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Historical Evolution of Fluid Therapy and Contemporary Challenges: From Intravenous Injection to Artificial Blood

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Abstract

Fluid therapy has evolved dramatically from its origins in 17th-century blood transfusion experiments to sophisticated, modern, perioperative fluid management protocols. This comprehensive review traces the historical development of intravenous fluid administration, beginning with William Harvey's circulation theory and Christopher Wren's pioneering venous injections, through the cholera epidemics that necessitated early fluid replacement therapy, to Sydney Ringer's groundbreaking electrolyte solutions. The evolution of blood transfusion from dangerous animal-to-human experiments to safe ABO-compatible transfusions paralleled the development of plasma substitutes and colloid solutions. Pediatric fluid therapy emerged as a specialized field in the early 20th century, with contributions from researchers like James Gamble and Daniel Darrow establishing the fundamental principles of water and electrolyte balance. Modern perioperative fluid management has been revolutionized by Enhanced Recovery After Surgery (ERAS) protocols, goal-directed fluid therapy, and evidence-based approaches that optimize patient outcomes. Contemporary challenges include the ongoing debate over crystalloid versus colloid solutions, the safety concerns surrounding hydroxyethyl starch preparations, and the continued quest for effective artificial blood substitutes. Recent advances in artificial oxygen carriers, particularly Professor Hiromi Sakai's hemoglobin vesicles (HbV) developed through three decades of research at Nara Medical University, have demonstrated promising Phase 1 trial results with acceptable safety profiles, offering potential solutions to blood supply shortages and compatibility issues with anticipated clinical implementation by 2030. This historical perspective illuminates how empirical observations evolved into evidence-based practice, while highlighting persistent challenges in optimizing fluid therapy for diverse clinical scenarios.

Keywords

Fluid Therapy, Blood Transfusion, Plasma Substitutes, Ringer's Solution, Enhanced Recovery After Surgery (ERAS), Perioperative Management, Artificial Blood

1. Introduction

Administration of intravenous fluids represents one of the most fundamental interventions in modern medicine, yet its evolution spans centuries of scientific discovery, clinical observation, and technological advancement. From the first tentative experiments with venous injection in the 17th century, to today's sophisticated perioperative fluid management protocols, the history of fluid therapy reflects humanity's growing understanding of physiology, pathophysiology, and the delicate balance required to maintain life.

The journey began with William Harvey's revolutionary description of blood circulation in 1628, which laid the theoretical foundation for intravenous therapy [1]. However, it took nearly two centuries before fluid replacement therapy found its first major clinical application during the cholera epidemics of the 1830s [2]. The subsequent development of blood transfusion, electrolyte solutions, and plasma substitutes represents a convergence of scientific inquiry, clinical necessity, and technological innovation that continues to this day.

Modern fluid therapy encompasses not merely the replacement of lost volume, but the precise management of electrolyte balance, acid-base status, and hemodynamic optimization. The emergence of Enhanced Recovery After Surgery (ERAS) protocols, goal-directed fluid therapy, and personalized medicine approaches reflects our current understanding that fluid management must be tailored to individual patient needs and clinical circumstances.

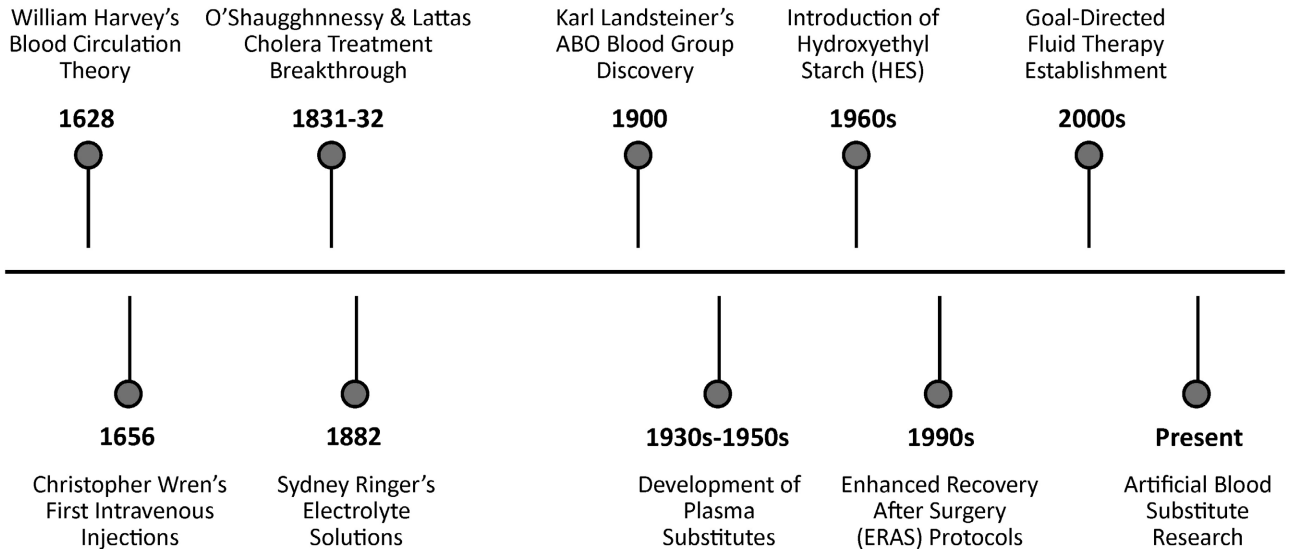
This historical analysis reveals that fluid therapy advancement has been predominantly driven by urgent clinical necessity—from cholera epidemics to battlefield medicine—which catalyzed scientific inquiry and accelerated technological innovation, demonstrating how medical crises serve as powerful catalysts for therapeutic breakthroughs.

2. History of Fluid Therapy (Figure 1)

2.1. Ancient and Medieval Foundations

The earliest recorded medical practices involving fluid therapy can be traced to ancient Egyptian medicine (3000 BCE), where physicians used rectal infusions and bladder irrigation techniques, as documented in the Edwin Smith Papyrus and Ebers Papyrus [3] [4]. These early practitioners recognized the importance of maintaining fluid balance, though their understanding was limited to observable symptoms rather than physiological mechanisms.

Islamic physicians during the medieval period made significant advances to our



Key milestones in the evolution of fluid therapy from the discovery of blood circulation to modern artificial blood research. Major discoveries include Harvey's circulation theory (1628) [1], Wren's pioneering intravenous injections (1656) [10], the cholera treatment breakthrough by O'Shaughnessy and Latta (1831-1832) [2] [89]-[92], Ringer's electrolyte solutions (1882) [109] [110], Landsteiner's ABO blood groups (1900) [46] [47], development of plasma substitutes (1930s-1950s) [67]-[74], introduction of hydroxyethyl starch (1960s) [75] [76], Enhanced Recovery After Surgery protocols (1990s) [154]-[157], establishment of goal-directed fluid therapy (2000s) [165] [166], and current artificial blood substitute research, including hemoglobin-based oxygen carriers (HBOCs), PFCs, and hemoglobin (Hb)-vesicles [215]-[217].

Figure 1. Historical timeline of the development of fluid therapy.

understanding of circulation and fluid dynamics. Al-Razi (854-925 CE) described detailed observations of fluid loss in fever patients, while Ibn Sina (Avicenna, 980-1037 CE) proposed sophisticated theories about blood circulation and fluid distribution that predated European understanding by centuries [5] [6]. Their works, preserved in Arabic texts and later translated into Latin, influenced European medical thought for over 500 years.

The Renaissance brought renewed interest in anatomical studies and physiological understanding. Andreas Vesalius (1514-1564) corrected numerous Galenic errors through systematic dissection, while Michael Servetus (1511-1553) described pulmonary circulation decades before Harvey's comprehensive theory [7] [8]. These anatomical advances laid the groundwork for understanding the circulatory system as a closed-loop network capable of supporting therapeutic interventions.

The concept of intravenous fluid administration emerged from ancient medical theories about bodily humors (fluids) and fluid balance. Hippocrates (460-370 BCE) proposed that health depended on the equilibrium of four bodily fluids: blood, phlegm, yellow bile and black bile. This "humoral pathology" theory, later refined by Galen (129-216 CE), suggested that disease resulted from imbalances in these fluids, leading to treatments involving bloodletting and purgation.

The scientific foundation for modern fluid therapy began with William Harvey's (1578-1657) groundbreaking work "De Motu Cordis" (1628), which demonstrated that blood circulates throughout the body rather than being consumed by

tissues, as previously believed [1] [9]. This discovery contradicted Galenic doctrine and established the theoretical basis for intravenous injection and transfusion.

2.2. Early Intravenous Experiments

The first recorded intravenous injection was performed by Christopher Wren (1632-1723) in 1656 [10]. Using a hollow goose quill attached to a pig's bladder, Wren injected wine, ale and opium into dogs' veins, observing their effects on behavior and physiology. While these experiments demonstrated the feasibility of intravenous administration, they also revealed the potential dangers, as several animals died from the procedures [11] [12].

Robert Boyle (1627-1691), working alongside Wren at the Royal Society, conducted parallel experiments using different substances and injection techniques [13]. Their collaborative work, documented in the Philosophical Transactions of the Royal Society, established basic principles of dose-response relationships and the importance of injection site selection [14] [15]. These early experiments also noted the rapid onset of action compared to oral administration, establishing intravenous delivery as a route for emergency interventions.

Johann Daniel Major (1634-1693) performed the first human intravenous injection in 1662, documenting his techniques in "Chirurgia Infusoria" (1664) [16]. His careful documentation included detailed drawings of injection apparatus, patient positioning, and the adverse reactions observed [17]. Major's work influenced German medical practice for decades, and established protocols that remained largely unchanged until the 19th century.

Simultaneously, Johann Sigismund Elsholtz (1623-1688) conducted similar experiments in Brandenburg, publishing "Clysmatica Nova" (1665) with detailed illustrations of injection apparatus and techniques [18] [19]. Elsholtz's contributions included the development of improved syringes, recognition of venous anatomical variations, and early descriptions of what we now recognize as anaphylactic reactions [20]. His work was more widely distributed than Major's, and influenced medical practice across German-speaking regions.

2.3. 17th and 18th Century Developments

These early experiments, while crude by modern standards, established several important principles: the need for sterile techniques (although germ theory was unknown), the importance of controlling injection speed, and the potential for both therapeutic benefit and serious harm [21] [22]. However, limited understanding about infection, blood compatibility and appropriate solutions limited the clinical application of intravenous fluid infusions for nearly two centuries.

The 18th century saw sporadic attempts to revive intravenous therapy, particularly in France, where physicians like François Magendie (1783-1855) conducted systematic studies on drug absorption and distribution [23]. Magendie's work on strychnine and other alkaloids demonstrated that intravenous administration

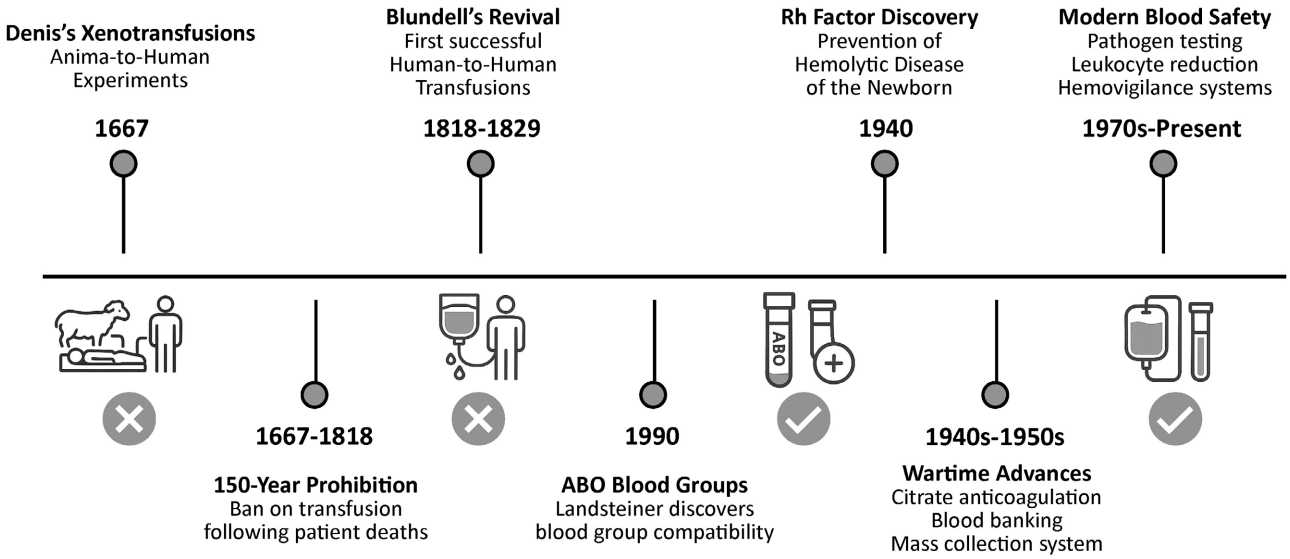
produced more predictable effects than other routes, laying the groundwork for modern pharmacokinetics [24] [25].

In England, Stephen Hales (1677-1761) made crucial contributions to understanding blood pressure and circulatory dynamics [26]. His experiments measuring arterial pressure in horses using glass tubes provided quantitative data about circulatory physiology that would later inform fluid resuscitation strategies [27] [28]. Hales also investigated the effects of different solutions on blood flow and pressure, noting that certain substances could restore circulation in moribund animals.

3. History of Blood Transfusion (Figure 2)

3.1. Ancient Beliefs and Early Concepts

Throughout history, blood has been viewed as carrying life force, personality traits, and healing properties. Ancient Egyptian texts describe drinking blood for therapeutic purposes, while Roman gladiatorial practices included consuming the blood of fallen warriors to transfer their courage and strength [29] [30]. These beliefs, while scientifically unfounded, demonstrate the early recognition of blood's vital importance, and foreshadow attempts at therapeutic blood replacement.



Development of blood transfusion from dangerous animal-to-human experiments to modern safe practice. Denis's xenotransfusions (1667) [33] [36] led to mortality and prohibition of blood transfusions lasting 150 years [40]. Blundell's revival (1818-1829) established human-to-human transfusion principles [39]-[45]. Landsteiner's ABO discovery (1900) [46] [47] and Rh factor identification (1940) [51]-[54] revolutionized compatibility testing. World Wars accelerated developments in transfusion medicine, including citrate anticoagulation, blood banking, and component therapy [57]-[65].

Figure 2. Evolution of blood transfusion safety.

Blood transfusion emerged as a logical extension of intravenous injection techniques, driven by observations that blood loss was often fatal and that replacing blood might restore life. The history of transfusion reveals both the promise and

peril of medical innovation when applied before the existence of adequate scientific understanding.

3.2. Animal-to-Human Transfusions

Richard Lower's animal experiments at Oxford University represent the first systematic investigation of blood transfusion [31]. Working with Robert Hooke and other members of the Royal Society, Lower developed techniques for direct vessel-to-vessel connections using quills and silver tubes [32] [33]. His experiments in 1665 resulted in successful transfusion of blood from one dog's carotid artery to another's jugular vein, with the recipient dog surviving and showing no apparent adverse effects.

Lower's success encouraged attempts at therapeutic transfusion in humans. His detailed documentation in Philosophical Transactions included observations about blood coagulation, the importance of matching donor and recipient sizes, and early recognition that some animals tolerated the procedure better than others [34]. These observations, while limited in comparison with contemporary understanding, established fundamental principles that remained valid for centuries.

3.3. The Denis Era and Early Human Transfusions

Jean-Baptiste Denis (1643-1704) performed the first recorded animal-to-human transfusion in Paris on June 15, 1667 [35]. The patient, a 15-year-old boy suffering from prolonged fever and weakened by repeated bloodletting, received approximately 9 ounces of lamb's blood through a silver tube connected to the lamb's carotid artery and the boy's brachial vein. The immediate improvement—restoration of consciousness, improved pulse, and return of appetite—encouraged Denis to attempt additional transfusions.

Denis performed at least four documented xenotransfusions between June and December 1667, with mixed results [36] [37]. His second patient, a laborer named Mauroy, received multiple transfusions of calf's blood for what Denis described as "madness" [29]. After initial apparent improvement, Mauroy died following a third transfusion, leading to accusations of murder and a highly publicized trial. The case ended in Denis's acquittal when investigation revealed that Mauroy's wife had poisoned him with arsenic, but the controversy effectively ended early transfusion experiments.

In London, Edmund King performed the first xenotransfusion in England on November 23, 1667, assisted by Richard Lower [38] [39]. Their patient, a Cambridge scholar suffering from mental illness, received 6 - 7 ounces of sheep's blood. While the patient initially improved, the procedure's association with the Denis controversy led to growing opposition. The Royal Society of London effectively banned transfusion experiments in 1678, followed by similar prohibition by the French Parliament, ending systematic transfusion research for nearly 150 years.

The ban on transfusion effectively halted advances in transfusions for nearly 150 years, demonstrating how premature application of new techniques can im-

pede medical advancement when safety concerns overshadow potential benefits [40].

3.4. Revival and Human-to-Human Transfusion

James Blundell (1791-1878), a London obstetrician, revived transfusion in the early 19th century, recognizing that species compatibility was crucial [41]. His experiments demonstrated that animal blood was incompatible with humans, and developed techniques for human-to-human transfusion using syringes and funnels.

Blundell's revival of transfusion was motivated by his obstetric practice, where he frequently witnessed deaths from postpartum hemorrhage [42]. His systematic animal experiments demonstrated that only blood from the same species was effective, leading him to conclude that "the blood of mammals is not so circumstanced that we can employ, with advantage to the human subject, that of lower animals" [43] [44].

Blundell's first human transfusion on December 22, 1818, involved a patient with severe gastric bleeding who had lost approximately 14 ounces of blood through vomiting [45]. Using a syringe and silver tube, Blundell slowly infused 12 - 14 ounces of fresh human blood from multiple donors. Although the patient showed temporary improvement—improved pulse, restored warmth, and regained consciousness—he died 56 hours later from continued bleeding. Despite the ultimate failure, Blundell had demonstrated the feasibility and immediate benefits of human blood transfusion.

Between 1818 and 1829, Blundell performed ten documented human transfusions with five survivals, establishing basic principles that remained valid for decades [45]. His innovations included the "Gravitator" (1824), a funnel-shaped apparatus that used gravity to drive blood flow, and the "Impellor" (1829), which employed atmospheric pressure. These devices reduced the complexity of transfusion and made the procedure more practical for emergency use.

3.5. ABO Blood Groups and Modern Transfusion

The discovery of ABO blood groups by Karl Landsteiner (1868-1943) in 1900 revolutionized transfusion medicine [46] [47]. Landsteiner's identification of A, B and O blood types (AB was discovered by his colleagues in 1902) explained the variable success of transfusions and provided a scientific basis for compatibility testing [48] [49].

Landsteiner's discovery emerged from his investigation of why blood from different individuals sometimes clumped together when mixed. Using blood samples from himself and five colleagues, he identified three distinct patterns of agglutination, leading to the classification of blood types A, B and C (later renamed O). His colleagues Alfred von Decastello and Adriano Sturli identified the fourth blood type, AB, in 1902 [50]. This work earned Landsteiner the 1930 Nobel Prize in Physiology or Medicine and established the foundation for safe transfusion

practice.

Discovery of the Rh factor by Landsteiner and Alexander Wiener in 1940 further refined compatibility testing and explained hemolytic disease of the newborn [51]-[53]. Their work with rhesus monkey blood led to identification of the Rh antigen system, adding another crucial layer to transfusion safety. Development of the Coombs test by Robin Coombs in 1945 provided a method for detecting incomplete antibodies, further improving the accuracy of compatibility testing [54].

3.6. World Wars and Advancements in Transfusion

World War I catalyzed rapid advances in blood storage and transfusion techniques. Albert Hustin's use of sodium citrate as an anticoagulant in 1914 enabled blood collection and storage, while Geoffrey Keynes developed portable transfusion apparatus for battlefield use [55]. The establishment of blood depots near the front lines demonstrated the feasibility of organized blood banking and saved thousands of lives.

World War II brought further innovations, including the development of plasma fractionation by Edwin Cohn, establishment of blood banks by Bernard Fantus at Cook County Hospital (1937), and the first systematic use of blood substitutes [56] [57]. The American Red Cross, under Charles Drew's leadership, organized massive blood collection programs that revolutionized blood banking and established principles still used today [58]-[61].

Post-war developments included the discovery of additional blood group systems, development of plastic blood bags by Carl Walter and W.P. Murphy (1950), and establishment of volunteer blood donation systems [62]. The introduction of component therapy in the 1960s—separating whole blood into red cells, plasma, platelets and clotting factors—maximized the utility of each donation and reduced transfusion reactions [63].

4. History of Blood Substitutes and Plasma Expanders

4.1. Early Development and Theoretical Foundations

The limitations and risks of blood transfusion drove the search for artificial alternatives that could provide volume expansion without the complications of blood compatibility, infectious disease transmission, and limited availability. This quest has spanned over 150 years with mixed success.

The concept of colloid osmotic pressure, described by Ernest Starling in 1896, provided the theoretical foundation for plasma substitutes [64]. Starling's principle explained how proteins in blood maintain intravascular volume by creating osmotic gradients that prevent fluid loss to tissues [65].

Early attempts at plasma substitution included various protein solutions and synthetic polymers. During the Spanish Civil War (1936-1939), Frederic Duran-Jorda pioneered the use of preserved blood and plasma, while simultaneously investigating protein hydrolysates as blood substitutes [66]. These early efforts established the principle that effective plasma substitutes must maintain oncotic

pressure, while avoiding toxicity and immune reactions [67].

4.2. First Generation Plasma Expanders

The first plasma substitute was developed in 1863 when Carl Ludwig used gum arabic dissolved in electrolyte solution for organ perfusion experiments. During World War I, William Bayliss used gum Arabic solutions to treat hemorrhagic shock, although toxicity reactions and edema limited its utility. The urgent need for blood substitutes during World War II accelerated the development of various plasma expanders [68].

4.3. Gelatin Solutions and Second-Generation Products

Modified gelatin solutions were developed in the 1950s to overcome the limitations of earlier substitutes. Gelofusine (B. Braun, 1962) and Haemaccel (Hoechst, 1968) became widely used in Europe for perioperative fluid management and trauma resuscitation [69]. These urea-linked gelatin solutions provided effective volume expansion with molecular weights of 30,000 - 35,000 daltons, although their short intravascular half-life of 3 - 4 hours required their repeated administration.

Clinical studies comparing gelatin solutions to crystalloids demonstrated the superior hemodynamic stability and reduced fluid requirements with gelatin, although higher costs and occasional anaphylactoid reactions limited their widespread adoption [69]. The development of modified fluid gelatin (Gelafusal) and polygeline (Haemaccel) provided alternatives with different safety profiles, although fundamental limitations of the short duration of effect and moderate allergic potential persisted [69].

4.4. Synthetic Colloids

Dextran solutions, developed in Sweden in the 1940 s, provided better safety profiles and became widely used for volume expansion and improvement of the flow properties of blood [70] [71]. Dextran development by Anders Grönwall and Björn Ingelman at the Pharmacia company represented a major advance in synthetic plasma expanders [71]. Dextran 70 (molecular weight 70,000) provided optimal volume expansion for a duration of 4 - 6 hours, while Dextran 40 (molecular weight 40,000) offered improved microcirculatory flow, but for a shorter duration [72]. Clinical trials demonstrated the effectiveness of dextran in surgical patients and trauma victims, although maximum dose limitations (1.5 g/kg/day) were established due to bleeding complications and renal toxicity [73] [74].

4.5. Third Generation Products: Hydroxyethyl Starch

Hydroxyethyl starch (HES) solutions, first developed by Thompson and Walton in 1963, represent the most sophisticated synthetic plasma substitute to date [75] [76]. The first-generation high molecular weight HES (450/0.7) provided excellent volume expansion lasting 8 - 12 hours, but caused significant coagulation abnor-

malities due to interference with factor VIII/von Willebrand factor complex [77] [78].

Second-generation medium molecular weight HES preparations (200/0.5) offered improved safety profiles with reduced coagulation effects, while maintaining good volume expansion properties [79]. The third-generation lower molecular weight HES (130/0.4) promised further safety improvements with minimal coagulation impact and reduced tissue storage, leading to widespread adoption in Europe and clinical trials worldwide [80].

However, the VISEP (2008), 6S (2012), and CHEST (2013) trials revealed increased mortality and acute kidney injury in septic patients receiving HES compared to crystalloids, leading to regulatory restrictions [81]-[83]. The European Medicines Agency subsequently suspended the use of HES products in 2013, although it later allowed its restricted use in 2018, while other jurisdictions maintained varying policies reflecting ongoing controversies about its risk-benefit ratio [84]. Current European guidelines permit restricted HES use in specific non-septic contexts, including elective cardiac surgery, liver transplantation, and major orthopedic procedures, where the risk-benefit ratio may favor its volume expansion properties, provided patients have normal renal function and coagulation status.

5. Fluid Therapy in Cholera Treatment

The cholera pandemics of the 19th century represented the first major test of intravenous fluid therapy, establishing fundamental principles of fluid resuscitation, while revealing both the potential benefits and limitations of early medical intervention [2]. The global impact of cholera and the development of fluid replacement therapy during these epidemics laid the groundwork for modern emergency medicine and critical care.

5.1. Cholera Pandemics and Epidemiology

Cholera, endemic to the Bengal region of India, spread globally during the 19th century due to increased trade and travel, causing six major pandemics between 1817 and 1923 [85] [86]. The first pandemic (1817-1824) remained largely confined to Asia, but subsequent waves reached Europe, North America and Africa, with devastating mortality rates. The second pandemic (1829-1837) killed over one million people in Russia alone, and prompted the first systematic medical investigations of the disease.

Cholera's pathophysiology involves massive fluid and electrolyte losses—up to 20 liters daily in severe cases—due to the effects of the cholera toxin on intestinal epithelium [87]. Without treatment, case fatality rates exceed 50%, but with appropriate fluid replacement, mortality can be reduced to less than 1%. This dramatic difference established fluid therapy as one of medicine's most effective interventions, and demonstrated the importance of understanding disease mechanisms for developing rational treatments.

Traditional treatments during early cholera outbreaks were not only ineffective, but often harmful [88]. Bloodletting, the dominant therapy based on the humoral theory, further depleted already volume-depleted patients. Mercury-based calomel purgatives worsened diarrhea, while opium-based compounds provided symptomatic relief, but did nothing to address the underlying fluid losses. These failures created desperation among physicians and opened minds to innovative approaches, such as intravenous fluid therapy.

5.2. O'Shaughnessy's Proposal

William Brooke O'Shaughnessy (1809-1889), a 22-year-old Irish physician sent to investigate cholera outbreaks, conducted detailed blood analyses of cholera patients and discovered massive losses of water and salts [89]. In 1831, he published his findings in The Lancet, proposing that intravenous injection of warm saline solutions that matched blood salt concentrations could restore normal physiology. Although O'Shaughnessy tested his theories in animal experiments, he did not attempt human treatment.

O'Shaughnessy's analytical work was groundbreaking in its precision and scientific rigor [89] [90]. Using chemical analysis techniques, he demonstrated that cholera patients lost approximately one-third of their normal water content and massive quantities of sodium salts. His proposal for treatment was remarkably prescient: "What is wanted is to restore the blood to its natural specific gravity, to restore its deficient saline matters, and to increase its temperature." The composition of the solution he recommended—containing sodium chloride and sodium carbonate—closely resembled modern oral rehydration solutions [90].

5.3. Latta's Clinical Application

Thomas Aitchison Latta (1796-1833), a Scottish physician, became the first to apply O'Shaughnessy's theories clinically [91]. Latta's technique involved inserting a silver cannula into the basilic vein and slowly injecting a saline solution warmed to approximately 112˚F (44˚C). His first patient received six pints of the solution (3.4 liters) over 30 minutes, with dramatic improvements in pulse rate, respiration and consciousness. However, when treatment was discontinued and the patient was transferred to another physician, continuing vomiting and diarrhea led to death within hours. This established a pattern that would be repeated throughout the cholera epidemic—temporary improvement during fluid administration, followed by relapse when treatment was stopped.

Subsequent patients treated by Latta and his colleagues demonstrated both the potential and limitations of early fluid therapy [92]. A 50-year-old woman received 330 ounces (9.3 liters) of the saline solution over 12 hours and made a complete recovery. However, other patients died despite treatment, leading to questions about appropriate patient selection, the timing of intervention, and adequacy of fluid replacement. Latta's detailed case reports, published in The Lancet, provided the first systematic documentation of the results of intravenous fluid

therapy [92].

5.4. Other Physicians' Contributions

John MacKintosh, working at the London Cholera Hospital, expanded on Latta's work with systematic treatment of 156 patients, achieving a 16% survival rate compared to 0% with conventional therapy [93] [94]. His detailed analysis identified factors associated with successful treatment: early intervention before complete collapse, adequate fluid volumes, and maintenance therapy to prevent relapse.

In continental Europe, physicians such as Hermann Klencke in Germany and Charles-Emmanuel Sédillot in France adapted Latta's techniques with varying degrees of success [95] [96]. The French Academy of Medicine initially opposed intravenous therapy, but gradually accepted its utility as evidence accumulated. Italian physician Arnaldo Cantani later developed subcutaneous saline infusion techniques that were safer and easier to perform, although less effective than intravenous routes [97].

The end of the cholera outbreak in 1833 and Latta's death from tuberculosis ended this early chapter in fluid therapy [88]. It was another 50 years before intravenous fluid therapy was widely adopted, although the principles established during the cholera epidemic—rapid volume replacement, electrolyte correction, and careful monitoring—remain fundamental to modern resuscitation [98] [99].

5.5. Modern Oral Rehydration Therapy

The development of oral rehydration therapy (ORT) in the 1960s represented a return to cholera's origins and vindicated O'Shaughnessy's original insights [100] [101]. Work by Robert Phillips in Dhaka and Norbert Hirschhorn at Johns Hopkins demonstrated that glucose-enhanced sodium absorption could match intravenous therapy's effectiveness, while being safer and more practical in resource-limited settings [102] [103]. The World Health Organization's standardized formula for oral rehydration solution (ORS), introduced in 1978 and refined in 2003, has, to date, prevented millions of deaths from diarrheal diseases worldwide [104] [105].

5.6. Birth of Ringer's Solution

The development of Ringer's solution represents one of the most serendipitous discoveries in medicine, arising from accidental observation and leading to fundamental understanding of electrolyte physiology and optimal fluid composition.

The serendipitous discovery of electrolyte requirements for optimal physiological function represents one of medicine's most fortunate accidents, fundamentally changing our understanding of cellular physiology and establishing the foundation for modern fluid therapy [106]. Ringer's work bridged the gap between empirical observation and scientific understanding, providing mechanistic in-

sights that remain relevant even today.

5.7. Sydney Ringer's Experiments

Sydney Ringer (1835-1910), a professor of physiology at University College London, was conducting experiments on isolated frog hearts in 1882, using them to study the effects of various substances on cardiac function [107]. When perfused with what Ringer believed was a pure saline solution, frog hearts typically stopped beating within 20 minutes. However, on one occasion, a heart continued beating for over four hours [108].

Investigation revealed that his laboratory assistant had mistakenly prepared the saline solution by using tap water from the New River Water Company rather than distilled water [108]. Analysis showed that the tap water contained small amounts of calcium and other minerals. This discovery led Ringer to systematically investigate the effects of various ions on cardiac function [106].

Ringer's investigation involved preparing solutions with precisely controlled ionic compositions and measuring cardiac contractile force, rate and rhythm using mechanical recording devices [106]. His apparatus included lever systems to measure the force of contraction, and timing mechanisms to assess rhythm changes. These experiments represented some of the earliest quantitative studies in cardiac physiology, and established experimental methods that would be used for decades.

5.8. Electrolyte Functions

Ringer's subsequent experiments, published in 1883, demonstrated that calcium was essential for cardiac contractility, while excessive potassium caused cardiac arrest [109]. He showed that sodium, calcium and potassium worked together to maintain normal cardiac rhythm and contractility—a discovery that laid the foundation for understanding cardiac electrophysiology [110].

The original experiments revealed the fundamental principles of cardiac electrophysiology that were decades ahead of their time [110]. Ringer demonstrated that calcium removal eliminated contractility without affecting electrical activity, while excess potassium caused progressive bradycardia and eventual asystole [110]. His work established the concept of calcium-sodium antagonism, and predicted findings that were not fully understood until the discovery of cellular ion channels and calcium-handling mechanisms in the mid-20th century [111].

The original Ringer's solution contained 0.75% sodium chloride, 0.014% potassium chloride, 0.012% calcium chloride, and 0.02% sodium bicarbonate [111]. This composition, while different from modern formulations, established the principle that physiological solutions should contain multiple electrolytes in appropriate concentrations.

5.9. Contemporary Research and Validation

Ringer's work was simultaneously validated and extended by other physiologists across Europe [112]. Walter Holbrook Gaskell at Cambridge University con-

firmed Ringer's findings using different experimental preparations, while Henry Pickering Bowditch at Harvard University demonstrated similar principles in mammalian cardiac tissue [113]. These independent confirmations established the universality of Ringer's discoveries and accelerated their clinical application.

5.10. Evolution of and Modifications to Ringer's Original Solution

Ringer's work inspired numerous modifications and improvements [106]. Frank Locke added glucose to create Locke's solution in 1901 [114] [115], while Maurice Tyrode developed Tyrode's solution in 1910, adding magnesium and phosphate for tissue culture applications [107] [116].

Locke's solution incorporated 0.1% glucose to provide a metabolic substrate for prolonged tissue survival, extending the viability of isolated tissues from hours to days [114] [115]. This modification proved crucial for early organ transplantation experiments, and established glucose as an essential component of physiological solutions. Tyrode's solution further refined electrolyte composition by adding magnesium chloride and monosodium phosphate, creating a solution that closely approximated the composition of extracellular fluid [107].

Development of Krebs-Henseleit solution by Hans Krebs and Kurt Henseleit in 1932 represented another major advance in intravenous solutions, optimizing the composition for metabolic studies and introducing systematic bicarbonate buffering [117] [118]. This solution became the standard for physiological research and influenced the development of the modern balanced crystalloid solutions used clinically today.

The most clinically significant modification came in 1932, when Alexis Frank Hartmann added lactate to create lactated Ringer's solution (Hartmann's solution) [119]. Working at Washington University, Hartmann was investigating the treatment of acidosis in pediatric diarrheal diseases when he discovered that lactate could serve as a metabolizable base, providing an alkali without the instability of bicarbonate solutions.

Hartmann's innovation solved multiple problems simultaneously: lactate provided buffering capacity, could be autoclaved without decomposition, and was metabolized to bicarbonate by the liver [99]. Clinical trials in children with acidotic diarrheal diseases demonstrated superior outcomes with lactated solutions compared to bicarbonate-containing solutions, leading to its rapid adoption worldwide. Modern lactated Ringer's solution remains essentially unchanged from Hartmann's original formulation, and is now the most widely used balanced crystalloid solution globally [120] [121].

6. Development of Pediatric Fluid Therapy

Pediatric fluid therapy developed as a distinct specialty in the early 20th century, driven by the enormous mortality from diarrheal diseases in children and recognition that children have unique physiological requirements that differ significantly from adults.

The recognition that children are not simply small adults represented a paradigm shift in medical thinking that occurred gradually throughout the early 20th century [122] [123].

6.1. Early Pioneers

John Howland (1873-1926) established the first academic pediatric department at Johns Hopkins University, emphasizing research alongside clinical care [124]. His work with William McKim Marriott on infantile diarrhea demonstrated that acidosis resulted from excessive bicarbonate loss, establishing the fundamental principles of acid-base physiology in children [125] [126].

James Lawder Gamble (1883-1959) revolutionized the understanding of fluid and electrolyte balance in hospitalized children [127]. His introduction of the "Gamblogram"—a graphical representation of plasma electrolyte composition using milliequivalents—provided a conceptual framework for understanding fluid and electrolyte disorders that remains valuable today [128] [129].

Marriott's detailed studies of infantile diarrhea in Baltimore revealed that acidosis was the primary cause of death, and not dehydration alone [130]. His systematic measurement of blood chemistry in sick infants demonstrated specific patterns of electrolyte loss and established the scientific foundation for replacement therapy. Marriott's work influenced a generation of pediatricians and established Johns Hopkins as the leading center for pediatric research globally.

Gamble's conceptual contributions extended far beyond clinical practice to fundamental understanding of cellular physiology and kidney function [131]. His studies of fasting and refeeding established the concept of intracellular versus extracellular fluid compartments, and demonstrated how different disease states affect fluid distribution. The Gamblogram visualization technique made complex electrolyte abnormalities comprehensible to practicing physicians, and established the use of milliequivalents as standard units for clinical chemistry [132].

6.2. Physiological Discoveries and Clinical Applications

Nathan Talbot's work at Massachusetts General Hospital established safety limits for pediatric fluid administration and developed the concept of "homeostatic limits" for fluid therapy [133] [134]. His mathematical models predicted the consequences of various fluid compositions and volumes, providing a scientific basis for safe practice limits that prevented both dehydration and water intoxication.

Allan Butler's metabolic studies at Boston Children's Hospital revealed the unique nutritional requirements of sick children, and led to the development of maintenance solutions containing appropriate ratios of glucose, electrolytes and amino acids [135] [136]. Butler's solutions were among the first designed specifically for pediatric metabolism rather than simple extrapolation of adult requirements.

6.3. Maintenance Fluid Requirements (Table 1)

Malcolm Holliday and William Segar's 1957 publication established standard formulas for calculating pediatric maintenance fluid requirements based on metabolic

Table 1. Pediatric maintenance fluid calculations.

Holliday-Segar Methods (1957)		Hourly Rate	Daily Volume
"4-2-1 Rule" for Maintenance Fluid Calculation			
First 10 kg	4 mL/kg/hour	4 × weight (kg)	100 mL/day
Second 10 kg	2 mL/kg/hour	2 × weight (kg)	50 mL/day
Each additional kg thereafter	1 mL/kg/hour	1 × weight (kg)	20 mL/day
Example Calculations			
5 kg infant	4 × 5 = 20 mL/hour	20 mL/hour	480 mL/day
15 kg child	(4 × 10) + (2 × 5) = 50 mL/hour	50 mL/hour	1200 mL/day
25 kg child	(4 × 10) + (2 × 10) + (1 × 5) = 65 mL/hour	65 mL/hour	1560 mL/day
Current Guidelines			
NICE (2020) and American Academy of Pediatrics (2018) recommend:			
Use isotonic solutions (e.g., 0.9% saline) rather than hypotonic solutions.			
Monitor serum sodium levels in children receiving IV fluids.			
Regular clinical reassessment to adjust fluid therapy as needed.			
Safety Considerations			
Hospital-acquired hyponatremia risks:			
SIADH (Syndrome of Inappropriate ADH secretion) common in hospitalized children.			
Hypotonic solutions may exacerbate water retention and hyponatremia.			
Symptoms include headache, nausea, seizures and, in severe cases, cerebral edema.			

Holliday-Segar method (1957) for calculating pediatric maintenance fluid requirements based on metabolic rate and body weight [137] [138]. The "4-2-1 rule" provides 4 ml/kg/hr for the first 10 kg, 2 ml/kg/hr for the next 10 kg, and 1 ml/kg/hr for each additional kilogram. Modern guidelines from NICE (2020) and AAP (2018) recommend isotonic rather than hypotonic solutions to prevent hospital-acquired hyponatremia [147]-[149]. This approach correlates fluid requirements with energy expenditure, recognizing that metabolic requirements per kilogram decrease with age and size.

rate and body weight [137]. Their "4-2-1 rule" (4 ml/kg/hr for the first 10 kg, 2 ml/kg/hr for the next 10 kg, and 1 ml/kg/hr for each additional kg) became the global standard for pediatric fluid management [138].

The Holliday-Segar method was based on careful studies of metabolic rate and insensible water losses in healthy children of different ages and sizes [139]. Their approach correlated fluid requirements with energy expenditure, recognizing that metabolic rate per kilogram body weight decreases with age and size. This method provided a simple, practical formula that could be applied globally, and became the foundation for pediatric fluid therapy protocols worldwide.

However, recent evidence suggesting the increased risk of hyponatremia with hypotonic maintenance solutions has led to revised guidelines recommending isotonic solutions for most hospitalized children, demonstrating how clinical practice evolves with new evidence [140].

The safety concerns about hypotonic solutions emerged from multiple case reports and systematic studies demonstrating hospital-acquired hyponatremia in

children receiving standard maintenance fluids [141]. The syndrome of inappropriate antidiuretic hormone secretion (SIADH), common in hospitalized children with various illnesses, increases water retention and leads to the risk of hyponatremia when combined with hypotonic fluid administration [142].

6.4. Specialized Pediatric Solutions

Daniel Darrow's work in the 1940s at Yale University emphasized the importance of potassium replacement in pediatric patients, leading to the development of Darrow's solution containing 35 mEq/L potassium—much higher than in adult solutions [143]. His recognition that children lose proportionally more potassium than adults during diarrheal illnesses revolutionized pediatric electrolyte management and reduced mortality from hypokalemic paralysis.

Darrow's clinical observations revealed that potassium depletion was a major cause of persistent ileus and respiratory failure in children with diarrheal diseases [144]. His systematic studies on potassium balance demonstrated that replacement requirements exceeded losses measured in stool and urine, leading to the recognition of transcellular potassium shifts during illness and recovery phases.

The Japanese approach to pediatric fluid therapy, developed by Takatsu and colleagues in the 1960s, involved numbered solutions (1 - 4) designed for sequential use depending on the patient's clinical status and treatment phase [145]. This system represents the early recognition that fluid requirements change during illness and recovery, anticipating modern goal-directed approaches to fluid management.

6.5. Modern Pediatric Guidelines and Evidence

Contemporary pediatric fluid management has been influenced by major clinical trials and systematic reviews that challenge traditional approaches [146]. The NICE guidelines (2015, updated 2020) recommend isotonic solutions for most hospitalized children, while the American Academy of Pediatrics (2018) provided similar recommendations based on accumulating evidence of hyponatremia risks [147] [148].

Recent studies have also questioned traditional approaches to fluid resuscitation in pediatric sepsis, with the FEAST trial demonstrating potential harm from fluid bolus therapy in African children with severe infection [149] [150]. These findings highlight the complexity of pediatric fluid management and the need for continued research to optimize treatment approaches in different clinical scenarios and geographic settings.

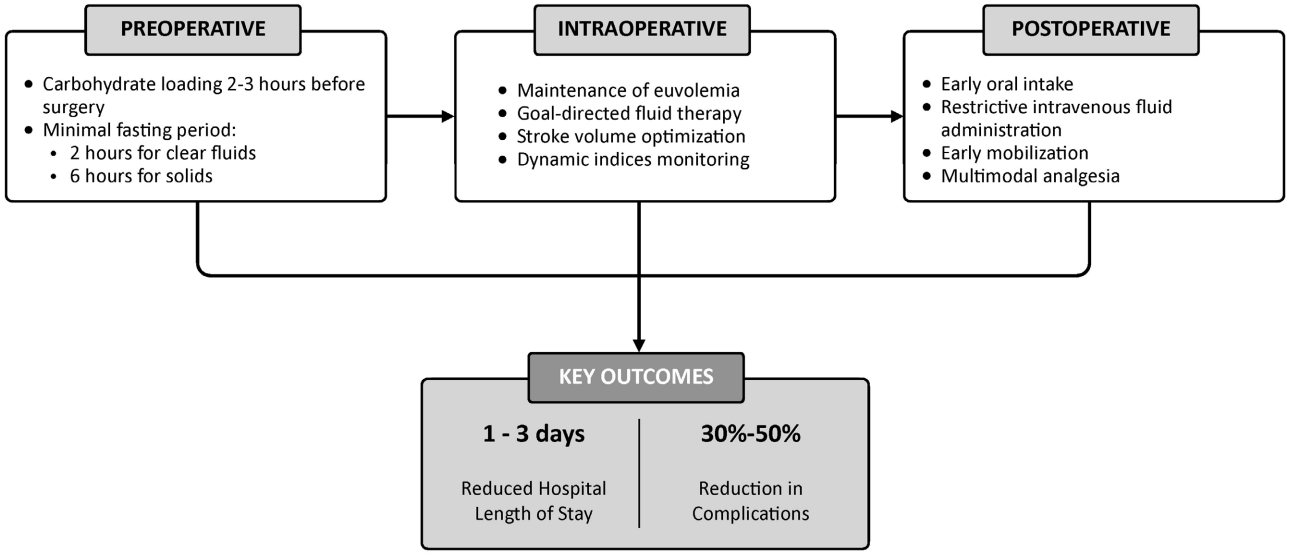
7. Modern Perioperative Fluid Management Including ERAS

Modern perioperative fluid management has evolved from intuition-based practices to evidence-driven protocols that have significantly impacted surgical outcomes, recovery times and healthcare costs. The transformation of perioperative fluid management from intuition-based practices to evidence-driven protocols represents one of the major advances in perioperative medicine of the past two

decades [151] [152]. This evolution has been driven by recognition that fluid management significantly impacts surgical outcomes, healthcare costs and patient satisfaction, leading to the development of sophisticated monitoring techniques and management algorithms.

7.1. Enhanced Recovery After Surgery (ERAS) Protocols (Figure 3)

Enhanced Recovery After Surgery (ERAS) protocols, pioneered by Henrik Kehlet in Denmark, represent a paradigm shift toward multimodal perioperative care designed to minimize surgical stress and accelerate recovery [153] [154]. Fluid management is a core component of ERAS, emphasizing several key principles.



Enhanced Recovery After Surgery (ERAS) fluid management principles, as established by Kehlet and the ERAS Society [153]-[156]. The protocol emphasizes preoperative carbohydrate loading 2 - 3 hours before surgery [154] [155], minimal preoperative fasting periods (2 hours for clear fluids, 6 hours for solids) [155], intraoperative maintenance of euvolemia using goal-directed fluid therapy based on dynamic indices [155] [156], and postoperative early oral intake with restrictive intravenous fluid administration [155] [156]. Implementation of the ERAS protocol reduces the duration of hospitalization by 1-3 days and the rate of postoperative complications by 30% - 50% [155] [156].

Figure 3. ERAS fluid management protocol.

The ERAS Society, founded in 2001, has published evidence-based guidelines for multiple surgical specialties, including colorectal, cardiac, orthopedic and gynecologic surgery [155] [156]. These guidelines are regularly updated based on emerging evidence and have been adopted worldwide, with demonstrated improvements in the duration of hospitalization, postoperative complications, and patient satisfaction. Implementation of ERAS protocols typically reduces the duration of hospitalization by 1 - 3 days, while reducing complications by 30% - 50% [157]. ERAS fluid management principles include avoiding preoperative fasting beyond 2 hours for clear fluids and 6 hours for solids, implementing carbohydrate loading 2 - 3 hours preoperatively to improve insulin sensitivity and reduce postoperative nausea, and maintaining intraoperative euvolemia, while avoiding both hypovolemia and fluid overload [158]. The concept of "zero fluid balance" aims

to prevent tissue edema while ensuring adequate organ perfusion.

Systematic reviews and meta-analyses have also consistently demonstrated that ERAS implementation reduces postoperative complications, duration of hospitalization and healthcare costs across multiple surgical specialties [159]. A 2019 Cochrane review of 17 randomized trials involving over 1800 patients found significant reductions in complications (RR 0.71, 95% CI 0.58 - 0.86) and duration of hospitalization (mean difference −2.28 days, 95% CI −3.09 to −1.46) with ERAS implementation [160].

However, it should also be cautioned that excessive fluid administration can lead to tissue edema, delayed wound healing, and prolonged recovery, while inadequate fluid replacement can cause organ hypoperfusion and dysfunction, requiring careful balance between restriction and adequacy.

7.2. Goal-Directed Fluid Therapy

Goal-directed fluid therapy (GDFT) uses hemodynamic monitoring to assess cardiac output, and fluid responsiveness to optimize fluid administration [161]. Parameters such as stroke volume variation, pulse pressure variation, and dynamic indices derived from arterial waveform analysis guide fluid and vasoactive drug administration.

GDFT protocols typically involve targeting specific hemodynamic parameters, such as stroke volume optimization, maintaining stroke volume variation at <13%, and achieving predetermined oxygen delivery targets [162]. Various monitoring systems have been developed, including esophageal Doppler (CardioQ), pulse contour analysis (FloTrac/Vigileo), and non-invasive cardiac output monitors (ClearSight), each with specific advantages and limitations [163].

Multiple randomized trials have demonstrated improved outcomes with GDFT, particularly in high-risk surgical patients [164]. The approach moves beyond traditional static parameters, such as central venous pressure, toward dynamic assessments of hemodynamic status and fluid responsiveness.

A 2016 systematic review of 38 randomized trials involving over 4000 patients demonstrated that GDFT reduces complications (OR 0.77, 95% CI 0.63 - 0.94), duration of hospitalization (mean difference −1.16 days), and may reduce mortality in high-risk surgical patients [165]. However, the benefits appear most pronounced in high-risk patients undergoing major surgery, with less clear evidence in routine surgical procedures [166].

7.3. Crystalloid vs. Colloid Debate (Table 2)

The choice between crystalloid and colloid solutions for fluid resuscitation in critically ill and surgical patients remains contentious despite decades of research. Large randomized trials, such as SAFE (2004), FEAST (2011) and CRISTAL (2013), have provided important insights, but have not definitively resolved the debate [150] [167] [168]. The SAFE trial found no difference in mortality between saline and albumin in ICU patients, while FEAST surprisingly demonstrated harm

Table 2. Comparison of crystalloid and colloid solutions.

Characteristics	Crystalloids	Colloids
Examples	Normal saline (0.9% NaCl) Lactated Ringer's solution Balanced solution (Plasma-Lyte)	Albumin (5%, 25%) Dextran (40, 70) Gelatins (Gelofusine) Hydroxyethyl starch (HES)
Duration of volume expansion	30 - 60 minutes *Rapid redistribution to interstitial space*	2 - 12 hours *HES: 4 - 6 hours; Albumin: 8 - 12 hours*
Cost	Low *~$1 - 4 per liter*	High *Albumin: ~$80 - 300 per unit* *HES: ~$50 - 90 per unit*
Risks	Hyperchloremic metabolic acidosis Tissue edema Electrolyte imbalance *Particularly with large volumes of normal saline*	Coagulation disorders Acute kidney injury (especially HES) Anaphylactic/anaphylactoid reactions Accumulation in tissues with repeated dosing
Clinical trial evidence	SMART trial (2018): Reduced kidney events with balanced crystalloids vs saline (14.3% vs 15.4%, p = 0.04)	SAFE trial (2004): No mortality difference between albumin and saline 6S, CHEST trial (2012): Increased kidney injury and mortality with HES in sepsis
Current recommendations	First-line fluid for most resuscitation scenarios Balanced solutions preferred over normal saline	Limited role in specific scenarios HES use restricted in many countries Albumin considered in select patients

Characteristics and clinical implications of crystalloid versus colloid solutions based on major clinical trials. Crystalloids include normal saline, lactated Ringer's solution and balanced solutions, such as Plasma-Lyte, providing short-duration volume expansion (30 - 60 minutes) at low cost, but with the risk of hyperchloremic acidosis and tissue edema [80]-[84] [167] [168]. Colloids, including albumin, dextran, gelatin and hydroxyethyl starch, provide longer duration volume expansion (2 - 12 hours), but at a higher cost and with risks of coagulation disorders, acute kidney injury (particularly with HES) and anaphylaxis. The SMART trial demonstrated reduced kidney injury with balanced crystalloids versus saline [169].

from fluid boluses in African children with severe infection [150] [167] [168].

More recent trials have focused on crystalloid composition rather than crystalloid versus colloid comparisons. The SMART trial (2018) demonstrated a reduction in major adverse kidney events within 30 days (14.3% vs 15.4%, p = 0.04) when balanced crystalloids were compared to saline in over 15,000 critically ill adults [169]. Similar findings in the SALT-ED trial in emergency department patients suggest that balanced crystalloids may have advantages over normal saline, although the effect sizes are modest [170].

Current evidence also increasingly favors balanced crystalloid solutions over normal saline due to the reduced risk of hyperchloremic acidosis and acute kidney injury [171]. The development of fourth-generation balanced solutions with physiological electrolyte compositions represents ongoing refinement of crystalloid therapy.

Modern balanced crystalloids include lactated Ringer's solution, Plasma-Lyte A, and newer formulations, such as Sterofundin and Jonosteril, that more closely approximate plasma electrolyte composition [172]. These solutions typically con-

tain 130 - 140 mEq/L sodium, 98 - 110 mEq/L chloride, and metabolizable anions (lactate, acetate, or gluconate) to provide appropriate strong ion differences and avoid the hyperchloremic metabolic acidosis associated with normal saline administration [173] [174] (**Table 3**).

Table 3. Major clinical trials in fluid therapy.

Trial (Year)	Patient Population	Interventions Compared	Primary Outcome	Key Findings
SAFE (2004)	ICU patients requiring fluid resuscitation (n = 6997)	4% Albumin vs. Normal saline	28-day all-cause mortality	No difference in mortality (Albumin: 20.9% vs. Saline: 21.1%)
FEAST (2011)	African children with severe infection and impaired perfusion (n = 3141)	Albumin bolus vs. Saline bolus vs. No bolus	48-hour mortality	Increased mortality with fluid boluses (Bolus: 10.5% vs. No bolus: 7.3%)
CRISTAL (2013)	ICU patients with hypovolemic shock (n = 2857)	Colloids (albumin, gelatins, dextrans, HES) vs. Crystalloids (saline, Ringer's)	28-day mortality	No difference in mortality (Colloids: 25.4% vs. Crystalloids: 27.0%)
SMART (2018)	Critically ill adults (n = 15,802)	Balanced crystalloids (LR, Plasma-Lyte) vs. Normal saline	Major adverse kidney events within 30 days	Reduced kidney events with balanced solutions (14.3% vs. 15.4%, p = 0.04)
BaSICS (2021)	Critically ill adults requiring fluid challenges (n = 10,520)	Balanced solution vs. Normal saline	90-day mortality	No mortality difference Confirmed safety of balanced solutions

Landmark randomized controlled trials that shaped modern fluid therapy practice. The SAFE trial (2004) found no mortality difference between albumin and saline in ICU patients [167]. The FEAST trial (2011) surprisingly demonstrated harm from fluid boluses in African children with severe infection [149]. CRISTAL (2013) showed no mortality difference between crystalloids and colloids [168]. The SMART trial (2018) demonstrated reduced major adverse kidney events with balanced crystalloids versus saline (14.3% vs 15.4%, p = 0.04) [169]. BaSICS (2021) confirmed the safety of balanced solutions without mortality benefits [171].

7.4. Individualized Fluid Management

Modern fluid management increasingly emphasizes individualized approaches based on patient-specific factors, including comorbidities, surgical procedure and real-time physiological monitoring [175]. Techniques such as transesophageal echocardiography, pulse wave analysis, and bioimpedance monitoring enable personalized fluid optimization.

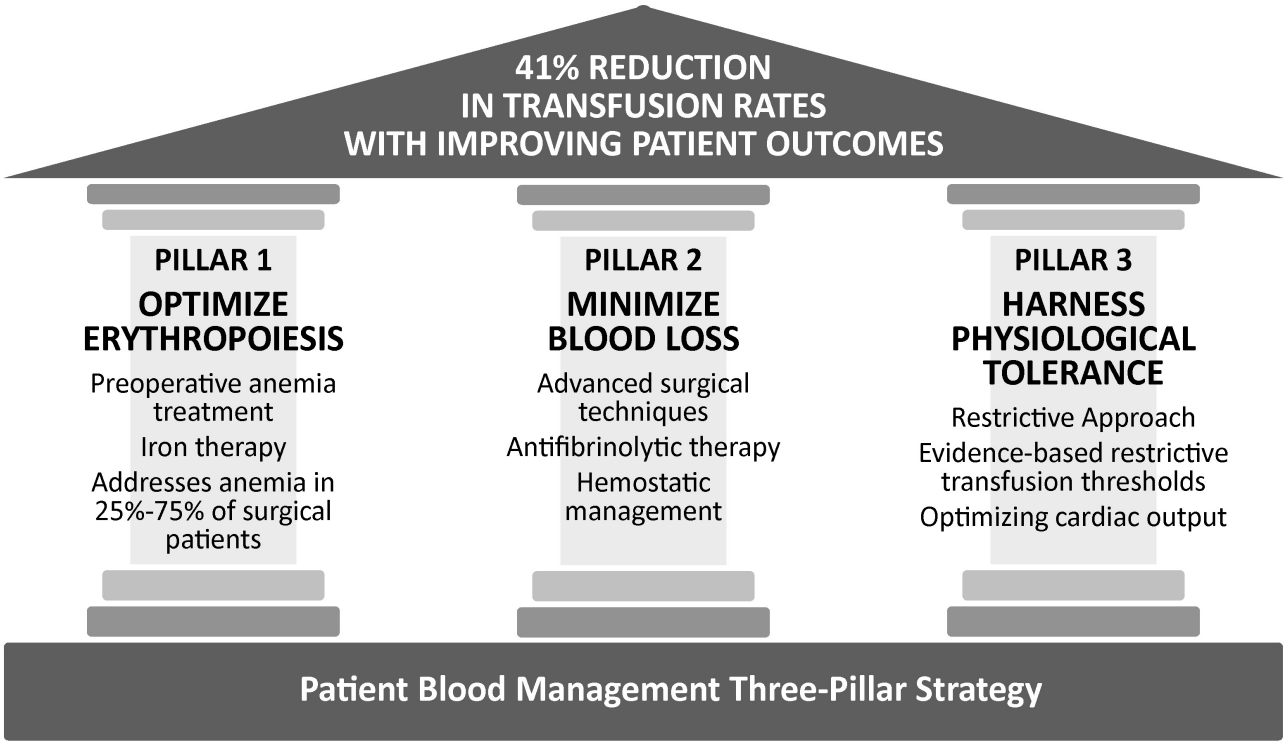
For example, patients with heart failure require restrictive fluid strategies with careful monitoring of central venous pressure and pulmonary artery wedge pressure to prevent pulmonary edema, while maintaining adequate preload for cardiac output optimization. Conversely, patients with chronic kidney disease may benefit from more liberal fluid administration to maintain renal perfusion and prevent contrast-induced nephropathy, though electrolyte balance requires meticulous attention due to impaired renal clearance.

Machine learning approaches are also being developed to predict fluid requirements and optimize management based on continuous monitoring data, electronic health records, and patient characteristics [176] [177]. Artificial intelligence systems can potentially integrate multiple data streams, including vital signs, la-

boratory values, surgical factors and patient comorbidities, to provide real-time recommendations for fluid management decisions.

8. Patient Blood Management and Modern Transfusion Strategies (Figure 4)

Patient Blood Management (PBM) represents a paradigm shift in transfusion medicine, evolving from traditional reactive approaches to proactive, evidence-based strategies that optimize patient outcomes while minimizing blood product utilization [178]. This comprehensive approach has gained international recognition and adoption, fundamentally changing how clinicians approach perioperative and critical care management. The integration of PBM principles with modern fluid management creates synergistic effects, where optimizing physiological tolerance to anemia through enhanced oxygen delivery and reduced consumption allows for more restrictive transfusion thresholds, thereby reducing the reliance on aggressive fluid resuscitation to maintain hemodynamic stability in anemic patients.



The three fundamental pillars of Patient Blood Management (PBM) as developed in Australia and endorsed by the World Health Organization [181]. **Pillar 1** focuses on optimizing erythropoiesis through preoperative anemia treatment with intravenous iron and erythropoiesis-stimulating agents, addressing anemia in 25% - 75% of surgical patients [189]-[191]. Systematic iron therapy increases hemoglobin by 1.5 - 2.5 g/dL within 2 - 4 weeks and reduces transfusion requirements [192]-[194]. **Pillar 2** emphasizes minimizing perioperative blood loss through meticulous surgical technique, tranexamic acid administration (reducing bleeding by 30% - 40%), and point-of-care viscoelastic testing [195] [196]. **Pillar 3** harnesses physiological tolerance to anemia through evidence-based restrictive transfusion thresholds (7 - 8 g/dL for stable patients) and optimization of oxygen delivery [197] [198]. Multimodal PBM implementation demonstrates 30% - 50% transfusion reduction, 20% - 30% complication reduction, and 1 - 2 day shorter hospital stays [199]-[201].

Figure 4. Three-pillar strategy of patient blood management.

PBM originated in Australia in the 1990s, driven by concerns about blood shortages, transfusion-related complications, and healthcare costs [179]. The Western Australia PBM initiative, launched in 2008 under the leadership of Axel Hofmann and Shannon Farmer, demonstrated significant reductions in red blood cell transfusion rates (41% reduction) and healthcare costs, while improving patient outcomes [180].

The Australian experience influenced its international adoption, with PBM programs implemented in Europe, North America and Asia. The World Health Organization endorsed PBM in 2010, recognizing it as essential for patient safety and healthcare sustainability [181]. Key professional organizations, including the Society for the Advancement of Blood Management (SABM) and the International Foundation for Patient Blood Management, have promoted evidence-based transfusion practices globally [182].

8.1. The Three-Pillar Strategy

PBM is built on three fundamental pillars that work synergistically to optimize patient outcomes while minimizing transfusion requirements [183]. This systematic approach addresses the entire perioperative period, from preoperative optimization through postoperative recovery.

8.1.1. Pillar 1: Optimize Erythropoiesis and Treat Anemia

Preoperative anemia represents one of the most significant modifiable risk factors in surgical patients, affecting 25% - 75% depending on surgical type, patient demographics, and underlying comorbidities [184]. The presence of even mild anemia (hemoglobin 10 - 12 g/dL) independently predicts increased morbidity, mortality, hospital length of stay, and transfusion requirements across diverse surgical populations [185]. Meta-analyses demonstrate a linear relationship between decreasing preoperative hemoglobin and adverse outcomes, with even hemoglobin levels of 12 - 13 g/dL showing elevated risk compared to normal values [185].

1) Pathophysiology and Etiology of Perioperative Anemia

Understanding anemia etiology guides appropriate treatment selection [186]. Iron deficiency constitutes the most common cause of preoperative anemia in surgical populations, accounting for 30% - 60% of cases [185] [186]. Absolute iron deficiency results from depleted total body iron stores (ferritin < 30 ng/mL), while functional iron deficiency occurs when adequate iron stores exist but cannot be mobilized for erythropoiesis due to hepcidin-mediated sequestration [187].

Hepcidin, a liver-produced hormone regulated by inflammation, represents the master regulator of iron homeostasis [187]. Inflammatory states—including malignancy, chronic infections, autoimmune disorders, and obesity—upregulate hepcidin synthesis, which then binds and degrades ferroportin (the sole cellular iron exporter) on duodenal enterocytes and macrophages. This blocks both dietary iron absorption and mobilization of stored iron, creating functional iron deficiency despite normal or elevated ferritin levels—the classical "anemia of chronic disease" [187].

Vitamin B12 and folate deficiencies contribute to macrocytic anemia in surgical patients, particularly in gastrointestinal surgery populations where malabsorption is common [188]. Recent studies reveal that 5% - 15% of preoperative anemic patients have B12 or folate deficiency, often coexisting with iron deficiency [188].

2) Iron Replacement Therapy

Iron replacement represents the cornerstone of preoperative anemia management for iron-deficient patients [189]. Route selection—oral versus intravenous—depends on time available before surgery, severity of deficiency, inflammatory status, and gastrointestinal tolerance.

Intravenous Iron Therapy: Intravenous iron preparations bypass hepcidin-mediated absorption blockade, delivering large iron doses directly into circulation for immediate incorporation into erythropoiesis [189]. Modern formulations—ferric carboxymaltose, iron isomaltoside, and low-molecular-weight iron dextran—allow administration of 500 - 1000 mg in single 15 - 30 minute infusions [189].

Multiple randomized trials demonstrate that preoperative IV iron significantly increases hemoglobin levels (mean increase 1.5 - 2.5 g/dL within 2 - 4 weeks) and reduces transfusion requirements [189]. The PREVENTT trial, while showing neutral primary outcomes, provided important insights about timing requirements (4 - 6 weeks optimal versus 10 - 14 days suboptimal) [190]. Recent meta-analyses of over 10,000 patients confirm IV iron reduces transfusion likelihood (RR 0.74, 95% CI 0.62 - 0.88) without increasing adverse events [191].

The PROVITA trial in cardiac surgery demonstrated that even ultra-short-term IV iron administration (2 - 7 days preoperatively) significantly reduced transfusion rates, establishing feasibility for urgent surgical scenarios [192].

3) Erythropoiesis-Stimulating Agents

ESAs—epoetin alfa, epoetin beta, darbepoetin alfa—directly stimulate red blood cell production and prove particularly valuable in inflammatory anemia where hepcidin limits iron availability, and in chronic kidney disease where endogenous erythropoietin production is impaired [193].

Cochrane systematic reviews demonstrate ESA efficacy in reducing perioperative transfusion rates when combined with iron supplementation [193]. ESAs are safe when hemoglobin targets do not exceed 13 g/dL, with recent evidence suggesting potential nephroprotective and cardioprotective effects independent of erythropoiesis [193].

4) Vitamin Supplementation and Comprehensive Management

Vitamin B12 (1000 mcg IM weekly or 1000 - 2000 mcg oral daily) and folate (1 - 5 mg daily) effectively correct deficiencies within 4 - 8 weeks [194]. Recent data emphasize testing all anemic surgical patients for vitamin deficiencies, as prevalence exceeds 15% in some populations and remains underdiagnosed [190].

5) Preoperative Anemia Clinics

Systematic preoperative anemia management requires organizational infrastructure supporting early identification (6-8 weeks preoperatively), comprehensive diagnostic evaluation, protocol-driven treatment, and reassessment [194].

Implementation of dedicated anemia clinics reduces transfusion rates by 20% - 50%, decreases length of stay by 1 - 2 days, and demonstrates cost savings of $1000 - 3000 per patient despite upfront investments [194].

8.1.2. Pillar 2: Minimize Perioperative Blood Loss

The second pillar addresses blood loss reduction through surgical technique optimization, pharmacological agents, and blood conservation technologies. Meticulous surgical hemostasis and minimally invasive approaches demonstrate 30% - 50% less blood loss than open procedures. Regional anesthesia reduces bleeding through sympathetic blockade and decreased venous pressure.

Tranexamic acid, an antifibrinolytic agent, reduces surgical blood loss by 30% - 40% when administered prophylactically (loading dose 10 - 15 mg/kg, then infusion 1 - 2 mg/kg/hour) [195]. Point-of-care viscoelastic testing (TEG®/ROTEM®) enables real-time coagulation assessment and goal-directed hemostatic therapy, reducing transfusion requirements by 30% - 50% [196].

Intraoperative cell salvage recovers and returns the patient's shed blood, proving cost-effective when blood loss exceeds 1000 mL [197]. Postoperative blood conservation includes minimizing phlebotomy through reduced laboratory testing frequency and smaller-volume collection tubes.

8.1.3. Pillar 3: Optimize Physiological Tolerance of Anemia

The third pillar recognizes that adequate tissue oxygenation depends on the entire oxygen delivery system. The body compensates for anemia through increased cardiac output, enhanced oxygen extraction, and regional blood flow redistribution [198].

Optimizing oxygen delivery involves supplemental oxygen administration and maintenance of adequate cardiac output through goal-directed fluid therapy. Reducing oxygen consumption through adequate analgesia, fever control, and infection prevention enhances anemia tolerance.

Restrictive transfusion strategies based on landmark trials establish safety of hemoglobin thresholds of 7 - 8 g/dL in stable patients, including those with cardiovascular disease [198] [199]. These evidence-based thresholds have reduced transfusion rates 30% - 50% without adverse outcomes. Single-unit transfusion strategies prevent unnecessary transfusions while achieving equivalent outcomes.

Postoperative anemia management includes intravenous iron to accelerate hemoglobin recovery, nutritional optimization, and continued adherence to restrictive transfusion thresholds [200]. Combined implementation of all three pillars creates synergistic effects, with multimodal PBM programs demonstrating 30% - 50% transfusion reduction, 20% - 30% complication reduction, and 1 - 2 day shorter hospital stays [201]-[203].

9. Artificial Oxygen Carriers: From Concept to Clinical Reality

The quest for artificial blood substitutes represents one of the most challenging endeavors in modern medicine, driven by fundamental limitations inherent in

conventional blood transfusion systems. The growing disparity between blood supply and demand, exacerbated by aging populations and declining donor participation, has created an urgent need for alternative oxygen-carrying solutions [204]. Beyond supply constraints, traditional blood transfusion faces multiple clinical challenges including ABO/Rh compatibility requirements, limited storage duration of 42 days for packed red blood cells, and persistent risks of pathogen transmission despite rigorous screening protocols [205]. These limitations become particularly critical in emergency situations, military conflicts, and remote medical settings where immediate blood availability can determine patient survival outcomes.

9.1. Historical Development of Artificial Oxygen Carriers

The scientific foundation for artificial oxygen carriers was established in 1966 when Clark and Gollan demonstrated the remarkable oxygen-dissolving capacity of perfluorocarbon (PFC) compounds [206]. Their groundbreaking experiments showed that laboratory mice could survive complete submersion in oxygenated perfluorocarbon solutions, breathing the liquid medium through their lungs. This discovery opened new possibilities for developing synthetic oxygen-carrying fluids that could potentially replace red blood cells in clinical applications.

The first commercial artificial blood product, Fluosol-DA-20, was developed by Green Cross Corporation of Japan and received FDA approval in 1989 [207]. This perfluorocarbon-based emulsion represented a milestone in blood substitute development, offering pathogen-free oxygen delivery with universal compatibility. However, clinical experience revealed significant limitations including low oxygen-carrying capacity (requiring high inspired oxygen concentrations), complement activation leading to pulmonary edema, and complex preparation requirements. These drawbacks ultimately led to its market withdrawal in 1994, highlighting the formidable challenges in artificial blood development [208].

Parallel development of hemoglobin-based oxygen carriers (HBOCs) during the 1980s and 1990s initially showed promise but encountered severe safety concerns. First-generation cell-free hemoglobin products, including PolyHeme, Hemopure, and Hemolink, demonstrated significant increases in myocardial infarction risk and mortality in clinical trials [209]. A comprehensive meta-analysis by Natanson and colleagues in 2008 revealed a 30% increase in death risk and threefold increase in myocardial infarction risk associated with these products, effectively halting their clinical development [210]. The mechanisms underlying these adverse effects were attributed to hemoglobin's intrinsic properties when released from the protective environment of red blood cells.

9.2. Two Major Approaches to Artificial Oxygen Carriers

9.2.1. Perfluorocarbon-Based Systems

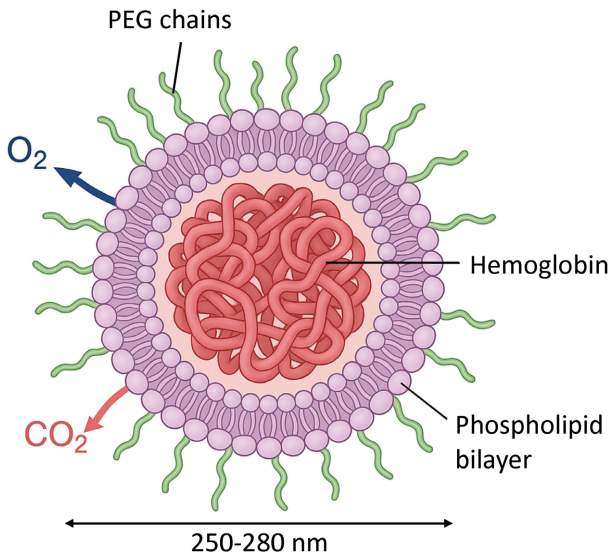
Perfluorocarbons possess unique physicochemical properties that make them attractive for oxygen delivery applications. These synthetic compounds demonstrate linear oxygen solubility relationships, allowing dissolution of up to 20 times

more oxygen than plasma at atmospheric pressure [211]. Unlike hemoglobin-based systems, PFCs do not chemically bind oxygen but rather dissolve it physically, creating a reservoir that releases oxygen in proportion to local tissue oxygen tension. Modern second-generation PFC emulsions have addressed many limitations of Fluosol-DA-20 through improved formulations with enhanced stability, reduced particle size, and minimal complement activation [212].

9.2.2. Hemoglobin-Based Oxygen Carriers

The fundamental challenge with cell-free hemoglobin lies in its inherent toxicity when removed from the red blood cell environment. Unencapsulated hemoglobin molecules readily extravasate through capillary walls, scavenge nitric oxide leading to vasoconstriction and hypertension, and undergo oxidative reactions producing methemoglobin and reactive oxygen species [213]. These mechanisms explain the cardiovascular toxicity observed with first-generation HBOCs and led to the development of encapsulation strategies to recreate the protective cellular environment.

Japanese Innovation: Hemoglobin Vesicles (HbV) (**Figure 5**).



Schematic cross-sectional representation of a hemoglobin vesicle (HbV) showing the innovative encapsulation design [214] [215] [217]. The vesicle consists of purified human hemoglobin encapsulated within a PEGylated phospholipid bilayer membrane with a diameter of 250 - 280 nanometers. Polyethylene glycol (PEG) chains extending from the outer surface provide stealth properties and prevent immune recognition. The lipid bilayer membrane maintains selective permeability, allowing bidirectional diffusion of oxygen (O_2) and carbon dioxide (CO_2) while containing hemoglobin molecules within the vesicle core.

Figure 5. Structural design and functional advantages of hemoglobin vesicles (HbV).

A revolutionary approach to hemoglobin-based oxygen carriers emerged from

the research laboratory of Professor Hiromi Sakai at Nara Medical University, Japan. Over three decades of dedicated research, Sakai and his team developed hemoglobin vesicles (HbV), representing a paradigm shift in artificial blood design [214]. These innovative nano-sized particles consist of purified human hemoglobin encapsulated within PEGylated phospholipid bilayer membranes, creating artificial red blood cells with diameters of 250 - 280 nanometers [215].

The unique structure of HbV addresses the fundamental problems of previous HBOC generations. The lipid bilayer membrane prevents hemoglobin extravasation while maintaining selective permeability for oxygen and carbon dioxide. This design significantly reduces nitric oxide scavenging, eliminates the hypertensive response characteristic of cell-free hemoglobin, and provides protection against oxidative damage [216]. Furthermore, HbV demonstrates remarkable stability with a shelf life of two years at room temperature and universal compatibility across all blood types, representing significant advantages over conventional blood products.

9.2.3. Clinical Development Progress

The clinical translation of HbV represents a methodical progression from laboratory concept to human application. Following extensive preclinical safety and efficacy studies in multiple animal models, Sakai's team conducted the first-in-human Phase 1 clinical trial from 2020 to 2022 [217]. This landmark study enrolled 12 healthy male volunteers across three dose-escalation cohorts receiving 10 mL, 50 mL, and 100 mL of HbV suspension respectively.

The Phase 1 results, published in Blood Advances in 2022, demonstrated encouraging safety profiles with no clinically significant blood pressure changes—a crucial distinction from previous HBOC failures [218]. The primary adverse events included mild infusion reactions typical of liposomal products and transient fever episodes, both manageable with standard premedication protocols. Pharmacokinetic analysis revealed a circulation half-life of approximately 8 hours, providing sufficient duration for emergency resuscitation until conventional blood products become available. Most importantly, the study confirmed the absence of hypertensive responses that had plagued earlier hemoglobin-based products.

9.2.4. Clinical Applications and Future Prospects

The successful Phase 1 trial has positioned HbV for expanded clinical development, with Phase 2 studies planned for 2025 targeting specific clinical scenarios where artificial oxygen carriers could provide maximum benefit [219]. These Phase 2 studies will focus on trauma patients with hemorrhagic shock, cardiac surgery patients with anticipated significant blood loss, and obstetric emergency cases where immediate blood availability is critical, representing clinical scenarios where HbV's universal compatibility and extended shelf life provide maximum therapeutic advantage. Primary applications include hemorrhagic shock resuscitation in trauma patients, where rapid volume replacement with oxygen-carrying capacity could improve survival outcomes compared to crystalloid or colloid solutions

alone.

The versatility of HbV extends beyond emergency medicine to specialized clinical contexts including disaster relief operations, military medicine, and remote healthcare delivery where blood banking infrastructure is unavailable. Additionally, the extended shelf life and universal compatibility make HbV particularly valuable for obstetric emergencies, where massive hemorrhage requires immediate intervention, and for organ preservation during transplantation procedures [220].

The development of artificial oxygen carriers represents the culmination of four centuries of progress in fluid therapy, from William Harvey's revolutionary description of blood circulation in 1628 to the pioneering intravenous saline therapy for cholera victims in the 1830s, through the establishment of modern transfusion medicine in the 20th century. Today, as we stand on the threshold of the artificial blood era, the work of Sakai and his colleagues embodies the convergence of historical knowledge, technological innovation, and clinical necessity.

The anticipated commercial availability of HbV by 2030 will mark a transformative milestone in medical history, potentially revolutionizing emergency medicine, trauma care, and surgical practice [221]. This achievement represents not merely a technological advancement but the fulfillment of a centuries-old medical aspiration to provide safe, effective, and universally compatible blood substitutes. As artificial oxygen carriers transition from experimental concepts to clinical reality, they embody the remarkable journey of fluid therapy from its humble origins in cholera treatment to the sophisticated life-saving interventions of modern medicine.

The story of artificial blood development exemplifies the iterative nature of medical progress, where each generation of researchers builds upon previous achievements while addressing fundamental challenges. From the early recognition of blood's vital role to the molecular engineering of hemoglobin vesicles, this journey reflects humanity's persistent quest to preserve and protect life through innovative medical solutions. The imminent clinical implementation of artificial oxygen carriers thus represents both a scientific triumph and a continuation of the humanitarian mission that has driven fluid therapy development throughout its remarkable 400-year evolution.

10. Conclusions

The historical evolution of fluid therapy represents a remarkable journey from ancient humoral theories to modern evidence-based medicine. From Christopher Wren's crude experiments with goose quills to today's sophisticated ERAS protocols and artificial intelligence-guided fluid management, each advance has built upon previous discoveries, while revealing new complexities and challenges.

The cholera epidemics of the 19th century demonstrated both the potential and limitations of fluid therapy, establishing principles that remain fundamental to modern resuscitation. Sydney Ringer's accidental discovery of electrolyte requirements revolutionized our understanding of cellular physiology, while the pediatric pioneers of the early 20th century established age-specific approaches that saved

countless lives.

Modern perioperative fluid management has evolved from the liberal fluid practices of the mid-20th century to today's precision medicine approaches. ERAS protocols and goal-directed fluid therapy represent the culmination of evidence-based practice, although debates continue about optimal fluid composition, administration timing and volume.

The quest for artificial blood substitutes illustrates both the promise and peril of medical innovation. Despite enormous investment and sophisticated technology, no product has successfully replicated blood's multiple functions, highlighting the complexity of physiological systems and the challenges of artificial blood replacement. However, promising developments, such as hemoglobin vesicles, continue to offer hope for future breakthroughs (**Table 4**).

Table 4. Classification of artificial blood substitutes.

Category	Mechanism	Advantages	Limitations
Hemoglobin-Based Oxygen Carriers (HBOCs) *PolyHb*, *DCLHb*, *Hemopure*	• Cell-free hemoglobin molecules • Cross-linked or polymerized to prevent rapid clearance • Directly bind and transport oxygen	• High oxygen-carrying capacity • Long shelf life (1 - 3 years) • No blood typing required • Reduced infection risk	• Vasoconstriction due to nitric oxide scavenging • Potential renal toxicity • Hypertension • Oxidative stress
Perfluorocarbon Emulsions (PFCs) *Fluosol*, *Oxygent*	• Synthetic compounds with high gas solubility • Dissolve oxygen physically rather than binding • Emulsified in water for intravascular use	• Dissolves large amounts of oxygen • Also transports CO_2 • Small particle size (<0.2 μm) • Completely synthetic (no biological contamination)	• Requires high inspired oxygen concentrations • Limited oxygen delivery at normal PaO_2 • Uptake by reticuloendothelial system • Flu-like symptoms
Hemoglobin Vesicles *Liposome-encapsulated Hb*, *HbV*	• Hemoglobin encapsulated in phospholipid vesicles • Mimics RBC structure and function • Isolates Hb from the sur rounding environment	• Reduced vasoactivity • Prevents nitric oxide scavenging • Maintains oxygen transport function • Cellular-scale oxygen delivery	• Complex manufacturing process • Limited stability • Potential immune response • High production costs
Stem Cell-Derived Red Blood Cells *iPSC-RBCs*, *CD34+ derived RBCs*	• Cultured from stem cells (iPSC, CD34+) • Differentiated through erythropoiesis pathway • Functionally identical to natural RBCs	• Potentially unlimited supply • Full biocompatibility • Normal oxygen carrying capacity • Customizable blood types	• Scalability challenges • Extremely high costs • Complex bioreactor requirements • Still in experimental phase

Current approaches to the development of artificial blood substitutes, with their mechanisms, advantages and limitations. Hemoglobin-based oxygen carriers (HBOCs), including polymerized hemoglobin (PolyHb), diaspirin cross-linked hemoglobin (DCLHb), and Hemopure provide high oxygen-carrying capacity, but cause vasoconstriction through nitric oxide scavenging [214]. Perfluorocarbon emulsions (PFCs), such as Fluosol and Oxygent, dissolve large amounts of oxygen, but require high inspired oxygen concentrations [212]. Hemoglobin vesicles represent promising encapsulation technology, reducing toxicity while maintaining oxygen transport function [214]. Stem cell-derived red blood cells offer a potential unlimited supply of red cells with full compatibility, but face scalability and cost challenges [221].

Patient Blood Management has caused a paradigm shift in transfusion medicine, demonstrating that proactive, evidence-based approaches can simultaneously improve patient outcomes, while reducing blood product utilization. This systematic approach exemplifies how modern medicine integrates multiple disciplines to optimize care.

Looking forward, fluid therapy will continue to evolve with advances in monitoring technology, personalized medicine, and artificial intelligence. Future directions may include real-time metabolomic monitoring (continuous assessment of cellular metabolic byproducts to guide fluid composition and timing), predictive algorithms for fluid requirements, and novel synthetic solutions designed for specific clinical scenarios.

The history of fluid therapy serves as a reminder that medical progress often comes through serendipitous discovery, careful observation and rigorous scientific testing. As we face new challenges in an aging population with complex comorbidities, the lessons learned from past successes and failures will continue to guide the development of safer and more effective fluid management strategies.

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Conflicts of Interest

The author declares that there are no conflicts of interest related to any commercial entities, including those mentioned in this manuscript.

References

[1] Harvey, W. and De Landau, H. (1628) Exercitatio anatomica de motv cordis et sangvinis in animalibvs. William Fitzer. https://doi.org/10.5479/sil.126677.39088002685501

[2] Snow, J. (1855) On the Mode of Communication of Cholera. John Churchill.

[3] Breasted, J.H. (1930) The Edwin Smith Surgical Papyrus. University of Chicago Press.

[4] Ghalioungui, P. (1987) The Ebers Papyrus: A New English Translation. Academy of Scientific Research.

[5] Iskandar, A.Z. (1962) Al-Razi's Contribution to Medicine. *Medical History*, **6**, 126-133.

[6] Aciduman, A. and Er, U. (2007) Avicenna's Views on Brain Anatomy, Intracranial Diseases, and Their Treatment. *Neurosurg Focus*, **23**, E8.

[7] O'Malley, C.D. (1964) Andreas Vesalius of Brussels, 1514-1564. University of California Press.

[8] Bainton, R.H. (1953) Hunted Heretic: The Life and Death of Michael Servetus. Bea-

con Press.

[9] Whitteridge, G. (1971) William Harvey and the Circulation of the Blood. Mac-Donald.

[10] Wren, C. (1665) Experiments on the Injection of Liquors into the Veins of Animals. *Philosophical Transactions of the Royal Society of London*, **1**, 128-130.

[11] Boyle, R. (1663) Some Considerations Touching the Usefulness of Experimental Natural Philosophy. Henry Herringman.

[12] Frank, H.A. (2000) Robert Boyle: Pioneer of Transfusion Medicine. *Transfusion Medicine Reviews*, **14**, 213-221.

[13] Hoff, H.E. and Guillemin, R. (1963) The First Experiments in Intravenous Therapy: Christopher Wren's Contributions. *Journal of the History of Medicine and Allied Sciences*, **18**, 13-21.

[14] Schmidt, J.E. (1959) Medical Discoveries: Who and When. Charles C Thomas.

[15] Cosnett, J.E. (1989) The Origins of Intravenous Fluid Therapy. *The Lancet*, **333**, 768-771. https://doi.org/10.1016/s0140-6736(89)92583-x

[16] Major, J.D. (1664) Chirurgia Infusoria. Joachim Reumann.

[17] Garrison, F.H. (1929) An Introduction to the History of Medicine. W.B. Saunders.

[18] Elsholtz, J.S. (1665) Clysmatica Nova. Georg Schultz.

[19] Magendie, F. (1824) Formulary for the Preparation and Mode of Employing Several New Remedies. Thomas and George Underwood.

[20] Olmsted, J.M.D. (1944) François Magendie: Pioneer in Experimental Physiology and Scientific Medicine in XIX Century France. Schuman.

[21] Porter, R. (1997) The Greatest Benefit to Mankind: A Medical History of Humanity. Norton.

[22] Temkin, O. (1973) Galenism: Rise and Decline of a Medical Philosophy. Cornell University Press.

[23] Singer, C. and Underwood, E.A. (1962) A Short History of Medicine. Oxford University Press.

[24] Hales, S. (1733) Statistical Essays: Containing Haemastaticks. W. Innys and R. Manby.

[25] Allan, D.J. and Schofield, R.E. (1980) Stephen Hales: Scientist and Philanthropist. Scholar Press.

[26] French, R. (1994) William Harvey's Natural Philosophy. Cambridge University Press.

[27] David, T.E. (1975) Blood and Wine: The Religious and Symbolic Association in Antiquity. *Journal of the History of Medicine and Allied Sciences*, **30**, 263-276.

[28] Scarborough, J. (1968) Roman Medicine and the Legions: A Reconsideration. *Medical History*, **12**, 254-261. https://doi.org/10.1017/s0025727300013296

[29] Lower, R. (1665) The Method Observed in Transfusing the Blood Out of One Animal into Another. *Philosophical Transactions of the Royal Society of London*, **1**, 353-358.

[30] Hooke, R. (1667) Method of Preserving Animals Alive by Blowing through Their Lungs with Bellows. *Philosophical Transactions of the Royal Society of London*, **2**, 539-540.

[31] Lower, R. (1669) Tractatus de Corde. Jo. Redmayne.

[32] Keynes, G. (1949) Blood Transfusion. John Wright & Sons.

[33] Denis, J.B. (1667) Letter Concerning a New Way of Curing Sundry Diseases by Trans-

fusion of Blood. *Philosophical Transactions of the Royal Society of London*, **2**, 489-504.

[34] Maluf, N.S.R. (1954) History of Blood Transfusion. *Journal of the History of Medicine and Allied Sciences*, **IX**, 59-107. https://doi.org/10.1093/jhmas/ix.1.59

[35] Tucker, H.H. (2011) Blood Work: A Tale of Medicine and Murder in the Scientific Revolution. W.W. Norton.

[36] Denis, J.B. (1668) Lettre écrite à monsieur montmort par monsieur denis touchant une folie invétérée qui a été guérie par la transfusion du sang. *Journal des Savants*, **3**, 153-159.

[37] King, E. (1667) An Account of the Experiment of Transfusion Practiced Upon a Man in London. *Philosophical Transactions of the Royal Society of London*, **2**, 557-559.

[38] Mollison, P.L. (1972) Blood Transfusion in Clinical Medicine. Blackwell Scientific.

[39] Blundell, J. (1818) Experiments on the Transfusion of Blood by the Syringe. *Journal of the Royal Society of Medicine*, **9**, 56-92. https://doi.org/10.1177/095952871800090p107

[40] Young, J.H. (1964) James Blundell (1790-1878) Experimental Physiologist and Obstetrician. *Medical History*, **8**, 159-169. https://doi.org/10.1017/s0025727300029409

[41] Blundell, J. (1819) Some Account of a Case of Obstinate Vomiting, in Which an Attempt Was Made to Prolong Life by the Injection of Blood into the Veins. *Journal of the Royal Society of Medicine*, **10**, 296-311. https://doi.org/10.1177/095952871901000p204

[42] Blundell, (1828) Observations on Transfusion of Blood. *The Lancet*, **12**, 321-324. https://doi.org/10.1016/s0140-6736(02)92543-2

[43] Blundell, J. (1980) The First Human Blood Transfusion. *American Journal of Obstetrics & Gynecology*, **136**, 985-987.

[44] Blundell, J. (1825) Researches Physiological and Pathological. E. Cox.

[45] Blundell, J. (1829) Successful Case of Transfusion. *The Lancet*, **1**, 431-432.

[46] Landsteiner, K. (1900) Zur kenntnis der antifermentativen, lytischen und agglutinierenden wirkungen des blutserums und der lymphe. *Centralbl Bakteriol*, **27**, 357-362.

[47] Landsteiner, K. (1961) On Agglutination of Normal Human Blood. *Transfusion*, **1**, 5-8. https://doi.org/10.1111/j.1537-2995.1961.tb00005.x

[48] Schiff, F. (1950) The ABO Blood Groups and Their Significance. *Vox Sanguinis*, **5**, 1-14.

[49] Stormont, C. (1968) The ABO Blood Groups: An Appreciation of Karl Landsteiner. *California Medicine*, **109**, 285-292.

[50] von Decastello, A. and Sturli, A. (1902) Ueber die isoagglutinine im serum gesunder und kranker menschen. *Münchner Medizinische Wochenschrift*, **49**, 1090-1095.

[51] Wiener, A.S. (1946) The Rh Factor and Racial Origins. *American Journal of Physical Anthropology*, **4**, 1-8.

[52] Landsteiner, K. and Wiener, A.S. (1940) An Agglutinable Factor in Human Blood Recognized by Immune Sera for Rhesus Blood. *Experimental Biology and Medicine*, **43**, 223-223. https://doi.org/10.3181/00379727-43-11151

[53] Wiener, A.S. (1943) Genetic Theory of the Rh Blood Types. *Experimental Biology and Medicine*, **54**, 316-319. https://doi.org/10.3181/00379727-54-14419

[54] Coombs, R.R.A., Mourant, A.E. and Race, R.R. (1945) A New Test for the Detection

of Weak and Incomplete Rh Agglutinins. *British Journal of Experimental Pathology*, **26**, 255-266.

[55] Hustin, A. (1914) Principe d'une nouvelle méthode de transfusion muqueuse. *Journal de Médecine de Bruxelles*, **12**, 436-439.

[56] Keynes, G. (1943) The History of Blood Transfusion, 1628-1914. *Journal of British Surgery*, **31**, 38-50. https://doi.org/10.1002/bjs.18003112107

[57] Cohn, E.J., Strong, L.E., Hughes, W.L., Mulford, D.J., Ashworth, J.N., Melin, M., *et al.* (1946) Preparation and Properties of Serum and Plasma Proteins. *Journal of the American Chemical Society*, **68**, 459-475. https://doi.org/10.1021/ja01207a034

[58] Fantus, B. (1937) The Therapy of the Cook County Hospital Blood Bank. *JAMA*, **109**, 128-131.

[59] DeGowin, R.L. (1982) A Brief History of Blood Transfusion. In: DeGowin, R.L., Ed., *Blood Transfusion*, Little Brown, 1-18.

[60] Drew, C.R. (1940) Banked Blood: A Study in Blood Preservation. Doctoral Dissertation, Columbia University.

[61] Love, W.C. (1969) Charles Richard Drew (1904-1950): His Contributions to Blood Transfusion. *Journal of the National Medical Association*, **61**, 467-469.

[62] Walter, C.W. and Murphy Jr., W.P., A. (1952) Closed Gravity Technique for the Preservation of Whole Blood in ACD Solution Utilizing Plastic Equipment. *Surgery, Gynecology & Obstetrics*, **94**, 687-692.

[63] Gibson, J.G., Peacock, W.C., Seligman, A.M. and Sack, T. (1946) Circulating Red Cell Volume Measured Simultaneously by the Radioactive Iron and Dye Methods. *Journal of Clinical Investigation*, **25**, 838-847. https://doi.org/10.1172/jci101771

[64] Starling, E.H. (1896) On the Absorption of Fluids from the Connective Tissue Spaces. *The Journal of Physiology*, **19**, 312-326. https://doi.org/10.1113/jphysiol.1896.sp000596

[65] Pappenheimer, J.R. and Soto-Rivera, A. (1948) Effective Osmotic Pressure of the Plasma Proteins and Other Quantities Associated with the Capillary Circulation in the Hindlimbs of Cats and Dogs. *American Journal of Physiology-Legacy Content*, **152**, 471-491. https://doi.org/10.1152/ajplegacy.1948.152.3.471

[66] Duran Jorda, F. (1939) The Barcelona Blood-Transfusion Service. *The Lancet*, **233**, 773-775. https://doi.org/10.1016/s0140-6736(00)60392-6

[67] Eliasson, R. (1952) Blood and Plasma Substitutes. *Acta Physiologica Scandinavica*, **25**, 1-191.

[68] Janeway, C.A., Gibson, S.T., Woodruff, L.M., Heyl, J.T., Bailey, O.T. and Newhouser, L.R. (1944) Chemical, Clinical, and Immunological Studies on the Products of Human Plasma Fractionation. VII. Concentrated Human Serum Albumin 123. *Journal of Clinical Investigation*, **23**, 465-490. https://doi.org/10.1172/jci101514

[69] Jenkins, M.T., Gottlieb, L.S., Choi, S. and Rosenberg, B.J. (1962) Gelatin as a Plasma Substitute: A Clinical Evaluation. *Anesthesia & Analgesia*, **41**, 314-318.

[70] Wilson, C.W. (1948) Fluorescence of Highly Insulating Dielectrics Produced by X- and Γ-radiations. *Nature*, **161**, 520-521. https://doi.org/10.1038/161520b0

[71] Grönwall, A. and Ingelman, B. (1945) Untersuchungen über dextran und sein verhalten bei parenteraler zufuhr. II. *Acta Physiologica Scandinavica*, **9**, 1-27. https://doi.org/10.1111/j.1748-1716.1945.tb03080.x

[72] Hint, H. (1968) The Pharmacology of Dextran and the Physiological Background for the Clinical Use of Rheomacrodex and Macrodex. *Acta Anaesthesiologica Belgica*, **19**,

119-138.

[73] Bergentz, S.E., Gelin, L.E., Rudenstam, J., *et al.* (1961) Dextran in the Treatment of Shock. *The New England Journal of Medicine*, **264**, 1230-1233.

[74] Bergström, K., Hedner, U. and Nilsson, I.M. (1961) Dextran and Blood Coagulation. *Thrombosis, Death & Haemorrhage*, **6**, 15-29.

[75] Thompson, W.L., Fukushima, T., Rutherford, R.B. and Walton, R.P. (1970) Intravascular Persistence, Tissue Storage, and Excretion of Hydroxyethyl Starch. *Surgery, Gynecology & Obstetrics*, **131**, 965-972.

[76] Walton, R.P., Thompson, W.L. and Sedar, A.W. (1973) Efficacy of Hydroxyethyl Starch Compared with Albumin for Postoperative Volume Expansion. *Anesthesiology*, **38**, 461-463.

[77] Lowe, G.D.O., Forbes, C.D., Prentice, C.R.M., *et al.* (1977) Comparison of Effects of Modified Gelatin and Dextran 70 on Coagulation and Fibrinolysis. *British Medical Journal*, **2**, 517-519.

[78] Lundsgaard-Hansen, P. (1980) Component Therapy of Surgical Hemorrhage: Red Cell Concentrates, Colloids and Crystalloids. *Bibliotheca Haematologica*, **46**, 147-169. https://doi.org/10.1159/000430555

[79] Vogt, N.H., Bothner, U., Lerch, G., Lindner, K.H. and Georgieff, M. (1996) Large-dose Administration of 6% Hydroxyethyl Starch 200/0.5 for Total Hip Arthroplasty. *Anesthesia & Analgesia*, **83**, 262-268. https://doi.org/10.1213/00000539-199608000-00011

[80] Perner, A., Haase, N., Guttormsen, A.B., Tenhunen, J., Klemenzson, G., Åneman, A., *et al.* (2012) Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in Severe Sepsis. *New England Journal of Medicine*, **367**, 124-134. https://doi.org/10.1056/nejmoa1204242

[81] Brunkhorst, F.M., Engel, C., Bloos, F., Meier-Hellmann, A., Ragaller, M., Weiler, N., *et al.* (2008) Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis. *New England Journal of Medicine*, **358**, 125-139. https://doi.org/10.1056/nejmoa070716

[82] Myburgh, J.A., Finfer, S., Bellomo, R., Billot, L., Cass, A., Gattas, D., *et al.* (2012) Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care. *New England Journal of Medicine*, **367**, 1901-1911. https://doi.org/10.1056/nejmoa1209759

[83] Zarychanski, R., Abou-Setta, A.M., Turgeon, A.F., Houston, B.L., McIntyre, L., Marshall, J.C., *et al.* (2013) Association of Hydroxyethyl Starch Administration with Mortality and Acute Kidney Injury in Critically Ill Patients Requiring Volume Resuscitation: A Systematic Review and Meta-Analysis. *JAMA*, **309**, 678-688. https://doi.org/10.1001/jama.2013.430

[84] European Medicines Agency (2013) Hydroxyethyl-Starch Solutions (HES) No Longer to Be Used in Patients with Sepsis or Burn Injuries or in Critically Ill Patients.

[85] Pollitzer, R. (1959) Cholera. World Health Organization.

[86] Barua, D. and Greenough, W.B. III. (1992) Cholera. Plenum Medical Book Company.

[87] Howard-Jones, N. (1972) Cholera Therapy in the Nineteenth Century. *Journal of the History of Medicine and Allied Sciences*, **27**, 373-395. https://doi.org/10.1093/jhmas/xxvii.4.373

[88] Greenough, W.B., Rosenberg, I.S., Gordon, R.S., Davies, B.I. and Benenson, A.S. (1964) Tetracycline in the Treatment of Cholera. *The Lancet*, **283**, 355-357. https://doi.org/10.1016/s0140-6736(64)92099-9

[89] O'Shaughnessy, W.B. (1831) Proposal of A New Method of Treating the Blue Epi-

demic Cholera by the Injection of Highly-Oxygenised Salts into the Venous System. *The Lancet*, **17**, 366-371. https://doi.org/10.1016/s0140-6736(02)94163-2

[90] O'Shaughnessy, W.B. (1831) Experiments on the Blood in Cholera. *The Lancet*, **17**, Article 490. https://doi.org/10.1016/s0140-6736(02)94389-8

[91] Latta, T. (1832) Malignant Cholera. Documents Communicated by the Central Board of Health, London, Relative to the Treatment of Cholera by the Copious Injection of Aqueous and Saline Fluids into the Veins. *The Lancet*, **2**, 274-277.

[92] Latta, T. (1832) Saline Venous Injection in Cases of Malignant Cholera. *The Lancet*, **2**, 208-209.

[93] MacKintosh, J. (1832) Treatment of Cholera by Injection. *The Lancet*, **1**, 368-370.

[94] MacKintosh, J. (1832) Further Observations on Injection in Cholera. *Edinburgh Medical and Surgical Journal*, **38**, 194-203.

[95] Klencke, H. (1832) Die cholera-epidemie des jahres 1832. Leipzig.

[96] Sédillot, C.E. (1836) Traité de médecine opératoire. Béchet.

[97] Cantani, A. (1865) Sull'iniezione sottocutanea. Naples.

[98] Awad, S., Allison, S.P. and Lobo, D.N. (2008) The History of 0.9% Saline. *Clinical Nutrition*, **27**, 179-188. https://doi.org/10.1016/j.clnu.2008.01.008

[99] Baskett, T.F. (2002) William O'shaughnessy, Thomas Latta and the Origins of Intravenous Saline. *Resuscitation*, **55**, 231-234. https://doi.org/10.1016/s0300-9572(02)00294-0

[100] Nalin, D.R. and Cash, R.A. (1970) Oral or Nasogastric Maintenance Therapy in Pediatric Cholera Patients. *The Journal of Pediatrics*, **77**, 307-311.

[101] Mahalanabis, D., Choudhuri, A.B., Bagchi, N.G., *et al.* (1973) Oral Fluid Therapy of Cholera among Bangladesh Refugees. *Johns Hopkins Medical Journal*, **132**, 197-205.

[102] Phillips, R.A. (1964) Water and Electrolyte Losses in Cholera. *Federation Proceedings*, **23**, 705-712.

[103] Hirschhorn, N., Kinzie, J.L., Sachar, D.B., Northrup, R.S., Taylor, J.O., Ahmad, S.Z., *et al.* (1968) Decrease in Net Stool Output in Cholera during Intestinal Perfusion with Glucose-Containing Solutions. *New England Journal of Medicine*, **279**, 176-181. https://doi.org/10.1056/nejm196807252790402

[104] World Health Organization (1980) A Manual for the Treatment of Diarrhoea. WHO.

[105] World Health Organization (2006) Oral Rehydration Salts: Production of the New ORS. WHO.

[106] Ringer, S. (1883) A Further Contribution Regarding the Influence of the Different Constituents of the Blood on the Contraction of the Heart. *The Journal of Physiology*, **4**, 29-42. https://doi.org/10.1113/jphysiol.1883.sp000120

[107] Miller, D.J. (2004) Sydney Ringer; Physiological Saline, Calcium and the Contraction of the Heart. *The Journal of Physiology*, **555**, 585-587. https://doi.org/10.1113/jphysiol.2004.060731

[108] Simmons, D.H. (2002) A Primer on Ringer's Solution. *Physiologist*, **45**, 305-306.

[109] Ringer, S. (1882) Regarding the Action of Hydrate of Soda, Hydrate of Ammonia, and Hydrate of Potash on the Ventricle of the Frog's Heart. *The Journal of Physiology*, **3**, 195-202. https://doi.org/10.1113/jphysiol.1882.sp000095

[110] Ringer, S. and Buxton, D.W. (1887) Concerning the Action of Calcium, Potassium, and Sodium Salts Upon the Eel's Heart and Upon the Skeletal Muscles of the Frog. *The Journal of Physiology*, **8**, 15-19. https://doi.org/10.1113/jphysiol.1887.sp000239

[111] Fye, W.B. (2003) Sydney Ringer, Calcium, and Cardiac Function. *Circulation*, **107**, 2280-2282.

[112] Gaskell, W.H. (1882) On the Rhythm of the Heart of the Frog, and on the Nature of the Action of the Vagus Nerve. *Philosophical Transactions of the Royal Society of London, Series B: Biological Sciences*, **173**, 993-1033.

[113] Coraboeuf, E. (1991) Bowditch and the Staircase Phenomenon, 1871. *Trends in Cardiovascular Medicine*, **1**, 227-231.

[114] Locke, F.S. (1901) Die Wirkung der metalle des blutplasmas und verschiedener zucker auf das isolirte säugethierherz. *Zentralblatt für Physiologie*, **14**, 670-672.

[115] Hearse, D.J., Stewart, D.A. and Chain, E.B. (1974) Recovery from Cardiac Bypass and Elective Cardiac Arrest: The Metabolic Consequences of Various Cardioplegic Procedures in the Isolated Rat Heart. *Circulation Research*, **35**, 448-457. https://doi.org/10.1161/01.res.35.3.448

[116] Tyrode, M.V. (1910) The Mode of Action of Some Purgative Salts. *Archives Internationales de Pharmacodynamie et de Thérapie*, **20**, 205-223.

[117] Krebs, H.A. and Henseleit, K. (1932) Untersuchungen uber die Harnstoffbildung im Tierkörper. *Biological Chemistry*, **210**, 33-66. https://doi.org/10.1515/bchm2.1932.210.1-2.33

[118] Krebs, H.A. (1970) The History of the Tricarboxylic Acid Cycle. *Perspectives in Biology and Medicine*, **14**, 154-172. https://doi.org/10.1353/pbm.1970.0001

[119] Hartmann, A.F. and Senn, M.J.E. (1932) Studies in the Metabolism of Sodium R-Lactate. I. Response of Normal Human Subjects to the Intravenous Injection of Sodium R-Lactate. *Journal of Clinical Investigation*, **11**, 327-335. https://doi.org/10.1172/jci100414

[120] Hartmann, A.F. and Senn, M.J.E. (1932) Studies in the Metabolism of Sodium R-Lactate. II. Response of Human Subjects with Acidosis to the Intravenous Injection of Sodium R-Lactate. *Journal of Clinical Investigation*, **11**, 337-344. https://doi.org/10.1172/jci100415

[121] Morgan, T.J., Venkatesh, B. and Hall, J. (2004) Crystalloid Strong Ion Difference Determines Metabolic Acid-Base Change during Acute Normovolaemic Haemodilution. *Intensive Care Medicine*, **30**, 1432-1437. https://doi.org/10.1007/s00134-004-2176-x

[122] Cone Jr., T.E. (1985) History of the Care and Feeding of the Premature Infant. Little, Brown.

[123] Pearson, H.A. (2002) History of Pediatric Hematology Oncology. *Pediatric Research*, **52**, 979-992. https://doi.org/10.1203/00006450-200212000-00026

[124] Davison, W.C. (1955) John Howland (1873-1926). *The Journal of Pediatrics*, **46**, 473-486.

[125] Howland, J. and Marriott, W.M. (1916) Acidosis Occurring with Diarrhea. *Archives of Pediatrics and Adolescent Medicine*, **11**, 309-325. https://doi.org/10.1001/archpedi.1916.04110110002001

[126] Gamble, J.L. (1950) William McKim Marriott (1885-1936). *The Journal of Pediatrics*, **36**, 239-241.

[127] Blattner, R.J. (1959) Favism. *The Journal of Pediatrics*, **55**, 531-533. https://doi.org/10.1016/s0022-3476(59)80292-4

[128] Gamble, J.L. (1942) Chemical Anatomy, Physiology and Pathology of Extracellular Fluid: A Lecture Syllabus. Harvard University Press.

[129] Finberg, L. (1982) Gamble and Ross on Teaching. *Pediatrics*, **69**, 122-124.

[130] Marriott, W.M. and Hartmann, A.F. (1933) Croonian Lectures on the Newer Aspects of the Pathology of Nutrition in Infancy. *The Lancet*, **221**, 1347-1352.

[131] Gamble, J.L., Ross, G.S. and Tisdall, F.F. (1923) The Metabolism of Fixed Base During Fasting. *Journal of Biological Chemistry*, **57**, 633-695. https://doi.org/10.1016/s0021-9258(18)85480-1

[132] Winters, R.W. (1965) Terminology of Acid-Base Disorders. *Annals of Internal Medicine*, **63**, 873-884. https://doi.org/10.7326/0003-4819-63-5-873

[133] Talbot, N.B., Sobel, E.H., McArthur, J.W. and Crawford, J.D. (1952) Functional Endocrinology from Birth through Adolescence. Harvard University Press.

[134] Crawford, J.D., Terry, M.E. and Rourke, G.M. (1950) Simplification of Drug Dosage Calculation by Application of the Surface Area Principle. *Pediatrics*, **5**, 783-790. https://doi.org/10.1542/peds.5.5.783

[135] Butler, A.M., Talbot, N.B., Burnett, C.H., *et al.* (1947) Metabolic Studies in Diabetic Coma. *Transactions of the Association of American Physicians*, **60**, 102-109.

[136] Levine, S.Z., Wilson, J.R. and Gottschall, G. (1928) The Osmotic Pressure of Serum and Cerebro-Spinal Fluid. *American Journal of Diseases of Children*, **35**, 195-200.

[137] Holliday, M.A. and Segar, W.E. (1957) The Maintenance Need for Water in Parenteral Fluid Therapy. *Pediatrics*, **19**, 823-832. https://doi.org/10.1542/peds.19.5.823

[138] Holliday, M.A., Ray, P.E. and Friedman, A.L. (2007) Fluid Therapy for Children: Facts, Fashions and Questions. *Archives of Disease in Childhood*, **92**, 546-550. https://doi.org/10.1136/adc.2006.106377

[139] Segar, W.E. and Moore, W.W. (1968) The Regulation of Antidiuretic Hormone Release in Man. *Journal of Clinical Investigation*, **47**, 2143-2151. https://doi.org/10.1172/jci105900

[140] Moritz, M.L. and Ayus, J.C. (2003) Prevention of Hospital-Acquired Hyponatremia: A Case for Using Isotonic Saline. *Pediatrics*, **111**, 227-230. https://doi.org/10.1542/peds.111.2.227

[141] Halberthal, M. (2001) Lesson of the Week: Acute Hyponatraemia in Children Admitted to Hospital: Retrospective Analysis of Factors Contributing to Its Development and Resolution. *BMJ*, **322**, 780-782. https://doi.org/10.1136/bmj.322.7289.780

[142] Neville, K.A. (2006) Isotonic Is Better than Hypotonic Saline for Intravenous Rehydration of Children with Gastroenteritis: A Prospective Randomised Study. *Archives of Disease in Childhood*, **91**, 226-232. https://doi.org/10.1136/adc.2005.084103

[143] Darrow, D.C., Pratt, E.L., Flett, J., Gamble, A.H. and Wiese, H.F. (1949) Disturbances of Water and Electrolytes in Infantile Diarrhea. *Pediatrics*, **3**, 129-156. https://doi.org/10.1542/peds.3.2.129

[144] Darrow, D.C. (1946) The Retention of Electrolyte during Recovery Fromsevere Dehydration Due to Diarrhea. *The Journal of Pediatrics*, **28**, 515-540. https://doi.org/10.1016/s0022-3476(46)80213-0

[145] Shime, N., Hosokawa, T., Aoki, Y., *et al.* (2010) Intravenous Fluid Therapy for Pediatric Patients: Current Issues. *Journal of Anesthesiology*, **24**, 730-740.

[146] Wang, J., Xu, E. and Xiao, Y. (2014) Isotonic versus Hypotonic Maintenance IV Fluids in Hospitalized Children: A Meta-Analysis. *Pediatrics*, **133**, 105-113. https://doi.org/10.1542/peds.2013-2041

[147] National Institute for Health and Care Excellence (2015) Intravenous Fluid Therapy in Children and Young People in Hospital (NG29). NICE.

[148] Feld, L.G., Neuspiel, D.R., Foster, B.A., Leu, M.G., Garber, M.D., Austin, K., *et al.* (2018) Clinical Practice Guideline: Maintenance Intravenous Fluids in Children. *Pediatrics*, **142**, e20183083. https://doi.org/10.1542/peds.2018-3083

[149] Maitland, K., Kiguli, S., Opoka, R.O., Engoru, C., Olupot-Olupot, P., Akech, S.O., *et al.* (2011) Mortality after Fluid Bolus in African Children with Severe Infection. *New England Journal of Medicine*, **364**, 2483-2495. https://doi.org/10.1056/nejmoa1101549

[150] Maitland, K., George, E.C., Evans, J.A., Kiguli, S., Olupot-Olupot, P., Akech, S.O., *et al.* (2013) Exploring Mechanisms of Excess Mortality with Early Fluid Resuscitation: Insightsfrom the FEAST Trial. *BMC Medicine*, **11**, Article No. 68. https://doi.org/10.1186/1741-7015-11-68

[151] Miller, T.E., Roche, A.M. and Mythen, M. (2015) Fluid Management and Goal-Directed Therapy as an Adjunct to Enhanced Recovery after Surgery (ERAS). *Canadian Journal of Anesthesia*, **62**, 158-168. https://doi.org/10.1007/s12630-014-0266-y

[152] Miller, T.E. and Myles, P.S. (2019) Perioperative Fluid Therapy for Major Surgery. *Anesthesiology*, **130**, 825-832. https://doi.org/10.1097/aln.0000000000002603

[153] Kehlet, H. (1997) Multimodal Approach to Control Postoperative Pathophysiology and Rehabilitation. *British Journal of Anaesthesia*, **78**, 606-617. https://doi.org/10.1093/bja/78.5.606

[154] Fearon, K.C.H., Ljungqvist, O., Von Meyenfeldt, M., Revhaug, A., Dejong, C.H.C., Lassen, K., *et al.* (2005) Enhanced Recovery after Surgery: A Consensus Review of Clinical Care for Patients Undergoing Colonic Resection. *Clinical Nutrition*, **24**, 466-477. https://doi.org/10.1016/j.clnu.2005.02.002

[155] Gustafsson, U.O., Scott, M.J., Hubner, M., Nygren, J., Demartines, N., Francis, N., *et al.* (2019) Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery after Surgery (ERAS®) Society Recommendations: 2018. *World Journal of Surgery*, **43**, 659-695. https://doi.org/10.1007/s00268-018-4844-y

[156] Engelman, D.T., Ben Ali, W., Williams, J.B., Perrault, L.P., Reddy, V.S., Arora, R.C., *et al.* (2019) Guidelines for Perioperative Care in Cardiac Surgery: Enhanced Recovery After Surgery Society Recommendations. *JAMA Surgery*, **154**, 755-766. https://doi.org/10.1001/jamasurg.2019.1153

[157] Ljungqvist, O., Scott, M. and Fearon, K.C. (2017) Enhanced Recovery after Surgery: A Review. *JAMA Surgery*, **152**, 292-298. https://doi.org/10.1001/jamasurg.2016.4952

[158] Smith, M.D., McCall, J., Plank, L., Herbison, G.P., Soop, M. and Nygren, J. (2014) Preoperative Carbohydrate Treatment for Enhancing Recovery after Elective Surgery. *Cochrane Database of Systematic Reviews*, No. 8, CD009161. https://doi.org/10.1002/14651858.cd009161.pub2

[159] Nicholson, A., Lowe, M.C., Parker, J., Lewis, S.R., Alderson, P. and Smith, A.F. (2014) Systematic Review and Meta-Analysis of Enhanced Recovery Programmes in Surgical Patients. *British Journal of Surgery*, **101**, 172-188. https://doi.org/10.1002/bjs.9394

[160] Wainwright, T.W., Gill, M., McDonald, D.A., Middleton, R.G., Reed, M., Sahota, O., *et al.* (2019) Consensus Statement for Perioperative Care in Total Hip Replacement and Total Knee Replacement Surgery: Enhanced Recovery after Surgery (ERAS®) Society Recommendations. *Acta Orthopaedica*, **91**, 3-19. https://doi.org/10.1080/17453674.2019.1683790

[161] Pearse, R.M., Harrison, D.A., MacDonald, N., Gillies, M.A., Blunt, M., Ackland, G., *et al.* (2014) Effect of a Perioperative, Cardiac Output-Guided Hemodynamic Therapy Algorithm on Outcomes Following Major Gastrointestinal Surgery. *JAMA*, **311**,

2181-2190. https://doi.org/10.1001/jama.2014.5305

[162] Marik, P.E., Cavallazzi, R., Vasu, T. and Hirani, A. (2009) Dynamic Changes in Arterial Waveform Derived Variables and Fluid Responsiveness in Mechanically Ventilated Patients: A Systematic Review of the Literature. *Critical Care Medicine*, **37**, 2642-2647. https://doi.org/10.1097/ccm.0b013e3181a590da

[163] Saugel, B., Cecconi, M., Wagner, J.Y. and Reuter, D.A. (2015) Noninvasive Continuous Cardiac Output Monitoring in Perioperative and Intensive Care Medicine. *British Journal of Anaesthesia*, **114**, 562-575. https://doi.org/10.1093/bja/aeu447

[164] Grocott, M.P.W., Dushianthan, A., Hamilton, M.A., Mythen, M.G., Harrison, D. and Rowan, K. (2013) Perioperative Increase in Global Blood Flow to Explicit Defined Goals and Outcomes after Surgery: A Cochrane Systematic Review. *British Journal of Anaesthesia*, **111**, 535-548. https://doi.org/10.1093/bja/aet155

[165] Rollins, K.E. and Lobo, D.N. (2016) Intraoperative Goal-Directed Fluid Therapy in Elective Major Abdominal Surgery: A Meta-Analysis of Randomized Controlled Trials. *Annals of Surgery*, **263**, 465-476. https://doi.org/10.1097/sla.0000000000001366

[166] Challand, C., Struthers, R., Sneyd, J.R., Erasmus, P.D., Mellor, N., Hosie, K.B., *et al.* (2012) Randomized Controlled Trial of Intraoperative Goal-Directed Fluid Therapy in Aerobically Fit and Unfit Patients Having Major Colorectal Surgery. *British Journal of Anaesthesia*, **108**, 53-62. https://doi.org/10.1093/bja/aer273

[167] Finfer, S., Bellomo, R., Boyce, N., *et al.* (2004) A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit. *The New England Journal of Medicine*, **350**, 2247-2256.

[168] Annane, D. (2013) Effects of Fluid Resuscitation with Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting with Hypovolemic Shock: The Cristal Randomized Trial. *JAMA*, **310**, 1809-1817. https://doi.org/10.1001/jama.2013.280502

[169] Semler, M.W., Self, W.H., Wanderer, J.P., Ehrenfeld, J.M., Wang, L., Byrne, D.W., *et al.* (2018) Balanced Crystalloids versus Saline in Critically Ill Adults. *New England Journal of Medicine*, **378**, 829-839. https://doi.org/10.1056/nejmoa1711584

[170] Self, W.H., Semler, M.W., Wanderer, J.P., Wang, L., Byrne, D.W., Collins, S.P., *et al.* (2018) Balanced Crystalloids versus Saline in Noncritically Ill Adults. *New England Journal of Medicine*, **378**, 819-828. https://doi.org/10.1056/nejmoa1711586

[171] Zampieri, F.G., Machado, F.R., Biondi, R.S., Freitas, F.G.R., Veiga, V.C., Figueiredo, R.C., *et al.* (2021) Effect of Intravenous Fluid Treatment with a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients: The BaSICS Randomized Clinical Trial. *JAMA*, **326**, 818-829. https://doi.org/10.1001/jama.2021.11684

[172] Myburgh, J.A. and Mythen, M.G. (2013) Resuscitation Fluids. *New England Journal of Medicine*, **369**, 1243-1251. https://doi.org/10.1056/nejmra1208627

[173] Stewart, P.A. (1983) Modern Quantitative Acid-Base Chemistry. *Canadian Journal of Physiology and Pharmacology*, **61**, 1444-1461. https://doi.org/10.1139/y83-207

[174] Morgan, T.J. (2004) The Meaning of Acid-Base Abnormalities in the Intensive Care Unit: Part III—Effects of Fluid Administration. *Critical Care*, **9**, 204-211. https://doi.org/10.1186/cc2946

[175] Malbrain, M.L.N.G., Marik, P.E., Witters, I., Cordemans, C., Kirkpatrick, A.W., Roberts, D.J., *et al.* (2014) Fluid Overload, De-Resuscitation, and Outcomes in Critically Ill or Injured Patients: A Systematic Review with Suggestions for Clinical Practice. *Anestezjologia Intensywna Terapia*, **46**, 361-380. https://doi.org/10.5603/ait.2014.0060

[176] Komorowski, M., Celi, L.A., Badawi, O., Gordon, A.C. and Faisal, A.A. (2018) The Artificial Intelligence Clinician Learns Optimal Treatment Strategies for Sepsis in Intensive Care. *Nature Medicine*, **24**, 1716-1720. https://doi.org/10.1038/s41591-018-0213-5

[177] Bose, E. and Magder, S. (2022) Artificial Intelligence and Machine Learning in Intensive Care Medicine. *Intensive Care Medicine*, **48**, 589-592.

[178] Goodnough, L.T., Shander, A. and Riou, B. (2012) Patient Blood Management. *Anesthesiology*, **116**, 1367-1376. https://doi.org/10.1097/aln.0b013e318254d1a3

[179] Shander, A., Hofmann, A., Ozawa, S., Theusinger, O.M., Gombotz, H. and Spahn, D.R. (2010) Activity-Based Costs of Blood Transfusions in Surgical Patients at Four Hospitals. *Transfusion*, **50**, 753-765. https://doi.org/10.1111/j.1537-2995.2009.02518.x

[180] Leahy, M.F., Hofmann, A., Towler, S., Trentino, K.M., Burrows, S.A., Swain, S.G., *et al.* (2017) Improved Outcomes and Reduced Costs Associated with a Health-System-Wide Patient Blood Management Program: A Retrospective Observational Study in Four Major Adult Tertiary-Care Hospitals. *Transfusion*, **57**, 1347-1358. https://doi.org/10.1111/trf.14006

[181] World Health Assembly (2010) Availability, Safety and Quality of Blood Products: Report by the Secretariat. 63rd World Health Assembly, WHO.

[182] Spahn, D.R., Theusinger, O.M. and Hofmann, A. (2012) Patient Blood Management Is a Win-Win: A Wake-Up Call. *British Journal of Anaesthesia*, **108**, 889-892. https://doi.org/10.1093/bja/aes166

[183] Meybohm, P., Froessler, B., Goodnough, L.T., Klein, A.A., Muñoz, M., Murphy, M.F., *et al.* (2017) "Simplified International Recommendations for the Implementation of Patient Blood Management" (SIR4PBM). *Perioperative Medicine*, **6**, Article No. 5. https://doi.org/10.1186/s13741-017-0061-8

[184] Musallam, K.M., Tamim, H.M., Richards, T., Spahn, D.R., Rosendaal, F.R., Habbal, A., *et al.* (2011) Preoperative Anaemia and Postoperative Outcomes in Non-Cardiac Surgery: A Retrospective Cohort Study. *The Lancet*, **378**, 1396-1407. https://doi.org/10.1016/s0140-6736(11)61381-0

[185] Baron, D.M., Hochrieser, H., Posch, M., Metnitz, B., Rhodes, A., Moreno, R.P., *et al.* (2014) Preoperative Anaemia Is Associated with Poor Clinical Outcome in Non-Cardiac Surgery Patients. *British Journal of Anaesthesia*, **113**, 416-423. https://doi.org/10.1093/bja/aeu098

[186] Muñoz, M., Acheson, A.G., Auerbach, M., Besser, M., Habler, O., Kehlet, H., *et al.* (2017) International Consensus Statement on the Peri-Operative Management of Anaemia and Iron Deficiency. *Anaesthesia*, **72**, 233-247. https://doi.org/10.1111/anae.13773

[187] Ganz, T. and Nemeth, E. (2012) Hepcidin and Iron Homeostasis. *Biochimica et Biophysica Acta* (*BBA*)-*Molecular Cell Research*, **1823**, 1434-1443. https://doi.org/10.1016/j.bbamcr.2012.01.014

[188] Green, R., Allen, L.H., Bjørke-Monsen, A., Brito, A., Guéant, J., Miller, J.W., *et al.* (2017) Vitamin B12 Deficiency. *Nature Reviews Disease Primers*, **3**, Article No. 17040. https://doi.org/10.1038/nrdp.2017.40

[189] Froessler, B., Palm, P., Weber, I., Hodyl, N.A., Singh, R. and Murphy, E.M. (2016) The Important Role for Intravenous Iron in Perioperative Patient Blood Management in Major Abdominal Surgery: A Randomized Controlled Trial. *Annals of Surgery*, **264**, 41-46. https://doi.org/10.1097/sla.0000000000001646

[190] Richards, T., Baikady, R.R., Clevenger, B., Butcher, A., Abeysiri, S., Chau, M., *et al.* (2020) Preoperative Intravenous Iron to Treat Anaemia before Major Abdominal Surgery (PREVENTT): A Randomised, Double-Blind, Controlled Trial. *The Lancet*, **396**, 1353-1361. https://doi.org/10.1016/s0140-6736(20)31539-7

[191] Elhenawy, A.M., Meyer, S.R., Bagshaw, S.M., *et al.* (2021) Role of Preoperative Intravenous Iron Therapy to Correct Anemia before Major Surgery: A Systematic Review and Meta-Analysis. *Systematic Reviews*, **10**, Article No. 36. https://doi.org/10.1186/s13643-021-01579-8

[192] Spahn, D.R., Schoenrath, F., Spahn, G.H., Seifert, B., Stein, P., Theusinger, O.M., *et al.* (2019) Effect of Ultra-Short-Term Treatment of Patients with Iron Deficiency or Anaemia Undergoing Cardiac Surgery: A Prospective Randomised Trial. *The Lancet*, **393**, 2201-2212. https://doi.org/10.1016/s0140-6736(18)32555-8

[193] Alsaleh, K., Alotaibi, G.S., Almodaimegh, H.S., Aleem, A.A. and Kouroukis, C.T. (2013) The Use of Preoperative Erythropoiesis-Stimulating Agents (ESAS) in Patients Who Underwent Knee or Hip Arthroplasty: A Meta-Analysis of Randomized Clinical trials. *The Journal of Arthroplasty*, **28**, 1463-1472. https://doi.org/10.1016/j.arth.2013.01.024

[194] Clevenger, B., Gurusamy, K., Klein, A.A., Murphy, G.J., Anker, S.D. and Richards, T. (2016) Systematic Review and Meta-Analysis of Iron Therapy in Anaemic Adults without Chronic Kidney Disease: Updated and Abridged Cochrane Review. *European Journal of Heart Failure*, **18**, 774-785. https://doi.org/10.1002/ejhf.514

[195] Ker, K., Edwards, P., Perel, P., Shakur, H. and Roberts, I. (2012) Effect of Tranexamic Acid on Surgical Bleeding: Systematic Review and Cumulative Meta-Analysis. *BMJ*, **344**, e3054-e3054. https://doi.org/10.1136/bmj.e3054

[196] Whiting, P., Al, M., Westwood, M., Ramos, I.C., Ryder, S., Armstrong, N., *et al.* (2015) Viscoelastic Point-of-Care Testing to Assist with the Diagnosis, Management and Monitoring of Haemostasis: A Systematic Review and Cost-Effectiveness Analysis. *Health Technology Assessment*, **19**, 1-228. https://doi.org/10.3310/hta19580

[197] Carless, P.A., Henry, D.A., Moxey, A.J., *et al.* (2010) Cell Salvage for Minimising Perioperative Allogeneic Blood Transfusion. *Cochrane Database of Systematic Reviews*, No. 4, CD001888.

[198] Hébert, P.C., Wells, G., Blajchman, M.A., Marshall, J., Martin, C., Pagliarello, G., *et al.* (1999) A Multicenter, Randomized, Controlled Clinical Trial of Transfusion Requirements in Critical Care. *New England Journal of Medicine*, **340**, 409-417. https://doi.org/10.1056/nejm199902113400601

[199] Carson, J.L., Terrin, M.L., Noveck, H., Sanders, D.W., Chaitman, B.R., Rhoads, G.G., *et al.* (2011) Liberal or Restrictive Transfusion in High-Risk Patients after Hip Surgery. *New England Journal of Medicine*, **365**, 2453-2462. https://doi.org/10.1056/nejmoa1012452

[200] Meybohm, P., Richards, T., Isbister, J., Hofmann, A., Shander, A., Goodnough, L.T., *et al.* (2017) Patient Blood Management Bundles to Facilitate Implementation. *Transfusion Medicine Reviews*, **31**, 62-71. https://doi.org/10.1016/j.tmrv.2016.05.012

[201] Meybohm, P., Herrmann, E., Steinbicker, A.U., Wittmann, M., Gruenewald, M., Fischer, D., *et al.* (2016) Patient Blood Management Is Associated with a Substantial Reduction of Red Blood Cell Utilization and Safe for Patient's Outcome: A Prospective, Multicenter Cohort Study with a Noninferiority Design. *Annals of Surgery*, **264**, 203-211. https://doi.org/10.1097/sla.0000000000001747

[202] Froessler, B., Rueger, A. and Connolly, M. (2018) Assessing the Costs and Benefits of Perioperative Iron Deficiency Anemia Management with Ferric Carboxymaltose in

Germany. *Risk Management and Healthcare Policy*, **11**, 77-82. https://doi.org/10.2147/rmhp.s157379

[203] Klein, A.A., Chau, M., Iohom, G., *et al.* (2020) Patient Blood Management in Europe: Surveys on Anaemia Prevalence, Iron Deficiency Diagnosis, and the Use of Intravenous Iron. *European Journal of Anaesthesiology*, **37**, 1015-1025.

[204] Shander, A. and Goodnough, L.T. (2006) Objectives and Limitations of Bloodless Medical Care. *Current Opinion in Hematology*, **13**, 462-470. https://doi.org/10.1097/01.moh.0000245692.32085.bd

[205] Vamvakas, E.C. and Blajchman, M.A. (2009) Transfusion-Related Mortality: The Ongoing Risks of Allogeneic Blood Transfusion and the Available Strategies for Their Prevention. *Blood*, **113**, 3406-3417. https://doi.org/10.1182/blood-2008-10-167643

[206] Clark, L.C. and Gollan, F. (1966) Survival of Mammals Breathing Organic Liquids Equilibrated with Oxygen at Atmospheric Pressure. *Science*, **152**, 1755-1756. https://doi.org/10.1126/science.152.3730.1755

[207] Spahn, D.R., van Brempt, R., Theilmeier, G., Reibold, J., Welte, M., Heinzerling, H., *et al.* (1999) Perflubron Emulsion Delays Blood Transfusions in Orthopedic Surgery. *Anesthesiology*, **91**, 1195-1195. https://doi.org/10.1097/00000542-199911000-00009

[208] Keipert, P.E., Otto, S., Flaim, S.F., Weers, J.G., Schutt, E.A., Pelura, T.J., *et al.* (1994) Influence of Perflubron Emulsion Particle Size on Blood Half-Life and Febrile Response in Rats. *Artificial Cells, Blood Substitutes, and Biotechnology*, **22**, 1169-1174. https://doi.org/10.3109/10731199409138812

[209] Buehler, P.W. and Alayash, A.I. (2008) All Hemoglobin-Based Oxygen Carriers Are Not Created Equally. *Biochimica et Biophysica Acta* (*BBA*)-*Proteins and Proteomics*, **1784**, 1378-1381. https://doi.org/10.1016/j.bbapap.2007.12.009

[210] Natanson, C., Kern, S.J., Lurie, P., Banks, S.M. and Wolfe, S.M. (2008) Cell-Free Hemoglobin-Based Blood Substitutes and Risk of Myocardial Infarction and Death. *JAMA*, **299**, 2304-2312. https://doi.org/10.1001/jama.299.19.jrv80007

[211] Riess, J.G. (2006) Perfluorocarbon-Based Oxygen Delivery. *Artificial Cells, Blood Substitutes, and Biotechnology*, **34**, 567-580. https://doi.org/10.1080/10731190600973824

[212] Riess, J.G. (2005) Understanding the Fundamentals of Perfluorocarbons and Perfluorocarbon Emulsions Relevant to *in Vivo* Oxygen Delivery. *Artificial Cells, Blood Substitutes, and Biotechnology*, **33**, 47-63. https://doi.org/10.1081/bio-200046659

[213] Alayash, A.I. (2019) Mechanisms of Toxicity and Modulation of Hemoglobin-Based Oxygen Carriers. *Shock*, **52**, 41-49. https://doi.org/10.1097/shk.0000000000001044

[214] Sakai, H. (2017) Overview of Potential Clinical Applications of Hemoglobin Vesicles (HBV) as Artificial Red Cells, Evidenced by Preclinical Studies of the Academic Research Consortium. *Journal of Functional Biomaterials*, **8**, Article 10. https://doi.org/10.3390/jfb8010010

[215] Kure, T. and Sakai, H. (2021) Preparation of Artificial Red Blood Cells (Hemoglobin Vesicles) Using the Rotation-Revolution Mixer for High Encapsulation Efficiency. *ACS Biomaterials Science & Engineering*, **7**, 2835-2844. https://doi.org/10.1021/acsbiomaterials.1c00424

[216] Sakai, H., Sato, A., Masuda, K., Takeoka, S. and Tsuchida, E. (2008) Encapsulation of Concentrated Hemoglobin Solution in Phospholipid Vesicles Retards the Reaction with NO, but Not CO, by Intracellular Diffusion Barrier. *Journal of Biological Chemistry*, **283**, 1508-1517. https://doi.org/10.1074/jbc.m707660200

[217] Sakai, H., Masada, Y., Horinouchi, H., Ikeda, E., Sou, K., Takeoka, S., *et al.* (2004)

Physiological Capacity of the Reticuloendothelial System for the Degradation of Hemoglobin Vesicles (Artificial Oxygen Carriers) after Massive Intravenous Doses by Daily Repeated Infusions for 14 Days. *The Journal of Pharmacology and Experimental Therapeutics*, **311**, 874-884. https://doi.org/10.1124/jpet.104.073049

[218] Azuma, H., Amano, T., Kamiyama, N., Takehara, N., Jingu, M., Takagi, H., *et al.* (2022) First-in-Human Phase 1 Trial of Hemoglobin Vesicles as Artificial Red Blood Cells Developed for Use as a Transfusion Alternative. *Blood Advances*, **6**, 5711-5715. https://doi.org/10.1182/bloodadvances.2022007977

[219] Jahr, J.S., Guinn, N.R., Lowery, D.R., Shore-Lesserson, L. and Shander, A. (2021) Blood Substitutes and Oxygen Therapeutics: A Review. *Anesthesia & Analgesia*, **132**, 119-129. https://doi.org/10.1213/ane.0000000000003957

[220] Yuki, Y., Hagisawa, K., Kinoshita, M., Ishibashi, H., Kaneko, K., Ishida, O., *et al.* (2021) Efficacy of Resuscitative Infusion with Hemoglobin Vesicles in Rabbits with Massive Obstetric Hemorrhage. *American Journal of Obstetrics and Gynecology*, **224**, 398.e1-398.e11. https://doi.org/10.1016/j.ajog.2020.09.010

[221] Mohanto, N., Panda, A.K., Pramanik, N., *et al.* (2022) Current Perspectives of Artificial Oxygen Carriers as Red Blood Cell Substitutes: A Review of Old to Cutting-Edge Technologies. *Molecular Pharmaceutics*, **19**, 2121-2142.