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# The Relationships of Hypocholesterolemia to Cytokine Concentrations and Mortality in Critically Ill Patients with Systemic Inflammatory Response Syndrome

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## ABSTRACT

*Background*: Decreased concentrations of total cholesterol, lipoproteins, and lipoprotein cholesterols occur early in the course of critical illness. Low cholesterol concentrations correlate with high concentrations of cytokines such as interleukin (IL)–6 and IL-10, and may be due to decreased synthesis or increased catabolism of cholesterol. Low cholesterol concentrations have been associated clinically with several adverse outcomes, including the development of nosocomial infections. The study was performed to test the hypothesis that a low cholesterol concentration predicts mortality and secondarily predicts the development of organ dysfunction in critical surgical illness.

*Methods*: A prospective study was undertaken of 215 patients admitted to a university surgical ICU with systemic inflammatory response syndrome (SIRS). Serial blood samples were collected within 24 h of admission, as well as on the morning of days 2, 4, and 7 of the ICU stay for as long as the patients were in the ICU. Demographic data and predetermined outcomes were noted.

*Results*: One hundred nine patients had at least two samples drawn and form the population for analysis. Sixty-two of the patients had three samples obtained, whereas 42 patients had four samples obtained. By univariate analysis, non-survivors were more severely ill on admission (APACHE III), more likely to have been admitted to the ICU as an emergency, more likely to develop a nosocomial infection, and more likely to develop severe organ dysfunction (MODS) (all, $p < 0.05$). Death was associated on day 1 with increased concentrations of sIL-2R, IL-6, IL-10, and sTNFR-p75 (all, $p < 0.01$), but there were initially no differences in serum lipid concentrations. However, by day 2, concentrations of IL-6, IL-10, and cholesterol had decreased significantly (all, $p < 0.05$) from day 1 in non-survivors but not in survivors; the difference in serum cholesterol concentration persisted to day 7 ($p < 0.05$). Persistently elevated concentrations of IL-6 and IL-10 were observed in patients who developed severe MODS. By logistic regression, increased APACHE III score, development of a nosocomial infection, and decreased cholesterol concentration were independently associated with mortality.

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*Conclusions:* **Decreased serum cholesterol concentration is an independent predictor of mortality in critically ill surgical patients. Repletion of serum lipids is a feasible therapeutic approach for the management of critical illness.**

SYSTEMIC INFLAMMATORY RESPONSES can result from activation of host defenses following either injury or infection. The systemic inflammatory response syndrome (SIRS) is characterized in part by widespread activation of immune cells and the elaboration of cytokines, such as tumor necrosis factor–alpha (TNF-$\alpha$) and interleukin-1 (IL-1), and other moieties [1]. Up-regulation of the pro-inflammatory response also consists of activation of coagulation, complement, and the kinin systems, activation of neutrophils and mononuclear cells, and disruption of the microcirculation. Vasoreactivity leads to tissue edema, hypovolemia, and hypoxemia; hemodynamic instability, acidosis, and shock may result. Also characteristic of SIRS is altered hepatic function with disrupted hepatocyte–Kupffer cell interactions [2], leading to disruption of reticulothelial host defenses as well as altered carbohydrate, protein, and lipid metabolism. Numerous mechanisms have been elucidated, but specific, effective treatment and prophylaxis remain elusive.

The systemic pro-inflammatory response is believed to be mitigated by an anti-inflammatory counter-regulatory response, consisting in part of the elaboration of glucocorticoids, IL-4, IL-10, and other factors. Although the components of the putative counter-regulatory response are increasingly well described, clinical outcomes remain variable and difficult to predict. The SIRS may resolve spontaneously following surgical stress, or may persist with deleterious clinical consequences [3], including an increased risk of the development of nosocomial infection, multiple organ dysfunction syndrome (MODS), or death. This risk is present regardless of whether the inflammatory response is sterile, or as a result of infection (sepsis).

The relationship of inflammation and its resolution with the progression of SIRS to MODS remains a matter of speculation. Adverse consequences may result from exuberant inflammation that overwhelms maximal compensatory mechanisms, from an inadequate anti-inflammatory response to a typical stimulus, or from temporal malalignment of the inflammatory "ebb and flow" (e.g., the "second-hit" phenomenon) [4]. Incomplete understanding of these inter-relationships and their impact on outcome may be due to several factors, e.g., lack of clinically relevant anti-inflammatory markers, failure to identify as yet markers that may be informative, irrelevance of detectable circulating markers, or faulty interpretation of observations already made (i.e., linear descriptions of complex, non-linear systems).

It has been observed that concentrations of total and lipoprotein cholesterol decrease markedly in the early phases of critical illness [5,6]. Moreover, there is increasing evidence that cholesterol metabolism is related to inflammation [7–9], and indeed, may regulate and be regulated by proinflammatory cytokines [10–13]. Low cholesterol concentration has been associated with relevant clinical outcomes including death, development of nosocomial infection, length of intensive care unit stay, and the magnitude of organ dysfunction [5,14]. This study was performed to test the hypothesis that low cholesterol concentration is related to the development of organ dysfunction and mortality in critically ill surgical patients admitted with SIRS, and to delineate further the relationships among pro- and anti-inflammatory cytokines and cholesterol metabolism.

## PATIENTS AND METHODS

The study was performed in the surgical ICU of New York–Presbyterian Hospital–New York Weill Cornell campus, after approval of the study by the Committee on Human Rights in Research of Weill Medical College of Cornell University. Eligible patients were those admitted with SIRS ($\geq$2 criteria), regardless of etiology or severity of illness. Oral informed con-

sent was obtained from all patients. Demographic data collected included age, gender, admission diagnosis, admission status (elective/emergency), whether phenytoin (raises cholesterol concentration) or statin drugs (lowers cholesterol concentration) were administered recently or concurrently, severity of illness (APACHE II, III) [15,16], development of a nosocomial infection (CDC criteria) [17], incidence (MOF) and magnitude (MMOD) of organ dysfunction (Marshall criteria) [16], ICU length of stay (ULOS), and mortality.

Serial blood samples were obtained within 24 h of ICU admission (day 1) and thereafter on the morning of days 2, 4, and 7 for as long as the patient remained critically ill and in the ICU. Samples were iced immediately and centrifuged; serum was frozen at −70°C for later analysis. Samples were analyzed for total bilirubin concentration, concentrations of total, HDL- and LDL-cholesterol, apolipoprotein A, and triglycerides by enzymatic methods (Roche Diagnostic Systems, Indianapolis, IN). Concentrations of IL-1, sIL-2r, IL-6, IL-10, TNF-$\alpha$, sTNFR p55, and sTNFR p75 were assayed by automated ELISA (Roche COBAS Core II, Roche Diagnostic Systems, Basel, Switzerland).

Statistical analysis was performed using commercial software (Statview 4.1 with SuperANOVA 1.1.1, ACIUS Inc., Cupertino, CA; True EpiSTAT, EpiSTAT Services, Richardson, TX). The primary endpoint was mortality, and the principal secondary endpoint was the magnitude of organ dysfunction. Univariate analysis of coordinate variables was performed by chi-square with Fisher exact test, and univariate analysis of continuous variables was performed by Mann-Whitney U-test. Changes in continuous variables with respect to time were analyzed by repeated-measures analysis of variance (ANOVA) with Bonferroni correction, and correlations were made by the Pearson method. Statistical significance was defined at $\alpha = 0.05$. Univariate results of possible statistical significance ($\alpha < 0.15$) were tested in multivariate models for independence of effect upon defined dependent outcome variables after auto-correlation was excluded by matrix correlations and the Durbin-Watson test. The factors influencing MMOD, analyzing MMOD as a continuous dependent variable, were tested by multivariate ANOVA. The factors influencing mortality were analyzed by logistic regression. Odds ratios and 95% confidence intervals were determined, and the sensitivity, specificity, and goodness of fit (model chi-square) were determined for each logistic regression model.

## RESULTS

Two hundred fifteen patients contributed 431 blood samples. Only a single sample was obtained from 106 patients; thus, this analysis is based on data from 109 patients who contributed at least two serial samples. Eighteen of the patients were taking phenytoin (which can increase serum cholesterol concentration), whereas nine patients were taking a statin drug

TABLE 1. DEMOGRAPHICS OF PATIENTS WHO HAD MULTIPLE SAMPLES DRAWN

| | *All* | *Survivors* | *Non-survivors* | *P-value* |
|---|---|---|---|---|
| N | 109 | 82 | 27 | |
| Age | 64.5 ± 1.6 | 63.7 ± 1.9 | 69.9 ± 2.9 | 0.4055 |
| Female gender (%) | 45.8 | 46.9 | 42.9 | 0.8267 |
| APACHE II | 19.8 ± 0.6 | 17.5 ± 0.6 | 26.6 ± 1.1 | <0.0001 |
| APACHE III | 66.2 ± 2.7 | 56.3 ± 2.3 | 96.4 ± 5.1 | <0.0001 |
| SIRS score | 2.8 ± 0.1 | 2.8 ± 2.1 | 2.9 ± 0.1 | 0.6952 |
| ULOS | 7.7 ± 1.0 | 6.5 ± 1.2 | 11.4 ± 1.9 | 0.0361 |
| MOF (%) | 78.9 | 71.9 | 100 | 0.0008 |
| MMOD | 6.1 ± 0.5 | 3.6 ± 0.4 | 13.3 ± 0.7 | <0.0001 |
| Emergent (%) | 62.4 | 56.1 | 81.5 | 0.0220 |
| Nosocomial infection (%) | 30.1 | 23.2 | 51.9 | 0.0076 |
| Admitted with sepsis (%) | 21.1 | 19.5 | 25.9 | 0.5870 |
| Statin (%) | 8.2 | 8.5 | 7.4 | >0.9999 |
| Phenytoin (%) | 16.5 | 14.6 | 22.2 | 0.3780 |

TABLE 2. DAY 1 SERUM CONCENTRATIONS FOR 109 PATIENTS, STRATIFIED BY SURVIVAL

| *Parameter* | *All* | *Survivors* | *Non-survivors* | P-*value* |
|---|---|---|---|---|
| Lipids/lipoproteins | | | | |
| Cholesterol | 135.1 ± 5.5 | 133.1 ± 4.9 | 140.8 ± 16.5 | 0.5496 |
| Triglycerides | 157.1 ± 15.6 | 139.3 ± 4.9 | 208.6 ± 56.6 | 0.0519 |
| HDL-cholesterol | 30.9 ± 1.7 | 32.2 ± 1.8 | 27.3 ± 4.0 | 0.1628 |
| LDL-cholesterol | 73.9 ± 4.0 | 73.3 ± 4.0 | 75.9 ± 10.6 | 0.6661 |
| VLDL-cholesterol | 31.4 ± 3.1 | 27.9 ± 1.5 | 41.7 ± 11.3 | 0.0519 |
| Apolipoprotein A | 81.8 ± 3.4 | 85.2 ± 3.6 | 71.7 ± 7.7 | 0.0831 |
| Apolipoprotein B | 64.8 ± 3.4 | 63.2 ± 2.7 | 69.6 ± 8.9 | 0.4779 |
| Cytokines | | | | |
| sIL-2R | 0.76 ± 0.06 | 0.63 ± 0.05 | 1.20 ± 0.20 | 0.0021 |
| IL-6 | 1121.1 ± 348.6 | 537.2 ± 185.5 | 2894.4 ± 1245.8 | 0.0031 |
| IL-10 | 17.9 ± 5.8 | 8.3 ± 2.1 | 46.9 ± 22.1 | 0.0038 |
| sTNFR-p55 | 6.4 ± 1.1 | 5.6 ± 1.2 | 8.6 ± 2.7 | 0.2504 |
| sTNFR-p75 | 9.9 ± 0.8 | 8.7 ± 0.6 | 13.9 ± 2.4 | 0.0034 |

(which can decrease serum cholesterol concentration); neither drug confounded the results. Sixty-two patients contributed three samples, whereas 42 patients contributed the maximum four samples. The mean age of the patients was 64 ± 2 years (Table 1). The mean APACHE III score was 66 ± 3 points, and the mean SIRS score was 2.8 ± 0.1 points. The mortality rate was 24.7%. Patients who died were significantly more ill (by APACHE scores) on admission, but there was no difference in the percentage of patients admitted with sepsis of any type. Patients who survived had a significantly shorter length of stay, whereas patients who died were more likely to have been admitted emergently to the ICU, to develop a nosocomial infection, to develop organ failure, and had a significantly higher MOD score (Table 1).

Admission data for biochemical analyses are presented in Table 2. Without stratification, the mean total cholesterol concentration was 135 ± 6 mg/dL. On admission, there were no differences between survivors and non-survivors for the concentration of any lipid or lipoprotein. In contrast, circulating concentrations of several cytokines were higher in the non-survivors, including sIL-2r, IL-6, IL-10, and sTNFr-p75 (Table 2).

Among patients who remained in the ICU for serial blood sampling, SIRS was persistent over time, and similar in magnitude between survivors and non-survivors (Table 3). Among the 109 patients studied twice, there were significant decreases in concentrations of cholesterol, IL-6, and IL-10 from day 1 to day 2. These decreases were significantly larger among non-survivors (Table 4, Figs. 1 and 2). By day 7, a significant decrease persisted only for the decrease in serum cholesterol (Table 5, Fig. 1).

The mean MMOD score was 6.1 ± 0.5 points, and differed significantly between survivors and non-survivors (3.6 ± 0.4 vs. 13.1 ± 0.7 points, $p < 0.0001$) (Table 1). Using the mean MMOD score of six points as a discriminator, serum cholesterol decreased from day 1 to day 2 in non-survivors compared with survivors, and increased in non-survivors to a significantly lesser degree by day 7 (Fig. 3). A higher MMOD score was associated with significantly higher serum concentrations of IL-6 and IL-10 that were not sustained (Fig. 3). There was no correlation ($r^2 = 0.07$) between serum bilirubin

TABLE 3. CHANGES IN SIRS SCORES OVER TIME

| *Day* | *1* | *2* | *4* | *7* |
|---|---|---|---|---|
| N | 215 | 109 | 62 | 42 |
| Survivors | 2.83 ± 0.09 | 2.74 ± 0.08 | 2.61 ± 0.16 | 2.57 ± 0.22 |
| Non-survivors | 2.89 ± 0.14 | 2.85 ± 0.14 | 2.45 ± 0.20 | 2.81 ± 0.21 |

The *p*-value was nonsignificant.

TABLE 4. CHANGES IN SERUM CONCENTRATIONS OF CYTOKINES AND LIPIDS, DAY 1 VERSUS DAY 2, FROM 109 PATIENTS

| | *All* | *Survivors* | *Non-survivors* | *P-value* |
|---|---|---|---|---|
| ΔIL-10 | −10.8 ± 3.7 | −5.5 ± 1.9 | −26.9 ± 13.6 | 0.0125 |
| ΔIL-6 | −724 ± 312 | −354 ± 175 | −1845 ± 1132 | 0.0388 |
| ΔsIL-2r | 0.052 ± 0.042 | 0.054 ± 0.043 | 0.043 ± 0.114 | 0.9104 |
| ΔsTNFR-p55 | −0.252 ± 0.844 | −0.677 ± 1.1 | 1.0 ± 0.9 | 0.3824 |
| ΔsTNFR-p75 | 0.390 ± 0.375 | 0.383 ± 0.357 | 0.410 ± 0.360 | 0.9756 |
| ΔAPO-A | −5.9 ± 1.7 | −4.4 ± 1.7 | −10.6 ± 4.5 | 0.1113 |
| ΔCholesterol | 2.8 ± 3.5 | 8.3 ± 3.3 | −13.9 ± 9.8 | 0.0066 |

See text for abbreviations.

concentration and cholesterol concentration (data not shown), inferring no influence of hepatic function on circulating lipids.

The results of linear multivariate analysis of the independent effects of circulating mediator concentrations on outcomes are shown in Table 6. Because the sample sizes are small and the data may not be arrayed with a normal distribution, the analyses are performed using the change in concentrations from baseline (day 1) concentrations. The results of multiple linear regression and multivariate ANOVA are identical. Interleukin-6 and IL-10 concentrations are associated with the development (magnitude) of MODS, whereas IL-10 and cholesterol concentration had an independent effect on mortality.

Analyses of independent effects on mortality assessed by logistic regression are shown in Tables 7 and 8. Logistic regression is a better mode to employ when data do not fit a normal distribution, but the analysis is not possible when the dependent variable is a continuous variable (i.e., MMOD). In Table 7, the effects of changing mediator concentrations (day 1 to day 2) are examined separately because their effect on outcome is modest, and might be obscured by major clinical influences. The influence of the decrease in cholesterol concentration upon mortality is confirmed, whereas the independence of effect of changing IL-10 concentration is lost, albeit barely. In this model, each decrease in cholesterol concentration of 1 mg/dL increases the chance of mortality by 2.8%. However, although the model is a good fit to the data (goodness of fit chi-square 4.00, $p = 0.68$), only 11% of the observed mortality is explained. Specificity is high but sensitivity is low, and only 81% of cases are classified correctly by the data.

In Table 8, a model that incorporates clinical factors (severity of illness, emergency status, development of a nosocomial infection) is presented. The independent effect of hypocholesterolemia upon mortality is reconfirmed (each decrease of 1 mg/dL increases mortality by 3%). However, each one-point increase in

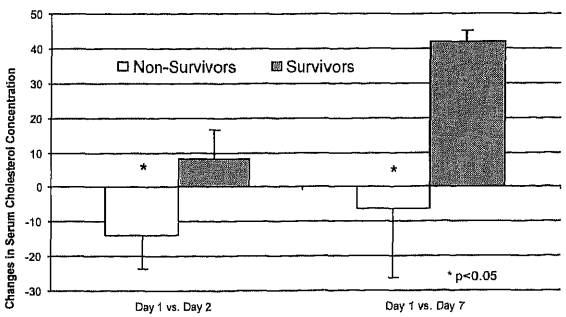


FIG. 1. Changes in serum cholesterol concentrations over time. A persistent decrease in serum cholesterol was noted among non-survivors. *$p < 0.05$ for survivors versus non-survivors.

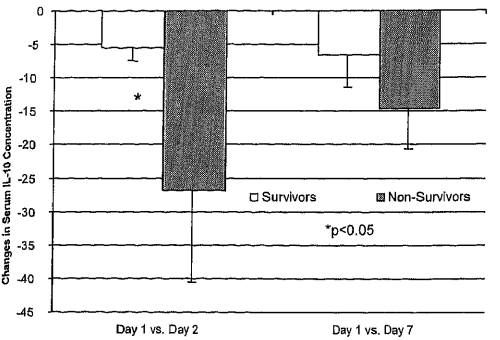


FIG. 2. Changes in serum IL-10 concentrations over time. Non-survivors had a marked decrease in IL-10 concentration on day 2. *$p < 0.05$ for survivors versus non-survivors.

APACHE III score increased mortality by 8%, emergency admission increased the risk of mortality by 27%, and the development of a nosocomial infection increased the chance of death by nearly ninefold. The model is again a good fit to the data, and 49% of the observed mortality is explained. Higher sensitivity increased the percentage of cases classified correctly to 86%. There was insufficient statistical power to assess the influence of the various factors on the development of nosocomial infection, owing to the occurrence of only 27 such cases. A model could be constructed to explain 65% of the variability of mortality by analyzing MMOD as an independent variable, but that was proscribed by the analytical plan.

## DISCUSSION

It is well established that serum lipid concentrations are decreased after surgical stress and during sepsis. Akgun et al. observed a significant 28% decrease in total cholesterol concentration among 11 male patients who underwent major elective surgery [18], reaching a nadir within 24 h and recovering over 7–10 days. Similar decreases were noted in serum concentrations of HDL- and LDL-cholesterol [18]. Interleukin-6 concentrations were increased, and there was a significant inverse relationship between IL-6 and total cholesterol concentrations. Several studies highlight the relationship between low serum cholesterol and sepsis [19–23]. Mentz and Magnette [20] stratified 120 septic patients into groups based on the fasting concentration of C-reactive protein (CRP), and compared the patients to 40 volunteers, finding an inverse relationship between concentrations of CRP and cholesterol. Fraunberger et al. [21] measured cytokine and lipid concentrations in seven patients with septic shock, and compared the results to healthy control subjects. Increased TNF production by the

TABLE 5. CHANGES IN SERUM CONCENTRATIONS OF CYTOKINES AND LIPIDS, DAY 1 VERSUS DAY 7, FROM 42 PATIENTS

| | *All* | *Survivors* | *Non-survivors* | *P-value* |
|---|---|---|---|---|
| ΔIL-10 | −9.4 ± 3.8 | −6.5 ± 4.8 | −14.5 ± 6.2 | 0.3204 |
| ΔIL-6 | −1236 ± 715 | −217 ± 286 | −3071 ± 1884 | 0.0549 |
| ΔsIL-2r | −0.081 ± 0.042 | −0.115 ± 0.118 | −0.021 ± 0.176 | 0.6514 |
| ΔsTNFR-p55 | 2.6 ± 2.3 | 3.8 ± 3.5 | 0.553 ± 1.5 | 0.5087 |
| ΔsTNFR-p75 | 2.1 ± 1.3 | 1.5 ± 1.7 | 0.553 ± 1.5 | 0.4986 |
| ΔAPO-A | −19.3 ± 4.0 | −22.6 ± 5.5 | −14.5 ± 5.7 | 0.1113 |
| ΔCholesterol | 8.1 ± 7.6 | 41.8 ± 3.3 | −6.3 ± 20.1 | 0.0341 |

See text for abbreviations.

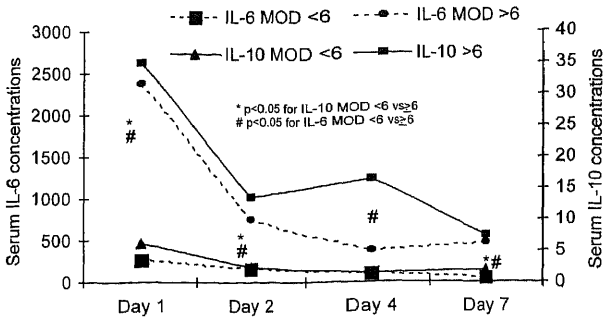


FIG. 3. Concentrations of IL-6 (pg/mL) and IL-10 (pg/mL) over time, stratified by the degree of organ dysfunction (MOD). Patients with a high degree of organ dysfunction had persistent elevations of the two cytokines.

patients in septic shock correlated with low total cholesterol concentration and concentrations of apolipoproteins $A_1$ and B. In companion *in vitro* studies, TNF increased the degradation of $^{125}$I-LDL in human fibroblasts and endothelial cells, and in HepG2 hepatoma cells [21]. Dunham et al. studied 28 mechanically ventilated trauma patients, finding lower serum cholesterol concentrations in non-survivors [23], a close correlation with the onset of nosocomial infection and an increasing magnitude of organ dysfunction, and increased cholesterol concentration during convalescence.

Decreased total cholesterol, HDL-, and LDL-cholesterol concentrations have been documented in patients infected with human immunodeficiency virus, with and without acquired immunodeficiency syndrome [24]. Patients with community-acquired pneumonia also manifest hypocholesterolemia [25,26]. Rodriguez Reguero et al. observed lipid profiles over a 6-month period in 60 patients with community-acquired pneumonia [25]. Concentrations of total and HDL-cholesterol and of apolipoproteins A1 and B were all decreased during the acute infection [25]. All values had normalized by day 15, except for the HDL-cholesterol concentration, which continued to increase toward baseline for the entire period of observation.

Hypocholesterolemia has also been associated with the development of nosocomial infections [14,26–28], especially in the postoperative period. Leardi et al. [27] found the risk of postoperative infection to be 73% among patients with a total cholesterol concentration of <105 mg/dL, compared with an incidence of infection of 35% ($p < 0.001$) with a higher cholesterol concentration. Delgado-Rodriguez et al. followed 1,267 general surgery patients prospectively for the development of postoperative infections, including surgical site infec-

TABLE 6. RESULTS OF LINEAR MULTIVARIATE ANALYSES

| | *MANOVA dependent (MMOD)* p-*value* | *MANOVA dependent (expired)* p-*value* | *Multiple linear regression (MMOD)* p-*value* | *Multiple linear regression (expired)* p-*value* |
|---|---|---|---|---|
| ΔIL-10 | 0.0268 | 0.0157 | 0.0266 | 0.0156 |
| ΔIL-6 | 0.0432 | 0.2347 | 0.0432 | 0.2345 |
| ΔsIL-2R | 0.7373 | 0.2737 | 0.7283 | 0.2696 |
| ΔsTNFR-p55 | 0.2968 | 0.1411 | 0.2966 | 0.1413 |
| ΔsTNFR-p75 | 0.5376 | 0.4901 | 0.5360 | 0.4913 |
| ΔAPOA | 0.3860 | 0.9626 | 0.3872 | 0.9637 |
| ΔCholesterol | 0.1693 | 0.0244 | 0.1694 | 0.0244 |

See text for abbreviations.

TABLE 7. MULTIPLE LOGISTIC REGRESSION, EXPIRED = OUTCOME (DEPENDENT) VARIABLE, PREDICTORS CHANGE DAY 1–2

| | | | | 95% CI | |
|---|---|---|---|---|---|
| *Predictor* | *Coefficient* | *Standard error* | *p-value* | *Lower* | *Upper* |
| ΔIL10 | −0.0148 | 0.0077 | 0.0560 | −0.0299 | 0.000375 |
| ΔIL6 | −0.0000379 | 0.0002572 | 0.8828 | −0.000542 | 0.000466 |
| ΔsIL2R | −0.4776 | 0.6901 | 0.4889 | −1.83 | 0.8749 |
| ΔsTNFR-P55 | 0.0378 | 0.0473 | 0.4242 | −0.0549 | 0.1305 |
| ΔsTNFR-P75 | −0.0421 | 0.0881 | 0.6332 | −0.2148 | 0.1307 |
| ΔAPOA | 0.0106 | 0.0264 | 0.6874 | −0.0412 | 0.0624 |
| ΔCholesterol | −0.0287 | 0.0145 | 0.0480 | −0.0572 | −0.000256 |

Model chi-square 12.4678 ($p$ = 0.0862)
Variation explained 11.04%
Goodness to fit 4.0022 ($p$ = 0.6764)

| | | 95% CI | |
|---|---|---|---|
| *Predictor* | *Odds* | *Lower* | *Upper* |
| ΔIL10 | 0.9853 | 0.9705 | 1.0004 |
| ΔIL6 | 1.0000 | 0.9995 | 1.0005 |
| ΔsIL2R | 0.6202 | 0.1604 | 2.3987 |
| ΔsTNFR-P55 | 1.0385 | 0.9466 | 1.1394 |
| ΔsTNFR-P75 | 0.9588 | 0.8067 | 1.1396 |
| ΔAPOA | 1.0107 | 0.9597 | 1.0644 |
| ΔCholesterol | 0.9717 | 0.9444 | 0.9997 |

Sensitivity 25.0%
Specificity 98.8%
Correct class 81.9%

See text for abbreviations.

tion, urinary tract infection, and bacteremia [14]. Low levels of HDL-cholesterol (≤20 mg/dL) were associated with odds ratios for surgical site infection and respiratory tract infection of 2.2 and 10.3, respectively. A total cholesterol concentration of <102 mg/dL was associated with an increased incidence of both surgical site and respiratory tract infections, primarily from gram-negative organisms.

The mechanism of hypocholesterolemia during infection is likely multifactorial, with both decreased synthesis and increased catabolism playing a role. Decreased lipoprotein synthesis occurs *in vitro* when hepatocytes are exposed to TNF and IL-6 [29]. Infection and inflammation induce oxidation of LDL-cholesterol [19,30]. Decreases in HDL-cholesterol may be related to high concentrations of phospholipase $A_2$ [31], or to downregulation of the ATP-binding-cassette transporter–1 gene [32]. Hypolipidemia reduces competition for binding of LPS to lipopolysaccharide-binding protein (LBP), leading to ligation of the CD14 complex and activation of mononuclear cells [33,34]. Conversely, binding of LPS to lipoproteins facilitates delivery of LPS to hepatocytes for detoxification, which if insufficient may lead to increased mononuclear cell activation [35].

The present study differs from our previous work in several important respects. In our initial study of 32 patients in a surgical ICU, mean total cholesterol was 117 mg/dL assayed once within 24 h of admission, and LDL-cholesterol was 35 mg/dL [6]. Patients with infections had lower LDL-cholesterol concentrations than those who did not [6]. In a followup study of 111 critically ill patients, also studied once within 24 h of admission, median total cholesterol concentration was 120 mg/dL, and there were significant inverse correlations between cholesterol concentration and serum concentrations of IL-6, IL-10, and sIL-2r [5]. Clinical outcomes including death, infection subsequent to ICU admission, length of ICU stay, and magnitude of organ dysfunction occurred more frequently (relative risks, 1.9–3.5) among

TABLE 8. MULTIPLE LOGISTIC REGRESSION, EXPIRED = OUTCOME (DEPENDENT) VARIABLE, PREDICTORS CLINICAL (CHOLESTEROL, IL10, IL6) CHANGE DAY 1–2

| | | | | 95% CI | |
|---|---|---|---|---|---|
| *Predictor* | *Coefficient* | *Standard error* | *P value* | *Lower* | *Upper* |
| APACHE III | 0.0822 | 0.0187 | 0.0001 | 0.0455 | 0.1190 |
| Emergent admission | 0.2433 | 0.7700 | 0.7520 | −1.2650 | 1.7525 |
| Nosocomial infection | 2.1642 | 0.7649 | 0.0047 | 0.6650 | 3.6634 |
| ΔCholesterol | −0.0311 | 0.0140 | 0.0265 | −0.0585 | −0.0036 |
| ΔIL10 | −0.0018 | 0.0101 | 0.8601 | −0.0216 | 0.0181 |
| ΔIL6 | −0.0002 | 0.0003 | 0.4029 | −0.0007 | 0.0003 |

Model chi-square 55.020 ($p \leq 0.000001$)
Variation explained 48.8%
Goodness to fit 6.4376 ($p = 0.5983$)

| | | 95% CI | |
|---|---|---|---|
| *Predictor* | *Odds* | *Lower* | *Upper* |
| APACHE III | 1.0857 | 1.0466 | 1.1263 |
| Emergent admission | 1.2755 | 0.2820 | 5.7692 |
| Nosocomial infection | 8.7077 | 1.9445 | 38.9935 |
| ΔCholesterol | 0.9694 | 0.9432 | 0.9964 |
| ΔIL10 | 0.9982 | 0.9786 | 1.0182 |
| ΔIL6 | 0.9998 | 0.9994 | 1.0003 |

Sensitivity 62.5%
Specificity 93.8%
Correct class 86.7%

See text for abbreviations.

patients with below-median cholesterol concentrations. The subjects studied herein were specifically selected to represent sicker, higher-risk patients than were studied previously, and they were studied serially rather than at a single point in time.

Our data confirm an association between cytokine activation and hypocholesterolemia, and indicate that a decrease in total cholesterol concentration is an independent predictor of mortality in critical surgical illness. Low concentrations of cholesterol have been associated previously with increased mortality in elderly persons [36,37], especially in association with a low serum albumin concentration. However, neither a contribution of age nor gender to outcome was detected in the present study. In surgical patients, Pacelli et al. retrospectively identified hypocholesterolemia as an independent predictor of mortality among 604 patients with intra-abdominal infection [38], and Gu et al. associated low total cholesterol concentrations with death in critically ill surgical patients [39].

Although the contribution of hypocholesterolemia to mortality is modest compared with known risk factors such as increased severity of illness and the development of nosocomial infection, low serum lipid concentrations represent a potential therapeutic target in sepsis. Various reconstituted lipid compounds have been administered experimentally as a potential therapy for sepsis. Levine et al. demonstrated that transgenic mice with elevated concentrations of HDL-cholesterol had more bound LPS, lower plasma cytokine concentrations, and improved survival after administration of endotoxin [40]. Intravenous infusion of a reconstituted HDL (rHDL) particle was also protective. In rabbits, administration of rHDL reduced TNF production in response to LPS [41,42] and reduced TNF production and acidosis after *E. coli*, but not *S. aureus* bacteremia [43,44]. Goldfarb et al. administered a lipoprotein phospholipid compound prophylactically in a porcine model of intra-abdominal infection [45]. Pretreatment de-

creased serum endotoxin and TNF concentrations, preserved cardiac output and left ventricular ejection fraction, and attenuated increases in systemic and pulmonary vascular resistances.

Pakjrt et al. studied coagulation responses to rHDL in human endotoxemia, finding that rHDL inhibited the activation of coagulation and aggregation of platelets, but did not affect the LPS-induced inhibition of fibrinolysis [46]. In a randomized, placebo-controlled crossover study, Pakjrt et al. administered rHDL 40 mg/kg as a 4-h infusion before a standardized endotoxin challenge (4 ng/kg) [46]. Administration of the lipid reduced the flu-like symptoms, but did not abrogate the febrile response. There was a marked reduction of the release of TNF, IL-6, and IL-8, and a modest reduction of the release of IL-1ra, soluble TNF receptors, and IL-10. Additionally, rHDL attenuated LPS-induced changes in leukocyte counts, and as well as neutrophil CD11b/CD18 expression. Prior to administration of LPS, monocyte CD14 receptor expression was downregulated, and harvested monocytes had a diminished expression of CD14 and production of TNF when stimulated with LPS [47].

In conclusion, critically ill patients with SIRS become hypocholesterolemic at an early point in their illness, which manifests as an independent risk factor for death. Repletion of serum lipids can be hypothesized to afford a therapeutic target for the management of sepsis or severe inflammatory states.

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