

Optimizing Trauma Care with Pre-Hospital Blood Transfusion

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Introduction

Hemorrhage-related deaths account for a large proportion of lives lost and are a primary cause of mortality worldwide [1,2]. Over a hundred years ago, early transfusion of whole blood post-trauma was discovered to be a life-saving measure [3-5]. Several resuscitation methods have been implemented over the years to deal with this issue. Fluid resuscitation started in the 1970s with regular saline solution and transitioned eventually to blood component therapy [6, 7]. This was done in accordance with the notion that correcting hypovolemia recovers organ perfusion. The total time to transfusion onset has been demonstrated to play a critical role in lowering mortality [8,9]. This is in addition to the early utilization of blood products in the resuscitation of trauma patients.

Depending on the clinical circumstances, the appropriate transfusion strategies to be used in emergency situations can vary greatly. The transfusion plan is established by the healthcare professionals based on their evaluation of the patient's clinical stability, the severity of the hemorrhage or blood loss volume, and the speed of the bleeding [10]. Early resuscitations with blood products is made possible by the ability to transfuse patients in the pre-hospital setting. This review examines the role of pre-hospital transfusion, its guiding principles, and developing approaches to fluid resuscitation.

Literature Review

Pre-hospital transfusion

Pre-hospital transfusion refers to the administration of blood or blood products to a patient outside of a hospital setting, typically in an Emergency Medical Service (EMS) setting. The purpose of pre-hospital transfusion is to provide critical intervention in the form of rapid and targeted treatment to patients who have suffered significant blood loss due to trauma or other medical conditions [11, 12]. Pre-hospital transfusion has gained increasing recognition in recent years as a potentially life-saving intervention for critically injured patients. Traditionally, pre-hospital care has focused on

stabilizing patients and transporting them to a hospital for further treatment [13-15]. However, this approach can be ineffective for patients who are bleeding profusely and require immediate transfusion [16-19].

The use of pre-hospital transfusion was first introduced by the military to improve survival rates for soldiers wounded in combat [20,21]. Since then, it has been adopted by EMS agencies around the world to improve outcomes for civilian trauma patients. One of the most important factors in the success of pre-hospital transfusion is the ability to identify patients who are most likely to benefit from this intervention. In the pre-hospital setting, where resources are scarce and sufficient volumes of blood are not easily accessible, it is extremely challenging to accurately evaluate patients who need blood transfusions. Inappropriate transfusion practices entail avoidable hazards and resource waste, especially of rare O negative units [22-27]. The most common indication for pre-hospital transfusion is severe hemorrhage, which can occur as a result of trauma, surgery, or other medical conditions. Patients who are in shock or have significant hypotension may also be candidates for pre-hospital transfusion. Any defined criterion is not enough; the clinical judgment of pre-hospital healthcare practitioners should also be taken into account when determining if transfusion is the best course of treatment.

Modalities involved in pre-hospital transfusion

Prompt hemorrhage management is the primary goal of pre-hospital transfusion in order to prevent hypovolemic shock and the lethal triad threat of coagulopathy, hypothermia, and acidosis. There are several different types of pre-hospital transfusions that may be used depending on the patient's condition and the resources available. One common approach is to administer Packed Red Blood Cells (PRBCs), which contain oxygen-carrying hemoglobin and can help to restore the patient's blood volume and oxygenation levels. Other blood products that may be used include Fresh Frozen Plasma (FFP), which contains clotting factors and can help to prevent bleeding, and platelets, which are essential for clot formation. For instance, in patients with penetrating injuries, clinical practice in the recent times has been dominated by a resuscitation approach that revolves around aggressive use of crystalloid as the primary fluid [28]. Since organ ischemia and decreased perfusion has a serious impact on mortality rates, it was thought that early, large-volume fluid resuscitation was essential in the treatment of hypotensive shock in trauma patients. A 3:1 replacement of crystalloid fluid to the amount of blood lost was the norm. Aggressive fluid resuscitation therefore gained popularity even before its effectiveness was well-examined and established [29,30].

However, in the past few years, it has been shown through various retrospective studies that intensive resuscitation, frequently commenced in the pre-hospital setting, may be deleterious to trauma patients [28,31-33].

The changing paradigm of fluid resuscitation techniques

While crystalloids can be helpful in restoring blood volume and hydration levels, despite their widespread use, they have some limitations and potential risks associated with their use. Unfortunately, this approach has now been linked to negative side effects that include electrolyte imbalance in the form of acid-base disturbances, hypothermia, dilutional coagulopathy, and rapid blood loss [34]. It is widely known that the amount of pre-hospital crystalloid infusion correlates with acute traumatic coagulopathy at the time of arrival to the hospital [35]. The use of excessive crystalloid volumes in the treatment of trauma patients can also cause resuscitation injury, inflammation damage, digestive and cardiac dysfunction, Acute Respiratory Distress Syndrome (ARDS), elevated extremity compartment pressures, clotting disturbances, abdominal compartment syndrome, and Multiple Organ Dysfunction Syndrome (MODS). They can also lead to pulmonary

edema, heart failure, and other complications, particularly in patients with pre-existing cardiac or renal dysfunction [36-44].

One of the main concerns with crystalloid use is the potential for fluid overload, which can occur when large volumes of crystalloid solutions are administered. In particular, large volumes of crystalloid solutions can dilute the patient's blood components and lead to complications such as decreased coagulation ability. Another potential risk associated with crystalloid use is the dilutional effect on blood components which include red blood cells and clotting factors. Dilutional coagulopathy can occur when large volumes of crystalloid solutions are administered, which can impair the patient's ability to form clots and increase the risk of bleeding [45]. This is particularly concerning in patients who require transfusions of blood products, as dilutional coagulopathy can worsen bleeding and make it more difficult to control. In addition to concerns related to fluid overload and dilutional coagulopathy, crystalloid use may also have other potential risks, including electrolyte imbalances and acid-base disturbances. For example, administration of large volumes of normal saline can lead to hyperchloremic metabolic acidosis, which can impair renal function and increase the risk of infection [46].

To address these concerns, several studies have examined the use of balanced crystalloid solutions, which contain electrolytes in ratios that more closely mimic those found in the body's extracellular fluid [47-49]. One such solution is Plasma Lyte A, which has been shown to have a lower incidence of hyperchloremic acidosis and lower rates of renal failure compared to normal saline [50].

Alternative strategies of fluid resuscitation

For patients with severe trauma to receive optimal fluid resuscitation, it is crucial to maintain an equilibrium between organ perfusion and hemostasis. Hemostatic resuscitation of bleeding trauma patients with early deployment of blood components is the current best practice, according to studies published in the past couple of decades [51-58]. More recent approaches for managing patients with severe hemorrhage has evolved from supportive, reactive care using crystalloids to proactive, urgent deployment of standardized procedures known as Massive Transfusion Protocols (MTPs) [59]. Newer resuscitation techniques, such as Damage Control Resuscitation (DCR), which underscore the importance of early application of blood products and concentrates on providing the patient with balanced resuscitation, have been developed as a result of an increased awareness of the risks involved with crystalloid use and the necessity for early inclusion of blood products [30,60]. The DCR paradigm stipulates that blood component transfusions (consisting of fresh frozen plasma, packed red blood cells, and platelets) be administered in a 1:1:1 ratio, (thereby resembling whole blood); priority be given to prompt hemorrhage management; and that crystalloid infusion be restricted to allow for a lower blood pressure until bleeding is controlled. In critical trauma patients, this approach has been associated with improved survival rates [61,62]. Up until bleeding can be surgically managed, DCR, which avoids crystalloids while accepting some degree of hypotension, is increasingly preferred [63-67].

Damage Control Resuscitation (DCR)

The core tenets of DCR are the mitigation and management of hypothermia, acidosis, and hypocalcemia, as well as permissive hypotension and swift and definitive hemorrhage control. Damage-control resuscitation aims to achieve definitive hemostasis, reduce iatrogenic resuscitation injury, and to preempt the acute traumatic shock from exacerbating [68]. According to Morrison et al., coagulopathy is one of the key distinctions between hypotensive resuscitation and normotensive resuscitation. Their study revealed that although the overall rate of mortality was not statistically different, the group that received hypotensive group had a much lower rate of mortality from bleeding due to coagulopathy within the initial 24 hours following injury [69]. This is because there were no deaths from bleeding following surgical hemorrhage repair. Three approaches-permissive hypotension, in which fluid is administered to raise the systolic blood pressure short of achieving normotension; controlled resuscitation, where a fixed volume of fluid is transfused; and delayed resuscitation, in which fluid is administered after bleeding has been controlled have been suggested to prevent clot disintegration and dilutional coagulopathy.

Hypotensive resuscitation, also known as permissive hypotension, achieves and sustains low tissue perfusion by minimal volume fluid resuscitation, such that the blood pressure is maintained in the lower-than-normal range, which is ideal for short time frames. Goal-directed resuscitation, where the systolic blood pressure or mean arterial pressure is targeted depending on individual patient profile, or controlled resuscitation, where preestablished rates are infused such that normotension is not reached, are two methods for achieving permissive hypotension [70].

During the early resuscitation of hypotensive trauma patients, controlled resuscitation defined as administering smaller crystalloid boluses for either a systolic pressure less than 70 mmHg or in the absence of a radial pulse is practicable and secure. Controlled resuscitation may be safer in pre-hospital transfusion for blunt trauma-patients and may even result in better prognosis, especially in patients with pre-hospital hypotension, according to two important clinical trials [71,72]. However, this approach carries the potential threat of tissue hypoperfusion even if it may prevent the negative consequences of early and high-dose fluid resuscitation [73].

Delayed resuscitation results in lower mortality rates and shorter hospitalizations. Aggressive fluid administration prior to surgery and hemorrhage management is believed to escalate blood loss, dislodge clots, and even result in a secondary hemorrhage [30].

In patients with Traumatic Brain Injury (TBI) and/or spinal injury, neither permissive hypotension/hypotensive resuscitation nor restricted/controlled resuscitation is recommended [74]. This is due to the fact that adequate perfusion must be sustained during resuscitation in so as to ensure tissue oxygenation of the compromised central nervous system and prevent secondary damage [65, 75,76]. To further understand the efficacy of these methods and to create treatment plans that examine the role of trauma-induced coagulopathy in the pathophysiology of trauma and pre-hospital transfusions, additional research is required.

Challenges and room for improvement

Protocols guiding the resuscitation with blood components, plasma protein, and associated products have emerged in the pre-hospital setting in accordance with the concept that the slightest delay can dramatically increase the mortality rate [77,78]. The need of the hour is to develop strategies that guarantee the safety of transfusion medicine procedures and accordingly meet the accreditation standards, thereby avoiding unnecessary waste and ensuring personnel competences.

Despite the potential benefits of pre-hospital transfusion, there are some challenges associated with this intervention. One of the biggest challenges is ensuring that blood products are administered safely and appropriately. Blood products must be stored and transported under specific conditions to maintain their efficacy and safety. Blood transfusions are also not able to be utilized routinely in the pre-hospital setting due to logistical and operational constraints [79]. Furthermore, there is also lack of information available on the pre-hospital indications for blood transfusions and evidence of the effectiveness of these practices is not widely available [80,81]. When transit times are short, performing transfusion can be done to the detriment of drug administration, because transfusions need separate intravenous lines. Less patients received tranexamic acid as a result of these factors following the implementation of pre-hospital blood products in their service, according to Jenkins et al [82]. In addition, pre-hospital transfusion can be expensive and resource intensive.

Most randomized-controlled trials in pre-hospital transfusion are based on plasma transfusions, even though it is the red blood cells and tranexamic acid that are predominantly used in most pre-hospital transfusion programs [83-87]. Elements including prolonged arrival times to the trauma center, simultaneous delivery of red blood cells and plasma and blunt-trauma patients may result in favorable patient outcomes with pre-hospital transfusion, despite mixed evidence [88-94]. Most importantly, priority should be given to timely transfer of patients to appropriate facilities where standard-of-care is received, and definitive care is offered [95-98].

Conclusion

In conclusion, pre-hospital transfusion has emerged as an important intervention for patients with significant blood loss due to trauma or other medical conditions. With proper implementation, pre-hospital transfusion has the potential to save lives and improve outcomes for critically injured patients. In situations where transport time to definitive care is prompt, delayed resuscitation is preferable; while in slow transport circumstances, goal-directed resuscitation with low-volume crystalloid seems advisable. However, the impacts of pre-hospital transfusions are undoubtedly multifaceted, hence studying more complex outcomes in addition to just mortality statistics will be crucial for understanding their implications.

References

- Cannon, Jeremy W. "Hemorrhagic shock." *N. Engl. J. Med.* 378.4 (2018): 370-379.
- Haagsma, Juanita A., et al. "The global burden of injury: incidence, mortality, disability-adjusted life years and time trends from the Global Burden of Disease study 2013." *Injury prevention* 22.1 (2016): 3-18.
- Primrose, A., and E. S. Ryerson. "The direct transfusion of blood: its value in haemorrhage and shock in the treatment of the wounded in war." *Br. Med. J.* 2.2907 (1916): 384.
- Bruce, R.L.. "The transfusion of whole blood: a suggestion for its more frequent employment in war surgery." *Br. Med. J.* 2.2897 (1916): 38.
- Transfusion. *Can Med Assoc J.* 1915 Dec;5(12):1084-91
- Cap, Andrew P. "The school of hard knocks: what we've learned and relearned about transfusion in a decade of global conflict." *Transfus. Med.* 24.3 (2014): 135-137.
- Gurney, Jennifer M., and Philip C. Spinella. "Blood transfusion management in the severely bleeding military patient." *Curr. Opin. Anaesthesiol.* 31.2 (2018): 207-214.
- Holcomb, John B., et al. "The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks." *JAMA surg.* 148.2 (2013): 127-136.
- Zink, Karen A., et al. "A high ratio of plasma and platelets to packed red blood cells in the first 6 hours of massive transfusion improves outcomes in a large multicenter study." *Am. j. surg.* 197.5 (2009): 565-570.
- Patil, V., and Shetmahajan, M. "Massive transfusion and massive transfusion protocol." *Indian j. anaesth.* 58.5 (2014): 590.
- Van Turenhout, Elisabeth C., et al. "Pre-hospital transfusion of red blood cells. Part 1: a scoping review of current practice and transfusion triggers." *Transfus. Med.* 30.2 (2020): 86-105.
- American College of Surgeons. Committee on Trauma. ATLS, advanced trauma life support for doctors: student course manual. *Am. Coll. Surg., 2008.*
- Zietlow, John M., et al. "Prehospital use of hemostatic bandages and tourniquets: translation from military experience to implementation in civilian trauma care." *J Spec Oper Med* 15.2 (2015): 48-53.
- Schober, Patrick, et al. "Hemorrhage treatment adjuncts in a helicopter emergency medical service." *Air Med. J.* 38.3 (2019): 209-211.
- Grissom, Thomas E., and Fang, R. "Topical hemostatic agents and dressings in the prehospital setting." *Curr. Opin. Anesthesiol.* 28.2 (2015): 210-216.
- Kelly, Joseph F., et al. "Injury severity and causes of death from Operation Iraqi Freedom and Operation Enduring Freedom: 2003-2004 versus 2006." *J. Trauma Acute Care Surg.* 64.2 (2008): S21-S27.
- Dylan, P. et al. "Causes of death in Canadian Forces members deployed to Afghanistan and implications on tactical combat casualty care provision." *J. Trauma Acute Care Surg.* 71.5 (2011): S401-S407.
- Eastridge, Brian J., et al. "Died of wounds on the battlefield: causation and implications for improving combat casualty care." *J. Trauma Acute Care Surg.* 71.1 (2011): S4-S8.
- Eastridge, Brian J., et al. "Death on the battlefield (2001-2011): implications for the future of combat casualty care." *J. Trauma Acute Care Surg.* 73.6 (2012): S431-S437.
- Cloonan, Clifford C. "Treating traumatic bleeding in a combat setting." *Military medicine* 169.12 (2004): 8.
- O'Reilly, David J., et al. "Prehospital blood transfusion in the en route management of severe combat trauma: a matched cohort study." *J. Trauma Acute Care Surg.* 77.3 (2014): S114-S120.
- Vitalis, V., et al. "Early transfusion on battlefield before admission to role 2: a preliminary observational study during "Barkhane" operation." *Inj.* 49.5 (2018): 903-910.
- Spinella, Philip C. "Warm fresh whole blood transfusion for severe hemorrhage: US military and potential civilian applications." *Crit. care med.* 36.7 (2008): S340-S345.
- Maegele, Marc, et al. "Changes in transfusion practice in multiple injury between 1993 and 2006: a retrospective analysis on 5389 patients from the German Trauma Registry." *Transfus. Med.* 19.3 (2009): 117-124.
- Miraflor, Emily, et al. "Emergency uncrossmatched transfusion effect on blood type alloantibodies." *J. Trauma Acute Care Surg.* 72.1 (2012): 48-53.
- Guerado, E., et al. "Protocols for massive blood transfusion: when and why, and potential complications." *Eur. J. Trauma Emerg. Surg.* 42 (2016): 283-295.
- Maegele, M., et al. "Early coagulopathy in multiple injury: an analysis from the German Trauma Registry on 8724 patients." *Injury* 38.3 (2007): 298-304.
- Melissa, K., and Roberts, E. "Permissive hypotension and trauma: can fluid restriction reduce the incidence of ARDS?." *J. Trauma Nurs. / JTN* 24.1 (2017): 19-24.
- Bickell, William H., et al. "Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries." *N. Engl. J. Med.* 331.17 (1994): 1105-1109.
- Haut, Elliott R., et al. "Prehospital intravenous fluid administration is associated with higher mortality in trauma patients: a National Trauma Data Bank analysis." *Ann. surg.* 253.2 (2011): 371-377.
- Hussmann, B., et al. "Does increased prehospital replacement volume lead to a poor clinical course and an increased mortality? A matched-pair analysis of 1896 patients of the Trauma Registry of the German Society for Trauma Surgery who were managed by an emergency doctor at the accident site." *Injury* 44.5 (2013): 611-617.
- Madigan, Michael C., et al. "Secondary abdominal compartment syndrome after severe extremity injury: are early, aggressive fluid resuscitation strategies to blame?." *J. Trauma Acute Care Surg.* 64.2 (2008): 280-285.
- Chatrath, V., et al. "Fluid management in patients with trauma: Restrictive versus liberal approach." *J. anaesthesiol. clin. pharmacol.* 31.3 (2015): 308.
- Maegele, M., et al. "Red blood cell to plasma ratios transfused during massive transfusion are associated with mortality in severe multiply injury: a retrospective analysis from the Trauma Registry of the Deutsche Gesellschaft für Unfallchirurgie." *Vox sang.* 95.2 (2008): 112-119.
- Cherkas, David. "Traumatic hemorrhagic shock: advances in fluid management." *Emerg Med Pract* 13.11 (2011): 1-19.
- Ronald, C. and Holcomb, J.B. "Hồi sức dịch truyền cho bệnh nhân sốc mất máu do chấn thương." *Crit Care Clin* 33.1 (2017): 15-36.
- Cantle, Paul M., and Bryan A. Cotton. "Balanced resuscitation in trauma management." *Surg. Clin.* 97.5 (2017): 999-1014.
- Ng, K. F. J., et al. "In vivo effect of haemodilution with saline on coagulation: a randomized controlled trial." *Br. j. anaesth.* 88.4 (2002): 475-480.
- Walker, Jeffrey, and Laura M. Criddle. "Pathophysiology and management of abdominal compartment syndrome." *Am. J. Crit. Care* 12.4 (2003): 367-371.

40. Rodas, Edgar B., et al. "Hyperacute abdominal compartment syndrome: an unrecognized complication of massive intraoperative resuscitation for extra-abdominal injuries." *Am. surg.* 71.11 (2005): 977-981.
41. Cotton, Bryan A., et al. "The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies." *Shock* 26.2 (2006): 115-121.
42. Schreiber, Martin A., et al. "Early predictors of massive transfusion in combat casualties." *J. Am. Coll. Surg.* 205.4 (2007): 541-545.
43. Tieu, Brandon H., et al. "Coagulopathy: its pathophysiology and treatment in the injured patient." *World j. surg.* 31 (2007): 1055-1065.
44. Christian, M. "Is there a place for crystalloids and colloids in remote damage control resuscitation?" *Shock* 41 (2014): 47-50.
45. Lobo, Dileep N., and Awad. S. "Should chloride-rich crystalloids remain the mainstay of fluid resuscitation to prevent 'pre-renal' acute kidney injury?: *con.*" *Kidney int.* 86.6 (2014): 1096-1105.
46. Schreiber, Martin A. "The use of normal saline for resuscitation in trauma." *J. Trauma Acute Care Surg.* 70.5 (2011): S13-S14.
47. McSwain Jr, et al. "Potential use of prothrombin complex concentrate in trauma resuscitation." *J. Trauma Acute Care Surg.* 70.5 (2011): S53-S56.
48. Cotton, Bryan A. "Alternative fluids for prehospital resuscitation: 'pharmacological' resuscitation fluids." *J. Trauma Acute Care Surg.* 70.5 (2011): S30-S31.
49. Young, Jason B., et al. "Saline versus Plasma-Lyte A in initial resuscitation of trauma patients: a randomized trial." (2014): 255-262.
50. Mesar, Tomaz, et al. "Association between ratio of fresh frozen plasma to red blood cells during massive transfusion and survival among patients without traumatic injury." *JAMA surg.* 152.6 (2017): 574-580.
51. Johansson, Pär I., and Jakob Stensballe. "REVIEWS: Hemostatic resuscitation for massive bleeding: the paradigm of plasma and platelets—a review of the current literature." *Transfusion* 50.3 (2010): 701-710.
52. Holcomb, John B., et al. "Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients." *Annals of surgery* 248.3 (2008): 447-458.
53. Johansson, P. I., and J. Stensballe. "Effect of haemostatic control resuscitation on mortality in massively bleeding patients: a before and after study." *Vox sanguinis* 96.2 (2009): 111-118.
54. Johansson, Pär I. "Goal-directed hemostatic resuscitation for massively bleeding patients: the Copenhagen concept." *Transfusion and apheresis science* 43.3 (2010): 401-405.
55. Riskin, Daniel J., et al. "Massive transfusion protocols: the role of aggressive resuscitation versus product ratio in mortality reduction." *J. Am. Coll. Surg.* 209.2 (2009): 198-205.
56. Holcomb, John B., et al. "Transfusion of plasma, platelets, and red blood cells in a 1: 1: 1 vs a 1: 1: 2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial." *Jama* 313.5 (2015): 471-482.
57. Gonzalez, Ernest A., et al. "Fresh frozen plasma should be given earlier to patients requiring massive transfusion." *J. Trauma Acute Care Surg.* 62.1 (2007): 112-119.
58. Saxena, R., et al. "Cutting-Edge Strategies in Massive Transfusion in Patients of Obstetric Hemorrhage." *J. Gen. Pract. (Los Angel)* 4 (2016): 280.
59. Butler, Frank K., et al. "Fluid resuscitation for hemorrhagic shock in tactical combat casualty care: *TCCC guidelines change* 14-01-2 June 2014." (2014).
60. Langan, Nicholas R., Matthew Eckert, and Matthew J. Martin. "Changing patterns of in-hospital deaths following implementation of damage control resuscitation practices in US forward military treatment facilities." *JAMA surg.* 149.9 (2014): 904-912.
61. Kaafarani, H. M. A., and G. C. Velmahos. "Damage control resuscitation in trauma." *Scand. J. Surg.* 103.2 (2014): 81-88.
62. Hodgetts, T. J., P. F. Mahoney, and E. Kirkman. "Damage control resuscitation." *BMJ Mil. Health* 153.4 (2007): 299.
63. Holcomb, John B., et al. "Damage control resuscitation: directly addressing the early coagulopathy of trauma." *J. Trauma Acute Care Surg.* 62.2 (2007): 307-310.
64. Beekley, Alec C. "Damage control resuscitation: a sensible approach to the exsanguinating surgical patient." *Crit. care med.* 36.7 (2008): S267-S274.
65. Gerhardt, Robert T., et al. "Remote damage control resuscitation and the S olstrand Conference: defining the need, the language, and a way forward." *Transfusion* 53 (2013): 9S-16S.
66. Harris, Tim, et al. "The evolving science of trauma resuscitation." *Emerg. Med. Clin.* 36.1 (2018): 85-106.
67. Holcomb, COL John B. "Fluid resuscitation in modern combat casualty care: lessons learned from Somalia." *J. Trauma Acute Care Surg.* 54.5 (2003): S46-S51.
68. Morrison, C. Anne, et al. "Hypotensive resuscitation strategy reduces transfusion requirements and severe postoperative coagulopathy in trauma patients with hemorrhagic shock: preliminary results of a randomized controlled trial." *J. Trauma Acute Care Surg.* 70.3 (2011): 652-663.
69. Kudo, Daisuke, Yoshitaro Yoshida, and Shigeki Kushimoto. "Permissive hypotension/hypotensive resuscitation and restricted/controlled resuscitation in patients with severe trauma." *J. Intensive Care* 5.1 (2017): 1-8.
70. Schreiber, Martin A., et al. "A controlled resuscitation strategy is feasible and safe in hypotensive trauma patients: results of a prospective randomized pilot trial." *J. trauma acute care surg.* 78.4 (2015): 687.
71. Brown, Joshua B., et al. "Goal directed resuscitation in the prehospital setting: a propensity adjusted analysis." *J. trauma acute care surg.* 74.5 (2013): 1207.
72. Garner, Jeff, et al. "Prolonged permissive hypotensive resuscitation is associated with poor outcome in primary blast injury with controlled hemorrhage." *Ann. surg.* 251.6 (2010): 1131-1139.
73. Isabelle, N., and Jean-François Chastang. "Overall fraction of disease attributable to multiple dependent risk factors: a new formula." *Lancet Neurol.* 20.12 (2021): 979-980.
74. Shackford, Steven R. "Prehospital fluid resuscitation of known or suspected traumatic brain injury." *Journal of Trauma and Acute Care Surgery* 70.5 (2011): S32-S33.
75. Wald, Steven L., and Steven R. Shackford. "The effect of secondary insults on mortality and long-term disability after severe head injury in a rural region without a trauma system." *J. Trauma Acute Care Surg.* 34.3 (1993): 377-382.
76. Meyer, David E., et al. "Every minute counts: time to delivery of initial massive transfusion cooler and its impact on mortality." *J. trauma acute care surg.* 83.1 (2017): 19.
77. Cotton, Bryan A., et al. "Room for (performance) improvement: provider-related factors associated with poor outcomes in massive transfusion." *J. Trauma Acute Care Surg.* 67.5 (2009): 1004-1012.
78. Karl, Alyssa, et al. "Variability of uncrossmatched blood use by helicopter EMS programs in the United States." *Prehosp. Emerg. Care* 20.6 (2016): 688-694.
79. Smith, Iain M., et al. "Prehospital blood product resuscitation for trauma: a systematic review." *Shock (Augusta, Ga.)* 46.1 (2016): 3.
80. Huang GS, Dunham CM. Mortality outcomes in trauma patients undergoing prehospital red blood cell transfusion: a systematic literature review. *Int J Burns Trauma.* 2017 15;7(2):17-26.
81. Sumida, Michael P., et al. "Prehospital blood transfusion versus crystalloid alone in the air medical transport of trauma patients." *Air Med. J.* 19.4 (2000): 140-143.
82. Yazer, M. H., et al. "Vox Sanguinis International Forum on the use of prehospital blood products and pharmaceuticals in the treatment of patients with traumatic haemorrhage." *Vox sanguinis* 113.7 (2018): 701-706.
83. Moore, Hunter B., et al. "Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an

- urban area: a randomised trial." *The Lancet* 392.10144 (2018): 283-291.
84. Christian, F.E., et al. "Pre-hospital plasma transfusion: a valuable coagulation support or an expensive fluid therapy?." *Crit. Care* 23.1 (2019): 1-4.
 85. Trudeau, J., et al. "Massive hemorrhage and emergency transfusion." *Clin. Guide Transfus., Can. Blood Serv.* (2017).
 86. Lier, H., and Grottko, O. "Prehospital plasma transfusion in civilian trauma patients in hemorrhagic shock." *Anaesthesist* 67 (2018): 950-952.
 87. Tucker, H., et al. "The role of plasma transfusion in pre-hospital haemostatic resuscitation." *Transfusion Medicine Reviews* 35.4 (2021): 91-95.
 88. Pusateri, Anthony E., et al. "Association of prehospital plasma transfusion with survival in trauma patients with hemorrhagic shock when transport times are longer than 20 minutes: a post hoc analysis of the PAMPer and COMBAT clinical trials." *JAMA surg.* 155.2 (2020): e195085-e195085.
 89. Gruen, Danielle S., et al. "Characterization of unexpected survivors following a prehospital plasma randomized trial." *J. trauma acute care surg.* 89.5 (2020): 908.
 90. Sim, Edward S., et al. "Massive transfusion and the response to prehospital plasma: It is all in how you define it." *J. trauma acute care surg.* 89.1 (2020): 43.
 91. Guyette, Francis X., et al. "Prehospital blood product and crystalloid resuscitation in the severely injured patient: a secondary analysis of the prehospital air medical plasma trial." *Ann. surg.* 273.2 (2021): 358-364.
 92. Anto, Vincent P., et al. "Severity of hemorrhage and the survival benefit associated with plasma: results from a randomized prehospital plasma trial." *J. Trauma Acute Care Surg.* 88.1 (2020): 141-147.
 93. Reitz, Katherine M., et al. "Prehospital plasma in injured patients is associated with survival principally in blunt injury: results from two randomized prehospital plasma trials." *J. trauma acute care surg.* 88.1 (2020): 33.
 94. Santry, Heena P., and Hasan B. A. "Fluid resuscitation: past, present, and the future." *Shock (Augusta, Ga.)* 33.3 (2010): 229.
 95. Karim, M.M., et al. "Prehospital trauma system reduces mortality in severe trauma: a controlled study of road traffic casualties in Iraq." *Prehosp. disaster med.* 27.1 (2012): 36-41.
 96. Murad, Mudhafar K., et al. "Prehospital trauma care reduces mortality. Ten-year results from a time-cohort and trauma audit study in Iraq." *Scand. j. trauma resusc. emerg. med.* 20.1 (2012): 1-10.
 97. Paravar, Mohammad, et al. "Prehospital care and in-hospital mortality of trauma patients in Iran." *Prehosp. disaster med.* 29.5 (2014): 473-477.
 98. Cantle, Paul M., and Bryan A. Cotton. "Prediction of massive transfusion in trauma." *Crit. care clin.* 33.1 (2017): 71-84.