ALBUMIN 5%
NEWBORN USE ONLY

2023

Alert	Albumin 4% (Albumex® 4) is discontinued in Australia and is replaced by albumin 5%, commercially available as Alburex® 5 AU.[1] Alburex® 5 AU is a clear, slightly viscous liquid and is either colourless, yellow, amber, or green in colour. Do not use it if it is cloudy or have deposits - this may indicate that the protein is unstable or that the solution has become contaminated. The vial should be returned unopened to Australian Red Cross Lifeblood.[1]
Indication	Volume resuscitation/expansion in hypovolemia. Partial exchange transfusion in polycythaemia (normal saline is preferred)
Action	The most important functions of albumin are maintenance of plasma oncotic pressure and a transport function. Albumin stabilises circulating blood volume and is a carrier of hormones, unconjugated bilirubin, enzymes, medicinal products, and toxins. The serum half-life of albumin averages 17 days in adults, 14-21 days in full-term infants and 5-7 days in the premature neonate.[2]
Drug Type	Human albumin, made from human plasma.
Trade Name	Alburex® 5 AU
Presentation	250 mL (12.5 g albumin) and 500 mL (25 g albumin) vials. Contains human albumin 50 g/L.
Dose	**Volume resuscitation/expansion** 10 to 20 mL/kg over 5 to 60 minutes titrated to clinical response. **Partial exchange for polycythaemia** [normal saline is preferred/recommended]: $Volume\ albumin\ 5\%\ (mL) = total\ blood\ volume\ x\ \frac{(observed\ Hct - desired\ Hct)}{observed\ Hct}$ Where total blood volume = 80 mL/kg; desired haematocrit (Hct) = 0.55 Infusion rate to match 1:1 with the rate of removal of blood. Note: Haematocrit (Hct) is also known as packed cell volume (PCV)
Dose adjustment	Therapeutic hypothermia – No information. ECMO – No information. Renal impairment – No dose adjustment; watch for circulatory overload due to volume infused. Hepatic impairment – No dose adjustment; watch for circulatory overload due to volume infused.
Maximum dose	
Total cumulative dose	
Route	Intravenous
Preparation	Administer undiluted. Dilution of Albumin 20% to Albumin 5% in case of unavailability of albumin 5% Albumin 20% can be diluted to albumin 5% prior to administration. **For each** 1 mL of Albumin 20% add 3 mL of crystalloid solution (sodium chloride 0.9% or glucose 5% or 10%). **DO NOT dilute with water since the lower tonicity will lead to intravascular haemolysis.**
Administration	**Volume resuscitation/expansion** Infuse over 5 to 60 minutes titrating to clinical response. **Partial exchange for polycythaemia** Infusion rate to match 1:1 with the rate of removal of blood. The glass vial must be vented during infusion administration. Warm product to room or body temperature if large volumes are to be infused. Record the name and batch number of the product in patient's notes to be able to track adverse events.
Monitoring	Continuous cardiorespiratory and temperature observations. Watch for signs of fluid overload. Urine output. Electrolytes and haemoglobin.
Contraindications	Hypersensitivity to albumin preparations or to any of the excipients.

Precautions	Cardiac failure, pulmonary oedema, severe anaemia, renal or post-renal anuria. The sodium concentration in this product is 140 mmol/L.[1] This should be noted when the product is used in patients requiring sodium restriction.
Drug Interactions	No specific interactions of human albumin with other medicinal products.[3]
Adverse Reactions	Allergic reactions. Fluid overload (pulmonary oedema, impaired gas exchange, worsening oxygenation, chronic lung disease, patent ductus arteriosus, myocardial dysfunction especially for infants with birth asphyxia). Neurological injury (cerebral oedema, intraventricular haemorrhage with rapid bolus). Sodium loading. Fluid retention.
Compatibility	**Fluids:** glucose 5%, glucose 10%, glucose 5% in sodium chloride 0.9%, glucose 5% in sodium chloride 0.45%, sodium chloride 0.9%, sodium chloride 0.45%.[3] **Y-site:** cloxacillin sodium, diltiazem HCL, esmolol HCL, hydrocortisone, ketamine HCL, lorazepam, meropenem, metoprolol tartrate.[3]
Incompatibility	Alburex® 5 AU must not be mixed in the syringe with any other medicinal products, including whole blood, packed red cells, or other albumins.[1] **Fluids:** Amino acid-glucose infusion.[3] **Y-site:** Fat emulsions, Fosfomycin, labetalol, meropenem/vaborbactam, micafungin, midazolam HCL, vancomycin HCL, verapamil HCL.[3]
Stability	
Storage	Store below 25°C (Do not freeze). Protect from light.
Excipients	Sodium acetyltryptophanate, sodium octanoate, sodium chloride, water for injections.[1]
Special Comments	Alburex® 5 AU is a clear, slightly viscous liquid and is either colourless, yellow, amber, or green in colour. Do not use it if it is cloudy or have deposits - this may indicate that the protein is unstable or that the solution has become contaminated. The vial should be returned unopened to Australian Red Cross Lifeblood.[1]
Evidence	**Background** Albumin 5% (available as Alburex® 5 AU by CSL Behring (Australia) Pty Ltd) is a solution containing 50 g/L of total protein of which at least 96% is human albumin. Alburex® 5 AU is manufactured from human plasma collected in Australia by Australian Red Cross Lifeblood. Alburex® 5 AU is mildly hypo-oncotic to normal plasma. It has an osmolality of 258 mOsm/kg, compared to normal plasma osmolality of 275–290 mOsm/Kg and albumin 4% osmolality of 260 mOsm/kg. It is isotonic with sodium content of 140 mmol/L. Sodium content in Alburex® 5 AU (3.2 mg sodium per mL) should be noted when the product is used in patients requiring sodium restriction.[1] **Efficacy** **<u>Volume expansion</u>** Albumin is contemplated in 3 scenarios: (1) neonatal resuscitation at delivery, (3) early hypotension in preterm neonates and (3) volume expansion for hypovolaemia/shock secondary to blood loss or sepsis in NICU or emergency. **<u>Volume expansion at delivery:</u>** There is no evidence from randomized trials to support the use of routine volume resuscitation at delivery. One large retrospective review found that 0.04% of newborns received volume resuscitation in the delivery room, confirming that it is a relatively uncommon event.[4] There is insufficient clinical evidence to determine what type of volume expander (crystalloid or blood) is more beneficial during neonatal resuscitation. The American Heart Association 2020 Neonatal resuscitation guidelines at delivery support the use of crystalloid over albumin expanders and blood over crystalloid solutions.[5] <u>AHA 2020 specific recommendations:</u> (1) It may be reasonable to administer a volume expander to newly born infants with suspected hypovolemia, based on history and physical examination, who remain bradycardic (heart rate less than 60/min) despite ventilation, chest compressions, and epinephrine. (2) Normal saline (0.9% sodium chloride) is the crystalloid fluid of choice. Un-crossmatched type O, Rh-negative blood (or crossmatched, if immediately available) is preferred when blood loss is substantial. An initial volume of 10 mL/kg over 5 to 10 minutes may be reasonable and may be repeated if there is inadequate response.[5]

Volume expansion for early hypotension in preterm neonates: A Cochrane review by Osborn et al found no evidence from randomised trials to support the routine use of early volume expansion in very preterm infants without cardiovascular compromise. There is insufficient evidence to determine whether infants with cardiovascular compromise benefit from volume expansion. There is insufficient evidence to determine what type of volume expansion should be used in preterm infants (if at all). The meta-analyses found no other significant clinical benefit in using albumin compared to saline.[6] If a volume expander is considered/needed, available evidence suggests that crystalloids are as effective as albumin to increase blood pressure in hypotensive preterm neonates. In a study, 63 mechanically ventilated preterm infants weighing 540 to 1950 g with hypotension were randomized to 5% albumin vs normal saline in the first 2 hours of life.[7] This study found isotonic saline was as effective as 5% albumin for treating hypotension in preterm infants, and it had the additional advantage of causing less fluid retention in the first 48 hours.[7] Oca et al, randomized 42 infants (term and preterm) with hypotension to either 5% albumin or normal saline. Normal saline was shown to be as effective as albumin for the correction of acute hypotension.[8]
In contrary, there is one randomized controlled trial that demonstrated some advantage of albumin, showing that preterm infants who received albumin 5% were more likely to correct their blood pressure at 1 hour post-bolus and required less inotropic support compared to those who received normal saline.[9]
ANMF consensus is similar to Shalish et al.[2] When fluid resuscitation is indicated, normal saline appears to be equally effective as a volume expander, less expensive, and more readily available. Thus, there is currently no evidence to recommend albumin in most conditions encountered in the NICU, with risks of harm if misused.

Volume expansion for in hypovolaemia/shock (e.g. secondary to blood loss): Volume expansion remains the first-line treatment in critically ill neonates whenever hypovolemia is suspected, even though, it is well acknowledged that bedside clinical and laboratory signs can be non-specific and may not represent hypovolemia.[2] AHA 2020 neonatal resuscitation guidelines at delivery favour the use of isotonic saline or packed red blood cells over albumin as a volume expander for neonates who fail to respond to adequate positive pressure ventilation.[5] It is hard to conduct studies in neonates with hypovolaemic shock. However, extrapolating the AHA 2020 recommendations, there is no physiological rationale to favour the use of albumin over crystalloids or packed red cells for the management of acute hypovolaemic shock.

Albumin in proinflammatory conditions: During pro-inflammatory states such as sepsis or post-surgery, the most important cause of decreased albumin is attributed to capillary leak, redistribution, and increased catabolism. Capillary permeability may increase 13-fold in sepsis, resulting in significantly augmented albumin transcapillary escape rates (TER), increased protein flow from the intravascular to extravascular compartment, and hypoalbuminemia within hours. Any albumin administered will rapidly leak into the interstitial space and exacerbate the oedema. In an adult study, 18 septic patients were administered albumin 5% or normal saline; although albumin effectively increased plasma volume by 122%, it also increased the interstitial space by 102%, thereby neutralizing any potential benefits.[10] There is currently no study that has evaluated the use of albumin in neonates with sepsis or during the postoperative period. Based on the weak biological plausibility, lack of clinical evidence and extrapolated data from adult meta-analyses,[11] albumin cannot be routinely recommended in neonates during pro-inflammatory states.[2]

Partial exchange transfusion (PET) for polycythaemia

A single RCT compared isotonic saline versus 5% albumin in 102 term infants as replacement fluid in partial exchange transfusion (PET) for the treatment of neonatal polycythaemia. PET with either resulted in a decline in haematocrit up to 24 hours after PET with no difference between groups and no adverse event reported.[12] A systematic review of PET for polycythaemia, most RCTs compared plasma preparations to no treatment.[13] The review reported there are no proven clinically significant short or long-term benefits of PET in polycythaemic newborn infants who are clinically well or who have minor symptoms related to hyperviscosity, and there may be an increased risk of NEC. ANMF consensus: Albumin solutions cannot be recommended as the preferred method of PET for polycythaemia.

Safety

	Human albumin product does not contain iso-agglutinins or blood group substances; hence the risk of minor or major incompatibility is not possible. Hypersensitivity reactions such as flushing, urticaria, fever and nausea rarely occur following its administration, since albumin preparations are considered non-immunogenic. However, possible harms associated with albumin infusion in neonates include fluid overload (pulmonary oedema, impaired gas exchange, worsening oxygenation, chronic lung disease, patent ductus arteriosus, myocardial dysfunction especially for infants with birth asphyxia), neurological injury (cerebral oedema, intraventricular haemorrhage due to rapid bolus administration), salt loading and fluid retention, and higher cost compared with crystalloids.[2] **Pathogen safety** Products made from human plasma may contain infectious agents such as viruses and theoretically Creutzfeldt-Jakob Disease (CJD) agents that can cause disease. Alburex® 5 AU manufacturing process includes pasteurisation (60°C for 10 hours) and multiple steps involving ethanol fractionation and depth filtration. The current process and procedures applied in the manufacture of this product are effective against human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis A virus (HAV) and human parvovirus B19. Despite these measures, such products may still potentially transmit disease.[1] **Pharmacokinetics** In healthy subjects, less than 10% of infused albumin leaves the intravascular compartment during the first 2 hours following infusion. There is considerable individual variation in the effect on plasma volume. In some patients the plasma volume can remain increased for some hours. However, in critically ill patients, albumin can leak out of the vascular space in substantial amounts at an unpredictable rate.[1]
Practice points	
References	1. Australian Product information. Alburex® 5 AU. CSL Behring (Australia) Pty Ltd. Accessed on 16 October 2023. 2. Shalish W, Olivier F, Aly H, Sant'Anna G, editors. Uses and misuses of albumin during resuscitation and in the neonatal intensive care unit. Seminars in Fetal and Neonatal Medicine; 2017: Elsevier. 3. MerativeTM Micromedex® Complete IV Compatibility (electronic version). Merative, Ann Arbor, Michigan, USA. Available at: https://www.micromedexsolutions.com/ (cited: October/16/2023). 4. Wyckoff MH, Perlman JM, Laptook AR. Use of volume expansion during delivery room resuscitation in near-term and term infants. Pediatrics. 2005;115(4):950-5. 5. Aziz K, Lee HC, Escobedo MB, Hoover AV, Kamath-Rayne BD, Kapadia VS, et al. Part 5: Neonatal Resuscitation: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2020;142(16_suppl_2):S524-S50. 6. Osborn DA, Evans NJ. Early volume expansion for prevention of morbidity and mortality in very preterm infants. Cochrane Database of Systematic Reviews. 2004(2). 7. So KW, Fok TF, Ng PC, Wong WW, Cheung KL. Randomised controlled trial of colloid or crystalloid in hypotensive preterm infants. Archives of Disease in Childhood-Fetal and Neonatal Edition. 1997;76(1):F43-F6. 8. Oca MJ, Nelson M, Donn SM. Randomized trial of normal saline versus 5% albumin for the treatment of neonatal hypotension. Journal of perinatology. 2003;23(6):473-6. 9. Lynch S, Mullett M, Graeber J, Polak M. A comparison of albumin-bolus therapy versus normal saline-bolus therapy for hypotension in neonates. Journal of Perinatology. 2008;28(1):29-33. 10. Ernest D, Belzberg AS, Dodek PM. Distribution of normal saline and 5% albumin infusions in septic patients. Critical care medicine. 1999;27(1):46-50. 11. Tseng C-H, Chen T-T, Wu M-Y, Chan M-C, Shih M-C, Tu Y-K. Resuscitation fluid types in sepsis, surgical, and trauma patients: a systematic review and sequential network meta-analyses. Critical Care. 2020;24(1):1-12. 12. Wong W, Fok T, Lee C, Ng P, So K, Ou Y, et al. Randomised controlled trial: comparison of colloid or crystalloid for partial exchange transfusion for treatment of neonatal polycythaemia. Archives of Disease in Childhood-Fetal and Neonatal Edition. 1997;77(2):F115-F8.

	13. Özek E, Soll R, Schimmel MS. Partial exchange transfusion to prevent neurodevelopmental disability in infants with polycythemia. Cochrane Database of Systematic Reviews. 2010(1).

VERSION/NUMBER	DATE
Original 1.0	19/10/2023
Current 1.0 (minor errata)	26/10/2023
REVIEW	19/10/2028

Authors Contribution

Original author/s	Srinivas Bolisetty
Evidence Review	Srinivas Bolisetty
Nursing Review	Benjamin Emerson-Parker, Eszter Jozsa
Pharmacy Review	Rebecca O'Grady, Susanah Brew
ANMF Group contributors	Martin Kluckow, Nilkant Phad, Bhavesh Mehta, Rebecca Barzegar, Mohammad Irfan Azeem, Thao Tran, Cindy Chen, Helen Huynh, Stephanie Halena, Michelle Jenkins, Simarjit Kaur, Renae Gengaroli, Karel Allegaert
Final editing	Srinivas Bolisetty
Electronic version	Cindy Chen, Ian Callander
Facilitator	Srinivas Bolisetty

Citation for the current version

Bolisetty S, Emerson-Parker B, Jozsa E, O'Grady R, Brew S, Kluckow M, Phad N, Mehta B, Barzegar R, Azeem MI, Tran T, Chen C, Huynh H, Halena S, Jenkins M, Kaur S, Gengaroli R, Allegaert K, Callander I. Albumin 5%. Consensus formulary by the Australasian Neonatal Medicines Formulary group. Version 1, dated 26 October 2023. www.anmfonline.org