REVIEWS

An overview on fluid resuscitation and resuscitation endpoints in burns: Past, present and future. Part 2 — avoiding complications by using the right endpoints with a new personalized protocolized approach

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Abstract

While organ hypoperfusion caused by inadequate resuscitation has become rare in clinical practice due to the better understanding of burn shock pathophysiology, there is growing concern that increased morbidity and mortality related to over-resuscitation induced by late 20th century resuscitation strategies based on urine output, is occurring more frequently in burn care. In order to reduce complications related to this concept of "fluid creep", such as respiratory failure and compartment syndromes, efforts should be made to resuscitate with the least amount of fluid to provide adequate organ perfusion. In this second part of a concise review, the different targets and endpoints used to guide fluid resuscitation are discussed. Special reference is made to the role of intra-abdominal hypertension in burn care and adjunctive treatments modulating the inflammatory response. Finally, as urine output has been recognized as a poor resuscitation target, a new personalized stepwise resuscitation protocol is suggested which includes targets and endpoints that can be obtained with modern, less invasive hemodynamic monitoring devices like transpulmonary thermodilution.

Key words: burns; fluid resuscitation; monitoring; treatment; resuscitation endpoint/target; de-resuscitation; abdominal pressure; abdominal hypertension; abdominal compartment syndrome; personalized care; protocol; algorith

As discussed in the first part of this review, following a severe burn injury, an overwhelming systemic inflammatory response, with an associated capillary leak syndrome, occurs. Due to fluid shifts that reach a maximum at 12 to 24 hours post injury, the severely burned patient experiences profound intravascular hypovolemia. During this initial "ebb" phase with profound intravascular underfilling, fluid resuscitation is of paramount importance. Moreover, the fluid needs can be enormous due to plasma and proteins leaking into the extravascular compartment. This results in a positive (daily and cumulative) fluid balance associated with well-known complications related to fluid-creep like renal and respiratory failure, gastro-intestinal dysfunction, abdominal hypertension and compartment syndromes [1].

As the systemic inflammatory response diminishes, a polyuric or "flow" phase is entered, where a negative fluid balance is seen, reflecting the loss of the initial resuscitation fluids [1].

Despite the fact that numerous articles regarding burn resuscitation have been published over recent decades, there is still no universal consensus on the optimal resuscitation fluid and how to achieve adequate resuscitation whilst avoiding the adverse effects of fluid overload. Thus, it is necessary to develop a dynamic fluid strategy, including an active de-resuscitation therapeutic protocol based on newly available physiologic parameters via transpulmonary thermodilution such as extravascular lung water (EVLW), pulmonary vascular permeability index (PVPI), in combination with capillary leak index (CLI) and intra-abdominal pres-

sure (IAP) [2–5]. The objective of this paper is to address the complications of fluid overload (especially intra-abdominal hypertension (IAH) and compartment syndromes) and to review the past and present literature regarding targets and endpoints for fluid resuscitation in burn care and to suggest a new algorithm for future clinical use. These recommendations are listed in Table 1.

METHODS

A MEDLINE and Pubmed search was performed using the search terms "resuscitation", "burn(s)", "burn management", "resuscitation endpoint/target", "preload", "resuscitation fluids", "fluid creep", "cardiac output", "deresuscitation", "extravascular lung water", "abdominal pressure", "abdominal hypertension", "abdominal compartment syndrome". Selected articles and their bibliographies were used to supplement the authors' knowledge and to identify other relevant citations.

ROLE OF ABDOMINAL HYPERTENSION

Intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) are major complications in burn patients and contribute to multi-organ dysfunction and death. IAH/ACS requires specific strategies to prevent, monitor, diagnose and manage such conditions [6]. IAH is defined as a sustained or repeated pathological elevation in IAP ≥ 12 mm Hg, and ACS as a sustained IAP > 20 mm Hg that is associated with new organ dysfunction [5].

Although the adverse consequences of increased intra-abdominal pressure (IAP) were documented by authors in the 19th century, it appears to have been neglected in clinical practice until the beginning of the 1980s. Several publications have underlined the consequences of elevated IAP [7–10], which triggered renewed interest and research. In 2004, the World Society of the Abdominal Compartment Syndrome (WSACS) was founded in an effort to promote research, provide education and improve the survival of patients suffering from IAH and ACS [11, 12]. The definitions and guidelines regarding IAH and ACS have been developed and recently updated in order to standardize terminology, clinical applications and research [5].

The incidence of IAH in severe burns is higher than other patient populations and is around 50 to 70% with an incidence of ACS around 20 to 30%. The cause of IAH and ACS in burn patients is multifactorial. The fact in 2015 is that big burns get big fluid volumes, well above the classic formula. Major burns (with large resuscitation fluid) are therefore at risk of IAH. As clinical signs to detect IAH are unreliable, early IAP monitoring is warranted to detect high-risk patients. As ACS is a late development (with high morbidity and mortality), there is a need to anticipate and prevent IAH. The initial idea was that if some fluid is good, more may be better,

whilst dealing with therapeutic dilemmas and choosing between renal protection vs. the risk for pulmonary edema. However, the burn specialist needs to be aware that every ml given in the first 16 hours is lost from circulation within minutes.

The major contributors of elevated IAP are indirect effects of systemic inflammation and capillary leak, causing bowel edema and distention, edema of the abdominal wall and fluid accumulation in the peritoneal cavity [6, 13–15]. Once IAP is elevated, venous hypertension may follow, further aggravating fluid translocation [16]. Furthermore, direct effects of the burn insult, such as eschars, may lead to a decreased abdominal wall and thoracic compliance [17, 18]. Table 2 lists the different risk factors related to IAH and ACS in burns. Because there is no inciting intraperitoneal injury, the elevated IAP in burn patients is an example of secondary IAH/ACS. This usually develops within 48 hours after the burn injury during the acute resuscitation phase, occurring again later on as fluid accumulates in the interstitium and peritoneal cavities, made worse by an ileus [19]. ACS is a life-threatening complication with mortality rate of 50–80%, even in treated patients [6, 20, 21]. Patients who reach the "flow phase" have a lower risk of IAH/ACS.

Several predisposing factors for IAH and ACS in burn patients have been identified. In 1994, it was reported that the incidence of ACS was linked with the extent of the burn injury. This relationship between TBSA and the development of ACS has been confirmed in other studies [13, 14, 22, 23]. Although not limited to this group of burn patients, ACS typically occurs when the TBSA is greater than 55–60% [22]. There is concern whether the development of IAH and ACS is iatrogenic, or if it can be avoided through different fluid strategies [14, 24, 25]. Excessive fluid resuscitation is without doubt a major predisposing factor and this has been confirmed in numerous studies [22, 23, 26–28]. In 2000, Ivy stated that a volume administration of > 250 mL kg^{-1} in the first 24 hours is a risk factor for ACS. This fluid quantity became known as the Ivy Index [23]. An inhalation injury is another important predisposing factor, presumably caused by aggravating the systemic inflammation and resulting in the need for a larger volume of fluid resuscitation [22, 23, 25]. Although the occurrence of IAH/ACS is usually in the burn shock resuscitation phase, each subsequent event requiring aggressive fluid resuscitation, such as sepsis or surgery, is a predisposing factor for IAH/ACS. As a result, IAH/ACS can also develop during the later course of the disease.

Preventing IAH and ACS is of paramount importance. By optimizing our resuscitation protocols we can influence one of the controllable predisposing factors. A prospective randomized trial showed it possible to significantly lower IAP by using human colloids (plasma) in comparison to crystalloids [29]. Similar results were found by Oda when using

Table 1. Recommendations regarding fluid resuscitation and resuscitation endpoints in severe burns patients

Fluids	
1. Normal saline	Given the fact that fluid resuscitation in burn management requires large volumes, the use of saline cannot be recommended in a burn resuscitation protocol
2. Balanced crystalloid	Based on the available evidence, balanced crystalloid solutions are a pragmatic initial resuscitation fluid in the majority of acutely ill (and burn) patients
3. Semi-synthetic colloids	Given the recent data concerning the use of semi-synthetic colloids (and starches in particular), their use in critically ill patients, including burn patients cannot be recommended
4. Albumin	Based on the available evidence, the use of albumin 20% can be recommended in severe burns, especially in the de-resuscitation phase guided by indices of capillary leak, body weight, (cumulative) fluid balance, fluid overload, extravascular lung water, and intra-abdominal pressure
5. Hypertonic solutions	To this day, there is insufficient evidence to reach consensus regarding the safety of hypertonic saline in burn resuscitation. Whenever using hypertonic saline in clinical practice, however, close monitoring of sodium levels is highly advised
Adjunctive therapy	
6. Vitamin C	Given the available evidence, the benefit of adjunctive high dose ascorbic acid treatment may be strongly suspected to be the limiting of fluid intake and prevention of secondary abdominal hypertension; while, equally important, no adverse effects have been reported
7. Plasmapheresis	The benefit of plasmapheresis on outcomes in burn patients still needs to be validated in large prospective, randomized trials. As such its use cannot be recommended
8. Intravenous immunoglobulins (IVIG)	The use of IVIG should be limited to cases of toxic epidermal necrolysis
Abdominal hypertension	
9. Intra-abdominal pressure (IAP)	During the resuscitation phase as well as the recovery phase intra-abdominal pressure (IAP) needs to be measured in burn patients at least 4 to 6 times per day
10. Medical treatment	Medical management (improvement of abdominal compliance, evacuation of intra-abdominal contents, evacuation of intra-luminal contents, limitation of fluid intake, optimization of organ perfusion) comes first and should be initiated whenever IAP increases above 12 mm Hg
11. Surgical treatment	Escharotomies should be performed in cases of circular thoracic or abdominal eschars. While surgical decompressive laparotomy is only a last resort in case medical management fails
Resuscitation endpoints	
12. Monitoring	Every severely burned patients (> 20% TBSA in adults or > 15% TBSA in children) should be adequately monitored with regard to fluid status, fluid responsiveness and organ perfusion
13. Urine output	Diuresis is a poor endpoint that may lead to over- or under estimation of fluid resuscitation and, as such, can no longer be recommended; however in situations with limited monitoring techniques, it can still be used to guide fluid resuscitation (see further under urine output algorithm)
14. Barometric preload	Barometric preload indicators, such as central venous pressure (CVP) or pulmonary artery occlusion pressure (PAOP), should not be used to guide fluid resuscitation in burn patients
15. Volumetric preload	Volumetric preload indicators (such as right ventricular or global end diastolic volume) are superior compared to barometric ones and are recommended to guide fluid resuscitation, especially in burn patients with increased IAP (see further under GEDVI algorithm)
16. Lung water	The use of extravascular lung water is recommended to guide de-resuscitation in burn patients not transgressing spontaneously from Ebb to Flow phase
17. Fluid responsiveness	Fluid resuscitation in burn patients should be guided by physiological parameters or tests that are able to predict fluid responsiveness (see further under PPV algorithm)
18. Perfusion	Fluid resuscitation should only be given/increased in case of evidence of tissue hypoperfusion (base deficit, lactate, etc.).
Stepwise approach	
19. PPV Algorithm	If a patient is sedated and mechanically ventilated, an algorithm based on pulse pressure variation (PPV) can be used in severe burns, on condition that PPV measurements are reliable (Fig. 3)
20. GEDVI algorithm	If PPV is unreliable, volumetric parameters obtained with transpulmonary thermodilution may be used to guide fluid resuscitation in severe burns. Here, the GEDVI is interpreted as a measure of preload and EVLWI as a safety parameter warning for pending pulmonary edema (Fig. 4). If the GEDVI is high, the measurement needs to be corrected with the global ejection fraction as this leads to a more accurate estimation of preload
21. Urine output algorithm	If PPV or volumetric parameters are unreliable, or when monitoring possibilities are limited, urine output may be used to guide fluid resuscitation in severe burns (Fig. 5)

CVP: central venous pressure; EVLWI: extravascular lung water index; GEDVI: global end diastolic volume index; IAP: intra-abdominal pressure; IVIG: intravenous immunoglobulins; PAOP: pulmonary artery occlusion pressure; PPV: pulse pressure variation; TBSA: total burned surface area

Table 2. Specific risk factors for abdominal hypertension in burns

A. Related to diminished abdominal wall compliance
Circular abdominal eschars (diminished abdominal wall compliance)
Circular thoracic eschars (diminished chest and abdominal wall compliance)
Edema of the abdominal wall (fluid creep)
Mechanical ventilation (especially desynchronization with the ventilator and the use of accessory muscles)
Use of excessive positive end expiratory pressure (PEEP) or the presence of auto-PEEP
Basal pneumonia, acute respiratory distress syndrome (primary ARDS related to inhalation injury and secondary ARDS)
Prone and other body positioning
High body mass index

B. Related to increased intra-abdominal contents
Gastroparesis
Gastric distention
Ileus (bowel edema)
Colonic pseudo-obstruction
Enteral feeding
Constipation (opioid creep)

C. Related to abdominal collections of fluid, air or blood
Liver dysfunction (forward and backward failure)
Third space fluid accumulation (ascites, pleural effusions)
Hematoma formation (coagulopathy)

D. 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 twice normal or a prothrombin time (PTT) below 50% or an international standardized ratio (INR) more than 1.5)
Sepsis (as defined by the American-European Consensus Conference definitions)
Severe sepsis or bacteremia
Septic shock
Massive fluid resuscitation (> 7–10 L of crystalloid/24 hours with capillary leak and positive fluid balance), risk of ACS increased when fluid intake > 250 mL kg^{-1} in first 24 hours (Ivy index)
Major burns (TBSA > 20% in adults or > 15% in children), risk of ACS increased when TBSA > 55–60%
Systemic inflammatory reaction after each surgical intervention with debridement and skin grafting
Loss of skin barrier and immune-deprivation (prone to infection)

*The combination of acidosis, hypothermia and coagulopathy has been labeled in the literature as the deadly triad [60, 61]

Table 3. Medical interventions and strategies in burn patients suggested by the World Society on Abdominal Compartment Syndrome (WSACS) in the management of intra-abdominal hypertension [5]

1. Improvement of abdominal wall compliance
Sedation and paralysis
Escharotomies
Avoiding positive fluid balance

2. Evacuation of intra-abdominal contents
Ultrasound guided percutaneous ascites drainage

3. Evacuation of intraluminal contents
Gastro- and colonoprokinetics
Stool softeners
Enemas
Adaptation of enteral nutrition speed

4. Correction of capillary leak and fluid balance
Hypertonic solutions
Albumin 20%
Colloids (not HES, hydroxyl-ethyl starch)
Diuretics
Renal replacement therapy with net ultrafiltration

5. Optimisation of organ perfusion
Dobutamine and/or norepinephrine

a hypertonic lactated saline solution [27]. However, a 2014 systematic review noted that despite the effect of colloids on decreasing resuscitation volume needs, no benefits in preventing IAH were observed [13]. The use of plasma or hypertonic saline may reduce the risk for the development of ACS and lower the volume of fluid administered, however close monitoring of sodium levels in the latter is highly advised [13, 27, 29]. Functional hemodynamics in combination with volumetric indices acquired by transpulmonary thermodilution may also be useful as a resuscitation endpoint [30–32].

It is recommended that the clinician should routinely monitor IAP every 4 to 6 hours throughout the resuscitation of patients with a TBSA of more than 20% [6]. The clinical diagnosis of ACS is a very late finding and the presence of

IAH should be detected before the development of this potentially lethal complication.

Recommendation: *During the resuscitation phase, as well as the recovery phase, intra-abdominal pressure (IAP) needs to be measured in burn patients at least every 4 to 6 hours*

Once an elevated IAH has been diagnosed, medical treatment should be immediately initiated in order to avoid progression to ACS. This consists of nasogastric decompression, the use of neuro-muscular blocking agents, percutaneous ascites drainage, diuretics or veno-venous hemofiltration [12]. Table 3 summarizes medical management options for IAH in burn patients. The clinician should also be aware of the interactions of pressures between different compartments referred to as polycompartment syndrome [33, 34].

If medical treatment fails or ACS is imminent, surgical treatment should be considered but never as a first choice (Fig. 1). Although a midline laparotomy is very effective in reducing IAP, its morbidity and mortality in burn patients is tremendous considering its wound healing challenges and high incidence of infectious complications [21]. One should be aware that in burn patients, decompressive laparotomy should not always be the preferred surgical salvage procedure. In case of circular truncal eschars, escharotomy may significantly improve the compliance of the abdominal and thoracic walls. This type of procedure may also be effective at decreasing IAP and improving ventilation [35, 36].

Recommendation: *Medical management (improvement of abdominal compliance, evacuation of intra-abdominal contents, evacuation of intra-luminal contents, limitation of fluid intake, optimization of organ perfusion) should be initiated*

Figure 1. A decompressive laparotomy (DL) in a patient with circular abdominal eschars. DL is not the first choice of treatment, especially not in cases of circular abdominal eschars with poor compliance of the abdominal wall as this will result in permanent exteriorization of abdominal content and difficulties in performing a temporary abdominal closure. The treatment of choice in this situation is to perform an abdominal (and thoracic) escharotomy

Figure 2. The vicious cycle of burn shock resuscitation. Urine output is a poor resuscitation endpoint as it may trigger over-resuscitation in the setting of intra-abdominal hypertension (IAH)

whenever IAP increases above 12 mm Hg. Surgical decompressive laparotomy should remain a last resort in cases where medical management has failed.

The recommendations are summarized in Table 1.

RESUSCITATION TARGETS AND ENDPOINTS

Clinicians need to regularly evaluate the optimal amount of fluid when resuscitating burn patients. The clinical interpretation of hemodynamic status can be very difficult in this population, which is problematic considering the potential harm caused by under- or over-resuscitation.

Resuscitation formulas are merely guidelines for the initial fluid resuscitation infusion rates, and these need to be adjusted based on physiological endpoints. Throughout the history of burn resuscitation, certain endpoints were used in an attempt to achieve optimal resuscitation. These endpoints comprise, for example, urinary output, systemic blood pressure, mean arterial pressure, lactate levels, cardiac filling pressures, cardiac output or volumetric indices such as thoracic blood volume index (TBVI) and global end-diastolic volume index (GEDVI) [37]. These endpoints or targets can be obtained by minimal or less invasive traditional monitoring methods as pulse contour analysis and/or transpulmonary thermodilution.

It is important to realize the limitations of any monitoring device, and accept that no monitoring device can improve patient-centered outcomes unless it is coupled to a treatment protocol that improves the outcome [38]. The most frequently used endpoints in burn resuscitation will be discussed here.

Recommendation: *Every severe burn patients (> 20% TBSA in adults or > 15% TBSA in children) should be adequately*
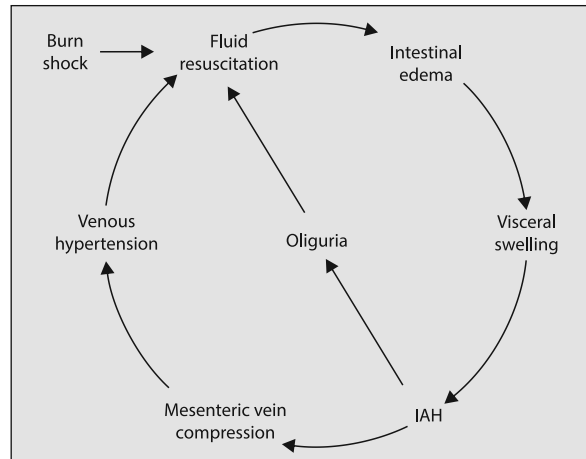
monitored with regard to fluid status, fluid responsiveness and organ perfusion.

The recommendations regarding the different resuscitation targets and endpoints are summarized in Table 1.

URINE OUTPUT

Urine output has classically been adopted as the primary endpoint to guide resuscitation in burn care. The prevailing view deemed it appropriate to target a diuresis of greater than 0.5 mL kg^{-1} h^{-1} in adults and 1 mL kg^{-1} h^{-1} in the pediatric population. This endpoint, however, has been brought into question by various studies. In a retrospective review, no correlation between urine output and invasively derived physiologic variables was found [39]. Moreover, urine output was unable to identify fluid responders after a fluid challenge. Other studies also suggest the inaccuracy of urine output as a resuscitation target [40, 41], perhaps even contributing to the phenomenon of fluid creep.

A better understanding of elevated IAP and its pathophysiology has led to new insights, with urine output being a potentially harmful endpoint in the presence of elevated IAP. In an experimental study in 1923, Thorington [42] described a concomitant decrease in urine output with increasing IAP caused by ascites, reflecting the pathophysiological effect of elevated IAP on renal function. Decreased urinary output can easily mislead the clinician, as while decreased urine output may be the result of intravascular hypovolemia, it equally could also be caused by IAH and ACS. In the latter situation, a vicious cycle is established with further fluid loading. This will cause even more intestinal edema and visceral swelling, leading to increasing IAP, venous hypertension and deteriorating renal function (Fig. 2). The monitoring of IAP will provide valuable information, warning the clinician in case of impending IAH or ACS.

Recommendation: *Urine output is a poor endpoint that may lead to over- or under estimation of fluid resuscitation and, as such, can no longer be recommended. However, in situations with limited monitoring techniques, it can still be used to guide fluid resuscitation.*

BAROMETRIC PRELOAD

Pulmonary artery occlusion pressure (PAOP) and central venous pressure (CVP), also known as the cardiac filling pressures (or barometric preload indicators), were used as measures of preload as they were considered to be a reasonable reflection of the end-diastolic volumes of the left and right ventricles [43].

The CVP, obtained via a central venous catheter, used to be measured in almost all ICUs around the world, while clinical decisions, such as fluid or diuretic administration, were frequently based on the interpretation of this parameter. This was encouraged by clinical guidelines such as the Surviving Sepsis Guidelines, which recommended using CVP as an endpoint of fluid resuscitation in sepsis [44]. PAOP is obtained by a pulmonary artery catheter, which not only measures pulmonary artery pressure and PAOP, but also cardiac output through thermodilution techniques, together with mixed venous oxygen saturation. This provides extensive information regarding hemodynamics and the oxygen supply/demand balance.

Recent studies have questioned the efficacy of CVP and PAOP as endpoints for resuscitation as these parameters do not correlate with ventricular filling pressures and ventricular end-diastolic volumes [45, 46]. This holds also true in burn patients with increased IAP and artificially increased CVP or PAOP [6, 33, 43].

In a systematic review by Marik [47], a very poor relationship was found between CVP and blood volume. Additionally, it was unreliable in its ability to predict the hemodynamic response to a fluid challenge. In a further study looking at the filling pressures in healthy subjects [48], there was no correlation between initial CVP/PAOP and end-diastolic ventricular volume index (EDVI), as well as stroke volume index. This lack of correlation was persistent following fluid loading. In contrast, initial EDVI and changes in EDVI following fluid loading correlate strongly with pre- and post-fluid loading changes in stroke volume index, suggesting the possible benefit of this volumetric index.

Mounting evidence demonstrates cardiac filling pressures are poor predictors of fluid responsiveness [47, 49, 50] while the use of a pulmonary artery catheter fails to influence outcomes in randomized controlled trials [51], thus rendering CVP and PAOP obsolete as standardized endpoints for fluid resuscitation. Therefore, their use should be reserved for specific indications (such as pericardial tamponade).

Recommendation: *Barometric preload indicators should not be used to guide fluid resuscitation in burn patients.*

VOLUMETRIC PRELOAD

Advances in technology (such as transpulmonary thermodilution) allow the monitoring of preload in static volumetric indices such as global end-diastolic volume (GEDV) and intrathoracic blood volume (ITBV). These parameters can be measured with the use of a conventional central venous catheter and a dedicated femoral artery catheter (PiCCO, Pulsion Medical Systems or EV1000, Edwards Lifesciences). During the taking of measurements, a known volume of cold normal saline is injected through the central venous line. The arterial catheter detects temperature differences and generates a thermodilution curve to which the Stewart Hamilton equation is applied to calculate cardiac output (CO) and volumetric preload indices, indexed according to body surface area [52]. Some pathologies may create inaccurate measurements such as intracardiac shunts, aortic aneurysms, aortic valvular stenosis, severe mitral or tricuspid regurgitation, pneumonectomy, pulmonary embolism, the presence of a balloon pump and unstable arrhythmias. Catheters may have to be placed in other locations due to the localization of burn wounds. If both a central venous catheter and an arterial PiCCO catheter are placed in an ipsilateral femoral site, a crosstalk phenomenon can occur as the cold bolus injected through the central venous catheter passes the thermistor of the arterial catheter, leading to errors in measurement. This may be avoided by withdrawing the arterial PiCCO catheter a few centimetres [52].

The GEDV consists of the volumes of all four cardiac chambers, while the ITBV is the total combined volume of the heart (GEDV) and pulmonary blood volumes, both measured at the end of diastole (with ITBV = $1.25 \times$ GEDV). Numerous studies have shown that these volumetric indices represent preload more precisely when compared to urine output [30, 31] or cardiac filling pressures [50, 53], which are prone to missing hypervolemia as it is poorly represented by the blood pressure, filling pressure and/or urine output in the early resuscitative phase [31]. By measuring the ejection fraction to correct these volumetric preload parameters, the ability of these parameters to assess changes in preload over time can be further improved [53].

Recommendation: *Volumetric preload indicators are superior when compared to barometric ones and are recommended to guide fluid resuscitation, especially in burn patients with increased IAP.*

Another parameter that can be derived from transpulmonary thermodilution is the extravascular lung water (EVLW), indexed to predicted body weight. This consists of the interstitial, intracellular and intra-alveolar water of lung tissue. This parameter, together with the pulmonary

vascular permeability index (PVPI), can be used to determine the presence of lung edema which can be very useful as a safety parameter during resuscitation [31]. This is particularly applicable in patients with inhalation injuries or in guiding fluid de-resuscitation if a patient fails to proceed to the "flow" phase [1–3]. Of course, as explained above, the cardiac index can also be derived from transpulmonary thermodilution, which can be used to determine the need for additional inotropic therapy.

Recommendation: *The use of extravascular lung water is recommended to guide de-resuscitation in burn patients not progressing spontaneously from an "ebb" to a "flow" phase.*

FLUID RESPONSIVENESS

Following a fluid challenge, patients may be classified as either a responder or a non-responder. Responders are patients who are on the ascending limb of the Frank Starling curve, during which the fluid challenge will result in an increase in stroke volume and cardiac index due to an increased preload. A fluid responder is defined by an increase in stroke volume of 10-15% following a fluid challenge [37].

To determine the benefit of fluid administration, several clinical and hemodynamic tests can be used. As mentioned above, although CVP does not predict fluid responsiveness [46, 47], studies have shown that dynamic parameters, obtained by invasive arterial monitoring and pulse contour analysis (such as pulse pressure variation [PPV] and stroke volume variation [SVV]) are highly predictive of fluid responsiveness in mechanically ventilated patients [54]. Most publications report that a PPV or SVV greater than 12% is highly predictive of fluid responsiveness. Classically, fluid responsiveness is defined as an increase in cardiac index of 15% or more after a fluid bolus. It should be emphasized that PPV and SVV are unreliable in patients with spontaneous breathing activity, cardiac arrhythmias, pericarditis, cardiac tamponade, right ventricular failure (high CVP), high PEEP or high IAP and low tidal volumes (< 6 mL kg^{-1}) [52].

An experimental study has shown that PPV and inferior vena cava flow fluctuations were dependent on IAP (the higher the IAP, the higher the SVV or PPV) [55]. Although this effect is probably related to concomitant changes in pleural pressure, further analysis showed that this was only related to a Δup phenomenon, which suggests that dynamic indices are not exclusively related to intravascular volume status in the presence of increased IAP [56]. This was confirmed in a review of all experimental studies regarding increased IAP and functional hemodynamics [56]. The conclusion was that an increase in IAP with 18 mm Hg doubles the SVV and PPV values. Subsequently, clinicians need to be cautious not to interpret increased PPV and SVV caused by IAH or ACS as hypovolemia with fluid responsiveness, and thus further over-resuscitating the patient.

Another method to determine fluid responsiveness is the passive leg raise (PLR) test, where a reversible autotransfusion is caused by simply raising the patient's legs to mimic the effects of a fluid challenge. Besides the ease and economic advantage, this test is completely reversible, whereas a fluid challenge could worsen resuscitation related morbidity. An increase in the cardiac index of 10% with a PLR test is an indicator of fluid responsiveness [57]. In contrast to predicting fluid responsiveness with PPV and SVV, the PLR test is reliable in patients with arrhythmias and spontaneous breathing activity. However, one must be cautious because the PLR can provide false negative results in patients with elevated IAP (and thus also burn patients), where venous return is impaired [58]. This can be avoided by performing the test in the Trendelenburg position, which gives the best endogenous transfusion in the presence of IAH. This technique is contraindicated in patients with intracranial hypertension, while a reflux of gastric content may also occur.

The end-expiratory occlusion test is another non-invasive, quick technique to predict fluid responsiveness in intubated patients. It increases cardiac preload and allows for the detection of preload dependence. Fluid responsiveness is predicted with a high sensitivity and specificity by an increase in pulse pressure > 5% during the end-expiratory occlusion and by an increase in cardiac index > 5% [59]. Just as the passive leg raise test, the end-expiratory occlusion test can be reliably interpreted in cardiac arrhythmias or spontaneously breathing patients.

Recommendation: *Fluid resuscitation in burn patients should be guided by physiological parameters or tests that are able to predict fluid responsiveness.*

HOLISTIC APPROACH: INTRODUCTION OF A NEW PROTOCOL

In an attempt to guide fluid resuscitation effectively in burn patients in the future, while avoiding deleterious effects of over-resuscitation, a multimodal protocol using a modified formula and multiple endpoints is suggested. Each burn patient deserves personalized (protocolized) care using a stepwise approach.

Fluid resuscitation should be initiated in adults with > 20% TBSA and children with > 15% TBSA. A modified Parkland formula is suggested, using a balanced crystalloid (for example, Plasma-Lyte®), to be given at 2 mL kg^{-1} %TBSA^{-1} in the first 24 hours in combination with albumin 20% at 0.2 mL kg^{-1} %TBSA^{-1}. Half of the total dose of crystalloids and colloids should be given in the first eight hours, and the other half between 8–24 hours. Over the next 24 hours Plasma-Lyte® is given at 0.75 mL kg^{-1} %TBSA^{-1} in combination with albumin 20% at 0.075 mL kg^{-1} %TBSA^{-1}. These resuscitation rates are fixed and fluids are gradually decreased over the next 24–48 hours of burn shock resuscitation. Basic
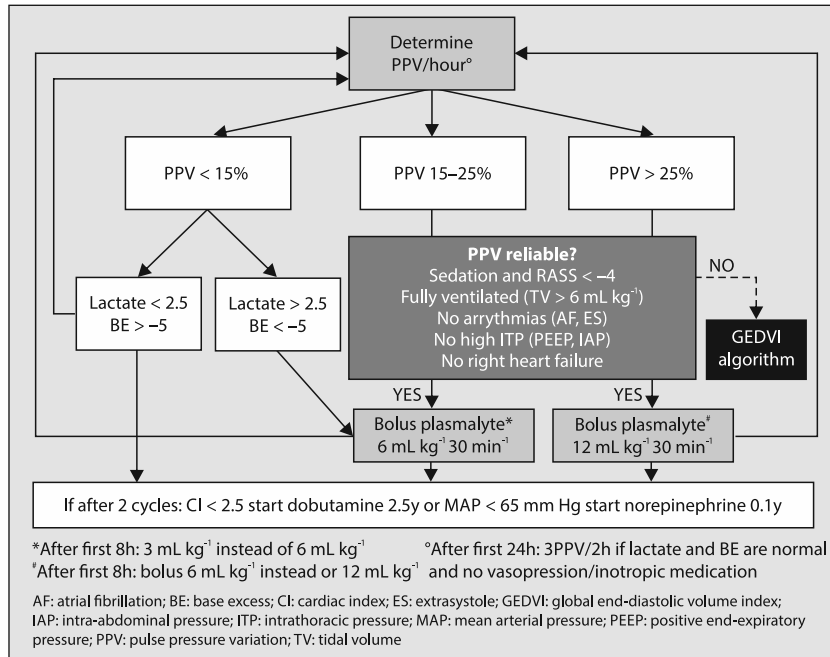
Figure 3. The Pulse Pressure Variation algorithm to guide resuscitation in severely burned patients. If the patient is mechanically ventilated and PPV is reliable, fluid resuscitation is guided by the PPV algorithm

fluids need to be supplemented in the form of a glucose containing solution such as Glucion® 5% at a constant rate of 30 mL kg^{-1} 24h^{-1} at all times. Enteral nutrition, if given, should be included in the basic fluid administration. Fluids are changed or adapted throughout resuscitation according to biochemical analysis and concomitant medical conditions (see algorithms as discussed further). During the first 24 hours, the resuscitation fluids, as calculated above, are kept at a constant rate, and when needed, fluid boluses can be given at 3, 6 and 12 mL kg^{-1} over 30 minutes, depending on the different thresholds as discussed further. De-resuscitation (with a gradual decrease in resuscitation fluids) is only started after the first 24 hours. Extra albumin 20% can be administered based on serum levels of albumin (target 30 g L^{-1}) or colloid oncotic pressure (COP, target at least 16–18 mm Hg).

PPV ALGORITHM

As discussed above, different endpoints in combination with lactate and base excess (BE) can be used in order to guide fluid resuscitation. If a patient is sedated and mechanically ventilated, pulse pressure variation (PPV) is used, whenever reliable. The subsequent PPV algorithm is presented in Figure 3. The clinician, however, needs to check whether the patient has conditions leading to incorrect interpretation of PPV, as discussed above, while before each fluid bolus, fluid responsiveness is tested [52]. In cases where PPV is unreliable, the GEDVI algorithm needs to be used.

GEDVI ALGORITHM

If PPV is unreliable, volumetric parameters are measured with the use of transpulmonary thermodilution using PiCCO technology. Here, the GEDVI is interpreted as a measure of preload and EVLWI as a safety parameter warning for impending pulmonary edema. The subsequent GEDVI algorithm is presented in Figure 4. The correct interpretation of volumetric parameters needs to be made in relation to the presence, or not, of the conditions mentioned above (valvulopathy, catheter position, extracorporeal circuit etc.) [52]. If the GEDVI is high, the measurement needs to be corrected with the global ejection fraction, as this leads to a more accurate estimation of preload [53] (Table 4).

URINE OUTPUT ALGORITHM

If PPV or volumetric parameters are unreliable, or when monitoring possibilities are limited, urine output (UO) can be used to guide fluid resuscitation. The subsequent UO algorithm is presented in Figure 5. The importance of measuring IAP needs to be underlined when using urine output as a resuscitation target as IAH and ACS decrease urine output.

In children with TBSA > 10–15%, with a bodyweight below 30 kg, the Parkland formula is used (4 mL kg^{-1} %TBSA^{-1}) in the first 24 hours. As with adults, half is given in the first eight hours. Basic fluid needs should always be given in glucose-containing fluids. The fluid rate in children is guided by urine output as presented in the UO algorithm in Figure 5,
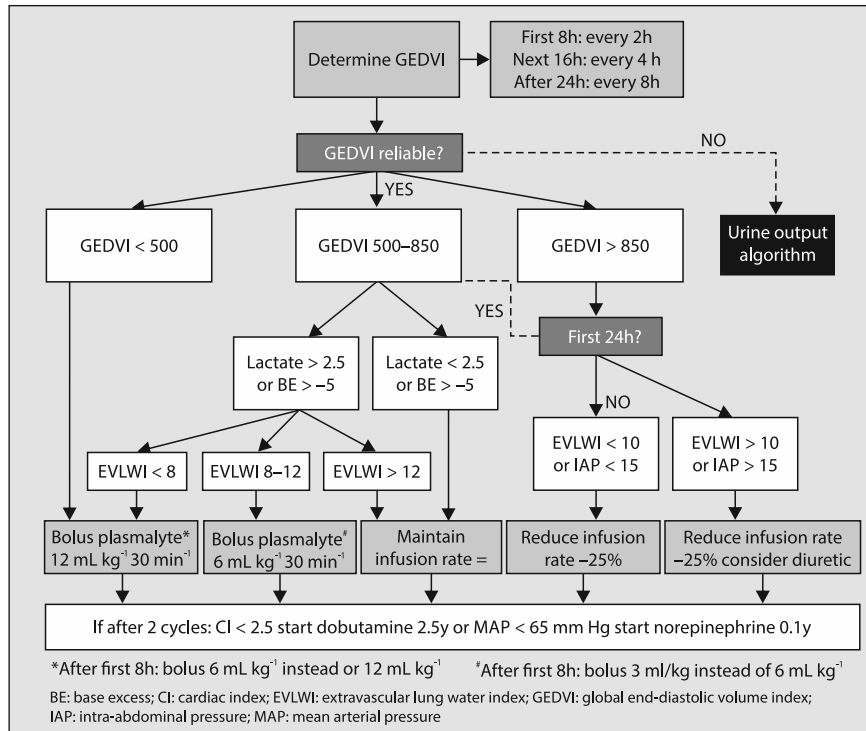
Figure 4. Global end-diastolic volume index algorithm to guide resuscitation in severely burned patients. If PPV is unreliable, the patient has a PiCCO catheter and GEDVI is reliable, fluid resuscitation is guided by the GEDVI algorithm

Table 4. Global ejection fraction corrected volumetric target values

Ejection fraction	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%
GEDVI-target (normal)	1175	1050	950	850	775	700	625	575	525	475	435
GEDVI-target (critically ill burns)	1450	1300	1150	1025	925	825	750	675	600	550	500

Critically ill: refers to an unstable patient with a clinical diminished preload; GEDVI: global end-diastolic volume index; normal: refers to a stable patient

however the target diuresis is 2 mL kg^{-1} h^{-1} in children weighing < 10 kg and 1 mL kg^{-1} h^{-1} in children between 11–30 kg.

CONCLUSIONS

During the last decades, burn resuscitation keeps evolving and new trends appear. Over the last fifteen years, much attention has been given to avoid over-resuscitation and subsequent morbidity and mortality. Fluid creep is recognized by nearly all physicians involved in burn care.

Efforts should be made to avoid excess crystalloid administration by revising resuscitation protocols. Physicians need to be aware of the harm caused by fluid overload during resuscitation. They should actively aim to avoid fluid accumulation, as this can be at least as harmful, if not more so, than under-resuscitation. Evidence suggests that the addition of a colloid, such as albumin 20%, may decrease fluid requirements and may potentially reduce resuscitation-related morbidity (especially renal, respiratory complications and compartment syndromes). However, the use of colloids in burn resuscitation continues to be a great source of controversy and discussion and, as explained in part 1 of this concise review, HES solutions should not be used. Ascorbic acid as an adjunctive therapy shows promising results, without presenting adverse effects. Its use should be considered in patients at risk of fluid overload or secondary IAH and ACS.

Moreover, the endpoints of burn resuscitation should be redefined. Although the traditional urine output target does not represent preload accurately as shown in numerous studies, barometric preload parameters also seem to lack this ability. The evidence suggests that advanced hemodynamic monitoring with pulse contour analysis and transpulmonary thermodilution may provide superior endpoints, such as pulse pressure variation (PPV) and global end diastolic volume index (GEDVI), in order to prevent under-resuscitation, while extravascular lung water index (EVLWI) can be used as a safety parameter to avoid over-resuscitation and to guide the de-resuscitation process.
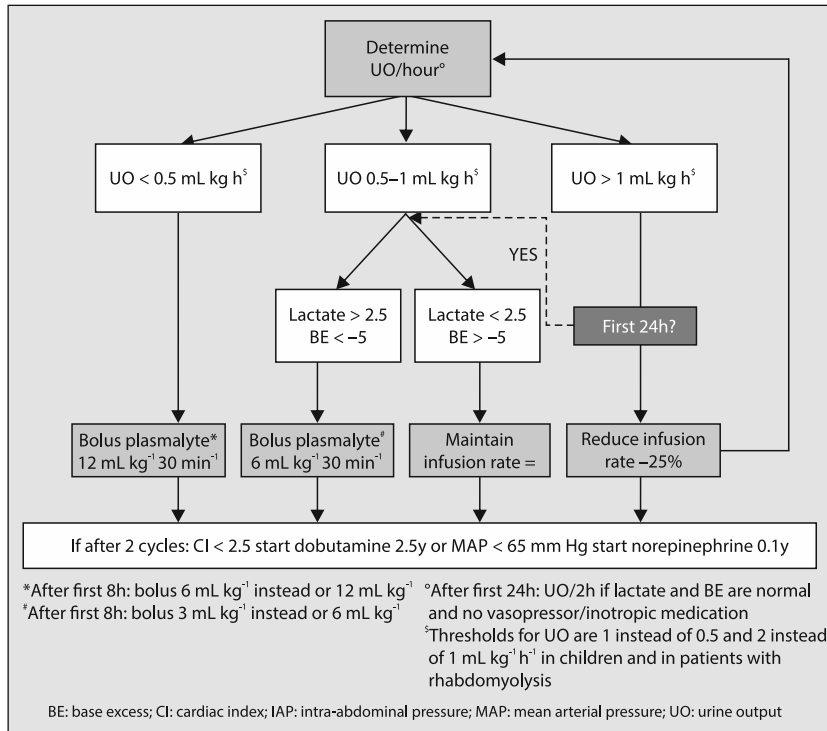
Figure 5. Urine output algorithm to guide resuscitation in severely burned patients. If the patient has no PiCCO catheter (or GEDVI is not reliable) and PPV is not reliable, fluid resuscitation is guided by the UO algorithm

The role of intra-abdominal hypertension and its pathophysiology has been extensively investigated over recent years, while efforts should be made to prevent and treat intra-abdominal hypertension and its most lethal complication — abdominal compartment syndrome. It should be emphasized that regular and routine monitoring of intra-abdominal pressure (IAP) is of paramount importance in severely burned patients. More studies are needed to establish the place of the proposed algorithms and personalized care in severely burned patients.

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