Damage Control Resuscitation

Identification and Treatment of Life-Threatening Hemorrhage

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Editor
Philip C. Spinella
School of Medicine
Washington University in St. Louis
St. Louis, MO
USA

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This textbook is dedicated to the many health-care providers and scientists who work tirelessly to improve outcomes for patients with traumatic injuries.

Preface

The Trauma Hemostasis and Oxygenation Research (THOR) Network, formed in 2010, is an international, multidisciplinary group of clinicians and investigators, with equal representation from both military and civilian experts. The overarching goal of the THOR Network is to improve outcomes for patients with traumatic injury through education, training, and research. While THOR has a focus on prehospital resuscitation, it also includes in-hospital resuscitation all the way through to completion of acute care. Damage control resuscitation (DCR) is a term coined by John Holcomb in 2007 that describes a bundle of care intended to improve outcomes for patients with severe traumatic bleeding. The individual principles of DCR have been practiced in one form or another for the last 100 years, with a handful of principles having fell out of favor for decades. Now, with a more modern understanding of pathophysiology, improvement in the safety of blood products, and reexamination of some previously well-established principles, there have been renewed interest and rapid adoption of DCR worldwide in well-resourced trauma centers.

This first edition of *Damage Control Resuscitation* is a significant accomplishment for the THOR Network, as it falls in line with the goal of education regarding the principles of DCR. This textbook covers both DCR and remote DCR (RDCR), where RDCR is the application of these same DCR principles in the prehospital phase of care or in austere environments. This distinction is important as treatment capabilities and therapeutic options can be radically different in prehospital/austere settings compared to robust trauma centers. This textbook and its future editions will serve as one of the main methods of disseminating knowledge and educating health-care providers on current concepts for resuscitation of patients with severe traumatic bleeding.

This textbook encompasses multiple aspects of DCR, including past, present, and future iterations. Some chapters are dedicated to the history of when and why individual aspects of DCR were developed, while other chapters cover the epidemiology of severe traumatic injuries. We also highlight the pathophysiology of "blood failure," which is a new term THOR Network has been promoting to describe the adverse consequences of traumatic injury and reduced oxygen delivery on hemostatic, endothelial, and immune function. Additional chapters are included that provide an in-depth detail on hemostatic resuscitation principles, which is a blood-based strategy for treating hemorrhagic shock, as well as chapters on dried plasma, dried

platelet surrogates, and recent developments in frozen red blood cells and oxygen carriers. We include how DCR principles are essential for emergency preparedness in scenarios where there are large numbers of patients with hemorrhagic lesions and how DCR principles might be appropriate in distinct populations, such as children, and for etiologies other than trauma. In addition, a handful of chapters are dedicated to patient management concepts, including respiratory and circulatory support, as well as learning health-care systems and how DCR can be applied to improve outcomes for patients with traumatic injuries. Lastly, a unique aspect of this textbook is a focus on training and education methods for implementation of both DCR and remote DCR principles.

In summary, the THOR Network is very proud of this first edition of the *Damage Control Resuscitation* textbook. As a network, we are passionately dedicated to the care of patients with traumatic injury in both military and civilian populations. We hope that this textbook serves as an educational basis for practitioners who strive to improve outcomes for their patients, that it motivates investigators to continue to explore innovative methods of DCR, and that it provokes all trauma care specialists to aspire to be the best clinicians, educators, and investigators that they can be.

St. Louis, MO, USA Philip C. Spinella, MD, FCCM

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Contributors

Hasan B. Alam, MD Department of Surgery, University of Michigan, Ann Arbor, MI, USA

Matthew A. Borgman, MD, FCCM Department of Pediatrics, Brooke Army Medical Center, Fort Sam Houston, TX, USA

David W. Callaway, MD, MPA Department of Emergency Medicine, Operational and Disaster Medicine, Carolinas Medical Center, Atrium Health System, Charlotte, NC, USA

Jeremy W. Cannon, MD Department of Surgery, Division of Traumatology, Surgical Critical Care and Emergency Surgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, MD, USA

Andrew P. Cap, MS, MD, PhD Medical Corps, U.S. Army, U.S. Army Institute of Surgical Research, JBSA-FT Sam Houston, TX, USA

Ravi Chauhan, MBChB, FRCA, FCAI Department of Anaesthesia, University Hospital Birmingham, Birmingham, UK

Academic Department of Military Anaesthesia and Critical Care, Royal Centre for Defence Medicine, Birmingham, UK

Allan Doctor, MD Departments of Pediatrics, Biochemistry and Bioengineering, University of Maryland School of Medicine, Baltimore, MD, USA

Ryan P. Dumas, MD Division of General and Acute Care Surgery, UT Southwestern Medical Center, Dallas, TX, USA

Department of Surgery, Division of Traumatology, Surgical Critical Care and Emergency Surgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Larry J. Dumont, MBA, PhD The Geisel School of Medicine at Dartmouth, Lebanon, NH, USA

University of Colorado School of Medicine, Denver, CO, USA

Vitalant Research Institute (VRI), Denver, CO, USA

Brian J. Eastridge, MD Department of Surgery, UTHealth Science Center San Antonio, San Antonio, TX, USA

Jez Fabes, MA BM BCh PhD FRCA Department of Anaesthesia, The Royal Free Hospital, London, UK

G. Michael Fitzpatrick, PhD Clinical Research and Development, Cellphire, Inc., Rockville, MD, USA

Sean M. Fox, MD, FACEP, FAAP Department of Emergency Medicine, Carolinas Medical Center, Atrium Health System, Charlotte, NC, USA

Arvin C. Gee, MD, PhD, FACS Division of Trauma, Critical Care, and Acute Care Surgery, Oregon Health and Science University, Portland, OR, USA

Elon Glassberg, MD MHA Medical Corps, Israel Defense Forces, Ramat Gan, Israel

Jennifer M. Gurney, MD Joint Trauma System, US Army Institute of Surgical Research, JBSA – FT. Sam Houston, TX, USA

John B. Holcomb, MD Department of Surgery, Division of Acute Care Surgery, University of Texas Health Science Center at Houston, Memorial Hermann Hospital, Houston, TX, USA

Tony Hudson, MA, MBBS, FRCP, FRCEM Emergency Department, Royal Devon and Exeter NHS Foundation Trust Hospital, Devon, UK

Donald H. Jenkins, MD, FACS, DMCC Department of Surgery, UT Health San Antonio, San Antonio, TX, USA

Kyle J. Kalkwarf, MD Department of Surgery, Division of Acute Care Surgery, University of Texas Health Science Center at Houston, Memorial Hermann Hospital, Houston, TX, USA

Kathleen Kelly, PhD Vitalant Research Institute (VRI), Denver, CO, USA

Geoffrey Ling, MD, PhD Department of Neurology, Johns Hopkins Hospital, Baltimore, MD, USA

Marc Maegele, MD Department of Traumatology and Orthopedic Surgery, Institute for Research in Operative Medicine (IFOM), Cologne-Merheim Medical Center (CMMC), University Witten-Herdecke (UW/H), Cologne, Germany

John C. Maitha, APA-C 75th Ranger Regiment, US Army Special operations Command, Savannah, GA, USA

Joe C. McCannon, AB Billions Institute, Cambridge, MA, USA

Kara McElvaine, BA Oregon State University, Corvallis, OR, USA

Michael A. Meledeo, MS, PhD Coagulation and Blood Research, United States Army Institute of Surgical Research, JBSA-Fort Sam Houston, TX, USA

Ethan A. Miles, MD 75th Ranger Regiment, US Army Special Operations Command, Columbus, GA, USA

Uniformed Services University of the Health Sciences, Bethesda, MD, USA

Allan Pang, MBChB Department of Anaesthesia, James Cook University Hospital, Middlesbrough, UK

Academic Department of Military Anaesthesia and Critical Care, Royal Centre for Defence Medicine, Birmingham, UK

Jacob R. Peschman, MD Department of Surgery, Medical College of Wisconsin, Milwaukee, WI, USA

Heather Pidcoke, MD, MSCI, PhD Department of Clinical Affairs, Cellphire, Inc., Rockville, MD, USA

Martin A. Schreiber, MD, FACS Division of Trauma, Critical Care, and Acute Care Surgery, Oregon Health and Science University, Portland, OR, USA

C. William Schwab, MD Traumatology, Surgical Critical Care and Emergency Surgery, Penn Presbyterian Medical Center, Philadelphia, PA, USA

Perlman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Anirban Sen Gupta, PhD Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH, USA

Stacy Shackelford, MD Combat Support Agency, Defense Health Agency, San Antonio, TX, USA

Reed Smith, MD Department of Emergency Medicine, George Washington University, Washington, DC, USA

Arlington County Fire Department, Arlington, VA, USA

Simon Stanworth, DPhil, FRCP, FRCPathHaematology NHS Blood and Transplant, Oxford University Hospitals NHS Trust, University of Oxford, Oxford, UK

Geir Strandenes, MD Department of Immunology and Transfusion Medicine, Haukeland University Hospital, Bergen, Norway

Patrick Thompson Paramedic, Cape Town, South Africa

Dominick A. Vitale, MD Trauma/Critical Care, Brooke Army Medical Center, Fort Sam Houston, TX, USA

Yuxuan Wang, MD Division of Trauma, Critical Care, and Acute Care Surgery, Oregon Health and Sciences University, Portland, OR, USA

Kevin R. Ward, MD Departments of Emergency Medicine and Biomedical Engineering, Michigan Center for Integrative Research in Critical Care, University of Michigan, Ann Arbor, MI, USA

Nathan J. White, MD, MS Department of Emergency Medicine, University of Washington, Seattle, WA, USA

Aaron M. Williams, MD Department of Surgery, University of Michigan, Ann Arbor, MI, USA

Tom Woolley, MD, FRCA, MBBS Academic Department of Military Anaesthesia and Critical Care, Royal Centre for Defence Medicine, Birmingham, UK

Mouayyad Zaza, MD Department of Surgery, Division of Acute Care Surgery, University of Texas Health Science Center at Houston, Memorial Hermann Hospital, Houston, TX, USA

Part I

DCR Clinical Concepts

The History of Fluid Resuscitation for Bleeding

1

Patrick Thompson and Geir Strandenes

Introduction

Damage control resuscitation (DCR) is a bundle of care first described by Holcomb et al. that is aimed at reducing death from hemorrhage for patients with severe traumatic bleeding. DCR principles include compressible hemorrhage control; hypotensive resuscitation; rapid surgical control of bleeding; avoidance of the overuse of crystalloids and colloids, prevention or correction of acidosis, hypothermia, and hypocalcaemia; and hemostatic resuscitation (blood-based resuscitation) [1]. RDCR is defined as the prehospital application of DCR concepts. The term RDCR was first published by Gerhardt and has been disseminated by the THOR Network [2, 3].

The number and severity of wounded in the wars in Afghanistan and Iraq coupled with the collection of clinical data inspired renewed thinking regarding the optimal methods to improve outcomes for casualties with traumatic hemorrhagic shock. Motivation for reassessment of the standard resuscitative approach for severe bleeding was a result of retrospective studies supporting the earlier use of blood products to include whole blood [4–7] and data by Eastridge that indicated the majority of casualties succumb to their wounds before reaching any medical facility with an advanced resuscitation capability, and the overwhelming majority of these patients (>90%) died from hemorrhage [8]. Advanced life-saving interventions performed in this pre-medical treatment facility (MTF) phase of care can improve outcomes by delivering a casualty to the surgeon with survivable injuries [9, 10].

P. Thompson (✉)
Paramedic, Cape Town, South Africa

G. Strandenes
Department of Immunology and Transfusion Medicine, Haukeland University Hospital, Bergen, Norway

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The history of DCR and RDCR starts well before the inception of the terms. The concepts behind the principles of DCR and RDCR stretch far back into the past. This chapter provides an outline of this history, but it is limited to the fluid resuscitation aspect of DCR/RDCR.

1600s

The history of fluid resuscitation starts with the discovery of the circulatory system. Until this point in time there was no intervention to the circulatory system as no one had yet conceived of the blood to be in "circulation"; it was incorrectly assumed that the blood was produced in the liver and consumed in the peripheries.

In 1628, William Harvey, an English physician educated in Italy at the University of Padua as a student of Hieronymus Fabricius and later at the University of Cambridge, publishes *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* translated as "An Anatomical Exercise on the Motion of the Heart and Blood in Living Beings" commonly called De Motu Cordis (On The Motion of Heart and Blood). This was the first complete, well-researched, description of the circulatory system including the pulmonary and the systemic circulation. The concept was in contradiction to Galen and the accepted understanding of the age. Harvey calculated cardiac output and demonstrated that it was impossible that the liver could possibly produce the volume of blood required as had been previously thought. This bold insight set the stage for new ideas surrounding treatment for hemorrhage.

Harvey's description of the circulatory system was rapidly accepted and it was not long until the idea of interventions via the circulatory system was envisioned. The first intravenous injections (IV) were administered by Christopher Wren and Robert Boyle in 1656 in Oxford. An animal bladder was attached to a Goose quill and wine, ale and opiates were injected into dogs. A mixture of opium and alcohol produced the first IV anesthesia with full recovery; this concept was not implemented into clinical practice and an early chance for pain-free surgery was lost.

Richard Lower conducted research in the cardiopulmonary system and was the first to describe the difference in blood after exposure to air via the lungs. In 1666, Lower reported the first blood transfusion. More specifically, Lower revealed that transfusion could be used as a life-saving treatment for exsanguination. Lower bled a dog to the point of death and then saved the animal with a whole blood transfusion from another larger dog. In 1667, blood was first transfused from animal to man by Jean Baptiste Denis and Lower. It must be noted that the transfusion of blood from a lamb into man was not as a treatment for hemorrhage but instead for "madness." After much medical and theological debate, the practice of transfusion was banned by the French and later the Pope. While transfusion fell into disrepute, the practice faded although the theory was passed on.

1700s

Just as it was important to identify and describe the circulatory system, it was equally important to identify and describe the condition of hemorrhagic shock; this has proven particularly difficult due to the complexity of the pathology. In 1731, French surgeon Henri Francois Le Dran in a publication titled, *Observation de Chirurgie*, describes the collapse of vital functions which ended in death after being hit by a missile. He called it *secousse* which translates from the French to Shock [11].

1800s

In 1817, Dr John Henry Leacock showed that blood was species-specific in cat and dog transfusions and argued for human-to-human transfusion.

> The consequences of haemorrhages where the functions are not dangerously affected, do not of course, require transfusion, since other remedies will suffice. But when the danger is imminent, and the common means are ineffectual, as when a parturient women trembles on the brink of the grave from uterine haemorrhage, *or* when a soldier is at the point of death from loss of blood, what reason can be alleged for not having recourse to this last hope, and for not attempting the recruit the exhausted frame and turn the ebbing tide of life.

This quote carries a clear message of the urgency of resuscitation after severe hemorrhage.

In 1818, James Blundell performed the first human-to-human transfusion. Blundell had postulated that transfusion could be used to treat postpartum hemorrhage and researched transfusion with animals. In 1829, Blundell published the first successful resuscitation of a woman from postpartum hemorrhage in *The Lancet*. He performed ten transfusions in the next 10 years. Blundell also improved the technique and equipment for transfusion using a syringe to conduct vein-to-vein transfusions.

Blundell noted that vein-to-vein transfusions were impractical due to clotting, and removal of air was essential. Attaching the donor's artery to the recipient's vein had however proven successful in Lower's experiments but required skill and time. To resolve this problem, the use of defibrillated blood was suggested by Prevost and Dumas in 1821, which allowed blood to clot, usually by stirring, and then the clots were removed and the remaining fluid now "defibrillated" could be used. Others sought an anticoagulant; J Neudorfer recommended sodium bicarbonate as an anticoagulant in 1860. Dr Braxton Hicks attempted a solution of sodium phosphate but was unsuccessful [12].

In 1849, C.H.F. Routh reviewed all the published blood transfusions to that date, in an article entitled "Remarks, statistical and general on transfusion of blood," which was published in the *Medical Times*. He reported that he was only able to find

48 recorded cases of transfusion, of which 18 had a fatal outcome. This gave a mortality of approximately 1 in 3, which was reported as being "rather less than that of hernia, or about the same as the average amputation" [12].

In 1865, Louis Pasteur recognized that bacterial and fungal contamination causes putrefaction, and in 1867, Joseph Lister discovered antiseptics to cure the dangers of infection. As a result of these discoveries, infection in transfusions moved toward a potential solution with the sterilization of instruments and antiseptic methods beginning to be introduced.

Crystalloids and Colloids

Another important development in fluid resuscitation started in 1831. William Brooke O'Shaughnessy examined cholera patients in Edinburgh and postulated that the disease resulted in hypovolemia and electrolyte loss; O'Shaughnessy experimented on dogs with Saline. In 1832, Thomas A Latta administered salt solution to cholera victims and published details in *The Lancet*: "The very remarkable effects of this remedy require to be witnessed to be believed. Shortly after the commencement of the injection the pulse, which was not perceptible, gradually returns, … the whole countenance assumes a natural healthy appearance" [13].

In 1885, Sydney Ringer strived to achieve optimum electrolyte concentrations for organs making Ringer's solution. In 1896, Ernest Starling described colloid osmotic pressure (Starling's principle) and the importance of colloids plasma proteins; this paved the way for the development of colloids.

American Civil War 1861–1865

In 1850, Samuel D. Gross makes one of the first descriptions of wound shock: "the rude unhinging of the machinery of life" [14, 15].

Two whole blood transfusion attempts were made on active duty wounded soldiers by Union surgeons and reported in the War Department's Medical and Surgical History of the War of the Rebellion. Surgeon E. Bentley reported a successful transfusion given to Private G. P. Cross at Grosvenor Branch Hospital, Arlington, Virginia, on August 15, 1864, and another by Assistant Surgeon B. E. Fryer at Brown Hospital in Louisville, Kentucky, operated on a Private J. Mott in August 1864 [16, 17].

Franco-Prussian War 1870–1871

Battlefield Transfusions

In 1865, Dr J. Roussel of Geneva first conducted a whole blood transfusion using direct arm-to-arm transfusion with a device he had developed called the "transfuseur," for treatment of a patient suffering from hemorrhage. The apparatus he used was described in the Gazette des hopitaux in 1867. Roussel stated later that it was

unfortunate that the device and procedure was not more widely utilized during the Franco-Prussian war, although it was used.

In 1867, Roussel claimed 16 successful whole blood transfusions out of 35 performed for the treatment of a variety of conditions. In 1882, in Paris, he reported on a total of 60 whole blood transfusions performed since 1865 in Switzerland, Austria, Russia, Belgium, England, and France. Roussel's transfuseur apparatus was subsequently officially adopted for use by the French Army and apparently used in times of war.

Developments were made on the equipment needed to conduct whole blood transfusions. Blundell used syringes made for him specially for the vein-to-vein transfusion process; he later developed two new devices: the "impellor" and later the "gravitator." Many other devices were invented and attempted. In 1873, Dr. J.H. Aveling used a device he invented for vein-to-vein whole blood transfusion which consisted of two cannulas joined by a bulb pump and one-way valve to ensure the correct direction of flow; he described the device as small enough to be carried around in a pocket. In 1872, Aveling attended to a lady, aged 21 years, "in extremis" from postpartum hemorrhage. She received 60 drachms of blood from her coachman and apparently soon recovered, certainly enough to reportedly be able to remark that she was dying! Dr. Aveling added in his report that: "the mental improvement of the patient was not as marked and rapid as I anticipated, but this was perhaps due to the quantity of brandy she had taken" [12].

In the United States, between 1873 and 1880, an attempt at a blood substitute was attempted with the milk of cows and goats. T.G. Thomas and J. S. Prout supported this treatment due to the problems with blood transfusion because of its "tendency to coagulation." By 1878, J.H. Britton, writing in *the New York Medical Record*, predicted that transfusion using milk would entirely supersede transfusions of blood [12].

The Spanish-American War 1898

The first descriptions of wound shock which was thought of as something separate from the injury came from the American Civil War, and it was during the Spanish-American War of 1898 that wound shock was first associated with sepsis; however, wound shock was seen as distinctive from hemorrhage [18].

The Anglo-Boer War 1899–1902

In 1900, during the Anglo-Boer War, British surgeons use strychnine and saline to treat shock. Porter describes treatment, "I wanted to pump in strychnine as before, but Cheyne was playing about with 3 or 4 drop doses. The man was very bad and looked like dying so I got 10 drops and gave it. Cheyne was astonished and said it was a very big dose, but I said the patient wanted it. Then Cheyne thought he would try transfusion, and put one and half pints of salt water into a vein" [19].

In 1900, the US Surgeon General recommended that patients in a state of shock were given normal salt solution rectally and subcutaneously and 1/60 grain of strychnine, covered with blankets and kept warm [20].

1900s

Physiology: Blood Groups

In 1900, Karl Landsteiner, while experimenting with the mixing of whole blood from different people, found some blood agglutinates and some lyse, and some are unaffected. In 1901, he found that this effect was due to the red blood cells coming into contact with incompatible blood serum antibodies. He labeled the blood groups according to agglutination A, B, and C, which was later changed to O. Landsteiner also found out that whole blood transfusion between persons with the same blood group did not lead to the destruction of blood cells, whereas this occurred between persons of different blood groups [21]. A fourth main blood type, AB, was found by A. Decastrello and A. Sturli.

Transfusion: Avoiding Transfusion Reactions

In 1907, Ludvig Hektoen recommends blood cross matching, the mixing of donor and recipient blood to determine compatibility. Ruben Ottenberg performs first "cross matched" and typed whole blood transfusion, and Ruben also recognized blood type O as the universal donor.

In 1908, French surgeon Alexis Carrel devised a way to prevent blood clotting. His method involved joining an artery in the donor directly to a vein in the recipient with surgical sutures; this was a highly skilled and complex process available only to skilled surgeons.

In 1913, Dr. Edward Lindeman revolutionized blood transfusion by using syringes and cannulas to transfuse whole blood instead of directly connecting the donors' and recipients' blood vessels at the Bellevue Hospital in New York [22]. In 1914, the first transfusion using citrated whole blood was performed by Professor L. Agote. In 1915, Richard Lewisohn uses sodium citrate as an anticoagulant to transform the transfusion procedure from direct to indirect with the capability of storage. Richard Weil demonstrates the feasibility of refrigerated storage of such anticoagulated blood. In 1916, Peyton Rous and J.R. Turner Jr. found that adding dextrose to the citrate extended the storage time to 4 weeks.

In 1916, W. Bayliss a professor of general physiology at University College London contributed a lecture to the Physiological Society; his abstract was published in the *Journal of Physiology* The abstract detailed animal models after bleeding that received salt solutions had only a transitory recovery; however, the effect was sustained when 5% gelatin of gum acacia was added. Interestingly, gum acacia contains a moderate amount of calcium and magnesium salts, which are cofactors in hemostasis [23].

WWI 1914–1918

In 1915, Oswald Hope Robertson travels to Europe as a medical student and performs first whole blood transfusion of the war at a volunteer hospital in Paris. After his graduation later that year, he works with P. Rous at the Rockefeller Institute. In 1917, Robertson joins the Harvard Medical Unit with Roger Lee at the Base Hospital No. 5 from Boston. Lee had sent Robertson to work with Rous at the Rockefeller Institute. Robertson is tasked with investigation of the treatment of shock; he initiated direct transfusions and wrote to Rous with an idea of larger-scale collection and storage. In 1917, he tested donors and used only type "O" universal donors as suggested by Lee; the donors were tested for disease. He collected blood via venipuncture into glass bottles with anticoagulant. He cooled the blood in ice chests and stored it for up to 28 days. Robertson moved the blood to where it would be needed. He personally administered blood to the wounded under fire and was awarded the Distinguished Service Order for bravery. Robertson also taught the techniques to other instructors responsible for transfusion and resuscitation training. In 1918, O.H. Robertson published his findings in the *British Medical Journal* [24].

In 1915–1916, Captain Ernest Cowell and Captain John Fraser began measuring soldiers' blood pressures and recorded that in wounded men with classic symptoms of shock, the average SBP was 90mmHg, and they labeled this primary shock. In the group which showed no signs of shock initially but later the BP dropped to 70–90 mmHg, this was called secondary shock. If the BP continued to decline and if it fell to 50–60, or below, the men died.

In 1916, Captain L. Bruce Robertson from Toronto, who had recently trained with Lindemann in New York, used direct whole blood transfusions with no blood typing or cross matching in the field. He published in the *British Medical Journal*, The transfusion of whole blood: "a suggestion for its more frequent employment in war surgery," where he states: "the additional blood often carries the patients over a critical period and assists his forces to rally to withstand further surgical procedures." Robertson publishes his experiences of resuscitation transfusions in 1917 in the *British Medical Journal*, and in 1918, in the *Annals of Surgery*, he describes 36 cases of transfusion including 3 fatal hemolytic transfusion reactions [24].

In 1917, after the Medical Research Council Shock Committee meeting, Bayliss recommends 5% gum acacia in a 3% sodium bicarbonate solution; this proved difficult to manufacture, and after further testing, it was agreed to place the 6% gum acacia in a 0.9% saline solution. Reports were circulated that gum acacia and Ringer's solution were capable of saving lives on the front. In 1918, Colonel Elliott and Captain Walker reported that gum-saline succeeded if infused on arrival at the Casualty Clearing Station, but if treatment was delayed for more than 8 hours, a blood transfusion was better.

In 1917, the Investigation Committee on Surgical Shock and Allied Conditions of the Medical Research Council was formed with Starling as first chair then Bayliss. The committee was established to examine treatment of shock. The

committee requests an update on the use of whole blood from Captain Oswald Hope Robertson. Both cold-stored and warm whole blood were transfused to casualties in WWI.

In 1917, Bayliss travels to France and meets Captain Fraser and Captain Walter B. Cannon of the USAMC and the Higginson Professor of Physiology at the Harvard Medical School. Cannon conducted autopsies to test the theory that wound shock was caused by blood pooling in the great veins of the abdomen and found this to be untrue. He began investigations with a Van Slyke blood gas analyzer on blood plasma and was able to show a correlation between wound shock BP and acidosis; the lower the BP, the greater the acidity of the plasma.

On August 17, 1917, at the first MRC Special Investigation Committee on Surgical Shock and Allied Conditions meeting, they publish the first definition of wound shock "a condition of circulatory failure due to deficient entry of blood into the heart."

The Medical Research Council Shock Committee urgently tried to discover the cause of shock and potential treatment. Cannon is convinced that high acid levels in the blood are causing the wound shock and an alkali treatment is needed. H.H Dale disagrees and suggests a more complex pathology: "namely, that substances with similar activity (to histamine) absorbed from wounds involving injury to tissues, in conjunction with hemorrhage, exposure to cold, and so forth, could well determine the onset of shock." Dale argues that the treatment of shock should include whole blood transfusion [25].

In 1918, Cannon is named the Director of Surgical Research at the Medical Laboratory at Dijon; there he trains resuscitation teams in the physiology of shock and resuscitation of shock with a strong emphasis on hypothermia management, which he learned from working on the front line with Cowell and Fraser. Cannon requests and receives the assistance of O.H. Robertson in his research. In 1918, the US Army Medical Department adopts whole blood transfusion with citrated blood to combat shock for American Expeditionary Forces.

Geoffrey Keynes developed "field durable" equipment that enabled whole blood transfusions to be carried out in the field outside of established medical facilities. In the field, the only way to transfuse casualties was from another soldier to the casualty. Keynes' equipment enabled regulating the flow of blood between the donor and the patient.

Post-WW1

In November of 1918, the Royal Army Medical Core convened a conference in Boulogne of surgeons and pathologists to evaluate treatments for shock and hemorrhage. The final conclusion was that whole blood was probably superior, but colloids warranted further investigation, and reactions to gum acacia were reported.

After the war, the MRC Shock Committee also independently reviews the evidence from the war and declares "that in all cases of hemorrhage with shock, transfusion of unaltered whole blood or citrated blood is the best treatment yet available" [26, 27]

Major W. Richard Ohler states after the war, "hemorrhage is the important single factor in shock and the amount of hemorrhage defines the amount of shock, when, therefore, the need is for oxygen carrying corpuses, no other intravenous solution will serve the purpose."

In 1921, Percy Lane Oliver, Secretary of the Camberwell Division of the British Red Cross, establishes the first emergency donor panel with some 20 strong donors to donate blood at short notice in London hospitals. Oliver calls it British Red Cross Blood Transfusion Service. In 1922, it is used 13 times; word spread and by 1925, the service is used 428 times. Sir Geoffrey Keynes is appointed as medical adviser to the organization. Similar systems are adopted in other countries; France, Germany, Austria, Belgium, Australia, and Japan being among the first. At the first Congress of the International Society of Blood Transfusion held in Rome in 1935, "It is to the Red Cross in London that the honor is due to having been the first, in 1921, to solve the problem of blood donation by organizing a transfusion service available at all hours, and able to send to any place a donor of guaranteed health, whose blood has been duly verified." In 1937, Bernard Fantus of the Cook County Hospital in Chicago establishes the first US civilian blood bank, in which whole blood was collected in bottles and stored in a refrigerator for up to 10 days [28].

In 1932, Alexis F. Hartmann and M.J.C. Senn suggest a 1/6 molar sodium-lactate solution to replace the sodium chloride in Ringer's solution; they showed that the lactate was metabolized in the liver, making sodium available to combine with available anions. The use of the solution meant the amount of chloride to be reduced, limiting hyperchloremic acidosis [29].

In 1929, Professor Vladimir Shamov of Kharkiv, USSR, reports experimental use of cadaveric blood transfusion and absence of toxicity. In 1930, Russian surgeon Sergei Yudin familiar with the work of Shamov transfuses his first patient, and he states, "My first experience was with the case of a young engineer who slashed both of his wrists in a suicidal attempt. He was brought to our hospital pulseless and with slow, jerky respiration. Transfusion with 420 cc. of blood taken from the cadaver of a man, aged 60, who had been killed in an automobile accident just six hours before, promptly revived him*"* [30]. Later that year, Yudin reports at the fourth Congress of Ukrainian Surgeons at Kharkiv in September on his first seven transfusions from cadavers. By 1932, Yudin reports 100 transfusions with blood kept for 3 weeks from cadavers, and in 1937, Yudin reports over 1,000 uses of cadaveric blood in *The Lancet* [28].

Spanish Civil War 1936–1939

By 1936, Frederic Duran-Jorda had created a transfusion service in Barcelona to meet the growing demand for blood transfusions; later that year, Norman Bethune visited the facility and then sets up a similar service based out of Madrid called the *Servicio canadiense de transfusión de sangre*. In 1914, Bethune suspended his medical studies and joined the Canadian Army's No. 2 Field Ambulance to serve as a stretcher-bearer in France. He was wounded by shrapnel, and after recovering, he returned to Toronto to complete his medical degree. Based on his experience in

WWI, he organized a mobile transfusion service stating: "Why bring the bleeding men back to the hospital when the blood should travel forward to them?" During the Spanish Civil War, 28,900 donors donated 9000 liters of whole blood. Donors are X-rayed for TB and their blood is tested for syphilis and malaria. Six donations of whole blood were mixed and filtered and then placed in 300 ml glass jars and stored at 2 °C for up to 15 days. With the advent of blood fractionation, plasma could be separated from whole blood and was used for the first time in this war to treat the battle wounded. In 1938, Duran-Jorda fleed to the United Kingdom and worked with Dr. Janet Vaughan at the Royal Postgraduate Medical School at Hammersmith Hospital to create a system of national blood banks in London.

Pre-WWII

In 1934, Alfred Blalock proposed four categories of shock: hypovolemic, vasogenic (septic), cardiogenic, and neurogenic. Hypovolemic shock, the most common type, results from loss of circulating blood volume due to loss of whole blood (hemorrhagic shock), plasma, interstitial fluid, or a combination [31].

In 1938, the Medical Research Council establishes four blood depots in London. Later, in the autumn, the War Office also created the British Army Blood Transfusion Service and the initial Army Blood Service Depot (ABSD) in Bristol under the control of Dr Lionel Whitby. The service also sets up a plasma-drying facility that produced 1200–1400 units a week.

WWII 1939–1945

Transfusion: UK Army Blood Transfusion Service

In 1938, Brigadier Lionel Whitby was appointed Director of an autonomous UK Army Blood Transfusion Service (ABTS). Unlike WWI where the blood was obtained from fellow soldiers, the plan changed to central civilian collection and then to a distribution network. The service was organized on three levels: (1) the Army Blood Service Depot (ABSD), producing all wet and dried products, crystalloids, grouping sera, blood collecting, and administering equipment and training; (2) Base Transfusion Units, which were chiefly concerned with distribution in each theater of operations; and (3) Field Transfusion Units, which worked in forward areas.

Plasma for Britain

In 1940, Dr Charles R. Drew, surgeon and researcher who had developed techniques for preserving liquid plasma, supervised the "Blood for Britain" program which delivered blood to treat those wounded during the Blitz. To encourage donation, Drew first used vehicles with refrigerators serving as donation centers.

Research

In 1940, on May 31, US Surgeon General Magee appoints Professor Walter B. Cannon of Harvard University as Chairman of the US National Research Council Committee on Shock and Transfusion. On November 3, 1941, this committee agreed "that it had been the consensus of the group that [US] Armed Forces should use whole blood in the treatment of shock wherever possible"; the results of that discussion were not made official until 2 years later, on November 17, 1943 [32].

Cannon also introduced the term "homeostasis" to describe the equilibrium maintained in the internal environment and is credited for the first proposal to cause deliberate hypotension in order to reduce internal hemorrhage until surgical control could be established [33].

Plasma: Fractionation

In 1940, Edwin Cohn, a professor of biological chemistry at Harvard Medical School, develops cold ethanol fractionation, the process of breaking down plasma into components and products. Albumin, gamma globulin, and fibrinogen are isolated and become available for clinical use. John Elliott develops the first blood container, a vacuum bottle extensively used by the Red Cross [34]. In 1941, Isodor Ravdin treats victims of the Pearl Harbor attack with Cohn's albumin for blood loss and shock [34].

Transfusion: The United States' Need for Whole Blood

In 1941, as US troops arrive in the United Kingdom, the United States reports that they are not able or prepared to supply US donated blood to Europe or Africa.

On June 28, 1941, the first Conference on Shock was conducted by the Subcommittee on Shock, 6 months before the United States entered the war. Treatment recommendations included control of hemorrhage with early application of a tourniquet, the application of heat to reverse hypothermia and analgesia. Regarding fluid therapy, when shock is imminent or present, blood, plasma, or albumin should be injected as promptly as possible. In massive hemorrhage, whole blood is preferable to blood substitutes.

In 1943, pressure grows on the United States to supply whole blood during D-Day Planning: *"*The Allied planning group were shocked to be told that the U.S. would not sanction the transport of any whole blood from the United States to Great Britain; logistical problems and the efficacy of human plasma were cited as the reasons for the U.S. obduracy*"* [35].

In March 1943, US Army Colonel Edward D. Churchill arrives for duty as Chief Surgical Consultant to the North African and Mediterranean operational theater. Churchill conducts a study on the resuscitation of shock and releases a report that states plasma is a first aid measure in support of whole blood which is the first-line

treatment for resuscitation of battlefield casualties. Whole blood is the only agent that prepares casualties for surgery and decreases mortality by reducing infection. Inadequate resuscitation with whole blood resulted in organ damage. There was a widespread misconception by US military medical leadership that plasma was as effective as whole blood [36]. Churchill, incensed by the US Surgeon Generals' position on blood products, briefed a *New York Times* reporter with the aim of publicizing the need for military blood banks [37]. In 1943, Colonel Elliott C. Cutler's memorandum to Brigadier General Paul R. Hawley, Chief Surgeon, European Theatre of Operations, stated that "Brigadier Whitby tells me that the use of wet plasma has practically been given up, and transfusion (of whole blood) used in its stead in the British Army" [38].

Colonel Frank S Gillespie (Liaison Officer for the United Kingdom in Washington DC)

> I have often wondered at the physiological differences between the British and American soldier. The former, when badly shocked, needs plenty of whole blood, but the American soldier, until recently, has got by with plasma. However, I seemed to observe a change of heart when I was in Normandy recently and found American surgical units borrowing 200–300 pints of blood daily from British Transfusion Units, and I'm sure they were temporarily and perhaps even permanently benefited by having some good British blood in their veins.

In December 1943, the second Conference on Shock was held. Dr E. I. Evans comments on the therapeutic effects of whole blood and blood substitutes in shock, "One of the chief problems is concerned with supplying whole blood in forward areas. Somewhere along the planning line somebody seems to have forgotten that plasma lacks oxygen-carrying power." Evans stated that this led to the wounded not surviving surgery.

Crystalloids: WWII

In WWII, crystalloids were mainly used for dehydration and electrolyte imbalance or if plasma or whole blood were not available.

Colloids: WWII

In WWI, use of gum acacia had resulted in toxic reactions and edema. During WWII, other colloids were researched for effectiveness, namely, gelatin, pectin, fish gelatin, amino acids, and oxidized cotton.

In the 1940s, dextran was being investigated by the United Kingdom, the United States, and Sweden. In 1942, A. Grönwall and Swedish biochemist B. Ingelman suggested using hydrolyzed dextran as a plasma substitute. A Swedish pharmaceutical company adopted the project in 1943. In 1944, under the direction of surgeon G. Bohmansson extensive clinical trials were initiated at the Regional Hospital in

Örebro. By 1947, about 4 years after the innovation, a 6% solution of dextran fraction had been approved for clinical use in Sweden and, shortly thereafter, in the United Kingdom.

Transfusion Transmissible Disease

In 1942, batches of yellow fever vaccine and plasma contaminated with hepatitis virus were linked to cases of viral hepatitis. Between 1942 and 1945, around 200,000 cases were reported. This identified the disease as a matter of prime importance to the Armed Forces during World War II and it became evident during these conflicts that effective methods of screening, treating, and preventing hepatitis in soldiers were urgently required.

Post-WWII

Review

In 1945, the Conference on Shock and Transfusion drew the following conclusions: Plasma was best used far forward. Whole blood was essential and rendered the casualty fit for surgery. Large wounds required large transfusions. Speed in administration was essential. Reduced volume of resuscitation was advocated for the central nervous system and chest injuries.

In 1949, W. Rankin, who had served in the US Army in both world wars, reviewed his experience as an Army General and Director of the Surgery Division of the US Army in World War II and cited four factors as being most important in the reduction of mortality and morbidity rates for battle injuries in World War II: (1) the availability of excellently trained young surgeons who could perform surgery in combat areas; (2) improved methods of resuscitation, including the ready availability of whole blood and plasma; (3) the availability of antibiotics and chemotherapeutic agents used as adjuncts to surgery; and (4) improved evacuation along the chain of care.

As a result of those improvements in care, the percentage of combat casualties dying of wounds was reduced to 3.3% from the World War I percentage of 8.1%. Furthermore, the mortality rates of patients with life-threatening wounds of the head, chest, and abdomen were reduced to approximately one-third of the rates in World War I [39].

Korean War 1950–1953

In 1950, 5 years after WWII, the US military blood program had been discontinued. There had however been a review regarding this state of affairs, and a new policy had been drawn up but not implemented. On July 3, 1950, within days of the onset

of hostilities, responsibility for collecting and distributing blood in the Far East Command was assigned to the 406th Medical General Laboratory in Tokyo, and on July 7, blood was delivered to the first hospital unit arriving in Korea. Military personnel in Japan and many Japanese civilians donated blood. Only low-titer (Anti A and B <256) group "O" whole blood was collected to reduce the logistical burden of typing and cross matching recipients. 39,000 units were collected; however, this was insufficient to meet the needs of the casualties.

As in WWII, the American Red Cross was asked to become the collecting agency for the US military again. The agency had a blood collecting program in operation, to supply blood to civilian hospitals in the United States and could build upon it; this too proved insufficient.

The Armed Forces Blood Program and a National Blood Program were set up and remained in operation until the end of active fighting in Korea. Some 400,000 units of whole blood were transfused by the end of the war.

Massive Transfusion of Group "O" Problems

Massive transfusions of low-titer group O whole blood to other blood groups resulted in the virtual replacement of the recipient's cells with cells of the O group. The recipient's plasma sometimes contained antibodies against red cells of their own hereditary blood group. Gradual hemolysis of native red cells by transfused antibodies was observed. The presence of anti-A and B antibodies from type O whole blood, however, sometimes made it impossible to crossmatch the patient. Severe reactions sometimes occurred when type-specific whole blood was given after large transfusions of low-titer O whole blood. In the light of this new observation, it was recommended that after transfusions of low-titer group O whole blood, no change should be made to blood of another group until at least 2 weeks had elapsed from the last group O whole blood transfusion [40].

Plastic Collection Bags

In 1950, Carl Walter and W.P. Murphy Jr. introduced plastic bags for whole blood collection; this important development made transport of blood easier and more efficient during war time.

Need for Whole Blood

In 1951, at a meeting of the Subcommittee on Shock, Committee on Surgery, NRC (National Research Council), Dr Walter L. Bloom stated: "It is interesting, and somewhat depressing, to note in various reports of conferences concerning the blood and blood-derivatives program in the Korean War how quickly the World War II experience seemed to have been forgotten and how the tendency was again

evident to concentrate on agents other than whole blood in the management of combat and other casualties." He went to add "that the entire philosophy of plasma expanders was questionable. The limitations of these substitutes should be defined, and they should be considered as suitable for emergency use only. The first need of combat casualties was for whole blood." A review of use showed that an average of two-and-a-half pints were used for every casualty wounded in action [41].

Transfusion Risks

In 1952, only 4 major hemolytic reactions resulting in acute renal failure were reported out of the 50,000 whole blood transfusions administered [42].

Plasma Problems

The Army, in need of a fluid therapy agent to stabilize casualties during evacuation to a medical treatment facility, faced a difficult decision because using plasma risked hepatitis. The risk had increased from WWII. In 1951, the incidence of hepatitis after plasma transfusion was 21%. Sterilization techniques had proved unsuccessful. On August 20, 1953, Circular No. 73, Department of the Army directed that because of the risk of serum hepatitis, the higher cost, and the need to use it for the production of specific globulins, plasma would not be used "to support blood volume" unless dextran was not available [40].

Serum Albumin

In 1951, with the increased need for volume expanders, 50,000 units of outdated serum albumin were obtained from the Navy and transferred to the San Francisco medical depot for shipment to Korea. Technically, outdated serum albumin proved satisfactory. One of its advantages was that the small size of the units made it possible for corpsmen to load their pockets with it. Also, serum albumin did not freeze, as reconstituted plasma did. Albumin heated for 10 hours at 60 °C carried no risk of hepatitis. Albumin could be made from contaminated plasma, which meant that a large quantity could be obtained from the available plasma no longer considered fit for use because of the risk of transmission of hepatitis [40].

Dextran

By 1950, the Swedish experience with dextran had reached 200,000 cases. In the 10 years of its use, there had been no postmortem evidence of tissue damage, and reactions were fewer than with the use of either blood or plasma. A compilation of articles from the literature by Pharmacia showed an impressive use of dextran

by reliable investigators in Denmark, Finland, Holland, as well as in Sweden. There was some evidence obtained from use of Swedish and British dextran that showed local and systemic allergic reactions; this was thought to be worse with the higher molecular weight dextran and the US-produced dextran of lower molecular weights. On October 1, 1952 at the meeting of Subcommittee on Shock, it was reported that 125 units of dextran had been used in Korea, with good clinical results and no significant reactions. A 6-month study had been started in Air Force installations in the United States. Dextran was used in increasing amounts until the end of the Korean War. In September 1953, a hitherto undescribed consequence of dextran injections was reported, a prolongation of the bleeding time, and the change in the bleeding time occurred within 3–9 hours after dextran had been given [40].

Vietnam War 1955–1975

In 1965, no formal military blood program existed in Vietnam. Transfusion requirements were met with shipments of 10 units of group O blood from Japan approximately every 10 days. Blood supply was provided by the 406th Mobile Medical Laboratory, Camp Zama, Japan. The decision was made to ship only low-titer group O whole blood. Later Group A was added and by 1966 all types of whole blood were utilized to meet demand. In Vietnam only low-titer group O whole blood was used far forward. From 1967 to 1969, around 230,323 units of whole blood were transfused; 24 hemolytic transfusions reactions were reported [43]. The Vietnam War was the first major wartime engagement for the Armed Services Blood Program (ASBP). Over the course of the conflict, the program collected nearly 1.8 million units of blood in support of troops in Vietnam. It was the first time that every unit of whole blood used to support the war was voluntarily donated by military personnel, their dependents, and civilians employed at military installations and not through civilian organizations.

Aggressive fluid resuscitation during the Vietnam War with red blood cells, plasma, and crystalloid solutions allowed patients who previously would have succumbed to hemorrhagic shock to survive. Renal failure became a less frequent clinical problem, vital organ function was better sustained, but fulminant pulmonary failure termed “DaNang lung” or “acute respiratory distress syndrome (ARDS)” appeared as an early cause of death after severe hemorrhage.

Acute Coagulopathy in Trauma

Miller et al. published data in 1971 from the War in Vietnam that showed coagulation defects in massive transfusion; this was treated unsuccessfully with FFP and then whole blood which was successful in limiting the bleeding tendencies [44].

Post-Vietnam War

Crystalloids

In the 1970s, additional studies by Shires et al. demonstrated that a prolonged period of hemorrhagic hypotension was associated with the development of microvascular injury with marked ECF deficit which could be corrected only by the administration of isotonic crystalloids in volumes two to three times the estimated blood loss due to loss of interstitial fluid from the extravascular space. This was the basis of the well-known "3 to 1" dogma for the treatment of hemorrhagic shock, which was adopted by the ATLS for the treatment of trauma casualties. It was recommended that the early treatment of hemorrhagic shock includes primarily the control of external bleeding and early intravenous administration of 2000 ml of crystalloids through a large bore catheter [45].

Their philosophy for resuscitation in patients with traumatic bleeding was misapplied and led to the overuse of crystalloids, to the detriment of patients with severe bleeding who commonly received 5–10 L of crystalloids before any blood product administration [46].

These outcomes were actually predicted by Shoemaker in 1976, when he challenged the notion that the interstitial compartment required resuscitation and instead emphasized the need for whole blood to treat significant bleeding when the hematocrit fell below 30%. The overuse of crystalloids occurred despite a call for moderation by Moore and Shires as early as 1967. In their editorial, Moore and Shires state, "Blood should still be replaced during major operative surgery as it is lost. The use of balanced salt solutions appears to be a physiological adjunct to surgical trauma, not a substitute for blood." Subsequent research has demonstrated that a crystalloid-based resuscitation strategy leads to increased inflammation and vascular permeability compared to WB [46].

Rise of Blood Components

By the 1980s and 1990s, the accepted ATLS treatment for hemorrhagic shock was aggressive use of crystalloids and colloids and component therapy. RBCs were to be used for patients who continued to actively bleed after 2L of fluids were given. Plasma and platelets were indicated if the patient was still bleeding after the RBCs were given and there was a laboratory abnormality indicating poor coagulation or platelet count, respectively.

From the 1990s onward, the evidence started to mount that this strategy may not be optimal. In 1990, Kaweski et al. published "The effect of prehospital fluids on survival in trauma patients." In 1992, Krausz et al. published "Scoop and run" or stabilize hemorrhagic shock with normal saline or small-volume hypertonic saline." In 1994, Bickell et al. published "Immediate versus delayed fluid resuscitation for

hypotensive patients with penetrating torso injuries." In 2004, Blumenfeld et al. published "Prehospital fluid resuscitation in trauma: the IDF-MC Consensus Panel Summary"; these and other papers started to question the strategy of aggressive crystalloid use.

Somalia Use of Fresh Whole Blood in Mogadishu Experience and How It Affected Iraq/Afghanistan Wars

In 1993, the US forces in Mogadishu Somalia were faced with a shark attack victim from the tenth Mountain Division who required bilateral lower extremity amputations and massive transfusion. With limited plasma and infrequent resupply of packed red blood cells, Colonel Denver Perkins initiated an emergency donor panel whole blood collection. The immediate resolution of clinical coagulopathy and improved physiology was apparent to all. This highlighted the efficacy of whole blood and led to around 120 units of whole blood collected and more than 80 units being transfused during the Black Hawk Down crisis. This event led to the inclusion of whole blood training for deploying forward surgical teams at the joint trauma training center starting in 1999 with a section on whole blood in the 2003 version of *Emergency War Surgery* handbook (personal communication, JB Holcomb).

Tactical Combat Casualty Care

In 1996, Butler et al. published "Tactical combat casualty care in special operations" which led to the establishment of TCCC guidelines; this initial guideline recommended 1000 ml of Hespan for a casualty in shock with bleeding controlled [47].

2000 To Present

2000

RDCR and DCR

After 9/11 and the commencement of the "War on Terror," coalition forces faced conflict in Afghanistan and Iraq. The initial resuscitation strategies were similar to those from the 1990s with the United Kingdom and the United States using clear fluids with a hypotensive resuscitation strategy based on maintaining a radial pulse, forward and during evacuation and blood components in medical treatment facilities.

During the conflicts and as casualty number and severity of injuries increased, mainly due to a rise in IED use, the concept of damage control resuscitation was resurrected from the shock wards of WWII and synthesized with emerging resuscitation strategies. This concept can be envisioned as the resuscitation of a patient to increase the chance of survival to, and survival of, damage control surgery [47].

Remote damage control resuscitation is the use of DCR concepts in prehospital and as early as possible in the evacuation chain [2]. Aspects of RDCR began with the prehospital use of RBCs to be effectively practiced by the UK MERT platform in Afghanistan after 2006 and by the US forces as part of their "Vampire Missions" that transfused patients upon transport starting in 2012.

Lethal Triad

Increasingly resuscitation strategies target the lethal triad of hypothermia, acidosis, and coagulopathy. The realization that this combined pathology has an impact on mortality has its roots in WWI. The modern concept was coined in 1982 by the American Trauma Society which proposed the "bloody vicious cycle," which included acidosis, hypothermia, and coagulopathy as an important cause of death in patients with coagulopathy in the early stage of trauma. This term was gradually replaced by other terms, such as "lethal triad" and "iatrogenic trauma coagulopathy," and is also the theoretical basis for damage control resuscitation [48].

2003

Acute Traumatic Coagulopathy

In 2003, Brohi et al., in a retrospective study of over 1800 patients, showed that just over 24% had significant coagulopathy, and this group had a threefold higher mortality. Brohi called the pathology *acute traumatic coagulopathy*. Later in 2007, Brohi identified that studies had shown that this coagulopathy exists on admission to hospital and is independent of severity score. He argued that the driver of this pathology is hypoperfusion causing activation of the protein C pathway and fibrinolysis. Resuscitation strategies started to target this coagulopathy [49].

2004

Resurgence of Whole Blood

In 2004, the 31st Combat Support Hospital in Baghdad began using ABO type specific whole blood as a salvage therapy when patients were near death. With experiential data that whole blood was more effectively reversing shock and coagulopathy than with RBCs of advanced storage age and plasma, this encouraged earlier use of whole blood [50]. In October of 2004, a massive transfusion guideline was developed that incorporated the early use of warm fresh whole blood (ABO specific) and blood components in a 1:1:1 ratio until whole blood was available [50].During 2004 at the 31st CSH, there was the incorporation of rapid screening tests for HIV, HCV, and HBV for ABO-specific whole blood that was collected from donors. Results of these rapid tests were available within 5 minutes and resulted prior to completion of the collection of the unit of whole blood [51].

ABO-specific whole blood was used instead of low-titer group O whole blood because at this time the AABB standards for whole blood stated that it must be

ABO-specific when transfused. The lessons learned from WWII to the Korean and Vietnam Wars regarding the efficacy and safety of low-titer group O whole blood were lost in the 1980s to the 2000 timeframe and the concern regarding the mild-to-moderate risk of incompatible plasma led the blood banking community to write standards that required whole blood to be ABO specific [50].

2005

Platelets

In 2005, the US Army for the first time makes apheresis platelets stored at 22 °C for 5 days available in Baghdad and soon thereafter expands the availability to all other combat support hospitals [52].

2007

Component Therapy

The optimal use and ratios of components in resuscitation of hemorrhagic shock was questioned with a trend toward increased use of plasma. In 2007, Borgman et al. publish "The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital." Borgman recommended early and increased use of red blood cells and plasma in a 1:1 ratio. This retrospective study evaluated 246 patients, with massive transfusion, and reported an independent association between higher ratio of plasma to RBCs and survival. There was also lower risk of death from hemorrhage in patients transfused with higher plasma to RBC ratios [4].

2008

ATLS

The 8th edition of the ATLS manual was changed to reflect developing strategies in resuscitation "Balancing the goal of organ perfusion with the risks of re-bleeding by accepting a lower than normal blood pressure has been called 'Controlled resuscitation', 'Balanced Resuscitation', 'Hypotensive Resuscitation' and 'Permissive Hypotension'. The goal is the balance, not the hypotension. Such a resuscitation strategy may be a bridge to but is also not a substitute for definitive surgical control of bleeding" [53].

2009

Data on WFWB

Spinella et al. published data indicating that ABO-specific warm fresh whole blood is independently associated with improved survival for patients with combat-related traumatic injuries and may improve 30-day survival [7].

Emergency Donation of WB

In 2009, Steve Williams of the Royal Caribbean Cruises implemented a fresh whole blood transfusion protocol using onboard guests and crew as volunteer donors [54].

Dried Plasma

French medical personnel in medical treatment facilities begin using dried, pathogen reduced, pooled plasma which was first reported in 2009 [55].

2011

Data on WFWB

Nessen et al. publish data indicating that warm fresh whole blood (WFWB) is associated with improved survival at two facilities, and it is the first manuscript from the Afghanistan/Iraq Wars to provide some data that the use of group O whole blood in non-group O patients is safe and effective [42].

In 2011, the THOR Network is established by Strandenes and Spinella. It is an international multidisciplinary network of providers ranging from medics to basic scientists with a goal to improve outcomes for patients with life-threatening traumatic bleeding. It initially focuses on whole blood but rapidly expands to include all aspects of resuscitation for patients with traumatic hemorrhagic shock [56].

2012

Dried Plasma

In 2012, US Special Forces medics begin to use freeze-dried plasma provided by the French Military (personal communication with Andre Cap).

2013

Whole Blood Storage

Pidcoke et al. publish that cold storage of whole blood at 4 °C maintains adequate hemostasis for at least 14 days. These findings are confirmed by Strandenes in Norway in 2015 [57, 58].

The Norwegian Naval Special Operations Commando starts bringing cold-stored whole blood on mission in the Gulf of Aden [58].

Dried Plasma

The Israeli Defense Forces implements the use of freeze-dried plasma (FDP) at the point of injury (POI) [59].

2014

TCCC Guidelines Change ranks resuscitation fluids and places whole blood as the optimum for hemorrhagic shock [60].

The THOR Network advocates for the resurrection of cold-stored LTOWB to improve its availability and safety compared to the use of warm fresh whole blood [61].

Field Transfusion

Strandenes et al. publish "Emergency Whole-Blood use in the field: a simplified protocol for collection and transfusion" in which he presents the Norwegian Naval Special Operation Commando unit specific RDCR protocol, which includes field collection and transfusion of warm fresh whole blood [62].

Dried Plasma

The Norwegian Helicopter Emergency Medical Service began using a German freeze-dried plasma product for civilian casualties [63].

Platelets

In 2014, the US Army Blood Research Program, led by Dr. Andre Cap, begins extensive in vitro studies convincingly demonstrating that apheresis platelets stored at 4 °C have superior hemostatic function and are not irreversibly activated as previously presumed compared to platelets stored at 22 °C [64].

2015

The Norwegian Helicopter Emergency Medical Service located in Bergen started transporting low-titer group O whole blood on every mission for civilian casualties [65].

The University of Pittsburgh becomes the first civilian trauma center to bring low-titer group O whole blood back after its disappearance in the 1970s after the Vietnam War ended [66].

The Norwegian Armed Forces transported cold-stored LTOWB to military facilities in Afghanistan (Personal communication with CDR Geir Strandenes).

ROLO Program

In 2015, the 75th Ranger Regiment's Ranger Group O Low Titer (ROLO) Whole Blood Program was developed and initiated in concert with international multidisciplinary civilian and military providers of the Trauma Hemostasis and Oxygenation Research (THOR) Network to bring emergency blood transfusion from the hospital environment to the battlefield. Thanks in large part to LTC Andre Cap, Chief of Blood Research at the Army Institute of Surgical Research, LTC Ethan Miles Command Surgeon, 75th Ranger Regiment, and LTC Jason Corley, Deputy Director of the Army Blood Program, the ROLO Whole Blood Program went from concept to implementation at the unit level in only 18 months [67].

2017

Cold Platelets

In 2017, the US Army began transfusing apheresis platelet units stored at 4 °C based on its superior hemostatic function compared to platelets stored at 22 °C [68, 69]. The storage duration for the 4 °C platelets started at 3 days with the plan to extend it over time after collecting data.

Blood Failure

Bjerkvig et al. publish on the concept of "blood failure," and the link between oxygen debt and traditional organ failure has long been recognized. Bjerkvig argues for the consideration of failure in two additional linked and very dynamic organ systems, the endothelium and blood, both very sensitive to oxygen debt. The degree of damage to the endothelium is largely modulated by the degree of oxygen debt. Hypoperfusion causes oxygen debt and is believed to begin a cascade of events leading to acute traumatic coagulopathy (ATC). This combination of oxygen debt-driven endothelial damage and ATC might be considered collectively as "blood failure." The article presents the implications of oxygen debt remote damage control resuscitation strategies, such as permissive hypotension and hemostatic resuscitation [70, 71].

2018

AABB Standards for Low-Titer Group O Whole Blood

The THOR Network petitions the AABB for acceptance of the use of low-titer group O whole blood for patients with severe bleeding of any etiology. A few months later, Standard 5.15.1 in the 31st edition of the AABB standards are changed allowing the use of low-titer group O whole blood. After this change in standards, many civilian trauma centers internationally begin to adopt the use of cold-stored LTOWB for patients with life-threatening bleeding [72].

Whole Blood Transfusions

From 2003 to 2018, there have been over 10,000 units of ABO-specific warm fresh whole blood transfused. Between 2017 and 2018, there have been over 300 units of cold-stored LTOWB stored at 2–6 °C transfused by the US military.

Conclusion

DCR and RDCR will continue to evolve as new evidence, research on the pathophysiology of hemorrhagic shock, technological advances, and drug development emerge. It is in looking back that we understand the path that has led us to where we are now. It is essential that the hard lessons learned from lives lost do not have to be learned again, as has so often been the case in the past.

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2 Epidemiology of Prehospital and Hospital Traumatic Deaths from Life-Threatening Hemorrhage

Stacy Shackelford and Brian J. Eastridge

Death from injury was described as the neglected epidemic of modern medicine by the Institutes of Medicine in 1966 [1]. Despite dramatic advances in acute trauma care over the last several decades, including resuscitation of massive hemorrhage, damage control surgery, and technological advances in critical care, the health burden of injury on our society, in both peacetime and wartime, remains substantial. From a public health perspective, injury remains the leading cause of death accounting for 59% of all deaths among individuals up to the age of 45 and is responsible for a domestic cost of more than $406 billion in medical care and lost productivity each year [2]. Medical treatment and loss of work productivity costs for civilian fatal and non-fatal injuries in the United States totaled more than $671 billion [3]. Since injury is disproportionately represented in a relatively young population, it stands as the single largest cause of years of life lost and productivity lost in the United States. In 2015, 214,000 persons in the United States suffered fatal injury; more than 2,800,000 persons were hospitalized and 27,600,000 persons were treated in emergency departments for non-fatal injuries. The majority of injury mortality occurs in the field with or without access to medical care [4–6]. According to a Centers for Disease Control and Prevention report in 2008, 62% of all people who died from injuries and 75% of people who died from gunshot wounds were pronounced dead outside of a hospital [7].

Understanding the epidemiology of death after trauma is vital to improving the outcomes of the injured patient. The concept of the distribution of mortality after injury along a chronological axis was initially characterized by Trunkey based upon his experience and research in his seminal work describing the trimodal distribution

S. Shackelford
Combat Support Agency, Defense Health Agency, San Antonio, TX, USA

B. J. Eastridge (✉)
Department of Surgery, UTHealth Science Center San Antonio, San Antonio, TX, USA
e-mail: eastridge@uthscsa.edu

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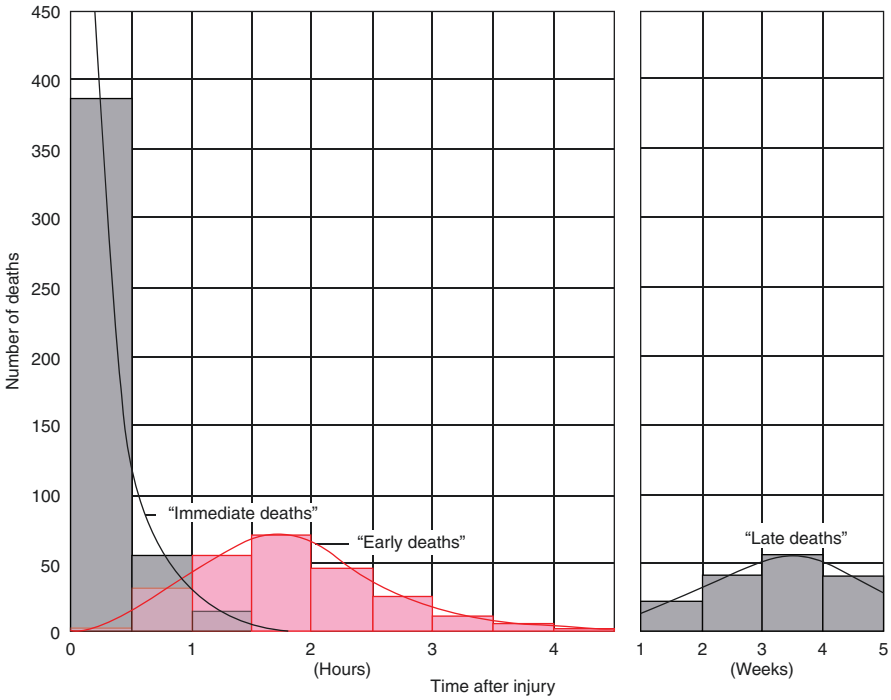

Fig. 2.1 The trimodal distribution of trauma deaths. (From Trunkey [8] with permission of Springer Nature)

of trauma death. This distribution of death after traumatic injury is classically described with death occurring during immediate, early, and late timeframes after injury [8] (Fig. 2.1).

In an associated review of 425 consecutive trauma autopsies, he found the most substantial etiology of mortality across the spectrum of injury was hemorrhage, which was responsible for 35.2% of deaths [9]. From this early work evolved concepts of injury prevention, expedited evacuation, and optimized acute healthcare delivery which formed the nascent architecture of regionalized trauma care and were the precursor to our current trauma systems across the United States. As initially described by Dr. Trunkey, "immediate" deaths occur within 1 hour of injury and were considered unpreventable through available medical interventions. Immediate deaths are most frequently caused by catastrophic whole body, central nervous system (CNS), heart, or great vessel injury. From a trauma system perspective, such immediate deaths are best addressed through an inclusive trauma system integrating injury prevention and safety interventions. "Early" deaths after trauma, usually occur within the time realm of prehospital or acute medical care occurring later than immediate but still within the first few hours after injury. Most early deaths are attributable to major CNS injuries or hemorrhage [10, 11]. As little can be done to ameliorate the effects of primary CNS injury, clinical efforts are directed

toward optimization of brain perfusion and minimizing secondary brain injury. Assuming these tenets, the mortality of injured patients who succumb to CNS injury is largely not preventable. On the other hand, some of the deaths secondary to hemorrhage during this interval are potentially preventable and highlight opportunities to advance medical interventions and trauma systems. The interval between injury and definitive control of the focus of bleeding is most critical for this group of injured patients. The third "peak" in trauma deaths corresponds to trauma patients who die days or weeks after injury, usually due to infection, multiple organ failure, or the latent effects of devastating brain injury. Optimal care in the early hours after injury may prevent the progression of such sequelae. Improvements in critical care have improved injury outcomes and minimized the mortality from these clinical entities as evidenced by recent publications have documented a diminution in the significance of this late third peak [12, 13]. It is especially notable that death after trauma is largely an acute phenomenon with approximately 40–64% of deaths occurring at the scene [4, 9, 11]. For those patients that make it to a trauma center and ultimately die, 34–52% succumb to their injuries within the first 24 hours, and the remainder distributed over the subsequent days to weeks [12, 14, 15].

Reducing the time between injury and life-saving interventions is a critical factor in optimizing injury survival. While the exact length of time that an individual patient can survive depends on their specific injuries, 1 hour has been frequently cited as a goal to deliver an injured patient to a facility capable of surgical management of bleeding in both the civilian sector and on the battlefield [16–18]. Although objective data to support the targeted 1 hour prehospital time have been elusive, few question the fact that earlier interventions save lives. On heels of Korean War, the US Army awarded Dr. R Adams Cowley, a cardiothoracic surgeon, a grant for $100,000 to study shock in humans. Most patients presented to his facility physiologically moribund, earning his four-bed unit the moniker of the "death lab." Owing to lessons learned from the Vietnam War, in 1968, he negotiated to have patients brought in to his facility by military helicopter to minimize prehospital time after injury. Based upon subsequent clinical experience with injury, in 1975, he published his perspective on the development of a comprehensive emergency medical system in the *Maryland State Medical Journal*. His quote that "the first hour after injury will largely determine a critically injured person's chances for survival" developed into the concept of the "golden hour" which has remained as one of the core guiding tenets of trauma care for emergency medical services for over the last four decades. Dr. Cowley coined the legendary term to promote the urgency between injury and care, recognizing that trauma patients who reached definitive care sooner had a better chance of survival [19]. He subsequently established Baltimore Shock Trauma Center and a statewide system of care served by Maryland state police helicopters piloted by Vietnam veterans.

Advances in both military and civilian trauma systems have focused attention on those deaths determined to be potentially preventable through medical means. Although numerous methods of defining "preventable death" have been established, there is no standard definition that has proved universally acceptable, highlighting the challenges of developing such metrics. Regardless of the definition of

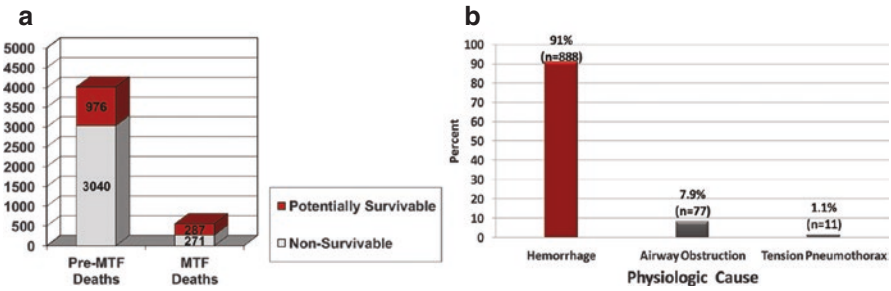

Fig. 2.2 (**a**) Battlefield mortality location (n = 4596). (**b**) Injury/physiologic focus potentially survivable acute mortality (n = 976). (From The Journal of Trauma and Acute Care Surgery, Eastridge et al. [20] Figure 4, with permission of Wolters Kluwer Health, Inc.)

preventable, hemorrhage consistently emerges as the most substantive pathophysiology associated with potentially preventable trauma mortality. In a large contemporary autopsy study of combat deaths from 2001 to 2011, 87% of the 4574 deaths occurred prior to arrival at a medical treatment facility (MTF), and of the prehospital deaths, 24% were considered potentially survivable based on a process of expert review of anatomic criteria established in the study [20] (Fig. 2.2a, b).

Of the pre-hospital casualties with potentially survivable injuries, 91% of the deaths were associated with a source of hemorrhage. Further stratification noted the site of lethal bleeding as follows: torso 67%, junctional 19%, and extremity 14%. The focus of bleeding in the torso hemorrhage death casualties was predominantly thoracic in 36% and abdominopelvic in 64%. Similar classification of the junctional hemorrhage deaths demonstrated 61% were associated with axilla and groin injuries, whereas 39% were associated with cervical injuries [20]. Another study utilizing the same methodology analyzed 558 combat casualties who succumbed to their injuries after reaching a military treatment facility. These died of wounds (DOW) casualties occurred at a rate of 4.6% over the study period, which is strikingly similar to the average civilian trauma center case fatality rate of 4.1%. Of the 287 (51.4%) DOW casualties deemed potentially survivable, 80% of the mortality was directly associated with a source of acute hemorrhage early in the hospital course [21].

By comparison, analyses of civilian trauma deaths, where blunt mechanism of injury is more prevalent, clinical studies also demonstrate that hemorrhage is the most substantial contributor to early trauma deaths. A 1998 analysis of trauma center mortality demonstrated that nearly all of the traumatic mortality directly attributable to hemorrhage occurred within 24 hours from injury [22]. A comparable review of in-hospital deaths classified as preventable or potentially preventable demonstrated that 40% were caused by hemorrhage [15]. Similarly, another metropolitan trauma center performed a review of 753 consecutive trauma deaths in their hospital. Of these deaths, 53% occurred within 12 hours and 74% within 48 hours. Of this population, 37% of the mortality was attributable to acute hemorrhage [14]. A study of civilian prehospital deaths in a large urban county designated 29% of the

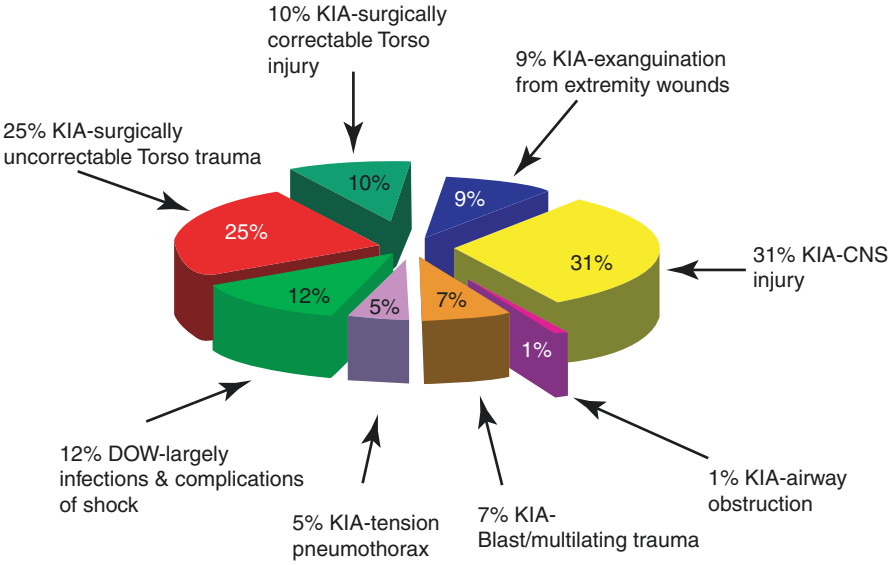

Fig. 2.3 How people die in ground combat. (Figure 1 Bellamy [24]. Based on the Wound Data Munitions Effectiveness Team (WDMET) during the Vietnam War between 1967 and 1969)

mortality as potentially preventable, with 64% of those deaths deemed potentially survivable attributed entirely or partially to hemorrhage [23].

The prevalence of prehospital deaths in recent conflicts in the southwest Asia remained essentially unchanged compared to previous US wars. The lack of effective management strategies to mitigate life-threatening hemorrhage secondary to trauma has long been recognized as a knowledge and capability gap requiring remediation. In a classic military manuscript, Dr. Bellamy reviewed the nature of ground combat deaths in a hypothetical model which incorporated data from World War II, the Korean War, and the Vietnam War into a prediction of the causes of death in combat [24]. Approximately 44% of deaths were associated with limb hemorrhage, thereby highlighting extremity bleeding as one of the most substantive causes of potentially preventable death on the battlefield (Fig. 2.3).

A turning point in military prehospital trauma care came in 1996 when a review of battlefield deaths and the medical requirements to support special operations forces led to the development of a new paradigm for combat casualty care on the battlefield [25]. The core principles of Tactical Combat Casualty Care (TCCC) were based upon the premise of eliminating preventable deaths and combining good medicine with good tactics. Phased care in the tactical environment included Care under Fire, Tactical Field Care, and Tactical Evacuation (TACEVAC) Care. Casualty and medic actions during the care under fire phase were directed toward tactical advantage and mission completion. Simple life-saving interventions targeting hemorrhage control are emphasized in this primary phase of TCCC, with only tourniquets and hemostatic dressings recommended as standard medical care in this

phase. These early iterations of Tactical Combat Casualty Care (TCCC) guidelines recommended immediate application of limb tourniquets as the first-line treatment of extremity hemorrhage. Over the ensuing decade, the US military gradually adopted widespread implementation of extremity tourniquets for all deployed forces, ultimately resulting in an 85% decrease in deaths attributed to limb hemorrhage [20]. This battlefield lesson was subsequently translated to the civilian population, fostered by the strong advocacy of the Hartford Consensus [26, 27] and by the evolution of community bleeding control courses, "Stop the Bleed" [28, 29].

While efforts to control isolated extremity hemorrhage after injury have been uniquely successful within the last decade, mitigation of junctional and torso hemorrhage in the prehospital environment remains elusive. A contemporary study to characterize the impact of prehospital time and junctional injury severity on survival utilizing the National Trauma Data Bank (NTDB) Research Data Set found that in patients sustaining junctional injury, increasing severity of anatomic disruption was associated with more significant hemorrhage and mortality. In this study, a mortality rate of 45% was exhibited in high grade junctional injury groups at prehospital times <30 minutes and remained substantial throughout subsequent prehospital time intervals [30]. In a parallel study, the investigators sought to illustrate the impact of prehospital time and torso injury severity on survival. This analysis demonstrated that significant torso injury was associated with higher rates of death, particularly in penetrating injury. In fact, the observed mortality rate for high grade torso injury with hemorrhage was >40% in as little as 15 minutes after injury [31]. Both of these studies underscore the critical nature of prehospital time in patients with junctional and torso hemorrhage. Understanding that evacuation times <30 minutes may not be realistic or attainable, particularly in tactical or austere environments, efforts should be directed toward the development and evolution of novel strategies to mitigate hemorrhage from junctional sources in the prehospital environment and temporize the window of survival.

Based upon the understanding that hemorrhage represents the most substantial etiology of potentially preventable deaths after trauma, efforts to develop mitigation strategies have evolved markedly in the last decade. The principle of damage control resuscitation was developed through an observation that combat casualties with massive hemorrhage that received more aggressive correction of shock and coagulopathy immediately after injury had improved survival [32]. Increasing plasma:RBC ratio from 1:8 to 1:1.4 was associated with a threefold decrease in mortality from 60% to 19% [32]. Notably, casualties resuscitated with low ratio were significantly more likely to die from ongoing hemorrhage than those managed with balanced plasma: RBC ratios. The concept of damage control resuscitation has subsequently been refined predicated upon optimizing physiology and preventing of the lethal elements contributing to post-injury hemorrhagic mortality: hypothermia, acidosis, and coagulopathy. Incumbent in the damage control resuscitation strategy are the techniques of hypotensive resuscitation (permissive hypotension) and hemostatic resuscitation (amelioration of the shock and coagulopathy of trauma) [33, 34].

While the concept of damage control resuscitation evolved across the battlefields of Iraq and Afghanistan, research to substantiate the observed successes of

fresh whole blood and balanced ratio transfusion practices drew additional attention to the timing of hemorrhagic deaths. Consistently, studies supported the fact that for patients who arrive at a trauma center, death from hemorrhage occurs within about 2 hours of hospital arrival [35–37]. Prospective trauma resuscitation studies in hemorrhaging patients showed that the median time to hemorrhagic death was 2.0 to 2.6 hours, with at least 50% of all deaths occurring within 3 hours of hospital arrival [38].

In contrast to the well-characterized outcome of injury mortality after reaching the hospital, there is a paucity of evidence that substantively defines injury-associated death in the prehospital environment or across the continuum of care. One important analysis that included both prehospital and in-hospital traffic injury mortality demonstrated an overall 35% decrease in motor vehicle crash-related deaths over a period of 36 years [19]. For those patients who died prehospital, the rate of death occurred at a logarithmically defined rate that was greatest in the early minutes after injury. Although total traffic deaths decreased over the period of the study, there was an increase in prehospital fatalities relative to hospital fatalities demonstrated [39] (Fig. 2.4).

This data is consistent with military studies and supports the need to focus on prehospital deaths with respect to hemorrhage control, resuscitation, and trauma system design.

Shorter prehospital time has been associated with improved survival in both military [16] and civilian trauma patients [30, 31]. In addition, recognizing that more rapid transport to surgical hospitals is not always possible, recent trauma system advances have also focused on bringing additional resuscitation capabilities (remote damage control resuscitation) to the seriously injured in the form of prehospital blood transfusion, advanced hemostatic interventions, and light, maneuverable surgical teams [16, 40]. Prehospital transfusion in particular has been associated with

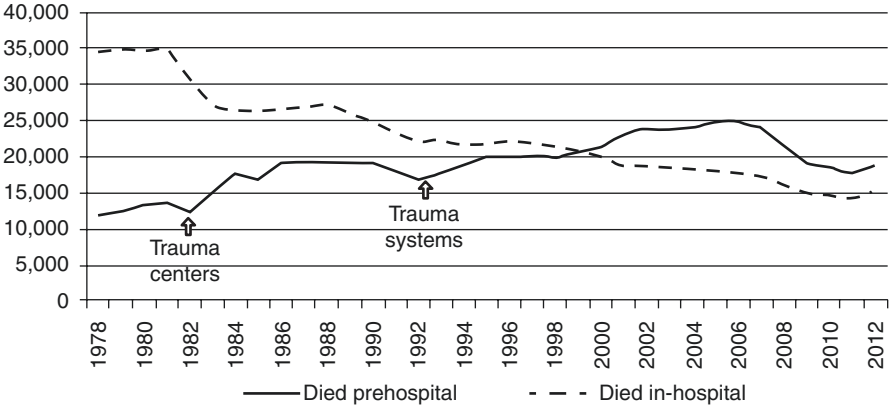

Fig. 2.4 US vehicle-related fatalities, pre-hospital and in-hospital, 1978–2013, total numbers. (From The Journal of Trauma and Acute Care Surgery, Champion et al. [39], Figure 3, with permission of Wolters Kluwer Health, Inc.)

improved survival in combat casualties [41]. Not all studies of prehospital transfusion have demonstrated a survival benefit. However, an analysis of the time to transfusion amongst evacuated US military combat causalities in Afghanistan demonstrated that blood product transfusion within 36 minutes of injury was associated with improved survival. Beyond this interval, mortality benefits from prehospital transfusion were not significant [42]. More recent efforts in battlefield resuscitation have focused on delivering whole blood to severely injured casualties within minutes of injury by combat medics equipped with cold-stored universal donor low-titer type O whole blood as well as the capability to collect fresh whole blood from pre-identified donors [43]. These and other evolving efforts hold much promise for the future of remote damage control resuscitation.

Conclusion

The majority of potentially preventable deaths after trauma are related to hemorrhage and occur early after injury, with the largest number of deaths occurring before hospital arrival. About one-fourth of trauma deaths may be potentially preventable through early medical and surgical interventions. Interventions dedicated to bleeding control and hemostatic resuscitation have demonstrated merit in decreasing hemorrhagic injury mortality. Advancing these novel strategies to the casualty in the field, particularly in tactical or austere environments, may prove beneficial for hemorrhage mitigation in order to temporize the window of survival to definitive care. Future studies of resuscitation and survival after traumatic injury must include analysis of prehospital deaths in order to fully understand the outcomes of early interventions.

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Blood Failure: Pathophysiology and Diagnosis

3

Nathan J. White and Kevin R. Ward

Introduction

Hemorrhage is the leading cause of preventable death from trauma in both civilian and military environments [1, 2]. It is estimated that hemorrhage may account for up to 90% of all potentially salvageable combat-related deaths in the US Military. Traumatic shock is a unique condition combining mechanical tissue injury with hemorrhage so that even organs that are not primarily affected by direct mechanical injury can be primarily and secondarily impacted by hemorrhage wherein these organs can fail in their primary function and in turn further impact other organ systems [3].

A convergence of military conflicts and science over the last 15 years, much of it coming from lessons learned from combat surgery combined with fundamental principles of forgotten physiology, has begun to transform our understanding of traumatic shock and our approach to its treatment. Among these is the recognition that impaired coagulation in the setting of traumatic shock that increases hemorrhage has been identified in 20–30% of trauma victims shortly after injury and when present can increase the incidence of organ failure, intensive care utilization, and even death [4]. This Trauma Induced Coagulopathy (TIC) has resulted in new treatment strategies such as Damage Control Resuscitation (DCR) which rely heavily on transfusion medicine therapies [5–7].

These insights have led to a new and growing concept that blood should be considered an organ system and that like other organ systems, when injured sufficiently it can fail and its failure, can in turn cause injury to other organs [8, 9].

N. J. White
Department of Emergency Medicine, University of Washington, Seattle, WA, USA

K. R. Ward (✉)
Departments of Emergency Medicine and Biomedical Engineering, Michigan Center for Integrative Research in Critical Care, University of Michigan, Ann Arbor, MI, USA
e-mail: keward@umich.edu

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Body organs are composed of distinct populations of cells integrated in a manner allowing them to perform certain critical functions. Blood consist of distinct cell types (red blood cells, white blood cells, platelets) and noncellular components (plasma). However, it is also intimately and inextricably integrated with the vascular endothelium which it constantly bathes and communicates with, each regulating many of the functions of the other. Thus, the blood-endothelial unit can be viewed an as organ system and is unique in that it connects all other organ system.

We will define hemorrhagic blood failure as an emergent state of blood leading to hemostatic dysfunction and a bleeding phenotype resulting from the physiologic and biochemical exhaustion of the blood-endothelium interface caused by a combination of hemorrhage-driven shock and tissue hypoxia, tissue injury, and blood cellular and plasma component loss.

This chapter will define the critical elements and pathophysiology of trauma-induced hemorrhagic blood failure and its diagnosis. Figure 3.1 will serve as a general framework for the mechanisms behind the initiation, evolution, and sustainment of blood failure. This framework not only helps to understand the process but also offers a means to work to develop new prevention, diagnostic, and treatment strategies.

These concepts will assist in understanding the basis for DCR and remote damage control resuscitation (RDCR) including the practice of hemostatic resuscitation. In the setting of traumatic hemorrhage, while there is no substitute for definitive surgical hemostasis, therapy provided prior to this time can greatly impact outcomes, including how rapid hemostasis can be achieved once surgery starts. This pre-surgical resuscitation phase or RDCR and DCR are designed to limit ongoing hemorrhage and to produce or preserve an adequate level of physiologic reserve to deliver a casualty to the hospital that can be salvaged with the follow-on strategy of DCR and Damage Control Surgery (DCS).

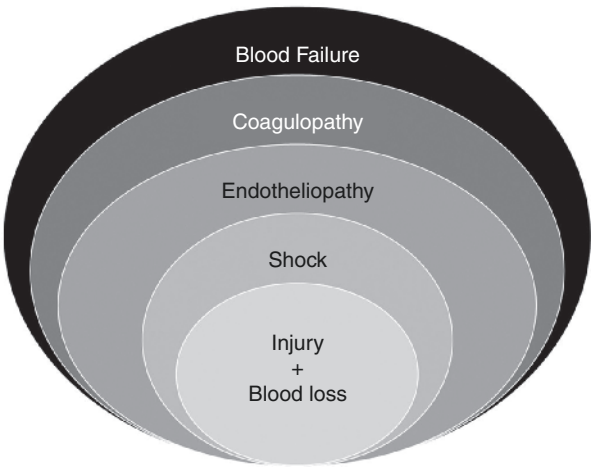

Fig. 3.1 Considering Blood as an organ: Framework for understanding the initiation, evolution, and sustainment of blood failure. (From White et al. [9], with permission of Wolters Kluwer Health, Inc.)

The Primary Role of Shock and Oxygen Debt

Victims of severe trauma who develop trauma-induced coagulopathy (TIC) prior to fluid resuscitation or the development of hypothermia show significant evidence of hypoperfusion as a function of elevated base deficits and lactate levels [5, 10, 11]. This is not surprising since severe shock resulting in tissue hypoperfusion manifested by elevated base deficits and lactate levels on admission have been known to be an independent predictor of morbidity and mortality after trauma. Hypoperfusion does not necessarily equate with the severity of injury as reflected in Injury Severity Scores although concomitant severe injury exacerbates the coagulopathy [12–15]. TIC can be exacerbated by plasma dilution with crystalloid resuscitation, hypothermia, and acidosis, which can be iatrogencially produced [5]. Certain traumatic tissue injuries such as those produced by blast and high velocity mechanisms as well as brain injuries may cause and/or exacerbate coagulopathy [16–18]. Many times it is difficult to distinguish their independent contributions to TIC.

Shock is traditionally defined as tissue oxygen delivery below tissue oxygen metabolic needs or demands. While conceptually easy to appreciate, it is important to have a deeper qualitative and quantitative understanding of shock which will impact resuscitative strategies and outcomes as they relate to blood failure. Shock caused by hemorrhage as well as other insults leading to tissue hypoperfusion and hypoxia results in tissues accumulating oxygen debt [19–22].

To date, oxygen debt is the only physiologic indicator that has clearly been linked to both morbidity and mortality in the form of multiple organ failure after shock [19–24]. The degree (depth and length) of oxygen debt have clear consequences as oxygen debt has been linked to the degree of reperfusion injury, inflammation, and acidosis. Oxygen debt can be viewed as a quantitate measure of whole body ischemia. A simple corollary at an individual organ level would be stroke or acute myocardial infarction where the greater the ischemic burden over time, the greater the final tissue damage and function during and after reperfusion.

Oxygen debt is the accumulation of oxygen deficit over time. Oxygen deficit is the difference between the amount of oxygen needed to meet metabolic demand and the amount of oxygen that is being delivered. An oxygen deficit occurs when less oxygen is being delivered relative to the required aerobic metabolic demand (shock) [19]. Figure 3.2 demonstrates the biphasic relationship of oxygen delivery (DO2) and oxygen consumption (VO2). As DO2 decreases, VO2 can remain constant due to an increasing ratio of oxygen that is extracted at the level of the tissue (OER) which is mirrored by a decrease in hemoglobin oxygen saturation (SvO2). However, as DO2 continues to decrease, there will eventually come a point where the OER cannot meet tissue VO2 demands resulting in a state of DO2-dependent VO2. At this point, metabolism transitions largely from aerobic to anaerobic metabolism. It is at this point that an oxygen deficit begins to accumulate as signaled by increased levels of anaerobically produced lactate levels and correlating increases in base deficit. Because oxygen deficit is the change in VO2 from baseline, oxygen deficit is, therefore, equal to the difference between baseline VO2 and the VO2 at a particular time point. This quantified deficit over time is oxygen debt (Fig. 3.3).

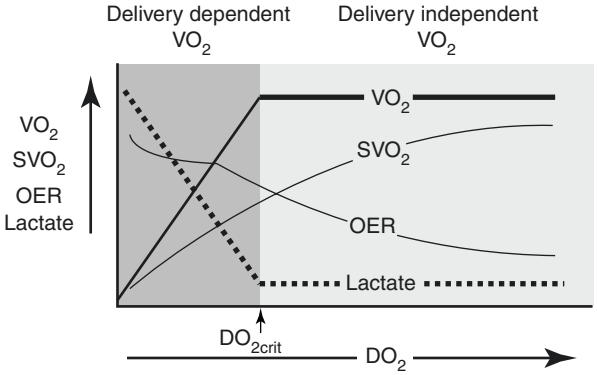

Fig. 3.2 The biphasic relationship of oxygen delivery (DO2) and oxygen consumption (VO2). As DO2 decreases, VO2 may remain constant due to an increase in the ratio of extracted oxygen (OER) at the tissue level. This is mirrored by a decrease in the venous hemoglobin oxygen saturation (SvO2). However, at some point, OER will not meet VO2 demands of the tissues resulting in a state of DO2-dependent VO2, whereby aerobic VO2 transitions largely to anaerobic VO2. At this point of critical DO2, an oxygen deficit occurs and an oxygen debt begins to accumulate reflected by an increase in byproducts of anaerobiosis such as lactate. While this biphasic relationship exists for the body as a whole, it also exists for each individual organ system. (From Ward [33], with permission of John Wiley and Sons)

As oxygen becomes limited and can no longer serve as the terminal electron acceptor (oxidant), ATP production significantly decreases. An increase in mitochondrial electron burden occurs destabilizing mitochondrial membrane electrochemical potentials which in turn allow electrons to leak from the membrane (Fig. 3.4) [25]. What little oxygen remains becomes available for pathologic reduction to form reactive oxygen species such as the superoxide radical which can react with nitric oxide when colocalized in the vascular space to form peroxynitrite. Peroxynitrite is highly toxic and capable of altering protein function by nitrosylating tyrosine moieties. Other highly damaging reactive oxygen species such as hydroxyl radicals form via hydrogen peroxide when antioxidant systems based on catalase and glutathione peroxidase are overwhelmed [26, 27]. Ongoing production of these oxidants which become exacerbated upon initial reperfusion (as more oxygen is available to react with previously increased pool of electrons) may cause irreversible cellular damage in the form of lipid peroxidation, protein nitrosylation, and DNA damage [26, 28, 29].

Adrenergic activation and catecholamine release induced by pain, neurovascular compensation, and tissue injury exacerbates tissue hypoxia secondary to vasoconstriction and endothelial injury during hemorrhage thus increasing oxygen debt [29]. Tissue injury with activation of pain and adrenergic pathways increase oxygen debt in the setting of hemorrhage over hemorrhage alone [30]. Adrenergic activation and catecholamine release also stimulate lactate production by activation of the Na^+-K^+-ATPase so that blood lactate levels are elevated and may be used as a supplementary tissue fuel source for vital organs [31].

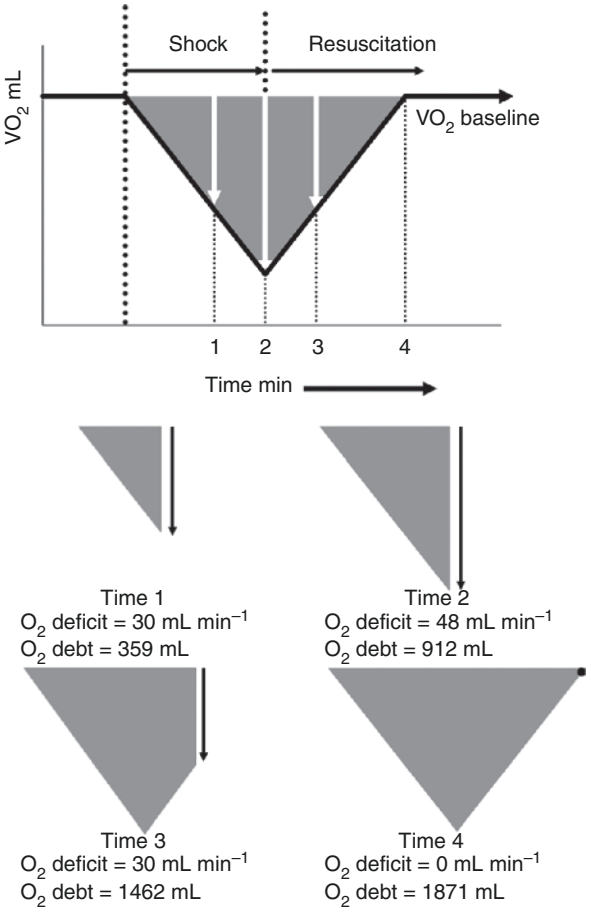

Fig. 3.3 Relationship between oxygen deficit and oxygen debt. Oxygen deficit is the difference between VO2 (indicated by the dashed line) and VO2 measured at a given time point (indicated by numbered arrows) during the shock period. The magnitude of the deficit is indicated by the length of the arrow. Oxygen debt is the accumulated sum of all oxygen deficits incurred and is represented by the area under the curve. It should be noted that halting the accumulation of the deficit does not repay back the accumulated debt. (From Barbee et al. [19], with permission of Wolters Kluwer Health, Inc.)

Since it is well-known that reperfusion injury drives subsequent inflammatory and immune dysfunction, it is important to underscore the strong relationship that exists between the degree/depth of oxygen debt and ensuing inflammation during the subsequent reperfusion injury. However, instead of being limited to a single organ, the insult affects multiple organs directly and indirectly via the reperfusion injury cascade [22, 32]. This will include the blood via damage to the endothelium as well as circulating coagulation proteins such as fibrinogen [33].

A common but very overlooked and misunderstood physiologic principle relating to oxygen debt is the need for timely repayment of a critical portion of oxygen debt [19–21, 24]. Similar to sleep and other physiologic debts, it is not possible to incur a significant oxygen debt with no consequences if it is not repaid. Halting the oxygen deficit by simply returning to a DO2- independent VO2 state, while essential is not sufficient in and of itself to achieve homeostasis (Fig. 3.3). In addition to meeting the basal metabolic demands of the body to restore aerobic metabolism and halt additional oxygen deficit accumulation, additional consumption is required to

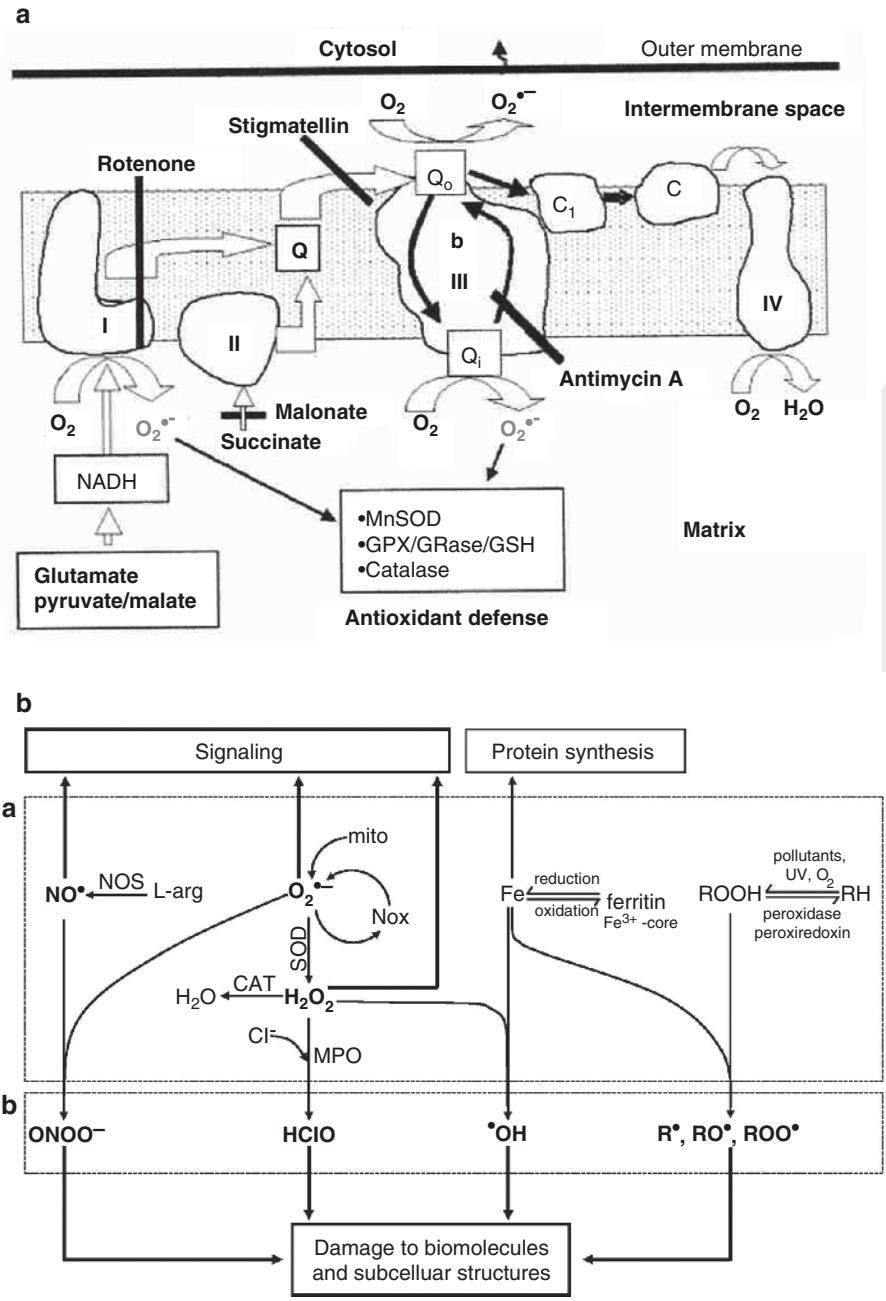

Fig. 3.4 Setting the stage for reperfusion injury. Hemorrhage-induced ischemia leads to electron build up and leak from the mitochondrial membrane (Panel **a**). The reintroduction of oxygen into previously ischemic tissue produces a host of reactive oxygen species (ROS) such as superoxide and hydroxyl radical and other compounds such as peroxynitrite which can induce signaling and cause oxidative damage to tissues and their cellular machinery (Panel **b**). (Adapted with permission from Best [120]; Weidinger and Kozlov [27])

replenish critical cellular energetic processes including the phosphogen and glycogen-lactic acid system which can be significantly depleted during shock [34]. The ability to repay these systems in a timely manner decreases significantly with increasing levels of debt and time.

It is important to note that while lactate clearance during resuscitation signals the halt of anaerobic metabolism and return of a DO2-independent VO2 state, it is not in and of itself a marker of debt repayment. This is because lactate production can be halted just above critical DO2, accompanied by lactate metabolism by organs such as the liver and kidney. However, debt has not been repaid. Just how much debt can be forgiven versus repaid and over what period of time is not entirely known (Fig. 3.5) [19, 20, 24]. Unfortunately, there are no current monitoring tools that allow care takers to know when oxygen debt has been repaid. Rapidly normalizing lactate and the body's OER makes the most sense physiologically to maximize chances of timely oxygen debt repayment [33, 35].

The principles of oxygen debt and its contribution to blood failure can serve as a basis for judging the limitations of various resuscitation strategies such as permissive hypotension in developing new resuscitation solutions or protocols. Their effects on

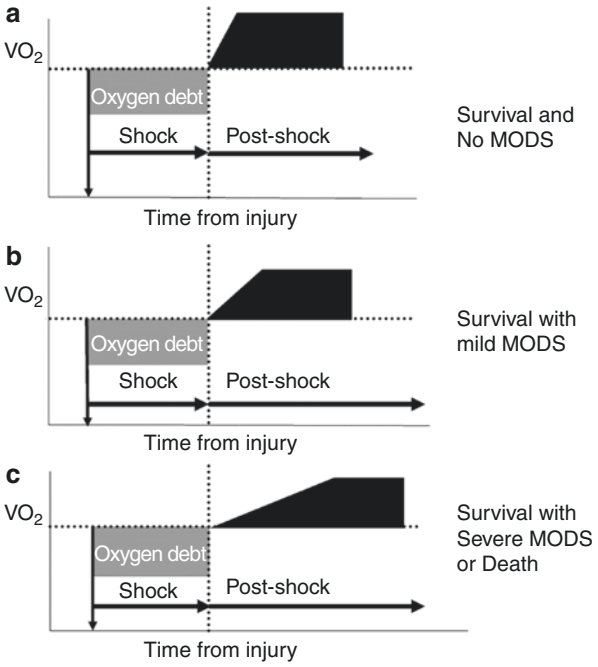

Fig. 3.5 Relationship between various oxygen debt repayment profiles and the likelihood of significant organ damage and/or death. Oxygen debt is represented by the area of the basal VO2 dashed line; oxygen debt repayment is the area above the basal VO2 dashed line. Resuscitation is marked by the dotted vertical line. The more rapid that critical portions of debt can be repaid (**a**), the better chance of survival and survival without organ failure. Delayed repayment (**b** and **c**) can result in varying levels of organ failure and ultimately death. The exact proportion of debt and the kinetics of repayment to avoid death and organ failure are not clearly known and there are challenges due to lack of technology in knowing both how much debt is accumulated and how much is repaid. (From Barbee et al. [19], with permission of Wolters Kluwer Health, Inc.)

limiting oxygen debt and in promoting repayment of critical portions to prevent or reverse blood failure are critical to consider. An understanding of oxygen debt also invites the opportunity to consider modulating oxygen consumption such as decreasing consumption through reducing metabolism as a means for reducing oxygen debt accumulation or in repaying debt more quickly.

The Microcirculation and Endothelium

The linkage between oxygen debt and traditional organ failure (hepatic, renal, lung, etc.) has been long recognized. It is therefore intuitive that the endothelial portion of the blood-endothelial unit is also affected by oxygen debt. The microcirculation with its endothelial lining is estimated to cover an area of up to 7000 m^2 and thus represents what might represent the body's largest organ system [36, 37]. The individual microcirculatory unit composed of the arteriole, capillary bed, and postcapillary venule is designed to ensure the delivery of oxygen and other nutrients to tissues in excess of their needs as well as to remove products of metabolism. With an estimated 10^{13} endothelial cells in an adult, the endothelium is constantly exposed to blood [36]. It is, therefore, logical that it would be prone to significant cellular injury resulting in dysfunction from trauma, hemorrhage, hypoperfusion, reperfusion injury, and inflammation [38, 39]. Complicating our understanding is the fact that there is no universal phenotype for the endothelium and that this phenotypic heterogeneity and the role it plays is likely to simply be a core property as it is with the parenchymal cells of other organ systems [38, 39]. For example, arteriole endothelium plays a major role in regulating vascular tone through signal transduction via shear stress to the vascular smooth muscle, while postcapillary venule endothelium is involved in leukocyte trafficking in response to injury [40]. Thus, injury to and dysfunction or failure of the endothelium can be termed "endotheliopathy" and thought of similarly to how we view injury to and impaired function of other organs (cardiomyopapthy, etc.). This endotheliopathy can be characterized by three main components: (1) paracellular permeability, (2) dysfunctional hemostasis, and (3) inflammation [41–43].

The endothelium regulates the integrity of the blood-organ barrier and clot formation including both anticoagulant and procoagulant functions. Endotheliopathy secondary to hypoxia results in endothelial cell surface activation by inflammatory mediators, in addition to adhesion of platelets, red blood cells, and leukocytes to activated endothelial cells. Endothelial cell activation also increases the production of coagulation pathway intermediates [9].

Under normal physiologic conditions, the endothelial cell surface maintains blood fluidity and regulates flow by multiple anticoagulant mechanisms. The surface-linked protein thrombomodulin binds thrombin converting it from a potent procoagulant to an anticoagulant by increasing its affinity for protein C above that

of fibrinogen [44, 45]. Activation of protein C can further reduce Factor V and VII levels. Once activated, protein C is also capable of interacting with endothelial cells to activate cell survival responses and maintain the endothelial barrier [46]. Synthesis of local prostacyclin (PGI2) and ADP metabolism to adenine nucleotides also inhibit platelet activation, adhesion, and aggregation. Vascular patency is impacted and regulated by the endothelium synthesizing nitric oxide which causes vasodilation to keep the microcirculation open. Nitric oxide also inhibits platelet function and tPA, which activates plasminogen to plasmin, the primary proteolytic enzyme of fibrin [41, 46]. As a result, nitric oxide formation secondary to hypoperfusion has competing effects on hemostasis.

Paracellular permeability leading to organ edema and failure is caused by hypoxia-induced breakdown of endothelial cell-cell tight and adherent junctions that regulate the endothelial blood-organ barrier in various tissues. While tissue specific, these barriers are, in general, maintained by structural components (i.e., adherens junctions), cellular components (i.e., smooth muscle cells and pericytes), and extracellular matrix proteins, all working to maintain the endothelium barrier [9]. This is important as the stress of hypoperfusion secondary to traumatic hemorrhage leads to antagonistic signaling of angioproteins 1 and 2 signal via the Tie-2 receptor to tighten (Ang-1) or loosen (Ang-2) the barrier that separates the strong procoagulant subendothelial tissues from blood [47]. An additional layer of protection is afforded by a thick surface matrix made up of membrane-bound glycoproteins and proteoglycans having heparin-like activity called the glycocalyx. The glycocalyx is a protective border on endothelial cells that regulates endothelial cell permeability and shear stress, meant to limit the interactions of the endothelium with circulating blood cells which in turn inhibits local thrombin activity [48]. However, with traumatic injury and severe shock, the injured endothelium initially promotes coagulation due to barrier disruption when activated by releasing Ang-2, tissue factor, von Willebrand factor, platelet activating factor, and PAI-I [48]. Thus, the balance of the state of quiescent anticoagulant or activate procoagulant phenotypes of the state of the endothelium is dependent on the degree of local and system injury.

Traumatic hemorrhage leading to tissue hypoxia and oxygen deficits will affect the microcirculation and its endothelium as described above by activating both pro- and anticoagulant responses to various degrees. Local acidosis and its severity can induce a decrease in nitric oxide and PIG2 production promoting vasoconstriction and platelet adhesion [49]. Shedding of the glycocalyx is among the first events. This shedding releases syndecans with their antithrombotic properties into the circulation [50–52]. Circulating catecholamines including epinephrine and high circulating syndecan-1 (a marker of endothelial glycocalyx degradation) have been positively correlated with the degree of glycocalyx shedding and mortality after trauma as evidenced by the degree of hyperfibrinolysis and coagulopathy underscoring the involvement of all components of the blood-endothelial unit leading to blood failure (Fig. 3.6) [53].

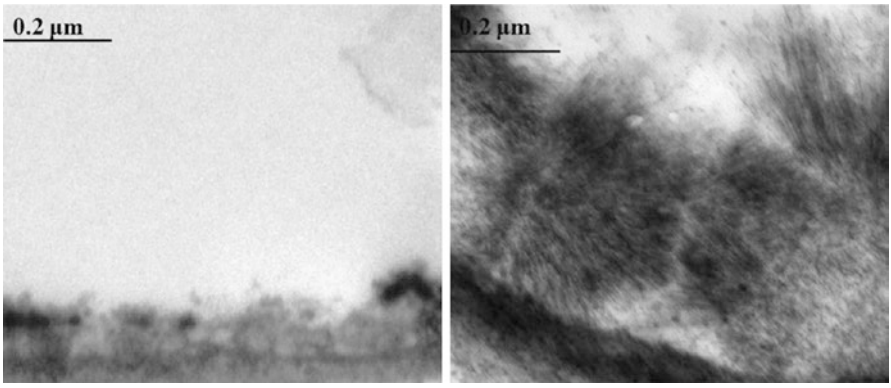

Fig. 3.6 Effect of hemorrhagic shock on the endothelial glycocalyx. Absence of the endothelial glycocalyx following hemorrhagic shock in a rat (left). Endothelial glycocalyx of experimental sham rat (right). (From Kozar and Pati [51], fig. 1, with permission of Wolters Kluwer Health, Inc.)

Glycocalyx shedding enables direct interactions between inflammatory blood cells and their mediators with the direct surface of the endothelium. This exposure is also capable of activating platelets as evidenced by increases in the platelet-derived inflammatory mediator soluble CD40 ligand that is also associated with sympathoadrenal and immune system activation and increased mortality [54]. Activated neutrophils migrate to the endothelial surface and contribute to oxidative damage of the surface through the release of neutrophil extracellular traps [55]. Endothelial cell surface oxidation may also promote direct red cell adhesion inducing local thrombosis and further microcirculatory hypoperfusion [56]. Lastly, oxidative stress from neutrophils is believed to directly impact circulating coagulation factors. For example, oxidation of a single key methionine in the Aα-C domain of fibrinogen to methionine sulfoxide by hypochlorous acid, produced by activated neutrophils can disrupt fibrin polymerization [57, 58]. Elucidation of the complex but integrated components of the blood-endothelial unit continue to argue for the concept and critical understanding of blood failure.

Given this, it is not surprising that the degree of endothelial damage is largely modulated by the degree of hypoperfusion or oxygen debt incurred which in turn ignites and feeds a spectrum of endothelial-driven coagulation responses that rapidly transitions to anticoagulation seen as the acute coagulopathy of trauma, as oxygen debt accumulates and shock worsens. These responses are coordinated at the blood-endothelial interface and are further modulated by circulating catecholamines, anaerobic metabolites, inflammation, oxidations, proteolysis, and cellular dysfunction. The end result of this unchecked process leads to what can be considered blood failure making it the first organ to fail as a result of traumatic shock (Fig. 3.7). Mitigation of oxygen debt accumulation and rapid repayment of oxygen debt should be viewed as essential and primary goals of trauma care at the earliest possible times.

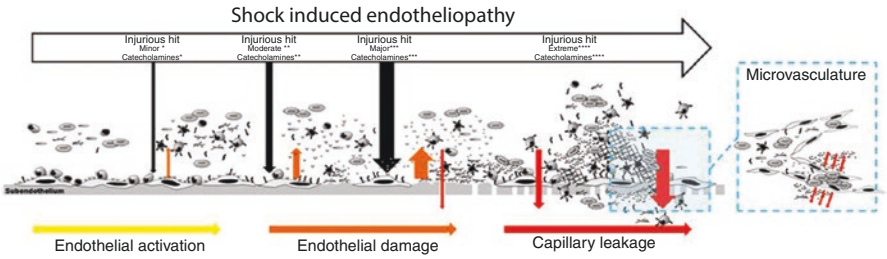

Fig. 3.7 Endotheliopathy of traumatic shock (see text for details). (With permission, Johansson et al. [121])

Blood Failure and Coagulopathy

Clinical observation strongly supports that coagulopathy as a manifestation of hemorrhagic blood failure is a serious evolving condition composed of many local and systemic responses to injury and shock. Primary among these responses in the release of tPA to activate fibrinolysis [59]. In addition, soluble thrombomodulin and activated protein C levels are increased. However, activated protein C levels are not sufficient in and of itself to anticoagulate normal plasma [60]. Platelets are also capable of activating sufficient FV to support hemostasis and overcome supraphysiologic levels of activated protein C [61]. While the procoagulant activity of thrombin generation is generally accepted to be elevated in trauma patients (even in the setting of coagulopathy) above those of healthy controls, the blood of trauma patients having prolonged prothrombin time/international normalized ratio (PT/INR) may not be truly reflective of reduced thrombin formation [62–64]. Abnormalities in plasma-based clotting assays like PT/INR may instead reflect complex interactions of fibrinogen depletion, fibrin degradation product interference with fibrin mesh formation, dysregulated thrombin generation, and excess plasmin activity manifested most obviously in fibrinolysis [9].

Perhaps most devastating in the evolution of hemorrhagic blood failure is increased proteolytic activity within blood. Multiple circulating proteolytic enzymes are increased after trauma including neutrophil elastase and plasmin [65]. Plasmin is a serine protease having proteolytic activity against a wide range of coagulation proteins, membrane proteins, and integrins. Plasmin proteolysis can activate FV, FVIII, and FXIIIa and can activate FXII, thus linking its activation to complement, inflammation, and immunity by direct generation of bradykinin from high molecular weight kininogen [66–68]. However, the most direct effect of plasmin on coagulation is its activity against both fibrinogen and fibrin, which contributes to rapid fibrinogen consumption and fibrinolysis after traumatic shock [69, 70]. The degree of fibrinolysis is positively associated with mortality and it appears to be proportional to the degree of shock [71].

Overall, severe trauma accompanied by shock appears to increase both thrombin generation and plasmin activation. While there may be some benefit to physiologic fibrinolysis after trauma, both an early increase in fibrinolysis and a later resistance to fibrinolysis are associated with increases mortality during traumatic shock [72]. Thus, while some degree of fibrinolysis may support vascular patency and tissue oxygen delivery during low flow states, it also exacerbates blood loss prior to surgical hemostasis. Studies such as the CRASH-2 trial demonstrate a mortality benefit in the setting of hemorrhage when tranexamic acid (an antifibrinolytic) is administered early after hemorrhage strongly suggesting that shock-induced blood proteolysis is an important component of coagulopathy and driver of blood failure [73]. Underscoring the integrated nature of the blood and endothelium as an organ system is that inhibition of plasmin activation with tranexamic acid in traumatic shock also appears to improve endothelial barrier function, reducing tissue edema and injury due in part to decreased bradykinin generation [74].

Another critical contributor to traumatic hemorrhage-induced blood failure is platelet dysfunction. Circulating platelets act to initiate clot formation at wounds by adhesion and aggregation during primary hemostasis. In addition, they provide a local environment that supports thrombin generation where they forcefully contract fibrin to stabilize evolving clots. When measured by impedance aggregation and viscoelastic methods, hemorrhage-induced platelet dysfunction has been strongly linked to mortality [75, 76]. The discreet mechanisms by which platelet dysfunction occurs is unclear given that the surface of dysfunctional platelets also seem to be paradoxically activated [77]. Since platelet-induced clot contraction is critical to clot strength after injury and hemorrhage, it explains the variability in clotting strength profiles encountered in the early time periods after trauma and resuscitation [78].

In summary, traumatic shock induces a spectrum of endothelial-driven coagulation responses that initially promote a procoagulant phenotype that is capable of rapidly devolving to an anticoagulation phenotype as oxygen debt accumulates and shock worsens. These responses are integrated at the blood-endothelial interface and are modulated by circulating catecholamines, anaerobic metabolites and acidosis, inflammation, oxidation, proteolysis, and cellular dysfunction (Fig. 3.8).

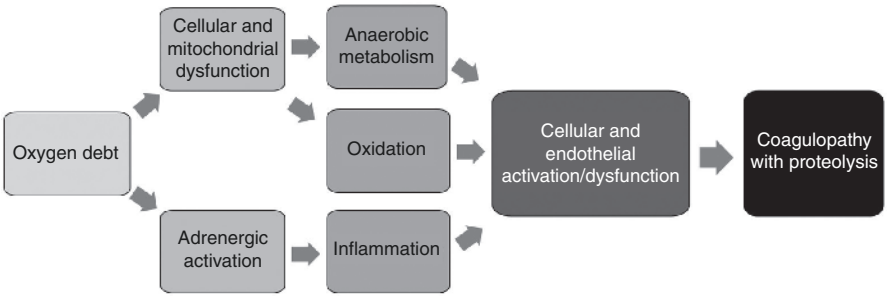

Fig. 3.8 Schematic of key linkages between oxygen debt, cellular dysfunction, and coagulopathy during hemorrhagic-induced blood failure. (From White et al. [9], with permission of Wolters Kluwer Health, Inc.)

Diagnosis and Monitoring of Blood Failure

Traumatic blood failure is defined as a cascading series of events within the blood compartment induced by injury and blood loss that culminate in the loss of the vital functions of the blood. Hemostasis is one vital blood function that can become dysfunctional contributing to increased mortality after severe injury. As explained earlier, the pathophysiology of altered hemostasis is complex and linked to a series of events initiated by traumatic shock.

It should be emphasized that the major factor initiating blood failure and its severity is the magnitude of traumatic shock. Rapid halting of oxygen-deficit accumulation and repayment of oxygen debt are essential in limiting the degree of blood failure. The ability to monitor for each aspect of blood failure would enhance the rapid application of therapies to prevent or treat it. Unfortunately, there are few readily available monitoring methods that have been demonstrated to be effective in accurately and rapidly detecting shock, hemostatic, immune and endothelial dysfunction.

Perhaps the most well-known tool that is beginning to move beyond the trauma center into the field is the use of point of care (POC) or near POC monitoring of whole blood lactate. As discussed earlier, lactate is capable of tracking the accumulation and degree of oxygen debt during injury, but it requires serial measurements [22, 79–81]. The quantitative and temporal ranges and limits of lactate to predict blood failure in humans have not been well defined. In addition, given the biphasic nature of the relationship between oxygen delivery and consumption, clearance of lactate does not ensure repayment of oxygen debt [19]. Experimentally, it appears that the faster lactate clearance is, the better chance there is of repaying debt or at least of critical portion of debt that improves survival [24, 82]. Thus, trajectory of clearance is important. Elevations of lactate should prompt aggressive efforts to halt hemorrhage and to provide a level or resuscitation that limits further lactate accumulation and begins to clear lactate. Use of permissive hypotension in the RDCR or DCR setting pose challenges to this strategy and must be balanced with the need to limit ongoing hemorrhage as well as the availability of blood products to use in resuscitation.

Other potential useful tools include tissue hemoglobin oxygen saturation (StO2) and compensatory reserve index (CRI) monitoring. Based on the relationship between oxygen delivery, oxygen consumption, and oxygen extraction, the use of StO2 monitoring is attractive. Spectroscopy techniques including near infrared spectroscopy (NIRS) and resonance Raman spectroscopy (RRS) attempt to exploit the fact that the majority of blood volume within a tissue is 70–80% venous [83]. The ability to monitor aggregate StO2 of a tissue is thus representative of the postextraction portion of the tissue compartment similar to monitoring of central or mixed venous oxygen saturation (Fig. 3.2). Thus, the potential exist for StO2 to detect reductions in tissue oxygenation prior to reaching critical DO2 as well as to ensure that during resuscitation that oxygen extraction ratios is increased into normal ranges helping to ensure that oxygen debt is being rapidly repaid as lactate levels fall [33, 84]. Certain caveats to the use of this strategy exist including choosing a

target tissue to monitor that is sensitive to reductions in blood flow and responsive to resuscitation. For NIRS, the use of skeletal muscle beds such as the deltoid or thenar eminence has been used. However, when used in this manner, NIRS will also capture myoglobin oxygenation spectra which cannot be differentiated from hemoglobin. This is important since the p50 of hemoglobin is 5 mmHg versus 26 mmHg for hemoglobin [84]. This fact may prevent NIRS from acting as a sensitive early warning monitoring modality. Its use in trauma to guide treatment has been met with mixed results with wide variability in baseline readings [85, 86]. While RRS using the buccal mucosa appears to overcome these issues, its use is still experimental and has only been tested in preclinical models [87]. If NIRS is used, attempts to normalized StO2 to values above 70% should be made with concomitant tracking of lactate levels. This same strategy should be utilized if monitoring of central venous hemoglobin oxygen saturation (ScvO2) is available in the in-hospital setting. Experimental models indicate that changes in clot strength during hemorrhage are impacted by changes in ScvO2 changes indicating, again, the sensitivity of hemostasis to tissue hypoxia [88].

CRI is a newly developed technique utilizing artificial intelligence to identify and track changes in the photoplethysmograph (PPG) of a pulse oximeter to detect vascular changes associated with cardiovascular decompensation due to central hypovolemia [89, 90]. Preliminary clinical data suggest CRI may be of value in identifying patients who are actively decompensating before changes in traditional vital signs such as systolic blood pressure occur [89]. In one study, abnormal CRI values were found to equal the ability to identify hemorrhage and correlated well with lactate levels themselves [91]. While promising, the ability of CRI to robustly detect and track the accumulation of lactate and its clearance require further study.

In summary, serial whole blood lactate and surrogates such as base deficit are currently the most rapid and efficient means to estimate and monitor the degree of oxygen debt and its resolution associated with traumatic shock and its resuscitation and should be used in conjunction with the coagulation-based laboratory methods described below. Laboratory methods have been used to identify and characterize these components of blood failure with variable success. In this section, we review the use of laboratory methods used to identify blood failure with an emphasis on identification of coagulopathy after injury.

Plasma-Based Laboratory Methods

The prothrombin time (PT) assay is a widely used and standard laboratory coagulation assay measuring the extrinsic coagulation pathway activation state. The test is primarily used to manage anticoagulation therapy using vitamin K antagonists. The PT has been used to identify the presence of a distinct “acute coagulopathy of trauma” present in approximately 25% of severely injured trauma patients [4]. A prothrombin time test (PT) of >18 seconds was used as the definition of coagulopathy and was associated with an approximately four- to sixfold increased mortality [4]. Since these initial reports, PT and the PT-based standardized International

Normalized Ratio (INR) have continued to be used as a primary laboratory method for identification of coagulopathy. A large multicenter study of PT ratio found that any increase beyond 1.2 represented an increased mortality for trauma patients, increasing from 7% to 22% [92]. However, increased INR may overestimate the presence of coagulopathy in stable trauma and surgical patients [93]. Further increasing the INR cutoff to >1.5 found increased specificity for both hemorrhagic and thrombotic complications in trauma patients [94].

The activated partial thromboplastin time (aPTT) is another standard plasma-based coagulation assay that measures the intrinsic pathway of clot formation. It was developed and is most widely used to manage anticoagulation therapy using unfractionated heparin. Prolongation of aPTT is predictive of mortality in trauma patients where it was found to be less sensitive but more specific [4]. While the aPTT is a part of most standard coagulation panels measured in trauma patients, its use for traumatic coagulopathy and blood failure has been limited. The PT/INR and aPTT are often measured together and are useful as screening tools when one or both are prolonged in trauma patients. However, since procoagulant activity is typically increased in the early stages of traumatic coagulopathy and blood failure, their usefulness to guide specific therapies are limited [62, 63]. This limitation likely stems from the fact that multiple coagulation abnormalities ranging from decreased activity of specific coagulation factors such as Factor V and VIII, endogenous heparinization, and loss of fibrinogen are present in trauma patients and can induce prolongation of one or both of these assays [52, 95, 96]. Thus, they are most useful as screening tools capable of identifying the risk of coagulopathy and should be used to initiate more specific laboratory investigation.

Of particular importance to the detection and treatment of blood failure is the concentration of the hemostatic protein fibrinogen which is negatively associated with mortality after trauma [96]. A popular method for measuring fibrinogen concentration in plasma is based upon the method of Von Clauss, where functional fibrinogen concentration in plasma is measured by its time to fibrin formation after activation by an excess of thrombin after sample dilution [97]. Fibrinogen is rapidly lost from the blood during hemorrhage requiring blood component transfusion, being the first coagulation protein to reach critically low functional levels in experimental models and during surgery with significant blood loss [98]. Trauma patients with decreased fibrinogen concentrations in the emergency department require more blood product transfusions and are more likely to die [96]. Standard cutoff values for fibrinogen replacement have increased steadily as more evidence of its importance has accumulated. Historical cutoff values of 100 mg/dl have increased to a recommended maintenance of 150–200 mg/dl by European guidelines [99]. A more recent large multicenter study of fibrinogen concentration in trauma patients found that mortality doubled when fibrinogen was less than 228 mg/dl, suggesting that replacement thresholds are likely to increase even further [100]. Despite strong associations with clinical outcomes in trauma, fibrinogen concentration is not measured directly in many trauma centers. However, clinically relevant hypofibrinogenemia is common and shows a strong correlation with other standard laboratory parameters such as hemoglobin concentration and base excess, which may indirectly suggest the need for early fibrinogen replacement [101].

Another important contributor to coagulopathy after trauma is increased proteolytic activation in the blood by generation of plasmin from plasminogen. Plasmin is a fairly nonspecific protease that has particular affinity for enzymatic degradation of fibrin. Plasmin's degradation of fibrin increases the fibrin-specific cleave product D-dimer in blood. D-dimer is commonly used clinically as a screening tool to identify venous thromboembolism in emergency department patients [102]. There is ample evidence supporting significant elevations of D-dimer in blood during blood failure with coagulopathy [71, 103, 104]. However, D-dimer tends to be elevated in most trauma patients, and thresholds for sensitive detection of coagulopathy and blood failure have not yet been reported.

Whole-Blood Laboratory Methods

Common plasma-based laboratory methods used for detection of coagulopathy after trauma cannot consider the cellular contributions to blood failure. This is important because cellular dysfunction, especially of blood platelets, is strongly associated with mortality after trauma [77]. Kutcher et al. used multiple electrode aggregometry to find that decreased platelet aggregation responses to any agonist in emergency department trauma patients was associated with a tenfold mortality increase [75]. Platelet contraction is also a primary contributor to changes in clot formation in emergency department trauma patients [18]. In addition, changes in hematocrit, mostly determined by red blood cell mass, can also directly affect clot formation and hemostasis [105, 106].

The whole-blood-based laboratory method that has gained significant traction in trauma medicine and transfusion practice is the viscoelastic hemostatic assay (VHA). The measurement is achieved using a cylindrical cup filled with whole blood into which a central pin is inserted and acts as a sensor. Either the cup or pin is rotated through a small angle at low frequency around the vertical axis. Blood contained within the cup is activated to clot, which couples the motion of the cup to the pin via fibrin causing a change in amplitude of rotation of the sensor (measured in mm) in either direction (Fig. 3.9). The resulting extremes in amplitude are plotted over time and are used to detect the elastic parameters of clot initiation, propagation, and durability over time. Originally developed by Hartert, this assay monitors the elastic properties of whole blood clots over time, reporting clot onset time, clot formation kinetics, clot firmness or amplitude, and clot degradation or fibrinolysis (Fig. 3.10) [107].

This method is advantageous because it includes contributions of all blood components to coagulopathy and offers a simplified functional view of coagulation to the clinician. The two major devices in clinical use are thrombelastography (TEG) and rotational thromboelastometry (ROTEM). These devices make similar measurements but differ enough so that they should not be used interchangeably [108]. Alternative methods using resonance frequency and ultrasound to measure viscoelastic properties of blood clots are available, but have not yet gained wide acceptance [109, 110]. However, caution should be taken when interpreting platelet function using whole

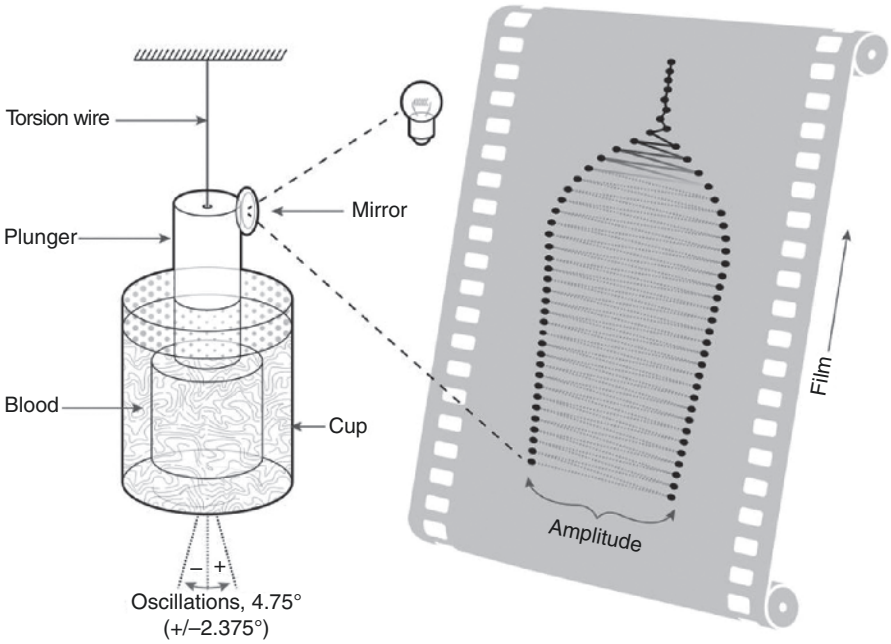

Fig. 3.9 Hartert's thrombelastograph device (H-TEG). The cylindrical container (cup) is rotated through a total angle of 4.75 around the vertical axis. Light from a slit lamp is reflected onto photographic film that moves at a rate of 2 mm/min to record rotation of the rod (the film roll is 15 m long and 100 mm wide). In practice, lines between the dots on the film are not visible because the intensity of the light and photosensitivity of the film are configured so that the film is blackened only when the light is stationary, that is, at the point of maximum rotation of the cup when there is a 1-second pause in the oscillatory movement. (From Hochleitner et al. [122], with permission of SAGE Journals)

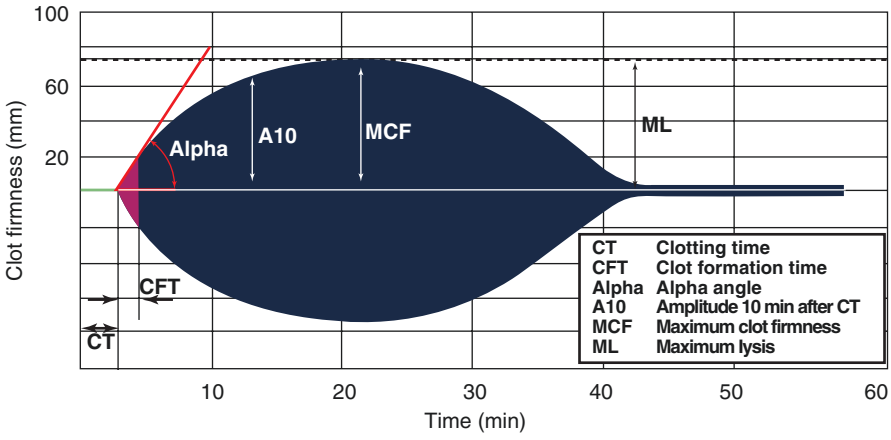

Fig. 3.10 Visual output of whole blood coagulation using viscoelastic hemostatic assay provided by rotational thromboelastography (ROTEM). (From Tanaka et al. [123], fig. 1, with permission of Elsevier [123])

blood VHAs. Activators such as tissue factor and kaolin used in these assays generate adequate thrombin to activate platelets fully, even if alternative platelet activation pathways, including arachidonic acid and ADP, are extrinsically blocked or internally deranged. The result is a lack of sensitivity to exogenous platelet inhibitors such as aspirin and clopidogrel. Alternative platelet-specific activators have been developed to overcome these limitations (e.g., platelet mapping assays) and have shown significant platelet dysfunction in trauma patients [76]. However, their accuracy and utility has not yet been defined in the trauma population.

Blood failure induces progressive impairments of clot formation over time that can be detected using VHAs. Davenport et al. found that the first ROTEM abnormality during traumatic coagulopathy was an absolute decrease of clot amplitude [111]. As coagulopathy develops, VHA parameters continue to evolve in predictable ways. Progressive prolongation of clot activation or onset times appear in addition to decreased clot amplitude reflecting decrease clot strength. Increasing fibrinolytic intensity induces further decreases of clot amplitude with increased terminal clot breakdown representing fibrinolysis [112]. Terminal coagulopathy representing a likely nonsurvivable injury is represented by a VHA curve assuming a diamond shape (death diamond) with prolonged clot onset time, low amplitude, and rapid terminal clot breakdown (Fig. 3.11) [113].

VHAs have demonstrated increased ability to predict transfusion needs, including massive transfusion, compared to plasma-based laboratory methods when measured in trauma patients at hospital admission [114]. A single center randomized

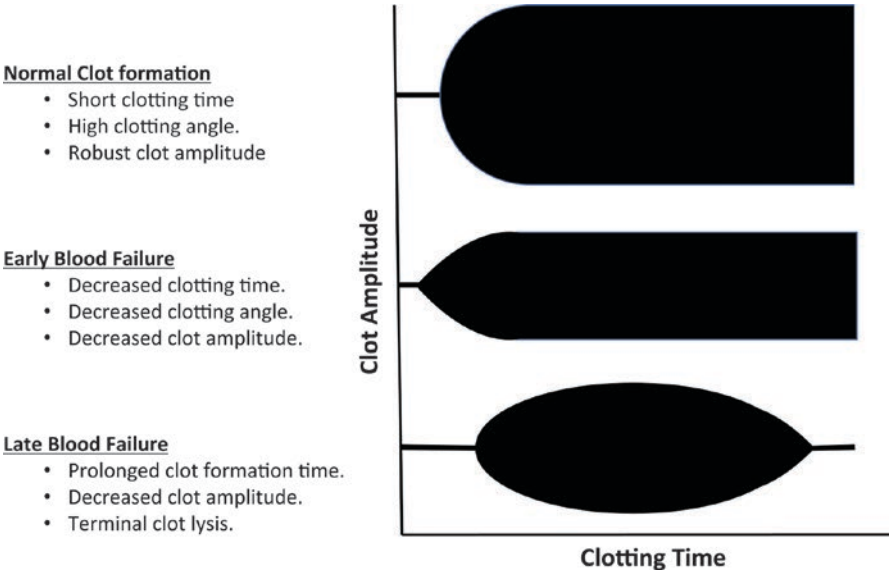

Fig. 3.11 Characteristic viscoelastic hemostatic assay profiles depicting normal clot formation and those associated with early and late blood failure including the "death diamond" of late blood failure characteristic of hyperfibrinolysis

controlled trial of goal-directed massive transfusion using VHA parameters vs. conventional coagulation tests also demonstrated improved survival with less blood products used [115]. VHAs can also be useful because their characteristics and behavior under different activating and inhibitory conditions can be used to diagnose sources of coagulopathy and guide hemostatic therapies. An increasing number of trauma centers use goal-directed transfusion algorithms based upon VHA measurements. They include transfusion of plasma or prothrombin concentrates for prolongation of clot onset times, transfusion of platelets and cryoprecipitate or fibrinogen concentrates for decreased clot amplitude, and the use of the antifibrinolytic drug tranexamic acid for clot lysis (Fig. 3.12) [116, 117].

While VHAs are increasingly being used to diagnose and guide therapy for the coagulopathy of blood failure after trauma, questions still surround their utility for this use. Perhaps the least clear application of VHAs for treatment of blood failure is their ability to identify clinically relevant fibrinolysis and guide subsequent antifibrinolytic therapy. Raza et al. reported that over 50% of trauma patients had clinically relevant

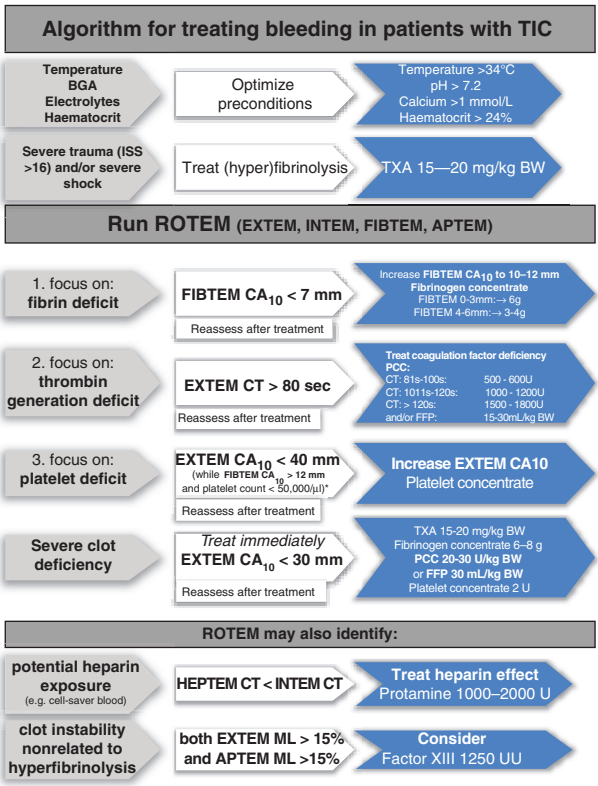

Fig. 3.12 Example of goal-directed transfusion therapy for treatment of trauma-induced coagulation (TIC) using viscoelastic hemostatic assays such as rotational thromboelastography. (From Schochl et al. [116], fig. 2, with permission of Wolters Kluwer Health)

fibrinolytic activation measured by plasmin-antiplasmin complex level, while only 5% of these patients demonstrated appreciable clot lysis on ROTEM [71]. In addition, there appears to be significant variation of the lysis parameters reported by TEG that suggesting that fibrinolysis is inhibited, when underlying significant fibrinolytic activation is likely present [103]. Systematic reviews of VHAs for diagnosis of coagulopathy and therapeutic guidance during blood failure offer some evidence that these tests can be useful, but lack of overall evidence, including lack of large multicenter prospective randomized trials, continues to limit their use [118, 119].

Conclusion

The blood-endothelial unit (Blood) is a complex organ and like other organs is prone to failure when severely injured. The link between the degree of traumatic shock and blood failure makes blood the primary target organ for treatment using the principles of DCR and RDCR. A more robust understanding of the tightly linked physiologic and biochemical elements responsible for blood failure and its resolution will hopefully create a new generation of diagnostic and therapeutic approaches to hemostatic resuscitation strategies for DCR and RDCR that improve outcomes.

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Prediction of Life-Threatening Hemorrhage

4

Dominick A. Vitale, Marc Maegele, and Matthew A. Borgman

Introduction

Trauma-related mortality is one of the top causes of overall mortality in a number of age groups including both the young and the elderly in industrialized countries [1, 2]. This burden carries not only a toll on society but also a financial toll on the healthcare system as a whole. Of these trauma-related deaths, up to 50% can be attributed to uncontrolled hemorrhage [3]. Massive uncontrolled hemorrhage has been shown to lead to a lethal triad of coagulopathy, hypothermia, and acidosis that can be irreversible [4]. Historically, the early identification of patients with shock and or coagulopathy has been poor. An estimated 10–25% of all multiple injured trauma patients present with shock or acute traumatic coagulopathy upon arrival [5–7]. This shock and coagulopathy is not only related to acute surgical bleeding but also as a result of profound local release of inflammatory mediators due to tissue trauma [8]. In response to the recognition of massive and life-threatening bleeding leading to significant mortality in the trauma population, most patients deemed to be in shock related to surgical or coagulopathic bleeding receive blood transfusions during their early resuscitation phase. Over the last few decades, the transition to a balanced resuscitation of red blood cells (RBCs), fresh frozen plasma (FFP), and platelets emulating whole blood has improved mortality in traumatically injured patients [9–14]. Trauma patients requiring massive transfusion (MT) (>10 RBCs in 24 hours) have also been reported to have a mortality of up to 40–60% and deplete

D. A. Vitale
Trauma/Critical Care, Brooke Army Medical Center, Fort Sam Houston, TX, USA

M. Maegele
Department of Traumatology and Orthopedic Surgery, Institute for Research in Operative Medicine (IFOM), Cologne-Merheim Medical Center (CMMC), University Witten-Herdecke (UW/H), Cologne, Germany

M. A. Borgman (✉)
Department of Pediatrics, Brooke Army Medical Center, Fort Sam Houston, TX, USA

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blood banks consuming over 70% of the blood products used for trauma purposes [15]. Meyer et al. showed that despite the American College of Surgeons Quality improvement guidelines recommendation of first cooler of blood product arrival by 15 minutes, odds of mortality increased by 5% with every passing minute waiting for blood products to arrive [16]. It is because of this that at least 85% of major US trauma centers have a massive transfusion protocol (MTP) established for the rapid mobilization of blood products from blood banks and early administration of products in a predefined ratio [17]. Despite everything we know about MTP and the survival benefit of early administration of blood products, there still does not exist a specific set of criteria for early (pre-hospital or ED) activation of the MTP.

Definition of Massive Transfusion

In order to understand the importance of MT with life-threatening hemorrhage (LTH) and its effect on outcomes, it's necessary to settle on the definition of MT and of an outcome. This unfortunately is not straightforward.

Historically, the definition of MT has been the need of 10 or more units of RBCs over a 24-hour period [18–20]. This definition has been reported to have multiple flaws in appropriately describing the trauma patient with LTH and may either underestimate or overestimate the severity of bleeding and therefore the risk of death from hemorrhage. First, as stated by Cantle and Cotton [18], this definition fails to account for plasma and platelet transfusions that are often co-administered. Second, it may leave out those patients who were so severely injured and clearly in hemorrhagic shock that only received a few units of RBC prior to death [18]. The need for an MTP activation is primarily to direct the blood bank to rapidly deliver blood products to the bedside of a hemorrhaging patient. While this would be essential for a patient needing 10 units of RBC within the first 2 hours, it may not be necessary for 10 units required over a 24-hour period. Recent efforts have been made to improve on the definition by changing the timeframe in which 10 units or more of RBC were transfused to within 6 hours, but this still carries the same flaws as its predecessor and introduces survival bias [18]. In response to these potentially biased definitions of MT, numerous authors have developed their own definitions of MT to improve both the research and clinical definition which may have significant downstream implications with regard to predictive models of need for MT in LTH [18, 21].

The Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study, which will be discussed in further detail in a later section, introduced the concept of Resuscitation Intensity (RI) [22]. This concept incorporates all types of fluid used in the initial resuscitation of trauma patients, to include each liter of crystalloid, each 0.5 L of colloid, and each unit of plasma, RBC, or apheresis platelets being defined as a single unit of resuscitation fluid. Rahbar et al. in 2013 showed that there was a threefold increase in mortality when a threshold of 3 units of resuscitation volume was administered over the initial 30 minutes. This translated to a 6-hour mortality of 14.4% vs. 4.5%, respectively,

and a 24-hour relative increase in mortality of 76%. Given the RI is based on a fluid requirement per unit time, it accounts for the survival bias seen in the historical definition while also allowing for multiple methods of resuscitation not limited to colloid; however, it may be difficult to compare those patients who receive a predominantly crystalloid resuscitation to those who receive a colloid hemostatic one [18, 22].

The Critical Administration Threshold (CAT), developed by Savage et al., is one of those models set out to redefine the concept of MT and remove the aforementioned survivor bias creating a more evidenced-based approach [23]. The CAT was defined as a threshold of 3 units of RBCs transfused over a 1-hour period. When compared to the traditional definition of MT as defined previously, CAT was more predictive of mortality (RR 3.6 vs. 1.8 for MT) [23]. Since CAT is a dynamic measure it can be followed throughout a patient's resuscitation as opposed to one point in time. The number of episodes in which a patient met the CAT threshold within the first 24 hours was also predictive of the odds of death. The most significant improvement of CAT over MT was the ability of CAT to identify those patients who were equally as injured but who did not meet the MT threshold of transfusion in the first 24 hours. Of the 169 patients studied in the original article from 2012, 15 patients were CAT positive but did not meet the MT threshold. The CAT ability to recognize these patients improves on the survivor bias of the old MT definition [3]. This model was prospectively validated by the same authors at a separate institution with similar results. CAT was shown to be a more sensitive tool for identifying those critically injured patients that would benefit from early activation of a MTP when compared to the traditional definition of MT [23]. Although this new approach improves survivor bias, the currently existing models for prediction of the need for MT in LTH all define MT in the historical sense.

Evidence of Improved Outcomes

MTPs have evolved over the last few decades. The purpose of these protocols in general is to minimize any delay of the administration of blood products to a hemorrhaging patient by prescribing a predetermined "batch" of blood units to be empirically delivered from the blood bank to the bedside. An ideal protocol proactively sends batches of blood products to the bedside of a severely bleeding patient, as opposed to a reactive process that requires individual ordering of each blood product, which inevitably results in delays. Any such delay has been associated with an increase in mortality [16].

Efficient MTPs require a coordinated effort between first responders, emergency room, trauma team, and blood bank personnel. Various protocols exist and are site- and regional-specific. Riskin and colleagues in 2009 showed a drastic mortality reduction from 45% to 19% after implementing a MTP [24]. Dente and colleagues also found that there was a drastic reduction in early mortality from 57% to 19% when patients were transfused in a standard <2:1 ratio RBC:FFP than when transfused >3:1 [25]. At many institutions, MTPs are initiated by ED staff or

trauma surgeons either prior to patient arrival from information reported by first responders or after primary survey in the trauma room immediately upon arrival. When an MTP is activated, blood banks immediately release uncross-matched RBCs, plasma, and platelets) often in a 1:1:1 unit ratio, typically 5–6 units of RBCs and plasma with 1 unit of apheresis platelets (equal to 5–6 units of whole blood derived platelets). Some centers provide different ratios of products and some even change the ratio delivered in each batch of blood products over time. After the initial MTP pack has been delivered, several blood tests (e.g., CBC, type and cross, comprehensive metabolic panel, standard coagulation assay, Ca^{2+}, lactate, blood gas) are often obtained in order to assess the resuscitation. Some centers use viscoelastic testing (rapid-TEG or ROTEM) to guide the use of specific blood products or hemostatic adjuncts. Several adjuncts to the MTP may also be listed in a protocoled resuscitation effort, including an antifibrinolytic (e.g., tranexamic acid (TXA)), cryoprecipitate, or in rare cases recombinant factors of coagulation including VII and VII, and 4-factor prothrombin complex concentrate (PCC) to aid warfarin reversal. In Europe, recent studies reported on the diversity of the guidelines for damage control resuscitation across a number of institutions [26]. Although some similarities existed among the trauma centers, there are numerous differences in the use of triggers, labs to guide resuscitation, adjuncts, and indications for cessation of MTPs. This only demonstrates the evolving nature of DCR and the complex environment of standardized algorithms in the setting of varied sources of evidence [26].

The debate over the most beneficial ratio of blood products during a massive resuscitation of a patient in hemorrhagic shock is ongoing. In the two largest studies to date, the results are mixed. In the prospective observational PROMMTT study, ratios of plasma: RBC and platelet: RBC were compared as both continuous and categorical values. Results indicate that increased ratios as a continuous variable were independently associated with an reduced 6-hour mortality [27]. When both ratios were analyzed as categorical values, a ratio of >1:1 was associated with reduced 6-hour mortality. This mortality benefit was lost, however, after 24 hours [27]. In the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial a mortality difference at either 24 hours or 30 days was not reported between patients receiving a 1:1:1 ratio vs. a 1:1:2 ratio of plasma, platelets, and RBCs, respectively [28]. The authors of the trial were able to conclude that the patients who did receive a 1:1:1 ratio had achieved hemostasis and experienced less death from exsanguination in the first 24 hours [28]. Borgman et al. evaluated patients who were predicted to need a MT and found that ratios of FFP:RBC >1:2 during the first 5 hours of admission improved survival, highlighting the importance of utilizing a predictive score to a trauma patient in order to identify who would benefit from an aggressive resuscitation strategy [29]. As noted earlier, ongoing monitoring of the resuscitation is essential and may ideally be guided by viscoelastic monitoring [30]. MTPs are generally stopped by the provider when it is determined that the patient is stabilized and there is no longer life-threatening bleeding; however, it is essential to continue to assess and monitor the patient for metabolic and coagulation derangements or potential new bleeding.

Predictive Models

Over 14 predictive models and scoring systems of life-threatening hemorrhage in order to improve timing to transfusion in trauma patients who present in shock or coagulopathy secondary to traumatic injury have been developed to date [3, 8, 15, 17, 18, 31–36]. These studies did not use the same definition of MT. A summary of both civilian and military data derived scoring systems presented in this chapter are presented at the end of each section in Tables 4.1 and 4.2, respectively. Additionally, the data for which these models are based upon are mostly retrospective from one or more institutions with a variety of experience with trauma and MT. Therefore, the limitations of retrospective studies (missing data, lack of standard protocols of treatments, and laboratory draws) apply. In a published study by Trickey et al. evaluating data from nine MT predictive models, it was found out that anywhere between 41 and 88% of cases had sufficiently completed datasets for the variables being studied [37]. This missing data and difficult patient populations can lead to significant selection bias. Those patients with complete datasets may be those that survived their early resuscitation more frequently or those patients in which the care team had the benefit of time and patient stability to gather all of the needed data points. Obtaining laboratory studies was not necessarily standardized and can be influenced by the patient presentation or the bias of the clinician. Despite these biases, the following models and scoring systems give the practitioner more objective data to assist with early activation of MTPs, which have been shown to improve survival in the critically injured. One major difference between some of the scoring systems is the patient population from which the data is collected, particularly between civilian and military trauma settings. In the civilian trauma centers with predominately blunt-injured patients, laboratory values, radiographic studies, and functioning blood banks are commonplace and resources tend to be abundant. In contrast, military patients have a higher incidence of blast and penetrating injury, and resources especially in more austere environments tend to be scarcer. Blood products may not be easily obtained and plasma and platelets are less available resulting in administration of whole blood in some circumstances [38]. Whole blood is also used in military facilities based on its potential superiority to blood components [39]. It is for these reasons the following major scoring systems have been presented in separate categories based on civilian and military databases from which they were derived and in no particular order of reliability or author preference.

With all of the available scoring systems, it can be difficult to determine which model works best or has the best fit for a specific trauma program in order to best communicate with blood banks and therefore improve outcomes. Clearly, if some laboratory or radiographic data is not available to the trauma team at the time of resuscitation, then some of the models will not be helpful. Each must be weighed against the individual situation and resources available but should not be substituted for clinical judgment. Clinical "gestalt" is not infallible as demonstrated by Pommerening et al. who showed that gestalt alone had a sensitivity of 66% and a 35% positive predictive value (PPV) making it a poor screening test, missing almost one-third of patients who would ultimately require MT [40]. This only serves to underscore the need for an objective measure to help supplement the decision-making process of activating MTPs.

Table 4.1 Civilian database derived MT score/model summarization of characteristics

Score/ model	ABC [6]	TASH [4]	PWH [29]	Vandromme [31]	Baker [24]	TBSS [8]
Design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
Number of patients	596	4527 [4] 1517[a] [30]	1.891[b]	514	654	119 113[a]
Setting	Civilian, single center	Civilian, multi center	Civilian, single center	Civilian, single center	Civilian, multi center	Civilian, single center
Variable type	Non-weighted, dichotomous	Weighted	Weighted	Non-weighted, sum predictors	Non-weighted, sum risk factors	Weighted, sum risk factors
Definition of MT	>10 units first 24 hours	>10 units ED to ICU	>10 units first 24 hours	>10 units first 24 hours		>10 units first 24 hours
SBP (mmHg)	≤90	<100 <120	≤90	<110	<90	<90–≥110 (4 categories)
Heart rate (bpm)	≥120	>120	≥120	>105	>120	
Hemoglobin (g/dl)		<7–<12 (5 categories)	≤7–>10 (3 categories)	≤11		
Base excess (mmol/l)		<−10–<−2 (3 categories)				
Base deficit (mmol/l)			>5			
Lactate (mmol/l)				≥5		0–≥7.5 (4 ranges)
INR				>1.5		
FAST	Positive	Positive	Positive			[c]Regions positive
Age (years)						≥60 and ≤59
Mechanism of injury	Penetrating				High-risk injury[c]	
GCS			≤8		<9	
Pelvic/ extremity fracture		Positive	Positive (pelvic)			Type A–C
Gender		Male				
AUROC	0.859	0.892 0.887[a]	0.889	0.91		0.985

FAST focused assessment with sonography of trauma, *INR* international normalized ratio, *AUROC* area under the receiving operator characteristic, *GCS* Glasgow coma score, *SBP* systolic blood pressure

[a]Independent internal validation

[b]95% of patients Chinese origin

[c]High risk injury, trauma to the ventral chest between the midclavicular lines, abdominal injury with diffuse tenderness, survival of a vehicular crash in which another occupant died, vehicular ejection, or penetrating torso injury

Table 4.2 Military database-derived MT score/model summarization of characteristics

Score/model	McLaughlin [19]	Larson [35]	Schreiber [36]	MASH [23]
Design	Retrospective	Retrospective	Retrospective	R
Number of patients	302 396[a]	1.124	558	1298 1186[a]
Setting	Military, single center	Military, multi center	Military, two center	Military, multi center
Variable type	Non-weighted, dichotomous, sum predictors	Non-weighted, sum of predictors	Non-weighted, individual predictive variables	Weighted, sum of predictors
SBP (mmHg)	<110	<110		<110
Heart rate (bpm)	>105	>110		≥100
RR (min)				≥30
Hemoglobin (g/dl)		≤11	≤11	
Hematocrit (%)	<32			
BD (mmol/l)		≤6		
INR			>1.5	
pH	<7.25			
Mechanism of injury			Penetrating	
FAST				Positive
Pre-hospital intervention				Blood products, tourniquet use, hemostatic agent use
Injuries sustained				Amputated limb #, femoral fracture #, open tibial fracture #, pelvic injury, arterial bleeding, HTX
GCS				<15
AUROC	0.839 0.747[a]		0.804	0.92 0.93[a]

AUROC area under the receiver operator curve, *INR* international normalized ratio, *GCS* Glasgow coma score, *BD* base deficit, *RR* respiratory rate, *SBP* systolic blood pressure, *bpm* beats per minute, *mmHg* millimeters of mercury, *HTX* hemothorax, *FAST* focused assessment with sonography for trauma

[a]Independent internal validation

Civilian Database Developed Models

Assessment of Blood Consumption (ABC) Score

The ABC score was proposed initially in 2009 by Nunez et al. as a way to easily and rapidly identify those patients who are severely injured that would benefit from early activation of a massive transfusion protocol [15]. The score has since been validated in a multicenter trial at three Level 1 trauma centers with positive results. The initial ABC score is an ED arrival score comprised of four non-weighted variables: focused assessment with sonography for trauma (FAST) positivity, penetrating mechanism, arrival systolic blood pressure (SBP) less than or equal to 90 mmHg, and heart rate

of greater than 120 beats per minute. These variables were dichotomous, either receiving a 0 or a 1. The scoring then assigned a 1 to any variable that was positive for a maximum total score of 4. The score was derived from the institutions trauma surgeons' clinical gestalt in predicting MT (10 units or more of RBCs in the first 24 hours after admission) and using a logistic regression model to evaluate the four variables for accuracy. Of the four components, SBP <90 mmHg had the highest correlation to MT activation with an OR of 13 ($p < 0.001$, CI 6.93–24.52), followed by positive FAST (OR 8.2, $p < 0.001$, CI 4.34–5.30), HR greater than 120 beats per minute (OR 3.9, $p < 001$, CI 2.00–6.85), and penetrating mechanism (OR 1.9, $p < 0.02$, CI 1.15–3.44) [15]. When this score was applied to 596 patients, the overall MT rate was 12% and mortality was 18.1%. When the ABC was compared to the TASH and McLaughlin scoring systems for the same cohort of patients, the ABC score had the highest overall accuracy with an AUROC (area under the receiver operator characteristic) curve of 0.859 [15]. When outcomes were stratified by ABC score, a score of 2 was deemed to be the appropriate cutoff value for activation of MT. When two or more parameters were present, the percentage of patients in the cohort requiring MT was 40%, compared to 10% with a score of 1, increasing to 48% with a score of 3, and 100% with a score of 4. A score of 2 had a sensitivity of 75% and specificity of 86%. Scores of 2 or greater accurately predicted the need for MT (10 units of RBCs in the first 24 hours of admission) in greater than 80% of patients.

The ABC score was validated in a retrospective multicenter study of 3 level 1 trauma centers in 1018 patients [41]. An ABC score of greater than or equal to 2 was used as the threshold for predicting MT, defined as need for 10 units or greater of RBC in the first 24 hours of admission. Sensitivity and specificity between the centers for predicting MT were 76–90% and 67–87%, respectively. Despite a low PPV of 55%, the NPV was as high as 97%. There was also no significant difference between trauma centers in the AUROC, ranging between 0.833 and 0.903, all highly accurate [41]. The ABC score is a simple and effective tool to aid in rapidly assessing a severely injured patient without taking away from the clinical care of the patient and delaying lifesaving fluid resuscitation waiting for time-consuming labs for decision-making. Although the PPV was seemingly low, identifying a patient as being severely injured and ordering MTP unnecessarily can be forgiven; however, the situation where a patient is in need of MT and no products are available early can put the patient at significant harm for death. The strong NPV of the ABC score translated to a less than 4% incidence of this disastrous situation [18].

Baker Model

The Baker model, from a US Level I trauma center, incorporates physiologic data present on patient arrival to the trauma bay and injury severity based on physical exam findings or mechanism of injury reports to predict need for any ED transfusion. The goal of the Baker et al. study was to attempt to limit the perceived overuse of cross-matching in the trauma bay by identifying risk factors for transfusion on presentation to the ED [36]. Four variables in the data collected correlated with the need to initiate transfusion: systolic blood pressure <90 mmHg, HR >120 bpm, GCS <9, and high-risk injury defined as chest trauma to the "box", abdominal

injuries with signs of peritonitis, death of an occupant in the same vehicle, ejection, and penetrating injuries to the torso [36]. In this retrospective review of 654 ED patients receiving blood transfusion within 24 hours of arrival, systolic blood pressure of <90 correlated with transfusion most frequently. Presence of all four factors resulted in a 100% transfusion rate, with three factors present the rate was 68%, two 42%, one 12%, and with none present, there was still a 2% transfusion rate. Although this model, as it is currently designed, does not specifically predict the need for MT, during the analysis, the average RBC transfusion over the first 24 hours was in excess of 10 units. Several limitations to the Baker et al. study were acknowledged including exclusion of bradycardic (HR <60 bpm) patients who died prior to blood draws to determine the need for transfusion resulting in only three risk factors and the admittedly enigmatic definition of "high-risk injury" [4].

Prince of Wales Score

Also known as the Rainer score, the Prince of Wales (PWH Score) was developed at the Prince of Wales hospital in Hong Kong [42]. The retrospective study comprised of 1891 civilian trauma patients, 95% of which were of Chinese nationality. MT was defined as >10 units of RBCs in a 24-hour period and of the patients studied, 92 fell within criteria. The data identified seven variables to be predictive of need for MT: SBP ≤90 mmHg, GCS ≤8, HR ≥120 bpm, CT or FAST positive, Hemoglobin ≤7 g/dl, base deficit (BD) >5 mmol/L, and displaced pelvic fracture. A score of ≥6 was 96.9% predictive of MT with sensitivity of 31.5%, specificity of 99.7%, PPV of 82.9%, and NPV of 96.6%. A score of >1 gave a sensitivity and specificity of 79.3% and 86%, respectively. The AUROC for the Rainer/PWH model was 0.889 [4]. The model is limited in that it cannot be directly transferrable to international use because a very specific and cohort with regional disease (high rate of thalassemia, dementia, renal failure) that complicate variable calculation as well as the fact that the score has yet to be validated or prospectively studied [42].

Trauma-Associated Severe Hemorrhage (TASH) Score

Yucel et al. devised the Trauma-Associated Severe Hemorrhage (TASH) Score from data obtained through the trauma registry of the German Trauma Society (TR-DGU) in 2006 [8]. The TASH model incorporates radiographic, laboratory, and physiologic parameters in assigning a score. MT was defined as 10 units of RBCs administered from presentation to ICU from the ED, which averaged 3.8 hours in this cohort. Only directly admitted patients were included in the analysis [8]. Using multivariate logistic regression and univariate statistical analysis, seven independent variables were found to correlate with probability of MT and were used in the TASH model [32]. These variables include: (1) sex of the patient, (2) systolic blood pressure (SBP), (3) heart rate (HR), (4) hemoglobin (Hb), (5) base excess (BE), (6) result of FAST examination of the abdomen, and (7) relevant injuries to the extremities and abdomen represented by the Abbreviated Injury Scale (AIS) Score. Each variable was weighted after multivariate logistic regression analysis and assigned a score, thus giving the user a TASH score of between 0 and 28. In the derivation arm, 4527 patients were studied and a score of ≥16 was shown to predict individual need

for MT of 50%. This was validated within the same database using 1517 patients, and similar predictive values were determined. When both datasets were evaluated for overall predictive accuracy, a score of ≥16 correctly predicted MT in 89.6% of patients leading to an AUROC of 0.864–0.910 in the validation data set [8].

In a later re-validation study by Maegele et al., significant improvements in the way patients were resuscitated resulting in overall improved mortality across participating centers were considered, and an additional 5834 patients from the same TR-DGU were studied [43]. Additional data were attempted to be introduced into the scoring system including INR, pH, temperature, lactate, and mechanism of injury as they were not reliably recorded in the TR-DGU with the previous study and no performance improvement was noted. Multivariate regression was also performed on the current TASH variables and no weighting score adjustments were made [44]. As a result of the re-validation study, the authors concluded that TASH can be easily used with readily available data within a reasonable amount of time. The timeframe for calculation was subsequently studied in response to criticism about its efficiency. In a German study of 40 patients at a single Level I trauma center, the TASH score was able to be calculated with return of all variables and need for MT determined reliably within 8 minutes of patient arrival to the trauma bay. It is unknown if this time to calculation can be externally generalized to other trauma centers [45]. Currently, the TASH model is being implemented with regularity across Germany and Europe [32]. Despite its limitations such as an extensive amount of patient dropout due to missed data including base excess which is shown to correlate with hemorrhage and outcome leading to potential selection bias as well as including variables that are highly subjective and operator dependent, the TASH model appears highly accurate [44].

Traumatic Bleeding Severity Score (TBSS)

Ogura et al. set out to improve upon previously established models for predicting need for MT such as the TASH and ABC models by incorporating a demographic which he claimed was left out and is underappreciated: patients over age 65 [17]. In Japan, the elderly (>65 years of age) population is booming and comprises approximately 22% of the total Japanese population. In a low volume trauma center that sees approximately 250 patients per year with mean ISS >16, 113 patients were enrolled with mean age for MT of 64 and 50 for non-MT, improving predictive value for the elderly population. Five independent variables were identified using logistic regression analysis to be predictive of MT of greater than 10 units of RBCs in the first 24 hours of admission and using a weighted scoring system a total score was obtained. These five variables were: age, SBP after 1 liter of crystalloid infusion, number of regions (of 4) that FAST was positive, presence of and type of pelvic fracture, and arterial serum lactate concentration. Of these five variables, a score of 0–57 was assigned. Scores ≥15 had 97% sensitivity and 96% specificity for need for MT. When these patients were compared to ABC and TASH models, the AUROC for the TBSS was 0.985 and 0.813 and 0.892 for the ABC and TASH, respectively. One major limitation of the study is the difference between transfusion practices in Japan compared to the United States. In Japan, a single unit of RBC is approximately one-third that of a unit of RBC in the United States by volume. This, according to the authors, will not affect the

calculation and accuracy of the TBSS; however, MT thresholds in other countries will need to be recalibrated adding that further external validation is needed [17].

Vandromme Model

The Vandromme Score was devised from civilian trauma data of 6638 patients from a single Level I trauma center in Birmingham, Alabama [44]. Various patient characteristics were used to identify patients at risk for MT, based on a number of combat studies on MT [46]. MT was defined as 10 units or more of RBCs within the first 24 hours of admission. Five clinical measurements were used to devise the score including: (1) INR >1.5, (2) Serum lactate ≥5, (3) HR >105 beats per minute, (4) Hb ≤11, and (5) SBP <110 mmHg. Using a best-fit predictive model with three or more positive predictive measures for MT resulted in a Specificity of 98%, Sensitivity 53%, PPV 33%, and Negative Predictive Value (NPV) 99%. With all clinical measures positive, the PPV improved to 86%. The authors could not conclude that this combination of clinical variables was predictive enough to support the use of the model. Further investigation was warranted in the future to improve upon the current data [44].

Military Database Developed Models

McLaughlin Score

The McLaughlin model was developed from retrospective data collected at one combat support hospital from the Joint Theater Trauma Registry (JTTR) established in 2004 and kept at the US Army Institute for Surgical Research (ISR) [31]. Combat injured trauma patients were evaluated and 3442 patient records were reviewed with 680 patients receiving at least one unit of RBCs. Of these transfused patients, 302 were identified to have received a MT, defined as ≥10 units of RBCs in the first 24 hours of patient arrival to the ED. Four risk factors for MT were found: SBP <110 mmHg, HR >105 bpm, pH <7.25, and Hematocrit <32%. All four components were non-weighted either receiving a 0 or a 1 value. A predictive equation was developed:

$$\log\left[p/(1-p)\right] = 1{,}576 + (0.825 \times \mathrm{SBP}) + (0.826 \times \mathrm{HR}) + (1.044 \times \mathrm{Hct}) + (0.462 \times \mathrm{pH})$$

When this model was internally validated at the same combat support hospital, the AUROC curve was 0.747 and the model's ability to accurately predict those who needed MT was only 66%. When the independent variables were analyzed, the incidence of MT went from 20% to 80% when one value was present to when all four were present [31]. McLaughlin admittedly pointed out several limitations to the original study including provider bias seen in which lab studies to order between patients of varying degrees of injury severity, missing data, lack of mortality data due to difficulty with long-term follow-up of Iraqi nationals, and significant differences between the developmental and validation groups in terms of injury severity

due to escalation of military conflict between the two study periods leading to a decreased sensitivity and PPV [31].

Larson Model

For this model, a retrospective review of Joint Theatre Trauma Registry (JTTR) data of 1124 combat casualties who had been transfused at least one unit of RBC was performed and 420 (37%) received a MT defined as ≥10 units of RBCs within 24 hours of admission [47]. Four data points from the available literature were used to predict need for MT: HR >105 bpm (Larson and colleagues chose >110 bpm for ease of remembering), SBP <110 mmHg, Hb ≤11 g/dL, and BD ≤6 mmol/L. The presence of at least two variables resulted in a sensitivity of 69% and a specificity of 65% [47]. Some limitations to the Larson model preclude its practical use. The majority of patients were penetrating and injuries were from combat related. Additionally, blood product administration times were absent confounding temporal relationships with timing of transfusions as well as the 5-year patient selection period spanning a time period during which a new clinical practice guideline was adopted implementing damage control resuscitation practices in theater [47].

Schreiber Model

Schreiber and colleagues performed a retrospective analysis of 558 combat casualties at two different combat support hospitals in Iraq [48]. Two-hundred and forty-seven patients required MT defined as transfusion of ≥10 units of combined whole blood and RBCs. After univariate analysis and stepwise logistic regression, three variables were identified as predictive of need for MT. The variables were: INR >1.5, Hb ≤11 g/dL, and penetrating mechanism of injury. Hb was however the most predictive of these variables with an OR for need for MT of 7.7. The mortality observed in the patients receiving MT was 39% vs. 1% in the non-MT patients. The AUROC was 0.804 [48]. Combat medic practice, transport times to combat support hospitals (CSH), patient age and demographics, i.e. young, healthy soldiers, all were confounding variables in its ability to translate the findings to civilian practice. Admittedly, although coagulopathy plays a major role in hemostatic control during MT, the availability of critical blood components such as platelets, FFP, and cryoprecipitate was variable due to the nature of the combat environment; however, whole blood was frequently used [48].

Military Acute Severe Hemorrhage (MASH) Score

The MASH Score was derived from the UK Joint Theatre Trauma Registry database. McLennan et al. evaluated 1298 combat casualties, 275 of which received MT which they defined as 6 units or more in a 4-hour time period or 10 units or more of RBCs in 24 hours [35]. Univariate regression analysis was used to identify variables predictive of MT, and they were included in the score derivation chart. The variables included not only physiologic criteria and injury patterns but treatment factors as well. Scores for all variables except for limb amputation and fracture number were

categorical receiving a 0 or 1. A MASH score of 3 points or more had a positive likelihood of MT of 8.08 (95% CI 6.69–9.79) and a negative likelihood of 0.20 (95% CI 0.15–0.25). The data was internally validated with similar results and an AUROC of 0.92 [35]. The major limitation of the study is its retrospective nature and numerous missing data points. Both radiographic evaluation and injury coding were retrospectively assigned to fit into the scoring algorithm. It is not known, based on the study method, if the results would be the same if data points were calculated based on real-time evaluations of the imaging and physical examination limiting its efficacy [35].

The models mentioned in this chapter, both military and civilian, were grouped based on the cohort from which the data was gathered. Despite the dichotomy in the cohort populations, there is no evidence that these models are not translatable but it does stand to reason that civilian models work best with civilian applications and military models with military applications. In addition to the above-mentioned scoring systems and models for predicting massive transfusion, there still exist numerous others not specifically described in this chapter. These include the Shock Index, Trauma Induced Coagulopathy Clinical Score, Massive Transfusion Score, Cincinnati Individual Transfusion Trigger study, the Emergency Transfusion Score, the Coagulopathy of Severe Trauma Score, Moore model, Wade model, Revised Trauma Score, and Modified Field Trauma Score [3, 18, 20, 32, 34, 46, 49]. There have even been models developed and incorporated into smartphone applications that are readily available for download to make the computation of predictive scores easier [50].

Use of Individual Values as Triggers for Massive Transfusion

Despite the predictive value of previously mentioned scoring systems, they are not always practical to apply. Acutely, gathering and calculating a score of up to ten variables may be impractical in any environment when time is critical. With a number of the scoring systems, accuracy for predicting the need for MT is predicated on having all or most of the variables present to give a total score. Callcut et al. sought out to determine if individual triggers for MT were as useful as commutative scoring systems. In a prospective observational study at a level 1 trauma center, 170 patients were studied that required immediate operative intervention [51]. They found that individual transfusion triggers, as defined from prior scoring systems such as the CITT and the ABC, were accurate in predicting both need for MT and need for any transfusion. The presence of any single transfusion trigger (INR >1.5, BD ≥6, SBP <90 mmHg, Temp <35.5 °C, Hb <11 g/dL) accurately predicted 77–88% of the patients who received MT [51]. The finding that INR was the strongest predictor of MT was also validated in other studies including the 2011 validation of individual triggers in the PROMMTT patient database [52]. The INR trigger was found to be present in 19% of total patients and 43% of those required MT (OR 3.4, 95% CI 2.5–4.7) followed by BD (OR 2.8, 95% CI 2.0–3.9) and SBP (OR 2.6, 95% CI 1.9–3.4) [52].

Thromboelastography (TEG)/ROTEM® was also evaluated as an additional marker of acute traumatic coagulopathy. Hampton et al. evaluated 795 patients in 3 Level I trauma centers to determine if adding LY30, clot lysis 30 minutes after maximum clot strength was achieved, could be an independent predictor of trauma-related mortality. Results indicated that adding LY30 did not significantly improve AUROC (0.86 with 4-variable analysis and 0.88 with 5-variable analysis) but did improve HL goodness-of-fit from 0.37 to 0.90 [53]. Schöchl et al. similarly studied coagulopathy using the ROTEM, reporting on the FIBTEM assay, which is a fibrin-based extrinsically activated test with tissue factor and the platelet inhibitor cytochalasin D. FIBTEM maximum clot firmness (MCF) and FIBTEM clot amplitude at 10 minutes (A10) were found to be equally predictive of need for MT (≥10 units of RBCs in 24 hours) with an AUROC of 0.84 and 0.83, respectively [54].

In the pre-hospital setting and within the first 15 minutes of trauma bay resuscitation, laboratory and radiographic information may not be available. Simple vital signs analysis may be the only option for the resuscitation team to determine if an MTP should be activated. Simple vital sign information from a pulse oximeter was suggested to be predictive of MT by Mackenzie et al. Heart rate, SpO2%, and photoplethysmograph (PPG) wave forms were shown to be predictive of MT, defined in this study as 4 units of RBCs in first 4 hours, with an AUROC of 0.94 [55]. Despite its low enrollment and loss of data due to unforeseen circumstances, the idea that a single device that can be reduced in size and easily transported is a promising research that may not only have pre-hospital civilian trauma implications but may improve transfusion practices in battlefield casualties where resources are limited [55].

Conclusion

Earlier recognition of severe hemorrhage and treatment of shock and coagulopathy along with early activation of MTP and administration of blood products improves survival. Therefore, adjunctive tools that can aid in identifying patients who need an MT and speed delivery of blood products to the bedside are valuable. The models and scoring systems that we have described in this chapter, and those not described, have all ventured to identify variables both physiologic, radiographic, and hematologic that can predict the need for MT. The majority of these studies were flawed by their retrospective nature, had differing arbitrary definitions a MT, and many still require prospective validation. Some of the best performing models statistically we discussed were the TASH and MASH scores, with an AUROC value of 0.91 and 0.92, respectively. However, these higher performing predictive models rely heavily on numerous variables with weighted scoring systems and complex algorithmic calculations that may make them unrealistic in time-sensitive certain situations. Despite their usefulness, no single model can be fully endorsed by any trauma organization. While there is no substitute for a trauma surgeon's clinical judgment and a high index of suspicion, or "gestalt," a rapid tool that immediately aids the trauma

team to initiate an MTP would certainly be useful. Future studies to identify various independent variables and the use of real-time assessment of shock and coagulopathy to guide resuscitation are necessary to further improve outcomes for patients with traumatic hemorrhagic shock.

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Remote Damage Control Resuscitation

5

Jacob R. Peschman, Elon Glassberg, and Donald H. Jenkins

Introduction

While the term remote damage control resuscitation (RDCR) may be relatively young, the principle is not [1]. For traumatically injured patients, providing basic care at the point of injury focused on controlling hemorrhage and transporting them to medical care as quickly as possible has been practiced in military conflicts for centuries. However, in order for the patient to receive advanced treatment, they must survive long enough to reach medical care. While many have recognized that limiting blood loss was key, the extent of what could be done in a prehospital setting remained very limited even in the twentieth and early twenty-first centuries. Interventions have typically centered around common sense; applying pressure, bandages, or basic first aid. In 1966, the National Academy of Sciences released "Accidental Death and Disability: The Neglected Disease of Modern Society" which focused significantly on the need to improve prehospital care and transport of injured patients in the United States [2]. In addition to recommendations concerning trauma system development, improving communications, and coordinating transportation programs to get patients to hospitals faster, it also highlighted the need for early bystanders to provide care to the injured patient. "Beyond the fifth grade of elementary school, every American citizen should be trained in basic first aid." As the trauma care in hospitals evolved starting with damage control surgery (DCS) in

J. R. Peschman
Department of Surgery, Medical College of Wisconsin, Milwaukee, WI, USA

E. Glassberg
Medical Corps, Israel Defense Forces, Ramat Gan, Israel

D. H. Jenkins (✉)
Department of Surgery, UT Health San Antonio, San Antonio, TX, USA
e-mail: JenkinsD4@uthscsa.edu

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the late 1980s and early 1990s, transforming into the principles now known as damage control resuscitation (DCR), it was immediately recognized that these principles must also be implemented before patients reach the hospital to improve their morbidity and mortality [3–6]. This need for improved prehospital care has evolved to include programs such as the American College of Surgeons' Advanced Trauma Life Support (ATLS) training, the National Association for Emergency Medical Technicians' PreHospital Trauma Life Support (PHTLS) program, and the Department of Defense's (DoD) Tactical Combat Casualty Care (TCCC). The new "Stop the Bleed" campaign sponsored by the American College of Surgeons goes one step further, targeting training to anyone, so that bystanders can apply basic principles of hemorrhage control before first responders reach the scene [7]. The modern basis of the bleeding control strategies taught in these programs, often without using the term, comes from RDCR and carries immense potential for impacting the lives of the traumatically injured in both the military and the civilian settings.

Sutton's Law and Opportunities in RDCR

"Go where the money is," the phrase known as Sutton's law, has been used in medical teaching for decades to remind medical students and residents to focus on the area with the greatest likelihood to answer a question or make an impact. In trauma care, this is addressing hemorrhagic shock early and efficiently. Shock is the state when there is inadequate oxygen delivery to maintain aerobic metabolism in cells. This leads to the development of an oxygen deficit. Oxygen debt is a term that has been proposed to reflect the accumulation of an oxygen deficit over time as a way to quantify an individual's degree of shock [8]. It has been known since the 1960s based on animal models that development of an oxygen debt following hemorrhage can lead to states where shock becomes irreversible and fatal [9]. Among survivors, the degree of debt and time to repayment correlate to morbidity including development of multiple system organ failure and coagulopathy [10, 11]. Therefore, prevention of building an oxygen debt, and repaying what has developed as early as possible, can improve patient outcomes [8, 12, 13]. The idea of reaching a state of irreversible shock following hemorrhage has been central to our understanding of when and why trauma patients die. When Dr. Trunkey first described the "trimodal" distribution of death following traumatic injury, targets for improvements in trauma care began to emerge [14]. Over 40% of trauma deaths occurred within the first hour, many before arriving to receive medical care, while the other "peaks" occurred at 1–4 hours and at >1 week due to late complications, primarily infection. In the time since, significant focus on the care we provide in the hospital has led to a change in this distribution. While the late peaks have flattened out or disappeared, early death remains responsible for the bulk of mortality [15, 16]. Data from the recent conflicts in Iraq and Afghanistan have shown the same in military systems. Nearly 90% of injury-related mortality occurs before casualties reach a medical treatment facility (MTF), with estimates that 25% of those injuries were potentially

survivable as they are primarily due to hemorrhage [17]. As Sutton's law suggests, the money is in intervening early, before the patient accrues an oxygen debt that cannot be repaid. This is where RDCR takes center stage.

The Distinct Field of RDCR

The Trauma Hemostasis and Oxygenation Research (THOR) Network is a multidisciplinary collaborative effort made up of clinicians, medics, educators, and researchers whose focus is to improve outcomes for the traumatically injured [18]. The group has taken a central role in not only defining RDCR but promoting the importance of research, education, and training on the topic. While some groups have advocated the inclusion of prehospital care as part of what is encompassed by standard DCR principles [19], the THOR Network has supported the distinction of RDCR from DCR for multiple reasons and has employed scientific principles to support its development [20]. DCR principles include rapid compressible hemorrhage control, rapid control of surgical bleeding, hypotensive resuscitation, balanced hemostatic resuscitation, avoidance of the overuse of crystalloid fluids, preventing and correcting hypoperfusion, acidosis, coagulopathy, hypothermia, and hypocalcemia. When DCR principles are applied in the prehospital setting, those providing the care and the resources available to them are different [21]. The practitioners are typically first responders and emergency medical personnel in civilian systems and combat medics, paramedics, hospital corpsmen, and even physicians in some military and civilian settings. Many of these providers can lack experience with patients in severe hemorrhagic shock. In the prehospital arena, there is also limited availability of many of the diagnostic (monitoring, laboratory) and therapeutic (blood component therapy, surgical capabilities) resources that are standard of care for hospital-based DCR. Airway management may also differ in the prehospital phase as the risks of intubation and positive pressure ventilation are magnified in the prehospital setting due to the inability to volume load and monitor for reduced preload and cardiac output in an intubated patient [22]. The threshold for intubation for RDCR is therefore different than when DCR is practiced in hospital. Management strategies may also differ in resource-rich areas with short evacuation times (e.g., urban cities) compared to austere environments with prolonged evacuations. Although the ultimate goal of reduced morbidity and mortality is the same in RDCR as in DCR, the short-term goal is to deliver a patient to a hospital, MTF, or forward surgical team with physiology that is salvageable and with the best chance of recovery. Another important reason to separately define DCR and RDCR is to appreciate the differences needed in future research efforts. We must study the application and outcomes of prehospital interventions with the different challenges and goals in mind. RDCR-specific data should ultimately be what drives, or tempers, widespread adoption of moving hospital therapies to prehospital settings or unique prehospital therapies themselves. Though the principles of DCR

will be the framework for the remainder of this chapter, the goal is to highlight the unique considerations in RDCR.

Definitions

One of the many successes of the ATLS program is that it provides a consistent unifying terminology for the assessment of the trauma patient. Terms such as primary survey, secondary survey, and "the ABCs" let different medical personnel, with different experiences and backgrounds, speak the same language. For international partnerships, this may even mean doing it regardless of the language they speak. Consistency in terminology is also important for identifying gaps and directing research efforts, as standardized definitions allow apples to be compared to apples. Several terms with specific descriptions as they apply to RDCR have been defined by the THOR Network and warrant familiarization [20]. A summary can be seen in Table 5.1. First, as has been alluded to, the addition of "remote" to damage control resuscitation denotes it as applying DCR principles to the prehospital setting and ending with the initiation of surgical care. The term "forward" can be similarly used but is more military specific. As a brief aside, using the term "forward" should be done with some caution to avoid any confusion with the military term of a forward surgical team (FST). These have gained widespread application since the "golden hour" policy put forth by the Secretary of Defense in 2009 to have surgical care available within 1 hour of any combat casualty [23]. An FST can provide DCR and DCS, when a trauma victim reaches this capability in a military system. Therefore, RDCR ends upon surgical control of bleeding at an FST. Resource availability is acknowledged with the terms "far-forward" or "austere," which denote environments where healthcare providers do not typically work and basic resources (such as shelter, power) and medical technologies may not be available. While these terms are often thought of as synonymous with larger distances and longer transport times, evacuation time should be distinctly described as "delayed" (>60 minutes) or

Table 5.1 Remote damage control resuscitation terminology

Term	Definition
Remote or forward	The pre-hospital setting or phase of resuscitation
Far-forward or austere	The environment where professional healthcare providers normally do not operate and basic equipment and capabilities necessary for resuscitation are often not available
Delayed evacuation	>60 minutes from wounding until reaching a medical treatment facility that is capable of providing DCS and DCR
Prolonged evacuation	>6 hours from wounding until reaching a medical treatment facility that is capable of providing DCS and DCR
Acute coagulopathy of trauma	Endogenous coagulopathy that occurs as a result of severe traumatic injury
Trauma-induced coagulopathy	Describe both endogenous and exogenous causes of coagulopathy following trauma

DCR Damage Control Resuscitation, *DCS* damage control surgery

"prolonged" (>6 hours) based from the time of injury until reaching an MTF that can provide DCR [15]. Trauma-induced blood failure is a term that THOR has established to describe the consequences of reduced function of the elements of blood and the endothelium that result in shock, endotheliopathy, coagulopathy, and immune dysfunction [11, 24]. Trauma-induced coagulopathy (TIC) has been categorized into primary and secondary etiologies [20]. The acute coagulopathy of trauma (ACT) has been defined as the primary mechanisms that occur due to the biologic response to trauma. ACT is distinct from secondary, iatrogenic, or exogenous factors that contribute to coagulopathy (dilutional and consumptive processes). Precise and explicit definitions of terms used to describe RDCR/DCR principles will facilitate education, training, and research aimed at reducing death and disability from severe traumatic hemorrhage [20].

Compressible Hemorrhage Control and Rapid Control of Surgical Bleeding

Stop bleeding as soon as possible. It is really that simple. While the means to do this will vary based on the location of injury, the sooner some form of compression can be applied to slow or stop bleeding until definitive surgical control of bleeding can be performed the better. This principle is so important in the prehospital setting, that, unlike ATLS and the ABCs of airway, breathing, and circulation, for the corpsman or combat medic, TCCC teaches MARCH [25, 26]. MARCH stands for massive hemorrhage, airway, respiratory, circulation, and hypothermia, taking note that massive hemorrhage is to be addressed even before airway. Ultimately, the role of the person attempting to control hemorrhage is to prevent hypoperfusion and augment the hemostatic response to injury. One method of hemorrhage control is to apply hemostatic adjuncts. Hemostatic adjuncts can be divided into two primary categories: "mechanical" hemostatic adjuncts which refer to devices that stop or slow hemorrhage and "injectable" hemostatic adjuncts which comprise medications and plasma derivatives that results in immediate hemostatic effects on the body's coagulation system [20]. A summary of the different hemostatic adjuncts available for RDCR can be seen in Table 5.2. While injectable hemostatic adjuncts typically require minimal specific training to be administered, which is discussed in more detail in the section on hemostatic resuscitation, mechanical adjuncts encompass a broad range of products with varying levels of invasiveness and complexity of application.

Mechanical hemostatic adjuncts are really the first line of treatment available to control hemorrhage. They function by applying direct compression to, in, or proximal to bleeding injuries. Gauze, with or without impregnation of hemostatic substances, and extremity tourniquets are the most frequently utilized mechanical hemostatic adjuncts available. They are also among the oldest. Gauze with direct manual compression or wound packing can be one of the best and most efficient ways of controlling hemorrhage. While fairly straightforward to teach and perform, a potential downside is that it prevents the person

Table 5.2 Hemostatic adjuncts in remote damage control resuscitation

Category	Adjunct	Mechanism of action
Mechanical	Gauze	External compression or wound packing directly to site of injury
	Topical hemostatic	External compression or wound packing directly to site of injury with gauze impregnated with substances with hemostatic properties (i.e., kaolin, chitosan)
	Extremity tourniquet	Direct or proximal external compression on arterial supply to extremity
	Junctional tourniquet	Proximal external compression to axilla or groin for injuries not amenable to extremity tourniquets
	Abdominal aortic tourniquet	Proximal external compression to the abdominal aorta for pelvic or junctional injuries not amenable to extremity tourniquets
	Pelvic binder	Prevention of mobility of pelvic fractures resulting in ongoing bleeding, decrease potential space for blood loss
	Expandable hemostatic agents	Percutaneously injectable expandable substance for temporary control of non-compressible deep wound or abdominal hemorrhage
	REBOA	Endovascular occlusion of aorta for non-compressible truncal or pelvic hemorrhage
Injectable	TXA	Antifibrinolytic agent which inhibits plasminogen
	PCC	Plasma-derived compound of coagulation factors II, IX, X, +/− VII
	rFVIIa	Activated form of coagulant factor VII
	Cryoprecipitate	Plasma preparation of coagulant factors, primarily fibrinogen
	Fibrinogen concentrate	Standardized concentration of fibrinogen in lyophilized powder form

applying pressure from continuing on with any other responsibilities, such as providing care to additional victims or to continue to fight/protect themselves during military conflicts or in civilian mass casualty scenarios. More recently, the addition of topical hemostatic agents such as kaolin (a white clay mineral) or chitosan (sugar molecule derived from shellfish exoskeleton) to gauze has been introduced. Data supports the hemostatic ability of these impregnated gauze products; however, most are single-arm studies without direct comparison to conventional gauze or among the various hemostatic compounds [27]. Injectable sponges for non-compressible junctional hemorrhage have also been adopted into TCCC training [28]. Tourniquet use dates back to the Roman era with more detailed descriptions in the 1700s [29]. While robust military data exists supporting the use of extremity tourniquets at the point of injury by non-medical personnel, civilian adoption had been much slower even as recently as 5–10 years ago due to concern for the perceived risks of incorrect tourniquet placement and inappropriately selected patients. Fortunately, these concerns have been proven unfounded [30, 31]. Subsequently, tourniquet use has been adopted and incorporated in the civilian ATLS and PHTLS as well as "Stop the Bleed," aimed at nonmedical personnel. This may finally meet the challenge

from the National Academy of Sciences by increasing awareness and comfort of performing hemorrhage control by bystanders equivalent to performing cardiopulmonary resuscitation [32].

More advanced mechanical hemostatic adjuncts are also available. Junctional tourniquets are designed for injuries near to the axilla, shoulder, or groins that would otherwise not be controlled by a standard extremity tourniquet. They tend to be bulkier and are more difficult to apply, so specific training is needed. However, the addition of junctional tourniquets to the prehospital armamentarium theoretically expands the number of potentially controlled extremity hemorrhage by an additional nearly 20% [17]. Though limited data currently exists on their efficacy outside of cadaver and animal studies [33–35], several products are available and training is included in military programs including TCCC [36]. Abdominal aortic tourniquets apply external pneumatic compression to the abdominal aorta, targeting otherwise non-compressible pelvic or lower extremity junctional hemorrhage. These have yet to see widespread adoption as they require more training to place and provide limited additional hemorrhage control to the previously described tourniquets and have the potential to limit respiration due to abdominal compression. Further evidence on their utility is needed as swine model reports remain mixed and other data remains limited to case reports [33, 37–39]. Pelvic binders, however, have been widely used for decades and have been incorporated in ATLS and TCCC [40]. Unlike a tourniquet, the principle behind a pelvic binder is to limit and prevent additional motion that can cause ongoing bleeding and to decrease the potential space for blood loss, not to directly compress the arterial supply proximal to a site of active hemorrhage. While widely applied, the actual data supporting their use is also limited, and risk for skin necrosis with prolonged placement is real. As such, trauma organization guidelines do recommend their use but with caution [41]. Two additional emerging mechanical agents warrant mention. Retrograde endovascular balloon occlusion of the aorta (REBOA) has already generated significant interest and growing adoption in hospital settings for DCR [42]. Japan has implemented it in limited settings by Emergency Physicians, prior to the availability of surgical support, with success in a small series [43]. While still in its infancy in many ways, the fact that it is deployable percutaneously, with the primary technical skill being placement of a standard femoral arterial line, the idea that at some point in the future the technology could be taught to combat medics and prehospital providers for field deployment for select patients holds significant interest [44]. Another emerging option for non-compressible hemorrhage is in percutaneously injectable expandable hemostatic material. The primary goal would be to cause rapid hemostasis in otherwise non-compressible infra-diaphragmatic abdominal hemorrhage. Such an expandable foam-based product is in development with DoD support [45]. The goal of all these products is to provide temporary control to sites that are otherwise not accessible externally allowing transport to a site where surgical capabilities exist, or as an adjunct for surgical control of massive bleeding. While data is limited, it seems the potential of these types of products is promising.

Avoiding the Overuse of Crystalloids

Another central principle of DCR that has significant applicability in RDCR is the concept of hypotensive resuscitation. Other terms in the literature that may be encountered include permissive hypotension, balanced resuscitation, or delayed resuscitation. Some variation may exist when the terms are applied however, the overarching concept is the same. As discussed above, prevention of ongoing hemorrhage is critical to the traumatically injured patient. An injured victim's initial response to bleeding is to form a platelet plug as part of primary hemostasis. As such, this initial clot that forms can be tenuous. Part of the original thought process behind hypotensive resuscitation was to avoid "popping" the clot that had formed by aggressively resuscitating a patient to a "normal" blood pressure with crystalloids [46]. Targeting a palpable radial pulse and appropriate mentation, typically equivalent to a systolic blood pressure of roughly 90 mmHg, has been the resuscitation strategy adopted by the US military [47]. Data reported by civilian trauma centers indicates hypotensive resuscitation decreases transfusion needs and improves mortality in penetrating torso trauma upon arrival to the hospital [48, 49]. The principle, however, has been found to have additional benefits, as targeting lower blood pressures also means less fluid being administered. In austere settings, this allows for better resource utilization, but beyond that in situations with limited access to blood or blood components, this also prevents overuse of crystalloid fluids, which has been shown to contribute to coagulopathy, abdominal compartment syndrome, acute respiratory distress syndrome, and increased mortality in trauma patients [50–53].

Despite significant support in the literature, there are several major limitations that must be further studied in relation to hypotensive resuscitation in RDCR. First is that most studies have been in the setting of relatively short evacuation times. Data to support its safety in prolonged or even delayed evacuations is lacking. Additionally, hypotensive resuscitation is contraindicated in patients with, or patients suspected to have, severe traumatic brain injury. Since hypotension and hypoxia are known to worsen outcomes following severe traumatic brain injury, incorporating hypotensive resuscitation in prehospital management of multisystem trauma patients requires thoughtful application and more research into patient selection, since some patients may have severe TBI without it being appreciated by prehospital providers. Additionally, as elderly patients become a larger proportion of the trauma patients seen at civilian trauma centers, appreciation of the changes in physiology due to comorbid conditions, medications, and aging require thought regarding the risk to benefit ratio for the application of hypotensive resuscitation in this cohort as decrease from the patient's *baseline* systolic blood pressure of just 10% on arrival to a trauma center has been shown to be more predictive of mortality in elderly injured patients than traditional fixed criteria physiologic parameters in a retrospective cohort. This data is supportive of a report by Eastridge that indicated an admission systolic blood pressure of <110 mmHg was associated with increased mortality. These knowledge gaps leave us with many questions about the optimal prehospital resuscitation endpoints we currently use, including the safe target

systolic blood pressure. As a result, a THOR position statement published in 2018 concluded that for patients without severe traumatic brain injury, the goal of resuscitation for patients at risk of traumatic hemorrhagic shock should be a SBP of 100 mm Hg, recognizing that a range of 90 mm Hg to 110 mm Hg may be more practical. The position paper also states that for patients with severe TBI the goal for resuscitation should be for a SBP >110 mmHg. Future investigation centering on the amount and types of fluid, correct endpoints of resuscitation, and long-term outcomes such as end organ failure and survival to hospital discharge with acceptable neurologic outcomes represent needed areas of RDCR research.

These questions of application also lead to interest in other means of measuring and monitoring the severity of injury and efficacy of resuscitation. Markers of oxygen debt may be more appropriate targets as endpoints of resuscitation during RDCR. Markers such as lactic acid and base deficit, both now available as point of care testing, may be worthwhile additions to the available tools for those providing in transit care [8, 12, 13]. While both are feasible, limited data exists in well-designed clinical studies as markers to guide resuscitation, rather than to predict outcomes [54]. Other endpoints of resuscitation under exploration that have been used in the hospital setting but may have application to RDCR, include point-of-care ultrasound which has multiple potential prehospital uses and non-invasive Tissue Saturation Oxygen Monitoring (StO2) [55, 56]. StO2 is a technology that utilizes a commercially available infrared spectrometry probe to measure real-time tissue perfusion. Current literature has shown tissue saturation levels <70% or over 90% have better correlation to multiple clinical outcomes in trauma patients than standard physiologic markers such as tachycardia, base deficit, and lactate, correlation to the need for blood product transfusion and mortality [57, 58]. Another emerging technology is Compensatory Reserve Index (CRI) which utilizes non-invasive photoplethysmography sensors to tracks analog arterial waveforms and has shown better correlation to early signs of blood loss than traditional physiologic parameters [59]. Research on the utility of these and other emerging technologies in RDCR, as well as their potential advantage to provide continuous real-time feedback for response to intervention, is currently ongoing and would greatly support expansion of their use.

Prevent and Correct Acidosis, Hypothermia, and Hypocalcemia

Directly addressing and preventing the development of the lethal triad of acidosis, hypothermia, and coagulopathy must be a central focus of RDCR. Hypothermia, while seemingly simple to address is critical and can be challenging in prolonged evacuations from austere environments where both time and the elements may be working against the patient and those providing care. Even in urban settings with short transport ties, preventing/treating hypothermia is important. A recent study published from Norway identified that >70% of trauma victims were hypothermic (defined as a body temperature of <36° C) on arrival of emergency medical service providers [60]. All attempts should be made to prevent hypothermia through removal of wet clothing, passive, and active rewarming efforts including utilizing heated

blankets and administration of warm fluids or ideally blood products when needed. Commercially available hypothermia prevention kits have been utilized by the US DoD since 2004 and are considered a central part of prehospital care and the teaching of TCCC [61]. Acidosis is the result of hypoperfusion and shock due to generation of acidic metabolites, lactate, and other unmeasured anions, during anaerobic metabolism, with the degree of acidosis correlating with mortality and prognosis [62]. While adaptive to some degree as it aids in offloading of oxygen from hemoglobin at the cellular level, it also has multiple negative effects on the body including increasing minute ventilation as compensation, decreasing responsiveness to catecholamines, and worsening coagulopathy. Directly correcting acidosis with base compounds, most commonly sodium bicarbonate, while logical intuitively should be avoided unless extreme states of acidosis are present resulting in severe hemodynamic instability. An additional factor that can contribute to acidosis is aggressive crystalloid fluid resuscitation. Normal saline has a pH of 5.5 and due to its chloride content it can cause a hyperchloremic metabolic acidosis. In addition, no benefit has been found with the use of hypertonic fluid. It was originally thought to have enhanced intravascular volume expansion ability with decreased volume administered. Data on hypertonic saline for hemorrhagic shock has been mixed, although in general, there is no benefit with its use over traditional crystalloids in a prehospital setting [63]. Lastly, though hypocalcemia is not part of the lethal triad, it is worth discussing. Hypocalcemia in patients with traumatic hemorrhagic shock may occur due to consumption as a co-factor for hemostasis and also due to citrate within blood product storage solutions. A review of military patients from the conflicts in Iraq and Afghanistan revealed that 70% of combat casualties that received blood were noted to be hypocalcemic on arrival to the MTF [64]. Hypocalcemia can contribute to several physiologic abnormalities, including hypotension, and has been reported to occur after as little as 2 units of red blood cells (RBCs). Some studies have found association between severe hypocalcemia, <0.9 mmol/L, and increased mortality in trauma patients, though at present no studies have shown that correcting this improves outcomes [65]. However, many institutions and organizations recommend calcium replacement in the setting of massive hemorrhage [65, 66]. Hypocalcemia should be directly addressed via the intravenous administration of calcium chloride or calcium gluconate. When ionized calcium concentrations cannot be measured, it is reasonable to empirically administer calcium intravenously for every 2–4 units of RBCs transfused.

Hemostatic Resuscitation

The final principle of DCR applied to RDCR is hemostatic resuscitation, which is the use of whole blood or a "whole blood equivalent" with individual blood components in a 1:1:1 unit ratio. Inherent in the principle of hemostatic resuscitation is avoidance, or at the very least limitation, of crystalloids and colloids. Military data strongly supports the use of fresh whole blood (FWB) for resuscitation [67, 68]. Walking blood banks are well suited for austere environments as they eliminate the

significant challenges of storage while providing the pinnacle of resuscitative fluids. Unfortunately, they also carry with them unique logistic challenges, issues with screening for infectious diseases, and maintaining adequate donor pools [69]. Prescreening programs and the expansion of low-titer O+ whole blood use, which has shown to be safe as a universal donor, improve some of these issues [70, 71]. However, transition of WBB programs to civilian settings has remain limited, with the Royal Caribbean Cruise Lines having perhaps the most successful large-scale implementation of a civilian walking blood bank program, with 37 transfusion cases reported [72]. Expansion of the use of low-titer cold-stored type O whole blood is starting to gain favor as the benefits of whole blood resuscitation continue to be reported [73–75]. For RDCR, especially in settings of delayed or prolonged evacuation whole blood may be preferred compared to the use of component therapy (RBC, plasma, platelet units) as it is logistically very challenging to appropriately store and transport all three blood components. Patients who require shorter evacuation times may be adequately temporized with just RBCs or even RBCs and plasma before hemostasis is achieved at an MTF, but for severely bleeding patients with longer transport times the most beneficial component may be platelets, and the only feasible way to resuscitate a trauma patient with all aspects of blood is to use whole blood. Whole blood for prehospital use has been shown to be feasible in well-developed trauma systems through coordinated efforts between trauma surgeons, blood banks, and emergency services [76–79]. The use of advanced technology such as drones will further enhance the availability of blood products in remote settings [80].

To supplement whole blood, or when whole blood is not available, use of freeze-dried plasma can be advantageous. Its use has been successfully implemented by the Germans, Norwegians, French, and Israelis [81–83]. The availability of plasma prehospital is also important because data indicates that its early use is associated with improved outcomes for patients with severe TBI [84]. A recent RCT published by Sperry et al. also indicates the use of plasma prehospital improved survival compared to the use of crystalloids [85]. Freeze-dried platelets are currently in development and have the potential to dramatically improve RDCR hemostatic resuscitation capabilities in austere environments [86, 87].

Lastly, injectable hemostatic adjuncts have potential for significant impact in the prehospital setting as either a complement to blood products or when blood products are not available. Tranexamic Acid (TXA) is an anti-fibrinolytic agent that inhibits plasminogen and plasmin, which are key factors for clot lysis. Both the MATTERs and CRASH-2 trials report decreased mortality when administered within the first 3 hours following trauma though potential for increased thrombotic complications exists [88, 89]. Prehospital TXA use in both military and civilian settings has shown the practice to be feasible with ongoing prospective randomized trials currently in progress [90–92]. Other potential injectables include Prothrombin Complex Concentrate (PCC), a plasma-derived compound coagulation factors II, IX, X +/− VII, activated recombinant factor VII (rFVIIa), fibrinogen concentrates, and cryoprecipitate. While each has gained interest in empiric use in trauma, little data supports their use. rFVIIa has significantly fallen out of favor despite some

evidence that it may decrease the need for massive transfusion, when given early [93]. Similarly, the utility of empiric PCC seems limited to reversal of warfarin and some of the newer oral anticoagulant agents as an adjunct to FFP [94]. These agents potentially could play a larger role as direct factor replacements based on functional coagulation studies such as Thrombelastography (TEG) or Rotational Thromboelastometry (ROTEM). The RETIC study attempted to analyze if ROTEM-directed coagulation factor concentrates affected outcomes compared to the use of plasma. Unfortunately, this trial was limited by differences in the time to treatment in both groups that could have been avoided with the use of thawed plasma [95]. Currently, there is no high-quality data to support the use of these hemostatic adjuncts based on TEG or ROTEM data.

Conclusion

"You may delay, but time will not."
Benjamin Franklin
Poor Richard's Almanack, 1758

Outside of prevention efforts, the opportunity to change the trajectory of a trauma victim's life for the better starts at the moment of injury. From that second on, an oxygen debt is accumulating that must be repaid, and time is the enemy. Applying the principles of RDCR brings active treatment to the patient while transporting them to a treatment facility as quickly as possible. In many ways, this is only possible by changing the historical perception that treatment starts in the trauma bay to a more modern approach where trauma care is optimized by initiating the resuscitation at the scene of the injury. Utilizing the prehospital transport time to control bleeding and treat blood failure may be the difference between a patient that has survivable injuries vs. an inevitable fatality. Many interventions and strategies are available to start addressing blood failure in a prehospital setting, but they require training of prehospital personnel and the resources to support them. Not only will the continued advancement of the practice and science of RDCR improve the care of trauma patients in the remote setting, it also holds great promise in improving prehospital care of all trauma patients, as well as patients with many other conditions such as gastrointestinal and peripartum hemorrhage. It is time for every trauma provider to make sure they are knowledgeable about RDCR and to champion its implementation and ongoing research.

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Permissive Hypotension

6

Allan Pang, Ravi Chauhan, and Tom Woolley

Introduction

> Trauma patients are a complex population, with each individual requiring a unique management strategy tailored to his/her needs – the acceptance of a single global blood pressure target would appear to be the antithesis of this principle. – M. Wiles [1]

Permissive hypotension (PH) in the context of life-threatening haemorrhage (LTH) is a resuscitation strategy which is used within damage control resuscitation (DCR), in which a lower than normotensive blood pressure is targeted until the source of haemorrhage is controlled [2]. The perceived benefit of PH is that it limits bleeding and prevents dislodging of any clot formed at the injury site by avoiding excessively high blood pressures. This must be balanced against the dangers of an under-perfused bleeding patient who will suffer from increasing physiological burden of reduced oxygen delivery resulting in endotheliopathy, coagulopathy, acidosis and hypothermia which can ultimately lead to multi-organ failure to include 'blood failure' [3, 4].

A. Pang (✉)
Department of Anaesthesia, James Cook University Hospital, Middlesbrough, UK

Academic Department of Military Anaesthesia and Critical Care, Royal Centre for Defence Medicine, Birmingham, UK
e-mail: allan.pang@doctors.org.uk

R. Chauhan
Department of Anaesthesia, University Hospital Birmingham, Birmingham, UK

Academic Department of Military Anaesthesia and Critical Care, Royal Centre for Defence Medicine, Birmingham, UK

T. Woolley
Academic Department of Military Anaesthesia and Critical Care, Royal Centre for Defence Medicine, Birmingham, UK

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The ultimate goal of DCR is the delivery of a casualty to higher echelons of care (i.e. a hospital with suitable surgical facilities available) with sufficient physiological reserve to survive definitive surgical haemostasis and further aggressive resuscitation. The paradigm of DCR has evolved over many iterations ultimately leading to the current practice of combined use of blood-based resuscitation and limiting systolic blood pressure (SBP) which is believed to be effective in promoting haemostasis and reversing shock.

This chapter will examine the evolution of PH and its part in DCR, the benefits and risks of PH and how future iterations of PH have started to evolve.

Evolution of the Management of Haemorrhagic Shock

Post-injury haemorrhagic shock remains the major cause of morbidity and mortality in patients suffering major trauma [5, 6]. Shock is a defined state of oxygen delivery that is inadequate to meet vital organ metabolic demands. Once perfusion falls and hence oxygen delivery of an organ falls below a sufficient level, anaerobic metabolism dominates, leading to an oxygen deficit at the cellular level. The product of the severity of shock and time spent in a shocked state is known as oxygen debt, which must be repaid. Failure to resolve this debt results in worsening organ dysfunction/failure, including blood failure, making ongoing resuscitation increasingly difficult and eventually impossible [7].

Emphasis on restoration of circulating volume to maintain perfusion remained the mainstay of clinical practice until the start of the twenty-first century. The basis of this was founded on canine models initially proposed by Wiggers [8, 9], who found that survival rates were poor following periods of prolonged severe haemorrhagic shock even after re-administration of blood that had been lost.

This was further developed by Reynolds [10] and Shires [11], who found that administration of whole blood with large amounts of crystalloid solution relative to the amount of blood loss (2 ml per 1 ml of blood loss) could result in the reversal of the state of shock and dramatically improve survival rates. This is the basis of the '3:1 rule' where 2–3 times of estimated blood loss would be administered in the form of crystalloid solution, early in the treatment of haemorrhagic shock. This was adopted by Advanced Trauma Life Support and taught until 1997 [12].

Concurrently, in the latter half of the twentieth century, work looking at management of patient with burns found that successful management resuscitation of burns patients required very large volumes of crystalloid fluid [13], forming the basis of the Parkland formula which is still widely used today [14]. There was a belief that the 'burns model' would serve as an excellent model for trauma resuscitation as both injury patterns appeared to lead to extracellular deficits.

This reinforced the strategy of large-volume resuscitation in the context of traumatic haemorrhage, and widespread liberal fluid resuscitation strategies were used. During the Vietnam War, aggressive crystalloid administration strategies, whilst believed to have saved many lives and reduced the incidence of renal

Table 6.1 Summary of fluid resuscitation strategies

Type of resuscitation strategy	Intervention to patient	Major clinical trials focusing on concepts
Restricted resuscitation	Limit the volume of fluid administered	Schreiber et al. [23]
Delayed resuscitation	Restrict fluid resuscitation until admission to hospital	Bickel et al. [25]
Hypotensive resuscitation	Titrate and control BP to less than normal range	Dutton et al. [28], Carrick et al. [30]

failure [15], were also thought to have been the cause of 'Da Nang lung', now known as acute respiratory distress syndrome (ARDS) along with other recognised syndromes associated with excess crystalloid use such as abdominal compartment syndrome [16].

Development of Permissive Hypotension

As early as 1918, it was suggested that restoring a normal blood pressure value had dangers of worsening haemorrhage by disrupting the formation of clots at the site of injury.

> Injection of a fluid that will increase blood pressure has dangers in itself. If the pressure is raised before the surgeon is ready to check any bleeding that might take place, blood that is sorely needed may be lost. – W. Cannon [17]

Despite this, it was not until a growing body of evidence in the 1990s and early 2000s started to challenge the dogma of large-volume crystalloid resuscitation. Three strategies began to emerge to deliver hypotensive resuscitation summarised in Table 6.1.

Restricted Resuscitation

Animal studies report that in simulated cases of uncontrolled haemorrhage, administration of large volume of crystalloids, whilst increased blood pressure, worsened bleeding at the injury site and mortality [18–20]. Two retrospective studies found that those who received a restrictive fluid regime during the resuscitation phase had better chance of survival [21, 22]. These findings should be interpreted with caution as there may be confounding factors between morality and the amount of fluid administered.

Recently, a multicentre prospective randomised pilot trial was conducted to compare outcomes of controlled resuscitation (250 ml of 0.9% saline) vs. standard resuscitation (2000 ml of 0.9% saline) in response to hypotension in trauma (<70 mmHg or absent radial pulse). They examined 192 patients and reported 24-h mortality to be higher in the standard resuscitation group (18% vs. 3%) in those who suffered from blunt trauma [23].

Delayed Resuscitation

A study looking at pre-hospital management of LTH found that the administration of fluid prior to surgical intervention did not have a significant influence on mortality rate [24]. Bickell et al.'s landmark study randomised 598 shocked patients with penetrating torso trauma into 2 groups: those who received early fluid administration (pre-hospital) and those who received delayed fluid administration (in-hospital).

The group with delayed fluid resuscitation had a better survival rate (70 vs. 62% (p = 0.04)) and suggested that it may also reduce intraoperative bleeding [25]. Within this group, in blood samples taken on arrival to hospital, there were also significantly higher haemoglobin and platelet concentrations with a shorter prothrombin, and partial thromboplastin times were longer. This may suggest that large volumes of crystalloid may not just attenuate secondary bleeding but also worsen coagulopathy.

Hypotensive Resuscitation

When targeting a lower than normal blood pressure, in animal models, both survival outcomes and control of haemorrhage improved [26, 27]. The models of haemorrhage often used in animal studies may not be entirely representative of a traumatic haemorrhage in humans. The animal models used are the most sensitive to re-bleeding (i.e. a lesion to a major artery with large volumes of crystalloid fluids given immediately) and are conducted under anaesthesia resulting in differences in vascular resistances and regional blood flow due to anaesthetic-induced vasodilatation. Despite this, collectively these studies do suggest that very aggressive and early resuscitation with clear fluids is detrimental and provides a useful starting point for clinical studies.

Clinical human studies, however, found it difficult to demonstrate benefits of hypotensive resuscitation. Dutton et al. [28] performed a prospective randomised controlled trial (RCT); 110 hypotensive trauma patients with presumed haemorrhagic shock were randomised to receive fluid resuscitation to a targeted SBP (hypotensive (70 mmHg) vs. normotensive (>100 mmHg)). There were no differences in 'in-hospital mortality' between these two groups; however, mean SBP in these two groups were higher than intended (100 mmHg vs. 114 mmHg).

This deviation from the intended study protocol shows how unpredictable SBP rises can be even with small aliquots of fluid administration. What was also seen in this study was the phenomenon of a spontaneous recovery of SBP following the control of the bleeding source without fluid administration along with pressure oscillations as seen in Fig. 6.1.

Morrison et al. looked at intraoperative control of blood pressure, comparing targeting mean arterial pressure (MAP) of 50 mmHg vs. 65 mmHg. In the preliminary findings [29], they found that within the hypotensive group, early post-operative mortality had improved and that there were less to develop coagulopathies. As with

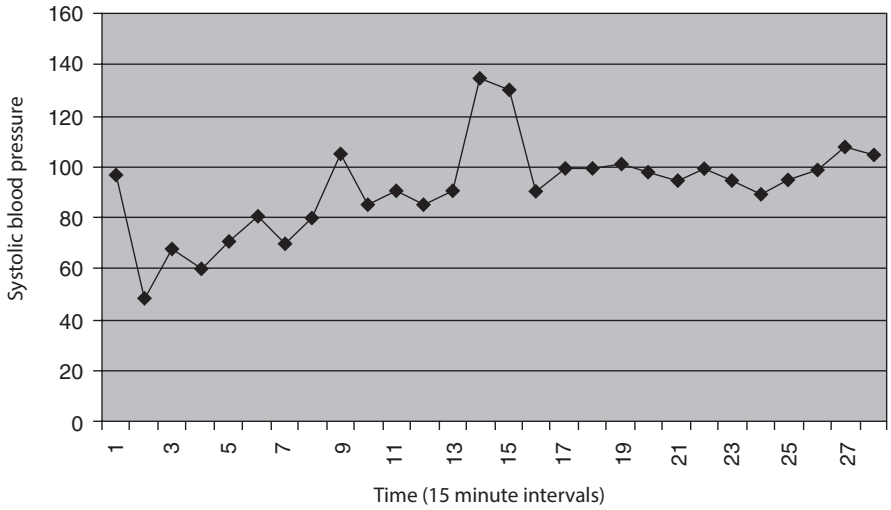

Fig. 6.1 An example of blood pressure oscillation and eventual equilibration in a patient from the low-pressure arm of the study. (From Dutton et al. [28], Fig. 3, with permission of Wolters Kluwer Health, Inc.)

Dutton's team, trying to maintain separation of MAP proved challenging, and in fact the mean MAP values in both groups were not statistically different. This study was terminated early as it was unable to demonstrate differences in 30-day mortality with the proposed sample size [30].

What should be noted is that many of these studies had established trauma networks with short pre-hospital times (<60 min) and access to surgery was readily available. This means that any period of hypotension is short and potentially the adverse effects of shock may not have as significant of an effect. However, this is not the case in many parts of the world, even within the economically developed nations, particularly in isolated rural regions, or within a military context.

Of the three strategies for hypotensive resuscitation mentioned previously, there is no strong evidence that any can be applied universally to bleeding trauma patients, and no human data exist to guide the duration of a hypotensive strategy. To add more confusion, it is also unclear whether the restrictive resuscitation/controlled resuscitation approach might be beneficial as a consequence of less crystalloid use or due to hypotension itself. The risks associated with hypotensive resuscitation, in particular hypoperfusion and end-organ damage, have been documented in the literature, although to counter this, certain animal studies dispute the significance [31].

A recent Cochrane Review demonstrated that no large-scale RCT has shown any benefit from hypotensive resuscitation in trauma [32]. This highlights the uncertainty behind the postulated mortality benefit. Despite the lack of evidence, the concept of hypotensive resuscitation for LTH has been adopted in many national trauma guidelines and has entered widespread practice as a result [33, 34].

Defining an Appropriate Target

Analogously, the question concerning what blood pressure to aim for has also been left unanswered. When evaluating PH, one cannot avoid trying to define blood pressure targets and as such consider a suitable range, i.e. the lower and upper limits acceptable in PH. A consensus group in 2002 suggested that the presence/absence of a palpable peripheral pulse (i.e. radial pulse) could be used as this end point [35].

As with most areas pertaining to PH, the evidence for defining these limits is scarce, especially when taking into consideration non-anaesthetised patients. What does seem to be clear is that patients suffering trauma (except for those with severe traumatic brain injury) do not necessarily seem to be disadvantaged from short periods of hypotension. [36–39] There is some experimental evidence that tissue autoregulation limits may be lower than originally suspected [40].

When considering blood pressure measurements, Emerson et al. in 1945 studied 112 battle casualties presenting to a field hospital [41]. They found that mortality in those arriving in shock with SBP < 85 mmHg was 35%, whereas those arriving with a SBP >85 mmHg was 11%. Of those who died and had additional blood volume measurements (n = 13), some assessments of the factors leading to death were made. Two of these cases had extremity injuries, one from a through-and-through gunshot wound to the thigh and one open bilateral lower limb fractures. Both of these cases should have been amenable to external haemorrhage control. The salient feature of these patients was the prolonged pre-hospital phase (7 h and 6 h from the time of injury) with systolic pressures of 50 mmHg and 60 mmHg, respectively, at time of admission. Notwithstanding 'adequate' volume resuscitation with blood, they never recovered from shock. Emerson and his colleagues wrote:

> These patients failed to respond to adequate shock treatment, although in neither case could this failure be attributed to lack of adequate transfusion therapy or to the presence of infection. The sequence of events suggests that failure of shock therapy in these cases is related to irreversible changes in the cardiovascular system resulting from prolonged tissue anoxia.

This observation would suggest that 85 mmHg might be too low to be the lower limit for a prolonged period. In the absence of any evidence, the currently accepted level of 80–90 mmHg should be the absolute lowest. Simultaneously, it could be argued that a higher goal of 100 mmHg may be more appropriate in order to ensure that 90 mmHg is never infringed.

In 2007 Eastridge et al. analysed 871,000 patients from the US National Trauma Data Bank [42]. When traumatic brain injury (TBI) was excluded, the authors correlated mortality and admission base deficit with admission SBP. Baseline mortality was <2.5%. Figure 6.2 compares mortality and base deficit against systolic blood pressure on arrival in the ED. The slope of the graph changed at 110 mmHg such that below 110 mmHg, there was a 4.8% increase in mortality for every 10 mmHg drop in SBP. A similar inflection point for base deficit appeared at 118 mmHg. They

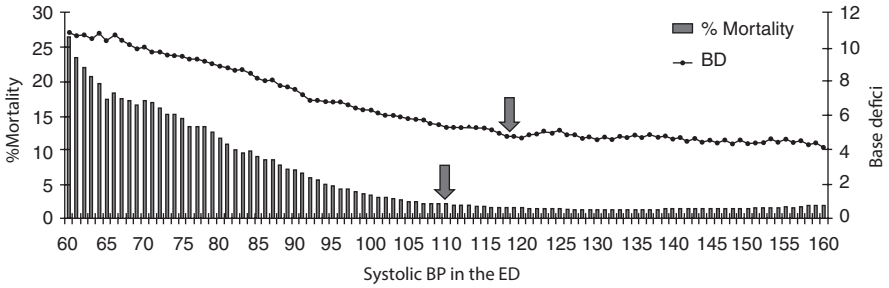

Fig. 6.2 Inflection points of mortality and base excess as SBP falls. (From Eastridge et al. [42], Fig. 2, with permission of Wolters Kluwer Health, Inc.)

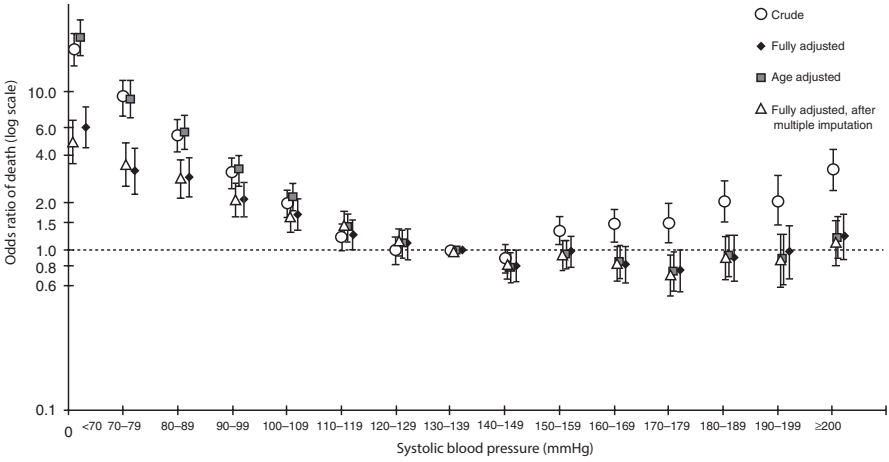

Fig. 6.3 Odds ratios of death and its association with SBP. (From Hasler et al. [43], with permission of Elsevier)

concluded that a SBP ≤110 mmHg is a more clinically relevant definition of hypotension and shock than 90 mmHg.

Similarly, Hasler et al. examined 48,000 patients from the UK Trauma Registry suffering from blunt trauma [43]. Figure 6.3 shows the odds ratio against systolic pressure on arrival, which documented that the odds of dying increased below an SBP of 110 mmHg and had doubled below an SBP of 100 mmHg, with a similar inflection point at 110 mmHg.

These studies indicate that an SBP on admission of <110 mmHg is associated with worsening outcomes. Thus, an SBP of 110 mmHg may indicate a 'lower limit of normal' and perhaps the upper limit of a pressure range target for resuscitation.

Duration of Hypotension

The use of PH as a resuscitative strategy is a balancing act between two poor outcomes. If we raise blood pressure, we risk uncontrolled haemorrhage; however, a low blood pressure risks under-perfusion and the physiological insult that comes with this. Initially the greatest danger is haemorrhage, and so we tolerate a low blood pressure to control this; however, as time passes, the magnitude of physiological derangement increases and may cause more harm.

This raises a question: At which point during the execution of permissive hypotension do the adverse effects associated with the strategy offset the benefits? It is reasonable to conclude that prolonged hypoperfusion/hypotension will worsen clinical outcomes and animal studies support this belief. The effects of permissive hypotension of 60-, 90- and 120-min duration were evaluated in rats with uncontrolled haemorrhage [44]. Survival times and organ function were nearly identical for those in the 60- and 90-min groups, yet in those rats treated with hypotensive periods longer than 90 min, the outcomes were significantly worse.

In another similar study of 24 pigs with controlled haemorrhage, those treated with severe hypotensive resuscitation (systolic BP 65 mmHg) for 8 h had persistently worse base excess and tissue oxygen saturation, and significantly higher mortality, compared to those resuscitated to systolic BP 90 mmHg or 80 mmHg [45]. The point at which the hypotensive strategy causes more harm is not yet addressed in any international consensus guideline and makes answering the question above difficult. The answer may lie in the nature of the trauma and the initial response of the patient.

Remote Damage Control Resuscitation

It is important to highlight differences in the strategies of patient management inherent in pre-hospital and in in-hospital phases of care. Very different monitoring capabilities and treatment options exist, including the availability of anaesthesia and immediate surgery.

Consequently, a difference in the approach to hypotensive resuscitation is required. DCR principles are applied mainly to hospitalised patients under general anaesthesia. Remote damage control resuscitation (RDCR), in most parts of the world, is applied to pre-hospital patients who are awake and at times spontaneously breathing. This leads to increased systemic vascular resistance in those patients who are awake and breathing relative to those who are anaesthetised and mechanically ventilated.

Anaesthetised patients are vasodilated by anaesthetic drugs and opioids and often have advanced haemodynamic monitoring, a multidisciplinary team caring for them and ongoing surgery (if required). This allows the in-hospital provider to maintain a higher cardiac output whilst keeping SVR and pressure targets low, thus maximising oxygen delivery to the tissues. This approach is nearly impossible in the pre-hospital setting and therefore caution to be applied when trying to apply evidence derived from an in-hospital setting to a pre-hospital setting.

Management with Concurrent Traumatic Brain Injury

The management strategy for LTH in a patient with associated traumatic brain injury (TBI) is an area of controversy. Debate exists as to whether or not the guidelines for permissive hypotension should be changed in the presence of TBI as no human evidence exists from prospective studies [46]. There is retrospective and observational data for patients with TBI that link increased mortality with reductions in mean arterial pressure [28, 47].

The 2016 guidelines published by the Brain Trauma Foundation, relating to in-hospital management of traumatic head injury, supports maintaining a systolic blood pressure above 110 mmHg, based on level 3 evidence. These guidelines do not offer direction on the suitability of this strategy in those with LTH [48]. What we do know is that aggressive fluid resuscitation in patients with LTH and TBI is unfavourable [49]. Studies involving rats, dogs and swine models have indicated that crystalloids used to raise cerebral perfusion (through raising the BP) result in damage to microvasculature leading to extravasation and ultimately raised intracranial pressure through cerebral oedema [50–52].

Vrettos et al. studied the effect of PH in both TBI and blunt abdominal trauma in pigs [53]. They simulated a TBI using a standardised fluid percussion model and uncontrolled haemorrhage by releasing a surgical knot on the aorta. At this point they randomised the pigs into two groups: those with aggressive crystalloid fluid resuscitation and those left hypotensive for 1 h (PH). All pigs in the aggressive fluid resuscitation group died; however, for those in the PH resuscitation group, 50% survived and were able to have their haemodynamic profile and consequently cerebral oxygenation restored to pre-injury levels when resuscitated.

The National Institute for Health and Care Excellence (NICE), UK, advises that in patients with both TBI and LTH, if haemorrhagic shock is dominant, then restrictive volume resuscitation should be continued; however, if TBI is dominant, a less restrictive volume resuscitation approach should be used to maintain cerebral perfusion pressure [54]. Interestingly, this guidance is followed by the following statement:

> Based on low quality randomised controlled trials, and the experience and opinion of the GDG (Guideline Development Group).

Potential Areas for Future Development

Hybrid Resuscitation

During prolonged evacuation, the balance of risk between exacerbating further bleeding against hypoperfusion evolves with time. Initially, the greater risk might be to disrupt a fragile nascent clot, and so it might be appropriate to severely restrict fluid administration allowing blood pressure to remain low. As clot strength increases with time, the risk of clot disruption diminishes; however, the impact of a

shocked hypoperfused state accumulates with time leading to acidosis, coagulopathy and end-organ damage/failure.

Experimental studies in anaesthetised pigs with haemorrhagic shock with the background of blast lung found that prolonged periods of hypoperfusion led to significant worsening survival time and mortality [55]. Further animal studies found a new paradigm of allowing a period of hypotension (60 min) followed by a normotensive resuscitation target using crystalloid fluid administration.

This was known as 'novel hybrid resuscitation', which was found to improve survival as well as reversal of a shocked state in the same animal model as described above [56]. The question that this piece of research was evaluating who to best to manage casualties where there were prolonged evacuation times (i.e. the military) and in 2006, the UK military adopted novel hybrid resuscitation as part of their clinical guidelines for prehospital care of traumatic haemorrhage.

This highlights that PH is realistically limited for casualties with short evacuation times with readily available surgical facilities. This approach to reverse shock by raising the BP target at 60 min addresses the fact that the therapeutic priority has shifted towards shock rather than limiting re-bleeding.

Use of Blood Products

Shock is characterised by an oxygen deficit which in the context of LTH is due to the failure of delivery to meet oxygen demand. The oxygen delivery equation is as follows:

$$\mathrm{O_2\ delivery} = \mathrm{arterial\ O_2\ content} \times \mathrm{cardiac\ output}$$

In the context of LTH, hypovolaemia is the precipitating factor in low cardiac output. Cardiac output is the product of heart rate and stroke volume. The use of clear IV fluids will increase preload and myocardial contractility leading to increased stroke volume and therefore cardiac output. Clear IV fluids also reduce viscosity of blood and thereby improve microvascular flow at the capillary bed. Whilst this is all initially beneficial to the patient, these effects are only temporary as crystalloid fluid freely redistributes across the capillary bed into the interstitial fluid (up to 2/3), minimising the effect on improving cardiac output. The temptation will be then to continue to administer clear fluids to maintain cardiac output, and as discussed previously, too much crystalloid fluid has detrimental effects.

The use of blood products would improve cardiac output by the same mechanisms as crystalloid fluids and will stay within the intravascular space longer whilst also increasing arterial oxygen content. There is an increasing body of evidence in the benefit of blood products early for patients with LTH [57].

The Trauma Hemostasis and Oxygenation Research (THOR) Network has recently published a position statement on the role of permissive hypotension in RDCR [58]. They advocate the early use of blood products, in particular, whole blood. This is based on a significant animal study [59] and several retrospective

studies [57, 60–62], which found improvements in mortality, base excess and coagulopathy when pre-hospital blood products were used compared against crystalloid fluid.

The group also evaluated what would be a suitable systolic blood pressure to aim for. Based on the evidence seen above [44, 45], a target systolic blood pressure of 100 mmHg should be used. By using blood products early, we can use this higher threshold to prevent the dangers of under-perfusion and oxygen debt.

Point-of-Care Assessment of Shock

It has long been recognised by physiologists and anaesthetists/intensivists that monitoring mean arterial blood pressure is a poor measure of the degree of haemorrhage and developing shock [63], principally because reflex increases in vascular resistance (to maintain or elevate pressure) cause a reduction in tissue blood flow that is underestimated or even hidden when blood pressure is the primary assessment. The above sentiments would hold true in the context of permissive hypotension.

Although monitoring methods are discussed elsewhere in this book, alternative hypothesised methods include measures of global blood flow (such as stroke volume or cardiac output) or tissue perfusion or oxygenation (such as lactate or base excess), which may give a more timely warning of hidden haemorrhage since the former are part of the initial effect of haemorrhage, whilst the latter change in response to the physiological alterations that delay the overt falls in arterial blood pressure. Similarly, changes in tissue perfusion may indicate a need for intervention and consequently techniques to change global flow.

At present, there is no single machine or measurement that gives a rapid, accurate answer to the degree of shock and response to fluid resuscitation. Many physiological indices have merit, but currently no empirical test has shown the outcome superiority of one over another. In the absence of prospective effectiveness trials, pre-hospital clinicians will continue to need to collect, digest and interpret all the information, overlaid by experience, in order to maximise the chance of a bleeding patient surviving.

Summary

Within the paradigm of RDCR and DCR, PH is a principal strategy. The goal of PH is to provide just enough preload to sustain cardiac output/oxygen delivery to prevent cellular injury and exacerbation of blood failure whilst also preventing adverse effects of hypothermia, dilutional coagulopathy, re-bleeding, endothelial injury and resultant inflammation.

Providing this balance is difficult and compounded in the pre-hospital phase of resuscitation where monitoring is challenging. The duration and depth of PH must also be balanced with the rate of bleeding and duration of time to surgical control of bleeding. In line with the quotation at the start of this chapter, when exploring resuscitation

approaches in trauma patients, consideration should be given to age, mechanism and severity of injury, presence or absence of shock and what treatment, if any, occurred at a pre-hospital or in-hospital setting and the availability of blood-based products.

There are currently no methods available that can inform the ability to achieve the balance needed to ensure adequate oxygen delivery whilst minimising the adverse effects of fluid resuscitation. This balance also changes with the primary use of blood products, where increased oxygen delivery, haemostasis and endothelial cell repair can be achieved with less risks of haemodilution, inflammation and endothelial injury.

Nevertheless, it is imperative to acknowledge that permissive hypotension is neither a treatment nor a substitute for definitive surgical haemorrhage control. To quote a recent manuscript by Nevin and Brohi, 'Permissive hypotension is a technique employed on the journey to a greater overall destination' [64].

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Hemostatic Resuscitation

7

Andrew P. Cap, Jennifer M. Gurney,
and Michael A. Meledeo

Introduction

Evidence from the battlefield and the civilian prehospital environments is clear: hemorrhage is the leading cause of preventable death in trauma. The goal of the trauma medical community at large has been to reduce the number of these preventable deaths to zero [1]. Saving the life of an exsanguinating patient requires two objectives: early hemorrhage control and appropriate, hemostatic resuscitation. The more rapidly these are accomplished, the greater the chances of survival. There is a distinct reciprocity between hemorrhage control and appropriate resuscitation: hemorrhage causes a quantitative and qualitative failure in the hemostatic function and, more broadly, of the global homeostatic function of blood and the endothelium that contains it. To understand the pathophysiology of hemorrhagic shock and how this drives therapeutic imperatives, the blood-endothelium unit should be thought of as an organ system and the shock state as organ failure. The rapid onset of blood organ failure quickly leads to failure of the other dependent organs, and death within minutes to hours, depending on the rate of hemorrhage.

The critical role of blood in supporting other organs has long been appreciated; however, the degree to which the dysfunction of the blood-endothelial organ contributes to hemorrhagic death, and the time course over which this develops, has

A. P. Cap (✉)
Medical Corps, U.S. Army, U.S. Army Institute of Surgical Research,
JBSA-FT Sam Houston, TX, USA
e-mail: andrew.p.cap.mil@mail.mil

J. M. Gurney
Joint Trauma System, US Army Institute of Surgical Research,
JBSA – FT. Sam Houston, TX, USA

M. A. Meledeo
Coagulation and Blood Research, United States Army Institute of Surgical Research,
JBSA-Fort Sam Houston, TX, USA

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only recently been acknowledged. Basic research combined with a focused empiricism approach to analyzing clinical data from military and civilian trauma systems has led to the development of "damage control resuscitation" (DCR) [2]. The concept of damage control has been embraced in the military's battlefield continuum of care; it describes a paradigm of early recognition and therapies to control hemorrhage facilitating the movement of casualties to higher capabilities. The DCR bundle in the military's battlefield trauma system include prehospital hemostasis with tourniquets or hemostatic dressings, rapid surgical control of bleeding and avoidance of crystalloids, and hemostatic resuscitation or a whole blood-based resuscitation with either whole blood or blood components in a 1:1:1 ratio that recapitulates whole blood [3, 4]. Hemostatic resuscitation is central to the DCR bundle of care.

Hemostatic resuscitation stands in stark contrast to prior resuscitation strategies that prioritized maintenance of circulating volume (generally with crystalloids) and restoration of oxygen delivery (with red blood cells) but neglected delivery of hemostatic products [5]. Hemostatic resuscitation has profound implications not only for treatment of the individual patient but also for the design and support of entire trauma and blood banking systems. The application of DCR principles, with hemostatic resuscitation as its core, in both military and civilian settings, has reduced trauma mortality and is revolutionizing trauma care. This chapter will discuss the physiologic principles underpinning DCR; the history of its empiric, clinical evolution; and the importance of whole blood and blood component transfusion strategies, in addition to factor concentrates and adjuncts to hemostatic resuscitation. The chapter also reviews potential treatment strategies for the future.

Coagulopathy Is a Manifestation of Blood Failure: The Need for Hemostatic Resuscitation

The term *blood failure* refers to the physiologic consequences of untreated hemorrhage (see Chap. 3 for a larger discussion of blood failure). Severe injury with resultant hemorrhage results in failure of oxygen delivery by blood (a quantitative deficiency), leading to accumulation of oxygen debt and a cascade of events driven by cellular hypoxia and metabolic failure (quantitative and qualitative deficiencies in blood function). Endotheliopathy develops within the first 30 min of hemorrhage-induced hypoperfusion and is characterized by release of tissue plasminogen activator (tPA) with activation of fibrinolysis, as well as loss of endothelial glycocalyx and associated dysfunction of endothelial regulation of permeability and interactions with the coagulation and immune systems [6]. From a historical standpoint, coagulopathy, as it relates to hemorrhage, was described and studied in both the Korean and Vietnam wars [7, 8]. Coagulopathy now is known to develop in parallel with endothelial dysfunction. The exposure of tissue factor on damaged tissue activates thrombin generation, which is dramatically amplified on the surfaces of activated platelets, leukocytes, and endothelial cells, as well as on microvesicles derived from these and other cells [9–11]. Activation of fibrinolysis is coupled with consumption of fibrinogen by the burst of thrombin activity, leading to clot formation but also to

increases in circulating fibrin monomer and fibrin degradation products [12, 13]. Oxygen debt directly alters coagulation function through effects on fibrinogen such as oxidative stress [14]. The combination of these factors can interfere with normal fibrin polymerization and the formation of stable clots. The net result is a quantitative loss of clotting capacity as well as a qualitative defect which is manifest in both traditional clotting time-based coagulation assays (e.g., prolongation of prothrombin time, PT) and viscoelastic assays of clotting. Traditional coagulation tests like the prothrombin time are also affected by the association of factors V and VIII with activated phospholipid surfaces where they serve as anchors for the assembly of the tenase and prothrombinase complexes, thus reducing their levels in circulating blood that is sampled for clinical testing. In some respects, this aspect of measured coagulopathy may be considered an artifact, though it does reflect the tremendous mobilization of resources to generate thrombin in vivo. Though plasma anticoagulant pathways that regulate thrombin generation, such as the protein C and S systems, are activated by elevated thrombin generation, prolongations in clotting times observed in hemorrhagic shock patients occur despite both elevated thrombin generation potential and evidence of prior and ongoing thrombin generation (e.g., elevated levels of thrombin-antithrombin complexes), as well as rapid fibrinogen consumption and degradation [15, 16].

In light of this, the early coagulopathy of trauma could be seen as a failure to regulate exuberant thrombin generation and fibrinolysis, leading to a fundamentally consumptive coagulopathy, rather than an anticoagulated state in which thrombin generation is inadequate to the hemostatic challenge [17–20]. In addition, platelets, the vital cellular effectors of hemostasis, are rapidly activated (in part by exposure to elevated thrombin levels) and consumed early in response to injury but then develop qualitative functional defects, such as loss of aggregation function, through a combination of metabolic failure and inhibitory signaling, which magnify the effects of coagulopathy in the plasma [21, 22]. Decreases in platelet number and function are correlated with increased trauma mortality [23, 24]. During hemorrhage the combination of the loss of blood cells and the movement of interstitial fluid into the vascular space results in hemodilution. Hemodilution is exacerbated by the loss of endothelial barrier function and decreased Starling forces and amplifies functional defects in coagulation and platelet function. Loss of red blood cell mass reduces the buffering capacity of blood, exacerbating lactic acidosis, and leads to loss of platelet margination to the edges of the blood flow stream where they can attach to damaged tissue and initiate hemostasis [25, 26]. Red cells provide the bulk of clot mass and contribute to blood viscosity; their loss in hemorrhage is thus a central feature of coagulopathic bleeding. The downward spiral of blood failure encompasses all of the sub-systems of the hemo-vascular organ including loss of vasomotor regulation, beginning with systemic vasoconstriction due to adrenergic hyperactivity [27] followed by vasoplegia, and an immunopathology, resulting in systemic inflammation and dysregulated innate and adaptive immunity [28–31]. The loss of hemostasis homeostasis in catastrophic hemorrhage described above reflects first and foremost the quantitative loss of whole blood, not just depletion of any single component. That central fact underlies the resultant pathophysiology and

implies a treatment approach: lost organ function must be replaced. Hemorrhage control cannot be successful without restoration of oxygen delivery and hemostatic function. Severe blood loss must be treated with blood transfusion. Indeed, hemostatic resuscitation can be thought of as the core organizing principle of DCR. Application of these concepts has required a major change in clinical practice and the organization of trauma systems. The evolution of this transformation is described below.

The History of Damage Control and the Coaptation with Hemostatic Resuscitation in Trauma Care

Damage control resuscitation represents the convergence of concepts and interventions that control bleeding and treat blood failure. Principals such as early mechanical hemorrhage control and hemostatic resuscitation are the pillars of DCR. The term "damage control" has its roots in the US Navy and is the concept of refocusing the efforts of a damaged ship's crew on fire control and leak containment. The translation of this concept to the massively hemorrhaging patient that will succumb to their injuries without rapid intervention is germane, especially when considering the military continuum of battlefield care. Damage control in the Navy are measures to keep a severely damaged ship afloat with temporary salvage techniques so that it might survive to arrive at a port for formal repairs. It is a process that requires quick decision-making and often painful trade-offs in stabilizing a devastating situation and curtailing losses. The *Damage Control Handbook*, published in 1945 by the Bureau of Naval Personnel, describes the rapid salvage approaches for damaged ships: "If the ship does not sink within a very few minutes after damage, she probably will survive for several hours." The parallels in trauma management, especially when it comes to interventions for hemorrhage, are readily apparent. Naval damage control has four goals: extinguish the fire, stop the flooding, repair machinery, and provide care to wounded personnel. These concepts applied to the care of traumatically wounded patients are stop the bleeding and minimize contamination, temporize nonlethal injury, stabilize the patient's metabolic disturbances, and then later perform definitive repairs. Hemostatic resuscitation is essential for bleeding control and minimizing metabolic disturbances; it is compulsory for effective DCR.

This principle of rapid salvage and stabilization of a bleeding patient instead of proceeding directly to definitive repair was described in 1983 by Stone et al. [32]. In this foreshadowing of the modern DCR approach, patients underwent abbreviated laparotomy for hemorrhage control to avoid additional bleeding from coagulopathy and the development of blood failure, although the term "blood failure" had not been described. Ten years later, the concept of damage control surgery was defined by Rotondo and Schwab as initial control of hemorrhage and contamination followed by intraperitoneal packing and rapid closure, allowing for resuscitation to normal physiology in the intensive care unit and subsequent definitive re-exploration [33]. This practice was widely adopted and is now considered the gold standard in the care of significantly injured patients. The initial description of the damage

control concept did not include hemostatic resuscitation; instead it emphasized high-volume infusion of crystalloids and red blood cell concentrates, with minimal and late use of plasma and platelets; whole blood was rarely used. Despite the recognition as early as 1982 that crystalloids caused hemodilution and acidosis and contributed to hypothermia (if not warmed prior to infusion), leading to worsened coagulopathy and a "bloody vicious cycle" [34, 35], the resurgence of hemostatic resuscitation to treat trauma-induced blood failure, aka "the blood vicious cycle," took an additional two decades to fully rediscover.

While surgical damage control was being refined and the damage control concept expanded to ICU care and other surgical disciplines, resuscitation strategies were slower to change. Resuscitation has classically been defined as an intervention designed to expand the intravascular space and restore oxygen delivery to vital organs. However, as alluded to above and as will be described further in this chapter, the convergence of the damage control surgery and hemostatic resuscitation has led to the evolution of resuscitation to now represent an intervention not only for oxygen carrying capacity but also for hemostasis and other aspects of blood function including maintenance of endothelial structure and function. Hemostatic resuscitation treats hemorrhagic shock and blood failure and is a key component of damage control. Both mechanical (surgical) hemorrhage control and hemostatic resuscitation are necessary for DCR; one without the other is insufficient for the hemorrhaging patient. Over the last two decades, these concepts have simultaneously evolved and coapted; hemostatic resuscitation was somewhat of a late addition to the DCR strategy – despite many of the concepts being employed since World War II. As blood failure become better elucidated, hemostatic resuscitation, which includes plasma, platelets, cryoprecipitate, and whole blood transfusion, complemented the damage control strategy and led to the integrated concept of DCR.

Damage Control and Hemostatic Resuscitation in Combat Casualty Care

Much of the current understanding of damage control resuscitation and hemostatic resuscitation have come from the recent military experiences in Iraq and Afghanistan. Damage control concepts have long been used by the military across the spectrum of care, and damage control should be viewed more as a strategy than a specific procedure. In the modern US military battlefield system of care, which evolved from roughly 2003 to 2018, the concept of damage control starts with the point-of-injury medic rapidly controlling hemorrhage with a tourniquet and hemostatic dressing use. Rapid evacuation to far-forward surgical care where abbreviated laparotomy and additional hemorrhage and contamination control procedures are performed is the next stage in the damage control spectrum of care. After hemostatic resuscitation with blood products and rewarming, the patient is evacuated to a higher level of care for definitive management. Important elements in the modern damage control strategy include early use of whole blood, minimal crystalloid infusion to avoid hemodilution, and active rewarming measures. These, combined with

moving surgical and resuscitative capabilities closer to the point of injury, encompass a "bundle of care" which mitigates the effects of massive hemorrhage. The development of this system – which now includes prehospital blood transfusion – required a paradigm shift in the understanding of the goals of resuscitation and the importance of treating early blood failure with hemostatic resuscitation.

Interestingly, resuscitation for combat casualties with whole blood and plasma was used in the beginning of the twentieth century up until the Vietnam War. Blood and plasma were transfused to wounded soldiers promptly after injury, and mobile blood banks were used to deliver whole blood to the forward line of battle [36, 37]. Ironically, at the end of the Vietnam War, there was a movement away from whole blood toward crystalloid and blood component resuscitation. This was a reductionist attempt to provide a goal-directed strategy to replace circulating and interstitial volume while sequentially treating identified physiologic deficiencies. Crystalloids were given to increase volume, red blood cell concentrates to replace oxygen-carrying capacity, plasma to replace factors, etc. Given the rapid physiologic decompensation of patients suffering traumatic hemorrhage, it might have been anticipated that a sequential, goal-directed strategy such as this would have been difficult to implement effectively, especially in austere military settings. This resuscitation strategy was a scientific, intellectual, and elegant approach to resuscitation which was rooted in the urge to deconstruct the pathophysiology and measure precisely before treating; interestingly, it was widely adopted without direct comparison to the antecedent whole blood approach or any comparative study.

Relearning Lessons of the Past

In both military and civilian environments, there have been significant investments to advance the understanding of the physiology of hemorrhage and the development of mitigating strategies for hemorrhage control. Devices, medications, operative strategies, and attempts at optimization of transfusion practices have been aimed at improved hemorrhage control in order to avoid the aberrant and frequently deadly physiologic lethal triad (acidosis, coagulopathy, and hypothermia) associated with hemorrhage. However; in a remote setting or far-forward battlefield with limited access to equipment and supplies, successful resuscitation requires a care provider's knowledge and recognition of hemorrhage physiology rather than technology and advanced materiel. It is critical that this knowledge be codified and passed on to avoid the cycle of relearning lost lessons.

Over the last two decades, there has been a paradigm shift in resuscitation strategies regarding both *what* is given as well as *when* it is given. The trauma community has learned that rapid transfusion using either whole blood or a combination of blood components that recapitulates the oxygen carrying and hemostatic function of whole blood will decrease death from hemorrhage. Additionally, the community has learned that resuscitation should begin as soon as the need is identified, at the site of injury if possible. Transfusion at the point of injury (POI), at a remove from the manpower and

logistical support of a hospital, is called remote damage control resuscitation (RDCR) and is now recognized as the lifesaving intervention having the most potential to decrease preventable deaths from severe hemorrhage early after injury [38, 39].

Much of what has been learned about RDCR comes from theaters of war, where the most concentrated source of hemorrhaging patients is found. While the terms *damage control resuscitation*, *hemostatic resuscitation*, and *remote damage control resuscitation* are part of the "resuscitation lexicon" that has emerged during the recent conflicts in the Middle East, their concepts date back to World War I. Transfusion practice evolution during military conflicts has demonstrated that the battlefield is often a source of advancement and innovation in medicine, fueled by intense and concentrated patient experiences as well as the national impetus to improve patient outcomes. The history of battlefield medicine has given great insight into what has worked and what has not. Unfortunately, lessons learned from the past have had to be relearned during the recent conflicts. One of the most obvious of these is the employment of tourniquets for extremity hemorrhage control, but these relearned lessons also include principles associated with transfusion therapies dating back to World War I, such as "The indications for blood transfusion are based on the fact that transfused blood is the best substitute for blood lost in acute hemorrhage," from the 1918 article *The transfusion of whole blood: a suggestion for its more frequent employment in war surgery* by Dr. LB Robertson [40]. This century-old article states that a seriously bleeding patient needs whole blood – *what was lost must be replaced*. While this seems apparent and even simplistic, resuscitation strategies employed since 1918 have varied significantly, incorporating usage of balanced salt solutions, colloidal volume expanders, blood component therapy, and finally, again, whole blood – despite the fact that Robertson and colleagues turned to blood because of the failure crystalloid- and colloid-based resuscitation. Many of the lessons learned from conflict over the years have not been effectively disseminated in peacetime to maintain continuity of best practices.

Resuscitation for the past several decades thus has consisted of crystalloid solutions (lactated Ringer's or normal saline) and packed red cells (if available), a strategy that remains pervasive in locations that have insufficient blood products or supply chain deficiencies. These products temporarily restore perfusion pressures and provide some oxygen delivery but forego support for hemostasis and aggravate endotheliopathy and reperfusion injury. Hemostatic resuscitation incorporating plasma and platelets and minimizing crystalloids on the other hand offers a significant number of other benefits besides restoring perfusion. Even beyond the coagulation factors in plasma, blood products promote homeostasis which is critical to preventing exacerbation of other aspects of blood failure [6, 41]. As important as procoagulant factors are, the anticoagulants such as antithrombin, protein C, and protein S control excess thrombin generation remote from sites of injury and maintain hemostatic and homeostatic balance [42, 43]. Rapid replacement of what has been lost in hemorrhage (all the elements of whole blood) assists with early reversal of shock, hemostatic dysfunction, and endotheliopathy (including associated capillary leak and inflammation).

Physiologic Requisite for Hemostatic Resuscitation

The advocacy for interstitial resuscitation puts the cart before the horse: replacing what was lost from the interstitium is irrelevant if blood failure is not adequately treated. Indeed, interstitial resuscitation as a primary resuscitation approach proved harmful, and even Shires and colleagues sought to correct the misperception that crystalloid use could substitute for blood [44]. Nevertheless, a return to hemostatic resuscitation with whole blood or balanced components would only evolve due to the high casualty volume and logistical challenges of maintaining blood supplies experienced by the US military in Iraq and Afghanistan, more than three decades after the end of the Vietnam War. Improved data capture and enthusiasm for outcomes-based research enabled rapid dissemination of new practices and widespread adoption of modern military blood transfusion strategies.

How did these paradigm shifts occur? As US military casualties began to mount in 2004, blood supplies reaching trauma hospitals and forward surgical teams were found to be inadequate in the management of severely injured patients. Supplying fresh frozen plasma (FFP) proved to be difficult due to challenges in cold chain management and high bag breakage rates. Platelet units were completely unavailable. Resuscitation with red blood cells and crystalloid alone led to high rates of exsanguination, and there were shortages of red cell units. Physicians turned to whole blood collected from walking blood banks to supplement the inadequate component therapy. The experience with fresh whole blood transfusion proved revelatory. Outcomes were visibly better [45]. The Armed Services Blood Program, concerned about the risk for transfusion transmitted disease from using untested blood collected from walking blood banks, responded to the need for an expanded component supply by moving apheresis platelet collection teams into theater and by increasing RBC and plasma shipments [46, 47]. Clinicians attempted to reproduce the results they had seen with fresh whole blood by incorporating plasma and platelets early in the resuscitation of bleeding patients. When supplies of these components were exhausted, they switched back to whole blood. Aware of the unique circumstances they found themselves in, these remarkable clinicians recorded in great detail the interventions they applied and the outcomes they observed. Data from these early studies, conducted between 2003 and 2007, inspired similar efforts in civilian populations which confirmed and extended the battlefield findings. Importantly, these early data collection efforts led to the creation of the DoD Trauma Registry, which has grown into the largest combat trauma registry in history and has provided data for many important studies.

While many analyses of combat trauma data have been published, several have proven to be extremely important for the subsequent development of DCR hemostatic strategies. The first of these studies, and by far the most frequently cited paper on resuscitation from the Iraq War experience, was the 2007 study published by Borgman and Spinella [48]. In this seminal work, the authors described how an increasing ratio of plasma to red cell units was associated with dramatically reduced risk of death in combat trauma patients. As the ratio of plasma to red cells increased from 1:8 to 1:1, mortality dropped from 65% to 19%. This paper gave rise to the

"1:1" plasma to red cell ratio concept. Perkins and Cap extended these findings with an analysis of the impact of adding apheresis platelets to hemorrhage resuscitation. They found that adding platelets in a ratio of ≥1:8 (i.e., about one apheresis unit for every 6 units of red cells) was associated with the highest survival (95%) compared with patients transfused the lowest ratio of platelets (64% survival) [49]. Spinella and colleagues showed that the best results were obtained when fresh whole blood was included in resuscitation, even when compared to component-based therapy that included platelets [45]. Multiple studies of whole blood use in Iraq and Afghanistan have confirmed that whole blood is associated with outcomes at least as good, if not better, than component-based therapy [50, 51].

Ultimately, damage control resuscitation (DCR) was understood to include the comprehensive treatment package of early hemostatic resuscitation with blood product transfusion, immediate arrest of ongoing hemorrhage (even if the therapy is not definitive), avoidance of crystalloids and colloids, maintenance of normothermia, use of hemostatic adjuncts, and physiologic stability to thwart the early coagulopathy of trauma and to decrease the likelihood of blood failure.

As hemostatic resuscitation began to take shape, the strategy of initial crystalloid resuscitation followed by a serial augmentation of red cells, plasma, and lastly platelets was abandoned and no longer considered optimal care [52–57]. While it remains unclear if the detrimental effects of crystalloid are secondary to dilution of clotting factors and platelets, injury to the endothelium, or another primary effect of these acidotic, potentially pro-inflammatory fluids, it has been shown that even small volumes (approximately 1.5 liters) of crystalloid are deleterious. Both crystalloid- and colloid-based resuscitations ultimately may result in a decline in oxygen delivery, exacerbating acidosis and coagulopathy and thereby increasing blood loss which increases the challenge of surgical hemorrhage control in addition to the other derangements in physiology. In hemostatic resuscitation, only low volumes of crystalloids and colloids are used in both the prehospital setting and through the entire resuscitation including intraoperative management and the immediate postoperative period.

Thus, data emerging from the large numbers of casualties treated in Iraq and Afghanistan supported the use of a hemostatic resuscitation consisting of whole blood or blood component products (packed red cells, plasma, and platelets) administered in ratios that mimicked whole blood and had better efficacy in treating the coagulopathy of trauma. Similar results were observed in a large, multicenter observational study of civilian trauma patients [58]. The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) study was a comparative efficacy investigation in ten trauma centers that demonstrated how early transfusion of higher plasma and platelet ratios (versus red cells) was associated with decreased mortality during the initial 6 h after admission [59]. PROMMTT demonstrated the challenges of survival bias in studies evaluating an exsanguinating patient cohort, the importance of coordinating efforts necessary to transfuse the optimal ratio of plasma and platelets within minutes of hospital arrival, and, most importantly, that suboptimal transfusion ratios are associated with early death. PROMMTT provided critical evidence that helped inform the design of the follow-on randomized trial

which has fueled the evolution of transfusion practices in the hemorrhaging trauma patient [59–63].

Hemostatic resuscitation has been shown to improve outcomes when surgical hemorrhage control is necessary; additionally, evidence is mounting suggesting that it can improve rates of successful nonoperative management in Grade IV and Grade V blunt liver injuries [64, 65]. In a retrospective analysis of more than 1400 blunt liver injuries before and after implementation of hemostatic resuscitation at a Level 1 trauma center, increased success rates of nonoperative management were observed; additionally, a significant improvement in survival was achieved [65].

As military resuscitation practice evolved over the course of the conflicts in Iraq and Afghanistan, hemostatic resuscitation approaches were translated to the prehospital environment, with medics at the point of injury and helicopter evacuation crews administering transfusions. From a physiologic standpoint, this transition had obvious appeal since it offered the possibility of reducing shock dose and preventing coagulopathy. Observational studies of both the US and British military experience as well as US civilian trauma system experience were indeed promising [66–69]. The most detailed such study, by Shackelford and colleagues of the US Joint Trauma System, observed a striking reduction in mortality among combat casualties transfused within 30–40 min of injury [70]. In addition, the "golden hour" decision by Secretary of Defense Robert Gates to increase the number of helicopter evacuation platforms in Afghanistan available to transport casualties to surgical care within 1 h, much applauded for its association with a reduction in combat mortality, was found to have had its beneficial effect primarily through the early delivery of blood transfusion to wounded personnel [71]. This experience supported the expansion of hemostatic resuscitation as part of an overall DCR approach to settings remote from hospital capabilities and the coining of the term "remote damage control resuscitation" or RDCR.

Since hemostatic resuscitation principles state that plasma should be the primary volume resuscitation fluid in order to reduce endothelial dysfunction, and restore lost coagulation factors, the Department of Defense funded two randomized studies of plasma-based prehospital resuscitation to evaluate whether moving the hemostatic resuscitation approach out of the hospital would improve trauma outcomes as suggested by the multiple observational studies discussed above [2, 56–58, 72, 73]. The COMBAT trial was a single-center study comparing plasma (2 units administered by paramedics) to normal saline in ground ambulance evacuation [74]. This study did not find a reduction in trauma mortality with early plasma transfusion, but evacuation times were so short (<20 min for both arms) that many patients could not receive the intervention before arrival at hospital (only 32% received both units of plasma during transport). This study was halted early due to futility. The PAMPER trial was a multicenter study that compared plasma (2 units administered by flight crew) to standard of care (generally crystalloids but include red cell units) in helicopter evacuation of trauma patients. This study found a substantial survival advantage for early plasma transfusion – reduction of 30-day mortality by one-third (22% vs. 32% mortality). The difference in findings between the two studies may be due to many factors, and cross-study comparisons are hazardous; however, the mortality

difference may have been due to the long evacuation times (approximately 40 min) in PAMPER compared to COMBAT [69]. Neither study identified any disadvantages to beginning transfusion support in the prehospital environment, and in both, most patients receiving early transfusion went on to require further blood transfusion support, indicating that triage algorithms could be successfully implemented by prehospital providers. Overall, the weight of currently available clinical evidence as well as our current understanding of hemorrhage, coagulopathy, and blood failure supports the implementation of RDCR, or early hemostatic resuscitation, in both civilian and military settings, particularly when transportation time to fully capable trauma hospitals exceeds 20 min.

What to Transfuse and When

While the choice of which product to deliver first depends on the condition and need of the patient, hemostatic resuscitation prioritizes platelets first, followed by alternating red cell units and plasma units in a ratio of 1:1:1 to best mimic whole blood, when whole blood is not available. For patients requiring transfusion, early delivery of plasma and platelets is associated with improved survival within the first 6 h. Additionally, maintaining the 1:1:1 ratio of platelets, plasma, and red cells has been shown to improve outcomes including reduced mortality and cessation of anatomic bleeding. This hemostatic damage control resuscitation is currently the standard operating procedure for massive transfusions within the military and many civilian centers [75].

In addition to what is being transfused, the timing of transfusion is critical. Many advances in trauma and critical care emphasize that the more expeditious the intervention, the more efficacious the therapy. Well-understood early interventions that result in improved treatment effects are antibiotics in sepsis, time to neurosurgical intervention for extra-axial traumatic hemorrhage, time to tourniquet placement for extremity hemorrhage, time to intervention for stroke therapy, time to revascularization in myocardial infarctions, and time to hemostatic transfusion in hemorrhage. Time is critical, and while it seems like an obvious statement: hemorrhaging patients die quickly; therefore, minutes matter. Time to hemostatic transfusion and time to hemorrhage control are the difference between a life and death for a patient with severe bleeding. Given that most deaths from hemorrhage occur in the prehospital environment, employing strategies to mitigate the effects of hemorrhage and improve hemorrhage control in the far-forward combat environment will have the highest impact mortality. Additionally, strategies used to control bleeding in the military population can be extrapolated into civilian practices and ideally have a large impact on preventable death from trauma.

Clearly then, there are several parameters to be considered when developing transfusion strategies for DCR, and these become even more critical in the RDCR setting. The product or products transfused should recapitulate to the extent possible the functionality of whole blood. Oxygen delivery and hemostasis must both be accomplished. Products like whole blood, plasma and platelets should be optimized primarily for their ability to support hemorrhage control. Speed and ease of use are vitally

important, particularly as the staff available to administer the transfusions becomes constrained as in the prehospital environment. During initial resuscitation, complexity should be minimized wherever possible to reduce risk of errors and improve speed, through use of broadly compatible products and minimization of testing.

Tools of the Trade: All Roads Lead to Whole Blood

Early in the recent wars in Iraq and Afghanistan, whole blood was utilized in US Military operations primarily by forward deployed teams that were equipped with a limited supply of packed red blood cells; whole blood transfusion during this period was driven by necessity rather than clinical indication [51, 76]. At the combat support hospitals, the highest level of care on the battlefield, whole blood was initially used when apheresis platelets were unavailable. Over time, through both focused empiricism and investigations of comparative efficacy which demonstrated improved survival with whole blood, battlefield hospitals began using whole blood not just when components were unavailable but because of the clinical superiority of whole blood [45, 51, 77].

While component therapy is a vast improvement over crystalloid and colloid for hemostatic resuscitation, there are deficiencies to the method that must be addressed. With multiple components transfused comes multiple doses of anticoagulant; whole blood is superior in this regard since anticoagulant-induced dilution is minimized with a single product. In a reconstituted whole blood made from 1:1:1 blood components, hematocrit and factor levels are lower than equivalent units of whole blood [78, 79]. Additionally, whole blood contains platelets, providing superior hemostatic function to component therapy in the variety of situations in which platelets cannot be supplied. Logistically, it is much easier to collect, transport, store, and transfuse a single product that meets the essential needs of a bleeding patient.

Because of the benefits to patient care and logistical simplicity, there continues to be enthusiasm for whole blood use in in both military and civilian settings: it is being considered, studied, and reestablished as the optimal therapy for hemorrhage. Cold stored, low titer Group O whole blood was introduced into Iraq in November 2016. In 2017, 311 units of cold stored LTOWB were transfused, and it was the preferred resuscitation product when compared to component therapy. Based on the usage of, and demand for, LTOWB, the authors concluded that it is not only feasible but has logistical advantages and will likely emerge as the preferred transfusion product for far-forward damage control resuscitation [80].

Combat casualties requiring massive transfusion have a mortality rate up to 33% and will receive the largest benefit from whole blood transfusion. In a large retrospective review of patients that received whole blood without platelet transfusion compared to those who received balanced component resuscitation (including platelet transfusion), those who received whole blood had a higher survival at both 24 h and 30 days. The use of fresh whole blood was associated with a 13% increase in 30-day survival and demonstrated that the volume of fresh whole blood transfused was independently associated with improved 30-day survival [45].

Whole blood can refer specifically to two types of products. The first is fresh whole blood (FWB), drawn on an emergency basis and transfused within a limited window post-collection (typically 24 h). This has the drawback of omitting formal pathogen screening which increases the risk of transfusion transmitted disease (TTD) [81]. This risk can be partially mitigated through the use of point-of-care rapid screening tests, though such testing can be impractical under the most austere conditions of combat casualty care. Blood group typing and matching can be performed with point-of-care tests, or FWB can be drawn only from pre-screened individuals who are group O low anti-A and anti-B titer donors (low titer O whole blood, LTOWB). LTOWB red cells will be compatible with recipients of other blood groups, and the risk of transfusing incompatible plasma is minimized by selecting donors with low titers against A and B blood group antigens. FWB can be collected and stored at refrigerated temperatures (1–6 °C) within the first 8 h for up to 21 days in CPD anticoagulant or 35 days with CPDA-1 anticoagulant. If whole blood is collected where it can be tested for TTDs, it can be provided as a standard refrigerated and fully tested product (cold whole blood, CWB). However, the stored blood suffers from the same "storage lesion" as has been previously described for blood components. Over time, stored whole blood red cells undergo shape change and lose function, platelets bind fibrinogen and release their intracellular contents (depleting functionality), and waste products accumulate in the plasma increasing acidity. Despite this, cold-stored blood still supports hemostasis and provides platelets in many scenarios in which they would be unavailable. Storing platelets at cold temperatures reduces their rate of functional decline as observed in the platelet storage lesion for the room temperature-stored standard-of-care platelet product.

Given that the vast majority of combat deaths occur in the prehospital environment, prior to reaching a surgical capability, these are the combat casualties who will most benefit from blood far forward. WB is the logical choice for a nearly perfect resuscitative product in the far-forward environment given that it has oxygen carrying capacity, coagulation factors, and platelets in the ratio that are lost during exsanguination. It is logistically easier to carry and transfuse one unit of whole blood compared to multiple units of components. In the current theaters of operation, the blood transfusion capability continues to mature at both point of injury and in the en route care environment. In 2013 the Norwegian Special Operations Forces instituted an RDCR protocol which included far-forward collection and transfusion of whole blood. A similar protocol for tactical DCR (TDCR) in order to transfuse low-titer Type-O WB at POI was adopted by US Army Ranger Regiment: Ranger O-low-titer Type O (ROLO). Currently, US Special Operations Forces carry low titer group O whole blood on select missions [82–84]. Transfusion far forward is an essential capability that saves lives of combat casualties.

In far-forward or prolonged field care conditions with life threatening hemorrhage, where hemostatic resuscitation is most critical, it becomes particularly apparent that whole blood is a superior option with respect to simplicity of logistics, usage, and outcomes. Carrying all blood components (RBCs, plasma, platelets) is all but impossible for the military medic, and even most medical transports cannot support the multiple temperature storage modalities required for proper maintenance of

individual components. Additionally, both collection and delivery of a single product reduce risk, including crossmatching risk reduction through use of low-titer O whole blood as mentioned above – a benefit in prolonged field care, at role 2 facilities, and even for humanitarian care where the recipient's type is unknown. However, the definition of what constitutes "low-titer" for anti-A and anti-B is still under some debate, with the maximum set to <256 by US Armed Forces until such time as more strong evidence emerges to re-evaluate this threshold established in World War II.

Leukoreduction has been recommended to reduce the immunomodulatory side effects of whole blood transfusion. Remy et al. showed that there was a distinct loss of platelet function even with "platelet-sparing" leukocyte filtration, an effect that must be considered in the cost-benefit analysis of whether or not to use leukoreduction [85]. The US military does not currently leukoreduce whole blood, though approximately 50% of civilian centers do so [86, 87].

Another consideration in the implementation of a LTOWB program for hemostatic resuscitation is how to manage the risk of alloimmunization to the D or other antigens in patients receiving uncross-matched blood. It is generally accepted that alloimmunization to the D antigen represents the greatest risk, as it is the most immunogenic antigen on red blood cells. In female patients of child-bearing potential, development of an anti-D antibody could lead to hemolytic disease of the fetus and newborn (HDFN), though only about 20% of D-negative recipients of D-positive red blood cells or whole blood develop antibodies. While a simple solution to this problem would appear to be available – transfusion of only D-negative LTOWB to females of child-bearing potential – the reality is that D-negative potential donors make up only 7% of the population and that D-positive group O whole blood is generally the only product available in sufficient quantities to resuscitate patients. Thus, decisions regarding what products to offer to which populations should be made based on a local risk assessment. Transfusion of D-positive LTOWB to females of unknown blood type can be justified due to the imperative to preserve the patient's life when weighed against the relatively low risk of causing harm to a future theoretical pregnancy. Furthermore, HDFN is treatable and does not automatically doom all future pregnancies. Finally, it is important to realize that the limitations on availability of D-negative LTOWB are similar to those for D-negative RBC units and that most of the emergency release blood available is D-positive [88].

The tangible benefits from both logistical and patient care perspectives make whole blood a superior option to component therapy following hemorrhage, especially in massive transfusion cases and in the prehospital setting.

Tools of the Trade: Component Blood Products

Red Cells

Red cells (erythrocytes) are the largest volumetric cellular fraction of blood, performing the critical functions of delivering oxygen to tissues, supplying critical enzymatic functions, and buffering the blood [89]. Their contribution to hemostasis

consists primarily in providing the bulk of clot mass and in pushing platelets to the edges of the blood flow stream and facilitating their interaction with damaged vessel walls in a process known as margination [26]. In the microvasculature, red cells contribute significantly to buffering the acidosis generated by hypoperfusion. Since coagulation enzyme activity drops with dropping pH, red cells play a crucial role in maintaining the activity of the coagulation system and reducing capillary bleeding. In addition, hypoxia triggers release of tPA from endothelial cells, activating fibrinolysis. Red cell delivery of oxygen to the vascular bed can mitigate this process which otherwise contributes significantly to development of acute traumatic coagulopathy [90, 91]. Thus, red cell transfusion is critical to recovery of oxygen deficit and hemostatic function.

As stated above, historically, red cells have been among the first products delivered in resuscitation, often at a higher ratio than plasma or platelets. They remain very common in transfusion, partly because of their support for oxygen delivery but also likely because they are easier to maintain in blood banking practice [92]. Red cells are isolated from whole blood via centrifugation and transferred into a preservative solution which by Food and Drug Administration regulations allows them to be maintained at temperatures from 1 to 6 °C for up to 42 days. However, multiple studies have indicated that red cells undergo a "storage lesion" over time; as red cells remain in storage prior to transfusion, they begin to shed microvesicles, to lose membrane integrity, to have diminished oxygen carrying capacity, and to suffer altered morphology [93, 94]. Aged red cell transfusion may result in greater likelihood of poor outcomes in trauma patients that require a large amount of RBC transfusions [95–98].

Red cells remain an important part of the balanced resuscitation prescribed by DCR, but they must be used with platelets and plasma to achieve primary and secondary hemostasis.

Plasma

The need for plasma in hemostatic resuscitation should be self-evident; plasma contains all of the necessary enzymes and substrates for producing a clot, factors which are rapidly depleted in trauma due to consumption, dilution (from autoresuscitation or crystalloid usage), and/or continued hemorrhage. Restoration of what has been lost in plasma is mandatory for continued hemostasis. As noted above, early use of plasma, even prehospital, has been shown to reduce mortality in severely injured trauma patient [48, 67].

Plasma can be collected via centrifugation of whole blood or can be obtained through apheresis, and there are several options for storing the plasma. For maximum retention of enzymatic function, plasma can be frozen immediately (within 8 h) after collection at temperatures below −18 °C. Alternatively, often for convenience and logistical purposes, plasma is isolated from whole blood within 24 h of collection and frozen, resulting in some diminished capacity of labile factors (particularly factors V and VIII) but overall preservation of fibrinogen, the primary

substrate for clot formation [99]. Frozen plasma can be kept for a year before expiration, but it requires sufficient time for thawing (30–40 min using conventional techniques), a substantial consideration in emergency scenarios. Alternatively, plasma can be thawed prior to use and stored refrigerated for up to 5 days (thawed plasma), or it can be stored as a refrigerated product and never frozen (liquid plasma). Liquid plasma can be stored for 26 days if collected in CPD anticoagulant or for 40 days if collected in CPDA-1. All thawed or liquid plasmas are deficient to various degrees in labile factors like FV and FVIII, but overall ability to support hemostasis in emergency settings appears to be adequate [100, 101]. The convenience of omitting the thawing step can mean the difference between timely plasma transfusion and the delivery of a temporally unbalanced resuscitation that appears to be associated with suboptimal outcomes [57, 102].

Plasma can also be dehydrated through one of several lyophilization or spray-drying processes, resulting in a relatively stable powder of plasma proteins that can be rehydrated on demand [103]. This allows for easier transport as cold chain requirements are reduced and no freezer is required for storage, and rehydration can occur much more rapidly than thawing an equivalent volume of frozen plasma. While dried plasmas are available in some countries, no dried plasma products are yet approved by the US Food and Drug Administration. Usage within the United States has been restricted to an investigational new drug application of the French lyophilized plasma in military special operations forces. Comparative efficacy of FDP versus other plasmas is still being studied, especially with regard to its utility at point-of-injury care [104–107]. See Chap. 8, *Dried Plasma*, for more information.

Plasma from group AB donors has long been considered universal due to its lack of anti-A or anti-B antibodies. Since only about 4% of US and European populations are AB, this plasma is in short supply. It has emerged that Group A plasma can be safely transfused to recipients of any group, even when anti-B titers are unknown [108]. Group A plasma is being widely adopted as an emergency release product in many trauma systems including the US military.

Platelets

After being neglected in resuscitation strategies for many years, pragmatically and in the literature, platelets deserve special mention for their critical function of rapidly initiating coagulation and hemostasis at the site of wounding. The vital role of platelets in hemostasis has long been recognized; therefore, it is not understood why these key elements were often omitted as an imperative component of hemorrhage resuscitation after the transition to component therapy. It appears that the reason is more logistical than biological: platelets are problematic from a supply standpoint. Once collected (e.g., by platelet apheresis in volumes of 200–300 ml from a single donor), they are typically stored at room temperature (approximately 22 °C) with gentle agitation. This already presents problems for austere and extreme environments with

limited power and unregulated temperatures, and these settings (e.g., theaters of war, high altitudes, polar stations, or space flights) are also associated with higher risks to life and limb where hemostatic blood products would be most valuable on scene. But even beyond the storage requirements, the shelf life of platelets is the most restrictive of the blood products: regulations limit platelets to a 5–7-day post-collection expiration, primarily because storage at room temperature gives ample opportunity for what would have been inconsequential contamination at collection to become a major problem after 5–7 days of bacterial growth. This restriction in particular makes platelet usage outside of large trauma centers extremely limited.

Platelets, like red cells, suffer from a "storage lesion" over time, although with platelets this occurs more rapidly, exacerbated by room temperature storage where metabolism functions markedly better than the refrigeration of red cells allows. In vitro aggregation function declines rapidly and is minimal after 72 h [109]. Mitochondrial exhaustion is apparent, and waste products are abundant [110]. Clinical outcomes are also affected [111].

Recognizing the importance of platelets in balanced hemostatic resuscitation, several avenues have been investigated to extend shelf life and improve function. In an effort to reduce the effect of platelet alpha 2b beta 3 receptors binding fibrinogen in the plasma solution in which they are carried, a variety of additive solutions have been used to dilute the fibrinogen and supply nutrients to the platelets during storage [112]. These have shown moderate success in improving the function over time, but there is still opportunity for reducing bacterial growth.

To overcome the contamination issues and limit biochemical activity during storage, the obvious solution is to store under refrigeration similarly to whole blood. This idea has once again been brought to the forefront of transfusion research after decades of being dismissed by the blood banking community due to studies in the late 1960s and early 1970s that demonstrated a reduced recovery and survival of transfused platelets that had been stored in refrigerated temperatures [113]. Recently, that paradigm for viability has been questioned, as studies have shown that the room temperature-stored platelets that freely circulate and boost the recovery and survival counts are largely non-functional in hemostasis [109]. In fact, the likely explanation for the diminished recovery of refrigeration-stored platelets is because they are, in fact, migrating to sites of injury and performing their intended function; this has been proven in animal studies that show these cold-stored platelets (in whole blood) localizing in thrombi on damaged endothelium [114, 115]. These in vitro and animal studies have led to human testing; a randomized control trial performed in Norway evaluated cold-stored platelets versus standard room temperature-stored platelets in cardiac surgery patients and found that cold platelet use was associated with reduced post-operative blood loss. Overall, cold-stored platelets (CSP) have been compared to room temperature (RT)-stored platelets across the following parameters and been found to be generally superior: aggregation to single or multiple agonists, adhesion to collagen under flow including reversal of antiplatelet drug effect, spreading on fibrinogen-coated surfaces, clot strength, clot retraction, clot architecture, thrombin generation, thromboelastography/thromboelastometry,

mitochondrial function, resistance to activation of apoptosis, maintenance of membrane integrity and granule content, response to regulatory stimuli, preservation of RNA, secretion of inflammatory mediators, risk of bacterial growth, and in vivo hemostasis in both animal models and human patients including those undergoing surgery and those with hypoproliferative thrombocytopenia due to chemotherapy or other bone marrow failure states [116–118]. These results have been replicated since the early 1970s through the present (2018) and in laboratory and clinical settings using multiple variations of CSP (platelet-rich plasma concentrate pools, buffy coat pools, apheresis units collected on multiple platforms, units stored in plasma or platelet additive solutions, gamma-irradiated or pathogen-reduced units) in the United States, Norway, Sweden, Australia, Germany, Korea, and China. In short, the superior hemostatic function and bacterial safety of CSP are well-established. The US Department of Defense has used CSP stored for up to 14 days in the hemostatic resuscitation of combat casualties in Afghanistan and Iraq, and the US FDA has granted a variance for the use of CSP in the treatment of bleeding patients [119]. CSP offers a way to expand access to hemostatic resuscitation safe from bacterial contamination for a broad range of patients previously without access to platelet transfusions.

As previously mentioned, perhaps the easiest solution to incorporating platelets into transfusion is through the use of whole blood. Whole blood is already stored refrigerated and contains platelets, plasma, and red cells all in one package. CSP and whole blood will soon be more broadly available and will transform hemostatic resuscitation in the far-forward setting.

Tools of the Trade: The Role of Laboratory Testing, Factor Concentrates, and Tranexamic Acid

Goal-directed therapies have been used for decades. For example, acute traumatic coagulopathy has been identified by some as an increase in prothrombin time (PT), and many efforts to provide reversal of this coagulopathy have focused on the goal of restoring PT to normal. In fact, resuscitation in the pre-DCR era used crystalloid and red cells first to establish tissue perfusion, followed by plasma and platelets as guided by the PT and platelet counts to correct objectively identified coagulation deficits. As we have seen, this approach led to late use of plasma and platelets and suboptimal resuscitation of bleeding patients. PT was recognized as an inadequate diagnostic [120], and thus more robust methods have gained ground in recent years, with viscoelastic tests of coagulation such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) analyzing an ex vivo blood sample for a variety of parameters providing additional therapeutic targets [121–123]. Varying the combinations of reagents in these assays can isolate specific coagulation-related problems. Point-of-care (POC) devices have also been introduced to provide limited information to guide treatment at the scene or en route [124].

The use of viscoelastic testing technology to facilitate early diagnosis of clotting aberrancies and guide goal-directed therapies has been suggested as being superior to empiric ratio-based component therapy, and factor adjuncts to resuscitation have received attention over the last decade. Recombinant factor VII initially showed promise for the treatment of trauma-induced coagulopathy [125, 126]; however, larger retrospective and prospective studies did not demonstrate a mortality benefit [127–129].

Studies have suggested that early fibrinogen supplementation may improve outcomes in traumatic hemorrhage. Cryoprecipitate from plasma contains fibrinogen, factor XIII, factor VIII, vWF, and fibronectin, and it is commonly used for resuscitation in cases where early fibrinogen and factors will provide the most benefit. Similarly, for cases where pharmaceutical anticoagulant reversal is required, prothrombin complex concentrates can restore thrombin activation, a procedure typically guided by prothrombin time and international normalized ratios. Identification of hyperfibrinolysis as a major bleeding problem following ischemia and plasminogen activator release has supported the use of tranexamic acid as an early adjunct (within 3 h of injury) in patients identified as at risk for bleeding complications to stabilize fibrin networks against exuberant plasmin-induced breakdown. Some groups have suggested the use of viscoelastic tests to limit the use of tranexamic acid to those manifesting evidence of fibrinolysis.

The use of factor concentrates and tranexamic acid guided by viscoelastic testing, while intellectually attractive, has not been adequately studied. One single-center randomized study evaluated this approach compared to use of plasma in the resuscitation of blunt trauma patients [102]. Although the authors found an advantage to use of concentrates, this was largely driven by the time delay in treatment in the plasma arm due to the need to thaw plasma. Clearly, this delay in treatment could be obviated by the use of thawed or liquid plasma or indeed whole blood. In addition, the study did not include penetrating trauma patients who may experience brisk bleeding and rapid decompensation that limits the utility of a testing-intensive resuscitation strategy. Also, there is little consensus on viscoelastic test thresholds for determining the use of factor concentrates or antifibrinolytics like tranexamic acid [130]. Finally, the viscoelastic tests like TEG and ROTEM are not practical for prehospital use. Although a single-center RCT recently demonstrated a survival benefit from the use of TEG-directed therapy, further study of this promising goal-directed approach is required before it can be broadly implemented [123].

Overall, empiric use of TXA in bleeding trauma patients is well-supported by the literature, though this represents off-label use in the United States. The CRASH-2 study randomized over 20,000 patients to either TXA or placebo and found a 9% reduction in relative risk of all-cause mortality and a 15% reduction in relative risk of hemorrhage mortality in patients receiving TXA [131]. In this study, TXA was given without viscoelastic testing guidance in a dose of 1 g over 10 min followed by 1 g over 8 h. TXA reduced mortality if given within 3 h of injury but was associated with higher mortality when given more than 3 h after injury. Current clinical guidelines suggest using TXA as given in CRASH-2, within 3 h of injury.

Currently, there are no high-quality data to support either the empiric or viscoelastic testing-based use of fibrinogen concentrate, prothrombin complex concentrates, or recombinant human activated factor VII (rhFVIIa) outside of the setting of a clinical trial. In the United States, fibrinogen concentrate is approved for the treatment of congenital hypofibrinogenemia. Prothrombin complex concentrates containing factors II, VII, IX, and X such as Kcentra are licensed for the reversal of vitamin K antagonists, and rhFVIIa is approved for the treatment of patients with hemophilia who have inhibitors to FVIII. In addition to the complexity and time requirement of reconstituting multiple vials of these products in the acute setting, and the considerable costs of these factors, the thrombotic risk of using these products off-label in the absence of high-quality clinical data supporting their safety or efficacy in unselected trauma patients argues for caution. Further study of these products in bleeding trauma patients is needed.

A frequently overlooked hemostatic adjunct is calcium. Hypocalcemia is present in a majority of trauma patients requiring urgent resuscitation due in part to the calcium chelating effects of intracellular phosphates and other substances released from damaged cells. Transfusion of citrated blood causes further calcium sequestration and can cause clinically significant hypocalcemia [132]. Hypocalcemia can cause not only cardiac arrhythmias but also dysfunctional coagulation and vasoplegia. Infusion of calcium early in resuscitation (e.g., one gram of calcium IV/IO as either 30 ml of 10% calcium gluconate or 10 ml of 10% calcium chloride) can mitigate these problems and boost not only coagulation function but also cardiac output and vascular tone.

Mitigation of Transfusion Hazards

While evidence suggests that blood and blood products should be given early following trauma, increased usage, especially in emergency scenarios, raises the likelihood of a transfusion-related complications. Transfusion-related acute lung injury is a concern with use of plasma, though this has been significantly mitigated by use of plasma from male donors or never-pregnant females or females documented to lack anti-HLA antibodies [133]. Over-transfusion, or transfusion-associated circulatory overload, has been documented, and thus transfusions should be carefully monitored and documented [134].

Potentially lethal hemolytic transfusion reactions can be mitigated through use of low-titer group O whole blood, group O red cells, and group AB or A plasma. Safety concerns associated with on-scene collection and transfusion (as has become possible in military practice) must be addressed through rigorous training in donor selection and repetition of collection procedures that emphasize competence in blood typing and infectious disease rapid testing, as well as the development of donor screening programs and rigorous record keeping. The potentially serious hazards of prehospital blood collection and transfusion are significantly diminished by using a pre-screened, blood group-identified donor pool [135].

Even when blood is collected in advance, screening can be a major expenditure with respect to both time and money, reducing the supply and availability of product in remote locations. New innovations in pathogen reduction technologies have been proposed to provide a rapid method to reduce the transfusion-transmitted disease risks associated with fresh whole blood, and these products and methods have been made available in locations suffering from virulent outbreaks including Ebola [136]. Photochemical inactivation of pathogens is the current approach, with the latest products using photosensitizers and ultraviolet light to damage nucleic acids. These technologies may also reduce the very small but real risk of transfusion-associated graft-versus-host disease through inactivation of the lymphocytes transfused from donor to recipient [137]. These pathogen reduction technologies are undergoing regulatory evaluation in the United States.

Conclusion

The preponderance of the available evidence suggests that hemostatic resuscitation is a core element of the DCR bundle of care. DCR is inclusive of early mechanical hemorrhage control, no crystalloid, and hemostatic resuscitation which is the holistic approach to treating blood failure by replacing the functionality of whole blood lost to hemorrhage. DCR and hemostatic resuscitation reduce trauma mortality compared to resuscitation strategies that do not address both the restoration of perfusion and of hemostasis in a timely manner. Emerging data from military and civilian experience demonstrate that translation of the DCR approach into the prehospital setting as RDCR extends the benefits of DCR further reduces trauma mortality. Significant challenges remain in the broad implementation of a "blood far-forward" paradigm such as the financial and logistical challenges to providing whole blood or components in the prehospital environment. Training prehospital personnel in hemostatic resuscitation procedures and transfusion is difficult and requires a substantial investment in skills maintenance. Training not only military personnel but also civilians in whole blood collection, establishment of emergency donor panels, and documentation of emergency transfusion is a major undertaking but one that could prove lifesaving in the event of civilian or military mass casualty events where the local blood supply is exhausted and resupply from other regions has not occurred. Research challenges include the need to identify better ways to store blood products in order to preserve their shelf life and function. Ultimately, these challenges must be overcome in order to make progress towards the goal of zero preventable deaths that military experience in elite units has taught us could be close to achievable.

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Dried Plasma

8

Mouayyad Zaza, Kyle J. Kalkwarf, and John B. Holcomb

Abbreviations

DCR	Damage control resuscitation
FDP	Freeze-dried plasma
FFP	Fresh frozen plasma
FLyP	French lyophilize plasma
LP	Lyophilized plasma
RBCs	Red blood cells
S/D	Solvent/detergent
SDP	Spray-dried plasma
TBI	Traumatic brain injury
TEG	Thrombelastography

Introduction

Hemorrhage remains the leading cause of preventable death in trauma patients [1]. Contrary to the classical teachings of the "golden hour," in patients with severe truncal hemorrhage, peak mortality occurs at 30 min [2]. For patients who survive long enough to make it to a hospital, the median time to death from hemorrhage is 90–150 min after admission [1, 3]. The lethal triad of hypothermia, acidosis, and acute coagulopathy of trauma is well recognized as a common pathway to irreversible shock and death [4, 5]. Rapid treatment utilizing damage control resuscitation

M. Zaza (✉) · K. J. Kalkwarf · J. B. Holcomb
Department of Surgery, Division of Acute Care Surgery, University of Texas Health Science Center at Houston, Memorial Hermann Hospital, Houston, TX, USA
e-mail: Kyle.J.Kalkwarf@uth.tmc.edu; John.Holcomb@uth.tmc.edu

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(DCR) with blood components mimicking whole blood in the setting of permissive hypotension, avoiding crystalloid and colloid, followed by prompt surgical hemorrhage control, is the best strategy to prevent traumatic hemorrhagic death and the onset of the lethal triad [1, 4, 6, 7]. Plasma transfusion is an essential part of this approach and remains a significant logistical challenge even today, hence the need for a reliable, shelf-stable, easy-to-carry and administer plasma product such as dried plasma.

Benefits of Early Plasma Transfusion

The role of plasma in DCR has been reaffirmed time and time again. In 1945, Beecher noted that "Plasma gives more time to get whole blood into the patient" [8]. Multiple US large center retrospective cohorts showed that 24–28% of severely injured trauma patients are found to be coagulopathic on admission. Coagulopathic patients have significantly higher mortality rates, while the degree of coagulopathy correlated with the severity of injury [9–11]. Analysis of the German Trauma Registry yielded similar results with rates of coagulopathy up to 34% as well as a direct correlation between the amount of crystalloid received prehospital and an increasing degree of coagulopathy [12]. Looking back at the first decade of war in Iraq, 33% of combat casualties were coagulopathic on admission, which correlated with a fivefold increase in mortality [13]. These data highlight the importance of recognizing the early onset of the coagulopathy of trauma at the time of injury, as well as endothelial damage, which plasma has been shown to correct [14]. Therefore, correction of coagulopathy should not be delayed until laboratory values are available to guide therapy and goals of care. The approach to the trauma patient should aim at preventing and correcting this coagulopathy as soon as possible to decrease its effects on mortality and progression of shock.

The importance of balanced resuscitation to include a high ratio of plasma delivered early became evident in the Iraq War where a survival advantage was noted in patients receiving close to 1:1 plasma-to-RBC ratio during massive transfusion compared to those who received less plasma [15]. During this conflict, over 335,000 units of blood products were transfused with nearly 110,000 being plasma [16, 17]. Analysis of combat casualties over 10 years revealed improved survival in those receiving a higher ratio of plasma and platelets to blood [13]. By 2010, clinical practice guidelines implemented by the Department of Defense (DoD) led to almost 100% of combat massive transfusions to be at a 1:1:1 ratio [18]. The PROMMTT trial then showed that early plasma administration was associated with reduced mortality in the first 6 h [3]. Following that, the PROPPR trial demonstrated that patients transfused with a higher plasma ratio achieved more hemostasis and had less early death due to exsanguination [19].

A retrospective review of patients receiving thawed plasma available in the ED showed shorter time to plasma transfusion (43 vs. 89 min), a reduction in blood transfused over 24 h, and decreased 30-day mortality [20]. A recent review of US combat casualties in Afghanistan rescued by medical evacuation (MEDEVAC) units

showed that early blood product transfusion prehospital or within minutes of injury resulted in greater 24-h and 30-day survival [21]. In a large civilian cohort from a level 1 trauma center, prehospital administration of blood products including RBCs and plasma has been shown to be feasible and beneficial with improved acid-base status on admission and decreased overall blood product use in 24 h as well as a reduction in the risk of death in the sickest patients over the first 6 h [22]. All these findings point toward the need for a method to deliver early plasma in a reliable fashion.

Plasma produces superior volume expansion when compared to crystalloids, allowing less volumes infused to match volume lost, faster hemodynamic recovery, and decreased third-spaced volume [23]. It is important to use plasma as the primary resuscitation fluid for patients who are bleeding [4]. Other benefits of plasma stem from its ability to mitigate the effects of shock on physiology. The role of plasma in the correction of the endotheliopathy of trauma has been reported in multiple studies and is likely more important than correcting coagulopathy. The mechanism of action is thought to be through promoting systemic vascular stability and preventing endothelial permeability, coagulopathy, and inflammation which eventually lead to shock and end-organ failure [24, 25]. Moreover, in a rat model of injury and shock, plasma was able to restore the endothelial glycocalyx, improve syndecan-1 expression, and correct lung injury caused by shock [26].

In a swine model of traumatic brain injury (TBI) and hemorrhagic shock, transfusion of fresh frozen plasma (FFP) decreased neurologic impairment and hastened recovery to baseline cognitive function when compared to saline infusion [27]. Neuroprotective effects of plasma in hemorrhagic shock and TBI are thought to be due to improved cerebral perfusion, decreased glutamate-mediated excitotoxicity, and reduction in mitochondrial dysfunction as demonstrated in animal models [28]. Plasma also reduced the size of brain lesions and swelling in multiple swine models of TBI and hemorrhagic shock [29, 30]. It also incurs neuroprotection by providing higher brain oxygenation and cerebral perfusion profiles [30]. In humans, a large retrospective cohort analysis showed that in the subgroup of patients with multifocal intracranial hemorrhage, early administration of plasma was associated with a survival benefit [31].

Logistical Challenges in Plasma Transfusion

Unfortunately, delivery of early balanced resuscitation is fraught with strategic and logistical challenges. In the USA, half of all trauma patients are cared for outside of levels 1 and 2 trauma centers, where blood products are frequently not readily available [32]. In the military, forward surgical teams (FST) were developed to provide immediate support and treatment to injured soldiers. They used to only carry red blood cells (RBCs) for transfusion, and more recently, they are able to provide plasma but not platelets [33]. Warm fresh whole blood (WFWB) is available in these circumstances and has been shown to improve survival in combat casualties treated by FST [33]. These challenges, along with misconceptions regarding the

role of blood products in resuscitation, led to the overuse of crystalloids and its own set of unique complications. Excessive crystalloid resuscitation has been shown to be detrimental, while balanced blood product resuscitation decreases the onset of acute respiratory distress syndrome (ARDS) and abdominal compartment syndrome and improves survival [32, 34].

The recognition of the importance of early, balanced DCR has led many trauma systems in the USA, and around the world, to search for novel approaches to provide blood products as soon as possible to severely injured trauma patients. These include carrying them in the prehospital setting and having them readily available in the ED. The logistical difficulties in providing FFP transfusions early in trauma are based on the need for reliable cold storage facilities, specialized transport equipment and personnel to provide them, and a lengthy thawing process. There is also a significant loss of up to 50% due to bag breakage during transport and thawing [35].

FFP is prepared through separation from whole blood and stored at −18 °C or colder with a shelf life of about 1 year. The thawing process requires a 30–37 °C agitated water bath or a warming device cleared by the US Food and Drug Administration; this takes 15–30 min [36]. Thawed FFP should be immediately used but can be stored between 1 and 6 °C for up to 5 days. All those factors preclude its immediate availability and delay administration in many settings such as austere environments, the battlefield, and smaller hospitals with limited blood banking capabilities. Of great importance and increasing realization is that these same limitations apply in the larger centers as well.

History of Lyophilized Plasma

The use of plasma in the resuscitation of trauma and hemorrhagic shock began with the work of Dr. John Elliot, who in 1936 devised a mechanism to separate plasma from red blood cells and store it in a vacuum bottle. He believed plasma was all that was needed to treat hemorrhagic shock [37–39]. Elliot utilized pooling by mixing the plasma of up to eight donors together to neutralize anti-A and anti-B antibodies and eliminate the need for cross-matching [38, 40]. Reports of treating shock with dried plasma go back as early as 1938 [41]. In 1940, the British Army called upon the American Red Cross to provide plasma shipped directly to London, and the blood plasma for Great Britain project started [42, 43]. The "Blood for Britain" campaign resulted in almost 15,000 units of blood donated from 1940 to 1941 in New York City alone with the majority used to produce liquid plasma, while the RBCs and platelets were discarded. The program was then stopped due to high incidence of bacterial contamination in liquid plasma [42, 43].

Meanwhile, Dr. Max Strumia was experimenting with turning Elliot's liquid plasma into a sterile powder and refined the drying process by inventing a device for freeze-drying under a vacuum [37, 44]. This was followed by production of several hundred units of dried plasma for testing by the US Army and Navy. In 1941, freeze-dried, or lyophilized, plasma was approved for use by the Council on Pharmacy and Chemistry of the American Medical Association. Boxes were designed containing

the dried plasma in a bottle accompanied by a bottle of sterile water for reconstitution [37]. Lyophilized plasma use started in WWII where millions of units were produced by the American Red Cross and administered by the US and British armies and also distributed to the Allied Forces [17, 37, 42]. It was the primary mode of resuscitating combat casualties for most of WWII.

The recognition of serum hepatitis as a result of pooled lyophilized plasma transfusion caused it to fall out of favor. It continued to be used in the Korean War but was abandoned altogether in the 1950s [37, 42]. The French military continued to produce lyophilized plasma through the mid-1980s when HIV transmission via blood transfusion was recognized. They resumed production in 1994 utilizing small donor pools (under 11 donors) and amotosalen with UV light processing for pathogen reduction [54]. During the same time, the German Red Cross started processing pooled plasma with a solvent/detergent (S/D) treatment as a method of pathogen inactivation. This continued through the early 2000s when the recognition of possible prion disease transmission caused them to switch to a single-donor approach [42, 45].

Efficacy and Safety of Dried Plasma

Production and Forms of Dried Plasma

Production of dried plasma is achieved in two ways: freeze-drying, also known as lyophilization, or spray-drying. Lyophilization is achieved by freezing the plasma under a vacuum in a glass container for several days, which decreases the water content to 1–2% [45]. Spray-dried plasma production utilizes atomization of liquid plasma via pressurized drying gas to droplets which are then exposed to hot gas (up to 150 °C) in a drying chamber followed by rapid evaporative cooling. This method can dry a unit of plasma (~250 mL) in approximately 25 min [17, 46]. Dried plasma can then be reconstituted to its original volume or a concentrated form. Multiple pathogen inactivation methods are available to use during the process, and the choice depends on the manufacturer's preference and experience.

Pathogen Inactivation

Newer and more accurate viral detection and pathogen inactivation methods have led to the improved safety of blood products, reducing the residual risk of transfusion-transmitted HIV-1 and HCV to approximately 1 in 2 million blood units [47]. Pathogen inactivation methods used for plasma include solvent/detergent (S/D) treatment and photochemical inactivation techniques [17]. S/D treatment, which is FDA-approved, binds lipid-enveloped viruses and bacteria to inactivate them followed by a filtration process to remove cells and debris, but it has no effect against non-enveloped viruses and prions [48]. Rigorous screening standards require testing donors for non-enveloped viruses twice at a 6-month interval to decrease the risk of

transmission. Moreover, photochemical inactivation utilizes a photosensitizer that binds the DNA and RNA of pathogens, including non-enveloped viruses, and nucleated cells, followed by ultraviolet light exposure to inactivate them [49]. INTERCEPT (Cerus Corp., Concord, CA) is an FDA-approved system, which uses amotosalen (a psoralen molecule) to bind DNA and RNA followed by UV light activation [50]. The Mirasol System (Terumo BCT, Lakewood, CO), which uses riboflavin as the photosensitizer, is currently approved for clinical use in Europe but only approved for investigational use in the USA and Canada [51]. Methylene blue can also be used with visible light exposure [52].

Standard S/D treatment causes a decrease in vWF activity (24%), factor V (37%), protein S (44%), and alpha-2 antiplasmin (79%). Similarly, amotosalen + UV light reduces factor VII (23%) and factor VIII (27%) [17, 48]. A newer S/D treatment product, Octaplas LG (Octapharma, Lachen, Switzerland), received FDA clearance in 2013 and employs a prion reduction step and a modified S/D process that better preserves factor levels [17].

Buffering and Reconstitution

Reconstituted porcine lyophilized plasma is alkalotic with a pH >8.5, making it highly lethal when injected in swine due to their lack of ability to buffer their plasma [53]. Human lyophilized plasma is also alkalotic with a pH near 8; however, it is well tolerated clinically in humans [54]. This increase in pH after lyophilization is attributed to the loss of bicarbonate during the drying process. Multiple acidic buffering solutions were studied to evaluate their effect on the hemostatic properties of lyophilized plasma. For example, when ascorbic acid (vitamin C) is added to lyophilized plasma (LP), 84% of the coagulation factor activity was maintained [55].

In a swine model of polytrauma and hemorrhagic shock, a significant decrease in interleukin-6 (IL-6) levels was observed in all LP-treated animals compared to those receiving FFP, suggesting an anti-inflammatory effect [55]. This was corroborated by another study using concentrated LP (50%) that showed buffering with ascorbic acid resulted in reduced serum levels of IL-6 and TNF [56]. Another study examined the effect of other buffers, such as citric acid and hydrochloric acid, on lyophilized plasma. No difference in physiology, coagulation parameters, or blood loss was noted, but animals receiving ascorbic acid had lower IL-6 levels and less oxidative DNA damage [57]. Using higher concentrations of ascorbic acid didn't affect the physiologic benefits of LP, but no improvement in the anti-inflammatory effects or further decrease in DNA oxidative damage was detected [53].

The type of fluid used to reconstitute dried plasma has not been shown to affect the degree of inflammation or oxidative DNA damage induced by shock in a swine model of polytrauma and hemorrhagic shock [58]. However, the type of fluid used for reconstitution does affect the hemostatic efficacy and ability of lyophilized plasma (LP) to mitigate the effects of shock. Animals treated with LP reconstituted with sterile water and lactated Ringer's (LR) had less blood loss compared to those reconstituted in normal saline (NS) and Hextend. The group that received Hextend had persistently elevated INR values and contained the only animal that did not

survive the experiment. Serum IL-6 levels were lowest in the sterile water group when compared to NS [59]. The optimal solution for buffering lyophilized plasma in humans is unknown and will require further investigation. For now, sterile water is used to reconstitute human LP.

Lyophilized Versus Fresh Frozen Plasma

The process of freezing and thawing plasma is not benign and has several detrimental effects on coagulation proteins. Never-frozen liquid plasma was found to have a superior coagulation profile and factor activity, as well as thrombin generation potential, when compared to plasma from thawed FFP [60]. Thawed plasma was compared at day 0 and after storage at day 5, and a significant degradation of clotting factors was detected in the older product, with a 40% reduction in thrombin generation potential and significantly decreased hemostatic profile on thrombelastography (TEG) analysis [61]. Thawed FFP decreased vascular permeability *in vitro* by a factor of 10; however, that effect decreased to only a factor of 2.5 when 5-day-old thawed plasma was used [62]. These findings reinforce some of the advantages of dried plasma over FFP.

Concentrated Dried Plasma

Concentrated, low-volume reconstitution of lyophilized plasma (50%) has been demonstrated to be safe in a swine polytrauma model of hemorrhagic shock with similar physiologic effects, hemostatic properties, and coagulation parameters (INR and TEG) [63]. This could have logistical advantages in packaging and transport on the battlefield as well as in austere environments. The effects of infusing this hypertonic, hyper-oncotic fluid are unknown in humans and will require careful evaluation.

Spray-dried plasma (SDP) at original concentration was compared with triple concentrated SDP in the resuscitation of a swine model of polytrauma and hemorrhagic shock. *In vitro* evaluation of coagulation parameters of SDP compared with FFP did not reveal any difference between the two products. However, triple-concentration SDP showed an increase in clotting factor activity and prolonged PT/PTT. Treatment with all three formulations corrected INR rapidly and increased clot strength (TEG-maximum amplitude (MA)). This confirmed that concentrated, low-volume SDP is as effective as FFP and regular SDP in reversing trauma-associated coagulopathy [64].

Coagulation Profile of Dried Plasma

The accepted standard for factor loss in frozen then thawed plasma is 25–40% [65]. *In vitro* analysis of swine FFP vs. lyophilized plasma (LP) coagulation tests (PT, PTT, INR, fibrinogen) did not reveal any statistically significant difference.

Reconstituted LP has been shown to maintain an average of 86% of coagulation factor activity when compared to FFP [66]. In comparison, spray-drying causes reduction in several factors including 25% for fibrinogen and protein S, 50% for vWF activity, and 70% for factors V and VIII. However, this has been shown to have no effect on the ability of SDP to generate thrombin [67]. On the contrary, after a year of storage at −25 °C, lyophilized plasma had no significant change in clotting factors activity when compared to fresh plasma [68]. Lyophilized plasma stored as long as 30 years had similar preservation of components [69].

Studies in Animal Models of Shock

Multiple studies demonstrate the safety and efficacy of lyophilized plasma (LP). In a series of studies using a swine model of polytrauma and hemorrhagic shock, LP demonstrated superior hemostatic efficacy to FFP when combined with RBCs in 1:1 ratio. Concentrated LP reconstituted to 50% of its volume was also well tolerated and equally effective in correcting shock physiology when compared to unconcentrated LP [56]. In another study, fresh whole blood (FWB), FFP, and LP all corrected coagulopathy equally in a swine model. There was 85% mortality in the crystalloid only group and no mortality in any of the blood products groups [66]. Another study showed that when compared with colloid alone, 7-day survival was superior in animals that received spray-dried plasma – this effect was equivalent to that seen in animals that received whole blood [70]. Moreover, animals receiving balanced LP-to-RBC had significantly less blood loss than those receiving FFP or LP alone, and LP was as effective as FFP in reversing coagulopathy in this animal model [55].

Lyophilized plasma (LP) demonstrated similar effects as FFP, both *in vitro* and *in vivo*, on reducing endothelial cell permeability, increasing trans-endothelial resistance, decreasing leukocyte-endothelial binding, and preserving adherens junctions. In an *in vitro* mouse model of hemorrhagic shock, LP and FFP both equally reduced pulmonary injury, inflammation, and vascular permeability [71]. Spray-dried plasma (SDP) also reduced vascular permeability and other indicators of endothelial damage as well as FFP [72]. FFP and SDP equally decreased shock-induced pulmonary vascular permeability *in vivo*. SDP was also equivalent to FFP in the correction of shock in a mouse model. They both reduced alveolar wall thickening, leukocyte infiltration, and the breakdown of EC junctions [73].

Neuroprotective Effects of Lyophilized Plasma

Plasma has been shown to have multiple neuroprotective effects in traumatic brain injury. In a swine model of polytrauma, hemorrhagic shock, and TBI, both lyophilized plasma (LP) and FFP were shown to decrease brain lesion size by 50% after 6 h of injury when compared to saline infusion; swelling was also 54% less in plasma-treated groups [74]. A follow-up study to evaluate the long-term effects of

resuscitation with FFP vs. LP on neurological outcomes showed similar recovery of cognitive function in studied animals. The brain lesion size was significantly smaller in LP group on experiment day 3, but this effect dissipated by day 10 [75]. Another large 30-day animal study recently showed similar neuroprotective results with faster return to baseline neurological function in animals treated with LP and FFP vs. NS [76].

Modern-Day Lyophilized Plasma

Since its reintroduction in the 1990s, lyophilized plasma has been used in a variety of settings around the globe. Currently, the largest two manufacturers of lyophilized plasma are the French Military and the German Red Cross. Multiple accounts of the use of lyophilized plasma have been reported, including administration at the point of injury, in the ED and in the ICU. French lyophilized plasma (FLyP) is used by US military special operations under an agreement between the French and US governments as an expanded access investigational new drug application [15, 17, 77]. German lyophilized plasma, known as LyoPlas N-w, has been carried by UK foot patrols since 2012. The use of LyoPlas N-w was easily integrated into the first responder care package. One case of successful usage by the British Military is reported in the literature [78]. The National Bioproducts Institute in South Africa also produces a pooled, S/D-treated, ABO-universal lyophilized plasma, Bioplasma FDP, which has been in use in South Africa since 1996, with a strong record of safety [79].

The Norwegian helicopter emergency medical service experience with the use of lyophilized plasma (LyoPlas N-w, AB) during a 12-month period reported transfusion of 16 patients having sustained blunt and penetrating trauma, as well as non-traumatic hemorrhage (ruptured AAA, upper GI bleeding, etc.). Two patients died on scene, and the remaining were alive at 30 days. No transfusion-related complications were reported. Lyophilized plasma is stored at room temperature in the fast-response car and in the helicopter, making it readily available. Pre-transfusion hypotension was seen in 62% of the patients, but only 12% were still hypotensive at the time of admission. Median systolic blood pressure increased after prehospital lyophilized plasma transfusion in all patient categories. 68% of the patients received emergency surgery after arrival at the hospital [80].

The Swedish Armed Forces also use lyophilized plasma, and the first civilian helicopter emergency medical systems in Sweden started carrying the product in 2015. They published a case report describing a patient with carotid artery injury due to a high-velocity gunshot wound to the neck and in-flight reconstitution and administration of lyophilized plasma (LyoPlas N-w) in a Medevac helicopter. The reconstitution of LyoPlas N-w powder took about 4 min in a dark Black Hawk helicopter cabin. The hemodynamic stability of the patient improved after administration [81].

The Israeli Defense Force Medical Corps (IDF-MC) introduced lyophilized plasma, in the form of LyoPlas N-w, to its protocol of prehospital trauma care and

transfusion in 2013 [82]. A case report of its use in a civilian after a motor vehicle accident described their first experience with point-of-injury administration of lyophilized plasma [83]. This was followed by a retrospective review of 109 patients who were transfused with lyophilized plasma from 2013 to 2016. The majority (83%) of patients received only one unit of LyoPlas N-w, and only 8.2% received prehospital blood transfusions. There were five instances (4.6%) of difficulty with administration after reconstitution mainly due to low flow rates. Side effects were reported in only one female patient who developed chills and shivering during infusion which stopped upon prompt discontinuation [84]. This study is a real-life example of utilizing prehospital lyophilized plasma in early resuscitation of trauma casualties demonstrating safety and feasibility.

French Lyophilized Plasma (FLyP)

Dr. Jean Julliard started producing freeze-dried plasma in 1945 after its inception by the US military in WWII. By 1950, the Centre de Transfusion Sanguine des Armées (CTSA) became the first European center to produce lyophilized plasma. During the Indochina War, almost 40,000 units of lyophilized plasma were delivered to the French military. Production was suspended in 1985 due to concerns for HIV transmission. In 1991, production restarted with the first Gulf War and has continued since that time [54].

Since 1994, French lyophilized plasma (FLyP) is made using a pool of less than 11 donors. Pooling based on blood type selection allows the dilution and neutralization of natural anti-A and anti-B hemagglutinins, making FLyP a universal donor product compatible with any recipient blood type. Since 2003, it is also being leukoreduced. Starting in 2010, plasma from women with a history of pregnancy is tested for HLA antibodies and excluded if positive. That was the same time that FLyP started undergoing amotosalen and UV light processing as a pathogen DNA/RNA inactivation method. This process was chosen over solvent/detergent treatment due to better preservation of clotting factors. The French hemovigilance program has been monitoring FLyP since 1994, and so far, no reactions or infectious complications have been reported out of more than 1100 units transfused [54].

FLyP is packaged in glass bottles, shelf-stable in ambient temperatures between 2 and 25 °C for 2 years, and easily rehydrated with 200 mL of water in less than 3 min, allowing for immediate transfusion with RBCs. FLyP contains all clotting factors and proteins. After more than 2 years of storage at ambient temperature, the fibrinogen and clotting factor levels of FLyP are equivalent to FFP [85]. Despite a certain level of factor reduction (20–25%), lyophilization has not been shown to alter *in vitro* hemostatic efficacy of plasma. When reconstituted, FLyP has a pH close to 8 [54].

In 2011, FLyP was authorized by the French Agency for the Sanitary Safety of Health Products (AFSSAPS) for use in civilians in austere settings or until thawed plasma became available [54]. Clinical efficacy of FLyP was studied in a prospective trial on 87 ICU patients in Afghanistan and was found to be safe and efficacious

in the management of polytrauma and shock [86]. Furthermore, the difference in administration times between FLyP and FFP in a level 1 trauma center was studied. Retrospective analysis showed significantly less time to product administration between patients receiving FLyP vs. FFP (median 15 vs. 95 min). This is consistent with similar reports in the literature of time to FFP transfusion [21]. Subsequently, time to achieve 1:1 resuscitation ratio with RBCs was shorter in FLyP group. There were also significantly less cases of massive transfusion utilization and RBC transfusion in the FLyP group compared to the FFP group (7 vs. 45%). No differences in hospital length of stay, ICU length of stay, or 24-h mortality between the two groups were noted [87].

Recently, a randomized open-label clinical trial of 48 patients who were assigned to receive 4 units of FLyP or FFP within 6 h of injury was completed. Patients in the FLyP group demonstrated less time from randomization to infusion compared to those in the FFP group (median 14 min vs. 77 min). This led to higher levels of fibrinogen achieved within 45 min of randomization, as well as a greater improvement in INR, factor V, and factor II levels. The difference in coagulation parameters between the two groups remained significant at 6 h. However, there was no difference detected in mortality between the two groups [88].

German Lyophilized Plasma (LyoPlas N-w)

In the 1990s, the German Red Cross Blood Service West produced solvent/detergent (S/D) treated lyophilized plasma using pooled plasma. Due to concern for Creutzfeldt-Jakob-type prion disease transmission, which is not inactivated by standard S/D treatment, pooled plasma was replaced with single-donor lyophilized plasma in 2007 [45]. This product is licensed under the name LyoPlas N-w (German Red Cross Blood Service West, Hagen, Germany).

Quarantined plasma from a single donor is stored frozen for at least 4 months until the donor returns for retesting for HIV, hepatitis C virus, hepatitis B virus, hepatitis A virus, and parvovirus B19. After the quarantine, the plasma is thawed and connected by sterile docking to the patented steam-sterilized "bottle-in-bag" system, which consists of a glass bottle and a rubber stopper inside a plastic bag. During transfer into the glass bottle, the plasma passes through a filter with a nominal pore size of 0.2 μm. Once 200 mL of plasma is transferred, the bottle is closed with the stopper and removed from the system. Plasma is then frozen to −30 °C followed by lyophilization in specially designed freeze-dryers. The lyophilization is accomplished by a stepwise increase of the temperature from −45 °C to +15 °C, resulting in water content below 1% [45].

Sterile water for reconstitution (200 mL) is included in the LyoPlas N-w kit and accomplished within 10 min depending on the plasma composition and water temperature. Transfusion can be accomplished via the glass bottle or the plastic bag, which allows for pressure infusion if needed. After storage at 2–8 °C for 24 months, LyoPlas N-w only had a 10% reduction in factor V, VIII, and vWF. All other factors remained stable. Storage at room temperature, however, led to 54% decrease in

fibrinogen levels and vWF activity. This is why the shelf life of LyoPlas N-w has been restricted to 15 months only. After reconstitutions, factor degradation increases over time at room temperature. At 48 h, factor VIII and protein S levels decreased by 66 and 50%, respectively. Only 10% degradation of those factors was noted in the first 6 h, however. This is why it is recommended to use LyoPlas N-w within 6 h of reconstitution [45].

From 2007 to 2011, a total of 237,850 units of LyoPlas N-w were provided to hospitals, doctors, and the German military compared to 343,821 units of FFP delivered during the same time period. This reflects the wide use of LyoPlas N-w in Germany (41% of all plasma used) under various clinical settings requiring transfusion and not just trauma resuscitation. The rates and types of transfusion-related complications reported between 2007 and 2011 were similar for FFP and LyoPlas N-w (0.018 vs. 0.023%). No viral transmission has been reported since its inception in 2007 [45].

Products Currently Under Development

The US Department of Defense (DoD) and the Biomedical Advanced Research and Development Authority (BARDA) are sponsoring multiple different programs to provide dried plasma products in different forms (lyophilized and spray-dried). The aim is to make the distribution, storage, and administration of plasma in combat and civilian environments safe and feasible [79].

Historically, there was a dried plasma product licensed in the USA under Plas-SD manufactured by Vitex (Melville, NY) which was required to have a black box warning due to the risk of adverse thromboembolic events caused by low levels of protein S. This was attributed to the solvent/detergent treatment. However, newer technology provided by Octaplas LG seems to have resolved the problem [79]. The Vitex product is no longer available.

HemCon Medical Technologies, Inc. (Portland, Oregon) was in the process of developing a dried plasma product for the US Army Medical Research and Materiel Command (Fort Detrick, MD) between 2008 and 2013. It was going to be a single-donor lyophilized plasma product derived from licensed FFP. In 2011, the product underwent a successful phase I clinical trial and was shown to have factors within the normal range [17, 89]. Unfortunately, the partnership ended in 2014 due to business reasons.

Teleflex Inc. (Limerick, PA) recently acquired Vascular Solutions (Minneapolis, MN) which replaced HemCon as the Army's partner in developing a single-donor, lyophilized plasma product since 2014 named RePlas. In 2017, they announced the commencement of the phase I clinical study of Ascending Doses of Autologous FDP vs FFP. This product is being developed in collaboration with the US Army Medical Materiel Development Activity (USAMMDA). They plan on having FDA approval by 2021 [17, 77, 90, 91].

Entegrion Inc. (Research Triangle Park, NC), in partnership with the Office of Naval Research, has been developing Resusix, a group AB, pooled, solvent/detergent spray-dried plasma under a US Navy, Marine Corps, and Defense Health

Agency program since 2008. S/D treatment using a process licensed from Octapharma (Lachen, Switzerland) that is effective against lipid-enveloped viruses and other pathogens is utilized. The S/D process also removes immunogenic lipids, and a filtration step removes cellular debris and proinflammatory microparticles. Phase I clinical trials were completed in 2016, and developers have a goal of being licensed by 2020 [17, 92, 93]. Nova Laboratories (Leicester, UK) will perform the spray-drying and packaging for the product [79].

Velico Medical (Beverly, MA), is developing a spray-drying device and proprietary bag system (Frontline ODP) that will enable blood banks to produce licensed, single-donor, spray-dried plasma units locally within 30 min. This program is conducted under a contract from BARDA, a part of the US Department of Health and Human Services, and is still in the preclinical phase [46, 93–95]. This product will provide a certain independence from manufacturers and allow local augmentation of production in times of need [79].

Future of Lyophilized Plasma

Damage control resuscitation is now the standard of care in the treatment of hemorrhagic shock. It is clear that trauma patients with serious injury will benefit from DCR within minutes of injury. Plasma transfusion is an integral part of this concept but suffers from several logistical constraints. This also makes it an area where significant advancements are necessary and can improve patient outcomes.

Early delivery of plasma is one avenue that seems to suffer the most. Many challenges exist that hinder this goal including physical requirements for storing and transporting FFP, required personnel, and thawing times. Certain steps taken by major trauma centers to remedy that have been successful, including having thawed plasma ready in the ED at all times and carrying thawed and liquid plasma in the prehospital setting. These measures are costly and require a large-scale operation. Smaller hospitals will not be able to accommodate such measures. Patients presenting to such facilities will suffer worse outcomes from delay in administration of plasma until it is available or until transported to a larger center. Physicians are forced to use crystalloid and colloid in such situations to stabilize patients. Furthermore, trauma casualties in remote locations requiring long transport times or austere environments requiring prolonged extrication will be at a huge disadvantage. Finally, soldiers and combat casualties are also negatively affected by the delay of plasma transfusion, which has been demonstrated over and over again.

The solution is to have a product that is readily available, easy to store and transport, and can be administered quickly and safely. Dried plasma provides all these advantages. It can be stored up to 2 years at room temperature and reconstituted within minutes. It's been shown to be safe and efficacious clinically and in animal models with similar coagulation properties to FFP.

A dried plasma product introduced in the USA will allow for earlier plasma administration starting prehospital and continuing into the hospital setting, which will likely improve patient outcomes, as demonstrated by the French experience

[87]. Dried plasma should certainly replace the recommended crystalloid administration in the ATLS guidelines, which were designed to accommodate all levels of practice and take into account the variable availability of blood products. Taking this concept one step further, it may prove beneficial and efficient to replace FFP altogether, especially when time to transfusion is a critical element of care, thus eliminating the need for cold storage facilities and complicated thawing equipment and procedures. The future of lyophilized plasma is exciting, and while it is an old product, it will likely see a new beginning.

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Platelets: Frozen and Freeze-Dried Current Products in Development and Regulatory Licensing Challenges

9

Heather Pidcoke, Kathleen Kelly, G. Michael Fitzpatrick, and Larry J. Dumont

Abbreviations

ACD	Anticoagulant Citrate Dextrose Solution
ADF	Australian Defense Force
ARC	Australian Red Cross
BARDA	Biomedical Advanced Research and Development Authority
BEST	Biomedical Excellence for Safer Transfusion
CABG	Coronary artery bypass grafting
CBER	Center for Biologics Evaluation and Research
CD41a	Cluster of differentiation 41a (GPIIb/IIIa)
CD42b	Cluster of differentiation 42b (GPIb)
cGMP	Current Good Manufacturing Practice
CLIP	Cryopreserved Platelets Versus Liquid Platelets Trial
CPP	Cryopreserved platelet product
DARPA	Defense Advanced Research Projects Agency
DMSO	Dimethyl sulfoxide
DoD	Department of Defense

H. Pidcoke
Department of Clinical Affairs, Cellphire, Inc., Rockville, MD, USA

K. Kelly
Vitalant Research Institute (VRI), Denver, CO, USA

G. M. Fitzpatrick
Clinical Research and Development, Cellphire, Inc., Rockville, MD, USA

L. J. Dumont (✉)
The Geisel School of Medicine at Dartmouth, Lebanon, NH, USA

University of Colorado School of Medicine, Denver, CO, USA

Vitalant Research Institute (VRI), Denver, CO, USA
e-mail: LDumont@vitalant.org

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FDA	Food and Drug Administration
FFP	Fresh frozen plasma
GPIb	Glycoprotein Ib
GPIIb/IIIa	Glycoprotein IIb/IIIa
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
LDH	Lactate dehydrogenase
LSP	Liquid-stored platelets
LyPt	Lyophilized platelets
LyPt-P	Lyophilized platelets stabilized with paraformaldehyde
LyPt-T	Lyophilized platelets stabilized with trehalose
MTFs	Medical treatment facilities
NATO	North Atlantic Treaty Organization
NHP	Non-human primate
NIH	National Institutes of Health
NLAF	Netherlands Armed Forces
NZWR	New Zealand white rabbits
PAS	Platelet additive solution
PVC	Polyvinyl chloride
RT	Room temperature, 20–24 °C
US	United States
WB	Whole blood

Early Platelet Product Development and Exploration of Alternative Storage Methods

Platelets are critical components of blood that restore and maintain normal hemostasis in the event of injury. Since Max Schultze first described platelets in 1865 and Giulio Bizzozero described platelet aggregation thrombus formation in 1882, there have been continuous efforts to understand the functional roles of platelets, provide them to patients, and maximize the effectiveness and safety of transfused platelets in a variety of clinical settings [1]. Despite this early understanding of platelet nature and function, the relationship between platelet count and hemostasis was not established until Duke's seminal publication in 1910. The clinical use of platelet concentrates first described in 1914 was primarily for the preparation of vaccines against bacterial infections [2, 3]. Clinical use of platelets to treat thrombocytopenic bleeding did not widely occur until the 1950s when direct transfusion of whole blood (WB) from the donor to the patient was replaced with platelet concentrates prepared from WB, refrigerated, and stored for up to 3 days [3–7]. Development of collection by apheresis in 1961 supported further advances in clinical use [8]. There was early recognition that platelet concentrates exposed to cold temperatures controlled hemorrhage, but did not increase platelet counts as effectively as fresh WB or fresh platelet concentrates [9–12]. During this time, Dr. Emil Freireich described survival benefits due to platelet transfusion to treat thrombocytopenic bleeding.

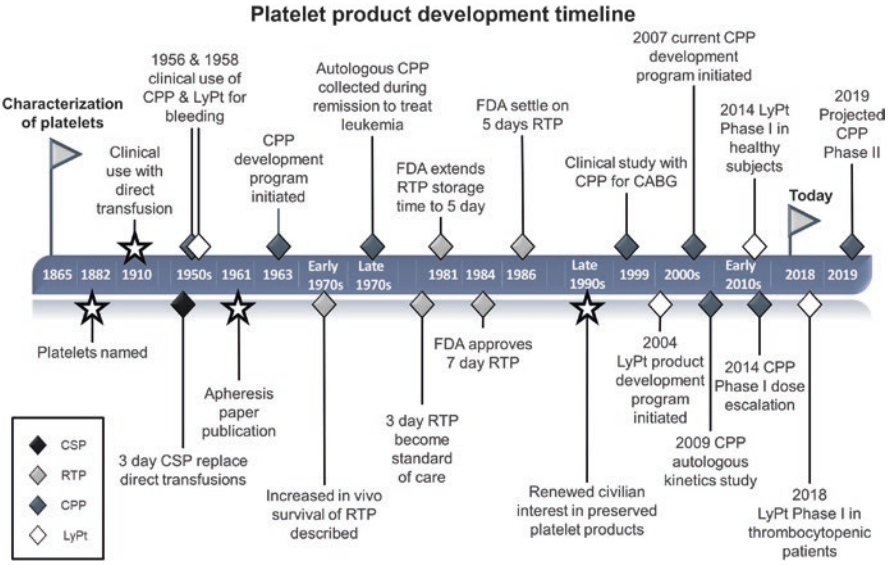

Fig. 9.1 Platelet product development timeline

Patients required several transfusions per week as the circulation time of refrigerated platelets was 1–2 days [13]. Studies with radiolabeled platelets indicated that in vivo cold-stored platelet survival was shorter than fresh preparations. The desire for longer storage and in vivo circulation triggered investigations into alternative storage techniques. Successful clinical use of lyophilized and cryopreserved platelets to control thrombocytopenic bleeding were first reported in the 1950s [9, 14–16]. The blood banking community eventually moved to room temperature storage to avoid the early clearance, thus prioritizing longer in vivo circulation over storage time (Fig. 9.1).

In 1956, Drs. E. Klein, P. Arnold, and colleagues reported that, even though platelet counts were not elevated, both cryopreserved and lyophilized platelets were effective in controlling thrombocytopenic bleeding in children with acute leukemia and aplastic anemia [14, 15]. The potential clinical benefit of these products for the management of thrombocytopenia was shown by Stefanini and Kistner in 1958 [16]. Deaths due to hemorrhage in thrombocytopenic patients undergoing chemotherapy was reduced by platelet transfusion. Development efforts focused on improving the in vivo circulation time of platelets to reduce the frequency of transfusions. Murphy and Gardner demonstrated that storage of platelets at room temperature (RT, 20–24 °C) resulted in remarkable improvements in platelet circulation, thereby decreasing the number of transfusions needed to support thrombocytopenic patients [11, 12, 17]. RT-stored platelets thus became the standard of care; however, availability quickly became an issue, and research focused on methods to extended storage time. Plastic bags with improved gas permeability, investigations into platelet storage solutions, and improvements in platelet apheresis collection systems became the primary developmental goals.

Despite technological improvements that improved in vivo circulation, ex vivo storage of platelet components was limited to 3 days with the consequence that availability of a reliable supply of platelets remained a continual challenge. Lyophilized, cryopreserved, and refrigerated platelets had the potential to extend ex vivo storage, but development efforts lagged due to the focus on circulation time and the inability to show hemostatic benefits in some thrombocytopenic animal models [9, 11, 18]. Although it was not known at the time, the disappointing function of these products was likely due to changes in the platelet membranes and other effects of cold activation and, in the case of lyophilization, excessive damage to the structural integrity [19–23]. Effective methods to protect platelets during lyophilization were decades away, but research into potential cryoprotectants began almost immediately [18, 24–26].

Investigators continued in vitro and animal studies to characterize cryopreserved platelets but recognized that a cryoprotectant such as glycerol and/or dimethyl sulfoxide (DMSO) was needed to improve results [18, 24–32]. Djerassi, Roy, and colleagues described a successful method of cryopreserving platelets using glycerol and DMSO [25, 26]. With these advances, studies documented preservation of morphology, viability, organelles, contractile proteins, clot retraction, lactate dehydrogenase (LDH), oxygen consumption, aggregation and release reactions, as well as measurable in vivo survival in human and animal models [33, 34]. Despite the move to RT-stored platelets and the use of directed donor HLA-compatible platelets to support alloimmunized patients, Schiffer and colleagues at the University of Maryland chose to use cryopreserved autologous platelets well in the 1980s [10, 35–40].

Challenges in Providing Room Temperature Platelet Concentrates

Platelet storage at RT was limited to 3 days until 1981, when the US Food and Drug Administration (FDA) issued a guidance allowing an extension to 5 days. In 1984, FDA amended the guidance to allow 7-day storage, but this was rescinded 2 years later due to adverse events related to bacterial contamination [41]. The 5-day storage period was accompanied by the requirement for routine bacterial testing, leaving little time for transport and storage of platelets to remote areas. The short shelf life of 22 °C stored platelets (roughly 3 days following infectious disease testing and processing) results in significant and constant pressures on availability [42, 43]. This in turn presents significant production, distribution, and logistical challenges to blood organizations [43, 44]. To cover urgent needs, hospital users maintain platelet inventory in excess of their daily demand [44]. One undesirable outcome is wastage due to expiration estimated at 7.7–12% in the USA and up to 25% in some centers [43–45].

Supplying room temperature-stored platelet concentrates to combat personnel created even greater challenges for the US military. Maintaining platelet concentrate agitation during storage and transport resulted in an additional logistical burden preventing platelet availability in austere environments. Alternative platelet-containing

products like cold-stored group O WB were available and used during the Korean and Vietnam conflicts; however, the only approved WB product for use within the USA was type-specific. As the blood type of acutely bleeding civilian prehospital patients is often unknown, WB fell out of civilian use in the 1980s. Military interest in cryopreservation and lyophilization persisted due to the need for longer storage times to accommodate extended transport times over large distances [32, 46–49].

Cryopreserved Platelet Product (CPP) Characterization and Development

US Military CPP Research and Development Programs

As an alternative to RT platelets, the US Office of Naval Research sponsored a CPP research program at the US Naval Blood Research Laboratory, Boston, MA, in the 1970s. Valeri and colleagues extensively characterized CPP in DMSO and evaluated in vitro and in vivo performance prior to advancing to clinical trials [32, 48, 50, 51]. A variety of parameters were measured including oxygen consumption, aggregation, release reactions, storage duration, ultrastructural alterations, and phagocytic function followed by evaluations of circulation and hemostatic effectiveness in canine, baboon, and other animal models [32, 48, 50, 51]. The Valeri method began with freezing single units of platelets prepared from WB in 5% DMSO at a freezing rate of 1 °C/min to −40 °C, followed by storage in the vapor phase of liquid nitrogen [52]. Frozen platelets were prepared for transfusion by thawing in a 37 °C water bath, washing, and resuspending in plasma. Valeri's group continued to develop and refine their methods ending with freezing of apheresis collected platelets in 6% DMSO that were frozen and stored at −80 °C. The units were thawed, washed, and resuspended in anticoagulant citrate dextrose (ACD) solution plasma prior to transfusion.

The culmination of this development program was a clinical trial in patients undergoing cardiopulmonary bypass surgery who were randomized to receive either CPP or RT platelets in the perioperative period. The trial was successful in demonstrating that CPP established hemostasis as effectively as control platelets and non-inferiority metric was met [53]. The results were published in 1999, but the cumulative preclinical and clinical data on the Valeri method for platelet freezing were not sufficient to obtain FDA approval. Valeri and colleagues continued development including the pivotal invention of the no-wash method, enabled by removal of the DMSO/plasma supernatant prior to freezing [54].

International CPP Research and Development Programs

The Netherlands Armed Forces (NLAF) also experienced considerable challenges in supplying platelets to austere environments. Having learned from the Valeri laboratory, the NLAF chose to augment standard blood products with CPP and other frozen blood products rather than rely on a walking blood bank for fresh WB and

apheresis platelet products. The NLAF began using frozen 6% DMSO platelets reconstituted in thawed plasma with thawed deglycerolized red cells and thawed fresh frozen plasma (FFP) in their deployed medical treatment facilities (MTFs) in 2001 [55]. They published their experience in 2016 after reviewing 4 years of hemovigilance and combat casualty outcomes data collected in Afghanistan beginning in 2006. Results were excellent, with only 1 observed mild transfusion reaction in 3060 transfused products. Twenty-four-hour and hospital stay mortality (14% compared to 44% in historical controls, $p = 0.005$) decreased significantly in massive transfusion patients. The authors concluded that the use of frozen products, including CPP, in massive transfusion is safe and effective [55].

Rapid dissemination of these findings was likely facilitated during the recent conflicts in Iraq and Afghanistan, because exchange of medical information was common among the North Atlantic Treaty Organization (NATO) coalition forces [56]. In Australia, the University of Queensland, the Australian Red Cross (ARC), the Australian Defense Force (ADF), and others are collaborating to expedite a CPP development program [57–59]. In addition to potential military applications, providing a platelet product with storage times of years, rather than days, could provide hemostatic platelets in smaller rural hospitals that cannot sustain an RT platelet concentrate inventory. One-third of Australia's population lives in remote areas where providing emergency services and blood products is challenging [60]. The recognition that longer-stored, potentially more hemostatic platelet-derived products are needed for both civilian and military centers mirrors similar viewpoints recently expressed by physicians in the USA and Europe [42, 61].

The ARC has studied CPP using various preparations in platelet starting material. The major differences included the initial storage solution (70% platelet additive solution, or PAS, versus 100% plasma), the final reconstitution fluid (70% PAS versus 100% plasma), and method of collection (apheresis versus buffy coat preparation) [62–66]. ARC reported differences in factor activity, protein content, microparticles, and other biological response modifiers in these CPP compared to standard RT platelets [64]. They noted that fibrinogen was higher in CPP, whereas factors V and VIII activity were decreased. The clinical significance of these findings regarding in vivo CPP function and outcomes was difficult to estimate given that these platelets are primed for activation and in vitro studies are difficult to correlate to clinical findings. The ARC investigators found that thrombin generation and clotting activity were faster, while clot strength was similar to fresh [64–66]. As reported by others, aggregation was attenuated compared to Day 2, but comparison was not made to aggregation after Day 3, when RT platelets typically respond poorly to agonists.

Reade and colleagues recognized the limitations of currently available clinical data for CPP. The University of Queensland, the ARC, and the ADF collaborated on a randomized, controlled multicenter clinical trial in a surgical bleeding population, Cryopreserved Platelets Versus Liquid Platelets (CLIP) Trial (ACTRN12612001261808) [57]. The investigators hypothesize that CPP will be at least as effective and safe as conventional RT platelets in the management of active bleeding related to surgery. The primary endpoints are protocol feasibility

in this setting and safety and acceptability [57]. Clinical efficacy as measured by 28-day mortality, blood loss, transfusion requirement, and thromboembolism will be assessed as secondary endpoints. Results are not yet available.

The US Army has sponsored a development program for CPP. Based on the Valeri no-wash method, a Current Good Manufacturing Practice (cGMP) manufacturing process has been developed [67]. Briefly, gamma-irradiated (25Gy) apheresis platelets in plasma from either the Trima apheresis system (Terumo BCT, Inc., Lakewood, CO, USA) or Amicus apheresis system (Fresenius-Kabi, Lake Zurich, IL, USA) are brought to 5.6 to 6.7% effective DMSO concentration by adding 27% sterile DMSO/saline concentrating by centrifugation at 1250× g for 10 min, removal of supernatant to a final volume of 20–35 mL in a freezing bag (Cryostore 500, OriGen Biomedical, Austin, TX, USA), placed into a polyvinyl chloride (PVC) overwrap bag, and stored in a cardboard freezing box. The box is placed flat on the floor of a chest-type mechanical 80 °C freezer. CPP are stable for up to 24 months at ≤ −65 °C. To prepare for transfusion, CPP is thawed in a 37 °C water bath for 8 min. After a 30-min rest period, 0.9% NaCl at 20–24 °C is added slowly in aliquots of 10 mL and 15 mL while gently mixing. The resuspended CPP contains approximately 2.0×10^{11} to 3.6×10^{11} irradiated platelets in a volume of ≥45 mL to ≤60 mL and approximately 1250–2530 mg residual DMSO. Thawed diluted CPP units are stable at RT for up to 4 h.

CPP In Vitro Phenotype

The phenotype of thawed CPP is distinct from RT 5-day liquid-stored platelets (LSP). CPP presented with increased microparticles content, phosphatidylserine exposure, and thrombin generation capabilities (thrombin peak, Table 9.1), suggestive of a more activated cell state. The more activated state of CPP is apparent in transmission electron micrographs (Fig. 9.2). Comparing fresh platelets (Fig. 9.2a) to CPP (Fig. 9.2b), while the ultrastructure of microtubules and open

Table 9.1 In vitro phenotype for 5-day LSP and CPP

	5-day LSP	CPP
Platelet concentration ($\times 10^3/\mu l$)	1521 ± 144	6295 ± 816
Microparticles (% of platelet events)	6 ± 3	42 ± 9
Phosphatidylserine exposure (% of platelet events)	7 ± 4	73 ± 4
Aggregation (ADP + EPI) (%)	75 ± 24	20 ± 13
Aggregation (collagen) (%)	83 ± 14	16 ± 12
TGA peak thrombin (nM) (SD)	72.3 (10.3)	159.6 (25.7)

From Cid et al. [68], with permission of John Wiley and Sons
For aggregation assay final concentrations: *ADP* adenosine diphosphate at 10 μM, *EPI* epinephrine at 5 μM; collagen at 10 μg/ml and platelet concentrations at 300×10^3 platelets/μl. For *TGA* thrombin generation assay with final concentration of 66×10^3 platelets/μl, 1pM tissue factor in pooled fresh frozen plasma
LPS liquid-stored platelet, *SD* standard deviation

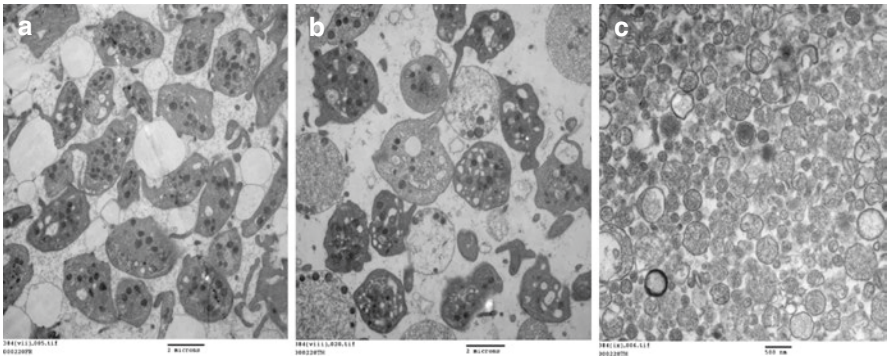

Fig. 9.2 Transmission electron microscopy of LSP and CPP and CPP supernatant reveal the increased activation morphology of CPP. Transmission electron micrograph of (**a**) LSP at 7000×, (**b**) CPP at 7000×, and (**c**) the CPP supernatant following high centrifugation to visualize microparticles at 19,500×. Bar = 2 μm in **a** and **b** and 500 nm in **c**. (From Dumont et al. [67], with permission of John Wiley and Sons)

canalicular system is maintained in many cells, the CPP (Fig. 9.2b) cell population has a larger representation of active platelets. Approximately 30–50% of 4000× fields appear as platelets, with more pseudopodia observable, occasional platelets with granule contents constricted to the center of the cell, and some platelets observed with few, if any, granules (Fig. 9.2b). No aggregates, per se, were observed (Fig. 9.2b). Confirming the increased microparticle contents of thawed CPP identified with flow cytometry (Table 9.1), the 2000× g CPP supernatant prepared with the 16,000× g centrifugation shows many spherical particles 500 nm and smaller (Fig. 9.2c).

Interestingly, CPP response to exogenous agonist compared to 5-day LSP in an aggregation assay is decreased (Table 9.1). Examining the clotting phenotype of CPP under shear flow over rabbit aorta in a flow chamber (with CPP restored platelet-depleted WB) revealed CPP maintained half of the platelet deposition capability of WB restored with 5-day LSP under medium shear (Fig. 9.3, CPP at 10.7 ± 3.1 and 5-day LSP at 22.9 ± 4.1 percent platelet coverage) [68]. Fibrin coverage is equivalent between both cell types (Fig. 9.3, 21–25%); however, CPP supported an almost threefold higher prothrombin cleavage which is maintained over 10 min of shear flow (Fig. 9.3, CPP at 606 ± 216 compared to LSP 221 ± 67) [68].

CPP Recovery and Survival

Autologous recovery and survival of CPP in healthy subjects have been evaluated compared to fresh autologous platelets transfused simultaneously following the method recommended by the Biomedical Excellence for Safer Transfusions (BEST) Collaborative, with some modifications for CPP [67, 69, 70]. As expected with an

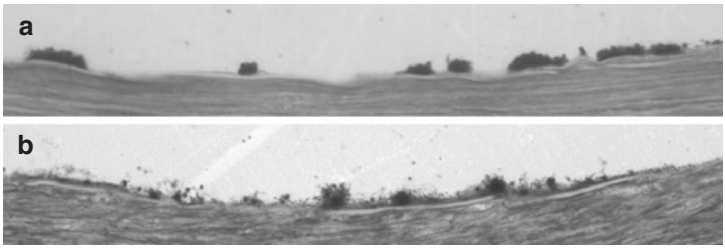

Fig. 9.3 Micrographs of platelet adhesion under flow conditions (Baumgartner model). Microscopic fields of perfusion experiments for platelet-depleted whole blood substituted with 200 × 10^9 platelets/L of 5-day LSP (**a**) or CPP (**b**) reveals CPP with decreased platelet coverage compared to LSP under shear (22 ml at 600/s for 10 min). (From Cid et al. [68], with permission of John Wiley and Sons)

Table 9.2 Transfused platelet recovery and survival

	Platelet recovery (%)	Platelet survival (d)
Fresh	63 ± 9	8.6 ± 1.1
CPP	33 ± 10	7.5 ± 1.2
P	<.0001	<.0001
% of fresh	52 ± 12	89 ± 15

From Slichter et al. [70], with permission of Elsevier
Data reported as mean ± standard deviation, $n = 32$

activated platelet product, CPP recovery was 52% of fresh platelets (Table 9.2); however, they circulated for 7.5 days or 89% of fresh platelets [70]. This is consistent with good clinical outcomes previously reported when similar CPP products were used for hypoproliferative thrombocytopenia as discussed above. CPP recoveries are lower and could result in the need for increased transfusions, but it is also possible that CPP may allow physicians to manage patients with a lower platelet count due to the improved hemostatic potential of this product. Further studies are needed to evaluate CPP safety and clinical utility, and these are currently in progress.

CPP Phase 1 Dose Escalation

Advancing CPP into clinical trials has been challenging. In a Phase 1 clinical trial (Safety Study of Dimethyl Sulfoxide Cryopreserved Platelets; ClinicalTrials.gov Identifier: NCT02078284) [71], patients with a WHO bleeding score ≥2 received from 0.5 to 3 units of CPP ($n = 24$) or 1 unit of LSP ($n = 4$). There were no related thrombotic or other serious adverse events and five mild transfusion-related adverse events. Among the CPP recipients, 14/24 (58%) had improved bleeding scores, including 3/7 (43%) patients who had intracerebral bleeding. CPP post-transfusion platelet increments were significantly less than LSP (Fig. 9.4); however, days to the next transfusion for CPP or LSP were the same [71]. A Phase 2 trial in cardiac surgery patients undergoing coronary artery bypass grafting (CABG) is planned for the near future (Fig. 9.1).

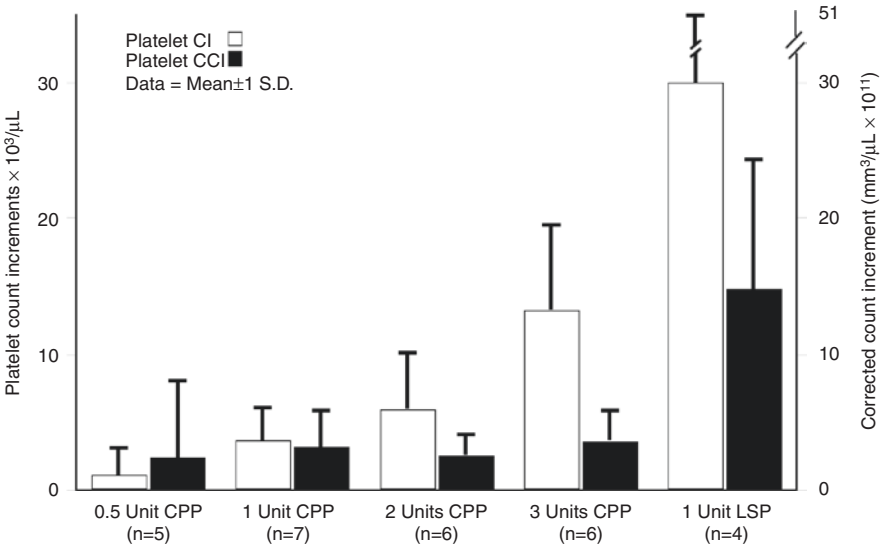

Fig. 9.4 CPP dose escalation. Platelet count increments (left axis) and corrected count increment (right axis) for Phase 1 CPP dose escalation trial. (From Slichter et al. [71], with permission of John Wiley and Sons)

Lyophilized Platelet (LyPt) Characterization and Development

Lyophilized Platelets Stabilized with Paraformaldehyde (LyPt-P)

In addition to the CPP program, the US military also funded development of several techniques to produce LyPt. Two have been the most extensively described and pursued. One technology, developed by Read and colleagues, used paraformaldehyde to fix platelets prior to lyophilization [72]. The authors reported that these LyPt-P were morphologically similar to fresh. Rehydrated LyPt-P expressed glycoprotein Ib (GPIb) and glycoprotein IIb/IIIa (GPIIb/IIIa) on cell surfaces and adhered via GPIb; displayed adhesion and spreading, although not to the extent of fresh platelets; restored bleeding time in thrombocytopenic rats from >15 to 0.5–1.5 min and in dogs on cardiopulmonary bypass from 8–12 to 2–4 min; incorporated in the bleeding time wounds in dogs; and when transfused in advance of an injury, were adherent to the area of injury but not to intact endothelium [72–74]. It is clear that factors V and VII bind to the surface of these lyophilized platelets and that they are able to catalyze thrombin generation [48, 75]. On the other hand, although bleeding times in the dog studies improved, they did not return to baseline, lyophilized platelet surface coverage of the injured lumen was approximately half of fresh, responses to agonists other than ristocetin were attenuated, and inside-out signaling was largely inhibited [48, 72–74, 76].

Paraformaldehyde platelets were also tested in a swine liver injury model of non-compressible hemorrhage as a surrogate for prehospital use and were found to substantially increase survival compared to saline administration (80% versus 20%, $p = 0.023$) [77]. The human LyPt-P product administered caused thrombotic complications in one animal, but this result was not unexpected as the authors noted; thrombosis is a known complication of xenographically mismatched transfusions to swine. Thrombosis occurs due to the interaction of human platelets with porcine von Willebrand factor [77].

To assess clinical efficacy and safety of the product in a xenographically matched model, Bode and colleagues developed a collaboration with clinical veterinarians to perform a pilot study in thrombocytopenic dogs with clinical signs of hemorrhage [78]. Canine patients were randomized to receive canine LyPt-P versus fresh canine platelets. Results were similar between groups regarding 24-h bleeding scores, transfusion reactions, additional transfusions, hospitalization time, and 28-day survival, suggesting that this pilot data supports use of lyophilized platelets to treat thrombocytopenic hemorrhage [78].

Lyophilized Platelets Stabilized with Trehalose (LyPt-T)

Another platelet lyophilization technology funded by the US Department of Defense (DoD), with early funding from Defense Advanced Research Projects Agency (DARPA) and National Institutes of Health (NIH), uses trehalose as a stabilizing agent prior to lyophilization (Thrombosomes®, Cellphire, Inc., Rockville, MD), a process described in 2001 by Wolkers, Crowe, and associates [79]. Trehalose, a disaccharide used by multiple organisms that can survive significant desiccation, stabilizes membranes by forming hydrogen bonds with polar residues in proteins and phospholipids. The hydrogen bonds replace the water shell surrounding the platelet membranes, mimicking the hydrated state and protecting macromolecules from damage [79–82]. Crowe and associates reported near-normal aggregation responses to thrombin, collagen, and ristocetin, although subsequent studies have not been able to fully reproduce these early findings. Other investigators attempted to use this same technology to cryopreserve nucleated cells, but were not successful until the cells were transfected with a crustacean cyst stress protein gene which acted synergistically with trehalose to protect cellular reproduction [82]. Trehalose stabilization appears to be adequate to protect non-nucleated platelets during desiccation, and the reconstituted LyPt-T product appears to retain similar morphology to fresh platelets (Fig. 9.5) although dense granules and alpha-granules are less distinct than fresh on TEM (Fig. 9.5a, b) and the SEM morphology is consistent with activated platelets (Fig. 9.5c, d) [83]. LyPt-T also displayed significant in vitro adhesion when imaged with Lucifer Yellow staining (Fig. 9.5e), participated in clot formation, and demonstrated in vivo hemostatic capacity [83–86].

LyPt-T are prepared from Group O, leukoreduced apheresis platelets that meet FDA and AABB (the organization formerly known as American Association of Blood Banks) requirements. Units from up to ten donors are pooled and concentrated

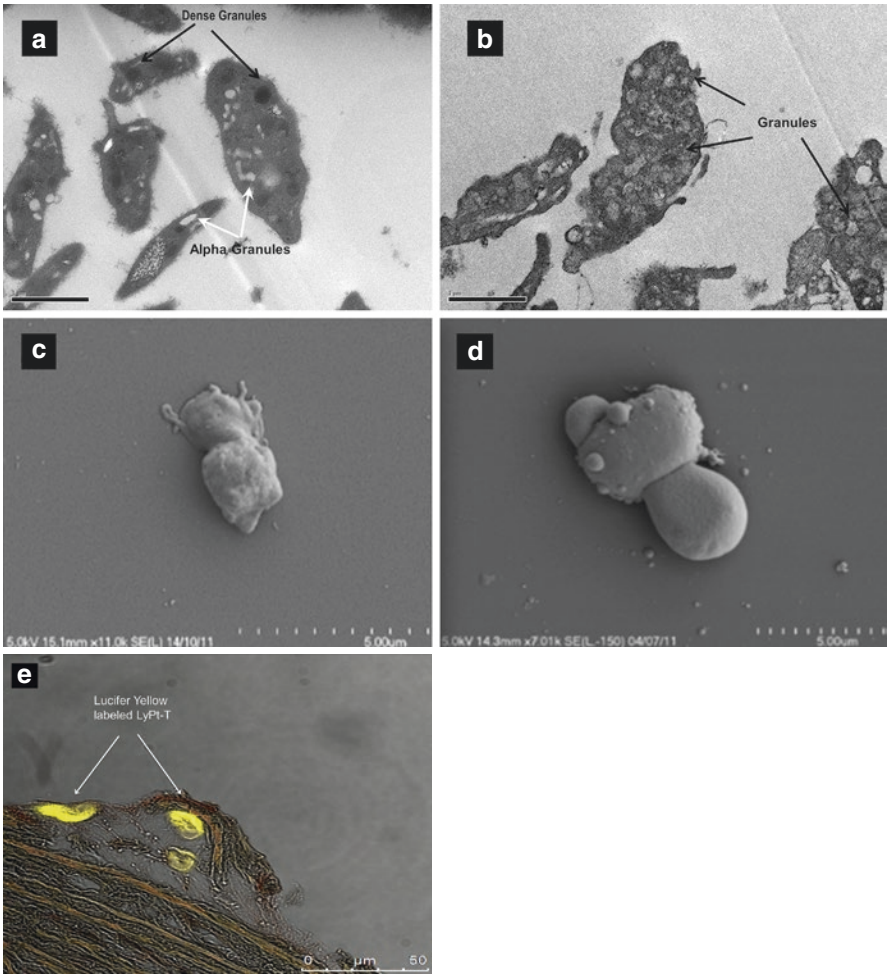

Fig. 9.5 Transmission electron microscopy and scanning electron microscopy demonstrated activated LyPt-T phenotype compared to fresh platelets. Transmission electron micrograph of (**a**) fresh platelets at 7000× and (**b**) LyPt-T at 7000×. Scanning electron micrograph of (**c**) fresh platelets at 2000× and (**d**) LyPt-T at 2000×. (**e**) Lucifer Yellow-stained LyPt-T demonstrated that particles incorporate into the developing thrombus at 40×. (From Joshi et al. [83], © Schattauer GmbH with permission)

by centrifugation. The supernatant plasma is removed, and the platelets are resuspended in a trehalose-containing proprietary buffer and incubated at 37 °C. After incubation, platelets are diluted to ~2.0×10^6 per µL with a proprietary bulking agent, dispensed into glass vials, and lyophilized with a proprietary process. Vials are stoppered under vacuum and transferred to a dry-heat oven for annealing. Fitzpatrick and associates demonstrated that 98.6% ± 0.4 of cells expressing both GPIIb/IIIa (CD41a) and GPIb (CD42b) were in the size range of 0.5–2.5 µm, revealing that

Table 9.3 In vitro phenotype of reconstituted LyPt-T[a]

Test	Conditions (units)	Results Mean ± 1SD
Safety		
Aerobic culture	Growth/no growth	NG
Anaerobic culture	Growth/no growth	NG
Endotoxin	EU (ml)	0.2 ± 0.1
Strength		
Particle count	Particles (ml)	$1.67 \times 10^9 \pm 5.7 \times 10^7$
Identity		
Percent of CD41a- and CD42b-positive particles	Overall particles (%)	57 ± 2.5
CD41a and CD42b double-positive in each size range	<0.5 μm (%)	0.3 ± 0.1
	0.5–2.5 μm (%)	98.6 ± 0.4
	>2.5 μm (%)	1.0 ± 0.4
CD62P: % positive	0.5–2.5 μm (%)	93.2 ± 2.5
Annexin V: % positive	0.5–2.5 μm (%)	96.5 ± 0.3
Phosphatidylserine exposure	μg (ml)	30.4 ± 2.6
Potency		
Aggregation in buffer	AA (%)	58.0 ± 1.6
	Thrombin (%)	50.7 ± 5.8
Thrombin generation potency units	TGPU/10^6 particles	1.9 ± 0.1
Thrombin generation maximum	Peak (nM)	70.8 ± 4.6
Thromboelastography	R (m)	8.8 ± 0.4
Thromboelastography	MA (mm)	38.4 ± 0.3
Stability		
Residual moisture content	(%)	0.7 ± 0.2

For aggregation assay final concentrations: Thrombin at 2.5 U/ml with; *AA* arachidonic acid at 500 μg/ml and LyP-T concentration at 375×10^3 particles/μl. For *TGA* thrombin generation assay with final concentration of 4.8×10^3 LyP-T/μl, 1pM tissue factor in solvent detergent treated pooled frozen plasma

SD standard deviation, *NG* no growth, *CD* cluster of differentiation, *TGPU* thrombin generation potency units, *MA* maximum amplitude

[a]Previously unpublished data

the majority of particles were not microparticles or aggregated particles (Table 9.3). GPIIb/IIIa expression was as expected at 98.71% ± 0.18, GPIb expression in the trehalose-treated lyophilized product was reduced at 44.77% ± 6.65, and Annexin V binding was 86.05% ± 2.65% [85]. Thrombin generation (Table 9.3) was similar to plasma controls [85]. Aggregation was diminished in plasma (data not shown) but somewhat better in buffer solution particularly in response to thrombin and arachidonic acid (Table 9.3). Clot strength was at the lower end of reference ranges with a maximum amplitude (MA) of 38.6 ± 1.8 mm (Table 9.3), and R-time was within reference ranges at 9.2 ± 1.1 m (Table 9.3) [85, 87]. Circulation kinetics were assessed in New Zealand white rabbits (NZWR) with the infusion of both human and species-specific ^{111}In-labeled lyophilized platelets (Table 9.4). Circulation time for both were similar with a precipitous drop occurring within the first 10 min compared to fresh rabbit platelets, and less than 40% of the product remaining in circulation at 2 h [85]. Safety and toxicology studies in rabbit, canine, and non-human

Table 9.4 Blood loss (CPM) over time[a]

Minutes	0	2	4	6	8	10	12	15	20	30
Saline	2.66	15.27	26.94	41.05	47.52	56.95	64.52	80.26	106.98	149.70
Buffer	11.79	22.32	32.03	42.83	55.11	64.54	74.33	86.40	109.16	153.80
Thrombosomes	12.27	20.46	24.81	25.95	27.22	26.98	27.93	28,16	30.49	34.86
LRP	14.09	22.43	28.67	32.10	34.87	36.74	37.44	38.27	41.71	47.19

CPM (counts per min). A whole blood sample was collected, radiolabeled, and reinfused prior to initiating the ear bleed study. Samples of shed blood were collected periodically as shown and CPM determined from the collected sample

[a]Previously unpublished data

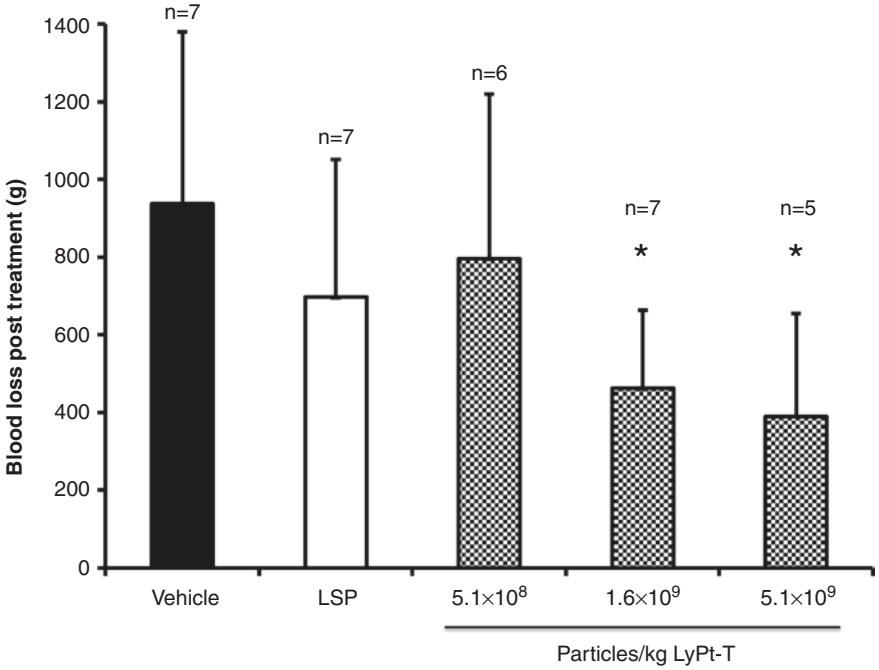

Fig. 9.6 LyPt-T dose response in a canine model of coronary artery bypass grafting (CABG). Dose response curve demonstrating reduced bleeding compared to liquid-stored platelets (LSP) after administration of LyPt-T in a canine model of CABG. (From Getz et al. [84])

primate (NHP) models demonstrated no adverse events or findings on macroscopic and microscopic examination [85]. Studies in multiple preclinical models have provided positive evidence of hemostatic effect: (1) thrombocytopenia (busulfan induced in NZWR) and a radiation induced LD50/30 in NZWR, (2) canine {CABG} (Fig. 9.6), and (3) acute hemorrhagic shock induced by traumatic livery injury in NHP [84–86].

Inaba and associates evaluated in vivo function of both human and swine LyPt-T compared to placebo in a porcine model of nonsurgical hemorrhage that combined controlled blood removal with lactated Ringer's replacement and an uncontrolled

bleeding phase produced by a liver injury [88]. Injury was followed by treatment with a three-arm study of human LyPt-T, porcine LyPt-T, and control porcine platelet concentrates. The model resulted in a significant increase in lactate, which is predictive of increased mortality risk in humans [89]. At 15 min, shed blood was calculated, and as expected, transfusion with xenographically mismatched platelets resulted in worse outcome. Transfusion of lyophilized swine platelets did not alter the amount of uncontrolled hemorrhage at 15 min but resulted in a significantly higher hematocrit at 48 h compared to the other two arms, suggesting a better hemostatic effect [88]. Further studies in animal models of injury and in clinical animal patients are planned and in progress to assess hemostatic function in the treatment of thrombocytopenic bleeding.

Funding for continued development of LyPt-T is now provided by a Biomedical Advanced Research and Development Authority (BARDA) contract. A Phase I safety study in healthy human volunteers (Evaluation of the Safety and Immunogenicity of Autologous Thrombosomes® in Healthy Human Subjects; A Microdose Escalation Study (Cohorts 1–4) and Repeat Microdose Immunogenicity Study (Cohort 5, ClinicalTrials.gov Identifier, NCT02223117) has been completed although results are not yet available in published form, and a second Phase 1 safety study (Thrombosomes® in Bleeding Thrombocytopenic Patients; ClinicalTrials.gov Identifier: NCT03394755) in thrombocytopenic bleeding oncology patients is currently enrolling subjects.

Regulatory Hurdles for Novel Platelet Products

Regulatory evaluation of novel products in the USA involves multiple in vitro evaluations, animal studies, and human trials. In the absence of a predicate product, a development program can cost in excess of several hundred million dollars after considering all exploratory, discovery, and post-market studies required. JG Vostal recently outlined FDA requirements for platelet products related to the FDA review process and stated that the more novel a product, the higher the concerns it raises regarding safety and efficacy, which in turn increases the financial burden of providing the data required by the FDA [90]. Products in development such as those described here require extensive in vitro characterization, to include platelet physiology, morphology, and biochemistry. These are followed by preclinical studies in multiple models and species and Phase 1 dose escalation trials to assess safety, if required. Additional in vitro studies are also needed to demonstrate that, regardless of the variability of the starting material, manufacturing methods and characterization of the product comply with the FDA and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) requirements for the validation of analytical methods, maintains consistency during the manufacturing process, and conforms to release and other cGMP criteria. This can be very challenging given the inherent biological diversity observed between individual donors when determining platelet count, hemostatic efficacy, ex vivo and in vivo survival, and other qualities of the platelet starting material.

In characterizing products, development teams must address qualities such as product identity, purity, potency, strength, reproducibility, and creation of scalable processes that do not change the essentials of the product manufacturing process. The products described face different and unique challenges. Each unit of CPP is a unique lot of product from a single donor, whereas each trehalose-stabilized lyophilized platelet dose is an aliquot from a lot manufactured from a platelet pool collected from up to ten individual donors. Depending on the proposed indication and novelty of the product, regulatory bodies may ask for additional studies, including in vivo radiolabeled recovery and survival studies, Phase 1 dose escalation safety trials, Phase 2 dose-finding studies, Phase 3 trials to establish efficacy to treat clinical disease, and, finally, Phase 4 post-market studies. Phase 1–3 studies invariably assess safety endpoints but are not usually powered to detect rare safety risks. For this reason, FDA is increasingly requiring Phase 6 post-market studies to evaluate innovative products.

With strict enforcement of patient blood management, blood product use is declining and associated profit margins are increasingly smaller. It is no wonder that companies involved in the blood industry must carefully evaluate whether or not to invest in expensive, decades-long product development efforts. Introduction of new products into an already competitive landscape compounds the difficulties as clinicians appropriately have moved to evidence-based decision-making, leading to further expense related to the conduct of clinical trials aimed at driving product adoption. Rapid changes in biomedical sciences increase the risk, because of the greater potential for a disruptive technology to change the field before market approval. With increasing complexity in the regulatory requirements comes the risk that regulatory barriers become so high that a product with a challenging business case but a high potential to save lives may never become commercially available. FDA has tried to address this problem by designating some novel products as "orphan drugs" if the patient population is small or if the expected return is lower than the required investment. In addition, the DoD (US Army Medical Materiel Development Activity, or USAMMDA; DARPA; and others), BARDA, and directed congressional appropriations may be able to generate funding streams to address the so-called product valley of death, describing the interval after a great idea has been shown to be feasible but is too risky to attract investment capital for further development. Without DoD or BARDA funding, the product development programs described in this chapter would not exist, yet they are aimed at addressing life-threatening injuries sustained in environments in which good treatment alternatives are scarce or absent.

The current proposed indication for use of CPP is "Treatment of acute hemorrhage in patients with a platelet deficiency or a platelet dysfunction when LSP are unavailable" and that of LyPt-T is "for the treatment of uncontrolled hemorrhage." FDA considers both CPP and LyPt-T to be hemostatic agents derived from human platelets rather than conventional blood products, but this classification remains within the scope of the Center for Biologics Evaluation and Research (CBER). Both products are primed to participate in clot formation, with accelerated thrombin

formation in in vitro assays. Available data does not suggest that these phenotypes are clinically dangerous as initiators of thromboembolic events and may indeed be helpful to treat active bleeding, but differences from the current standard of care have prompted increased FDA scrutiny and requirements. The preclinical work for both products has been extensive, expensive, and time-consuming. Movement of these products into clinical trials has been equally challenging. Rapid changes in clinical practice have increased the complexity of identifying study populations where equipoise exists and there is an appropriate balance between risk of harm and potential benefit. To address the proposed indication for these products, study subjects must be actively bleeding, and while this requirement may seem simple at first glance, the identification of bleeding patient populations in the face of continual improvements in blood-sparing techniques has been problematic. The difficulties in accurately assessing bleeding endpoints are well-recognized due to lack of common definitions, subjective quantification of blood loss, and a high degree of outcome variability [91].

Despite these uncertainties, the FDA's regulatory review process may soon take on a more streamlined aspect as the FDA and the US DoD have agreed to work closely together in support of critically needed breakthrough technologies. Potential benefits of this approach may include more frequent and accelerated reviews by the FDA, consultation on development from an FDA team not involved in product review, consideration of interim limited indications to allow early use in settings without viable alternatives, and greater weight given to animal and non-US data if production methods are sufficiently similar. Successful execution of Phase 1 safety trials and Phase 2 efficacy studies undoubtedly will remain required elements of development programs; however, FDA may reevaluate the necessity and timing of Phase 3 studies on a case-by-case basis. If so, it is likely that FDA will rely more heavily on surveillance or prospectively designed randomized controlled interventional Phase 4 post-market studies.

Summary

Cryopreserved and lyophilized platelets have a long, but limited, history of human use that dates back to the 1950s yet involves a small number of total study subjects. Despite decades of research characterizing the quality and nature of these products, questions remain regarding the relationship between in vitro performance and in vivo function to control bleeding. That said, results to date indicate promising in vivo hemostatic potential in several animal models. Although the data is retrospective and cannot definitively establish causality, human use of cryopreserved platelets in military settings also appears to be associated with benefit. The regulatory pathway for these products, particularly in the case of CPP, has been decades long, and more trials are needed to provide high-quality data to regulatory bodies. These products could be life-saving in settings where other good alternatives are limited or not available.

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Frozen Red Blood Cells

10

Yuxuan Wang and Martin A. Schreiber

Introduction

Trauma is the leading cause of death in the United States in persons younger than 44 years, with traumatic hemorrhage and trauma-induced coagulopathy contributing to mortality in the first 24 h [1]. Ongoing research in trauma resuscitation has revealed that goal-directed resuscitation with a protocolized balanced blood product transfusion strategy results in improved early survival and less deaths due to exsanguination [2–5].

Regardless of transfusion strategy, the need for red blood cells (RBCs) and their oxygen-carrying capacity is critical to survival. An American Association of Blood Banks (AABB) Blood Survey Report from 2013 showed a 12% decrease in whole blood and RBC collection when compared to 2011, even though the utilization of whole blood and RBCs decreased by 5% [6, 7]. Even with improvement in hemorrhage control strategies in trauma, other means of storing RBCs need to be explored due to the limited shelf life of liquid-packed RBCs and the development of storage lesions over time. One example of this is frozen RBCs (fRBCs).

History

The first published study of successful cryopreservation of RBCs was by Dr. Audrey Smith in 1950, who discovered that human blood diluted with equal parts of 30% glycerol-saline and frozen to −80 °C did not undergo the usual hemolysis caused by freezing and thawing [8]. She observed that glycerol, a sugar alcohol that is

Y. Wang · M. A. Schreiber (✉)
Division of Trauma, Critical Care, and Acute Care Surgery, Oregon Health and Sciences University, Portland, OR, USA
e-mail: schreibm@ohsu.edu

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permeable to cell membranes, acted as a cryoprotective agent (CPA) during the freeze-thaw process. It was thought that the principle protective action was their ability to prevent the excessive concentration of electrolytes and other substances that otherwise occurs with freezing [9]. Although other CPAs such as dimethyl sulfoxide and hydroxyethyl starch have been used to prevent cryoinjury, glycerol is the more commonly studied and utilized CPA [9, 10]. Mollison and Sloviter published the first successful transfusion of thawed fRBCs and found a post-thawing preservation of 80–90% of the original cellular volume [11].

This resulted in enthusiasm for the process, as it was seen that cryopreservation could allow the long-term storage and stockpiling of large quantities of blood for prolonged periods, thus alleviating the issue of seasonal or unexpected catastrophic shortages and establishing greater availability of rare blood types.

Cryopreservation

The cryopreservation process requires three steps after screening and pathogen testing of the packed RBCs (pRBCs):

1. Glycerolization phase
2. Storage phase
3. Deglycerolization phase

Glycerol is a very effective cryoprotectant for cells in which they can diffuse into fairly quickly, such as human erythrocytes. The uptake of glycerol by human erythrocytes are both an active and passive process [12–15]. Once intracellular, glycerol will form firm hydrogen bonds with intracellular water, inhibiting it from turning into ice. In turn, this will suppress the rise in sodium chloride concentration to prevent extreme hypertonicity [16, 17].

Currently, two methods are commonly used to cryopreserve RBCs: the high glycerol concentration (HGC) method with 40% weight/volume (W/V) or the low glycerol concentration (LGC) method with 20% W/V.

The HGC method allows for an initial slow freezing rate (~1–3 °C/min) and storage in −80 °C freezers but adds to the thawing time. The LGC method requires rapid cooling (>100 °C/min) to −140 °C in liquid nitrogen but reduces the thawing time [18]. Advantages of the HGC method include storage up to 37 years and the relative ease of transportation in freezers [19]. One advantage of the LGC method is that it results in less hemolysis upon thawing than the HGC method [20]. Prior to transfusion, frozen RBCs require deglycerolization due to increased hemolysis caused by a more rapid endosmosis of water than exosmosis of glycerol [21].

The deglycerolization phase involves washing the glycerolized RBCs with hypertonic sodium chloride solution. The diluted RBCs are then placed in a centrifuge and the supernatant fluid is removed. The RBCs are washed twice with isotonic sodium chloride solution. Historically, the entire process required 1 l of wash solution and took almost 3 h [22].

Multiple methods were developed to speed up the process, and in 1963, Dr. Charles Huggins invented the cytoglomerator, which uses a dilution/agglomeration technique. It first involves removal of glycerol by adding non-electrolyte solutions contacting glucose and fructose to glycerolized RBCs while stirring. This decreases the ionic strength of the environment, causing RBCs to clump together, or agglomerate, once stirring stops. After decantation of the supernatant, isotonic saline is added to the agglomerated RBCs for disaggregation [23]. The average time was 50 min with 6.8 l of washing fluids used. In 1967, Haemonetics developed a blood processor called the M115 cell processor with a polycarbonate bowl with an attached shaker for mixing of the washing solutions. This process took 35 min and only used 2 l of washing fluid [24]. Both of these systems, however, are open systems, and the RBCs must be administered within 24 h of post-thaw and washing [25–27]. Haemonetics later developed a closed-system automated cell processor in 1998; the ACP 215 is able to use thawed pre-wash blood stored at 1–6 °C for up to 14 days and produce acceptable-quality post-wash RBCs that can be stored up to 7–14 days [28, 29]. This device utilizes sterile connecting devices, in-line 0.22 micron bacterial filters for solution delivery, and a disposable polycarbonate bowl to deglycerolize RBCs. The post-wash RBCs are then stored in standard blood storage solutions, either additive solution (AS)-3 (saline, adenine, glucose, citrate, and phosphate) or saline-adenine-glucose-mannitol (SAGM). The entire freeze-thaw-wash process takes about 2 h and is currently the most prevalent method of processing fRBCs [30].

Benefits

Inventory and Availability

Over 75 million units of blood are donated every year worldwide, with blood services depending on the altruism of the donors [31]. In the United States, blood donation, distribution, and transfusion services all operate within a blood supply network consisting of collection centers (hospital and community) and transfusing facilities. Basic economics of supply and demand apply, with the hope that blood banks will always have enough blood in storage for emergent demands. Since 1971, national surveys have been administered for the blood supply network to assess supply and demand. Recent National Blood Collection and Utilization Survey (NBCUS) Reports published by the US Department of Health and Human Services have described a decrease in donor blood collection, with an 11.6% decrease between 2013 and 2015 [32]. This echoes a steady decrease in demand as well, which has been a trend seen in earlier surveys [33]. This is likely due to a focused effort to reduce transfusions, such as minimally invasive surgeries, restrictive transfusion practices, success with cytokine-based therapies, and immunosuppression for aplastic anemia [33]. However, this raises concern that hospitals do not have enough supply to accommodate for surge demand in times of crises or major disaster. One example is the Zika virus outbreak in 2016, where blood

collection was halted in Puerto Rico until nucleic acid testing could be implemented under investigational new drug protocols. With their inherent supply cut off, Puerto Rico depended on the importing of blood products from the non-Zika-affected blood centers in the mainland United States. Another important issue is wastage of blood products, which may occur from time expiry, wasted imports, blood that was medically or surgically ordered but not used, stock time expiration, hemolysis, or miscellaneous reasons. The 2011 NBCUS survey reported a 12% wastage rate, with causes attributed to unacceptable test results, units sacrificed by collectors for unspecified reasons, and outdated units [34]. Recent results from three level I trauma centers' utilization of blood products during massive transfusion protocols also showed an RBC wastage rate of 9% [35]. Even with the FDA extension of liquid RBC shelf life from 21 to 42 days, fRBCs can still be stored for over 10 years, thus decreasing the wastage of blood through outdating by thawing the blood needed ahead of time [21].

Ever since the terrorist attack on September 11, 2001, a focus has been placed on the availability of blood products to prepare for possible future catastrophic events. This event initiated the American Red Cross (ARC), America's Blood Centers (ABC), and other government agencies to produce weekly data reflecting that blood centers and hospitals each maintain on average a 3- to 5-day supply of RBCs to create an estimated 10-day reserve [36]. However, a 2006 ABC newsletter showed less than half of their centers maintained a blood supply of 3 or more days. In addition, seasonal shortages are common, especially in the winter and summer months due to inclement weather, seasonal viral infections, decrease in donor pool, and vacations [37]. These seasonal shortages could be alleviated by the availability of fRBCs in blood centers and hospitals.

Storage Lesion Elimination

The term "storage lesion" refers to changes in RBCs while in storage and is characterized by reversible and irreversible defects. Ex vivo storage affects RBC energy metabolism, redox metabolism, and the cell membrane, thus creating a "phenotype" of morphologic, structural, and functional changes [38]. The RBC storage phenotype is characterized by depletion of 2,3-DPG, ATP, glutathione, and loss of normal shape, with an accumulation of reactive oxygen species, lactate, potassium, inflammatory lipids, and extracellular vesicles (EV) [39]. The major driving forces of the phenotypic lesion are caused by a defective ATP-centered metabolism and oxidative stress. RBC membrane stability and deformability are reliant on energy from ATP, which is not in constant supply in storage, causing some RBCs to undergo hemolysis or eryptosis. Posttransfusion, deformed RBCs may be engulfed by macrophages in the spleen, liver, or bone marrow [40]. However, certain aspects of the storage lesion may be reversed upon transfusion, such as 2,3-DPG levels, ATP, and electrolyte imbalances [41]. The buildup of EVs and inflammatory lipids in stored blood activates neutrophils to produce an inflammatory cascade after transfusion and could be involved in the pathogenesis of transfusion related lung

injury [42, 43]. Another hypothesis is that the release of cell-free hemoglobin and microparticles may decrease the amount of nitic oxide and deficiency in nitric oxide synthase activity [44].

Standards set by the AABB require RBCs to be frozen within 6 days of collection, therefore halting the metabolism of erythrocytes and theoretically decreasing the likelihood of red blood cell storage lesions. Fabricant et al. and Hampton et al. performed prospective randomized studies comparing transfusion of standard liquid RBCS or cryopreserved RBCs in trauma patients. Patients who received fRBC transfusions had higher tissue oxygenation levels and 2,3-DPG levels with lower interleukin 8, tumor necrosis factor alpha, and D-dimer concentrations when compared with liquid RBCs [45, 46]. A multi-institutional study across five level 1 trauma centers comparing fRBCs and liquid RBCs in 256 trauma patients demonstrated decreased levels of alpha-2 macroglobulin, haptoglobin, c-reactive protein, and serum amyloid-P in the fRBC patients, but no difference in tissue oxygenation, organ failure, infection rate, and mortality [47]. Recently, McCully et al. noted that patients with BMI >30 who received fRBC had increased tissue oxygenation and lower free hemoglobin when compared to those who received liquid RBC [48]. These multi-institutional clinical trials highlight the benefits of fRBCs in a civilian setting.

Blood Washing

One major hazard of blood transfusion is the transmission of pathogens, especially hepatitis. It was not until 1963 when the discovery of a screening test for hepatitis B was discovered [49]. Prior to this, it was found that fRBCs had a reduced likelihood of transmitting serum hepatitis or hepatitis B [50]. This was attributed to the washing step, as it was found that the hepatitis B antigen was in the eluent. Washing also reduced the number of WBCs and plasma, thus reducing the risk of transfusion reactions [51]. This caused an increase in the utilization of fRBC in dialysis centers and patients undergoing renal transplantation [52]. However, with the ever-improving infectious disease screening process of blood banks, and the use of pre-storage leukoreduction, liquid RBCs are just as safe from an infectious point of view as fRBCs [53].

Rare Blood

The most irrefutable benefit of fRBCs is the preservation of a bank of rare blood types [52]. Since the 1960s, the medical community recognized patients with complex serology whose options for blood transfusion are severely limited. In 1960, Valeri's group at the Naval Blood Research Laboratory built a 200-unit rare phenotype frozen RBC repository in conjunction with the AABB, with the state of New York following suit in 1968 [53]. The America Rare Donor Program was formed in 1998 to provide rare blood for those patients in need [54]. The Laboratory

of the Dutch Red Cross Blood Service also began storing rare fRBCs and reached a maximum of 300 units for the year of 1981 [55]. Another benefit is the storage of autologous blood for those with transfusion-dependent disorders. These patients can store their own blood in preparation for elective surgery or other unplanned events [56, 57].

Clinical Use

Throughout history, wars have played an important role in the development and advancement of medical care. The first documented successful blood transfusion took place in the US Civil War, when, in 1864, Dr. Fryer transfused 16 ounces to a soldier who underwent an above-knee amputation [58, 59]. By the first World War, knowledge of citrate as an anticoagulant was available, but not utilized for quite some time [60]. Rous and Turner in the first year of World War I created a mixture of 5.4% glucose and 3.8% sodium citrate to protect RBCs from hemolysis for 4 weeks [61]. In 1917, a military physician named Oswald Robertson designed an icebox with glass containers filled with whole blood mixed with the Rous-Turner solution, thus becoming the world's first blood banker [62]. By the World War II, whole blood was able to be fractionated into plasma and was used to treat burn victims in Pearl Harbor after the Japanese attack [63]. During the early years of World War II, the general belief was that plasma was enough to compensate for hemorrhagic shock [64]. As the war raged on, focus was turned back to whole blood, which carried through the Korean War. Noticeably, the mortality rate of wounded soldiers after reaching a hospital decreased from 10% in World War I to 2.6% in the Korean War [65, 66].

In the time between the Korean and Vietnam Wars, the US Navy commissioned the Blood Research Laboratory in 1956, later renamed the Naval Blood Research Laboratory (NBRL) in 1965, which was tasked with developing long-term preservation of RBCs, especially for use on naval ships. That same year, the NBRL established the first frozen blood bank at Chelsea Naval Hospital in Massachusetts, adopting the HGM [53].

The first clinical trial utilizing fRBCs was performed by Haynes et al. at Chelsea Naval Hospital, where more than 1000 units of fRBCS stored up to 44 months were transfused to more than 355 patients. In addition to equivalent clinical results as compared to liquid RBCs, they found a decreased rate of transfusion-related hepatitis and adverse febrile reactions [21].

In 1966, a frozen blood bank at the Navy Station Hospital in Da Nang, Republic of South Vietnam, was established. Their objective was to receive a limited supply of frozen Group O, Rh-negative blood from the United States for use in selected casualties, using a Huggins cytoglomerator for the processing of fRBCs. A total of 307 units of fRBCs were transfused. In vitro studies showed a 27% red cell loss, with a final volume of 210 mL with a hematocrit of 87%. In vivo studies showed an immediate posttransfusion mean hemoglobin increase of 3.68 mg/100 mL as compared to 0.72 mg/100 mL for liquid RBCs. Measured serum creatinine and bilirubin

level were acceptable. The authors concluded that fRBCs during wartime are an alternative to the walking donor system, which is fraught with possible logistical complications such as transportation, communication, personnel, blood-borne pathogen transmission, and donor safety [67]. During the 1991 Gulf War, approximately 7000 frozen units were available on two US Naval hospital ships, but none were used. The Joint Trauma System Performance Improvement Branch analyzed data from the Department of Defense Trauma Registry and Massive Transfusion Database in Afghanistan and found 63 patients between January 2010 and September 2011 who received massive transfusions that required the use of fRBCs. When compared to a control population of 525 patients who did not receive fRBCs during their massive transfusions, there were no significant differences in complications including transfusion reactions, coagulopathy, renal failure, deep vein thrombosis, or respiratory failure [68]. Currently, the US Naval Hospital Ship Mercy carries a stock of 2850 fRBC units at all times, and in 5 months, over 200 deglycerolized units were transfused to patients in various settings [69]. The US Military Joint Trauma System Clinical Practice Guideline regarding fRBCs supports the use of fRBCs, with the primary indication as a supplement to liquid RBCs during periods of increased transfusion requirements in order to decrease hemorrhagic morbidity and mortality in casualties [68].

Internationally, the Laboratory of the Dutch Red Cross Blood Service began freezing RBCs in the early 1960s. Using the LGM, they initially began freezing phenotypically uncommon or rare RBCs. They also froze O-positive and O-negative units to increase their inventory in anticipation of the possible shortages in the summer and winter months [64]. During the first Gulf War in 1991, the Netherlands Military Blood Bank realized that shipment of liquid RBCs was cost-ineffective and would not guarantee availability at all times, unlike fRBCs. To test this, they froze and sent 1360 units of fRBCs and frozen platelets to Iraq in 2005. They learned that a military hospital blood bank facility can be deployed without regular shipments of liquid blood products and can meet the needs of a surgical team by thawing and washing a certain amount weekly, creating a hybrid liquid-frozen blood bank, although it is not known how busy the surgical team was during that time [69].

Civilian usage of fRBCs began with the invention of the cytoglomerator by Dr. Huggins, making Massachusetts General Hospital the first civilian center to use fRBCs on a large scale [13]. Between 1971 and 1972, his blood bank froze over 15,000 units, and 14,406 units were transfused in the subsequent years, with Huggins claiming that no cases of hepatitis occurred [55]. Gerald Moss, a student of Dr. Huggins, ran the Cook County Blood Bank in Chicago using almost exclusively fRBCs. By 1975, they were freezing and thawing more than 10,000 units of RBC a year [55].

Drawbacks/Future Directions

One of the biggest drawbacks of fRBCs is the preparation. Whereas liquid RBCs are ready to use after removal from a 1–6 °C cooler, fRBCS need to be deglycerolized and prepared, which takes at least 50 min even with the new ACP 215 [70]. This

detracts from the utility of fRBCS in emergent scenarios. This problem can be mitigated by maintaining a portion of the RBCs thawed for immediate use. A second drawback is cost, which is about three times the cost of liquid preservation, with the majority due to instruments used in processing, disposables, and solutions [71]. This ties into the third drawback, which is the in vivo recovery rate of 75% at 24 h after transfusion of fRBCs [72]. Although this is at the threshold of the FDA's current standard of transfusion recovery rate, the extra cost associated without the benefit of increased recovery can cause reservations in widespread adaptation of this technique of blood storage. However, the prospective randomized multicenter trial revealed that hematocrits performed 12 h after transfusion were identical in the liquid and fRBC groups. This suggests that the senescent cells that are removed in the deglycerolization process are similarly removed by the body after transfusion resulting in equivalent loss in vivo. A recent paper by Chang et al. found that after deglycerolization, cryopreserved blood developed storage lesions at a faster rate when compared with liquid never-frozen pRBCs, thus negating one of the benefits of fRBCs if they are not transfused within 14 days after deglycerolization [73].

The processing and usage of fRBCs peaked in 1978/79, where the majority of their use was in dialysis centers for potential cadaveric renal transplant recipients. It was originally thought that sensitization to donor histocompatibility could affect graft survival and fRBCs had a lower amount of leukocytes than liquid RBCs to provoke this immune response. However, Opelz and Terasaki in 1978 published a study of 1360 cadaver donor transplants comparing 4-year graft survival in never-transfused patients and those who had over 20 pretransplant transfusions. The results showed that graft survival was 30% in those who never received transfusions as compared to over 65% in those who received transfusions, suggesting that prior exposure to donor histocompatibility, antigens enhanced graft survival [74]. As a result of this study, utilization of fRBCs began their steady decline. The demand for fRBCs also declined after the discovery of the human immunodeficiency virus (HIV) in 1983. By 1992, 9621 cases of acquired immunodeficiency syndrome attributed to blood transfusions were identified, and it was not until 1985 when a screening process for HIV was created. Since the cryopreserved blood was not tested for HIV, fear of transmission has curtailed their use [75].

Regarding rare blood use, with the advent of longer liquid RBC storage, the Dutch Red Cross now averages transfusing 30 units per year. Even the American Red Cross Rare Donor Registry decreased their inventory size from 18,000 to 9800 between 1981 and 1990 [55].

In the wake of the terrorist attack on the World Trade Center in New York City, New York, and the Pentagon in Arlington, Virginia, a total of 2800 people were killed and 4000 were injured. Despite the New York Blood Center having between 18,000 and 22,000 units available and the Washington DC metropolitan area having 12,000 units available during that time, only a mere 258 units of RBCs were transfused [63]. A few hours after the attacks, the Red Cross ceased distribution of blood from its regional centers, forcing local hospitals to look elsewhere for blood. Around the same time, the National Institutes of Health opened up their blood bank, and ceased collections within 24 h due to adequate filling of its inventory. In addition, blood donors were lining up outside of local donation centers to contribute to the

blood supply inventory. With no evidence of blood shortage, the Red Cross did not cease donations for weeks, with their justification being the creation of a "National Blood Reserve" of a 7- to 10-day supply of liquid RBCs followed by fRBCs, resulting in collection of 287,000 extra units of blood [53]. The Red Cross purchased 70 Haemonetics ACP 215 machines, only to find out that many of the extra units of blood were preserved in additive solutions that were not licensed to be used with the machine. Only 9500 of the planned 100,000 units were frozen, and many of the extra units were sold or given away as they neared their expiration date. In total, almost 600,000 extra units of blood were collected with over 300,000 units destroyed. Due to the high wastage of donated blood, the state of New York experienced a decrease in the number of donors due to their perception that their donated blood was wasted [53].

A task force composed of the Blood Centers of America, the American Hospital Association, the Centers for Disease Control and Prevention, the US Department of Defense, the DHS, the FDA, the ABC, and the ARC formed the Interorganizational Task Force on Domestic Disasters and Acts of Terrorism to address three lessons learned from 9/11:

1. There must be control of excess collections to prevent waste of donated blood units.
2. Facilities should maintain adequate inventories to prepare for "disasters at all times in all locations."
3. All blood centers should have a 7-day supply of RBCs at all times [53].

Significantly less than half of the hospitals and blood centers have a 7-day supply of RBCs. If a disastrous event was to deplete of the entire blood supply in a community, it would take 2–3 days to screen and process freshly donated blood for transfusion, whereas fRBCs can be thawed in less than an hour. If each blood center had a frozen blood bank as an adjunct to a disaster preparedness plan, a solid and dependable supply could supplement the need in times of surge and decrease waste by having the ability to freeze RBCs.

Conclusion

Frozen RBCs have demonstrated benefits over liquid RBCs with improved biomarkers, less infection, and most importantly, a very long shelf-life. Frozen RBCs remain an important solution for disaster scenarios, for austere conditions, and for patients with rare blood types.

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Oxygen Carriers

11

Anirban Sen Gupta and Allan Doctor

Introduction

In austere battlefield conditions and remote civilian locations, trauma-associated uncontrolled hemorrhage and acute coagulopathy remain one of the leading causes of mortality [1–6]. In such scenarios, transfusion of whole blood and blood components (e.g., RBCs, platelets, and plasma), as per Damage Control Resuscitation (DCR) guidelines, can significantly reduce trauma-associated morbidities and mortalities [7–9]. However, the limited availability and portability, special storage requirements, and high contamination risks of these blood products present severe logistical challenges that preclude facile, ubiquitous pre-hospital application in military and civilian scenarios, for either immediate (e.g., point-of-injury or en route) or prolonged field (e.g., extended, in place) care at the point-of-injury [10–17]. A robust volume of research is currently being dedicated toward resolving these issues and enhancing the availability and applicability of donor-derived blood products in the field [18–21]. In parallel, enabled by transformative advances in the areas of synthetic chemistry, biomaterials, and nanofabrication, an exciting area of research has emerged that focuses on the development and evaluation of semisynthetic or synthetic "bioinspired" surrogates of blood products that can be manufactured at large scale (i.e., sufficient availability); can be sterilized without compromising biofunction, and stored as small volume deliverables over long periods of time across broad ambient temperature ranges and environmental conditions (i.e., easy storage

A. Sen Gupta (✉)
Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH, USA
e-mail: anirban.sengupta@case.edu

A. Doctor
Departments of Pediatrics, Biochemistry and Bioengineering, University of Maryland School of Medicine, Baltimore, MD, USA

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and portability); can be easily reconstituted and administered "on demand" in far-forward scenarios (i.e., pre-hospital applicability); can potentially avoid the need for type matching (universal application with minimal immunogenic risk); can circulate safely upon intravascular administration without systemic risks; and can mimic, leverage, and amplify endogenous mechanisms of blood component function to mitigate the effects of traumatic exsanguinating hemorrhage [22–24]. This field of research has developed in the areas of functionally mimicking blood's cellular as well as non-cellular components and continues to focus on resolving translational challenges with regard to biocompatibility, safety, pre-hospital availability, and universal applicability.

The research endeavors on preserving and transporting donor-derived blood started during World War I, and blood transfusions became widely available by World War II. Based on this advance, multiple blood banks were established in the USA from the 1950s onward, and blood donation was promoted as a form of civic responsibility. Subsequent development of processes and methodologies for isolation and storage of various blood components has significantly enhanced utilization of whole blood and its components. Currently, transfusions of whole blood as well as various isolated components are clinically approved for application in civilian and battlefield trauma (e.g., in Damage Control Resuscitation), surgical settings (e.g., transplants), chronic and acute anemias, and disease-associated, drug-induced, or congenital bleeding disorders [25–32]. RBC transfusion is clinically significant in efficient mitigation of hemorrhagic shock, as part of the Massive Transfusion Protocol (MTP) in hypoperfused patients with critically limited oxygen delivery [33–37]. It has also been demonstrated that pre-hospital use of RBC transfusion (if available) can significantly improve survival in critically injured subjects [38, 39]. Such transfusions are dependent on donor-derived RBC products (e.g., packed Red Blood Cell or pRBC). However, according to the Red Cross, only ~40% of US population is eligible to donate blood at any given time, and only 10–15% actually donate. In addition, blood-based products have formally limited shelf-life due to accrual of processing and storage-related damage as well as risks of pathogenic contamination. Currently, RBCs have a maximum shelf-life of 42 days, while platelet suspensions have a shelf-life of 5 days, at room temperature [40]. Also, RBCs (and platelets) develop storage lesions over time, which affect their stability, in vivo circulation lifetime, and post-transfusion physiology [41, 42]. Significant research is underway to enhance the shelf-life of blood products by cold storage, freezing, lyophilization, etc. and to develop pathogen reduction technologies like psoralen-based or riboflavin-based UV irradiation, as well as extensive serological testing of donor blood, leukoreduction, and specialized storage protocols [13, 19, 31, 43–48]. Nevertheless, portability of blood products, especially to remote battlefield and civilian locations, especially for pre-hospital point-of-care use, continues to be a major logistical challenge [14, 17, 49].

Such challenges can be potentially addressed by bioinspired engineering of semisynthetic or synthetic surrogates of blood components [22, 50, 51]. In fact, major interest in such synthetic surrogates developed during the HIV crisis of the 1980s due to fear of contaminated blood products, and this research has been

ongoing, with several designs and products that have progressed through pre-clinical and clinical evaluations. However, currently no such product is clinically approved by the FDA for human applications in the USA, although certain products have been approved for human use in South Africa and, under special circumstances, dispensed for compassionate use provision in the USA and Europe. Of note, a 2008 meta-analysis of 16 clinical trials of 5 different HBOCs indicated increased risk of both myocardial infarction and death in subjects who received such products [52]. Although this report raised significant concern with regard to the clinical safety and utility of these particular HBOCs, the design of this analysis has been debated and, importantly, this work has directed significant re-emphasis to better understanding the pros and cons of these products at fundamental physiological and mechanistic levels. To this end, the current categorization of such products has shifted from "blood substitutes" to "oxygenation therapeutics" so as to emphasize the important role of such products in scenarios where donor-derived RBCs may not be sufficiently available (e.g., far-forward military setting) as well as for niche scenarios, such as ex vivo perfusion of transplantable organs. In this framework, we will focus on reviewing "hemoglobin-based oxygen carriers" (HBOCs), comprehensively discussing relevant designs, current state-of-art and novel molecules in development, along with emphasizing criteria for successes and challenges.

Hemoglobin (Hb) Function in RBCs for Oxygen Transport

In blood, the primary function of RBCs is the transport of oxygen (O_2) and to some extent carbon dioxide (CO_2) to and from tissues, by virtue of binding of the gases to hemoglobin (Hb) within RBCs. The average amount of Hb in adult human RBCs (mean corpuscular hemoglobin, or MCH) is 27–31 picograms per cell (~250 million Hb molecules). Hb is a tetrameric protein comprised by two α- and two β-polypeptide chains, each bearing an iron-containing heme prosthetic group that is capable of reversibly binding one oxygen molecule (O_2). Figure 11.1a shows a multi-scale representation of an RBC, Hb within an RBC, and the chemical structure of an iron-containing "heme" group within Hb. The O_2-binding kinetics to Hb is positively cooperative, such that a small variation in oxygen partial pressure (pO_2) as blood transits from lung to tissue (Fig. 11.1b) results in a large change in oxygen that is captured (in lung) and then released (in tissue) by Hb as exhibited by the classic sigmoidal shape of the O_2-binding equilibrium curve (OEC, Fig. 11.1c) [53, 54]. O_2-carrying iron in Hb is in its reduced "ferrous" (Fe^{2+}) state. Approximately 10% of the O_2 molecules release as superoxide, generating methemoglobin (MetHb), in which the iron is oxidized to the "ferric" state (Fe^{3+}) and rendered unable to bind oxygen [55]—this process is accelerated in the setting of increased O_2 delivery and/or during other conditions characterized by oxidative stress. Due to this reason, in RBCs, Hb oxygenation/deoxygenation cycling is closely coupled to RBC energetics and anti-oxidant systems (e.g., driven by enzyme NAD-cytochrome b5 reductase), such that the Fe^{2+}-containing Hb is maintained in its O_2-binding state. Failure

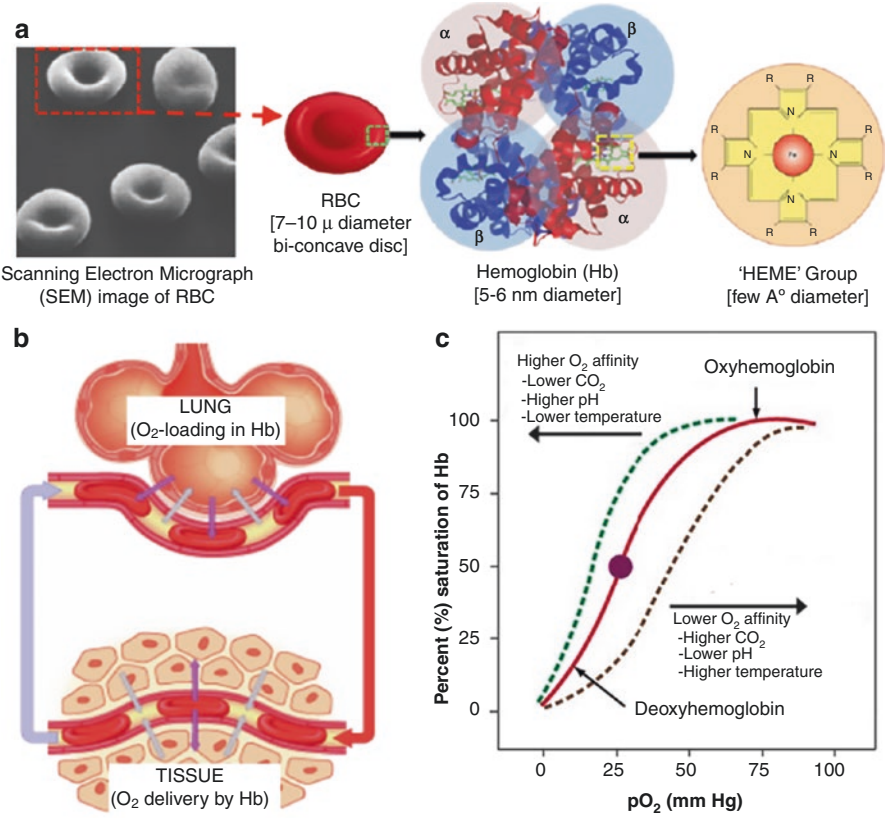


Fig. 11.1 (**a**) Multi-scale representation of RBCs and Hemoglobin (Hb), showing a scanning electron micrograph (SEM) image of RBC depicting the biconcave discoid structure, along with sequential schematic of RBC structure, Hb structure, and "Heme" structure; (**b**) shows a schematic of RBC movement between lung (oxygen loading site) and tissue (oxygen off-loading site), while (**c**) shows corresponding oxygen equilibrium curve (OEC) characteristics of Hb. (From 2017 Military Supplement: Hemoglobin-based Oxygen Carriers Current State-of-the-Art and Novel Molecules, Anirban Gupta, Shock Injury, Inflammation and Sepsis, Oct 3, 2018, Publish Ahead of Print, Figs. 1–4, with permission of Wolters Kluwer Health, Inc.)

to reverse MetHb formation not only diminishes oxygen-carrying capacity, but the cooperativity is also impaired, leading to increased O_2 affinity for remaining ferrous hemes (in "partial met" tetramers), and this also leads to dysregulated vascular tone and inflammatory reactions. Furthermore, Hb in RBCs have the unique capability to undergo conformational changes to allow O_2 saturation (loading) in the lungs (higher O_2 affinity) and then O_2 release in tissue (lower O_2 affinity). This reversible conformational regulation of O_2-binding affinity of Hb is aided by allosteric effector molecules like 2,3-diphosphoglycerate (2,3-DPG), which forms in RBCs as a glycolytic intermediate. Therefore, maintaining such oxygen-carrying thermodynamic and kinetic characteristics of Hb is one of the important and challenging design considerations in the context of developing a "bioinspired" Hb-based RBC

surrogate [56]. In this context, an essential factor is to maintain the intraerythrocytic physicochemical milieu of Hb, since outside of the protective RBC environment (i.e., in plasma, which fundamentally differs from that in RBCs with regard to pH, redox potential, key ion/small molecule abundance, etc.), the Hb tetramer is prone to rapidly oxidize and disassemble into its dimeric and monomeric protein units, which in turn results in rapid clearance from circulation into extravascular space and kidneys. This results in reduced circulation residence time and increased risk of nephrotoxicity. Extraerythrocytic Hb is also devoid of oxygen affinity regulatory effectors, such as 2,3-DPG, as well as protective anti-oxidant enzymes and reducing equivalents. As a result, free Hb in plasma exhibits dysregulated tissue oxygenation capacity compared to RBC-encapsulated Hb and is also prone to rapid MetHb accrual (without reversal systems available in RBCs), thereby degrading its oxygen transport ability. Unencapsulated Hb is also a potent nitric oxide (NO) scavenger, which is produced by endothelial cells as a principle effector molecule to achieve vasodilation in response to multiple physiologic reflexes that optimize tissue perfusion; notably, this pathologic Hb-NO interaction has been implicated in hypertensive and (paradoxical) perfusion-limiting side effects of unencapsulated Hb. Hence, providing efficient tissue oxygenation while maintaining reasonable circulation lifetime, minimizing hypertensive side effects, and avoiding Hb-induced toxicity are the three prominent design requirements for HBOCs. The following sections review and discuss the various design approaches that attempt to address these requirements.

Hb-Based Oxygen Carrier (HBOC) Systems

HBOCs are semisynthetic systems that utilize biologically generated Hb as the oxygen-carrying component and are formulated either as chemically modified cell-free suspensions or conjugated and cross-linked with polymers along with protective enzymes or encapsulated within microparticulate or nanoparticulate vehicles [51, 57]. The Hb used in these systems is usually derived from outdated human or bovine RBCs or from recombinant sources [57–63]. In the case of outdated human or bovine RBCs, the Hb is isolated via cell lysis, purified by sterile filtration and chromatographic techniques, and sterilized (e.g., by low heat) [64]. Using cell-free Hb presents the advantage of minimum antigenicity and improved oxygen diffusivity, due to the lack of interference by cell membrane. In fact, reported in the early twentieth century, suspension of cell-free Hb in lactated Ringer's solution was used to intravenously treat 15 patients; however, a large number of them developed renal toxicity and cardiovascular complications [64]. Similar results were also found in the 1950s when US Navy treated several patients with cell-free Hb [65]. Cell-free Hb was also found to have a very short circulatory residence time because the Hb tetramer rapidly dissociates into dimeric and monomeric forms that can bind non-specifically to plasma proteins or are captured by scavenging proteins devoted to this purpose (haptoglobin, hemopexin) and thus undergo rapid clearance by the reticulo-endothelial system (RES) into spleen and liver, as well as renal clearance

into kidneys, leading to Hb-induced toxicities in these organs [66, 67]. Additionally, cell-free Hb and its dissociated derivatives can also extravasate into the subendothelial domain of the circulatory system and rapidly sequester nitric oxide (NO), resulting in its conversion into nitrate (dioxygenation reaction) and of oxy-Hb to MetHb [68]. NO is an essential endogenous vasodilator (e.g., endothelial-derived relaxant factor) and therefore such NO scavenging results in vasoconstriction and cardiovascular complications, paradoxically, thereby diminishing tissue O_2 delivery. Furthermore, 2,3-DPG absence in plasma (as well as lack of Bohr and Haldane-based OEC "shifting," which is enabled in "intact" RBCs) leads to unnaturally high cell-free Hb oxygen affinity, limiting O_2 off-loading across physiologic O_2 gradients—further diminishing tissue O_2 delivery. Cell-free Hb can also change blood osmolarity, leading to alteration of blood volumes and associated side effects. Altogether, for these reasons, cell-free human Hb appears problematic for in vivo oxygen-carrying applications. Instead of human Hb, studies have also been conducted with bovine Hb, but this also presents similar issues of stability, extravasation, NO scavenging, and renal clearance and toxicity. Historically, an innovative approach to address some of these issues was by development of "designer" recombinant Hb (e.g., in *E. coli*) where targeted mutations decrease the likelihood of tetramer dissociation, optimize heme redox behavior, and modulate propensity for NO consumption, but an optimal combination of mutations that results in free-Hb performance similar to that observed for intraerythrocytic Hb remains elusive [69–71]. Recombinant technologies are also prohibitively expensive, in comparison to human or bovine sourcing for Hb. Therefore, a substantial volume of research has been directed to achieve in vivo stabilization and performance optimization via chemical modification of purified Hb utilizing techniques (alone or in combination) such as cross-linking, polymerization, and macromeric surface conjugations. The goals of these modifications are to reduce Hb dissociation, extravasation, and renal clearance, while maintaining reasonable circulation lifetime and O_2-transport capacities.

Chemically Modified HBOCs

Hb tetramers can be cross-linked both intra- and intermolecularly. For example, intramolecular cross-linking in human Hb formed between its two α-subunits using acylation with bis-(3,5 dibromosalicyl)-fumarate (also known as Diaspirin) led to a product called HemAssist from Baxter, USA [57, 72, 73]. This product showed an increase in circulation residence time up to 12 h compared to <6 h for unmodified Hb, but in human trials, cross-linked Hb unfortunately led to a 72% increase in mortality compared to saline, and clinical trials were discontinued [74]. An analogous approach to cross-link the α-subunits of recombinant Hb using Glycine led to a product called Optro from Somatogen, USA, but this also resulted in increased risks of cardiac arrest and mortality [75–77]. Instead of site-specific intramolecular cross-linking only, polymerized Hb has also been created from using bifunctional cross-linking reagents like glutaraldehyde-based cross-linking of bovine

Hb (e.g., Hemopure originally from Biopure, USA, now HbO_2 Therapeutics, USA) or human Hb (e.g., PolyHeme from Northfield Labs, USA) and o-raffinose-based cross-linking of human Hb (e.g., the product HemoLink from Hemosol, Canada) [78, 79]. Such polymeric cross-linking creates higher-molecular-weight cell-free Hb that retains "simple" oxygen-binding properties (physiologic OEC shifting is not retained) while minimizing dissociation and rapid clearance observed for unmodified Hb tetramers, when free in plasma. One challenge in these approaches is to precisely control polymer molecular weight and geometry, and rigorous purification steps are necessary to ensure product quality. PolyHeme was reported to progress into Phase III clinical trials in the USA in treating trauma-associated blood loss and showed a decreased need of natural blood transfusions [77]. Clinical trials with HemoPure also showed a reduced need of additional blood transfusions in cardiac surgery [80]. HemoPure has received clinical approval in South Africa and Russia for acutely anemic human patients and is occasionally used on a compassionate basis in the USA. An analogous product from the same company (HbO_2 Therapeutics, USA) called Oxyglobin is currently approved in the USA for veterinary use, but has not gained widespread acceptance. HemoLink also advanced to Phase III clinical trials but was discontinued in 2003 when patients receiving treatment experienced adverse cardiac events. In fact, as noted in the meta-analysis which led to FDA stopping clinical trials for this HBOC class, all of these products in their clinical studies have shown various degrees of transient hypertension, organ damage through microvascular constriction and dysfunction, gastro-intestinal distress, nephrotoxicity, neurotoxicity, and increased mortality [52, 80–82].

Instead of intramolecular cross-linking and intermolecular polymerization, Hb modification has also been carried out with macromeric bioconjugation to increase stability and vascular residence time while reducing immune recognition [83–85]. Important examples of this approach are found in polyethylene glycol (PEG) modification (e.g., the products Hemospan from Sangart Inc., USA, and PEG-Hb from Enzon, USA) and poly(oxyethylene) modification of pyridoxylated cross-linked Hb (e.g., the product PHP from Apex Bioscience, USA). PEG-ylated Hb products have undergone extensive clinical trials, and the studies showed risks of bradycardia and elevation of hepatic pancreatic enzymes even at low doses [86]. Nonetheless, the Phase I and Phase II clinical trials showed that Hemospan was well tolerated in humans for efficient oxygen delivery, and Phase III trials in orthopedic surgery patients were carried out in Europe [87]. The trials suggested that the risk of cardiovascular and renal dysfunction still persisted with such chemically modified Hb products. During the past two decades, it has been identified that cell-free Hb (including chemically modified versions) are potent scavengers of nitric oxide (NO) via rapid irreversible binding (rate constant ~10^7 M^{-1} s^{-1}), which in turn can affect systemic and pulmonary vascular tone, resulting in vasoconstriction, hypertension, and lowering of cardiac output [88, 89]. A resolution of this issue has been attempted by (NO pre-loading) Hb modifications, such as S-nitrosylation of cysteine residues in the β-subunits of Hb; however, this approach is critically constrained by natural limits imposed by simple stoichiometry [90]. Of note, RBCs contain anti-oxidant enzymes, such as catalase (CAT) and superoxide dismutase (SOD) that mitigate

oxidative stress arising from Hb-generated superoxide. In an interesting approach, these enzymes have been cross-linked to polymerized Hb to form PolyHb-SOD-CAT, which has shown combined advantages of long circulation time and reduced oxidative damage [91, 92]. Another interesting approach is to incorporate regulatory molecules such as 2,3-DPG and methemoglobin reductase along with Hb in appropriate HBOC systems, to prevent hemoglobin oxidation [93]. In recent years, a product named HemoTech has been reported that uses purified bovine Hb cross-linked *intra*molecularly with ATP and *inter*molecularly with adenosine, and conjugated with reduced glutathione (GSH) [94]. This unique design employs pharmacologically active molecules (ATP, adenosine, and GSH) as the chemical modifiers, in that ATP is intended to regulate vascular tone through purinergic receptors, adenosine is intended to counteract the Hb-based vasoconstriction via stimulating adenosine receptors, and GSH is intended to protect heme from NO and various reactive oxygen species. Pre-clinical and early-phase clinical studies have shown that HemoTech works as an effective oxygen carrier in treating blood loss, anemia, and ischemic vascular conditions, and further studies are warranted [95]. Another polymeric Hb reported in recent years is OxyVita®, which is produced through modification of a zero-linked polymerization mechanism using carbodiimide chemistry on bovine tetramer hemoglobin to produce "super-polymeric" macromolecules [96]. In yet another recent approach, a polynitroxylated PEG-ylated hemoglobin (PNPH) nanostructure design has been reported, named VitalHeme™ (SynZyme Technologies LLC, Irvine, CA), where PEG-ylated hemoglobin is covalently modified with catalytic-caged NO [97]. These designs reportedly allow for higher Hb stability in vivo and are currently under pre-clinical investigation. Figure 11.2 shows some of the prominent designs based on chemical modification of cell-free Hb that have undergone (or are still undergoing) pre-clinical and clinical evaluation for oxygen transport. In spite of promising pre-clinical results, many of the chemically modified Hb products have been withdrawn from clinical studies and discontinued in production, due to indication of clinical risks stemming from chemical heterogeneity and variable stability of final product, suboptimal vascular residence time, non-ideal oxygen loading and off-loading capabilities, rapid irreversible conversion to methemoglobin, and increased cardiovascular and renal dysfunction issues. While some of the newer products are refining their design and processing to address these issues, a "next-generation" approach has focused on Hb encapsulation within various micro- and nanocarrier vehicles, to more closely mimic the physiological encapsulated state of Hb in RBCs.

Encapsulated HBOC Systems

During the past two decades, particulate drug delivery platform technologies (microparticles and nanoparticles) have revolutionized the packaging and delivery of pharmaceutical compounds, by encapsulating active compounds/biologics to protect them from plasma-induced effects, increase their circulation time, and allow sustained availability to cells, tissues, and organs. This design concept has also been

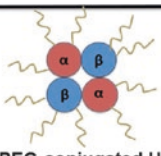
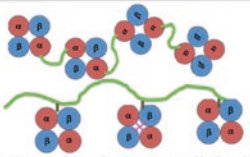
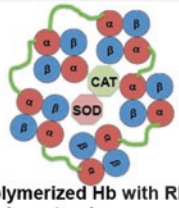
Chemically modified Hb based HBOCs	Materials used	Representative Design Names
 Pure cell-free Hb	Cell-free Hb obtained from human, bovine, salmon and recombinant sources	Cell-free Hb
 Intramolecularly crosslinked Hb	Cell-free Hb crosslinked between subunits, with agents like glycine, glutaraldehyde, O-raffinose, 3,5-dibromosalicyl fumarate, pyridoxal-5-phospate etc.	HemAssist (Baxter) Hemopure (BioPure) Optro (Somatogen) Hemolink (Hemosol) etc.
 PEG-conjugated Hb	Cell-free Hb conjugated on the surface by Maleimide-activated Polyethylene glycol (i.e. Hb-Mal-PEG)	Hemospan (Sangart) etc.
 Intermolecularly crosslinked and polymer-tethered Hb	Cell-free Hb intra- and inter-molecularly crosslinked or tethered from polymer chains by agents like glutaraldehyde, poly-oxy ethylene, O-raffinose etc.	PolyHeme (Northfield Lab) Pyridoxylated Hb or PHP (Apex Bioscience) etc.
 Polymerized Hb with RBC-relevant redox enzymes	Cell-free inter-molecularly crosslinked or polymer-tethered in multiple copies and associated with enzymes like superoxide dismutase (SOD), catalase (CAT) etc that can maintain redox environment for efficient Hb activity .	Poly-Hb-SOD-CAT etc.

Fig. 11.2 Representative approaches and design schematics for HBOCs based on chemical modification (cross-linking, surface modification, polymerization, etc.) of Hb that have undergone significant pre-clinical and clinical evaluation. (From 2017 Military Supplement: Hemoglobin-based Oxygen Carriers Current State-of-the-Art and Novel Molecules, Anirban Gupta, Shock Injury, Inflammation and Sepsis, Oct 3, 2018, Publish Ahead of Print, Figs. 1–4, with permission of Wolters Kluwer Health, Inc.)

adapted to create HBOCs that encapsulate Hb within suitable particulate vehicles. In fact, the pioneering concept and demonstration of "bio-artificial cells" was presented as early as the 1950s and 1960s by Chang and colleagues, by encapsulating Hb as well as other proteins and enzymes within polymeric membrane-based microvesicles. The membrane material originally used was collodion (cellulose nitrate) and later changed to biodegradable polyethylene glycol-polylactide (PEG-PLA) [98, 99]. These Hb-loaded microvesicles, aptly termed "hemoglobin

corpuscles," showed oxygen equilibrium curves similar to RBCs and also allowed coencapsulation and activity of RBC-relevant enzymes like 2,3-diphosphoglycerate (2,3-DPG), carbonic anhydrase, and CAT [100–102]. However, in these systems, a major challenge was posed by the rapid macrophagic uptake and clearance of these micrometer-sized vesicles from circulation, resulting in suboptimal circulation residence time for in vivo use. Reducing the diameter to ~1 micron only marginally improved the circulation lifetime, and a significant research effort has been directed toward further improving the vascular residence time by modifying the surface of the vesicles with lipids and polysaccharides. In another similar design approach, Djordjevich et al. reported on encapsulation of Hb in micron and submicron size lipid vesicles (liposome-encapsulated Hb or LEH), with membrane made of phospholipids and cholesterol [103–105]. A number of variations of this design have followed, e.g., "neohemocytes," "TRM-645 Neo Red Cells," etc., where the primary focus has been to maintain uniform Hb-encapsulation levels and uniform size distribution of the vesicles, minimize vesicle destabilization or fusion over time, and enhance storage stability of the vesicles while maintaining the RBC-analogous oxygen transport properties of the encapsulated Hb [106–108]. During the 1990s, the "Stealth Liposome" technology was clinically established, where lipid nanovesicles (100–200 nm in diameter) were surface-functionalized with polyethylene glycol (PEG) to enhance storage stability, reduce opsonization, and prevent rapid macrophagic uptake, and this significantly enhanced the circulation residence time [109, 110]. Consequently, this technology was adapted to form Hb-encapsulated PEGylated liposomal vesicles (HbV) [111–113]. 1,2-Dioctadecadienoyl-sn-glycero-3-phosphatidylcholine (DODPC) was used as the major membrane phospholipid for HbV preparation, such that γ-irradiation-induced radiolysis of water molecules in the vesicles generated hydroxy (-OH) radicals that promoted intermolecular polymerization of dienoyl groups to produce highly stable liposomes that could withstand freeze-thawing, freeze-drying, and rehydration processes. The HbV design has shown substantial improvement of circulation lifetime (~60 h in some animal models), and several refinements of this design have been recently reported [114–118]. The oxygen transport ability of these HbV systems was found to be similar to natural RBCs, with comparable oxygen saturation and release kinetics. Also, the liposomal encapsulation of Hb attenuated its NO scavenging effect and thereby appears to reduce the associated negative effects on vasculature. Hb encapsulation in liposomal vesicles also prevented glomerular clearance of Hb (since liposomes are too big for renal clearance) and therefore reduced nephrotoxicity. The current optimized HbV product contains about 30,000 Hb molecules encapsulated within one PEGylated liposomal vesicle of ~250 nm in diameter. In comparison, a natural RBC is ~7 μ in diameter and ~2 μ in thickness, containing about 250 million Hb molecules. HbVs have undergone extensive pre-clinical evaluation in suitable animal models for potential use as an RBC surrogate in transfusion and resuscitative mitigation of massive hemorrhagic shock and hemodilution incidents, and oxygenation of ischemic as well as transplanted tissues and organs. Although these studies have shown promise of HbVs as RBC surrogate oxygen carrier, these systems still present issues of broad size distribution of the vesicles, variation in Hb-encapsulation efficiencies,

as well as variable pharmacokinetics and complement-mediated immune response in vivo. Further research is currently directed toward resolving these issues for potential clinical translation of HbV designs as well as other analogous designs of liposome-encapsulated hemoglobin (LEH) systems as RBC surrogates (114–118). Interestingly, instead of encapsulating Hb, others have attempted to encapsulate oxygen (O_2) directly within phospholipid microvesicles (2–4 μm in diameter) to deliver O_2 to deoxygenated RBCs in circulation [119, 120]. Although these oxygen-loaded microbubbles were found to be stable for a few weeks in storage with only small extent of oxygen loss, in vivo they were found to have a very short circulation lifetime (<1 h). Therefore, treatment with these systems would require multiple dosing, which may prompt negative effects of dysregulated oxidative stress and associated toxicity and immune response. Therefore, long-term safety profile of such technologies needs to be rigorously evaluated.

Encapsulation of Hb has also been studied in other microparticle and nanoparticle systems other than lipid vesicles. In pioneering work by Chang et al., Hb was encapsulated within polymeric nanoparticles (80–200 nm in diameter) made from PEG-PLA and analogous block-copolymers [121, 122]. These polymeric nanoparticles allow oxygen transport kinetics of Hb at levels similar to natural RBCs, and the polymeric material could be engineered to be biocompatible and biodegradable. Furthermore, enzymes that maintain the redox environment for Hb stability and function regulation (e.g., carbonic anhydrase, CAT, SOD, MetHb reductase, etc.) could also be encapsulated within the same nanoparticles toward further mimicry of "natural" RBCs [123]. This design approach has also been adopted for other polymer systems including poly(ε-caprolactone)/poly(L-lactic acid) (PCL/PLA) copolymers, poly(L-lysine) (PLL), poly(lactic-co-glycolic acid) (PLGA)/PEG copolymers, etc. [124, 125]. Amphiphilic block-copolymer systems also provide the ideal building blocks for designing polymer vesicles, otherwise known as polymersomes, analogous to liposomes. These polymersome systems have been recently utilized to create polymersome-encapsulated Hb (PEH) systems [126]. Hb loading in these PEH systems is reportedly 1–2 mg/mL, compared to human blood (i.e., within RBC) concentration of ~150 mg/mL. Utilization of hollow fiber-based membrane extrusion system has provided an automated way to manufacture these PEH systems [127]. These PEH systems are reportedly capable of encapsulating both bovine and human Hb, and have shown oxygen equilibrium kinetics and other biophysical parameters similar to RBCs. This suggests considerable promise toward the application of such PEH systems as RBC surrogates, but currently very limited in vivo evaluation data is available for these systems. A potential issue with polymersome systems may be their higher shell thickness compared to liposomes, which may increase oxygen diffusion time beyond the (low millisecond) time window required for physiologic gas exchange during circulatory transit. Modulation of polymer molecular weight of the shell components, and therefore of the shell thickness, can provide a unique way to influence oxygen flux properties of PEH systems. Higher stability of polymersomes compared to liposomes, both in storage and in vivo, is an additional advantage for use as Hb-encapsulated RBC surrogate systems. Ongoing and future studies with these systems should be directed toward

establishment of batch-to-batch consistency, sterilization metric and storage stability evaluation, post-sterilization Hb bioactivity determination, in vivo pharmacokinetics and biodistribution determination, and therapeutic evaluation in appropriate animal models (e.g., hemorrhagic shock, ischemia, etc.). Figure 11.3 shows some representative designs and components for encapsulated Hb systems that have undergone and are currently still undergoing in vitro and in vivo evaluation for RBC-mimetic oxygen carrier application.

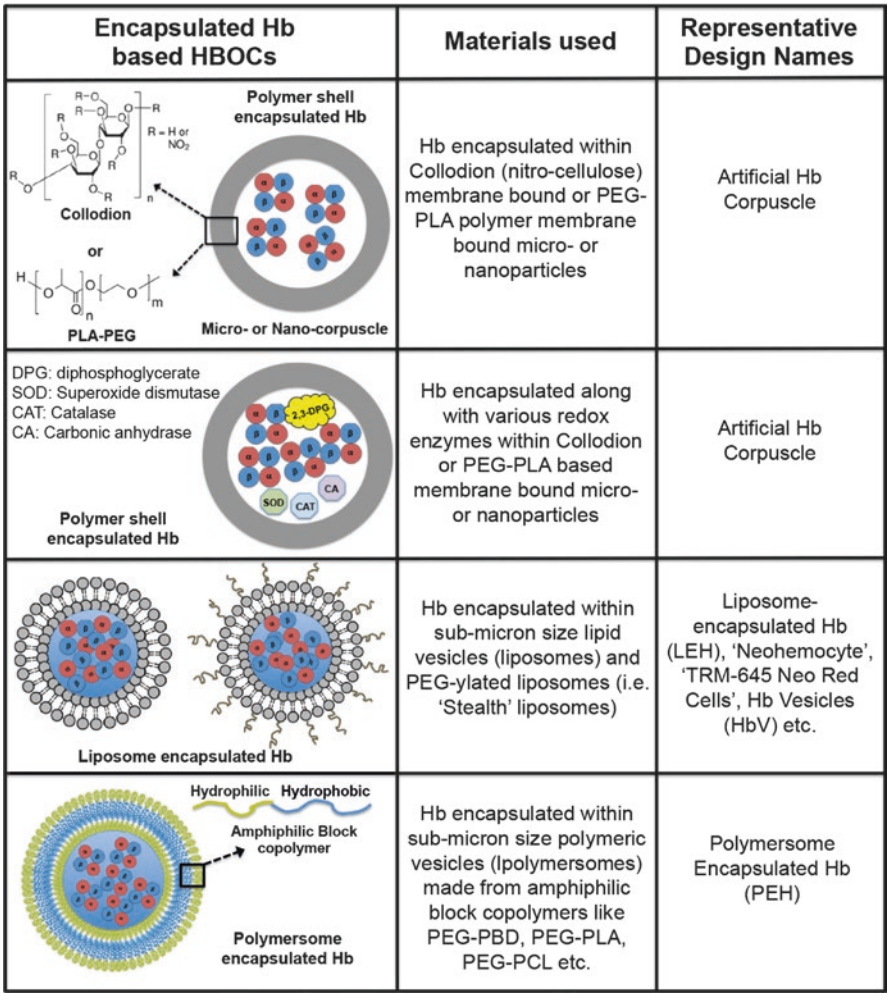


Fig. 11.3 Representative approaches and design schematics for HBOCs based on encapsulation of Hb in microparticle and nanoparticle systems that have undergone significant pre-clinical evaluation and hold clinical promise. (From 2017 Military Supplement: Hemoglobin-based Oxygen Carriers Current State-of-the-Art and Novel Molecules, Anirban Gupta, Shock Injury, Inflammation and Sepsis, Oct 3, 2018, Publish Ahead of Print, Figs. 1–4, with permission of Wolters Kluwer Health, Inc.)

Novel Molecules and Designs Incorporating Hb as O_2 Carrier

The focus of this section is to not distinguish between "chemically modified" and "encapsulated" Hb systems, but rather describe and review emerging novel designs and technologies that incorporate Hb for oxygen transport purposes. In one interesting approach, instead of Hb, PEG-ylation was carried out on bovine carboxyhemoglobin (CO-Hb), and the resultant PEG-CO-Hb system has been evaluated for oxygen transport (and CO transport) properties [128–130]. The rationale behind this design is that endogenous CO produced from (hypoxia-enhanced) heme-oxygenase activity is reported to render cytoprotective and homeostatic effects, such as inhibition of apoptosis and inflammation and reduction of oxidative stress and vasodilatory activity [131]. The PEG-CO-Hb product (Sanguinate, Prolong Pharmaceuticals, South Plainfield, New Jersey, USA) has undergone pre-clinical evaluation in small animal models, and is now in Phase I/II clinical trials for sickle cell anemia, thrombotic thrombocytopenic purpura (TTP), and ischemia after subarachnoid hemorrhage, with promising safety profile and oxygenation parameters. In another approach, core-shell cluster structures were formed by conjugating human serum albumin (HSA) on Hb using Hb surface lysines conjugated to HSA cysteine-34 using α-succinimidyl-ε-maleimide cross-linker [132]. These Hb-HSA clusters reported lower risk of rapid clearance and extravasation and thus improve circulation residence time. Further modification of these Hb-HSA core-shell nanoclusters was recently reported in which antioxidant enzymes and platinum nanoparticles were embedded in HSA pockets for Hb protection [133]. Thus far, this nanocluster design has been evaluated only in vitro, for oxygen-binding capacity, redox properties, and stability, with promising results. However, rigorous in vivo pharmacokinetics, toxicology, biodistribution, and oxygenation studies, along with demonstrating batch-to-batch compositional and functional consistency, are needed to establish in vivo utility. In another approach, Hb has been loaded in microparticles by coprecipitation with calcium carbonate ($CaCO_3$), followed by glutaraldehyde cross-linking and $CaCO_3$ dissolution, resulting in Hb payload density approaching that of RBCs [134]. However, although these Hb microparticles demonstrate oxygen equilibrium kinetics similar to free Hb (affinity too high for O_2 release under physiologic conditions), the circulation lifetime is significantly extended, compared to free Hb. Analogous Hb microparticles carrying about 80% Hb content compared to RBCs have been reported where Hb and $MnCO_3$ were coprecipitated, immediately followed by human serum albumin addition for encapsulation and stabilization of the particles [135]. These particles have shown reduced risks of NO scavenging and associated effect on vasoconstriction. In yet another recent approach, Hb was covalently conjugated directly to the hydrophobic or hydrophilic domain of block-copolymers, and the resultant conjugates were self-assembled to form Hb-loaded micelles [136, 137]. In another interesting design, $MnCO_3$ nanoparticles were used as templates to deposit layer-by-layer (L-B-L) assemblies of Hb and dialdehyde heparin (DHP), followed by cross-linking to stabilize the layers and selective dissolution of the template core [138]. A similar approach was also used to

form L-B-L-coated nanotubes where alternate layers of Hb, DHP, and the enzyme CAT were deposited, to create systems for potential application in treating oxidative stress [139]. These complex nanostructures have been characterized in vitro for their morphology, stability, cytotoxicity, and in some cases biofunctionality, but pre-clinical evaluation for oxygen carrying efficacy in vivo is not yet reported. Another recent exciting development in the area of novel HBOC molecules is the utilization of large-molecular-weight extracellular Hb isolated from marine invertebrates like polychaete annelid (e.g., the product HEMOXYCarrier from Hemarina, France) [140]. Pre-clinical studies with this unique Hb molecule have shown reduced microvascular vasoconstriction and no significant impact on mean arterial blood pressure, compared to other HBOCs that utilize bovine or human Hb [139]. Further investigation of this system is currently ongoing to evaluate its potential as a clinical oxygen carrier therapeutic system.

In recent years, some Hb-encapsulation approaches have also focused on adapting the physico-mechanical properties of natural RBCs that significantly influence their biological functions. Healthy RBCs have a biconcave discoid morphology, with a diameter of ~8 μm and a thickness of ~2 μm. These RBCs are also highly flexible (Young's modulus 0.1–0.2 kPa) that enables them to change their morphology when passing through microvascular circulation [141, 142]. The mechanical integrity and viscoelastic nature of RBCs during their cyclical deformation is rendered by a two-dimensional spectrin network that exhibits context-variable stiffness and tethering to the cytosolic membrane surface. Oxygen loading results in RBCs having significantly more deformability than oxygen unloading, and this enables the flexibility RBCs require to efficiently transit the microvasculature. RBC size, shape, and flexibility also influence their movement and distribution in the blood flow field, where they mostly reside in the center of the parabolic flow field in mid to large vessels, while in small vessels and capillaries, RBCs distribute throughout for efficient oxygen exchange [143, 144]. These considerations have recently led to biomaterials-based mimicry of RBC's physical (size, shape, and flexibility) attributes into Hb-encapsulating synthetic constructs. For example, polyelectrolyte-driven layer-by-layer assembly has been used to create microparticles that mimic the shape and deformability of natural RBCs [145]. In this approach, Hb and BSA were electrostatically deposited on the surface of discoid PLGA particles of ~7 μm diameter and 400 nm shell thickness, and then the PLGA core was selectively dissolved to yield RBC-shaped Hb-loaded particles that have high elastic deformation. Similar RBC-mimetic flexible particles have been fabricated using PEG hydrogel system in a stop-flow-lithography (SFL) approach where the mechanical properties of resultant particles could be controlled by modulating cross-linking density of the hydrogel systems [146]. In a different approach, RBC shape-mimetic particles were fabricated from acrylate hydrogels using a "particle replication in non-wetting templates" (PRINT®) technology [147]. These particles were made in 2–3 μm molds, such that, upon hydration, the particles swelled to disks with ~6 μm diameter and ~1.5 μm thickness. Also, the meniscus

effect from the molds resulted in the particles being thinner in the middle and thicker at the edges, resembling the biconcave morphology of RBCs. RBC morphology and flexibility mimicking particle designs made through these two techniques have demonstrated in vitro elastic deformation capabilities sufficient for transport through narrow channels, and controllable circulation lifetime in vivo, depending on their elastic modulus. Although these particles have been reported to be capable of Hb encapsulation via physical trapping or covalent bonding, detailed oxygen transport capabilities and associated in vivo transfusion applications have not been reported. In another interesting approach, liposome-encapsulated actin-hemoglobin (LEAcHb) constructs were prepared using a polymerized actin core, to mimic morphology of natural RBCs [148]. Although these particles were much smaller (~140 nm) than RBCs, the biconcave shape along with the mechanical support of the membrane improved the half-life to ~72 h. In natural RBCs, the negative surface charge electrostatically prevents RBC aggregation over a distance of 20 nm, and this rationale has led to some research in mimicking RBC-relevant surface charge on Hb-encapsulating PEG-PLA nanoparticles (<200 nm in diameter) using cetyltrimethylammonium bromide (CTAB) or anionic sodium dodecyl sulfate (SDS) surfactants [149]. Of note, cationized particles were found to have a half-life of ~11 h (8-fold higher than untreated particles), while the anionized particles were quickly eliminated, giving a half-life of <1 h. In yet another particularly innovative approach, a biosynthetic artificial RBC (ErythroMer) has been developed following a formal "bioinspired" design principles and is reported to closely emulate RBC physiology, particularly under physiologic stress by preserving cooperative O_2 binding/dissociation and by linking O_2 affinity to biochemical cues of aerobic sufficiency, while inhibiting methemoglobin (metHb) accumulation and NO sequestration [150]. Importantly, this design is crafted to enable sterile, lyophilized storage suitable for rapid reconstitution even in remote/austere environments. Moreover, due to unique shell properties, this polymeric particle is expected to be immuno-silent, with limited complement activation or other immune-related reactions. ErythroMer is based upon a novel amphiphilic polymeric system that employs polyethylene imine (PEI) grafted to palmitic acid that self-assembles to form payload-bearing toroidal-shaped nanoparticles (termed nanobialys, ~200 nm diameter) that encapsulate Hb, as well as maintain both physiologic, context-responsive O_2 affinity and a reductive environment to retard the rate of metHb accrual by coencapsulation of the synthetic allosteric inhibitor RSR-13 and leuko-methylene blue [150]. These novel Hb-containing particles, termed, have shown promising oxygen transport in vivo in rodent models of hemorrhagic shock/resuscitation and near-complete exchange transfusion. Detailed biocompatibility studies (e.g., for PEI which can pose cytotoxicity issues), circulation lifetime and stability, Hb-loading capacity and oxygen transport capabilities, etc. must be further evaluated to establish the clinical potential of such designs as RBC surrogates in transfusion medicine. Figure 11.4 shows design schematics of these novel emerging designs and structures for Hb-based oxygen carriers.

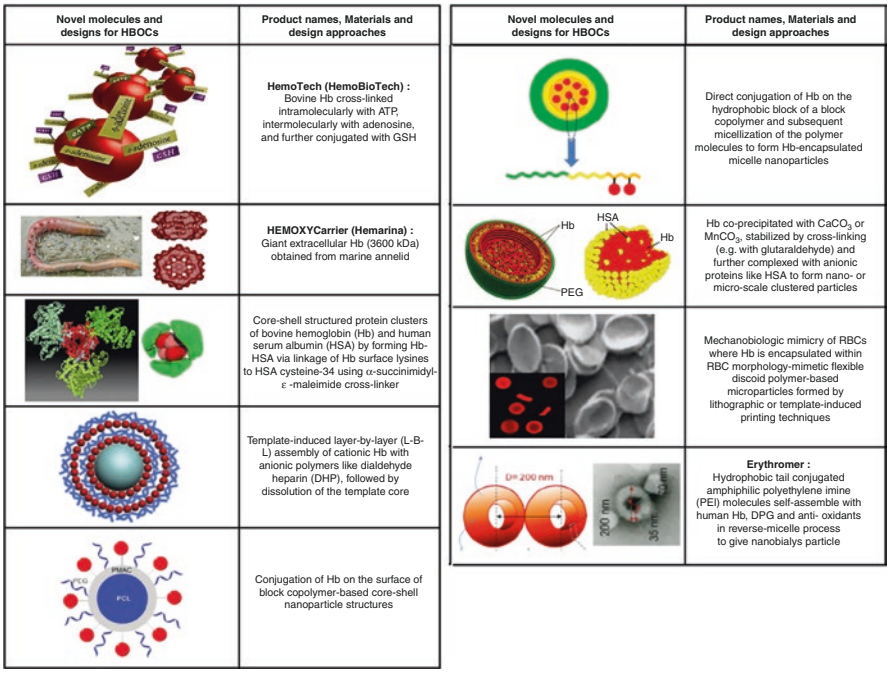


Fig. 11.4 Representative schematics for novel HBOC molecules and designs, including new polymerization strategies, new sources of Hb, and novel encapsulation and biomimetic strategies that are currently under development and pre-clinical evaluation. (From 2017 Military Supplement: Hemoglobin-based Oxygen Carriers Current State-of-the-Art and Novel Molecules, Anirban Gupta, Shock Injury, Inflammation and Sepsis, Oct 3, 2018, Publish Ahead of Print, Figs. 1–4, with permission of Wolters Kluwer Health, Inc.)

Current State-of-Art and Future Perspectives

In traumatic injuries and hemorrhage, tissue oxygenation is severely compromised, resulting in drastic, progressive damage to vital tissues and organs. Therefore, rapid hemorrhage control and restoration of tissue oxygen are critical to optimizing outcomes. To this end, timely transfusion of whole blood or balanced ratio administration of blood components (RBCs, platelets, and plasma) has become the current clinical standard. However, these blood products currently present significant logistical challenges with regard to widespread usage in austere battlefield and prehospital settings, where trauma- and hemorrhage-related morbidities and mortalities become significant, particularly in the context of prolonged field care scenarios. One potential solution is the bioengineering of semisynthetic or synthetic surrogates of blood components that are specifically designed for facile use in this challenging environment. In this framework, one important category of technology is that of Hb-based oxygen carriers (HBOCs), which provide the oxygen transport properties of RBCs while enabling higher availability (via in vitro large-scale manufacture),

universal applicability (no need for blood type matching), reduced contamination risks (due to sterilization), and longer shelf-life under ambient conditions (for some designs). While a wide variety of approaches have been dedicated to creating HBOCs, with some advancing to clinical trials, major risks associated with cell-free Hb (e.g., short circulation lifetime, renal clearance and associated toxicity, NO scavenging and associated vasoconstrictive/hypertensive side effects, etc.) have led to negative clinical outcomes and deep concerns for viability of this therapeutic class. As a result, no HBOC has attained FDA approval for human use, although one product (HemoPure or HBOC-201) is approved for (restricted) human use in South Africa and has been, under special circumstances, dispensed for compassionate use provision in the USA and Europe [151]. Other HBOC products (PolyHeme, Hemospan, and HemoTech) all advanced to different levels of clinical trials (e.g., Phase I for HemoTech, Phase II for Hemospan, and Phase III for PolyHeme); however, further studies are needed to establish their clinical safety and efficacy profiles. In many clinical studies, functional efficacy comparison has been to natural RBC transfusion, and, though HBOCs have demonstrated a reduction in the number of RBC transfusions, it remains to be answered whether HBOCs are suitable as "RBC substitutes" or rather as "oxygen carriers" in scenarios in which natural RBCs are either unavailable or undesirable. Future considerations of clinical study design should utilize this framework to compare HBOCs to relevant "standard of care" (e.g., saline or plasma expanders in pre-hospital trauma) instead of RBCs, to most appropriately evaluate real-world comparative risk/benefit in this context. Other questions that remain are whether these chemically modified and polymeric HBOC designs based on cell-free Hb have adequately addressed issues of NO scavenging (associated hypertensive effects) and heme toxicity. Newer HBOC designs, both chemically modified cell-free Hb (e.g., HemoTech) and encapsulated Hb (e.g., LEH, PEH, ErythroMer etc.), are still undergoing rigorous pre-clinical evaluation to elucidate and establish batch-to-batch consistency, mechanism of action, pharmacokinetics and biodistribution, tissue oxygenation capability, and in vivo safety profiles. In this framework, it remains to be seen if "encapsulated" Hb designs are superior to chemically modified cell-free systems, in terms of allowing coencapsulation of oxygen affinity regulatory and redox environment preserving molecules. It is important to note here that such multicomponent design will add manufacturing costs and thus the cost–benefit analysis need to be rigorously validated in appropriate pre-clinical models, before clinical studies and translation. Going forward, there is a significant need to systematically study cell-free chemically modified polymeric Hb designs versus encapsulated Hb designs (with or without effector molecule and anti-oxidant enzyme coencapsulation) in a suite of established anatomically and physiologically relevant pre-clinical animal model to compare circulation residence time, tissue oxygenation efficacy, NO scavenging-associated hypertensive risks and heme-associated toxicity, and importantly, suitability for pragmatic field use (both acutely and in prolonged field care scenarios).

Regarding Hb sourcing, most designs have utilized either human or bovine Hb, although some newer designs have adapted utilization of recombinant Hb where the physicochemical and biological properties can be precisely engineered, as well as

giant Hb sourced from marine invertebrates with salutary properties. One critical aspect regarding Hb sourcing for efficient HBOC design is the regulation of oxygen loading/off-loading capacity of the Hb used. For human Hb, this is regulated by allosteric effector molecules like 2,3-DPG, which maintains the P_{50} of human Hb at 26–28 mm mercury. However, oxygen affinity for cell-free human Hb (i.e., in absence of DPG) is much higher (OEC curve shifts to left), and this will lead to reduced oxygen release across any given physiologic gradient [152]. In contrast, oxygen affinity of bovine Hb is not critically dependent on DPG but rather on chloride ions, which are present in abundance in all mammals including humans. Bovine Hb has also been reported to have higher thermal stability than human Hb during isolation and processing [153]. Furthermore, while human Hb is sourced from outdated human units, bovine Hb can be obtained from dedicated farms and slaughterhouses and hence has more availability. Therefore, from availability, processing, and oxygen transport regulation standpoint, bovine Hb may provide benefit over human Hb and is used for Hemopure (or HBOC-201). However, both human and bovine sourcing share risk of infectious transmission, although this risk can be mitigated by appropriate processing and novel pathogen reduction technologies. Other alternative sources of Hb (recombinant technologies, annelid supramolecular extracellular Hb, etc.) should incorporate isolation and manufacturing costs, as well as physicochemical comparison of oxygen loading/off-loading aspects (with respect to human Hb), in order to successfully translate the corresponding HBOC designs to the clinic. Importantly, HBOCs designed with cell-free non-human Hb should also carefully analyze product immunogenicity, compared to encapsulated version of the same Hb. Other than Hb-based systems, oxygen carriers based on perfluorocarbons (PFCs) and iron (Fe^{2+})-containing porphyrin systems have also undergone significant pre-clinical and limited clinical evaluation, but an ideal oxygen carrier system for safe and effective in vivo use from this approach is yet to be realized. It is also important to note that the various HBOC systems should not be categorized as "artificial blood," but rather as a critical component of such a system. It is now unambiguously clear that attention to hemostatic blood components (platelets and plasma) is critical to successful resuscitation for hemorrhagic shock, and a significant volume of research has evolved in the area of platelet surrogates and plasma expanders, reviewed elsewhere [23, 24, 154–158]. Exciting advancements have also been made in recent years to develop "donor independent" RBCs (and platelets) from stem cells, AKA "blood pharming" [159–164]. In continuing evaluation and clinical translation of these technologies, it should be very important to consider and resolve manufacturing challenges (e.g., scaling up of complex multicomponent designs while maintaining batch-to-batch consistent quality and functional efficacy, etc.) as well as meticulously design pre-clinical studies in physiologically relevant animal models and clinical studies where current "standard of care" in the specific application is compared. Through such studies, it is envisioned that Hb-based oxygen carriers will revolutionize combat casualty care in pre-hospital and en route scenarios, as well as allow emergency management of civilian trauma in remote locations or when blood products are not immediately or sufficiently available.

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Intravenous Haemostatic Adjuncts

12

Jez Fabes and Simon Stanworth

Background and Methods

This chapter will address the use of four intravenous haemostatic agents as part of the resuscitative management of patients with major traumatic bleeding. It will describe the mechanisms of action and evidence to support the efficacy and safety of these agents in acquired bleeding. Although the focus will be on traumatic haemorrhage, emergency teams and clinicians are faced with major bleeding in many settings beyond trauma, and inevitably questions arise about the broader applicability of these agents.

The search methodology for this chapter has been based on search parameters undertaken for a Cochrane review [1] and by use of terms to cover all haemostatic agents in Medline and the Transfusion evidence library. In brief, the published Cochrane review describes a systematic review of the effectiveness of pro-haemostatic agents in acquired bleeding, other than rFVIIa. Searches for recent clinical trials of rFVIIa was undertaken by running the searches undertaken by prior Cochrane reviews and by reviewing cross-references in identified articles.

J. Fabes (✉)
Department of Anaesthesia, The Royal Free Hospital, London, UK
e-mail: jfabes@doctors.org.uk

S. Stanworth
NHS Blood and Transplant, Oxford University Hospitals NHS Trust, University of Oxford, Oxford, UK

P. C. Spinella (ed.), *Damage Control Resuscitation*,
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Tranexamic Acid

Haemostatic Agent Nature and Administration

Tranexamic acid (TXA; Cyklokapron) is a synthetic lysine analogue available as a 100 mg/mL solution. It now resides on the World Health Organization's List of Essential Medicines [2]. Recognised side effects are reported to include gastrointestinal upset, nausea, allergic reaction, visual disturbance, hypotension with rapid i.v. administration and seizures at high doses. Relative contraindications include a history of previous convulsions, renal failure (dose adjustment required), pregnancy, patients at high risk of thrombosis and massive haematuria. There is no evidence of teratogenicity in animal studies with the manufacturer recommendation that use in pregnancy should only occur if potential benefit outweighs risk. TXA crosses the placenta [3].

Pharmacology and Action

The antifibrinolytic action of TXA is mediated by reversible binding to lysine binding sites on plasmin and plasminogen and thereby competitively inhibiting binding to fibrin. This impairs the ability of plasmin to break down fibrin, inhibiting fibrinolysis and thereby maintaining the fibrin meshwork and promoting clot stability. The small size of TXA means that distribution is to all body compartments. Clearance is predominately through renal excretion of the unchanged drug with a plasma half-life of two hours [4].

TXA has approximately eight times the antifibrinolytic efficacy of the older synthetic lysine analogue ε-aminocaproic acid that requires a loading dose followed by continuous infusion to maintain therapeutic plasma concentration. As such, the use of ε-aminocaproic acid is now reserved for situations where TXA is not immediately available. The older antifibrinolytic agent aprotinin is no longer recommended in the trauma scenario due to a lack of benefit [5] and a consistently negative impact on mortality [6].

Indications, Efficacy and Safety

Hyperfibrinolysis, driven by protein C activation secondary to tissue hypoperfusion and injury, is a key component of trauma-induced coagulopathy (TIC) and is associated with a high mortality [7–10]. The CRASH-2 trial [5] (Clinical Randomisation of Antifibrinolytic therapy in Significant Haemorrhage) provides the main evidence base for antifibrinolytic intervention in adult blunt and penetrating trauma. This randomised controlled trial of over 20,000 trauma patients with, or at risk of, significant bleeding allocated patients to clinician-blinded doses of either placebo or 1 g TXA over 10 minutes followed by a further placebo or 1 g dose over 8 hours. TXA significantly reduced all-cause mortality from 16.0% to 14.5% (relative risk 0.91) and haemorrhagic deaths by 0.8% (relative risk 0.85), predominately through an

impact on exsanguination on the day of injury in those receiving TXA within 3 hours of injury [11, 12]. Importantly, administration after 3 hours significantly increased the risk of mortality secondary to bleeding (4.4% vs. 3.1% placebo mortality; relative risk 1.44).

While evidence in elective sugery shows that TXA reduces the need for blood transfusion [13], this is not borne out in Cochrane analysis of randomised trials in acute trauma [12]. However, the survival benefit of TXA in CRASH-2 may have led to surviving patients receiving blood where equivalent patients in the placebo arm would have died and hence not been transfused - eliminating any benefit of TXA on overall transfusion. Meta-analysis of 12 studies investigating TXA in orthopaedic trauma surgery showed a reduction in packed red blood cell (PRBC) for transfusion requirement (odds ratio 0.41) and bleeding mass without any increase in symptomatic thromboembolism (TE) [14]. Additional data supports the use of TXA in mature civilian trauma systems with a reduction in all-cause mortality and multiorgan failure in severely shocked patients, but not those without shock [15]. However, a *post-hoc* analysis of CRASH-2 suggests that TXA is of benefit regardless of severity of injury and should not be restricted to high risk or major haemorrhage patients [16].

The beneficial effects of TXA appear to be more pronounced the sooner it is given after injury, with delivery within an hour providing the greatest mortality benefit [11]. Meta-analysis of the CRASH-2 and WOMAN trials of TXA in trauma and major obstetric haemorrhage (MOH), respectively, showed that immediate TXA administration improved survival by more than 70% with efficacy decreasing by 10% for every 15-minute treatment delay until 3 hours, after which there was no benefit [17]. Administration of TXA beyond 3 hours after injury appears to be associated with an increased risk of harm [11] through fatal haemorrhage, although this was a post-hoc subgroup analysis with reduced precision. This has led the UK National Clinical Guideline Centre to recommend that empiric administration of TXA should be avoided more than 3 hours after injury without evidence of ongoing hyperfibrinolysis [18, 19].

Consideration should be given to the provision of TXA in a pre-hospital setting to minimise the time to delivery, although at present there is no robust evidence to support this approach [20–22]. Prospective data demonstrates that pre-hospital administration of TXA has beneficial effects on ROTEM indices of TIC with enhanced clot stability and reduced fibrinolysis [23]. TXA may also have a role in isolated traumatic brain injury. Prospective data from two randomised controlled trials (RCTs) of TXA vs. placebo in isolated traumatic brain injury demonstrates a reduction in haemorrhagic progression [24, 25] with a further RCT showing a non-significant trend towards improved mortality and outcome [26]. Retrospective observational data from Japan shows a significant reduction in 28-day mortality (10.0% vs. 18.4%) including in a subgroup with primary brain injury (6.0% vs. 13.2%) where TXA was given within 3 hours of injury [27].

The European guidelines on management of major bleeding and coagulopathy following trauma [28, 29] recommend TXA administration as early as possible to the trauma patient who is bleeding or at risk of significant haemorrhage (GRADE 1A [30]). These guidelines also highlight administration within 3 hours of injury in the bleeding trauma patient (Grade 1B) and that consideration should be given to

administration of the first dose of TXA *en route* to hospital (Grade 2C). The UK National Clinical Guideline Centre also recommends that TXA may be used in paediatric trauma by extrapolation from the CRASH-2 study and the good safety profile of TXA in paediatric patients [18].

TXA is a cheap and readily available intervention with a cost of around £45 [18, 31] per life year gained. However, Europe-wide audit [32] of trauma practice in 2015 showed that only 66% of centres are using tranexamic acid frequently; future audits will hopefully demonstrate an increase in uptake.

Dosing

Pharmacokinetic modelling of TXA levels in high injury severity patients receiving a single 1 g dose of TXA demonstrates that concentrations are likely to fall to a subtherapeutic level without additional dosing or infusion [33]. The European guidelines recommend a loading dose of 1 g infused over 10 minutes, followed by an i.v. infusion of 1 g over 8 hours [28, 29]. However, there is no efficacy or pharmacokinetic data supporting this dose, and higher doses are used in other settings, such as cardiac and orthopaedic surgery. Paediatric dosing uses the adult protocol for children over 12 years of age; younger children should receive 15 mg/kg (to a maximum of 1 g) followed by an infusion of 2 mg/kg per hour for 8 hours or until the bleeding stops, whichever is longer [34, 35].

Safety

The safety profile of TXA in trauma is good, with no evidence for an increased risk of venous thromboembolic events [12, 17, 36] and a reduction in the rate of arterial events [5]. High doses of TXA are a recognised precipitant for convulsive events in a dose-dependent manner although total TXA doses around 100 mg/kg may be required [37]. In the CRASH-2 cohort, however, there were not reported seizure events.

While hyperfibrinolysis is uncontrovertibly damaging, ineffective fibrinolysis has been suggested by some researchers to be harmful with evidence of a nadir in mortality with measures of fibrinolysis at 30 minutes between 0.81% and 2.9% [38, 39]. There is a reported concern regarding harm in patients receiving TXA without evidence of hyperfibrinolysis through fibrinolysis shutdown (LY30 below 0.8%). A retrospective review of trauma cases showed that those with fibrinolysis shutdown were more likely to have received TXA or cryoprecipitate [40]. The risk-benefit profile of TXA may be enhanced in the future through rapid viscoelastic testing (VET) markers of fibrinolysis such as measures of functional fibrinogen [41]. However, current recommendations are that provision of TXA in the context of haemorrhagic TIC should not be delayed to obtain VET-based evidence of hyperfibrinolysis [42].

Future Studies

The prospective Cal-PAT study assessing the feasibility of pre-hospital TXA administration to trauma patients with evidence of haemorrhagic shock has released interim data. This shows a significant reduction in blood product usage, a trend

towards lower 24-hour mortality (3.9% vs. 7.2%) without any increase in adverse events [43]. The ongoing PATCH study of pre-hospital TXA will also give further insight into this area [44].

The CRASH-3 study, [45] an international, randomised, placebo-controlled trial that has now completed recruitment, will assess the impact of early TXA administration on death and disability in isolated traumatic brain injury (TBI) patients. This will complement the ongoing study into pre-hospital TXA in moderate-to-severe TBI [46].

Further insight in this area may be derived from the ongoing ULTRA study [47] of the efficacy of TXA in preventing aneurysm rebleeding in non-traumatic subarachnoid haemorrhage and the recently analysed TICH-2 trial [48] of TXA in spontaneous intracerebral haemorrhage.

Fibrinogen Concentrate and Cryoprecipitate

Haemostatic Agent Nature and Administration

Fibrinogen concentrate (FgC; Fibryga, RiaSTAP) is provided in variable pathogen-inactivated doses around 1 g per vial in powdered form for i.v. use once reconstituted. Fibryga should be administered within 4 hours of reconstitution, while RiaSTAP contains human albumin and should be administered within 8 hours of reconstitution. FgC is derived from pooled human plasma and demonstrates comparable pharmacokinetics to native fibrinogen with a half-life of 80 hours (70 hours in paediatric patients).

Cryoprecipitated AHF (antihaemophilic factor), commonly known as cryoprecipitate, is derived from separating the cold-insoluble protein fraction from fresh frozen plasma (FFP) by centrifugation and constitutes a subset of clotting proteins present in a single unit of whole blood. This 5–20 mL volume can be frozen and stored for up to 1 year prior to use. A single unit of cryoprecipitate contains 150–250 mg fibrinogen, 100–150 units of vWF, fibronectin, 80 units of factor VIII and 50–75 units of factor XIII. Pooled cryoprecipitate, as used clinically, contains the cryoprecipitate from 5 to 10 units of FFP. Cryoprecipitate requires 10–30 minutes to thaw and should be administered through a standard transfusion filter within 4 hours. Blood group compatibility (but not Rhesus type) is preferred.

Indications, Efficacy and Safety

Fibrinogen, clotting factor 1, is the final common substrate in the clotting pathway and is enzymatically converted by thrombin to fibrin. Fibrin promotes clot stability and platelet activation through GPIIb/IIIa activation and also functions as antithrombin I, thereby regulating clot proliferation. Fibrinogen is distributed solely to the vascular compartment without any systemic reserve; hence, the 8–10 g of fibrinogen in the pre-morbid patient is very sensitive to haemorrhagic losses, consumption and dilution. Protein C activation is a key component of TIC and leads to significant

hypofibrinogenaemia [49, 50] such that fibrinogen deficiency is the commonest and earliest-detected clotting factor abnormality in TIC. Additionally, the physiological environment of trauma with haemodilution, acidosis, hyperfibrinolysis and hypothermia compound the situation through impaired fibrinogen function [51, 52].

Hypofibrinogenaemia, variably defined but typically as less than 1.5 or 2 g/L [53], is present in 25–70% of patients with haemorrhagic shock [49], more severe injuries and anaemia [54] and is associated with greater transfusion requirement [55] and worse outcomes [49, 53, 56, 57]. While it is clear that fibrinogen replacement in hypofibrinogenaemic coagulopathy improves outcomes [49, 56, 58, 59], prior to the availability of clotting results the initial approach to management of TIC and bleeding is contentious [60, 61]. The source of fibrinogen in initial resuscitation may be provided through either fibrinogen concentrate, FFP (which contains approximately 2 g/L fibrinogen), or cryoprecipitate.

While FFP administration maintains fibrinogen concentrations, it will not correct hypofibrinogenaemia [62] without infusion of around 30 mL/kg [63] and may worsen coagulopathy [50, 64, 65] and outcomes [61] with associated multiorgan failure [66, 67]. Because of these issues, FgC and cryoprecipitate have been assessed as alternative sources of fibrinogen. The choice between FgC or cryoprecipitate for fibrinogen supplementation is not clear with systematic reviews demonstrating no significant difference in outcomes [68, 69]. There is broad heterogeneity in institutional practice with cryoprecipitate [70], which is currently the leading source of fibrinogen in the UK, in contrast to the rest of Europe where FgC is more prevalent [71]. A key limitation of cryoprecipitate is delay in administration of typically 2 or more hours, by which time mortality may be 50% [72]. However, the CRYOSTAT study demonstrated that with appropriate infrastructure it is possible to administer cryoprecipitate within 90 minutes and generate fibrinogen levels above 1.8 g/L. [73]

Fibrinogen concentrate has the advantage of more rapid availability due to easy reconstitution and the lack of need for blood group matching as well as a smaller administration volume and hence lower risk of TRALI and TACO than FFP. FiiRST, a prospective study of FgC in haemorrhagic shock secondary to trauma, has shown the feasibility of administration within one hour of admission with no evidence of an increase in complications [74]. The early-fibrinogen in trauma (E-FIT) study will shortly report on the feasibility of providing FgC within 45 minutes of admission and maintenance of fibrinogen levels above 2 g/L in the face of ongoing bleeding across multiple UK trauma centres. While retrospective data of FgC administration in trauma shows a likely impact on survival, especially in patients with a higher injury severity score [75, 76], systematic reviews of FgC in surgery [77], trauma [78, 79] or haemorrhage [80] have not found any mortality benefit so firm conclusions cannot be drawn as yet. Similarly, while FgC in comparison to FFP [61] or cryoprecipitate [69] in broader haemorrhage settings demonstrates clinical efficacy, direct prospective comparisons are required.

Two grams of fibrinogen rather than high-dose FFP is appropriate in significant haemorrhage while clotting results are pending [81]. This is sufficient to maintain fibrinogen levels in the face of dilution by an initial transfusion of four units of PRBC. Clotting factor-only approaches to the management of TIC with FgC and/or

prothrombin complex concentrate (PCC) show clinical and viscoelastic testing (VET) efficacy with reduced transfusion requirement and mortality [82, 83]. Consequently, some national guidelines [84, 85] now support FgC as the primary intervention for fibrinogen replacement although the European guidelines [28] for the initial resuscitation of coagulopathy still support an FFP:RBC ratio of 1:2 or greater (Grade 1B evidence). Initial resuscitation based on admission Hb level is also likely to be of value [28] (Grade 1C) with consideration of a threshold of 10 g/L for intervention [54]. At present, robust, prospective data supporting either FFP-based strategies or direct fibrinogen supplementation is lacking [86]. The choice of the form of fibrinogen administered to patients will be dependent on local guidelines, institutional practice, product availability, clinician preference and expertise. Health economics are also likely to play a role as per gram of fibrinogen FgC is four times the cost of cryoprecipitate ($1140 vs. approximately $414) [87].

Where FgC or cryoprecipitate is administered, a point of care (POC)-based targeted approach to transfusion should be implemented. VET-guided fibrinogen substitution permits a reduction in blood product exposure and treatment cost without impairment of clinical outcomes [81, 88, 89]. Furthermore, POC- or VET-guided administration of FgC and PCC, without the use of FFP, may lead to a reduced requirement for PRBC and platelet transfusion with good clinical outcomes [59, 89]. Similar findings have been demonstrated in a range of perioperative settings with a 90% reduction in FFP usage and a reduction in the incidence of massive transfusion [90].

Fibrinogen Dose

The critical threshold of hypofibrinogenaemia is not clear, although the significant increase in risk profile around 2 g/L [53, 91] may represent a sensible supplementation threshold. Numerous approaches to fibrinogen supplementation dosing have been proposed, but no method is currently validated [92]. Hence, patients with haemorrhage and evidence of hypofibrinogenaemia (plasma fibrinogen below 2 g/L or ROTEM MCF below 7 mm [93]) should receive supplementation with repeat POC testing to titrate further intervention. While the PT and APTT are rarely deranged in hypofibrinogenaemia [94] and Clauss [95] assays have long turnaround times, FIBTEM [93, 96] and functional fibrinogen [97] assays are effective at identifying hypofibrinogenaemic coagulopathy and can be used to guide therapy. The initial dose of 3–4 g FgC or 15–20 units of cryoprecipitate recommended by the European guidelines on management of major bleeding and coagulopathy [28] would be expected to increase the plasma fibrinogen level by 1.5–2 g/L and the ROTEM MCF by 6–8 mm [90].

Safety

Overall FgC appears safe without a significant increase in the incidence of TE [98]. Recorded adverse reactions are non-specific and include fever, erythema, pruritus, musculoskeletal weakness and vomiting. Hypersensitivity reactions are recognised, however, and are a contraindication to use. As a human plasma product there is an inherent risk of transmission of viral and prion (i.e. creutzfeldt-jakob disease (CJD))

diseases, although with pathogen inactivation during preparation this risk is low. Safety data regarding fibrinogen infusion in a range of settings is being addressed by an upcoming Cochrane review of the efficacy and safety of prohaemostatic agents [1].

The risk of infectious transmission with a single unit of cryoprecipitate is equivalent to that of a unit of FFP or PRBCs; however, the pooling of cryoprecipitate from multiple sources means the risk per 'pool' is that of all constituent units summated. While this risk is very low, with a single case in the UK to date, progress in pathogen inactivation techniques may reduce this risk further [99]. Hypersensitivity reactions are recognised, and these are likely to be comparable in frequency and severity to those seen with FFP. The fractionated nature of cryoprecipitate results in a lower alloantibody count and therefore a lower risk of haemolytic transfusion reaction than FFP which can be reduced further with group matching.

Future Studies

The Pilot Randomized trial of Fibrinogen in Trauma Haemorrhage (PRooF-iTH) study is currently enrolling and will report on the efficacy and safety of first-line treatment with fibrinogen concentrate in trauma haemorrhage [100].

The Fibrinogen Concentrate in Trauma Patients, Presumed to Bleed (FI in TIC) study has completed recruitment and will provide RCT evidence comparing prehospital FgC to placebo in trauma [101].

The ongoing FEISTY trial is assessing the feasibility and efficacy of fibrinogen supplementation using VET-guided administration of FgC or cryoprecipitate [102].

CRYOSTAT-2 is currently recruiting to assess the impact of high-dose cryoprecipitate in the initial resuscitation of major traumatic haemorrhage [103].

Prothrombin Complex Concentrate

Haemostatic Agent Nature and Administration

Four-factor prothrombin complex concentrate (PCC; Beriplex, Octaplex, Kcentra) is derived from donor-pooled human plasma and contains human albumin, human antithrombin III and heparin. All formulations are reconstituted from lyophilised powder and infused slowly at room temperature.

Four-factor PCC contains significant levels of vitamin K-dependent clotting factors (II, VII, IX, X) and protein C and S. The composition of each 500 unit vial of PCC depends on the manufacturer and should be checked prior to administration, but typically contains:

- Factor II: 550 units
- Factor VII: 350 units
- Factor IX: 500 units

- Factor X: 750 units (NB Octaplex 500 units)
- Protein C: 550 units
- Protein S: 450 units

Of note, mass spectrometric analysis of Kcentra demonstrated 92 plasma proteins not included on the product insert, any number of which may contribute to the action of PCC in TIC and other settings [104]. Interestingly, in this analysis, Factor VII concentrations were very low (less than 1% that of prothrombin) highlighting the batch variability of this complex.

Indications, Efficacy and Safety

The role of PCC may prove to be limited outside of vitamin K antagonist (VKA)-related coagulopathy as thrombin generation is generally well maintained during trauma [105]. Furthermore, as clot instability is the major issue in TIC, platelets and fibrinogen are likely to be paramount in importance [106, 107]. However, PCC is likely to be an important part of concentrate-based approaches to TIC management, especially where there is evidence of delayed onset of thrombin generation.

PCC provides rapid factor replacement within a small administration volume and is indicated in patients with VKA-acquired coagulopathy, VKA-associated bleeding and urgent reversal of VKAs. There is very little evidence regarding the use of PCC outside the context of emergency reversal of VKA and potentially novel oral anticoagulants (NOACs), although it is licensed in most European countries for the management of acquired coagulopathy. Reversal of VKA-associated coagulopathy can be achieved within minutes [108, 109] compared to a number of hours with FFP. PCC can be administered rapidly and is a negligible volume in comparison to other transfusion products.

The rapid action of PCC and factor concentrates in enhancing thrombin generation and clot strength coupled with a minimisation of volume expansion and factor dilution might be expected to reverse coagulopathy more quickly than FFP.

Support for this comes from a limited number of retrospective studies assessing the empirical management of coagulopathic patients (defined as an INR $\geq$ 1.5). The addition of PCC to FFP-based management of TIC led to a reduction in PRBC and FFP use, more rapid correction of coagulopathy and a 5% absolute reduction in mortality [110]. Similar benefits were seen with the addition of PCC to FFP-based management of coagulopathic traumatic brain injury [111] with the additional advantage of shorter time to surgical intervention, an effect also seen in emergency general surgery [112]. A further retrospective study showed that the use of PCC in high-energy pelvic and limb fractures led to more rapid correction of coagulopathy and consequent surgical intervention as well as a reduction in PRBC and FFP requirement [113].

PCC is most commonly used as part of a factor concentrate-based management approach with fibrinogen and other concentrates, with additive effects on VET markers of coagulopathy [114]. A large retrospective database review [59] of clotting factor concentrates (FgC and PCC) compared to FFP in TIC showed

a comparable mortality, but the concentrate-only approach required significantly less PRBC and had an 80% absolute risk reduction for the incidence of multiorgan failure and shorter ventilation requirement. Similarly, a retrospective analysis [82] of data from the DIA-TRE-TIC study [115] showed that a clotting factor-based approach reduced PRBC and platelet exposure with an attendant reduction in multiorgan failure (18% vs. 37%) and sepsis compared to FFP-based management. A further retrospective study [88] showed TEG-guided concentrate-based management led to an avoidance of RBC transfusion in 29% of patients in the FgC-PCC group vs. 3% in the FFP group with comparable data for platelet transfusion.

The only prospective data regarding PCC use comes from the RETIC trial [116], a single-centre open-label RCT in Austria that assessed the impact of VET-guided management using clotting factor concentrates vs. FFP in trauma. While the limitations of this study make it difficult to draw conclusions regarding the efficacy of the two approaches, PCC was required in 16% of patients in the clotting factor concentrate arm compared to 100% of those receiving FFP, demonstrating it may play a key role as a component of algorithm- and VET-based strategies.

There is insufficient data available to make firm recommendations on the best approach to the management of either initial resuscitation or that following availability of clotting results when considering use of PCC. The current European guidelines [28] state that management could include FFP or clotting factors or a combination of both and supports the use of PCC in the setting of delayed coagulation initiation as represented by prolonged clot initiation (ROTEM-CT or TEG-R) times where fibrinogen levels are normal (Grade 2C).

Safety

The safety profile of PCC outside emergency reversal of VKAs is unknown [117, 118], but an association with raised thrombin levels and low antithrombin is recognised [119, 120]. PCC is known to increase subsequent arterial and venous thrombotic complications [121] and disseminated intravascular coagulation [122], suggesting early thromboprophylaxis should be implemented where PCC has been used. The use of PCC in reversal of VKA-related coagulopathy has an associated TE risk of around 4% [123, 124]. Complications in VKA reversal with PCC are lower than for FFP [125] with RCT evidence of fluid overload and similar cardiac complications in 12.8% of patients receiving FFP compared to 4.9% of those treated with PCC [126]. The use of a potent procoagulant in this patient cohort with a high TE risk must be balanced against benefit; dose titration may be achieved through VET measures of clot reaction time once fibrinogen is replete although there is insufficient data at present to support specific thresholds for VET measures of clot initiation time [42].

Hypersensitivity reactions rarely occur and may be severe requiring cessation of infusion, while low-grade reactions may respond to a slower rate of infusion. As a product of human plasma, transmission of infectious agents is possible despite donor testing and pathogen inactivation. A history of heparin-induced thrombocytopaenia is a contraindication to use, and prior episodes of disseminated intravascular coagulation are a relative contraindication unless bleeding is life-threatening.

Recombinant Activated Factor VII

Haemostatic Agent Nature and Administration

Recombinant activated human factor VII (rFVIIa; eptacog alfa, Novo-Seven) is produced through recombinant cell lines. It is comparable to the endogenous activated clotting factor VII although with a shorter plasma half-life (2 vs. 5 hours).

Physiological levels of the activated serine protease FVIIa, complexed with tissue factor (TF), act through catalysis of the activation of clotting factors IX and X in the extrinsic clotting pathway. At supraphysiological levels, it appears that rFVIIa functions on the activated platelet surface to enhance factor X activation and thrombin generation, independently of TF [127]. As such, deranged levels of substrates or cofactors like calcium, factor X, fibrinogen, prothrombin and platelets are likely to impair rFVIIa efficacy [128]. The activity of rFVIIa *in vitro* is very dependent on the physiological environment which should be borne in mind regarding its likely clinical efficacy. rFVIIa activity is reduced by 90% and the rFVIIa:TF complex by 60% in a pH of 7.0 [129], although rFVIIa appears to be resistant to temperature changes with full activity *in vitro* at 33 °C.

Indications, Efficacy and Safety

Prospective controlled interventional studies in trauma are challenging to perform [130] and as such the majority of evidence for rFVIIa is of low quality. Two parallel RCTs [131] assessing rFVIIa efficacy in blunt and penetrating trauma requiring six or more units of PRBC within 4 hours have been performed using high rFVIIa doses (200, 100 and a further 100 mcg/kg). Both cohorts receiving rFVIIa required less PRBC transfusions and were more likely to avoid massive transfusion (above 20 PRBC units; 14% vs. 33%), although only the blunt trauma cohort reached significance. A subgroup analysis of those patients requiring higher FFP doses showed that rFVIIa reduced the incidence of MOH and/or ARDS (3% vs. 20%). However, no mortality benefit from rFVIIa was found in these studies or the larger follow-up RCT [130], although the reduction in PRBC requirement was reproduced in keeping with retrospective studies in traumatic [132–134] and other forms [135] of haemorrhage. Additionally, some retrospective studies have identified that, while rFVIIa significantly reduces initial haemorrhagic mortality, longer-term mortality is unchanged due to multiorgan failure [136, 137]. Additionally, while early studies suggested efficacy in isolated traumatic intra-cranial haemorrhage, the literature is now inconsistent [138–141] with some evidence of harm and a lack of prospective data to support its use [142].

Two meta-analyses [143, 144] and a systematic review [145] of rFVIIa across all off-license uses confirmed a lack of mortality benefit despite a reduction in blood loss and PRBC transfusion requirement. A trend towards better outcomes was noted where rFVIIa was used therapeutically rather than prophylactically and at doses no greater than 90 μg/kg. Interestingly, this systematic review also identified a reduction in the incidence of ARDS in trauma patients treated with rFVIIa (risk

difference − 0.05) which may be attributable to the reduction in allogenic blood product transfusion required.

In keeping with the physiological sensitivity of rFVIIa, some experts feel that only a subset of patients respond to rFVIIa and this may explain the mixed results to date and the failure to demonstrate a mortality benefit in heterogeneous trauma cohorts. This has been noted in retrospective case reviews [146–149] demonstrating that patients with a pH under 7.2, platelet count under 100×10^9/L and systolic blood pressure under 90 mmHg at the time of rFVIIa administration have a poor response. For maximum efficacy, rFVIIa should therefore be given concurrent to efforts to optimise these conditions.

The high cost of rFVIIa at £3,700 in 2007 [150] for a single dose and limited evidence base for efficacy mean that guidelines for off-license use in trauma should be instituted and administration reserved for where life-threatening haemorrhage and coagulopathy have persisted despite all other routine measures. The European guidelines support the use of rFVIIa where resuscitation has achieved a platelet count above 50×10^9/L, fibrinogen above 1.5–2.0 g/L, haematocrit above 0.24 with concomitant administration of antifibrinolytics, correction of acidosis, core body temperature and ionised calcium levels along with surgical haemostasis have failed [28, 29]. This is supported by prospective multicentre data showing that an rFVIIa dose of 100 μg/kg was increasingly effective and led to better survival when a larger number of these criteria were met prior to rFVIIa administration [151]. Additional indications for use may include life-threatening bleeding where conventional therapy cannot be tolerated, is inappropriate or refused or where no other therapy is available.

Dose

There is significant variability in the published rFVIIa dose used [150] with no assay to determine optimal dose for a given patient or scenario. Expert opinion [152] based on data available in 2006 led to the recommendation of an initial dose of 200 μg/kg followed by two doses of 100 μg/kg. This formed the basis for the dosing regime in the existing RCTs of rFVIIa in trauma [130, 131] with pharmacokinetic modelling data to support the efficacy of this dose [153]. Meta-analysis of rFVIIa in major surgical haemorrhage showed that a dose of 50 μg/kg or above was required for significant treatment benefit [154]. However, some evidence in trauma cohorts supports a lower dose (48 μg/kg vs. 62 μg/kg) of rFVIIa as equally efficacious [155] and potential benefit for INR correction with doses as low as 20 μg/kg [141]. The best duration of therapy is also unknown and must be determined empirically by response to therapy, correction of coagulopathy and clinical correlation. Higher cumulative doses of rFVIIa in off-label settings associate with a higher incidence of thrombosis [145, 147]; hence the minimum effective dose should be sought for any given scenario.

Safety

The concern regarding arterial and venous TE complications with rFVIIa has been present since the expansion in off-license use [156]. A major issue with the current evidence base for rFVIIa is the limited range of licensing and hence its predominant

use for off-license indications often without clear guidelines or criteria for administration [157] and limited coordinated collection of complications. The prospective RCTs that have been performed with rFVIIa did not show an increase in the incidence of TE events in trauma [130, 131, 158]. This may be explained by the action of rFVIIa predominately in concert with the endogenous coagulation system and localisation of activity to those areas with tissue damage and TF expression; hence, the risk of systemic thromboembolic events may be minimised.

However, meta-analyses [143, 144] of off-license rFVIIa use demonstrated a trend towards increased overall thromboembolic complications with a statistically significant increase in arterial events (relative risk 1.45 [143]). Systematic review of off-license rFVIIa confirmed this increase in arterial events for medium- and high-dose rFVIIa [145], with comparable evidence from observational data [147]. One retrospective dose-correlation study showed no difference in the incidence of TEs between 30 and 100 μg/kg doses in a range of coagulopathic bleeding patients [159].

While the evidence for TE events in haemophilia, even at high doses, suggests that rFVIIa is safe, this young cohort of patients differs significantly from the patient cohort receiving off-license use of rFVIIa who more commonly have TE risk factors. A review of TEs in RCTs of rFVIIa use in off-license indications also showed that arterial events were more common among those greater than 75 years old (10.8% vs. 4.1%) [160]. This might explain the lack of increase in TE events in the trauma RCTs discussed above as the majority of this patient cohort were young and therefore at lower TE risk. The TE risk from rFVIIa is highest in patients with lower degrees of coagulopathy, pre-morbid risk factors for TE and those with direct vascular injuries [161].

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Colloids and Crystalloids

13

Arvin C. Gee and Martin A. Schreiber

Abbreviations

ARDS	Acute respiratory distress syndrome
ATLS	Advanced Trauma Life Support
DCR	Damage control resuscitation
FDA	Federal Drug Administration
HES	Hydroxyethyl starch
HSD	6% dextran-70 in 7.5% sodium chloride
HTS	Hypertonic saline
kDa	Kilodaltons
LR	Lactated Ringer's
mEq/L	Milli-equivalents per liter
mmHg	Millimeters of mercury
mOsm/L	Milli-osmoles per liter
MW	Molecular weight
NS	Normal saline
RBC	Red blood cell
TCA	Tricarboxylic acid

Introduction

Trauma is one of the leading causes of early mortality in the United States in persons under 50 years of age [1, 2]. Exsanguination is the leading cause of preventable death in this population. Exsanguination accounts for an even larger percentage of traumatic

A. C. Gee · M. A. Schreiber (✉)
Division of Trauma, Critical Care, and Acute Care Surgery, Oregon Health and Science University, Portland, OR, USA
e-mail: geea@ohsu.edu; schreibm@ohsu.edu

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deaths in a battlefield setting than it does in the civilian setting [3, 4]. Trauma surgeons have been investigating methods to stem the degree of hemorrhage and to prevent as many of these deaths as possible. The concept of an abbreviated initial operation to arrest the lethal triad of coagulopathy, metabolic acidosis, and hypothermia was first described in 1983 by Stone and colleagues [5]. Since that time, there has been increasing promulgation of operative strategies that aim to temporize traumatic injuries and not necessarily provide definitive repair. This operative strategy has been termed "damage control surgery" and has been continuously refined based on the care of injured warfighters during the last two decades of conflict. Concurrently with the refinement of damage control surgery, there has been a parallel refinement in the fluid resuscitation known as damage control resuscitation (DCR) [6].

During World War I, battlefield surgeons recognized the importance and utility of whole blood in the treatment of acutely injured persons [7]. This practice continued through World War II and the Korean War, but it was noted that there was difficulty with storing whole blood that leads to significant wastage. Over time the use of whole blood was replaced by component therapy as it facilitated storage and minimized waste. As use of component therapy increased, crystalloid fluid use also increased for restoration of the circulatory volume. Unfortunately, with the large volume of crystalloid therapy there was a concomitant rise in the incidence of acute lung injury through an increase in the amount of extra-vascular lung water [8]. This recognition and efforts to avoid displacing established clots and avoiding coagulopathy lead to a decrease in the volume of crystalloids used, but crystalloids remained a mainstay of trauma resuscitation codified in the Advanced Trauma Life Support (ATLS) guidelines prior to the 10th edition. Blood products were used sparingly due to concerns with acute transfusion reactions and immune system depression.

Over the last several years there has been a resurgence in the utilization of blood products based largely upon the US military experience in Iraq and Afghanistan. Studies emerged that elucidated a survival benefit in patients who received a high plasma to red blood cell (RBC) transfusion ratio [9, 10] in both military combat and civilian trauma populations. This was subsequently studied in the US civilian trauma population in the PROPPR randomized controlled trial which demonstrated improved hemostasis and decreased death from exsanguination when a transfusion ratio of 1:1:1 plasma/platelets/RBCs was given compared to 1:1:2 [11]. This has resulted in recommendations for balanced resuscitation with blood products, including whole blood transfusions, and more judicious use of crystalloid fluids, during the damage control surgery/resuscitation phase of care.

The ideal fluid for use in the DCR setting would be one that provides a reproducible expansion of the intravascular space, limits interstitial edema, such as in the intestines and lung, aids in the restoration of hemostasis, has little systemic accumulation, has minimal side-effects, and is cost-effective. The ideal fluid would enhance the ability to subsequently close the open abdomen following damage control procedures. Post-traumatic complications such as an open abdomen/intra-abdominal hypertension (Fig. 13.1) and acute respiratory distress syndrome (Fig. 13.2) add significant morbidity to the patient and increases the cost of care. Unfortunately, no such synthetic fluid

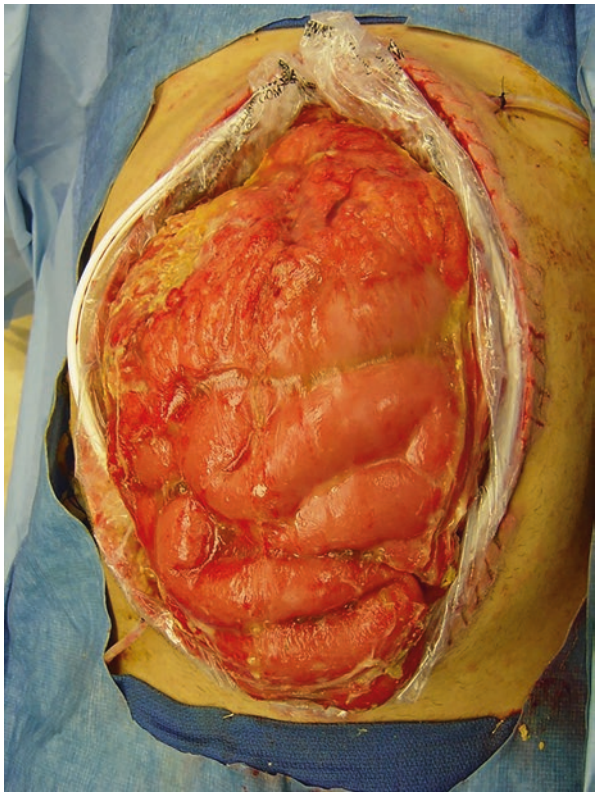

Fig. 13.1 An example of the sequela of intra-abdominal hypertension and bowel edema after a large volume crystalloid and blood product resuscitation following an abdominal gunshot wound. Note the persistent bowel dilation and fibrinous exudate

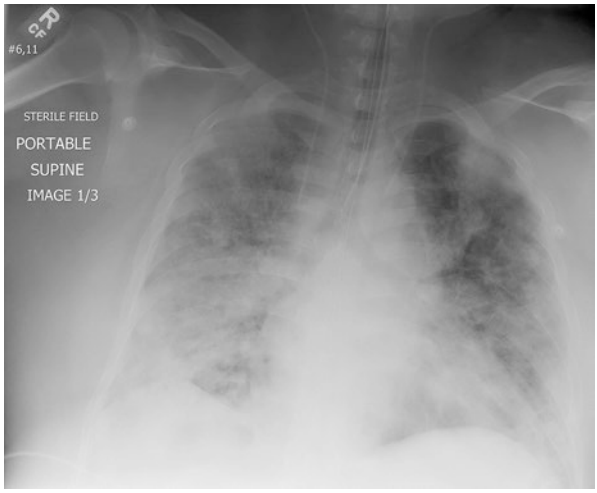

Fig. 13.2 Chest x-ray with bilateral infiltrates in acute respiratory distress syndrome that developed following a large volume crystalloid resuscitation

currently exists and we are left with a variety of different fluids that may be used in the DCR setting. This chapter will review the various types of fluids commonly available for use during DCR. Recommendations for the use of blood product transfusions in targeted hemostatic resuscitation are covered in other chapters.

Colloids

Colloids are crystalloid solutions containing a soluble high molecular weight compound. These compounds are usually derived from a carbohydrate- or glycol-based polymer but also include albumin (a product of blood fractionation) and gelatins which are derived from collagen [12]. The carbohydrate-, glycol-, and gelatin-based colloids are synthetic, whereas albumin is a natural purified substance. While colloids are often thought of as being uniform, they are actually a diverse class of fluids with different physical properties and pharmacokinetics. The molecular weight of the macromolecule plays a large part in determining the viscosity of the fluid. Of the colloids, albumin is the only one with a fairly uniform molecular size and the synthetic polymers are mixtures that are purified to be of a specific mean weight. The colloidal macromolecules are dissolved within an electrolyte solution to minimize disruption of the patient's serum electrolytes are generally formulated to be iso-osmolar to serum. The characteristics of some of the common colloid fluids are found in Table 13.1 [12–14].

The macromolecules are designed to be too large to traverse the glycocalyx and generally remain within the vasculature for a period of time. The actual plasma half-life of the colloid is dependent upon its molecular weight, route of metabolism, and degree of organ dysfunction. The concentration of the colloid in plasma increases the oncotic pressure within the vasculature relative to the interstitial and intracellular spaces and forces a net movement of water into the vascular space. The higher the oncotic pressure generated, the greater the amount of volume expansion.

Table 13.1 Common colloid fluids

Name (product name)	Osmolarity (mOsm/L)	Oncotic pressure (mmHg)	Estimated % volume expansion	Electrolyte composition	pH
Albumin, 5%	330	20–29	80	Na 100–145 mEq/L Cl 100–145 mEq/L	6.7–7.3
Albumin, 25%	330	100–120	200–400	Na 100–145 mEq/L Cl 100–145 mEq/L	6.7–7.3
6% hydroxyethyl starch (MW 670 kDa) in lactated Ringer's (Hextend)	273	25–30	100	Na 143 mEq/L Cl 124 mEq/L Lactate 28 mEq/L Ca 5 mEq/L K 3 mEq/L Mg 0.9 mEq/L	5.9
6% hydroxyethyl starch (MW 600 kDa) in normal saline (Hespan)	308	25–30	100	Na 154 mEq/L Cl 154 mEq/L	5.9
6% Dextran-70 in hypertonic saline (7.5%)	2566	75	120	Na 1283 mEq/L Cl 1283 mEq/L	5.7

Because the colloid draws in water from the body tissues, it results in a greater volume expansion than the actual volume of fluid infused. The decreased fluid requirement makes colloids attractive in theory due to mitigation of many of the complications associated with large volume infusions. By requiring less fluid volume per unit of volume expansion and long-term room temperature storage, colloids provide logistical benefits. Additionally, the decreased fluid volume weighs less, which is an important consideration in austere and prehospital environments where there are limitations in how much equipment and supplies can be carried in both military and civilian environments.

Albumin

Albumin is the most abundant protein in plasma and has an average molecular weight of 66 kDa. It is made by the liver and physiologically functions to aid in the transport of small molecules. It provides a pH buffer, maintains oncotic pressure, and aids in the binding and transport of divalent cations. Albumin's role in maintaining oncotic pressure, and hence circulating blood volume, is the property that makes it useful in fluid resuscitation. Albumin is found in the extracellular fluid as well and can have increased translocation from the vasculature due to increased vascular permeability in the setting of shock. This translocation can contribute to the worsening of soft tissue edema and organ dysfunction.

Since albumin is derived from donated human blood, it does carry a theoretical risk of infectious disease transmission. The blood is screened at the time of donation for prior exposure to several different infectious diseases after which the albumin is purified by either cold fractionation with ethanol or chromatography and is then heat pasteurized. Although the fractionation and pasteurization processes lead to significant reductions in viral particles, there remains a theoretical risk for viral and prion disease transmission [15]. As a resuscitation fluid, albumin is relatively expensive due to the processing required. It is a stable solution that can be stored at room temperature. The purification process also removes the immunogenic elements found in whole blood, although allergic reactions, including anaphylaxis, have been described.

There have been many studies evaluating the use of albumin in humans, but there are a few that are relevant for patients with traumatic hemorrhagic shock and DCR. In 2004, Finfer and colleagues published the results of the SAFE study which evaluated the use of a 4% albumin solution against normal saline for fluid resuscitation of critically ill patients admitted to the ICU, in a multicenter, randomized, and double-blinded study. The trial was adequately powered to evaluate the primary endpoint of 28 day all-cause mortality [16, 17]. There was no difference in the primary or secondary endpoints. However, in a subsequent post-hoc subgroup analysis, the SAFE study investigators found that traumatically brain injured patients who had been in the albumin resuscitation arm had a higher mortality rate at 2 years as compared to those who received normal saline as their resuscitative fluid [18]. The investigators attributed this to increased intracranial pressure during the first post-injury week [19]. A subsequent Cochrane Review in 2013 pooled the data from 24 studies of all types of critically ill

patients, yielding 9920 patients, to evaluate the use of albumin for resuscitation. The pooled relative risk was reported to be 1.01 (95% CI 0.93–1.10), thus failing to find a mortality difference when albumin was compared to a crystalloid solution [20]. Given the lack of benefit, as compared to crystalloid solutions, and potential risk of harm in traumatic brain injured patients, albumin is not a common first line product for fluid resuscitation in patients with life-threatening bleeding requiring DCR.

Hydroxyethyl Starch

Hydroxyethyl starches (HES) are highly branched glucose-based polymers that are derived from amylopectin. Hydroxyethyl groups are synthetically added to the hydroxyl groups using ethylene oxide. The addition of multiple hydroxyethyl groups stabilizes the starch to degradation and metabolism. The amylopectins can come from a variety of plant sources and when purified have a wide range of molecular weights due to variations in the polymer length. HES is cleared via renal excretion, and its half-life in plasma is dependent upon renal function and tissue deposition.

Animal and clinical studies have been difficult to interpret due to the different sizes of starches being studied. Given the significant structural differences between the various HES products, findings with one product may not be applicable to all the others. Two commercially available formulations, Hextend and Hespan, both use an HES mixture with an average molecular weight of 600–670 kDa and are the most commonly studied for the use in trauma resuscitation. There is a newer variant of HES known as tetrastarch that has a mean molecular weight of 130 kDa. Tetrastarch was formulated with the intent of having a shorter half-life than other HES polymers. This product has not been evaluated for use in the trauma resuscitation setting, but it has been associated with negative outcomes in septic ICU patients but may have less risk for anaphylaxis [12, 21, 22].

As with all colloids, HES produces a volume expansion via an increase in vascular oncotic pressure. Hextend and Hespan's ability to expand the circulatory volume is similar to that of 5% albumin [12]. Both of these solutions contain 6% HES since studies have suggested that HES solutions with concentrations greater than 10% high molecular weight HES have increased rates of death, acute kidney injury, and need for renal replacement therapy [23]. These risks have led to FDA black box warnings on all forms of HES [24, 25]. For many clinicians, HES fluids have long raised concerns about anaphylaxis, coagulopathy, and uncontrolled massive hemorrhage [26], although these concerns have been largely based upon case reports. Olgivie and co-workers attempted to examine the safety, efficacy, and effect on coagulation of Hextend with a non-randomized, non-blinded study in 2008. In this study, they found that the patients who received Hextend had a lower mortality rate and no evidence of coagulopathy or transfusion requirement [26, 27]. The design of the study limits the ability to interpret if there is a survival benefit, but the results do show that Hextend does not affect PT or PTT in the 500–1500 ml volumes studied. Thrombelastography was not used in this study, so we do not know if other aspects of hemostasis were affected by Hextend, which has been associated with decreased factor VIII and von Willebrand factor when used in higher doses [12, 28]. Given the

lack of clear clinical benefit and potential risk of harm with HES, it is difficult to recommend its use outside of an austere or logistically challenged environment.

Dextran

Dextrans are biosynthetic, highly branched, polysaccharides. Similar to HES, dextrans can have a wide range of molecular weights, but are purified to specific molecular weights. In the DCR setting, dextran-70 (70 kDa average molecular weight) is the most commonly used and studied. As with albumin and HES, dextrans can provide a significant increase in the intravascular volume relative to the infused volume and are primarily excreted in the urine. Dextrans as a class have been associated with anaphylaxis, coagulopathy, and renal failure by precipitation in the renal tubules. They also impair blood cross-matching by obscuring the RBC surfaces.

There have not been many studies to evaluate the use of dextran in the trauma setting due to concerns about coagulopathy. In 1991, Mattox and co-workers evaluated the use of 6% dextran-70 in 7.5% sodium chloride (HSD) in a multicenter trial. This study compared the use of 250 ml of the dextran solution vs 250 ml of a crystalloid solution prior to standard resuscitation. In this study, they did not note coagulopathy with the doses and volumes used. There was no clear mortality benefit for the study cohort overall, but the subgroup that did require an operation demonstrated a survival benefit. Also importantly, the standard therapy appeared to be associated with a higher incidence of acute respiratory distress syndrome (ARDS), renal failure, and coagulopathy [29]. This lead to a blinded multicenter randomized study of prehospital use of 7.5% hypertonic saline, normal saline, and HSD (ROC study). This study was stopped early after a planned safety review for futility and patient safety. Patients in the HTS and HTS/dextran arms who did not receive blood transfusions in the first 24 hours after injury were found to have a higher mortality rate [30]. It was not clear to the study's authors why there was this effect, but they postulated that shock was masked by HTS resuscitation resulting in delayed transfusions. Early mortality was higher in the HTS groups, but later mortality was lower leading to no overall difference. Based on these studies, dextran is not recommended for DCR.

Given the lack of a robust benefit with the use of colloids in the setting of resuscitations along with their higher cost, colloid solutions are not recommended as the first line fluid for use in DCR. Currently in the US Military Tactical Combat Casualty Care (TCCC) Guidelines, Hextend remains a part of the treatment recommendations, but only if blood products are not available, and remains preferred over crystalloids due primarily to prehospital logistics [31].

Crystalloids

Crystalloids are electrolyte-containing fluids that have been in use for nearly 200 years. They have been the mainstay of resuscitation prior to the development of DCR strategies since crystalloid fluids are widely available and

Table 13.2 Common crystalloid fluids

Name (product name)	Electrolytes (mEq/L)					Buffer	Osmolarity (mOsm/L)	pH
	Sodium	Chloride	Potassium	Calcium	Magnesium			
0.9% NaCl (normal saline)	154	154	0	0	0	None	308	4.5–7.0
3% NaCl (hypertonic saline)	513	503	0	0	0	None	1027	4.5–7.0
7.5% NaCl (hypertonic saline)	1283	1283	0	0	0	None	2560	4.5–7.0
Lactated Ringer's	130	109	4	2.7	0	Lactate 28 mEq/L	273	6.7
Plasma-Lyte A and Normosol-R	140	98	5	0	3	Acetate 27 mEq/L Gluconate 23 mEq/L	294	7.4

relatively inexpensive. Crystalloids can be broadly classified into two categories: saline and balanced salt solutions. Saline solutions contain only sodium chloride whereas balanced salt solutions are electrolyte solutions that contain other cation and anions in addition to the sodium and chloride and generally contain a pH buffer. Commonly used balanced salt solutions for resuscitation include lactated Ringer's, Normosol-R, and Plasma-Lyte-A. The composition of these commonly used crystalloids is summarized in Table 13.2 [12, 32]. Unlike colloids, crystalloids diffuse rapidly out of the vascular space and into the extravascular spaces.

Saline Solutions

In the resuscitative setting, commonly used concentrations of saline are 0.9%, 3%, and 7.5% NaCl. 0.9% NaCl is generally known as normal saline (NS), while the latter three concentrations are collectively referred to as hypertonic saline (HTS). All saline solutions have a measurable pH in the acidic range (4.5–7.0) due to their lack of a buffering component. The low pH is due to the dissolved carbon dioxide in the solution and the presence of sodium and chloride ions act to stabilize the dissociation of carbonic acid. Additionally, there is likely leaching of acid from the polyvinylchloride (PVC) containers that further drop the pH of saline [33]. When used in a maintenance infusion rate and volume, the acidity of saline is readily buffered by plasma and generally is of little consequence. However, when saline is administered rapidly and in large volumes during DCR, it can both overwhelm and dilute the buffering capacity of plasma. Additionally, in the DCR setting, the patient may already have developed some degree of acidosis from shock and loss of buffering capacity from hemorrhage.

Isotonic and hypertonic solutions contain significantly higher concentrations of chloride anions than is normally present in plasma. With rapid and/or high volume infusions, this often leads to a hyperchloremic metabolic acidosis which in turn contributes to the acidosis experienced by a patient in shock. This can frequently lead to a prolonged over resuscitation when clinicians are working to correct the acid-base disorder present during shock. The acidosis may lead to increased vascular permeability, edema, and development of coagulopathy [34]. The hyperchloremia may also lead to immune dysfunction, decreased glomerular filtration rate, and increased risk of acute kidney injury [23, 35]. In an observational study of abdominal surgery patients, Shaw and co-workers found that patients who received NS (as compared to those receiving Plasma-Lyte) on the day of their operation had a significantly higher mortality rate and complication rate. In this study, NS was associated with post-operative infections, need for renal replacement therapy, blood transfusions, and electrolyte and acid-base disturbances [36]. The authors postulated that the use of NS leads to increased morbidity and greater resource utilization incurring a higher cost of care.

Hypertonic saline solutions have been attractive in resuscitation due the potential benefit of increasing a patient's circulating volume by drawing water from the interstitial tissues into the blood stream via osmotic pressure. This increase in blood volume requires a lower infusion volume due to the higher concentration of sodium chloride in the HTS solutions. Similar to colloid solutions, this would provide a logistical benefit to these solutions by weight and volume reduction. However, due to the rapid diffusion of crystalloid out of the vascular space, the volume expansion may be much shorter in duration than with colloid-based volume-expanding fluids. In general, a decreased infusion volume with HTS still can result in less fluid overload and extravascular lung water as compared to NS.

There have also been some animal model studies suggesting that HTS infusion has beneficial immunomodulatory effects [37, 38]. Use of 7.5% saline in the prehospital setting was evaluated in the ROC study as mentioned earlier. There was no significant benefit observed for patients receiving HTS as compared to those who received NS [30]. Another prehospital study of HTS found that prehospital administration of HTS to brain injured patients did not yield any short- or long-term benefits [39]. HTS does remain useful in acutely controlling intra-cranial hypertension but prolonged use may lead to a transient rebound hyponatremia [28]. Due to a reduction in fluid resuscitation and the potential to reduce bowel edema, HTS has been considered as a therapeutic agent to expedite abdominal closure after damage control laparotomy. This is currently being studied in a multicenter trial.

Balanced Salt Solutions

Balanced salt solutions have a lower osmolarity and a lower chloride concentration compared to saline solutions and contain other electrolytes in addition to sodium and chloride. The lower chloride infusion decreases the likelihood of developing hyperchloremia and the complications associated with it. Another

common characteristic of balanced salt solutions is that they are buffered with lactate or acetate to a pH of 6.5–7.5. The lactate and acetate are eventually metabolized via the TCA cycle, but lactate metabolism occurs in the liver and kidney while most cells can metabolize acetate. Prior to being metabolized, the infused lactate can lead to elevated plasma concentrations of lactate, while theoretically concerning, this has not been shown to have any clinical significance. However, large volume infusion of buffered fluids can lead to metabolic alkalosis, hypotonicity, or cardiotoxicity, particularly in the setting of impaired hepatic metabolism [23]. Lactated Ringer's (LR) solution contains racemic lactate, and the D-enantiomer had been previously shown to be pro-inflammatory in an in vitro model by increasing neutrophil activation and leukocyte gene expression in a pro-inflammatory pattern [40]. Several clinical studies have found racemic LR to be anti-inflammatory in other disease processes such as acute pancreatitis [41]. The effects of LR on immunomodulation should be considered when it is used as a resuscitative fluid, particularly at faster infusion rates or greater infusion volumes [40, 41].

Two clinical observational studies have shown that, when compared to NS, use of a balanced salt solution was associated with a lower incidence of acute kidney injury, need for dialysis, and infections [36, 42]. To date there has not been a randomized controlled trial that evaluates saline and balanced salt solutions in a prospective fashion. Use of a calcium-containing balanced salt solution with red blood cell transfusions may theoretically lead to clotting due to the chelation of the calcium by citrate used to prevent clotting in the packed red blood cell unit [23, 34]. There are no data to suggest that one balanced salt solution is better than others for use in DCR.

Both NS and HTS solutions have significant potential downsides for use in the DCR setting. Balanced salt solutions appear to have a better benefit-to-risk comparison than saline solutions and should be used as the crystalloid fluid of choice for DCR. Although balanced salt solutions appear to have a better safety profile, they still must be used judiciously, as they result in third spacing and complications associated with hypervolemia such as ileus, pulmonary failure, ARDS, intra-cranial hypertension, and intra-abdominal hypertension [43–45].

Summary

A primary goal of DCR is terminating life-threatening hemorrhage and the development of coagulopathy and shock. As noted earlier, there is no perfect resuscitation fluid as each currently used commercially available fluid has its own set of benefits and risks. Neither colloids nor crystalloids directly restore the blood's ability to clot or carry oxygen. Transfusion of blood components or whole blood provides for both of these as well as expansion of the circulatory blood volume.

US Tactical Combat Casualty Care revised its guideline in 2014 prioritizing resuscitation fluids for life-threatening hemorrhage as follows (in order of most to least preferred: whole blood, plasma, RBCs, platelets (in 1:1:1 ratio), plasma or

RBCs only, Hextend, and crystalloids (LR or Plasma-Lyte A)). In a non-austere environment, a balanced salt solution should be preferred over Hextend or other colloids as there is little evidence to suggest differences in outcome, colloids are significantly more expensive, and there are no logistical issues that would favor colloids.

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14

Airway Management of Patients with Life Threatening Haemorrhage: Principles of Safe and Effective Care

Tony Hudson

Abbreviations

BURP	Backwards upwards rightwards pressure
DO_2	Oxygen delivery
EAD	Extraglottic airway device
ELM	External laryngeal manipulation
EMS	Emergency medical services
$EtCO_2$	End-tidal carbon dioxide
ETI	Endotracheal intubation
ETT	Endotracheal tube
HEMS	Helicopter emergency medical services
LMA	Laryngeal mask airway
MILS	Manual in line stabilisation
MTF	Medical treatment facility
NMBA	Neuromuscular blocking agent
NPA	Nasopharyngeal airway
OPA	Oropharyngeal airway
PALM	Pharmacologically assisted laryngeal mask
RSI	Rapid sequence intubation
TBI	Traumatic brain injury
TCCC	Tactical combat casualty care
TECC	Tactical emergency casualty care

T. Hudson (✉)
Emergency Department, Royal Devon and Exeter NHS Foundation Trust Hospital, Devon, UK
e-mail: anthony.hudson1@nhs.net

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Introduction

Airway care of the patient with life threatening haemorrhage has two fundamental objectives: to prevent respiratory insufficiency (hypoxaemia or hypercarbia) and to facilitate damage control resuscitation interventions. Immediate care must ensure a patent airway, protection of the airway and lungs from contamination and when necessary, assistance with ventilation. This must be achieved from the onset of haemorrhage and may require a range of interventions from basic airway manoeuvres to advanced airway procedures. Subsequently, there may be a requirement to deliver general anaesthesia to permit invasive haemorrhage control procedures. In this chapter, we discuss the range of techniques to manage both phases of airway care safely and effectively in the presence of life threatening haemorrhage.

Airway Care in the Remote Damage Control Resuscitation (RDCR) Setting

Background

Many of the studies of preventable deaths from trauma that highlight the importance of haemorrhage control also demonstrate that airway obstruction is a significant cause of preventable death in the pre-hospital setting [1, 2]. One extensive review of military battlefield trauma deaths concluded that airway obstruction represented the second most common category of death due to potentially survivable injury that occurred prior to arrival at a medical treatment facility (MTF) [3]. It is therefore imperative that providers of care in the pre-hospital environment have the necessary skills to recognise and manage airway compromise in the presence of life threatening haemorrhage.

Environment

For many patients with life threatening haemorrhage, damage control resuscitation will start in the pre-hospital environment (remote damage control resuscitation). This environment may be an urban setting with short transport times to sophisticated medical facilities. In many parts of the world, however, pre-hospital care is delivered in remote, austere and sometimes dangerous environments. There are many challenges associated with delivering remote damage control resuscitation, including safe and effective airway care, in such settings. There may be a lack of monitoring, equipment, communications, transport and medical supplies. Extended evacuation times may necessitate that providers undertake not only the time-critical, life-saving, airway interventions but also provide ongoing protection of the airway en-route to appropriate medical facilities.

Who Provides Care?

Initial airway care of the patient with life threatening haemorrhage is not the exclusive domain of any given medical provider but will fall to whoever has the necessary skills to recognise and manage airway compromise. In some health care systems, particularly civilian Emergency Medical Services (EMS) and Helicopter Emergency Services (HEMS), a small cadre of highly trained paramedical or medical staff can be deployed to supplement the basic airway skills of other providers on the few occasions when more sophisticated interventions are required. In more hostile, military environments, this may not be feasible and so basic healthcare providers may need to have a wider range of airway skills appropriate to the casualties they may encounter. Military initiatives such as the Tactical Combat Casualty Care (TCCC) training program and the Civilian Tactical Emergency Casualty Care (C-TECC) program seek to address these problems and emphasise the time-critical nature of not only haemorrhage control measures but also airway interventions. Such courses and an investment in the overall doctrine necessary to deliver these skills have been shown to have a significant impact upon outcomes from trauma. One study of military trauma outcomes following the introduction of a TCCC program demonstrated a dramatic reduction of preventable deaths on the battlefield [4].

Airway Care in Life Threatening Haemorrhage

Airway obstruction due to a reduced level of consciousness (due to reduced brain perfusion) is a significant risk for patients with life threatening haemorrhage. The priority of airway care for such patients is therefore to maintain a patent airway to facilitate adequate ventilation and tissue oxygen delivery whilst achieving haemorrhage control. Fick's principle highlights that tissue delivery of oxygen (DO_2) is proportional to the haemoglobin concentration, oxygen saturation and cardiac output. (Fig. 14.1) A sustained fall in oxygen delivery below a critical point will precipitate accumulation of lactic acid and an "oxygen debt" which may lead to irreversible tissue ischaemia and coagulopathy [5]. Hence key damage control resuscitation strategies to ensure adequate tissue oxygen delivery for patients with life threatening haemorrhage are to maximise oxygen saturations, retain (and when possible, replace) haemoglobin, improve preload and cardiac output with plasma and minimise the detrimental effect upon cardiac output of any interventions undertaken.

$$DO_2 = 1.34 \times Hb \text{ X } SaO_2 \times CO$$

DO_2 (oxygen delivery), Hb (haemoglobin concentration), SaO_2 (oxygen saturation), CO (cardiac output)

Fig. 14.1 Oxygen delivery (DO_2)

Principles of Safe and Effective Airway Care

Indications for Intervention

Many patients with life threatening haemorrhage need no immediate airway intervention, either in the pre-hospital setting or upon arrival at a medical treatment facility. Whilst basic airway skills can be delivered by providers with relatively limited training and experience, there are some patients who will need more sophisticated interventions. The proportion of patients requiring these advanced interventions varies by population studied. One review of 6875 combat casualties arriving at Combat Support Hospitals during Operation Iraqi Freedom found that 4.8% had undergone advanced airway interventions, delivered by a variety of providers, in the pre-hospital phase [6]. In another study of pre-hospital airway interventions in UK civilian practice, a significant proportion (57%) of trauma patients who had undergone initial airway intervention by EMS personnel still had airway compromise (partial airway obstruction or evidence of airway contamination) on arrival of an advanced care team and required advanced airway interventions [7]. Thus, providers of airway care in the pre-hospital environment must be trained not only in basic airway skills but also recognition of when more advanced interventions are required. Consideration needs to be given of which advanced airway skills and equipment will then be used and which providers will be required to deliver them.

Airway Assessment and Basic Care

All patients with haemorrhagic shock are at risk of developing airway compromise and therefore require rapid initial assessment and ongoing observation for impending airway compromise. The starting point of all airway care are the traditional methods of visual inspection of the airway and associated ventilatory efforts, listening for typical noises of airway obstruction and when necessary feeling for the movement of air. These methods may be more time consuming and inaccurate than generally realised, particularly in austere or hostile environments [8]. Monitoring with continuous waveform capnography will help assess the net results of airway patency and ventilatory effort and is essential if advanced airway interventions are subsequently performed [9]. Pulse oximetry will provide information about oxygenation and circulation of blood although is often unreliable in the low flow states found in life threatening haemorrhage. Providers should avoid overreliance upon such adjunctive monitoring and be prepared to make repeated clinical assessments of airway patency, ventilatory effort and mentation. A stepwise approach to airway care should be used to ensure that simple strategies are the starting point after which an escalation of intervention can be employed to achieve a patent airway. Positioning of patients plays a vital role in initial airway care. In many settings, providers will want to position the patient in the supine position to facilitate airway care, interventions to address life threatening haemorrhage and casualty transport, but for many patients this represents a suboptimal position. Patients with life threatening obstetric haemorrhage may suffer aorto-caval

obstruction when placed in the supine position and so should be managed in a tilted position. Patients with life threatening haemoptysis or haematemesis may aspirate blood if placed in the supine position. Similarly, patients with soiling of the airway or inability to maintain an airway in a supine position may be best managed in the lateral position to allow gravity to assist with postural drainage and opening of the airway. Many providers are naturally concerned about the potential risk of the lateral position for patients with suspected spinal injury, but a systematic review identified no evidence to suggest that placing patients with spinal injury into a lateral position carries a risk of neurological deterioration provided appropriate precautions are taken [10]. Simple airway opening manoeuvres such as jaw thrust, chin lift or head tilt may be required in the presence of airway obstruction but only jaw thrust is suitable for trauma patients with suspected cervical spine injury. Numerous studies have shown that cervical spine injury is rare in the presence of penetrating neck injury or gunshot wounds to the head and that in such settings airway management should take priority over cervical spine immobilisation [11, 12].

Airway Adjuncts

In some patients, a patent airway can only be maintained by the use of simple airway adjuncts, either a nasopharyngeal (NPA) or an oropharyngeal airway (OPA). Nasopharyngeal airways have the advantage of being relatively easy to insert, are better tolerated in patients who are not completely obtunded (hence less likely to cause gagging or vomiting) and can be inserted when a patient has trismus. Conversely, there is some evidence that incorrectly sized NPAs are ineffective or can actually precipitate airway obstruction [13]. Furthermore, there are case reports of intracranial passage of NPAs in patients with associated major head injury and of significant epistaxis with incautious insertion of the device [14, 15]. The relatively low risks of insertion must be balanced with the perceived benefits in each setting. OPAs are widely used as airway adjuncts but are usually only tolerated by deeply unconscious patients. In the event that these basic strategies fail then providers will need to escalate to more invasive methods of airway care.

Advanced Airway Care

Surgical Airways and Extraglottic Airway Devices (EADs)

Airway care in remote or austere settings often falls to relatively inexperienced providers with limited training or equipment and hence strategies to manage airway problems must take their level of training and experience into account. For this reason, many military organisations have chosen to train their pre-hospital medical providers in the skills required to perform surgical airway insertion (cricothyrotomy) when there are direct airway injuries or providers are unable to perform alternative advanced techniques such as the use of extraglottic airway devices (EAD) or drug-assisted

endotracheal tube placement. There are many advantages of cricothyrotomy as an advanced airway intervention in an RDCR setting. It is a relatively easily learned and remembered technique that in its simplest form requires little equipment or post-procedural care [16]. There are a variety of techniques from simple dissection and insertion of a cuffed tracheal tube ("scalpel, finger, bougie") to Seldinger devices and techniques that require more equipment and training. There would currently appear to be no clear advantages of any given technique or equipment [17]. Military studies have shown success rates of up to 93% [18–20]. A potentially compelling advantage is that this procedure can also be performed under local anaesthetic or with appropriate sedation (using agents least likely to cause hypotension or respiratory depression). When an airway has been secured, patients can be allowed to breathe spontaneously as muscle paralysis is not required to facilitate this procedure. There are clear haemodynamic benefits of spontaneous negative pressure ventilation over positive pressure ventilation for patients with life threatening haemorrhage. Cricothyrotomy is less widely used in civilian pre-hospital care settings due to lower rates of ballistic facial injury, concerns about potential harm of the procedure, increasing use of extraglottic airway devices and wider availability of drug- assisted intubation skills.

Another advanced strategy of airway care is the use of an extraglottic airway device (EAD). Such devices are relatively easy to use and can be rapidly inserted with little risk of harm in deeply unconscious patients. They can be used for either spontaneous or assisted ventilation. They may require little or no ancillary equipment, particularly when a version is used that does not require cuff inflation after insertion. Although they all feature some sort of cuff or seal to limit the risk of aspiration of gastric contents or airway contaminants, they cannot be considered to offer a secure airway. Furthermore, to allow insertion, patients must either be deeply unconscious or drugs must be administered to obtund airway reflexes otherwise vomiting may occur. This can make them complex to employ in patients with dynamic airway compromise. Some providers suggest the use of pharmacologically assisted laryngeal mask (PALM) placement although this does expose the patient to all the risks of sedation or even paralysis without the advantages of achieving a secure, cuffed endotracheal tube [21]. The safety and efficacy of this technique remain unclear. There is no doubt, however, that as rapidly inserted airway interventions for unconscious patients or as "rescue" devices in the case of failed endotracheal intubation, EADs have a role to play in the advanced airway care of patients with life threatening haemorrhage [22].

Endotracheal Intubation and Positive Pressure Ventilation

When Should Patients with Life Threatening Haemorrhage Be Intubated?

Patients with life threatening haemorrhage who are unable to be oxygenated by use of any of the basic airway manoeuvres or adjuncts described above, or whose airway cannot be protected from contamination of blood, debris or gastric contents will need placement of an endotracheal tube to maintain oxygenation. This is usually

Table 14.1 Indications for endotracheal intubation in RDCR

Immediate:
Failure to achieve oxygenation or ventilation by other techniques
Inability to protect airway
Urgent:
To perform damage control surgery/invasive haemorrhage control procedures
Impending airway obstruction, e.g. burns
Neuroprotective ventilation
To facilitate transfer
Combative head injury patients
Humanitarian – distressing multiple injuries

facilitated by a process of drug-assisted sedation and paralysis to achieve rapid sequence intubation (RSI). Paralysed patients must then be ventilated by positive pressure ventilation. In the presence of haemorrhagic shock, any induction agent can exacerbate the hypotensive state and positive pressure ventilation will further reduce cardiac output. Given these risks, controversy exists about the efficacy of pre-hospital intubation, with some retrospective studies seeming to show that it confers no survival advantage whilst other prospective studies have suggested improved outcomes [23–25]. Furthermore, some studies have even suggested that a strategy of rapid transport to hospital by police or private transport rather than Emergency Medical Services is associated with lower mortality for trauma patients, perhaps highlighting the time-critical need to achieve haemorrhage control as the greatest priority [26, 27]. On arrival at a medical treatment facility, patients who have not already been intubated are likely to need rapid sequence intubation to allow invasive haemorrhage control procedures as part of a coordinated damage control resuscitation strategy. The significant risk of haemodynamic compromise of this procedure should be mitigated whenever possible by a policy of aggressive blood product resuscitation in the peri-intubation phase.

A summary of the indications for endotracheal intubation is shown in Table 14.1.

When Should Patients with Life Threatening Haemorrhage Not Be Intubated?

Life threatening haemorrhage is not in itself an indication for intubation and positive pressure ventilation despite the perception that this brings order to a sometimes chaotic and challenging situation. When undertaken in awake hypotensive trauma patients in the field, pre-hospital intubation and positive pressure ventilation have been shown to be associated with increased in-hospital mortality [28]. Whilst many such patients will eventually require intubation to facilitate haemorrhage control procedures, this should be deferred, whenever safely possible, until the patient can be adequately resuscitated. Providers of airway care, particularly in remote settings where blood products may be less widely available, must therefore be trained in a range of appropriate airway strategies to manage the airway without resorting to intubation. Reduced

level of consciousness due to life threatening haemorrhage should also not in itself mandate intubation in the pre-hospital setting as this does not necessarily correlate with ability to maintain an airway. If adequate oxygenation can be maintained and the airway protected from contamination using appropriate measures (e.g. postural drainage or suction) in a patient who is self-ventilating, then consideration should be given to transporting the patient to an appropriate medical treatment facility as rapidly as possible without performing intubation. When advanced airway practitioners are deployed into the pre-hospital environment, it must be recognised that they possess the vital skills and experience not only to perform intubation but also to identify when patients with life threatening haemorrhage can safely be managed without intubation. Providers must weigh the potential benefits of intubation and positive pressure ventilation against the significant risks of these procedures, particularly critical organ hypo-perfusion and cardiac arrest, in the presence of life threatening haemorrhage and consider whether alternative, lower risk, airway management strategies (including EAD placement or cricothyrotomy) can be employed pending the availability of more definitive resuscitation facilities.

Rapid Sequence Intubation in the Presence of Life Threatening Haemorrhage

If intubation must be performed in the presence of life threatening haemorrhage, there are specific considerations that minimise risk and optimise outcomes:

Blood Product Resuscitation

Given the hypotensive effects of induction agents and reduction of cardiac output caused by positive pressure ventilation, it is vital that patients with life threatening haemorrhage are resuscitated by blood product administration, whenever possible, prior to intubation and ventilation. If blood products cannot be made available, then crystalloid or colloids should be used to improve preload prior to intubation.

Pre-oxygenation/Apnoeic Oxygenation

Patients with haemorrhagic shock will rapidly desaturate during the intubation process unless appropriate measures are taken to maximise pre-oxygenation and minimise the duration of apnoea. A strategy of effective pre-oxygenation (with associated denitrogenation) is vital to maximise the time until haemoglobin desaturation. In time-critical settings, this is best achieved by eight deep breaths within 60 seconds with high flow oxygen delivered using a non-rebreathing facemask although this technique may not be suitable for heavily pregnant or uncooperative patients [29]. Studies have also suggested that the process of apnoeic oxygenation by delivery of high flow oxygen via nasal speculum during apnoea significantly delays onset of hypoxaemia [30, 31].

Pre-treatment

An opiate, usually fentanyl or remifentanil, is routinely used as a pre-treatment agent during RSI of haemodynamically stable patients to obtund the sympathetically

mediated hypertensive reflex of endotracheal intubation. In the presence of haemorrhagic shock, these drugs carry significant risk of precipitating hypotension and should therefore be omitted.

Sedation/Induction

All induction agents can provoke hypotension in the presence of life threatening haemorrhage [32]. Ketamine or etomidate are commonly used as they cause less haemodynamic compromise than other agents and exert rapid effects, even in the presence of shock [33]. One review of anaesthesia in haemodynamically compromised emergency patients concluded that ketamine represented the best choice of induction agent, particularly in austere and remote healthcare settings [34]. Ketamine, although negatively inotropic in vitro, causes less hypotension than most other agents due to a mechanism of endogenous catecholamine release [35, 36]. Ketamine can, however, provoke hypotension in shocked patients who are catecholamine depleted and so induction doses must be reduced for such patients. One review of ketamine administration as an induction agent for pre-hospital RSI highlighted that patients with a shock index (heart rate/blood pressure) ≥ 0.9 pre-intubation, were more likely to become hypotensive than those with a lower shock index <0.9 [37]. Etomidate is also widely used although it has been withdrawn from use in some countries due to concerns about adrenal suppression [38]. Whichever agent is chosen, providers must be fully conversant with the safety profile and modifications of dose regimes required in the presence of haemorrhagic shock.

Paralysis

Administration of a neuromuscular blocking agent (NMBA) to achieve paralysis greatly facilitates laryngoscopy and passage of an endotracheal tube between the vocal cords. Indeed, trauma patients who are able to tolerate this procedure without drug administration have been observed to have dismal outcomes [39]. The resultant apnoea carries the risk of respiratory acidosis, hypoxia during the intubation process and hypotension when positive pressure ventilation is initiated. Suxamethonium or rocuronium have the most rapid onset of action and hence are the neuromuscular blocking agents of choice for intubation of patients with life threatening haemorrhage. When given at appropriate doses both have similarly rapid onset of paralysis [40]. In the shocked state, higher range doses are required to achieve rapid onset of paralysis. A Cochrane review found no statistical difference in intubation conditions when succinylcholine was compared to rocuronium at a dose of 1.2 mg/kg but concluded that succinylcholine was clinically superior as it has a shorter duration of action [41]. This may be a disadvantage in some settings. Rocuronium has fewer contraindications, causes no muscle fasciculation (and hence no increase in oxygen consumption) and has a much longer duration of action. Resuscitation teams must decide whether a short acting agent that then allows resumption of spontaneous, negative pressure ventilation during transport would be advantageous in the context of life threatening haemorrhage or whether more prolonged paralysis (and hence maintenance of positive pressure ventilation) is required to facilitate transport or surgical intervention. Other important

considerations include the availability of a reversal agent for rocuronium (sugammadex) and product storage requirements [42].

Intubation

Laryngoscopy to achieve endotracheal intubation for patients with life threatening haemorrhage carries risk of direct airway injury or failure to achieve intubation. For trauma patients with potential associated cervical spine injury there is a requirement to maintain manual in line stabilisation (MILS). The resulting suboptimal anatomical position of the airway may significantly impede direct visualisation of the glottic opening. This may be improved by use of external laryngeal manipulation (ELM) or the application of "backwards, upwards, rightwards pressure" (BURP) [43, 44]. Both techniques have potential to significantly improve visualisation of the vocal cords and a gum elastic bougie should routinely be used to guide endotracheal tube placement. Fibre optic and video laryngoscope devices may give better views than direct laryngoscopy but may not be available in austere settings or effective in the presence of significant contamination of the upper airway.

Cricoid pressure is traditionally applied during paralysis in an attempt to protect from regurgitation of gastric contents prior to ETI placement although some authors highlight potential risks of this manoeuvre [45]. It is clear that delays incurred whilst trying to visualise the glottis or due to multiple attempts at laryngoscopy carry the risk of hypoxia and so multiple attempts (more than three) or unnecessary delays must be avoided [46]. Choice of endotracheal tube size is also vital to ensure success and minimise risk of harm. Pregnant patients may have respiratory tract mucosal oedema and capillary engorgement that can reduce the size of the glottic opening and so smaller endotracheal tubes should be used. Confirmation of correct placement of the endotracheal tube is best achieved using continuous wave form capnography to measure end-tidal carbon dioxide ($EtCO_2$). [9] Whilst other techniques including auscultation may be employed, they carry significant risk of failing to identify oesophageal intubation.

Positive Pressure Ventilation

A key concept in the safe and effective management of the airway for patients with life threatening haemorrhage is the impact of positive pressure ventilation on intrathoracic pressure. The adverse effect of positive pressure ventilation on cardiac output is well described [47]. Intrathoracic pressure becomes raised during the inspiration phase of positive pressure ventilation. In patients with haemorrhagic shock this will reduce the already compromised venous return and hence reduce right ventricular output, pulmonary blood-flow and cardiac output [48]. In human models of simulated shock states, the advantages of negative pressure ventilation have been demonstrated using negative pressure impendence devices [49]. In porcine models of haemorrhagic shock the impact of positive pressure ventilation on cardiac output has been explored and compared to spontaneous, negative pressure ventilation. In one model of haemorrhagic shock, intubated animals undergoing positive pressure ventilation were demonstrated to have greater reduction in cardiac output and body temperature than non-intubated, spontaneously breathing animals [50]. There appeared

to be no survival advantage from intubation and positive pressure ventilation, emphasising that intubation and ventilation are not treatments for haemorrhagic shock but the unavoidable consequences of advanced airway care. When positive pressure ventilation is initiated, providers must employ a ventilation strategy that minimises the impact upon cardiac output. One porcine model of ventilation strategies in severe haemorrhagic shock demonstrated that reduction of end expiratory pressure was the factor that had greatest influence upon haemodynamic stability although decreasing tidal volumes and increasing respiratory rates also had beneficial effects [51]. Positive pressure ventilation in the presence of haemorrhagic shock has also been suggested to be an independent cause of a more pronounced systemic inflammatory response although the effect of this upon acute traumatic coagulopathy remains unclear [52].

Post-intubation Care

Following successful intubation, patients with life threatening haemorrhage will need appropriate on-going care, monitoring and reassessment of the impact of this intervention. In RDCR settings there will be a priority to transport the patient to an appropriate medical facility during which time sedation will need to be maintained and consideration given to maintaining paralysis with a long acting NMBA. Sedation is typically maintained with further bolus administration of a sedative agent such as ketamine that will have least impact upon haemodynamic stability and also provide analgesia. Ventilator settings must be optimised to minimise impact upon cardiac output and confer lung protection. Low tidal volumes (6–8 ml/kg) are typically used and respiratory rates adjusted to maintain appropriate $EtCO_2$ levels, with initial rates of 8–10 breaths per minute. Positive end expiratory pressure (PEEP) should be maintained at 0 mmHg pending adequate resuscitation, unless there is significant concomitant lung injury that requires PEEP to improve oxygenation. In this scenario the least amount of PEEP needed to maintain oxygen saturations above 90% is reasonable. Post-intubation care for patients intubated in a medical facility, or arriving from the field already intubated, will similarly require maintenance of sedation, paralysis and analgesia and careful management of ventilator strategies. When effective haemorrhage control and resuscitation have been achieved, administration of opioid agents such as fentanyl may improve tissue perfusion and protect from reperfusion injury by achieving dilation of the microcirculation [53].

Special Situations: Head Injury

Patients with life threatening haemorrhage who also have traumatic brain injury (TBI) present special challenges to providers of airway care and ventilatory support. Such patients may initially be combative and resistant to attempts to provide appropriate airway care and in some instances, may have trismus, making assessment and support of the airway extremely difficult. Simple airway manoeuvres may be adequate but there may be a need for pharmacological assistance to facilitate simple interventions. Despite historical concerns about the use of ketamine in head injured patients, available evidence suggests that it is safe for such patients and may even

have a neuroprotective effect [54, 55]. Use of low dose ketamine may allow improved pre-oxygenation prior to progression to rapid sequence intubation. Hypotension associated with administration of induction agents for rapid sequence intubation and positive pressure ventilation has been shown to have a detrimental effect upon cerebral perfusion and survival following TBI. A single episode of hypotension below 90 mmHg has been shown to be independently associated with more than a doubling of mortality in the presence of TBI [56]. Any hypoxaemia associated with onset of apnoea or attempts to secure endotracheal intubation has also been shown to have a significant effect upon survival, with a single excursion of oxygen saturation below 90% associated with more than a doubling of mortality [57]. The combination of both hypotension and hypoxia has been demonstrated to be associated with a six-fold risk of mortality in TBI [58]. Furthermore, any over-enthusiastic hyperventilation of patients with TBI following intubation will provoke hypotension and vasoconstriction and hence reduce cerebral blood flow with consequent detrimental impact upon outcome [59]. Providers must be mindful of these pitfalls when performing airway care in the presence of suspected head injury for the patient with life threatening haemorrhage.

Impact of Airway Interventions in Life Threatening Haemorrhage upon Outcomes

There can be no doubt that rapid intervention with basic airway skills to maintain oxygenation in patients with severe haemorrhage can be life-saving, particularly in the presence of direct airway injury or reduced levels of consciousness due to head injury or poor brain perfusion. But more advanced interventions, particularly when performed prematurely in under-resuscitated patients, can have harmful consequences. Interpretation of outcomes for patients with life threatening haemorrhage who undergo advanced airway interventions are potentially confounded by uncertainty about the causation of poor outcomes. Are they due to the underlying haemorrhagic shock state and any associated injuries or pathologies or are they due to the dangers of the airway intervention process and any associated delays? Evidence of the impact of pre-hospital intubation in less critically injured patients illustrates the potentially harmful consequences of this intervention. In one retrospective database review, adult trauma patients who were intubated before arrival in hospital, but who on retrospective review were considered to be only moderately injured, were matched with similarly injured patients who did not undergo intubation [60]. Intubated patients were found to have spent longer on scene, had more volume replacement, more coagulation derangement and lower haemoglobin concentrations than the non-intubated patients, suggesting that the potential harm of this intervention must be considered by providers. As long ago as 1943 the potential hazards of anaesthesia in the presence of haemorrhagic shock were emphasised in descriptions of the use of barbiturate anaesthesia in shocked trauma patients at Pearl Harbour [61]. One retrospective database review of trauma patients who received massive transfusion on arrival in hospital attempts to compare outcomes of these patients with life

Table 14.2 Potential pitfalls of RSI in the presence of life threatening haemorrhage

Intervention	Potential adverse effect
Sedation agents	Hypotension, respiratory depression, hypoxaemia
Neuromuscular blocking agents	Apnoea, hypoxaemia, respiratory acidosis
Intubation attempts	Hypoxaemia, unrecognised oesophageal placement of endotracheal tube, iatrogenic airway injury
Positive pressure ventilation	Reduced cardiac output, hypothermia, inflammatory response
Inadvertent hyperventilation	Cerebral vasoconstriction

threatening haemorrhage who received RSI before arrival in hospital with those who didn't [62]. The authors observed an association between pre-hospital RSI and higher risk of mortality and concluded that this effect was likely to be due to the effect of RSI and ventilation but noted that it may have been due to the patient factors that caused providers to perform intubation in the field rather than waiting until arrival at hospital. A systematic review and meta-analysis of pre-hospital intubation comparing mortality rates of adult trauma patients who underwent pre-hospital intubation with those who were intubated in the emergency department also noted an association between pre-hospital intubation and higher mortality rates [63].

Intubation of shocked trauma patients also carries risk when performed in hospital. A study of the outcomes for adult trauma patients intubated on arrival at hospital noted higher mortality rates for those who suffered post-intubation hypotension [64]. Overall, these studies would seem to support concern that emergent intubation of patients with life threatening haemorrhage carries significant risk of harm and that consideration should be given to deferring intubation, in the absence of airway obstruction, evidence of hypoxaemia, hypercarbia or other compelling indications, until measures can be taken to resuscitate the patient.

The potential pitfalls of intubation in the presence of life threatening haemorrhage are summarised in Table 14.2.

Summary

Airway care is a key component of damage control resuscitation for patients with life threatening haemorrhage. Oxygenation and ventilation must be maintained at all times and when necessary, providers will need to employ a range of airway management strategies, including rapid sequence intubation, to achieve this. Providers must be aware of the potential harm and delays that more complex interventions may cause and when oxygenation can be maintained by simple interventions, should consider deferring definitive airway care until appropriate resuscitation products and facilities are available. The risk of intubation and positive pressure ventilation causing a life-threatening reduction in cardiac output is substantial for all patients with haemorrhagic shock. When rapid sequence intubation is undertaken to facilitate invasive haemorrhage control techniques, every possible care must be taken to minimise the risks of this procedure.

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Damage Control Resuscitation for Severe Traumatic Brain Injury

15

Aaron M. Williams, Geoffrey Ling, and Hasan B. Alam

Introduction

Traumatic brain injury (TBI) remains a leading cause of death and disability worldwide [1, 2]. In the United States alone, approximately 1.7 million people are affected by TBI each year, and TBI ultimately contributes to approximately 30% of all injury-related deaths [3, 4]. In both civilian and military traumatic settings, TBI is frequently accompanied by other traumatic insults, including vascular injury and life-threatening hemorrhage (LTH), which is the leading cause of preventable death in trauma [5]. The presence of severe TBI, in addition to LTH, presents a unique clinical scenario in which providers should be well-versed. Severe TBI alone can contribute to widespread impairment of hemostasis, endothelial function, coagulation, and immune function [6–8]. In the setting of LTH, severe TBI can contribute to potentiation of the lethal triad—acidosis, coagulopathy, and hypothermia—in trauma. To improve patient outcomes, pre- and in-hospital care of patients with LTH and severe TBI requires avoiding hypoxia and hypotension to minimize secondary brain injury and optimizing intracranial hemodynamics [4, 9].

Within recent years, damage control resuscitation (DCR) has become a highly popular treatment strategy with increasing relevance in both military and civilian trauma [10]. Originally termed by the United States Navy, "damage control" refers to providing only those interventions deemed necessary to control hemorrhage and minimize gross contamination [11], with the goal of restoring a patient to a survivable physiologic status through early definitive resuscitation and aggressive correction of metabolic derangements, hypothermia, and acidosis [10]. Achieving these

A. M. Williams · H. B. Alam (✉)
Department of Surgery, University of Michigan, Ann Arbor, MI, USA
e-mail: willaaro@med.umich.edu; alamh@med.umich.edu

G. Ling
Department of Neurology, Johns Hopkins Hospital, Baltimore, MD, USA
e-mail: geoffrey.ling@usuhs.edu

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means is possible through application of several key concepts for LTH, including permissive hypotension, prioritizing blood product transfusion over crystalloids, and aggressive correction of shock and coagulopathy with whole blood or blood product component therapy in 1:1:1 unit ratios to simulate whole blood [12, 13]. As TBI and LTH often coexist in severe trauma, both civilian and military providers must be well-versed in the application of DCR in the setting of severe TBI and LTH. Although such a management strategy is well-established for LTH, alternative treatment strategies and management considerations should be applied to patients with concurrent severe TBI.

This chapter highlights [1] the effects of severe TBI on hemostasis, immune function, endothelial function, and shock (oxygen deficit) which results in cell death, [2] resuscitation principles for pre- and in-hospital care of patients with LTH and severe TBI, [3] resuscitation strategies involving blood products and crystalloids/colloids, and [4] novel neurotherapeutic agents which appear promising to improve clinical outcomes in the setting of severe TBI and LTH.

The Impact of TBI on Shock, Coagulopathy, Endotheliopathy, and Immune Dysfunction

Following the direct impact of TBI, normal hemostasis, inflammation, and endothelial cell and immune functions are immediately disrupted. Although these alterations are observed in traumatic injuries without TBI, the presence of concurrent severe TBI and LTH can substantially increase the magnitude of impaired hemostasis, massive inflammation, and endotheliopathy compared to these isolated conditions alone [14–17]. All of these impairments ultimately contribute to the development of impaired hemostasis, which occurs in over 60% of patient with severe TBI [18, 19].

Development of coagulopathy appears to be related to the rapid induction of a hypercoagulable state, with subsequent transformation to a hypocoagulable state. In the simplest of terms, platelet activating factor (PAF) and brain tissue factor (TF), both potent procoagulants, are released by the brain following injury, resulting in a consumption of coagulation factors and platelets [6]. Despite this oversimplification, the proposed pathophysiologic mechanisms are highly complex and are suspected to include hypocoagulation, platelet consumption and dysfunction, decreased coagulation factor activity, hyperfibrinolysis, and excessive inflammation (Fig. 15.1) [6, 16, 17, 20–27]. This sequence of TBI-induced coagulopathy has been linked to detrimental outcomes with mortality rates ranging from 17% to 86% [18, 28]. Although the prevailing dogma is that severe TBI promotes a significant coagulopathy, there is some prospective observational data to suggest that TBI may not necessarily produce a coagulopathy out of proportion to injury in other body region in recent years [29]. Nonetheless, the presence of severe TBI, in addition to LTH, presents a unique scenario in which providers should be well-versed to provide the best clinical outcomes for severe TBI patients.

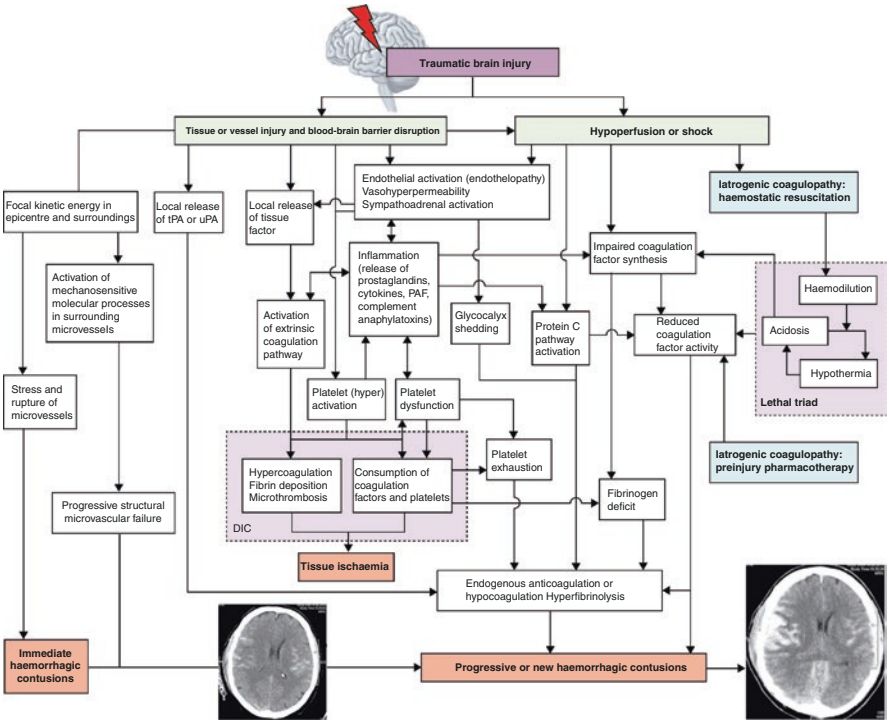

Fig. 15.1 Current understanding of the systemic mechanisms underlying coagulopathy and hemorrhagic contusions after traumatic brain injury. Numerous complex, highly interactive pathways are involved in contributing to the development of coagulopathy following traumatic brain injury including direct impact, microvessel injury, blood-brain barrier disruption, platelet dysfunction, endotheliopathy, protein C activation, hyperfibrinolysis, and iatrogenic coagulopathy. (From Maegele et al. [6], Copyright (2017), with permission with permission of Elsevier)

Initial Injury and Platelet Activation and Disruption

Severe TBI typically results in immediate disruption of brain microvasculature and the blood-brain barrier (BBB), resulting in an immediate hemorrhagic contusion [6]. The closely surrounding area, known as the penumbra, is also a highly sensitive area which can result in delayed microvessel failure causing progressive hemorrhagic contusion [30]. Following microvasculature and BBB disruption, complex interactions between platelets and damaged endothelium or the subendothelial matrix may occur, leading to the release of massive inflammatory mediators, including prostaglandins, cytokines, and PAF [6, 31, 32]. Such mediators can contribute to additional BBB breakdown along with the release of additional PAF and other procoagulants [33]. As a downstream effect, platelet hyperactivation may ensue followed by subsequent platelet consumption and exhaustion, causing both primary and secondary platelet depletion [20, 34]. Platelet dysfunction secondary to inhibition of adenosine diphosphate or arachidonic acid receptors may also occur, even in

the setting of normal platelet counts [20, 23, 34]. Furthermore, this platelet dysfunction can further coagulopathy by influencing coagulation and inflammatory pathways through complement-mediated mechanisms [35–37].

Brain Tissue Factor and Activation of the Coagulation Cascade

Brain tissue factor (TF) release and activation may also play a significant role in the development of inflammation and systemic coagulopathy [6, 38]. In the absence of severe TBI, any brain TF released is normally isolated by the BBB. Following severe TBI, however, TF is shed in the systemic circulation and can be bound extensively by factor VIIa, propagating the extrinsic coagulation pathway [6, 39]. Following subsequent thrombin activation, platelet dysfunction and exhaustion can occur [39]. In severe cases, however, disseminated intravascular coagulation (DIC) may ensue, occurring as early as 6 hours following severe TBI. With the onset of DIC, massive systemic activation of both the intrinsic and extrinsic clotting pathways may occur, resulting in further consumption of coagulation factors and platelets, leading to further coagulopathy. Furthermore, the combination of brain TF and TF released from other associated traumatic injuries can further platelet activation, along with endothelial-derived and platelet-derived micro-particles, enabling formation of procoagulant complexes [14, 24, 40]. As this cascade is propagated, fibrinogen and platelet concentrations may significantly decrease and can result in further coagulopathy and the potentiation of any existing bleeding [41, 42].

Hyperfibrinolysis

Although platelet and coagulation factor consumption contribute to TBI-induced hypocoagulable conditions [41, 42], several alternative mechanisms promoting hyperfibrinolysis have been proposed. In rodent models, both endogenous tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA), well-known mediators of fibrinolysis, have been demonstrated to be increased in brain tissue following TBI [43]. Furthermore, a depletion of alpha-2-plasmin inhibitor, resulting in an increase in plasmin, has also been demonstrated [24]. As plasmin is the cleavage product of plasminogen and a key mediator of fibrinolysis, its increased levels are suspected to make patients with severe TBI particularly susceptible to impaired hemostasis [6].

Endothelial Dysfunction (Endotheliopathy) and Other Mechanisms

When severe TBI is coupled with polytrauma and LTH, additional mechanisms related to endothelial dysfunction or endotheliopathy also come into play [23]. In this setting, massive endothelial damage secondary to shock and injury can result in

severe glycocalyx shedding, which has been shown to induce auto-heparinization [44]. This may ultimately lead to endogenous anticoagulation of TBI patients [44]. In addition, elevated catecholamines often occur secondary to a hyperadrenergic state and endothelial dysfunction, and have been correlated with coagulopathy following TBI [23, 45, 46]. Furthermore, patients with concurrent TBI and LTH have also been shown to exhibit activation of downstream protein C pathways, which can promote further inflammation, hyperfibrinolysis, and inhibition of coagulation factors Va and VIIIa [24, 47].

Lastly, liberal fluid resuscitation for patients with LTH often promotes iatrogenic hypocoagulation secondary to hemodilution, acidosis, and hypothermia (most fluids are room temperature and have a low pH), which can further worsen the lethal triad of trauma—metabolic acidosis, hypothermia, and coagulopathy [48–50]. Acidosis alone can markedly affect the interplay of coagulation factors, while hypothermia is known to inhibit fibrinogen synthesis and thrombin generation [48–50].

Prehospital Resuscitation of the TBI Patient

To achieve optimal patient outcomes, management of severe TBI begins at the time of injury. Initial priorities include in-field triage, stabilization of the patient, and transfer to definitive care facilities. During this process, the major goal should be to minimize secondary brain injury and optimize intracranial hemodynamics. As effective prehospital resuscitation has been linked to short-term and long-term outcomes [51–53], first-responders, emergency medical services, and in-field providers must be well-versed in severe TBI management in the setting of LTH.

Initial prehospital care prioritizes a patient's "airway" and "breathing." A definitive airway should be established in all patients with an inability to protect the airway, inability to maintain oxygenation and ventilation, and a Glasgow Coma Scale (GCS) less than nine. Prehospital hypoxia has been shown to worsen severe TBI outcomes along with furthering neuroinflammation and promoting neurobiomarker release potentiating poor TBI outcomes [16, 54–56]. An oxygen saturation level of at least 90% or a pO_2 greater than 60 mmHg should be targeted [57]. Oxygen values less than these have been shown to increase TBI-associated mortality fourfold [58]. Furthermore, normal ventilation rates, including an end-tidal CO_2 ($ETCO_2$) of 35–40 mmHg, should be targeted for patients with severe TBI. Hyperventilation ($ETCO_2$ <35 mmHg) should be avoided for routine use or elevated intracranial pressure (ICP) prophylaxis [59–61], and only implemented for patients with signs of impending cerebral herniation [62].

Following stabilization of patient's airway and breathing, the next priority becomes "circulation." Hemorrhage from trauma is the primary cause of hypovolemia and hypotension. In the prehospital setting, hypotension, which is defined as a systolic blood pressure (SBP) less than 90 mmHg, can be markedly dangerous in patients with severe TBI [63]. Each episode of hypotension has been shown to have deleterious effects on the brain [63]. The goal of fluid resuscitation in this setting is to optimize cerebral hemodynamics and further oxygen delivery to the brain. For

patients with concurrent LTH, early and definitive hemorrhage control is key to minimize ongoing hemorrhage. Although the traditional definition of hypotension (<90 mmHg) was previously the target SBP according to the prior Brain Trauma Foundation (BTF) guidelines (3rd edition), new literature has emerged which supports a higher level, which varies by age, to improve outcomes [64–66]. The prior threshold of 90 mmHg is thought to underestimate hypotension-induced secondary brain injury [65]. The 4th edition of the BTF guidelines now states that a SBP greater than 100 mmHg, depending on age, should be targeted for patients with concurrent severe TBI [57]. For patients between 50 and 69 years old, a SBP of greater than 100 mmHg should be targeted [57]. For patients between the ages of 15 and 49 or greater than 70 years old, however, a SBP greater than 110 mmHg should be maintained [57]. Currently, these recommendations remain in contrast with the Tactical Combat Casualty Care (TCCC) guidelines, which still suggest a SBP target of 90 mmHg.

Furthermore, there are no current recommendations regarding the optimal fluid for resuscitation [53]. Isotonic crystalloids are the fluid used most often in the prehospital setting given resource and logistical constraints. However, blood product administration may provide definitive resuscitation for patients with concurrent LTH and can improve neurologic outcomes following severe TBI. Several alternative choices for patients with severe TBI exist and may have logistical advantages. Such resuscitative strategies will be discussed later in the chapter.

Early neurologic assessment, including GCS, should be performed to help guide severe TBI management. Patients should be frequently monitored for signs of Cushing's triad, including hypertension, bradycardia, and irregular respirations. They should also be monitored for signs of impending cerebral herniation, which includes dilated, unreactive, and asymmetric pupils, and a motor exam with extensor posturing or progressive neurologic deterioration. In patients with concerning signs, hyperventilation ($ETCO_2$ 30–35 mmHg) should be employed until clinical improvement is observed and should only be used as a temporizing maneuver [53]. In addition, hypertonic saline, which ranges from 3% to 30%, may be administered to aid in ICP management if deemed a concern [67–70]. A bolus of 250 mL or 2 mL/kg of 7.5% saline has been commonly used in studies. Although found to be inferior to hypertonic saline in ICP reduction, mannitol (0.5–1.0 mg/kg) may be used for patients with cerebral herniation if intravascular volume can be maintained. However, none of these agents have trial evidence supporting improved survival or neurologic outcomes compared to each other. Lastly, combination of hypertonic saline with dextran (250 mL bolus of 7.5% saline/6% dextran) has been studied but also failed to show any clinical benefit compared to normal saline alone [68].

Patients with severe TBI and LTH may also present with hypothermia and is associated with increased fluid resuscitation and blood product transfusions due to severity of their illness. Therefore, prehospital hypothermia should be avoided as much as possible [71, 72]. Furthermore, prehospital hypothermia is independently associated with morbidity and mortality, including pneumonia and adult respiratory distress syndrome (ARDS) [71, 72].

Sedation and analgesia may also be required for transporting patients to a higher level of care. According to the 4th edition of the BTF guidelines, barbiturates and propofol may be used as sedation for patients with TBI. Both agents can reduce ICP and help terminate seizure activity. High-dose barbiturates may be used to control elevated ICP that fails to respond to medical and surgical therapy. However, providers must be aware that it may cause hemodynamic stability during use. Propofol may also be used as a sedative given its rapid onset, short duration of action, ability to decrease ICP, and preservation of CO_2 reactivity and cerebral autoregulation [73]. Propofol, however, has failed to show improvement in mortality for 6-month outcomes [74]. Providers must also be aware of propofol infusion syndrome, which can occur at high doses and can cause significant morbidity.

In recent years, there has been an emerging use of ketamine for prehospital induction, maintenance, and sedation for patients with TBI [75]. Ketamine was historically avoided due to concerns that it caused an increase in ICP. However, recent evidence suggests otherwise. A systematic review by Zeiler et al. failed to demonstrate that ketamine increases ICP [76]. In some cases, ketamine use actually decreased ICP. Furthermore, no significant adverse effects were noted related to ketamine administration. Recent studies appear to demonstrate that ketamine may actually have neuroprotective effects in TBI by inhibiting spreading depolarization, decreasing neurotoxic metabolites, and attenuating oxidative stress and apoptosis [75, 77–80]. Although ketamine is currently not listed in the 4th edition BTF guidelines, it appears to be one of the most commonly used prehospital sedatives in the field. Evidence continues to accumulate supporting its use.

Lastly, antibiotics may be administered for patients with associated penetrating injuries related to TBI. Gram positive organisms, including *Staphylococcus aureus,* and gram-negative bacteria may be involved [81]. As such, cephalosporins are the most preferred antibiotics; however, some recommend ceftriaxone, metronidazole, and vancomycin for extended durations for penetrating brain injury [81].

In-Hospital Resuscitation of the TBI Patient

Once transported to definitive care facilities, severe TBI patient should be transported to the intensive care unit (ICU) for critical care monitoring and management. In the ICU, oxygenation and ventilation should remain key priorities. If not already established, a definitive airway should be considered if indicated (GCS $\leq$8). Oxygenation should be maintained with a pO_2 >60 mmHg or oxygen saturation >90%, while normocapnia ($ETCO_2$ 35–40 mmHg) should be targeted in the absence of cerebral herniation [57]. If hyperventilation is indicated for cerebral herniation, it should only be conducted for a period of 24 hours. Following ensuring a secure airway and breathing, a patient's circulation should be re-evaluated. As stated previously, a SBP of greater than 100 mmHg should be targeted for patients between 50 and 69 years old [57]. However, a SBP greater than 110 mmHg should be maintained for patients between the ages of 15 and 49 or greater than 70 years old [57].

Once stabilized, focus should turn to managing neurologic deficits. Early imaging, including computed tomography (CT), should be obtained to assess the degree intracranial injuries and prognosticate patients. There is some evidence, although weak, to support using ICP monitoring for patients with severe TBI to reduce in-hospital and 2-week post-injury mortality [57]. When ICP monitoring is used, an ICP of less than 22 mmHg should be targeted [57]. Maintaining a cerebral perfusion pressure (CPP) of 60–70 mmHg is critical to provide adequate perfusion to the brain [57]. Several modalities exist to achieve lowering ICP if a concern, including hypertonic saline bullets (30 cc of 23.4% saline), hypertonic saline infusions (3% saline), and mannitol in select patients. An external ventricular drain (EVD) may be used for continuous CSF drainage to lower ICP [57]. This may be used within 12 hours after injury for patients with an initial GCS <6–8 [57, 82]. Other modalities to lower ICP exist, but have weak supporting evidence. According to the BTF guidelines, early hemicraniectomy can be considered in select patients as a last resort [57, 83]. Although long-term outcomes remain controversial and may lead to unfavorable outcomes, this procedure has been shown to reduce ICP and minimize days in the ICU [83]. The latest study suggests that decompressive craniectomy should be used only in patients with refractory intra-cranial hypertension (ICP >25 mmHg) that have failed all medical treatments, rather than as an early treatment [84]. This approach, however, varies widely internationally and different approaches in terms of timing may be considered, especially for adult versus pediatric patients.

Several other management options may be considered. Antiepileptic drugs, including Levetiracetam, have been shown to decrease the incidence of early post-traumatic seizures when administered within 7 days of injury and may be used [85, 86]. Enteral nutrition should be initiated as early as possible to decrease mortality [87, 88]. Lastly, hypothermia [89] and steroids [90] are no longer indicated in these settings, although previously thought to be beneficial.

Resuscitation Strategies for Severe TBI and LTH Patients

Resuscitation strategies remain complex in patients with concurrent LTH and severe TBI. However, initial critical steps for prehospital and in-hospital resuscitation include hemorrhage control and volume expansion to restore systemic perfusion and oxygenation. In the absence of TBI, patients with LTH should receive DCR strategies with focus on hypotensive resuscitation. The injured brain in patients with concurrent TBI, however, is highly susceptible to secondary insult including hypotension and hypoxia. Therefore, maintenance of an adequate SBP and CPP, as previously mentioned, is required [57], and the concept of DCR with hypotensive resuscitation is contraindicated in this setting.

Unfortunately, the optimal resuscitation strategy for patients with LTH and severe TBI in the prehospital setting is rather limited. Crystalloids and colloids are readily available, but blood products are often unavailable in the field due to logistical constraints. In the setting of LTH, blood products can be life-saving and improve outcomes if administered early in ratio-based resuscitation (1:1:1) [12, 91]. For

patients with TBI, resuscitation guidelines are not as clear. The BTF guidelines recommend crystalloid for any TBI patient with hypotension in prehospital settings [57]. However, the evidence for this recommendation is weak and warrants further investigation.

Here, we present different resuscitation strategies, including crystalloids, colloids, and blood products, for patients with concurrent LTH and severe TBI. Each strategy has its own benefits and limitations, which providers should consider carefully during the development of their management protocols.

Crystalloid Resuscitation Strategies

Historically, blood products are often unavailable for resuscitation of patients with LTH and severe TBI in the prehospital setting. As such, crystalloids and colloids are the two major types of resuscitative fluids administered to improve circulating volume, shock, and oxygen delivery. Crystalloids are a relatively cheap way to achieve rapid improvement in SBP. However, once administered, crystalloids can decrease oncotic pressure and promote significant interstitial tissue edema when given [92]. As such, a large volume is required to maintain an increase in plasma volume, which can be logistically challenging in an austere environment or resource-constrained settings [93]. Judicious use should always be considered as cerebral edema, a life-threatening complication contributing to TBI-associated mortality, can ensue.

Current Advanced Trauma Life Support (ATLS) guidelines recommend the use of crystalloid, including either normal saline (NS) or lactated ringer's (LR), for initial resuscitation [94]. In the setting of LTH, this can be life-saving. However, the optimal fluid for resuscitation in patients with TBI is unknown at this time [95]. Several animal studies suggest that LR resuscitation is associated with improved physiological outcomes and decreased secondary bleeding [96, 97], while NS resuscitation may lead to hypochloremic acidosis, which can cause systemic vasodilation and coagulopathy [98]. Despite this, some consider NS to be the preferred fluid for TBI patient resuscitation given its increased osmolarity compared to LR [95]. Within recent years, prospective observational studies have demonstrated increased mortality with LR use compared with NS in patients with TBI [95]. Although most would consider NS use for patients with TBI, these controversies remain, and randomized controlled clinical trials are needed to further elucidate LR and NS resuscitation for patients with TBI in the prehospital phase.

Colloid Resuscitation Strategies

In contrast to crystalloids, colloids (albumin, dextran, and hydroxyethyl starch) are able to increase intravascular oncotic pressure by drawing water from interstitial tissues and maintain existing volume in the intravascular space [99]. In theory, colloid administration may help prevent over-resuscitation resulting in interstitial edema and aid in maintaining microcirculatory flow [100]. As such, colloids could

potentially be used to help minimize the risk of cerebral edema. However, the use of colloids remains controversial in patients with TBI, as some suspect that the increased permeability of a damaged BBB can result in unfavorable outcomes. Despite this, colloids are generally preferred in tactical combat casualty care as they can provide the resuscitative volume needed to improve intravascular volume and "theoretically" minimize the total volume required to achieve this [101].

Although initially thought to be a promising colloid agent, albumin has provided suboptimal results for patients with LTH and severe TBI. The Saline versus Albumin Fluid Evaluation (SAFE) trial demonstrated that 4% albumin can cause increased ICP and mortality among TBI patients [102]. Although not fully explained by the study, some suspect that this increased mortality is attributed to colloid extravasation into the brain parenchyma following TBI-associated BBB damage, which may worsen any initially existing TBI-induced cerebral edema [103, 104]. Some studies, however, have demonstrated benefits when using higher concentrations of albumin (20%), leading to decreased neurologic deficits and brain tissue necrosis in experimental models of TBI.

Hextend, a colloid volume expander consisting of 6% hetastarch in LR, has demonstrated promise in clinically realistic large animal studies. Following administration, Hextend can decrease brain swelling compared to NS resuscitation alone [105]. In small animal studies, 10% hetastarch has demonstrated decreased brain tissue necrosis and neurologic severity scores (NSS) [106]. However, its use has yet to be confirmed in randomized human trials of patients with concurrent LTH and severe TBI. Despite this, Hextend is currently considered the first-line fluid of choice among colloids and crystalloids for use in far-forward combat resuscitation given its markedly beneficial effects in preclinical animal studies and low volume [93, 101]. However, further studies are required to further elucidate its safety and beneficial effects in trauma patients.

Blood Product Resuscitation Strategies

The optimal resuscitation strategy for patients with LTH and severe TBI in the prehospital settings involves early administration of either whole blood or red blood cells (RBCs), fresh frozen plasma (FFP), and platelet concentrates while minimizing crystalloid use. Such blood products and derivatives have demonstrated superiority to crystalloids and colloids by providing definitive resuscitation through improving oxygen-carrying capacity, replacement of clotting factors, and anti-inflammatory mechanisms [12, 107]. Furthermore, blood product administration can mitigate the effects of the lethal triad including trauma-induced coagulopathy, hypothermia, and acidosis. In the setting of isolated LTH, blood products should be administered either as whole blood or in a 1:1:1 fashion to target DCR through hypotensive resuscitation (SBP target of 90 mmHg) for patients with hemoglobin deficits, ongoing hemorrhage, and hemodynamic instability. However, when concurrent severe TBI exists with LTH, achieving DCR requires targeting a SBP greater than 100 mmHg, depending on age, and an adequate CPP, as previously discussed

[57]. Currently, no well-defined transfusion thresholds based on evidence guide transfusion practices in patients with severe TBI/closed head injury. It is well known, however, that patients with severe TBI requiring blood product transfusions demonstrate poor clinical outcomes [108]. As such, judicious blood product transfusion should be considered to minimize morbidity and mortality.

Red Blood Cell Transfusion

Within recent years, RBC transfusion for anemia in patients with severe TBI has become a controversial topic. Post-traumatic anemia and poor clinical outcomes in patients with severe TBI has been an inconsistent finding [109]. It is well known that decreased oxygen delivery to the brain following severe TBI can result in progression of ischemia, causing secondary brain injury [108]. As oxygen delivery to the brain is primarily dependent on the hemoglobin (Hb) concentration, decreased Hb has been suspected to cause exacerbation of TBI [108]. However, the exact Hb threshold at which RBCs should be administered for transfusion has remained a matter of debate [110, 111].

Currently, there are clear clinical guidelines indicating that a Hb less than 7 g/dL mandates RBC transfusion [109]. Randomized control trials analyzing the role of restrictive transfusion (Hb <7 g/dL) compared to liberal transfusion (Hb <10 g/dL) demonstrate that patients with restrictive Hb transfusion thresholds had more favorable outcomes and less thromboembolic events [112, 113]. Although previously employed, there appears to be no benefit to liberal transfusions for severe TBI patients targeting a Hb greater than 10 g/dL. In fact, liberal transfusion may be deleterious [114]. Some studies have indicated that liberal transfusion thresholds can even lead to progressive hemorrhagic injury, contributing to higher morbidity and mortality [115]. Although further work to elucidate the optimal Hb threshold is ongoing, most providers would agree that the current standard involves restrictive blood transfusion thresholds in patients with non-active bleeding. For patients with active bleeding, it is reasonable to maintain a Hb of at least 9 g/dL.

Fresh Frozen Plasma Transfusion

Plasma-based resuscitation strategies have demonstrated improved outcomes in trauma patients within recent years. Following LTH, clotting factor levels can decrease by nearly 30% from baseline after replacing a patient's blood volume with RBC transfusions [116]. Any further hemorrhage beyond this point can severely impact a patient's ability to maintain hemostasis, leading to trauma-induced coagulopathy, which is present in nearly 25% of trauma patients [18]. Within recent years, the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial assessed clinical outcomes in severely injured trauma patients receiving high and low plasma and platelet transfusion ratios (1:1:1 versus 1:1:2 plasma: platelet: RBC) [117]. Although no differences were found in 24-hour or 30-day mortality, the 1:1:1

group experienced fewer deaths by exsanguination at 24 hours [117]. This improvement has been thought to be secondary to FFP's ability to decrease vascular permeability and promote improvement in endotheliopathy.

In the setting of concurrent LTH and severe TBI, no randomized control trial data exists for plasma-based resuscitation strategies. However, well-performed preclinical animal and clinical observational and prospective studies appear to suggest a benefit. In porcine models of concurrent LTH and severe TBI, FFP improves secondary brain injury through decreased lesion size and improved neurologic recovery [118]. Lyophilized plasma, an alternative strategy that meets military constraints (e.g., long shelf-life, stable without need for refrigeration, low volume), has also been investigated demonstrating comparable therapeutic effects to FFP on secondary brain injury and neurologic recovery in porcine models [119]. Such benefits are suspected to be due to improvement in volume expansion and cerebral perfusion, attenuation of glutamine-mediated excitotoxicity, decreased mitochondrial dysfunction, as well as repair of endothelial and BBB injury [120]. Repair of endothelial injury following LTH with plasma-based resuscitation strategies has been confirmed in animal lung models [121, 122]. It is also suspected that FFP resuscitation can directly affect gene regulation by upregulating genes involved in metabolic and platelet signaling, and downregulating genes involved in inflammatory pathways [123].

Several human studies have confirmed beneficial effects with plasma-based resuscitation; however, others report detrimental effects. Peininger et al. demonstrated that a high plasma:RBC ratio is an independent predictor of improved survival among 1250 trauma with concurrent LTH and severe TBI [91]. However, others have demonstrated that high plasma:RBC transfusion ratios are associated with improved survival in patients without TBI [124]. A few studies, however, have reported adverse outcomes with FFP transfusion, demonstrating worsening secondary brain injury and higher mortality rates in TBI [125]. Although some controversy remains, further work is required to further elucidate the effects of FFP in human trauma patients with concurrent LTH and severe TBI. Investigation is also needed to compare the safety and efficacy of different formulations of plasma such as FFP, liquid plasma, and solvent detergent plasma. Processing differences for plasma lead to alterations in product characteristics and immune effects [126, 127]. It is unknown if these in vitro differences have any clinical relevance.

Platelet Transfusion

Similar to plasma-based resuscitation strategies, platelet resuscitation strategies have demonstrated improved outcomes in patients with LTH within recent years. Similarly, the PROPPR trial demonstrated that high platelet ratio transfusions (1:1:1 versus 1:1:2 plasma: platelet: RBC) patients can significantly decrease deaths by exsanguination at 24 hours in severely injured trauma patients [117].

Evidence for platelet-based resuscitation strategies has been emerging for patients with concurrent LTH and severe TBI. It is well-known that platelet

consumption and dysfunction occurs secondary to alteration in local and systemic coagulation pathways following TBI [6]. In recent years, ratio-based platelet resuscitation strategies have demonstrated improved outcomes in trauma patients with TBI. Spinella et al. conducted a retrospective review analyzing 2,312 trauma patients with massive hemorrhage, with and without TBI, focusing on patients who received high or low platelet to RBC units (<1:2 vs. ≥1:2) [124]. TBI patients who received high platelet ratios were found to have improved 30-day survival compared to patients with low platelet:RBC ratios [124]. Similarly, in a 3-year retrospective analysis of patients with TBI as the only major injury, Oroujikoar et al. found that TBI patients receiving ratio-based platelet resuscitation had higher survival rates compared to patients with non-ratio based resuscitation strategies [128]. For severe TBI patients requiring massive transfusion for concurrent LTH, it is suspected that ratio-based platelet resuscitation can help aid in intravascular volume resuscitation, platelet replenishment, as well as prevention of dilutional coagulopathy [128]. This correction of coagulopathy, through platelet resuscitation, may also help improve clinical outcomes for patients with intracranial bleeding, as well as improve time to definitive operative repair if needed [129]. The benefits of plasma transfusion may also occur with platelet transfusion since there is almost an entire unit of plasma within a unit of apheresis platelets.

Within recent years, several animal studies have attempted to investigate the mechanisms of action by which platelets provide therapeutic effects in TBI at the level of the brain. In a rodent model, platelets have been demonstrated to promote BBB healing by activating oligodendrocyte precursor cells (OPCs) [130]. OPCs are predominantly responsible for differentiation into oligodendrocytes, which can then repair injured areas of demyelination secondary to TBI [130]. Further studies investigating this arena are currently being employed.

Whole Blood Transfusion

Although previously considered the historic resuscitation for LTH, whole blood had, until recently, disappeared from mainstream use for definitive resuscitation. Unfortunately, this transition from whole blood to blood component transfusion had occurred without clinical evidence of superior or equal efficacy and safety. Within recent years, however, there has been a resurgence of whole blood for transfusion in both military and civilian centers for LTH. Currently, there are 20 trauma centers implementing whole blood for transfusion in LTH, and this list is rapidly expanding.

Although data continues to emerge to support its use, whole blood may provide many biological and logistical advantages compared to blood product component therapy [131]. First, whole blood contains balanced and increased cellular components of RBCs, platelets, and plasma [132]. This avoids additives and anticoagulants that can contribute to dilutional coagulopathy noted with individual therapies [132]. Furthermore, whole blood contains a 30% higher oxygen

carrying capacity when compared to individual blood component therapy [133]. In terms of hemostatic function, platelets in whole blood stored at 2–6 °C have improved platelet aggregation and stronger clots compared to those stored at 20–24 °C [134–138].

Although there may be may logistical and biological benefits to whole blood transfusion, there is limited data regarding its use in LTH and TBI. Further studies, however, are required to help further support its adoption in the near future.

Complications of Blood Product Transfusion

Although blood products can be life-saving and improve outcomes when administered early and in ratio-based resuscitation, they should be administered judiciously as several possible complications may occur. The most common complications include either acute or delayed, non-hemolytic reactions, which are relatively minor. For patients with severe TBI, transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO) can contribute to significant morbidity and mortality [139–141]. TRALI results from immune complex-mediated damage to the pulmonary vasculature resulting in increased permeability and edema, which can manifest as dyspnea and bilateral pulmonary edema. In TACO, increased hydrostatic pressure results in increased edema, manifesting as respiratory distress, hypoxemia, and volume overload [108]. Treatment for TRALI and TACO involves initial supportive measures and mechanical ventilation, while TACO also mandates diuresis [108].

Novel Therapeutics Agents for Improving Clinical Outcomes

Within recent years, identifying pharmacologic agents to improve outcomes in patients with concurrent LTH and severe TBI has become an area of interest. As far-forward settings and austere environments are often resource-limited and logistically constraining, definitive resuscitative strategies with blood products are not always possible. Pharmacologic agents improving survival and minimizing neurologic injury, coagulopathy, inflammation, and oxidative stress have been investigated. Such agents are low volume, environmentally stable, cheap, and easy-to-use and have the potential to be high impact treatment strategies. Among numerous agents, valproic acid (VPA) appears to be a promising prehospital neurotherapeutic agent which could be used in patients with concurrent LTH and severe TBI. It has demonstrated its significant therapeutic effects in preclinical animal models. Other agents, including anti-inflammatory, anti-edema, and antioxidant agents, have demonstrated promise, although their therapeutic profiles are more selective and targeted. Further studies investigating the therapeutic effects of these agents are ongoing but are likely to be potential treatment strategies in the near future [142].

Valproic Acid

VPA, a historic anti-convulsant drug approved by the Food and Drug Administration (FDA) in 1978, has become a promising agent for patients with LTH and severe TBI in recent years. VPA is a histone deacetylase inhibitor (HDAC inhibitor or HDACI), which causes histone and non-histone acetylation affecting gene expression and protein function. When added to other resuscitative fluids, VPA has been demonstrated to improve outcomes in preclinical models. In rats, NS + VPA (300 mg/kg) resuscitation improved survival to 80% compared to 17% in animals resuscitated with NS alone [143]. In swine subjected to LTH and polytrauma, Hextend + VPA improved survival to 50% compared to 25% in Hextend-treated animals alone [144].

In recent years, large animal models have been used to further demonstrate VPA's effects in traumatic models including concurrent LTH and severe TBI. In swine subjected to TBI and LTH, animals resuscitated with NS + VPA (150 mg/kg) demonstrated smaller brain lesion size, decreased neurologic injury, improved neurologic recovery, and faster normalization of cognitive function [145]. With the addition of polytraumatic injuries, similar findings have been observed. Animals resuscitated with NS + VPA (150 mg/kg) showed less neurological impairment and smaller brain lesion size after treatment compared to those resuscitated with NS alone [146].

In mediating these effects, VPA has been shown to alter the BBB following injury and promote gene regulation in the brain and peripheral blood mononuclear cells (PBMCs) [147]. Following administration in swine subjected to TBI and LTH, VPA treatment improves protein expression profiles leading to improvement of BBB integrity [148]. Brain tissue harvested at 8 hours following VPA treatment has even demonstrated upregulation of genes involved in neurogenesis and neuroregulation and downregulation of genes involved in apoptosis and inflammation [148]. Similarly, in swine subjected to TBI, polytrauma, and LTH, VPA-treated animals demonstrated altered gene expression in PBMCs [149]. VPA treatment upregulates gene pathways involved in cellular growth and proliferation, and downregulates pathways involved in alteration of cell cycle checkpoints, apoptosis, acute phase reactants, and the inflammatory response [149]. In similar models, VPA treatment has also been demonstrated to reduce collagen, arachidonic acid, and adenosine diphosphate-induced platelet aggregation, suggesting that VPA can decrease platelet aggregation and affect clot dynamics (strength and rate) [150].

Initial human studies have demonstrated great promise as well. The safety and tolerability of high-dose VPA has recently been tested [151] and will be moving to a phase II clinical trial in the coming years.

Anti-inflammatory Agents

Astrocyte and microglial activation, cytokine release, and BBB disruption can contribute significantly to the development of neuroinflammation following TBI. Within recent years, inhibiting neuroinflammation has been a potential target to improve

clinical outcomes following TBI. Anti-inflammatory pharmacologic agents, including minocycline, have become promising candidates. Minocycline is a second-generation tetracycline that exhibits potent anti-inflammatory and neuroprotective properties and has been shown to be effective in preclinical models through suppression of IL-1B, IL-6, microgliosis, and neuronal apoptosis [152]. In the past several years, minocycline has been demonstrated to reduce serum neurofilament levels in patients with spinal cord injury (SCI) in clinical trials [153]. Although several studies have demonstrated improvements in long-term behavior following neurologic injury, others have demonstrated only transient effects on recovery [152]. Others, however, are concerned that despite decreasing microglial activation, increased neurodegeneration may be observed with minocycline use [154, 155]. However, further studies in this arena are ongoing.

Synthetic peroxisome proliferator-activated receptor (PPAR) agonists are another potentially efficacious anti-inflammatory agent for the treatment of TBI and SCI. Following activation, PPARs can translocate from the cytoplasm to the nucleus to augment gene expression, suppressing COX2 and iNOS, two pro-inflammatory mediators [156–158]. Fenofibrate has been shown to reduce inflammation, oxidative stress, and cerebral edema following TBI through PPAR-alpha agonism [159]. However, Pioglitazone and Rosiglitazone, PPAR-gamma agonists, have also been demonstrated to decrease astrocytic and microglial activation and to promote neuroprotective proteins HSP27 and Mn-SOD, facilitating improved behavior and histological outcomes following TBI [160, 161]. Such effects have even been observed in various TBI models including cortical impact, diffuse TBI, and lateral percussive injury [160, 162, 163].

Anti-edema Agents

Cerebral edema is a significant contributor to early morbidity and mortality following TBI. It can lead to a significant increase in ICP, preventing the brain from appropriate cerebral perfusion and oxygenation [164]. When severe TBI is coupled with aggressive fluid resuscitation, cerebral edema can worsen even further [164]. Several agents have been used to help prevent against cerebral edema in these settings. In severe TBI, the administration of mannitol, an osmodiuretic, has been demonstrated to decrease brain edema for in-hospital patients [165]. However, prehospital data is currently lacking and mannitol use may be contraindicated for severe TBI patients with concurrent LTH given the risk of hypotension. Other pharmacologic agents, including cannabinoid receptor agonists, have demonstrated promise in the preclinical setting [166–168]. Following TBI, dexanabinol (HU-211) has been shown to reduce brain edema by decreasing neuroinflammation and improving BBB integrity in a murine model of closed head injury. Furthermore, selective activation of cannabinoid receptor-2 has been shown to reduce neuroinflammation, reduce cerebral edema, enhance cerebral blood flow, and even improve neurobehavioral outcomes following murine models of controlled cortical impact-induced TBI and endovascular-induced subarachnoid hemorrhage [168, 169].

Antioxidative Agents

Oxidative damage to the brain can occur as early as minutes following TBI. Several key pathways involve free radical production from the enzyme xanthine oxidase, arachidonic acid cascade, and mitochondrial leak/generation. Following production, these free radicals can cause significant oxidative damage to proteins, DNA, and RNA. In recent years, targeting inhibition of free radical production and scavenging circulating free radicals has been investigated [170].

Cyclosporine A (CsA), a drug commonly used as immunosuppression in transplantation, inhibits mitochondrial permeability transition pores, which can prevent the production of free radical species [142]. Initial preclinical studies have demonstrated promise, as it has been able to provide neuroprotection in preclinical models by inhibiting lipid peroxidation and mitochondrial damage contributing to neurotoxicity [142]. Other drugs, including phenelzine, an FDA-approved monoamine oxidase inhibitor, have demonstrated similar results and may act synergistically to CsA [171]. These drugs are suspected to act via attenuation of mitochondrial dysfunction and neuronal damage and to decrease glutamate and lactate levels [172–174]. Other promising antioxidant therapies, including dimethyl fumarate, ubiquinol, and N-acetylcysteine, have demonstrated efficacy in preclinical models when administered within several hours following injury [175–177]. Unfortunately, many of these have failed to demonstrate translation into human TBI patients secondary to their limited therapeutic window. However, some view this limitation as an excellent opportunity for prehospital neurotherapeutic resuscitation if able to be administered early [178]. Further studies are required to further refine these therapeutic strategies targeting prevention of oxidative damage.

Conclusions

In conclusion, LTH and severe TBI remain leading causes of preventable deaths in trauma. Although DCR has become a highly popular treatment strategy for LTH, the presence of concurrent severe TBI requires alternative treatment strategies and management considerations. It is important to understand that the presence of severe TBI can significantly contribute to systemic coagulopathy. Improving patient outcomes requires being well-versed in the pre- and in-hospital care of patients with LTH and severe TBI, which aim to minimize secondary brain injury and optimize cerebral hemodynamics. Several novel resuscitative treatment strategies have demonstrated great promise in improving outcomes in patients with LTH and TBI, but require further testing and exploration in the coming years. To ensure streamlined delivery, all of these options should be carefully considered and incorporated into an Institutional TBI-Management Protocol in collaboration with the various stakeholders (emergency medicine, trauma surgeons, neurosurgeons, pharmacy, blood bank, nursing, etc.). These protocols should also be periodically updated as new information becomes available.

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Emergency Preparedness Aspects of DCR for Civilian Mass Casualty Scenarios

16

David W. Callaway, Reed Smith, and Sean M. Fox

Introduction

The goal of Mass Casualty Incident (MCI) preparedness and response is to reduce potentially preventable death during times of acute health system strain from patient volume and acuity [1–3]. An MCI is defined as an event which "generates more patients at one time than locally available resources can manage using routine procedures or resulting in a number of victims large enough to disrupt the normal course of emergency and health care services and would require additional non-routine assistance." [4] Though extensively studied in the military, the epidemiology of mortality in civilian Traumatic-MCI (T-MCI) is more variable. In the civilian setting, despite a decade of high-profile dynamic T-MCIs, there exists no standard injury pattern [5]. For example, a 2014 Emergency Medical Services database analysis revealed that although 40.7% of self-reported MCIs were categorized as "traumatic," motor vehicle accidents accounted for 63% of the calls (i.e., blunt mechanism). In contrast, Smith et al. reported a majority of mortality from Civilian Public Mass Shootings was secondary to penetrating torso and neurologic trauma (i.e., penetrating mechanism) [6, 7]. Accordingly, health systems must implement an all-hazards approach to T-MCI, be prepared for much broader threats, and develop robust polytrauma response paradigms.

D. W. Callaway (✉)
Department of Emergency Medicine, Operational and Disaster Medicine, Carolinas Medical Center, Atrium Health System, Charlotte, NC, USA

R. Smith
Department of Emergency Medicine, George Washington University, Washington, DC, USA

Arlington County Fire Department, Arlington, VA, USA

S. M. Fox
Department of Emergency Medicine, Carolinas Medical Center, Atrium Health System, Charlotte, NC, USA

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Damage control resuscitation (DCR) is the current standard of care for treatment of patients suffering from trauma-related massive hemorrhage. DCR is a bridging strategy that aims to minimize blood loss, hypothermia, acidosis, and coagulopathy through *early* hemorrhage control, *aggressive* hemostatic resuscitation, and *rapid* movement to surgical hemorrhage source control to enable definitive surgical stabilization. *Early, aggressive*, and *rapid* are the key phrases in the Emergency Department. However, the complexity, patient volume, and systems impact of T-MCI create unique challenges to DCR implementation.

This chapter will focus on the tiered application of damage control resuscitation, including remote DCR (RDCR) principles, as a key pillar of civilian T-MCI emergency readiness and response. The emergency management framework is a standard tool for developing a systems approach to DCR integration into the full spectrum of T-MCI and disaster response. For the purposes of this chapter, the doctrine will broadly divide disasters into *readiness* and *response* phases applied across the operational arenas of prehospital care, first receiver facilities (FRF), and trauma centers.

Readiness

In the hemorrhaging trauma patient, the development of oxygen debt that causes endotheliopathy and immunologic and hemostatic dysfunction is referred to as "blood failure" [8]. Up to 25% of major trauma patients presenting to the ED suffer from acute traumatic coagulopathy (ATC) with resultant increased mortality [9]. Although, the mechanisms of ATC are complex, it is thought to be caused by hypoperfusion that leads to increased activated protein C and hyper-fibrinolysis. Thus, the DCR approach of hemostatic resuscitation is based on the principle of balanced blood product administration, limitation of crystalloid/colloid infusions, plus pharmacologic adjuncts in order to limit "blood failure," and death from hemorrhage. Early initiation of hemostatic resuscitation at point of injury and continuation through FRF and on to the trauma center improves 24-hour and 30-day survival in trauma [10, 11]. However, the logistics of hemostatic resuscitation and DCR are challenging given the variable resources across systems, and success relies heavily on a systems commitment to readiness.

Readiness is broadly comprised of mitigation and preparedness activities. A critical initial step in T-MCI readiness is articulating the DCR priorities within the mitigation and preparedness context in order to align key response stakeholders from the prehospital, first receiver, and trauma center communities. Mitigation is the process of clearly defining the problem set, conducting a system gap analysis, articulating a plan for whole of community and regional healthcare response, and executing pre-disaster measures to reduce risk. Mitigation activities should build capabilities (i.e., training, equipment, etc.) and address physical assets with limited capacity (i.e., ambulances, hospital beds, blood collection/distribution, etc.). Delineation of priorities and goals allows for an accurate system gap analysis (Table 16.1). A common operating framework with common language allows all stakeholders to align

Table 16.1 Example DCR gap analysis: blood product availability

Topic	Risk	Impact	Priority	Current	Proposed	Gap
General	*Determine the range of potential disasters likely to be faced*	*Predict the effect of these disasters on population, critical infrastructure, and government operations*	1,2,3, etc. (1 = highest priority)	*Quantitative or qualitative description of current system*	*Desired future state*	*Material, administrative, logistical, regulatory, and policy gaps*
Prehospital RBC availability	Routine trauma T-MCI surge	Delayed DCR and potential increased mortality and overall system blood product use	8	25%	2 U	e.g., policies, quality assurance, blood storage
Prehospital plasma availability	Routine trauma T-MCI surge	Delayed DCR and potential increased mortality and overall system blood product use	5	Very few	2 U	e.g., policies, quality assurance, blood storage
Prehospital LTOWB	Routine trauma T-MCI surge	Delayed DCR and potential increased mortality and overall system blood product use	3	Very few	4 U	e.g., policies, quality assurance, blood storage
First receiver facility PRBC availability	Routine trauma T-MCI surge	Inability to provide state of the art trauma resuscitation or offload trauma centers in T-MCI	6	4 U (units)	8 U	e.g., Blood stewardship program
First receiver facility plasma availability	Routine trauma T-MCI surge	Inability to provide state-of-the-art trauma resuscitation or offload trauma centers in T-MCI	4	2 U (units)	4 U	e.g., Blood stewardship program

(continued)

Table 16.1 (continued)

Topic	Risk	Impact	Priority	Current	Proposed	Gap
Trauma Center blood product availability	Routine trauma T-MCI surge	Required for standard of care trauma resuscitation	1	4 concurrent MTP	8 MTP 20 U LTOWB	e.g., No LTOWB policy or procedure, no financial model supporting
Local blood supplier product availability	Routine trauma T-MCI surge	Direct access required if >15 patients requiring MTP	2	40 U PRBC 20 U FFP 10 U PLT	60 U RBC 40 U FFP 20 U PLT 50 U LTOWB	e.g., Financial model for FWB
Regional blood bank product availability	T-MCI surge	Direct access required if >20 patients requiring MTP	7	60 U PRBC 40 U FFP 20 U PLT	80 U RBC 60 U FFP 20 U PLT 100 LTOWB	e.g. Financial model for FWB, regulatory compliance issues, ability to safely scale walking blood banks

Note the content and numbers listed are for illustrative purposes only
MTP Massive transfusion packs, *RBC* Red blood cells, *FFP* Fresh frozen plasma, *PLT* Platelets, *LTOWB* Low Titer Group O Whole Blood, *U* Unit

expectations and resources [12]. Intentional collaboration and coordination across disciplines and health systems is vital for developing this common operating framework. Preparedness is a multiphase, continuous cycle of planning, organizing, training, equipping, exercising, evaluating, and taking corrective action in an effort to ensure effective coordination during T-MCI incident response [13]. Preparedness requires building the resilience of each link in the chain of survival through focused application of DCR capability and capacity building exercises. The Parisian response to the November 13, 2015, terror attack illustrates the importance of preparation. As the attack unfolded, the French government activated their "White Plan" for the first time in the nation's history. This robust plan, developed in the mitigation phase, had been frequently exercised; such familiarity allowed for a RDCR and fixed facility DCR plan to be deployed immediately.

Prehospital

Early RDCR saves lives. Civilian prehospital T-MCI mitigation and preparedness activities should enable strategies that allow for rapid initiation of stabilizing trauma care at or near the point of wounding despite limited resources and personnel,

followed by coordinated continuity of care across the entire medical response system. However, the complexity of the civilian healthcare system means that medical directors of EMS/fire agencies must clearly determine how to implement the basic principles of RDCR. They must then develop training standards, identify funding sources, standardize and ensure compatibility of equipment, and create sustainment plans that span community groups and professional first responders.

Unification around common response language is critical to successful interagency RDCR implementation. The US military demonstrated that the tiered prehospital application of RDCR principles through the systematic application of the Tactical Combat Casualty Care (TCCC) operational paradigm reduces mortality from trauma in combat [2]. The shared common language of TCCC allowed for clear outcomes, standardized training, and accountability. In the civilian pre-trauma center arena, the Committee for Tactical Emergency Casualty Care (C-TECC) high-threat trauma chain of survival offers a parallel framework for the integration of RDCR principles into T-MCI response [14–16].

The TECC guidelines provide a foundation for comprehensive civilian prehospital DCR plans [17]. The guidelines are based on the application of RDCR principles in a threat-based matrix comprised of three dynamic phases: direct threat, indirect threat, and evacuation care [18]. In direct threat care, the focus is on responder safety and the first principle of RCDR-aggressive control of life-threatening hemorrhage using a combination of direct pressure and tourniquets. Success requires preparing all levels of care providers, from the citizen through the highly trained Emergency Medical Providers to execute hemorrhage control in high-threat environments. In the indirect threat care phase, the external threat to victim and responder is present but is not direct and immediate. During this phase, depending on the resources and situation, additional aspects of RDCR can be initiated. The final phase of TECC is termed evacuation care and occurs when the injured and the provider are in areas where there is little ongoing threat. During this phase, all aspects of RDCR should be considered. Experience from the US military suggests that early, aggressive resuscitation with blood products, including whole blood, reduce mortality from trauma [19, 20]. However, in domestic operations data supporting whole blood use in trauma remains sparse [21]. Based upon community resources, operational constraints, and risk tolerance, appropriate resuscitation strategies may range from low-crystalloid resuscitation to prehospital administration of whole blood. During the readiness phase, leaders must determine where on this RDCR continuum their system will fall and create strategies to fill their gaps.

Readiness activities must acknowledge the logistical challenges of RDCR and create solutions for scenarios where full operational medical resources may not be brought to bear. On a basic level, this means aggressively implementing whole of community hemorrhage control programs such as Stop the Bleed or FEMA's Until Help Arrives. On a high level, it means examining decisions regarding out of hospital resuscitation standards. For example, for RDCR to have the greatest effect on survival, prehospital systems must embrace field blood transfusion programs, systemic and topical hemostatic adjuncts, tourniquets, and educating providers about the risks of using positive pressure ventilation for hemorrhagic shock patients.

Protocols, procedures, training, and guidance for EMS providers on airway and prehospital blood management and administration must be developed. Transfusion-related material should include the medical aspects of transfusion, strategies for management of transfusion expenses, mitigation of regulatory compliance issues, strategies for quality control and medical quality assurance, training on transfusion indications, protocols for judicious product utilization, and strategies for recycling/rotation of blood products back to the blood bank to limit waste.

In addition, medical systems readiness must address the need for interoperable and coordinated communication. RDCR implemented on scene must be able to be communicated to first receiver facilities to efficiently transition from field RDCR to inhospital DCR. Without an effective communication system between prehospital public safety assets and fixed medical facilities, the gap in information will be a true barrier to real-time implementation. Additionally, the content and data points shared in this field report should be clearly defined. By defining and training to this communication flow, the real-time dissemination of medical information will allow for successful RDCR and DCR across the multiple levels of provider care.

First Receiver Facilities (FRF)

First receiver facilities (FRF) are defined as non-Level 1 trauma centers that by design or circumstance provide initial live-saving care for victims of T-MCI. While trauma centers are often the focus of preparedness funding, there are only 217 level 1 trauma centers in the United States [22]. As a result, first receiver facilities with limited resuscitation and operative capabilities may find themselves on the front line of T-MCI response and fill a key role in the TECC Chain of Survival. The response to the 2017 Las Vegas attack clearly demonstrated that non-level 1 trauma centers play a major role in mitigating the consequences of T-MCI. The Sunrise Medical Center in Las Vegas, a level 2 trauma center, received over 150 patients in less than an hour. Non-trauma facilities in the Valley Hospital System care for an additional 228 victims [23].

First receiver facilities often have only limited resuscitation resources (e.g., blood products such as platelets) and limited surgical coverage and may have little experience in managing T-MCI. The whole of community readiness process must acknowledge these limitations, catalogue existing resources, and intentionally strengthen this link in the chain of survival.

One model is to consider FRF as casualty collection points (CCP) where additional stabilization may occur prior to transfer to definitive care. Readiness efforts can focus on the nuanced application of RDCR. At the FRF, the key DCR operational goals should be hemorrhage control, hemostatic resuscitation (if possible), hypotensive resuscitation, hypothermia prevention, and rapid distribution of casualties to regional trauma centers. Material acquisition should focus on targeted purchases including tourniquets, hemostatic agents, and fluid warmers. Education programs should emphasize team training on key components of RDCR. Process development should focus on building robust transfer mechanisms. And,

administration efforts should create expedited staff credentialing procedures to maximize utilization of fixed resources such as operating theaters.

In addition to playing a stabilizing role, FRFs should also investigate mechanisms to receive patients from trauma centers. Trauma centers could proactively move existing patients or transfer incident patients after initial stabilization. This "safety valve" model allows for urgent rather than emergent surge capacity and can offload postoperative caseloads from the trauma center.

While the above are important components of a robust readiness system, the major response gap at FRF is rapid access to adequate blood transfusion capabilities required for hemostatic resuscitation. Multiple studies have reported that earlier and increased use of RBCs, plasma, platelets, and whole blood are associated with improved outcomes [11, 20, 24, 25].

Again, reality and community limitations must be considered. So even in the absence of blood product availability, readiness activities can integrate other DCR components into the T-MCI resuscitation plan such as albumin-based resuscitation or low-volume crystalloid administration [26]. Since the landmark study by Bickell et al. in 1994, multiple studies have challenged the survival benefit of large volume or empiric intravenous fluid administration in trauma [27]. While maintenance of perfusion pressure is a core resuscitation principle, crystalloids result in dilutional anemia and coagulopathy, activate the inflammatory cascade, accelerate hypothermia, worsen acidosis, and result in interstitial edema due to increased permeability of capillary gap junctions [28–30].

During the readiness phase, it is critical that FRF develop continuity of operations plans (COOP). Ideally these plans improve daily operations in order to strengthen crisis response. For DCR, a key component of the COOP is close coordination with local and regional blood banks to create robust donor and vendor systems. The COOP must be realistic and tailored to community resources. For example, if the primary DCR plan is to initiate RBC and FFP transfusion augmented by TXA and restricted crystalloid use, some critical points include:

- Identification of total blood products in the hospital at any given time
- Test time from ordering to preparation to delivery to administration
- Verification of blood product access priority
- Determining number of units allocated per patient
- Validating product resupply process and timing

Trauma Center

Trauma centers are central to the readiness process, serving as the coordinating node, deep knowledge experts, and system advocates. Trauma centers play an important role leveraging regional trauma committees, utilization and evaluation of regional referral networks, coordination of educational activities, integration of virtual care, and strengthening of logistical support. They must encourage and support the integration of non-trauma first receiver facilities into the broader DCR strategy.

Trauma centers also play a critical role in pushing RDCR strategies closer to the point of injury. If prehospital damage control and blood transfusion is to be successful in the United States, the blood collection centers must be fully integrated as leaders and partners in these programs. Organizations such as the American Association of Blood Banks need to develop guidance for blood collection centers to assist in implementation and management of field blood use, addressing the inherent regulatory issues, financial cost sharing, product tracking and accountability, field quality control programs, and all guidance on supply and recycling/rotation.

Trauma programs at large academic centers, as key subject matter experts, can play a leading role in building these coalitions to drive comprehensive DCR strategies. They can also play an important role in driving public policy around DCR such as utilization of whole blood, development and distribution of alternative resuscitation products such as freeze dried plasma, and development of tiered community DCR protocols.

At trauma centers, hemostatic resuscitation with component therapy or Low Titer Group O Whole Blood (LTOWB), hemostatic adjuncts, and rapid damage control surgery should be the standard of care. In T-MCI scenarios, patient volumes and compressed operational timelines can strain standard logistical and administrative support functions that enable DCR. Trauma programs must insure internal readiness through practiced implementation of the Hospital Incident Command System (HICS). The HICS creates a dedicated, standardized leadership function that allows for proper inter- and intra-facility coordination.

In order to provide timely DCR capabilities in T-MCI, health system leaders must be proactive in their inclusion of the hospital-based blood bank and blood suppliers in the HICS. Health system leaders must build relationships with local and regional blood suppliers in order to "activate" these resources in T-MCI surges. As part of blood capacity readiness activities, systems should focus on building robust, yet flexible blood stewardship programs that support routine operations and allow for flexible surge capacity. These programs should include massive transfusion protocols (MTP) that have been demonstrated to improve outcomes and reduce blood product wastage, as well as goal-directed trauma resuscitation with viscoelastic testing [31–33].

Response

The 2017 mass shooting in Las Vegas, NV, demonstrated the complex, dynamic nature of T-MCI response. The whole of community response to the attack included layperson interventions, law enforcement patient transport, integrated warm zone operations, non-trauma center engagement, and trauma center surge capacity. Las Vegas is the case study for whole of community application of the RDCR-DCR-damage control surgery (DCS) continuum in T-MCI. Readiness activities create the critical foundation for response and allows for flexibility during highly dynamic T-MCI scenarios.

Prehospital

The focus of RDCR is to extend the "physiologic system failure" time from point of injury to life-stabilizing/life-saving surgical care. Across the spectrum of high-threat T-MCI response, public safety entities face the same operational roadblocks to implementation. The high-threat patient care model is conducted in four separate phases: *access, assess, stabilize, and evacuate*. Each phase has unique considerations as applied across the *Direct Threat/hot zone* (i.e., area where the direct ongoing threat to the patient and responder exceeds the benefit of comprehensive trauma intervention), the *Indirect Threat/warm zone* (i.e., area of ongoing, indirect threat that can be mitigated in order to allow for targeted trauma care intervention), or the *evacuation zone*. Of note, given the increased targeting of first responders and current threat matrix, responders should not consider any area a *cold zone*.

In the *access* and *assessment* phases, common barriers to care including ongoing threat, geographic restraints, overwhelming patient numbers, and equipment requirements. Though scene safety remains an important tenant of prehospital response, Emergency Medical System (EMS) and fire rescue are increasingly embracing a role in the integrated assault rescue model as they move to provide care in the *warm zone*. The two most common integrated response systems are the Rescue Task Force and the "Warm Corridor" models. The Rescue Task Force framework pairs law enforcement and medical/rescue specialists to create dynamic response teams that move to casualties. In the "Warm Corridor" paradigm, law enforcement officers conduct preliminary clearance of areas then post at designated locations within line of sight of other officers to reduce the risk to responding medical teams. Regardless of the model deployed, the target outcome is to provide more robust capabilities and earlier EMS access to casualties in the warm zone [34–36].

The *stabilization* phase is the phase of response that, despite the barriers of ongoing threat, wounding patterns, and limited manpower and equipment, has a clear path forward in the evidence- and best-practice-based DCR application guidelines of TECC. The *evacuate* phase has immediate operational challenges that become more complex in T-MCI (e.g., staging of ambulances, destination protocols, the use of alternative evacuation platforms, etc.).

The first casualty management step in T-MCI is identification and categorization of victims through proper scene management and triage. In high-threat T-MCI, these are dynamic processes. Traditional triage tools that immediately place ambulatory patients in green/low-acuity categories are dangerously limited in T-MCI with high volumes of penetrating trauma. In addition, US experience reveals that victims often flee the scene and self-present to hospitals, that ongoing threats can limit medical first responder response and prompt law enforcement transport of casualties, and stabilizing RDCR is often delayed during the evacuation phase.

Current triage tools were designed to determine priority for surgical intervention. However, they do not adequately account for modern DCR practices. Studies suggest that markers of severe injury including multiple proximal amputations, penetrating torso trauma especially with evisceration, and torso trauma with decompensated hemorrhagic shock are predictors of blood transfusion and surgical

care. These components must be considered early in the T-MCI response in order to both determine correct destination protocols but also proactively engage system/regional blood bank resources.

The second phase is rapid and coordinated victim evacuation to appropriate stabilizing care. A "RDCR evacuation system" provides for rapid, multimodal transport of casualties to definitive care or deploys advanced resuscitation assets closer to the point of injury. In the civilian setting, EMS is traditionally responsible for patient transport. However, in high-threat T-MCIs where access and egress may be compromised, casualty evacuation and transport require more operational flexibility. In certain circumstances such as penetrating torso trauma, speed of transport may be paramount. Several US studies suggest that, in urban environments, the utilization of private vehicles or police transport compared to EMS for victims of penetrating torso trauma results in equivalent or improved mortality [37–40]. Specific to high-threat T-MCI, in the response to the 2012 Century Theater shooting fleeing victims and bystanders prevented Fire and EMS from accessing seriously injured casualties. As a result, law enforcement transported 75% of the patients during the first 30 minutes of response [41]. No adverse outcomes were reported.

Finally, in addition to structured nonmedical victim transport, systems should also have the capacity to provide RDCR interventions on scene or during transport. In scenarios with prolonged transport times or limited access to definitive care, slowing "physiologic system failure" is critical. Table 16.2 details RDCR transport planning components. In the civilian setting, many RDCR principles such as mechanical hemorrhage control, hypothermia prevention, limited crystalloid infusion, and prehospital tranexamic acid (TXA) are gaining broader acceptance [42–45]. However, there remains a significant RDCR capability gap related to the ability to perform balanced blood product resuscitation in the prehospital. Few EMS systems have prehospital blood protocols and only an estimated 25% of helicopter EMS systems have blood programs [46].

Emerging combat and civilian data suggests that prehospital blood component therapy in trauma is safe and feasible and may improve clinical outcomes [47, 48]. The London Ambulance Service demonstrated that civilian prehospital RBC administration in trauma was feasible, reduced blood product transfusion in 24 hours, improved base excess/acid base balance on admission, and may improve survival [49]. Some US EMS agencies are even moving to LTOWB administration in the prehospital setting [50]. Clearly, with proper quality assurance and processes, the ability to mobilize large stores of LTOWB in the prehospital setting could fundamentally change the future of resuscitation in T-MCI. Currently, prehospital blood transfusion programs that, at minimum, allow for transfusion of RBCs and plasma should be considered the minimum capability of comprehensive prehospital RCDR [51].

Prehospital strategies to mitigate the acute coagulopathy of trauma are growing. Many prehospital systems currently use of tranexamic acid as a hemostatic adjunct to prevent and/or treat hyper-fibrinolysis and coagulopathy. Given the low cost and cube space of TXA, this intervention is relatively easy to scale in T-MCI. In addition

Table 16.2 Trauma system DCR transport components (example components)

Process	Justification
Multimodal patient transport protocols (e.g., law enforcement transport)	Allows for more rapid movement of patients to definitive care Rapid scene decompression of T-MCI
Dynamic trauma destination protocols	Allows for rapid redistribution of patients based on bed availability Alignment of resources with injury patterns Reduces care variability Improves efficiency in transport
Trauma evaluation protocols that limit time in the prehospital and non-trauma center care space (e.g., limited radiology utilization)	Improves efficiency in transport Reduces presurgical time Minimizes impact on non-trauma center patient flow
Aggressive blood product utilization protocols by transport teams	Addresses DCR balanced transfusion requirements Mitigates capability gap in non-trauma center ED
Direct to OR/IR protocols	Reduces time to definitive care Creates frontline emergency department capacity Reduces cost of additional ED visit Improves staff: patient utilization ratio
Blood product replenishment protocols (e.g., transport agencies replenishing community hospital)	Maintains DCR capabilities of non-trauma center hospital Cost-efficient solution for maintaining DCR capability within trauma system
Coordinated, interoperable communication systems and defined communication content	Allows efficient information flow among public safety and health systems Defined communications flow and content from field providers allows for seamless transition from RDCR to full DCR in healthcare facilities

to TXA, many agencies are aggressively pursing options to administer plasma in the field. Fresh frozen plasma (FFP) and thawed plasma (TP) have been utilized by several US prehospital systems with varying degrees of success [11, 47, 52]. The logistics of prehospital plasma administration, especially in T-MCI, are daunting. Several studies demonstrate that more durable and field expedient plasma formulations such as freeze-dried and spray-dried plasma are safe and effective [53, 54]. However, in the United States, there is currently no FDA-approved freeze-dried plasma option. In order to effectively provide RDCR during T-MCI, prehospital systems should have in place mechanisms to rapidly access plasma either through hospital-based resupply or destination protocols. Finally, hypothermia prevention in trauma is critical as a drop in core temperature of 1 °C decreases clotting factor function 10%, impairs platelet function resulting in spiraling coagulopathy, and increases morbidity and mortality in trauma patients [55, 56]. Many EMS systems now endorse limited patient exposure during the evacuation phase followed by rapid application of commercial hypothermia prevention kits.

First Receiver Facility Response

The FRF should focus on executing their COOP and emergency management plans. The mission is to provide EMS agencies with more robust pre-trauma center capabilities and offload trauma center volume. Given the resource limitations of smaller non-level 1 trauma centers, in the face of overwhelming numbers, these facilities should focus on the basic components of RDCR including hemorrhage control, hypothermia prevention, limited crystalloid resuscitation, and limited use of radiology studies to only guide triage and transportation priorities.

As noted, many FR facilities lack robust blood transfusion capabilities. With planning, a properly designed trauma system can account for these limitations through a variety of mechanisms. For example, many community hospital blood banks can rapidly provide the FR facility with 1–2 units of uncrossmatched PRBCs. However, access to plasma requires thawing of fresh frozen plasma (FFP) and a minimum delay of ≥45 minutes. In these circumstances, systems can deploy critical care transport teams to FR facilities equipped with thawed plasma or liquid plasma as part of their resuscitation armamentarium in order to achieve early balanced resuscitation [57, 58]. Pre-trauma center plasma administration has the added benefit of early agent reversal in anticoagulated patients with TBI [59].

First receiver facilities universally do not have access to platelets in an operationally relevant time frame. This deficiency limits the ability to reasonably meet 1:1:1 ratio benchmarks in T-MCI. Fortuitously, the American Association of Blood Banks (AABB) recently changed their standards to include LTOWB as a transfusion option for hemorrhagic shock in trauma patients with unknown blood types [60]. This advancement, combined with the fact that under certain storage solutions, LTOWB can be stored at 4C for up to 35 days can mitigate the platelet gap and could dramatically improve system preparedness for large-scale DCR implementation.

Trauma Center

Trauma centers are the lynch pins in T-MCI response. The key role trauma centers play in reducing mortality in T-MCI is the ability to manage noncompressible hemorrhage through comprehensive DCR and damage control surgery (DCS) to a large surge of adult and pediatric patients on short notice. In general, hemorrhage control interventions in the emergency department (ED) are limited and the priority should be rapid movement to the operative suite or interventional radiology. However, two relatively rapid, potentially life-saving techniques are important when applied early in the DCR armamentarium, pelvic circumferential compression devices (PCCD) for high-energy pelvic fractures [61–63], and Retrograde Endovascular Balloon Occlusion of the Aorta (REBOA) [64, 65]. In appropriate patients, stabilization of pelvic fractures reduces blood product requirements and mortality. While PCCDs likely provide improved mortality, some data suggests that properly applied improvised pelvic binders with bedsheets provides similar outcomes and this technique should be practiced in order to scale the capability during high-volume surge [66]. In T-MCI, REBOA offers a less resource intensive option than ED thoracotomy to

stabilize selected in extremis patients with torso trauma, expanding capabilities and buying time to move to operative repair or interventional radiology.

Trauma center blood banks are critical in the T-MCI response. The blood banks should execute their MCI policy and immediate begin to prepare MTP packs as well as initiate COOP plans to coordinate access to additional regional blood products. Additional staff will be required as timely, large volume blood product distribution to the ED, operating suite, and ICUs will be essential. Complicating operations, trauma centers must also be prepared to provide blood resuscitation for a diverse patient population in the T-MCI setting. For example, the elderly trauma victim on antiplatelet and warfarin therapy, perhaps with prior blood transfusion histories, creates clinical and administrative complexity.

Trauma programs in high-risk areas must also consider the possibility that a MCI may be large enough that it exhausts the local blood supply. While all efforts should be made to have blood products from the region transported to centers where casualties are being resuscitated, it is optimal to have a contingency plan just in case there are no blood products available and there are still casualties with survivable injuries to resuscitate. In countries where it is permitted, an emergency plan to collect warm fresh whole blood from donors near or within the trauma center can be developed. The collection and use of warm fresh whole blood has been a standard practice in military hospitals since the Civil War, but its use in civilian hospitals has been limited due to regulatory restrictions from using blood that has not been formally tested for transfusion transmitted diseases. In Norway, an emergency plan for the use of warm fresh whole blood has been developed and activated at least once in 2018 when the blood supply was near exhaustion. In countries or regions where the risk is high for the exhaustion of the blood supply in MCI events emergency fresh warm whole blood programs should be considered.

Another complex scenario is the appropriate administration of balanced blood products to the traumatized child. Though there is evidence that higher plasma and platelet to red blood cell ratios are associated with lower mortality rates in teenagers, the pediatric specific literature is often undermined by the small study population sizes and the fact that many of the attempts to achieve the 1:1:1 ratio are not successful due to the logistics of obtaining the thawed plasma [67, 68]. Given the infrequency of severe pediatric trauma and the mixed data, the application of DCR in a single, severely injured child is challenging. Trauma centers cannot rely on ad hoc pediatric resuscitation. They must develop and train specific pediatric DCR plans then build the operational systems in order to scale these during a T-MCI. Specifically, consideration should be made for pediatric MTP logistics (e.g., weight-based blood administration, hypothermia prevention protocols).

Conclusions

Damage control resuscitation is the standard of care for the systematic management of the critically injured trauma patient in MCIs. Early hemorrhage control, hypotensive resuscitation, hemostatic resuscitation, limited crystalloid administration, pharmacologic adjuncts, and aggressive hypothermia prevention can mitigate blood failure and improve survival.

In the wake of the Pulse Nightclub shooting, Orlando Regional Medical Center (ORMC), the local level 1 trauma center, absorbed greater than 50 casualties over the span of a few hours. The location of the shooting resulted in rapid transport to a level 1 trauma center. And, the timing of the attack (i.e., late evening) allowed for ORMC to surge into multiple open operating theaters. However, lessons from the 2015 Paris attacks and the 2017 mass shooting in Las Vegas demonstrate reliance on a single trauma center can create a fragile response system. These incidents instead demonstrated that proper mitigation and planning must be undertaken in the readiness phase in order to enable the appropriate application of a whole of community response to a T-MCI. *All* healthcare systems that potentially manage trauma patients should implement a comprehensive, tiered DCR strategy as part of their emergency preparedness activities.

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DCR for Non-trauma Patients

17

Ryan P. Dumas and Jeremy W. Cannon

Introduction

Since the introduction of the truncated laparotomy in 1983 [1] and subsequent popularization of damage control surgery (DCS) by Rotondo et al. in 1993 [2], similar concepts have been applied to resuscitation, termed damage control resuscitation (DCR) [3, 4]. DCR combats the "lethal triad" of trauma coagulopathy and has become the standard of care for severely injured trauma victims with exsanguinating hemorrhage [4–8]. When combined with DCS, this approach has been associated with improved patient outcomes [9]. The fundamental importance of hemostatic resuscitation was underscored by the PROPPR trial in which patients in the 1:1:1 group achieved hemostasis sooner and had decreased mortality from hemorrhage within the first 24 hours [10].

Despite these potential benefits, the application of DCR principles remains variable [11, 12]. Evidence-based clinical recommendations for the application of DCR are the subject of a new Eastern Association for the Surgery of Trauma (EAST) guideline [13]. The emphasis on trauma applications is understandable given the demographics of hemorrhage-related deaths in the United States; however, peptic ulcer disease, ruptured abdominal aortic aneurysm, and maternal hemorrhage also

R. P. Dumas
Division of General and Acute Care Surgery,
UT Southwestern Medical Center, Dallas, TX, USA

Department of Surgery, Division of Traumatology, Surgical Critical Care and Emergency Surgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

J. W. Cannon (✉)
Department of Surgery, Division of Traumatology, Surgical Critical Care and Emergency Surgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, MD, USA
e-mail: jeremy.cannon@uphs.upenn.edu

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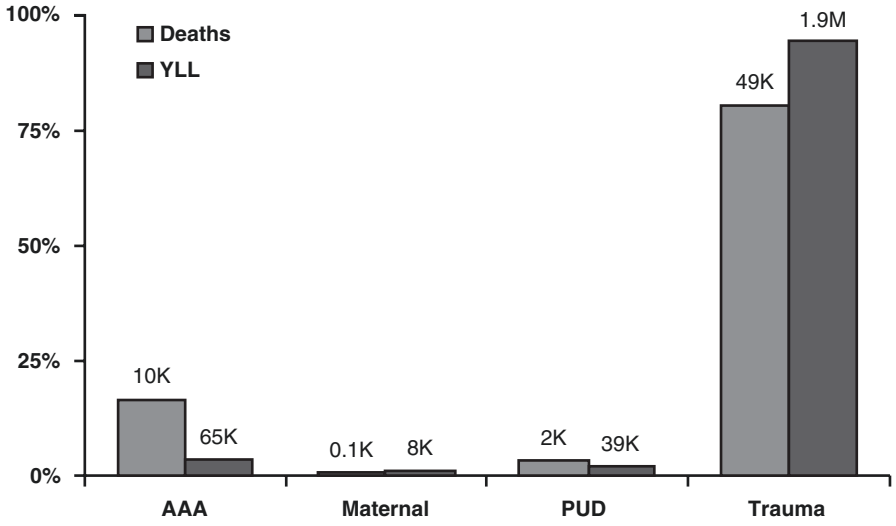

Fig. 17.1 Annual deaths and years of life lost (YLL) from hemorrhage in the United States. Each entity is shown as a relative percent, and the absolute numbers of deaths and YLL are shown above each bar (K denotes 1,000, M denotes 1,000,000). Perioperative deaths in the United States from other entities are not known and thus are not shown on this figure. AAA Abdominal Aortic Aneurysm, PUD Peptic Ulcer Disease. (Data from Cannon JW. Hemorrhagic shock. N Engl J Med 2018. 378:370–9)

claim numerous lives every year (Fig. 17.1). In addition, some studies estimate that perioperative hemorrhage in cardiac, vascular, oncologic surgery, and other operations for benign conditions are responsible for between 60% and 70% of patients undergoing massive transfusions [14, 15]. Thus, it is very important to consider how the principles of DCR may apply in these non-trauma populations [16]. This chapter will review the use of DCR principles in various nontraditional patient populations including pediatric patients, geriatric patients, and non-trauma patients.

Pediatrics

The principles of DCR should be in the forefront of every practitioner's mind taking care of a bleeding pediatric patient. The core tenets of DCR in this population remain the same: hemostatic resuscitation while limiting crystalloid administration, recognizing and treating causes of hypothermia, coagulopathy and acidosis, and rapid definitive hemostasis [17]. There are, however, multiple unique elements of pediatric morphology and physiology that make DCR in this population particularly challenging. Pediatric patients are thinner, have less subcutaneous fat, and have an increased surface area to body mass ratio and are thus vulnerable to hypothermia [18]. Furthermore, although pediatric patients have relatively more circulating volume (10% body weight vs. 7% in adults), the absolute pediatric blood volume is quite small [19, 20]. Thus, even seemingly small volumes of blood loss can represent a catastrophic hemorrhage in a child. Finally, although pediatric patients have

increased cardiac reserve and are able to compensate for up to nearly 50% of blood loss before developing hypotension, once this reserve is spent, they tend to progress quickly to cardiac arrest [21]. Evidence suggests that pediatric patients may also respond differently to inflammation as compared to adults [22] and that children less than 12 months of age have immature hemostatic systems and may have different blood transfusion requirements [23]. Additionally, procoagulant factor levels are reportedly low in pediatric patients until 6 months of age although the functional significance of these differences remains unclear [24]. Similarly, difference in platelet function, aggregation, and adhesion are also described [25].

With these important differences in mind, the following paragraphs summarize our current understanding of the application of adult DCR principles to pediatric patients. Historically, DCR has been used in pediatric patients undergoing burn resection and reconstruction for craniosynostosis [26]. More recently, data from combat operations in Iraq and Afghanistan have shed more light on the application of DCR in injured children [27, 28] while the ongoing *MA*ssive *T*ransfusion *I*n *C*hildren (MATIC) study promises to illuminate modern pediatric resuscitation in civilian practice for both trauma and non-trauma patients (http://pediatrics.wustl.edu/matic/AboutMATIC).

Permissive Hypotension

Permissive hypotension has historically been one of the core tenets of DCR but remains one of the most controversial. The evidence for permissive hypotension in adults is mixed [29, 30]; thus, its application remains unclear [17]. Despite two randomize controlled trials that support use of permissive hypotension [31, 32] in trauma patients, a 2014 Cochrane Review concluded that there was insufficient evidence to support the use of hypotensive resuscitation strategies [33]. The most recent analysis from 2018, however, suggests there may still be a role and benefit for hypotensive resuscitation but that the majority of the studies are underpowered to detect a difference [34]. From the original study by Bickell et al. [23], it appears that delayed resuscitation is likely best applied to patients with penetrating torso injuries in an urban environment with extremely short prehospital times. To date, there are no pediatric trials that have studied the use hypotensive resuscitation on pediatric patient outcomes and there is insufficient evidence to support the use of permissive hypotension. Thus, best practice in the perioperative period is likely to target age-adjusted normotension. Table 17.1 summarizes the normal vitals ranges in pediatric patients.

Table 17.1 Normal pediatric physiology [105, 106]

	Respiratory rate (breaths per minute)	Heart rate (beats per minute)	Systolic blood pressure (mm Hg)
0–9 months	32	136	75
10–24 months	26	124	90
2–4 years	24	114	97
4–8 years	23	103	102
8–12 years	20	94	107
12–16 years	20	85	115

Minimize Crystalloids

There is evidence, however, to support the deleterious effects of crystalloid infusions in pediatric patients. Prehospital IV fluid administration has been associated with increased transfusion requirements, abnormal laboratory coagulation parameters, as well as a trend toward increased mortality [35]. In a recent large study of over 1300 pediatric trauma patients in Iraq and Afghanistan, investigators identified an association between crystalloid volume and both increased length of stay and prolonged ventilator days [36].

Coagulopathy and Shock

There is general consensus that the acute coagulopathy of trauma present in adults is also present in pediatric trauma patients. In a recent retrospective review of over 800 pediatric patients, early coagulopathy was present approximately one-third of patients and was associated with a significant increase in mortality [37]. Similar results have been reported in pediatric patients treated during combat operations [38]. Not surprisingly, hypotension and injury severity score with associated with early coagulopathy in pediatric patients [37].

Transfusion

Similar to adult patient populations, a massive transfusion protocol (MTP) should be implemented in all pediatric tertiary care centers [18, 21]. In pediatric patients, massive transfusion is defined as one of the following: transfusion >100% of estimated blood volume in 24 hours, ongoing transfusion of >10% of blood volume per minute, or replacement of 50% of estimated blood volume in 3 hours or less [23]. Importantly, a threshold of 40 cc/kg of all blood product transfused during the first 24 hours identified children at risk for mortality [27].

Although the evidence for MTP use in pediatric patients is still emerging, developing and employing an MTP for bleeding pediatric patients are likely beneficial [24]. The optimal target ratios of packed red blood cells, plasma, and platelets for the empiric phase of an MTP have yet to be firmly defined. It seems, however, that in pediatric patients, there may be more latitude in the exact ratio than in adults [28, 39]. Likewise, the optimal order of blood product administration has yet to be precisely defined. So long as volume overload is avoided, it is likely safe to lead with plasma and platelets followed by red blood cells. In the absence of an established best practice, there remains a lot of variation in the implementation of pediatric MTPs [23]. Fortunately, MTP for trauma in pediatric patients remains a relatively uncommon event compared to adults [40]. There is some evidence to support the use of TXA in pediatric trauma [41]; however, a recent survey of pediatric hospitals found that only 15% use antifibrinolytic therapy routinely [42].

Geriatrics/Elderly

Elderly patients represent an ever-growing demographic in our society. Although the elderly represents one-eighth of the population, they consume one quarter of trauma and critical care expenditures [43]. Patients over the age of 65 undergo approximately two million operations annually [44]. Studies have shown worse outcomes for elderly patients undergoing emergency operations [45] and when compared with their younger peers, elderly trauma patients are characterized as having worse outcomes [46]. Likewise, for those patients aged 65–79 undergoing a massive transfusion (defined as ≥10 units packed red blood cells over 2 consecutive calendar days [as an approximation for 24 hours given the nature of the data collection format for the registry]) for any indication, 30-day mortality was 27.7% and for patients over the age of 80 was 36%, compared to a mortality of just over 10% in patients ages 18–39 in a recent epidemiologic analysis [15]. This association between massive transfusion, age and mortality was also confirmed by another recent study [14]. Thus, we believe there are some important considerations when applying DCR principles to this population although to date, no study has specifically evaluated DCR outcomes in the elderly [47].

Elderly patients undergoing DCR for any indication are generally unwell at baseline with more medical comorbidities [48] and more frequent use of anticoagulants and antiplatelet agents [49, 50]. Progressive loss of physiologic reserve in this population has been coined "homeostenosis" [51]. A number of physiologic changes have been described and quantified, such as decreased pulmonary reserve [52], cardiovascular changes [53], and worsening renal function (Table 17.2) [54]. Hypoperfusion in the elderly may occur despite normal appearing vital signs [47].

Table 17.2 Changes in geriatric physiology with aging [51]

Neurologic
Decreased brain mass
Impaired autoregulation
Cardiovascular
Decreased maximum HR
Decreased maximum CO
Large arteries decreased compliance
Increased peripheral vascular resistance
Increased systolic blood pressure
Pulmonary
Decreased FEV1 and FVC
Increased VQ mismatch
Decreased inspiratory and expiratory pressures
Decreased alveolar surface area
Renal
Decreased solute secretion
Decreased renal mass
Decreased response to ADH, renin, and aldosterone
Temperature regulation
Decreased shivering
Decreased vasoconstriction
Decreased sweat production

Demetriades et al. showed that the majority of severely injured elderly patients did not meet traditional definition for trauma team activations based on presenting vitals [55]. Furthermore, traditional vital sign ranges that may predict mortality in patients less than 65 years of age may not be as useful in the elderly [56]. Due to preexisting atherosclerosis, elderly patients have a blunted vasoconstrictive responses [47]. It is very important to highlight, however, that the degree of physiologic change varies widely from patient to patient [51]. Further complicating the clinical picture, traditional endpoints of resuscitation such as urine output may not be as reliable in the elderly. Elevated lactate and base deficit levels should prompt increased monitoring as these laboratory indicators can herald occult hypoperfusion in the elderly. In elderly blunt trauma patients, elevated lactate and base deficit are associated with a fourfold increase in mortality [57]. Finally, geriatric patients, like pediatric patients, are very susceptible to hypothermia. A recent study found that patients over the age of 55 were more likely to arrive to the ICU hypothermic and hypothermia was found to be an independent risk factor for mortality [58].

Permissive Hypotension

Because vital signs are not a useful indicator of hypoperfusion in the elderly, the practice of permissive hypotension in this population is controversial. Permissive hypotension in the elderly has been studied in a retrospective fashion and was not associated with increased survival [59, 60]. However, the quality of the evidence is low and randomized controlled trials are lacking.

Crystalloids

Like in adults and pediatrics, however, the evidence supporting limiting crystalloid infusions in geriatric patients is more robust. In elderly patients in hemorrhagic shock, attempts should be made to limit crystalloid to two liters during the emergency department phase of patient care [61, 62].

Transfusions

Elderly patients have different cardiac physiology including impaired ventricular filling, decreased maximal cardiac output, and a decreased maximal heart rate [63]. Additionally, geriatric patients have a smaller blood volume and blunted cardiovascular responses [64]. Some studies also support more aggressive transfusion thresholds in non-bleeding geriatric patient with myocardial infarction [63]. Whether or not these benefits extended to patients undergoing DCR remains unclear.

Other non-trauma indications for DCR in the elderly patient population includes aortic surgery, cardiac surgery, and gastrointestinal hemorrhage. Recent studies have attempted to mitigate bleeding risk and the need for transfusion in these patient

populations. For example, a recent randomized controlled trial of elderly patients undergoing combined coronary artery bypass grafting and aortic valve surgery found that prophylactic tranexamic acid reduced blood transfusion requirements perioperatively [65].

Anticoagulant and antiplatelet therapy in the aging population is also an important consideration during DCR of the elderly patient. These medications are widely prescribed and carry a substantial bleeding risk [50]. Particularly, the use of these medications increases the risk of intracranial hemorrhage. Additionally, these patients are also at risk for delayed hemorrhage following a negative CT scan examination of the head. Studies have shown that anticoagulant use increases the risk of mortality by sixfold in patients with a traumatic brain injury [66]. Although it is beyond the scope of this chapter, prompt reversal of therapeutic anticoagulation should be part of DCR for bleeding-injured and non-injured patients alike.

Obstetrics

Despite common perception, in large epidemiologic studies in industrialized nations, massive transfusion due to obstetrical bleeding is low 1.8% [15], and obstetrics patients have the lowest mortality following MTP (2.8%) [14]. When maternal bleeding does occur, however, it can be very dramatic and acute care surgeons are likely to be consulted to aid in the multidisciplinary care of these patients [67].

Before discussing some of the considerations of DCR in obstetrics patients, like elderly and pediatric patients, it is important to highlight some physiologic differences in pregnant mothers (Table 17.3). Changes during pregnancy, both hormonal and physiologic, most significantly affect the cardiovascular system. Despite a large increase in circulating blood volume, the major contributor is plasma volume with a relatively smaller increase in red cell mass. This is important when considering the pathophysiology of hemorrhagic shock. Whereas hemodynamic changes may be evident in Class II and III shock in nonpregnant patients, in pregnant patients, hemodynamic changes may not become visible until 1500–2000 cc of blood loss. Like blood volume in pregnancy, maternal cardiac output and oxygen consumptions are similarly increased [68].

One of the more important and simple considerations for non-obstetric practitioners to remember during DCR of an obstetric patient is the physiologic impact of

Table 17.3 Changes in maternal physiology during pregnancy [107]

Plasma volume	Increases
Red blood cell mass	Increases
White blood cell count	Increases
Peripheral vascular resistance	Decreases
Heart rate	Increases
Systolic blood pressure	Decreases
Cardiac output	Increases
Clotting factors	Increase
Respiratory rate	Increases
Glomerular filtration rate	Increases

the gravid uterus on the pregnant mother. Recumbent positioning has been found to reduce cardiac preload by as much as 25% [69]. To mitigate this risk, hypotensive obstetric patients should be bumped up with rolls placed under the right flank to relieve any pressure on the inferior vena cava. Finally, lower extremity venous access for resuscitation, such as femoral artery cannulation, should be avoided.

Postpartum Hemorrhage

Defined as blood loss greater than 500 cc following a vaginal delivery and more than 1000 cc following a caesarian section, postpartum hemorrhage (PPH) occurs in approximately 2.9% of all deliveries of which 79% are attributable to uterine atony [70]. The reason behind current increased rates of PPH is thought to be due to medication given during induction to augment labor such as high-dose and prolonged courses of oxytocin (in contrast to postpartum prophylactic dosing of oxytocin to prevent PPH) [71] and increased rates of caesarian sections [72]. There are a number of options for the treatment of PPH based on the DCR paradigm. These therapies include uterotonics (e.g., postpartum oxytocin at prophylactic dosing), interventional therapies, and surgical control. Recently, resuscitative endovascular balloon occlusion of the aorta (REBOA) has emerged as a useful adjunct for temporary aortic occlusion in patients with postpartum hemorrhage [73].

Transfusion

The majority of the recommendations and principles of hemostatic resuscitation applied to trauma patients can be applied to pregnant mothers. Similar to trauma patients, a high ratio of plasma to red blood cells may be beneficial in this patient population, but further research is needed [74]. TXA has not been studied in obstetric patients with life-threatening hemorrhage. Instead, the use of TXA in this patient population has primarily been studied as a prophylactic agent used to prevent PPH. A recent meta-analysis published in 2015 ultimately favored the use of TXA and found that the incidence of blood loss greater than 500 cc was less in patients receiving TXA versus placebo [75]. The benefits of TXA for patients with obstetric hemorrhage were also found in a study that examined its use in PPH treatment. Duration of hemorrhage and blood loss was significantly lower in patients receiving TXA following hemorrhage [76]. Finally, the benefits of TXA were confirmed in a recent randomized controlled trial published in 2017 [77] with over 20,000 patients. The investigators found that death due to bleeding was significantly lower in patients receiving TXA. The use of recombinant activated factor VII (rVIIa) for PPH has fallen out of favor as several trials in the obstetric literature have shown no survival benefit and increased complications [78], although numerous case reports touting the benefits of rVIIa can be found in the literature [79]. Finally, monitoring fibrinogen is especially important in obstetric hemorrhage in which certain kinds of placental pathology cause rapid

fibrinolysis and it is a good indicator of PPH severity [78]. Consensus guidelines support the use of fibrinogen concentrate for ongoing PPH over the use of cryoprecipitate [80].

Gastrointestinal Hemorrhage

In recent years, the emphasis in this patient population has been on a restrictive transfusion strategy using hemoglobin targets. A large randomized trial of patients with upper gastrointestinal bleeding treated with a restrictive transfusion strategy (transfusion for Hb <7 vs. Hb <9) for upper gastrointestinal bleeds had improved outcomes [81]. The benefits of such a strategy was confirmed by a recent 2017 meta-analysis [82]. However, on close examination of the studies considered, patients with massive hemorrhage and hemodynamic instability were excluded, and the benefit of a restrictive strategy was dominated by patients with portal hypertension in which over-resuscitation is known to increase portal pressure thereby increasing the likelihood of rebleeding.

Germane to the application of DCR in patients with gastrointestinal hemorrhage, a large epidemiologic study in Australia and New Zealand found that 13.9% of 3500 MTP activations were for this indication [14]. Thus, it is imperative to distinguish those patients with massive GI bleeding and hemorrhagic shock who require a ratio-based resuscitation strategy to optimize hemostasis. As with other indications for DCR, studies have shown that significant practice variation in transfusion thresholds persists [83]. A platelet threshold of fifty thousand has been proposed although this recommendation is largely based on expert opinion [84]. Furthermore, transfusing patients on antiplatelet agents with platelets stored at room temperature may not improve patient outcomes [85]. A 2014 Cochrane Review of TXA for variceal bleeding found some evidence to supports its use although the quality of the evidence was low [86]. One small randomized controlled trial with TXA showed no difference in blood loss between placebo and TXA-treated patients with lower gastrointestinal bleeds [87].

These resuscitative measures are designed to reverse accumulating oxygen debt and augment hemostasis. Other temporizing measures include balloon tamponade of bleeding varices [88], esophageal stenting [89, 90], and even REBOA [91, 92]. However, in most cases, early endoscopic control is imperative for definitive hemostasis. In patients who have failed endoscopic treatment or who have pathology not amenable to endoscopic control, angioembolization or surgical hemostasis may be required.

Perioperative and Operative DCR Considerations

During DCR of massively bleeding trauma and non-trauma patients in the operating room, acute care surgeons should actively follow markers of resuscitation such as base deficit and lactate and, if available, thromboelastography data. Although

high-quality evidence in support of using thromboelastography to monitoring coagulation parameters during DCR is lacking [93], the technology is available and has found its way into the armamentarium of both acute care surgeons and obstetricians alike and algorithms have been developed in efforts to fine-tune DCR [94]. Studies indicate these tests may be helpful for the early detection of coagulation abnormalities and fibrinogen administration [95]. One caveat is that "normal values" may be different in different patients [96].

During massive transfusion, calcium is chelated by citrate present in all stored blood products. If hypocalcemia occurs patients can become hypocoagulable. Targeting a blood pressure that optimizes end-organ perfusion is also optimal. While permissive hypotension may still have a role outside the operating room in select patient populations, the use of intraoperative permissive hypotension is not supported by the literature. Randomized controlled trials evaluating hypotensive resuscitation in trauma patients [97] and in non-trauma patients requiring during laparotomy have not indicated any benefit. Surgeons should ultimately target normotension during these operations.

Intraoperative red blood cell salvage is an important component of intraoperative DCR [98, 99], despite an unclear benefit on mortality; a 2015 Cochrane Review showed a decrease transfusion requirement in the first 24 hours following injury and no differences in cost or infectious complications with the use of cell salvage technology.

In non-trauma patients undergoing massive transfusion and non-massively transfused trauma patients the ratio of blood products transfused may not be as critical. Although it decreased mortality in non-trauma patients in the first 48 hours after injury, a high ratio of plasma:RBC (>1:2) did not improve overall survival in massively transfused non-trauma patients [100]. Similar results were published by Sambasivan et al. in 2011, whose study of trauma patients found that a high ratio of FFP and platelets to RBCs increased ventilator days and length of stay and did not affect mortality in non-massively transfused trauma patients [101].

Prior to the MATTERs and CRASH-2 studies [102, 103], investigators explored the perioperative use of TXA. A recent review found that TXA prophylaxis was associated with reduced blood loss and reduced transfusions in elective cardiac, transplant, orthopedics, neurosurgery, and obstetrics procedures [104].

Conclusion

DCR is a well-established bundle of care for severely bleeding patients. Its principles, although predominately studied in trauma patients, can be applied to other patient populations. Keeping varying physiology in mind, the core principles of hemostatic resuscitation, limiting crystalloid infusion, careful consideration of permissive hypotension, as well as prompt identification of the need for and activation of MTP can be applied to pediatric patients, geriatric patients, and those with peripartum, gastrointestinal, and perioperative hemorrhage alike. Identifying hypoperfusion in the elderly is challenging and relying on vitals without careful analysis of

laboratory values may be misleading. During perioperative DCR, use of red cell salvage techniques, REBOA, and hemostatic adjuncts such as TXA should be considered if significant blood loss is anticipated. More work is needed to understand the demographics of massive bleeding and hemorrhagic shock in non-trauma patients and to optimize the hemostatic resuscitation of these patients.

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Part II

Education and Training Methods for DCR

Optimal Methods of Teaching and Training DCR/RDCR

18

Ethan A. Miles and John C. Maitha

The practitioner of RDCR (remote damage control resuscitation) is tasked with taking a team sport (DCR) which is typically practiced by large well-trained teams in major medical centers and perform the key tasks in a remote and typically dangerous environment often by themselves with nothing but a small aid bag on their back. The prehospital provider may be a military medic, a civilian EMS paramedic, a wilderness search and rescue team, or a rural physician. Regardless of level of formal education, the majority of procedures and knowledge may be taught to most medical providers. If given quality training and medical direction, individuals can be expected to successfully provide the majority of the key components of RDCR in any environment.

The medical director must include four key components to allow the prehospital provider to practice: (1) training and education, (2) certification, (3) licensure, and (4) credentialing. The training and education of RDCR should be done with the ultimate goal in mind of credentialing the individual to perform the key components described in this chapter. Written and hands-on testing of RDCR is a key component in the process of credentialing and requires definitive goals in the performance of RDCR given the unique environment in which the individual provider is expected to perform. By setting specific goal directed steps, the student can clearly identify performance steps required for successful completion of the training. Given the severity of consequences and lack of alternate treatment in the resuscitation of patients with hemorrhagic shock in the remote setting, scope of practice tends to be much wider than typically encountered. Ultimately though, it is up to the medical director to determine the scope of practice given in RDCR to the practitioner.

Utilizing the crawl, walk, and run methodology allows the instructor to ensure the student has a solid understanding at each phase of instruction and allows for

E. A. Miles (✉)
75th Ranger Regiment, US Army Special Operations Command, Columbus, GA, USA

Uniformed Services University of the Health Sciences, Bethesda, MD, USA

J. C. Maitha
75th Ranger Regiment, US Army Special operations Command, Savannah, GA, USA

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simple resets when knowledge gaps are discovered. In training RDCR, the crawl phase consists of developing a core basis of understanding of DCR as well as the development of the required procedural skills in a lab or classroom setting. The walk phase advances to the application of DCR principles into the student's expected environment and how the skills learned may be utilized in their setting; decision-making should be emphasized at this point. The run phase recreates the student's expected environment as closely as possible (i.e., in a helicopter at night, under simulated enemy fire, or in the back of an ambulance while moving) with timed scenarios designed to challenge both the knowledge gained as well as the actual skills application (i.e., multiple casualties with limited equipment in CCP-casualty collection point).

There are two goals of RDCR training. The first goal is to develop an adequate understanding of life-threatening hemorrhage (LTH), hemorrhagic shock and its consequences, components of RDCR, when to use the components of RDCR, and how they affect the patient. The second is to master the basics of TCCC and fully integrate RDCR principles into a standardized trauma patient primary assessment. When training RDCR in the initial education phase, great emphasis should be placed on how the physiology applies to practical application vs. an in-depth review of processes which do not directly impact decision-making in the field. The graphic below is an example of how the concepts of LTH, hemorrhagic shock, and oxygen debt [1] are taught at the 75th Ranger Regiment during RDCR training with specific emphasis on how to manage each pathway. See Fig. 18.1.

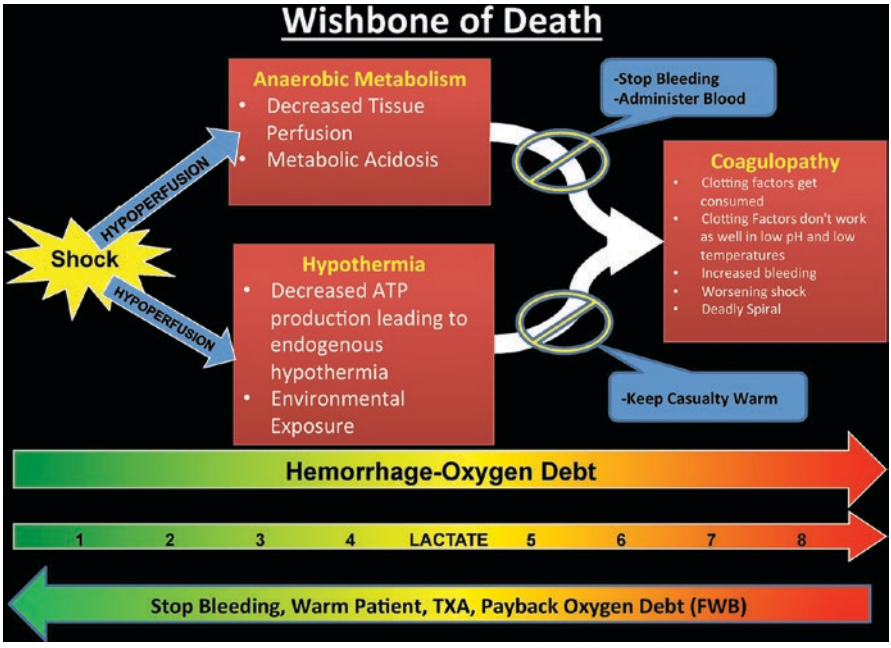

Fig. 18.1 The RDCR treatment approach to delay the secondary effects of trauma

By gaining a solid understanding of how the principles of DCR apply to the casualty in the field, the student may then conceptualize the importance of each step in the process of RDCR.

Following the completion of the first goal of initial education of the lethal triad effects a focus on the primary trauma assessment should be started. Without mastery of a basic trauma assessment RDCR is futile. The purpose of the trauma assessment is to treat life-threatening injuries and then apply RDCR to treat the secondary effects of trauma.

Models for Training

Multiple models exist for utilization in training RDCR, and best-training practices typically combines the models to take full advantage of each. The main models currently utilized are task trainers, human patient simulators (HPS), live role players (LRP), live tissue training (LTT), and virtual training. While no single model provides a perfect training solution, a solid understanding of the benefits and downsides of each will help the trainer piece together the optimal training path for student success.

Dedicated task trainers such as IV arms and wound-packing simulators are best utilized during initial skills training in order to facilitate the student learning the physical steps of the procedure. During this step, students are often familiarized with a piece of equipment such as an IO device and instructed through the entire procedure. The second portion of training where dedicated task trainers are helpful is during the run phase where the individual skill has been mastered and the student needs a model to complete a particular step in the trauma lane and move on to focus on the RDCR portion. An example of this would be the utilization of a sternal IO trainer when using a live role player, thus allowing the student to perform the task as they would in a live patient without incurring the risk of performing an IO in a live role player.

The HPS provides a training model, which can be fairly appropriate for most tasks in RDCR training. In training RDCR, the advantages of an HPS include full size and weight (which pushes the student to use proper movement and hypothermia prevention techniques), realism of injury with newer models, and vital sign feedback without instructor coaching and allow the majority of the individual tasks to be performed on a single model. The downsides of the HPS tend to be technical reliability, time involved in setup/refitting, lack of variability in wound patterns, HPS operator proficiency, and a rapidly fading realism effect. The HPS is best used during the "walk" phase where the student is starting to bring together multiple steps of the assessment and intervention phase in RDCR. This allows the student to get multiple trauma lane runs in, which facilitates committing the key steps of the process in the right order.

Live role players (LRPs) provide an optimal model for a realistic training model in several areas. Distinct advantages include live patient feedback, accurate model for measuring vital signs, and obtaining vascular access with autologous blood

transfusion If using a properly trained LRP, the student often pays much more attention to hypothermia prevention, safe realistic patient movement techniques, and pain control. Disadvantages of LRPs include a limited number of procedures you can perform; limited vital sign variability and injury patterns generally rely on moulage which has limited ability to replicate massive hemorrhage. LRPs are generally utilized best during the run phase and can significantly contribute to the chaos of MASCAL event training.

Live Tissue Training (LTT), using animal models to recreate trauma models, provides several distinct advantages to include; absolute realism with hemorrhage control, live real-time physiologic feedback, ability to perform WB transfusions, and variability of real wounding patterns. Disadvantages include restriction of use, smaller patient size, anatomic differences, difficulty with integration into large unit level exercises, backside veterinary support and cost. While this training is often restricted, its value when combined with a comprehensive training program is significant. This type of training should not be utilized as a one size fits all, rather it should be utilized only after careful consideration of the goals of training and in conjunction with the models outlined above.

Human cadavers provide the highest accuracy for an anatomically correct training model. The cadaver provides an ideal model to learn anatomy and perform many key procedures such as IO placement, airway adjuncts, surgical airway, needle decompression, and chest tube insertion. The cost and sensitivity have a potential to significantly impact availability of use. Cadavers are typically best utilized during the crawl phase when the student is gaining a detailed anatomic understanding of injury patterns and lifesaving interventions.

When selecting models to use in training RDCR, care should be taken to match the models for the objectives. In the majority of training, a combination of models will be needed to train (and retrain) students as they refine their ability to run a trauma lane. By objectively grading at each phase, the instructor can utilize the best model to facilitate optimal training in area identified as a weak spot for the student. The chart below shows a simple diagram identifying individual model strengths and weaknesses to facilitate a proper combination for training based on what is available. See Fig. 18.2.

Goals in RDCR Training

The first goal of training is the early recognition and intervention in LTH, which is the first step in the MARCH (Massive Hemorrhage, Airway, Respiration, Circulation and Hypothermia/Head Injury) process. Students should be taught to recognize injury patterns that pose a high risk for massive hemorrhage loss or continued noncompressible hemorrhage. Additionally, the provider should train on the management of the designated medical team as well as the management of nonmedically trained responders during this time.

	NPA	SGA	Cric	Needle Decompression	CT	TQ	Wound Packing	Cax package Transport	IV	IO	Blood Admin	Casualty Assessment	Vital Signs
Role Player	*****	0	0	0	0	****	0	*****	****	0	*****	****	****
HPS	***	***	**	***	**	****	***	****	***	***	**	***	***
LTT	***	0	***	****	****	**	****	**	**	***	****	****	***
Task Trainer	**	***	**	**	**	**	***	0	***	***	**	0	0
Cad	****	****	*****	*****	*****	****	(***)	****	*	*****	0	*	0
Real World Patient	*****	*****	*****	*****	*****	*****	*****	*****	*****	*****	*****	*****	*****

0 = Not available/ Not doable

* = Marginally useful

** = Useful for motor memory task, but not realistic

*** = Somewhat realistic

**** = Very realistic

***** = Same as real

Scale from zero to five, zero the lowest, quantifying training model realism.

Fig. 18.2 Training model strengths and weaknesses to maximize individual RDCR skill training effectiveness

The Crawl Phase

During the crawl phase students should complete multiple MARCH assessments while communicating to the instructor common injury patterns on casualties to engrain the algorithmic approach. The crawl phase can include verbal prodding from the instructor to facilitate emphasis and focus on injury patterns during each step of the casualty assessment.

- The start of the crawl phase should emphasize the primary trauma assessment.
- The Tactical Combat Casualty Care Guidelines and many military medics use the MARCH pneumonic to identify initial life-threatening injuries. The MARCH pneumonic is effective in the RDCR arena because it is designed to treat and identify the initial and secondary effects of trauma.
- This phase should not be stressful to the student promoting a learning environment of question and answers between student and instructor.
- The crawl phase should emphasize perfecting the algorithmic approach using the MARCH pneumonic, or equivalent, with numerous trauma assessments on other classmates absent injury or combat equipment. Multiple repetitions of the student touching or verbally implying where an appropriate intervention should be applied in the primary trauma assessment will build a strong foundation for DCR. Technical application of interventions for minor and complex wounding should be added during the walk and run phases. Perfecting the basic algorithmic approach without distractions will greatly increase the effectiveness of run phase as the instructor can focus on decision-making verses technique and sequence correction.

- Skill stations or round robin style training should be utilized to cover in detail the capabilities of the equipment used to stop immediate life threats and provide instruction on implementing DCR interventions following treatments of initial life threats. See Table 18.1 for round-robin example.
- An effective method to maintain proficiency and updated information on the latest medical developments for the MARCH primary survey is to review the Tactical Combat Casualty Care Guidelines. The guidelines are updated periodically with the latest medical literature and recommendations from deployed military medics. A free website to access updated guidelines, skill sheets, and videos can be found at www.naemt.org or you can download the free "Deployed Medicine" application for Android or iPhone devices.
- If the DCR training course includes live tissue training (LTT), a tabletop block of instruction is required. The table top or wet lab block of instruction should cover indication, contraindications, and alternative methods for each procedure performed. Proctor standardization on a training model is highly recommended prior to the start of the tabletop instruction so every student performs individual procedures to the same standard. See Table 18.2 for example of a tabletop block of instruction.
- An example training schedule for training initial trauma assessments and DCR can be found in Table 18.3.

Table 18.1 Example of an individual RDCR technical skill rotation

Time	Skill station – round robin
25 minutes	Intermediate airways
25 minutes	Buddy transfusion – blood
25 minutes	Junctional tourniquets
25 minutes	Hypothermia management
25 minutes	IV fluid warmer
25 minutes	Extremity tourniquets
25 minutes	Evacuation packaging
25 minutes	Peripheral saline lock
25 minutes	IO device insertion (sternal)
25 minutes	Monitoring devices – SP02, ETC02

Table 18.2 Example of a minor surgical skill training rotation utilizing LTT

Time	Table top task list
25 minutes	Surgical airway
25 minutes	Tourniquet application
25 minutes	Hemostatic application
25 minutes	Tourniquet conversion
25 minutes	Needle thoracentesis
25 minutes	Chest tube insertion
25 minutes	Intravenous access
25 minutes	Intraosseous infusion (nonsternal)
25 minutes	Lateral canthotomy
25 minutes	Blood transfusion

Table 18.3 Comprehensive training schedule to teach RDCR in 1 week

Day 1	Time	Event	Location	Instructor	Uniform
Crawl phase	0900–1000	TCCC updates			Field
	1000–1100	Deployment casualty AARs			Field
	1100–1200	Skill stations			Field
	1200–1300	Lunch			Field
	1300–1600	Skill stations			Field
	1600–1700	Pain management class			Field
	1700–UTC	Aid bag/equipment preparation			Field
Day 2	Time	Event	Location	Instructor	Uniform
Crawl phase	0800–0900	Trauma airway class			Field
	0900–1000	Thoracic trauma class			Field
	1000–1100	RDCR class			Field
	1100–1200	Blast/burns/crush management			Field
	1200–1400	Day trauma lanes – moulage			Body armor
	1400–1500	Lunch			Field
	1500–1700	Day trauma lanes – moulage			Body armor
	1700–UTC	LTT/equipment preparation			Field
Day 3	Time	Event	Location	Instructor	Uniform
Crawl phase	0800–0900	Animal care brief			Field
	0900–1000	Head trauma/hypothermia class			Field
	1000–1100	Orthopedic trauma			Field
	1100–1200	Spinal trauma			Field
	1100–1200	Proctor standardization			Field
	1200–1300	Lunch			Field
	1300–1400	LTT patient preparation			Field
	1400–1700	LTT tabletop instruction			Field
	1700–UTC	AAR			Field
Day 4	Time	Event	Location	Instructor	Uniform
Walk phase	0800–0900	K9 trauma management			Field
	0900–1000	MASCAL/CCP operations			Field
	1000–1100	Mission brief/planning/rehearsals			Field
	1100–1200	Lunch			Field
	1300–1400	LTT patient preparation			Field
	1400–1700	Day time trauma lanes			Body armor
	1700–1800	Range recovery/chow			Field
	1800–1900	LTT patient preparation			Field
	1900–2000	Mission brief/planning/rehearsals			Field
	2000–UTC	Nighttime trauma lanes			Body armor
		AAR following training completion			Field
Day 5	Time	Event	Location	Instructor	Uniform

(continued)

Table 18.3 (continued)

Day 1	Time	Event	Location	Instructor	Uniform
Run phase	1200–1300	LTT patient preparation			Field
	1300–1400	Mission brief/planning/rehearsals			Field
	1400–1800	Daytime MASCAL exercise			Body armor
	1800–1900	Ranger recovery/chow			Field
	1900–2000	LTT patient preparation			Field
	2000–2100	Mission brief/planning/rehearsals			Field
	2100–UTC	Nighttime MASCAL exercise			Field
		AAR following training completion			Field

The Walk Phase

Progression to the walk phase is accomplished by producing an injury pattern on the chosen training model consistent with massive hemorrhage (extremity amputation) or noncompressible hemorrhage (penetrating trauma to the torso or junctional bleed). Without verbal prodding by the instructor, the student should rapidly identify all sources of significant bleeding and intervene to stop any potential compressible bleeding. The focus of the student during the walk phase is effectively implementing the MARCH process while completing the appropriate treatment tasks to a specific time standard. Verbal prodding by the instructor should be eliminated and focused towards assessing the student's critical thinking process. The walk phase ends when the student can effectively complete a MARCH assessment, identify life threats without verbal ques. and apply all necessary interventions within the specified time standard.

Advances to the application of DCR principles into the students expected environment and how the skills learned may be utilized in their setting; decision-making should be emphasized at this point. The priority of the walk phase is to integrate the basic skills and didactic instruction taught during the crawl phase into a simple trauma patient scenario. The question and answers between student and instructor should be minimized and more focus should be placed on correcting student deficiencies.

- To increase the intensity and stress of the scenario, the students should be in the uniform that the expected environment requires (body armor, helmet, extrication tools, etc.).
- In general, The walk phase takes place during the day time.
- The most effective casualty models for the walk phase are moulage and patient simulators. Both training models can provide the most realistic feedback to the student and better drive the algorithmic process.
- Casualty scenarios should be dictated by the medical director but have input from prehospital providers. The most effective trauma scenarios come from After Action Reviews (AARs) articulated from prehospital providers who operate in the student's expected environment. It is particularly effective to review the

management during the scenario in comparison with the actual management provided to the casualty in the real-world event. This provides the student with a greater sense of realism and can review outcomes of the real-world casualty.

The Run Phase

During the run phase, the instructor may add in distraction injuries such as superficial skin wounds to determine the student's ability to discriminate hemorrhage requiring immediate intervention from superficial wounding. In addition to performing hemorrhage control interventions, at the run stage, the student should start activating the RDCR response system (calling for blood, casualty transport team, managing first responders, etc.). Goal times will vary based on complexity of injury pattern, but in general the following times should be achievable. See Table 18.4.

The run phase should provide enough realism and complexity for the instructor to evaluate the student's ability to medically manage a casualty scenario. The student should focus on completing advanced medical tasks while assigning basic tasks to adjacent team members. Providing complex wounding patterns and short evacuation times can create situations where the student requires a team approach to care and maximize the RDCR response system. Attention should be given to areas where efficiencies can be increased, for example, hemostatic pressure dressing can be held while directing first responders, activating the RDCR system, and preparing equipment. The run phase should end when the student can effectively apply medical interventions, manage a team through the RDCR process, and complete the treatment process to the point of casualty evacuation.

- The student uniform should include all equipment required to accomplish the mission in the expected environment. The mission environment should be established as chaotic as possible. Add explosions, pneumatic gun fire, smoking barrels, aircraft hulks, or adverse terrain for a stressful training iteration.
- Casualty scenarios should be complex and polytraumatic, require multiple interventions, and create a scene where casualty reporting is difficult.
- Casualty movement should be physically challenging. Incorporate difficult patient movement scenarios from prior prehospital provider experiences to add realism but also limit unrealistic scenario movements.
- Minor feedback should be required or provided and evaluation of task completion is the priority.

Table 18.4 Estimated time standards indicating efficacious application of LTH interventions

RDCR task	Time standard
Tourniquet placement	60 seconds
Wound packing	60 seconds to pack and 3 minutes of pressure (for current hemostatics)
Junctional tourniquet placement	90 seconds
Pelvic binding	60 seconds

Training RDCR

Once hemorrhage is controlled as best as possible given the patients' injuries, life-threatening airway (A) and respiration (R) issues are identified and treated. The focus of training then turns to meeting goals of RDCR. Through pattern recognition (established during prior repetitive patient assessments) and early assessment of vital signs the student should arrive at a diagnosis of hemorrhagic shock and start the process of goal driven resuscitation. Early placement of pulse oximetry, ETCO2, and blood pressure measurement greatly assists in this process. Depending on the model used, the proctor may have to utilize verbal cluing for clinical and vital signs in order to drive the scenario in the desired direction. The ability to produce desired vital signs in a HPS (human patient simulator) presents a distinct advantage during this phase as the student is able to arrive at their own conclusions based off of his or her assessment rather than looking to the proctor for clues. See Fig. 18.3.

Current goals include:

- Systolic BP 100 (when using Whole Blood for resuscitation)
- Pulse <100
- SpO2 >90
- Lactate <5
- Clinical signs – normal mentation, normal skin tissue perfusion, and appropriate pulse quality

Once hemorrhage control is complete and initial assessment determines that hemorrhagic shock is present or pending, the resuscitation phase of training begins. Multiple interventions need to be performed in rapid order during this phase and the student should focus on efficiencies in performance. For example, it has become standard practice within the 75th Ranger Regiment that if an IO is used for RDCR then it is initially flushed with 1 gram of TXA, thus combining the flush step of performing an IO with the administration of TXA step in RDCR. Time to accurate intervention continues to be assessed with the following goals (each time standard is based from the time the student makes it to the C portion of the MARCH process). See Fig. 18.4.

- IV or IO access: C + 3 minutes
- First Dose of TXA: C + 5 minutes
- First unit of blood begins: C + 10 minutes
- Walking donor drawn: 15 minutes after recognition of injury if using a team member to draw and C + 15 minutes if student is drawing blood
- Patient warming/hypothermia prevention: C + 5 minutes

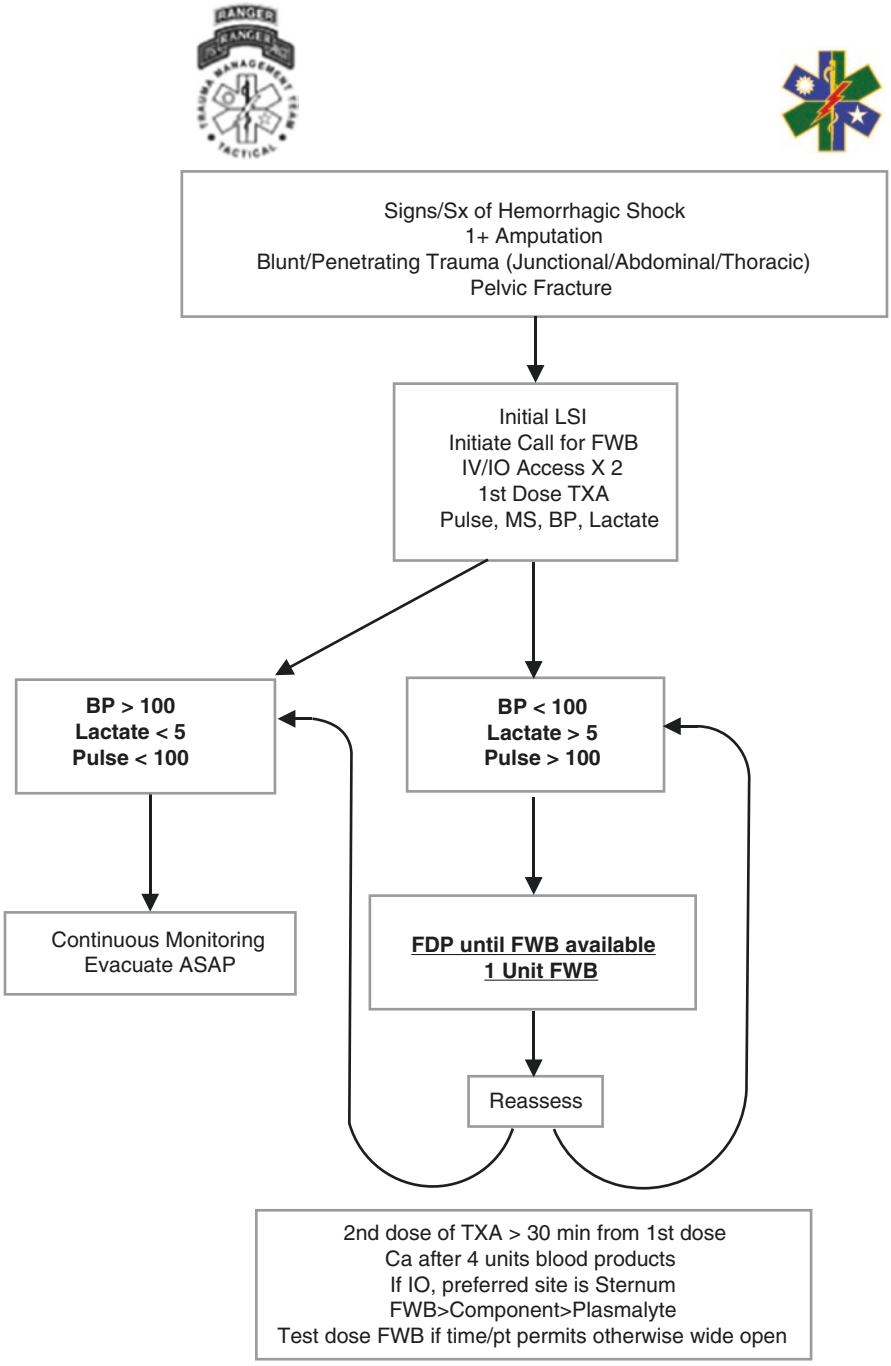

Fig. 18.3 75th Ranger Regiment Hypovolemic Shock Protocol [6]. (From Fisher et al. [6], with permission of Oxford University Press)

Intervention	Goal	
LSI (TQ/ Wound Pack)	60 sec	
Hemostatic	901 min +3 min pressure	
VS Check	After LSI	
IV/IO	C+3min	
TXA	C+5min	
WB	C+10min	
Hypothermia Prevention	C+5min	
ROLO Draw	15min	

Fig. 18.4 Estimated treatment timeline goals in the spectrum of RDCR care

Skills Teaching

The core skills involved in RDCR are hemorrhage control and the physiologic administration of blood products and medications to treat shock and blood failure. While there are numerous methods involved in hemorrhage control, explanation of the methods is beyond the scope of this chapter. The main concept to keep in mind with hemorrhage control is mastery of the basics; new techniques should never take the place of the basic tenets of tourniquet application and proper hemostatic wound packing.

The first step of the RDCR process is to effectively control all immediate life threats and establish intravenous (IV) or intraosseous (IO) access for whole blood or blood product transfusion. In the MARCH algorithm step C (circulation) is the appropriate point to direct, if nonmedical personnel are available, or personally obtain access.

- Vascular line size should be no less than 18 gauge.
- IO access should be taught to include the sternal and humeral head sites.

- Emphasis should be placed on training non-medical providers in IV/IO skills. A team approach to RDCR is always more effective and provides faster treatment. Having a nonmedical provider establish access for a blood transfusion saves time.

While medication administration is a fairly straightforward process, practicing the exact steps pays dividends when seconds count during patient treatment. Field and hospital-based training should focus on either practicing with the exact medications or by using simulated medications. By requiring each step to be actually performed, the student gains a better appreciation for the setup of his or her equipment and ways to speed or smooth out the process. Experimentation and cross talk should be encouraged during this stage of training, facilitating best ways to setup an individual's equipment.

FWB transfusions can be a daunting task if the student or trainer has minimal experience; however, this is a relatively simple procedure, which can be learned rapidly. Starting with an equipment familiarization, the student should layout the kit in order of the steps being performed. Many aftermarket blood transfusion kits are packaged with excess materials that are irrelevant to collection in the RDCR environment. The procedure requires very little equipment and focus should be on the basic steps to eliminate any unnecessary procedures involved.

- One method for streamlining the procedure is to:
  1. Start by placing a 14–16 g IV in the antecubital fossa.
  2. Apply a saline lock adapter plug.
  3. Insert the hard needle from the donor bag is placed through the saline lock.
  4. Release the clamp on the donor bag line.
  5. Blood will begin to fill the donor bag.
  6. This technique allows for continuous or intermittent blood collection in the event the casualty requires movement.

When drawing a unit of FWB, the student must learn to accurately judge volume to determine when the bag is full and collection should cease. Overfilling could result in wasted time and increased risk of clot formation within the bag. Underfilling a collection bag could result in an overall increase in relative citrate administration, thereby increasing risk of citrate toxicity and hypocalcemia. A simple method for determining how full a bag should be is to bring a kitchen scale to training and fill the bag to the 600 gm mark. This method gives the student an accurate frame of reference, which generally imparts a lasting ability to judge the fullness of a bag by eyesight and feel. A simple procedure in the field is to use a zip tie secured around the middle of the bag with a 6.5-inch circumference and fill until flow stops. This method reliably results in a full blood bag without overfilling [2]. In general students become quite proficient at estimating ideal volume after just a few draws. When drawing a unit of FWB for use in RDCR, speed of draw is a critical consideration. While adhering to the safety precautions outlined in this chapter, students should be prompted and allowed multiple attempts while being timed in order to

facilitate rapid blood collection in the field. One simple method is to have competitions between groups to see who can fill a bag the quickest with the highest volumetric accuracy. Administration of the unit of blood back in to the donor is a very simple process, and doing so significantly instills confidence in the student to perform transfusions in a real-world patient. Administration should be performed as soon as possible after donation, but no longer than 4 hours after the draw.

With these steps trained, the student should be able to rapidly obtain IV and IO access, administer TXA, and draw/transfuse a unit of FWB within a 15-minute timeframe. Task completion (if using pre-drawn WB) within a 15-minute time standard is ideal and will provide the best outcome for a combat casualty [3]. Additional products utilized in the RDCR process should be added to the training based on the unit's medical protocols and what products are available. Cold stored-low titer O whole blood (CS-LTOWB) may be simulated by placing a label on a 500 ml bag of normal saline and carried in a cooling container. Simulated freeze-dried plasma (FDP) is commercially available for use in training; however, caution in training must be taken as the simulated FDP dissolves much quicker than actual FDP. Expired units of packed red blood cells (PRBCs), plasma, and platelets can often be obtained from blood banks which allows for hands on practice with these items, thus facilitating efficient administration in a simulated patient.

All of the skills discussed in this section should be realistically trained among the team that will be working on patients together. This team may include nonmedical personnel as well, who can greatly accelerate the speed at which the RDCR process flows. Nonmedical personnel should be trained to the highest level possible as oversight from medical direction allows. For example, nonmedical personnel within the 75th Ranger Regiment are routinely taught how to properly identify a donor, collect a unit, document, and assist in the administration of a unit of FWB. When utilizing a team approach, it is vital to have set standard operating procedures (SOPs) for all to follow and to train those SOPs within the actual group who will be working together.

- Standard operating procedure (SOP) example
- Identify donors
- Unit Collection
- Utilizing a team approach
- Documentation and administration of FWB

Safety in Training

Training RDCR poses few, but potentially serious, risks to health. Proper care must be taken whenever performing autologous blood transfusions to avoid blood mismatch errors. It essential that training standard operating procedures (SOPs) are created and upheld during all training to prevent blood transfusion mismatch. For an increased measure of safety, the medical director may elect to only draw and transfuse one individual at a time, thereby decreasing the chance for mismatching drawn units. However, in the authors' experience, multiple students can safely perform

autologous transfusions at the same time by adhering to basic safety precautions. In fact, in the advanced stages of training, having multiple students perform autologous transfusions at the same time encourages efficiency and speed by facilitating timed challenges. Three simple procedures greatly assist in preventing a potentially lethal mismatch: (1) When drawing a unit from a donor, the bag and the donor should be labeled with the same unique mark (letters or numbers work well). The donors' arm or forehead can be labeled for ease of recognition. (2) The donor bag should be signed by the donor at time of draw. (3) Physical separation of students and whole blood to decrease the chances of unintentionally mixing units of blood. The first two steps allow for a simple timeout to be performed prior to reinfusion of the blood into the donor. During this timeout, the donor verifies his or her signature and the administrator verifies that the mark on the bag matches the mark on the patient.

Another potential risk in training autologous whole blood transfusions is the potential for citrate toxicity and allergic reaction. While these reactions are rare, providers should be prepared to respond and treat allergic reactions. Mild citrate reactions are not uncommon and generally consist of a mild cough during reinfusion. For mild reaction, the transfusion can be slowed, stopped, or continued with close monitoring. Rarely anaphylactic reactions can occur with transfusion [4], which is even more rare with autologous blood transfusion [5]. These reactions can be treated with standard allergic reaction protocols. The medical director overseeing training should have epinephrine and diphenhydramine available for treatment. With any reaction, the administration can be stopped and remaining blood discontinued. A single unit of blood donation is very well tolerated without significant side effect in the overwhelming majority of healthy individuals.

Additional risks include infection, thrombus formation, and contaminated needle stick. Using standard precautions as performed with any routing medical procedure greatly reduces these risks. Care should be taken to ensure sterile procedure even if in austere training environment, and personal protective equipment should be used at all times.

While there are definitive risks involved with RDCR training, simple precautions greatly reduce these risks and allow for high-quality training. The medical director in charge of training should ensure establishment of SOPs as discussed above and be adequately prepared to respond to complications. The benefit gained by students performing live transfusions prior to real-world execution should not be underestimated due to discomfort with the risks discussed above. While there is a steep learning curve to RDCR, the training discussed in this chapter is essential to being able to execute DCR in the remote environment and no current technology is a suitable replacement for autologous transfusions in the training environment.

Qualification Standards

In order to authorize medical personnel to perform the tasks involved with RDCR, the medical director must set standards of training. Each unit will have some variation in protocols, training time, and expectations. The key to quality training is that

each of the section and tasks discussed in this chapter should have defined standards which may include time standards, following key steps in and SOP, and ability to provide reasoning for actions in the RDCR process. One method for doing this is to perform a written test covering key concepts of RDCR. This written test captures knowledge of the subject and decision-making ability with a resulting written score. Following the written score, skills stations covering each of the defined tasks (hemorrhage control, IV/IO access, blood draw, medication administration, etc.) can be easily set up to test the student's ability to perform each step safely and quickly and to the standards set by the medical director in the SOP. Finally, a graded trauma lane which evaluates the student's overall ability to bring the knowledge and skills to a simulated real-world scenario serves as a final test. Depending on the students' level of training and expected environment to operate in, the graded trauma lanes can include multiple patients, extremes of environment (night, cold, in evacuation platforms) and distracting events (simulated gunfire). Once complete with the assessments, the medical director will have a comprehensive picture of each student's capabilities. At a minimum, skills should be evaluated annually with regularly scheduled (minimum of quarterly) interval training on the above skills and knowledge.

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Learning Healthcare System Principles to Facilitate Spread of DCR

19

Kara McElvaine, Joe C. McCannon, and C. William Schwab

Introduction

The fields of healthcare and public health regularly generate new innovations and evidence-based practices designed to alleviate suffering, improve quality of care and help the system function more efficiently. But while there is no shortage of well-established ideas about how to improve performance, disseminating what works remains a challenging and, at times, elusive enterprise [1–4].

The medical community and the reader alike now know what Damage Control Resuscitation (DCR) is and how vital it can be when used "with the right patient, in the right place, at the right time" [5, 6]. However, many brilliant and powerful healthcare interventions like DCR are not implemented broadly or reliably, particularly when the added complexity of cooperation across disciplines, environments, and specialty domains are introduced. As such, those seeking to introduce DCR into their system must think critically about the ways by which they, along with their teams, will introduce and embed the intervention within and throughout their system, ultimately creating a sustainable process. There is a clear intrinsic motivation within all providers for delivering innovations like DCR—indeed, any interruption in delivery of this approach risks less than optimal outcomes and ultimately the loss of human life or a reduction in the quality of life.

K. McElvaine (✉)
Oregon State University, Corvallis, OR, USA
e-mail: mcelvaik@oregonstate.edu

J. C. McCannon
Billions Institute, Cambridge, MA, USA

C. W. Schwab
Perlman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Traumatology, Surgical Critical Care and Emergency Surgery, Penn Presbyterian Medical Center, Philadelphia, PA, USA

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Adopting the principles of a learning healthcare system (LHS) can create an engine for embedding research-based and evidence-supported interventions and practices like DCR into clinical care. This chapter will provide an overview of an LHS, describe how it constantly learns, and offer an example from Intermountain Healthcare. Following these, a description of how an LHS can ideally implement and improve the practice of DCR will be discussed. An important facet of DCR is the need to bring DCR to the patients most in need and at an early interval after life-threatening injury and exsanguination. Thus, we will address how different components of the trauma LHS (prehospital, en route, and in-hospital care) must integrate data, experience, and report outcomes to continuously learn, identify gaps, and direct further research and improvement. Prior to concluding, the chapter will briefly look at what it might take to introduce DCR at national scale.

An Introduction to Learning Healthcare Systems

According to the Institute of Medicine, an LHS is a system "in which science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process, and new knowledge captured as an integral by-product of the delivery experience" [7]. This kind of undertaking requires all involved to grapple with the critical work of iterative testing, sound measurement, systems analysis, and change management [8]. It also requires understanding the factors that limit learning and implementation of effective models. These include:

- The incorrect belief that simply publishing new innovation is sufficient to lead to its adoption [1]
- The sheer volume of new information (publications, studies, protocols) that most healthcare professionals in the healthcare system have to process
- Management incentives, such as ranking by individual performance rather than by team performance, that create fear and limit learning
- The logistical and operational challenges of introducing innovations into new settings and contexts, with all of their attendant differences
- The fundamental imbalance in access to care, quality of care, and care outcomes experienced in particular geographies and by different groups (e.g., people of color) and cultures in the American healthcare system [9, 10]. These inequities are sometimes replicated with relation to acquisition of new knowledge and practice**,** *thereby hindering learning and spread and heightening maldistribution of outcomes* [9, 11, 12]

Equity here is defined as achieving equally high outcomes for all patients removing the predictability of success or failure that in some areas of healthcare correlate with social or cultural factors; any learning system must address sources of inequity, including cultures that preference certain races, classes, and genders [13, 14].

Learning systems that effectively introduce new innovations operate in an exceptional way that proactively mitigates for these barriers. Specifically, LHSs understand the inherent patterns of behavior and cultural norms in the systems and

organizations in which they operate; refine their interventions thoughtfully to meet the needs, requirements, and values of all adopting audiences; pursue many strategies to raise awareness and deepen will for change; and offer many forms of support for adult learning and implementation of new practice via a variety of adult learning methods [15, 16]. Lastly, LHSs have styles of operating that are highly tolerant of rapid iteration, adaptation, and learning [17].

Below is a simplified table intended to compare typical and less effective learning systems with the extraordinary, transformational learning systems at a high level (Table 19.1). It is not meant to be exhaustive, but rather to provide a comparison of the more traditional and proposed learning systems in healthcare today.

Table 19.1 Comparing typical with exceptional learning systems

Typical learning systems	Exceptional and transformational learning systems
The aim of the network is to facilitate general learning *No sense of direction or urgency, so making progress is not the goal*	The system-level aim of the network is crisp and quantifiable *The aim focuses action and induces cooperation toward a shared vision of success*
The system is oriented to focus upward in the hierarchy; leadership receives data and reports *The system's capacity to learn is limited because the orientation is toward leadership rather than the front lines and the patient*	The system is oriented to focus on the needs of the patient/customer; leadership removes barriers to progress in the field *Frontline providers are empowered to deliver quality care based on their deep contextual wisdom*
The system catalogues explicit knowledge (libraries) *Inadequately contextualized information, not designed to help practitioners change behavior*	The system facilitates the exchange of tacit knowledge *Focused on sharing the emergent tricks of the trade and pragmatic how-to's*
The system furnishes aggregate information *Bright spots and areas for improvement are combined, so opportunities for learning are lost*	The system measures site-level performance and disaggregates data by race and class wherever possible *Allows for learning about local adaptations, and helps motivated teams improve*
A large investment is made in teaching and training *Fosters passive learning*	Experimentation and improvisation are encouraged or required; there are high expectations for testing and adjustment *Providers constantly apply new knowledge and learning to meet outcome goals for patients*
Consensus is the primary approach to decision-making *While important under certain circumstances, consensus can be time consuming*	Agility is valued, and a variety of decision-making approaches are used depending on the stakes/risk involved *Allow stakeholders and caregivers to have the license to explore different approaches toward shared aims*
New networks are created *Work intensive and potentially inefficient*	Existing networks are harnessed *Other communities are likely working on the same problem. Collaborating is mutually beneficial*
The system is centrally managed *Can be an impediment to rapid learning*	System management is distributed; losing control is viewed as success *Frontlines are laboratories for learning*

Sources: [18–20]

Leadership

In order to launch and maintain an effective DCR program using the principles described above, leadership at every level must support the constant improvement of knowledge, experience, and study of DCR with all stakeholders throughout the delivery system. There are many existing definitions of leadership, but when it comes to establishing and maintaining learning health systems, we appreciate Marshall Ganz's definition: "Leadership is accepting responsibility to create conditions to enable others to achieve shared purpose in the face of uncertainty" [21]. The function of leadership in a transformational LHS is to create an ongoing practice of identifying, recruiting, and developing leaders at all levels and supporting one another's personal growth and professional development [17, 22, 23]. A workplace or community with more leaders of this type will be more effective and interconnected than those with a more traditional linear reporting structure.

Looking to Ganz's definition and the literature on leadership and leadership in healthcare, what might it look like to create conditions to enable others to achieve? We propose that leaders must take a hard look at existing policies, standard procedures, and incentive systems to understand what behaviors and attitudes are being reinforced [21, 23]. There is no such thing as a neutral system—the structure of any organization and community expectations for performance are always buttressed by deeper intersubjective beliefs. Methods like design thinking's empathy interviews, colleague shadowing, and 360 feedback processes can be powerful experiences to gain an understanding of those deeper beliefs.

Measurement and Data Systems

Any attempt at systemic quality improvement will need to create and tend to multidisciplinary measurement to ensure that teams are making progress toward prioritized goals. Effective measurement systems are designed to give frontline clinicians expedient access to formative data and empower those frontline clinicians to use data to inform their delivery of care. Less effective measurement systems, on the other hand, tend to provide summative data oriented toward leadership, which are used for clinician evaluation and even punishment based on outcomes. These ineffective measurement systems are not designed to aid frontline learning, which makes them less accessible in the critical moments of delivery of care.

In the highest performing LHSs, data systems are structured from the bottom-up rather than the top-down. Provider-level data counters inertia with a sense of urgency and can motivate staff into action [21, 24, p., 278]. Aggregate data showing exclusively high-level system performance hides trends and reduces the likelihood of learning. This approach of acting and reflecting at the team and individual provider data reinforces the clinical gaps, reveals areas for improvement, and at times, demonstrates how to promote learning. Using patient data to generate clinical evidence is extremely important to an LHS. Registries, which allow for timely analysis of and quick access to patient data, are also enormously useful [18, 24].

This process starts with gathering data while treating patients and developing information that leads to actions to be incorporated into future practice. Quality improvement gradually becomes a routine and perpetual process, helping all stakeholders optimize outcomes with and for patients by using evidence-based practices and interventions.

What a Learning Healthcare System Can Look Like: Intermountain Healthcare's LHS

Intermountain Healthcare (IHC) is a nonprofit healthcare system in Utah, which employs over 32,000 staff in 22 hospitals and 180 clinics [25, 26]. Under the leadership of former Chief Quality Officer Brent James, IHC began using lean management principles in 2009 and started dabbling in quality improvement in 1986 [26, 27]. See the timeline below for a brief overview of their quality improvement journey (Fig. 19.1).

One of the most powerful ways that IHC intentionally organized as an LHS was in the adoption of this mantra: *Make it easy to do it right.* By way of example, Brent James cited Dr. Alan Morris: "Morris has all sorts of hunches that he tests. His ICU is a little learning lab. At one point, he had three trials running, all using a standard protocol as a control" [7, 27, p. 7]. Here, Morris is clearly committed to improving his practice and outcomes for his patients, and the structure of IHC empowered him to allocate the necessary time for the development of protocols which could then be shared and used throughout IHC's system [28].

IHC's structure and measurement systems are fully oriented to the needs of their patients—it is explicitly the role of leadership to remove barriers to progress in the

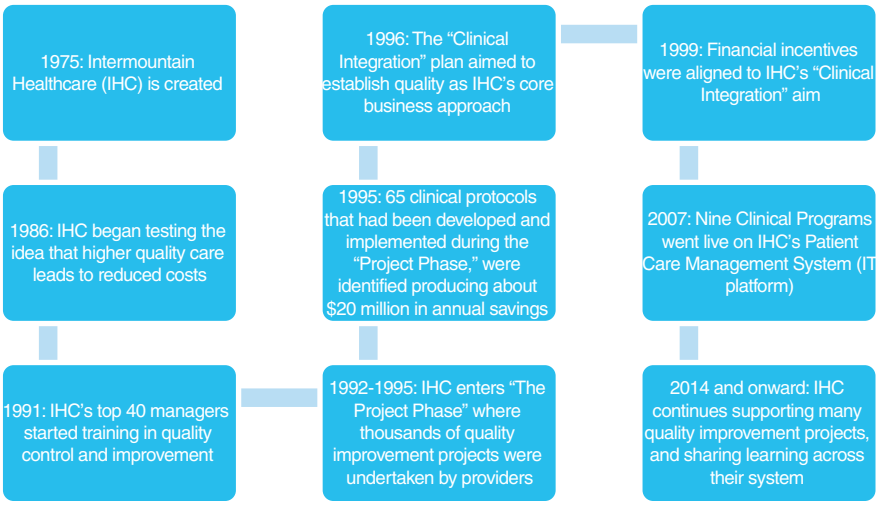

Fig. 19.1 A BRIEF Timeline of Intermountain Healthcare's improvement journey

field. Their integrated management structure supported this orientation. In the 1990s, they built a clinical management structure parallel to the existing administrative structure. James' strategy was to merge the two structures over time: "we should give the two structures tight links and shared goals, and then let them collapse together, into a single structure. We hope that over time they will experience and see the redundancy and ask themselves 'why are we holding two meetings?' and merge of their own accord" [8, 27, p. 8].

The third pivotal action that IHC took was building a brilliantly structured Patient Care Management IT infrastructure to make "bottom-up" data available for front-line providers to use in decision-making while delivering care. Aligning data management with clinical processes helped to encourage physician buy-in. In James' words, "you manage what you measure… doctors manage patients, not money" [5, 27, p. 5]. The mechanics of this type of measurement and logical processing infrastructure are beyond the scope of this chapter, but are covered well in other pieces [27, p. 9 and 30].

Additional examples of healthcare systems successfully employing the other tenants of an LHS include Virginia Mason, ThedaCare, Mayo Clinic, and Ascension Health [29–32].

Putting These Models to Work for DCR

Hypothesis: Damage Control Surgery (DCS), DCR, and the observation that moving the control of bleeding and mitigating the pathophysiologic and biologic consequences of exsanguination and severe injury "forward" to prehospital and early hospital settings can prevent death and disability after injury [33, 34]. DCR is applicable to all geographical environments, and its concepts and therapeutic pieces can be initiated by all levels of providers, including bystanders through the chain of survival to in-hospital teams of specialists (Fig. 19.2). This chain of steps required of DCR provides the vehicle and motivation to amalgamate several components of emergency response and large contingencies of providers and professionals. If successful, national effort to implement DCR universally could be a best practice catalyst for leading the development of a national trauma system.

The recent report from the NASEM, *A National Trauma Care System: Combining the Military and Civilian Systems to Achieve Zero Preventable Deaths After Injury*, identified that preventable death after major trauma is an unrecognized problem that is epidemic in proportion [18]. Evidence from the US Military Medical System and Joint Trauma System's Department of Defense Trauma Registry identified that of the 4596 combat-related deaths, 976 patient deaths were preventable if early control of bleeding or interventions to support physiology and coagulation were applied until surgical control of bleeding was accomplished [35, 36]. Civilian reports on preventable death highlighted the scale in the civilian sector and a crude estimate of 25,000–30,000 patients of the approximately 147,790 trauma fatalities in 2014 in the United States were potentially preventable; uncontrolled bleeding was the most common cause [18, 37]. The report is lengthy and contains dozens of recommendations to

Fig. 19.2 DCR and the LHS: chain of survival after critical injury. The trauma system is a continuum of care from discovery of the injured patient through recovery and reentry to society. The early providers of trauma care are essential for the commencement of DCR and its continuation till the patient is stabilized and definitive care completed in the hospital. (From National Academies of Sciences, Engineering, and Medicine [18])

address this problem-motivating federal leadership, establishing a national trauma system with standards, policy, and incentives to affect regional and local change, creation of a trauma research agenda, and assuring an expert workforce. Key to many of these recommendations is the adoption of the framework of the LHS to enable the system-wide changes to lower the preventable death toll.

Bleeding to death after injury remains the greatest challenge to the emergency medical and trauma systems. DCS and subsequently DCR were empirically developed by clinicians struggling to keep patients alive with horrific wounds and in a physiologic death spiral [38–41]. DCR forms a bundle of care rather than a specific

therapy and has its place and perhaps its greatest impact if used in the *earliest* phases of trauma care: prehospital, en route, and hospital/trauma center arrival. Its concepts, especially *rapid* transport to definitive care and early tactical *control of bleeding*—manual pressure and tourniquets—are simple and applicable in all environments and deployable by the earliest responders to the injury incident. Sustaining life and mitigating the pathophysiology of blood failure until the onset of DCS is the goal [33]. Twenty years of advancing the DCS paradigm and over a decade of innovation with DCR provide a "test of time" to the efficacy of these modalities [42]. Combined Damage Control Resuscitation and Damage Control Surgery (DCR-S) has produced survival advantages and reductions in blood usage, promoted biologic homeostasis, and improved outcomes in both the military and civilian settings, including austere and remote environments [43–46]. Professional societies' endorsement and publication of evidence-based clinical guidelines supporting the combined DCR-S pathway for improving patient survival are widespread [18, 41].

The need to improve trauma care systems should be at the forefront of our efforts as heralded by "A National Trauma Healthcare System: Integrating Military and Civilian Trauma Systems to Achieve Zero Preventable Deaths After Injury" [18]. Furthermore, taking on the challenge to eliminate preventable deaths from bleeding demands advancing the application of DCR-S to every injured patient at risk and across the all delivery environments. This will require local and regional cooperation but would be best guided and refined as a national effort. At this time, DCR-S appears to be a powerful catalyst that drives the further development of emergency and trauma systems, ultimately advancing the public's health.

Visions of an Ideal Application of DCR Across the Country

Leadership and professional societies have endorsed the combined concepts of DCR and DCS. The amassed evidence, affirmations by interdisciplinary thought leaders, and favorable experiences by respected peer groups should motivate the leadership and providers of entities not familiar with DCR to learn and apply the concepts and principles of DCR. Thus on a regional, local, and organizational level, education and training of DCR should follow the best practices and management guidelines currently available [41]. Across the spectrum of early trauma care, all stakeholders should be motivated to understand DCR and what, where, and when to clinically initiate and apply it.

In support of the clinical providers, the clinical scenes, the necessary support, and organizational agencies such as regional EMS medical councils, EMT and advanced paramedic training and certification programs, and blood banking, information technology, data registry, and information technology personnel should be informed of the DCR program and modify data collection elements, tools, and reporting so that concurrent review of DCR can be monitored and refined to identify gaps and performance improvement opportunities. Leadership and user groups should also be active in surveillance and identifying issues that require modification of practice guidelines, refinement of training, and areas for subsequent research.

Data and experience with DCR should be disseminated to a national agency that is capable of managing large data cohorts and provide feedback and comparisons across the participating agencies. This promotes objective feedback and points to large areas of improving need as well as informs investigators and researchers to further needs and refinements overall. The larger national picture also provides further motivation by demonstrating accomplishment of set goals to all involved.

Moving from national professional societies to more regional and local efforts must be used to identify barriers to learning and reluctance to accept (usually lack of awareness and knowledge and/or poor leadership models) and implement DCR (tactical impediments, educational barriers, resourcing). Solutions to removal of these barriers are best done by involvement of all professionals throughout the system, and patients that system has served, thus forging consortium of motivated stakeholders. Ideally, each stakeholder recognizes their special place and integral role in the DCR-S chain of survival. This approach seems to be very powerful in the salvage of the individual and, nationally, a means to lower preventable death and disability after injury.

A Portrait of the Future: DCR Carried Out on an LHS Framework

What could it look like if DCR were carried out within an LHS? Here is one possible narrative: The informed bystander discovers and calls 911 for help and, initially and subsequently with a first responder, accomplishes hemorrhage control (pressure on bleeding, where applicable tourniquet application), and removes the patient to a safe area if necessary; the prehospital providers supplement the bystanders with rapid assessment, enhancement of communication, rapid extrication, packaging, and transport of the patient. The time to transport promotes enrooted care and monitoring, intravenous access, and starting limited fluid therapy to administer necessary drugs and set the stage for commencement of blood product and procoagulant therapies upon arrival or in some environments en route. The recording of data into an EMR designed with templates/parameters to enhance understanding mechanism of injury, physiology, times, and therapies has been promoted by remote technology that has recognized a DCR patient and alerted the onsite team and receiving trauma teams. In the operating room at the receiving hospital, teams activate protocols to receive the patient directly and commence DCS, and as needed, anesthesia and nursing teams apply very advanced life support technology and continue DCR. Simultaneously, the massive transfusion protocol within the hospital is initiated, and the regional telemedicine center is notified.

Any provider that initiates DCR treatment electronically alerts the regional medical helicopter to the potential for rendezvous with the ground transporting unit and enables advance therapies including blood component transfusion by the aeromedical team. Time and communication data and recordings are captured. In rural and remote locations, telemedicine and telepresence capability can be delivered by the emergency telemedicine center that also delivers other complementary care direction such as ICU and consultative responses to providers requesting such services.

Data is captured or entered from monitors, vehicular gauges, and clocks throughout the prehospital and transport routes. As needed, prehospital providers can rapidly access medical command centers and bidirectional audiovisual connection projects the scene and patient. Patient data, physiologic trends, and applied therapies are chronologically recorded and shared with a medical command physician or other provider with expertise in the medic and prehospital teams practice domain. If necessary, telepresence is initiated and allows the medical command to deliver tacit knowledge and, as necessary, direct more invasive procedures. Constant communication and visual imaging is being used and recorded for subsequent study and performance improvement efforts.

Injuries requiring DCR will need DCS or invasive techniques and the operating theater or room is the destination of choice. This "Operating Space" has multiple modalities, including advanced imaging (whole-body LODOX scan, CT, MRI, angiographic, biplane capabilities), and can adapt to multiple teams with adequate space, supporting staffs, and equipment. Upon completion, the patient is moved to the ICU and for ongoing care, resuscitation, and further diagnostic studies. At all times, therapies and physiologic trends are recorded. In the ICU, data is captured, and where appropriate, video recording is used for performance improvement efforts; these are integrated into the EMR, registry, and other databases. The trauma registry team becomes active in the review and abstraction of data and completes a primary review of DCR preselected data elements. Any immediate concerns are brought to the care teams and performance improvement personnel, and further information about the patient, event, and treatments is added to the confidential PI record. This registry data populates performance improvement professionals and electronically alerts clinicians of other clinical management guidelines, potential research studies, and on-call specialists at the local hospital and available at the level I or II trauma center.

In keeping with the LHS model, the data and knowledge generated by the idealized process described above is used to inform other professionals across regional and national networks. This frontline work will also regularly generate new research questions, and related testing and piloting, to help advance the field and refine patient management and system development.

National Scale

While this chapter focuses mainly on the spread and implementation of DCR within organizations and local networks, spreading DCR nationally is an important aspiration. For that to happen, much of the thinking outlined above would need to be applied at a national level by a national organization (or consortium of organizations) that decides to pursue this goal. Specifically, they would need to:

- Conduct thorough and ongoing analysis of variation in implementation across the national system in order to identify "bright spots" that might act as mentors to others and groups in need of more intensive support.

- Secure a clear, shared commitment from national bodies to prioritize national spread, including arriving at an aim and supporting pursuit of it through contextually and culturally aligned incentives and technical supports.
- Maintain a coordinated system for spreading DCR, embracing the principles of an LHS, so that organizations and systems across the country can rapidly learn the practical details of implementation from one another in a supportive learning environment.
- Provide timely access to data on nationwide performance, including tracking and providing access to new innovations in implementation.

Implementing evidence-based practice across any setting or geography is hard work that requires active learning, which itself can only happen when every professional in the system is thoroughly supported and empowered to make local adaptations that allow the intervention to thrive [47]. This, above all, will be critical in spreading the important work of DCR. We hope the application of LHS principles can contribute to broader adoption of DCR-S efforts across a nation. To be sure, these approaches require intentional planning and reflection, as well as allocation of resources for collecting data and learning, but as noted above in other areas of healthcare and public health, they can support meaningful progress and give us some optimism for the future.

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