



# Prehospital Resuscitation with Low Titer O+ Whole Blood by Civilian EMS Teams: Rationale and Evolving Strategies for Use

# 29

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## 29.1 Introduction: Civilian Setting Resuscitation Strategies for Bleeding over the Past Half Century

*For the Life of all flesh, is the blood thereof.* (Leviticus 17:14, the Bible)

Most modern out-of-hospital emergency medical services (EMS) systems, as we have come to recognize them today, were established in the 1960s and 1970s when a cadre of intrepid physicians ventured into the streets and later published their successful experiences with lifesaving approaches to managing acute coronary syndromes, trauma care, and cardiopulmonary arrest on-scene [1–3]. These lifesaving reports helped to propel the widespread adoption of EMS systems and the concomitant introduction of specially trained (non-physician) emergency medical technicians called “paramedics” in many parts of the globe [1–5]. In addition, nursing personnel also ventured into the realm of on-scene emergency response, particularly in the arena of air medical services, often retrieving trauma patients in non-urban, distant settings.

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J.-L. Vincent (ed.), *Annual Update in Intensive Care and Emergency  
Medicine 2020*, Annual Update in Intensive Care and Emergency Medicine,  
[https://doi.org/10.1007/978-3-030-37323-8\\_29](https://doi.org/10.1007/978-3-030-37323-8_29)

365

By the early 1980s, the standard of care for hypotensive trauma patients, be it blunt or penetrating injury, was the application of the pneumatic anti-shock garment and the infusion of intravenous isotonic fluids, generally crystalloids [6–8]. These interventions were provided for the purposes of restoring a “normalized” blood pressure with an intent to “re-perfuse the tissues” [6–8].

These adopted practices had their roots in elegant laboratory experiments that demonstrated the value of infusing crystalloid-like fluids, along with blood, to mitigate mortality after large (life-threatening) volumes of blood had been removed from the study animals [9, 10]. Subsequently, the evolution of prehospital EMS and air medical rescue programs facilitated the ability to bring these interventions to patients as early as possible. In turn, almost all systems of prehospital trauma care began immediate infusion of isotonic crystalloid fluids such as lactated Ringer’s solution, normal saline, or modified products such as PlasmaLyte or Normosol either on-scene or en-route to a trauma center. In certain venues, intravenous resuscitation for hypotensive trauma patients included other intravascular volume-restoring interventions including colloids such as albumin and hypertonic saline–dextran infusions [11]. While innumerable arguments soon ensued regarding which product was superlative to the others, the very early prehospital administration of non-hematologic intravenous fluids became a seemingly universal standard of care in most trauma care systems by the 1980s.

In the mid-1980s and early 1990s, however, clinical trials were conducted that appeared to refute the value of the pneumatic anti-shock garment as well as prehospital fluid resuscitation. Ironically, this inability to confirm a survival advantage was particularly applicable to their use for penetrating truncal injuries, a condition in which the main cause of death was usually related to internal hemorrhage [7, 8]. Not only were both prehospital interventions of no apparent advantage, but there were also inferences and observed trends that mortality might even be higher with these interventions, even though they did raise blood pressure [7, 8].

Later, in the 1990s, new experimental models sought to examine internal hemorrhage that was uncontrollable prior to its operative intervention [12–16]. These laboratory studies demonstrated that isotonic and hypertonic intravenous fluid infusions prior to bleeding control were indeed detrimental. The original 1950–60s animal models of fluid infusions that showed improved outcomes with intravenous crystalloid fluids largely involved scenarios in which the animal’s blood was removed in large volumes. However, there was no longer an ongoing loss of blood after the large volume blood removal [9, 10]. In other words, they were mimicking scenarios in which bleeding would have been controlled prior to intravascular volume infusion. Those original studies also generally included a certain degree of restoration of whole blood along with the crystalloids [9, 10].

In the subsequent uncontrolled bleeding models that demonstrated a detrimental effect, it was shown directly that early infusions of fluids that were not blood-based generally created multiple problems including hydraulic acceleration of hemorrhage and a dislodging of early soft clots that had not yet had a fibrinous transformation [12–16]. There was also dilution of clotting factors, but at the time, that association with detrimental outcomes was simply considered an inferential factor [8].

Nevertheless, the notion to restore patients to normotensive status, particularly those with head injuries, remained a persistent practice, even well into the early 2000s [6, 17, 18]. The focus remained on expediting mechanical bleeding control (surgical hemostasis) at a trauma center, be it for intracranial, intrathoracic, or intra-abdominal bleeding. However, while more judicious with their infusions, clinicians still sought to maintain a degree of hemodynamic support in the preoperative phase with intravenous fluids, be they colloids or crystalloids.

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## 29.2 The Recent Evolution of Non-Mechanical Bleeding Control Interventions

Vanguard work largely coming out of the U.S. military experience in the Middle East during the 2000s, not only focused on the application of tourniquets for external hemorrhage control but also clot-stimulating dressings and other forms of mechanical bleeding control. While the clot-forming dressings implied a form of non-mechanical intervention, they were still used in the prehospital setting for large wounds and accompanied direct compression of the hemorrhage site.

Based on that same military experience as well as other clinical trials primarily based on the European continent, the concept of non-mechanical bleeding control began to evolve quite strongly. For example, the CRASH-2 trial supported the use of tranexamic acid early on after injury [19]. The tranexamic acid was used presumably to enhance intravascular clotting non-mechanically. However, the overall mechanism of action remained unclear, and it was also shown that delayed infusion was associated with worse outcomes [19]. Nevertheless, those early tranexamic acid trauma studies did begin to indicate that very early interventions to enhance clotting would become important adjuncts in the preoperative management of trauma patients.

Concurrently, other pivotal publications further enhanced that line of thinking and fostered the notion of so-called damage control resuscitation in which case-controlled study outcomes appeared to be much better with the infusion of red blood cells (RBCs) and plasma in more of a 1:1 ratio versus the more traditional 8:1 ratio [20]. Later the addition of platelets, creating a triplet damage control resuscitation strategy of 1:1:1 (cells:plasma:platelets), evolved and eventually spread into the civilian population [21].

More recently, the concept of just providing early plasma infusion alone as in the prehospital setting has been independently associated with improved outcomes [22]. In addition, early results from studies of soldiers with traumatic brain injury (TBI) indicate a lifesaving effect of tranexamic acid in that setting [23], and early reports from other unpublished studies may indicate that the early infusion of 2 g tranexamic acid may be superior to only 1 g initially followed by a second gram infused slowly over the next few hours.

These evolving data help to further drive a renewed focus on infusing products that might induce non-mechanical bleeding control in the prehospital setting. The CRASH-3 trial (tranexamic acid for TBI) has now been published, further

reinforcing the focus on these concepts [24]. As will be discussed in the next section, it has also stimulated a movement away from using intravenous fluids that are not blood-based (e.g., crystalloid/colloid) and a focus more toward the use of plasma and whole blood as a form of “remote damage control” resuscitation [25–28].

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### 29.3 The Detrimental Effects of Isotonic/Hypertonic Fluid Infusions

Evolving experimental work has now demonstrated that non-hematological fluid infusions have deleterious effects beyond the hydraulic acceleration of hemorrhage and the dislodging of early soft clot formation. More recently, it has been demonstrated that such intravenous fluids, can be detrimental to the glycocalyx, the important coating over the vascular endothelium [25, 26, 29].

The glycocalyx is a “fuzzy” layer of glycoproteins and sugar moieties located on the external side of the plasma membrane of most cell types. The composition of the glycocalyx, which can be altered in disease states and with non-blood component fluid infusions, influences numerous properties of the cell membrane, including coagulation, cell–cell recognition, and the cell’s interface with the microenvironment. Experimentally, its erosion along the vascular endothelium can lead to leaking capillaries, corrupted platelet function, dysfunctional coagulation, and subsequent risk for multiple organ failure [25, 26, 29]. Therefore, like heart failure or kidney failure, “blood failure” can occur in the face of severe hemorrhage as manifested by oxygen debt (acidosis), platelet dysfunction, coagulopathy, and an “endotheliopathy.”

Recent evidence suggests that blood products, including both whole blood and plasma, help to maintain the integrity of the glycocalyx, protect its properties and its ability to form clots and also promote other forms of non-mechanical hemostasis, whereas crystalloids disrupt it [25, 26, 29]. Recent clinical studies support the life-saving effect of early on-scene plasma infusion, and follow-up studies confirm that the addition of RBCs to plasma enhance that effect [22, 30]. These findings indicate that the original demonstration of potential harm from colloids/crystalloids is related to more than just the simple dilution of the clotting factors and the accompanying factors of hydraulic acceleration of bleeding and soft clot disruption. There are also potential detrimental effects from infusion of fluids at ambient temperatures and numerous other physiological sequelae.

Even if infusion of traditional crystalloid and colloid fluids is discouraged, there are remaining challenges in terms of infusing products that maintain the glycocalyx and other critical factors that mitigate bleeding and subsequent complications. A recent study in an urban setting (Denver) showed no distinct advantage to the particular type of plasma product that was studied [31]. However, that neutral result might be because of the short distances to the trauma center or the time to prepare the product for infusion [31]. While they can be maintained on ambulances for much longer periods, freeze-dried products may also have their limitations, and

**Table 29.1** Comparison of component blood products versus whole blood

	Component therapy	Whole blood
<i>Composition</i>	1 unit of packed red blood cells + 1 unit of platelets + 1 unit of fresh frozen plasma + 1 unit of cryoprecipitate	1 unit of low titer O+ whole blood
<i>Volume and temperature</i>	680 ml and cold	500 ml and warm
<i>Hematocrit</i>	29%	38–50%
<i>Platelet count</i>	80 K	150–400 K
<i>Coagulation factors</i>	65% of initial concentration	100%
<i>Fibrinogen</i>	1000 mg	1000 mg

storage of fresh frozen plasma (FFP) still requires thawing and its shelf-life is limited.

With the evolution of using blood products and particularly 1:1:1 damage control resuscitation in hospital, the thought might be to consider the same in the prehospital setting, but storage of those blood products would be unfeasible [27, 28]. It would be very expensive to continue to maintain these products at all times, even on helicopters, let alone ground ambulances. This is exacerbated by the very short half-life of stored platelets (e.g., 3–5 days) and even fresh plasma after thawing (e.g., 5 days). In addition, infusion of all these individual components is not an easy task and infusion of whole blood would not only make more sense logistically (one versus multiple infusions that need to be checked and verified), but it is actually more effective in terms of longevity of platelet counts, clotting functions (Table 29.1), and perhaps even outcomes [32]. In fact, the 1:1:1 approach was actually a secondary strategy that came about in the early 2000s when whole blood products were in short supply. The original intent was always to use blood in the field.

However, on the surface, use of whole blood brings its own challenges in terms of prevalent misconceptions. Even though portable devices are now available that can rapidly warm refrigerated whole blood in a matter of minutes, many clinicians, wary of the risk of transfusion reactions, believe that whole blood cannot be used before blood-typing and crossmatching are accomplished. Nevertheless, as discussed in the next section, there may be a solution to those concerns.

## 29.4 The Rationale for Prehospital Use of Low Titer O+ Whole Blood

While O-negative whole blood has traditionally been called the “universal donor” because of its lack of A, B, and Rh antigens, it is only found in about 8% of the U.S. population (i.e., about 4% of males) and may be less than 3% worldwide. Therefore, blood banks and decision-making clinicians prefer to protect the use of O-negative for the benefit of certain cancer patients, neonates, and women of childbearing age.

In contrast, O-positive blood constitutes the blood line for about 40% of the U.S. population and likely more elsewhere. Recent evidence suggests that a very large

proportion of persons with O-positive blood may have very low titers of A and B antibodies and, specifically, not enough to create an immediate hemolytic or life-threatening negative transfusion reaction. The latest available data suggest that transfusion reactions are very rare when using O+ low titer whole blood in which the IgM or IgG anti-A and anti-B titers are less than 256 [27, 28]. While many other venues are using titers <128, most are beginning to use blood with titers of <256 [27, 28].

In fact, military experience and records from over half a million transfusions now indicate that using donor blood with O+ titers <1000 may be safe as another type of “universal donor” and that as many as 60–70% of persons with O+ blood would fall into that low titer category [33–35]. This constitutes roughly a third of the population. Until recently, O+ men (about 20% of the general U.S. population) have preferably been used as low titer O+ blood donor targets because, compared to men, there is a lower proportion of women with eligible low titer O+ blood. A significant percentage of women also have human leukocyte antigen (HLA) which may predispose the recipient to the risk of another complication, namely a rare but finite risk for transfusion-associated lung injury (TRALI). Nevertheless, the level of HLA correlates with the number of past pregnancies and thus some predictors exist to anticipate its presence. In essence, there are many women with the potential to safely donate low titer O+ whole blood, creating another excellent source for donors. In addition, the risk for creating TRALI would again be so much lower than the high risk of dying from the severe hemorrhage that indicated the transfusion in the first place.

The latest data indicate that the civilian risk of mild hemolytic transfusion reactions due to plasma-incompatible transfusions, using titer-screened donors, is approximately 1:80,000 [27, 28, 35–37]. Therefore, infusion of low titer O+ whole blood can be performed with relative confidence. In addition, with fewer donor exposures than currently occur with the multiple component transfusions (such as the typical 1:1:1 massive transfusion protocols), this enhances the safety profile [35–37].

In terms of isoimmunization and Rh type, the traditional concern is hemolytic disease of the fetus and newborn in women of childbearing age. But recent studies now indicate that this concern is largely mitigated by the immunosuppression of trauma patients and by the administration of anti-D immune globulin to those women receiving the whole blood (i.e., RhIg) [38–40]. Therefore, women of childbearing age who receive Rh+ packed cells or low titer O+ whole blood should be evaluated for RhIg administration candidacy and obstetric and pathology consultation within 24 h. Nevertheless, their risk of having fetal complications is so far outweighed by the lifesaving need that would indicate infusion of the blood [27, 28]. In San Antonio, for example, among 124 patients receiving massive transfusion over a 30-month period, only 26 were women and only 18 of those were of childbearing age. More than half of those women (10/18) died [40]. Furthermore, the one woman of childbearing age who was found to have a D-negative blood type was actually one of the mass transfusion survivors.

The ability to provide whole blood without having to obtain prior typing and crossmatching creates a scenario in which prehospital administration of whole blood may not only be feasible but actually preferred for those who are likely to be exsanguinating. Based on the prior discussion, whole blood would be more feasible and expeditious than mixed component therapy. It is also more effective, and its potential longevity is much greater [27, 28, 32–34]. For all those reasons, the rationale for using low titer O+ whole blood is fairly clear. However, additional challenges remain: (1) finding and obtaining adequate sources of the blood; (2) sustaining and managing its effectiveness to prevent waste of the donated blood; (3) appropriate triggers for infusing the blood; (4) appropriate equipment and related training; (5) sustainable funding; and (6) strategic distribution of the stored blood among the response teams who would be providing the transfusions. In the following section, several strategies for implementation will be described for consideration by those contemplating prehospital use of whole blood, particularly those considering ground ambulance use.

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## **29.5 Some Current Experiences with Implementation of Prehospital Whole Blood**

Several EMS systems and air medical rescue programs have now successfully implemented the prehospital use of low titer O+ whole blood including the City of San Antonio Fire Department in San Antonio, Texas and the Broward County Sheriff's Office Department of Fire Rescue in Broward County, Florida. Other civilian and military programs globally have already incurred far more experience with the use of whole blood in the prehospital setting and some of the strategies used by these two agencies for implementation reflect lessons learned, good and bad, from that experience. Nevertheless, as the San Antonio Fire Department and Broward County Sheriff's Office Department of Fire Rescue are the bases of operations for the authors, the following discussion is provided to present two different but current parallel examples of this kind of initiative currently in evolution.

### **29.5.1 Source of the EMS System Blood Supply**

While the Broward County teams currently obtain their blood supply through a commercial agency, San Antonio has a very unique, special model. The city is fortunate to be the home of a longstanding military medical research complex with veteran military trauma researchers who have led many of the advances in trauma care over the past two decades including application of tourniquets, damage control resuscitation, and the use of whole blood in resuscitation. The military medical complex includes a military-staffed trauma center, and there is also a collaborating major university-affiliated trauma center that serves the San Antonio civilian population, which has advanced much of the current work in whole blood resuscitation.

In their efforts to implement a civilian trauma resuscitation system that sustains a substantive supply of whole blood for use in the prehospital setting at the “point of injury,” a collaboration was constructed between that university-affiliated trauma hospital and the State of Texas regional trauma advisory council for South Texas (STRAC). In turn, that collaboration helped to create a blood donation program called “Brothers in Arms” funded by a San Antonio Medical Foundation grant. This program, developed and managed by the affiliated South Texas Blood and Tissue Center (STBTC), identifies men with low titer O+ blood types. Those identified are subsequently asked to volunteer to participate in the program. A large source of donors now actually includes many of the EMS rescuers and firefighters who eventually provide the medical rescue and transfusions in the prehospital setting.

Using safe intervals between blood donations from the individuals involved as well as the other usual safeguards and best practices in testing blood donations, “Brothers in Arms” and the affiliated blood bank program itself is quite a unique endeavor, and represents a whole new service line in the San Antonio area as it includes specialized equipment for whole blood retrieval and preservation, testing, packaging and distribution directly to the involved EMS units or stations.

### **29.5.2 Deciding How to Distribute the Blood Supply**

In collaboration with local trauma center teams, the San Antonio Fire Department team identified various areas of the city of San Antonio from where the highest volumes of patients with life-threatening hemorrhage had originated [27]. For example, they determined areas of the city where patients who later received multiple transfusions in-hospital were retrieved and, in turn, used EMS response vehicles covering those areas of the city as the targets for storing and utilizing the blood product [27]. Among several dozen EMS response units in the city, 8 of the units, each staffed with paramedics, were chosen to carry the blood in the initial round of evaluation.

In the case of Broward County Sheriff’s Office Department of Fire Rescue, they have now developed a specialized air rescue program to deliver the blood due to the expansive and complex geography in their EMS response jurisdiction and the ensuing concern for extensive delays transporting the severely bleeding patient to the closest trauma center. While they are currently planning a move to add whole blood onto the ground units as well, the air rescue program is the current focus for the new program.

In San Antonio, each of the 8 units assigned was provided with just one 500-ml standard container of whole blood for transfusion. The blood was kept in a portable cooler that maintains the blood at 0 to 6 °C (Credo ProMed<sup>®</sup>, Pelican BioThermal, LLC, Plymouth, MN, USA) and is monitored for any breach of temperature control. Broward County uses a different cooler (BloodBoxx<sup>®</sup> by Thermal Logistics Solutions, Combat Medical, Harrisburg, NC, USA) at 0–4 °C with automated monitoring for temperature breaches.

The carried unit of whole blood is considered to be fully transfusable and effective for several weeks. The blood can be maintained in a viable state for up to



**Fig. 29.1** Low titer O+ whole blood in the out-of-hospital setting. Whole blood can now be stored and maintained for significant periods of time on ambulances (photo courtesy of the Broward County Sheriff, Broward County, Florida, USA)



21 days at 1–6 °C in the anticoagulant, citrate–phosphate–dextrose, or for 35 days at 1–6 °C in citrate–phosphate–dextrose–adenine substrate [27, 28] (Fig. 29.1). However, to preempt the possibility of wasting any blood unused by EMS, the blood in San Antonio is rotated back every 14 days to the civilian trauma center (and other area medical centers) for the usual in-hospital transfusions. Experience to date from the San Antonio Fire Department is that 75% of the blood is used prehospital and over 200 patients were treated in the first year of operation. With 8 EMS response units carrying the blood, this translates into about 6 units being used every 2 weeks at a cost of about US\$500 (€450) each or about US\$75,000 per year. The agency is not charged if the blood is rotated back into the hospital system. In contrast, Broward County Sheriff's Office Department of Fire Rescue pays for all of its blood products, used or unused, but in both cases, the cost has been deemed worthwhile especially with preliminary data indicating trends toward substantial lifesaving. Accordingly, both agencies plan on expanding their fleet of ground units carrying the blood.

### 29.5.3 Criteria and Triggers for EMS Infusing Whole Blood and Tranexamic Acid

The San Antonio Fire Department EMS crews will infuse blood into not only patients with blunt and/or penetrating trauma but also those with medical conditions associated with substantial blood loss such as severe gastrointestinal hemorrhage. To date, about 25% of the recipients of the whole blood had non-traumatic etiologies and the use included women of childbearing age and even pregnant patients [41].

Regardless of etiology, both San Antonio and Broward County EMS crews will use the blood product for patients with presumed large volume hemorrhage manifested by the following: systolic blood pressure <70 mmHg; systolic blood pressure <90 mmHg and a heart rate of  $\geq 110$  beats per minute; a witnessed post-traumatic or non-traumatic circulatory arrest <5 min prior to EMS arrival on-scene and

continuous use of cardiopulmonary arrest (CPR) chest compressions throughout the resuscitation efforts; or a patient with likely bleeding who is  $\geq 65$  years of age and who has a systolic blood pressure  $\leq 100$  mmHg and heart rate  $\geq 100$  beats per minute.

In addition to the infusion of the 500 ml of blood over an approximate 3–4 min period, the patient simultaneously receives 1 g of tranexamic acid through another site of vascular access. Children  $< 6$  years of age are not treated according to the prescribed protocol, but they can still be given the blood after the medical director has been contacted for approval.

### 29.5.4 Infusing the Blood and Tranexamic Acid

Both the Broward County and San Antonio programs use a specialized infuser device called the Qinflow<sup>R</sup> that immediately warms the blood from near freezing to 38 °C, reaching body temperature in a matter of seconds while delivering the blood at a rate of 200 ml/min through standard large bore peripheral intravenous catheters. In that respect, most patients receive the full benefit of the transfusion within minutes.

## 29.6 Conclusion

In addition to growing concerns about early resuscitation with crystalloids and other non-hematologic fluids, there is also a growing rationale and evolving evidence that bringing whole blood to the prehospital setting is not only feasible and superior to the component therapy approach but also lifesaving. Using low titer O+ whole blood avoids many of the prior concerns about using blood without blood type and crossmatching. Several strategic initiatives, as discussed in this chapter, may help to expedite and facilitate that lifesaving effect for other communities.

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