

Narrative & Reflective Essays

Brief History of the Development and Clinical Use of Albumin

Brian L. Erstad, PharmD¹ 

¹ Pharmacy Practice and Science, University of Arizona

Keywords: albumin, human serum albumin, bovine albumin, clinical practice, clinical practice guidelines, history

Journal of Acute Care Pharmacotherapy

Vol. 1, Issue 1, 2025

This paper provides a brief history of the development and early clinical use of albumin to offer background and context for current ongoing debate concerning appropriate albumin indications. When the United States military began mobilizing resources in anticipation of entering World War II, albumin was thought to be a good choice for subsequent investigation as a blood substitute since it was known at the time to be responsible for approximately 80 to 85% of the oncotic pressure of blood despite constituting only 65% of plasma proteins. The protein chemist Edwin Cohn led the effort to fractionate and develop an albumin product appropriate for storage and administration by the military. A large number of investigations associated with albumin development resulted in multiple subsequent publications near the end of the war effort. The next major event in the history of albumin is a workshop convened because of concerns related to the increasing use and cost of albumin. The publication of the findings of the workshop led to the first guideline pertaining to the clinical use of albumin, which set the stage for future randomized trials, meta-analyses, and clinical practice guidelines.

INTRODUCTION

By the late 1800s there were investigations of salt solution transport across blood vessels when the British physiologist Ernest Starling described his experiments of the effects of serum “proteids” (i.e., proteins) on “osmotic” (i.e., oncotic pressure) fluid movement across a semipermeable membrane.¹ Starling discussed the oncotic and hydrostatic forces within the intravascular and extravascular spaces that formed the basis of the original Starling equation describing fluid movement across capillary walls. In 1918, the physiologist Frank Mann described his experiments on how the impairment of circulatory control of blood volume during surgical shock could be effectively restored by colloids to a much greater degree than physiological sodium chloride solutions but none were as effective as whole blood or serum.² However, investigations specific to the colloid albumin did not occur until albumin was isolated from blood by fractionation during World War II. The purpose of this paper is to provide a brief history of the development and early clinical use of albumin to offer background and context for current ongoing debate concerning appropriate albumin indications. In particular, this review will demonstrate how the broad indications for albumin in prescribing information were based on small observational trials conducted in the first couple of decades following its fractionation. Additionally, this review will show how these broad indications led to widespread albumin prescribing and periodic shortages over time despite clinical practice guidelines. The narrative will begin with the fractionation of albumin in the early 1940s and conclude with a description of the first guidelines for clinical use of albumin published in

1977 followed by a discussion of how the recommendations in those early guidelines compare to current guideline recommendations.

FRACTIONATION OF ALBUMIN

By the spring of 1940, the United States military began mobilizing resources in anticipation of entering World War II. What followed was a close relationship by the military, educational institutions (particularly Harvard Medical School), and industry to develop a substitute for human plasma given the challenges of distributing and storing blood and plasma in combat settings.³ Albumin was thought to be a good choice for subsequent investigation as a blood substitute since it was known at the time to be responsible for approximately 80% of the oncotic pressure of blood despite constituting only 65% of plasma proteins. Bovine albumin was the initial focus of plasma fractionation and initial clinical studies although fatal cases of serum sickness as well as fractionation of human albumin by Dr. Edwin Cohn of Harvard Medical School led to discontinuation of further investigations of its use.

Dr. Edwin Cohn was a protein chemist who had been working on a process that separated different proteins from plasma, led the blood substitute efforts involving human albumin. A colleague of Cohn's, Dr. John Oncley, helped with refinement of the fractionation process, hence referral of the process as Cohn-Oncley fractionation. Cohn's “blood machine” was able to separate blood into red cells, plasma, and the buffy coat (platelets and white blood cells) with subsequent isolation of the albumin from plasma. Using blood collected by the American Red Cross, Cohn initially

Table 1. Development of Albumin in the United States for World War II.

Spring 1940	Mobilization of medical resources in US in anticipation of entering WW II
May 1940	Meeting of Committee on Transfusions, Division of Medical Sciences involved discussion of a substitute, preferably synthetic, for human plasma
November 1940	Subcommittee on Blood Substitutes brought in Dr. Edwin Cohn of Harvard Medical School for his ongoing work on plasma fractionation in conjunction with Dr. John Oncley
Late 1940	Dr. Cohn develops a method for bovine albumin fractionation and clinical investigations begin
February 1941	Dr. Charles Drew appointed first blood bank director of American Red Cross and implemented use of bloodmobiles
May 1941	First use of human albumin in a 20-year-old man at Walter Reed with traumatic shock
May 1941	Subcommittee on Blood Substitutes recommended that Cohn's human albumin undergo confirmatory testing with use by services if no issues
July 1941	Production of human albumin at Harvard was approximately 500-800 g/week
January 1942	Recommendations to Army and Navy to immediately adopt human albumin for clinical use
February 1942	Of 125 patients given 4247 g of human albumin, 4 had mild and 1 had moderately severe reaction
July 1942	Fatal case of serum sickness in volunteer receiving bovine albumin
February 1943	Second fatal case of unusual serum sickness in volunteer receiving bovine albumin led to termination of program
March 1943	Sodium chloride content in human albumin was increased from 0.15 molar (300 mOsm/L) to 0.3 molar (600 mOsm/L) to increase stability and decrease cloudiness especially common in hot temperatures
Late 1943	Requisitions by military for human albumin began to decrease in conjunction with increasing availability and use of plasma for resuscitation purposes

Adapted from Reference 3: AMEDD Center of History & Heritage. CHAPTER XII. The Bovine and Human Albumin Programs. <https://achh.army.mil/history/book-wwii-blood-chapter12> (Accessed March 20, 2025).

developed three fractionation products: One tube was 10 g of albumin in 11 mL water slightly discolored from globulins and very viscous but stable, another tube had 10 g of crystalline albumin, and a third tube had a 25% clear albumin solution. Cohn argued for the crystalline form based on easy storage and shipment in preference to the 25% solution preferred by others.³ The 25% solution was approximately one-sixth the size of dried plasma with diluent and was amenable to rapid gravity infusion. Cohn insisted that the 25% human albumin product had a label stating to avoid administration in patients with severe dehydration without simultaneous administration of fluids and electrolytes. After initial testing in humans, albumin became available for clinical use by the military with the American Red Cross mobilizing voluntary blood donations for processing albumin and pharmaceutical companies such as Armour, Lederle, and Cutter involved in large-scale production efforts. Table 1 provides an overview of the development of albumin for World War II.³

ALBUMIN USE FOLLOWING WORLD WAR II

By 1945, there was development of a so-called *salt-poor* form of albumin using 0.04 molar acetyl tryptophanate. The term *salt poor* remains in use to this day albeit with solutions containing varying amounts of sodium and chloride usually in near normal serum ranges at least for products available in the United States. Additionally, these early studies demonstrated the importance of sterilizing albumin

solutions in the final container with heat treatment to 60°C for 10 hours to eliminate potential microbial pathogens.

The end of World War II led to a reduction in the demand for blood leading the American Red Cross to get out of the blood business until 1947 when it was resumed purportedly to help fund raising given the success of the blood program during World War II with at least seven million volunteers participating in donation efforts.⁴ The availability of albumin fractionated from the blood of these donation efforts set the initial stage for more widespread use.

More than 35 articles concerning fractionation and initial investigations of albumin and other fractionation products were published prior to 1950 in a series of papers in the *Journal of Clinical Investigation* alone. For example, there was a series of 24 articles published from 1944 to 1945 in the latter journal concerning the chemical, clinical, and immunological products of plasma fractionation. The first article in this series was a paper by Cohn et al. describing studies on products of human plasma fractionation including albumin, immune globulins, hemagglutinins for blood typing, and thrombin, fibrinogen, and fibrin as hemostatic agents and tissue substitutes for grafting.⁵ Table 2 describes conclusions of three studies involving albumin for disease states that were part of the 24 article series.⁵⁻⁸ In addition to the previous series, other researchers using blood donated by the American Red Cross published studies concerning the distribution and degradation of albumin in humans using various tracer techniques such as albumin labeled with radioiodine.^{9,10} By the 1960s, assays were avail-

Table 2. Conclusions of Studies Published by 1945 of Human Albumin for Disease States.

Reference 6	Chronic protein depletion	Large amounts of albumin are required to raise serum albumin levels regardless of specific cause
Reference 6	Nephrosis	Administered albumin appears in the urine of patients with nephrosis but not those with normal kidney function
Reference 6	Cirrhosis	Repeated albumin administration increases serum albumin levels but only temporarily
References 7,8	Shock	Albumin is effective for shock but less likely to remain in circulation in patients with shock due to active bleeding or burns; need whole blood if acute anemia

able for serum albumin that led to other studies evaluating the synthesis and clinical effectiveness of albumin administration in patients with disease states such as cirrhosis.¹¹

FIRST WORKSHOP AND CLINICAL PRACTICE GUIDELINE INVOLVING ALBUMIN

By the 1970s, the rapid increase in albumin usage led to a workshop convened under the auspices of the Division of Blood and Blood products of the FDA and the Division of Blood Diseases and Resources by NIH.¹² As background for the workshop, a survey involving 101 hospitals (1.4% of those registered by the American Hospital Association) had been conducted, which revealed that 1 of every 250 patients received albumin with 18,845 units of 50 mL 25% albumin given to 2,889 patients and 1,650 units of 250 mL of 5% albumin given to 520 patients. The published proceedings of the workshop provide an extensive discussion with references to the accumulated research related to albumin at that time. The workshop proceedings served as the basis for a subsequent two-part paper authored by Dr. James Tullis, a noted hematologist who had worked with Dr. Cohn as a researcher in training on the fractionation process. Part 1 describes albumin's chemical and physiological nature, synthesis and degradation, distribution, general use patterns (i.e., markedly increasing use often based on limited evidence), production of the final product with mention of its high degree of safety as noted by low risk of serious adverse effects.¹³ Part 2 of the Tullis articles provides guidelines for clinical use of albumin.¹⁴ Of note, only one small randomized trial involving albumin was available at the time the recommendations were compiled in these guidelines published in 1977.¹⁵ Table 3 provides an overview of the recommendations in Part 2 of the Tullis guideline.

RECOMMENDATIONS FOR ALBUMIN IN CURRENT CLINICAL GUIDELINES

Currently, there are several guidelines involving albumin promulgated by different specialty practice organizations and associations. The most notable difference between these guidelines and those of Tullis is the use of levels of evidence to formulate recommendations in current clinical practice guidelines. In contrast, the Tullis guideline had general recommendations for appropriate or occasional use based primarily on small observational trials and expert

opinion. This difference in guideline formulation precludes meaningful comparisons between those of Tullis and current evidence-based organizational guidelines.

The most recent guideline published in 2024 by the International Collaboration for Transfusion Medicine Guidelines Intravenous Albumin Guideline Group contains 14 recommendations concerning the most common uses of albumin involving the areas of critical care (adult, pediatric, and neonatal), cardiovascular surgery, kidney replacement therapy, and cirrhosis.¹⁶ The first important point to note about the 2024 guideline is that there was only 1 “strong” recommendation, albeit based on low certainty of evidence, which is that albumin is *not recommended* to reduce mortality in pediatric patients with infection and hypoperfusion. The remaining 13 recommendations were all “conditional” based on low or very low certainty of evidence. In 10 of these 13 recommendations, albumin was *not suggested* (e.g., as first-line therapy for volume replacement or to increase albumin concentrations in critically ill patients, to remove extravascular fluid in conjunction with diuretics, to improve respiratory function in patients with acute respiratory distress syndrome, to prevent or treat hypotension in patients undergoing renal replacement therapy, for priming the bypass circuit or volume replacement in patients undergoing cardiovascular surgery) or *not routinely suggested* (to reduce complications in outpatients with cirrhosis and uncomplicated ascites). The only recommendations suggesting the use of albumin were to prevent circulatory dysfunction in patients with cirrhosis having at least 5 liters of fluid removed by large volume paracentesis and to reduce mortality in patients with cirrhosis and spontaneous bacterial peritonitis. There are ongoing challenges related to the appropriate use of albumin in patients with cirrhosis including how to best diagnose acute kidney injury using albumin infusions.^{17,18}

DISCUSSION

As noted above, all but one of the randomized trials involving albumin were performed following the publication of the Tullis guidelines in 1977. However, as with many of the other randomized trials conducted in early era of critical care the trials were often small and underpowered for clinically important endpoints, particularly mortality.¹⁹ Therefore, until the publication of the landmark Saline versus Albumin Fluid Evaluation (SAFE) trial there was a series of

Table 3. Summary of Appropriateness of Indications for Albumin in First Published Guideline.

Appropriate Use	Explanation
Shock	Albumin dosing should be based on patient responsiveness but in the absence of active bleeding doses should not exceed those estimated in normal plasma volumes; the preferred form is 5% albumin but if 25% is used it should be administered with crystalloid
Burns	Crystalloids should be the primary fluid in the first 24 hours with increasing amounts of 25% albumin over time to maintain a plasma albumin level of 2.5 +/- 0.5 g/dL or a plasma oncotic pressure of 20 mm Hg
Adult respiratory distress syndrome	For a post-diuretic decrease in plasma volume, 25% albumin should be given to maintain vital signs
Cardiopulmonary bypass	An albumin and crystalloid pump prime can be used to achieve a hematocrit value of 20% and a plasma albumin level of 2.5 g/dL with subsequent monitoring to keep a colloid oncotic pressure of 20 mm Hg
Occasional Use	Explanation
Acute liver failure	May be useful if rapid loss of liver function
Red blood cell suspension media	May be useful for exchange transfusion or use of very large volumes of red blood cells to avoid excessive hypoproteinemia using doses of albumin up to 12.5 g/250 mL unit of red blood cells
Ascites	Albumin or crystalloid may be useful with removal of more than 1500 mL of ascitic fluid using the same dosing as for shock; serous effusions due to peritonitis may necessitate albumin administration for hypoalbuminemia
After surgery	May be needed for hypoproteinemia after surgery
Acute nephrosis	Patients not responding to traditional therapy may respond to a loop diuretic with 100 mL of 25% albumin repeated daily for 7 to 10 days to try to limit edema
Renal dialysis	May be useful in post-dialysis patients with severe anemia who are prone to hypotension and shock using the dosing for shock
Uses requiring additional data	Explanation
Detoxification	Albumin best for binding hydrophobic drugs that possess a ring structure with at least 80% binding in normal concentrations; only established use as binding agent is severe jaundice in hemolytic disease of newborn
Unjustified use	Explanation
Undernutrition	Breakdown of albumin is too slow and its content of essential amino acids especially tryptophan is poor
Chronic nephrosis	Albumin has no value long-term regardless of hypoalbuminemia
Chronic cirrhosis	Albumin has no demonstrable value

Adapted from Reference 14: Tullis JL. Albumin. 2. Guidelines for clinical use. JAMA. 1977;237(5):460-3. doi: 10.1001/jama.237.5.460

meta-analyses attempting to define appropriate uses of albumin.²⁰ However, the quality of these meta-analyses is in large part reflective of the quality of their underlying studies.

In conclusion, the published studies immediately following the fractionation of albumin for World War II and up to the first set of clinical practice guidelines provide an historical perspective for future studies and proposed clinical uses of albumin. With a few notable exceptions related to patients with liver disease, routine administration of albumin lacks justification as a first-line therapy for most areas of common use.

CONFLICTS OF INTEREST

The author reports no conflicts of interest to disclose.

FUNDING

None

ACKNOWLEDGEMENTS AND CREDITS

None

Submitted: September 02, 2025 EST. Accepted: October 28, 2025 EST. Published: December 01, 2025 EST.



This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CCBY-4.0). View this license's legal deed at <http://creativecommons.org/licenses/by/4.0> and legal code at <http://creativecommons.org/licenses/by/4.0/legalcode> for more information.

REFERENCES

1. Starling EH. On the absorption of fluids from the connective tissue spaces. *J Physiol.* 1896;19(4):312-326. doi:[10.1113/jphysiol.1896.sp000596](https://doi.org/10.1113/jphysiol.1896.sp000596)
2. Mann FC. Further experimental study of surgical shock. *JAMA.* 1918;71(15):1184-1188. doi:[10.1001/jama.1918.02600410006002](https://doi.org/10.1001/jama.1918.02600410006002)
3. AMEDD Center of History & Heritage. CHAPTER XII. The Bovine and Human Albumin Programs. Accessed March 20, 2025. <https://achh.army.mil/history/book-wwii-blood-chapter12>
4. Starr D. *Blood*. 2nd edition. Alfred A. Knopf, Inc.; 2002.
5. Cohn EJ, Oncley JL, Strong LE, Hughes WL, Armstrong SH. Chemical, clinical, and immunological studies on the products of human plasma fractionation. I. the characterization of the protein fractions of human plasma. *J Clin Invest.* 1944;23(4):417-432. doi:[10.1172/JCI101508](https://doi.org/10.1172/JCI101508)
6. Janeway CA, Gibson ST, Woodruff LM, Heyl JT, Bailey OT, Newhouser LR. Chemical, clinical, and immunological studies on the products of human plasma fractionation. VII. concentrated human serum albumin. *J Clin Invest.* 1944;23(4):465-490. doi:[10.1172/JCI101514](https://doi.org/10.1172/JCI101514)
7. Cournand A, Noble RP, Breed ES, et al. Chemical, clinical, and immunological studies on the products of human plasma fractionation. VIII. clinical use of concentrated human serum albumin in shock, and comparison with whole blood and with rapid saline infusion. *J Clin Invest.* 1944;23(4):491-505. doi:[10.1172/JCI101515](https://doi.org/10.1172/JCI101515)
8. Warren JV, Stead EA, Merrill AJ, Brannon ES. Chemical, clinical, and immunological studies on the products of human plasma fractionation. IX. the treatment of shock with concentrated human serum albumin: a preliminary report. *J Clin Invest.* 1944;23(4):506-509. doi:[10.1172/JCI101516](https://doi.org/10.1172/JCI101516)
9. Sterling K. The turnover rate of serum albumin in man as measured by I131-tagged albumin. *J Clin Invest.* 1951;30(11):1228-1237. doi:[10.1172/JCI102542](https://doi.org/10.1172/JCI102542)
10. Berson SA, Yalow RS, Schreiber SS, Post J. Tracer experiments with I131 labeled human serum albumin: distribution and degradation studies. *J Clin Invest.* 1953;32:746-768. doi:[10.1172/JCI102789](https://doi.org/10.1172/JCI102789)
11. Wilkinson P, Sherlock S. The effect of repeated albumin infusions in patients with cirrhosis. *Lancet.* 1962;2(7266):1125-1129. doi:[10.1016/S0140-6736\(62\)90895-4](https://doi.org/10.1016/S0140-6736(62)90895-4)
12. Sgouris JT, René A, eds. *Proceedings of the Workshop on Albumin, Feb 12-13, 1975*. National Heart and Lung Institute, National Institutes of Health, Dept of Health, Education, and Welfare; 1975.
13. Tullis JL. Albumin. 1. Background and use. *JAMA.* 1977;237(4):355-360. doi:[10.1001/jama.237.4.355](https://doi.org/10.1001/jama.237.4.355)
14. Tullis JL. Albumin. 2. Guidelines for clinical use. *JAMA.* 1977;237(5):460-463. doi:[10.1001/jama.237.5.460](https://doi.org/10.1001/jama.237.5.460)
15. Skillman JJ, Restall DS, Salzman EW. Randomized trial of albumin vs. electrolyte solutions during abdominal aortic operations. *Surgery.* 1975;78(3):291-303.
16. Callum J, Skubas NJ, Bathla A, et al. Use of intravenous albumin: A guideline from the International Collaboration for Transfusion Medicine Guidelines. *Chest.* 2024;166(2):321-338. doi:[10.1016/j.chest.2024.02.049](https://doi.org/10.1016/j.chest.2024.02.049)
17. Angeli P, Labenz C, Piano S, et al. Albumin infusion in hepatorenal syndrome-acute kidney injury: New evidence challenges recent consensus. *J Hepatol.* 2025;83(3):800-802. doi:[10.1016/j.jhep.2025.04.011](https://doi.org/10.1016/j.jhep.2025.04.011)
18. Nadim MK, Kellum JA, Forni L, et al. Acute kidney injury in patients with cirrhosis: Acute Disease Quality Initiative (ADQI) and International Club of Ascites (ICA) joint multidisciplinary consensus meeting. *J Hepatol.* 2024;81(1):163-183. doi:[10.1016/j.jhep.2024.03.031](https://doi.org/10.1016/j.jhep.2024.03.031)
19. Cook D. Is albumin safe? *N Engl J Med.* 2004;350(22):2294-2296. doi:[10.1056/NEJMe048095](https://doi.org/10.1056/NEJMe048095)
20. Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med.* 2004;350(22):2247-2256. doi:[10.1056/NEJMoa040232](https://doi.org/10.1056/NEJMoa040232)