

Persistent Occult Hypoperfusion Is Associated with a Significant Increase in Infection Rate and Mortality in Major Trauma Patients

Jeffrey A. Claridge, MD, Traves D. Crabtree, MD, Shawn J. Pelletier, MD, Kathy Butler, RN, Robert G. Sawyer, MD, and Jeffrey S. Young, MD

Objective: To investigate the hypothesis that occult hypoperfusion (OH) is associated with infectious episodes in major trauma patients.

Methods: Data were collected prospectively on all adult trauma patients admitted to the Surgical/Trauma Intensive Care Unit from November of 1996 to December of 1998. Treatment was managed by a single physician according to a defined resuscitation protocol directed at correcting OH (lactic acid [LA] > 2.4 mmol/L).

Results: Of a total of 381 consecutive patients, 118 never developed OH and 263 patients exhibited OH. Seventeen patients were excluded because their LA never corrected, and they all subsequently died. One hundred seventy-six infectious episodes occurred in 97 of the 364 patients remaining. The infection rate in patients with no elevation of LA was 13.6% (n = 118) compared with 12.7% (n = 110) in patients whose LA corrected by 12 hours, 40.5% (n = 79; $p < 0.01$ compared with all other groups) in patients whose LA corrected between 12 and 24

hours, and 65.9% (n = 57; $p < 0.01$ compared with all other groups) in patients who corrected after 24 hours. Among the patients with infections, there were 276 infection sites with 42% of infections involving the lung and 21% involving bacteremia. There was no difference in proportion of infections occurring at each site between groups. The mortality rate of patients who developed infections was 7.9% versus 1.9% in patients without infections ($p < 0.05$). Of the patients who developed infections, 69.8% versus 25.8% ($p < 0.001$) did not have their lactate levels normalized within 12 hours of emergency room admission. Logistic regression demonstrated that both the Injury Severity Score and OH > 12 hours were independently predictive of infection.

Conclusion: A clear increase in infections occurred in patients with OH whose lactate levels did not correct by 12 hours, with an associated increase in length of stay, days in surgical/trauma intensive care unit, hospital charges, and mortality.

In the United States, traumatic injury is the leading cause of loss of life before 65 years of age¹ and the second leading cause of direct medical costs.² Numerous studies have demonstrated infection to be the leading cause of morbidity and mortality in patients who survive at least 48 hours.³⁻⁷ Infection has been shown to play a significant role in the majority of late deaths after trauma.^{8,9} It is clear that in trauma patients, infection remains one of the leading causes of morbidity and mortality, prompting diligent efforts to identify risk factors for development of infection. Our hypothesis was that persistent occult hypoperfusion (OH) is a risk factor for the development of infections in severely traumatized patients. We defined OH as serum lactic acid (LA) > 2.4 mmol/L in the patient who exhibits no signs of clinical shock. At our institution, we follow a regimented protocol for the correction of OH and our goal is to correct LA as quickly as possible.

To date, there have been no studies evaluating the correlation between the correction of OH and the subsequent

development of infections. It was our hypothesis that the infection rate would be higher in patients who had longer periods of OH, and that OH could be a useful marker for further identifying patients at risk for developing infections. Thus, the purpose of this study was to evaluate the relationship of OH and infections in severely traumatized patients.

MATERIALS AND METHODS

Trauma patients admitted to the surgical and trauma intensive care unit (STICU) between November of 1996 and December of 1999 were evaluated. The study was conducted at the University of Virginia Health System, a Level I trauma center, and was approved by the University of Virginia Human Investigation Committee. Demographic and patient care data were collected daily by the trauma registry staff, which is managed by a full-time registered nurse. Data collected included age, Injury Severity Score (ISS), emergency department Glasgow Coma Scale score (ED GCS), survival probability (Ps), and emergency department admission systolic blood pressure. The ISS was determined by the methods originally described by Baker et al¹⁰ and later revised in 1985.¹¹ Sp was calculated by using the equation $Sp = 1/(1 + e^{-b})$, where $e = 2.7183$ (base of Napierian logarithms), and $b = b_0 + b_1$ (Revised Trauma Scale score) + b_2 (ISS) + b_3 (A), where b_0 , b_1 , b_2 , and b_3 are weights derived from study data and $A = 1$ (age > 54 years) and $A = 0$ (age < 54 years).¹²

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From the Trauma Research and Surgical Infectious Disease Laboratories, University of Virginia Health System, Charlottesville, Virginia.

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Address for reprints: Jeffrey S. Young, MD, Department of Surgery, University of Virginia Health System, Post Office Box 10005, Charlottesville, VA 22906-0005.

TABLE 1. Initial variable separated by time of LA correction

Variable	Normal LA Group I	LA Corrects <12 h Group II	Corrects 12–24 h Group III	Corrects >24 h Group IV
N	118	110	79	57
Age (yr)	45.1 ± 1.9	40.9 ± 1.8	43.6 ± 2.1	45.2 ± 2.6
ISS	20.3 ± 1.0	21.1 ± 0.9	24.9 ± 1.2	28.8 ± 1.6 ^a
ED systolic blood pressure (mm Hg)	120 ± 5	124 ± 4	123 ± 5	116 ± 5
ED GCS	11.2 ± 0.5	11.5 ± 0.5	10.4 ± .6	8.8 ± .8 ^b
Ps (%)	85 ± 3	86 ± 3	76 ± 4	75 ± 4

^a Denotes $p < 0.01$ compared with groups I and II.

^b Denotes $p < 0.05$ compared with group II.

Data regarding infectious complications were collected by members of the surgical infectious disease laboratory and kept in a separate database from the trauma registry. The investigators performed daily or every-other-day evaluation of all hospitalized surgical patients. This investigation included chart review, review of daily microbiologic data, and other laboratory data, antibiotic data, and patient evaluation. Criteria for infection varied depending on the site of infection. Pneumonia was diagnosed when a predominant organism was isolated from appropriately obtained sputum cultures in the setting of purulent sputum production and/or a new or changing pulmonary infiltrate on chest x-ray film. Bloodstream infections were diagnosed based on isolation of a predominant organism from blood cultures obtained under sterile conditions. Criteria for urinary tract infections included isolation of $> 10^5$ organisms/mL urine or $> 10^4$ organisms with symptoms. Criteria for catheter-related infection included isolation of > 15 colony forming units from catheter tips cultured only in the setting of suspected infection. Primary peritoneal infections and wound infections were generally diagnosed based on the physician's evaluation of the respective site, frequently without obtaining cultures.

Patient care was directed by a single physician, whose goal was to normalize LA as quickly as possible by controlling hemorrhage, optimizing preload or increasing cardiac performance. Serum LA levels were obtained on admission and at set intervals (every 4–6 hours) until the values returned to less than 2.4 mmol/L, or until death. Our resuscitation protocol was previously described by Blow et al.¹³ Briefly, patients with LA > 2.4 mmol/L, patients who showed signs of inadequate perfusion despite reasonable fluid resuscitation, or both, underwent pulmonary artery catheterization. Pulmonary capillary wedge pressures and cardiac indices were obtained at regular intervals. These numbers guided further treatment, including the use of pressers until the LA was within normal limits.

Statistical Analysis

All univariate comparisons were unpaired, and all tests of significance were two tailed. For univariate analysis, continuous variables were compared by the Student's t test, with equal or unequal variance as determined by F test analysis of the variability of each parameter. Multiple groups were compared by means of analysis of variance with Tukey/Kramer post hoc analysis. Categorical data were compared by using χ^2 testing or Fisher's exact test if necessary, based on sample

size. All values were expressed as the mean \pm SE of the mean (continuous variables) or as a percentage of the group from which they were derived (categorical variables). On univariate analysis, $p < 0.05$ was considered significant.

We then performed logistic regression to identify risk factors for infections in traumatically injured patients admitted to the STICU. Backward stepwise logistic regression analysis was used to estimate the odds ratio (OR) of inpatient infections (dependent variable) and the presence or absence of potential prognostic factors (independent variables). The OR was defined as the exp (beta-coefficient) with 95% confidence intervals. An initial Pearson correlation coefficient was determined for all continuous variables to screen for highly correlated parameters. Statistical analysis was performed by using SAS software (SAS Institute, Inc., Cary, NC).

RESULTS

Over a 25-month period from November of 1996 to December of 1998, 381 consecutive STICU patients were evaluated. Seventeen patients with a 100% mortality rate were excluded because their LA never corrected. Analysis was done on the 364 patients remaining. The overall mortality of these patients was 3.3%, with 50.0% of them dying while septic.

Univariate Analysis Comparing Four Different Correction Times of LA

One hundred eighteen patients never developed OH and 246 patients exhibited OH. Initially, four groups were analyzed according to duration of OH. Group I ($n = 118$) had a normal LA during the initial hospital course. The remaining groups (II–IV) exhibited OH (LA > 2.4 mmol/L) on admission. Group II ($n = 109$) corrected LA within 12 hours of admission. Group III ($n = 79$) corrected LA within 12 to 24 hours. Group IV ($n = 57$) corrected LA more than 24 hours after admission. Table 1 illustrates the ages, ISS, initial systolic blood pressure, ED GCS, and Ps among each group. There was no difference in mean ages among groups. The ISS of group IV demonstrated a statistically higher score compared with groups I and II. Initial systolic blood pressure demonstrated no difference among groups. ED GCS only demonstrated a significant decrease in GCS in patients in group IV compared with group II. Ps was similar among groups.

Outcomes for each group are illustrated in Figures 1 and 2. The percentage of patients in each group developing infection was 13.6% in group I, 12.7% in group II, 40.5% in group III,

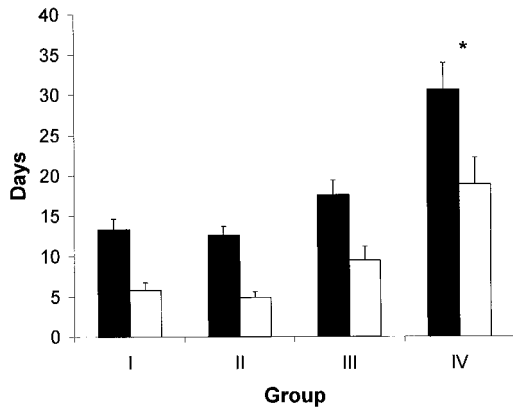


FIG 1. Length of stay (LOS) and STICU days evaluated in relationship to the time of LA correction. Group I represents patients whose lactate levels were never abnormal, group II represents patients whose lactate levels corrected by 12 hours, group III represents patients whose lactate levels corrected within 12 to 24 hours, and group IV represents patients whose lactate levels corrected after 24 hours. The asterisk denotes a *p* value < 0.01 comparing LOS and ICU days of group IV with all other groups. White bars, LOS; black bars, ICU days.

and 65.9% in group IV, with groups III and IV demonstrating statistical significance compared with all other groups. The mortality rate was also statistically higher in group IV at 11.8%. The mortality rate of groups I to III was 0.8%, 1.9%, and 3.9%, respectively. Length of stay (LOS) and STICU days were statistically higher in group IV compared with all other groups. The LOS in the groups I to IV were 13.3 ± 1.3 days, 12.6 ± 1.1 days, 17.6 ± 1.8 days, and 30.6 ± 3.3 days (*p* < 0.01), respectively. The STICU days among groups I to IV were 5.8 ± 0.9 , 4.9 ± 0.7 , 9.5 ± 1.7 , and 18.9 ± 3.3 (*p* < 0.01), respectively.

Univariate Comparison of Patients Whose LA Corrected by 12 hours versus >12 hours

Further comparison was made between two groups of patients, those whose LA corrected by 12 hours and those who corrected at >12 hours. Table 2 illustrates the results. These results demonstrated that 227 patients had OH < 12 hours and 136 patients had OH > 12 hours. The infection rate in

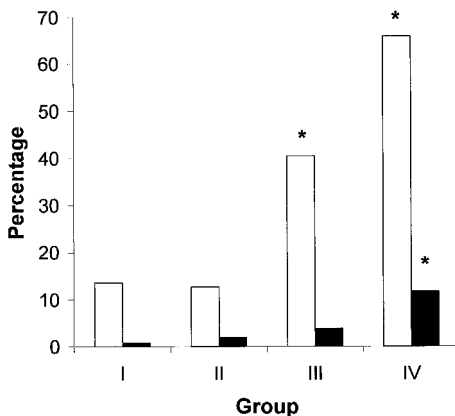


FIG 2. Infection rates and mortality rates in relationship to the time lactate corrects. Group I represents patients whose lactate levels were never abnormal, group II represents patients whose lactate levels corrected by 12 hours, group III represents patients whose lactate levels corrected within 12 to 24 hours, and group IV represents patients whose lactate levels corrected after 24 hours. The asterisks denote a *p* value < 0.01 compared with all other groups. White bars, infections (%); black bars, mortality rate (%).

TABLE 2. Univariate comparison between patients whose lactate levels correct by 12 hours and patients whose lactate levels correct after 12 hours

Variable	LA Corrects by 12 h	LA Corrects >12 h	<i>p</i> Value
n	227	136	
Age (yr)	43.1 ± 1.3	44.3 ± 1.6	Not significant
ISS	20.7 ± 0.7	26.5 ± 1.0	<0.0001
ED GCS	11.4 ± 0.4	9.7 ± 0.5	0.0061
ED systolic blood pressure	121.7 ± 3.0	119.7 ± 3.5	Not significant
Ps	85.5 ± 1.9%	76.3 ± 3.8%	0.0052
LOS (days)	12.9 ± 0.8	23.1 ± 1.8	<0.0001
STICU days	5.3 ± 0.5	13.5 ± 1.5	<0.0001
Hospital costs (\$)	19658 ± 2050	36240 ± 5552	0.0064
Infections	12.7%	49.3%	0.0001
Mortality	1.3%	7.1%	0.0063

patients with OH < 12 hours was 12.7% versus 49.3% in patients with OH > 12 hours (*p* = 0.001). The mortality rate of patients with OH < 12 hours was 1.3% versus 7.1% in patients with OH > 12 hours (*p* = 0.0063).

Univariate Comparison of Patients with and without Infections

Ninety-seven patients (26.7%) developed infections, and 267 patients did not develop infections. These results are illustrated in Table 3. The mean age of patients who developed infections was 44.7 ± 2.0 years versus 43.1 ± 1.2 years in patients without infections. This is not statistically different. The ISS were statistically higher in patients with infections at 29.1 ± 1.3 versus 20.6 ± 0.6 in patients without infections. The ED GCS was statistically lower in patients with infections at 8.4 ± 0.6 versus 11.6 in patients without infections. The emergency department admission systolic blood pressure was statistically lower in patients who developed infections at 111 ± 5 mm Hg versus 124 ± 3 mm Hg in patients without infections. The Ps of patients who developed infections was statistically lower at $73.2 \pm 3.4\%$ compared with $85.3 \pm 1.8\%$ in patients without infections. LOS, STICU days, and hospital charges were all statistically higher in patients with infections compared with patients without infections. There was also a significant increase in the mortality rate of patients

TABLE 3. Comparison of trauma patients with infections to patients without infections

Variable	Patients with Infections	Patients without Infections	<i>p</i> Value
n	97	267	
Age (yr)	44.7 ± 2.0	43.1 ± 1.2	Not significant
ISS	29.1 ± 1.3	20.6 ± 0.6	<0.0001
ED GCS	8.4 ± 0.6	11.6 ± 0.3	<0.0001
ED systolic blood pressure (mm Hg)	111 ± 5	124 ± 3	0.02
Ps	73.2 ± 3.4%	85.3 ± 1.8%	0.0007
LOS (days)	29.7 ± 2.3	12.1 ± 0.7	<0.0001
STICU days	18.0 ± 1.9	4.9 ± 0.5	<0.0001
Hospital costs (\$)	52199 ± 7886	16962 ± 1505	<0.0001
LA not corrected by 12 h	69.8%	25.8%	<0.001
Mortality rate	7.9%	1.9%	<0.05

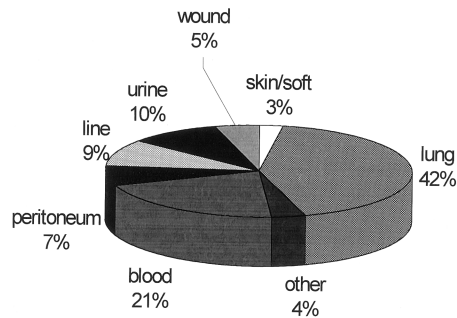


FIG 3. Breakdown of sites for all patients with infections. There were 276 infectious sites in 97 patients. Skin/soft, skin/soft tissue.

who developed infections at 7.9% versus 1.9% in patients who did not develop infections.

Evaluation of Infections

There were 176 infectious episodes occurring in 97 patients. Among the patients with infections, there were 276 infection sites, with 42% involving the lung and 21% involving bacteremia. This is further illustrated in Figure 3. Of the patients who developed infections, 69.8% versus 25.8% ($p < 0.001$) did not have their lactate levels corrected within 12 hours of emergency room admission. The breakdown of infections by site in those patients whose LA corrected by 12 hours, compared with those who corrected after 12 hours, is illustrated in Table 4. These results reveal no difference in proportion of infections occurring at each site between groups. There was no statistical difference in the time of admission to initiation of treatment for infection between patients whose LA corrected by 12 hours compared with those who corrected at >12 hours. In addition, there was no difference in the time of operation to the time of treatment for infection between these two groups. However, LOS after initiation of treatment for infection was 17 ± 2 days in patients whose lactate corrected by 12 hours compared with 31 ± 2 days in patients whose LA corrected after 12 hours from admission ($p < 0.0001$).

Multivariate Analysis of Patients with Infections versus Patients without Infections

To determine the impact of initial hospital variables on predicting infections, multivariate linear regression was used to evaluate LA, ISS, GCS, systolic blood pressure, and Ps. The

TABLE 4. Breakdown of infections in relation to time of lactate level correction^a

Site of Infection	Lactate Corrected by 12 h (%)	Lactate Corrected >12 h (%)
Lung	39 (50)	78 (39)
Blood	13 (17)	44 (22)
Urine	10 (13)	17 (9)
Line	8 (10)	18 (9)
Wound	3 (4)	10 (5)
Skin/soft tissue	1 (1)	6 (3)
Vagina	1 (1)	2 (1)
Colon	0 (0)	2 (1)
Pleura	1 (1)	2 (1)
Other	0 (0)	2 (1)
Total	78 (100)	198 (100)

^a No statistical difference between any variable.

TABLE 5. Results of multivariate linear regression analysis of the risk of infection after severe traumatic injury requiring admission to the intensive care unit

Variable	Odds Ratio	95% Confidence Interval	p Value ^a
Ps	1.32	0.68–2.56	NS
ED GCS	1.55	0.82–2.96	NS
ED systolic blood pressure	0.994	0.988–1.000	NS
ISS	1.05	1.02–1.08	0.0004
LA	5.33	3.07–9.26	<0.0001

^a NS, not significant.

results are illustrated in Table 5. The presence of OH at >12 hours and increasing ISS were both predictive of infection. The OR for infection for LA not correcting by 12 hours was 5.33, with a 95% confidence interval of 3.07 to 9.26 ($p = 0.0004$). The OR of each additional ISS point was 1.05, with a 95% confidence interval of 1.02 to 1.08 ($p < 0.0001$).

DISCUSSION

These results indicate that patients with prolonged hypoperfusion have an increased risk of infection and mortality. Evaluation of the four groups previously outlined demonstrated that patients with OH at > 24 hours had significantly higher ISS than patients without OH and those who corrected by 12 hours, but no difference in patients who corrected within 12 to 24 hours. The ED GCS was significantly lower in patients whose LA corrected at > 24 hours compared with patients who corrected by 12 hours, but no other group showed a significant difference. No other recorded variables demonstrated significant difference between groups. However, in analyzing outcomes, the infection rate was significantly different, compared with all other groups, in patients whose LA corrected within 12 to 24 hours and those correcting at > 24 hours. The infection rate was 40.5% in patients whose lactate corrected within 12 to 24 hours and was 65.9% in patients whose LA corrected after 24 hours. The infection rate of patients with no abnormality was 13.6% and was 12.7% if LA corrected by 12 hours. These findings illustrate that even 12 hours of OH increase the risk of infection. Close monitoring of LA facilitates identification of patients at increased risk earlier and more reliably than other markers we evaluated.

In this study, 26.7% of patients admitted to the STICU developed at least one infection and subsequently had a 7.9% mortality rate. These results are consistent with other studies.¹⁴ The lung was the most common site (42%) of infection, followed by bacteremia (21%). This finding is consistent with a study from another group, which demonstrated that 30 to 60% of patients with ISS > 25 will suffer from pneumonia in the posttrauma period.¹⁵ Although there were many differences found between patients whose LA correct by 12 hours compared with those whose LA did not, there was no difference in the sites of infection between these two groups.

Logistic regression analysis demonstrated that both ISS and OH at >12 hours were independently predictive of sub-

sequent infectious episodes. Age, ED GCS, emergency department admission systolic blood pressure, and Ps were not predictive of subsequent infection. This report is the first study to clearly demonstrate this correlation between prolonged lactic acidosis and infections.

Several reports have studied the correlation between the severity of injury and serum LA levels.^{16–19} A correlation between blood lactate levels and the development of circulatory septic shock has been reported.^{20–23} We believe that a prolonged state of hypoperfusion is similar to prolonged ischemic time in models studying ischemic/reperfusion injury. Inadequate organ perfusion after severe traumatic injury leads to oxygen debt and an increase in LA, reflecting anaerobic metabolism. Other studies have shed light on the fact that persistent lactic acidosis increases the risk of mortality. In a study²⁴ of 76 consecutive patients admitted with multiple trauma, the survival of patients inversely correlated to the length of time it took to correct LA. There was 100% survival in patients whose LA corrected by 24 hours, 77.8% survival in patients whose LA corrected within 24 to 48 hours, and only a 13.6% survival in patients whose LA corrected at > 48 hours. Another study demonstrated that LA at day 3 was predictive of acute respiratory distress syndrome and multiple organ failure.²⁵ Our group has previously reported¹³ that OH at > 24 hours is associated with higher rates of respiratory complications, multiple organ failure, and death after trauma. We have also recently reported²⁶ that the presence of OH in trauma patients undergoing early intramedullary fixation of femur fractures is associated with a twofold higher incidence of postoperative complications. The results of this study further add to the possible importance of aiming therapy at improving perfusion and correcting lactic acidosis.

Our results support the hypothesis that prolonged hypoperfusion creates a condition of immunosuppression that renders the host more susceptible to bacteria and subsequent infections. It has been shown that trauma and thermal injury induce an immunosuppressed state in the host.²⁷ Napolitano and Campbell²⁸ suggested that trauma induces alterations in the inflammatory cytokine cascade that affect the immune response to subsequent septic challenge.

One theory is that trauma “up-regulates” the response to injury, increasing the amount and activity of proinflammatory mediators. Tumor necrosis factor- α (TNF- α) has been extensively studied; however, its exact role after trauma remains unclear.^{29–33} Recently, both cell-bound and -soluble TNF receptors have been discovered and may play a role in the biological activity of TNF.^{34,35} Wang et al.³⁶ demonstrated an increase in TNF- α and IL-6 during hemorrhage in humans. Ayala et al.²⁹ demonstrated that IL-6 and TNF- α were both increased after hemorrhage and concluded that induction of IL-6 by trauma may be partially independent of those mechanisms in hemorrhage that are involved in the release of TNF- α . On the other hand, Hoch et al.³⁷ demonstrated that severe injury produces a rapid, large increase in circulating concentrations of IL-6 and IL-8, with only minimal increase in TNF in the postresuscitation period in one third of patients with severe injury. IL-8 has been shown to have important effects on neutrophil function, especially in the role of leu-

kosequestration and activation in the lung.^{37,38} Roumen et al.³⁹ determined that IL-6 was significantly higher than IL-1 and TNF- α in traumatized patients and correlated extremely well with the development of adult respiratory distress syndrome and multiple system organ failure. A study by Ertel et al.⁴⁰ demonstrated that after major trauma, IL-6 levels were significantly increased and remained elevated up to 21 days. In addition, IL-6 levels correlated with the appearance of infectious complications after major injury. These studies indicate that trauma induces an exaggerated or “up-regulated” cytokine response.

Another theory is that trauma induces an immediate state of immunosuppression. IL-10, an anti-inflammatory cytokine produced by CD4+ T-helper cells, was increased after injury and correlated with subsequent septic events and decreased resistance to infection.⁴¹ Others have demonstrated that serious injury induced diminished production of IL-12 and a shift to the Th-2 phenotype, with the increased production of IL-4 and IL-10. Keel et al.⁴² concluded that trauma leads to reduced responsiveness of blood monocytes to lipopolysaccharide and a decreased secretion of proinflammatory-reacting lymphokines. Majetschak et al.⁴³ recently discovered that the extent of trauma tissue damage leads to a graded depression of immunocyte function and seems to be amplified by surgical treatment. These studies support the theory that trauma creates a state of immunosuppression that may create a condition in which patients are more susceptible to infections.

In summary, we have demonstrated that OH longer than 12 hours is a clear risk factor for the development of infections, with a subsequent increase in mortality, LOS, STICU days, and hospital costs. Logistic regression analysis demonstrated that ISS and LA correcting at > 12 hours are independently predictive of subsequent infections. These results strengthen the importance of correcting OH rapidly and suggest the importance of more aggressive treatment in attempts to improve LA to normal by 12 hours to minimize both mortality and infections. We believe that aggressive resuscitation to correct LA improves the outcome of a significant subset of patients. There likely exists a group of patients that will not correct their hypoperfusion and will go on to poor outcomes. However, this group may be small. Even though a significant percentage of patients did not correct their LA by 12 or 24 hours despite a management scheme that focuses on it, there are other confounding factors in addition to patient physiology contributing to this. Subspecialty operations, long radiology evaluations, “road trips” for studies, and boarding of patients in units unfamiliar with our protocols are factors that likely prolong the state of hypoperfusion. Diligence on our part will move more patients from the high-risk groups (correction > 12 hours) to the low-risk groups (correction < 12 hours) and continue to decrease infections and improve outcome.

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DISCUSSION

Dr. Christopher C. Baker (Chapel Hill, North Carolina): Congratulations Dr. Claridge, on the fine presentation. It is my honor to discuss this paper by Dr. Young and his colleagues from the University of Virginia.

Their paper examines the hypothesis that I have held for 25 years but have been unable to prove in a definitive fashion in humans—I've tried to prove it in animals without much success—namely, that the duration of extensive hypoperfusion affects the risk for sepsis and mortality following trauma.

In this paper that you just heard, the authors describe a large group of trauma patients that were studied carefully to test this hypothesis. It's a fairly sick group of patients, in that 4.5% of their patients never resuscitated and died early.

The authors found the infection rate increased primarily in those who failed to correct their lactic acidosis before 12 hours. It was this group in which the increased mortality rate was most significant, particularly in those who failed to correct by 24 hours.

The study is well defined and clearly presented in both the article and the presentation. I have several questions to ask the authors.

First, why did the patients with hypoperfusion fail to correct their acidosis? Is this due to a combination of injury and hypothermia or other underlying processes?

Second, what was the mean time of correction of lactate in the group IV patients who did not correct within the first 24 hours?

The authors mentioned cost, and I would suggest that they probably should be talking about charges.

Finally, did the authors correlate their findings with EDVI? We have found this to be a very helpful measure of the adequacy of resuscitation.

I have one final comment. The authors provide an excellent discussion of cytokines in the article in which they point out the important difference between soluble cytokines and membrane-bound cytokines. Given the cytokines that they mentioned, do they think there is any one cytokine—for instance, IL-6, IL-8, or IL-10—which is more important in the failure to resuscitate than others in these patients?

Dr. Michael Chang (Winston-Salem, North Carolina): I have two quick questions. The first thing that struck me when I looked at this abstract was that a number of us in the audience would quibble with the terminology of 'occult hypoperfusion.' To a number of us, we would just call this 'obvious hypoperfusion' if the lactate is still elevated.

The question is, everything looked good right until we got to the conclusions where you made the statement that correcting occult hypoperfusion should improve outcome. All of us that do research in this area have the same problem, and that is that association does not imply causality. Could you comment on that, please?

Dr. Mark A. Malangoni (Cleveland, Ohio): I enjoyed your paper very much. I was impressed by two things: One, your high incidence of pneumonia, which most other studies have shown has correlated with ventilator days. You didn't mention that, and I wonder if you did any analysis to see if this is really a factor in patients who remained on the ventilator for a prolonged period of time or not? You must have some patients in your other groups that were on ventilators for prolonged periods of time, and I'd be interested in your comments there.

You also had a very high incidence of bloodstream infections, which is unusual in trauma patients, and I wonder if you could comment on the cause of that. Are these real bloodstream primary bacteremias or are they really catheter-related infections?

Dr. Frank W. Cross (London, England): I think this a very important paper. I enjoyed it very much.

The large increase in mortality in the OH group seems to me disproportionate to the rather small increase in the Injury Severity Score in the same group, and I wonder if there may be some increased incidence of intercurrent illness in these patients, i.e., preexisting conditions, which might contribute to their mortality?

Dr. Turner M. Osler (Burlington, Vermont): I assume you tried to resuscitate all of these patients. What you may have shown is that those who can't be resuscitated died.

Dr. Robert N. Cooney (Hershey, Pennsylvania): I'd like to congratulate the authors on an excellent study.

However, I have one major concern that relates to the concept of occult hypoperfusion. The authors have assumed that a persistent elevation in plasma lactate is caused only by an imbalance between oxygen delivery and consumption. This is not true. There is considerable evidence in the literature that hyperlactatemia may also be caused by primary mitochondrial dysfunction with normal tissue oxygen levels.

Since both trauma and sepsis are inflammatory conditions and are associated with the release of inflammatory cytokines, it may be that posttraumatic inflammation induces mitochondrial dysfunction, which accounts for the persistent elevation in lactate and is associated with the development of subsequent infectious complications. I believe this possibility needs to be considered as an alternative explanation for your findings.

Dr. Philip S. Barie (New York, New York): I congratulate the authors. These results are certainly in concordance with our own work regarding the resolution of the proinflammatory response vis-à-vis resuscitation in the first 24 hours.

I share Dr. Cooney's concern and would raise another possibility that is based on the work of Britton Chance with magnetic resonance spectroscopy and Dennis Gore's paper in the *Annals of Surgery* a couple of years ago. This may in fact be protein catabolism and metabolism failure. I believe we have to be careful about equating an increased lactate concentration with hypoperfusion. What we may actually be seeing here is derangement of the protein catabolic response as it relates to the pyruvate kinase pathway, and not hypoperfusion at all.

However, we were only provided data on systolic blood

pressure in the Emergency Department. I wonder whether there might be a component that's been overlooked here, which might be blood loss and shock on the operating table or even hypotension during the period of time of resuscitation in the intensive care unit. If those periods of hypotension had been added, would the situation have been changed?

Finally, what were the resuscitation data and were there any patients in whom early resuscitation failure led to a change in resuscitation strategy with salvage?

Dr. Rao R. Ivatury (Richmond, Virginia): Are you sure this is truly occult hypoperfusion, and is there any evidence for that, or could it be some cytotoxicity as well? Could you comment on that?

What exactly are the causes of failure to correct the lactate levels? Looking at the other numbers, you were pretty aggressive in your resuscitation, so why were you not successful? Were there complicating events that were overlooked?

Finally, most of us feel that global markers are no longer able to explain everything in the trauma patient who is massively traumatized, so could you comment on the role of tissue-specific resuscitation as well?

Dr. Orlando C. Kirton (Hartford, Connecticut): I echo many of the concerns of the previous discussants. The term "occult hypoperfusion" for many refers to a more regional than a global phenomenon. And I would echo that I'd like Dr. Claridge's team to be measuring much more of a global phenomenon.

I do have concerns on which I would ask the authors to comment. Regarding the resuscitation protocol, was the tempo of resuscitation similar and, specifically, what were the algorithms used? Were they identical among all groups?

Also, please comment regarding whether you should have utilized another measurement tool, i.e., tonometry or near infrared spectroscopy as a better measure of occult hypoperfusion phenomena.

Dr. Jeffrey A. Claridge (closing): Thank you very much for your comments, especially Dr. Baker for his discussion. I will attempt to answer them as best I can.

First, regarding the term 'occult hypoperfusion,' although it is true that perhaps not every patient was occult at all times, in general, we aimed to resuscitate everyone. However, at times, these patients are not in consistent signs of shock. So, in other words, they would look normal if you were just to do normal hemodynamic monitoring, such as blood pressure, urinary output, and heart rate. However, at times, of course, they exhibit signs of shock.

To follow up why they did not correct, one of the questions we often get asked is, 'Is there a subset of patients who would not respond anyway, and do sick patients die?' While that is

probably true, we feel that there is a subset of patients who would respond with more aggressive management.

Rapid correction is clearly beneficial. So that if you find a patient who's out 6 hours and he or she hasn't corrected yet, I think it's wise to be more aggressive and aim to correct by 12 hours.

As far as looking at the cytokines, the reason why we discussed that in the article was because we were clearly trying to find the role of cytokines. Dr. Baker mentioned the important ones, specifically TNF and IL-6, and we had the lengthiest discussion about them in our study. TNF seems to show a short elevation. It probably has more of a role in sepsis as opposed to IL-6, which we feel may have more of a role in trauma and posthemorrhage injury.

Regarding the question of whether the association means outcomes, of course we cannot say that changing this will result in a change in outcomes. It would be very hard for us to make, on the basis of this data, a randomized study saying that we were not going to aim to correct occult hypoperfusion in a subset of patients until 24 hours versus 12 hours. I think the data is definitely strong enough to convince ourselves that it is in the best interests of the patients to correct them by 12 hours.

Regarding some of the reasons why patients don't correct, we feel that prolonged ER times, prolonged trips to angio, prolonged trips sitting in radiology, perhaps prolonged transit to the operating room, or surgery by another service other than the trauma service—such as orthopedics and neurosurgery, where we are not the overall managers of the patient—may further prolong the patient's degree of hypoperfusion.

We anticipated the question regarding our resuscitation protocol. Basically, we have a protocol that is actually set up by 12 hours. If patients have persistent, consistent signs, i.e., persistent and consistent elevations of lactate acid greater than 2.4 separated by 4 hours, we then go ahead and put in a Swan-Ganz catheter and start them on dopamine and dobutamine, with a more aggressive fluid management directed by the Swan-Ganz catheter numbers. We have not yet looked at EDVI.

As far as looking at ventilator days, yes, there is a correlation between the length of ventilator days and incidence of pneumonia. However, we did not specifically look at the ventilator days as a predictor of infection in this group. Also we didn't look at the number of blood transfusions.

Regarding the question about catheter-related infections as primary bloodstream infections, these were analyzed (two thirds were by some other source, and one third were catheter-related); there was a small number in which we actually never determined the source.

I believe I've answered most of the questions. Thank you very much.