“Fluid Creep” Is Really a New Phenomenon in Critically Ill Patients

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Abstract

The importance of accurate monitoring and assessment of the fluid balance with regard to the outcome of the patient has been shown in several studies. Maintaining a balance between fluid intake and output plays an important role in the management of a critically ill patient. This article reviews the incidence, consequences, and possible aetiologies of fluid creep in modern practice and uses this information to propose some therapeutic strategies to reduce or eliminate excessive fluid resuscitation.

Keywords

Fluid Creep, Resuscitation, Critically Ill Patients

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1. History of Fluid Creep

Intravenous (IV) fluid therapy remains the most ubiquitous intervention administered in acutely ill hospitalized patients [12] Fluid therapy is routinely prescribed across a broad range of clinical settings including in the management of critically ill patients with infections, hypovolemia, and in those with hemodynamic deterioration deemed to be volume responsive; and for the peri-operative replacement of significant fluid deficits and losses. In these contexts, fluid therapy is general perceived to have benefit for patients [14, 15].

Acute resuscitation is a unique aspect of burn, trauma and sepsis care and the ability to effectively resuscitate patients is critical to survival and overall outcome. The profound inflammatory response generated by a burn far surpasses that seen in trauma or sepsis, and the resultant fluid needs can be extreme. Before recognition of the magnitude of fluid shifts and the massive fluid requirements of severely burned patients, failed resuscitation was the leading cause of death.

Excessive initial resuscitation is a likely contributor to fluid creep that may not be apparent until much later. As described recently, “fluid begets more fluid”; the higher the starting point in terms of initial fluid rate, the higher the final 24-h resuscitation volume [41].

The fluid needs for critically ill patients are not static and evolve in accordance with their phase of acute illness [13]. In particular; patients are susceptible to progressive, excessive and in may circumstances unnecessary fluid accumulation and overload termed “fluid creep” [1]. This was first described in patients with major burn injury; however, can essentially be applied to any patient who has been subject to overly judicious fluid administration. While iatrogenic fluid accumulation is important to monitor and unnecessary fluid overload important to avoid whenever possible, the optimal methods to mitigate and/or even actively remove accumulated fluid remains uncertain. [18, 33]. The excessive removal or too conservative use of fluid early during convalescence can precipitate hypotension or organ hypoperfusion and may contribute to long-term risk of
황기. A fourth component not originally described by below and Figure 1): pressure gradient, which normally favors translocation of pressure, and $\pi_i$ is the interstitial oncotic pressure [11].

The first half of Starling’s Law represents the hydrostatic pressure gradient, which normally favors translocation of fluid across the membrane and out of the vasculature. The second half represents the COP gradient across the capillary wall. The relative influence of COP on fluid flux is modulated by the oncotic reflection coefficient, which represents permeability of the vasculature to oncotically active substances such as plasma proteins. Edema forms when Starling’s forces are imbalanced, and there are three edema-protective mechanisms that oppose further edema formation when this process begins: 1) increases in interstitial hydrostatic pressure, 2) reductions in interstitial oncotic pressure, and 3) increases in capillary oncotic pressure. A fourth component not originally described by Starling is lymphatic flow, which may increase by nearly 10 times to prevent the accumulation of pulmonary edema. [11].

3. Pathophysiology of Fluid Overload

This section will address the question: ‘When to de-resuscitate?’ As early as 1942, the concept of a dual metabolic response to bodily injury was introduced. In direct response to initial proinflammatory cytokines and stress hormones, the Ebb phase represents a distributive shock characterized by arterial vasodilatation and trans-capillary albumin leakage abating plasma oncotic pressure. Arterial under-filling, microcirculatory dysfunction, and secondary interstitial edema lead to systemic hypoperfusion and regional impaired tissue use of oxygen. In this early stage of shock, adequate fluid therapy comprises adequate goal directed filling to prevent evolution to multiple organ dysfunction syndromes (MODS). As compensatory neuroendocrine reflexes and potential renal dysfunction result in sodium and water retention, positive fluid balances are inherent to the Ebb phase. Patients with higher severity of illness need more fluids to reach cardiovascular optimization. Therefore, at this point fluid balance may be considered a biomarker of critical illness. Patients overcoming shock attain homeostasis of proinflammatory and anti-inflammatory mediators classically within three days. Subsequent hemodynamic stabilization and restoration of plasma oncotic pressure set off the Flow phase with resumption of diuresis and mobilization of extravascular fluid resulting in negative fluid balances [5].

Transcapillary fluid flux is governed by a set of physical forces and properties summarized by Starling’s equation of both the capillary bed and the interstitium. A balance is normally present so that edema does not form. Capillary hydrostatic pressure forces fluid out; this is counterbalanced by colloid osmotic pressure dependent on plasma proteins concentration that holds fluid in the capillary lumen. Interstitial fluid pressure and interstitial colloid osmotic pressure are the other forces controlling fluid flux. Thus the forces driving fluid out of the capillary bed are capillary hydrostatic pressure and interstitial oncotic pressure; these are opposed by plasma colloid osmotic pressure and interstitial hydrostatic pressure [41].

The postulated mechanism of harm is the development of interstitial edema, with resultant increase morbidity and mortality. Interstitial edema may result from aggressive fluid therapy to replace the non-existent ‘third space’ loss. In such cases there may be altered distribution of protein due to destruction of glycocalyx6 and altered Starling forces leading to the accumulation of fluid in the interstitial compartment. This results in impairment of the lung, cardiac, kidney and gastrointestinal function [9].

Many patients become edematous if liberal fluid therapy continues. Interstitial edema will impede capillary blood flow and lymphatic drainage. Moreover, prolonged edema will further impair diffusion of cellular oxygen and metabolite. Finally, cell dysfunction contributes to progressive organ failure. Increased interstitial pressure and compromised blood flow are more pronounced in encapsulated organs such as liver and kidney. Fluid overload also increases the risk of intra-abdominal hypertension, which is strongly associated with development of AKI [3].

4. Risk Factor of Fluid Creep

Whereas reports of ACS and other edema-related complications demonstrate unequivocally the potentially disastrous consequences of fluid creep, they provide little...
insight into its etiology. Some patients groups who routinely required an additional fluids as patients with inhalation injuries, multiple trauma, patients with electrical burns, and those in whom resuscitation was delayed. patients with alcohol or drug addiction. In addition, inexperienced clinicians often make substantial errors in estimating fluid balance and adjusting fluid infusions on the basis of patients’ response, which can result in significant under- or over-calculation of fluid requirements [1].

5. Type and Phases of Fluid Therapy

For a given dose of fluid administered, toxicity may depend on the type and composition of fluid being administered and on patient susceptibilities and physiology. Both patient-specific and context-specific differences should be considered when selecting the type of fluid therapy to be administered. The debate regarding the relative risks and benefits of colloid and crystalloid solutions has raged on for years. Although various forms of crystalloid solutions have been used in humans since the 1830s, it was approximately 100 years more before the technology to isolate albumin from serum was available. In World War II, fractionated bovine albumin was first used on the battlefield as a resuscitation fluid. Synthetic colloids such as HES and gelatins have until recently been considered reasonable alternatives to albumin, due to their theoretical advantages such as mitigating the infectious risks of human blood products, improving blood rheology and micro-vascular flow, and modulating neutrophil aggregation [12].

Despite the wide variety of IV fluid types available for use in clinical practice, the same general principles behind IV fluid therapy remain similar today as they did in the 19th century – to restore cardiac output and blood pressure, organ and microcirculatory tissue perfusion and ensure adequate tissue oxygen delivery [16].

A conceptual framework outlining four distinct yet inter-related phases of resuscitation has recently been proposed. These phase have been described as Rescue (or Salvage), Optimization, Stabilization and De-escalation (ROS-D) and are intended to span the initial acute resuscitation to illness resolution [20, 21]. Logically, fluid therapy follows similar phases during acute resuscitation.

Rescue – This phase, also referred to as salvage, is characterized by life threatening shock characterized by hypotension and impaired organ perfusion. In this phase, patients are given rapid fluid bolus therapy as the mainstay of treatment to rapidly reverse volume-responsive shock states and improve organ perfusion while concomitantly identifying and treating the underlying precipitate (i.e., major trauma or sepsis or gastrointestinal bleeding). These patients are best transferred to settings with enhanced invasive (i.e., arterial catheter; central venous pressure; central venous oxygen saturation) and non-invasive (i.e., echocardiography, pulse pressure or stroke volume variation) monitoring capabilities to guide ongoing resuscitation and organ support (i.e., vasoactive therapy; mechanical ventilation) [13].

Optimization - In this phase, the patient is no longer at imminent risk of life-threatening shock; however, often requires fluid therapy to optimize cardiac function, sustain tissue perfusion, mitigate organ dysfunction and achieve physiological endpoints [22]. The optimal endpoints for resuscitation remain uncertain; however, consensus generally supports restoration of central venous oxygen saturation and clearance of arterial lactate as dynamic goals of resuscitation that correlate with improved patient outcome [27, 28]. During Optimization, “fluid challenge” therapy using fluid volumes of 250 - 500 mL over 15 – 20 minutes are often utilized to evaluate the effect of additional fluid therapy on targeted endpoints of resuscitation. Microcirculatory capillary blood flow (i.e., use of sublingual orthogonal polarization spectral [OPS] imaging) is commonly found abnormal among critically ill patients. Recent observational data have shown disturbance in sublingual microcirculatory flow failed to correlate with patient survival, possibly due to a significant dissociation observed between sublingual and intestinal microcirculatory perfusion following fluid resuscitation [23, 24]. These data reinforce the critical importance of the constant need for clinicians to monitor, reassess and reevaluate the necessity for ongoing fluid therapy.

Stabilization – During this phase, the main goals are to provide ongoing organ support, prevent worsening organ dysfunction and avoid iatrogenic complications. The need for fluid during this phase is largely aimed at maintaining intravascular volume homeostasis and replacing ongoing fluid losses. Implicit during this phase is the need to monitor and assess volume status and fluid balance [13].

De-escalation - The final phase is characterized by ongoing recovery whereby patients are weaned from ventilator and vasoactive support and where accumulated fluid is mobilized and removed. This “de-resuscitation” is aimed to achieve a negative fluid balance and relieve or avert the “quantitative” toxicity of fluid therapy. Late conservative fluid management strategies and achievement of a negative fluid balance have been associated with improved patient outcome, including reduced duration of mechanical ventilation, early ICU discharge and survival [17].

Unfortunately, there is a paucity of evidence on measures to
guide how to effectively and safely remove resuscitation fluid. In addition, as aforementioned, the ideal mechanisms to remove accumulated fluid (i.e., diuretic therapy, extracorporeal ultrafiltration) and optimal rate at which fluid can be safely removed remain to be determined [13].

6. Response to Fluid Therapy

The optimal target endpoints for fluid therapy

The optimal target endpoints for fluid therapy during resuscitation remain controversial. Recent data suggest static metrics of resuscitation, such as thresholds in central venous pressure (CVP), as currently recommended by the Surviving Sepsis Campaign [26], may not accurately correlate with restoration of intravascular volume and improvement in tissue oxygen delivery and may be associated with worse outcome [27]. Additional measures such as achieving a normalized central venous oxygen saturation (> 65%-70%) and rapid serum lactate clearance (> 20% in 2 h) in response to fluid resuscitation (± additional hemodynamic support) have been recommended and correlate with improve outcome, both of these endpoints also have important caveats to consider [28]. Rather, functional hemodynamic measures such as stroke volume variation, pulse pressure variation [29], bedside ultrasonic interrogation of cardiac output or respiratory variation in inferior vena cava diameter and additional novel dynamic metrics such changes in cardiac output associated with passive leg raising, changes in end-tidal CO2 and end-expiratory endotracheal tube occlusion can better predict the hemodynamic response to fluid loading [12].

The administration of intravenous fluids is widely regarded as the first step in the resuscitation of critically ill and injured patients who have evidence of impaired organ perfusion [5]. The purpose of fluid resuscitation is to increase venous return and stroke volume [30]. Fluid administration increases the stressed blood volume, increasing the gradient between the mean systemic filling pressure (MSFP) and right atrial pressure (CVP), thereby increasing venous return. In patients who are on the ascending limb of the Frank-Starling limb, the increased venous return results in an increase in stroke volume and cardiac index [30]. Fluid administration serves no useful purpose in those patients whose stroke volume fails to increase following a fluid challenge (non-responders) [5]. In these patients, fluid administration may even be harmful. Furthermore, due to the redistribution of fluid, the hemodynamic response in fluid responders is short lived with the stroke volume returning to baseline 30 to 60 minutes following the initial fluid challenge. In healthy individuals, 85% of an infused bolus of crystalloid has been reported to redistribute into the interstitial space after four hours [31]. In critically ill patients with endothelial injury and leaky capillaries, less than 5% of a fluid bolus remains intravascular after 90 minutes [32, 5].

A decline in UOP is an almost universal indication to increase intravenous fluids. The value of UOP as an accurate and sole indicator of appropriate fluid resuscitation has however been disputed over the past two decades. In an attempt to tailor resuscitation to achieve both the normalization of base deficit (BD) and lactic acid (LA) levels and, at the same time, above normal levels of cardiac index (CI) and oxygen delivery (DO2) and/or consumption (VO2), practitioners have shifted to a “goal-directed” therapy, even when vital signs and urine output are adequate [41].

7. Factors Affecting the Response to Fluid Therapy

The response to fluid therapy depends on many factors such as intravascular volume, myocardial compliance and contractility, vascular resistance, and capillary permeability [3]. Trans-pulmonary thermo-dilution and pulse contour analysis by PiCCO catheter for fluid status monitoring is more precise. Dynamic changes such as systolic pressure variation, pulse pressure variation, and stroke volume variation derived from PiCCO catheter have also been shown to be predictive of fluid responsiveness in mechanically ventilated patients, but they lose their value in patients with spontaneous breathing activity and arrhythmias. Passive leg raising induced changes in cardiac output and in arterial pulse pressure can also predict fluid responsiveness. Brain natriuretic peptide (BNP) is a potential marker for fluid therapy. It can identify patients with fluid overload and congestive heart failure. It has also been shown to correlate with mortality and morbidity in critically ill patients. BNP represents the tolerability of heart to intravascular volume. It has been correlated with echocardiographic and bioimpedance measures of fluid overload in patients receiving RRT. Even without apparent fluid overload detected by the other methods, higher BNP means intolerability of heart and fluid balance should be kept negative if the hemodynamic status is stable [3].

8. Effect of Fluid Creep

A relationship between a positive fluid balance and an unfavorable ICU outcome has been described before in general ICU populations. Mitchell and colleagues demonstrated a decrease in ventilator and ICU days in patients treated with fluid restriction and increased diuresis compared with a wedge pressure-guided fluid protocol. Upadya and colleagues demonstrated that a negative fluid
balance was independently associated with weaning success in mechanically ventilated patients. In an earlier analysis of the SOAP database, Sakr and colleagues demonstrated that mean fluid balance was an independent determinant of ICU outcome in patients with acute lung injury and adult respiratory distress syndrome. In patients with sepsis, the relationship between a positive fluid balance and a negative outcome has also been described. Alsous and colleagues demonstrated an increased mortality risk in patients failing to achieve a negative fluid balance within the first 3 days of treatment (relative risk, 5.0; 95% confidence interval, 2.3 to 10.9). Rinaldo Bellomo et al, in the RENAL study, concluded that extra intravenous fluids may do much more harm than good. They found a negative fluid balance in ICU patients was strongly associated not only with survival and shorter ICU and hospital stays [42].

A growing body of evidence strongly suggests that fluid overload may be detrimental to critically ill patients. Relatively little attention has been paid to the consequences of fluid overload such as respiratory failure, increased cardiac demand, and peripheral edema. Recent studies on patients with acute lung or kidney injury have reported that fluid overload has been associated with adverse outcomes. Although uniform definitions of fluid overload and well-designed randomized clinical trials are lacking, there seems to be a need to avoid overzealous fluid resuscitation in a subset of patients [4, 25]. Intravenous fluids play a critical role in the resuscitation of the critically ill patient with sepsis, but the overzealous fluid resuscitation has been associated with increased complications, increased length of ICU and hospital stay, and increased mortality [6].

Increased fluid volumes independently increase the risk of pneumonia, bloodstream infections, acute respiratory distress syndrome, multi-organ failure, and death. A large percentage of resuscitated patient exceed the Ivy Index, defined as 24 h volumes exceeding 250 mL/kg, a well acknowledged independent predictor of mortality based on multivariate logistic regression. Several studies have now determined that intra-abdominal hypertension will develop once a threshold of cumulative crystalloid fluid reaches 250 to 350 mL/kg during the acute resuscitation phase. More precisely, a resuscitation volume greater than 237 cc/kg over the course of 12 h (16 l during a 12-h period in a 70-kg man) appears to be the threshold for the development of ACS.5 Over-resuscitation of the severely and multi-injured patient often results in fluid overload and “resuscitation morbidity” characterized by anasarca, orbital compartment syndrome, extremity compartment syndrome, and abdominal compartment syndrome (ACS) as well as pulmonary edema requiring a prolonged and potentially complicated hospital stay. If not treated promptly and effectively, many of these complications will increase morbidity and mortality [41].

Intravenous fluid administration is important for stabilizing hemodynamic status and improving tissue oxygenation. However, once there has been adequate fluid resuscitation, further fluid administration may increase intravascular pressure along with vascular permeability, causing fluid leakage which results in tissue edema, decreased oxygenation index. Positive fluid balance could increase extravascular lung water, prolong mechanical ventilator days, and contribute to the occurrence of ventilator-associated pneumonia. In addition, the positive fluid balance could also result in intra-abdominal hypertension along with abdominal compartment syndrome contributing to the development of organ dysfunction. Furthermore, positive fluid balance is associated with delayed renal recovery and increased risk of acute kidney injury [2, 10]. It also increasing the risk of pressure sores and impaired wound healing. It may also cause disturbances of electrolyte status, such as hypernatremia and hypokalaemia from excessive administration of intravenous normal saline. Acute renal failure coexisting with sepsis may worsen outcomes as well as lead to positive fluid balance [8]. Accurate documentation of fluid status enabling judicious fluid prescribing is therefore fundamental to safe inpatient care [7].

Large volume fluid resuscitation results in severe tissue edema and clinical signs of volume overload. Tissue edema impairs oxygen and metabolite diffusion, distorts tissue architecture, impedes capillary blood flow and lymphatic drainage, and disturbs cell-cell interactions [35]. These effects are pronounced in encapsulated organs, such as the liver and kidneys, which lack the capacity to accommodate additional volume without an increase in interstitial pressure, resulting in compromised organ blood flow [36].

Kelm et al. [37]. Demonstrated that 67% of patients resuscitated by means of the EGDT protocol had clinical evidence of fluid overload after 24 hours, with 48% of patients having persistent features of fluid overload by the third hospital day. Multiple studies have demonstrated that a positive fluid balance is independently associated with impaired organ function and an increased risk of death [34]. This was recently demonstrated in an elegant study by Murphy et al. [17]. Conversely, achievement of a negative fluid balance is associated with improved organ function and survival. This has been referred to as the Ebb and Flow phases of shock. The Ebb phase was characterized by Cuthbertson in 1932 as: “Ashen faces, a thready pulse and cold clammy extremities…”, while during the Flow phase
“the patient warms up, cardiac output increases and the surgical team relaxes [5].

Renal function in particular is strongly affected by fluid overload and IAH, and renal interstitial edema may impair renal function, even in the absence of IAH [38, 39]. Therefore, fluid overload leading to IAH and associated renal dysfunction may counteract its own resolution. The adverse effects of fluid overload and interstitial edema are numerous and have an impact on all end organ functions, although some clinicians still believe that peripheral edema is only of cosmetic concern. 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 leakage, associated with higher severity of illness and mortality [40]. Previous studies correlated EVLWI with albumin extravasation in patients after multiple traumas. Responders to LCFM overcome the distributive shock and make a transition to the flow phase. On the other hand, nonresponders stay in the grip of the Ebb phase and progress to GIPS, resulting in positive fluid balances, organ failure and death [5].

![Figure 1. Vicious cycle of futile fluid loading to increased IAP and further ongoing fluid administration.](image1)

![Figure 2. Pathological effect of fluid overload on end-organ dysfunction.](image2)
9. Strategies for Prevention and Treatment of Fluid Creep

Although the exact causes of fluid creep remain undetermined, controlling its magnitude and complications certainly requires several strategies, which may include restriction of early fluid resuscitation, tighter titration of fluid administration, colloid administration, and possibly the use of adjunctive pharmacologic agents as well as markers of resuscitation other than urinary output failure and death [41].

Restrict Early Fluid Resuscitation: Although the prompt institution of fluid resuscitation after injury is an important contributor to improved survival, excessive initial resuscitation is a likely contributor to fluid creep, which may not be apparent until much later. Close communication with first responders and referring physicians—possibly including telemedicine or other visual evaluation—is essential and helps professionals regulate resuscitation as soon as possible after injury. Use of widely accessible programs for calculating fluid requirements may also help inexperienced clinicians avoid over-resuscitation. Consider Routine Colloid, or “Colloid Rescue.” Many patients are successfully resuscitated with crystalloid alone, without excessive volumes. However, edema-related complications correlate with the absolute volume of fluids infused; the volumes required with colloid-assisted resuscitation appear to be less than those with crystalloids alone, and this has been associated with lower abdominal pressures and incidence of clinical ACS. Use Resuscitation Protocols. This protocol is illustrated in Figure 3 have been found helpful in reducing excessive resuscitation and improving staff awareness of fluid resuscitation guidelines [1].

Figure 3. Resuscitation Protocols.
10. Conclusion

Fluid balance monitoring is a part of the scope of nurses’ practice. The incorrect calculation of fluid balance means that every patient management decision was influenced by inaccurate fluid balance information. Therefore, nurses working in ICUs are responsible and accountable for the accurate recording and calculation of fluid balance when caring for critically ill patients.

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