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Introducing a three hit model of shock

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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 characterised by arterial vasodilatation and transcapillary albumin leakage abating plasma oncotic pressure. Arterial underfilling, 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 goal directed filling to prevent evolution to multiple organ dysfunction syndrome (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, as proposed by Bagshaw et al [1].

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. Recent studies showed that conservative late fluid management (CLFM) with 2 consecutive days of negative fluid balance within the first week of stay is a strong and independent predictor of survival [2]. In contrast, patients with persistent systemic inflammation maintain transcapillary albumin leakage and do not reach the flow phase mounting up positive fluid balances. In this context the global increased permeability syndrome (GIPS) has been introduced, characterized by high capillary leak index (CLI, expressed as CRP over albumin ration), excess interstitial fluid and persistent high exrtravascular lung water (EVLWI), no CLFM achievement and progressing organ failure [3]. GIPS represents a 'third hit' following acute injury with progression to MODS [4].

The dual response to acute inflammatory insult is characterized by a crucial turning point on day 3. Presumably, homeostasis of cytokines the third day after shock onset allows initiation of healing the microcirculatory disruptions and 'closure' of capillary leakage. This interpretation is supported by observations demonstrating normalization of microcirculatory blood flow on day 3 in patients with abdominal sepsis. Lower extravascular lung water (EVLWI) and pulmonary vascular permeability indices [5] at day 3 of shock were shown to correlate with better survival.

As a result of capillary leakage and impaired flow phase, overzealous administration of fluids in the GIPS phase will lead to gross fluid overload and tissue edema. Interstitial edema raises the pressure in all four major body compartments: head, chest, abdomen and extremities. As a result, venous resistance of organs within compartments increases and perfusion pressure decreases contributing to progression of organ failure. As different compartments interact and reciprocally transmit compartment pressures, the concept of polycompartment syndrome was suggested [6-8].

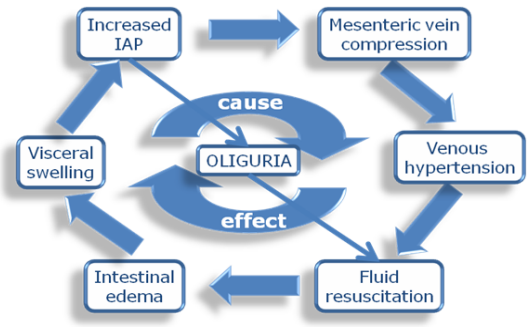

Figure 1. Vicious cycle leading to IAH and ACS (avoid futile crystalloid resuscitation)

The abdomen plays a central role in GIPS and polycompartment syndrome as positive fluid balances are a known risk factor for secondary intra-abdominal hypertension (IAH) which in turn is associated with deleterious effects on other compartments and organ functions (Figure 1). Renal function in particular is strongly affected by IAH. Furthermore, renal interstitial edema in absence of IAH may impair renal function, too. Therefore, fluid overload leading to IAH and associated renal dysfunction may counteract its own resolution. 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.

led to improved outcomes and lower positive fluid balances in states of capillary leakage. Restrictive fluid management may necessitate a greater use of vasopressor therapy, resuscitation with hyperoncotic solutions (e.g. albumin 20%) and early initiation of diuretics and renal replacement therapy.

Within the concept of dual response to shock, it is possible to identify patients with persistent capillary leakage not to reach the flow phase. In this context, GIPS reflects a 'third hit' of shock, after acute injury and MODS. In those patients, superfluous fluid administration results in edema formation, progression of organ failure and worse outcome and may be considered toxic (Figure 2 and Table). Therefore, as soon as hemodynamics allow, early transition to conservative fluid management and even fluid removal on the basis of EVLWI-guided protocol is mandated (late goal directed fluid removal) [2-4, 9].

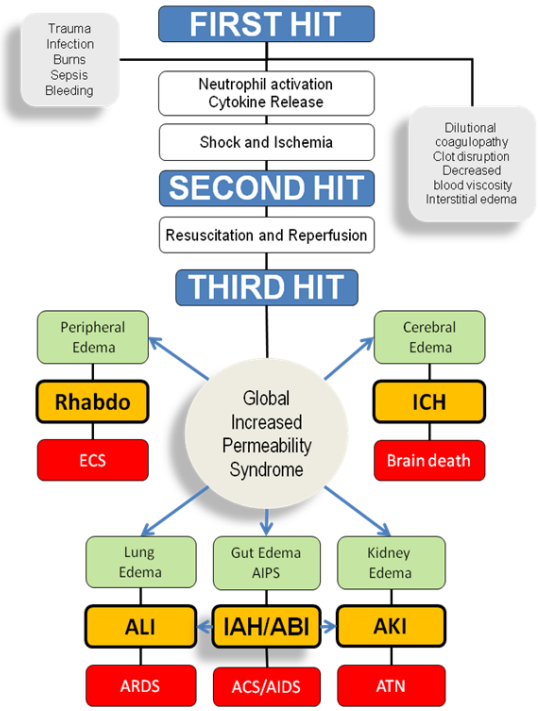

Figure 2. Three hit model of shock.

Figure Legend. Rhadbo: rhabdomyolysis, ECS: extremity compartment syndrome, ICH: intracranial hypertension, ALI: acute lung injury, ARDS: acute respiratory distress syndrome, IAH: intra-abdminal hypertension, ABI: acute bowel injury, ACS: abdominal compartment syndrome, aids: acute intestinal distress syndrome, AKI: acute kidney injury, ATN: acute tubular necropsis, GIPS: global increased permeability syndrome

A high EVLWI indicates a state of capillary leakage, associated with higher severity of illness and mortality. Recent studies correlated EVLWI with albumin extravasation in patients after multiple trauma. Responders to CLFM 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. In this hypothesis, (change in) EVLWI has a prognostic value as a reflexion of the extent of capillary leakage, rather than as a quantification of lung function impairment by lung water [9]. The recent observations may have direct consequences regarding fluid management in the critically ill patients with IAH. Patients at risk for GIPS as assessed by CLI, IAP, changes in EVLWI and fluid balance, require restrictive fluid strategies and even fluid removal guided by extended hemodynamic monitoring including lung water measurements (late goal directed fluid removal). Previously, the application of EVLWI-guided fluid therapy

Table: The 3 hit model of shock

	FIRST HIT	SECOND HIT	THIRD HIT
Cause	Inflammatory insult	Ischemia reperfusion	GIPS
Phase	Ebb	Flow	No flow
Fluids	Life saving	Biomarker of critical illness	Toxic
Monitoring	Functional hemodynamics (SVV, PPV)	Organ function (EVLWi, IAP)	Perfusion (ICG-PDR)
Treatment	Early adequate goal directed fluid management (EAGD)	Late conservative fluid management (LCFM)	Late goal directed fluid removal (LGFR)
Fluid balance	Positive	Neutral	Negative

KEY MESSAGES

Capillary leak is an inflammatory condition with diverse triggers that results from a common pathway that includes ischemia-reperfusion, toxic oxygen metabolite generation, cell wall and enzyme injury leading to a loss of capillary endothelial barrier function. In such a state, plasma volume expansion to correct hypoperfusion predictably results in extravascular movement of water, electrolytes and proteins. Peripheral tissue edema, visceral edema and ascites may be anticipated in proportion to the volume of prescribed resuscitation fluid. A variety of strategies are available to the clinician to reduce the volume of crystalloid resuscitation utilized while restoring macro- and microcirculatory flow. Regardless of the resuscitation strategy, the clinician must maintain a heightened

awareness of the dynamic relationship between capillary leak, fluid loading, peripheral edema, intra-abdominal hypertension and the abdominal compartment syndrome.

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