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Nosocomial Infections after Severe Trauma Are Associated With Lower Apolipoproteins B and AII

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Abstract

BACKGROUND—Infection following severe trauma is a significant cause of morbidity and mortality days to weeks after the initial injury. Apolipoproteins play important roles in host defense and circulating concentrations are altered by the acute inflammatory response. The purpose of this study was to determine if patients who acquire infection following severe trauma have significantly lower apolipoprotein levels than trauma patients who do not become infected.

METHODS—We conducted a case-control study on a prospectively identified cohort of adult patients admitted to our intensive care unit after severe trauma (Injury Severity Score ≥ 16). We compared plasma apolipoprotein levels between patients who acquired an infection within 30 days after trauma (cases) and those that remained infection free (controls).

RESULTS—Of 40 patients experiencing severe trauma, we identified 22 cases that developed an infection within 30 days after injury. Cases had significantly lower post-trauma plasma levels of apolipoprotein-B ($p=0.02$) and apolipoprotein-AII ($p=0.02$) compared to controls. Consistent with previous studies, cases also received greater volumes of crystalloid infusions ($p<0.01$) and blood transfusions ($p<0.01$). Cases also had a more profound inflammatory response as measured by Interleukin-6 levels ($p=0.02$).

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CONCLUSIONS—Infection after severe trauma is associated with decreased circulating apolipoproteins as compared to uninfected controls. Profoundly decreased plasma apolipoproteins B and AII could potentially contribute to the impaired immunity after severe trauma. Apolipoproteins are potential targets for identifying those patients at risk of infection after trauma and for interventions aimed at preventing nosocomial infections.

Infections cause the majority of morbidity and mortality in trauma patients who survive the initial trauma and subsequent resuscitation [1]. To decrease patient morbidity, mortality, and health care costs from post-trauma infections requires identification of those at risk of infection and development of appropriate preventive interventions. Risk factors identified for infection after trauma include the severity of the initial trauma [2,3], blood transfusions [4,5] and the magnitude of the initial inflammatory response [6,7]. These risk factors are useful for calculating the expected mortality after trauma [2,8], but offer limited insights into the mechanisms underlying the risk of infection.

Apolipoproteins participate in specific host defense mechanisms against a broad range of microbes important in post-trauma infections. Previous studies on the systemic inflammatory response syndrome and sepsis revealed decreases in circulating apolipoproteins correlated with the severity of infection [9]. These observations suggest that in trauma, where a profound inflammatory response is associated with the development of infection [7], apolipoproteins could be decreased and potentially play a direct role in the diminished host defense observed after trauma. To date, there are no studies evaluating the changes in circulating apolipoproteins after trauma and their association with infection risk.

Severe trauma causes profound disruptions in homeostasis measurable by alterations in soluble mediators of inflammation [6,10], defects in phagocyte function [11–14], and abnormal coagulation [15] that are thought to contribute to the immunosuppression that follows severe trauma [16]. Because serum lipoprotein concentrations, including high density lipoprotein (HDL), low density lipoprotein (LDL), and very low density lipoprotein (VLDL), are also altered by the acute inflammatory response [17], we postulated that circulating levels of lipoproteins might be altered following severe trauma. Whereas lipoproteins and their protein constituents (apolipoproteins) have been primarily studied for their role in the development of cardiovascular disease [18,19], increasingly they are being recognized as contributors to host defense against bacterial pathogens, including the prevention of invasive bacterial disease [20–26] and lower levels could contribute to the risk of infection. The goal of this study was to determine if patients who acquired an infection after severe trauma had decreased amounts of circulating apolipoproteins after trauma compared to patients who remained infection free.

Materials and Methods

Patients

Enrollment criteria were admission to the Trauma-Surgical Intensive Care Unit (TSICU) at the University of New Mexico (UNM) Hospital after trauma, injury severity score (ISS) 16, 18 years of age or older, negative pregnancy test, and patient consent or consent by a legally authorized representative. Blood was collected in standard heparin containing tubes within the first day of admission and on the subsequent second and third days after admission. Plasma removed after centrifugation was aliquotted and stored at -80°C until analysis. All samples and information were obtained in accordance with the guidelines and protocols approved by Human Research Protections Office at the UNM Health Science Center. A subset of this study's patient population was previously characterized [11]. This study is a nested case-control study that is a pre-planned secondary analysis of a convenience sample of prospectively identified patients who had suffered severe trauma. All

patients were able to provide consent or had a legally authorized representative who was able to provide consent. Even if a patient was able to provide assent a legally authorized representative was contacted before a patient was enrolled in the study. Patients were enrolled from July of 2008 through October of 2011. Clinical data were obtained from review of the electronic medical record (EMR). Injury severity scores were calculated as previously described [2,3]. APACHE II scores were calculated from values obtained in the EMR. In patients with missing values, APACHE II scores were not calculated (n=9). The subjects characterized in this study are part of an ongoing effort to better understand the changes in immune function after severe trauma.

Apolipoprotein concentration measurement

We measured Apolipoprotein B by enzyme-linked immunosorbent assay (ELISA) according to manufacturer's instructions (AlerCHEK™, Inc, Springvale, Maine, USA).

Apolipoproteins AI, AII, B, CII, CIII, and E were measured simultaneously using Millipore™ brand multiplex beads. Patient samples were analyzed at either 1:100 or 1:1000 dilutions.

Infection Definition

Infection was defined by the presence of a positive culture within 30 days of admission after trauma combined with the appropriate clinical findings as described by the Centers for Disease Control (CDC) criteria [27]. The EMR was evaluated to determine if the appropriate clinical criteria were present. Patients were defined as cases if they met infection criteria and those without positive microbial cultures or lack of appropriate supportive clinical findings within 30 days after severe trauma were defined as controls.

Statistical Analysis

Graphics, including receiver operating characteristics curves (ROC), were generated using Prism software version 5.0 (GraphPad, La Jolla, CA, USA). Statistical analysis was performed using SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA). Statistical significance was determined at $\alpha = 0.05$. Unless otherwise noted, p values were rounded to two decimal places. Categorical variables were tested for significance using a Fisher's Exact Test. Continuous variables were first analyzed for normality using the Shapiro-Wilk Normality Test. Variables that had a normal distribution were tested using a two-sample ANOVA, variables that did not meet normal distribution criteria were tested using the Wilcoxon Two Sample Test and are indicated as such with a ‡. Statistical consultation with Dr. Murray-Krezan of the University of New Mexico's Clinical and Translational Science Center was supported in part by the National Center for Research Resources and the National Center for Advancing Translational Sciences of the National Institutes of Health through Grant Number 8UL1TR000041, The University of New Mexico Clinical and Translational Science Center.

Results

Severely injured trauma patients are at high risk of infection

Patients enrolled in our study had a high incidence of infection (55%, Table 1). Subjects were 41 ± 16 years of age (mean $\pm$ SD), predominantly male (70%), and the majority suffered blunt trauma (88%). Patients acquired an infection a median of 5.5 days after trauma (IQR 3–9). We identified 29 positive cultures from 22 different patients. Cultures were obtained from tracheal aspirates, urine, blood, and wounds and corresponded to diagnosed infections of pneumonia, urinary tract infections, and blood stream infections. Three infections including wound infections and a case of meningitis were also identified. Organisms were primarily Gram negative with *Escherichia coli* and *Acinetobacter*

baumannii being the most prevalent (Table 1). *Staphylococcus aureus* accounted for three infections and in one patient was isolated from multiple sources. Reported culture results in Table 2 are from a patient's first recorded infection. Several subjects had multiple infections over the study period including additional Gram positive infections, especially *Staphylococcus aureus*. The three primary *S. aureus* infections represent approximately 14% of identified infections.

Subjects infected after trauma have significant physiologic disturbances within the first 24 hrs

Clinical characteristics measured within the first day of hospitalization were compared between cases (acquired infection by day 30) and controls (infection free following severe trauma). Both groups had elevated glucose, white blood cell counts, lowered blood pH, and abnormally low PaO₂/FiO₂ ratios (Table 2). Of these, pH ($p = 0.02$) and the PaO₂/FiO₂ ratio ($p = 0.03$) were statistically different between study groups. Cases had significantly lower initial Mean Arterial Pressures (MAPs) when compared to controls 78 ± 27 versus 100 ± 16 (mean $\pm$ SD, $p = 0.01$). Table 2 shows that cases had significantly higher injury severity scores (ISS) ($p = 0.01$) and higher APACHE II scores ($p=0.01$).

Infected patients require more hospital resources

Patients who acquire infections after trauma utilize significantly more resources than patients who remain infection free [28]. We examined fluid administration (blood products and crystalloid solutions), days in the hospital, days in the intensive care unit, and ventilator-dependent days. Table 2 shows that cases received nearly twice as much pre-admission volume of crystalloid solutions compared to controls (4.0 ± 1.7 vs. 2.2 ± 1.6 , Mean liters of fluid $\pm$ SD, $p<0.01$). Cases received significantly greater amounts of blood products compared to controls ($p<0.01$). Twenty-seven patients received blood products with only 11 receiving plasma. All patients acquiring an infection received blood products. Subsequent infection led to prolonged lengths of stay ($p<0.01$) compared to controls, including days in the ICU and more ventilator dependent days (Table 2).

Patients received prophylactic antibiotics independent of CDC criteria for infection

Consistent with the incidence of severe injuries including open fractures, 65% of all enrolled subjects received prophylactic antibiotics within the first day of trauma (Table 1). In addition, 88% received antibiotics within 7 days after trauma, typically first generation cephalosporins. Even in the absence of overt infection, some patients received full courses of antibiotics for obviously contaminated injuries such as penetrated viscera. There was no significant difference in antibiotic administration between cases and controls (Table 1).

Trauma induces an exuberant inflammatory response

Using a Luminex based multiplex assay, we found that cases had significantly higher amounts of Interleukin-6 (IL-6) within the first 3 days after trauma (Figure 1) compared to controls. Interleukin-10 (IL-10) levels were significantly higher in cases within the first two days after trauma (Figure 1). The highest levels of both IL-6 and IL-10 were measured within the first day after trauma.

Post Trauma apolipoproteins B and AII levels are lower in cases compared to controls

Cases had lower plasma apolipoprotein B (apoB) compared to controls post-trauma ($p=0.02$, Figure 2). Mean and median apoB levels for cases were below the established lower limit of normal. We examined the effect of trauma on apolipoproteins AI, AII, CII, and E using a multiplex assay on samples from days 1–3 post-trauma. Cases had significantly lower apolipoprotein AII (apoAII) ($p=0.02$, Figure 3). ApoAI levels were lower in cases, however

this did not reach statistical significance ($p = 0.053$). Apolipoproteins CII and E levels were not significantly different between cases and controls (Figure 3).

Day 1 apolipoprotein levels correlate with risk of infection

To further analyze the relationship of apolipoprotein levels and the risk of infection we examined receiver operating characteristic (ROC) curves of apolipoproteins and nosocomial infection. ROC curves of apolipoprotein levels and infection revealed a significant association of apoAII ($p=0.02$) and apoB ($p=0.03$) with later infection (Figure 4). We compared this to other known risk factors of infection including IL-6 (as a measure of inflammation), ISS, and blood transfusion volume. Area under the curve calculations and p -values for each marker tested are shown in Figure 4. The relationship between apoAI and infection was not statistically significant at $\alpha = 0.05$ ($p = 0.051$) with an area under the curve of 0.69. Neither apoCII, nor apoE were associated with risk of acquiring infection. The difference in the median values of apoAII and apoB between cases and controls was approximately 20 mg/dL. We found that an absolute reduction in apoAII of 20 mg/dL was associated with significantly increased odds for the development of infection (OR 2.7; 95% CI 1.1–6.6). For apoB, a drop in plasma concentration of 20 mg/dL was also significantly associated with increased odds of infection (OR 1.9; 95% CI 1.1–3.6). IL-6, ISS, crystalloid administration, and blood transfusions were also associated with increased odds of infection (Figure 4). These data demonstrate that early changes in apolipoproteins are associated with the risk of later nosocomial infection.

Discussion

The primary goal of this case-control study was to determine if apolipoprotein levels were reduced early following severe trauma in patients who acquired an infection compared to trauma patients who remained infection free. We found significant differences in both early apoAII and apoB levels between those who became infected within 30 days of severe trauma and those that remained infection free. These findings suggest that low apolipoprotein levels are associated with a risk of infection after trauma. Whether these changes contribute to impaired host defense or indicate profound alterations in metabolism and physiology that contribute to impaired host defense is currently unknown.

Apolipoproteins play important roles in the innate immune response to bacterial infection, particularly against *S. aureus* [26] and *E. coli* [20]. In the current study, *E. coli* was the predominant organism and *S. aureus* was the predominant Gram positive organism causing infection consistent with the causes of most nosocomial infections. The role of apoAI in host innate defense against *E. coli* includes inhibition of bacterial growth and clearance of endotoxin [20]. ApoAI is involved in complement activation and killing of the Gram negative pathogen *Yersinia enterocolitica* [21]. Both apoAI and apoAII support paraoxonase activity that plays a role in disrupting virulence factor regulation by *Pseudomonas aeruginosa* [22–24]. ApoB also disrupts *Staphylococcus aureus* virulence regulation thus inhibiting invasive infection [26]. HDL, which contains apoAI and apoAII, disrupts *S. aureus* toxin function [25]. Our observations suggest that decreased control of bacterial virulence combined with defects in phagocytosis, impaired coagulation, and monocyte deactivation creates an environment that favors disseminated infections.

Our data indicate that lower plasma apolipoprotein B and AII levels associate with the risk of acquired infection following severe trauma. Several factors likely contribute to the lowering of these host defense proteins in our cases including dilution by transfusion of blood and crystalloid solutions, IL-6 mediated suppression of apoB synthesis, and increased consumption of lipoproteins required to produce cortisol following this profound stress. Our cases received increased blood products, and while this is a known contributor to infection

[29], the mechanism is not defined. Although dilution of plasma apolipoproteins is one potential answer, other circulating constituents such as glucose, white blood cell count, platelets and creatinine were not different between cases and controls (table 2), in fact IL-6 and IL-10 were elevated (Figure 1). Because our cases had significantly elevated IL-6 levels and IL-6 is known to decrease apoB synthesis [30], the profound acute phase response is likely to be a contributor to lower plasma lipoprotein levels. In addition, the increased injury severity scores in our cases indicates that stress induced cortisol levels are likely to be higher contributing to consumption of lipoproteins to provide the cholesterol necessary for cortisol synthesis. All of the study participants had disruptions in normal nutrition as necessitated by their care. The impact of this disruption on apolipoprotein levels is not known.

Measuring apolipoprotein levels is clinically available now and validated for use in cardiovascular risk assessments. We show that severely injured trauma patients with apoB levels less than 50% of the lower limit of normal have the highest risk of subsequent hospital acquired infections following trauma. These findings identify a role for apolipoproteins in the altered host defense after trauma and suggest they may be valuable as a predictor of infections in severely injured trauma patients. The ROC curves presented in figure 4 reveal that apolipoproteins measured as single entities predict infection as well as IL-6 levels, Injury severity score, or crystalloid infusion volume. Combining apoB and apoAII together strengthens their predictive value (data not shown). Apolipoprotein measurement has the potential to be a better marker for development of infection because it has the advantage of being easily measured with currently existing laboratory infrastructure, does not rely on the calculation of a complex multifactorial clinical score (such as the APACHE II score), and is objective with a clear normal range established through studies on cardiovascular risk.

We have identified novel changes in the innate host defense of patients who become infected after trauma. Our findings suggest a mechanism involving the depletion of host defense elements, potentially allowing host microbiota to cause invasive infections. This identifies a need for interventions that target this deficiency in addition to enhanced clinical practices that reduce nosocomial infections. Patients in our study were all admitted to the trauma-surgical intensive care where despite measures including private patient rooms, rigorous attention to hand hygiene, and prophylactic antibiotics, a significant subset acquired infections that contributed to prolonged lengths of stay and therefore to increased health care costs. The high propensity of these patients to become infected in the presence of optimal infection control measures suggests that patients may be infected with bacteria that were part of their normal flora. This is consistent with previous data where *S. aureus* and Gram negative bacteria such as *E. coli* are the primary nosocomial pathogens [31][28]. If patients are acquiring specific immune defects accounting for their increased rates of infection, then additional interventions must be designed and employed to prevent these infections. Our findings offer an additional potential contributor for explaining post-trauma immunosuppression and should be considered when designing and evaluating protocols to reduce nosocomial infections after trauma.

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Figure 1.
Interleukin-6 and Interleukin-10 responses post trauma.

Figure 2.
Circulating plasma apolipoprotein B levels in patients the first 3 days after trauma.

Figure 3.
First day after trauma plasma concentrations of apolipoproteins AI, AII, CII, and E.

Marker	AUC	95% CI	<i>p</i>	OR (CI)	per Unit
Apolipoprotein-AII	0.73	0.55 to 0.90	0.02	2.7 (1.1-6.6)	20 mg/dL
Apolipoprotein-B	0.72	0.54 to 0.90	0.03	1.9 (1.1-3.6)	20 mg/dL
Interleukin-6	0.76	0.59 to 0.93	0.02	2.2 (0.9-5.0)	10 pg/mL
Injury Severity Score	0.73	0.57 to 0.89	0.01	2.1 (1.1-4.0)	10
Pre-Admission Fluid	0.77	0.62 to 0.92	<0.01	1.9 (1.2-3.0)	1 Liter
Blood Transfusions	0.90	0.80 to 1.00	<0.01	2.0 (1.3-3.1)	400 mLs

AUC, Area Under the Curve; CI, Confidence Interval; ISS, Injury Severity Score; OR, Odds Ratio

Odds Ratios are given per change in unit. For Apo-AII and Apo-B the unit changes are decreases, for all other markers the changes are increases.

Figure 4.

Receiver Operating Characteristic curves of markers significantly different between controls and infected subjects after severe trauma.

Table 1

Patient and Infection Characteristics

Patients (n)	All (40)	Controls (18)	Infected (22)	p
Age, Median (IQR)	38 (25–55)	30 (23–46)	48 (29–56)	0.10 [‡]
Gender, n (%)				
Male	28 (70%)	13 (72%)	15 (68%)	1.00 [‡]
Female	12 (30%)	5 (28%)	7 (32%)	
Trauma Type, n (%)				
Blunt	35 (88%)	14 (78%)	21 (96%)	0.16 [‡]
Penetrating	5 (12%)	4 (22%)	1 (4%)	
Antibiotic use, n (%)				
First 24 hours	26 (65%)	11 (61%)	15 (68%)	0.74 [‡]
First week	35 (88%)	14 (78%)	21 (95%)	0.11 [‡]

First Infections	Days after trauma		
	n	Mean +/- SD	Median (IQR)
All	29	7 +/- 5	6 (3–9)
Pneumonia	11	8 +/- 6	7 (4–9)
Urinary Tract Infection	10	12 +/- 7	11 (6–16)
Blood Stream Infection	5	6 +/- 2	6 (4–8)
Other Infection	3	6 +/- 1	6 (5–7)

First Cultured Organisms			
Gram Negative	n	Gram Positive	n
<i>Escherichia coli</i>	8	<i>Staphylococcus aureus</i>	3
<i>Acinetobacter baumannii</i>	4	<i>Staphylococcus epidermidis</i>	2
<i>Enterobacter cloacae</i>	2		
<i>Enterobacter faecalis</i>	2		
<i>Pseudomonas aeruginosa</i>	2	Fungi	n
<i>Klebsiella pneumoniae</i>	2	<i>Candida parapsilosis</i>	1
<i>Bacteroides fragilis</i>	1	<i>Candida albicans</i>	1
<i>Citrobacter koseri</i>	1		
<i>Enterobacter aerogenes</i>	1		
<i>Proteus mirabilis</i>	1		
<i>Serratia marcescens</i>	1		

[‡] Fisher's Exact Test,

[‡] Wilcoxon Two Sample Test

Table 2

Clinical Characteristics

Physiology Measures	Controls			Infected by day 30		
	Mean +/- SD	Median	IQR	Mean +/- SD	Median	IQR
Systolic Blood Pressure (mmHg)	129 +/- 18			100 +/- 35		
Diastolic Blood Pressure (mmHg)	85 +/- 18			67 +/- 24		
Mean Arterial Pressure (mmHg)	100 +/- 16			78 +/- 27		
Heart Rate (bpm)	103 +/- 18			107 +/- 33		
Temperature (°Celsius)	36.3 +/- 0.6			35.7 +/- 1.2		
Respiratory Rate		20	18 – 25		22	15 – 26
Oxygen Saturation (%)		99	96 – 100		96	93 – 98
Clinical Scores	Mean +/- SD	Median	IQR	Mean +/- SD	Median	IQR
Glasgow Coma Scale		15	14 – 15		12	3 – 15
Injury Severity	26 +/- 12			35 +/- 11		
APACHE II	8.8 +/- 6.4			16 +/- 6.8		
Laboratory Measures	Mean +/- SD	Median	IQR	Mean +/- SD	Median	IQR
Glucose (mg/dL)	(60 – 100)	135	122 – 165		144	131 – 188
White Blood Cell Count ($\times 10^3$)	(4.0 – 10.6)	15	9.8 – 21		14	12 – 25
Platelet Count ($\times 10^3$)	(150 – 400)	233	201 – 281		237	159 – 298
Creatinine (mg/dL)	(0.80 – 1.30)	1.1	0.8 – 1.3		1.0	0.8 – 1.2
Hematocrit (%)	(F 36 – 48), (M 42 – 53)	39 +/- 5.6		39 +/- 5.2		
Arterial Blood Gas pH	(7.39 – 7.42)	7.33 +/- 0.07		7.26 +/- 0.08		
PaO ₂ /FIO ₂		313 +/- 137		218 +/- 100		
Fluid Resuscitation	Mean +/- SD	Median	IQR	Mean +/- SD	Median	IQR
Pre-admission Crystalloid administration (L)	2.3 +/- 1.6	1.9	1.0 – 3.3	4.0 +/- 1.7	3.8	2.9 – 5.2
Blood Products Transfused (L)		0.0	0.0 – 1.2		2.4	1.4 – 7.8
Packed Red Blood Cells transfused (L)		0.0	0.0 – 1.2		2.1	1.2 – 4.5

Physiology Measures	Controls				Infected by day 30				p
	Mean +/- SD	Median	IQR		Mean +/- SD	Median	IQR		
Plasma transfused (L)		0.0	0.0 – 0.0			0.0	0.0 – 2.0		<0.01 ‡
Outcomes		Median	IQR			Median	IQR		p
Length of Stay (days)		11	5 – 15			30	22 – 54		<0.01 ‡
ICU Length of Stay (days)		3	1 – 4			17	12 – 25		<0.01 ‡
Ventilator Dependent Days		0	0 – 1			16	9 – 21		<0.01 ‡

Data meeting criteria for normality (Shapiro-Wilk $p > 0.05$) are represented as Mean +/- SD.
Data not meeting this criteria are presented as the median with the interquartile range (IQR).
These were evaluated using the Wilcoxon Two Sample Test and are signified by a ‡.