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Chapter

Resuscitation Endpoints in Traumatic Shock: A Focused Review with Emphasis on Point-of-Care Approaches

Kathryn C. Kelley, Kyle Dammann, Alex Alers, Thomas B. Zanders, Charles Bendas and Stanislaw P. Stawicki

Abstract

Trauma resuscitation is a blend of art and science, with the traumatologist at the helm of a large, multidisciplinary team, making split-second decisions and overseeing various parallel processes. Despite tremendous progress over the past few decades, the "art" component continues to play a large part in the overall trauma resuscitation process, with the "science" part slowly but steadily increasing its footprint as a determinant of processes and decisions. Thus, it becomes critical for all clinicians to be able to recognize the evidence-based factors which can be most valuable in guiding trauma resuscitations. This chapter serves as an overview of the current clinical findings, resuscitative endpoints, imaging techniques, and physiologic indices that are most helpful in order to promptly recognize and treat traumatic shock as well as projecting forward to look at novel techniques and biomarkers. Though a single universal marker that accurately and consistently identifies traumatic shock has yet to be discovered, certain factors discussed, such as lactate and base deficit, have been proven to be much more reliable than others.

Keywords: traumatic shock, trauma resuscitation, resuscitative endpoints, imaging techniques, biomarkers in shock

1. Introduction

Trauma is among the leading causes of death across the globe [1, 2]. Yet despite the ubiquitous nature of this public health problem [3–5], our understanding of traumatic shock and the associated outcome determinants and markers continues to be incomplete at the increasingly granular, mechanistic level [6, 7]. For the purposes of this chapter, the term "traumatic shock" refers to any of the number of etiologies that would lead to shock in a trauma patient—most commonly seen is acute hemorrhage, but also other types of shock should also be mentioned, including neurogenic shock and possible late manifestations of obstructive shock and septic shock. There is a wealth of literature related to biomarkers and techniques used in identification of shock—including specifically sepsis and neurogenic shock—but there remains a paucity of studies specifically related to trauma patients.

The goal of this chapter is to provide an overview of the most commonly used endpoints of resuscitation in traumatic shock, beginning with clinical bedside assessments then progressing through various laboratory tests, and finally a discussion of other means of evaluation (e.g., sonography, novel biomarkers, and other miscellaneous approaches).

2. Methods

A total of 9152 candidate publications was identified during a comprehensive literature search using PubMed, Google Scholar™, EBSCOHost, and Bioline International. Search terms included various combinations of "resuscitative endpoints," "traumatic shock," "biomarkers in shock," "study," and "clinical trial." Within the larger subset of candidate publications, 70 studies were deemed suitable in the development of this chapter's content.

3. Clinical evaluation

The most important, and still very much essential, component of determining if a patient is in state of shock is the performance of an accurate clinical examination. There is no substitute for the judgment of an experienced clinician who is attuned to the most subtle manifestations of early (or compensated) shock.

The number one cause of death in the first hour after trauma is hemorrhage, and nearly 40% of all trauma related deaths are secondary to bleeding and its complications [8]. As such, hemorrhagic shock, a unique form of hypovolemic shock, has been the main focus of considerable trauma research and management applications, both in civilian and military settings. However, the astute and well-experienced clinician recognizes that trauma patients are not immune to other types of shock and that different types of shock are not mutually exclusive. Clinical manifestations of shock vary broadly and are based on the underlying etiology, the degree of organ perfusion, and previous organ dysfunction [9]. Understanding of the physical exam findings which may help differentiate between types of shock is a skill paramount to any clinician involved in trauma care. Proper attention to physical exam findings may guide initial therapy before other adjuncts such as imaging studies or laboratory measurements are available.

A complete, "head-to-toe" examination, such as is described for the secondary survey for trauma patients, will reveal multiple findings correlating with hypoperfusion of several organs. Altered mental status, manifesting as confusion, delirium, or coma, reveals decreased cerebral blood flow, most often at mean arterial pressures less than 50 mmHg [10, 11]. The differential diagnosis for any trauma patient who is altered must not only include traumatic brain injury or possible toxin ingestion but also take into account that this mental status change could be an initial presentation of shock. The cardiovascular system is one of the main players in the initial evaluation of shock. Sympathoadrenal stimulation typically causes an increase in heart rate. However, "misleading" heart rate might be present when managing high endurance athletes, geriatric patients, pregnant trauma victims, cardiovascular drug users, those with preexisting cardiovascular disease, or those in neurogenic shock [12–15]. Bradycardia, jugular venous distention, and new onset heart murmur might be present in cardiogenic shock [15, 16]. Distant/muffled heart sounds and pulsus paradoxus might be present in obstructive shock from cardiac tamponade [17]. Obstructive shock from tension hemothorax and/or pneumothorax might be evidenced by distant breath sounds, tracheal deviation, and hypotension [18, 19]. Dyspnea and hypoxia might clue the clinician in on a possible pulmonary embolus and obstructive shock.

Classical teaching would presume that shock is associated to arterial hypotension. Although this might be prevalent in patients suffering from any etiology of shock, arterial hypotension may happen without shock, and hypoperfusion and organ ischemia may happen despite normal blood pressure. Increase in systemic vascular resistance, leading to pale or dusky skin, peripheral cyanosis, damage to small capillaries producing petechiae, decrease in temperature, and delayed capillary refill, is present in almost all forms of shock, except for distributive. Patients in "cold" shock almost universally have alterations in peripheral perfusion. Capillary refill, also termed peripheral perfusion status, can be an easy and rapid assessment of resuscitation status. Abnormal peripheral perfusion has been found to identify normotensive patients with more severe organ dysfunction and correlated with high lactate levels [20]. However, basing resuscitation solely on peripheral perfusion status would not be recommended as this was not found to improve mortality compared to lactate-based resuscitation in septic shock patients [21]. Initial respiratory alterations in shock include an increase in minute ventilation leading to hypocapnia and respiratory alkalosis. Increased work of breathing and attempted respiratory correction of metabolic acidosis, coupled with impaired respiratory muscle function from hypoperfusion, lead to respiratory failure. Although acute kidney injury is commonplace in patients suffering from shock, identifying oliguria requires insertion of a urinary catheter and measurement of output for at least 1 hour; both of these interventions are necessary yet time-consuming. In the absence of prompt intervention, global hypoperfusion leads to failure of multiple organ systems and increases the morbidity and mortality associated to shock [22].

Rapid yet thorough physical examination can lead the clinician to institute therapy to alleviate different causes of shock. Cessation of hemorrhage and volume repletion are the most common maneuvers needed in the trauma bay. However, other culprits of shock are alleviated by, for example, prompt decompression of a tension pneumothorax or cardiac tamponade, rapid administration of fibrinolytic in massive pulmonary embolus, quick activation of the catheterization lab for myocardial ischemia, and fast initiation of vasoactive medications in the setting of heart failure, among others. Adjuncts to the physical exam, such as imaging studies and laboratory values, are valuable assets in the race against time during the management of the patient in shock.

4. Serum lactate

In a study of over 2800 patients, a comparison of four different fundamental serum markers of acidosis was conducted (**Figure 1**) [23]. Although not the first published report of lactate being superior to other well-established serum markers, the authors were able to perform a unique side-by-side comparison of serum lactate versus three other common markers of metabolic acidosis—base deficit, anion gap, and serum bicarbonate [23]. The study demonstrated superiority of lactic acid (AUC, 0.75) and base deficit (AUC, 0.72) over the other indicators (bicarbonate AUC, 0.68, and anion gap AUC, 0.66) [23].

At-risk populations, including the geriatric patients and those with elevated comorbidity-polypharmacy scores (CPS), are at elevated risk of poor outcomes, including morbidity, mortality, and readmissions [24–27]. More specific to the context of trauma, patients with end-stage renal disease, severe peripheral vascular disease, and chronic respiratory failure may present with physiologically misleading vital signs, as evidenced by a study of >30,000 patients examining post-injury vital signs across various age groups [14]. In such setting,

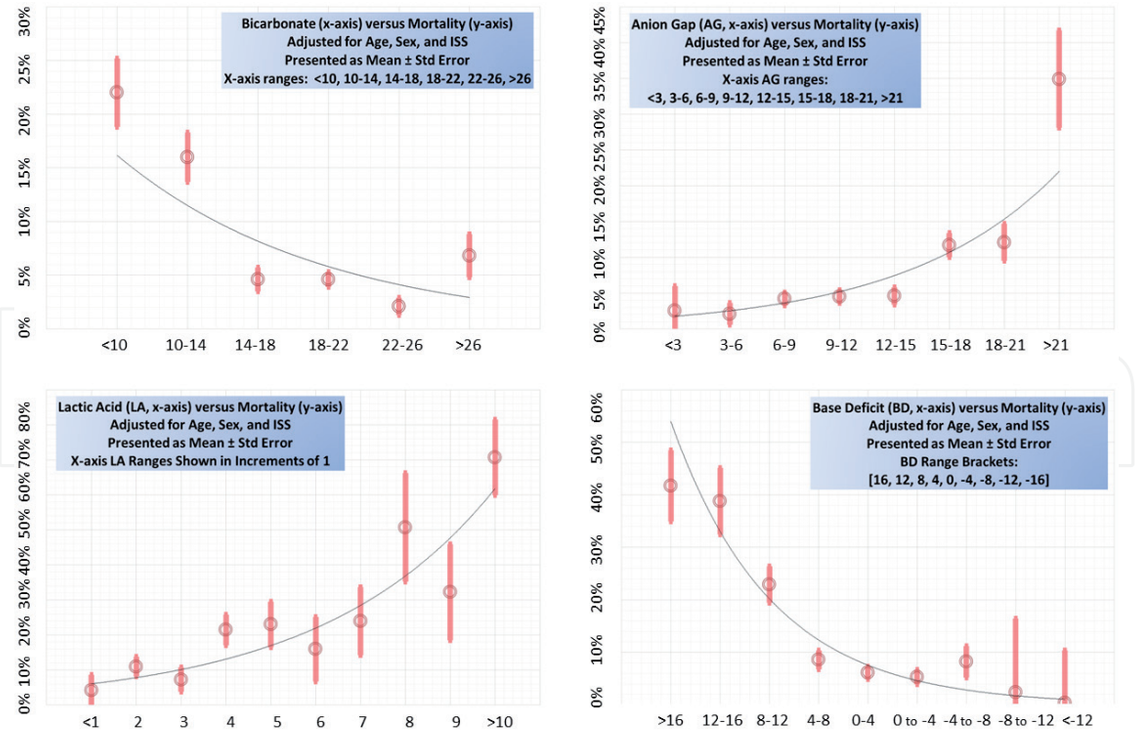


Figure 1.
Traditional serum markers of traumatic shock (clockwise from top left: Bicarbonate, anion gap, base deficit, and lactic acid). Each marker is shown in the context of its associated mortality. If note, all data are adjusted for age, sex, and ISS.

serum lactate may help identify individuals who may be in compensated shock and otherwise exhibit "normal" vital signs [28].

5. Base deficit

Base deficit, calculated directly from pCO_2, HCO_3^-, and pH via blood gas analysis, is often cited among the most reliable predictors of acute metabolic stress following traumatic injury [29, 30]. This particular option may provide enhanced diagnostic utility in at-risk populations, such as the elderly patients who remain normotensive despite significant injury burden [28]. Also, in one study of trauma patients ≤55 years old without head injury, a base deficit ≥8 mmol/L was associated with a 25% mortality rate [30]. However, studies have found that base deficit is less reliable in immediate identification of shock, and more reliable 24 hours after presentation, when irreversible effects of shock have already taken place [30]. Since the numerical value of base deficit is easily influenced by a multitude of other factors related to metabolic acidosis, such as GI losses, diabetic ketoacidosis, and renal dysfunction, serum lactate has been deemed overall more reliable than base deficit [30].

6. Anion gap and other measures of acidosis

In theory, both anion gap and serum bicarbonate should provide a reasonable reflection of systemic acid–base milieu, with clearly established evidence of the correlation between these parameters and increasing metabolic stress [31]. The more recent four-way comparison study shows that although both anion gap and serum bicarbonate fall short of the diagnostic utility of serum lactate or the base deficit, they

still provide relevant clinical information for the trauma practitioner. This is especially true in the setting where no other labs may be available [23]. The lethal triad of hemorrhagic shock consists of hypothermia, coagulopathy, and acidosis [32–34]. As such, monitoring of the acid–base status not only assists in guiding further resuscitation, but correction of the acidosis is imperative to improve survival of hemorrhagic shock.

7. Alternative measurements of metabolic stress

Serum pH measurement is yet another option for assessing acute metabolic stress during the immediate post-trauma period, with non-survivor pH ranging between 6.91 and 7.21 across several studies [29]. However, Joynt et al. identified a weakness in using gastric intramucosal pH to distinguish shock survivors from nonsurvivors [35]. At the 48-hour mark, it was found that serum lactate was again a better indicator of survival than serum pH. It is also important to note that improvement in base deficit has been found to be superior to pH in determining improvement in acidotic state [36].

Strong ion gap has additionally been identified as a helpful marker, with one study demonstrating its utility in mortality prediction for victims of major vascular trauma [29]. In that particular study, the strong ion gap ≥5 mEq/L correlated strongly with adverse clinical outcomes (AUC, 0.991) [29]. Other reported experiences suggest that strong ion gap may also offer predictive value in the setting of both adult and pediatric burn injuries [37, 38].

8. Sonography for hemodynamic/shock assessment

Vital signs are key in the initial shock assessment and, however, are often insufficient for evaluating volume status in patients with multiple comorbidities [39]. For this reason, ultrasound has become the standard of care to supplement the initial assessment and gauge resuscitative measures. Although dependent on the user's skillset, both inferior vena cava collapsibility (intravascular volume status surrogate) [40–42] and ventricle contractility (ejection fraction surrogate) can be accurately visualized without needing to record or calculate specific measurements [43]. After volume status is determined, fluid responsiveness (FR) should be assessed. Passive leg raise is a classic way of determining this, as cardiac output or stroke volume is increased by 10% when FR [44]. A more accurate assessment of FR via sonography is measuring variation in stroke volume, from the velocity time integral (VTI) [45]. VTI is the velocity and distance which blood ejects after each contraction, also known as stroke distance [46]. VTI variation more than 14% is highly specific for positive [47]. Finally, significant body of literature exists on the relationship between collapsibility of central veins (e.g., veins peripheral to vena cava) and intravascular volume status. Although less reliable with the more peripheral locations (e.g., subclavian vein more accurate than femoral vein collapsibility), this approach still provides useful clinical information and hemodynamic trends [48–51]. Understanding the above concepts allows one to understand the importance of ultrasound in emergent/trauma settings today.

9. Novel biomarkers in traumatic shock

For most trauma resuscitations involving patients who may be in shock, the use of lactic acid and base deficit as measurements of the overall physiological

derangement will be sufficient. However, there is significant room for improvement in terms of diagnostic and predictive accuracy. Many innate similarities exist in the inflammatory responses seen in traumatic shock and sepsis, and many inflammatory signals in tissue injury and end-organ damage are found in responses to both of these conditions. Although not yet extensively studied in the specific subset of trauma patients, novel biomarkers that have been proposed in the diagnosis of shock include sTREM-1 and suPAR [52, 53].

More studied in the setting of sepsis, sTREM1 (a.k.a. soluble triggering receptor expressed on myeloid cells), is a recently discovered immunoglobulin, whose presence has been proven to be greatly upregulated in the presence of bacteria or fungi in cell culture, peritoneal lavage fluid, and tissue samples from patients infected with these microorganisms [52]. Recent studies have shown sTREM1 to be both a diagnostic and prognostic indicator in critically ill patients with shock. sTREM1 has found to be non-inferior to CRP, procalcitonin, IL-6, and TNF-α in identifying postoperative patients with sepsis [52]. suPAR (a.k.a. soluble urokinase-type plasminogen activator system) is found in the blood and organic fluids in all humans and takes part in various immunological functions, such as cell adhesion, migration, chemotaxis, proteolysis, immune activation, tissue remodeling, and signal transduction [52, 53]. suPAR thus reflects the extent of immune activation in a specific individual, serving as a nonspecific prognostic biomarker [53]. It has been associated with hospital length of stay, transfer to the ICU, presence and severity of acute conditions, and risk of death [53]. The TRIAGE III Trial performed in 2018 in Denmark studied suPAR as a prognostic biomarker in patients presenting to the emergency department, finding that suPAR enhanced early risk stratification of patients, but did not lead to any significant changes in short- or long-term all-cause mortality [53].

An increase in extracellular histone levels, which are elevated in response to traumatic injury, correlates with fibrinolysis and activation of anticoagulants [54]. Extracellular histones bind phospholipids, damage cell membranes, and lead to influx of calcium; the sustained intracellular elevation of calcium leads to cell damage and release of cell contents. Circulating histones can lead to distant organ injury, most notably in the lungs, and can ultimately lead to multisystem organ failure [55]. Increases in histone levels from time of admission to 6 hours have been found to be predictive of mortality, paralleling an ongoing release of intracellular antigens that is likewise seen in sepsis [54]. In a 2012 study of 132 critically injured trauma patients, patients within the highest quartile of extracellular histone levels at admission had significantly higher Injury Severity Scores, lower GCS scores, a 1.8-fold higher rate of acute lung injury, a 3.2-fold higher incidence of multisystem organ failure, and 2.1-fold greater mortality [54]. However, further clinical studies on larger scales are needed to confirm whether elevated histones are a reliable indicator of traumatic shock.

Certain biomarkers hold promising potential for rapid early detection of traumatic brain injury (TBI) and neurogenic shock, although no studies with a specific subset of trauma patients have been performed. TBI can often be difficult to assess, as GCS can rapidly decline and standard neurological imaging may poorly characterize minor or occult injuries which could later contribute to clinical decline [56]. S100β is a neurologically derived calcium-binding protein which has increased serum expression following traumatic brain and orthopedic injuries and has also been used to rule out TBI due to its strong negative predictive value [56, 57]. Glial fibrillary acidic protein (GFAP), a cytoskeletal scaffold in astrocytes, is another promising biomarker more specific to TBI than S100β and also has differential expression patterns from low range (3–5) to stable range (13–15) of GCS values [58].

While multiple biomarkers are being investigated for CNS injury, one novel class of regulators, microRNAs (miRNAs), show promise as a potential biomarker for shock. miRNAs are noncoding sequences of genetic material which modulate gene expression in organ development, homeostasis, and disease pathology [59]. For example, miRNAs are associated with the pathogenesis of heart failure through modulation of neurohormonal signaling, and their plasma levels parallel lactate and predict outcomes following cardiac arrest [60–62]. Whether such markers are associated with cardiogenic shock following traumatic injury is unknown and should be investigated. miRNAs have also been implemented as biomarkers for the diagnosis of acute pulmonary embolism [63]. Large pulmonary emboli exhibit similar pathophysiology to acute obstructive shock; therefore, it may be plausible that miRNAs could be a predictor for obstructive shock in a traumatic setting. Additionally, miRNAs have involvement in the pathogenesis of adrenal disease [64]. As the sympathoadrenal axis plays a role in early shock, it may be valuable to investigate adrenal miRNA expression patterns after traumatic injury. One limitation which may limit the future use of miRNAs for the analysis of shock includes the lack of point-of-care testing, requirement of cumbersome miRNA isolation methods, and time-consuming analysis with PCR or microarray technology. However with advancing technology and the importance of miRNA in multiple fields, rapid isolation protocols will soon be on the horizon.

10. Physiological indices

Critical care scoring systems have been well-established to improve care of patients with traumatic shock in the ICU [65]. The following scoring systems give a few examples of how patient prognosis is established. There is no one best scoring system for critical patients, and experts recommend using multiple scores to better risk stratify each patient [65]. Multiple online calculators are readily available to assist in obtaining the score, and typically the most severe values within 24 hours of admission are the figures used for the calculation. The acute physiology and chronic health evaluation (APACHE IV) physiological score was established using more than 110,000 critical care patients and 142 variables to predict mortality and length of stay [65]. Important variables in the calculation include chronic health conditions, admission information and diagnosis, patient age, vital signs, blood gas and ventilation settings, urine output, GCS, and data from CBC and BMP lab work [65]. In comparison to the APACHE, the Simplified Acute Physiology Score (SAPS3) also evaluates how resources are being used between different ICUs based on time spent in ICU [66]. SAPS3 utilizes multiple components, many of which are similar to APACHE scoring system. Important aspects include length of stay before ICU, infections or surgeries while in critical care unit, GCS, vitals, CBC, CMP, blood gases, hospital location prior to ICU admit, and major therapeutic options, such as vasopressors before ICU transfer [66].

Similar to the other scoring systems, sequential organ failure assessment (SOFA) uses multiple organ systems to evaluate patient mortality risk. Variables utilized are the following: cardiovascular, MAP and pressor requirements; CNS, GCS; coagulation, platelet count; hepatic function, bilirubin; renal function, creatinine and urine output; and respiratory function, mechanical ventilation and the PaO2/FiO2 ratio [65]. When viewed as a whole, one can appreciate the similarities and the advantages that each of these scoring systems provides, further emphasizing the importance of using multiple scores in order to improve both clinical awareness and judgment.

11. Miscellaneous topics

Since current laboratory tests do not reliably supply enough diagnostic information about patients that experience acute hemorrhage, which includes trauma patients in hemorrhagic shock, global hemostatic coagulation tests, such as ROTEM/TEG, have emerged as an alternative to traditional coagulation tests such as PT/INR [67]. Though PT/INR can accurately identify the initiation of clotting, these tests do not identify hemostatic capacity in terms of clot formation and maximal thrombin generation [67]. The two semiautomated commercial devices currently on the market for thromboelastography are the ROTEM analyzer and the TEG analyzer; both devices can effectively measure the maximum fibrin clot formation, thus serving as an estimate of the capacity of the coagulation cascade [67]. Thromboelastography has become a valuable asset in identifying coagulopathies and guiding hemostatic therapy and could potentially even prevent unnecessary blood transfusions [67]. These tests are quickly emerging as possible point-of-care devices that can monitor hemorrhage in either the ICU or ED settings [67]. Along with thromboelastography, clot waveform analysis also seems to be a promising resource in monitoring hemorrhagic shock.

In principle, clot waveform analysis (CWA) is based on the aPTT assay and was first described when aPTT and PT were assessed with light transmission [67]. However, the distinct difference with CWA is that the readout from photo-optic registration is prolonged, creating a graph registered over time, whereas aPTT is solely the clotting time [67]. The tracing produced in clot waveform analysis thus reflects the entire process of clot formation and clot lysis [67]. CWA has been used to monitor the course of disseminated intravascular coagulation (DIC) and may be sensitive to even mild deficiencies in Factors II, V, VII, IX, X, and XII, which may prove the test useful in identifying hemophilias A and B [67]. Some studies have even found CWA to be more accurate than CRP and procalcitonin in monitoring the severity and prognosis of sepsis [67]. More clinical data and prospective studies are required, however, to support this evidence. Other emerging technologies that may prove to be highly valuable in the resuscitation of trauma patients are the FloTrac™/Vigileo™ system and the PiCCOplus™ system.

The FloTrac™/Vigileo™ and PiCCOplus™ systems have emerged as dynamic indicators that can accurately predict fluid responsiveness in critically ill patients [68, 69]. By utilizing stroke volume variation (SVV), or the percentage of changes in stroke volume (SV) during the ventilatory cycle, both systems have been shown comparable outcomes in predicting fluid responsiveness [69]. These systems serve as an alternative to static indicators such as central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP), which have been classically shown to be poor predictors of fluid responsiveness [68].

12. Conclusions

Despite tremendous progress in the management of trauma, universally applicable and highly reliable markers for adequacy of resuscitation remain elusive. For most trauma resuscitations involving patients who may be in shock, the use of lactic acid and base deficit as measurements of the overall physiological derangement will be sufficient.

DOI: http://dx.doi.org/10.5772/intechopen.90686

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