of respondents who would not prescribe iron between each determinant and baseline scenario and comparison between the four scenarios according to each determinant were derived from this GLMM using linear contrasts.

[b]$p < 0.05$ (for the comparison between determinant and baseline scenario).

probably higher for the critically ill patients (20). One the other hand, patients recovering from critical illness have a stable and compensated physiology, their condition is theoretically not immediately life-threatening anymore and their main challenge is the functional recovery. The threats of anemia and transfusions differ, thus, between the acute and the recovery phases of critical illness, and transfusion decision-making should differ accordingly.

Restrictive transfusion strategies are recommended in most critically ill children, based on four randomized controlled trials (RCTs) among which one implied a general population of critically ill children and none focused on children stabilized and ready to be discharged from PICU (4, 21–23). The hemoglobin thresholds triggering transfusions in our survey indicate that restrictive transfusion practices could be common at PICU discharge. However, the outcomes used to assess the safety of a restrictive transfusion strategy in the above-mentioned RCTs were mostly parameters related to PICU stay and do not reflect post-PICU outcomes. Thus, currently available data do not allow proper assessment of the impact of a restrictive transfusion strategy "after" critical illness. Post-PICU outcomes (including cognitive outcomes [13, 24]) should be evaluated when assessing the safety and efficacy of a restrictive RBC transfusion strategy in children recovering from critical illness. Indeed, anemia persisting after PICU discharge could be associated with worse outcomes which might justify higher transfusion thresholds after critical illness.

RBC Transfusion Strategy in Children With Congenital Heart Disease

The pediatric intensivists surveyed in our study used higher hemoglobin thresholds for children with congenital heart disease at the time of PICU discharge, especially in the presence of cyanotic heart disease. However, the transfusion practices stated in our survey are more restrictive than previously reported: in a survey conducted in Canada aiming to assess transfusion practices just after pediatric cardiac surgery (i.e., during the acute phase of critical illness), the mean pretransfusion hemoglobin was 8.8 ± 1.3 g/dL in a scenario involving a 5-month-old infant with a noncyanotic condition and was 11.1 ± 1.4 g/dL if a cyanotic heart disease was present. In our survey on the management of anemia at the time of PICU discharge (i.e., after the acute phase of critical illness), the mean transfusion threshold was 7.6 ± 0.1 g/dL after a biventricular

TABLE 5. Number and Proportion of Respondents Who Would Not Prescribe Erythropoietin (Regardless of the Hemoglobin Level) According to the Baseline Scenario and to Each Determinant

Determinant	Scenario 1: Hemorrhagic Shock	Scenario 2: Postcardiac Surgery (Biventricular Physiology)	Scenario 3: Postsurgery With a High Risk of Bleeding	Scenario 4: Polytrauma	*p*
1/Baseline scenario: respondents who would "not" prescribe erythropoietin (*n*/*n*tot [%])					
	145/209 (69.4)	117/162 (72.2)	119/162 (73.5)	117/156 (75)	0.61[a]
2/Effect of the determinants: respondents who would "not" prescribe erythropoietin (*n*/*n*tot [%])					
Low mean corpuscular volume	144/198 (72.7)	115/158 (72.8)	117/152 (77.0)	114/147 (77.6)	0.56[a]
Low ferritin level	145/199 (72.9)	115/158 (72.8)	116/151 (76.8)	113/147 (76.9)	0.65[a]
Low reticulocytosis	123/201 (61.2)[b]	99/157 (63.1)[b]	101/153 (66.0)	94/147 (64.0)[b]	0.81[a]
Asthenia	147/198 (74.2)	111/158 (70.3)	115/152 (75.7)	108/147 (73.5)	0.69[a]
Tachycardia	146/197 (74.1)	113/157 (72.0)	113/150 (75.3)	108/147 (73.5)	0.90[a]
Sickle cell disease	153/198 (77.3)	117/158 (74.1)	116/151 (76.8)	110/145 (75.9)	0.87[a]
Upcoming surgery with a high risk of bleeding	112/200 (56.0)[b]	86/158 (54.4)[b]	88/152 (57.9)[b]	87/146 (59.6)[b]	0.70[a]
Oxygen therapy	146/197 (74.5)	111/158 (70.3)	115/152 (75.7)	111/147 (75.5)	0.59[a]
Cyanotic congenital heart disease	143/197 (72.6)	109/158 (69.0)	107/152 (70.4)	104/147 (70.8)	0.86[a]
Left ventricular dysfunction with reduced ejection fraction	141/204 (71.6)	110/158 (69.6)	110/153 (71.9)	104/147 (70.8)	0.95[a]
Chronic kidney disease	46/194 (22.6)[b]	39/159 (24.5)[b]	39/155 (25.2)[b]	45/150 (30.0)[b]	0.32[a]
Lengthy PICU stay (30 d)	141/194 (72.7)	106/155 (68.4)	109/151 (72.2)	106/146 (72.6)	0.74[a]

*n*tot = number of participants who answered the question.

[a]Calculated using generalized linear mixed model (GLMM, binomial distribution, logit link function) with scenarios, determinants (including baseline), and determinants × scenarios as fixed effects and respondents as random effect to account for the correlation between the four scenarios within respondents. Comparison of the proportions of respondents who would not prescribe erythropoietin between each determinant and baseline scenario and comparison between the four scenarios according to each determinant were derived from this GLMM using linear contrasts.

[b]$p < 0.05$ (for the change in proportion when compared with the baseline scenario).

repair of a complete atrioventricular canal, with a mean increase of 1.8 g/dL if cyanotic heart disease was present. Even if pediatric intensivists may use a more restrictive transfusion strategy at PICU discharge for children with a congenital heart disease when compared with the acute phase of their PICU stay, we believe that the discrepancies between the Canadian survey (distributed in 2009) and ours may be related to the impact of recent RCTs (published in 2011–2017) showing that a restrictive transfusion strategy is safe in children with congenital heart disease.

RBC Transfusion and Oxygen Delivery

RBC transfusions are frequently prescribed to improve oxygen delivery (25). This may explain why we observed a significant increase in the mean hemoglobin trigger in situation involving oxygen requirement and even more so if left ventricular dysfunction was present. This is of interest given that several characteristics of stored RBCs may impair their ability to improve oxygen delivery to the tissues (26). In our survey, scenarios proposed involved stable children for whom oxygen delivery matched oxygen requirements. The increase in the hemoglobin threshold for these stable children leaving the PICU with oxygen requirement or with left ventricular dysfunction is not evidence based; this increase may be related to transfusion criteria used for unstable children which may not be appropriate for stabilized children ready for PICU discharge.

Balancing RBC Transfusion With Tolerance of Anemia

Respondents used higher hemoglobin levels to prescribe RBCs when tachycardia and asthenia were present, both of which can be the result of anemia. Several physiologic metrics and biomarkers have been proposed as markers for anemia intolerance which could be used as transfusion thresholds, but there is currently no evidence that supports their use in transfusion decision-making, neither during nor after the acute phase of critical illness (27). As suggested in the recent Transfusion and Anemia Expertise Initiative (TAXI) consensus conference, research programs are required to determine the efficacy and safety of transfusion strategies based on physiologic thresholds (27).

Iron

Iron deficiency is frequently reported in the critically ill patient, but its diagnosis during or just after critical illness is

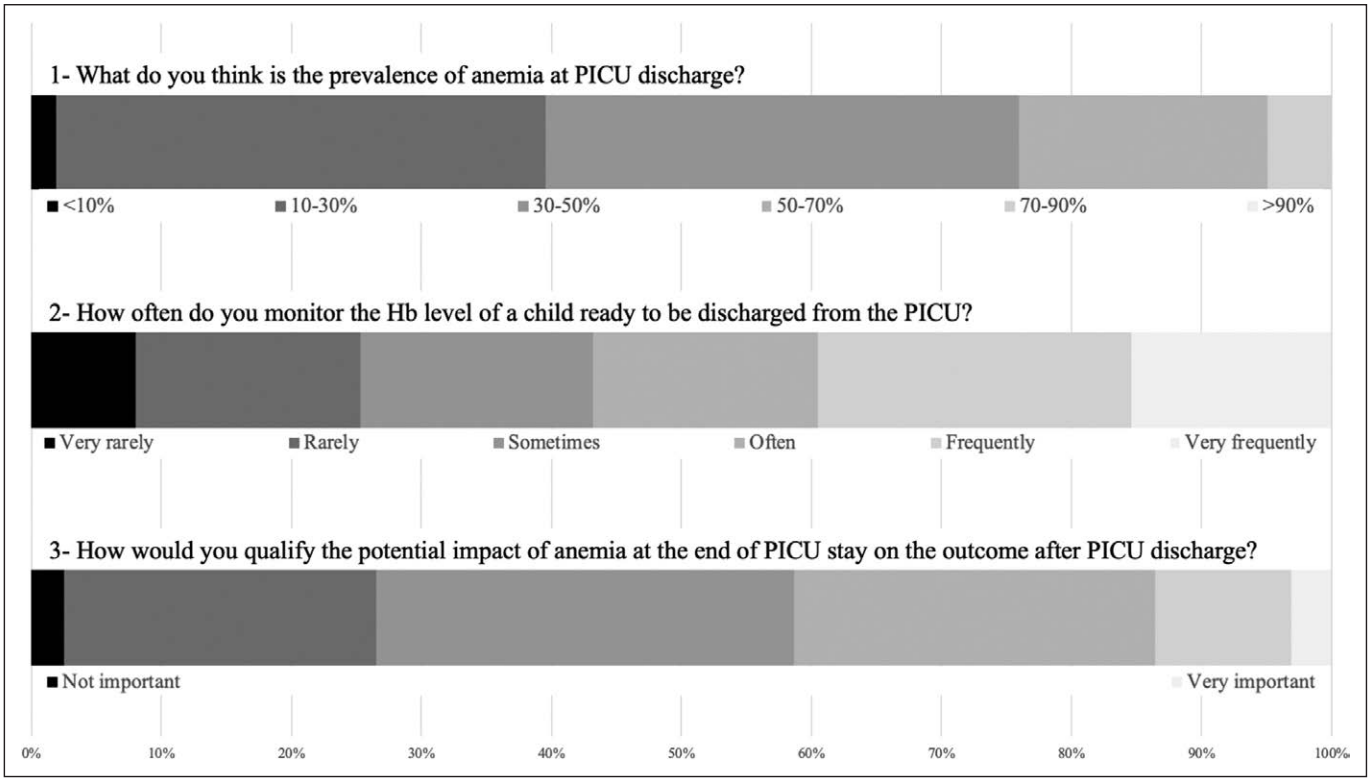

Figure 2. Stacked bar chart illustrating the opinion of respondents on anemia at PICU discharge. Hb = hemoglobin.

complex (28). In our survey, we evaluated the effect of two commonly used markers of iron deficiency: microcytosis and low ferritin level. Microcytosis is not specific of iron deficiency and occurs late because of the lifespan of circulating erythrocytes (29); ferritin is a sensitive parameter that allows assessment of iron stores in healthy subjects but may be elevated in the context of inflammation regardless of iron stores, and the threshold one should use to diagnose iron deficiency in the context of inflammation is not clear (29, 30). Despite these limitations, and despite the fact that no single measurement is currently available that will characterize the iron status of a child (30), the higher stated rates of iron prescription in cases with a low MCV and low ferritin level may indicate that the pediatric intensivists who completed our survey are sensitive to iron dysmetabolism and its markers in critically ill children.

Iron prescription in PICU is challenging because of the complexity of iron metabolism during critical illness and because of the potential toxicity of iron supplementation: potential complications include chronic iron overload, generation of free radicals, and increased risk of infection (31). Pediatric intensivists aware of these risks could be reluctant to prescribe iron in children with SCD (at increased risk of iron overload), oxygen therapy (free radicals), or tachycardia (which could be surrogate markers of ongoing infection), which could explain why fewer participants stated that they would prescribe iron in these conditions.

To date, no evidence exists to guide iron prescription during or after critical illness.

Erythropoietin

Erythropoietin is not recommended during the acute phase of critical illness (32). That is probably why so few respondents stated that they would prescribe erythropoietin at PICU discharge, even though it is not known if erythropoietin could help children to recover from anemia after critical illness.

Three variables were associated with an increase in erythropoietin prescription: a low reticulocyte count and upcoming surgery with a high risk of bleeding (slight effect), as well as CKD (marked effect). These findings are certainly related to the mechanism of action and the usual indications for erythropoietin. Indeed, patient blood management strategies are of crucial importance to reduce perioperative RBC transfusions and include erythropoietin to manage non-nutritional anemia in children as well as adults (33, 34). Furthermore, in children with CKD, the efficacy of erythropoietin in lowering blood transfusion requirements is unquestionable and is recommended to treat anemia after all correctable causes have been addressed (35, 36).

Limitations

Several limitations of our survey must be recognized. First, the participation rate impairs the external validity of our sample, especially for pediatric intensivists from Australia/New Zealand where participation was very low. However, although there is substantial variability in the range of response rates reported in web surveys of health professionals, low response rates (even under 20%) are not uncommon, particularly for physician surveys (37). Second, our study was inherently limited

by the inability to provide data for nonrespondents: we were thus unable to adjust our analyses to control for a potential nonresponse bias. Third, the sample selection was not random: the questionnaire was distributed to pediatric intensivists who were selected because of their responsibilities or their affiliation to specific societies and may not be representative of all pediatric intensivists working in North America, Europe, Australia, or New Zealand. Thus, our sampling frame could be an inaccurate representation of our population of interest (16). Fourth, participants who answered all the questions could be different from those who skipped some questions, making some replies from a lesser number of respondents less generalizable. Fifth, our survey reports stated transfusion practice, which could be different than actual practice. Sixth, PICU discharge thresholds may vary widely across institutions, and the time of PICU discharge may not be a common point in illness trajectory from one hospital to another. Even if we took care to clearly define the day of PICU discharge (i.e., day 5) and to describe the clinical condition of the child at this moment, the notion of "discharge readiness" may be interpreted heterogeneously across respondents, and this interpretation bias could lead to more heterogenous and less reliable results. Finally, after PICU discharge, non-PICU physicians might manage anemia differently than pediatric intensivists: our survey is thus a partial assessment of the way anemic children are treated after critical illness. Regardless, this survey is the first to assess the management of anemia "after" critical illness, was internationally distributed and included a large number of participants from across the world which increases its external validity, and used a systematic approach to develop the questionnaire that is an asset as this reduces the risk of missing key domains and of misunderstanding (38).

CONCLUSIONS

We surveyed 217 pediatric intensivists and found that they continue to apply restrictive transfusion strategies at PICU discharge, similar to those recommended during the acute phase of critical illness; this therapeutic behavior is based on evidence from studies conducted during the PICU stay and does not comprise evaluation of post-PICU outcomes. Iron is less frequently prescribed than RBCs, and the administration of erythropoietin is uncommon, probably reflecting the lack of evidence for their use during and after PICU stay and possibly the fact that anemia after critical illness might be underestimated by pediatric intensivists. As recent data indicate that anemia is highly prevalent at PICU discharge, it is urgent to develop strategies to guide its management, especially if this anemia persists significantly after PICU stay and is associated with adverse outcomes, which is still unknown. Further research is required that addresses these important questions.

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