The evolution of burn fluid resuscitation

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1. Introduction

When considering the management of a significant burn injury, there are few more crucial interventions than adequate fluid resuscitation. Burns have been a problem for humanity for thousands of years, but only relatively recently have we understood the precise pathophysiology which makes fluid therapy so important. That is not to say that there is no more to learn, or indeed that we always get it right. Moreover, we are still without a consensus on which fluids and resuscitation formulae are optimal, particularly in the initial 24 h following injury. Debate on such issues is however healthy and serves as a stimulus for valuable research.

Recent practice has highlighted the potential problems of over- as well as under-resuscitation, with the phenomenon of ‘fluid creep’, gaining credence. The invasiveness of resuscitation monitoring has been gradually increasing, with some camps believing the old stalwart of urinary output monitoring to be no longer sufficient, particularly for major burns. The reader will learn the importance of capillary permeability in burn pathology and would be right to ask of the potential within its manipulation. The manipulation of circulating inflammatory mediators is another ‘hot bed’ of modern burns research. Historical trends are given a nod, since looking into the distant past enables appreciation of what is a substantial trend or development, and what is not.

2. Historical trends: roots and herbs to ‘fluid creep’

Burns have been a problem for mankind since the discovery of fire. Indeed there is evidence from cave paintings that burn wounds were treated with roots and herbs by Neanderthal man some 50–60 thousand years BC.¹ Hippocrates (400 BC) used rendered pig fat and resin in bulky dressings, alternating with vinegar and oak bark soaks.² Galen (129–216 AD) simply advocated vinegar and exposure. Early burn excision was introduced by Paré (1510–1590 AD), and Hildanus (1607 AD) attempted to describe burn pathophysiology and the treatment of contractures.³ The illustrious Guillaume Dupuytren (1777–1835) was the first to classify burns systematically.⁴ Early modern developments in burns management followed large urban fires in the New Haven Rialto Theatre
In the 1960s, Knaysi described the rule of nines for TBSA calculation and Moyer introduced hypertonic salt solutions (Moylan later demonstrated that resuscitation fluid containing sodium was 13 times more effective upon cardiac output resuscitation than fluid without sodium). Also prominent throughout the 1960s were Baxter and Shires. Many important developments which remain relevant today can be attributed to these two. They were first to realise that protein released in the first 24 h exacerbated oedema formation, and described the phenomenon of intra-cellular oedema, due to sodium-potassium pump disruption. They related fluid volume changes to cardiac output using radioisotope dilution techniques, and not least introduced the Parkland formula, which completely omitted colloids in the first 24 h. Its development followed canine burn models displaying the efficacy of restoring extra-cellular fluid to within 10% of control volumes in the first 24 h. This formula, 40 years after its description, remains the most widely subscribed to.

Pruitt has written that “over the past half century, the use of such physiologically based formulae has essentially eliminated early post-burn renal failure, reduced the incidence of burn shock, decreased the occurrence of life-threatening electrolyte abnormalities and minimized tissue loss in the zone of stasis”. Despite the success of formulae like the Parkland, the modern age does not rest on the laurels of old formulae (with some feeling therapeutic promise, but H2 antagonists may have a future role. Serotonin amplifies the adverse effects of histamine, noradrenaline, prostaglandin, and angiotensin II in burn patients. An antagonist of serotonin (ketanserin) led to improved cardiorespiratory parameters in a porcine burn shock model. Prostaglandins cause vasodilatation, and in burned tissue PGE2 and PGII2 accentuate oedema formation, but there is no convincing evidence of the efficacy of prostaglandin inhibitors in animal burn models. Kinins (particularly bradykinin) increase venule permeability, contributing to oedema formation. Although circulating kinin levels can be reduced with protease inhibitors, there is little impact on oedema formation.5

### 3. Fluid pathophysiology in burns: mediating the mediators

The basic tenet of burn physiology is an inflammatory response, both local and systemic, which leads to fluid shift from the intravascular compartment to the interstitium, primarily due to changes in capillary permeability. Arturson noted that burn TBSA exceeding 25% led to generalised increase in capillary permeability. When this figure exceeds 30% TBSA, there is a generalised decrease in sodium ATPase activity leading to systemic disruption of the intra-/extra-cellular ion gradient, lasting at least several days, and only partially corrected by adequate resuscitation. At 50%, one half of the initial resuscitation fluid may leak into non-thermally injured tissue. Warden has comprehensively summarised the multiple mediators believed to be involved in the body fluid response to burns, and how their modulation may have therapeutic potential. These mediators act by increasing either vascular permeability or microvascular hydrostatic pressure. The end result is oedema, exacerbated by the necessary fluid resuscitation, particularly in the shocked patient. Mediators thought to be of importance include histamine, bradykinin, prostaglandins, leukotrienes, vasoactive amines, products of platelet activation, and the complement cascade.

Circulating histamine leads to early loss of protein and fluid from the blood by increasing intra-cellular junction space in venules. H1 receptor inhibitors have shown little therapeutic promise, but H2 antagonists may have a future role. Serotonin amplifies the adverse effects of histamine, noradrenaline, prostaglandin, and angiotensin II in burn patients. An antagonist of serotonin (ketanserin) led to improved cardiorespiratory parameters in a porcine burn shock model. Prostaglandins cause vasodilatation, and in burned tissue PGE2 and PGII2 accentuate oedema formation, but there is no convincing evidence of the efficacy of prostaglandin inhibitors in animal burn models. Kinins (particularly bradykinin) increase venule permeability, contributing to oedema formation. Although circulating kinin levels can be reduced with protease inhibitors, there is little impact on oedema formation.5

Neely describes three main phases of post-burn care starting with the resuscitation period (0–36 h), then the early post-resuscitation period (2–6 days) and finally the inflammation-infection period which persists from about day 7
until wound closure. Admittedly with modern care, wound closure may be obtained at quite an early stage, minimising the infection risk in the final phase. In the resuscitation phase intravascular volume loss follows increases in vascular permeability and burned tissue osmotic pressure. Cardiac output may fall due to hypovolaemia and, in severe burns, decreased myocardial contractility (and possibly myocardial oedema). Circulating catecholamines lead to increases in systemic vascular resistance and heart rate but volume must be adequately restored for a sustainable normalisation of cardiac output.

Burn injuries could be considered as four dimensional, as should the way we approach their management. Time of course is the fourth dimension, and improper management (particularly fluid resuscitation) in the first 24 h might result in a preventable increase in burn extent and depth. This is due to tissue in the zone of stasis joining the zone of necrosis as sluggish blood flow is not corrected (as per Jackson’s burn wound model).

### 4. The current consensus: there is no consensus

It’s actually not as bad as the title suggests. Despite the controversies and debates which will be outlined in due course, there is a reasonable degree of uniformity in the quality of burn care in modern society (if not necessarily the technique). Burn injuries which would previously have been fatal are now survivable with the timely administration of optimal care based on fundamental principles of resuscitation and surgical intervention. Such principles are well described by Cinat and Smith (in Achauer and Sood’s recent textbook), and reflect the dictum prescribed by the British Burn Association, and the Emergency Management of Severe Burns (EMSB) manual (published by the Australian and New Zealand Burns Association). A brief outline of EMSB teaching is presented, but such teachings do not wish practitioners to be automatons that dare not stray outside their limits. Patients after all do not respect limits.

Intravenous fluid resuscitation is currently advocated in adults with greater than 15% TBSA burn, and in children with 10% TBSA burn. Two large cannulae should be introduced, preferably through non-burned skin. Lactated Ringer’s (or Hartmann’s) solution is advised as the initial resuscitation fluid with volumes calculated using the Parkland formula.

**Volume in 1st 24 hours = 3–4mls/kg/%TBSA**

(half in 1st 8 h; half in the following 16 h).

It is important to remember that times are based on when the burn injury occurred, not time of presentation or initiation of resuscitation. It is also regularly stressed throughout the literature that formulae can only serve as an approximate guideline and clinicians should pay close attention to physiological parameters and resuscitation end-points, particularly urine output. As a minimum, an output of 0.5 ml/kg/h should be achieved in an adult, and 1 ml/kg/h in a child. Other parameters to be monitored include pulse, blood pressure, oxygen saturation and some or all of the following depending on the patient and burn characteristics:

1. arterial pH,
2. base deficit,
3. serum lactate,
4. central venous pressure,
5. pulmonary artery wedge pressure,
6. cardiac index,
7. mixed venous PO2.

In particular, central venous pressure measurement is recommended in elderly patients and those with significant comorbidity. A multinational study has noted that only about 12% of burns centres frequently use pulmonary artery catheter monitoring in patients with burns >30% TBSA, despite the data derived from such monitoring being of known value for direction of therapy. Indeed, wedge pressure calculation is felt to be more reliable than central venous pressure monitoring, and cardiac output calculation preferable to urinary output based resuscitation.

Certain patients and certain injuries sometimes merit more than the routine resuscitation volumes. In electrical (particularly high voltage) or crush injuries, rhabdomyolysis can lead to renal damage and necessitates essentially doubling the desired urinary output per hour. Urinary alkalisation and mannitol administration may also be considered in such cases. Greater volumes are also necessary in cases with associated inhalation injury, delayed resuscitation, associated trauma, patients on diuretics, and generally patients with very deep or diffuse burns. Burn shock is managed with boluses of fluid although there is a risk of fluid boluses increasing microvascular pressure which can increase fluid loss into the burned tissue. Inotropic support is advocated if perfusion is not maintained without excessive fluid. This is more likely in elderly patients, those with heart disease, and those on positive pressure ventilation. Dobutamine is often the first line agent.

The unique challenge of the burned child results from a limited physiological reserve, necessitating extra precision in resuscitation. Generally formal resuscitation begins at a lower TBSA than in the adult, with the need for maintenance fluids contributing to a relative increase in resuscitative requirements. Warden has noted the problems of over-resuscitation, and ‘saw-tooth resuscitation’ in children. These problems are felt to be partly due to non-burns specific formulae being used by ‘first responders’, including the generic resuscitation formula advocated by the Paediatric Advanced Life Support (PALS) teachings.

‘First responders’ include casualty departments and in those with relative inexperience in burns management, unfamiliarity with resuscitation formulae is often coupled with inaccuracy in burn size estimation. Collis, Smith and Fenton analysed the accuracy of burn size estimation and subsequent fluid resuscitation for more than 300 patients transferred to Yorkshire Regional Burns Unit over a 3 year period in the 1990s. The authors found that smaller burns were often overestimated by casualty departments, with a tendency to also underestimate large burns. On average, patients received 1.5 times the recommended fluid volume based on the
Casually TBSA estimation, rising to over twice the recommended volume following TBSA estimation in the burns unit. The problems of very junior staff rotating through casualty were acknowledged, and recommendations included continuing education, assessment of burns by senior staff, and increasing the profile of burns unit transfer and resuscitation policies. One of the roles of regional burns units must surely be to reach out to peripheral emergency departments to educate and distribute policies.

That is not to say that beyond the casualty department are all the answers. There is evidence that resuscitation within burns units can be suboptimal. Csontos recently addressed the concern that the Parkland formula (despite its popularity) underestimates the fluid requirements of the acute burn patient.78 The files of 47 patients with burns of at least 15% were analysed. In patients with low BMI or TBSA, the Parkland formula underestimated need, whereas with high BMI or TBSA, the Parkland formula was overgenerous. Holm in 2000 recognised a lack of evidence based medicine in our approach to burn shock resuscitation.

"Today, more than three decades after Baxter and Shires, we still do not know the answer to the basic questions: what kind of fluid to give, when to give it, and how much?"

Holm also found evidence of the Parkland formula substantially underestimating requirements, and felt that resuscitation based on invasive haemodynamic monitoring should be more routinely utilised (admittedly the invasive approach has shown limited survival benefit to date).61 Despite its apparent limitations, Parkland remains immensely popular. Baker and colleagues conducted a questionnaire study of the consistency of resuscitation practices in the United Kingdom and Ireland.87 Seventy eight percent of the responding units used the Parkland formula, with 11% favouring Muir and Barclay, and a further 11% using both. The popularity of the Parkland formula was reflected in a similar study in the USA.

5. Colloid versus crystalloid: an age-old debate

The old chestnut rumbles on. The fact that the answer to the crystalloid/colloid question continues to elude us suggests that there may never be a satisfactory answer presented. The issue was addressed in the latter (USA) study mentioned above.87 In three quarters of the units surveyed, Hartmann’s solution was the mainstay of resuscitation, with 12% preferring human albumin solution (HAS) (10% in paediatric units). One half of units did not routinely change the type of fluid at 24 h if intravenous resuscitation was continuing. The authors felt that the 1998 Cochrane Review (which linked albumin to a 6% increase in mortality) had a significant impact on resuscitation practices. However colloids have been found to reduce the risk of fluid overload complications including intra-abdominal hypertension.

The Cochrane Central Register of Controlled Trials argued a lack of evidence for albumin compared to cheaper alternatives, but most burn surgeons seem to agree that albumin supplementation is indicated for burn patients with very low albumin levels.8 Warden has remarked that “…it makes no more sense to use one particular fluid for all patients than it does to use one particular antibiotic for all infections”.6 The same author advises isotonic crystalloid for most burns under 40% TBSA without inhalational injury. Otherwise, hypertonic saline may be used for the first 8 h, followed by lactated Ringer’s. With massive burns, very young patients, or severe inhalation injury, three 8 h blocks are suggested, with hypertonic saline initially, followed by Ringer’s, and then 5% albumin.3

Perel and Roberts recently performed a Cochrane Review of studies comparing resuscitation with colloids and crystalloids in critically ill patients.60 Of 63 randomised controlled trials included, 55 contained mortality figures. In patients with shock following burns, trauma or surgery, there was no evidence that colloid administration reduced mortality figures compared to crystalloid. Since colloids are more expensive, the justification for their use was therefore questioned.

In a retrospective analysis by Cochran and colleagues from the University of Utah, patient characteristics and outcomes following albumin resuscitation were compared with a control group which did not receive albumin.21 Age, TBSA of burn and inhalation injury were related to increased mortality. Interestingly, when these factors were controlled, albumin resuscitation was associated with decreased mortality. In the control group an average of 6.4 ml/kg/%TBSA of crystalloid was used for resuscitation, amounting to 160% of a Parkland formula volume. It was proposed that the Parkland formula may be somewhat out of date, since resuscitation of very large burns is now common place, and clinicians are now more aggressive with analgesia and sedation, which might result in a greater demand for fluid. The authors described significant flaws in the 1998 Cochrane Review, including the inclusion of only three burn studies with only 163 patients in total, and variability in the justification for albumin in each study. A 2004 meta-analysis by Vincent, Navickis and Wilkes, which looked at 71 trials, showed decreased morbidity and mortality with albumin resuscitation (although the patients were critically ill from a variety of conditions, not solely burns).22 Cochran insists that the gold standard answer to the albumin question lies within a prospective randomised controlled trial.

Warden asserts that in patients with inhalation injuries, 50% TBSA or more, and at the extremes of age, a protein based component to resuscitation is essential. For very young children, major burns often lead to the rapid development of hypoproteinaemia, and in the other groups, protein is felt to reduce oedema formation and haemodynamic instability.5 Regarding the timing of colloid, Warden describes three principal schools of thought:

1. protein solutions should not be given in the first 24 h since they promote accumulation of oedema, particularly in the lungs;
2. proteins (albumin specifically) should be initiated with crystalloid at the commencement of resuscitation;
3. protein solutions should be commenced between 8 and 12 h post-burn, with crystalloid alone initially due to the massive fluid shifts at the most acute stage.
how often they should be repeated. Serum lactate is of known laboratory tests, particularly which tests are relevant and there is a dearth of studies indicating the utility of frequent inadequate, interventional options need to be considered. The precise limits of adequate resuscitation?

how often should it be measured and which levels represent benefit in monitoring critically ill patients including burns, but much of the important research into burn fluid pathophysiology. There is a growing consensus that we may have the fluid creep phenomenon, but consensus must also acknowledge that burn care is as good as it has ever been.

Research into issues such as capillary wall modulation is being undertaken by authors like Kumar. Kumar felt that ideal resuscitation is that which “utilizes minimal fluid for optimal resuscitation.” Any more fluid than that required for normovolaemia will increase tissue turgor and necrosis, increasing burn depth. Thus there is a very delicate balance whereby too much or too little fluid will adversely affect Jackson’s zone of stasis, leading to necrosis. This led Kumar to contemplate manipulation of capillary permeability. Such a strategy, if successful, may make the resuscitation balance a little less delicate, and the zone of stasis a little less sensitive. He admits the need for extensive research particularly into new drugs like aprotonin, a serine protease inhibitor, but suggests that simple medications like vitamin C may have therapeutic potential.

Warden has described four main areas of burn shock research in need of attention, finding some common ground with Kumar:

(1) the pathological course of capillary permeability changes, including the contributions of cellular and humoral factors;
(2) pharmacology which will significantly alter capillary leakage;
(3) how resuscitation fluid composition is related to changes in pulmonary function;
(4) the effect of resuscitation on late organ dysfunction.

As burn treatments evolve we see the development of advanced therapies such as plasma exchange. Plasma exchange is used in the Shriners Burns Hospital in Cincinnati for major burns refractory to conventional resuscitation volumes (typically patients needing twice the Parkland formula volume who have also converted to hypertonic saline). We also see less advanced therapies and innovations which can produce significant impacts in their own right. Malic has recently described a ‘resuscitation burn card,’ a single use, credit card sized aid for quickly calculating the percentage TBSA, with a surface area nomogram on one side, and a Lund and Browder chart with resuscitation formulae on the reverse. This seemed to improve the accuracy of burn size estimation by less experienced practitioners.

Holm believes there is no evidence to support delay of colloid administration after 8–12 h (when colloid extravasation into skin has been shown to stop), yet it tends to be withheld for 24 h. Early colloid administration actually seems to have a volume sparing pulmonary benefit. Kumar proposed that at the early stages of transfusion, large molecule proteins like globulin would be preferable to albumin, which leaks from the widened capillary pores. When capillary permeability returns to normal, albumin could be introduced to maintain normal protein proportions.

Dextran is a colloid available in several molecular sizes, including 40,000, 70,000 and 150,000 Da. It has been used in burn shock resuscitation, and the low molecular weight type can improve the flow of the microcirculation by reducing red blood cell aggregation. Dextran does however carry risks including allergic reactions and interference with blood typing. Fresh frozen plasma also has proponents (including Demling and Slater). It contains protein fractions exerting oncotic and non-oncotic actions, but it too is not without risk.

Although lactated Ringer’s remains the crystalloid of choice worldwide, the efficacy of hypertonic saline in burn shock has been known for years. It reduces the shift of intravascular water to the interstitium leading to decreased oedema and less purported need for escharotomies and intubations in major burns. The clinician needs to be wary and monitor serum sodium concentration regularly, since the level can breach 160 mEq/dl, and deaths have been reported due to hypernatraemia and serum hyperosmolarity. It contains protein fractions exerting oncotic and non-oncotic actions, but it too is not without risk.

What about hypertonic saline colloid to really muddy the water? In 1996 Guha and colleagues concluded that net volume loading could be significantly decreased (in sheep with large TBSA burns) using colloid, and even further using hypertonic saline colloid. The latter solution also reduced the incidence of hyponatremia.

6. The future: transcending the plateau

Holm noted that burn survival has not improved for over a decade, indicating our position on a modern treatment plateau. Perhaps our quality of care is almost as good as it gets, but certain areas of therapy are believed to hold potential for significant development. Not least of these is the topic of resuscitation monitoring. Early recourse to invasive monitoring has been associated with more aggressive resuscitation and decreased mortality. Suggestions for improved organ perfusion monitoring include gastric mucosal pH and regional PO2 monitoring which have shown success in other critically ill groups. The need for nationally (and preferably internationally) planned randomised controlled trials to address questions regarding invasive monitoring and organ perfusion end-point parameters is described as urgent. In addition there is a dearth of studies indicating the utility of frequent laboratory tests, particularly which tests are relevant and how often they should be repeated. Serum lactate is of known benefit in monitoring critically ill patients including burns, but how often should it be measured and which levels represent the precise limits of adequate resuscitation?

Of course if monitoring informs us that resuscitation is inadequate, interventional options need to be considered.
particularly over the colloid/crystalloid issue which seems to be in no danger of swift resolution. More importantly, the modern plateau has not sated our research needs, with many crucial questions still demanding attention. ‘Hot’ issues include the invasiveness of resuscitation monitoring, which laboratory tests are relevant and when, manipulation of inflammatory mediators and capillary wall integrity, and advanced therapies like plasma exchange.

Thus modern trends in fluid therapy for burns indicate positive and exciting directions. Viewed on an historical time-line starting with the first ever burned human many thousands of years ago, it is likely that the past century would merit much more than a passing nod. Credit must be given to the pioneers of burns research, and we hope that over the next few decades their successors will fulfil the promises within modern ideas, and transcend the plateau.

Conflict of interest
There are no conflicts of interest.

REFERENCES