# Burn Resuscitation

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One of the great advances in burn care, developing a strategy for treating burn shock resuscitation, occurred in the 1960s and 1970s. Before this period, most people with extensive burns (>30% TBSA) would simply die within hours or, if they survived, would suffer from renal failure. Currently, burn shock resuscitation has become an afterthought that is relegated to residents and nursing staff. Calculations are performed based on protocols, and it is known that fluid rate titration should be based on urine output. Recently, however, concerns have arisen that suggest that over-resuscitation has become common. "Fluid creep" has become the term to describe a trend in giving patients too much fluid.[1–4] The issue of "fluid creep" seems to be substantiated by increased numbers of publications describing complications such as compartment syndromes, especially abdominal compartment syndrome.[5–8] These realizations suggest that there still is a long way to go in understanding the mechanisms of burn shock. The purpose of this review will be to summarize the presentation, discussions, and conclusions of burn resuscitation at the recent "State of the Science Meeting," which took place in Washington, DC, October 26, 2006.

The goal of the review will be to ask several questions:

- Have we made progress in our resuscitation formulas?
- Can we do a better job with resuscitation?
- Do we need to do a better job?
- What is the pathophysiology of burn shock?
- Is there agreement on resuscitation formulas?
- What is the best resuscitation fluid?
- How do newer technologies assist with resuscitation?
- What should the endpoints of resuscitation be?
- Can we alter the capillary leak of burn shock?

The answers to these questions are, unfortunately, not simple. We have made progress, but not enough. There is not even universal agreement on which formula to use. We know that the ultimate goal is optimal perfusion but we still do not have adequate indicators of perfusion. One guideline for resuscitation has been clearly defined: urine output. Are we following urine output like we should? Often enough, we are not. Is urine output good enough? Maybe urine output leads to over-resuscitation. Does it really matter if we do a good job with resuscitation or not? Most patients tolerate our inaccuracies and do just fine despite our mistakes. According to the recent publication by the Institution of Medicine, this attitude will not be tolerated.[9] There are increased efforts to reduce medical errors. We cannot tolerate doing an "adequate" job when we can put forth a "good" or excellent" effort. The challenge to our colleagues, then, is to improve our knowledge of the science of resuscitation to reduce errors and improve the outcomes of our patients.

## HISTORY

The first documented interest in studying burn shock resuscitation was tied to burn disasters. Underhill published his experience with the Rialto Theater fire in 1921.[10] He documented the understanding that burn shock was related to fluid loss. The Coconut Grove disaster in 1942 was an impetus for many developments in burn care. One of the topics of the landmark publication of Moore was related to fluid shifts in burn resuscitation.[11] They suggested that edema contributes to the shock state after a burn. They also suggested that resuscitation should be tied to the body weight and the severity of burn and introduced a "body-weight burn budget" formula for resuscitation. The first burn resuscitation formula based on body surface area burn and bodyweight was described by Evans in 1952.[12] The "Evans Formula" was the standard for years. In 1965, Moyer et al suggested that burn edema sequesters a large amount of

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fluid.[13] They introduced the first crystalloid-only resuscitation. They also suggested that extracellular sodium depletion plays a role in burn shock. Arturson was another key investigator who suggested that capillary leak was the major cause of fluid shifts after a burn injury.[14]

Clearly, a major focus of research during the 1960s and 1970s was the investigation of fluid shifts during the first 24 hours after burn injury. There has not been such an effort since that time. One of the key figures in burn resuscitation was Charles Baxter, who was instrumental in developing the Parkland Formula, which today is the most frequently used resuscitation formula. Baxter, along with Shires, performed isotope studies to indicate that the fluid leaking from the capillaries had a similar protein content to serum.[15] This finding suggested that providing protein during burn shock resuscitation was not indicated because most of the supplemental proteins would leak into the interstitial space. He and his colleagues understood that fluid requirements should be dictated by the urine output of the burn patients. They determined that patients required 4 ml/kg/% TBSA burn in 24 hours.[16] As a rough indicator of the 24-hour requirements, they suggested that fluid delivery could be divided so that one half of the fluids could be given in the first 8 hours and the second half in the remaining 16 hours. He also realized that this was an approximation and the best indicator of fluid requirements should be based on urine output. The "Parkland Formula" has remained the most commonly used formula today.

Dr. Baxter spent much of his early career studying the mechanisms of burn shock. One of his key findings was that, in response to a burn injury, there is a "cellular shock" that is manifested by a change in the transmembrane potential of the cell.[16] In patients with burns greater than 30% TBSA, there is a systemic decrease in the transmembrane potential of the cell. The cause of the transmembrane decrease is related to an increase in intracellular sodium. The burn has effects on the membrane-associated ion channels. Further studies are needed to elucidate these effects but research has tended to focus on other aspects of the response to injury.

Around the same time as Dr. Baxter's work, Dr. Pruitt and Dr. Moncrief characterized the hemodynamic effects of burn shock with and without resuscitation.[17] They developed the Brooke Formula (named after the military base in San Antonio, Texas) with a resuscitation volume that was lower than the Parkland Formula (2 ml/kg/% TBSA burn). They also stressed that the actual fluid volume given should be titrated to the physiologic response (urine output). Although the initial formula suggested the use of a colloid for resuscitation, it was eventually changed to the "Modified Brooke Formula," suggesting the use of lactated Ringers (LR) solution at 2 ml/kg/% TBSA burn.

Also in the early 1970s, Monafo started examining the efficacy of using a hypertonic saline solution (240 – 300 mEq of $Na^+$) for resuscitation.[18,19] The concept was that hypertonic saline would shift water from the intracellular to the intravascular space. The other benefit would be that with a lower volume of resuscitation there would be less edema and its associated complications. Initially, there was great interest in using a hypertonic sodium chloride solution but interest waned in the subsequent years. At least two prospective trials have been performed with varying results.[20,21] A more recent study suggested that there was an increase in renal failure with hypertonic saline.[22] Another study suggested that the use of a hypertonic saline resuscitation reduces the risk of abdominal compartment syndrome by reducing the volume of resuscitation.[23] In the early 1990s, Warden suggested the use of a "modified hypertonic resuscitation" using LR solution with 50 mEq of $NaHCO_3$ per liter.[24] This creates a sodium concentration of 180 mEq. The results of another study suggested that addition of $NaHCO_3$ would not alter the outcome of resuscitation.[25] The interest in hypertonic resuscitation has recently been rekindled with findings that suggest that hypertonic saline may enhance the immune response to injury.[26]

More recently, the concept of using colloids for resuscitation has been revived. Fresh frozen plasma, Dextran 40, Dextran 70, and other colloid formulas have been proposed.[27–31] Recent studies using colloids have not substantially influenced the practice of burn resuscitation since the development of the Parkland Formula.

In 1978, approximately 30 years before the current State of the Science Meeting, a National Institutes of Health "Consensus Conference" on burn shock resuscitation was held to determine the optimal resuscitation for a burn patient.[32] Although there was no consensus on the best resuscitation formula, what was agreed upon was that the resuscitation fluids should be minimized to decrease iatrogenic complications. The consensus conference acknowledged that physiologic parameters, including urine output, were important for monitoring the efficacy of resuscitation and suggested that replacing sodium was the key to an adequate resuscitation. Since that conference, there has been no concerted efforts to improve burn shock resuscitation.

## THE PATHOPHYSIOLOGY OF BURN EDEMA

The pathophysiology of burn edema has been extensively studied. Demling[33] has recently published an excellent review from which I will summarize key issues. Burn edema forms rapidly after a burn injury; the extent varies with the depth of injury. For instance, after a superficial burn, the maximal amount of edema forms after 12 hours. Ninety percent of the edema, however, is present by 4 hours. The rapid increase in edema is caused by increased perfusion to the injured area. This increases local blood flow that in turn "pushes" more fluid out of the capillaries. To a great extent, the edema tends to reside within the dermis. Resorption of water begins around 4 hours and is complete by 4 days. The edema dissipates in a partial thickness burn more rapidly than in a full thickness burn due to the functional lymphatic network and increased perfusion of a partial-thickness burn.

Edema formation in deep burns is different, mainly because of the damage to dermal vascular and lymphatic plexus. The rate of tissue edema peaks later (maximal at 18 hours) and resorption is much delayed because of damage to the lymphatics. Approximately 25% of the excess water is still present at one week. The edema fluid also tends to reside in the subcutaneous tissue (because the skin itself is destroyed).

The fluid mechanics of edema are best understood by the modern version of the Starling Equation:

$$Q = K_f\,(Pcap - Pi) + \sigma\,(\pi p - \pi i)$$

Although there is a general simplistic view that an increase in capillary permeability drives injury-related edema, all factors of the formula are affected after a burn.

**Q** refers to the "fluid filtration rate," which peaks within 1 to 2 hours after a burn injury. The increase in fluid filtration rate (Q) persists for days after a burn but is soon balanced by very efficient resorption by lymphatics. Clearly, if there is damage to the local lymphatics then resorption of fluids will be delayed.

**$K_f$** refers to "capillary filtration coefficient," which depends on the capillary surface area and hydraulic conductivity. This coefficient increases to two to three times normal after a burn injury.

**Pcap** refers the "capillary hydrostatic pressure," which is increased in superficial burns as a result of the increase vasodilation in response to local mediator release. The Pcap increases from a normal of 24 mm Hg to 48 mm Hg after a burn injury.

**Pi** refers to the "interstitial hydrostatic pressure" which, surprisingly, becomes negative after a burn either from the breakdown of large proteins into smaller osmotically active particles that create a vacuum-like effect or because of the "Hydraulic Theory of Interstitial Matrix Pressure," which suggests that coiling of tethered collagen and hyaluron macromolecules creates a negative pressure.

**$\sigma$** refers to the "reflection coefficient" and describes the permeability characteristics of the capillary to macromolecules. A reflection coefficient of 1 indicates that no large molecule will pass across the capillary (ie, it is impermeable). A value of 0 means that there is free flow of macromolecules across the capillary. Normal **$\sigma$** is 0.9 for the skin and 0.7 for the lung. The peak in permeability occurs within the first day post-burn and persists for days.

**$\pi$p** refers to "plasma oncotic pressure" or "plasma colloid osmotic pressure." The plasma oncotic pressure decreases significantly as protein levels drop during resuscitation. The value drops by around 50% in a major burn.

**$\pi$i** refers to "Interstitial Oncotic Pressure" or "Interstitial Colloid Osmotic Pressure", which increases after burn injury due to proteins leaking into the interstitium.

Another factor is important in the production of edema: interstitial compliance. With destruction of the tissues, the interstitial compliance increases due to destruction of local collagen and other extracellular matrix molecules. This contributes to edema by increasing the compliance of the tissues to extra fluid. Other factors in the formation of edema are the lymphatics and the production of free oxygen radicals from leukocytes. The oxygen-free radicals lead to further tissue destruction, mediator production and prolonged changes in capillary permeability.

## THE CURRENT STATE OF RESUSCITATION

Most burn centers use a crystalloid solution (LR) along with some variation of the Parkland Formula for resuscitation (Table 1) and adjust resuscitation based on urine output. Resuscitation of a burn patient remains problematic. The fact that there are multiple formulas for resuscitation implies that our current resuscitation guidelines do not apply to all situations. There have been several publications that suggest that our resuscitation efforts frequently lead to over-resuscitation.[1–4] Many centers deliver much more fluid than 4 ml/kg/% TBSA burn, thus suggesting that "fluid creep" does indeed occur. The excessive fluid delivery has led to descriptions of increased complications such as abdominal compartment syndrome.[5–8] Why does "fluid creep" occur?

**Table 1.** Burn resuscitation formulas, current and past

| |
|---|
| Crystalloid formulas: Usually use lactated Ringer's solution, although newer isotonic fluids may be used. |
| Parkland (Baxter) formula: 4 ml/kg/% TBSA burn, give half in the first 8 hours and half in the next 16 hours. Adjust rate based on urine output. For second 24 hours, give 20% to 60% of calculated plasma volume as colloid. (The recommendation for the second 24 hours is usually not followed.) |
| Modified Brooke formula: 2 ml/kg/% TBSA burn, give half in the first 8 hours and half in the next 16 hours. Adjust rate based on urine output. For the second 24 hours, give 0.33 to 0.5 ml/kg/% TBSA burn as colloid plus $D_5W$ to maintain urine output. |
| Hypertonic formulas: No colloid. |
| Monafo: 250 mEq/liter $Na^+$ + 150 mEq lactate + 100 mEq $Cl^-$. Adjust rate based on urine output. For second 24 hours, give one third of isotonic salt orally. |
| Warden: lactated Ringer's plus 50 mEq $NaHCO_3$ (180 mEq of $Na^+$) per liter for first 8 hours (based on the Parkland Formula). Switch to lactated Ringer's when pH normalizes or at 8 hours. Adjust rate based on urine output. |
| Colloid formulas |
| Burn budget formula of F.D. Moore: lactated Ringer's 1000–4000 ml + 0.5 normal saline 1200 ml + 7.5% of body weight colloid + 1500–5000 ml $D_5W$. For second 24 hours, use same formula except for colloid 2.5% of weight. |
| Evans formula: normal saline at 1 ml/kg/% TBSA burn + colloid at 1 ml/kg/% TBSA burn. For second 24 hours, give half of first 240 hour requirements + $D_5W$ (dextrose 5% in water) 2000 ml. |
| Brooke formula (original): lactated Ringer's at 1.5 ml/kg/% TBSA burn + colloid at 0.5 ml/kg/% TBSA burn. Switch to $D_5W$ 2000 ml for second 24 hours. |
| Slater formula: lactated Ringers 2000 ml + fresh-frozen plasma at 75 ml/kg/24 hours. Adjust rate based on urine output. |
| Haifa formula: plasma at 1.5 ml/kg/% TBSA burn + lactated Ringer's at 1 ml/kg/% TBSA burn. Adjust rate based on urine output. |
| Demling formula: Dextran40 in normal saline at 2 ml/kg/hr for 8 hours. Fresh-frozen plasma at 0.5 ml/kg/hr starting at 8 hours. Lactated Ringer's should be given to maintain urine output. |

The answer is not clear, but it is known that actual urine output levels frequently are greater than the targeted 0.5 to 1 ml/kg/hr. Is the lack of adherence to urine output attributable to a lack of training or are staff members not paying attention to urine output? One hypothesis for over-resuscitation is that, with increased use of narcotics, there are increased fluid demands.[34] The term "opioid creep" has been coined to correspond to "fluid creep." This interesting hypothesis needs to be tested.

Other factors may be the related to the timing and initial volume of resuscitation. Delay in resuscitation increases fluid requirements[35]; therefore, with the regionalization of burn units, delays may lead to increasing fluid requirements. A comment during the State of the Science Meeting was that once over-resuscitation has been initiated, it is impossible to "turn off" the need for a high fluid resuscitation rate. This interesting hypothesis needs to be tested. Improved instruction and communication should help reduce initial over-resuscitation. Another key question is: is urine output an adequate monitor of resuscitation? Dries suggested that urine output might not be an accurate indicator of adequate resuscitation.[36] Are other parameters any better? Clearly, these questions need to be answered.

Age is another important factor affecting the volume of resuscitation. The actual fluid required for pediatric burn resuscitation turns out being approximately 6 ml/kg/% TBSA burn.[37,38] Small children have relatively large daily basal fluid requirements. This volume contributes to the fluid needed for burn resuscitation. For instance, a 10-kg child (body surface area of 0.5 meters squared) needs approximately 1000 ml/day for daily basal fluid requirements. If that child sustains a 50% TBSA burn, the Parkland Formula indicates that they need $4 \times 10 \times 50 = 2000$ ml in 24 hours. Addition of the basal requirement to the Parkland formula yields 6 ml/kg/% TBSA burn. In an adult or older child, the daily basal requirements become much smaller in comparison, and are already included in the resuscitation formula. For example, a 100-kg human needs approximately 3000 ml per day in basal fluids. If he or she sustains 80% burns the Parkland formula suggests $4 \times 100 \times 80 = 32{,}000$ ml for the first 24 hours. The 3000 ml is relatively inconsequential in influencing the fluid rate for resuscitation.

Anecdotal reports of using alternative solutions, such as Ringer's ethyl pyruvate solution, as an alternative crystalloid solution for other types of shock have recently been published.[39,40] The theory is that pyruvate, the second-to-last product of glycolysis, helps to improve the cell's capability to deal with metabolic stress. Studies by Fink have suggested that Ringer's ethyl pyruvate solution has anti-inflammatory

and anti-oxidant activities. There have been no reports of using this solution in burn shock resuscitation. Additional reports indicate that LR solution contains both L and D-lactate isomers.[41–43] The D-lactate isomer has been found to be toxic to the cells and increases apoptosis.[42,43] The L-lactate isoform lacks toxicity and thus might be better for routine resuscitation. These findings have not been confirmed in clinical studies.[41] Other fluids that may have some benefit include β-hydroxybutyrate in a Ringer's solution,[43] "Normosol," (Richard Kagan, MD, Shriners Hospitals for Children Cincinnati, personal communication), "Isosal-D,"[44] or "Gelofusine" (used for burn resuscitation in China).[45] Prospective randomized trials on these solutions are lacking.

The use of colloids in resuscitation has long been debated. The first formula described by Evans used albumin (NS at 1 ml/kg/% burn + colloid at 1 ml/kg/% burn).[12] The original Brooke formula also used colloid (LR at 1.5 ml/kg/% burn + colloid at 0.5 ml/kg/% burn), but the formula was later switched to LR at 2 ml/kg/% TBSA burn.[17] As described previously, Slater suggested that the use of fresh-frozen plasma in addition to LR (LR 2l/24 hours + FFP at 75 ml/kg/24 hours).[27]

Demling reported the use of a complicated formula of Dextran 40 in normal saline at 2 ml/kg/hr with LR added to maintain adequate urine output. He then added FFP at 0.5 ml/kg/hr starting at 8 hours and continuing for 18 hours.[27] The Haifa group uses serum for their resuscitation formula.[31] Many other burn units will utse the Parkland formula (or another crystalloid resuscitation) and then give small amounts of human albumin after 12 to 24 hours if the patient fails to resuscitate adequately. Although maintaining normal albumin levels is not justified, once levels drop to less than 2.0 mg/dl, the use of albumin may be indicated, and albumin does not decrease the incidence of multiple organ dysfunction.[46,47] The issue of the relative roles of crystalloid versus colloid resuscitation is still unresolved.

The other question related to resuscitation is whether inotropic support (such as dopamine, dobutamine, epinephrine, norepinephrine, or vasopressin) is indicated during burn shock. "Goal-directed resuscitation" was popular for managing sepsis during the 1990s,[48] but controlled trials suggested that it did not improve patient outcomes.[49] Several publications that suggest that a major burn releases a "cardiac depression factor" that impairs cardiac function,[50,51] so inotropic support might be of value in selected cases. Determining which patients, if any, would benefit from cardiac support may improve the outcomes of burn shock resuscitation.

## ENDPOINTS OF RESUSCITATION

The most important message derived from the State of the Science Meeting was that endpoints of resuscitation are poorly defined. Cancio et al[52] tried to find variables to predict who would not respond to resuscitation and were unable to do so. No single formula should be used to dictate fluid resuscitation during burn shock. There are many other factors that influence fluid requirements during resuscitation besides TBSA burn involvement. Other factors, such as burn depth, inhalation injury, associated injuries, age, delay in resuscitation, need for escharotomies/fasciotomies, and use of alcohol or drugs influence fluid requirements. Clearly, the formulas are just indicators for the initiating fluid resuscitation rate. Fluid rates need to be adjusted based on physiologic endpoints, such as urine output (1/2 ml/kg/hr for adults and 1 ml/kg/hr for small children). The value of using urine output to adjust fluid rates during burn shock has been challenged.[36] Studies also suggest that the adjustment of resuscitation fluids based on urine output is inconsistent.[1–4] Methods for improving our response to urine output as an endpoint are in order.

Other indicators of resuscitation have been challenged in recent years. The use of invasive monitoring, such as the central venous pressure (CVP) or pulmonary artery catheter (PAC) theoretically should help, especially in the elderly, but studies do not support their use.[53–56] One study suggests that the CVP is influenced more by intraabdominal pressures than actual right atrial pressures.[57] Pulmonary artery catheters (PAC) have the capability to provide more information, but recent studies suggest that the PAC does not change mortality in other diseases.[53–56]

Invasive monitors continue to become more sophisticated. Pulmonary artery catheters have the capability of measuring continuous cardiac output and mixed venous oxygen saturation. It is also possible to measure such parameters as ventricular-arterial coupling.[55] There have been a few studies using what is described as intermittent transpulmonary thermodilution using the "COLD system" (Pulsion Medical Systems, Munich, Germany). This system uses two systems of thermodilution, 0.3 mg/kg indocyanine green dye mixed with iced 5% glucose solution through a central line in the superior vena cava and a "thermistor-tipped fiberoptic catheter" placed in the femoral artery is used to measure such parameters as intrathoracic blood volume, cardiac output, total blood volume index, and extravascular lung water.[55–58] Although preliminary studies suggest that these devices may aid in resuscitation, the one randomized trial did not support these findings.[56] A surprising conclusion

was that the use of the Baxter (Parkland) formula led to under-resuscitation! This conclusion is certainly in contrast to the concerns about "fluid creep."

Another potential aid in estimating cardiac output, "pulse contour analysis," is based on the shape of an arterial waveform.[59–62] Pulse contour analysis has been found to be effective using both femoral and radial arterial catheters.[61] These devices have not been prospectively tested in burn patients. Other methods include measuring transesophageal echocardiography,[62] partial carbon dioxide rebreathing,[62] and impedance electrocardiography.[63] Comparisons of these various techniques demonstrate that they are somewhat reliable for determining cardiac output.[62] Although these devices are interesting, their use for burn resuscitation is undefined.

Tissue perfusion monitors, such as gastric tonometers[64] or devices to measure $O_2$ and $CO_2$ saturations in the subcutaneous tissues[65] (both below the burn and in normal skin), also have been tested. These devices are of marginal utility in dictating resuscitation; they demonstrate low perfusion despite other signs of adequate resuscitation. All of these findings suggest that we do not have adequate devices to monitor the adequacy of resuscitation. A major focus for the future will be to develop more reliable endpoints for resuscitation.

## ORAL RESUSCITATION

Oral resuscitation was one of the earliest methods of providing fluids for patients. Oral resuscitation is a potential source of fluids in two situations—burns in the third world and in the case of a disaster when intravenous supplies may not keep up with medical demand. Resources in many countries cannot support the use of intravenous fluids for many of their population. With a sizeable burn, these patients often are not resuscitated and thus die. Oral resuscitation fluids can be created in kitchens and are very inexpensive to create and administer. There are two excellent reviews that detail the specifics of oral resuscitation in burn patients.[66,67] What has piqued interest in oral resuscitation has been the success of using oral fluids to treat cholera and other epidemic forms of diarrhea. The World Health Organization (WHO) has developed guidelines for using oral resuscitation for severe diarrheal diseases.[68,69] These same formulations should be helpful for burn patients. The key question is at what size burn is oral resuscitation ineffective? Anecdotal studies suggest that oral resuscitation is helpful for at least patients with smaller burns.[70] The value of oral resuscitation for larger burns has not been established. It is conceivable that encouraging early oral fluid intake prior to intravenous access could improve resuscitation in massive burns. This strategy also would be helpful for soldiers suffering from burns while they await definitive care. The combination of oral and intravenous fluids would place less of a burden on supplies in a mass casualty situation.

A major problem with oral resuscitation, which may be related to the use of narcotics, is that vomiting may limit the volume delivered to the patient.[71] One suggestion made at the State of the Science Meeting was that oral opioid antagonists might improve gastrointestinal function. Clearly, early feeding is tolerated through nasoduodenal feeding tubes. The placement of nasoduodenal or nasogastric tubes may facilitate oral resuscitation.

Another quandary of oral resuscitation is what type of fluid do we provide? Studies have suggested the use of hypo- and hypertonic solutions (Table 2). The current WHO solution is somewhat hypotonic, and the literature suggests that hypotonicity really does not matter for severe diarrheal disease.[72] Studies also suggest that the addition of glucose will aid in the delivery of water.[73] The ideal solution and the best mode of delivery are currently not known (Table 2 and 3). Finally, there has been a description of delivering resuscitation fluids per rectum ("proctoclysis").[74] The "Murphy's Drip" solution, originally described in 1913, is made of NaCl (1.77 g) and $CaCl_2$ (1.77 g) in 473 ml (1 pint) and delivered per rectum as 1–2 pints every hour. Although these techniques are not frequently used, further studies are needed to test oral and rectal resuscitation strategies. The use of simplified resuscitation formulas could greatly enhance survival in third world countries.

## PHARMACOLOGIC MANIPULATION OF RESUSCITATION

The other key question of burn shock is whether the shock process can be reversed or inhibited by pharmacologic manipulation. Although burn shock involves the loss of fluid across from the intravascular to the interstitial space, the exact pathophysiology of the capillary leak is not entirely known. Local mediators such as histamine, serotonin, prostaglandins, and others have been implicated in the development of capillary leakage.[75–77] Many studies have been performed that use blockers of these different mediators to prevent capillary leakage.[78–80] However, these mediators appear to reduce, but do not eliminate, edema. Preinjury treatment is obviously not feasible for treating our patients. Postinjury studies have not proven to be of much value.

**Table 2.** The content of various solutions used for oral resuscitation (adapted from Cancio et al[68])

| Formula | Carbohydrate | $Na^+$ | $Cl^-$ | $K^+$ | Buffer | mOsM |
|---|---|---|---|---|---|---|
| WHO ORS (1975) | 111 | 90 | 80 | 20 | 30 | 331 |
| WHO ORS (2002) | 75 | 75 | 65 | 20 | 10 | 245 |
| Gatorade | 250 | 20 | 20 | 3 | 3 | 280 |
| Pedialyte | 139 | 45 | 35 | 20 | 30 | 250 |
| Rehydralyte | 139 | 75 | 65 | 20 | 30 | 325 |
| Fox's Na Lactate | 0 | 161 | 0 | 0 | 161 | 321 |
| Moyer's Citrated NaCl | 0 | 85 | 63 | 0 | 29 | 160 |
| Monafo's HTS | 0 | 300 | 200 | 0 | 100 | 600 |
| Liquidsorb | 222 | 60 | 44 | 4 | 28 | 370 |
| Jiang's Burn Drink | 252 | 48 | 28 | 0 | 20 | 347 |
| Ricelyte | 3 (%wt/vol) | 50 | 45 | 25 | 34 | 200 |
| AstroAde (NASA) | 0 | 164 | 76 | 0 | 40 | 253 |
| Lactated Ringer's | 0 | 130 | 109 | 4 | 28 | 270 |
| 0.9% NaCl | 0 | 154 | 154 | 0 | 0 | 308 |

*WHO ORS*, World Health Organization Oral Rehydration Solution; *HTS*, hypertonic saline.
Carbohydrates in mM, Osmolarity in mOsM.

Another promising substance in reducing the amount of fluid required for burn shock resuscitation is high-dose Vitamin C.[81,82] The clinical studies, performed in Japan, suggest that Vitamin C treatment might be an inexpensive and effective means for reducing fluid requirements for burn patients.[83] These studies have not been duplicated in other institutions. Multi-institutional prospective randomized trials are needed to substantiate these findings.

Finally, both plasmapheresis and exchange transfusions have been used to decrease inflammation and edema formation.[84–86] The theory of "removing the evil humors" makes sense, because the techniques can reduce cytokine levels. Plasmapheresis was reserved for adults and exchange transfusions were utilized for children. While these studies were encouraging, burn teams rarely use these techniques, due to the extensive personnel and equipment requirements.

## RESUSCITATION: THE FUTURE

In reality, there has been little progress made in understanding and treating burn shock in the last two to three decades. The formulas have not changed since the 1970s, and the attention paid to monitoring resuscitation may have deteriorated. There has been an increase in over-resuscitation and its associated complications. One may wonder whether our teams are trained as well in adjusting fluids as they were in the past. One new idea is to develop "closed-loop" resuscitation, in which the amount of urine produced is measured and intravenous fluids are adjusted automatically by a computer.[87] Publications that suggest that "closed-loop" resuscitation does as well as human monitors.

The simple question of which type of resuscitation fluid is the best still needs to be answered. Crystalloid use is inexpensive and is effective for the majority of patients. Some patients, however, benefit from the addition of colloid. Who are these patients and when should colloids be added? What are we to do if there is a burn-related disaster? We would quickly run out of our intravenous solutions. Do we need to have easily produced alternatives? The use of oral resuscitation formulas and treatment protocols is also necessary if we can improve the outcome of burns in the

**Table 3.** Recipes for homemade oral resuscitation fluids (adapted from Cancio et al[68])

| Base Ingredient | Volume | Sugar | Salt* | Baking Soda |
|---|---|---|---|---|
| Clean water | 1 liter | 8 tsp | ½ tsp | ½ tsp |
| Gatorade | Quart Bottle | No addition | ¼ tsp | ¼ tsp |
| Lactated Ringer's | 1 liter | 8 tsp sugar or glucose | No addition | No addition |

*In the absence of baking soda, double the salt, tsp = teaspoon).

outcome of burns in the third world. Studies are necessary to develop the optimal types of solution and to improve the tolerance of oral resuscitation.

One must also wonder whether urine output is really an accurate enough indicator of tissue perfusion. Frequently, the patient may have adequate urine output but is hemodynamically unstable. Abdominal compartment syndrome is thought to be a problem of "over-resuscitation" but frequently occurs in the face of inadequate urine output. The other monitors of tissue perfusion (gastric, rectal, skin tonometers) are of limited utility. A challenge for the future will be to develop monitors of tissue perfusion that are more accurate than our current standards.

We must also develop a better understanding of the hemodynamic demands of burn shock so that we can truly understand whether supplementation with inotropic support is indicated or of true value. The ability to alter the cellular responses to a burn injury would also be helpful. Is vitamin C treatment worthwhile? Can we develop an effective blockade of capillary leak that is effective hours after burn injury? Data needs to be obtained on the molecular and cellular mechanisms of burn shock. One of the key problems has been that there has been little interest in resuscitation research for the last several decades. Maybe it is time to rekindle that interest in burn resuscitation.

## RECOMMENDATIONS FROM THE STATE OF THE SCIENCE MEETING

Listed below is a summary of the key issues stressed by the participants of the State of the Science Meeting. Several key questions were asked of the participants so the questions will be listed along with key areas for future concern. It is hoped that these points will be used as guidelines for future investigations related to burn shock resuscitation.

The most important area of research should be to define endpoints of resuscitation:

- urine output alone is probably not an adequate endpoint, and
- multiple endpoints exist that may conflict. The interpretation of these endpoints should be better defined.

The role of invasive and noninvasive monitoring needs to be defined:

- Should pulmonary artery catheters be used?
- What is the role of newer monitoring techniques?

Better indicators of perfusion need to be determined:

- Current measures of tissue perfusion (gut or skin) are inadequate.
- What are the roles of base deficit and lactate levels?
- What is the role of the laser Doppler?
- What are the cellular markers of resuscitation?
- What is the best resuscitation solution?
- LR solution has problems but is still used by the vast majority of burn units.
- Some units use other types of crystalloid solutions, such as acetate.
- Colloid solutions are used in about 5% of the units throughout resuscitation.
- Most units add a colloid (usually albumin) during the first 24–48 hours, with a trend to adding albumin earlier during resuscitation. One person stated: "everyone cheats" by adding colloids to the resuscitation.
- A multicenter trial to examine the role of colloids in resuscitation is warranted.
- The role of hypertonic saline but its role still needs to be evaluated.
- Avoiding over-resuscitation is an important goal.
- Over-resuscitation is a major cause of complications such as compartment syndromes and acute respiratory distress syndrome.
- Once over-resuscitation has started, it is difficult to stop.
- Better teaching of prehospital personnel, emergency department staff, house staff, and nursing will reduce early over-resuscitation and its complications.
- Quality improvement projects should be set up to reduce over-resuscitation. The urine output target should continue to be 0.5 ml/kg/hr for adults and 1 ml/kg/hour for children $<30$ kg.
- Any center that participates in a resuscitation study will improve compliance with urine output goals.
- The influence of narcotics, alcohol and other drugs on over-resuscitation should be investigated.
- The role of computer-based "closed-loop" resuscitation systems should be investigated.
- Research should focus on the pathophysiology of both burn shock and edema formation.
- Research focus on cardiovascular changes in burn shock, including causes of myocardial depression.
- Research should define the cellular and molecular changes in the response to burn injury.
- Mathematical modeling may be a methodology for research.
- Oral resuscitation techniques should be investigated.

- Oral resuscitation should improve survival in third-world countries.
- Oral resuscitation may be a strategy for early resuscitation when intravenous access is unavailable (soldiers burned in action or during a disaster).
- Studies should focus on ways to improve tolerance of oral resuscitation strategies, including types of fluids and methods of delivery.
- Narcotics may decrease tolerance to oral resuscitation. Their role in oral intolerance to fluids should be investigated.
- The role of inotropic agents during resuscitation needs to be determined.
- Goal-directed resuscitation has not been proven effective in the intensive care unit.
- A study to evaluate the role of inotropes should be performed.
- Vasopressin may be an important inotrope to study during resuscitation.
- Research should focus on methods to stop the capillary leak during burn shock.
- The role of narcotics in capillary leak should be determined.
- A multicenter trial to examine the role of vitamin C during burn shock resuscitation should be performed.
- A "cocktail" should be developed to treat capillary leak. For instance, vitamin E (a vitamin with antioxidant effects) might reduce the leak.
- The role of activated protein C (Xigris, Eli Lilly, Incorporated, Indianapolis, IN) was mentioned as an interesting agent to reduce capillary leak. At present it is cost-prohibitive.
- Endpoints of resuscitation need to be defined prior to these studies.

## CONCLUSION: TOP 5 PRIORITIES FOR BURN RESUSCITATION RESEARCH

There are still gaps in our knowledge of burn resuscitation. Although there are many issues that should be investigated, the following questions should receive top priority (Table 4):

1. The top priority for burn resuscitation research is to define the endpoints of resuscitation. It has become obvious that urine output is not good enough but at the same time, newer measures of cardiovascular function also have been questioned. This needs to precede all other resuscitation studies.
2. There should be investigations that clearly identify the reasons for "fluid creep" in burn resuscitation. Have we become complacent or are there physiologic reasons for the increase in delivered fluids? Will performance improvement strategies reverse this trend?
3. The pathophysiology of burn edema should be determined. We need to determine what initiates the leak and determine why there are changes in the entire cardiovascular system.
4. The role of oral resuscitation should be investigated. Improving oral resuscitation strategies should enhance survival in third-world countries and after disasters.
5. The last topic for investigation is to test an agent that will reduce the capillary leak that occurs during burn shock. The investigation of high dose vitamin C seems to make the most sense for the first trial.

**Table 4.** The top five topics for investigation in burn shock resuscitation

| |
|---|
| Define the endpoints of burn shock resuscitation. |
| Develop a better understanding of the pathophysiology of burn shock edema. |
| Determine the cause of "fluid creep." |
| Develop a oral resuscitation protocol. |
| Perform a multicenter trial with an agent that reduces the capillary leak of burn shock. The role of high-dose vitamin C seems to make the most sense at this time. |

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