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## Transfusion Strategies for Patients in Pediatric Intensive Care Units

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### ABSTRACT

#### BACKGROUND

The optimal hemoglobin threshold for erythrocyte transfusions in critically ill children is unknown. We hypothesized that a restrictive transfusion strategy of using packed red cells that were leukocyte-reduced before storage would be as safe as a liberal transfusion strategy, as judged by the outcome of multiple-organ dysfunction.

#### METHODS

In this noninferiority trial, we enrolled 637 stable, critically ill children who had hemoglobin concentrations below 9.5 g per deciliter within 7 days after admission to an intensive care unit. We randomly assigned 320 patients to a hemoglobin threshold of 7 g per deciliter for red-cell transfusion (restrictive-strategy group) and 317 patients to a threshold of 9.5 g per deciliter (liberal-strategy group).

#### RESULTS

Hemoglobin concentrations were maintained at a mean ( $\pm$ SD) level that was  $2.1\pm 0.2$  g per deciliter lower in the restrictive-strategy group than in the liberal-strategy group (lowest average levels,  $8.7\pm 0.4$  and  $10.8\pm 0.5$  g per deciliter, respectively;  $P<0.001$ ). Patients in the restrictive-strategy group received 44% fewer transfusions; 174 patients (54%) in that group did not receive any transfusions, as compared with 7 patients (2%) in the liberal-strategy group ( $P<0.001$ ). New or progressive multiple-organ dysfunction syndrome (the primary outcome) developed in 38 patients in the restrictive-strategy group, as compared with 39 in the liberal-strategy group (12% in both groups) (absolute risk reduction with the restrictive strategy, 0.4%; 95% confidence interval,  $-4.6$  to 5.4). There were 14 deaths in each group within 28 days after randomization. No significant differences were found in other outcomes, including adverse events.

#### CONCLUSIONS

In stable, critically ill children a hemoglobin threshold of 7 g per deciliter for red-cell transfusion can decrease transfusion requirements without increasing adverse outcomes. (Controlled-trials.com number, ISRCTN37246456.)

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UP TO 50% OF CHILDREN WHO ARE HOSPITALIZED in an intensive care unit (ICU) receive red-cell transfusions,<sup>1,2</sup> yet children whose condition is stable may tolerate the decreased oxygen delivery associated with a moderate degree of anemia. On the one hand, transfusions containing leukocytes could have limited benefit in such children and might result in organ dysfunction through stimulation of the inflammatory cascade by the transfused leukocytes.<sup>3</sup> On the other hand, children in the ICU could benefit from transfusions because of enhanced oxygen delivery, just as adults with early septic shock benefit from transfusions.<sup>4</sup>

A randomized trial involving 838 critically ill adults suggested that a restrictive transfusion strategy may be superior to a liberal strategy.<sup>5</sup> There are no data from rigorous trials to guide transfusion decisions in critically ill children. Several surveys of pediatric intensivists have recently documented large variations in stated<sup>6,7</sup> and observed<sup>1,2</sup> practices with respect to red-cell transfusion.

Universal leukocyte reduction, recently introduced in many countries, may decrease the proinflammatory effects of transfusions.<sup>8</sup> We postulated that a restrictive transfusion strategy with the use of prestorage leukocyte-reduced red-cell units (i.e., red cells that have first been filtered to remove leukocytes and have then been stored in the usual manner) in stable, critically ill children would substantially decrease exposure to transfusions without worsening organ dysfunction.

## METHODS

### PATIENTS AND SITES

We enrolled patients at 19 tertiary-care pediatric ICUs in four countries (see the Appendix). Stable, critically ill children between 3 days and 14 years of age who had at least one hemoglobin concentration of 9.5 g per deciliter or less within the first 7 days after admission to the pediatric ICU were eligible for enrollment. The condition of patients was considered stable if the mean systemic arterial pressure was not less than 2 SD below the normal mean for age and if cardiovascular treatments had not been increased for at least 2 hours before enrollment. All consecutive children were screened. Exclusion criteria are listed in Figure 1. The study protocol was approved by the research ethics board at each participating institution, and for all pa-

tients, written informed consent was obtained from a parent or surrogate decision maker.

### STUDY DESIGN AND TREATMENT PROTOCOLS

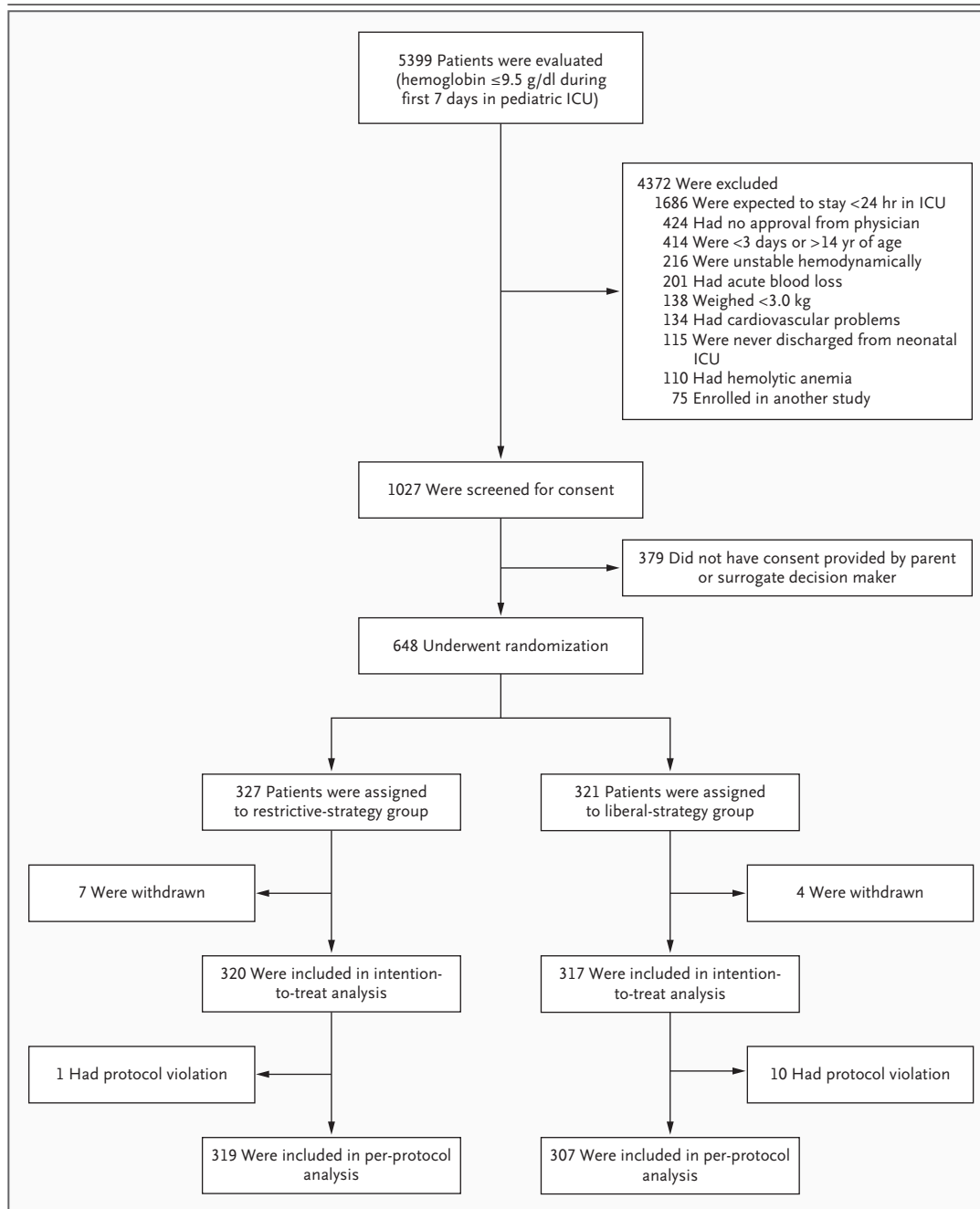
Randomization was centralized, with assignment data posted on the Internet. Patients were assigned to the study groups in blocks of 2 or 4 that were randomly distributed and stratified according to center and three age groups ( $\leq 28$  days, 29 to 364 days, and  $>364$  days). Physicians, nurses, and research staff were unaware of the block-randomization strategy.

In the restrictive-strategy group, the hemoglobin threshold for transfusion was set at 7 g per deciliter, with a target range after transfusion of 8.5 to 9.5 g per deciliter. In the liberal-strategy group, the threshold was 9.5 g per deciliter, with a target range of 11 to 12 g per deciliter. In both groups, red cells were transfused within 12 hours after the threshold value had been reached. Red-cell transfusions were administered in accordance with a formula that accounted for the patient's weight and the average hemoglobin concentration in red-cell units at each participating site. Only prestorage leukocyte-reduced red-cell units were used.

Attending physicians followed strategies for red-cell transfusion outlined for each group. No other clinical care protocols were used in the study. The transfusion protocol was applied for up to 28 days of the stay in the pediatric ICU or until the time of death, whichever occurred first. The protocol could be temporarily suspended, at the discretion of the attending physician, during periods of active and clinically significant blood loss, surgical intervention, severe hypoxemia, or hemodynamic instability and was promptly resumed once the condition of the patient no longer fulfilled the suspension criteria. Suspensions were not considered a breach of adherence to the protocol. Data monitoring and collection were unchanged during suspension. Clinical staff and parents were aware of the assignments to study groups, but the statistician and members of the data and safety monitoring committee were unaware of the assignments.

### BASELINE ASSESSMENT, MONITORING, AND OUTCOME MEASURES

Baseline assessments were undertaken at the time of randomization. Hemoglobin concentrations, the number of red-cell transfusions, the types of med-



**Figure 1. Enrollment and Outcomes.**

Some patients in pediatric intensive care units (ICUs) had more than one exclusion criterion. In addition to the causes listed for exclusion, other causes were a postconception age of less than 40 weeks (69 patients), severe thrombocytopenia (68), hypoxemia (65), a decision to withhold or withdraw critical care (59), predicted survival of less than 24 hours (54), previous enrollment in the study (33), brain death (25), extracorporeal membrane oxygenation (22), hemofiltration (21), blood exchange transfusion (20), plasmapheresis (17), an inability to receive blood products (14), and pregnancy (1). Among the 11 patients who were withdrawn from the intention-to-treat analysis, data were missing for 3 patients and could not be validated for 8 patients. Eleven patients were excluded from the per-protocol analysis because their hemoglobin level was below the threshold level during more than 20% of their stay after the first post-randomization day — our definition of noncompliance.

ications given, the use of mechanical ventilation and dialysis, and surgical interventions were recorded daily during the 28-day follow-up period. Hemoglobin concentrations were measured at least once within 6 hours after every red-cell transfusion. Data were collected by trained study personnel.

The primary outcome was the proportion of patients who died during the 28 days after randomization, had concurrent dysfunction of two or more organ systems (termed multiple-organ-dysfunction syndrome, or MODS), or had progression of MODS, as evidenced by the worsening of one or more organ dysfunctions, as defined by Proulx et al.<sup>9</sup> We also collected information on a number of secondary outcomes, including daily scores on Paediatric Logistic Organ Dysfunction (PELOD) assessment,<sup>10</sup> sepsis,<sup>9</sup> transfusion reactions,<sup>11</sup> nosocomial respiratory infections,<sup>12</sup> catheter-related infections,<sup>13</sup> adverse events, length of stay in the ICU and hospital, and mortality. Established diagnostic criteria were used.<sup>9,11-13</sup>

#### STATISTICAL ANALYSIS

We estimated that we would need to enroll at least 626 children in order to detect an absolute reduction of 10 percent in the risk of new or progressive organ dysfunction in the group treated according to the restrictive transfusion strategy, with an overall one-sided alpha of 5% and a power of 90%.<sup>14,15</sup>

One planned interim safety analysis was undertaken by a blinded, independent data and safety monitoring board after 50% of patients had been enrolled. Only unexpected rates of death, adverse events, and nosocomial infections were considered, and no statistical analysis was done. The board recommended continuation of the trial.

We compared the two groups with respect to the total number of transfusions per patient and the proportion of patients who did not have red-cell transfusions after randomization. We used analysis of variance with repeated measures to highlight differences in hemoglobin concentrations over time. We then calculated the number needed to treat to prevent one red-cell transfusion in the restrictive group.

The statistical analysis of the primary outcome measure was conducted with the use of an intention-to-treat approach. We calculated the 95% confidence interval (CI) for the absolute risk reduction<sup>16</sup> in the proportion of patients with new or progressive MODS. We established a priori that we would infer that a restrictive strategy was not

inferior to a liberal strategy for red-cell transfusions if the upper limit of the 95% CI for the absolute reduction in the risk of the primary outcome did not exceed a 10% margin of safety.<sup>17</sup> We generated Kaplan–Meier curves and used the log-rank test to compare the time to the development of new or progressive organ failure in the two groups. We calculated adjusted odds ratios for treatment effects with the use of logistic regression; the multivariate model included age, country, and score on the Pediatric Risk of Mortality (PRISM) assessment.<sup>18</sup> To minimize the probability of missing true differences, we also conducted a per-protocol analysis of the primary outcome in patients who met or exceeded an 80% rate of adherence to the protocol for red-cell transfusion. Adherence was defined as the proportion of days after randomization on which at least one hemoglobin concentration was over the transfusion threshold.

All analyses of secondary outcomes were based on the intention-to-treat principle. We compared daily PELOD scores, using the worst scores after baseline, the average total number of organs that were dysfunctional per patient, and other secondary outcomes listed above. Continuous variables were compared with the use of the Student t-test or the Wilcoxon rank-sum test. Categorical variables were analyzed with the use of the chi-square test.

We examined subgroups of patients who were at potential risk for adverse effects of anemia, categorized according to diagnosis, age, severity of illness (as estimated by the PRISM score), country, and study status (i.e., whether patients had been temporarily suspended from the trial).

Continuous data are expressed as means  $\pm$ SD. We report two-sided 95% CIs and P values. No adjustments of P values were made for multiple comparisons. Data were analyzed with SAS software, version 9.1 (SAS Institute).

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## RESULTS

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#### PATIENTS AND TREATMENT ASSIGNMENT

From November 26, 2001, to August 28, 2005, a total of 5399 children had a hemoglobin concentration of 9.5 g per deciliter or less during the first 7 days of admission to the ICU and were eligible for inclusion. Of these children, 4372 (81%) met at least one exclusion criterion (Fig. 1). For 379 of the remaining 1027 patients (37%), the parents or surrogate decision makers declined to provide consent. We therefore randomly assigned 648 children to

**Table 1. Baseline Characteristics of the Patients.\***

Variable	Restrictive-Strategy Group (N=320)	Liberal-Strategy Group (N=317)
<b>On admission to pediatric ICU</b>		
Age — mo	35.8±46.2	39.6±51.9
Weight — kg	14.0±14.8	15.1±15.3
Male sex — no. (%)	190 (59)	191 (60)
PRISM score†	9.4±6.7	9.1±6.7
Mechanical ventilation — no. (%)‡	253 (79)	252 (79)
<b>Red-cell transfusions before randomization</b>		
Patients — no. (%)	45 (14)	59 (19)
Volume of transfusions per transfused patient — ml/kg	16.9±11.8	14.7±10.7
No. of red-cell units per transfused patient	1.4±0.8	1.3±0.9
Length of storage of red-cell units — days	14.9±11.8	15.2±10.6
<b>Day of randomization</b>		
Hemoglobin — g/dl	8.0±1.0	8.0±0.9
Length of stay in ICU — days	2.3±1.7	2.3±1.8
Age — no. (%)§		
≤28 days	11 (3)	8 (3)
29–364 days	143 (45)	142 (45)
>364 days	166 (52)	167 (53)
Country — no. (%)§		
Belgium (3 sites)	66 (21)	66 (21)
Canada (10 sites)	205 (64)	203 (64)
United Kingdom (3 sites)	26 (8)	23 (7)
United States (3 sites)	23 (7)	25 (8)
Surgery — no. (%)		
Cardiac	63 (20)	62 (20)
Abdominal	15 (5)	16 (5)
Other surgery or transplantation	45 (14)	48 (15)
Severity of illness (PRISM score)†	4.8±4.4	4.8±4.3
Septic state — no. (%)¶		
Systemic inflammatory response syndrome	157 (49)	155 (49)
Sepsis	67 (21)	66 (21)
Severe sepsis	31 (10)	30 (9)
Septic shock	13 (4)	21 (7)
Multiple-organ-dysfunction syndrome — no. (%)¶	107 (33)	108 (34)
Respiratory dysfunction	234 (73)	246 (78)
Cardiovascular dysfunction	76 (24)	75 (24)
Hematologic dysfunction	42 (13)	39 (12)
Neurologic dysfunction	22 (7)	18 (6)
Hepatic dysfunction	7 (2)	6 (2)
Gastrointestinal dysfunction	7 (2)	5 (2)
Renal dysfunction	9 (3)	11 (3)
PELOD score (day 1)¶	6.3±6.8	5.2±6.2
No. of dysfunctional organs (day 1)	1.3±0.9	1.3±0.8

\* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding.

† Scores on the Pediatric Risk of Mortality (PRISM) assessment range from 0 to 76, with higher scores indicating a greater risk of death.

‡ Patients underwent either invasive or noninvasive mechanical ventilation.

§ Randomization was performed in blocks according to center and age.

¶ Organ dysfunction was determined as defined by Proulx et al.<sup>9</sup>

|| Scores on the Paediatric Logistic Organ Dysfunction (PELOD) assessment range from 0 to 71, with higher scores indicating more severe organ dysfunction.

**Table 2. Red-Cell Transfusions, Temporary Protocol Suspensions, and Cointerventions.\***

Variable	Restrictive-Strategy Group (N=320)	Liberal-Strategy Group (N=317)	P Value
<b>Red-cell transfusion and hemoglobin concentration after randomization</b>			
All patients			
No red-cell transfusion — no. of patients (%)	174 (54)	7 (2)	<0.001
No. of red-cell units per patient	0.9±2.6	1.7±2.2	<0.001
Lowest hemoglobin level in ICU — g/dl†	8.7±0.4	10.8±0.5	<0.001
Patients undergoing red-cell transfusion			
Any transfusion — no. of patients (%)	146 (46)	310 (98)	<0.001
1 transfusion — no. of patients (%)	104 (32)	194 (61)	
2 transfusions — no. of patients (%)	18 (6)	82 (26)	
>2 transfusions — no. of patients (%)	24 (8)	34 (11)	
No. of red-cell units per transfused patient	1.9±3.4	1.7±2.1	0.24
Volume of red-cell units per transfused patient — ml/kg	23.6±52.5	20.0±19.3	<0.04
First red-cell transfusion			
Time from randomization to first transfusion — days	1.7	0.1	<0.001
Hemoglobin level — g/dl			
Before first transfusion	6.7±0.5	8.1±0.1	<0.001
After first transfusion	9.4±1.2	11.2±1.1	<0.001
All red-cell transfusions			
Total no. of transfusions‡	301	542	<0.001
Average length of storage — days	16.0±10.5	15.7±10.3	0.62
Adherence to threshold hemoglobin level — no. of patients (%)§	319 (100)	307 (97)	0.006
<b>Temporary suspension of research protocol¶</b>			
Patients — no. (%)	39 (12)	20 (6)	0.01
PRISM score at randomization	6.5±4.8	7.2±5.2	0.63
Transfusion during suspension — no. of patients (%)	36 (11)	11 (3)	<0.001
No. of transfusions during suspension‡	71	61	0.41
Reason for suspension — no. of patients			
Acute respiratory distress syndrome with hypoxemia	6	1	
Shock	5	1	
Acute blood loss	7	2	
Surgery	12	8	
Hemofiltration primed with red cells	6	1	
Other	10	7	
Length of suspension — days	3.3±5.2	1.9±1.6	0.85

the two study groups. Of those, 11 (2%) were withdrawn after randomization, leaving 637 patients (320 in the restrictive-strategy group and 317 in the liberal-strategy group) in the intention-to-treat analyses. Patients in the two study groups had similar characteristics at baseline (Table 1).

#### INTERVENTION

Hemoglobin concentrations at the time of randomization were similar in the restrictive-strategy group and the liberal-strategy group (8.0±1.0 vs. 8.0±0.9 g per deciliter). There were significant differences between the groups in the time until the first trans-

Table 2. (Continued.)

Variable	Restrictive-Strategy Group (N=320)	Liberal-Strategy Group (N=317)	P Value
<b>Cointerventions</b>			
Fresh-frozen plasma — no. (%)	23 (7)	25 (8)	0.74
Platelets — no. (%)	26 (8)	29 (9)	0.65
Albumin — no. (%)	90 (28)	81 (26)	0.46
Corticosteroids — no. (%)	107 (33)	124 (39)	0.12
Administration of fluid (intake minus output) — ml/kg			
On first day	15.8±35.5	21.3±38.5	0.06
During stay in ICU	119±236	100±177	0.27
Vasoactive drugs — no. (%)**	106 (33)	99 (31)	0.61

\* Plus-minus values are means ±SD.

† The average difference between the restrictive-strategy group and the liberal-strategy group was 2.1±0.2 g per deciliter from randomization to discharge from the pediatric ICU.

‡ The number is for all transfusions after randomization, including those given during suspension; 71 transfusions in the restrictive-strategy group and 61 in the liberal-strategy group were given while patients were suspended from the study. One patient in the liberal-strategy group received 29 transfusions during study suspension.

§ It was expected that red cells would be transfused if the hemoglobin concentration fell below 7 g per deciliter in the restrictive-strategy group or below 9.5 g per deciliter in the liberal-strategy group.

¶ Attending physicians were permitted to transfuse more red cells than indicated in the study protocol if one of the following events occurred: severe acute respiratory distress syndrome with refractory hypoxemia; shock; instability in the patient's condition; acute blood loss; surgery; blood exchange-transfusion (manual or automated); hemofiltration, if priming was done with blood; or extracorporeal membrane oxygenation or plasmapheresis.

|| The median length of suspension was 1 day in both groups.

\*\* Agents included dobutamine, dopamine (at least 5 µg per kilogram of body weight per minute), epinephrine, milrinone, nitroglycerin, nitroprusside, norepinephrine, phenylephrine, and vasopressin.

fusion (1.7 vs. 0.1 days) and in the hemoglobin concentration before the first transfusion (6.7±0.5 vs. 8.1±0.1 g per deciliter) (P<0.001 for both comparisons) (Table 2). The hemoglobin concentrations were maintained above the threshold more than 94% of the time, with an average difference of 2.1±0.2 g per deciliter between the restrictive-strategy group and the liberal-strategy group (overall average lowest levels, 8.7±0.4 and 10.8±0.5 g per deciliter, respectively) until discharge from the pediatric ICU (P<0.001) (Fig. 1 of the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org)).

The protocol was temporarily suspended for 59 patients: 39 in the restrictive-strategy group and 20 in the liberal-strategy group (Table 2). Overall, 301 transfusions were administered in the restrictive-strategy group, as compared with 542 in the liberal-strategy group (a 44% decrease in the restrictive-strategy group, P<0.001); 71 and 61 transfusions, respectively, were given while strict transfusion protocols were temporarily suspended.

In the restrictive-strategy group, 174 patients (54%) received no red-cell transfusions, as compared with 7 patients (2%) in the liberal-strategy

group (P<0.001). Children in the restrictive-strategy group were also exposed to fewer transfusions than were children in the liberal-strategy group (0.9±2.6 vs. 1.7±2.2 transfusions per patient, P<0.001). With the restrictive protocol, the number needed to treat in order to prevent one red-cell transfusion was two patients. Cointerventions were similar in the two groups before and after randomization (Table 2).

#### PRIMARY OUTCOME

The number of patients with new or progressive MODS after randomization was 38 in the restrictive-strategy group and 39 in the liberal-strategy group (12% of both groups). The absolute reduction in risk was 0.4% (95% CI, -4.6 to 5.5 with the restrictive strategy); the upper limit of the 95% CI did not exceed 10%.

The risk of new or progressive MODS increased with the severity of illness, as reflected by the PRISM score, in both groups (Table 3). The time-to-event analysis for new or progressive MODS generated a hazard ratio of 0.95 for the restrictive transfusion strategy as compared with the liberal strategy (95% CI, 0.61 to 1.49; P=0.84).

**Table 3. Primary and Secondary Outcomes of the Patients.\***

Variable	Restrictive-Strategy Group	Liberal-Strategy Group	Absolute Risk Reduction, Odds Ratio, or Difference in Means (95% CI)	P Value
<b>Primary outcome</b>				
New or progressive MODS — no./total no. (%)†	38/320 (12)	39/317 (12)	0.4 (−4.6 to 5.5)	NI‡
Age†				
≤28 days	1/11 (9)	0	−9.1 (−26.1 to 7.9)	1.00
29–364 days	14/143 (10)	20/142 (14)	4.3 (−3.2 to 11.8)	0.28
>364 days	23/166 (14)	19/167 (11)	−2.5 (−9.6 to 4.7)	0.51
Country§				
Belgium	3/66 (5)	4/66 (6)	0.74 (0.16 to 3.43)	0.70
Canada	32/205 (16)	28/203 (14)	1.16 (0.67 to 2.00)	0.60
United Kingdom	2/26 (8)	5/23 (22)	0.30 (0.05 to 1.73)	0.17
United States	1/23 (4)	2/25 (8)	0.52 (0.04 to 6.18)	0.61
Severity of illness (PRISM score)†¶				
0 (lowest quartile)	3/64 (5)	4/64 (6)	1.5 (−6.3 to 9.4)	1.00
1–4 (second quartile)	13/128 (10)	11/111 (10)	−0.3 (−7.9 to 7.4)	0.94
5–7 (third quartile)	6/54 (11)	6/67 (9)	−2.2 (−13.0 to 8.7)	0.69
≥8 (highest quartile)	16/74 (22)	18/75 (24)	2.4 (−11.1 to 15.9)	0.73
Suspended protocol — no./total no. (%)	18/39 (46)	13/20 (65)	18.9 (−7.3 to 45.0)	0.17
<b>Secondary outcomes</b>				
Measures of severity of organ dysfunction				
No. of dysfunctional organs	1.6±1.4	1.5±1.2	−0.1 (−0.26 to 0.13)	0.87
PELOD score**				
After randomization	9.8±11.9	8.4±10.9	−1.4 (−3.1 to 0.4)	0.16
On day 1	6.3±6.8	5.2±6.2	−1.1 (−2.1 to −0.1)	0.09
Highest daily score after day 1	10.2±13.3	8.9±11.9	−1.2 (−3.2 to 0.8)	0.34
Change in score	3.8±10.9	3.8±9.9	−0.1 (−1.7 to 1.5)	0.97
Average daily score	5.0±6.1	4.2±5.1	−0.8 (−1.7 to 0.1)	0.13

**SECONDARY ANALYSES**

None of the measures of the severity of organ dysfunction differed significantly between the two groups (Table 3). The number of deaths 28 days after randomization was the same in the two groups (14). No significant differences were observed with respect to nosocomial infections, mechanical ventilation, the duration of the stay in the ICU, or reactions to red-cell transfusion. There were 221 adverse events in the restrictive-strategy group and 203 in the liberal-strategy group ( $P=0.44$ ); of those events, 28 and 22, respectively, were serious adverse events ( $P=0.42$ ). Patients with one or more adverse events included 97 in the restrictive-strategy group and 90 in the liberal-strategy group ( $P=0.59$ ), and 19 patients in each group had one

or more serious adverse events ( $P=0.98$ ). A complete list of adverse events can be found in the Supplementary Appendix.

We also performed a per-protocol analysis of the primary outcome.<sup>19</sup> A total of nearly 99% of patients met the 80% adherence criterion, and the results of the per-protocol analysis differed only slightly from those of the intention-to-treat analysis (absolute risk reduction with the restrictive strategy, 0.8%; 95% CI, −4.3 to 5.9).

**DISCUSSION**

We found that as compared with a liberal transfusion strategy, a restrictive strategy with a hemoglobin threshold of 7 g per deciliter resulted in a

Table 3. (Continued.)

Variable	Restrictive-Strategy Group	Liberal-Strategy Group	Absolute Risk Reduction, Odds Ratio, or Difference in Means (95% CI)	P Value
Clinical outcomes — no./total no. (%)†				
Death				
In ICU	11/320 (3)	8/317 (3)	−0.9 (−3.6 to 1.7)	0.50
From any cause during 28-day study	14/320 (4)	14/317 (4)	0 (−3.2 to 3.2)	0.98
Nosocomial infections	65/320 (20)	79/317 (25)	4.6 (−1.9 to 11.1)	0.16
At least 1 adverse event	97/320 (30)	90/317 (28)	−1.92 (−9.0 to 5.2)	0.59
Reactions to red-cell transfusion	3/320 (1)	6/317 (2)	1.0 (−0.9 to 2.8)	0.34
Duration of care — days‡				
Mechanical ventilation	6.2±5.9	6.0±5.4	−0.14 (−1.1 to 0.8)	0.76
ICU stay after randomization	9.5±7.9	9.9±7.4	0.46 (−0.7 to 1.7)	0.39

\* Plus-minus values are means ±SD.

† The comparison between the restrictive-strategy group and the liberal-strategy group is given as an absolute reduction in risk.

‡ Noninferiority (NI) was checked only for the primary outcome (the number of patients who had new or progressive multiple-organ-dysfunction syndrome [MODS], including death, after randomization). The absolute risk reduction for new or progressive MODS in the restrictive-strategy group versus the liberal-strategy group was 0.4% (two-sided 95% CI, −4.6 to 5.5) by intention-to-treat analysis; we also calculated a two-sided 97.5% CI of −5.4 to 6.2. Some experts also consider that a per-protocol analysis should be done in a noninferiority trial. In the per-protocol analysis, we excluded 11 patients who did not meet the 80% adherence criterion; the number of patients with the primary outcome was 37 of 319 (11.6%) in the restrictive-strategy group and 38 of 307 (12.4%) in the liberal-strategy group (absolute risk reduction, 0.8%; two-sided 95% CI, −4.3 to 5.9). In all analyses, the upper limit of the confidence interval was lower than the safety margin of error of 10% approved by consensus before the study was undertaken, which means that noninferiority was statistically significant.

§ The comparison between the restrictive-strategy group and the liberal-strategy group is given as an odds ratio.

¶ Scores on the Paediatric Risk of Mortality (PRISM) range from 0 to 76, with higher scores indicating a higher risk of death.

|| The comparison between the restrictive-strategy group and the liberal-strategy group is given as a difference between the means.

\*\* Scores on the Paediatric Logistic Organ Dysfunction (PELOD) assessment range from 0 to 71, with higher scores indicating more severe organ dysfunction. The PELOD score can be estimated over the entire stay in the ICU or over 1 day (daily PELOD). The change in the PELOD score is the difference between the daily PELOD score at study entry and the worst daily PELOD score thereafter. Patients whose PELOD score did not change or decreased after randomization were considered to have a change of 0.

96% reduction in the number of patients who had any transfusion exposure and a 44% decrease in the number of red-cell transfusions administered, without increasing the rates of new or progressive MODS, in stable, critically ill children. There were also no clinically important differences between the two groups in any secondary outcomes.

Our study showed that a restrictive transfusion strategy was safe in pediatric patients whose condition was stable in the ICU and that such a strategy was as safe as a liberal transfusion strategy. However, outcomes in critically ill adults differ from our findings in children. In a trial of two transfusion strategies in critically ill adults, the rates of worsening organ failure and other complications were significantly higher with a liberal transfusion strategy.<sup>5</sup> This study in adults also documented more in-hospital deaths in the liberal-strategy group than in the restrictive-strategy group, whereas the number of deaths was the same with the two strategies in our pediatric patients (14 in each group).

The differences between our results and those in adults may be due to several factors. First, critically ill adults may be more vulnerable than critically ill children to adverse consequences of red-cell transfusions. Second, the trial in adults did not use prestorage leukocyte-reduced red cells, as were used in our trial. Leukocytes in transfused red cells may harm vulnerable patients by generating cytokines and activating an inflammatory response.<sup>20-24</sup> Two randomized trials involving adults who had vascular disease or who had undergone cardiac surgery showed decreased rates of organ dysfunction in patients receiving leukocyte-reduced red cells.<sup>25,26</sup> In addition, two before-and-after trials that evaluated a universal prestorage leukocyte-reduction program showed reduced rates of febrile episodes among more than 14,000 adults<sup>27</sup> and decreased rates of post-transfusion bronchopulmonary dysplasia, retinopathy of prematurity, and necrotizing enterocolitis in premature infants.<sup>8</sup> Hence, in our study, prestorage leukocyte reduction may have helped prevent harmful

effects of transfusions, especially in the liberal group.

Three smaller trials in pediatric subpopulations have also evaluated various transfusion strategies. In a trial involving 147 pediatric patients undergoing cardiac surgery, a hematocrit of 21% during cardiopulmonary bypass was associated with a poor neurodevelopmental outcome, as compared with a hematocrit of 27%.<sup>28</sup> In a subgroup of patients in a study of 100 preterm infants who were randomly assigned to a restrictive or liberal transfusion strategy, the risk of intraparenchymal brain hemorrhage, periventricular leukomalacia, and apnea was higher in the restrictive-strategy group.<sup>29</sup> In a trial that included 451 premature infants who were randomly assigned to a restrictive or liberal transfusion strategy, the rate of death or severe morbidity was 2.6 percentage points higher in the restrictive-strategy group, but the difference was not significant.<sup>30</sup> From published reports, it is unclear whether red cells underwent prestorage leukocyte reduction in these three pediatric trials.

To minimize potential biases, we concealed treatment assignments, ensured complete follow-up, and assessed objective clinical outcomes. We lost only 11 patients to follow-up (2%), a rate low enough to prevent any bias attributable to sample-size slippage.<sup>31</sup> Despite varying practice patterns before this study, the adherence rates in the many participating centers exceeded 97% in both groups. Inferences related to clinical outcomes derived from this study are strengthened by the consistency of observations in both primary and secondary outcomes and across major subgroups. We did note that in the restrictive-strategy group, there were significantly more suspensions of the transfusion-threshold protocol, which may reflect the uneasiness of attending physicians about maintaining very sick patients at low hemoglobin concentrations. Suspensions were a result of the acute respiratory distress syndrome, worsened shock, or increased bleeding but did not cause these complications. Despite the increased number of sus-

pensions, we nevertheless documented a significant reduction in the number of red-cell units transfused in the restrictive group.

Our trial had at least one limitation. Although death is the reference outcome in studies of critically ill adults, the low mortality rate among children — only about 4%<sup>10</sup> — would not allow us to design a study with sufficient power to detect a meaningful change in death rates. In critical care medicine, organ failure is a clinically significant outcome.<sup>32</sup> We used a composite of death and development of new or progressive organ failure, which should be relevant to pediatric intensivists.

In conclusion, we found that a restrictive transfusion strategy can safely decrease the rate of exposure to red cells as well as the total number of transfusions in critically ill children, even though suspensions of transfusion strategies were permitted under prespecified conditions. We were unable to detect meaningful differences in any clinical outcomes, both overall and among all subgroups examined. We recommend a restrictive transfusion strategy in pediatric patients whose condition is stable in the ICU. This recommendation, however, is not applicable to premature infants, older adults, patients with coronary artery disease, or children with severe hypoxemia, hemodynamic instability, active blood loss, or cyanotic heart disease.

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#### APPENDIX

The following investigators participated in this study: **Executive Committee:** J. Lacroix (chair), P.C. Hébert, J.S. Hutchison, H.A. Hume, M. Tucci, F. Gauvin, J.P. Collet, B.J. Toledano, P. Robillard, and T. Ducruet. **Data Safety and Monitoring Board:** G.É. Rivard (committee chair, hematologist, Sainte-Justine Hospital), J.P. Collet (trial methodologist, McGill University), M.C. Guertin (biostatistician, Institut de Cardiologie de Montréal), C. Litalien (pediatric intensivist, Sainte-Justine Hospital), D.J. Cook (chair of the Canadian Critical Care Trials Group, trial methodologist and intensivist, McMaster University), and A. Proietti (trial manager, ex officio). **Data Management Committee:** J. Lacroix (chair), T. Ducruet (biostatistician), D. Paquin (database coordinator), and A. Proietti (trial manager, ex officio). **Study Managers:** A. Proietti, D. David, and R. Trahan. **Institutions and Site Investigators** (the number of study patients is given in parentheses). *Belgium:* Cliniques Universitaires Saint-Luc, Brussels (29) — S. Clément de Cléty; Hôpital Universitaire des Enfants Reine-Fabiola, Brussels (90) — D. Biarent; *Universitair Ziekenhuis, Ghent* (7) — A. De Jaeger. *Canada:* Stollery Children's Hospital, Edmonton, AB (93) — A. Joffe;

British Columbia Children's Hospital, Vancouver (47) — P. Skippen, D. Wensley; Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC (11) — C. Cyr; Children's Hospital of Eastern Ontario, Ottawa (41) — D. Creery, H. Writer; Children's Hospital of Western Ontario, London (6) — Y. Ouellette; Hamilton Health Science Corporation, Hamilton, ON (26) — K. Choong, H. Kirpalani; Hospital for Sick Children, Toronto (76) — J.S. Hutchison; Kingston General Hospital, Kingston, ON (12) — E. Tsai; Montreal Children's Hospital, Montreal (33) — R. Gottesman; Sainte-Justine Hospital, Montreal (67) — F. Gauvin. *United Kingdom*: Birmingham Children's Hospital, Birmingham (13) — K. Morris; Great Ormond Street Hospital for Children, London (28) — M.J. Peters; Queen's Medical Centre, Nottingham (8) — H. Vyas. *United States*: Children's Hospital Medical Center, Cincinnati (15) — B. Jacobs; Children's Hospital of Michigan, Detroit (33) — K. Meert; University of Virginia Children's Hospital Center, Charlottesville (2) — D. Willson. **Writing Committee**: J. Lacroix (chair), members of the Executive Committee, A. Joffe, D. Biarent, K. Meert, M.J. Peters, and site investigators.

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