Prior Statin Therapy Is Associated With a Decreased Rate of Severe Sepsis

Yaniv Almog, MD; Alexander Shefer, MD; Victor Novack, MD; Nimrod Maimon, MD; Leonid Barski, MD; Miruna Eizinger, MD; Michael Friger, PhD; Lior Zeller, MD; Abraham Danon, MD, PhD

Background—Statins have anti-inflammatory properties that are independent of their lipid-lowering abilities. We hypothesized that statin therapy before the onset of an acute bacterial infection may have a protective effect against severe sepsis. The aim of this study was to determine whether patients treated with statins develop severe sepsis less frequently.

Methods and Results—In this prospective observational cohort study, consecutive patients admitted with presumed or documented acute bacterial infection were enrolled. The primary outcomes were the rate of severe sepsis and intensive care unit (ICU) admission. Of the 361 patients enrolled, 82 (22.7%) were treated with statins before their admission. Both groups had a similar severity of illness on admission. Severe sepsis developed in 19% of patients in the no-statin group and in only 2.4% of the statin group (P < 0.001). Statin treatment was associated with a relative risk of developing severe sepsis of 0.13 (95% CI, 0.03 to 0.52) and an absolute risk reduction of 16.6%. The overall ICU admission rate was 10.2% (37/361); 12.2% of the no-statin group required ICU admission, whereas in the statin group only 3.7% were admitted to the ICU (P = 0.025), reflecting a relative risk of ICU admission of 0.30 (95% CI, 0.1 to 0.95).

Conclusions—Prior therapy with statins may be associated with a reduced rate of severe sepsis and ICU admission. If supported by prospective controlled trials, statins may have a role in the primary prevention of sepsis. (Circulation. 2004;110:880-885.)

Key Words: sepsis ■ anticholesterolemic agents ■ inflammation ■ primary prevention

Sepsis and septic shock are the 10th most common causes of death in the United States.1 It is estimated that there are approximately 400 000 to 500 000 sepsis episodes each year in the United States alone, and only 50% to 70% of these patients survive.1-3 Even though there are many confounding variables related to definitions and methodology, the incidence of sepsis and sepsis-related deaths appears to be increasing.1

It is generally accepted that sepsis syndrome reflects the delicate balance between extensive triggering of defense mechanisms by invading microorganisms and both direct and indirect effects of these microorganisms and their products.4,5 Most investigators would agree that sepsis and the systemic inflammatory response syndrome are accompanied by the inability to regulate the inflammatory response and that the cause of this perturbation is still unknown.5-7 Over the last 3 decades, numerous trials have failed to demonstrate that blocking specific inflammatory mediators is beneficial in sepsis.5-6 Given the acute onset and unpredictable nature of sepsis, primary prevention was never attempted in the management of this syndrome.

Statins have diverse immunomodulatory and anti-inflammatory properties independent of their lipid-lowering ability. A recent study demonstrated that simvastatin pretreatment profoundly improves survival in a murine model of sepsis.8 Another retrospective study showed that statin therapy reduced both overall and attributable mortality in patients with bacteremia.9 Many cellular and animal models as well as human data suggested a wide variety of mechanisms for these effects.10-14 We recently hypothesized that statins may have a protective effect against sepsis by virtue of these anti-inflammatory properties.15 Despite these observations, the possible role of statins in the management of sepsis has not been studied. This study was therefore conducted to evaluate whether patients treated with statins develop severe sepsis less frequently and to determine whether this presumed protective effect may reduce the rate of admission to the intensive care unit (ICU).

Methods

Patients

The ethics committee of Soroka University Medical Center approved the study before its initiation. From January 2003 to September 2003, 418 consecutive patients admitted with presumed bacterial infection were screened; of those, 369 met inclusion criteria and were enrolled.
Three hundred sixty-one patients were followed and included in the final analysis of this prospective observational study. Eligible patients were aged ≥40 years and admitted to the Department of Medicine with a known or presumed bacterial infection on the basis of clinical, radiological, and laboratory findings at the time of screening.

Selection Criteria
We included patients with pneumonia, urinary tract infection, or cellulitis. Pneumonia was defined as fever associated with new alveolar consolidation on chest radiography (Appendix 1). Urinary tract infection was defined as fever and urinary complaints associated with leukocyturia and bacteriuria (Appendix 1). Cellulitis was defined as fever associated with characteristic skin findings (Appendix 1). The criteria for severe sepsis and sepsis-induced organ dysfunction were those defined by the Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) investigators16 (Appendix 2). Exclusion criteria were age <40 years, patients in whom the level of care was limited by their relatives or physicians because of a debilitating illness and a limited functional capacity, pregnancy, human immunodeficiency virus infection, malignancy, statin therapy for <1 month before admission, and non–sepsis-related neutropenia.

Study Design
Patients were divided into 2 groups on the basis of whether they were taking statins for ≥1 month before their admission (statin group). The second group comprised those who were not taking statins before their admission (no-statin group). No study-related interventions were made, and patients’ care was provided by teams that knew whether the patients were taking statins before their admission but were unaware of the study objective, end points, or protocol. Blood sugar was managed similarly in both groups and according to routine protocols used in the general wards and in the ICU. The outcome assessors and data gatherers were coinvestigators who did not care for the patients. Decisions to admit a patient to the hospital or accept a patient to the ICU were made solely on clinical grounds by independent physicians. Several coinvestigators screened all new admissions on a daily basis and continued to follow the study patients independent of the teams caring for them. Ward teams were asked to report whenever they believed that a patient required ICU admission as common clinical practice would dictate. Patients were followed for 28 days or until death.

Evaluation of Patients
Baseline characteristics including clinical and demographic data, site of infection, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, preexisting conditions, laboratory test results, and long-term drug therapy were assessed within 24 hours of enrollment. Clinical, microbiological culture, laboratory, and organ failure indices were recorded on a daily basis. All data were recorded in each patient’s study file and subsequently computerized. On completion of data collection, each file was reviewed by an additional blinded investigator who was unaware regarding the group to which the patient belonged or the final outcome of that patient. A blinded infectious disease specialist retrospectively reviewed all charts and determined whether the empirical antibiotic therapy chosen on admission was appropriate and according to recommended guidelines. In addition, the sensitivity of blood culture isolates was correlated with the initial antibiotic selection.

Statistical Analysis
The primary end point was the rate of severe sepsis, which was assessed at the end of hospitalization or on ICU admission. Our prospectively defined primary analysis included all patients who were enrolled in the study and analyzed according to the status of statin treatment. The trial was designed to follow 370 patients to detect a 15% reduction in the absolute risk of developing severe sepsis. The sample size analysis assumed a 25% severe sepsis rate in hospitalized patients with an infectious disease with 80% power level and 95% CI. For univariate analysis, we used a t test for comparison of continuous variables and Pearson χ² test for categorical variables. Logistic regression models were used for multivariate analysis, in which we included all variables found to be related to outcomes in univariate analysis. Reported models include all variables that remained significantly related to outcomes. All reported probability values are 2 sided.

Results
Of the 369 enrolled patients, 8 patients were excluded by the blinded investigator: 2 in the statin group and 6 in the no-statin group. The patients who were excluded comprised 3 with presumed pneumonia because the admission chest film was later interpreted as normal and 5 with presumed urinary tract infection because their postadmission urinalysis was normal. None of the patients in either group had to be excluded because they were taking statins for <1 month. We included in the final analysis 361 patients. Their mean (±SD) age was 69.8 ± 11.8 years, and the mean (±SD) APACHE II score was 11.1 ± 7.2. The diagnostic categories on admission to the hospital were as follows: pneumonia in 177 patients (49%), urinary tract infection in 140 (38.8%), and cellulitis in 44 (12.2%).

Of the 361 patients, 27 (7.5%) died within 28 days of admission: 24 in the no-statin group and 3 in the statin group. Twenty-two patients died in the hospital, of which 20 belonged to the no-statin group and 2 to the statin group, reflecting an overall in-hospital mortality rate of 6.1%. The overall ICU admission rate was 10.2% (37/361): 12.2% of the no-statin group required ICU admission, whereas in the statin group only 3.7% were admitted to the ICU (P = 0.025), reflecting a relative risk of ICU admission of 0.30 (95% CI, 0.1 to 0.95). Of the 279 patients in the no-statin group, 53 had severe sepsis. Of those, 34 were admitted to the ICU and 19 were not. This subgroup was not admitted to the ICU because the patients had either single- or double-system failure, and they were managed by the ward teams.

Table 1 describes the baseline clinical and demographic characteristics of both groups. There were no differences between the groups in terms of APACHE II score, site of infection, or antibiotic therapy before admission and long-term steroid therapy. As expected, patients in the statin group had significantly higher rates of hypertension, ischemic heart disease, diabetes, dyslipidemia, and chronic renal failure. Seventy percent of the patients (n = 57) treated with statins were taking simvastatin, of whom 14% (8/57) were taking 10 mg/d, 58% (33/57) were taking 20 mg/d, and 28% (16/57) were taking 40 mg/d. Twenty-one percent of the patients (n = 17) treated with statins were taking pravastatin; of those, 29% (5/17) were taking 10 mg/d, 65% (11/17) were taking 20 mg/d, and 6% (1/17) were taking 40 mg/d.

Table 2 shows the characteristics of the patients who developed severe sepsis and those who did not. Of the 55 patients who developed severe sepsis, 53 belonged to the no-statin group and only 2 to the statin group. Of the 361 patients, there were 33 with positive blood cultures (9.1%). In the sepsis group (55 patients), the positive culture rate was 31% (17/55), whereas in the group without severe sepsis that rate was 5.2% (16/306). The 2 patients in the statin group with sepsis had a positive blood culture. Appropriateness of antibiotic therapy rate assessed by adherence to guidelines...
revealed that in the statin group the rate was 87.8% (72/82), whereas in the no-statin group that rate was 86% (240/279) \((P=0.68)\). The rate of appropriate antibiotic selection based on sensitivity of blood culture isolates was 83% (5/6) in the statin group, whereas in the no-statin group that rate was 85% (23/27) \((P=0.91)\). Of the 132 patients with urinary tract infection, 88 (67%) had a positive urine culture.

The Figure describes the incidence of the primary and secondary outcomes. During the study period, 53 patients of 279 in the no-statin group developed severe sepsis, reflecting a rate of 19\% (95\% CI, 14.4\% to 23.6\%). Of the 82 patients in the statin group, only 2 patients developed severe sepsis, reflecting a rate of 2.4\% (95\% CI, 0\% to 5.7\%). The absolute risk reduction was 16.6\% \((P<0.001)\), and the relative risk reduction was 87\% (95\% CI, 48\% to 97\%).

Twenty-eight day mortality rate in the no-statin group was 8.6\% (24/279 patients); in the statin group the rate was 3.7\% (3/82) \((P=0.14)\). Thus, statin treatment was associated with a relative risk of death of 0.43 (95\% CI, 0.13 to 1.38). The mortality rates of both groups were consistent with the expected APACHE II adjusted mortality rates.

Table 3 shows the results of the logistic regression model used to adjust for variables identified, by univariate analysis, to be associated with severe sepsis. The final model included the 3 variables that were identified by univariate analysis and remained significant after application of the model. In the final model, the protective effect of statins against severe sepsis remained statistically significant \((P=0.01; \text{odds ratio}, 0.07; 95\% \text{CI}, 0.01 \text{ to } 0.51)\). A higher APACHE II score and low serum albumin concentration were associated with an increased rate ratio of developing severe sepsis. Furthermore, an additional multivariate analysis, in which previous statin treatment and APACHE II score on admission were included, also revealed that patients treated with statins had a significantly lower rate of ICU admission \((P=0.046; \text{odds ratio}, 0.22; 95\% \text{CI}, 0.05 \text{ to } 0.97)\).

**Discussion**

In this prospective observational study, we found that therapy with statins for \(\geq 1\) month before the onset of an acute bacterial infection is probably associated with a reduced rate of severe sepsis and ICU admission.

Patients treated with statins, as expected, had a statistically significant higher frequency of hypertension, chronic ischemic heart disease, diabetes, and chronic renal failure. Despite
these significant differences in comorbidities, the protective effect of statins was marked. The quality of prehospital care is difficult to assess, and statin therapy may be a surrogate of closer medical attention. However, the fact that no difference was observed in preadmission antibiotic therapy and APACHE II score on admission probably suggests that the prehospital care did not affect the observed outcomes. In the final model, statin therapy remained an independent factor associated with a reduced rate of severe sepsis.

The lipid profiles of patients in the statin group were significantly higher than those of the no-statin group. Human and animal data suggest that lipids and lipoproteins may bind endotoxins and attenuate the intensity of the inflammatory response. These presumed protective effects of elevated lipids may provide an alternative explanation to our findings. In view of the abundant anti-inflammatory properties of statins and their beneficial effects in a wide variety of clinical conditions, it seems that the suggested protective effect of statins is a biologically more plausible explanation. Reevaluating existing records and specimens from some of the larger-scale statin trials may be helpful in clarifying the issue. A placebo-controlled study will probably be required to finally resolve the controversy.

The characteristics of the patients who had severe sepsis were very similar to those reported in previous studies in terms of APACHE II score, positive blood culture rate, and 28-day mortality. Taken together, these data suggest that our sample was carefully selected and that adherence to definitions was strict. Appropriateness of antibiotic therapy is an important factor that affects the outcome of patients with sepsis. Both methods that were used to assess it showed that there was no difference between the groups in this respect, suggesting that the empiric selection of antibiotics did not contribute to the observed difference in severe sepsis rate. Our study was not originally designed to demonstrate differences in mortality. Indeed, the difference in mortality between the 2 groups did not reach statistical significance. Our findings suggest that statins, by virtue of their presumed ability to reduce the sepsis rate and possibly by additional mechanisms not yet fully elucidated, may reduce mortality in patients admitted with bacterial infections. Larger prospective randomized controlled trials will be required to demonstrate whether the suggested protective effect conferred by statins reduces mortality.

### TABLE 2. Comparison of Patients With and Without Severe Sepsis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients With Severe Sepsis (n=55)</th>
<th>Patients Without Severe Sepsis (n=306)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70.5±11.3</td>
<td>69.7±11.9</td>
<td>0.63</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>60</td>
<td>46.4</td>
<td>0.06</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>19.2±9.5</td>
<td>9.6±5.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Site of infection, %</td>
<td></td>
<td></td>
<td>0.72*</td>
</tr>
<tr>
<td>Lung</td>
<td>49.1</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Urinary tract</td>
<td>41.8</td>
<td>38.2</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>9.1</td>
<td>12.7</td>
<td></td>
</tr>
<tr>
<td>No. of dysfunctional systems, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>27.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>31.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>33.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive blood culture, %</td>
<td>30.9</td>
<td>5.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In-hospital mortality, %</td>
<td>38.2</td>
<td>0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>28-day mortality, %</td>
<td>41.8</td>
<td>1.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean±SD. *P value for comparison of overall distribution of infection sites.

### TABLE 3. Multivariate Analysis of Risk Factors Associated With Severe Sepsis*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rate Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin treatment</td>
<td>0.07 (0.01–0.51)</td>
<td>0.01</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>0.37 (0.19–0.72)</td>
<td>0.004</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>1.19 (1.13–1.26)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Logistic regression.
We did not attempt to explore the mechanism responsible for this possible protective effect. It is well established that statins have a wide variety of potent anti-inflammatory properties. Abundant in vitro, cellular, animal, and human data regarding the pleiotropic effects of statins have led us to hypothesize recently that statins may have a protective effect against sepsis and to propose several possible mechanisms for this effect.

Large-scale multicenter studies have addressed the effects of statins in the primary prevention of atherosclerosis and ischemic heart disease and have uniformly demonstrated strong primary and secondary protective effects. The mechanism for this protective effect is believed to be related to their lipid-lowering ability as well as anti-inflammatory and immunomodulatory effects. An interesting observation in many of these trials was the reduction in all-cause mortality, including noncoronary mortality in statin-treated patients. None of these studies directly evaluated the incidence of or mortality from sepsis. These data, collectively evaluating tens of thousands of patients, indirectly support the concept that statins may confer additional protection not related to atherosclerotic diseases.

Our study was prospective but not randomized or controlled and was based on the fact that a certain proportion of the patients admitted to our Department of Medicine are treated with statins. Therefore, an unknown factor or factors may have affected allocation to statins and consequently influenced the measured outcomes. In view of these limitations, no causality could be determined between statin therapy and decreased sepsis rate. Moreover, the investigator following the patients was aware of whether the patients were taking statins. Thus, some bias may have been introduced into our sample, particularly in terms of meeting severe sepsis criteria. To minimize this possible bias, we enrolled consecutive patients using strict predefined criteria for both the primary infectious disease and severe sepsis. In addition, each file was reviewed by a second investigator who was blinded regarding the group to which the patient belonged or the outcome of that patient. Furthermore, the decision to present or admit a patient to the ICU from the regular wards was made by independent teams.

In summary, in this observational study we found that statin therapy is probably associated with a reduced rate of severe sepsis. Future rigorous prospective controlled trials will determine whether this reduced rate is indeed due to a protective effect provided by statins and the precise significance of this novel primary prevention approach to sepsis.

Appendix 1

Definitions of Infectious Diseases Used in the Study

Pneumonia

Pneumonia was defined as an infiltrate on chest radiography and a temperature of ≥37.5°C. In addition, ≥1 clinical criterion (cough, new sputum production, dyspnea, or chest pain or rales coincident with the area of radiological opacity) and laboratory criterion (leukocyte count ≥12×10⁹/L band forms >10%) had to be met.

Urinary Tract Infection

Urinary tract infection was defined as ≥1 of the following criteria: fever (38°C), urgency, frequency, dysuria, or suprapubic tenderness and ≥1 of the following: (1) positive dipstick for leukocyte esterase and/or nitrate, (2) pyuria (urine specimen with ≥10 white blood cells per millimeter or ≥3 white blood cells per high-power field of unspun urine), or (3) organisms seen on Gram’s stain of unspun urine.

Cellulitis

Cellulitis was defined as fever (38°C) and erythema, pain, swelling, and warmth of the affected skin.

Appendix 2

Modified Systemic Inflammatory Response Syndrome Criteria

Patients had to meet ≥3 of the following 4 criteria:

- Core temperature of >38°C (100.4°F) or <36°C (96.8°F)
- Heart rate of >90 bpm, except in patients with a medical condition known to increase the heart rate or those receiving treatment that would prevent tachycardia
- Respiratory rate of >20 breaths per minute or a partial pressure of arterial carbon dioxide (PaCO₂) of <32 mm Hg or the use of mechanical ventilation for an acute respiratory process
- White cell count of >12,000/mm³ or <4,000/mm³ or a differential count showing >10% immature neutrophils.

Criteria for Dysfunctional Organs or Systems

Patients had to meet ≥1 of the following 5 criteria:

- Cardiovascular system: the arterial systolic blood pressure had to be <90 mm Hg or the mean arterial pressure <70 mm Hg for ≥1 hour despite adequate fluid resuscitation, adequate intravascular volume status, or the use of vasopressor in an attempt to maintain a systolic blood pressure of >90 mm Hg or a mean arterial pressure of >70 mm Hg
- Renal system: urine output had to be <0.5 mL/kg body wt/h for 1 hour, despite adequate fluid resuscitation
- Respiratory system: the ratio of partial pressure of arterial oxygen (PaO₂) to fraction of inspired oxygen (FiO₂) had to be <250 in the presence of other dysfunctional organs or systems or <200 if the lung was the only dysfunctional organ
- Hematologic system: platelet count had to be <80,000/mm³ or have decreased by 50% in the 3 days preceding enrollment
- Unexplained metabolic acidosis: the pH had to be <7.30 or the base deficit had to be >5.0 mmol/L in association with a plasma lactate level that was >1.5 times the upper limit of the normal value for the reporting laboratory.

References

885


Prior Statin Therapy Is Associated With a Decreased Rate of Severe Sepsis
Yaniv Almog, Alexander Shefer, Victor Novack, Nimrod Maimon, Leonid Barski, Miruna Eizinger, Michael Friger, Lior Zeller and Abraham Danon

Circulation. 2004;110:880-885; originally published online August 2, 2004;
doi: 10.1161/01.CIR.0000138932.17956.F1
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/110/7/880

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/