Immediate Care of the Wounded

Clifford C. Cloonan, MD, FACEP
COL (ret) U.S. Army

Associate Professor
Department of Military & Emergency Medicine
Uniformed Services University of the Health Sciences

"It will be tragic if medical historians can look back on the World War II period and write of it as a time when so much was learned and so little remembered."[1]

Beecher H. Early Care of the Seriously Wounded Man. JAMA. 1951;145(4):193-200]
Henry K. Beecher - Father of the prospective, double-blind, placebo-controlled clinical trial.

"It is highly desirable that anyone engaged in war surgery should keep his ideas fluid and so be ready to abandon methods which prove unsatisfactory in favour of others which, at first, may appear revolutionary and even not free from inherent danger."[2]

Bailey H, ed. Surgery of Modern Warfare. 2nd ed. Edinburg: E & S Livingston; 1942; No. 1. – Hamilton Bailey, Reknown British Surgeon

Circulation

"…the only good thing that can be said of shock is that by enfeebling the circulation it may prevent so great a loss of blood as might otherwise occur."[3(p.9)]

J.J. Chisolm, Confederate Surgeon – Manual of Military Surgery

All bleeding stops…eventually[4]. [Attributed to Guy de Chauliac (1300-1370)]

Introduction

Exsanguination is the single most common cause of death on the battlefield; therefore the prevention of exsanguination at or near the point of wounding must be the single most important medical task. No hospital, no matter how advanced, and no surgeon, no matter how skilled, can save a wounded patient who has exsanguinated. Thus it is true, as Dr. Nicholas Senn, founder of the Association of Military Surgeons of the United States, once said, *"The fate of the wounded lies in the hands of the ones who apply the first dressing."* Most of those who die on the battlefield do so within minutes of wounding. Few of these patients with rapidly exsanguinating wounds can be saved regardless of the level of care provided; most would die even if they were wounded right outside a Level I trauma center. As noted by Col. Gray during World War I, *"The haemorrhage that takes place when a main artery is divided is usually so rapid and so copious that the wounded man dies before help can reach him."*[3(p.44)]

Furthermore, a sizeable number who could have been saved had care been immediately available die because the circumstances of combat preclude the rapid delivery of such care. An analysis of 98 Vietnam casualties who died from exsanguination revealed that nearly 20% had sustained injuries that, in ideal circumstances, could have been controlled with a tourniquet and/or appropriately applied direct pressure.[5-7] But some casualties with potentially lethal hemorrhage can be saved and it is upon this group the combat medical provider must focus.

Hemorrhagic Shock

The primary circulatory problem on the battlefield is shock; specifically hemorrhagic shock. Causes of hypovolemic shock such as massive burns and dehydration from a variety of causes, and neurogenic, cardiogenic, septic, and anaphylactic shock all occur in combat casualties but much more rarely. Hemorrhagic shock, therefore, is the primary focus of the following discussion. The other forms of shock will be briefly discussed at the end of this section.

Pathophysiology and Manifestations of Hemorrhagic Shock

A first century Roman savant, Aulus Cornelius Celsus, has been credited with describing hemorrhagic shock in vivid terms that remain accurate today.[8] He reputedly said, "When much blood is lost, the pulse becomes feeble, the skin extremely pale, the body covered with a malodorous sweat, the extremities frigid, and death occurs speedily." In the late 1800s, Samuel Gross described shock as being "a rude unhinging of the machinery of life"[9, 10] and John Warren called shock "A momentary pause in the act of death."[11] Despite great advances in hospital-level care, assessment and management of shock in the field remain little changed since at least World War II.

Types of Shock

Many different types of shock have been described. Shock is generally classified by cause or by underlying pathophysiology. Two or more types are often combined in a single patient, for example, hypovolemia may occur with septic shock and cardiogenic shock may occur when other types of shock exist. Regard-

less of the classification, the underlying defect is <u>always</u> inadequate tissue perfusion. Other causes of hypovolemic shock include dehydration, burns, and "third spacing" of fluid into the peritoneum or other extravascular spaces. Although the focus of the discussion herein is hypovolemic shock, other types of shock such as cardiogenic shock, neurogenic or vasogenic shock, anaphylactic and septic shock do occur in combat casualties,.

Stages of Shock

Shock is typically described as occurring in stages, although there are rarely distinct boundaries or well-defined characteristics that differentiate one stage from the next. Shock exists on a continuum that is unique in any given patient. The stages of shock, as described in most texts, are compensated, decompensated, and "irreversible" shock.

Compensated Shock

Compensated shock involves some degree of decreased tissue perfusion however the body's compensatory responses are sufficient to overcome the decrease in available intravascular volume. Cardiac output and a normal systolic blood pressure are maintained by sympathetic stimulation. In this stage the rate and depth of respirations increase, leading to decreased PCO_2 (compensatory respiratory alkalosis). This decrease is in response to decreased tissue perfusion and its resultant lactic acidosis. Sympathetic constriction of the large veins increases the amount of blood in the arterial system contributing to the maintenance of blood pressure and cardiac output (CO); essentially providing a venous capacitance autotransfusion.

Increases in heart rate (variable) and in cardiac contractility also maintain cardiac output. The quality of the pulse remains normal to somewhat weakened in strength (pulse pressure is normal to slightly decreased). Sympathetic constriction of the arteries leads to an increased peripheral vascular resistance that also helps to maintain blood pressure. This arteriolar constriction decreases capillary flow producing the cool skin so characteristic of patients in shock. Catecholamine release also produces bronchodilation, with associated improved air exchange.

The primary physical findings in compensatory shock are slightly delayed capillary refill and cool, slightly pale, skin. Other manifestations of shock may include mild to moderate thirst and depression, with no alteration in mental status. If the underlying cause remains untreated and continues unabated, the compensatory mechanisms eventually collapse. The progression of shock in the microcirculation produces a sequence of changes in capillary perfusion. Oxygen and substrate delivery to the cells supplied by these capillaries decreases, resulting in anaerobic metabolism that produces a lactic acidosis. When severe hypotension is present, oxygen delivery is markedly reduced and tissue oxygen extraction (percent of available oxygen extracted) is increased to meet demand. It should be noted that acidosis facilitates oxygen extraction at the cellular level by shifting the oxygen-hemoglobin dissociation curve to the right. For this reason shock-associated acidosis should never be treated with sodium but rather by restoring cellular perfusion.

Capillaries become "leaky" and protein-containing fluid leaks into the interstitial spaces (leaky capillary syndrome). Arte-

riovenous (AV) shunts open, particularly in the skin, kidneys and gastrointestinal tract, diminishing flow to the arterioles and capillaries in these organs. Sympathetic stimulation produces the pale, sweaty skin and rapid, thready, pulse (significantly narrowed pulse pressure) that Celsus described in the first century. It also elevates blood glucose levels and dilates coronary, cerebral, and skeletal muscle arterioles while constricting others. Blood is thus shunted to the heart, brain, and skeletal muscle with decreased capillary flow to the kidneys and abdominal viscera (autoregulation).

Decompensated Shock

Without prompt restoration of circulatory volume, compensated shock progresses to decompensated shock. Decompensated shock is manifested by a marked increase in heart rate, significantly prolonged capillary refill, and reduced blood flow to critical organs. At this stage, patients complain of marked thirst and although their mental state may remain clear, they are likely to be apathetic unless stimulated. Urine output decreases and eventually decreased blood flow to the brain alters mental status. As the shock state continues, the precapillary sphincters relax, expanding the vascular space. Postcapillary sphincters resist local effects and remain closed, causing blood to pool or stagnate in the capillary system producing capillary engorgement. Because increasing hypoxemia and acidosis lead to opening of additional venules and capillaries, the vascular space expands greatly.

With decompensated shock complete restoration of normal blood volume may be inadequate to fill the vascular "container" (this has implications for fluid resuscitation). The capillary and venule capacity may become great enough to reduce the volume of available blood for the great veins, further decreasing venous return and cardiac output. The viscera (lung, liver, kidneys and gastrointestinal mucosa) become congested due to stagnant blood flow. The respiratory system continues to attempt to compensate for the acidosis by increasing ventilation resulting in a partially compensated metabolic acidosis (decreased partial pressure of carbon dioxide [PCO_2]). Clotting mechanisms are affected leading to a hypercoagulable state that may result in disseminated intravascular coagulation. Uncorrected this stage of shock progresses to "irreversible" shock.

"Irreversible" Shock

At this point, the body is no longer able to maintain systolic pressure and both systolic and diastolic pressures begin to drop. The blood pressure may become unrecordable, the pulse will become very weak or even imperceptible, and the pulse pressure will be narrowed to such an extent that it may not be detectable with a blood pressure cuff.

"Irreversible" shock is manifested by extreme tachycardia or, in some cases, bradycardia, serious dysrhythmias, frank hypotension, and evidence of multiple organ failure. The skin is pale, cold, and clammy and capillary refill is markedly delayed. Patients in severe shock may complain bitterly of thirst, if they are able to speak. As cerebral blood flow decreases, there may be alteration in mental status manifested by apathy and such patients may appear to suffer very little. At this stage, patients may even become comatose although in previously healthy, physically fit, young adult soldiers, this tends to occur very late, if at all, and is often followed rapidly by death. In combat casualties, as a general

rule, it is dangerous to assume that shock is the cause of altered mental status before ruling out other causes such a head injury.

In "irreversible" shock, the partial pressure of oxygen (PO_2) may drop but the PCO_2 usually remains normal or low unless there is associated head or chest injury that leads to hypoventilation. Pulmonary capillaries become permeable, leading to pulmonary edema and acute respiratory failure or adult respiratory distress syndrome (ARDS). Cardiac ischemia may be present as a result of decreased hemoglobin, lower oxygen saturation, and decreased coronary perfusion secondary to diastolic hypotension. This ischemia may result in myocardial infarction and life-threatening dysrhythmias.

"Irreversible" shock is manifested by the progression of cellular ischemia and necrosis and by subsequent organ death despite restoration of oxygenation and perfusion. If capillary occlusion persists for more than 1-2 hours, the cells nourished by that capillary bed undergo irreversible changes. The unperfused cells can no longer use oxygen and metabolism stops. Hepatic failure usually occurs first, followed by renal failure, and then heart failure. Gastrointestinal bleeding and sepsis may result from mucosal necrosis. Pancreatic necrosis may lead to further clotting disorders and severe pancreatitis. Pulmonary thrombosis may produce hemorrhage and fluid loss into the alveoli, leading to death from respiratory failure.

Despite these well-described pathophysiologic changes, the irreversibility of "irreversible" shock has been questioned. The term, "irreversible shock" certainly has relevance in terms of pathophysiology but in any given patient

it is simply not possible to know at what point shock has become "irreversible." Indeed, a World War II army medical team sent to Anzio to study shock in nearly 3,000 casualties made the following observation:

> *The degree of wound shock, as we saw it...precisely paralleled the blood loss. Conversely, clinical recovery from shock resulted promptly from the administration of whole blood. Although we made intensive search at the bedside of thousands of wounded men...we never found a clear case of irreversible shock, so easily spoken of in published articles on this subject...The shock we saw was caused by blood loss...it was cured by blood administration.*[12(p. 672-681)]

Individual Manifestations of Shock

Although the various stages of shock are described in terms of specific physiologic states the manifestations of shock in a particular patient are determined, in large part, by that patient's pre-existing physiologic status. Factors that influence the response to a specific shock-producing insult include (1) age and relative health (2) pre-existing physical condition, and (3) pre-existing diseases and use of medications that may impair the body's ability to mount an appropriate physiologic response. Elderly patients are less able to compensate and thus tend to develop hypotension early. Children and physically fit young adult soldiers are able to compensate longer but they tend to decompensate precipitously.

Those who provide care at or near the point of wounding need to be aware that mortally wounded soldiers may not comprehend the severity of their injuries

and may only display outward signs of shock just before death. Even vital signs may misleadingly remain within the normal range for a surprisingly long time. The military historian S.L.A. Marshall describes one such circumstance as follows, "Millsaps [started across the river with one volunteer]...The man soon began to fall behind. Millsaps asked: "Something wrong with you? He answered: "I don't think so." Then Millsaps stripped the man's jump jacket away and found six bullet holes in his upper right arm and shoulder; the soldier had not been aware of his wounds until that moment. The soldier collapsed [and died]. Millsaps continued on alone."[13(p.183)]

Identifying the Patient in Hemorrhagic Shock at or Near the Point of Wounding

Shock should be assumed in the patient who has a weak, rapid, pulse (narrow pulse pressure), and a wound consistent with a shock state. It should be noted that severe extremity wounds are often associated with shock. The Board for the Study of the Severely Wounded in World War II found that, "…[T]he greatest loss of hemoglobin occurs in wounds that involve compound fractures of long bones or traumatic amputations."[12(p.676)] Certainly it was patients with these types of wounds who survived long enough to reach the shock tents on the beach at Anzio. In fact, this study showed that the blood loss associated with compound long bone fractures was greater than that seen in traumatic amputation.

It is again worth pointing out that except for patients with head wounds, the badly injured are nearly always lucid. Importantly the degree of thirst that is present in shock is often unappreciated; substan-

tial thirst is almost always present in severe shock.

When obtained at a single point in time, there is no single sign or symptom that can be used to reliably separate those in shock from those not; or to grade the severity of shock in an individual patient. There is simply no pathognomic sign or symptom of shock. Most important in making the diagnosis of shock is observation and repeated assessment over time. Particular attention should be given to observing the trend of the pulse and the pulse pressure (systolic minus diastolic blood pressure). A rising pulse rate, a falling blood pressure, and a narrowing pulse pressure should always alert the medical provider to the likelihood of shock, especially if associated with a cool skin, in a patient who has been in a warm environment.

Specific Tests for Shock

Blood Pressure

The general inability to use, with any beneficial effect, a single measurement of blood pressure to diagnose shock has long been recognized. Sir Zachary Cope, a pre-eminent surgeon of his day with considerable military experience in World War I, made the following observations about the utility of the blood pressure in diagnosing shock:

> *Though in general, blood loss increased with tissue damage, large blood loss might occur with small wounds... [There is] difficulty in recognizing those who had lost moderate amounts of blood, for patients who only had 70 or 80 percent of normal blood-volume might still maintain a normal blood pressure, though usually (but not always) they at the same time had a fast pulse*

and a pale face. A few of the patients [in shock] even presented a raised systolic blood pressure, while of those with a blood pressure of under 100 mm. Hg., some had rapid pulses, others only slightly more rapid than normal. A few, and these generally patients over fifty years, showed a pulse rate under seventy. In younger people the blood pressure was better maintained but the pulse rate tended to be faster...As a rule the blood pressure was proportional to the degree of injury and the reduction of blood volume, but occasionally extreme vasoconstriction maintained the blood pressure at a deceptive level, for example, 95 mm Hg, although in such cases the pallor was intense."[14]

More recently Capan and Miller, in their article on resuscitation, make the comment that, "equating a normal systemic blood pressure (or pulse) with normovolemia during initial resuscitation may lead to loss of valuable time for treating the underlying hypovolemia."[15] During World War II, Henry K. Beecher said,

Possibly, too much attention has been given to the fact that on many occasions [patients in shock may have a normal blood pressure]...[T]his has led to a tendency to dismiss the blood pressure as a helpful sign even when it is low - a fatal error, on some occasions. More helpful than the level of the blood pressure, is the direction of its swing - a falling blood pressure, a rising pulse rate, are in most cases an urgent indication of the need for blood."[16]

Dr. Colin Mackenzie, in his article "Anesthesia in the Shocked Patient" observes that, "It has been repeatedly shown that blood pressure and heart rate are unreliable indicators of shock in young trauma patients."[17] A recent study by Shoemaker et al. comparing invasive with non-invasive monitoring of intensive care unit (ICU) patients found that the average mean arterial pressure (MAP) initially recorded in survivors was only slightly higher than that of nonsurvivors.[18]

One final concern with relying on blood pressure to assess for shock is the accuracy of the blood pressure measurement itself. Potential problems include (1) the reliability of the provider who obtains the blood pressure, (2) the reliability of the equipment used to obtain the blood pressure, [19, 20] and (3) the ability of the equipment to perform outside of the normal physiologic range. Moskowitz and Reich note that, "The skill of the practitioner in detecting Korotkoff sounds and the speed of cuff deflation are potential sources of error in blood pressure measurement."[21] Hypotension produces hypoperfusion of the extremity with a resultant underestimation of blood pressure when assessed using the standard method.[22] Creamer et al.[23] demonstrated that the cuff pressures of patients in cardiogenic shock were poorly correlated with those obtained by direct monitoring of MAP.

Pulse Rate and Pulse Pressure

Regarding the efficacy of pulse rate and pulse pressure in the assessment of shock during World War II, The Board for the Study of the Severely Wounded noted that pulse rate is influenced by too many factors to be of great value by itself in the estimation of shock severity.[24] The Board did indicate, however, that the quality of the pulse and its upward or downward trend are most important. In a study on shock conducted by the

Board[24], the average, minimum and maximum pulse rates were the same in all degrees of shock. This surprising finding was explained as follows:

1. The tachycardia in the lesser degrees of shock may have been due in part to excitement, and

2. In some cases, the elevated pulse rate (and accompanying vasoconstriction) may have been adequate to ward off the signs of shock.

3. Further, even patients judged to be in severe shock could have a pulse rate as low as 60 beats per minute.

Of greater significance than the pulse rate was its volume, which often is decreased so far in severe shock that the pulse can no longer be felt [narrow pulse pressure]. Beecher et al. noted that as the severity of shock increases there is a significant and progressive decline in the pulse pressures as the severity of shock increases.[24]

The importance of measuring and tracking the pulse pressure of patients in shock was also emphasized by Sir Zachary Cope, who said, *"...a rapid pulse of low volume was a more constant indication of danger than a fall of blood pressure; a fall of blood pressure was sometimes a comparatively late event in circulatory failure after wounding."[14]* Occasionally patients in shock present with a normal or paradoxically decreased pulse rate. This condition has often been associated with ruptured ectopic pregnancy.[25, 26] and penetrating abdominal trauma.[27-29] but it has also been seen in hemorrhagic shock due to other causes[30-32].

Despite a long-standing recommendation to use the ability to obtain a pulse at the radial, femoral, and carotid arteries to estimate blood pressure (palpable radial pulse $\geq$ 80 mm Hg systolic blood pressure, palpable femoral pulse $\geq$ 70 mm Hg, and palpable carotid pulse $\geq$ 60 mm Hg systolic), there appears to be no scientific basis for this common belief. A 2000 study by Deakin and Low[33] published in the British Medical Journal compared the presence or absence of radial, femoral, and carotid pulses with intra-arterial blood pressure measured in the operating room. They found that, "The mean blood pressure and reference range obtained for each group indicate that the guidelines overestimate the systolic blood pressure associated with the number of pulses present." This author was unable to find any other studies that address the efficacy of this commonly used procedure to estimate blood pressure but empirically there appears to be a general correlation.

General Appearance and Mental State

Previously healthy, physically fit soldiers are so capable of compensating and autoregulating blood flow to the brain that even when blood loss has been massive, the usual mental lethargy that has often been described in shock may be absent and instead the patient may demonstrate unexpectedly normal mental acuity. This might easily deceive an inexperienced observer into thinking that shock is not present. Cope found that *"In shock the mental state was usu-*

ally rational...[14] The Board for the Study of the Severely Wounded during World War II stated that assessing mental status was not useful by itself but was helpful when combined with other findings, and noted that there was some correlation between mental status and degree of shock.[24]

Orthostatic Vital Signs

Orthostatic vital signs are used specifically to assess for hypovolemia. Orthostatic vital signs consist of blood pressure and pulse measurements obtained first when the patient is lying down and then from a standing or sitting position. Although typically used to assess intravascular volume status the validity of this test is in dispute. Commonly used parameters are the following differences between lying and standing measures:

> *>15-20 beat-per-minute increase in pulse rate*

> *>10-20 mm Hg decrease in systolic blood pressure*

> *>10-15 mm Hg decrease in diastolic blood pressure*

- The greater the difference, the higher the specificity and the lower the sensitivity for finding clinically significant hypovolemia

Although orthostatic vital signs are widely used to detect intravascular hypovolemia, a study by Baraff et al.[34] found that, *"No combination of orthostatic vital sign changes with a specificity of 95% or higher was sensitive enough to reliably detect an acute 450 ml blood loss."* Koziol-McLain et al. found that many normal (euvolemic) patients had orthostatic vital signs that

were consistent with hypovolemia, and they concluded that although the "tilt" test might differentiate patients with massive volume deficits from those without, attempting to do this test in critically injured patients was both unnecessary and unsafe.[35]

In a study assessing the usefulness of the tilt test in identifying significant intravascular volume depletion, Levitt et al. concluded that defining a "positive" tilt test appears to be impossible, and that although it is considered to be "the standard of care in evaluation of the hypovolemic patient," orthostatic vital signs have not been scientifically validated.[36] In a 2000 review, Dabrowski et al. questioned the accuracy of this test in diagnosing early shock when they noted that approximately 50% of normovolemic patients in the Koziol-McLain et al. study[35] exhibited positive orthostatic changes.[37]

Witting et al. found that in order to reliably separate patients with no blood loss from those with a 450-mL blood loss, the criteria for pulse had be set at a 20-point difference from lying to standing.[37] Even this sizeable difference produced a large number of false positives (normal patients identified as being abnormal). The authors also concluded that measurement of blood pressure as part of this test was without value and might actually provide misleading information.

None of this should be interpreted to mean that orthostatic vital signs are *unable* to identify many, if not most, patients in moderate to severe shock. It is, however, probably inappropriate to subject most patients in severe shock to this test because standing causes decreased perfusion of the brain and, at this stage, other findings will surely be present. If orthostatic vital signs are measured and

are grossly positive, particularly when other findings also suggest shock, the results should, most certainly, not be ignored.

Capillary Refill Test

Despite being one of the characteristic assessments in making a diagnosis of shock, delayed capillary refill has been shown to be an unreliable indicator of decreased intravascular volume. Unfortunately the efficacy of this test has not been well studied, particularly in settings where it is most relied upon, the prehospital and emergency department environments. In these settings, there is wide variability in a number of important factors including lighting, temperature, and skill level and experience of the provider making the assessment.

Furthermore, significant gender and age differences in response to this test have been shown, even in otherwise normal patients. Schriger and Baraff, in one of the few studies of this commonly used test, found that, "The upper limit of normal for adult women should be changed to 2.9 seconds and the upper limit of normal for the elderly should be changed to 4.5 seconds."[39] The authors also questioned whether the temperature dependence of the test may compromise its reliability in the prehospital setting. This study lead Knopp to make the following editorial comment, *"Given current 'normal values' and the variables of environmental temperature, age, sex and questions regarding the interpretation [which is affected by such things as lighting], one is left with the impression that at present capillary refill testing may be unreliable."*[40]

The preceding is not intended to imply that assessing for capillary refill has no place in the diagnosis of shock. It is rather to emphasize that many factors can render this test incapable of identifying early shock and to point out that capillary refill testing will over-diagnose shock, particularly in women and the elderly, and in cold, poorly lit, environments. As with orthostatic hypotension, if a patient with other signs and symptoms of shock and a mechanism of wounding consistent with shock has a positive test, e.g. delayed capillary refill, the patient is, almost certainly, in shock.

Hemoglobin Concentration Test

Although not a test that would generally be done at, or immediately near, the point of wounding, a test for hemoglobin concentration can certainly be conducted at a Battalion Aid Station. The effectiveness of this test in diagnosing shock has not been established. During World War II, Beecher found *"no early correlation between hemoglobin or hematocrit levels and circulating blood volume."*[1(p.194)]

There is some evidence, however, to suggest that an early low hemoglobin and hematocrit concentration might be of value as an indicator of acute, severe, blood loss. In a study of the effect of fluid resuscitation on hematocrit, Glick et al. found, despite the current teaching that hematocrit does not decrease immediately after acute hemorrhage, a 17% decrease in hematocrit at 15 minutes after the bleeding of splenectomized dogs that stabilized with no further drop during the remainder of the study.[41]

Knottenbelt, in a study of 1000 trauma patients, also demonstrated that, although it is traditionally taught that the body takes hours to respond to blood loss by moving fluid into the capillary circulation from interstitial spaces, patients who present with low initial he-

moglobin may have suffered significant hemorrhage.[42] In this study, a correlation between low initial hemoglobin levels and mortality in trauma patients was found. When there is significant hemorrhage and hypotension, extracellular fluid is readily drawn into capillaries, producing the low hemoglobin that is often seen on initial presentation in victims of severe trauma. This anemia is not caused by the dilutional effect of the initial fluid resuscitation bolus. Unfortunately there are also patients in hemorrhagic shock who present with hemoglobin and hematocrit concentrations within the normal range, so this test cannot be solely used to diagnose shock.

Once again, however, a patient who presents immediately after injury with a low hemoglobin/hematocrit and other signs or symptoms of shock should be presumed to be in shock. It is ill-advised to ignore positive tests, even ones that are not particularly sensitive or specific, especially when they are being applied to a population with a relatively high probability of having the condition for which the test is being conducted.

Future Tests for Shock

Based upon the finding that in experimental porcine hemorrhagic shock, changes in intestinal perfusion are the most rapid, sensitive indicators of acute blood volume loss,[43] wounded soldiers in the not-too-distant future might be given a "pill" to swallow that will monitor gut pH and will transmit this information to an external sensor that could track changes in intestinal perfusion as an early marker for shock. Someday, measurement of gut pH by prehospital personnel will allow for early, accurate, diagnosis and treatment of shock.

Fluid Resuscitation

Non-Blood Fluids

In order to have the best understanding of where we are today in terms of non-blood fluid resuscitation of patients in hemorrhagic shock, it is important to know the history of this practice. In 1832, while England was in the midst of a cholera epidemic, a 22-year-old doctor named William B. O'Shaughnessy recognized the underlying pathophysiology of cholera that was leading to death and he proposed a solution.[44, 45] He noted that, *"...the [two] indications of cure...are...to restore the blood to its natural specific gravity [and] to restore its deficient saline matters...The first of these can only be effected by absorption, by imbibition [drinking], or by the injection of aqueous fluid into the veins."* *"When absorption is entirely suspended...in those desperate cases,"* O'Shaughnessy recommended, *"the injection into the veins of water holding a solution of the normal salts of the blood."* Dr. Thomas Latta was the first to apply O'Shaughnessy's advice.[45] Reading the reports of doctors who had implemented his suggestions, Dr. O'Shaughnessy stated in the *Lancet* on 2 June *1832 "...the results of the practice [intravenous infusion of a saline solution]...exceed my most sanguine anticipations."[47]*

Since 1832, the benefits of non-oxygen carrying electrolyte solutions have remained undisputed when the primary need is *"to restore the blood to its natural specific gravity [and] to restore its deficient saline matters"* <u>and</u> [underlining added for emphasis] when the oral route, for whatever reason, is not a viable alternative.[44] The use of saline and related fluids for the treatment of hem-

orrhagic shock did not come into practice until following the 1883 recommendation of Charles E. Jennings' (a British clinician and physiologist). He stated that in "…most of the instances where [blood] transfusion is called for, I unhesitatingly advise the intravenous injection of [saline] fluid as being certain in its action, comparatively free from danger, and not requiring any special skill in its performance."[48, 49(p.193)]

In the early 1880s another British physiologist, Sidney Ringer, developed his "Ringer's Solution" that evolved into Ringers lactate, a resuscitation fluid that remains the American College of Surgeons' Advanced Trauma Life Support (ATLS) recommended trauma resuscitation fluid.[50(p.97)]

The scientific basis for infusing non-oxygen carrying fluids into patients in hemorrhagic shock has been established in numerous animal studies. When animals are exsanguinated in a controlled manner (Wigger's or modified Wigger's method) in a laboratory setting, those resuscitated with either or both crystalloid and colloidal intravenous fluids have a better probability of survival than those not similarly treated.[51(p.138-139)]

Only relatively recently have human studies been done that could establish with any certainty that trauma patients treated with intravenous fluids have a better chance of survival than those not similarly treated.[52, 53] Despite the widespread and long history of use of saline and related fluids to resuscitate patients with blood loss there has, for some time, been evidence that in some trauma victims the use of these fluids is worse than useless. Throughout the first half of the 20th Century, despite a lack of corroborative studies, military physicians with substantial experience in caring for

combat casualties observed that administration of intravenous fluids to patients with uncontrolled hemorrhage was potentially detrimental.[54, 55(pp 25,189), 56] During World War I, Gordon Watson, Consulting Surgeon to the British Second Army, observed that the effects of infused saline were "too often transitory – a flash in the pan – followed by greater collapse than before."[49(p.100)] During the Spanish Civil War, Dr. Douglas Jolly noted that,

> "There is always a commendable desire in the Classification Post [read Battalion Aid Station] to do something active in cases of severe abdominal haemorrhage. Sometimes this "first-aid" takes a dangerous form – i.e. the administration of large quantities of intravenous saline or glucose. The patient has already lost so much of his circulating haemoglobin that he cannot afford to have the remainder washed into the peritoneal cavity…The presence of gum Arabic [read Dextran] in the saline makes no real difference.[55(p.189)]

Recently these early empiric observations by military medical officers have been confirmed with controlled scientific studies. In 1991, Bickell et al. demonstrated the detrimental effect of aggressive intravenous crystalloid resuscitation in pigs with uncontrolled hemorrhage.[52, 57] In 1994 this was followed up with a human trial demonstrating that patients with penetrating wounds of the torso (uncontrolled bleeding) who were resuscitated with intravenous fluids prior to arrival at a hospital fared worse than those who were not given intravenous fluids.[52]

These findings have generally been confirmed by other investigators, who also

found that animals with uncontrolled hemorrhage fare worse if aggressively resuscitated with fluids.[58-60] Some of these studies show that animals resuscitated with minimal to moderate fluids to specific physiologic endpoints do better than both those aggressively resuscitated and those not given any fluids. A study by Kim et al. showed improved survival when animals with uncontrolled bleeding were resuscitated to a pressure of 40 mm Hg with Ringers lactate and a colloidal plasma substitute as compared to resuscitation with just Ringers lactate; both groups had better survival than those given no fluid resuscitation.[60] In 1999, Soucy et al. reported improved survival in rats with tail resections when resuscitation was accomplished with a "moderate" volume (80 ml/Kg) given at a fast rate (17.8 ml/Kg/min) as compared to non-resuscitated rats (60% survival as compared with 16.7% survival).[61] Other studies have also shown the benefit of moderate volume resuscitation over no resuscitation, particularly when evacuation time to surgery is long.[62, 63]

Unfortunately because of difficulties with obtaining informed consent, the results of Bickell's human trial have not been confirmed. It should be noted that in Bickell's human trial, the prehospital transport times were very short (< 15 minutes) and the times from wounding to surgery were generally under an hour. Concerns have been expressed regarding application of the "no prehospital fluids to patients with uncontrolled truncal hemorrhage" rule when the time from wounding to surgery is hours, as is the usual case in combat.[64] The dilemma of maintaining perfusion to the brain (and other vital organs) in patients with prolonged hypovolemia, especially in those with closed head injuries, remains. Further study is required to confirm the best

approach to the management of hemorrhagic shock in casualties with the prolonged transport times and long delays until definitive surgery typical of combat situations. The appropriate mean arterial pressure that would minimize ongoing blood loss yet allow for adequate organ perfusion to prevent multiorgan dysfunction has yet to be determined.[65]

The American College of Surgeons' ATLS guidelines[50] continue to recommend that initial resuscitation of patients with blood loss be done with intravenous crystalloid at a ratio of 3 mL for every 1 mL of estimated blood loss. This "three-for-one" rule is derived from the observation that most patients in hemorrhagic shock require as much as 300 mL of electrolyte solution for each 100 mL of blood loss. Applied blindly, these guidelines can result in excessive or, in some cases, inadequate fluid administration.[66] The use of bolus therapy with careful monitoring of the patient's response can moderate these extremes. Estimation of external blood loss, even by medical personnel, is notoriously inaccurate and internal blood loss cannot be estimated except during surgery.

The ATLS correlation of various physiologic parameters to specific amounts of blood loss is not well supported by good studies and really can't be used to make the 3 mL crystalloid for every 1 mL blood loss calculation.[50] In a study using splenectomized canines, Glick et al. examined the efficacy of various fluid resuscitation strategies and the effect of fluid resuscitation and hemorrhage on hematocrit concentration.[41] In the group treated with the recommended replacement of blood loss with crystalloids at a 3:1 ratio, there was a significant decrease in platelets and a significant increase in the prothrombin time com-

pared with those resuscitated at a 1:1 ratio. Although the 3:1 group did achieve a transient supranormal hemo-dynamic state, this had no distinct bene-fit over time. The conclusion of this study was that the recommended 3:1 resuscitation strategy had no advantage over a 1:1 replacement strategy <u>even in a controlled hemorrhage model</u>.

The following is the fluid resuscitation approach to the combat casualty in hemorrhagic shock that was recom-mended by Henry K. Beecher in World War II. It is based upon his own obser-vations and those of the other members of the Board for the Study of the Se-verely Wounded of nearly 3,000 combat casualties, 72 of which were in severe hemorrhagic shock. It is surprisingly similar to the current recommended ap-proach:

Resuscitation should be graded. It is important to rapidly restore a good blood color and the systolic pressure to an arbitrary level of about 85 mm of mercury in subjects whose blood pres-sure had previously been normal. Once these things have been accomplished, the rate of infusion of blood or blood substitutes depends on several factors:

(1) Delayed blood transfusion: If blood for transfusion or operation will not be available for a matter of hours, infusion of plasma or other blood substitute should be rapid enough only to maintain the aforementioned state (systolic B.P. of 85). More rapid admini-stration of plasma will elevate the blood pressure to the level where bleeding will be renewed or in-creased, with further and perhaps disastrous loss of irreplaceable (for the time being) hemoglobin.

(2) Delayed operation: If a patient must await surgical intervention for a considerable period, even though blood may be available, there is <u>no need to transfuse more rapidly than necessary to achieve these conditions, with one addi-tion: when blood is available it is desirable to administer it</u> until the skin loses the chill of shock and becomes warm. As long as the systolic blood pressure is not be-low a level of about 85 mm of mercury, the mucous membranes of good color, the skin warm and the pulse of good quality, there is <u>no need to administer further blood until surgical treatment is available</u>. To administer blood beyond the quantity necessary to achieve the condition mentioned, before surgery is available, inevi-tably means that more blood must be used than would otherwise be the case. Blood or plasma will leak into traumatized regions and be needlessly wasted; the hazard of an unnecessary number of transfusions will be incurred … Moreover, reasonable economy of blood means that it will be more abundantly available when need for it is urgent (systolic blood pressure below 80 mm mercury, pulse of poor quality and patient cold and pallid).

(3) Surgery available: When surgery is available, further transfusion of blood is advisable so that the ris-ing blood pressure is achieved at the time the anesthesia is started.[1]

They felt that,

> *Complete restoration to normal blood volume or blood pressure is not a necessary preliminary to successful surgery in previously healthy young men...Operation [should be] undertaken as soon as experience has shown that the patient will tolerate it, indicated chiefly by a rising blood pressure (85 mm mercury or above), a falling pulse rate, a warm skin and good color of the mucus membranes. Delay in surgical intervention beyond the accomplishment of these things requires the constant support of the patient by blood or blood substitutes and, in the end, the use of needlessly large total quantities of these agents. Delay means that infection will have progressed. This is closely allied to a rising death rate. Some patients, more often those with penetrating wounds of the abdomen, will fail to show any response to whole blood. Generally these patients are found to have continuing concealed bleeding or wide contamination of the peritoneal cavity. The failure of response to the usual resuscitative measures calls for a critical decision: the necessity of undertaking operation in the patient in poor condition. This bold decision may be life saving.*[1]

Current Point-of-Wounding Fluid Resuscitation Guidelines

Based upon recent information (above) regarding fluid resuscitation, changes have recently been made in the curriculum for combat medics. Those changes are specifically based on input provided to the AMEDD Center & School 91W Health Care Specialist Program at Fort Sam Houston, Texas, by COL John Holcomb, the current director of the United States Army Institute for Surgical Research. This input was provided in the form of a white paper entitled, *Hypotensive resuscitation - algorithm for AMEDD combat fluid resuscitation,* which was followed by a recent publication on the same topic in the Journal of Trauma.[67]

The bases for the following recommendations are:

(1) The consensus of the 2001 Combat Fluid Resuscitation Conference, which was held at the Uniformed Services University of the Health Sciences (USUHS), Bethesda, Maryland, in June 2001[68] and

(2) Recent studies that demonstrate the value of moderate volume resuscitation, particularly when transport times may be long.[58, 63, 69-73]

There was unanimous agreement among the attendees at the 2001 Combat Fluid Resuscitation Conference that hypotensive resuscitation strategies were tactically relevant, physiologically sound and should be utilized. There was also general, although not universal, agreement on the type of fluid to utilize while performing hypotensive resuscitation, and there continues to be general agreement that a low volume fluid administration is optimal (how low remains disputed). The fluid resuscitation algorithm used in the 91W Health Care Specialist Program at Fort Sam Houston that follows is based on the following assumptions:

- The tactical situation may or may not allow for medical care

- Hemorrhage control is of paramount importance

- Stethoscopes and blood pressure cuffs are rarely available or useful to the frontline medic

- A palpable radial pulse and normal mentation are adequate and tactically relevant resuscitation endpoints to either start or stop fluid resuscitation. Both can be easily and adequately assessed in noisy and chaotic situations.

- Intravenous (IV) access is important for delivery of fluids and medication and should be obtained early on any casualty with a significant injury. Only those casualties meeting criteria for resuscitation are given fluids through a single 18-gauge saline lock. When IV access is not possible, intraosseous infusion is a reasonable alternative

- The capacity for prehospital fluid resuscitation depends on the amount, both weight and volume, of fluid that can be carried by each medic and/or soldier. Mission constraints will dictate how much fluid is available on the battlefield.

- When intravascular volume expansion is indicated, Hextend® can achieve this endpoint faster, with less fluid, and for a longer time than Ringers lactate.

Based on these assumptions, the Army Medical Department's (AMEDD's) new algorithm for fluid resuscitation[76] is as follows:

1) Superficial wounds (>50% of injured) - No immediate IV access or fluid resuscitation is required

2) Any significant extremity or truncal wound (neck, chest abdomen or pelvis), with or without obvious blood loss or hypotension, and irrespective of blood pressure:

   a. If the soldier is coherent and has a palpable radial pulse, blood loss has likely stopped. Start a saline lock; do not give any fluids but re-evaluate as frequently as the tactical situation permits.

   b. Significant blood loss from any wound *and* the soldier has no palpable radial pulse, *or* is not coherent (note: mental status changes due to blood loss only, *not* head injury):

      i. STOP THE BLEEDING using direct pressure: hands and gauze rolls, hemostatic dressings, hemostatic powder, [*QuikClot – see following discussion on hemostatic agents*], with or without adjuncts like Ace bandages—is primary when possible. Extremity injuries may require the temporary use of an effective arterial tourniquet. However, >90% of hypotensive patients suffer from truncal injuries, which are unavailable to these resuscitative measures.

      ii. After hemorrhage is controlled to the extent possible, obtain IV access and start 500 mL Hextend®.

      iii. If the casualty's mental status improves and a pal-

pable radial pulse returns, stop IV infusion, maintain saline lock, and observe for changes in vital signs.

iv. If no response is seen, give an additional 500 mL Hextend®. If a positive response is obtained, stop IV infusion, maintain saline lock, and check vital signs.

v. Titrating fluids is desirable but may not be possible given the tactical situation. Likewise, the rate of infusion is likely to be difficult to control. Based on the effective volume of Hextend® vs. Ringers lactate and coagulation concerns with increasing amounts of Hextend®, no more than 1000 mL Hextend® should be given to any one casualty (approximately 10mL/kg). This amount is the intravascular equivalent of 6 L Ringers lactate. If the casualty is still unresponsive and without a radial pulse after 1000 mL Hextend®, consideration should be given to triaging supplies and attention to more salvageable casualties.

vi. Based on response to fluids, casualties will separate themselves into responders, transient responders, and non-responders.

Responders: Casualties with a sustained response to fluids probably have had a significant blood loss but have stopped bleeding. These casualties should be evacuated at a time that is tactically judicious.

Transient and non-responders are most likely continuing to bleed. They need rapid evacuation and surgical intervention as soon as tactically feasible. If rapid evacuation is not possible, the medic may need to triage his attention, equipment and supplies, to other casualties as determined by the tactical situation. No more than 1000 ml of Hextend should be given to any one casualty.

(3) Head injuries impose special considerations. Hypotension (systolic blood pressure [SBP] < 90 mmHg) and hypoxia (SpO2 <90%) are known to exacerbate secondary brain injury. Both are exceedingly difficult to control in the initial phases of combat casualty care. Given current recommendations on the care of head injuries, we cannot at this time recommend hypotensive resuscitation, as outlined above, for the soldier with obvious head injuries. Should the combat situation allow for continuous individual patient attention, the medic can attempt to keep SBP > 90mmHg via external blood pressure monitoring and evacuate the casualty to the next higher level of care as soon as possible. The impasse for the forward-area

medic is obvious and will have to be addressed as thinking and research on these issues progress

Crystalloids versus Colloids

Although recently overshadowed by the discussion about whether IV fluids have any value at all in the prehospital setting (see above), the long-standing dispute over whether crystalloids or colloids are the better resuscitation fluid remains. The origins of this dispute go back to Ernest H. Starling and William M. Bayliss, two British physiologists, in the early 1900s.[49] Bayliss concluded that the reason saline was generally ineffective in resuscitating patients in hemorrhagic shock was because most of it leaked out of the intravascular space; this he had clearly demonstrated in his laboratory.

A modern discussion of the physiology of crystalloid and colloidal solutions can be found in Prough's article on the subject in 1996.[75] Bayliss did the first experiments with colloidal solutions and it was he who introduced into clinical practice the first colloidal resuscitation fluid, a solution of 6−7% gum acacia in normal saline.[76] James Hogan, an American contemporary of Bayliss, advocated, instead of gum acacia, the use of gelatin solution for the treatment of shock.[77] Bayliss strongly advocated the use of his new colloidal solution for the treatment of patients in hemorrhagic shock during and after World War I. Gum acacia, however, was not widely accepted by military surgeons because they were unimpressed with its efficacy for this indication.

Plasma was introduced during World War II for the treatment of shock and was widely used, although not all physi-

cians found it equally efficacious. It is recorded in the proceedings of The Board for the Study of the Severely Wounded that,

> *The…statement of the Committee on Transfusions…that blood plasma is approximately as effective in the treatment of hemorrhagic shock as is whole blood, appears to have found origin in the conclusions drawn from laboratory experiments that were purposely designed so that the number of variables could be rigidly limited. Transference of these conclusions to a situation that introduced a number of additional variables [e.g.. combat casualties] was an error of human reasoning.*[78(p.5-7)]

Following World War II, DeBakey and Carter were quoted by Henry Beecher as having said the following about plasma:

> *Unfortunately, the early enthusiasm that accompanied this development* [use of plasma to treat hemorrhagic shock] *was so forceful that it pushed aside sound clinical judgment and led to the widespread misconception that plasma could be used as an effective and complete physiologic substitute for whole blood in the management of shock in the seriously wounded.…With increasing experience in the treatment of shock, it became more and more evident that plasma could not be used as a complete substitute for whole blood.*[56]

It is perhaps because of the lack of any clearly definitive evidence of superiority of crystalloids over colloids (or vice-versa) that the argument as to which is most effective has been sustained so long and has occasionally generated

such heat (without much light). Proponents of either position can cite numerous supporting studies. What is known is that when the efficacy of these fluids in reducing death from hemorrhagic shock in trauma patients is assessed, there is no clear winner and the available evidence tilts toward crystalloids as being slightly more efficacious.

In 1989, Velanovich conducted a meta-analysis of eight randomized prospective trials comparing crystalloid with colloid resuscitation. In this analysis patients resuscitated with crystalloids had an overall 5.7% relative reduction in mortality with a 12.3% reduction among patients in trauma trials.[79] A decade later, Choi et al. conducted an extensive systematic review of the effects of isotonic crystalloids compared with colloids in fluid resuscitation but found no overall difference in mortality, pulmonary edema, or length of stay between groups.[80] Although a trend suggestive of lower mortality in favor of crystalloids emerged, it was not statistically significant. When the trauma subgroup was analyzed separately, crystalloid resuscitation was associated with lower mortality than colloid resuscitation [79]. Choi et al. cautioned that these results should be carefully interpreted and should be used primarily to direct further inquiry. The authors concluded that although inference can be drawn that crystalloids are superior to colloids in resuscitating trauma victims the data were not conclusive enough to suggest abandoning colloid administration in practice. In closing they said, "Larger well-designed randomized trials are needed to achieve sufficient power to detect potentially small differences in treatment effects if they truly exist."

Other studies have reached similar conclusions. Prough found no major clinical differences in extravascular lung water induced by either fluid and concluded that either one is suitable for treating simple hemorrhagic shock without undue concern regarding pulmonary edema. *"[I]n the absence of hypervolemia,"* stated Prough, *"there appears to be no clinical difference in pulmonary function after administration of crystalloid or colloid solutions."*[75]

One area of controversy remains regarding the question of crystalloids versus colloids and that is in the situation of closed head injury. Which of these fluids is more likely to increase intracranial pressure? Sodium does not freely traverse the blood-brain barrier so it exerts an osmotic pressure across this barrier. For this reason an acute reduction of serum sodium will decrease plasma osmolality thereby increasing the water content of the brain. The converse is the case if there is an acute increase in serum sodium.

For some time colloidal solutions were thought to increase intracranial pressure less than crystalloid solutions because they do not cross the blood-brain barrier. Prough, however, points out that, "In fact, the choice of fluids (crystalloids or colloids) for gradual (nonresuscitative) rates of fluid infusion exerts remarkably little effect on cerebral edema after experimental head trauma."[75] What has been shown to affect brain water content in the setting of fluid resuscitation following closed head injury is the sodium concentration of the resuscitation fluid. Serum sodium concentration, rather than oncotic pressure has the greatest effect on intracranial pressure.[81-84] A general discussion regarding hypertonic saline for resuscitation of hemorrhagic shock and the effect of hypertonic fluid resuscitation on brain injured trauma victims follows in the next section.

Because there is no conclusive evidence that colloids are superior to crystalloids in terms of reducing mortality from hemorrhagic shock and, given their significantly greater cost and, in some instances associated complications, a recommendation that favors crystalloids over colloids for resuscitation seems quite reasonable. On the other hand, because colloids do tend to remain intravascular, an equivalent expansion of the intravascular space can be achieved with a smaller volume of colloid than crystalloid solution.

Pollack in his review of prehospital fluid resuscitation of the trauma patient, noted that, "A standard 1-L plastic bag of normal saline measures approximately 2744 cm^3 and weighs 1.1 kg."[85]. This led him to comment, regarding crystalloid resuscitation, *"this mode of treatment therefore can become physically burdensome on the battlefield to a medic with a limited capacity...for carrying resuscitative equipment."* Thus weight alone may recommend colloids in instances where combat medics have to carry IV fluids on their backs – perhaps.

Hypertonic Saline

Hypertonic Saline Dextran

Hypertonic saline resuscitation fluids, alone or combined with a colloid, have recently re-energized the discussion regarding which non-blood solution is most effective for resuscitating patients in hemorrhagic shock. Actually this issue is not new. Even before the entry of the United States into World War I "...*it was realized that the injection of physiologic salt solution or Ringers lactate*

was only temporarily effective in shock and hemorrhage and that the 'internal transfusion' accomplished by hypertonic salt solution, which withdrew fluid from the tissues and thus increased the blood volume, was equally ineffective."[86(p.8)] As noted in the preceding discussion, hypertonic saline solutions have been shown to reduce or at least prevent brain swelling in patients with closed head injury who receive fluid resuscitation.[87, 88]

It has been suggested that an ideal alternative to crystalloid and colloid fluids would be inexpensive, produce minimal edema, and effectively resuscitate patients in shock. Hypertonic saline, particularly if combined with a colloid, appears to have some of these characteristics. A number of studies have shown that 7.5% hypertonic saline, in relatively small volumes, is an effective resuscitation fluid for patients in hemorrhagic shock.[89-95] Some animal studies have shown that the beneficial effects of hyptertonic saline alone are not sustained, but when combined with a colloid they are longer lasting.[75, 96, 97]

The literature supports the assertion that hypertonic saline solutions are safe. Although hypertonic saline administration may result in serum sodium levels as high as 155 mEq/L patients seem to tolerate acute increases without harm and central pontine myelinolysis has not been observed in clinical trials of hypertonic resuscitation.[75]

Morbidity and Mortality Associated with Fluid Resuscitation

By far the most important study endpoint of interest for those involved in treating combat casualties is mortality. The main question about any resuscita-

tion fluid is not, "Does it improve specific physiologic parameters such as blood pressure?" but "Does it decrease mortality in patients in hemorrhagic shock?" Unfortunately there is little supporting evidence for the effect on mortality of any of the current resuscitation fluids including hypertonic saline.

Hypertonic Saline Dextran (HSD or more specifically 7.5% sodium chloride in 6% Dextran70) has been advocated as an ideal combat resuscitation fluid because several studies have shown that it increases myocardial contractility and improves redistribution of fluid from the extravascular to the vascular compartment and because considerably smaller volumes are needed to restore intravascular volume. One of the few human trials to examine the effect of hypertonic resuscitation on mortality was a 1991 prospective multi-center study that compared outcomes of trauma patients treated with normal saline with those treated with hypertonic saline dextran.[91] Both groups received equal volumes of fluid in the prehospital phase followed by standard isotonic infusions in the emergency department. Unfortunately there was no control group (i.e., no group that did not receive fluids) so a comparison of fluid vs. non-fluid resuscitation was not possible in this study. Although patients receiving hypertonic saline dextran had higher systemic blood pressures than the normal saline group on emergency department arrival there was no significant difference in overall mortality between the two groups at 24 hours. Further, there were no clinically significant complications of hypernatremia or dextran-related allergic reactions among patients receiving hypertonic saline dextran. The authors concluded that hypertonic saline dextran is safe, although further study, especially

in patients with concomitant head injury, is warranted.

In assessing the efficacy of any of these resuscitation fluids it is important to differentiate between controlled hemorrhagic shock, where the bleeding has stopped or been made to stop, and uncontrolled hemorrhagic shock, where bleeding is ongoing. Gross et al. found that hypertonic saline used to treat controlled hemorrhagic shock increases blood pressure and cardiac output but when used to treat uncontrolled hemorrhagic shock causes hemodynamic deterioration and increases both bleeding and mortality.[98, 99]

In 1995 Krausz noted that, in several clinical studies in which hypertonic saline dextran or hypertonic saline alone was used to treat trauma patients, mortality was not decreased.[100] Previously he had noted that the early administration of hypertonic saline in uncontrolled hemorrhage actually increases mortality.[101] When hypertonic saline was used to treat trauma patients with a Glasgow Coma Scale (GCS) score <8 (suggesting head injury) Krausz noted a small decrease in mortality; that decrease, however, was not statistically significant. Based on his review of the studies available at that time (mid-1990s) Kraus concluded that, "The efficacy of [hypertonic saline] has not clearly been established in clinical trials…Further human trials are required to better define the patient population that would benefit most from the prehospital administration of [hypertonic saline]."[100]

Hypertonic saline has also been recommended to resuscitate burn victims (see below for a complete discussion of fluid resuscitation of burn victims at or near the point of wounding). A prospective, double-blinded controlled animal study

was conducted by Guha et al. to assess the fluid balance and hemodynamic effects of Ringers lactate, hypertonic saline, 6% hetastarch, and hypertonic saline dextran on animals with large body surface area burns.[102] This study concluded that, "Net volume loading can be reduced markedly by initial resuscitation of large body surface area burn injury using a colloid (hetastarch), and can be further reduced by use of hypertonic saline colloid." Each of the test fluids was effective at resuscitation, although more rapid resuscitation was achieved with hypertonic saline dextran; all fluids were effective within one hour. There were, however, large, significant differences, in the amount of fluid infused. In the first 8 hrs after burn, 10 mL/kg of hetastarch reduced the net fluid balance by 48%, and 10 mL/kg of hypertonic saline dextran reduced net infused volume by 74% compared with lactated Ringers solution. The authors concluded that the volume-sparing effects of hetastarch and hypertonic saline dextran must be tested and confirmed in longer-term studies before being considered clinically important.[102]

Resuscitation Fluids and Endpoints for Different Types of Trauma

No single resuscitation fluid or resuscitation protocol is ideal for every type of trauma. Patients with controlled hemorrhage differ from those with uncontrolled hemorrhage[103], those with penetrating injury are different from those with blunt injury; those with shock and closed head trauma are different from those in shock without head injury; and patients in hypovolemic shock from hemorrhage are different from those in hypovolemic shock from burn injury

(see discussion below on hypovolemic shock due to burn injury).

Historically brain-injured trauma patients have been treated differently than those without brain injury. In the past, fluid restriction was recommended for brain injured patients but today this approach is recognized to cause variations in volume status and this may lead to tissue perfusion deficits. Because cerebral ischemia is one of the major causes of secondary brain injury the current focus is on aggressive maintenance of cerebral perfusion pressure (CPP). In severe head trauma maintenance of CPP at > 80 mm Hg has an associated mortality of 35−40%. Each additional 10-mm Hg decrease in CPP is associated with a 20% increase in mortality. Increasing the CPP through fluid resuscitation appears to improve morbidity and mortality.[65]

Patients with a combination of primary blast injury burn injury, and penetrating trauma present an especially unique challenge, both in terms of early diagnosis and approach to fluid resuscitation. It is difficult for even experienced professional health care providers, much less medics or corpsmen, to ascertain whether a casualty has sustained a significant primary blast injury so tailoring a specific point-of-wounding resuscitation protocol for these patients is problematic.

Casualties with significant burn injuries should receive early and relatively aggressive fluid resuscitation (see discussion below on hypovolemic shock due to burn injury) but those with primary blast injury of the lungs should be volume resuscitated with caution because they are likely to develop pulmonary edema if fluid resuscitation is too aggressive. Because of this risk Yancy

Phillips and Joan Zajtchuk, in their Textbook of Military Medicine chapter on the management of primary blast injury, recommend that, "Because the transudation of hypooncotic fluid is more likely in an injured lung, medical personnel should consider replacing the [primary blast injured] casualty's lost fluids with blood or a colloid solution rather than with a crystalloid solution."[104(p.303)] Although this seems to be a reasonable recommendation, no studies show that colloids (or blood) are any less likely than crystalloids to lead to pulmonary edema in patients with blast injury to the lung.[105]

Difficulties notwithstanding, it seems likely that each of these situations would probably best be treated with a unique fluid resuscitation protocol. Recently, Pepe and Eckstein commented that, "Evolving experience, both empiric and scientific, has demonstrated that the best treatment for 'the trauma patient' requires discrimination between the mechanism of injury, the location of anatomic involvement, and the extent, or 'staging,' of that specific process."[106]

On the battlefield, however, where there is an omnipresent threat of injury and death to both combat medic and patient, the medic does not have the time or capacity to differentiate among groups of patients, apply a different treatment for each, and/or carry several types of resuscitation fluids. Good data is needed to support the selection of a single resuscitation fluid and protocol that can be applied to all combat trauma victims. Because most combat casualties suffer primarily from hemorrhage caused by penetrating injury, without associated closed head injury, the fluid and resuscitation strategy that is most effective for this condition is likely the most appropriate choice.

Further complicating the question regarding what is the ideal combat fluid resuscitation fluid is the fact that IV fluids are not just used for the treatment of combat trauma but are more commonly used by medics to treat dehydration from a variety of causes (heat injury, diarrhea, vomiting, etc). The fact that combat casualties, unlike civilian trauma patients, may be significantly dehydrated at the time of wounding should also be taken into consideration when selecting the most appropriate resuscitation fluid.[107] Whatever resuscitation fluid is selected must, therefore, be not only safe and effective in the treatment of combat trauma, but must also be safe and effective when used to treat other, more common, conditions.

Route/Means of Intravenous Access

Although there is some controversy about the value of fluid resuscitation in the field for combat casualties, there is general agreement that it is valuable to establish vascular access at or near the point of wounding. Even if IV fluids are not required early intravascular access is still important for the following reasons:

1) Fluids and/or blood must often be given at the medical treatment facility in conjunction with hemorrhage control, and it is usually easier and faster to gain IV access in patients who are not volume depleted.

2) IV access is often necessary for purposes other than fluid administration, e.g., administration of analgesia or antibiotics.

Adequate analgesia is best achieved by titrating intravenous morphine to the level of pain, thereby minimizing both

patient discomfort and risk of opiate overdose (if morphine is given IM, especially to hypotensive and/or hypothermic casualties it is poorly absorbed from the muscle leading to repeated dosing and the risk of delayed onset of opiate overdose).

Studies by Spaite et al. have shown that civilian prehospital care providers can obtain IV access without significantly delaying evacuation, especially if access is gained during evacuation[108, 109] near the point-of-wounding access to the intravascular space is generally obtained by direct venous cannulation, usually in the upper extremities, and often in the antecubital fossa. Cannulation should always be obtained with a short 18-gauge (or larger) catheter so that large volumes of fluids and/or blood can be administered later if necessary.[110-112] As Poiseuille's equation [Flow = $\Delta P \pi r^4 / 8 \eta l$] states flow through a pipe (e.g. IV catheter) is directly proportional to the radius but inversely proportional to the length of the pipe. While the diameter of an IV catheter is by far the most important in terms of rate of flow a catheter of one inch length will have twice the flow rate of a two inch catheter with a similar diameter.

Even if clinically indicated fluid administration in the field can be problematic because care providers must then manage not only the casualty but the IV fluids and lines as well. IV management during combat/evacuation can lead to:

1) An unfortunate shift in the focus of care from the patient to the IV,

2) Difficulty ensuring that the IV line is not pulled out, and, at the very least

3) Inadequate control of the rate of fluid administration [vehicle evacuation in the forward battle areas is almost always accomplished without medical attendants using tactical, not medical, vehicles].

In summary, the average casualty who has had an IV line inserted in the field is unlikely to arrive at a medical treatment facility with a functional line, much less having received a controlled rate of fluid delivery. This is not as much of a problem as it might seem because, as discussed above, for the average combat casualty there is no evidence that volume resuscitation in the field improves survival. Under current guidance for combat medics if fluids are not to be administered, IV access can be obtained using a saline lock (see above, point-of-wounding fluid resuscitation guidelines). Without a line and a bag of IV fluids to be protected a saline lock is much more likely to remain functional during evacuation.

Another option is to obtain intraosseous access. In a recent review, Dubick and Holcomb discuss the safety, efficacy, insertion times, and flow rates associated with intraosseous vascular access.[113] Although intraosseous infusion has been used for many years in pediatric resuscitation[114], this method has recently been rediscovered as a means for prehospital fluid resuscitation in adults.[115, 116] In 1922, Drinker et al. demonstrated that red blood cells could be infused into the bloodstream through the intraosseous route.[117] In the early 1930s, this technique was demonstrated to be effective in humans [118, 119] and a few years later it was brought to the battlefield in World War II. Turkel, in 1956, commented that "Many of our fighters [in WWII]…were saved by the

intrasternal transfusion method administered to them by enlisted nonmedical but medically trained men.[120]

Today the two main routes of intraosseous access in adults are the medial malleolus and the sternum. The intramedullary space of the medial malleolus is somewhat difficult to access because of relatively thick overlying cortical bone but a device known as the bone injection gun [B.I.G.®] eliminates this problem by firing a spring-loaded hollow dart through the cortex to the correct depth.[121, 122]

The red bone marrow-containing intramedullary space of the sternum can be accessed through a flat, relatively thin bony cortex located just under the skin. This route is ideal but there is the potential risk of injury to major underlying vasculature in the mediastinum. A sternal intraosseous infusion device [F.A.S.T.®] allows for safe and rapid placement of an intraosseous needle into the sternal intramedullary space.[123-125]

With these devices an intraosseous infusion can be safely and reliably started in less than a minute. Because of relatively high resistance to flow through the intramedullary space into the intravascular space, it is not possible to administer large volumes of fluid rapidly via this route. It has, however, been previously pointed out that rapid, large-volume fluid resuscitation is harmful when bleeding has not been controlled, so this is often not an issue.

Hypertonic saline dextran has been recommended as the preferential intraosseous infusion fluid when volume resuscitation is indicated because of its ability to rapidly expand the intravascular space with minimal infused volume. Currently, there is only one study compar-

ing intravenous and intraosseous routes of administration of hypertonic saline dextran. Chavez-Negrete et al. compared intravenous-infused and intraosseous-infused hypertonic saline dextran in patients with gastrointestinal hemorrhage.[126] Sternal intraosseous and intravenous hypertonic saline dextran were equally effective and there was no difference between the two groups in terms of blood pressure response. No complications were noted in either group.

The intraosseous route of fluid administration is generally considered safe. In 1947 Heinild et al. reviewed nearly 1,000 pediatric intraosseous infusions and found few complications.[127] More recently Orlowski et al. assessed the risks of intraosseous fluid resuscitation-induced fat and bone marrow emboli and found that although emboli did occur they were not clinically significant.[128] Other studies and reviews have confirmed the relative safety of the intraosseous route.[129-131]

A recent study by Alam et al., however, has raised some concern about a potential risk associated with intraosseous infusion of hypertonic saline dextran.[132] In this study multiple intraosseous infusions of hypertonic saline dextran to dehydrated pigs caused severe necrosis of the tibia. The clinical relevance of this finding to human trauma patients is unknown.

Any parenteral fluid access site that is obtained at, or near, the point of wounding must be replaced as soon as a new site can be established in a clean environment. When access is obtained in a combat zone, the patient's risk of developing infectious complications increases.[133] During recent combat operations in Afghanistan, several cases of sepsis were reportedly associated with

field-started intravenous lines [conversations of author with combat medical personnel]. Osteomyelitis has been reported following intraosseous infusion[134] and is a risk in field-started intraosseous infusions that are left in place longer than 24 hours.

When fluid resuscitation is indicated intraosseous infusion via either the sternal or medial malleolus routes is a reasonable option either as a backup method to the intravenous route or as a primary means of access. There are certainly other methods of obtaining access to the intravascular space but in general none are appropriate at, or near, the point of wounding.

Oral Rehydration

Oral rehydration of hypovolemic wounded soldiers should not be overlooked – simple solutions often are. In alert patients without nausea, or even in those with mild nausea, a careful oral rehydration may be reasonable.

Attendees of a 2001 workshop organized by the International Committee of the Red Cross on prehospital care for war and mine wounded agreed that any wounded patient, regardless of wound type or severity, who had not lost consciousness could be given oral fluids. No specific guidelines were developed, however, and the workshop concluded with the thought that oral rehydration is a primary area for future research. [135(p.89)]

Although there is concern about the potential for aspiration either during evacuation or surgery, no reliable scientific data confirm that drinking water actually poses such a risk. In the past decade or so the long-standing recommendation that there be a long period of preoperative fasting has been changing, particularly with regard to water.[136-140] The general consensus is that water, <u>in any quantity</u>, is without risk 2 hours or more before surgery. There have been suggestions that even combat casualties with abdominal wounds can have sips of water as tolerated. In sum there appears to be no good evidence to support withholding water from wounded patients and providing water seems reasonable from a physiological standpoint.

Transfusion Near the Point of Wounding

Since prior to World War I blood has been recognized as the ideal resuscitation fluid for patients in hemorrhagic shock. The reason other fluids have, at times, assumed a leading role in the resuscitation of combat casualties, particularly far forward, is because of the problems that are associated with administration of blood on the battlefield. Even with modern technology administration of blood and blood products is risky and logistically difficult. The risks and complications of transfusion therapy include hemolytic reactions; immediate ABO and delayed non-ABO reactions; allergic and anaphylactoid reactions; febrile reactions; noncardiogenic pulmonary edema; hypothermia; citrate toxicity; acid-base imbalance; hyperkalemia or hypokalemia; bacterial contamination; and transfusion-transmitted diseases such as human immunodeficiency virus (HIV), hepatitis, cytomegalovirus, West Nile virus, and Creutzfeldt-Jakob disease to name a few.[66]

In a recent review of blood transfusion medicine avoidable transfusion errors were deemed an important, if uncommon, cause of iatrogenic death and injury in U.S. hospitals.[141] Given the chaotic circumstances that often prevail in combat, it is probable that the rate of such errors is even higher when transfusions occur on the battlefield.

Fatal misidentification errors in the United States are estimated to occur in 1 in 600,000 to 1 in 800,000 transfusions and non-fatal errors occur in 1 in 12,000 to 1 in 19,000 cases.[142, 143] An error incidence of 335 per 5.5 million units of red cells transfused is reported from the United Kingdom with transfusion of an incorrect blood component accounting for almost 70% of adverse events between 1999 and 2000.[144] This study also reported 97 cases of ABO blood group incompatibility that led to immediate major complications in 29 patients and death in 4 patients.

Every medical intervention, including blood and blood product administration, has risks. The basic question is, "When the risks are balanced against the benefits, does the equation favor forward administration of blood to combat casualties at or near the point of wounding?" The Israel Defense Forces (IDF) would answer in the affirmative. Although it was generally not Israeli policy to supply blood to forward area medical units, an exception was made during the Israeli incursion into Lebanon in 1982, where heavy casualties and difficult evacuations associated with urban combat (i.e., in Beirut) were anticipated.[144] During this operation, 85% of Israeli casualties were airlifted from the battle zone and 95% received some treatment before air evacuation (almost always this included having an IV started). Every Israeli helicopter carried blood for

transfusion and blood transfusions were begun in 5% (29 of 543) of patients who required an IV; 124 units of blood were administered in transit.[145]

The decision to administer blood far forward in this particular military operation was probably made because, unlike previous Arab-Israeli wars in which evacuation times to fixed hospitals were relatively short, in the Lebanon operation, evacuation times were long. As discussed in a 1999 study by Barkana et al., the IDF Medical Corps has been using blood in prehospital resuscitation of trauma patients since the 1980s.[146] In the IDF experience, time from wounding to hospital admission almost always exceeds 1 hour, and often runs 2–3 hours. The IDF uses Rh-positive type O packed red blood cells that are supplied by the central civilian blood bank and are kept in a special field refrigerator. The blood is maintained by military medical units whose members do not have any "expert" training in the maintenance of blood products. Before use, 250 mL saline is added to facilitate administration. IDF forces are somewhat unique in that physicians are stationed very far forward, often at or near the point of wounding. It is the physician who determines whether or not to administer blood, based upon ATLS guidelines.

The Barkana et al. study offered no conclusions about the efficacy of this practice because no comparison was made between casualties receiving prehospital blood with those not receiving blood.[146] The authors were able to conclude, based on their experience, that (1) blood can be administered safely at or near the point of wounding by individuals not specially trained or experienced in blood administration and (2) prehospital administration of O-positive packed red

blood cells is efficacious and indicated in selected patients.[146]

There are four major reasons to transfuse blood or blood components into a hemorrhaging patient:

1. To improve systemic oxygen transport
2. To restore critical red cell mass
3. To correct bleeding caused by dilutional thrombocytopenia, platelet dysfunction, or pathologic platelet consumption
4. To correct bleeding caused by a factor deficiency or pathologic consumption of coagulation proteins.

In short, the goals of transfusion therapy are to maintain physiologic support of the circulation and oxygen transport while avoiding the deficiencies of hemostatic factors or other physiologic deficits.[65]

Today, for reasons that are not entirely clear, blood is no longer routinely administered forward of units with surgical capability. This has not always been the case. During the Spanish Civil War, "In some classification posts [read Battalion Aid Station] blood transfusions were given to badly shocked men – usually with conserved blood but sometimes by direct transfusion."[54(p.24)]

It was during the Spanish Civil War that Dr. Norman Bethune established the first known mobile blood bank unit; it successfully delivered whole blood to casualty stations and provided *"transfusions at the front while the fighting was in progress."[147(p.124)148]* It was also observed during this war that, although the *"administration of large quantities of intravenous saline or glucose [or solutions containing gum Arabic]"* was

"dangerous," this was not the case for blood transfusion which "…may be given in the Classification Posts [and although]…blood may drive out blood…[if] the patient is not long in reaching the operating theatre, the net result is some gain.[54(p.189)]

During World War II, the British established Field Transfusion Units, the smallest units in the British Army. These units were entirely self-contained, were fully equipped for transfusion in the field, and consisted of an officer and three enlisted men, one of whom drove the truck and was responsible for the operation of the refrigerator. These units were attached wherever they were most needed during a campaign, usually operating at field surgical units, but also at field dressing stations and casualty clearing stations.[149]

Although it is not possible to comment on the specific benefit gained by the administration of blood forward of units with surgical capability, it is clear that overall blood administration was credited with saving a large number of lives in World War II and Korea. "Prompt and liberal use of whole blood" was deemed responsible for saving the lives of innumerable casualties in World War II and the Korean War and is considered "one of the great pioneering achievements of World War II.[149]

COL Edward D. Churchill, the Consultant in Surgery, Fifth U.S. Army in World War II, in his study of whole blood and plasma and their relative role in the resuscitation of combat casualties, concluded that, *"…whole blood [is] the agent of choice in the resuscitation of the great majority of battle casualties"* and that, *"…whole blood [is] the only therapeutic agent that [will] prepare seriously wounded casualties for the*

surgery necessary to save life and limb."[149(p.57)]

Following World War II, Henry K. Beecher noted that, "Too much preoccupation in the clinical treatment of patients with the unsolved problems of shock can have the indirect but very closely associated result of leaving the physician without access to the therapy well proved to be effective in the treatment of shock: blood as needed."[55] He also observed that, *"The shock we saw was caused by blood loss (or loss of fractions of the blood). It was cured by blood administration."*[55]

Regarding the efficacy of blood transfusion in the field, a modern retrospective chart review by Hall et al. found that trauma patients who received packed red blood cells in the field had outcomes similar to those who did not, despite the fact that the group who received blood had significantly worse injuries (in particular more serious intra-abdominal injuries) than the group who did not receive blood.[150] From these results, the authors concluded that early administration of blood may be of value, and recommended further study.

Despite overwhelming support for early blood transfusion by military surgeons with considerable experience in resuscitating combat casualties, there have been recent studies on blood transfusion that should give pause. Vincent et al., in a recent, extensive review of blood transfusion in critically ill patients, found a dose-response relationship between number of red blood cells infused and mortality.[151] All other variables being equal, receipt of a blood transfusion increased mortality risk by a factor of 1.4. This study illustrates the associations between transfusion and diminished organ function as well as between

low hemoglobin level, transfusion, and mortality. The authors recommended further study of transfusion in ICU patients, as well as exploration of alternatives to transfusion.

Multiple components contained in stored blood can increase levels of pro-inflammatory mediators that may lead to neutrophil activation and promote the development of multi-organ failure.[152-154] The implication of these findings for combat casualties is unclear. Certainly, the non-trauma ICU patients in the above study by Vincent et al. are quite different from combat casualties.[151] There is also a difference between the effectiveness and side effects of stored packed red blood cells, whole blood, and fresh blood.

During World War II, it was recommended that all transfusions be given with fresh blood in order to "make up for the lack of standardized equipment and the shortage of shipping space …in evacuation hospitals." This proposal was incorporated into Circular Letter No. 108, Office of the Surgeon General, U.S. Army, dated 27 May 1943, which stated that, *"…fresh whole blood [should be administered] in general hospitals in oversea[s] theaters within 4 hours after it had been collected and for the transfusion of stored blood [it should be] collected…and used within 7 hours…"*[149(p.180)] Also during World War II, COL Elliot Cutler recommended, *"transfusion of severely wounded casualties with blood secured from lightly wounded casualties."*[149(p.192)]

Clearly fresh whole blood, and even stored whole blood, is different from packed red blood cells. These differences could certainly account, at least in part, for the apparent difference between the findings of Vincent et al. in ICU pa-

tients and the observed effects of whole blood given to combat casualties in World War II.

COL John B. Holcomb, an army surgeon, commented very favorably on the beneficial effects of whole blood transfusions given to exsanguinating combat casualties in Mogadishu, Somalia in September and October 1993. He said that whole blood had a nearly *"miraculous effect"* when given to patients who were exsanguinating.[155] [Holcomb JB, Colonel, US Army. Personal communication, August 2003]

For at least the past four decades, the general US military policy has been to use packed red blood cells for resuscitating combat casualties both because packed red blood cells are believed to be as effective as whole blood and because they have logistical advantages. Despite this stated policy, fresh whole blood has, in fact, been used by US Forces in every conflict with significant casualties since World War II, including Operation Iraqi Freedom; Army doctrine is being changed to reflect this reality.[156] In short, the experience of military surgeons in the 20th Century supports the use of whole blood in resuscitation of combat casualties.

Autologous Transfusion

One way to avoid many of the risks of blood transfusion is to use the patient's own blood. There are two ways to do this:

1. Collect the blood in advance of the need (not really an option for combat casualties) and
2. Return the patient's own lost blood back to the circulatory system through autotransfusion.

In a patient with a chest wound, this can be done by collecting blood directly from a thoracostomy tube, using a suction device, into a citrate-containing bag. The blood can then be directly reinfused through a macroaggregate filter. Another method of blood collection involves the use of a cell saver unit that collects blood into a system that

- Includes an anticoagulant and
- Uses centrifugation and a washing mechanism to provide washed red blood cells for infusion.[65]

Autotransfusion was effectively used to treat combat casualties with chest wounds during the war in Bosnia in 1992. Jevtic et al. described 19 cases of autotransfusion of blood collected from chest tubes inserted into 29 casualties with penetrating chest trauma.[157] The average quantity of returned blood delivered was 1,500 mL but in two patients, both of whom survived, $\geq 4,000$ mL autotransfused blood was administered.

Although autotransfusion avoids a number of the potential risks of using donor blood (e.g., viral infection) there are several potential complications that are more common in autotransfusion. These include coagulopathy caused by excessive anticoagulant and disseminated intravascular coagulation caused by administration of activated products of coagulation and fibrinolysis. Typically, these complications are seen when >1500 mL shed blood is reinfused.

Autotransfusion of blood from the abdominal cavity can be used in the operating room, but this route of blood administration is not an option in the prehospital environment so is not discussed here.[65] Based upon the above observa-

tions, consideration should be given to increasing the emphasis at the Battalion Aid Station on autotransfusion of blood recovered from the chest via a thoracostomy tube.

Blood Substitutes

One challenge of the modern battlefield is the high degree of troop dispersion and the resulting long evacuation distances and times. In recent combat operations, the time from point of wounding to surgery has approached 24 hours. This means that wounded soldiers will have to be sustained much longer before they receive surgery. Ideally, part of this sustainment effort would be accomplished with blood administration, preferably fresh whole blood; but logistical, technical, and provider skill level issues preclude this being a viable option.

One option that is aggressively being pursued is the development and fielding of an oxygen-carrying resuscitation fluid. The search for a safe and effective oxygen-carrying resuscitation fluid has become the Holy Grail of military medicine. Millions of dollars have been spent over the past 35 years in hopes of finding a safe and efficacious blood substitute. The search actually began in the early 1600s, almost soon as it was discovered that blood circulated in the body and was vital to life.[158] In 1665, Christopher Wren tried using wine as a blood substitute, without beneficial effect. The beginnings of the modern search for an effective blood substitute began in the 1930's with Amberson, who infused stroma-free hemoglobin.[159]

The greatest efforts in this area began in the early 1970s, with the work of Rabiner et al [160] and Savitsky et al.[161] Unfortunately, despite some success, there were many problems, such as high

oxygen affinity (with limited off-loading of oxygen at the cellular level), short intravascular half-life, and renal toxicity. Development in the 1980s of modified polymerized hemoglobin solutions was the start of present-day research efforts in this area. These new solutions are more stable, have better oxygen delivery characteristics, and have fewer side effects; although some problems remain.

Six companies currently have hemoglobin-based blood substitutes (Baxter [HemAssist™], Hemosol [Hemolink™, hemoglobin raffimer], Northfield [PolyHeme®], Somatogen [Optro™], Sangart [Hemospan™], and BioPure [Hemopure®, HBOC-201, or hemoglobin glutamer-250)]) that have completed patient safety studies, and some have begun efficacy trials. None of these products requires type and cross-match, all have relatively short half-lives (about 24 hours) and fairly long shelf lives, and none appears to be associated with any risk for transmission of disease. There is, however, some concern about the possibility of prion transmission by products made from bovine hemoglobin. Biopure's Hemopure® is currently approved for some indications in human patients in South Africa, and Phase III testing for US Food and Drug Administration (FDA) approval is ongoing.

Two crosslinked hemoglobin solutions are currently in production: pyridoxylated hemoglobin (PLP-Hb) and diacetylated crosslinked hemoglobin (DCLHb), and other products are in development. PLP-Hb is a dimer and DCLHb is a purified human tetrameric hemoglobin molecule. In a number of these products hemoglobin is encapsulated in liposomes; these liposome-encapsulated hemoglobins are stable during storage and have a plasma half-life of 4–20

hours without associated renal toxicity or antigenicity.[158]

Hemoglobin used in these solutions comes from (1) human red blood cells (expired donated blood), (2) bovine red blood cells, or (3) recombinant hemoglobin sources. All of these hemoglobin-based oxygen-carrying solutions have a high affinity for oxygen. Indeed, the problem has not been with these solutions binding oxygen in the lungs but with releasing that bound oxygen to the tissues that need it. Another problem with many of these solutions is that most have at least some degree of vasopressor effect secondary to binding nitric oxide (endothelial-derived relaxing factor). As noted earlier, increasing blood pressure when hemorrhage is uncontrolled simply leads to a faster rate of blood loss.

Although there was much anticipation that DCLHb would become the first of several hemoglobin-derived, oxygen-carrying blood substitutes to successfully treat hemorrhagic shock, a multi-center trial evaluating the efficacy of DCLHb was terminated when it became clear that there was a significant increase in mortality associated with the use of this solution.[162] At 28 days, 46% of those infused with DCLHb died, compared to 15% mortality in those infused with saline. The incidence of multiple organ dysfunction was also considerably higher in the DCLHb group, and the authors concluded that DCLHb was not effective for fluid resuscitation.

Another hemoglobin-based, oxygen carrying solution, which consists of polymerized tetrameric human hemoglobin, is currently undergoing final testing and appears efficacious and safe.[163, 164] A study of this polymerized human hemoglobin solution in a relatively small number of trauma patients found that

this solution had a considerably lower 30-day mortality (25%) compared with an historical control of patients who refused blood transfusion for religious reasons (64.5%).[164] Final (Phase III) studies are currently underway evaluating this oxygen-carrying blood substitute in the prehospital treatment of trauma patients. If the results of this trial are favorable, this solution and/or others could have a substantial impact on the treatment of combat casualties at or near the point of wounding.

Non-hemoglobin-based oxygen carrying solutions are also being developed as possible blood substitutes; most of these are perfluorocarbon-based. Oxygen and carbon dioxide are highly soluble in perfluorocarbons, which makes these solutions able to carry oxygen to the tissues and carbon dioxide back to the lungs. In comparison to hemoglobin-based oxygen-carrying solutions, perfluorocarbons are much more effective at unloading oxygen at the tissue level. Perfluorocarbon emulsion solutions transport oxygen in a fundamentally different way than do hemoglobin based solutions. Hemoglobin based solutions exhibit a sigmoidal oxygen dissociation curve. The oxygen carrying capacity of perfluorocarbon emulsions, in contrast, is characterized by a linear relationship between PO_2 and oxygen content. Thus, sufficient oxygen delivery can only occur when patients are breathing 70 to 90% oxygen. Therefore, unlike hemoglobin-based solutions, in which supranormal levels of oxygen provide little additional benefit (and provide little added oxygen delivery to red blood cells), when perfluorocarbon emulsion solutions are used, elevated PO_2 such as that achieved with hyperbaric oxygen, is quite beneficial. Unfortunately this property means that perfluorocarbons are likely to be less valuable as a point-of-wounding resuscita-

tion fluid because oxygen, which is needed to maximize the effectiveness of these solutions, is generally not available.

Advantages of perfluorocarbons include the following:

- Some of these solutions can be stored at room temperature
- They are relatively cheap to produce
- They are completely free of biological material so they cannot be contaminated by infectious agents

Because fluorocarbons may unfavorably alter the reticuloendothelial system by long-term retention and can lower immunity [165-169] they are coated with substances, such as lecithin, which makes them soluble and reduces the extent to which they affect the immune system.

One such agent is the intravascular oxygen carrier, Oxygent™ (Alliance Phar-

maceutical Corp., San Diego), which is prepared from perfluorooctyl bromide (C8F17Br) with egg yolk lecithin as the surfactant. This product, which is compatible with all blood types and has a shelf life of as long as 2 years, has moved from Phase II clinical trials to Phase III trials.[170] Preliminary data indicate that use of Oxygent obviates or minimizes the need for blood, with results being statistically significant to 3-weeks post-administration.

Although this, or another, effective blood substitute may someday be available for administration at or near the point of wounding, the promise of this prospect is unlikely to be fulfilled in the near future. When an efficacious oxygen-carrying blood substitute does become available, it will represent a major military medicine milestone that will likely have a significant impact on combat casualty survival.

Pneumatic Antishock Garment

The pneumatic antishock garment (PASG), also known as military antishock trousers (MAST), is a device that encircles the abdomen and lower extremities with air bladders that can be inflated. The concept for this device originated from the "G" suits worn by pilots of high-performance aircraft; these suits inflate during high-gravitational-pull maneuvers to prevent loss of consciousness caused by pooling of blood in the lower extremities.

The original belief was that this type of device could be used to treat shock by a

mechanism of "autotransfusion" of blood from the lower extremities into the central circulation. The PASG certainly does raise the blood pressure of patients in shock, and in animal models with controlled hemorrhage it prolonged survival from otherwise fatal exsanguination [171], but it does so not by autotransfusion but by raising total peripheral vascular resistance and increasing afterload.[172, 173] Given that raising blood pressure in trauma patients with uncontrolled hemorrhage has been shown to be undesirable since at least the Spanish Civil War, it should have been a foregone conclusion that the PASG might actually worsen survival in trauma vic-

tims with on-going hemorrhage; unfortunately this was not the case.

Until relatively recently, the PASG was one of the most widely used and most-studied devices in emergency medicine and prehospital care.[174-176] Pneumatic Antishock Garments (PASGs) were a mandatory item of equipment on every ambulance in some states. Today, however, the PASG has developed such a bad reputation that it is rarely used at all. In some ways, the PASG is an excellent case study in why it is important to conduct randomized controlled human trials of all medical equipment, medical procedures, and pharmaceuticals before introducing them into widespread use. In the short span of about 25 years, the PASG went from invention, to widespread use, to obscurity.

PASG – Pneumatic Antishock Garment, From Operatiopnal Medicine 2001

Interestingly, it was one of the greatest early advocates of the PASG, Dr. Ken Mattox, who ultimately conducted the studies [177-180] that showed increased mortality in patients with penetrating abdominal injuries when the PASG was used. In patients with large-vessel involvement, survival rates were 49% for the PASG group and 65% for the control group. Not only was the PASG shown to be worse than ineffective, its use was associated, in some instances, with the development of compartment syndrome in previously normal lower extremities.[181-184] Furthermore, even during the period when its use was recommended, the PASG was known to be harmful to patients with closed head injury, thoracic injury, pregnancy, and/or pulmonary edema.

It should be noted that the Mattox and Bickell study [179] of the PASG was done in an urban environment with very short prehospital transport times. Whether the results would have been different had the transport times been longer is unknown, but there is no obvious reason why they would have been. Despite its problems, the PASG continues to be recommended by some [including this author] to apply compression over large, soft-tissue injuries in the lower extremities for hemorrhage control (PASGs reduce arterial and venous bleeding beneath the garment by decreasing vessel wound size, transmural pressure, and blood flow)[174, 176, 184, 185] to stabilize lower extremity fractures, and to help stabilize unstable pelvic fractures (see discussion below on pelvic fracture stabilization). There is some scientific support for these recommendations.[185, 186]

The limitations of the PASG prompted McCallum and Rubes in 1996 to suggest removal of the PASG from ambulances because of its "low utility and utilization."[187] Although PASGs have, in fact, been removed from most military medical equipment sets, their utility in helping to control lower extremity hemorrhage and stabilize lower extremity and pelvic fractures suggest that they should be kept available for these purposes. Prehospital medical personnel simply need to be taught that PASGs should not be used solely to treat hemorrhagic shock.

Hemmorrhage Control

"Hemorrhage, which produces such terror in the bystanders . . . should never unnerve the surgeon, who requires all of his self possession . . . to cope successfully with this ebbing away of life."[188]

Direct Pressure

Hemorrhage control is generally achieved by the application of direct pressure on the bleeding site. When possible, this is combined with elevation of the bleeding site above the level of the heart, which lowers the pressure at the point of bleeding. Digital pressure applied over proximal arterial pressure points also helps to control bleeding by lowering the pressure at the bleeding site(s). Performed correctly and, when possible, simultaneously, these hemorrhage control techniques can control significant, even brisk arterial, hemorrhage.

Until recently there has been no good method for teaching these techniques to prehospital medical personnel and so when treating hemorrhage in combat casualties, these personnel often apply insufficient pressure for an insufficient period of time. Fortunately, there has recently been increased emphasis on hemorrhage control at the 91W Health Care Specialist Program at the AMEDD Center & School at Fort Sam Houston, Texas and this has, in part, been made possible by the introduction of training devices that simulate realistic hemorrhage.[189]

Unfortunately, no matter how well this task is taught, the circumstances of combat make it unlikely, in many cases, that a medic/corpsman will be able to apply the requisite force long enough to achieve hemorrhage control. Maj. Meredith Mal-

lory noted during a conference held at the end of the Korean War that, *"In the case of lower extremity wounds, which give rise to the most severe hemorrhage controllable by tourniquet, it has been my observation that too few doctors, much less their assistants, have a concept of the constricting pressure required about the thigh to abolish the flow of blood."[190]* Prolonged pressure is physically demanding and prevents whoever is doing it from engaging in other tasks (like defending himself and his patient).

Although obvious pulsatile hemorrhage from a severed artery usually catches the attention of medical personnel and is dealt with promptly, if not adequately, what is often underappreciated is that casualties with large soft-tissues injuries and extensive venous ooze are also at very real risk of exsanguination -- if not in so dramatic a fashion.

During the Korean War, Artz, Sako and Howard noted that at the 46th Surgical Hospital there were 20 deaths among 138 severely wounded patients. Of these, 7 (35%) died of uncontrolled hemorrhage, 4 (20%) from uncontrolled postoperative oozing, and 3 (15%) from uncontrolled major vessel injury.[191] Patients were noted to have died from persistent oozing from massive muscle wounds. Persistent bleeding from a scalp wound can also contribute to exsanguination. One death during recent combat operations in Afghanistan was attributed to failure to control persistent venous ooze.[192]

Sustained application of direct pressure may be facilitated by a field-expedient method, that of placing a sandbag inside a clean cover and putting it directly over the top of the pressure dressing on the wound. This is basically what is done in a hospital setting after an arterial catheterization has been performed. There are, however, two problems with this recommendation:

1. A sandbag is not always available, and
2. A fully filled, full-size sandbag may be too heavy and may disperse pressure over too large an area.

A new product, named the BioHemostat®, is currently in development, which may solve both of these problems and may also be so effective as to negate, in many instances, the need for a tourniquet. Developed in 2001 by a team led by Marcus E. Carr, MD, PhD at Virginia Commonwealth University, the BioHemostat® combines a traditional pressure dressing with an attached bag that is filled with a water-absorbing polymer that can absorb, within 3 minutes, up to 1400 times its weight in blood (or water).[193]

When the bag expands, it can apply up to 90 mm Hg direct pressure, and if properly applied, will exert this force almost directly on the site of bleeding. This exerts a tourniquet-like effect on the bleeding vessel while allowing collateral vessels to continue to perfuse distal parts. Expansion of the polymer is triggered either by absorbed blood or water injected into the polymer-containing bag to cause immediate expansion. The pressure in the bag is controllable by the amount of water added. The addition of a hemostatic agent to this dressing could further enhance its' hemostatic properties.

Whether this device, or any other, will solve the problem of applying sustained focused direct pressure on the wound is unknown, but anything that could accomplish this task while freeing up the medic/corpsman would be a very useful at or near the point of wounding.

Tourniquets

A tourniquet is a constricting or compressing device that is used to control venous and arterial circulation to an extremity for a period of time. The tourniquet has been recognized as effective at controlling hemorrhage since at least the time of the Greeks [194] and it was described briefly in Roman literature but, perhaps because it lead to gangrene, it did not come into general clinical use until sometime in the mid-1500s when Ambrose Paré is credited with it's discovery as a useful medical device when accompanied by ligature of the bleeding vessel.[194] In 1628, William Harvey, an English surgeon, described the human circulatory system in detail, thus paving the way for future technological developments in hemorrhage control.

In 1718, Louis Petit, a French surgeon, developed a screw device, designed to apply pressure to specific arterial points in order to limit bleeding. It is from the French verb "tourner" (to turn), that Petit named his device a "tourniquet." Since its introduction by Paré into clinical practice, the ligature, or tourniquet, has been a standard medical item for military surgeons and has remained largely unchanged from its original form. A tourniquet on display at the National Museum of Civil War Medicine in Frederick, Maryland is remarkably similar to the one that was, until quite recently, standard Army issue to medical personnel (it still remains in the inventory).

Although a properly applied tourniquet is clearly effective at controlling distal extremity hemorrhage, the liberal use of tourniquets has long been discouraged because of their associated risks. Dr. Julian Chisolm, a senior Confederate surgeon, made the following comments about tourniquets in his book, *Manual of Military Surgery:*

> *[Tourniquets]…[u]nless very tightly applied…are of no service, as they do not control the bleeding, and if firmly applied, they act as a general ligature around the extremity, and can be used but for a short time without injury to the limb…. Should a soldier have a large artery wounded and the hemorrhage be excessive . . . the orderly should be instructed how to make a judicious finger pressure. This is much better than the tourniquet.[195]*

Following World War I, COL Gray noted the following in his book, *Early Treatment of War Wounds:*

> *When an important artery or vein has been divided…[and] if…the casualty clearing station is some distance away [from a surgical facility]…[a difficult decision must be faced regarding the application of] a tourniquet that must of necessity remain in position for many hours…. Blind grouping in the dark in a haphazard attempt to seize [a bleeding vessel] in the grasp of a pressure forceps is useless, and generally results in the loss of much additional blood. Unless the operator feels confident [in his ability to clamp a bleeding vessel] it is better to rely on a properly applied tourniquet.[3](p.45)*

Generally, hemostatic clamps have no role in the prehospital control of hemorrhage because it is rare that a hemorrhaging vessel clearly presents itself for clamping. It

continues to be true, as Dr. Gray said, "Blind grouping in the dark" for a bleeding vessel is worse than useless.

It was his experience with tourniquets during the Spanish Civil War that lead Dr. Douglas Jolly to comment that, *"More limbs and lives are lost at the front from the improper use of the tourniquet than are saved by its proper use."[54(p.24)]* During World War II, the use of tourniquets evolved as experience was gained.[196(p.427-428)] In Volume 1 of *Activities of Surgical Consultants* the following comments were made regarding the use of tourniquets in World War II:

> *Early in the war, they were used far too frequently and removed far too often. After a tourniquet had been applied by a corpsman on the battlefield, it was examined by the first medical officer who saw the casualty and frequently it was removed by this medical officer. If the tourniquet was not removed, it was the policy to loosen it routinely every 30 minutes. In some cases, death occurred from the cumulative effects of the bleeding which ensued each time the tourniquet was loosened. The fatalities usually took place during evacuation by ambulance, on trips lasting several hours, when the medical corpsman loosened the tourniquet every 30 minutes as he had been instructed to do. Many deaths which could have been avoided were thus precipitated because no facilities were at hand to control the hemorrhage which frequently followed the removal of the tourniquet. Later, the policy was reversed, and once a tourniquet had been applied, it was not loosened or removed, particularly if the casualty was in shock, until facilities were at hand for the immediate control of hemorrhage and the replacement of blood loss. It was found*

to be safe, when a large vessel had been damaged, to leave the tourniquet in place for periods of from 4 to 6 hours during cold weather and for somewhat shorter periods in warm weather. Rubber tubing proved more satisfactory than the Army-issue webbing tourniquet.[196]

This last comment regarding the general ineffectiveness of the Army-issue webbing tourniquet is interesting because it seems that despite being recognized as unsatisfactory during World War II, the tourniquet has remained in the inventory to the present. It is also interesting to note that during a recent Advanced Trauma Applications for Combat Casualty Care (ATACC) conference in St. Petersburg Florida, a panel discussion on tourniquets concluded that the ½ inch surgical tubing recommended as a tourniquet during World War II was the best available field expedient tourniquet; although concerns were raised about the high tissue pressures that could be generated by the use of this tubing as a tourniquet.[197]

During World War II, MAJ Luther H. Wolff, MC, and Capt. Troglier F. Adkins, MC carried out a study on the use of tourniquets, with a particular focus on patients in shock. The results of this study formed the basis of the following regime, which was in general use when World War II ended (and which remained standard practice until quite recently):

Patients with tourniquets in situ should have the highest priority for transportation to the nearest hospital. The emergency medical tag should indicate that a tourniquet is in place. Marking the forehead with a red T was an additional precaution.

An effective tourniquet should be placed on an actively bleeding extremity at the earliest possible moment.

At the end of 2 hours, if the patient was not in shock and if all circumstances were favorable, the medical officer might cautiously loosen the tourniquet if facilities were available for immediate control of hemorrhage. If bleeding was negligible or did not recur, the tourniquet might be removed, but the patient was kept under continuous observations and the tourniquet was left in place for immediate reapplication.

On no account should a tourniquet on a patient in shock be removed within 4 to 6 hours of its application unless the blood volume had been at least partly replaced by plasma or whole blood. After this time, the removal or loosening of the tourniquet was a matter of individual judgment. In many instances, sufficient clotting and spasm had occurred by this time to prevent further bleeding.

When a tourniquet was in place, the temperature of the affected limb was lowered as much as possible short of actual freezing.[196(p.427-428)]

The recommendation, during World War II, of 4 to 6 hours of tourniquet time, was empirically derived. Col Gray's opinion, based on his experiences from World War I, was that *"...about 80 per cent of limbs whose blood supply has been cut off by a tourniquet for a period of three hours...eventually come to amputation."[3(p.45)]*

A study during the Korean war of 79 major extremity vascular injuries showed that 47% were admitted with a tourniquet in place for between 40 minutes and 14 ½

hours; the average time being 4 hours.[198] Since the Korean War, a large number of studies have been done to determine the optimal maximum tourniquet time before irreversible tissue damage occurs.[199-209] Most of these studies have been done to evaluate the effect of tourniquet time on patients undergoing elective orthopedic surgery and thus patients were relatively normovolemic at the time of the tourniquet application. To what extent these studies can be applied to tourniquet use in combat casualties is unclear.

In a recent animal study of pneumatic tourniquet times and the effect of periodic episodes of reperfusion on muscle injury, Pedowitz demonstrated that 2 hours was a time threshold for tourniquet compression injury. The degree of tissue injury also depended upon cuff inflation pressure.[210] Physiologic and morphologic nerve abnormalities were caused by a 2-hour tourniquet time and necrosis was observed. With a 4-hour total tourniquet time, skeletal muscle injury beneath the cuff was significantly decreased by hourly, 10-minute reperfusion intervals.

Interestingly, this study found that if the tourniquet time was longer than 2 hours, episodes of reperfusion tended to exacerbate, not reduce, muscle injury. It is generally taught that muscles are more sensitive than nerves to long tourniquet time and that tourniquet times > 2 hours and the use of high pressure (>350 mm Hg in lower extremities and 250 mm Hg in upper extremities) increases the risk of nerve damage. It is also generally taught that if > 2 hours is required, the tourniquet should be deflated for 5 minutes during every 30 minutes of inflation time. Contradicting this recommendation is a 1999 study by Mohler et al. that demonstrated that intermittent reperfusion does not reduce neurological injury.[211] This study also showed that although tourniquet-induced muscle

damage may resolve, nerve damage, if it occurs, does not.

Forward healthcare providers should be instructed that, although combat casualties may experience only minimal discomfort when the tourniquet is first applied, the great majority will begin to experience increasingly severe pain at the tourniquet site after 30−60 minutes. This pain is described as a dull, burning, aching sensation that becomes increasingly worse until the tourniquet is removed.[212] Patients requiring tourniquet placement should be given adequate analgesia prior to transport.

As previously stated, as long ago as World War II it was noted that the standard-issue 1.5-inch-wide, cotton-strap tourniquet (nonpneumatic; NSN 6515-00-383-0565), was not particularly effective.[196(p.427-428)] It is difficult even for a trained healthcare provider to achieve arterial hemostasis with this tourniquet, but when applied by the wounded soldier himself it is essentially impossible to achieve hemostasis, especially if only one hand is available for application. During the post-Korean War conference, "Recent Advances in Medicine and Surgery (19-30 April 1954) at the Army Medical Service Graduate School Walter Reed Army Medical Center, Maj. Mallory made the following comments about the standard army tourniquet:

> *Present methods are time-consuming, inaccurate as to pressure exerted and often require excessive manipulation of the injured part (especially when applied by a single person). Self-application is virtually impossible…the tourniquet to be effective must be applied before the patient reaches the aid station. This requires that it be done in or very near the battle area. This further demands that the method be very simple and rapid and*

applicable by anyone – characteristics not possessed by the present means…We need, critically, a better tourniquet device (underlying added for emphasis).[213(p.61)]

During this same conference it was recommended that, *"Not infrequently, a tourniquet may be used as an emergency procedure; and, after further evaluation, bleeding may be controlled by a pressure dressing."*[198] Later during this conference LTC Hughes stated that, *"…a tourniquet should be applied only tight enough to control hemorrhage and left in place until it can be removed by a medical officer with blood or plasma expander available to resuscitate the patient. When packs or pressure dressings will suffice, the tourniquet should be removed and the pressure dressing applied only tight enough to control the hemorrhage."*[198] Interestingly this recommendation is virtually identical to that which was recently agreed to for far-forward medical care providers.

With regard to the current Army-issue tourniquet, early feedback from Navy corpsmen in support of the U.S. Marine Corps during Operation Iraqi Freedom in Spring 2003 is that once again the 1.5 x 42-inch non-pneumatic tourniquet (NSN 6515-00-383-0565) which was still issued at that time has proven ineffective. Corpsmen report that the tourniquet tended to slip around the thigh or arm while attempts were made to tighten it, causing medical personnel to resort to green slings and sticks to tighten around pressure points to stem the flow of arterial bleeding in the extremities.[214]

Calkins et al. recently evaluated available tourniquets and commented that the web-strap tourniquet is inconsistent in stopping arterial blood flow, even when applied by someone other than the injured patient him/herself.[215] Recognition of this fact has

led Special Operations medics to craft their own tourniquets from triangular bandages and suitable field-expedient windlasses; it also led researchers to try to find a better tourniquet. Calkins et al. found that both a ratchet-style and Velcro bladder tourniquet were effective and could be applied singled-handedly. Despite the potential of the bladder tourniquet to develop into a "smart tourniquet," i.e., capable of periodic self deflation and re-inflation, Calkins et al. recommended the ratchet-style tourniquet for field use, primarily due to its durability, simplicity, ease-of-use, size, and weight.[215]

The revival of interest in the tourniquet in the mid-to-late 1990's led to an aggressive effort to develop, evaluate, and field an effective tourniquet that could easily be applied one-handed by a wounded soldier. The preliminary result of this endeavor was the selection of a tourniquet that came to be referred to as the Army One Handed Tourniquet. Unfortunately, while this tourniquet could be applied one-handed (even this tourniquet was not particularly easy to apply one-handed) it was not particularly effective at occluding arterial flow in the lower extremities.[216]

Other tourniquets continued to be developed and deployed. The two most widely deployed being the Combat Application Tourniquet, or CAT, and the Special Operations Forces Tactical Tourniquet, or SOFTT. In his 10 May 2005 statement to the Senate Committee on Appropriations, Defense Subcommittee, LTG Kiley, Surgeon General, United States Army, noted that since April 1, 2004 193,897 tourniquets have been issued to deploying troops; 112,697 of these tourniquets being either the Combat Application Tourniquet (CAT) and the SOFTT (Special Operations Forces Tactical Tourniquet). He went on to say that beginning April 1, 2005 all new soldiers will received spe-

cific instructions on the CAT during Basic Combat Training.[217]

Most recently developed and fielded is the Mechanical Advantage Tourniquet, or M.A.T., produced by Cybertech. Although somewhat heavier and more bulky than some of the previously fielded tourniquets this author and others feel that this tourniquet is the best of the most recently fielded tourniquets. This tourniquet is very easy to use, it can be rapidly applied with little difficulty using one-hand, and, most importantly, it is effective at occluding arterial hemorrhage in both upper and lower extremities.[218] This said, the Combat Application Tourniquet is also quite effective, and although in this author's view somewhat more difficult to use, it is lighter and less bulky.

Based upon currently available scientific data, tourniquet times in excess of 2 hours should be assumed to be associated with the loss of the distal limb. This may not be true in every instance; certainly some limbs will still be salvageable after 2 hours of tourniquet time, especially if the limb has been kept cold. In fact forward medical personnel should be advised, whenever possible, to cool limbs (while avoiding freezing of the tissue) to which a tourniquet has been applied in order to increase the possibility of limb salvage. There will also be situations where otherwise viable limbs will be lost even when the tourniquet time has been kept to less than 2 hours.

Navein and Coupland, in their 2003 Journal of Trauma article, noted that a limb occluded for less than 2 hours is almost always salvageable while a limb occluded for more than 6 hours is almost certainly not salvageable. They conclude that decision making in tourniquet application should involve viewing tourniquets in one of three ways. First, those that are "tactical

tourniquets", which are applied quickly using materials immediately at hand, to control potentially lethal hemorrhage when time and circumstances do not allow for a detailed assessment and/or when manpower, or resources are not available. Such tourniquets are to be removed at the earliest possible time and the patient reassessed to determine if a tourniquet is actually needed. Second, there are those tourniquets that are "trial tourniquets"; tourniquets that have definitely been determined to be needed and have been applied in a careful manner with the intention to leave in place for up to 2 hours. Finally they describe "tourniquets of last resort". These are the tourniquets that are applied and left in place after a "trial tourniquet", which had already been left in place for two hours, is removed and bleeding continues unabated by other hemorrhage control efforts.[219]

The recommendation that is offered here is that forward healthcare providers should be given the following instructions:

1. Make every possible effort to evacuate, in less than 2 hours, all patients who require placement of a tourniquet to a facility where surgical control of hemorrhage can be provided

2. Tourniquet times in excess of 2 hours have a high associated probability of distal limb loss.

3. Although tourniquet placement may be necessary, it should always be done with an understanding that no tourniquet time is considered "safe," i.e., there is always a risk of injury any time a tourniquet is applied.

Research and development should be continued to develop and field an automatic pneumatic tourniquet that inflates to the

minimum effective inflation pressure required for hemorrhage control. If clinical studies confirm the efficacy of periodic tourniquet deflation, this new tourniquet should also be able to be set to periodically deflate and re-inflate to allow for some distal blood flow. The real barriers to fielding such a tourniquet today is that such a tourniquet should also be relatively inexpensive, very durable, and easy to use.

Other Methods of

Hemorrhage Control

Fibrin Dressing

Driven by the recognition that the only place in which combat-related deaths can really be significantly reduced is in the prehospital environment, the U.S. Department of Defense medical research community has increasingly focused on prehospital care issues; in particular on hemorrhage control and management of shock. Recent well-publicized, prolonged, deaths from hemorrhage of soldiers who were in the care of medics/corpsmen (e.g., during the 1993 operation in Mogadishu, Somalia and in 2002 at Robert's Ridge during Operation Anaconda in Afghanistan) have spurred these efforts. One initiative has been the development and fielding of the dry fibrin sealant dressing. Although research in this area has recently been re-energized and now focused on the far-forward use of fibrin, the use of fibrin for hemorrhage control had begun to be explored as early as World War II.

> *When thrombin first became available, Lt. Edgar A. Bering, Jr., Mc, USN and Dr. Bailey had applied it in solution to bleeding points in several cranial and spinal operations. It did no harm...but its effect was entirely transient. Lieutenant Bering then conceived the idea of using fibrinogen, converted into fibrin foam, as a matrix...The first applications of fibrin foam were made in cases in which bleeding was difficult to control and the application of muscle was not feasible. The hemostatic effect was evident...It was agreed that the material was of extraordinary value as a hemostatic agent in neurosurgery. It...proved of great value in hemophiliacs, in controlling bleeding from traumatic lacerations, and in maintaining hemostasis during minor surgical procedures such as tooth extractions."[85(p.364)]*

Early enthusiasm for the use of thrombin to help control hemorrhage was tempered by concerns about hepatitis transmission, and in 1946, all pooled blood products were withdrawn from military stocks and the FDA removed the last human fibrinogen from the market in 1977.[220] Recently, new methods have been found to inactivate viruses in pooled plasma and more extensive purification has enabled production of safe hemostatic agents from pooled blood products.

Increased focus on improving prehospital hemorrhage control was the catalyst for development of dry fibrin sealant dressing (DFSD) by COL John Holcomb, MD. The DFSD is designed for direct application to bleeding surfaces for control of serious hemorrhage [221-225]. The dry thrombin and fibrinogen used on the dressing provide, in great excess, the last two clotting factors in the coagulation cascade so when blood from a hemorrhaging vessel comes in contact with the dressing, a strong, clot-like adhesive is quickly formed.[220] The fibrin dressing has been shown to effectively control both external[221] and internal hemorrhage[223, 224, 226-230] in animal models.

In an unblinded, randomized, prospective trial using a caprine ballistic wounding model, the DFSD reduced both total blood loss and blood loss per kilogram of body weight as compared to a standard gauze dressing. By 20 minutes post-injury, the mean blood pressure in the DFSD-treated group had returned to its pre-injury level while at the same point in time, the mean blood pressure of the gauze-dressing-treated group remained near its post-injury low.[225] All dressings in the study were applied in the same manner as conventional gauze dressings.

There is some evidence to suggest that the DFSD is more sensitive to precise application for optimal function than is the standard gauze battle dressing. In a preliminary study of the efficacy of the DFSD in a simulated land-mine injury in a caprine model done by LTC Paul Dougherty at the Joint Special Operations Medical Training Center at Fort Bragg in 1999, it appeared that the DFSD did not perform as well as a conventional dressing unless the dressing was tucked down into the depth of the wound to ensure that the fibrin was in close proximity to the point of bleeding. Although this study may not have been completed and no other discussion of optimal position of the DFSD appears in the literature, COL Holcomb, developer and strong proponent of the DFSD, admitted that, *"These agents [hemostatic dressings] are not magic; they must be placed in apposition to the major bleeding source."*[155]

During recent military operations in Iraq (Operation Iraqi Freedom) the DFSD was fielded under a special investigative protocol approved by the FDA that ceased following conclusion of major combat operations. During this approved protocol, the DFSD was fielded to Special Operations combat medics involved in ongoing combat operations in Operation Iraqi Freedom, but it was not used in any instance.

In any case, given their higher level of medical training, the field performance of this dressing when used by Special Operations Combat Medics and Special Forces medics may not be equivalent to that which may later be observed in conventional medics/corpsmen.

It is hoped that someday this dressing and other hemostatic agents will help to increase the number of survivors of combat wounding. Unfortunately the cost of the DFSD is quite high (currently $1,000 per dressing) and the price is not expected to fall below $300 per dressing[155] even when it goes into full-scale production. This high cost will likely restrict the widespread usage of this dressing and thus, even if it is highly effective, it is unlikely to have a significant impact on survival because it won't be widely available at or near the point of wounding.

QuikClot[TM]

In 2002, a study was conducted at USUHS to evaluate the efficacy of several different, commercially available hemostatic agents in reducing blood loss after lethal uncontrolled hemorrhage in Yorkshire swine.[231] A complex groin injury that included complete division of the femoral artery and vein was inflicted, and after 5 minutes the animals were randomized to the following groups: (1) no dressing, (2) standard dressing, (3) standard dressing plus aggressive resuscitation, (4) standard dressing plus Rapid Deployment Hemostat[TM] (RDH, Marine Polymer Technologies], (5) standard dressing plus QuikClot[TM] hemostatic agent (Z-Medica), (6) standard dressing plus TraumaDEX[TM] (Medafor, Inc.).

In this Alam study all groups received one liter intravenous saline except Group 3, which received unlimited saline, with the goal of maintaining a systolic blood pressure >100 mm Hg. There were six animals in each group. Application of a wound dressing decreased mortality in all groups as compared to the no dressing group (Group 1), which had 83% mortality. Because of the small size of the groups, this difference was only significant for the QuikClot[TM] hemostatic agent, which had 0% mortality. Application of the standard dressing alone decreased mortality to 33.4%.

RDH[TM] is a poly-N-acetylglucosamine derived from algae that is backed by 4"x 4" gauze. QuikClot[TM] is a granular zeolite that adsorbs water (creating significant heat of adsorption) and promotes clot formation when it is poured onto a bleeding site. TraumaDEX[TM] is a powder-like agent that consists of bioinert microporous particles that absorb water and promote clotting by producing a gelling action.

In May 2002, the FDA approved QuikClot[TM] for clinical use. Based, in part, upon the findings in this study the United States Marine Corps decided to consider fielding QuikClot[TM] to medical personnel preparing to engage in impending combat operations in Iraq. Because of some concern about the potential for injury that might occur as the result of the exothermic heat of adsorption that is created when water (or blood) is added to QuikClot[TM], a study was done by Dr. Hasan B. Alam at USUHS to assess the degree of burn injury that might be produced during clinical use of this product.

In vitro, depending upon the amount of blood/saline and depending on the rate of addition, the temperature varied considerably. In the lab, with just the right mixture of blood, saline, and QuikClot[TM] the exothermic reaction reached as high as 65°C (149°F). Fortunately, in vivo, the maximum recorded temperature in tissue did not exceed 45°C (113°F). As noted by Dr. Alam, this was probably because the large volume of blood and the surrounding tissue acted as a heat sink and the distribution of QuikClot[TM] over a wider area minimized the amount of heat at any specific point.[232]

An interdisciplinary, multiservice panel of medical personnel chaired by COL Dave Burris was convened at USUHS in February 2003 to review Dr. Alam's findings and to make a recommendation to the U.S. Marine Corps regarding the advisability of fielding QuikClot[TM] to corpsmen. QuikClot[TM] was recommended for fielding with certain provisions. This panel concluded the following:

- QuikClot[TM] causes a variable amount of local tissue damage when used in animal models. Damage varies from none to as much as 5 mm into surrounding tissues. Localized burn injury to regional blood vessel walls and nerves could lead to morbidity if the casualty survives.

- In one animal study, wounds closed primarily after the use of this agent became infected. Because combat wounds should not be closed primarily, the significance of this finding is unclear.

- Given the risks of tissue damage, QuikClot[TM] should not be used when there is no life-threatening hemorrhage.

- QuikClot[TM] controls hemorrhage. The risk of tissue damage is offset by the potential to save life in otherwise uncontrollable external hemorrhage.

- QuikClot^{TM} should only be used to treat external wounds.

- QuikClot^{TM} should only be used after properly applied standard methods of hemorrhage control have failed.

- QuikClot^{TM} should be an accountable item that requires reporting each time a packet is utilized.[233]

Based upon the demonstrated efficacy of QuikClot^{TM} and upon the panel's recommendation, QuikClot^{TM} was fielded for use to U.S. Navy corpsmen supporting the U.S. Marine Corps during combat operations in Iraq.

The following comments regarding Quik-Clot^{TM} were included in an early U.S. Marine Corps Operation Iraqi Freedom After Action Report on the performance of various items of equipment including Quik-Clot^{TM}. [234] These comments do not reflect a comprehensive assessment of the effectiveness of QuikClot^{TM} in treating casualties, but they are worth consideration.

2D Tank Battalion Surgeon LT Bruce Webb (USN) stated that QuikClot^{TM} was ineffective (specifically, it was ineffective on arterial bleeding). Battalion corpsmen attempted to use QuikClot^{TM} in three separate occasions:

- Wounded Iraqi civilian. Shot near brachial artery. QuikClotTM was applied per the instructions. The substance dried but was flaking off. Standard direct pressure applied by corpsman proved more effective on the patient.

- Iraqi civilian shot in back with punctured spine. QuikClotTM applied to severe bleeding. Pressure from bleeding sprayed QuikClotTM away. Ac-

cording to LT Webb, "QuikClotTM was everywhere but the wound."

- Iraqi civilian, female, shot in femoral artery. She suffered severe arterial bleeding. Patient bled out. Quik-ClotTM unable to be applied effectively due to pressure of blood flow from wound. Patient died.

- An LAR Marine was shot in the femoral artery. QuikClotTM was applied to the heavily bleeding wound. The pressure from the blood soon caused the QuikClotTM to be pushed out of the wound and rendered ineffective. A tourniquet was applied instead. The patient died.

It was noted that QuikClot^{TM} may work if applied in a "buddy system" manner, with one individual applying the QuikClot^{TM} substance while another quickly applies sterile gauze to the wound. However, applying the QuikClot^{TM} as directed appeared to be ineffective. Direct pressure and tourniquets were used instead. It was noted in the report that the Marine Expeditionary Unit medical officer who was interviewed had a more favorable opinion of the efficacy of QuikClot^{TM} and the author of the report recommended that further study of this item be done (unfortunately data regarding the use of this item were not collected in a rigorous fashion and thus it will not be possible, even in a retrospective way, to truly assess the efficacy of QuikClot^{TM} when used to treat combat casualties during Operation Iraqi Freedom).

HemCon^{TM}

After Dr. Alam's initial study of available hemostatic dressings the FDA approved another hemostatic agent, the HemCon^{TM} hemostatic dressing. HemCon^{TM} is a chitosan-based, poly-N-acetyl-d-glucosamine

-- a naturally occurring substance. This hemostatic dressing is described by Alam et al[232] and is discussed in a review of hemostatic dressings for first responders by Neuffer et al.[235]

Pusateri et al. conducted a study of the efficacy of this product in controlling severe hemorrhage from a hepatic injury in a swine model.[236] They compared the chitosan dressing to gauze sponges in terms of ability to reduce hemorrhage and improve survival. Following induction of a large liver injury, the animals were resuscitated with Ringers lactate back to their baseline MAP at a rate of 260 mL/min (note that this is very aggressive fluid resuscitation). The dressings were applied directly to the areas of bleeding and compression was applied. The amount of post-treatment blood loss was determined by suctioning of the shed blood from the abdominal cavity.

Post-treatment blood loss was significantly reduced in the chitosan dressing group as compared to the gauze sponge group (p<0.01) and survival was also significantly better in the chitosan dressing group (7/8 compared to 2/7). Whether this dressing would be more effective than a properly applied standard battle dressing at controlling hemorrhage in an extremity injury in a combat casualty is unknown, however. Given that current resuscitation protocols call for limited to no volume resuscitation until hemostasis is achieved, it is unclear how this dressing would have compared to gauze if no effort had been made to raise the MAP back to pre-injury levels.

It is worth noting that Alam et. al.,[232] in their review of the various hemostatic agents considered for use by the U.S. military, concluded that, "Clearly hemostatic agents are not a substitute for, but an adjunct to, the standard treatment, and ade-

quate training of the user will be a key factor in obtaining the desired benefit." This is most certainly true. They go on to point out that, "For the first time since the Crimean War, the KIA rate has markedly dropped below the historic 20%" with there being an overall KIA rate during Operation Iraqi Freedom of only 12.2% (citing a Washington Post article by Loeb dated 28 December 2003) – implying that the use of hemostatic dressings contributed to this decline.

While the assertion in the Alam article that the KIA rate has declined dramatically during Operation Iraqi Freedom may be true there is good reason to suspect that it is not; at least not to anywhere near the extent stated. First, at the time of their article's publication the conflict was still ongoing so the final numbers, whatever they are, have not been tabulated and analyzed. Second, this author is unaware of any systematic, comprehensive, study of battle and disease-non-battle injuries and deaths that has been conducted during this war at the time of this writing (an article in the Washington Post is anecdotal at best). Finally, and perhaps most importantly, any decline in the KIA rate, if one actually exists, is far more likely the result of the widespread use of soft and hard body armor in this conflict. None of this is to suggest that there is no value in the procurement and distribution of hemostatic agents to pre-hospital combat health care providers. It is rather intended to make clear that there is no substitute for training and for the proper application of basic first-aid procedures for hemorrhage control and to underscore that injury prevention or attenuation is far more important than the availability and use of these new hemostatic agents.

Factor VII Injection

Future methods of hemorrhage control may include the use of recombinant Factor VII and/or other procoagulants. Factor VII has long been available for use in hospital settings to treat bleeding patients with inherited or acquired coagulation factor deficiencies. The major problem that has significantly limited the use of Factor VII for hemorrhage control, even for this group of patients, has been the risk of disease transmission. Historically, Factor VII was derived from pooled blood products and was associated with a high risk of hepatitis, and more recently, HIV, transmission. Recombinant Factor VIIa (rFVIIa), which is now available, does not have these risks. It is indicated for the treatment of hemorrhage in patients with a genetic Factor VII or Factor IX deficiency (hemophilia A and B) with significant bleeding; albeit at great expense. In the United Kingdom, approximate costs of rFVIIa (converted to U.S. dollars from 2002 U.K. pounds) were $1,130 for 1.2 mg; $2,260 for 2.4 mg, and $4,520 for 4.8 mg). For treatment of severe hemorrhage in an adult, the cost of one dose exceeds $5,600.[237]

Animal studies have demonstrated the efficacy of rFVIIa in reducing mortality in lethal uncontrolled hemorrhage models.[238, 239] Recombinant Factor VIIa has recently been successfully used off-label to treat patients with exsanguinating, and otherwise uncontrollable, hemorrhage due to trauma.[240-242] Occasionally, the results have been quite remarkable despite the fact that, because the rFVIIa was given as a last resort, a number of the patients ultimately died, often from causes other than continued hemorrhage.

Not surprisingly, the major concern with administration of rFVIIa to patients without a known deficiency is the risk of thrombotic complications. Exposure of subendothelial tissue factor at the site of injury initiates the coagulation cascade, and in extensive injury this may trigger a disseminated intravascular coagulation (DIC)-like picture that consumes clotting factors and leads to sustained bleeding. Traditionally, this has been a contraindication to the use of rFVIIa. Despite these concerns, clinical experience with rFVIIa has been relatively free of serious adverse events in general and specifically there has been a low risk of serious thromboembolic complications.[241]

Today, rFVIIa is not even approved for use in U.S. hospitals to treat general trauma patients, nor is it approved for use in the prehospital setting. There is, however, some reason to believe that such treatment might someday be considered at or near the point of wounding. Given the young age and pre-existing good health of the great majority of combat casualties, it may be that rFVIIa, or a related procoagulant, could someday be safely given in the field by prehospital personnel.

Other Methods of Hemorrhage

Control

Stabilization of fractures, especially pelvic fractures, is very effective at reducing or even stopping, continued bleeding. Major pelvic fracture can be associated with uncontrolled hemorrhage and mortality as high as 50%. Venous bleeding, which accounts for as much as 90% of pelvic hemorrhage, responds favorably to pelvic bone stabilization.[243]

New external pelvic stabilizers are now available that can be applied at the bedside, but such devices will almost certainly never have a role in the stabilization of pelvic fractures outside of a medical treatment facility. Stabilization of pelvic fractures can, however, be achieved with

devices that prehospital personnel either already carry, such as the PASG [181, 184, 244] or bed sheet [245], or could carry (e.g., Geneva pelvic belt, London pelvic splint, Trauma Pelvic Orthopedic Device (T-POD), etc…).

Stabilization of long-bone fractures, particularly femur fractures, can also mini-

mize the occasionally significant blood loss often associated with these injuries. Finally, stabilization of large, soft-tissue injuries of the thigh and buttocks through bandaging and splinting can help control bleeding even when there is no associated fracture.

Other Types of Shock

As noted above, hemorrhagic shock is the primary circulatory problem of concern in the management of the combat casualty at or near the point of wounding. Other forms of shock occur in combat casualties, although they are much less common. Although disease and non-battle injury continue to be significant causes of morbidity and lost man-days in the combat zone, they are an uncommon cause of death and are outside the scope of this discussion. Therefore, the other forms of shock, i.e., hypovolemic shock from other than hemorrhage, neurogenic, cardiogenic, anaphylactic, and septic shock will only be discussed here in the context of those shock states found in combat.

Hypovolemic Shock – Non-Hemorrhagic

Burns

As noted elsewhere in this series [246], combat-related burns have historically accounted for about 3% of all combat injuries. When considering modern warfare since World War II, particularly armored/mechanized warfare, this percentage has been as high as 10.5% (1973 Yom Kippur War) [247]. During the conflict in the Falklands 14% of all UK casualties were burned and 34% of Royal Navy casualties

suffered burn injuries, reflecting the high incidence of burn injury associated with naval warfare.[248]

Increased use of petroleum-powered vehicles on the modern battlefield has contributed to an increase in the number of burn injuries in land combat from both combat and non-combat causes. Although not used against U.S. forces in recent conflicts, fuel-air explosives and enhanced blast weapons are increasingly being used and will likely contribute to an increase in burn injuries in the future.

In armored warfare, a combined injury of burn, primary blast, and penetrating injury is called the "Anti-Tank Missile Syndrome." The management of combined injury is problematic because each individual mechanism may ideally require different fluid resuscitation strategies (see earlier discussion on this issue above).

Burns cause hypovolemia and shock through a variety of means. In burns, the intravascular and interstitial spaces are depleted as fluid exudes from the skin and vasoactive inflammatory mediators cause intravascular fluid to leak into surrounding tissues. All of this can happen soon after burn injury. When burns cover approximately 20% total body surface area (TBSA), hypovolemic shock may occur.

Delays in resuscitation of burn victims can be costly. It has been shown that the time to intravenous access and initiation of fluid resuscitation is a major predictor of mortality in pediatric patients with greater than 80% TBSA burns.[249] In one study, it was demonstrated that if intravenous access was not established within 2 hours from the time of injury, there was a significant increase in mortality.[250] The recommendation of this study was that if initial attempts at vascular access were unsuccessful, intraosseous access should be obtained and fluid administered.

Many different fluid resuscitation formulas for burn resuscitation have been described. These differ in the amount of crystalloid and colloid to be given, and in the tonicity of the fluid. A recent review article by Nguyen et al. notes that colloid administration with albumin or plasma protein substitutes helps maintain oncotic pressure after acute resuscitation but in randomized trials has not been shown to improve clinical outcomes.[251] According to these authors, the consensus is that the administration of colloid is unnecessary for patients with less than 40% TBSA burns and during the first 8 hours for patients with larger burns. No single fluid resuscitation protocol has proven superior at reducing the severe systemic edema that accompanies fluid resuscitation of severe burn injury; a partial list includes the following:

- Parkland Formula The most commonly used formula in adults, the Parkland formula employs crystalloid resuscitation with 4 mL/kg/%TBSA burn, using Ringers lactate in the first 24 hours post-burn.

- Brooke Formula The Brooke formula recommends 2 mL Ringers lactate/kg/% TBSA burn plus 2000 mL

of 5% dextrose in water (D5W) during the first 24 hours post burn.

- Consensus Formula Promulgated by the Advanced Burn Life Support Course, the Consensus fluid formula recommends 2-4 mL Ringers lactate/kg/TBSA burn for the first few hours post-burn, with half of the calculated volume given in the first 8 hours and half over the remaining 16 hours.252

Hypertonic saline, both alone and combined with a colloid (Dextran), has also been recommended for the treatment of burn victims (see above), but because 7.5% NaCl/6% Dextran-70 is not currently FDA-approved, it will not be discussed further here.[253] In general, crystalloid resuscitation with isotonic Ringers lactate is considered the best option in the acute phase.

When, for whatever reason, intravenous or intraosseous infusion of fluids is not possible, oral rehydration of moderately burned patients with the World Health Organization Oral Rehydration Solution is an option worth considering; certainly one that should receive further study. In an Egyptian study by El-Sonbaty, an oral rehydration solution called Rehydran-n (CID Co. Giza, Egypt) was used to treat children with 10−20% TBSA burns.[254] Rehydran-n is formulated as a 5.5-gram packet, which, when dissolved in 200 mL water, gives a concentration of 90 mEq sodium, 20 mEq potassium, 30 mEq bicarbonate, 80 mEq chloride and 111 mEq glucose per liter.

All of the children in the study did well, despite developing low serum sodium levels. Because these low sodium levels were almost certainly due to the low sodium content of the Rehydran-n solution, El-Sonbaty recommended that the 5.5-gram

packet be constituted with 150 mL instead of 200 mL water to increase the sodium content to120 mEq/L. The author concluded that the advantages of this approach include (1) simplicity of use (2) low cost (3) possibility of use as a first-aid treatment until patient arrives at a hospital (4) no risk of fluid overload, and (5) avoidance of all the difficulties and complications of intravenous infusions. Oral rehydration with a suitable solution, therefore, may reasonably be recommended for moderately burned combat casualties who can tolerate oral fluids and in whom intravenous access cannot be obtained. More severely burned patients will have a burn-induced ileus and will not be able to tolerate oral fluids.

Intravascular volume status of burn patients must be re-evaluated on a frequent basis during the acute phase. Monitoring urine output closely is the best indicator of adequate resuscitation. Unfortunately, this can't be done easily or accurately in the prehospital environment. Urine output in children should be maintained at 1 mL/kg/h, whereas for adults, 0.5 mL/kg/h is sufficient. Although early and substantial fluid resuscitation is indicated for patients with significant burns, it is essential to avoid over-aggressive resuscitation, which can lead to pulmonary edema. This is especially important in casualties with inhalation burn injuries, who are at increased risk of pulmonary edema due to increased pulmonary vascular permeability.

None of the recommended burn protocols should be considered a substitute for constant reassessment of urine output and volume status within the context of the patient's overall clinical picture. An increased fluid requirement in a burned combat casualty should raise the index of suspicion for concomitant injury. If there is an increased fluid requirement occult

penetrating or blunt injury, inhalation burn injury, or other causes of hemodynamic instability should be sought. Resuscitation should begin as soon as possible after the time of burn injury. Unfortunately, especially in the combat environment, delays in adequate resuscitation are, and will remain, common and this may lead to unnecessary loss of life.[249]

Cardiogenic Shock

Cardiogenic shock results when cardiac action cannot deliver a circulating blood volume adequate for tissue perfusion. The most common cause of this in the general population is myocardial ischemia or infarction. In the combat setting, cardiogenic shock in a young soldier is more likely caused by cardiac tamponade or cardiac contusion from blunt chest trauma.

Pericardial tamponade as a cause of combat-associated death was recognized and well described during the Civil War. The Confederate Surgeon General even noted that some combatants with this injury might survive stating that,

> *When the heart is injured [and yet the man lives a short period]…the pericardium soon becomes filled with blood; the action of the heart is mechanically impeded, and, sooner or later, depending upon the size of the wound and the facility for letting out blood, it ceases its pulsation. Reports of cases are not very rare in which small, oblique incised wounds of the heart have been recovered from…"* [255(p.281)]

The true incidence of both cardiac tamponade and cardiac contusion in modern combat casualties is unknown. There are certainly case reports of pericardial tam-

ponade found at autopsy. During World War II, the 2nd Auxiliary Surgical Group recorded that only 3.3% (75 of 2267) of those with thoracic wounds had cardiac or pericardial involvement, and in those cases where there was pericardial involvement tamponade was not present in all cases. Given that thoracic injuries only constitute 7% of all combat injuries[256] (probably less than this in current operations due to widespread use of body armor) and assuming that all of these 75 WWII casualties had pericardial tamponade this means that at most only .231% of all combat casualties in World War II had pericardial tamponade.[257]

It is noted in the above cited WWII report that, "In comparison to the frequency with which it is noted in civilian cardiac wounds, tamponade has been an infrequent finding." The absence of tamponade was attributed to the large wounding missiles used in combat, which create a hole in the pericardium so large that tamponade does not occur [257]. Whether this would be the case today, with an increased use of improved conventional munitions, is unknown. In this historical account of a busy combat surgical unit, it is worth noting that in more than 50% of the cases in which cardiac injury was ultimately diagnosed, the cardiac wound was undiagnosed prior to surgery.

When both pericardial tamponade and hemorrhagic shock are present, it is very difficult to make the proper diagnosis, even in a hospital setting. The classic triad associated with pericardial tamponade: (1) hypotension, (2) muffled heart sounds, and (3) distended neck veins (Beck's triad) are either not present (distended neck veins) or are readily attributable to hemorrhagic shock (hypotension); and finally what exactly constitutes muffled heart sounds is unclear and, in any case, accurate diagnosis of this finding in a busy

emergency department, much less a combat environment, seems unlikely. The presence of *pulsus paradoxus* (>10 mm Hg decrease in systolic blood pressure during inspiration), which is sometimes found in pericardial tamponade, could help make this diagnosis. Unfortunately, given the training of the average combat medic, the available equipment, and the chaos of the combat environment, it is not likely that *pulsus paradoxus* could be used to reliably diagnose pericardial tamponade in the field.

The definitive treatment of pericardial tamponade involves thoracotomy, with opening of the pericardium and repair of the underlying injury. Pericardiocentesis, which is advocated by current ATLS guidelines, is a temporizing, not definitive, measure. The technique, as described in the ATLS manual, requires monitoring of the patient's ECG "…before, during, and after the procedure." Evidence of a "current of injury" on the ECG (extreme ST-T wave changes or widened and enlarged QRS complex) indicates that the pericardial needle should be withdrawn. [49] This cannot be done at or near the point of wounding.

Although pericardiocentesis, without early thoracotomy, can certainly be performed at or near the point of wounding, the question is, "Should it be recommended?" The ATLS pericardiocentesis recommendation assumes that a surgeon, with the ability to perform the appropriate definitive procedure, is either immediately available or can be quickly reached. This is rarely the case when combat casualties are cared for at or near the point of wounding.

Special Operations Medics are taught to perform pericardiocentesis whenever either Beck's triad [hypotension, distended neck veins, muffled heart sounds] is present or when hypotension alone is coupled

with a wound likely to cause pericardial tamponade in a patient in whom other resuscitative efforts have been unsuccessful. Unfortunately, in a combat setting, most patients who have tamponade are likely to be hypovolemic from other penetrating wounds so distended neck veins are unlikely, and, as noted above, hearing "muffled heart sounds" in a combat setting is problematic.

Is pericardiocentesis in a combat setting a reasonable recommendation for Special Operations medics who are trained to, or above, the paramedic level? Is it a reasonable recommendation for the average combat medic? Is it a reasonable recommendation for any level of provider at or near the point of wounding? These are difficult questions. Reasonable answers require an assessment of the likelihood of benefit (based upon the incidence of the condition in the population and the efficacy of the procedure) as compared to the likelihood of "cost" (risk of iatrogenic injury if done correctly or incorrectly and if indicated or not indicated).

Pericardial tamponade appears to be a very uncommon condition in combat casualties; the exact incidence is unknown. It seems likely that when it occurs, it would be rare to find all elements of Beck's triad present. It is probable that in combat casualties, pericardial tamponade would usually be combined with some degree of hemorrhagic shock and/or pre-existing hypovolemia from dehydration. The incidence of hemorrhage shock, as a cause of fluid-unresponsive hypotension, is certainly much higher than the incidence of pericardial tamponade.

All of this raises the likelihood that, if the above guidelines are followed, that pericardiocentesis will be performed many times more often than required. Thus a potentially large number of patients who

would not benefit from the procedure (assuming that any would benefit) would be exposed to the risks of iatrogenic injury (pneumothorax, inducing pericardial tamponade, and inducing potentially fatal cardiac arrhythmias).

If there were evidence that performing pericardiocentesis at or near the point of wounding would benefit patients with pericardial tamponade, it might still be reasonable to recommend the procedure, inherent risks notwithstanding; unfortunately there is not.

When Dr. Ken Mattox, a contemporary leading trauma surgeon, was asked whether he would recommend the performance of pericardiocentesis by combat medics at or near the point of wounding, he said that he would not. Absent almost immediate surgical correction of the underlying condition, Dr. Mattox did not feel that pericardiocentesis would improve survival (personal conversation with author circa 1999).

Without clear benefit, only the risks remain, so until clear evidence of benefit is found, pericardiocentesis should not be performed at, or near the point of wounding. A small bolus of fluid, however, may help improve cardiac output in a patient with cardiac tamponade because increasing the preload will help overcome the resistance to distention of the left ventricle.

Blunt trauma to the chest can cause dysrhythmias and/or can produce a cardiac contusion with resultant impaired cardiac function, both of which can lead to reduced cardiac output and, in some cases, cardiogenic shock. These rarely occur on the battlefield, which is fortunate because it is generally not possible for combat medics to diagnose or treat casualties with these conditions. In the proper settings,

prehospital personnel should consider cardiogenic shock in the differential of a combat casualty with hypotension.

Neurogenic Shock (Spinal Cord Shock)

In the civilian setting, the great majority of spinal column injuries are caused by blunt trauma, with about 45% being caused by motor vehicle crashes, 20% by falls, and 15% by sporting accidents. Only 15% are due to penetrating trauma.[258] In the Soviet combat experience in World War II, over 99% of all spine injuries were caused by penetrating wounds – a significant difference.[259] The exact incidence of spine injury in combat casualties is difficult to ascertain as a significant number of casualties with such an injury die at, or near, the point of wounding. In World War II only 1.5% of casualties arriving alive at a general hospital had spinal cord injuries.[260] More recently, during the Vietnam War, it was found that approximately 13% of all combat casualties have, among their injuries, a penetrating neck wound[261] – but only a relatively small percentage of these have an injury to the spine, and even a smaller number have an injury to the cord. Due to the increased use of body armor and the associated relative decrease in the numbers of penetrating combat injuries, the relative percentage of combat-associated blunt trauma spinal cord injuries from falls and vehicle and aircraft crashes is likely to rise in more modern conflicts.

Neurogenic shock, in which the normal vasomotor tone derived from sympathetic afferent nerves is lost and blood pressure drops, can occur in both partial and complete spinal cord injury from both blunt and penetrating causes. Some data suggest that neurogenic shock is more likely to

occur from blunt than from penetrating injury.[258]

Traumatic spinal cord injury is associated with significant alterations in blood pressure, pulse rate, and cardiac rhythm. The immediate, acute response, to spinal cord injury is a systemic pressor response with a widened pulse pressure. This occurs within a few seconds of injury and persists for several minutes. Activation of the sympathetic nervous system and adrenal medulla is responsible for this initial, transient, pressor response.[262] This hypertensive response is often followed by a prolonged hypotensive phase (neurogenic shock) caused by an interruption of neuronal sympathetic activity.

Because the sympathetic nerves exit from above L-1, any patient with a spinal cord injury above that level could potentially have some degree of neurogenic shock. The sympathetic cardiac nerves exit the spinal cord between C-1 and T-5, so cord injury at or above T-5 may be associated with significant bradycardia that may further worsen any hypotension. Bradycardia may also be caused by a trauma-induced reflex parasympathetic discharge. Cardiovascular instability can persist for days to weeks.[263]

Sympathetic tone is most important to maintaining the blood pressure in the erect position so in the wounded supine/prone casualty, the loss of sympathetic tone has a less of an effect on tissue perfusion than might be anticipated. Most studies of neurogenic shock define hypotension as being present when systolic blood pressure is < 100 mm Hg, yet systolic blood pressure > 90 mm Hg is certainly adequate for tissue perfusion; the currently recommended threshold for volume-resuscitation of patients with uncontrolled hemorrhagic shock is systolic blood pressure < 85 mm Hg.

In a study by Zipnick et al of patients with penetrating spinal cord injuries primarily from gunshot wounds, only 5 of 75 patients (6.6%) with penetrating spinal cord injury had clear-cut, isolated, hypotension that could be attributed to neurogenic shock. Although most patients (78%) had complete spinal cord injury, only 18 (24%) were hypotensive in the field; an additional 5 patients developed hypotension after reaching the emergency department (hypotension was defined in this study as systolic blood pressure < 100 mm Hg) for a total of 23.[258] Of these, 18 had significant blood loss to explain their hypotension. Patients with cervical and upper thoracic injuries had significantly lower heart rates in the emergency department than did those with lower cord injury, but the lowest mean heart rate was 71 beats per minute.

Patients with cervical and upper thoracic spine injuries did not have a greater risk of initial hypotension; in fact, patients with lumbar cord injuries were most likely to be hypotensive, presumably because of a higher amount of blood loss. The authors noted that, *"Whereas patients with blunt spinal cord injuries are at risk for concomitant blood loss injuries, 70% of those with hypotension have neurogenic shock. This is far different in patients with penetrating spinal cord shock injuries in whom pure neurogenic shock is relatively rare."[258]*

Casualties in neurogenic shock, while suffering from the same basic underlying pathology of inadequate tissue perfusion that is present in all the other forms of shock, are different from those with some degree of hypovolemia in that there is no vasoconstriction (indeed this is the underlying problem). Replacement of vasoconstriction with vasodilation means that clinically, patients in neurogenic shock have warm, pink, dry skin instead of cold, cyanotic, moist skin. Other clues to a diagnosis of neurogenic shock, aside from hypotension with warm dry skin, are varying degrees of paralysis, and, if the spinal lesion is above C-5, some degree of respiratory difficulty that varies from abdominal (diaphragmatic) breathing to apnea.

From the perspective of the healthcare provider resuscitating the combat casualty at or near the point of wounding, the question is, "Does it matter, in terms of fluid resuscitation, if the casualty has a spinal cord injury and may have neurogenic shock?" The answer is, "Probably not." First, it should be assumed that all combat casualties, irrespective of mechanism, have ongoing hemorrhage. Zipnick et al. conclude their study with the comment that, *"Patients with early hypotension following penetrating spinal injury should be assumed to have a major blood loss injury...hypotension should not be ascribed to spinal cord injury until an exhaustive search for blood loss is completed and is clearly negative".[258]* This comment is applicable to victims of blunt trauma as well. Second, the current combat medic resuscitation protocol fluid resuscitation is dictated by mental status changes, the presence or absence of a radial pulse, and response to a fluid challenge. This protocol is reasonable for the casualty with neurogenic shock as well because the most important objective, in the short term, is to maintain adequate cerebral perfusion. Because the initial assumption should be that hypotension in a combat casualty with a possible cord injury is the result of hemorrhage, if fluid resuscitation is indicated, the type of fluid used should be the same as that recommended for hemorrhagic shock.

Given the underlying pathophysiology in neurogenic shock, it would seem reasonable to suggest using the PASG, if one is

available, because the PASG mechanically increases afterload. The problem is, as has been pointed out, that even when neurogenic shock is present, there is often concomitant hemorrhagic shock, often with uncontrolled blood loss, and the PASG is contraindicated in such a circumstance.

Furthermore the literature fails to demonstrate the efficacy of PASG to treat neurogenic shock. There is one situation in which it would still seem reasonable to recommend PASG in the management of a patient with presumed neurogenic shock, and that is in any circumstance in which such a patient would be lifted in a head-up configuration during extraction or evacuation, such as might occur during Stokes litter evacuation of a casualty onboard ship or in urban terrain. In this situation, a patient who might have been maintaining quite adequate cerebral perfusion while in the supine position could suffer a catastrophic drop in pressure when placed in a head-up position during evacuation. The PASG, by providing external compression, could counter the hypotension caused by venous pooling during a head-up evacuation.

Anaphylactic Shock

Although anaphylactic shock can certainly occur in the forward battle area from a wide range of etiologies, it is exceedingly unlikely that it would occur as a direct result of enemy action so it will not be discussed here beyond noting that it can occur as a result of medications administered to combat casualties.

Septic Shock

Although septic shock certainly may occur in combat casualties it generally occurs days after wounding and so would rarely be a cause of shock that would be treated at, or near, the point of wounding. In the case of penetrating abdominal wounds septic shock may, however, occur in less than 24 hours in some instances. In a study by Klein et al. [264] there were eighty-eight episodes of wound associated infection identified among 624 consecutively admitted battlefield casualties. Ninety-one per cent of infections occurred despite administration of a prophylactic antibiotic and in 65% of cases multiple antibiotics were being administered; so early antibiotic administration does not eliminate the risk of septic shock. In fact the practice of antibiotic wound prophylaxis may, overall, have a negative effect on battlefield wound infections by doing little-to-nothing to prevent them and by increasing the risk of infection with a resistant organism.

In a setting such as occurred during the Afghanistan conflict in the 1980's in which the International Committee of the Red Cross (ICRC) ran hospitals for the wounded that were some distance from the fighting in Pakistan, the wounded might take many days to arrive. In such a situation it is certainly possible for wounds to become infected and for septic shock to occur prior to hospital treatment. It was found in that during this conflict wounds sutured in the field tended to putrefy [265] and in this kind of a setting septic shock may be seen.

Thankfully septic shock is extremely rare on the modern battlefield due to reasonably rapid evacuation of casualties. When evacuation is much delayed, for whatever reason, septic shock certainly can occur in patients before they reach a hospital. Septic shock occurs when exotoxins (gram-positive toxic shock) or endotoxins (gram negative sepsis), enter the systemic circulation causing hypovolemia, cardiovascu-

lar depression, and systemic inflammation. Lipopolysaccharide's, contained in the cell wall of gram-negative bacteria, are one of the major causes of septic shock but gram-positive organisms can also cause septic shock and recently there has been a rise in the number of cases of sepsis in hospitalized patients caused by gram-positive organisms.[266, 267]

Hypotension in septic shock results from hypovolemia, inflammatory-mediated vasodilation, and cardiac depression. The hypovolemia of septic shock is both absolute, from gastrointestinal volume losses, sweating, and decreased oral intake, and relative from capillary leak and third spacing. Inflammatory-mediated vasodilation causes pooling of blood in the vascular bed similar to that occurring in neurogenic shock. Septic shock depresses cardiac function even early in the course of septic shock and eventually results in decreased cardiac output further worsening hypoten-

sion. Hypoxemia from capillary leak-induced acute respiratory distress syndrome (ARDS) and pneumonia and/or pulmonary aspiration, worsens the problem of hypoperfusion in septic shock. Very large volumes of fluids may be required to resuscitate a patient in septic shock. Fluid resuscitation should be continued until the mean arterial pressure is above 60 mm Hg, urine flow is adequate, and mentation is improving. Unlike most other forms of shock in which inotropic drugs that increase myocardial contractility and vasoconstricting drugs that increase systemic vascular resistance are generally either useless or contraindicated, in septic shock both may be helpful. Broad spectrum antibiotics are indicated but the management of septic shock in combat casualties usually involves the excision of necrotic and infected tissue so urgent evacuation to a surgical facility is the most important factor.

Summary

The ability to prevent exsanguination and to recognize and treat hemorrhagic shock is fundamental to quality point-of-wounding care. The single most important factor is the training of prehospital personnel of all skill levels. As important as knowing what to do for the combat casualty, is knowing what *not* to do. It is especially important to emphasize to prehospital personnel, who are by nature action-oriented, that each medical intervention carries with it some degree of risk. They must also understand that the relative value of each intervention varies with the frequency of the condition(s) for which the intervention(s) is/are being performed. If a condition is unlikely to be present in a patient, any intervention intended to treat

that condition will expose the patient to risk with little hope of benefit. Because it is not possible to train prehospital personnel to make individual risk-benefit analyses at the point of wounding, their training must be protocol driven and those protocols must be evidence-based.

There must also be discipline in the system to ensure that the protocols are being followed, and this requires some degree of inspection and oversight. Today, unlike in many areas of the civilian sector, care provided by prehospital personnel in support of military operations is not monitored for quality assurance. In most instances, no one evaluates the medical decisions and interventions that are made at

or near the point of wounding. This needs to be done in both peace and war because without such evaluation, real improvements in care are unlikely to occur.
Prehospital personnel must be able to recognize quickly and reliably the patient who is in shock or likely to go into shock. As noted above, this is no easy task. To accurately diagnose shock, it is necessary to integrate a wide range of data from mechanism of injury, anatomic location of wounding, general appearance and behavior of the patient, and physiologic data gathered over time. As previously stated, there is no single test that is pathognomic for shock. Each of the generally recommended tests -- blood pressure, pulse, capillary refill, orthostatic vital signs, and hemoglobin/hematocrit -- lack both the sensitivity and specificity necessary to reliably diagnose shock at or near the point of wounding. In the proper setting, an increase in both rate and depth of respirations and increasing thirst in a combat casualty should be considered evidence of shock until proven otherwise – the value of these findings in diagnosing shock is often under-appreciated.

None of this is to suggest that any of the other tests for shock lack value. Their value lies in being used both in conjunction with other findings that would suggest shock and in being used repeatedly over time. When used to create a pattern or to define a trend, these tests can effectively be used to diagnose shock. Unfortunately in many cases, the combat lifesaver, medic or corpsman that is usually present at or near the point of wounding often has neither the training, equipment, nor time to, quickly and accurately diagnose shock. Furthermore, the circumstances of combat often render this impossible even when the capability exists. This means that prehospital personnel must be taught that when there is any question about the possibility

of shock, they should manage the patient as if shock were present.

The single most important treatment for a patient in hemorrhagic shock is to stop the bleeding – *all bleeding* if possible. All else, in some instances even the airway, are of secondary importance. Without hemoglobin to carry oxygen, a patent airway is of little use. Hemorrhage control must be achieved as quickly as possible, utilizing whatever technique or techniques are both effective and medically and tactically appropriate. Ideally, methods such as direct pressure, use of pressure points, and elevation of bleeding extremities should be attempted initially.

Immediate use of a tourniquet is indicated if there is exsanguinating arterial hemorrhage in an extremity, or if the tactical circumstances preclude the application of less harmful, but more time and resource consuming, methods. The continued need for a tourniquet that has been applied as a temporizing measure *must* be re-evaluated at the earliest possible time and if other methods are capable of controlling hemorrhage, the tourniquet should be removed. The question of whether or not tourniquets should be periodically loosened to allow for some distal blood flow needs to be studied, but the experience during World War II was that this practice was implicated in enough combat deaths that it was stopped. Unless good studies show real benefit and unless training, procedures, and new equipment can ensure that the World War II experience with this practice will not be repeated, it should not be advocated.

The non-pneumatic strap tourniquet (NSN 6515-00-383-0565) that has been in the Army inventory since at least World War II *must* be removed and replaced. How many times is it necessary to prove that this tourniquet is ineffective? Finding an

effective replacement should continue to be a high priority medical research effort. Prehospital medical personnel must be trained to effectively apply tourniquets and they must be trained to fully understand the risks and implications of tourniquet application.

Ancillary methods of hemorrhage control such as the use of a dry fibrin sealant dressing, QuikClot™, the chitosin dressing, and/or the BioHemostat dressing may significantly improve the ability of prehospital personnel to control hemorrhage in a combat environment, but this needs to be proven. Most importantly, enthusiasm for these new hemorrhage control devices should not cause prehospital personnel to abandon conventional and proven methods of hemorrhage control or to preferentially use these new and, as yet, largely unproven devices. The reported case, during Operation Iraqi Freedom, of a Marine with a femoral artery injury, who was treated with QuikClot™ first and then a tourniquet is most disconcerting. Although the exact details of this incident are unknown, it appears that QuikClot™ was used as the initial hemorrhage control method, when instead a tourniquet should have been applied. Unfortunately, the Marine died. There is no way of knowing whether he would have survived had the first intervention been to apply a tourniquet, but given the available information it at least seems possible.

After all controllable hemorrhage has ceased, the next question is fluid resuscitation. Is it needed at all and if so, how much and what kind? It is appropriate, for a variety of reasons, that all combat casualties with more than trivial injuries have vascular access established. Intravascular or intraosseous access should be obtained. Intravascular cannulation should be established with a short, at least an 18-gauge or larger, catheter, and this should be set up

as a saline lock that can be used for drug and/or fluid administration as required. Intraosseous access can be obtained either through the medial malleolus with the Bone Injection Gun (BIG®), the VidaPort® system, or similar devices, or through the sternum with the Pyng F.A.S.T.® intraosseous infusion device or other similar device. These devices are generally easy to use, and a properly trained person can obtain intraosseous access in under a minute. Both drugs and fluids can be administered through the intraosseous route, but because of the resistance to flow, fluids cannot be administered as rapidly through the intraosseous route as through the intravenous route.

The current recommended fluid resuscitation protocol promulgated by COL Holcomb for the AMEDD Center & School 91W Health Care Specialist program, which is very similar to that recommended by Beecher et al. in World War II [16] seems reasonable and, in general, is supported by scientific evidence. For patients with ongoing hemorrhage that is uncontrollable in the prehospital setting, low volume, "hypotensive" resuscitation is recommended. How low, for how long, remains to be determined. The key to survival in such patients is rapid evacuation to a location where surgical control of hemorrhage can be achieved.

Although Hextend® or any other similar colloidal solution is recommended for management of hemorrhagic shock, for the reasons previously stated (weight and cube issues primarily), this recommendation may not be optimum for the following reasons:

1. There is no scientific evidence that these resuscitation fluids, when compared with normal saline or Ringers lactate, improve survival in

hemorrhagic shock (in fact there is some evidence to the contrary).

2. The efficacy and safety of these fluids in the management of dehydration of all causes (burn, heat injury, gastrointestinal loss, etc…) and for the treatment of other conditions for which intravenous fluids might be indicated (or used) is unknown.

3. These colloidal solutions are very expensive as compared to crystalloids. Because, in many instances, aggressive fluid resuscitation of combat casualties is now recognized as ill-advised, the need to carry large quantities of fluids is not as great as previously thought, so the weight and cube issue is, perhaps, not as important as it was before. However, because it is unlikely that the selection of one intravenous fluid over another will significantly alter the survival of combat casualties, this should not be allowed to become a contentious issue.

The question remains as to what role hypertonic saline dextran might play in the management of combat casualties. Hypertonic saline dextran is currently being evaluated in human trauma trials. Because of its demonstrable ability to improve outcomes in head-injured patients, plus its ability to rapidly expand the intravascular bed when given through intraosseous access and when given in small volumes, hypertonic saline dextran may ultimately be the single fluid of choice in combat casualty care. Unfortunately, many of the same concerns raised about Hextend®, Hespan®, and other colloidal solutions apply to hypertonic saline dextran as well. Until these concerns can be addressed with good scientific studies, there should be no rush to embrace this resuscitation fluid. One or more of the new oxygen-

carrying, hemoglobin-based, resuscitation fluids may prove effective in the treatment of hemorrhagic shock on the battlefield. This has yet to be proven but there is great promise in these new fluids that minimize or eliminate many of the risks and logistical difficulties associated with blood transfusion while preserving oxygen-carrying capability.

The basic underlying defect in all forms of shock is inadequate tissue perfusion. The new solutions will be able to directly address this defect. It is hoped that the introduction of such a solution or solutions will not have the same effect that the introduction of saline had in causing surgeons [or in this instance, prehospital personnel] to become cavalier about hemorrhage control. Kim Pelis, in her article, *Blood Standards and Failed Fluids: Clinic, Lab, and Transfusion Solutions in London, 1868-1916*, notes that following the introduction of saline to treat blood loss, "Surgeons, with…unrestrained operative enthusiasm…spilled great quantities of blood [that was] conveniently replaced with a few to several pints of saline solution."[48] It is virtually certain that no matter how good these oxygen-carrying solutions become, they will never be as good as the patient's own blood. Most assuredly, the patient does best if his or her own blood is retained, if not by preventing hemorrhage in the first instance, then by returning it into the circulation after it has been lost.

Autotransfusion of blood drained from chest tubes appears to be done infrequently in most forward areas for a variety of reasons. Given that this procedure is demonstrably efficacious, relatively easy to do, and logistically supportable, this practice should probably be done more often when clinically indicated. Finally, there is the question of far forward administration of blood. The numerous highly favorable comments about far for-

ward early administration of blood to combat casualties during the Spanish Civil War, World War II, and the Korean War and the more recent favorable comments about the near "miraculous" effect of whole blood when used to treat casualties in Mogadishu should give rise to questions as to why blood is rarely used today forward of a surgical facility. There are most certainly significant logistical and training challenges to far forward blood administration, but surely these are no more onerous than in the past and certainly technological advances have made them less so.

With regard to the management of types of shock other than hemorrhagic, it seems reasonable that only in the instance of burn shock, and perhaps in the unlikely instance of septic shock, should the above-described recommended fluid resuscitation protocol be altered. Burn patients are unique in that they have an ongoing fluid loss that cannot be medically or surgically controlled, and they require early, aggressive, and sustained fluid resuscitation. It is probably of no major consequence, in terms of outcomes, which of the generally accepted fluid resuscitation formulas for burns is used. Ringers lactate is the recommended fluid of choice for at least the first 8 hours in all of the widely accepted resuscitation protocols. In reality, the cir-

cumstances of combat make it unlikely that it will be possible to accurately estimate the percent of TBSA burn and even if this could be done accurately by a combat medic in the heat of combat or during evacuation it is unlikely, for a variety of reasons, that it would be possible to accurately administer the calculated amount of fluid. Most importantly, prehospital personnel need to know that seriously burned patients need early and relatively aggressive fluid resuscitation and, unless there is a contraindication (i.e. concomitant pulmonary blast injury and/or inhalation burn injury) at least two liters of Ringers lactate (or normal saline if Ringers lactate is not available) should be administered quickly and, if the evacuation is long, another liter should be administered. If intravenous access can't be obtained, these fluids should be given through intraosseous access. The total amount of administered fluid must be recorded and this information transmitted to the receiving medical treatment facility. As noted above, the World Health Organization oral rehydration solution may be an option for use in moderately burned combat casualties in whom intravenous fluid is not possible for any reason. Like badly burned patients, patients in septic shock may require substantial volumes of fluid.

References

1. *Beecher H. Early Care of the Seriously Wounded Man. JAMA. 1951;145(4):193-200.*

2. *Bailey H, ed. Surgery of Modern Warfare. 2nd ed. Edinburg: E & S Livingston; 1942; No. 1.*

3. *Gray CHM. The Early Treatment of War Wounds. London Warwick Square E.C.: Henry Frowde Hodder & Stoughton Oxford University Press; 1919.*

4. *Deitch EA, Fisher HR. Tools of the Trade and Rules of the Road: A Surgical Guide. Philadelphia: Lippincott Williams & Wilkins; 1997.*

5. *Bellamy RF. Death on the battlefield and the role of first aid . Military Medicine. 1987;152:634-635.*

6. *Bellamy R. Committee on Fluid Resuscitation for Combat Casualties, Institute of Medicine. Fluid Resuscitation: State of the Science for Treating Combat Casualties and Civilian Injuries. Washington, DC: National Academy Press; 1999.*

7. *Bellamy RF. The causes of death in conventional land warfare: implications for combat casualty care research. Mil Med. Feb 1984;149(2):55-62.*

8. *McNutt S, Denninghoff KR, T T. Shock: Rapid Recognition and ED Intervention. Emergency Medicine Practice. 2000;2(8):1 - 24.*

9. *Gross SD. Systems of Surgery: Pathological, diagnostic, therapeutique, and operative. Philadelphia: Lea & Febinger; 1872.*

10. *Britt LD, Weireter LJ, Jr., Riblet JL, Asensio JA, Maull K. Priorities in the management of profound shock. Surg Clin North Am. Aug 1996;76(4):645-660.*

11. *Warren JC. Surgical Pathology and Therapeutics. Philadelphia; 1895.*

12. *Beecher H, Simeone F, Burnett C, Shapiro S, Sullivan E, Mallory T. The Internal State of the Severely Wounded Man on Entry to the Most Forward Hospital. Surgery. Oct 1947 1947;22:676.*

13. *Marshall SLA. Men Against Fire: The Problem of Battle Command in Future War. Glouchester, MA: Peter Smith Publishers; 1978.*

14. *Cope Z. Surgery. In: Cope Z, ed. Shock and Resuscitation. London: Her Majesty's Stationary Office; 1953:78-88.*

15. *Capan LM MS. Trauma - Initial evaluation and resuscitation. Anesthesiol Clin N Amer. 1996;14:197-238.*

16. *Beecher HK. Preparation of battle casualties for surgery. Ann Surg. 1945;121:769-792.*

17. *Mackenzie CF. Anesthesia in the shocked patient. Internet [Internet]. Accessed 15 September, Accessed September 15, 2003.*

18. *Shoemaker WC, Wo CC, Bishop MH, Thangathurai D, Patil RS. Noninvasive hemodynamic monitoring of critical patients in the emergency department. Acad Emerg Med. Jul 1996;3(7):675-681.*

19. *O'Brien ET, Beevers DG, Marshall HJ. ABC of Hypertension. 3rd ed. London: BMJ Books; 1995.*

20. *O'Brien E, Mee F, Atkins N, O'Malley K. Inaccuracy of seven popular sphygmomanometers for home measurement of blood pressure. J Hypertens. Jul 1990;8(7):621-634.*

21. Moskowitz DM RD. Hemodynamic monitoring: Anesthesia for the cardiac patient. Anesthesia Clin N Amer. 1997;15:551-571.

22. Ramsey M. Noninvasive blood pressure monitoring methods and validation. In: Gravenstein JS NR, Ream AK, Smith NT,, ed. Essential Noninvasive Monitoring in Anesthesia. New York: Grune and Stratton; 1980:37-51.

23. Creamer JE, Edwards JD, Nightingale P. Hemodynamic and oxygen transport variables in cardiogenic shock secondary to acute myocardial infarction, and response to treatment. Am J Cardiol. Jun 1 1990;65(20):1297-1300.

24. Beecher HK. Resuscitation of men severely wounded in battle. In: Coates JB Jr. DM, Giddings WP, McFetridge EM,, ed. Surgery in World War II: General Surgery. Vol 2. Washington, DC: Medical Department of the US Army in World War II, Office of the Surgeon General; 1955:3-39.

25. Snyder HS. Lack of a tachycardic response to hypotension with ruptured ectopic pregnancy. Am J Emerg Med. Jan 1990;8(1):23-26.

26. Hick JL, Rodgerson JD, Heegaard WG, Sterner S. Vital signs fail to correlate with hemoperitoneum from ruptured ectopic pregnancy. Am J Emerg Med. Oct 2001;19(6):488-491.

27. Thompson D, Adams SL, Barrett J. Relative bradycardia in patients with isolated penetrating abdominal trauma and isolated extremity trauma. Ann Emerg Med. Mar 1990;19(3):268-275.

28. Vayer JS, Henderson JV, Bellamy RF, Galper AR. Absence of a tachycardic response to shock in penetrating intraperitoneal injury. Ann Emerg Med. Mar 1988;17(3):227-231.

29. Snyder HS, Dresnick SJ. Lack of tachycardic response to hypotension in penetrating abdominal injuries. J Emerg Med. Jul-Aug 1989;7(4):335-339.

30. Barriot P, Riou B. Hemorrhagic shock with paradoxical bradycardia. Intensive Care Med. 1987;13(3):203-207.

31. Adams SL, Greene JS. Absence of a tachycardic response to intraperitoneal hemorrhage. J Emerg Med. 1986;4(5):383-389.

32. Little RA. 1988 Fitts lecture: heart rate changes after haemorrhage and injury--a reappraisal. J Trauma. Jul 1989;29(7):903-906.

33. Deakin CD, Low JL. Accuracy of the advanced trauma life support guidelines for predicting systolic blood pressure using carotid, femoral, and radial pulses: observational study. Bmj. Sep 16 2000; 321 (7262): 673-674

33. Baraff LJ, Schriger DL. Orthostatic vital signs: variation with age, specificity, and sensitivity in detecting a 450-mL blood loss. Am J Emerg Med. Mar 1992;10(2):99-103.

34. Koziol-McLain J, Lowenstein SR, Fuller B. Orthostatic vital signs in emergency department patients. Ann Emerg Med. Jun 1991;20(6):606-610.

35. Levitt MA, Lopez B, Lieberman ME, Sutton M. Evaluation of the tilt test in an adult emergency medicine population. Ann Emerg Med. Jun 1992;21(6):713-718.

36. Dabrowski GP, Steinberg SM, Ferrara JJ, Flint LM. A critical assessment of endpoints of shock resuscitation. Surg Clin North Am. Jun 2000;80(3):825-844.

37. Witting MD, Wears RL, Li S. Defining the positive tilt test: a study of healthy adults with moderate acute blood loss. Ann Emerg Med. Jun 1994;23(6):1320-1323.

38. Schriger DL, Baraff L. Defining normal capillary refill: variation with age, sex, and temperature. Ann Emerg Med. Sep 1988;17(9):932-935.

39. Knopp RK. Capillary refill: new concerns about an old bedside test. Ann Emerg Med. Sep 1988;17(9):990-991.

40. Glick YA, Wilson LD, Aiello J. Hematocrit and metabolic changes caused by varied resuscitation strategies in a canine model of hemorrhagic shock. Am J Emerg Med. Jul 2002;20(4):303-309.

41. Knottenbelt JD. Low initial hemoglobin levels in trauma patients: an important indicator of ongoing hemorrhage. J Trauma. Oct 1991;31(10):1396-1399.

42. Scalia S, Burton H, Van Wylen D, et al. Persistent arteriolar constriction in microcirculation of the terminal ileum following moderate hemorrhagic hypovolemia and volume restoration. J Trauma. Jun 1990;30(6):713-718.

43. O'Shaughnessy WB. Proposal for a new method of treating the blue epidemic cholera. Lancet. 1830;1:366.

44. Foex BA. REVIEW How the cholera epidemic of 1831 resulted in a new technique for fluid resuscitation. Emerg Med J. 2003;20(316-318).

45. Cosnett JE. The origins of intravenous fluid therapy. Lancet. 1989;1:768-771.

46. O'Shaughnessy WB. Letter. Lancet. 1832;ii:281.

47. Jennings CE. On Transfusion of Blood and Saline Fluids , Author's preface to the second edition". 2nd Rev. ed. London; 1883.

48. Pelis K. Blood Standards and Failed Fluids: Clinic, Lab, and Transfusion Solutions in London, 1868-1916. Hist Sci 2001. 2001;39:185-213.

49. American College of Surgeons Committee On Trauma. Advanced Trauma Life Support Program for Physicians. Chicago, IL: American College of Surgeons; 1997.

50. Wiggers CJ. Physiology of Shock. New York, NY: Commonwealth Fund; 1950.

51. Bickell WH, Wall MJ, Jr., Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. N Engl J Med. Oct 27 1994;331(17):1105-1109.

52. Martin RR, Bickell WH, Pepe PE, Burch JM, Mattox KL. Prospective evaluation of preoperative fluid resuscitation in hypotensive patients with penetrating truncal injury: a preliminary report. J Trauma. Sep 1992;33(3):354-361; discussion 361-352.

53. Cannon W FJ, Cowell E,. Preventive treatment of wound shock. JAMA. 1918;70:618.

54. Jolly DW. Field Surgery in Total War. New York: Paul B Hoeber, Inc., Medical Book Department of Harbor & Brothers; 1939.

55. Beecher H. Notes on the History of Resuscitation in the Mediterranean Theater of Operations. Surg Gynec Obst. May 1947;84:989-996.

56. Bickell WH, Bruttig SP, Millnamow GA, O'Benar J, Wade CE. The detrimental effects of intravenous crystalloid after aortotomy in swine. Surgery. Sep 1991;110(3):529-536.

57. Dronen SC, Stern SA, Wang X, Stanley M. A comparison of the response of near-fatal acute hemorrhage models with and without a vascular injury to rapid volume expansion. Am J Emerg Med. Jul 1993;11(4):331-335.

58. Owens TM, Watson WC, Prough DS, Uchida T, Kramer GC. Limiting initial resuscitation of uncontrolled hemorrhage reduces internal bleeding and subsequent volume requirements. J Trauma. Aug 1995;39(2):200-207; discussion 208-209.

59. Kim SH, Stezoski SW, Safar P, Capone A, Tisherman S. Hypothermia and minimal fluid resuscitation increase survival after uncontrolled hemorrhagic shock in rats. J Trauma. Feb 1997;42(2):213-222.

60. Soucy DM, Rude M, Hsia WC, Hagedorn FN, Illner H, Shires GT. The effects of varying fluid volume and rate of resuscitation during uncontrolled hemorrhage. J Trauma. Feb 1999;46(2):209-215.

61. Leppaniemi A, Soltero R, Burris D, et al. Fluid resuscitation in a model of uncontrolled hemorrhage: too much too early, or too little too late? J Surg Res. Jul 1 1996;63(2):413-418.

62. Burris D, Rhee P, Kaufmann C, et al. Controlled resuscitation for uncontrolled hemorrhagic shock. J Trauma. Feb 1999;46(2):216-223.

63. Wiedeman JE, Rignault DP. Civilian versus military trauma dogma: who do you trust? Mil Med. Apr 1999;164(4):256-260.

64. Henry S, Scalea TM. Resuscitation in the new millennium. Surg Clin North Am. Dec 1999;79(6):1259-1267, viii.

65. Landers DF DK. Trauma -- Vascular access and fluid resuscitation in trauma: Issues of Blood and Blood Products. Anesthesiology Clinics of North America. 1999;17(1):125-139.

66. Holcomb JB. Fluid resuscitation in modern combat casualty care: lessons learned from Somalia. J Trauma. May 2003;54(5 Suppl):S46-51.

67. Champion HR. Combat fluid resuscitation: introduction and overview of conferences. J Trauma. May 2003;54(5 Suppl):S7-12.

68. Stern SA, Dronen SC, Birrer P, Wang X. Effect of blood pressure on hemorrhage volume and survival in a near-fatal hemorrhage model incorporating a vascular injury. Ann Emerg Med. Feb 1993;22(2):155-163.

69. Kowalenko T, Stern S, Dronen S, Wang X. Improved outcome with hypotensive resuscitation of uncontrolled hemorrhagic shock in a swine model. J Trauma. Sep 1992;33(3):349-353; discussion 361-342.

70. Capone A, Safar P, Radovsky A, Wang YF, Peitzman A, Tisherman SA. Complete recovery after normothermic hemorrhagic shock and profound hypothermic circulatory arrest of 60 minutes in dogs. J Trauma. Mar 1996;40(3):388-395.

71. Dubick MA, Atkins JL. Small-volume fluid resuscitation for the far-forward combat environment: current concepts. J Trauma. May 2003;54(5 Suppl):S43-45.

72. Rhee P, Koustova E, Alam HB. Searching for the optimal resuscitation method: recommendations for the initial fluid resuscitation of combat casualties. J Trauma. May 2003;54(5 Suppl):S52-62.

73. Holcomb J. Algorithm for AMEDD Combat Fluid Resuscitation. http://www.drum.army.mil/sites/tenants/division/CMDGRP/SURGEON/journals/HYPOTENSIVE%20RESUSCITATION.htm. Accessed 16 November, 2005, 2005.

74. Prough DS. Practical solutions for difficult problems: Crystalloids versus colloids in the perioperative period. Anesthesiology Clinics of North America. 1996;14(2):341 - 368.

75. Bayliss WM. Methods of raising a low arterial pressure. Proc Royal Soc London. 1917;89:380-393.

76. Hogan J. The intravenous use of colloidal (gelatin) solutions in shock. JAMA. 1915;64:721-726.

77. Beecher HK BC, Shapiro SL, Simeone FA, Smith LD, Sullivan ER, Mallory TB,. The Physiologic Effects of Wounds. Washington D.C.: The Board for the Study of the Severely Wounded North African-Mediterranean Theater of Operations, Office of the Surgeon General, Department of the Army; 1952.

78. Velanovich V. Crystalloid versus colloid fluid resuscitation: a meta-analysis of mortality. Surgery. Jan 1989;105(1):65-71.

79. Choi PT, Yip G, Quinonez LG, Cook DJ. Crystalloids vs. colloids in fluid resuscitation: a systematic review. Crit Care Med. Jan 1999;27(1):200-210.

80. Traverso LW, Bellamy RF, Hollenbach SJ, Witcher LD. Hypertonic sodium chloride solutions: effect on hemodynamics and survival after hemorrhage in swine. J Trauma. Jan 1987;27(1):32-39.

81. Warner DS, Boehland LA. Effects of iso-osmolal intravenous fluid therapy on post-ischemic brain water content in the rat. Anesthesiology. Jan 1988;68(1):86-91.

82. Zornow MH, Scheller MS, Todd MM, Moore SS. Acute cerebral effects of isotonic crystalloid and colloid solutions following cryogenic brain injury in the rabbit. Anesthesiology. Aug 1988;69(2):180-184.

83. Zornow MH, Todd MM, Moore SS. The acute cerebral effects of changes in plasma osmolality and oncotic pressure. Anesthesiology. Dec 1987;67(6):936-941.

84. Pollack CV, Jr. Prehospital fluid resuscitation of the trauma patient. An update on the controversies. Emerg Med Clin North Am. Feb 1993;11(1):61-70.

85. Kendrick DB. Blood Program in World War II. Washington, DC: Medical Department of the US Army Office of the Surgeon General; 1964.

86. Battistella FD, Wisner DH. Combined hemorrhagic shock and head injury: effects of hypertonic saline (7.5%) resuscitation. J Trauma. Feb 1991;31(2):182-188.

87. Walsh JC, Zhuang J, Shackford SR. A comparison of hypertonic to isotonic fluid in the resuscitation of brain injury and hemorrhagic shock. J Surg Res. Mar 1991;50(3):284-292.

88. Gunn ML, Hansbrough JF, Davis JW, Furst SR, Field TO. Prospective, randomized trial of hypertonic sodium lactate versus lactated Ringer's solution for burn shock resuscitation. J Trauma. Sep 1989;29(9):1261-1267.

89. Jelenko C, 3rd, Williams JB, Wheeler ML, et al. Studies in shock and resuscitation, I: use of a hypertonic, albumin-containing, fluid demand regimen (HALFD) in resuscitation. Crit Care Med. Apr 1979;7(4):157-167.

90. Mattox KL, Maningas PA, Moore EE, et al. Prehospital hypertonic saline/dextran infusion for post-traumatic hypotension. The U.S.A. Multicenter Trial. Ann Surg. May 1991;213(5):482-491.

91. Monafo WW, Chuntrasakul C, Ayvazian VH. Hypertonic sodium solutions in the treatment of burn shock. Am J Surg. Dec 1973;126(6):778-783.

92. Shackford SR, Davis JW, Gunn ML, Hansbrough JF. Serum osmolar and electrolyte changes associated with hypertonic resuscitation. Prog Clin Biol Res. 1989;299:321-330.

93. Vassar MJ, Perry CA, Gannaway WL, Holcroft JW. 7.5% sodium chloride/dextran for resuscitation of trauma patients undergoing helicopter transport. Arch Surg. Sep 1991;126(9):1065-1072.

94. Vassar MJ, Perry CA, Holcroft JW. Analysis of potential risks associated with 7.5% sodium chloride resuscitation of traumatic shock. Arch Surg. Oct 1990;125(10):1309-1315.

95. Kramer GC, Perron PR, Lindsey DC, et al. Small-volume resuscitation with hypertonic saline dextran solution. Surgery. Aug 1986;100(2):239-247.

96. Smith GJ, Kramer GC, Perron P, Nakayama S, Gunther RA, Holcroft JW. A comparison of several hypertonic solutions for resuscitation of bled sheep. J Surg Res. Dec 1985;39(6):517-528.

97. Gross D, Landau EH, Klin B, Krausz MM. Quantitative measurement of bleeding following hypertonic saline therapy in 'uncontrolled' hemorrhagic shock. J Trauma. Jan 1989;29(1):79-83.

98. Gross D, Landau EH, Assalia A, Krausz MM. Is hypertonic saline resuscitation safe in 'uncontrolled' hemorrhagic shock? J Trauma. Jun 1988;28(6):751-756.

99. Krausz MM. Controversies in shock research: hypertonic resuscitation--pros and cons. Shock. Jan 1995;3(1):69-72.

100. Krausz MM, Landau EH, Klin B, Gross D. Hypertonic saline treatment of uncontrolled hemorrhagic shock at different periods from bleeding. Arch Surg. Jan 1992;127(1):93-96.

101. Guha SC, Kinsky MP, Button B, et al. Burn resuscitation: crystalloid versus colloid versus hypertonic saline hyperoncotic colloid in sheep. Crit Care Med. Nov 1996;24(11):1849-1857.

102. Landau EH, Gross D, Assalia A, Krausz MM. Treatment of uncontrolled hemorrhagic shock by hypertonic saline and external counterpressure. Ann Emerg Med. Oct 1989;18(10):1039-1043.

103. Phillips YY III, Zajtchuk JT, eds. Chapter 9 The management of primary blast injury. Washington DC: Department of the Army, Office of the Surgeon General and the Borden Institute; 1989. Bellamy RF, Zajtchuk R, eds. Textbook of Military Medicine Conventional Warfare: Ballistic, Blast, and Burn Injuries.

104. Wightman JM, Gladish SL. Explosions and blast injuries. Ann Emerg Med. Jun 2001;37(6):664-678.

105. Pepe PE, Eckstein M. Reappraising the prehospital care of the patient with major trauma. Emerg Med Clin North Am. Feb 1998;16(1):1-15.

106. Dubick MA, Kramer GC. Hypertonic saline dextran (HSD) and intraosseous vascular access for the treatment of haemorrhagic hypotension in the far-forward combat arena. Ann Acad Med Singapore. Jan 1997;26(1):64-69.

107. Spaite DW, Valenzuela TD, Meislin HW, Criss EA, Hinsberg P. Prospective validation of a new model for evaluating emergency medical services systems by in-field observation of specific time intervals in prehospital care. Ann Emerg Med. Apr 1993;22(4):638-645.

108. Spaite DW, Valenzuela TD, Criss EA, Meislin HW, Hinsberg P. A prospective in-field comparison of intravenous line placement by urban and nonurban emergency medical services personnel. Ann Emerg Med. Aug 1994;24(2):209-214.

109. Sadler R, Waxman K, Eisner ME, Mason GR. Comparative flow rates of intravenous catheters. Mil Med. Jul 1984;149(7):415-416.

110. Aeder MI, Crowe JP, Rhodes RS, Shuck JM, Wolf WM. Technical limitations in the rapid infusion of intravenous fluids. Ann Emerg Med. Apr 1985;14(4):307-310.

111. Guisto JA, Iserson KV. The feasibility of 12-gauge intravenous catheter use in the prehospital setting. J Emerg Med. Mar-Apr 1990;8(2):173-176.

112. Dubick MA, Holcomb JB. A review of intraosseous vascular access: current status and military application. Mil Med. Jul 2000;165(7):552-559.

113. Smith RJ, Keseg DP, Manley LK, Standeford T. Intraosseous infusions by prehospital personnel in critically ill pediatric patients. Ann Emerg Med. May 1988;17(5):491-495.

114. Valdes MM. Intraosseous fluid administration in emergencies. Lancet. Jun 11 1977;1(8024):1235-1236.

115. Iserson KV. Intraosseous infusions in adults. J Emerg Med. Nov-Dec 1989;7(6):587-591.

116. Drinker CK, Drinker KR, Lund CC. The circulation in the mammalian bone marrow. Am J Physiol. 1922;62:1-92.

117. Tocantins LM, O'Neill JF, Price AH. Infusions of blood and other fluids via the bone marrow in traumatic shock and other forms of peripheral circulation failure. Annals of Surgery. 1941;114:1085-1092.

118. Doug EA, Tysell JE. Massive intramedullary infusions. JAMA. 1942;120:1212-1213.

119. Turkel H. Transfusion by Way of Bone Marrow. International Medical Digest. February 1956 1956;68(February):11-14.

120. Olsen D, Packer BE, Perrett J, Balentine H, Andrews GA. Evaluation of the bone injection gun as a method for intraosseous cannula placement for fluid therapy in adult dogs. Vet Surg. Nov-Dec 2002;31(6):533-540.

121. Calkins MD, Fitzgerald G, Bentley TB, Burris D. Intraosseous infusion devices: a comparison for potential use in special operations. J Trauma. Jun 2000;48(6):1068-1074.

122. Halvorsen L, Bay BK, Perron PR, et al. Evaluation of an intraosseous infusion device for the resuscitation of hypovolemic shock. J Trauma. Jun 1990;30(6):652-658; discussion 658-659.

123. Macnab A, Christenson J, Findlay J, et al. A new system for sternal intraosseous infusion in adults. Prehospital Emergency Care. 2000;4(173-177).

124. Macnab A. A new system for sternal intraosseous infusion in adults. Prehosp Emerg Care. 2000;4:173-177.

125. Chavez-Negrete A, Majluf Cruz S, Frati Munari A, Perches A, Arguero R. Treatment of hemorrhagic shock with intraosseous or intravenous infusion of hypertonic saline dextran solution. Eur Surg Res. 1991;23:123-129.

126. Heinild S, Sondergaard T, Tudvad F. Bone marrow infusion in childhood: Experiences-from a thousand infusions. J Pediatr. 1947;30:400-412.

127. Orlowski JP, Julius CJ, Petras RE, Porembka DT, Gallagher JM. The safety of intraosseous infusions: risks of fat and bone marrow emboli to the lungs. Ann Emerg Med. Oct 1989;18(10):1062-1067.

128. Fisher R, Prosser D. Intraosseous access in infant resuscitation. Arch Dis Child. Jul 2000;83(1):87.

129. LaSpada J, Kissoon N, Melker R, Murphy S, Miller G, Peterson R. Extravasation rates and complications of intraosseous needles during gravity and pressure infusion. Crit Care Med. Dec 1995;23(12):2023-2028.

130. Sawyer RW, Bodai BI, Blaisdell FW, McCourt MM. The current status of intraosseous infusion. J Am Coll Surg. Sep 1994;179(3):353-360.

131. Alam HB, Punzalan CM, Koustova E, Bowyer MW, Rhee P. *Hypertonic saline: intraosseous infusion causes myonecrosis in a dehydrated swine model of uncontrolled hemorrhagic shock. J Trauma.* Jan 2002;52(1):18-25.

132. Lawrence DW, Lauro AJ. *Complications from i.v. therapy: results from field-started and emergency department-started i.v.'s compared. Ann Emerg Med.* Apr 1988;17(4):314-317.

133. Rosovsky M, FitzPatrick M, Goldfarb CR, Finestone H. *Bilateral osteomyelitis due to intraosseous infusion: case report and review of the English-language literature. Pediatr Radiol.* 1994;24(1):72-73.

134. Coupland R, Molde A, Navein J. *A Report from the Workshop Organized by the ICRC on "Pre-hospital Care for War and Mine Wounded".* Geneva Switzerland: International Committee of the Red Cross; 2001.

135. Splinter WM, Schaefer JD. *Unlimited clear fluid ingestion two hours before surgery in children does not affect volume or pH of stomach contents. Anaesth Intensive Care.* Nov 1990;18(4):522-526.

136. Splinter WM, Schaefer JD, Zunder IH. *Clear fluids three hours before surgery do not affect the gastric fluid contents of children. Can J Anaesth.* Jul 1990;37(5):498-501.

137. *Evaluation and preparation of pediatric patients undergoing anesthesia. American Academy of Pediatrics. Section on Anesthesiology. Pediatrics.* Sep 1996;98(3 Pt 1):502-508.

138. Ferrari LR, Rooney FM, Rockoff MA. *Preoperative fasting practices in pediatrics. Anesthesiology.* Apr 1999;90(4):978-980.

139. O'Sullivan G, Scrutton M. *NPO during labor. Is there any scientific validation? Anesthesiol Clin North America.* Mar 2003;21(1):87-98.

140. Regan F, Taylor C. *Blood transfusion medicine. Bmj.* Jul 20 2002;325(7356):143-147.

141. Linden JV, Wagner K, Voytovich AE, Sheehan J. *Transfusion errors in New York State: an analysis of 10 years' experience. Transfusion.* Oct 2000;40(10):1207-1213.

142. Krombach J, Kampe S, Gathof BS, Diefenbach C, Kasper SM. *Human error: the persisting risk of blood transfusion: a report of five cases. Anesth Analg.* Jan 2002;94(1):154-156, table of contents.

143. Williamson LM, Lowe S, Love E, et al. *SERIOUS HAZARDS OF TRANSFUSION ANNUAL REPORT 1997 - 1998 1999.*

144. Dolev E. *Medical services in the Lebanon War, 1982: an overview. Isr J Med Sci.* Apr 1984;20(4):297-299.

145. Noy-Man Y, Hornung S, Barbash G, Margaliot S. *Medical air evacuation during the Lebanon War, 1982. Isr J Med Sci.* Apr 1984;20(4):303-304.

146. Barkana Y, Stein M, Maor R, Lynn M, Eldad A. *Prehospital blood transfusion in prolonged evacuation. J Trauma.* Jan 1999;46(1):176-180.

147. Gordon S, Allan T. *The Scalpel, The Sword.* Toronto: McClelland & Stewart; 1989.

148. Franco A, Cortes J, Alvarez J, Diz JC. *The development of blood transfusion: the contributions of Norman Bethune in the Spanish Civil War (1936-1939). Can J Anaesth.* Oct 1996;43(10):1076-1078.

149. Kendrick D. *Medical Department United States Army in World War II, Blood Program in World War II. In: Coates J, ed. Medical Department United States Army in World War II.* Washington, D.C.: Office of the Surgeon General, Department of the Army; 1964:364.

150. Hall K, Dronen S, Syverud S. The use of packed red cells in the field: Does it make a difference? Ann Emerg Med. April 1990 1990;19(4):449.

151. Vincent JL, Baron JF, Reinhart K, et al. Anemia and blood transfusion in critically ill patients. Jama. Sep 25 2002;288(12):1499-1507.

152. Zallen G, Offner PJ, Moore EE, et al. Age of transfused blood is an independent risk factor for postinjury multiple organ failure. Am J Surg. Dec 1999;178(6):570-572.

153. Moore FA, Moore EE, Sauaia A. Blood transfusion. An independent risk factor for postinjury multiple organ failure. Arch Surg. Jun 1997;132(6):620-624; discussion 624-625.

154. Aiboshi J, Moore EE, Ciesla DJ, Silliman CC. Blood transfusion and the two-insult model of postinjury multiple organ failure. Shock. Apr 2001;15(4):302-306.

155. Holcomb J, Army CU. Personal Correspondence August 2003 - Comment on Dry Fibrin Sealant Dressing. In: COL Clifford C. Cloonan IC, Dept. of Military and Emergency Medicine Uniformed Services University of the Health Sciences, ed; 2003.

156. Mosebar RH, Directorate of Combat and Doctrine Development, AMEDD Center and School, Fort Sam Houston, San Antonio, Texas. Personal Communication - Use of fresh whole blood in U.S. combat casualties. COL Clifford C. Cloonan, Interim Chair, Dept. of Military and Emergency Medicine Uniformed Services University of the Health Sciences, Bethesda, MD; 2003.

157. Jevtic M, Petrovic M, Ignjatovic D, et al. Treatment of Wounded in the Combat Zone. J Trauma. 1996;40(3 (Suppl)):173S-176S.

158. Creteur J, Sibbald W, Vincent JL. Hemoglobin solutions--not just red blood cell substitutes. Crit Care Med. Aug 2000;28(8):3025-3034.

159. Amberson WR, Jennings JJ, Rhode CM. Clinical experience with hemoglobin-saline solution. J Appl Physiol. 1949;1:469-489.

160. Rabiner SF, O'Brien K, Peskin GW, Friedman LH. Further studies with stroma-free hemoglobin solution. Ann Surg. Apr 1970;171(4):615-622.

161. Savitsky JP, Doczi J, Black J, Arnold JD. A clinical safety trial of stroma-free hemoglobin. Clin Pharmacol Ther. Jan 1978;23(1):73-80.

162. Sloan EP, Koenigsberg M, Gens D, et al. Diaspirin cross-linked hemoglobin (DCLHb) in the treatment of severe traumatic hemorrhagic shock: a randomized controlled efficacy trial. Jama. Nov 17 1999;282(19):1857-1864.

163. Gould SA, Moore EE, Hoyt DB, et al. The first randomized trial of human polymerized hemoglobin as a blood substitute in acute trauma and emergent surgery. J Am Coll Surg. Aug 1998;187(2):113-120; discussion 120-112.

164. Gould SA, Moore EE, Hoyt DB, et al. The life-sustaining capacity of human polymerized hemoglobin when red cells might be unavailable. J Am Coll Surg. Oct 2002;195(4):445-452; discussion 452-445.

165. Nanney L, Fink LM, Virmani R. Perfluorochemicals. Morphologic changes in infused liver, spleen, lung, and kidney of rabbits. Arch Pathol Lab Med. Aug 1984;108(8):631-637.

166. Bucala R, Kawakami M, Cerami A. Cytotoxicity of a perfluorocarbon blood substitute to macrophages in vitro. Science. May 27 1983;220(4600):965-967.

167. Rosenblum WI, Moncure CW, Behm FG. Some long-term effects of exchange transfusion with fluorocarbon emulsions in macaque monkeys. Arch Pathol Lab Med. Apr 1985;109(4):340-344.

168. Lutz J, Barthel U, Metzenauer P. Variation in toxicity of Escherichia coli endotoxin after treatment with perfluorated blood substitutes in mice. Circ Shock. 1982;9(2):99-106.

169. Castro O, Nesbitt AE, Lyles D. Effect of a perfluorocarbon emulsion (Fluosol-DA) on reticuloendo-thelial system clearance function. Am J Hematol. Jan 1984;16(1):15-21.

170. Oxygent Product Fact Sheet. Alliance Pharmaceutical Corporation [Internet]. http://www.allp.com/Oxygent/ox_fact.htm   Accessed October 19, 2003.

171. Traverso LW, Lee WP, DeGuzman LR, Bellamy RF. Military antishock trousers prolong survival after otherwise fatal hemorrhage in pigs. J Trauma. Nov 1985;25(11):1054-1058.

172. Bariot P, Riou B, Viars P. High versus low inflation pressures of medical anti-shock trousers (MAST) in severe hemorrhagic hypovolemia. Le Journal Européen des Urgences. 1989;1(117-120).

173. Bickell WH, Geer MR, Rubal BJ. Hemodynamic response to rapid pneumatic antishock garment deflation. Ann Emerg Med. Aug 1986;15(8):886-889.

174. Kaback KR, Sanders AB, Meislin HW. MAST suit update. Jama. Nov 9 1984;252(18):2598-2603.

175. Davis SM. Antishock trousers: a collective review. J Emerg Med. 1986;4(2):145-155.

176. McSwain NE, Jr. Pneumatic anti-shock garment: state of the art 1988. Ann Emerg Med. May 1988;17(5):506-525.

177. Hymes WA, Itani KM, Wall MJ, Jr., Granchi TS, Mattox KL. Delayed tension pneumopericardium after thoracotomy for penetrating chest trauma. Ann Thorac Surg. Jun 1994;57(6):1658-1660.

178. Mattox KL, Bickell W, Pepe PE, Burch J, Feliciano D. Prospective MAST study in 911 patients. J Trauma. Aug 1989;29(8):1104-1111; discussion 1111-1102.

179. Bickell WH, Pepe PE, Bailey ML, Wyatt CH, Mattox KL. Randomized trial of pneumatic antishock garments in the prehospital management of penetrating abdominal injuries. Ann Emerg Med. Jun 1987;16(6):653-658.

180. Mattox KL. Response: the MAST lesson: contemporary example of society and academic responses to paradigm shifts. Pharos Alpha Omega Alpha Honor Med Soc. Winter 2000;63(1):26-29.

181. Aprahamian C, Gessert G, Bandyk DF, Sell L, Stiehl J, Olson DW. MAST-associated compartment syndrome (MACS): a review. J Trauma. May 1989;29(5):549-555.

182. Brotman S, Browner BD, Cox EF. MAS trousers improperly applied causing a compartment syndrome in lower-extremity trauma. J Trauma. Jul 1982;22(7):598-599.

183. Kunkel JM. Thigh and leg compartment syndrome in the absence of lower extremity trauma following MAST application. Am J Emerg Med. Mar 1987;5(2):118-120.

184. Connolly B, Gerlinger T, Pitcher JD. Complete masking of a severe open-book pelvic fracture by a pneumatic antishock garment. J Trauma. Feb 1999;46(2):340-342.

185. Moreno C, Moore EE, Rosenberger A, Cleveland HC. Hemorrhage associated with major pelvic fracture: a multispecialty challenge. J Trauma. Nov 1986;26(11):987-994.

186. Flint L, Babikian G, Anders M, Rodriguez J, Steinberg S. Definitive control of mortality from severe pelvic fracture. Ann Surg. Jun 1990;211(6):703-706; discussion 706-707.

187. McCallum AL, Rubes CR. Prehospital interventions. Emerg Med Clin North Am. Feb 1996;14(1):1-12.

188. Chisolm JJ. A manual of military surgery, for the use of surgeons in the Confederate States army; with an appendix of the rules and regulations of the Medical department of the Confederate States. 2nd ed. Richmond, Va. (reprinted in San Francisco, CA): West & Johnson (reprinted by Norman Publishing); 1861 (republished 1989).

189. Mabry RL. Use of a Hemorrhage Simulator to Train Military Medics. Military Medicine. November 2005 2005;170(No. 11):921-925.

190. Mallory M. Emergency treatment and resuscitation at the battalion level. Medical Science Publication No. 4: Recent Advances in Medicine and Surgery (19-30 April 1954) Based on Professional Medical Experiences in Japan and Korea 1950-1953. Vol 1. Washington D.C.: Office of the Surgeon General Office of Medical History; 1954:61.

191. Hughes C. Hemorrhage. Recent Advances in Medicine and Surgery (19-30 April 1954) Based on Professional Medical Experiences in Japan and Korea 1950-1953. Vol No. 4: Medical Science Publication; 1954:244.

192. Butler F. Combat casualty death due to failure to control venous ooze. In: Cloonan C, ed. Tampa, Florida; 2003:Personal communication between CAPT Frank Butler and COL Cliff Cloonan at SOMA conference December 2003.

193. Frontiero M. VCURES developing high-tech bandage for U.S. Army: BioHemostat May Replace Battlefield Tourniquet, Reduce Amputations [press release]. Richmond, VA: Virginia Commonwealth University. Virginia Commonwealth University. Available at: Available at http://www.vcu.edu/uns/Releases/2001/oct/100801.htm. Accessed September 14, 2004, 2004.

194. Majno G. The Healing Hand - Man and Wound in the Ancient World. Cambridge, Massachusetts, and London, England: Harvard University Press; 1975.

195. Chisolm JJ. A manual of military surgery, for the use of surgeons in the Confederate States army; with an appendix of the rules and regulations of the Medical department of the Confederate States. Richmond, Va. (reprinted in San Francisco, CA): West & Johnson (reprinted by Norman Publishing); 1861 (republished 1989).

196. Coates J, ed. Medical Department, United States Army - Surgery in World War II, Activities of Surgical Consultants. Washington, D.C.: Office of the Surgeon General, Dept. of the Army; 1962; No. 1.

197. Walters T. Tourniquet Use Consensus Panel. Paper presented at: Advanced Trauma Applications for Combat Casualty Care (ATACCC) 2003 Conference; August 18-20 2003, 2003; St. Pete Beach, Florida.

198. Hughes CW. Hemorrhage. Medical Science Publication No. 4: Recent Advances in Medicine and Surgery (19-30 April 1954) Based on Professional Medical Experiences in Japan and Korea 1950-1953. Volume 1. Vol 1. Washington D.C.: Office of Medical History, Office of the Surgeon General; 1954:244.

199. Aho K, Sianio K, Kianta M, al e. Pneumatic tourniquet paralysis: Case report. J Bone Joint Surg 65B. 1983:441-443.

200. Dobner J, Nitz A. Postmeniscectomy tourniquet palsy and functional sequelae. Am J Sports Med. 1982;10:211-214.

201. Gutin B, Warren R, Wickiewicz T, O'Brien S, Altchek D, Kroll M. Does tourniquet use during anterior cruciate ligament surgery interfere with postsurgical recovery of function? A review of the literature. Arthroscopy. 1991;7(1):52-56.

202. Heppenstall RB, Balderston R, Goodwin C. Pathophysiologic effects distal to a tourniquet in the dog. J Trauma. Apr 1979;19(4):234-238.

203. Jacobson MD, Pedowitz RA, Oyama BK, Tryon B, Gershuni DH. Muscle functional deficits after tourniquet ischemia. Am J Sports Med. May-Jun 1994;22(3):372-377.

204. Klenerman L. Tourniquet paralysis. J Bone Joint Surg. 1983;65B:374-375.

205. Patterson S, Klenerman L. The effect of pneumatic tourniquets on the ultrastructure of skeletal muscle. J Bone Joint Surg. 1979; 61B:178-183.

206. Pedowitz R, Gershuni D, Schmidt A, al e. Muscle injury induced beneath and distal to a pneumatic tourniquet: A quantitative animal study of effects of tourniquet pressure and duration. J Hand Surg. 1991;16A:610-621.

207. Sapega AA, Heppenstall RB, Chance B, Park YS, Sokolow D. Optimizing tourniquet application and release times in extremity surgery. A biochemical and ultrastructural study. J Bone Joint Surg Am. Feb 1985;67(2):303-314.

208. Saunders K, Louis D, Weingarden S, al e. Effect of tourniquet time on postoperative quadriceps function. Clin Orthop. 1979;143:194-199.

209. Tountas C, Bergman R. Tourniquet ischemia: Ultrastructural and histochemical observations of ischemic human muscle and of monkey muscle and nerve. J Hand Surg. 1977;2:31-37.

210. Pedowitz R. Tourniquet-induced neuromuscular injury. A recent review of rabbit and clinical experiments. Acta Orthop Scand Suppl. 1991;245:Acta Orthop Scand Suppl.

211. Mohler LR, Pedowitz RA, Myers RR, Ohara WM, Lopez MA, Gershuni DH. Intermittent reperfusion fails to prevent posttourniquet neurapraxia. J Hand Surg [Am]. Jul 1999;24(4):687-693.

212. Middleton RW, Varian JP. Tourniquet paralysis. Aust N Z J Surg. May 1974;44(2):124-128.

213. Mallory MM. "Emergency Treatment and Resuscitation at the Battalion Level". Recent Advances in Medicine and Surgery (19-30 April 1954) Based on Professional Medical Experiences in Japan and Korea 1950-1953: Medical Science Publication No. 4; 1954:p. 61.

214. Field Report Marine Corps Systems Command Liaison Team, Central Iraq. 2003.

215. Calkins D, Snow C, Costello M, Bentley TB. Evaluation of possible battlefield tourniquet systems for the far-forward setting. Mil Med. May 2000;165(5):379-384.

216. Wenke JC, Walters TJ, Greydanus DJ, Pusateri AE, Convertino VA. Physiological evaluation of the U.S. Army one-handed tourniquet. Mil Med. Sep 2005;170(9):776-781.

217. Medical Hearing. Committee on Appropriations, Subcommittee on Defense, United States Senate. 1st Session, 109th Congress ed. Washington, D.C.: Congressional Record; 2005.

218. ONR/MARCORSYSCOM Tourniquet Evaluation. Panama City, Florida: Naval Sea Systems Command, Navy Experimental Diving Unit; 2005.

219. Navein J, Coupland R, Dunn R. The Tourniquet Controversy. J Trauma. 2003;54(5):S219-S220.

220. Holcomb J, Pusateri A, MacPhee M, Hess J. New Technologies in Hemorrhage Control. Current Opinion in Critical Care. 1997;3:488-493.

221. Larson MJ, Bowersox JC, Lim RC, Jr., Hess JR. Efficacy of a fibrin hemostatic bandage in controlling hemorrhage from experimental arterial injuries. Arch Surg. Apr 1995;130(4):420-422.

222. Holcomb J, Pusateri A, Harris R, Reid T, al e. Dry fibrin sealant dressing reduces blood loss, resuscitation volume, and improves survival in hypothermic coagulopathic swine with grade V liver injuries. J Trauma. 1999;47:233-242.

223. Holcomb JB, Pusateri AE, Harris RA, et al. Effect of dry fibrin sealant dressings versus gauze packing on blood loss in grade V liver injuries in resuscitated swine. J Trauma. Jan 1999;46(1):49-57.

224. Chan MW, Schwaitzberg SD, Demcheva M, Vournakis J, Finkielsztein S, Connolly RJ. Comparison of poly-N-acetyl glucosamine (P-GlcNAc) with absorbable collagen (Actifoam), and fibrin sealant (Bolheal) for achieving hemostasis in a swine model of splenic hemorrhage. J Trauma. Mar 2000;48(3):454-457; discussion 457-458.

225. Holcomb J, MacPhee M, Hetz S, Harris R, Pusateri A, Hess J. Efficacy of a Dry Fibrin Sealant Dressing for Hemorrhage Control After Ballistic Injury. Arch Surg. 1998;133:32-35.

226. Holcomb JB, Pusateri AE, Harris RA, et al. Dry fibrin sealant dressings reduce blood loss, resuscitation volume, and improve survival in hypothermic coagulopathic swine with grade V liver injuries. J Trauma. Aug 1999;47(2):233-240; discussion 240-232.

227. Morey AF, Anema JG, Harris R, et al. Treatment of grade 4 renal stab wounds with absorbable fibrin adhesive bandage in a porcine model. J Urol. Mar 2001;165(3):955-958.

228. Cornum RL, Morey AF, Harris R, et al. Does the absorbable fibrin adhesive bandage facilitate partial nephrectomy? J Urol. Sep 2000;164(3 Pt 1):864-867.

229. Holcomb JB, McClain JM, Pusateri AE, et al. Fibrin sealant foam sprayed directly on liver injuries decreases blood loss in resuscitated rats. J Trauma. Aug 2000;49(2):246-250.

230. Jackson MR, Friedman SA, Carter AJ, et al. Hemostatic efficacy of a fibrin sealant-based topical agent in a femoral artery injury model: a randomized, blinded, placebo-controlled study. J Vasc Surg. Aug 1997;26(2):274-280.

231. Alam HB, Uy GB, Miller D, et al. Comparative analysis of hemostatic agents in a swine model of lethal groin injury. J Trauma. Jun 2003;54(6):1077-1082.

232. Alam HB, Burris D, DaCorta J, Rhee P. Hemorrhage Control in the Battlefield: Role of New Hemostatic Agents. Military Medicine. January 2005 2005;170(1):63-69.

233. Burris D, Colonel UA, Chair of the QuikClotTM Interdisciplinary Review Panel Health Sciences, USUHS, Bethesda MD. Summary of Recommendations of QuikClotTM Interdisciplinary Review Panel. In: LCDR J.A. DaCorta EM, Marine Corps Warfighting Lab, Quantico, VA, ed. Bethesda MD: Uniformed Services University of the Health Sciences; 2003.

234. Field Report Marine Corps Systems Command Liaison Team, Central Iraq, 20 April to 25 April 2003. Central Iraq: U.S. Marine Corps Systems Command.

235. Neuffer MC, McDivitt J, Rose D, King K, Cloonan CC, Vayer JS. Hemostatic dressings for the first responder: a review. Mil Med. Sep 2004;169(9):716-720.

236. Pusateri AE, McCarthy SJ, Gregory KW, et al. Effect of a chitosan-based hemostatic dressing on blood loss and survival in a model of severe venous hemorrhage and hepatic injury in swine. J Trauma. Jan 2003;54(1):177-182.

237. New and Emerging Technology Briefing. Recombinant Factor VIIa in Haemostasis. National Horizon Scanning Centre, University of Birmingham, UK. Available at: http://www.publichealth.bham.ac.uk/horizon/2002reports/RecombinantVIIa.pdf.

238. Lynn M, Jerokhimov I, Jewelewicz D, et al. Early use of recombinant factor VIIa improves mean arterial pressure and may potentially decrease mortality in experimental hemorrhagic shock: a pilot study. J Trauma. Apr 2002;52(4):703-707.

239. Martinowitz U, Holcomb JB, Pusateri AE, et al. Intravenous rFVIIa administered for hemorrhage control in hypothermic coagulopathic swine with grade V liver injuries. J Trauma. Apr 2001;50(4):721-729.

240. O'Neill P, Bluth M, Gloster E, et al. Successful Use of Recombinant Activated Factor VII for Trauma-Associated Hemorrhage in a Patient without Preexisting Coagulopathy. J. Trauma. 2002;52(2):400-405.

241. Martinowitz U, Kenet G, Segal E, et al. Recombinant Activated Factor VII for Adjunctive Hemorrhage Control in Trauma. J Trauma. 2001;51(3):431-439.

242. Weiskopf R. Intraoperative Use of Recombinant Activated Coagulation Factor VII [Editorial Views]. Anesthesiology. 2002;96(6):1287-1289.

243. Buckle R, Browener B, M M. Emergency reduction for pelvic ring disruptions and control of associated hemorrhage using the pelvic stabilizer. Techniques in Orthopaedics. 1995;9:258-266.

244. Mucha P, Welch T. Hemorrhage in major pelvic fractures. Surg Clin North Am. 1988;68:757-773.

245. Warme WJ, Todd MS. The circumferential antishock sheet. Mil Med. May 2002;167(5):438-441.

246. Cioffi WG, Rue LW, Buescher TM, Pruitt BA. Chapter 11: The management of burn injury. In: Bellamy RF, Zajtchuk R, eds. Textbook of Military Medicine Conventional Warfare: Part I, Warfare, Weaponry, and the Casualty Volume 5 Ballistic, Blast, and Burn Injuries. Vol 5. Washington D.C.: Office of the Surgeon General and the Borden Institute; 1989:349-377.

247. Eldad A, Torem M. Burns in the Lebanon War 1982: "the blow and the cure". Mil Med. Mar 1990;155(3):130-132.

248. McLean AD. Burns and military clothing. J R Army Med Corps. Feb 2001;147(1):97-106.

249. Ramzy PI, Barret JP, Herndon DN. Thermal injury. Crit Care Clin. Apr 1999;15(2):333-352, ix.

250. Wolf SE, Rose JK, Desai MH, Mileski JP, Barrow RE, Herndon DN. Mortality determinants in massive pediatric burns. An analysis of 103 children with > or = 80% TBSA burns (> or = 70% full-thickness). Ann Surg. May 1997;225(5):554-565; discussion 565-559.

251. Nguyen TT, Gilpin DA, Meyer NA, Herndon DN. Current treatment of severely burned patients. Ann Surg. Jan 1996;223(1):14-25.

252. Demuth ME, Dimick AR, Gillespie RW, et al. Advanced Burn Life Support Course Provider's Manual. Chicago, IL: American Burn Association; 1994.

253. Dubick MA, Bruttig SP. Hypertonic saline dextran: A development update. US Army Med Dept J. 8-96 1996;11/12.

254. El-Sonbaty MA. Oral rehydration therapy in moderately burned children. Ann Burn Fire Disaster. 1991;4:29-32.

255. Chisolm JJ. A manual of military surgery, for the use of surgeons in the Confederate States army; with an appendix of the rules and regulations of the Medical department of the Confederate States.

Originally printed in Richmond, Va. (reprinted in San Francisco, CA): Originally published by West & Johnson (reprinted by Norman Publishing); 1861 (reprinted in 1989).

256. *Chapter III - Care of the Wounded. In: Neel MGS, ed. Vietnam Studies - Medical Support of the U.S. Army in Vietnam 1965-1970. Washington,D.C.: Department of the Army - US. Government Printing Office; 1991.*

257. *Forsee JH. Forward surgery of the severely wounded (A history of the activities of the 2nd auxillary surgical group). Washington, DC: Office of the Surgeon General; 1945.*

258. *Zipnick RI, Scalea TM, Trooskin SZ, et al. Hemodynamic responses to penetrating spinal cord injuries. J Trauma. Oct 1993;35(4):578-582; discussion 582-573.*

259. *Goldberg DG. Chapter I, "Short Historical Survey/Coverage of the Surgical Treatment of Bullet Wounds and Damages of Spine and Spinal Cord. Experience of Soviet Medicine in a Great Patriotic War 1941-1945: Translated and Published by the U.S. Foreign Technology Division:45.*

260. *Spurling RG. Part I - Administrative Considerations in Neurosurgery Chapter III "The European Theater of Operations". In: Coates JB, Spurling RG, Woodhall B, eds. Surgery in World War II: Neurosurgery. Vol I. Washington D.C.: Office of the Surgeon General; 1958:82.*

261. *Arishita GI, Vayer JS, Bellamy RF. Cervical spine immobilization of penetrating neck wounds in a hostile environment. J Trauma. Mar 1989;29(3):332-337.*

262. *Young W, DeCrescito V, Tomasula JJ, Ho V. The role of the sympathetic nervous system in pressor responses induced by spinal injury. J Neurosurg. Apr 1980;52(4):473-481.*

263. *Piepmeier JM, Lehmann KB, Lane JG. Cardiovascular instability following acute cervical spinal cord trauma. Cent Nerv Syst Trauma. Fall 1985;2(3):153-160.*

264. *Klein RS, Berger SA, Yekutiel P. Wound infection during the Yom Kippur war: observations concerning antibiotic prophylaxis and therapy. Ann Surg. Jul 1975;182(1):15-21.*

265. *Coupland RM, Howell PR. An experience of war surgery and wounds presenting after 3 days on the border of Afghanistan. Injury. Jul 1988;19(4):259-262.*

266. *Opal SM, Cohen J. Clinical gram-positive sepsis: does it fundamentally differ from gram-negative bacterial sepsis? Crit Care Med. Aug 1999;27(8):1608-1616.*

267. *Masur H. Sepsis Caused by Gram-Positive Cocci in ICUs: A Burgeoning Problem. Medscape. Accessed 18 September, 2004.*