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Association for the Advancement of Blood & Biotherapies

Association Bulletin #26-03

Date: May 14, 2026

To: AABB Members

From: Jose Cancelas, MD, PhD – President
Debra BenAvram – Chief Executive Officer

Re: Neonatal Red Blood Cell Transfusion and Mannitol Exposure

Association Bulletins provide a mechanism for publication of documents that have been approved by the Board of Directors for distribution to individual and institutional members, such as:

- Standards that were adopted after publication of the most recent edition of *Standards*.
- Statements of AABB policy intended for distribution to members.
- Guidance, recommendations, and reports that have been developed by AABB Committees or National Office staff for distribution to members.

This bulletin contains information related to the use of Red Blood Cell (RBC) units for neonatal transfusion that are stored in an additive solution (AS) containing mannitol.

This bulletin:

- Does not contain specific recommendations, nor does it create a standard or accreditation requirement.
- Was developed by an ad hoc working group of AABB member physicians with relevant expertise in transfusion medicine, including members of the Clinical Transfusion Medicine Committee.
- Provides important information and resources to AABB-accredited facilities to inform clinical practice decisions related to the use of RBC units for neonatal transfusion that are stored in an additive solution (AS) containing mannitol.

Please note, any references to products in this Association Bulletin are for informational purposes only and do not imply endorsement.

Key Points

- The use of RBC units with a mannitol-containing additive solution (AS) for neonatal transfusion is globally widespread.

- Clinical data demonstrate that mannitol-containing RBC units do not cause harm in extremely low birthweight, neonatal, and pediatric patients receiving routine small-volume transfusions (<20 ml/kg).
    - Small-volume transfusions are typically administered at ≤5 mL/kg/hour.
- For large-volume transfusions (≥20 ml/kg) there are no controlled data demonstrating harm; however, available evidence is insufficient to exclude risk, particularly with rapid transfusion, impaired renal clearance, or very high cumulative exposure.
    - Consider the risks of fluid imbalance and electrolyte disturbances, including hyperkalemia, when rapid emergency large-volume transfusions are necessary.
        - When possible, limit the rate to 30 mL/kg/hour (0.5 mL/kg/minute).
        - If a faster rate of transfusion is necessary, other steps, such as washing and volume reduction of cellular blood components may be taken to mitigate risk, depending on available time and resources.
    - Clinicians should be educated and prepared to treat the side effects of large-volume transfusions.
- Washing or volume reduction may reduce mannitol exposure, but these interventions can negatively impact RBC quality, delay availability, or be impractical in emergencies or settings such as extracorporeal circuits.
- Concern about mannitol exposure is based primarily on physiologic plausibility and experience with therapeutic mannitol dosing, rather than direct evidence of toxicity from mannitol-containing RBC transfusions.
- Emergent transfusion for significant anemia should not be delayed.

Introduction

Whole blood is collected into an anticoagulant, typically citrate, and is subsequently separated into RBC units that are stored with an AS that contains varying amounts of adenine, dextrose, and (sometimes) mannitol, to preserve and sustain the red cells (see Table 1). AS extends the shelf life of red cells up to 42 days by aiding the cell's intracellular metabolism and diminishing red cell lysis.[1] Although transfusion practitioners recognize the importance of AS to support inventory management, there are incomplete data to establish safety in all at-risk patient populations, including preterm neonates. There is considerable variability in the selection of AS and product specifications for neonates. It is unclear how much understanding clinicians have of the issues regarding AS. As always, there are important balances between perceived risks and benefits.

It has been hypothesized that when mannitol is administered therapeutically, the dose (250 mg/kg - 2 g/kg) may cause harm in premature infants and neonates related to their unique immature physiology. Although relatively low amounts of mannitol are present in AS (Table 1), the potential for harm has led some care facilities to provide mannitol-free RBC units (AS-3).

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Table 1: Additive Solution Formulations							
Constituents (mM)	**SAGM**	**AS-1**	**AS-3**	**AS-5**	**MAP**	**PAGGSM**	**AS-7**
NaCl	150	154	70	150	85	72	-
$NaHCO_3$	-	-	-	-	-	-	26
Na_2HPO_4	-	-	-	-	-	16	12
NaH_2PO_4	-	-	23	-	6	8	-
Citric acid			2	-	1		-
Na-citrate	-	-	23	-	5	-	-
Adenine	1.25	2	2	2.2	1.5	1.4	2
Guanosine	-	-	-	-	-	1.4	-
Dextrose (glucose)	45	111	55	45	40	47	80
Mannitol	30	41	-	45.5	80	55	55
pH	5.7	5.5	5.8	5.5	5.7	5.7	8.5
Anti-coagulant	CPD	CPD	CP2D	CPD	ACD	CPD	
FDA Licensed	No	Yes	Yes	Yes	No	No	Yes
Countries used	Europe	USA	USA	USA	Japan	Germany	Not Yet
	UK		Canada				
	Canada						
	New Zealand						

Table adapted from Roseff et al[3] and Sparrow et al.[4]
SAGM: saline-adenine-glucose-mannitol; AS: additive solution; MAP: mannitol-adenine-phosphate; PAGGSM: phosphate-adenine-glucose-guanosine-saline-mannitol, FDA: Food and Drug Administration; CE: Conformité Européene.

Most countries outside of the United States (US) use AS with mannitol (SAGM). Changes in the US market for blood collection bags have reduced the availability of mannitol-free AS. Also, the global changeover to DEHP-free component bags will further limit the availability of RBC storage solutions without mannitol. These changes are prompting concern by the some in the US pediatric transfusion medicine community who relied on mannitol-free AS RBC units for many years.

This AABB Association Bulletin reviews the available published studies that address the safety and possible risks of transfusing neonates with RBCs stored in an AS that contains mannitol. It is worth noting that there is a paucity of published work on this topic; therefore, abstracts that have not undergone the full peer-review process have been included in this Association Bulletin.

Additive Solutions

The developmental history of different AS formulations available across the globe has been a long one (Table 1). The first AS for RBCs, developed in the late 1970s, contained saline-adenine and glucose (SAG). In later formulations (SAGM, AS-1, AS-5, and others), mannitol was added to help protect the red cell membrane and reduce hemolysis. These AS formulations allow for up to 6 weeks of refrigerated storage of RBC units at a hematocrit of approximately 55 to 60%.[2] SAGM is the preferred AS in many high-resource countries/regions such as the European Union

(EU), Australia, and Canada. The US Food and Drug Administration (FDA) has approved four AS formulations for use in the US (AS-1, AS-3, AS-5, and AS-7). One manufacturer that supplies a hypoxic and hypocapnic collection and storage system for RBC units uses AS-3 in its US kit (as of 2026) and PAGGSM in Europe.

Physiologic Effects of Mannitol in Neonates

Mannitol is a potent osmotic diuretic, and its general clinical use in neonates—particularly in preterm infants—has been associated with potential risks due to immature renal and cerebral physiology.[5] When administered in therapeutic doses, mannitol induces brisk diuresis and shifts in intravascular volume, which may cause cerebral blood flow fluctuations. These hemodynamic changes are particularly concerning in extremely and very low birthweight infants and neonates, whose cerebral autoregulation is immature and whose blood-brain barrier integrity is not fully developed. This vulnerability increases the risk of intraventricular hemorrhage and ischemic injury.[6] In addition to cerebrovascular instability, large or repeated doses of mannitol can result in: electrolyte imbalances, including hyponatremia and hypokalemia; osmotic nephrosis, due to immature renal tubular function; and cardiac decompensation and arrhythmias, secondary to fluid shifts and electrolyte changes.

These effects have been seen in pediatric and adult neurocritical care settings.[1,7] However, it is important to note that the amount of mannitol exposure from typical doses of AS-containing RBC units is much lower than the therapeutic doses used for treatment of cerebral edema or increased intracranial pressure in neonates.

For example:

- The therapeutic dose of mannitol for reducing intracranial pressure in neonates is approximately 250 - 500 mg/kg, administered intravenously over 30 minutes. This may be repeated every 6 - 8 hours as clinically indicated.
- RBC units stored in SAGM, AS-1, or AS-5 contain 525 - 825 mg of mannitol per RBC unit or ~1.5 - 3 mg mannitol per mL of red cells.
- For a neonatal transfusion of 10 - 20 mL/kg, this translates to a mannitol exposure of less than 15 - 60 mg/kg — a dose that is much smaller than the therapeutic range used for osmotic diuresis.
- In contrast, neonates and extremely and very low birthweight infants who are exposed to a full RBC unit (equivalent to a large-volume transfusion), receive a mannitol dose that could cause osmotic diuresis and affect renal function or cerebral blood flow.

Mannitol and RBC Transfusions

The dose at which RBC transfusion may cause harm to an infant is difficult to pinpoint, as the risk is dependent on the volume and rate of transfusion, the patient's underlying renal and

hepatic status, the clinical setting, and the patient's capacity to metabolize mannitol.[1] Studies in neonates have demonstrated the safety and efficacy of RBCs stored in AS with mannitol for small-volume transfusion <20 mL/kg,[8-10] but moderate to high-certainty evidence establishing the safety of large-volume transfusions is limited.[3,11,12]

Luban et al calculated that the concentrations of solutes within AS could reach toxic levels when large volumes were transfused.[1] In a single institution retrospective study comparing the use of CPDA-1 vs AS RBC transfusion to infants undergoing extracorporeal membrane oxygenation (ECMO), the authors found transfusion of AS-1 or AS-3 RBC units to be tolerated as well as CPDA units as assessed by a comparison of changes in electrolyte levels.[13] This suggests that further modification such as washing or removal of supernatant in AS units may be unnecessary in some circumstances.

A retrospective study reported on 32 neonates who received large-volume transfusions of RBC units stored with SAGM in the context of cardiothoracic surgery.[14] The patients received 27.3 - 104.6 mL/kg, but it is unclear whether the units were washed or filtered before transfusion. The patients were assessed for bleeding, metabolic disturbances, and other clinical complications for up to 7 days after surgery. Although most patients experienced adverse events, by day 7 many complications were waning, with only inotropic support still needed by a majority of patients. This study demonstrated that patients may receive mannitol-containing additive solutions with no apparent long-term consequences. Nonetheless, given the size of the study and the fact that there was no mannitol-free comparison cohort, it is difficult to assess the level of risk.

As a result, to mitigate the risk of fluid shifts and systemic electrolyte disturbances including hyperkalemia, the rate of emergency large-volume transfusions should be limited to 30 mL/kg/hour (0.5 mL/kg/minute) compared to routine small-volume transfusion typically administered at ≤5 mL/kg/hour. If a faster rate of transfusion is necessary, other steps, such as washing or volume reduction of cellular blood products, may be taken to mitigate the risk, depending on available time and resources.

Real-World Evidence and Practice

Although large-volume pediatric transfusions with mannitol occur at many centers globally, pretransfusion washing with ECMO or cardiopulmonary bypass circuits may occur, making it difficult to assess the impact of mannitol. Some sites wash RBC units before large-volume transfusions to remove potassium but resuspend the units in SAGM. This practice indicates the safety of mannitol in large-volume transfusions, but no data from a comparator cohort are available. Thus, several real-world examples of large-volume transfusions with mannitol exist, but objective evidence of safety with prospective studies does not exist.

Possible Strategies to Mitigate the Impact of Mannitol-Containing Additive Solution

There is no global standard for the use of RBC units with respect to AS for neonatal patients.

- **Australia:** The Australian Red Cross produces RBC units only in SAGM and utilizes these units for all neonatal transfusions (small- or large-volume). For large-volume transfusions, a RBC unit may be washed (to remove free potassium) and resuspended in SAGM.[15]
- **Brazil:** The standard additive solution is SAGM. In case of large-volume transfusions, intrauterine transfusions (IUTs), and neonatal exchange transfusions, RBC units are washed to reduce mannitol dose.[16]
- **Canada:** RBC units and aliquots in SAGM are utilized for all standard transfusion needs. For neonates receiving massive transfusion or those with renal insufficiency, the practice is variable with some sites recommending removal of additive solution and other sites using RBC units with no modification.[17]
- **Israel:** RBC units in CPDA-1 are utilized for small-volume transfusions.[16]
- **Malaysia:** RBC units in CPD are utilized for small-volume transfusions.[16]
- **Saudi Arabia:** RBC units in CPD are utilized for small-volume transfusions.
- **United Kingdom:** Guidelines recommend RBC units and aliquots in SAGM for small-volume, large-volume, and emergent transfusion needs in neonates and pediatric patients.[7] However, for IUTs and neonatal exchange transfusions, which are planned procedures, RBC units stored in CPD are recommended.
- **United States:** Practice varies widely by institution.[11,12,16] Some centers utilize RBC in AS without further manipulations, others retain a dual inventory (AS or CPD/CPDA-1 RBCs), and some provide washed or supernatant-reduced RBCs when time permits. Thus, no standard practice exists in the US. For IUTs, centers remove supernatant or wash RBC units to increase unit hematocrit and remove extracellular contents, including AS with or without mannitol.[18,19]

Although this list notes the different types of RBC units available in each country, there are many options for limiting AS exposure (see Table 2). Some centers may try to retain a dual inventory (AS or CPD/CPDA-1 RBCs). However, supply chain issues including possible discontinuation of CPDA-1 and AS-3 bag production and implementation of DEHP-free bags, will likely limit availability of mannitol-free RBC units. In some cases clinical teams may utilize their cell salvage blood recovery/autotransfusion systems or extracorporeal circuits for washing or ultrafiltration of RBC units outside of the blood bank laboratory, before use.[20-23] However, washing of RBC units leads to mechanical damage and increased fragility and/or hemolysis of red cells.[24,25] With discontinuation of the Terumo COBE® 2991 Cell Processor, RBC units may be washed using the ACP® 215 automated cell processor (AABB Bulletin 25-02), or perform manual saline-washing of RBC units using multiple rounds of centrifugation or single-spin supernatant removal.[26,27] However, modification of blood components such as washing in the transfusion service requires FDA registration, additional equipment, validation, staffing resources, and time that may not be available at all centers or in emergency situations.

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Table 2: Considerations for Strategies Limiting Additive Solution Exposure

Strategy	Advantages	Challenges
Utilize RBCs stored with Additive Solution	Readily available with 42-day shelf life	• Limited data on patient outcomes for large-volume transfusions
Use of CPD or CPDA-1 RBCs	Avoids mannitol exposure	• Limited availability • Shorter shelf life (21-35 days) • Higher potassium accumulation in older units, increasing the risk of hyperkalemia[28]
Washed RBCs	Reduces all additive solution constituents	• Requires processing time, equipment, and validation • Risk of red cell damage and hemolysis • Not feasible for emergency transfusion
Supernatant removal (single-spin method)	Reduces additive solution content and may cause less red cell damage compared to washing	• Requires processing time, equipment, and validation • Not feasible for emergency transfusion
Bedside washing using blood recovery/autotransfusion systems	Reduces all additive solution constituents	• Requires processing time, equipment, and expertise • Risk of red cell damage and hemolysis
Extracorporeal ultrafiltration	Removes excess fluid and additives	• Requires processing time, equipment, and expertise

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Acknowledgment

AABB thanks the following members for their work on this Association Bulletin.

- Jennifer Andrews
- Meghan Delaney
- Jed Gorlin
- Cassandra Josephson
- Lani Lieberman
- Courtney Lawrence
- Hollie Reeves
- Nabiha Huq Saifee