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# Role of permissive hypotension, hypertonic resuscitation and the global increased permeability syndrome in patients with severe haemorrhage: adjuncts to damage control resuscitation to prevent intra-abdominal hypertension

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## Abstract

Secondary intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) are closely related to fluid resuscitation. IAH causes major deterioration of the cardiac function by affecting preload, contractility and afterload. The aim of this review is to discuss the different interactions between IAH, ACS and resuscitation, and to explore a new hypothesis with regard to damage control resuscitation, permissive hypotension and global increased permeability syndrome.

The recognition of the association between the development of ACS and resuscitation urged the need for new approach in traumatic shock management. Over a decade after wide spread application of damage control surgery damage control resuscitation was developed. DCR differs from previous resuscitation approaches by attempting an earlier and more aggressive correction of coagulopathy, as well as metabolic derangements like acidosis and hypothermia, often referred to as the 'deadly triad' or the 'bloody vicious cycle'. Permissive hypotension involves keeping the blood pressure low enough to avoid exacerbating uncontrolled haemorrhage while maintaining perfusion to vital end organs. The potential detrimental mechanisms of early, aggressive crystalloid resuscitation have been described. Limitation of fluid intake by using colloids, hypertonic saline (HTS) or hyperoncotic albumin solutions have been associated with favourable effects. HTS allows not only for rapid restoration of circulating intravascular volume with less administered fluid, but also attenuates post-injury oedema at the microcirculatory level and may improve microvascular perfusion. Capillary leak represents the maladaptive, often excessive, and undesirable loss of fluid and electrolytes with or without protein into the interstitium that generates oedema. The global increased permeability syndrome (GIPS) has been articulated in patients with persistent systemic inflammation failing to curtail transcapillary albumin leakage and resulting in increasingly positive net fluid balances. GIPS may represent a third hit after the initial insult and the ischaemia reperfusion injury. Novel markers like the capillary leak index, extravascular lung water and pulmonary permeability index may help the clinician in guiding appropriate fluid management.

Capillary leak is an inflammatory condition with diverse triggers that results from a common pathway that includes ischaemia-reperfusion, toxic oxygen metabolite generation, cell wall and enzyme injury leading to a loss of capillary endothelial barrier function. Fluid overload should be avoided in this setting.

**Key words:** damage control, damage control resuscitation, coagulopathy, component transfusion therapy, abdominal hypertension, capillary leak, global increased permeability syndrome, abdominal compartment syndrome, fluids, crystalloids, colloids, hypertonic

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Haemorrhage accounts for 30–40% of trauma fatalities and is the leading cause of preventable death in trauma [1]. Originally coined by the US Navy in reference to techniques for salvaging a ship which had sustained serious damage [2], the term 'damage control' has been adapted to truncating initial surgical procedures on severely injured patients in order to provide only interventions necessary to control haemorrhage and contamination in order to focus on re-establishing a survivable physiologic state. These temporised patients would then undergo continued resuscitation and aggressive correction of their coagulopathy, hypothermia, and acidosis in the intensive care unit before returning to the operating room for the definitive repair of their injuries. This approach has been shown to lead to better-than-expected survival rates for those with severe near-exsanguinating abdominal trauma [3–9], and its application has been extended to include thoracic surgery [10] and early fracture care [3–7, 11].

Discussions of damage control surgery usually centre on the type and timing of surgical procedures. Damage control surgery helped to save the most critically injured/shocked trauma patients. These early survivors frequently developed the lethal abdominal compartment syndrome within hours of ICU admission. Prospective observational studies identified the association between ACS and traumatic shock resuscitation. The suggestion was to minimize the amount of crystalloid infusions and administer early fresh frozen plasma balanced with the transfused red blood cell volumes. Recently, the methods of resuscitation of patients with near-exsanguinating haemorrhage have come under increasing scrutiny assessing their ability to adequately correct the acidosis, hypothermia, and coagulopathy identified in these patients [8, 9]. Damage Control Resuscitation (DCR) driven by ACS research followed the widespread application of damage control surgery after 10 years. DCR differs from previous resuscitation approaches by attempting an earlier and more aggressive correction of coagulopathy as well as metabolic derangements. The concept centres around the assumption that coagulopathy is present very early after injury, and earlier interventions to correct it in the most severely injured patients will lead to improved outcomes. DCR embraces several key concepts, including but not limited to permissive hypotension, the early and rapid delivery of component transfusion therapy instead of isotonic fluid for plasma volume expansion, that supports early correction of coagulopathy [12]. This resuscitation strategy begins in the emergency room, and continues through the operating room and into the intensive care unit.

Understanding the physiologic sequelae of near-exsanguinating haemorrhage and the complex interaction of hypothermia, acidosis, and coagulopathy is central to an appreciation of the potential benefits of DCR [13]. Additionally, as with any new therapy, there exists some controversy with regard to its efficacy, impact on outcomes, and the underpinning scientific evidence.

This narrative review will examine the basis of permissive hypotension and limited crystalloid resuscitation in patients managed with DCR, and explore the resuscitation-related risk factors for developing intra-abdominal hypertension (IAH) and the abdominal compartment syndrome (ACS), like the global increased permeability syndrome (GIPS).

## PERMISSIVE HYPOTENSION

The concept behind permissive hypotension involves keeping the blood pressure low enough to avoid exacerbating uncontrolled haemorrhage while maintaining perfusion to vital end organs, in particular the heart and brain. While hypotensive resuscitation is integrating into DCR, the practice itself is not new. Walter B. Cannon and John Fraser remarked on the potentially beneficial effect of permissive hypotension on both blood volume and outcome as early as 1918 when serving with the Harvard Medical Unit in France during World War I. They made the following observations on patients undergoing fluid resuscitation: "*Injection of a fluid that will increase blood pressure has dangers in itself. Haemorrhage in a case of shock may not have occurred to a marked degree because blood pressure has been too low and the flow too scant to overcome the obstacle offered by the clot. If the pressure is raised before the surgeon is ready to check any bleeding that may take place, blood that is sorely needed may be lost*" [14]. Dr. Cannon's endpoint of resuscitation prior to definitive haemorrhage control was a systolic pressure of 70–80 mm Hg, using a crystalloid/colloid mixture as the resuscitation fluid of choice – a paradigm that clearly serves as the forerunner of current practice.

In World War II, H.K. Beecher and colleagues promulgated Cannon's hypotensive resuscitation principles in the care of casualties with truncal injuries, opting for a systolic pressure of 85 mm Hg prior to definitive haemorrhage control. "*When the patient must wait for a considerable period, elevation of his systolic blood pressure to about 85 mmHg is all that is necessary….and when profuse internal bleeding is occurring, it is wasteful of time and blood to attempt to get a patient's blood pressure up to normal. One should consider himself lucky if a systolic pressure of 80-85 mmHg can be achieved and then surgery undertaken*"[15].

While these anecdotal reports from earlier generations of surgeons are interesting, more scientific attempts to examine outcomes for permissive hypotension after serious injury have been mixed. The best known study displaying a benefit for delayed aggressive fluid resuscitation (after operative intervention with surgical haemostasis) was published in 1994 by Bickell et al. [16]. This randomised controlled trial of patients with penetrating truncal injuries compared mortality rates of patients who received immediate versus delayed administration of intravenous fluids, and discovered improved survival, fewer complications, and shorter hospital stays in the delayed resuscitation group. They demonstrated that, regardless of the victim's blood pressure, survival was better in their urban 'scoop and run' rapid transport system when no attempt at pre-hospital resuscitation was made [16]. The same group published a follow up abstract in 1995, which was a subgroup analysis of the previous study, dividing patients into groups by their injury type. This study demonstrated a lack of effect on survival, in most groups, for patients treated with delayed fluid resuscitation, with a survival advantage only for patients with penetrating injuries to the heart ($P = 0.046$) [17]. This called into question whether Bickell's study was generalisable to the trauma population at large. Four years later, Burris et al. also suggested that patients could benefit in the short term by resuscitating to a lower blood pressure [18]. Other studies attempting to replicate these results were unable to find a difference in survival [19, 20]. Furthermore, the generalisability of results obtained in those with penetrating injury to those with blunt trauma remains unclear.

In 2006, Hirshberg et al. utilised computer modelling to demonstrate that the timing of resuscitation has different effects on bleeding, with an early bolus delaying haemostasis and increasing blood loss, and a late bolus triggering rebleeding [21]. Animal models exploring the effect of fluid administration on re-bleeding have been equally contradictory, with some demonstrating that limiting fluids reduces haemorrhage [22], while others demonstrate that fluids do not increase bleeding [23]. Moreover, the limited use of fluids during resuscitation efforts is in direct opposition to guidelines put forth by the American College of Surgeons Committee on Trauma Advanced Trauma Life Support protocol [24].

Relatedly, several other important questions regarding the utility and appropriateness of permissive hypotension in diverse settings including blunt injury, multicavity injury, the elderly or those with baseline hypertension remain to be explored. Issues including identifying a lower systolic or mean pressure safety limit as well as a time limit similarly remain unanswered. Importantly, hypotension has been shown to be detrimental in those with severe traumatic brain injury; failing to restore euvolemia can accentuate the injury by decreasing the cerebral perfusion pressure and cerebral oxygen delivery to injured regions that have acutely lost autoregulatory capability [25, 26].

Unfortunately, no professional society-supported evidence-based recommendations exist with regard to permissive hypotension. In their absence, the findings from historical military medical sources, modern urban transport studies, and recent laboratory animal models suggest that trauma patients without definitive haemorrhage control should have a limited rise in blood pressure until definitive surgical control of bleeding can be achieved. In deciding to pursue permissive hypotension prior to definitive control, the clinician must weigh the potential benefits of reduced haemorrhage against the detrimental downstream effects of prolonged ischaemia and subsequent oxygenated reperfusion injury. Until more detailed studies have been conducted, firm guidelines cannot be articulated and additional studies are warranted to identify the ideal target patient population to benefit from permissive hypotension.

## ISOTONIC CRYSTALLOIDS

Resuscitation denotes in large part medical therapy aimed at restoring lost fluid volume, and principally hinges on isotonic crystalloid solutions. Globally, 0.9% normal saline solution (NSS) predominates as the crystalloid fluid used for resuscitation when one includes both medical and surgical patients. While isotonic crystalloids solutions are ideal for those who have significant free water and lesser amounts of electrolyte losses, their role in the resuscitation of those with near-exsanguinating haemorrhage has come under intense scrutiny. Observations that include anasarca, IAH, ACS, diplopia, abdominal pain, and the sequelae of open abdomen management including enteroatmospheric fistulae, multiple readmissions, multiple reoperations and a prolonged reduced quality of life have fuelled a reappraisal of the role of crystalloid in massive haemorrhage resuscitation [27]. Its place as the mainstay of initial therapy for the patient in haemorrhagic shock is predicated on the early work of Carrico and Shires, which rests upon observations of fluid and salt shifts in the intracellular and extracellular spaces with resuscitation after haemorrhagic shock [28, 29]. An important additional consideration is the ischaemic cellular milieu that is established during haemorrhage and prior to resuscitation.

Oxygenated reperfusion of previously ischaemic beds generates toxic oxygen metabolites including but not limited to singlet oxygen, hypochlorous acid, tauric acid, superoxide, and peroxide leading to intracellular injury and lipid peroxidation [30]. This is worsened by the activation of inflammatory cells and the burst of inflammatory mediators, including cytotoxic compounds produced by activated neutrophils, which are in abundance in tissues highly susceptible to injury such as the lung, liver, and the gastrointestinal tract; both reperfusion and metabolic acidosis serve as potent triggers of these cascades. The clinical expression of these inflammatory sequelae is identified as systemic inflammatory response syndrome (SIRS), acute lung injury (ALI), Acute Respiratory Distress Syndrome (ARDS), and ultimately multiple system organ failure (MSOF).

It is important to point out that since this process has already commenced when the trauma patient arrives in shock, any intervention that improves tissue perfusion (reverse shock) will produce some degree of tissue injury. One may then evaluate resuscitation fluid options partly on the basis of minimising reperfusion injury instead of solely on the basis of the efficacy of restoration of mean arterial pressure and similar endpoints of resuscitation. Little data exists with regard to reperfusion injury mitigation on the basis of fluid selection and this offers a potential venue for future research. Multiple studies have identified that different fluids will create different effects on acid-base balance as well as unmeasured ions, the presence of which seems to correlate well with early mortality after both penetrating and blunt injury [27, 31, 32].

Also of note, recent reports have described potential mechanisms for the detrimental effects of early, aggressive crystalloid resuscitation, as crystalloids have been found to have profound systemic and cellular complications [33]. Rhee has demonstrated that isotonic resuscitation can elicit severe immune activation and up-regulation of cellular injury markers and worsen the acidosis and coagulopathy of trauma [34]. These actions may in turn lead to an increased likelihood of developing the ARDS, SIRS, and MSOF [22]. Although not specific for trauma and conducted in the post-resuscitative period, the Fluid and Catheter Treatment Trial (FACTT) by the ARDSNet group demonstrated significantly fewer ventilator days in a group of critically ill patients that received less crystalloid [35].

One of the prime mechanisms by which crystalloids can contribute to poor outcome in severe trauma is the exacerbation of the components of the 'death triad' or 'bloody vicious cycle' of acidosis, hypothermia, and coagulopathy [36]. Crystalloids can cause a dilutional coagulopathy, and they do little for the oxygen carrying capacity needed to correct anaerobic metabolism and the oxygen debt associated with shock, although there is some controversy here given that some people do not believe that there is an oxygen debt to be repaid. The use of un-warmed fluids can also be implicated as a major cause for hypothermia. Also, because of its supra-physiologic concentration of chloride, crystalloids have been associated with hyperchloremic acidosis and the worsening of trauma patients' existing acidosis [37].

As a result of the pathologic changes associated with injury, capillary permeability increases, causing a loss of colloid oncotic pressure and a net egress of fluid to the interstitial and intracellular spaces [33]. Isotonic, hypotonic, and small molecular weight colloid solutions (including albumin) given post-injury have been shown to leak across the capillary bed causing oedema, with only a fraction remaining within the intravascular system.

These induced fluid shifts are magnified by conventional fluid resuscitation protocols and may create untoward effects in injured organs by initiating or exacerbating visceral oedema. In the lungs, fluid extravasation and increased permeability of the pulmonary capillaries can lead to pulmonary oedema, high peak and plateau pressures, hypercarbia and hypoxemia [38]. In the GI (gastro instetinal) tract, splanchnic oedema can increase intra-abdominal pressure and cause a decrease in tissue oxygenation, increased gut susceptibility to infection, and impaired wound healing [39]. Figure 1 illustrates the vicious cycle of fluid loading. In the most extreme case, increased GI fluid sequestration can lead to the abdominal compartment syndrome, a not uncommon complication of large volume crystalloid resuscitation in critically-ill and injured patients [40] (Fig. 2). In addition to changes due to interstitial leakage of fluid and resultant tissue swelling, excessive administration of fluids can also cause imbalances at the cellular level, causing cellular swelling with resultant dilution of intracellular proteins and dysfunction of protein kinases ultimately leading to impaired metabolism in multiple cell lines, including hepatocytes, pancreatic islet cells, and cardiac myocytes [33]. Clearly, options other than isotonic crystalloids should be explored to mitigate against induced hyperchloremic acidosis, capillary leak and the undesirable effects of oedema in key organ systems [32].

## COLLOIDS

The year 2012 was significant in evidence based medicine in relation to closing the colloid *vs* crystalloid fluid debate that had been going on for decades [41]. But is this really the case? The publication of the **CHRYSTMAS study**, comparing the use of hydroxyethyl starch (HES 130/0.4 waxy maize) *vs* saline in 196 patients with septic shock was the start of a series of multicentre studies on fluid management in the critically ill [42]. While the CHRYSTMAS trial showed that less fluid was needed in the HES group (1,370 ± 886 vs 1,709 ± 1,164 mL; $P = 0.02$) to reach haemodynamic stability, no differences were found in mean and cumulative fluid balance over the first four days, nor in renal and coagulation side effects. This was followed by the **6S trial**, a prospective state-of-the-art study comparing balanced HES (130/0.42 potato) vs Ringer's acetate solution in 798 patients with severe sepsis [43]. Albeit no differences in median trial fluid volumes (3,000 mL in both arms) were observed, the HES treated patients were more likely to die at day 90 and to require RRT. This study was carefully designed, avoiding HES overdosage, using balanced solutions in both arms, with broad inclusion criteria and many patients exhibiting shock. However, no data was provided on haemodynamic monitoring or whether fluids were guided in a protocolised way. The **CHEST study** concluded the series of big trials including 7,000 general ICU patients

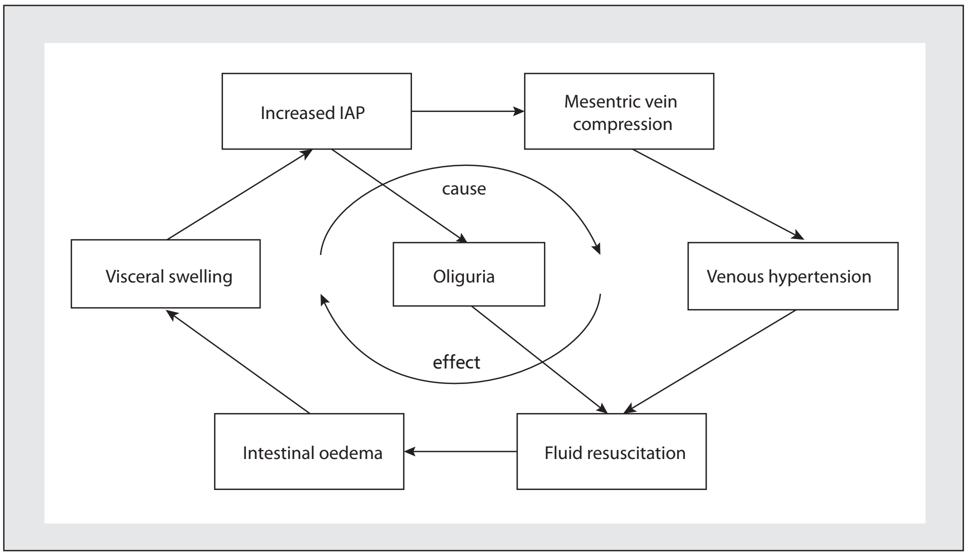


**Figure 1.** Vicious cycle of fluid loading leading to intra-abdominal hypertension and abdominal compartment syndrome; IAP — intra-abdominal pressure

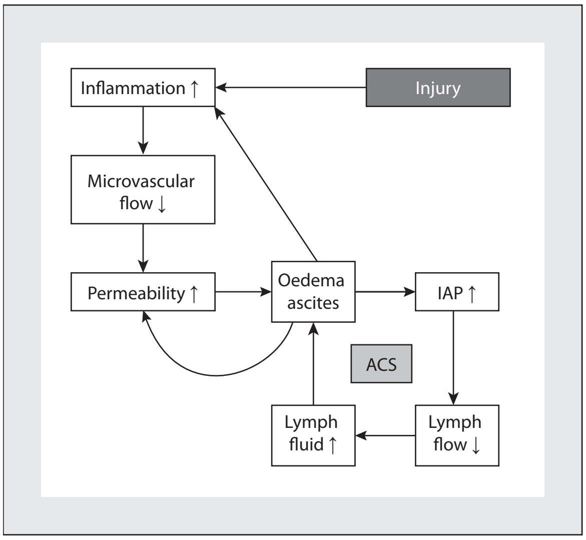


**Figure 2.** Pathophysiology of abdominal compartment syndrome ACS — abdominal compartment syndrome; IAP — intra-abdominal pressure

randomised to either HES 130/0.4 vs saline [44]. After the first four days, the average amount of study fluids per day was 526 ± 425 mL (HES) vs 616 ± 488 mL (NaCl) ($P < 0.001$), while the amount of non-study fluids was 851 ± 675 mL (HES) vs 1,115 ± 993 mL (NaCl) ($P < 0.001$), resulting in a net fluid balance of 921 ± 1,069 mL (HES) vs 982 ± 1,161 mL (NaCl) ($P = 0.03$). Afterwards, the results of the **CRISTAL study** became available showing that colloids – when given in patients with hypovolaemic shock — are lifesaving (significant reduction in 90-day mortality) [45]. In light of this evidence, it is unclear how to take it from here and what to do about common sense. The majority of physicians are aware of the current knowledge of the risk-benefit assessment of HES, but how do they take this into account at the bedside? What follows is a practical guide in different patient populations [46]. In (abdominal) sepsis, starches should no longer be used, normal saline is to be avoided, and as an alternative balanced crystalloids form the first choice, while hypertonic albumin may have a role in de-resuscitation. In general ICU patients, HES can be used only for a short time after onset of shock and its use is limited to acute volume resuscitation (< 24h) for haemodynamic instability in case of hypovolaemia and complying with maximum dose [47]. One needs to use reliable algorithms of fluid responsiveness and predefined haemodynamic endpoints. HES should not be used in acute or chronic renal failure or oliguria not responsive to fluids (6h), and the best alternative is a balanced crystalloid. In postoperative hypovolaemic patients, there may still be a place for HES taking into account the considerations listed above and saline should preferably not be used [48].

So, in conclusion, common sense must prevail and fluids should be treated just as any other drug, with indications and contra-indications and possible adverse effects [49]; fluid requirements change over time; the approach should be targeted and protocol driven; isotonic balanced salt solutions are a pragmatic initial resuscitation fluid in the majority of acutely ill patients; and, last but not least, fluid overload must be avoided at all costs [50].

## HYPERTONIC SALINE

One potential fluid for use in limited volume resuscitation that could be used instead of HES is hypertonic saline (HTS) [51]. The ability of HTS to raise blood pressure at much lower infusion volumes than isotonic fluids is relevant to combat, in that soldiers can bear less fluid-related weight and subsequently more ammunition or other supplies. Also, resupply of combat medics would be more efficient by allowing the medic to carry more equivalent doses at a similar weight.

HTS presumably acts to expand intravascular volume by increasing serum osmolarity, inducing a fluid shift across cell membranes into the extracellular and then intravascular space along a sodium driven concentration gradient. Work by Mazzoni et al. showed that HTS resuscitation reversed the capillary endothelial swelling that occurs early after hypotensive shock, and thus not only improved systemic haemodynamics, but improved microcirculatory blood flow that was not amenable to conventionally driven isotonic fluid resuscitation [52].

Hypertonic saline has also been shown to have profound immunomodulatory properties. Animal studies have been carried out which demonstrate the beneficial effects of HTS on attenuating the markers of injury and inflammation in both the lungs and the gut [53, 54]. Human studies by Rizoli et al. and Bulger et al., among others, have corroborated these findings. Rizoli found that in haemorrhaged trauma patients, administration of hypertonic saline resulted in decreased neutrophil activation, reduced serum TNF-α levels, increased levels of the anti-inflammatory cytokines IL-1ra and IL-10, and attenuation of the shock-induced norepinephrine surge. Moreover, they also found that these effects lasted for over 24 hours, long after the transient rise in serum osmolarity had normalised [55]. Bulger also found immune-modulation in HTS-administered trauma patients, which supported preclinical studies by Rizoli and Rotstein demonstrating that the anti-inflammatory effects were due to a transient inhibition of neutrophil CD11b expression [56–58].

In summary, HTS simultaneously allows for rapid restoration of circulating intravascular volume with less administered fluid and attenuates the post-injury oedema at the microcirculatory level and may improve microvascular perfusion but is not associated with an outcome advantage when used to restore systemic flow. Different effects, however, are noted when HTS is used as an adjunct to cerebral perfusion pressure management in those with traumatic brain injury and intracranial hypertension.

## *HTS IN TRAUMATIC BRAIN INJURIES (TBI)*

Given the prevalence of head injury in the trauma population, and the fact that it so often accounts for post-injury mortality (40–60% of post-injury mortality) [58], it is appropriate to explore whether resuscitation strategies can impact upon the high mortality rate. Several studies have found HTS to be a safe option in brain-injured trauma patients. Shackford et al. [59] noted that HTS was associated with a favourable fluid balance and control of intracranial pressure. Simma et al. [60] also found HTS advantageous in the treatment of head-injured children and reported improved outcomes including fewer interventions necessary to keep ICP ≤ 15 mm Hg, shorter ICU length of stay, and fewer days of mechanical ventilation compared to their standard approach. Furthermore, they also noted umbrella effect benefits including a reduced incidence of ARDS, pneumonia, sepsis and arrhythmias. The presumed benefits of HTS including preserved microvascular flow, decreased tissue oedema, and attenuated inflammatory response, may be particularly useful in brain-injured patients where cerebral oedema and intracranial hypertension lead to deleterious outcomes when aggressive fluid resuscitation is needed to maintain global haemodynamics [61]. More recently, several studies have compared HTS to mannitol for the control of intracranial hypertension, noting improved control with HTS [62]. Whether improved clinical outcome will accrue as a result of such practice remains unclear, but it is intuitively attractive to consider that HTS may present advantages in that it serves as a volume expander while mannitol results in systemic volume loss. Dehydration may not be ideal in those with more than isolated brain injury.

## *HTS IN CLINICAL PRACTICE*

Several studies have been carried out to determine the safety and efficacy of hyperosmotic solution in trauma resuscitations. Mattox et al. [63] was the first in the USA to conduct a multicentre trial to compare hypertonic saline with dextran (HSD) to standard resuscitation. Their study demonstrated that HSD was safe, with lower incidence of ARDS, renal failure, and coagulopathy, but was not able to demonstrate a difference in overall survival due to insufficient sample size [63]. In 1997, Wade et al. [64, 65] conducted a meta-analysis of controlled clinical studies which showed an increased survival of HSD over 0.9% NSS in 7/8 clinical trials [64, 65]. Although there are many benefits to be derived from HSD in trauma resuscitations, there are also certainly many risks and concerns associated with this type of treatment. A review by Dubick et al. [66] in 2005 highlighted several of the undesirable side effects noted with HSD. The first of these is the risk of uncontrolled bleeding, which can be seen with administration of any fluid that raises intravascular pressure. Hyperchloremic acidosis is seen in patients administered HTS due to its supraphysiologic concentration of chloride. Cellular dehydration is another concern involved with administering hypertonic fluids, especially in trauma patients. Neurological deficit from transient hypernatremia, specifically central pontine myelinolysis (CPM), is a theoretical risk which has not been borne out in human trials. There is currently no evidence in the literature of the CPM seen in the rapid correction of hyponatremia in the setting of hypertonic saline administration [67]. CPM has not been reported in human trials using HTS for TBI. As such, most sources suggest keeping the serum sodium below 155 mEq $L^{-1}$ and not raising it beyond 10 mEq $day^{-1}$. Lastly, the use of HSD in repeated doses has been examined and, again, the evidence suggests a great deal of tolerance based mainly on animal studies. The authors concluded that HSD administration, while not without some expected negative consequences, poses a minimal risk compared to other available treatment modalities [66]. Therefore, given the weight of favourable data, of which only a portion has been described here, the use of hypertonic saline as a potential tool in the resuscitation of severely traumatised individuals should be further explored, especially in settings where capillary leak presents difficulties in maintaining plasma volume [68].

## CAPILLARY LEAK

Capillary leak represents the maladaptive, often excessive, and undesirable loss of fluid and electrolytes with or without protein into the interstitium that generates oedema [68–70]. Recall that there are several discrete compartments into which fluid, electrolytes and protein are partitioned, including intravascular extracellular, intravascular intracellular (small), extravascular intracellular (large), and extravascular extracellular (vast). The insterstitium consists of a collagen matrix that is laced with proteoglycan filaments and a variety of enzymes including matrix metalloproteinases (the glycocalyx) [71]. This space functionally behaves as gel that allows molecule transit by diffusion, but tends to inhibit the free flow of fluids based on maintenance of colloid oncotic pressure equilibrium between the vascular and extravascular compartments. However, under normal physiologic conditions, some water and electrolytes are driven across the capillary bed into the interstitium [72]. Two other terms are useful in understanding capillary dynamics — filtration and reflection coefficient.

The filtration coefficient is defined by the inherent properties of the capillary surface. A high value indicates a highly water permeable capillary, while a low value indicates the converse; capillary injury generally increases the filtration coefficient. The filtration coefficient is the product of two components: capillary surface area and the permeability of the capillary wall to water. The permeability factor is often expressed as the 'hydraulic conductivity' of the capillary wall. The reflection coefficient may be considered as a correction factor. It describes the permeability of the capillary in terms of the percentage of potentially transmitted particles that are reflected off the capillary endothelium.

It is evident that, in normal circumstances, water and solute is driven across the arteriolar side of the capillary bed into the interstitium and then reclaimed across the wall on the venular side of the capillary bed [73]. This process may be readily understood on the basis of Starling forces. Fluid movement due to filtration across the capillary wall is dependent on the balance between the hydrostatic and oncotic pressure gradients across the capillary and are described by $\pi_c$ and $\pi_i$, the respective pressures within the capillary and the interstitial spaces driving water and solute movement. This pressure is developed by the number of oncotically active particles (principally proteins) unable to pass across the capillary wall which functions as a semi-permeable membrane separating these two compartments. Additionally, some fluid and small proteins including albumin are reclaimed by interstitial lymphatic transport instead of directly re-entering the vascular space [74]. Increases in interstitial water and solute volume occur when the normal balance of Starling forces is perturbed. Such perturbations fall into two main categories: 1) increases in the hydrostatic gradient, and 2) decreases in the oncotic gradient between the capillary and the interstitial space.

## EFFECTS OF VOLUME EXPANSION

In the critically ill, both increases in hydrostatic pressure and decreases in vascular colloid oncotic pressure occur with plasma volume expansion, acute hypoproteinemia secondary to dilution, as well as pre-existing or acquired severe protein-calorie malnutrition [69]. These oedema-promoting effects are exacerbated by capillary leak associated with inflammation or infection under the influence of a cascade of cytokines including but not limited to IL-1, IL-2, IL-4, IL-6, IL-10, TNF-α, and TGF-α. Capillary leak occurs when the tight junctions between capillary endothelial cells are loosened resulting in functional pores along the capillary bed. These pores are estimated to be approximately 7 nm in size; the three-dimensional structure of 60 kDa albumin spans a radius of approximately 5 nm. Thus, water, electrolytes, and protein may readily flow from the vascular to the interstitial space.

Regardless of the inciting incident, there is a common pathway that results in capillary leak. A common theme is hypoperfusion followed by oxygenated reperfusion of previously poorly perfused tissue beds (i.e. reperfusion injury). Shock regardless of cause is emblematic of this maladaptive process involving toxic oxygen metabolites including singlet oxygen, peroxynitrile, hypochlorous acid, superoxide, and hydrogen peroxide. Once shock is established, sympathetically driven vasoconstriction shunts blood away from the periphery and less essential systems (skin, muscles, kidney, etc.) to preferentially perfuse the heart and brain. This flow redistribution leads to tissue hypoperfusion of peripheral and less essential tissue beds. If unchecked, cellular dysoxia leads to cellular hypoxia and eventually cell death.

However, this process is typically interrupted, at least in part, by fluid resuscitation. Plasma volume expansion of the stressed volume seeks to restore both macro-circulatory and microcirculatory flow [75]. As flow returns to previously hypoperfused tissues, it does so in conjunction with oxygen – concomitantly both critical for cellular respiration and injurious to vulnerable tissue beds. Macrophages, monocytes, mast cells, platelets, and endothelial cells produce a multitude of cytokines. At the forefront of this process are TNF-α and IL-1, which initiate several cascades. They are proinflammatory, they directly or indirectly activate coagulation, complement, trigger nitric oxide synthesis and release, activate platelet-activating factor, and modulate biosynthesis of prostaglandins and leukotrienes. All of these activities alter pre-capillary arteriolar tone and, therefore, tissue perfusion. Protein complements C3a and C5a are believed to contribute directly to the release of additional cytokines and to cause vasodilatation and increasing vascular permeability. Certain prostaglandins, leukotrienes and endothelin gene products incite endothelial damage, leading to capillary leak.

Recruitment of neutrophils under the influence of the tissue hypoperfusion creates a bed that is primed for the delivery of oxygen to lead to the generation of toxic oxygen metabolites as mentioned earlier. These inflammatory moieties directly damage lipid membranes as well as interstitial enzyme complexes including matrix metalloproteinases. The lipid and enzyme destruction further destabilises the normal barrier between the vascular and interstitial compartments. At the same time, release of heparan sulfate occurs, indicating ongoing capillary endothelial injury, probably under the influence of oxidative damage. It is important to recall that some cells will undergo apoptotic death regardless of intervention; the remainder of the cells in a dysoxic bed will either survive or die, based on a balance between the salutary and deleterious effects of resuscitation. The cumulative effect is to promote capillary leak through a capillary endothelium bereft of its integrity. These effects directly relate to the efficiency of resuscitation based on the fluid selected for plasma volume expansion.

During conditions of capillary leak, plasma volume expansion with crystalloid solutions further aggravates extravascular fluid accumulation as the vascular oncotic pressure is further decreased secondary to dilution. Recall that in health, only 25% of a normotonic crystalloid infusion remains in the vascular space; 75% readily diffuses into the interstitial space. Clearly, in conditions of capillary leak, even less of a crystalloid plasma volume expansion bolus effectively supports circulating volume. Besides creating peripheral oedema, visceral organ oedema and ascites is readily promoted across the permeable peritoneal space; pleural effusion is the counterpart sequel within the thorax. The clinician detects these untoward consequences as peripheral oedema, IAH, and, if unrelieved, the ACS (Fig. 2).

Aggressive fluid resuscitation as espoused by the Early Goal Directed Therapy (EGDT) paradigm may exacerbate the issue of capillary leak syndrome and its relationship to IAH and ACS [76]. Since EGDT promotes rapid resuscitation, and the majority of the fluid utilised in the protocol was crystalloid, rapid ascites formation and an increase in secondary IAH and ACS should be anticipated. Indeed, secondary IAH and ACS are increasingly identified in conjunction with medical diseases such as pneumonia when the patient has presented to the ED in septic shock and been treated with significant plasma volume expansion [77]. Increased awareness of these sequelae of resuscitation in the medical critical care community will no doubt increase the recognition of IAH and ACS (Table 1). Pressure-volume dysregulation within the abdominal compartment may help to explain the role of the intestine in patients undergoing massive resuscitation who ultimately develop multiple organ failure.

**Table 1.** Risk factors for the development of IAH and ACS

| Related to capillary leak and fluid resuscitation |
| --- |
| Acidosis* (pH below 7.2) |
| Hypothermia* (core temperature below 33°C) |
| Coagulopathy* (platelet count below 50 G $L^{-1}$ OR an activated partial thromboplastin time (APTT) more than two times normal OR a prothrombin time (PTT) below 50% OR an international standardised ratio (INR) more than 1.5) |
| Polytransfusion/trauma (> 10 units of packed red cells/24 hours) |
| Sepsis (as defined by the American – European Consensus Conference definitions) |
| Severe sepsis or bacteremia |
| Septic shock |
| Massive fluid resuscitation (> 3 L of colloid or > 10 L of crystalloid/24 hours with capillary leak and positive fluid balance) |
| Major burns |

*The combination of acidosis, hypothermia and coagulopathy is termed the 'deadly triad' after injury

## GLOBAL INCREASED PERMEABILITY SYNDROME

Patients with critical illness of injury generally evidence grossly positive fluid balance as a reflection of resuscitative efforts. However, since there is little efficiency to crystalloid resuscitation as noted earlier, fluid balance may be considered a biomarker of critical illness, as proposed by Bagshaw et al. [78]. Indeed, one may clearly link a net fluid burden with distant organ dysfunction (Fig. 3).

In general, patients who are successfully resuscitated from shock attain homeostasis of proinflammatory and anti-inflammatory mediators within three days [50]. Subsequent haemodynamic stabilisation and restoration of plasma oncotic pressure allows diuresis and mobilisation of extravascular fluid resulting in negative fluid balances. Conservative late fluid management (CLFM) with two consecutive days of negative fluid balance is a strong and

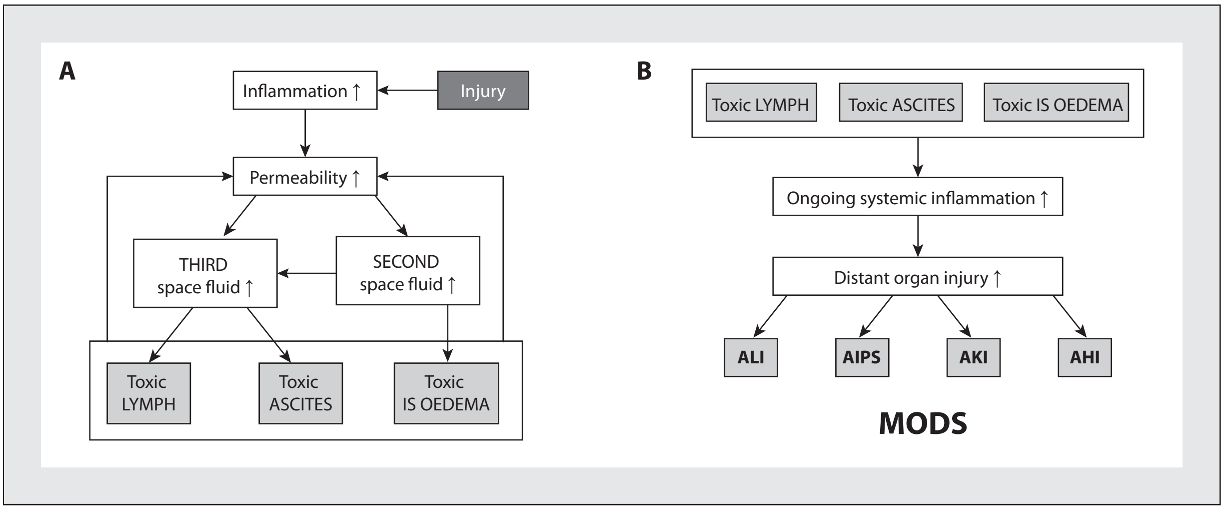


**Figure 3.** Pathophysiology of multiple organ dysfunction syndrome (MODS). **A** — inflammation leading to accumulation of multicompartment fluids; **B** — fluid accumulation leading to MODS; ALI — acute lung injury; AIPS — acute intestinal permeability syndrome; AKI — acute kidney injury; AHI — acute hepatic injury; MODS — multiple organ dysfunction syndrome; IS — interstitial

independent predictor of survival [71, 79, 80]. Presumably, homeostasis of cytokines the third day after shock onset allows initiation of healing the microcirculatory disruptions and 'closure' of capillary leakage. This interpretation is supported by observations demonstrating normalisation of microcirculatory blood flow on day 3 in patients with abdominal sepsis. Lower extravascular lung water (EVLWI) and pulmonary vascular permeability indices at day 3 of shock have been shown to correlate with better survival [81].

In contrast, patients with persistent systemic inflammation fail to curtail transcapillary albumin leakage and accrue increasingly positive net fluid balances. In this latter patient population, the global increased permeability syndrome (GIPS) has been articulated and is characterised by a high capillary leak index (CLI, C-Reactive Protein over albumin ratio), excess interstitial fluid and persistently elevated extravascular lung water (EVLWI), and progressive organ failure [50]. GIPS represents a mechanistic explanation for MODS following acute injury [82] (Fig. 4). As a result of capillary leakage and impaired flow phase, overzealous administration of fluids in patients with GIPS will lead to gross fluid overload and anasarca. Interstitial oedema raises the pressure in all four major body compartments: head, chest, abdomen, and extremities. As a result, trans-organ flow gradients decrease as venous resistance increases, contributing to the progression of organ failure. As different compartments interact and reciprocally transmit compartment pressures, the concept of polycompartment syndrome has been advanced [83–85].

The abdomen plays a central role in GIPS and polycompartment syndrome as positive fluid balances are a known risk factor for secondary IAH which in turn is associated with untoward remote organ effects [86]. Renal function

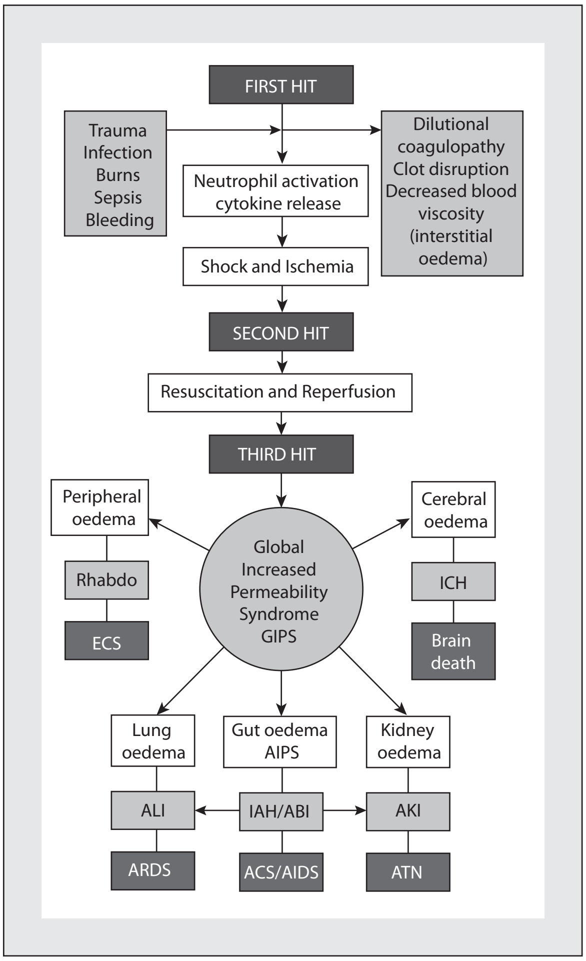


**Figure 4.** Modelling of shock. First hit refers to INJURY, second hit to REPERFUSION, and third hit to UNREPAIRED CAPILLARY LEAK. Rhabdo — rhabdomyolysis; ECS — extremity compartment syndrome; ICH — intracranial hypertension; ALI — acute lung injury; ARDS — acute respiratory distress syndrome; IAH — intra-abdominal hypertension; ABI — acute bowel injury; ACS — abdominal compartment syndrome; AIDS — acute intestinal distress syndrome; AIPS — acute intestinal permeability syndrome; AKI — acute kidney injury; ATN — acute tubular necrosis; GIPS — global increased permeability syndrome

**Table 2.** Effects of fluid overload on end-organ function

| |
|---|
| **CARDIOVASCULAR SYSTEM** |
| Myocardial oedema<br>Conduction disturbance<br>Impaired contractility<br>Diastolic dysfunction |
| **HEPATIC SYSTEM** |
| Hepatic congestion<br>Impaired synthetic function<br>Cholestasis<br>Impaired Cytochrome P 450 activity<br>Hepatic compartment syndrome |
| **GASTRO-INTESTINAL SYSTEM** |
| Gut oedema<br>Malabsorption<br>Ileus<br>Abdominal perfusion pressure decreased<br>Bowel contractility decreased<br>IAP increase and development of IAH, ACS<br>Successful enteral feeding decreased<br>Intestinal permeability increased<br>Bacterial translocation |
| **CENTRAL NERVOUS SYSTEM** |
| Cerebral oedema<br>Impaired cognition<br>Delirium<br>Intracranial pressure increased<br>Cerebral perfusion pressure decreased<br>Intra-ocular pressure increased |
| **RESPIRATORY SYSTEM** |
| Pulmonary oedema<br>Impaired gas exchange<br>Hypercarbia<br>$PaO_2$ and $PaO_2/FiO_2$ decreased<br>Extravascular lung water increased<br>Prolonged ventilation<br>Difficult weaning<br>Work of breathing increased |
| **RENAL SYSTEM** |
| Renal interstitial oedema<br>Renal venous pressure increased<br>Renal blood flow decreased<br>Interstitial pressure increased<br>Glomerular filtration rate decreased<br>Uremia<br>Renal vascular resistance increased<br>Salt retention<br>Water retention<br>Renal compartment syndrome |
| **ABDOMINAL WALL** |
| Tissue oedema<br>Impaired lymphatic drainage<br>Microcirculatory derangements<br>Poor wound healing<br>Wound infection<br>Pressure ulcers |
| **ENDOCRINE SYSTEM** |
| Release pro-inflammatory cytokines<br>(IL-1b, TNF-α, IL-6) |

in particular is strongly affected by IAH. Furthermore, renal interstitial oedema in the absence of IAH may impair renal function and create an intrarenal compartment syndrome. Therefore, fluid overload leading to IAH and associated renal dysfunction may counteract its own resolution [87]. The adverse effects of fluid overload and interstitial oedema are numerous and impact all end-organ functions (Table 2), laying to rest the notion that peripheral oedema is only of cosmetic concern [88].

As adverse effects of fluid overload in states of capillary leakage are particularly pronounced in the lungs, monitoring of EVLWI may offer a valuable tool to guide fluid management in the critically ill. A high EVLWI indicates a state of capillary leak, and is associated with a greater severity of illness and increased mortality. Recent studies have correlated EVLWI with albumin extravasation in patients after multiple trauma. Changes in EVLWI may have prognostic value as a reflection of the extent of capillary leakage rather than as a quantification of lung function impairment by lung water. Patients at risk for GIPS as assessed by CLI (defined as serum C-reactive protein levels divided by serum albumin), IAP, changes in EVLWI and fluid balance, benefit from restrictive fluid strategies and even fluid removal guided by extended haemodynamic monitoring including lung water measurements (late goal directed fluid removal) [50, 80, 89]. Indeed, the application of EVLWI-guided fluid therapy leads to improved outcomes and lower positive fluid balances in states of capillary leak [90]. Restrictive fluid management may be enabled by a more liberal use of vasopressor therapy, more prevalent resuscitation with hyperoncotic solutions, and goal-directed fluid removal after resuscitation is completed [50, 79, 80, 82]. The 3 hit model of shock is summarized in Table 3.

## CONCLUSIONS

Capillary leak is an inflammatory condition with diverse triggers that results from a common pathway that includes ischaemia-reperfusion, toxic oxygen metabolite generation, cell wall and enzyme injury leading to a loss of capillary endothelial barrier function. Fluid overload should be avoided in this setting. Plasma volume expansion to correct hypoperfusion results in extravascular movement of water, electrolytes and proteins. Peripheral tissue oedema, visceral oedema and ascites may be anticipated in proportion to the volume of prescribed crystalloid resuscitation fluid. A variety of strategies are available to the clinician to reduce the volume of crystalloid resuscitation used while restoring macro- and micro-circulatory flow, including the use of hypertonic solutions in those with traumatic brain injury. Hydroxyethyl

**Table 3.** A three hit model of shock

| | FIRST HIT | SECOND HIT | THIRD HIT |
|---|---|---|---|
| Cause | Inflammatory insult | Ischaemia reperfusion | GIPS |
| Phase | Ebb | Flow | No flow |
| Fluids | Life saving | Biomarker of critical illness | Toxic |
| Monitoring | Functional haemodynamics like stroke volume or pulse pressure variation | Organ function (EVLWI, IAP) | Perfusion |
| Treatment | Early adequate goal directed fluid management (EAGD) | Late conservative fluid management (LCFM) | Late goal directed fluid removal (LGFR) |
| Fluid balance | Positive | Neutral | Negative |

EVLWI — extravascular lung water index; IAP — intra-abdominal pressure

starches (HES) should no longer be used in the setting of capillary leak related to sepsis or burns.

Regardless of the resuscitation strategy, the clinician must maintain a heightened awareness of the dynamic relationship between injury, capillary leak, intra-abdominal hypertension, and abdominal compartment syndrome. Specific identification of patients with the Global Increased Permeability Syndrome may help improve ICU-related outcomes after injury.

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