

Clinical Practice Guideline: Endpoints of Resuscitation

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J Trauma. 2004;57:898–912.

STATEMENT OF THE PROBLEM

Severely injured trauma victims are at high risk of development of the multiple organ dysfunction syndrome (MODS) or death. To maximize chances for survival, treatment priorities must focus on resuscitation from shock (defined as inadequate tissue oxygenation to meet tissue O₂ requirements), including appropriate fluid resuscitation and rapid hemostasis. Inadequate tissue oxygenation leads to anaerobic metabolism and resultant tissue acidosis. The depth and duration of shock leads to a cumulative oxygen debt.¹ Resuscitation is complete when the oxygen debt has been repaid, tissue acidosis eliminated, and normal aerobic metabolism restored in all tissue beds. Many patients may appear to be adequately resuscitated based on normalization of vital signs, but have occult hypoperfusion and ongoing tissue acidosis (compensated shock), which may lead to organ dysfunction and death. Use of the endpoints discussed in this guideline may allow early detection and reversal of this state, with the potential to decrease morbidity and mortality from trauma.

Without doubt, resuscitation from hemorrhagic shock is impossible without hemostasis. Fluid resuscitation strategies before obtaining hemostasis in patients with uncontrolled hemorrhage, usually victims of penetrating trauma, remain controversial. Withholding fluid resuscitation may lead to

death from exsanguination, whereas aggressive fluid resuscitation may disrupt the clot and lead to more bleeding. “Limited,” “hypotensive,” and/or “delayed” fluid resuscitation may be beneficial, but clinical trials have yielded conflicting results.^{2,3} This clinical practice guideline will focus on resuscitation after achieving hemostasis and will not address the issue of uncontrolled hemorrhage further.

Use of the traditional markers of successful resuscitation, including restoration of normal blood pressure, heart rate, and urine output, remain the standard of care per the Advanced Trauma Life Support Course.⁴ When these parameters remain abnormal, i.e., uncompensated shock, the need for additional resuscitation is clear. After normalization of these parameters, up to 85% of severely injured trauma victims still have evidence of inadequate tissue oxygenation based on findings of an ongoing metabolic acidosis or evidence of gastric mucosal ischemia.^{5,6} This condition has been described as compensated shock. Recognition of this state and its rapid reversal are critical to minimize risk of MODS or death. Consequently, better markers of adequate resuscitation for severely injured trauma victims are needed. This guideline committee sought to evaluate the current state of the literature regarding use of potential markers and related goals of resuscitation, focusing on those that have been tested in human trauma victims. This manuscript is part of an ongoing process of guideline development that includes periodic (every 3–4 years) review of the topic and the recommendations in light of new data. The goal is for these guidelines to assist clinicians in assuring adequate resuscitation of trauma patients, ultimately improving patient outcomes.

Goals of the Guideline

1. To demonstrate that the proposed endpoints are useful for stratifying the patients' severity of physiologic derangement.
2. To demonstrate that the proposed endpoints are useful for predicting risk of development of MODS or death.
3. To determine the endpoints for resuscitation that would predict survival without organ system dysfunction if a defined level is achieved within a certain time frame.
4. To improve patient survival and morbidity (organ

Submitted for publication April 14, 2003.

Accepted for publication March 17, 2004.

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DOI: 10.1097/01.TA.0000133577.25793.E5

system dysfunction) by use of appropriate resuscitation endpoints.

Information regarding risk of death could lead to consideration of limiting therapy that may be futile. In trauma victims who have not suffered a cardiac arrest or who do not have injuries that are incompatible with life, there is little literature on determining medical futility. Consequently, this guideline does not make any recommendations regarding when to limit therapy.

Proposed Endpoints

The proposed endpoints of resuscitation fall into 2 categories: global and regional. The global O₂ delivery issue has been examined by studies of supranormal O₂ delivery and studies of the utility of mixed venous O₂ saturation. Other global hemodynamic parameters that have been explored include right ventricular end-diastolic volume, left-ventricular stroke work index, and left-ventricular power output. Similarly, global acid-base status has been explored using base deficit and lactate levels.

On the regional level, compensated shock disproportionately decreases blood flow to the splanchnic and other tissue beds to maintain cerebral and coronary blood flow. Examination of gut-related parameters may be useful as a marker of the severity of shock and may also demonstrate the pathophysiologic connection between gut ischemia and later MODS. Gastric ischemia can be monitored using gastric tonometry. Intramucosal pH (pHi) or the gap between intramucosal and arterial pCO₂ can be utilized. Skeletal muscle and subcutaneous tissue blood flow is similarly decreased during shock. Tissue po₂, pCO₂, and pH can be monitored using near infrared spectroscopy or tissue electrodes.

From a clinical perspective, in addition to direct clinical utility, other issues to consider for potential resuscitation endpoints include: general availability, cost, speed, invasiveness, and risk.

PROCESS

The process utilized by this committee was developed by the Practice Management Guidelines Committee of the Eastern Association for the Surgery of Trauma (www.east.org). The committee agreed upon the potential endpoints to be considered. Literature for review included: human, trauma patients, and some attempted connection between the proposed endpoint and patient outcome (morbidity, survival, etc), not just process variables. Some non-trauma studies of critically ill patients were also included, particularly if the parameter seemed promising in other surgical patients. Similarly, some non-human studies of promising techniques are discussed, though these were not included in the main review or recommendations. Medline and EMBASE were searched from 1980 to 2001.

Articles were distributed among committee members for formal review. Each article was entered into a review data sheet that summarized the main conclusions of the study and

identified any deficiencies in the study. Furthermore, reviewers classified each reference by the methodology established by the Agency for Health Care Policy and Research of the U.S. Department of Health and Human Services as follows: Class I: prospective, randomized, double-blinded study; Class II: prospective, randomized, nonblinded trial; Class III: retrospective series, meta-analysis.

An evidentiary table (Table 1) was constructed using the 74 references that were identified: Class I, 12 references; Class II, 38 references; and Class III, 24 references. Recommendations were made on the basis of the studies included in this table. Level I recommendations, usually based on class I data, were meant to be convincingly justifiable on scientific evidence alone. Level II recommendations, usually supported by class I and II data, were to be reasonably justifiable by available scientific evidence and strongly supported by expert opinion. Level III recommendations, usually based on Class II and III data, were to be made when adequate scientific evidence is lacking, but the recommendation is widely supported by available data and expert opinion.

RECOMMENDATIONS

Recommendations Regarding Stratifying Physiologic Derangement

Although the original goal of this guideline was to determine separate recommendations regarding the four goals listed in Section I, the literature on 1) stratifying patients' severity of physiologic derangements, 2) risk of MODS and death, and 3) predicting survival if certain values of the parameters are achieved, generally combines these issues. Consequently, the following recommendations refer to the first three goals of this guideline in aggregate. Recommendations related to goal 4, improving patient survival and morbidity, are presented separately.

Level I

1. Standard hemodynamic parameters do not adequately quantify the degree of physiologic derangement in trauma patients. The initial base deficit, lactate level, or gastric pHi should be used to stratify patients with regard to the need for ongoing fluid resuscitation, including packed red blood cells and other blood products, and the risks of MODS and death.
2. Oxygen delivery parameters should be observed since the ability of a patient to attain supranormal correlates with an improved chance for survival relative to patients who cannot achieve these parameters.

Level II

1. The time to normalization of base deficit, lactate, and pHi is predictive of survival. Observation of at least one of these parameters should be used clinically for prognostication.
2. Persistently high base deficit or low pHi (or worsening of these parameters) may be an early indicator of

Table 1 Endpoints of Resuscitation

First Author	Year	Title	Class of Evidence	Conclusions
Oxygen Delivery				
Shoemaker, WC	1988	Prospective trial of supranormal values of survivors and therapeutic goals in high risk surgical patients. <i>Chest</i> 94: 1176-86.	I	Resuscitating to preordained oxygen transport variables may reduce morbidity and mortality in high-risk surgical patients.
Boyd, O	1993	A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgery. <i>JAMA</i> 270:2699-2707.	I	A 75% reduction in mortality (5.7% vs 22.2% $p = 0.015$) and halving of the mean number of complications per patient in the protocol group ($p = 0.008$)
Hayes, MA	1994	Elevation of systemic oxygen delivery in the treatment of critically ill patients. <i>N Engl J Med</i> 330:1717-22.	I	Nine patients achieved goals with volume alone and all survived. Remainder were randomized: 50 to control, 50 to therapy. In house mortality was lower in the control group than the treatment group (34% vs 54%) $p = 0.04$.
Bishop, MH	1995	Prospective, randomized trial of survivor values of cardiac index, oxygen delivery, and oxygen consumption as resuscitation endpoints in severe trauma. <i>J Trauma</i> 38:780-787.	I	Cardiac output, oxygen delivery, and oxygen consumption therapeutic goals achieved within the first 24 hrs were associated with decreased mortality, organ dysfunction, and ICU and vent days.
Durham, RM	1996	The use of oxygen consumption and delivery as endpoints for resuscitation in critically ill patients. <i>J Trauma</i> 41:32-40.	I	The incidence of organ failure and death is similar for patients resuscitated based in O2 transport parameters vs conventional parameters. Given adequate volume resuscitation, O2-based parameters are more useful as predictors of outcome than as endpoints of resuscitation.
Velmahos, GC	2000	Endpoints of resuscitation of critically injured patients: normal or supranormal? A prospective randomized trial. <i>Ann Surg</i> 232:409-18.	I	No difference in mortality, organ failure, sepsis, length of stay between the two groups. Death rate was zero among patients who achieved optimal values compare to 30% among those who didn't. Age younger than 40 years old was the only independent factor of the ability to reach optimal values.
Shoemaker, WC	1973	Physiologic patterns in surviving and nonsurviving shock patients: Use of sequential cardiorespiratory variables in defining criteria for therapeutic goals and early warning of death. <i>Arch Surg</i> 106:630-636.	II	Cardiorespiratory patterns of non survivors surgical/trauma patients were characterized by reduced cardiac output, high pulmonary vascular resistance, and reduced oxygen transport. They proposed that these should be used as defined criteria for therapeutic goals.
Shoemaker, WC	1988	Tissue oxygen debt as a determinant of lethal and non-lethal postoperative organ failure. <i>Crit Care Med</i> 16:1117-1120.	II	The maximum cumulative oxygen debt is significantly less in patients without organ failure than that of nonsurvivors and survivors with organ failure. Oxygen consumption is not different between the 3 groups intraoperatively.
Fleming, A	1992	Prospective trial of supranormal values as a goal of resuscitation in severe trauma. <i>Arch Surg</i> 127:1175-1181.	II	Supranormal oxygen delivery vs normal. No change in mortality. Fewer organ failures, shorter intensive care unit length of stay, less ventilator days. Randomization unclear.
Moore, FA	1992	Incommensurate oxygen consumption in response to maximal oxygen availability predicts postinjury multisystem organ failure. <i>J Trauma</i> 33:58-67.	II	Fifteen of these patients (38%) did not meet this oxygen consumption goal at 12 hours. The patients had elevated lactate levels and also predicted multiple organ failure.
Bishop, MH	1993	Relationship between supranormal circulatory values, time delays, and outcome in severely traumatized patients. <i>Crit Care Med</i> 21:56-63.	II	Severely traumatized patients may improve survival if supranormal values of oxygen delivery and oxygen consumption are achieved by 24 hours.
Heyland, DK	1996	Maximizing oxygen delivery in critically ill patients: A methodologic appraisal of the evidence. <i>Crit Care Med</i> 24: 517-524.	II	Mortality is unchanged when oxygen delivery and consumption are driven to "supraphysiologic" levels in critically ill patients.
McKinley, BA	2002	Normal versus supranormal oxygen delivery goals in shock resuscitation: the response is the same. <i>J Trauma</i> 53:825-832.	II	Non-randomized study of 2 oxygen delivery goals (600 vs 500 ml/min/m ²) implemented with a computer-based protocol. The outcomes were the same, although less fluid was needed in the lower oxygen delivery cohort.
Shoemaker, WC	1983	Use of physiologic monitoring to predict outcome and to assist clinical decisions in the critically ill postoperative patients. <i>Am J Surg</i> 146:43-50.	III	Goals of resuscitation to achieve median values of cardio-pulmonary parameters retrospectively derived from a survivor group were associated with improved outcome.
Mixed Venous Oxygen Saturation				
Gattinoni, L	1995	A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. <i>N Engl J Med</i> 333: 1025-32.	I	Maximization of cardiac index > 4.5 or mixed venous O2 > 70% did not reduce morbidity or mortality in critically ill patients.
Additional Invasive Hemodynamic Monitoring Parameters				
Scalea, TM	1990	Geriatric blunt multiple trauma: improved survival with early invasive monitoring. <i>J Trauma</i> 30:129-136.	II	Emergent invasive monitoring identifies occult shock early, limits hypoperfusion, and will help prevent multiple organ failure and improve survival.
Abou-Khalil, B	1994	Hemodynamic responses to shock in young trauma patients: Need for invasive monitoring. <i>Crit Care Med</i> 22:633-639.	II	Young trauma patients have substantial but clinically occult myocardial depression after shock and most of these patients require inotropes to optimize and clear circulating lactate. Early invasive monitoring is necessary to define the adequacy of the cardiac response and individually tailor therapy. Patients who do not optimize and clear their lactate within 24 hours may not survive.
Chang, MC	1994	Gastric tonometry supplements information provided by systemic indicators of oxygen transport. <i>J Trauma</i> 37:488-94.	II	Low pHi correlates with morbidity and mortality in surgical patients. These values may be used in conjunction with oxygen transport variables to manage these patients.
Chang, MC	1997	Cardiac preload, splanchnic perfusion, and their relationship during resuscitation in trauma patients. <i>J Trauma</i> 42:577-82.	II	Patients in the normal group had a lower incidence multiple organ failure and death. Also the patients in the normal group maintained a higher right ventricular end-diastolic volume index (RVEDVI) throughout the resuscitation. Conclusions: Supranormal levels of preload during shock resuscitation are associated with better outcome. Keeping the RVEDVI > 100 may improve outcome.
Chang, MC	1998	Redefining cardiovascular performance during resuscitation: Ventricular stroke work, power, and the pressure-volume diagram. <i>J Trauma</i> 45:470-478.	II	Prospective study of critically ill trauma patients. Resuscitation with fluids, blood, and inotropes with a goal of rapid normalization of lactate level. Survivors had lower heart rates, stroke work, left ventricular power, and ventricular-arterial coupling.

Table 1 (Continued)

First Author	Year	Title	Class of Evidence	Conclusions
Cheatham, ML	1998	Right ventricular end-diastolic volume index as a predictor of preload status in patients on positive end-expiratory pressure. <i>Crit Care Med</i> 26:1801-1806.	II	Right ventricular end-diastolic volume index better predicts volume state and response to volume infusion than wedge pressure.
Chang, MC	2000	Maintaining survivors' values of left ventricular power output during shock resuscitation: a prospective pilot study. <i>J Trauma</i> 49:26-33.	II	Maintaining left ventricular power > 320 during resuscitation was associated with improved base deficit clearance and lower rates of organ dysfunction.
Chang, MC	2002	Improving ventricular-arterial coupling during resuscitation from shock: Effects on cardiovascular function and systemic perfusion. <i>J Trauma</i> 53:679-685.	II	Prospective study of critically-ill trauma patients. Resuscitation with fluids, blood, and inotropes based on left ventricular power output ventricular-arterial coupling led to rapid base deficit clearance and improved myocardial efficiency.
Kincaid, EH	2001	Determining optimal cardiac preload during resuscitation using measurements of ventricular compliance. <i>J Trauma</i> 50:665-669.	III	Prospective study of critically-ill trauma patients who needed a pulmonary artery catheter. Ventricular compliance curves were constructed during volume loading using right ventricular end-diastolic volume measurements.
Arterial Base Deficit				
Rutherford, EJ	1992	Base deficit stratifies mortality and determines therapy. <i>J Trauma</i> 33:417-23.	II	Based deficit is an expedient and sensitive measure of both the degree and duration of hypoperfusion. It is a useful clinical tool and enhances predictive ability of revised trauma score and TRISS.
Sauaia, A	1994	Early predictors of postinjury multiple organ failure. <i>Arch Surg</i> 129:39-45.	II	Age, injury severity score and >6u red blood cell transfusion in the first 12 hrs post injury were early predictors of multiple organ failure. Base deficit and lactate were also helpful.
Bannon, MP	1995	Central venous oxygen saturation, arterial base deficit, and lactate concentration in trauma patients. <i>Am Surg</i> 61: 738-45.	II	Base deficit and lactate are better than central venous oxygen saturation (ScvO2) as indicators of blood loss as measured by peritoneal shed blood volume, prep hypotension and transfusion requirement.
Davis, JW	1996	Admission base deficit predicts transfusion requirements and risk of complications. <i>J Trauma</i> 41:769-74.	II	Admission base deficit can be used to identify patients at risk for increasing transfusion requirements and intensive care unit + hospital length of stay.
Botha, AJ	1997	Base deficit after major trauma directly relates to neutrophil CD11b expression: a proposed mechanism of shock-induced organ. <i>Intens Care Med</i> 23:504-9.	II	The degree of metabolic acidosis after trauma correlates with CD11b receptor expression on circulating neutrophils.
Davis, JW	1998	Base deficit is superior to pH in evaluating clearance of acidosis after traumatic shock. <i>J Trauma</i> 44:114-8.	II	Base deficit reveals differences in metabolic acidosis between survivors and non-survivors not identified by pH determination. Base deficit is a better mark of acidosis clearance after shock.
Eberhard, LW	2000	Initial severity of metabolic acidosis predicts the development of acute lung injury in severely traumatized patients. <i>Crit Care Med</i> 28:125-31.	II	The emergency department base deficit and the total crystalloid volume in 24h predict the development of acute lung injury while total number of transfusions does not.
Brill, SA	2002	Base deficit does not predict mortality when it is secondary to hyperchloremic acidosis. <i>Shock</i> 17:459-462.	II	Hyperchloremic metabolic acidosis is a common cause of metabolic acidosis in the intensive care unit and is associated with lower mortality than metabolic acidosis from other causes. Hyperchloremic metabolic acidosis can be induced by lactated Ringer's resuscitation and may lead to inappropriate clinical interventions due to the incorrect presumption of ongoing tissue hypoxia.
Randolph, LC	2002	Resuscitation in the pediatric trauma population: admission base deficit remains an important prognostic indicator. <i>J Trauma</i> 53:838-842.	II	Retrospective study of pediatric trauma patients admitted to an intensive care unit. Admission base deficit is associated with shock, poor outcome, and mortality. Failure to clear base deficit was associated with 100% mortality.
Davis, JW	1988	Base deficit as a guide to volume resuscitation. <i>J Trauma</i> 28:1464-7.	III	Base deficit is a useful guide to volume replacement in the resuscitation of trauma patients.
Siegel, JH	1990	Early physiologic predictors of injury severity and death in blunt multiple trauma. <i>Arch Surg</i> 125:498-508.	III	Both extracellular base deficit and the volume of blood transfused in the first 24 hours were significant predictors of mortality.
Falcone, RE	1993	Correlation of metabolic acidosis with outcome following injury and its value as a scoring tool. <i>World J Surg</i> 17: 575-9.	III	Multivariate analysis revealed that only Trauma Score and age are predictive of survival. Base deficit is an important predictor of volume of blood needed.
Davis, JW	1997	Effect of alcohol on the utility of base deficit in trauma. <i>J Trauma</i> 43:507-10.	III	The presence of alcohol results in significantly worse base deficit despite lower injury severity score and higher predicted survival in alcohol positive patients. Despite this finding base deficit <-6 remained a significant predictor of major injury regardless of alcohol level.
Davis, JW	1998	Base deficit in the elderly: a marker of severe injury and death. <i>J Trauma</i> 45:873-7.	III	Base deficit < -6 is a marker of severe injury and significant mortality in all trauma patients, but it is particularly ominous in patients 55 years of age and older. Patients older than 55 years may have significant injuries and mortality risk without manifesting a base deficit out of the normal range.
Kincaid, EH	1998	Elevated arterial base deficit in trauma patients: a marker of impaired oxygen utilization. <i>JACS</i> 187:384-92.	III	A persistently high arterial base deficit is associated with altered O2 utilization and increased multiple organ failure and mortality.
Krishna, G	1998	Physiological predictors of death in exsanguinating trauma patients undergoing conventional trauma surgery. <i>ANZ J Surg</i> 68:826-9.	III	Strong predictors of death (after multiple logistic regression outcome could be predicted with 92.5% accuracy) were: Base deficit >12 mEq/L or T < 33 C or a combination of T 35.5 to 33.5 AND a base deficit of 5-12 mEq/L.
Dunham, CM	2000	Base deficit level indicating major injury is increased with ethanol. <i>J Emer Med</i> 18:165-71.	III	The presence of alcohol results in worsening of the base deficit independent of other variables. Risk of major injury increases when base deficit is <-4.1 in alcohol positive patients vs. <-1.1 in alcohol negative patients.
Rixen, D	2000	Metabolic correlates of oxygen debt predict posttrauma early acute respiratory distress syndrome and the related cytokine response. <i>J Trauma</i> 49:392-403.	III	Maximum oxygen debt (i.e. increased base deficit and lactate) correlates with early acute respiratory distress syndrome and death.
Kincaid, EH	2001	Admission base deficit in pediatric trauma: a study using the National Trauma Data Bank. <i>J Trauma</i> 51:332-5.	III	In injured children admission base deficit predicts injury severity and predicts mortality. Base deficit less than -8 could represent potentially lethal injury and uncompensated shock.
Rixen, D	2001	Base deficit development and its prognostic significance in posttrauma critical illness: An analysis by the trauma registry of the Deutsche Gesellschaft Fur Unfallchirurgie. <i>Shock</i> 15:83-89.	III	Base deficit is an early indicator to identify patients that will show hemodynamic instability, high transfusion requirements, metabolic and coagulatory decompensation as well as probability of death. This was true for both initial admission and intensive care unit admission. With a worsening of base deficit form hospital to intensive care unit admission there was an increased mortality.

Table 1 (Continued)

First Author	Year	Title	Class of Evidence	Conclusions
Dunne, J	2002	Lactate and base deficit in trauma: does alcohol impair their predictive accuracy? <i>J Trauma</i> 53:188 (abstract).	III	Using a large database of trauma patients, the authors found that many patients had ingested alcohol or other drugs. Lactate and base deficit levels still were predictive of outcome.
Eachempati, SR	2002	Factors associated with mortality in patients with penetrating abdominal vascular trauma. <i>J Surg Res</i> 108: 222–226.	III	In patients with penetrating abdominal trauma, the only factor that independently predicted mortality was base deficit. Blood pressure on admission and blood loss were predictive in univariate analysis.
Eachempati, SR	2003	Serum bicarbonate as an endpoint of resuscitation in critically ill patients. <i>Surg Inf</i> 4:193–197.	III	Using a large dataset from trauma patients, the authors found a strong correlation between base deficit and serum bicarbonate levels.
Arterial Lactate Levels				
Vincent, JL	1983	Serial lactate determinations during circulatory shock. <i>Crit Care Med</i> 11:449–451.	II	Serial lactate determinations are more prognostic of survival than a lone initial value.
Abramson, D	1993	Lactate clearances and survival following injury. <i>J Trauma</i> 35:584–589.	II	Time to normalize lactate is prognostic of survival.
Manikis, P	1995	Correlation of serial blood lactate levels to organ failure and mortality after trauma. <i>Am J Emerg Med</i> 13:619–622.	II	Initial lactate and peak lactate were higher in non-survivors. Initial lactate, peak lactate and duration of lactic acidosis correlated with organ failures.
Mikulaschek, A	1996	Serum lactate is not predicted by anion gap or base excess after trauma resuscitation. <i>J Trauma</i> 40:218–224.	II	Lactate, base excess, and anion gap do not correlate after resuscitation.
McNelis, J	2001	Prolonged lactate clearance is associated with increased mortality in the surgical intensive care unit. <i>Am J Surg</i> 182:481–485.	III	Retrospective study of postoperative intensive care unit patients. Time to clear lactate correlated with mortality.
End-tidal Carbon Dioxide				
Tyburksi, JG	2002	End-tidal CO ₂ -derived values during emergency trauma surgery correlated with outcome: a prospective study. <i>J Trauma</i> 53:738–743.	II	Prospective study of trauma patients who required an urgent operation. Survivors had higher end-tidal CO ₂ levels, lower arterial-end tidal CO ₂ differences, and decrease alveolar dead space ratio.
Gastric Tonometry				
Gutierrez, G	1992	Comparison of gastric intramucosal pH with measures of oxygen transport and consumption in critically ill patients. <i>Crit Care Med</i> 20:451–7.	I	pHi, mixed venous pH and PO ₂ , oxygen extraction ratio, lactate all different between survivors and nonsurvivors. Final values—pHi and SvO ₂ worse in nonsurvivors.
Gutierrez, G	1992	Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. <i>Lancet</i> 339:195–9.	I	Keep pHi > 7.35 vs standard care. No benefit if initial pHi <7.35. Improved survival in patients with normal initial pHi.
Ivatury, RR	1995	Gastric mucosal pH and oxygen delivery and oxygen consumption indices in the assessment of adequacy of resuscitation after trauma. <i>J Trauma</i> 39:128–34.	I	pHi may be an important marker for resuscitation adequacy and an early indicator of post-resuscitation complications.
Ivatury, RR	1996	A prospective randomized study of end points of resuscitation after major trauma: global oxygen transport indices versus organ. <i>JACS</i> 183:145–54.	I	pHi marker of adequate resuscitation. Normalized later than oxygen delivery, lactate, and base deficit.
Gomersall, CD	2000	Resuscitation of critically ill patients based on the results of gastric tonometry: A prospective, randomized controlled trial. <i>Crit Care Med</i> 28:607–614.	I	Compared standard therapy with standard therapy plus colloids and dobutamine for low pHi. No difference in outcome.
Doglio, GR	1991	Gastric mucosal pH as a prognostic index of mortality in critically ill patients. <i>Crit Care Med</i> 19:1037–40.	II	Low pHi predicts increased risk of death, sepsis, multiple organ failure. Worst if persists at 12 h.
Maynard, N	1993	Assessment of splanchnic oxygenation by gastric tonometry in patients with acute circulatory, failure. <i>JAMA</i> 270:1203–10.	II	Although a variety of resuscitation endpoints correlated with surviving critical illness, only pHi at 24 h proved an independent predictor of death by logistic regression.
Weil, MH	1999	Sublingual capnography: a new noninvasive measurement for diagnosis and quantitation of severity of circulatory shock. <i>Crit Care Med</i> 27:1225–1229.	II	Prospective, criterion study of acutely-ill patients and normal volunteers. Sublingual PCO ₂ correlates with lactate level, presence of shock, and survival.
Baron, BJ	2002	Diagnostic utility of sublingual PCO ₂ for detecting hemorrhage in patients with penetrating trauma. <i>Acad Emerg Med</i> 492 (abstract)	II	In a prospective, observational study, sublingual CO ₂ levels correlated with blood loss.
Gys, T	1988	The prognostic value of gastric intramural pH in surgical intensive care patients. <i>Crit Care Med</i> 16:1222–4.	III	pHi < 7.32 may correlate with short-term mortality.
Boyd, O	1993	Comparison of clinical information gained from routine blood-gas analysis and from gastric tonometry for intramural pH. <i>Lancet</i> 341:142–146.	III	Prospective study of patients who required a pulmonary artery catheter. Base deficit and bicarbonate levels correlated well with pHi.
Roumen, RMH	1994	Gastric tonometry in multiple trauma patients. <i>J Trauma</i> 36:313–316.	III	Gastric pHi may predict morbidity in severely injured patients.
Miller, PR	1998	Threshold values of intramucosal pH and mucosal-arterial CO ₂ gap during shock resuscitation. <i>J Trauma</i> 45:868–72.	III	In trauma patients, the ability to predict death and multiple organ failure is maximized when pHi < 7.25 and gastric mucosal to arterial carbon dioxide gap is greater than 18 mm Hg.
Subcutaneous Oxygen and Carbon Dioxide Electrodes				
Jonsson, K	1987	Assessment of perfusion in postoperative patients using tissue pO ₂ measurements. <i>Br J Surg</i> 74:263–7.	II	Subcutaneous tissue oxygen tension was measured as an index of perfusion in 44 postoperative patients. 12 of 30 patients were found to be underperfused by the authors' definition and was not recognized by clinical criteria.

Table 1 (Continued)

First Author	Year	Title	Class of Evidence	Conclusions
Waxman, K	1994	A method to determine the adequacy of resuscitation using tissue oxygen monitoring. <i>J Trauma</i> 36:852–856.	II	Monitoring tissue PO ₂ during an inspired O ₂ challenge may be a useful test to determine the adequacy of resuscitation. A negative O ₂ challenge was considered indicative of flow dependant O ₂ consumption, seen in 60% of patients during acute resuscitation.
Tatevossian, RG	2000	Transcutaneous oxygen and CO ₂ as early warning of tissue hypoxia and hemodynamic shock in critically ill emergency patients. <i>Crit Care Med</i> 28:2248–53.	II	Continuous PtO ₂ and PtCO ₂ monitoring evaluate tissue perfusion and serve as early warning in critically ill patients.
Gote, H	1990	Tissue oximetry as a possible predictor of lethal complications after emergency intestinal surgery. <i>Surg Res Comm</i> 7:243–249.	III	Subcutaneous PO ₂ was measured in 10 patients undergoing emergency intestinal surgical procedures using a tonometer implanted in the abdominal wall. Subcutaneous PO ₂ values were higher in the survivors.
Drucker, W	1996	Subcutaneous tissue oxygen pressure: a reliable index of peripheral perfusion in humans after injury. <i>J Trauma</i> 40 (3 Suppl):S116–22.	III	An optode probe which uses fluorescent techniques accurately measures the partial pressure of oxygen in subcutaneous tissues. This measurement correlates with the adequacy of resuscitation and tissue perfusion.
Near Infrared Spectroscopy				
Cairns, CB	1997	Evidence for early supply independent mitochondrial dysfunction in patients developing multiple organ failure after trauma. <i>J Trauma</i> 42:532–6.	II	Patients with severe trauma who developed multiple organ failure were found to display abnormal mitochondrial oxidative function. At 12 hours of resuscitation, patients with or without organ failure did not have different oxygen delivery or consumption. Lactate was higher in multiple organ failure group. 89% of patients with organ failure have abnormal near infrared values compared to 13% of patients without organ failure.
Torella, F	2002	Regional tissue oxygenation during hemorrhage: Can near infrared spectroscopy be used to monitor blood loss? <i>Shock</i> 18:440–444.	II	Human volunteers undergoing donation of 470 ml blood were studied. Blood loss correlated with regional hemoglobin saturation in the cerebral cortex and left calf muscle, as well as oxygenation index (oxygenated–deoxygenated hemoglobin concentration).
McKinley, BA	2000	Tissue hemoglobin O ₂ saturation during resuscitation of traumatic shock monitored using near infrared spectrometry. <i>J Trauma</i> 48:637–42.	III	Hb O ₂ saturation was monitored noninvasively and simultaneously in skeletal muscle and subcutaneous tissue. Skeletal muscle O ₂ tracked systemic O ₂ delivery. Authors suggest that it could be used in combination with base deficit and lactate to guide resuscitation.

complications, e.g., ongoing hemorrhage or abdominal compartment syndrome. These findings should prompt rapid reassessment of the patient.

3. The effects of ethanol intoxication, seizures, sepsis, a hyperchloremic metabolic acidosis, or a pre-existing metabolic acidosis, as well as administration of sodium bicarbonate, on base deficit levels should be considered when using this parameter as an endpoint of resuscitation.

Level III

1. Right ventricular end diastolic volume index (RVEDVI) measurement may be utilized as a better indicator of adequate volume resuscitation (preload) than central venous pressure or pulmonary capillary wedge pressure (PCWP).
2. Measurements of tissue (subcutaneous or muscle) O₂ and/or CO₂ levels may be used to identify patients who require additional resuscitation and are at an increased risk for MODS and death.
3. Serum bicarbonate levels may be substituted for base deficit levels.

Recommendations Regarding Improved Patient Outcomes

Level I

There are insufficient data to formulate a Level I recommendation.

Level II

1. During resuscitation, O₂ delivery should be increased to normalize base deficit, lactate, or pH_i during the first 24 hours. The optimal algorithms for fluid resuscitation, blood product replacement, and the use of inotropes and/or vasopressors have not been determined.

SCIENTIFIC FOUNDATION Oxygen Delivery

Shoemaker et al.,^{7,8} reviewed the hemodynamic profiles of high-risk surgical patients who survived versus those who did not. They found that survivors had significantly higher O₂ delivery and cardiac index (CI) values than nonsurvivors. The values in the survivors included: CI (≥ 4.5 L/min/m²), O₂ delivery (≥ 600 mL/min/m²), and O₂ consumption (≥ 170 mL/min/m²). In a prospective study of high-risk surgical patients, using these parameters as goals for resuscitation resulted in decreased complications, length of stay, and hospital costs.⁹ This group then recommended adding to the “ABCs” of resuscitation: “D” for increased delivery of O₂ and “E” for ensuring extraction and utilization of O₂ by tissues.¹⁰

In severely injured patients, this group similarly found that attaining supranormal hemodynamic parameters improved survival and decreased the frequency of organ failures.¹¹ They then prospectively tested the hypothesis that using the values of survivors as goals for resuscitation rather

than the values for these parameters found in normal, non-injured patients would improve survival. Fleming et al.,¹² randomized trauma patients to be resuscitated to the supranormal values above versus standard hemodynamic variables. The supranormal group had fewer organ failures and shorter hospital stays, particularly when the values were attained within 24 hours of injury. Mortality was slightly better at $p = 0.08$. In a randomized trial in victims of severe trauma, Bishop et al.,¹³ found that resuscitating to supranormal values of cardiac index, O₂ delivery, and O₂ consumption, compared with normal vital signs, urine output, and central venous pressure, decreased the risk of MODS and death. Oxygen delivery was augmented by volume loading, followed, if necessary, by dobutamine infusion and blood transfusions up to hemoglobin of 14 gm/dL.

Others have tried to duplicate these findings with limited success. Moore et al.,¹⁴ utilized a resuscitation protocol aimed at maximizing O₂ delivery. Patients who did not reach the established goals within 12 hours were at increased risk for developing MODS. Durham et al.,¹⁵ found that resuscitation of critically ill patients to the O₂ delivery and/or consumption parameters defined by Shoemaker did not improve the rate of MODS or death compared with conventional parameters. Patients in both groups had similar goals for preload based on PCWP or RVEDV and hemoglobin concentration. Patients who did not attain the supranormal O₂ delivery values were at high risk of developing MODS, regardless of group assignment. In trauma patients, Velmahos et al.,¹⁶ found that early optimization of O₂ delivery parameters did not improve outcome. In this study, 40% of the control patients achieved these parameters spontaneously compared with 70% of the protocol patients. None of the patients who attained these parameters died, compared with 30% of those who did not, regardless of group assignment. In these studies, attaining these parameters seemed to be more predictive of survival than useful as a goal of resuscitation, particularly if fluid resuscitation was adequate.

The means used to attain the O₂ delivery goals may be an important issue that has not been adequately explored. In the original studies by the Shoemaker group, the protocol consisted of volume loading with crystalloids and blood, followed by enhancement of cardiac output with dobutamine.^{7,8} In a heterogeneous group of medical and surgical critically ill patients, Hayes et al.,¹⁷ found that use of dobutamine to help augment O₂ delivery may actually have increased mortality. In contrast, Boyd et al.,¹⁸ found that, after fluid resuscitation, increasing O₂ delivery with dopexamine in high-risk surgical patients improved mortality and rate of complications.

The optimal O₂ delivery goal has recently been questioned. McKinley et al.,¹⁹ using a bedside computerized decision support tool, found that there was no difference in outcome between groups resuscitated to an O₂ delivery goal of 600 mL/min/m² versus 500 mL/min/m². The latter group required less fluid for resuscitation. Outcome was not compared with other endpoints, however.

Several methodological issues regarding these studies should be noted. First, these studies cannot be totally blinded. Second, patients in the control groups often attain the same physiologic endpoints as those in the treatment groups. Third, control of other aspects of management is variable. Fourth, entrance criteria vary from one study to another.

Heyland et al.,²⁰ reviewed the evidence for supra-physiologic goals for O₂ delivery in surgical patients and found no overall benefit. There was a suggestion of benefit if the goals were achieved preoperatively. More recently, Kern and Shoemaker²¹ reviewed all randomized clinical trials of hemodynamic optimization in high-risk patients, both medical and surgical. They grouped the studies by the timing of intervention (before or after the onset of organ dysfunction) and mortality in the control group. They found improved overall mortality with supranormal O₂ delivery goals only in the studies with interventions initiated before the onset of organ failure and mortality of >20% in the control group. Thus, it seems that optimization of hemodynamic variables should be initiated as early as possible during resuscitation. The greatest benefit seems to be in the sickest groups of patients.

In summary, patients who achieve supranormal oxygen delivery goals have a better chance of survival than those who do not achieve these goals. There is no convincing evidence that attempting to attain these goals directly improves survival. The best algorithm for attaining the goals is yet to be determined.

Mixed Venous Oxygen Saturation

Use of mixed venous O₂ saturation (SvO₂) levels should reflect the adequacy of O₂ delivery to tissues in relation to global tissue O₂ demands. In a general population of critically ill patients, Gattinoni et al.,²² resuscitated patients to a normal CI (2.5–3.5 L/min/m²), supranormal CI (>4.5 L/min/m²), or normal SvO₂ ($\geq 70\%$). There were no differences in mortality or MODS. There are few specific data on the use of mixed venous oxygen saturation in trauma victims.

Additional Invasive Hemodynamic Monitoring Parameters

Occult cardiac dysfunction and systemic hypoperfusion may occur in many trauma patients. To explore this question, Scalea et al.,²³ instituted a protocol of early invasive hemodynamic monitoring of high-risk geriatric blunt trauma victims. They found that monitoring identified occult shock early and may have helped to prevent MODS and death. These investigators⁵ even found that young victims of penetrating trauma often had evidence of hypoperfusion. They utilized a protocol of volume resuscitation, inotropes, and blood transfusions to increase O₂ delivery until lactate concentration normalized and O₂ consumption was no longer flow dependent. Patients who did not normalize lactate or reach their hemodynamic goals by 24 hours were at high risk of dying.

Recognizing that fluid resuscitation is the primary treatment for trauma patients in hemorrhagic shock, indicators of adequate intravascular volume, i.e., optimized preload, are needed. Central venous and pulmonary capillary wedge pressures are useful, but have limitations in critically ill patients due to changes in ventricular compliance (edema, ischemia, or contusion) and intrathoracic pressure (mechanical ventilation). The group at Bowman Gray School of Medicine has explored the use of several parameters that can be measured or calculated using a pulmonary artery catheter.

In the face of potentially variable ventricular compliance and intrathoracic pressure, measurement of RVEDVI may more accurately reflect left ventricular preload than CVP or PCWP. This value can be determined using a right ventricular ejection fraction/oximetry volumetric catheter. Cheatham et al.,²⁴ demonstrated that CI correlates better with RVEDVI than PCWP at up to very high levels of positive end-expiratory pressure. This same group²⁵ examined 79 consecutive critically ill trauma patients. Patients with splanchnic hypoperfusion as defined by low gastric mucosal pH (pHi) had a high risk of developing MODS and death. These patients also had lower RVEDVI than those with normal pHi. PCWP, CI, O₂ delivery index, and O₂ consumption index did not correlate with pHi. Chang et al.,²⁶ examined hemodynamic parameters in patients with normal versus low pHi after severe trauma. Normalized pHi and high RVEDVI were strongly associated with better outcomes. Recently, Kincaid et al.,²⁷ suggested that the optimal RVEDVI for each patient could be calculated based on measurements of ventricular compliance.

Chang et al.,²⁸ compared the hemodynamic variables left ventricular stroke work index (LVSWI = stroke index \times mean arterial pressure \times 0.0144) and left ventricular power output (LVP = cardiac index \times [mean arterial pressure - central venous pressure]), which encompass blood pressure and flow, with the standard, purely flow-derived, hemodynamic and O₂ transport variables (CI, O₂ delivery index, O₂ consumption index) as predictors of outcome in critically-ill trauma patients. The only variables that significantly correlated with lactate clearance and survival were heart rate, LVSWI and LVP. Using the ventricular pressure-volume relationships, they found that survivors also had better ventricular-arterial coupling, as determined by a lower ratio of afterload (aortic input impedance) to contractility (ventricular end-systolic elastance). They then prospectively resuscitated patients with the goal of achieving the survivors' level of LVP (>320 mm Hg \times L/min/m²).²⁹ This group of patients (n = 20) was compared with a group of patients from a previous prospective study (n = 39). The patients resuscitated to the LVP goal normalized their base deficit sooner and had a lower risk of developing organ system failure. The difference in survival did not reach statistical significance. In a separate study, these investigators³⁰ found that improved ventricular-arterial coupling during resuscitation was associated with improved myocardial efficiency (ratio of stroke work to total myocar-

dial energy output as measured via the pressure-volume loop) and decreased base deficit.

In summary, novel hemodynamic parameters that can be calculated by measurements obtained from the pulmonary artery catheter can be predictive of increased chances for survival. The utility of these parameters to directly improve survival is yet to be determined.

Arterial Base Deficit

Inadequate tissue O₂ delivery leads to anaerobic metabolism. The degree of anaerobiosis is proportional to the depth and severity of hemorrhagic shock, which should be reflected in the base deficit and lactate level. Arterial pH is not as useful since the body's compensatory mechanisms attempt to maintain a normal pH.³¹ A recent study by Eachempati et al.,³² suggests that serum bicarbonate concentrations, which may be more readily available than arterial blood gases, correlate very well with base deficit values.

Because it is rapidly available, the base deficit has been extensively studied. Davis et al.,³³ retrospectively found that higher base deficit was associated with lower blood pressure on admission and greater fluid requirements. They stratified patients' level of illness as mild (base deficit 2–5 mmol/L), moderate (base deficit 6–14 mmol/L), or severe (base deficit >14 mmol/L). Two-thirds of patients with an increasing base deficit had ongoing blood loss. Rutherford et al.,³⁴ added that base deficit correlated with mortality and enhanced the predictive value of the TRISS methodology.³⁵ Falcone et al.,³⁶ further found a good correlation between base deficit and blood product requirements, although they did not find base deficit to independently correlate with mortality. Sauaia et al.,³⁷ found that base deficit, lactate, and transfusion requirements were predictive of the development of multiple organ failure. Age and injury severity score (ISS) were also important variables.

The importance of a normal base deficit may vary with different patient populations. Davis et al.,³⁸ found that a base deficit of ≥ 6 mmol/L is a marker of severe injury in all patients, but a normal base deficit was associated with an ISS of >16 in patients older than 55 years more often than in younger patients.

Base deficit changes over time may add to the utility of this parameter. Davis et al.,³¹ found that changes in base deficit over time were more predictive of survival than pH levels. Kincaid et al.,³⁹ further found that, among trauma patients who normalized their lactate levels, those that had persistently high base deficit had greater risk of MODS and death than patients with normal base deficit. These patients also demonstrated impaired O₂ utilization, as evidenced by lower O₂ consumption and O₂ utilization coefficient. Rixen et al.,⁴⁰ similarly found that an increase in base deficit between arrival at the hospital and admission to the intensive care unit identified trauma patients with hemodynamic instability, high transfusion requirements, metabolic and coagulation abnormalities, and an increased risk of death.

Using a multivariate analysis, Siegel et al.,⁴¹ found that base deficit and initial 24 hour blood transfusion requirements were independently predictive of mortality. Lactate levels and injury severity scores were not. The combination of Glasgow Coma Scale and base deficit produced the best predictive model.

In victims of penetrating trauma, Eachempati et al.,⁴² found that the worst base deficit in the first 24 hours, blood pressure on admission, and estimated blood loss were predictive of mortality by univariate analysis. Only base deficit remained predictive by multivariate analysis.

To determine preoperative factors that could predict outcome in the most severely injured patients, Krishna et al.,⁴³ retrospectively examined 40 patients with multivisceral trauma (ISS >35) who required urgent operations for hemorrhage. Using base deficit, core temperature, and ISS, they could predict outcome with 92.5% accuracy. Severe hypothermia (<33°C), severe metabolic acidosis (base deficit >12 mmol/L), and a combination (temperature <35.5°C and base deficit >5 mmol/L) were strong predictors of death.

Elevated base deficit is not only predictive of mortality, but of complications, such as the need for blood transfusions and organ failure, particularly the acute respiratory distress syndrome (ARDS). Davis et al.,⁴⁴ found that admission base deficit correlated with need for blood transfusion (72% if base deficit \geq 6 mmol/L versus 18% if base deficit <6 mmol/L), length of stay, and the development of ARDS, renal failure, coagulopathy, and MODS. Eberhard et al.,⁴⁵ found that the initial base deficit was significantly higher in patients who developed acute lung injury compared with those who did not. Rixen and Siegel⁴⁶ found that both high lactate and base deficit during the first 24 hours of admission were associated with high interleukin-6 levels and the development of ARDS, especially within the first 4 days of admission. Botha et al.,⁴⁷ found that base deficit values correlated with neutrophil CD11b expression, suggesting that inflammatory processes are involved in the relationship between severity of post-traumatic shock and later development of MODS and death.

Bannon et al.,⁴⁸ prospectively studied 40 patients who required operations for truncal injuries to see what factors would best determine which patients were at the greatest risk of developing hemodynamic instability and need for blood transfusion. They found that both base deficit and lactate levels correlated with transfusion requirements, whereas mixed venous O₂ saturation did not.

Almost all studies of base deficit have focused on adults. Kincaid et al.,⁴⁹ found that base deficit could also reflect injury severity and risk of mortality in pediatric patients. Admission base deficit correlated with systolic blood pressure, ISS, and revised trauma score. Base deficit >8 mmol/L corresponded with a 25% mortality risk. This was corroborated by Randolph et al.⁵⁰

In addition to anaerobic metabolism, base deficit levels may be increased by a number of factors. Alcohol intoxica-

tion can worsen base deficit for similar levels of injury severity and hemodynamics after trauma. Dunham et al.,⁵¹ suggest that a base deficit of \geq 4.1 mmol/L should be concerning in intoxicated patients, whereas a base deficit of 1.1 is concerning in non-intoxicated patients. Davis et al.,⁵² on the other hand, found no difference in length of stay regardless of alcohol level. A base deficit of \geq 6 mmol/L was still predictive of a significant injury and need for blood transfusion. Using an even larger database (15,179 patients), Dunne et al.,⁵³ found that, although 21% of patients had ingested alcohol and 7% had used other drugs, admission lactate and base deficit remained as significant independent predictors of outcome.

Development of a hyperchloremic metabolic acidosis from resuscitation with normal saline or lactated Ringer's solution can increase base deficit independent of injury severity.⁵⁴ Acidosis secondary to hyperchloremia is associated with a lower mortality than that from other causes, particularly anaerobic metabolism.

Eachempati et al.,³² have shown that serum bicarbonate levels, which may be more readily available from some labs, correlate well with base deficits. Administration of sodium bicarbonate will at least transiently improve base deficit and bicarbonate levels and confound their use as endpoints for resuscitation. There is little role for sodium bicarbonate in the treatment of hemorrhagic shock.

Pre-existing metabolic acidosis (e.g., renal failure), sepsis, and seizure activity can also alter base deficit levels.

Initial base deficit levels and time to normalization of these levels correlate well with need for transfusion and risk of MODS and death. Persistently high or worsening base deficit levels may be an early indicator of complications, e.g., ongoing hemorrhage or the abdominal compartment syndrome. There are currently no data to suggest that using base deficit as an endpoint for resuscitation improves survival.

Arterial Lactate

Vincent et al.,⁵⁵ showed that not only were initial lactate levels important, but the response of the lactate level to an intervention, such as fluid resuscitation, would add predictive value in patients with noncardiogenic circulatory shock. Abramson et al.,⁵⁶ studied patients who had severe trauma and were resuscitated to supranormal values of O₂ transport.⁸ They found that the time needed to normalize serum lactate levels was an important prognostic factor for survival. All patients who had normalized lactate levels at 24 hours survived; those patients who normalized their levels between 24 and 48 hours had a 25% mortality rate; those that did not normalize by 48 hours had an 86% mortality rate. McNelis et al.,⁵⁷ found a similar trend in post-operative surgical patients admitted to the ICU. Manikas et al.,⁵⁸ further found that initial and peak lactate levels, as well as the duration of hyperlactatemia, correlated with the development of MODS after trauma.

In theory, the severity of metabolic acidosis secondary to tissue hypoperfusion should be similarly reflected in lactate levels and anion gap or base deficit. In 52 critically ill trauma patients, Mikulaschek et al.,⁵⁹ found that lactate levels were higher in nonsurvivors than in survivors. Similar correlations were not true for anion gap or base deficit. Correlations between these variables were poor. The total number of patients was small and the lactate levels were used to guide resuscitative efforts.

In summary, the initial lactate level and time to normalization of lactate correlate with risk of MODS and death. Improved survival using lactate as an endpoint for resuscitation has not been shown.

End-Tidal Carbon Dioxide Levels

Reduced cardiac output and/or abnormal distribution of pulmonary blood flow can lead to increased pulmonary dead space. This can then lead to an increase in the difference between arterial and alveolar CO₂, as measured by end-tidal CO₂. Tyburski et al.,⁶⁰ prospectively studied 106 trauma patients who required operations. Survivors had higher end-tidal CO₂, lower arterial-end tidal CO₂ differences, and decreased alveolar dead space ratio (estimated as arterial-end tidal CO₂ difference/arterial pCO₂) compared with nonsurvivors.

This preliminary study suggests that further study of end-tidal CO₂ measurements in trauma patients is warranted.

Gastric Tonometry

The stomach has been called the “canary of the body.”⁶¹ As systemic perfusion decreases, blood flow to the most vulnerable organs (brain and heart) is maintained at the expense of other organs (skin, muscle, kidneys, and intestines). In theory, detection of subclinical ischemia to these organs would allow identification of patients who require additional resuscitation despite seemingly normalized vital signs. Use of gastric tonometry is based on the finding that tissue ischemia leads to an increase in tissue pCO₂ and subsequent decrease in tissue pH. Because CO₂ diffuses readily across tissues and fluids, the pCO₂ in gastric secretions rapidly equilibrates with that in the gastric mucosa. For gastric tonometry to be accurate, it is necessary to withhold gastric feedings and suppress gastric acid secretion. A semi-permeable balloon attached to a special nasogastric tube is placed into the stomach. The balloon is filled with saline and CO₂ is allowed to diffuse into the balloon for a specific period of time. The pCO₂ in the saline is then measured. Continuous CO₂ electrodes are also available. Intramucosal pH (pHi) can be calculated based on the Henderson-Hasselbach equation. The difference between intragastric pCO₂ and arterial pCO₂ (the pCO₂ gap) or pHi correlates with the degree of gastric ischemia.

In a group of 59 surgical ICU patients, Gys et al.,⁶² found that pHi correlated with sepsis score. Patients with pHi <7.32 had a mortality of 37% whereas those with higher pHi all survived. Doglio et al.,⁶³ showed that lower pHi correlated with development of MODS and increased mortality in crit-

ically ill patients, particularly if the low pHi persisted for >12 hours. Maynard et al.,⁶⁴ suggested that pHi was a better predictor of mortality in a general ICU population than arterial pH, base deficit, and lactate levels. Interestingly, CI, O₂ delivery, and O₂ uptake were not different between survivors and nonsurvivors. In contrast, Boyd et al.,⁶⁵ found that markers of metabolic acidosis (base deficit and bicarbonate levels) correlated well with pHi. Finding base deficit of >4.65 had a 77% sensitivity and a 96% specificity of predicting pHi of <7.32. In 22 medical and surgical ICU patients, Gutierrez et al.,⁶⁶ compared pHi to O₂ transport parameters in survivors and nonsurvivors. Survivors and nonsurvivors had similar O₂ delivery, but nonsurvivors had greater O₂ consumption, O₂ extraction ratio, and lactate levels; and lower pHi, mixed venous pH, and mixed venous pO₂. All patients who died had pHi values <7.32.

In a separate study, Gutierrez et al.,⁶⁷ randomized critically ill patients to standard treatment versus a protocol that included increasing O₂ transport or decreasing O₂ demand if the pHi decreased below 7.35 or 0.1 units below the previous value. Survival was similar between groups if the initial pHi was low, but the protocol improved survival in those patients with initially normal pHi. In contrast, Gomersall et al.,⁶⁸ resuscitated patients in a general ICU using a standardized protocol to maintain mean arterial pressure >70 mm Hg, systolic blood pressure >90 mm Hg, urine output >0.5 mL/kg/hr, hemoglobin >8 g/dL, blood glucose <12 mmol/L, and arterial O₂ saturation >94%; uncompensated respiratory acidosis was corrected. Patients were then randomized to continued standard therapy or to additional fluid resuscitation and/or dobutamine to achieve pHi ≥7.35. There were no differences between groups in mortality, MODS, or length of stay.

In trauma patients, Roumen et al.,⁶⁹ prospectively studied 15 blunt trauma patients who required operations. Eight had low pHi (≤7.32) initially or subsequently. Three of these 8 developed complications and 2 died. All 7 with normal pHi had uncomplicated recoveries. They found no correlation between initial pHi and ISS, shock, lactate, or acute physiologic and chronic health evaluation (APACHE) II scores. Chang et al.,²⁶ similarly found that pHi <7.32 was a good predictor of MODS and mortality. Based deficit and mixed venous O₂ saturation were also independently associated with mortality. At 24 hours, the only factor that was different between patients who developed MODS and those who did not was pHi. All patients who developed MODS had pHi <7.1.

Threshold values for pHi and for the gastric mucosal-arterial CO₂ gap were explored by Miller et al.,⁷⁰ using a cohort of 114 trauma patients. The ability to predict MODS and death was maximized with pHi <7.25 and gap of >18 mm Hg. Some have suggested that the CO₂ gap is a better indicator of gut “dysoxia” than pHi, which is a calculated variable that may be altered by arterial bicarbonate levels.⁷¹

Using pHi as an endpoint (≥ 7.3) for resuscitation was compared with supranormal O_2 transport variables (O_2 delivery index of $600 \text{ mL}/\text{min}/\text{m}^2$ and a O_2 consumption index of $>150 \text{ mL}/\text{min}/\text{m}^2$) in a prospective, randomized study of 57 trauma patients by Ivatury et al.^{72,73} The resuscitation protocol included volume loading with crystalloid and blood followed, if necessary, with inotropic support using dobutamine. Treatment goals were achieved in almost all patients. Time taken to optimize pHi or O_2 transport variables was similar. The only parameter that remained different between groups was pHi. Considering both groups, delay in achieving pHi goals was more predictive of organ system failure, complications, and death than achieving the O_2 transport goals. The gap between gastric mucosal and arterial CO_2 was similarly predictive. In the postresuscitation period, persistently low or decreasing pHi was an early signal of complications.

Technologic limitations of measuring gastrointestinal pcO_2 should be kept in mind. The original, manual technique using a semi-permeable balloon is cumbersome. An airflow tonometer in which the balloon is automatically filled with air and the air is removed after a set period of time is also now approved by the Food and Drug Administration. Both methods could theoretically change the environment within the stomach by either adding O_2 or removing CO_2 . Fiberoptic systems using a spectrophotometric method for continuous monitoring are being developed. Wall et al.,⁷⁴ found that the airflow and fiberoptic devices correlated well with each other in vitro, but simultaneous samples in vivo during hemorrhagic shock and resuscitation in dogs differed significantly. The fiberoptic values were greater than the airflow values. The authors recommend using the fiberoptic approach since it does not interfere with the local gas environment. Imai et al.,⁷⁵ recently reported on the utility of a different type of CO_2 electrode that could continuously measure pcO_2 in the stomach.

An intriguing new approach to determine regional hypercarbia during shock is the use of sublingual pcO_2 monitoring. Weil et al.,⁷⁶ demonstrated that sublingual pcO_2 correlated with lactate levels, presence of shock, and survival in a small group of acutely ill patients. Povoas et al.,⁷⁷ compared duodenal and sublingual pcO_2 to mesenteric blood flow during hemorrhagic shock in pigs. Strong correlations were found between both pcO_2 values and mesenteric blood flow. In victims of penetrating trauma, Baron et al.,⁷⁸ showed that sublingual pcO_2 was elevated in patients with ongoing bleeding. Additional studies in humans are in progress.

In summary, gastric tonometry can provide data that can be used to predict risk of MODS and death. Normalization of pHi or pcO_2 gap as endpoints for resuscitation resulted in similar outcomes as attempts at achieving supranormal O_2 delivery.

Tissue Oxygen and Carbon Dioxide Electrodes

Measurements of transcutaneous O_2 and CO_2 levels may also be predictive of death in critically ill patients based on

the same principles of gastric tonometry. Drucker et al.,⁷⁹ utilized an optical sensor (optode) placed into subcutaneous tissues to examine peripheral perfusion. They first demonstrated that this probe worked as well as a standard Clark electrode and then demonstrated in animals that the subcutaneous po_2 decreased rapidly during hemorrhagic shock and increased with resuscitation. The values did not always return to baseline, suggesting ongoing peripheral vasoconstriction. Finally, in 18 trauma patients, they found that many still had low subcutaneous po_2 levels despite adequate resuscitation by standard clinical criteria.

Göte et al.,⁸⁰ measured subcutaneous po_2 in 10 patients undergoing emergency intestinal surgical procedures using a tonometer implanted in the abdominal wall. They found that subcutaneous po_2 values were higher in the survivors.

Tatevossian et al.,⁸¹ measured transcutaneous po_2 and pcO_2 in critically ill trauma patients. Patients who died had lower transcutaneous po_2 values, higher transcutaneous pcO_2 values, and longer periods of time with transcutaneous pcO_2 values $>60 \text{ mm Hg}$. All patients who had transcutaneous pcO_2 values $>60 \text{ mm Hg}$ for >30 minutes died.

Waxman et al.,⁸² took this concept one step further by measuring deltoid muscle po_2 via a needle-mounted probe before and after an O_2 challenge. Their hypothesis was that patients who were adequately resuscitated would respond with an increase in tissue po_2 since flow-dependent O_2 consumption would not be present. Tissue po_2 would not increase if flow dependent O_2 consumption is present and cells consume all additional O_2 . Responders ($n = 6$) during acute trauma resuscitations had lower ISS, higher revised trauma scores, and shorter hospital stays than nonresponders ($n = 9$). In 14 trauma patients already in the intensive care unit, response to the O_2 challenge test correlated very well with evidence of flow dependency via pulmonary artery catheterization. Jonsson et al.,⁸³ had previously used a similar technique to show that many patients who underwent abdominal surgical procedures were suboptimally perfused.

In summary, limited data suggest that transcutaneous and muscle po_2 and pcO_2 may be able to predict risk of death from trauma.

Near Infrared Spectroscopy (NIRS)

Measurement of skeletal muscle oxyhemoglobin levels by NIRS offers a non-invasive method for monitoring adequacy of resuscitation in terms of normalizing tissue oxygenation. In pigs undergoing hemorrhagic shock, Cohn et al.,⁸⁴ showed that gastric tissue O_2 saturation, measured continuously with a prototype side-illuminating NIRS nasogastric probe, decreased rapidly, correlating with superior mesenteric artery (SMA) blood flow. The correlation of SMA flow with tonometric CO_2 in the jejunum was not as good.

In human volunteers donating 470 mL of whole blood, Torella et al.,⁸⁵ found that cerebral cortex and calf muscle O_2 saturation measured by NIRS decreased in proportion to blood

loss. The oxygenation index ([oxygenated hemoglobin]-[deoxygenated hemoglobin]) also decreased proportionally.

McKinley et al.,⁸⁶ studied O₂ saturation of hemoglobin in tissue ($\text{StO}_2 = \text{HbO}_2/(\text{HbO}_2 + \text{Hb})$) during resuscitation in trauma patients. They found that StO_2 correlated with systemic O₂ delivery, base deficit, and lactate. This correlation was better than that found with gastric mucosal pCO₂ and pCO₂ gap.

NIRS technology allows the simultaneous measurement of tissue pO₂, pCO₂, and pH. During hemorrhagic shock, Puyana et al.,^{87,88} found in pigs that intra-abdominal organs respond differently than each other. Small bowel pH changed most rapidly during shock and resuscitation. Gastric mucosal pH, pCO₂, and pCO₂ gap were not as sensitive. Their data suggested that simultaneous measurements of tissue pO₂, pCO₂, and pH of solid organs, particularly the liver, may provide even better prediction of outcomes and better endpoints for resuscitation.^{89,90}

Sims et al.,⁹¹ found that placement of a fiberoptic multiparameter sensor into skeletal muscle could also be useful for monitoring the severity of hemorrhagic shock, as well as the adequacy of resuscitation, in pigs. They found that both pO₂ and pCO₂ changed rapidly during shock and resuscitation, whereas pH decreased, but did not return to baseline. The pH correlated best with blood loss. Persistently low pH and hypercarbia in muscle resulted from ongoing bleeding and incomplete resuscitation despite normalized blood pressure.

In addition to monitoring tissue oxygenation, NIRS can provide information regarding mitochondrial function. Normally, tissue oxyhemoglobin levels, reflecting local O₂ supply, are tightly coupled to cytochrome *a*,*a*₃ redox, reflecting mitochondrial O₂ consumption. Cairns et al.,⁹² found that 8 of 9 trauma patients who developed multiple organ failure had decoupling of these values, whereas only 2 of 16 patients who did not develop multiple organ failure had decoupling.

In summary, preliminary studies suggest that NIRS measurement of tissue pO₂, pCO₂, and pH has potential for predicting risk of MODS and death after trauma.

Physical Examination

Despite all the interest in laboratory values, as well as data from invasive and non-invasive monitoring devices, used to determine the adequacy of resuscitation, one should not discount the value of a good physical examination. Kaplan et al.,⁹³ examined the ability of two intensivists to diagnose hypoperfusion by physical examination of patients' extremities. The intensivists described the patients' extremities as either warm or cool. Compared with patients with warm extremities, those with cool extremities had lower CI, pH, bicarbonate levels, and SvO₂; and higher lactate levels.

SUMMARY

During resuscitation from traumatic hemorrhagic shock, normalization of standard clinical parameters such as blood pressure, heart rate, and urine output are not adequate to

guarantee survival without organ system dysfunction. Numerous parameters including hemodynamic profiles, acid-base status, gastric tonometry, and regional measures of tissue O₂ and CO₂ levels have been studied. Many can be useful for predicting risk of organ failure and death. Studies comparing use of these parameters as endpoints for resuscitation protocols, however, have failed to show clear benefit in terms of patient outcomes. At present, it seems prudent to use one of these endpoints rather than relying on standard clinical parameters.

FUTURE INVESTIGATION

The ideal parameter to use as an endpoint for resuscitation would be reliable, easy to use, non-invasive, safe, and cheap. Well-controlled clinical trials comparing parameters as endpoints for resuscitation are needed, but these are difficult to control because of lack of blinding, bias (by investigators and device manufacturers), and need for strict control of resuscitation protocols. In addition, comparing to a standard of care may become more difficult, perhaps even unethical, given that use of at least one parameter has become practically standard.

The next critical, unanswered question, once appropriate endpoints are determined, is how to achieve them. How do we know that the patient is adequately volume loaded? Once volume loaded, which inotropes and/or vasopressors are best for achieving the chosen endpoint? What should the optimal hematocrit be early in resuscitation?

Another set of important unanswered questions relate to subsets of trauma patients. The search for the "holy grail," i.e., a single endpoint that works for all trauma patients, may be unrealistic. For example, acid-base parameters may not work in patients with acid-base disturbances that are acute (alcohol intoxication) or chronic (renal failure). For older patients, beta-blockade and heart rate control may be valuable and use of inotropes that increase myocardial work along with massive volume loading may be detrimental.

Answering these questions will require systematic approaches to the problem in the context of coordinated research efforts. Multi-center studies should be instituted to achieve the large numbers of patients that will be needed to complete the studies in a timely fashion and to assure utility of the technique across a variety of patient populations and physician practices.

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EDITORIAL COMMENT

Dr. Tisherman and his colleagues from EAST have produced a provocative document in which they explore endpoints of resuscitation with respect to establishment of guidelines for clinical practice. The desire to establish scientifically based, evidence-supported, directed therapeutic modalities is a lofty and highly sought objective, an objective of potential usefulness and impact if fully implemented. It is difficult to argue with a desire to identify which measure or measures of physiology or metabolic biochemistry in acutely traumatized patients will tell us that the “resuscitation” has achieved its objective. The identification requires or assumes that the actual definition of “resuscitation endpoint” has been established and specified.

To that end, the very objective appears elusive. It may be restoration of normal tissue perfusion and homeostasis or the more clinically oriented outcome measures of morbidity, mortality, or incidence of multi-organ system dysfunction, the latter often a consequence of failure to achieve the necessary restoration of perfusion and tissue oxygenation.

One could also ask: is it attainment of an identified “endpoint” or the means of attaining the endpoint that has the greater influence on the clinical outcome measure, i.e., the “real” outcome measure? Some reference to the modes and methods of resuscitation with respect to endpoint identification and measurement, an interpretation in context, would seem appropriate in an undertaking of this magnitude.

Granted there are few randomized prospective trials to draw on, the use of mixed population studies, mostly class II and III evidence does not clarify but further confuses the question at hand: what is an endpoint for resuscitation?

Inclusion of data about surgical patients and surgical ICU patients in the analysis tends to further confuse the question. Patients who may have sustained acute changes in volume status under relatively controlled circumstances in the operating room or an observed or monitored situation are quite unlike the trauma victims with acute hypovolemia. The latter most frequently have an element of time delay in the restoration of intravascular volume, time to develop an oxygen debt in the tissues, time to effect hypoxia at the tissue levels with the result that negative metabolic sequelae develop. It is well accepted that the pathophysiology of shock—acute hypovolemic hemorrhage—is highly complex and multidimensional. It is somewhat of a stretch to consider that a single metric or combination of interdependent variables would be easily identified and clinically operationalized to effect a more desirable outcome. The underlying question remains: at what point in the resuscitation does the therapy transition from active treatment, end of resuscitation, to maintenance? Given a factor of time to restore cellular or organ function, can the transition point be specified? If not, the endpoint in this context remains elusive.

Which monitored variable, when restored to the patient’s baseline (not all patients will have the same normalized baseline, and it is frequently unknown and therefore assumed), actually reflects adequate restoration of tissue perfusion and overall organ functional stability, homeostasis? Absent a great deal of class I data, this is a difficult question to answer. Yet it must be addressed with well-designed, appropriately statistically powered randomized clinical trials. On the need for this approach I fully agree with the authors. However, absent these necessary studies, this piece reads as a review of potential measures, derived from underpowered studies of heterogeneous populations with data of wide-ranging quality from which level I recommendations are difficult to infer. This very “meta-analysis” approach to the design of guidelines, regression to expert opinion, reflects the class III data used to formulate the lower-level recommendation offered. Specification of the endpoints in terms of the acute resuscitation effort or the eventual patient outcome is required; if the former is done to defined evidence-based protocols, the latter surely will be improved. Despite the analysis presented, we have not identified useful and usable endpoints for either component, a point well made by this effort, which must be viewed as a work in progress.

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