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Individualizing Optimal Fluid Resuscitation in Patients with Major Burns: Emerging Role for Hydrocortisone, Proteinuria and Brain Natriuretic Peptide

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During the last decades tremendous progress has been made in the acute resuscitation of patients with major burns [1,2]. The recognition that large amounts of fluids should be infused during the first hours to days, due to capillary leakage which is the pathologic hallmark of a burn injury [3,4], is one of the most important reasons for the improved survival in these patients. Important formulae like the Parkland formula were of enormous help [3]. These efforts today provide the basis for new strategies to decrease capillary leakage and strategies to further improve fluid resuscitation. Thus the focus shifts from a uniform resuscitation towards a more individualized resuscitation strategy.

At the time of severe burn injury, the body responds with a massive inflammatory reaction driven by cytokines which induce the endothelial cells to lose their binding, leading to capillary leakage [5,6]. This inflammatory response will differ between individuals like it differs between septic patients and as a consequence the extent and duration of the capillary leakage will differ. Differences in burn size, depth and type, presence of inhalation injury, age, sex, genetic background and others all play a role. Also comorbidity differs between patients. All these parameters eventually influence the inflammatory response on the one hand and need for fluid resuscitation on the other. Two important questions thus are in which patients do we need to intervene on an increase in capillary leakage and how can we intervene. As capillary leakage decreases, so does the need for large amounts of fluid. Since too large amounts of fluids have several negative side effects on organ function, an important third question is therefore how to monitor the fluid status of a patient and tailor fluid amounts to individual patients' needs.

The next paragraphs address recent studies that may be useful for identifying patients with major burns (percentage total body surface area burned 20% or higher, according to the American Burns Associations' burn severity grading system) who are at risk for excessive capillary leakage, on interventions to reduce capillary leakage and on parameters that might be used to monitor fluid status and to tailor amount of fluids to be supplied. The focus in these paragraphs will be on the emerging role for hydrocortisone, proteinuria and Brain Natriuretic Peptide (BNP) to optimize individual patient's fluid resuscitation.

Parameters Indicating the Need for Intervention to Reduce Capillary Leakage

Decisions to start an intervention generally are based on balancing risks and expected benefits of this intervention in an individual patient. Clinical or laboratory parameters are used to judge this balance. In patients with burns the traditional clinical parameters that have proven to be of value to assess risk and thus prognosis and the need for fluid resuscitation due to capillary leakage, besides age and gender, are burn size and depth. The Parkland formula and the Baux score are based on these clinical parameters [3,5].

Proteinuria is a laboratory parameter that has been known for decades to be closely related to the severity and clinical progress of burn injury [6]. More recently, new interest for this prognostic parameter has been advocated [7-9]. Proteinuria is known to reflect systemic capillary leakage [10]. Capillary leakage with insufficient fluid resuscitation will lead to a low intravascular volume and Brain Natriuretic Peptide (BNP) levels

are strongly related to fluid retention [11]. We thus hypothesized that patients with high proteinuria may have more capillary leakage and that the more severe cases will have low BNP levels. Proteinuria in combination with BNP levels were measured in patients with severe burns to investigate whether low levels of BNP in combination with increased levels of proteinuria predict worse outcome [10]. In this study, averaged proteinuria at day 1 and 2 correlated positively with initial Sequential Organ Failure Assessment Scores **(SOFA score)**, indicating that patients with a higher proteinuria had a worse prognosis, which is in line with the literature [6-9]. Moreover, measurement of BNP levels had additional value. Patients with high proteinuria and low BNP levels, performed worse, as measured by SOFA scores, than patients with low proteinuria and high BNP levels, probably indicating increased capillary leakage. Patients with the other two possible profiles performed intermediate. Proteinuria in combination with BNP in the first days after admission thus could be used to characterize patients with an exaggerated capillary leakage which could be useful to identify those patients that might benefit from interventions to reduce capillary leakage most.

Apart from cardiovascular markers such as proteinuria and BNP levels, various other prognostic markers have been recognized. Burn injury induces an inflammatory and a hormonal stress response. The inflammatory response is evident from changes in peripheral blood counts such as monocytes and T-cells [12,13] and in interleukin levels [14,15]. Several authors showed that in particular interleukines 6, 8 and 10 are elevated within days after burn injury and that these levels correlate with the severity of the injury. These inflammatory response parameters are reported not only to depend on burn size but also to differ between individuals [12-16]. These differences may be explained in part by differences in each individual genetic make-up [17,18]. Burn trauma also induces coagulopathy and combining a patient's early coagulation and inflammatory status in addition to standard clinical indices improves prognostic models [19]. Since capillary leakage is probably invoked by cytokines measuring those cytokine profiles and/or genetic testing also might be of use in determining in which patients interventions aimed at reducing capillary leakage may be beneficial.

Finally, a hormonal stress response with hypercortisolism is seen after burn injury. It is unclear however, whether cortisol indices can be used to judge the necessity to start therapy for reduction of capillary leakage. Tissue cortisol levels are increased in burn patients, but, they do not correlate to plasma cortisol [20]. Moreover, use of hydrocortisone as intervention in severely burned patients to improve hemodynamic stability based on corticotropin tests for adrenal insufficiency did not predict the effects of hydrocortisone intervention [21].

Several strategies thus can be proposed to assess an individual patient's need for interventions aimed at reducing capillary leakage. Proteinuria and BNP levels in combination can be used to judge the extent of capillary leakage immediately after the burn injury. Moreover, these parameters are instantly and easily available. Alternatively cytokine profiles, cellular response, coagulation parameters or cortisol levels, maybe in combination can be used for this purpose.

Hydrocortisone and Other Strategies to Decrease Capillary Leakage

Capillary leakage characterizes the main effect of the inflammatory response in severely burned patients. This inflammatory response is thought to be driven by cytokines [22,23]. Several studies showed various interventions to be capable of reducing capillary leakage or inducing reductions in fluid requirements. First, prompt wound excision and fluid resuscitation has been shown to decrease the extent of the inflammatory response [24]. In man, N-acetylcysteine and the combination of recombinant human growth hormone and propranolol [25,26] and in animals pentoxifylline and ulinastatin also attenuated the inflammatory response [27,28]. High doses of ascorbic acid given early significantly reduced resuscitation fluid volume requirements [29]. Finally, London et al. showed in-vitro and in animals that strengthening the Slit-Robo4 signalling pathway stabilizes the endothelial intercellular junction by preventing the dissociation of p120-catenin from VE-cadherin in response to inflammatory mediators [30]. This approach reduced mortality and was independent from changes in cytokine levels, suggesting that reducing capillary leakage is pivotal in reducing mortality in septic or injured patients.

Though suppressing the inflammatory response might not be the only means to prevent capillary leakage to overwhelm the patient, so far studies have only either been performed in small groups of patients or interventions are not yet applicable in man. Recently however, several studies with low-dose hydrocortisone started immediately after admission were reported to improve outcome in patients with major burns [21-23,31,32]. Hydrocortisone differentially regulates cytokine responses and modulates transcriptional processes [18,33]. This provides a physiological understanding of the mechanism of action of hydrocortisone on cytokine responses and thus on capillary leakage.

We recently investigated the effects of low-dose hydrocortisone (starting dose of 300 mg/24 h tapered off in 13 days) on organ function scores in 39 patients [31]. Organ function scores improved faster in patients receiving hydrocortisone. Moreover, we investigated the effects of hydrocortisone on proteinuria and BNP. Interestingly, hydrocortisone induced first a decrease in proteinuria, which was followed by and correlated to an increase in BNP, suggesting a reduction of capillary leakage. We found this in patients in whom hydrocortisone was started when they were norepinephrine-dependent as well as in patients in whom hydrocortisone was started on admission and who were compared to controls without hydrocortisone intervention. No significant differences in adverse events were noted between hydrocortisone and control groups. These data suggest hydrocortisone to be beneficial by decreasing capillary leakage. Indeed, we also found a reduction in fluid requirement in the hydrocortisone group.

Huang et al. [32] showed in a relatively large study, in 69 patients with 70% or more total body surface area (TBSA) burns, a 200 mg/24 h dose of hydrocortisone given in the acute phase and continued for 7 days to be safe and effective and to reduce

interleukin-6 and tumor necrosis factor-α. Remarkably, they also observed a reduced incidence of pulmonary infections and stress ulcers. This study infers that hydrocortisone attenuates the inflammatory response after a severe burn.

Others included norepinephrine dependent patients with burns to study the effects of hydrocortisone. In these studies, hydrocortisone was thus started several days after admission. Fuchs et al. compared 10 patients in whom 200 mg/24 h hydrocortisone was given with 9 controls and found a reduced need for catecholamines and improved outcome [22]. Winter et al. showed a bolus of 100 mg followed by an infusion of 0.18 mg/(kgh) of hydrocortisone to reduce doses of norepinephrine and fluid requirements in surviving but not in non-surviving patients [23]. Venet et al. found hydrocortisone to reduce vasopressor administration compared to a placebo group (N=27, mean TBSA burned 62%) [21].

Low-dose hydrocortisone thus seems to be safe and effective in severely burned patients and one of its effects might be a reduction in capillary leakage. Since capillary leakage is crucial in the pathophysiology of the systemic response to a burn injury and since it is present within hours to days after injury, an early start with low-dose hydrocortisone may be beneficial, as shown by us and others [31,32]. The optimal dose, timing and duration of hydrocortisone still needs to be defined further, and future studies will need to clarify the precise role of hydrocortisone versus other strategies for each individual's needs. Given its positive effects in reducing capillary leakage, hydrocortisone therapy will decrease fluid demands and new strategies to monitor and guide fluid resuscitation in the course of the burn injury are required.

Monitoring Fluid Status: Serial Measured and Individualized BNP as a Simple and Useful Tool

Current formulae indicate the amounts of fluid to be given during the first days after injury but do not specify how to return to normal amounts. These formulae also do not take into account interventions that cause the inflammatory response and consequent capillary leakage to subside. Frequently, resuscitation volumes exceed the fluid amounts based on these formulae [1]. With hydrocortisone therapy administered fluids can be lowered more rapidly [31]. Since too high administered amounts of fluids cause organ dysfunction, after adequate resuscitation in the acute phase, cumulative fluid balance should be aimed as low as possible. Adjustments to estimate fluid needs must be made based upon a burn patient's physiologic response to resuscitation. Most often urine production is used. Other clinical signs of volume status, such as heart rate, blood pressure, capillary refill and colour of uninjured skin can also be taken into account. These clinical parameters however lack accuracy. Strategies thus are needed to monitor fluid status and the more so to tailor and help guiding reductions in the amounts of fluids to be ordered.

Preferably, a parameter for monitoring fluid status correlates with fluid status, whereas a parameter for tailoring fluid status needs to meet several criteria: Changes in fluid status are translated in simultaneous changes of the parameter, the parameter defines a lower as well as an upper limit and the parameter can be measured safely over a longer period of time.

Several methods have been tested to monitor and/or to guide fluid status: chest radiography, bio-impedance vector analysis, central venous pressure, thoracic and vena cava diameter ultrasound, Pulse index Contour Continuous Cardiac Output (PiCCO) system and brain natriuretic peptide [34]. All these parameters have their benefits and draw-backs [34,35]. In patients with severe burns some of these methods cannot be used because of the location of the burn or the invasive nature withholds their use for a longer period because of increased risk for infection.

Natriuretic peptides are interesting markers for fluid resuscitation as they are secreted from the myocardium under increased wall stretch [36]. BNP is nowadays used in the diagnosis of heart failure and is strongly related to fluid retention [11]. The height of BNP levels is known to be affected by various conditions [37]. **Table 1** summarizes these conditions in categories of permanent, persistent and variable (adapted from Henein et al. [37]). Permanent conditions are characteristic for each individual patient and will not change in time. Although BNP levels in a specific patient thus may be elevated due to this condition, the BNP level itself will be patient specific. In the course of the first days of the admission it will become clear in what range the optimal BNP levels of this patient vary. Persistent conditions influence BNP levels during the course of their presence, which however will last for at least several days. These conditions do not change with the burn injury and thus define a specific level for the patient's individual optimal fluid balance, though changes in BNP still correlate with changes in fluid status. These conditions are well recognized and thus can be accounted for. Thus, in the absence of variable rhythm disorders, the most important variable that affects changes in BNP values from one moment to the other is fluid status. Therefore, while monitoring the absolute fluid status with BNP levels in a patient depends on several conditions, sequential measurement of BNP comes close to the above mentioned criteria to tailor fluid status and to help guiding reductions in ordered amounts of fluids. BNP levels change with fluid status simultaneously, and can be measured safely for longer periods of time due to its non-invasive nature.

Our first practices with BNP in severe burns concerned its usefulness in the differential diagnosis between ARDS and congestive heart failure in a patient with inhalation injury and severe burns. Low plasma BNP levels excluded cardiogenic pulmonary edema and justified the infusion of extra fluids [38]. Subsequently, we investigated whether BNP levels can be used to monitor and/or guide fluid balance in patients with severe burns [10]. It was hypothesized that in case of capillary leakage, loss of fluid causes BNP levels to be low, and to increase upon fluid resuscitation. Indeed, BNP levels increased during the first three days of resuscitation in which the highest amounts of fluid were administered. Furthermore, those patients who received less fluids and thus were hemodynamic stable as the amounts

of fluids were determined based on adequate urine production and blood pressure, had increased BNP levels. Probably, these higher levels of BNP reflect more intravascular volume due to less capillary leakage. The clear association of a high level of BNP and less received fluid volume found in this study, suggests that BNP can be used in the individual patient to adjust fluid orders to actual demands. The main draw-back of BNP levels is its dependence on patient characteristics which makes it difficult to define general lower and upper limits. This draw-back can be overcome by taking the co-morbidities as summarized in **Table 1** into account. Moreover, serial measurement of BNP allows defining an individual's BNP value in a stable phase with clinically optimal fluid balance as target levels for that patient.

Tailoring Fluid Resuscitation and Hydrocortisone Dose during the First 2-3 Weeks after Major Burns

From the considerations discussed above it follows that serial measurements of proteinuria and BNP can be used to monitor the course of capillary leakage invoked by burn injury and the response to fluid resuscitation. This paragraph proposes a framework for the use of these parameters to tailor hydrocortisone dose and fluid resuscitation on an individual basis. To make this model practically applicable, targets and limits for proteinuria and BNP are proposed, derived from experiences at our institution, to indicate the start of hydrocortisone and to taper hydrocortisone dose as well as tailor fluid status by increasing or decreasing ordered amounts of fluid resuscitation **(Table 2)**.

The combination of high proteinuria and/or low BNP levels characterize patients at risk to develop an exaggerated increase in capillary leakage, indicating that they may benefit from hydrocortisone. In our study on the effects of hydrocortisone on proteinuria and BNP the patients who were shown to benefit had proteinuria of more than 0,6 g/24 h and/or BNP levels below 75 ng/L (approximately 400 ng/L NT-pro-BNP) during the first 2 days post burn [31]. Investigating the prognostic use of proteinuria and BNP, we found patients with a profile of either proteinuria more than 0,9 g/24 h and/or BNP levels below 119 ng/L at day 3 after admittance to perform worse compared to patients who had both a lower proteinuria and higher BNP level [10]. These data are in line since both proteinuria and BNP increase the first days after burn injury. Thus, the lower cut-off values of proteinuria of more than 0,6 g/24 h and/or BNP levels below 75 ng/L during the first 2 days post burn, can be used to select patients with major burns with increased risk for capillary leakage and in whom to start hydrocortisone early. To avoid delay for 24 h for urine tests, one may also use limits for urinary protein concentrations during the first 2 days after admittance, which in these groups was >0,4 g/L.

The optimal starting dose of hydrocortisone still needs further research. Current evidence however, indicates that low-dose schemes are beneficial i.e. hydrocortisone doses of 200-300 mg/24 h with or without a priming dose of 50-100 mg [21-23,31,32]. Some studies used a continuous dose for 7 days [22,23,32], whereas others used a tapering scheme [21,31]. Tapering schemes are standard in many other inflammatory diseases and also fit best in an individual treatment. Proteinuria can be used to taper hydrocortisone. In patients on hydrocortisone proteinuria decreases, in contrast to the increase in proteinuria in control patients [31]. We observed (unpublished data) that after stopping hydrocortisone early hemodynamics destabilize and proteinuria increases, whereas restarting hydrocortisone has the opposite effect, prolonging the duration of hydrocortisone infusion. It thus seems logical to taper hydrocortisone in small steps of for instance 25 mg/24 h under the condition that proteinuria is stable or decreases. This limits the use of hydrocortisone while individualizing the effect of hydrocortisone on the course of the patient's capillary leakage **(Table 2)**. We thus found the tapering scheme to lower proteinuria in the acute phase with a subsequent plateau phase in the week thereafter and finally to decrease proteinuria further [31].

The effect of hydrocortisone on capillary leakage will reduce the needed amounts of administered fluids. In general, a more optimal resuscitation scheme may have even higher amounts of fluids to be given in the acute phase with a switch to lower amount as soon as possible, ultimately leading to a lower total cumulative fluid balance. In patients with major burns BNP levels increase with fluid resuscitation and reach maximal levels after 3-7 days [10,31]. In our experience, we see in most patients an optimal fluid balance coinciding with BNP levels of 150-225 ng/L (or NT-pro-BNP 600-800 ng/L); both to be adapted individually based on co-morbidity **(Table 1)** and serial measurements. These

Table 1 Conditions in which BNP levels are elevated.

Permanent factors (*Sustainable*)	Persistent factors (*longer duration*)	Variable factors (*Shorter duration*)
General - Age - Weight **Cardiac** - Congenital heart disease - Diminished left ventricular ejection fraction - Hypertrophic cardiomyopathy - Aortic / Mitral stenosis - Aortic/Mitral regurgitation **Pulmonary** - COPD - Asthma - Bronchitis - Lung cancer - Pulmonary Embolism - Pulmonary Arterial Hypertension - Sleep Apnoe	- Pneumonia - Sepsis - Renal insufficiency - Anemia - Burns - Acute coronary syndrome - Tako Tsubo cardiomyopathy - Myocarditis/ Pericarditis - ARDS	- Hydration status - Atrial fibrillation - Ventricular fibrillation - Supraventricular tachycardia - Bradycardia

Conditions are categorized according to their changeability in time in three categories: permanent (general, cardiac and pulmonary), persistent (longer duration) or variable (shorter duration) factors

Table 2: Tailoring fluid resuscitation and hydrocortisone dose during the first 2-3 weeks after major burns.

Start hydrocortisone in patients with proteinuria >0,4 g/L or >0,6 g/24 h and/or NT-pro-BNP<400 ng/L (BNP<75 ng/L) at day 1 or 2 post burn			
Tailoring fluid resuscitation		**Tailoring hydrocortisone dose**	
Start fluid resuscitation according to hospital protocol (e.g. 4 ml/kg/%TBSA (Parkland formula))		Start intravenous infusion 200 mg/24 h for two days (eventually together with bolus of 50-100 mg)	
If NT-pro-BNP	**Action**	**If proteinuria**	**Action**
<600 ng/L	Continue or increase infusion rate	Increases compared to the day before	Continue dose
600-1000 ng/L	Continue or decrease infusion rate (10-20%)	Stable or decreases during 2 consecutive days	Decrease dose by 25 mg/24 h until 100 mg/24 h; thereafter by 25 mg/24 h every day
>1000 ng/L	Decrease infusion rate (20-40%)		
Target NT-pro-BNP 600-800 ng/L.		Target proteinuria<0.5 g/24 h.	
Adapt to higher level according to co-morbidity **(Table 1)**			
After 3 weeks lower BNP levels should be aimed for			
Measure NT-pro-BNP every 4-6 h during the first 1-3 days; thereafter every 12-24 h		Measure proteinuria every day as g/24 h; initially (the mean of 2) urinary protein concentration values can be used.	

values can be used as target to increase fluid volumes as long as these values are not reached and to start decreasing fluid volumes as soon as these targets are reached **(Table 2)**. Reflecting on our own studies, we could have decreased ordered amounts of fluids in an earlier phase [10,31].

The proposed target and limits for proteinuria and BNP are based on experience in our institution. Several factors may affect these targets and limits such as kind of resuscitation fluids used, delay in time to admittance and operation procedures. The values thus may vary between centers and can be specified further. The basis of the framework however, is based on pathophysiological mechanisms and may offer the opportunity to further improve survival in patients with major burns.

Conclusion

Significant progress in acute resuscitation in major burns has been made providing the basis for further improvements based on individual host defence responses and response to therapy. Capillary leakage invoked by an inflammatory response is an important therapeutic target. Capillary leakage can be anticipated by measuring proteinuria and BNP levels and/or cytokine profiles immediately after the burn injury. Low dose intravenous hydrocortisone therapy has important potential to reduce capillary leakage and concomitant high amounts of fluid needs. Serial measurement of proteinuria and BNP is a promising therapeutic tool to guide hydrocortisone dose and needs in fluid resuscitation.

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