Learning Objectives

1. Summarize the incidence, impact, and pathophysiology of sepsis
2. Discuss the suggested pleiotropic mechanism of statin therapy in septic patients
3. Propose evidence-based indications for the use of statins in sepsis
4. Identify possible limitations for the use of statins in sepsis
I. **Definition**
1) Interaction between host and infecting organism
2) Leads to Systemic Inflammatory Response Syndrome (SIRS) (refer to Appendix A)
3) Results in acute organ dysfunction

II. **Classification**
1) **SIRS**: at least two of the following: leukocytosis, fever, tachypnea, tachycardia
2) **Sepsis**: SIRS criteria PLUS suspected/documented infection
3) **Severe Sepsis**: Sepsis PLUS acute organ dysfunction
4) **Septic Shock**: Severe sepsis PLUS refractory hypotension/hypoperfusion in spite of adequate fluid resuscitation

III. **Epidemiology/Outcomes**
1) Incidence
   i. 3% of all U.S. hospitalizations from 2003 to 2007
   ii. Incidence rate of severe sepsis increasing: 52% in 2003 to 64% in 2007
2) Mortality
   i. Sepsis mortality: 20-50%
   ii. Severe sepsis mortality rate continues to decrease:
      1. 45% in 1993
      2. 37% in 2003
      3. 29% in 2007
3) Health Care Costs
   i. Cost of severe sepsis increasing: $15.4 billion in 2003 to $24.3 billion in 2007
   ii. $13,000 per case of sepsis
   iii. $19,000 per case of severe sepsis

IV. **Pathophysiology of Sepsis**
1) Toll-Like Receptors
   i. Transmembrane proteins expressed by macrophages and epithelial cells
   ii. Recognize Pathogen-Associated Molecular Patterns (PAMPs) from invading organism
      1. Most commonly lipopolysaccharide (LPS) and peptidoglycan
   iii. Activation of receptors leads to nuclear factor κB (NFκB) production \( \rightarrow \) cytokine cascade
      1. Increased interleukins (IL-1, IL-6, IL-8), tumor necrosis factor α (TNFα), plasminogen-activator inhibitor (PAI-1), and tissue factor (TF)
         a. **Interleukins**: increase production of TF/PAI-1 in addition to inducing endothelial damage \( \rightarrow \) vascular instability \( \rightarrow \) systemic/pulmonary vasodilation
         b. **TNFα**: increase chemokine/pyrogen production \( \rightarrow \) direct tissue injury
         c. **TF**: activates conversion of prothrombin to thrombin \( \rightarrow \) procoagulation
         d. **PAI-1**: prevents conversion of plasmin to plasminogen \( \rightarrow \) impaired fibrinolysis
      2. Decreased levels of protein C
         a. **Protein C**: inactivates factors Va/VIII \( \rightarrow \) anticoagulation
V. Treatment of Sepsis

1) Surviving Sepsis Campaign: initiative to improve the management, diagnosis, and treatment of sepsis
   i. Early Goal Directed Therapy: absolute reduction of 12.6% in 60-day mortality
      [OR 0.67(0.46-0.96) p=0.03] as compared to standard therapy (refer to Appendix B)
   ii. Focuses on supportive therapy rather than resolution of underlying inflammatory process

2) Treatment options for underlying inflammatory process are limited
   i. Corticosteroids: recommended only in septic shock, non-responsive to fluids or vasopressors
   ii. Activated recombinant protein C (Xigris®): recently withdrawn from the market

3) Ideal treatment of underlying inflammation
   i. Impacts multiple parts of inflammation cascade
   ii. Cost effective
   iii. Low side effect profile
VI. **HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme-A) reductase inhibitors aka “statins”**
1) Most widely prescribed medications with ~$16 billion in total sales per year
2) Most commonly used in primary and secondary prevention of coronary artery disease

<table>
<thead>
<tr>
<th>Statin</th>
<th>Class (Type)</th>
<th>Protein Binding (%)</th>
<th>Metabolism</th>
<th>T₁/₂ (hr)</th>
<th>Binding Sites*</th>
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</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>I</td>
<td>&gt;95</td>
<td>CYP3A4</td>
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<td>9</td>
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<tr>
<td>Simvastatin</td>
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<td>95-98</td>
<td>CYP3A4</td>
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<tr>
<td>Pravastatin</td>
<td>I</td>
<td>43-67</td>
<td>Sulfation</td>
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<tr>
<td>Fluvastatin</td>
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<td>98</td>
<td>CYP2C9</td>
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<tr>
<td>Atorvastatin</td>
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<td>CYP3A4</td>
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<tr>
<td>Rosuvastatin</td>
<td>II</td>
<td>90</td>
<td>CYP2C9</td>
<td>19</td>
<td>12</td>
</tr>
</tbody>
</table>

*Number of Binding sites on HMG-CoA reductase

3) **Suggested pleiotropic mechanisms for use in sepsis**
   i. Decreased LPS-induced and *S. aureus* α-toxin-induced leukocyte migration → decreased virulence
   ii. Suppression of toll-like receptor expression → decreased cytokine production
   iii. Decreased production of NFκB, IL-6, IL-8 and TNFα → decreased inflammation
   iv. Reduction of TF and PAI-1 → diminished procoagulant response
   v. Upregulation of endothelial nitric oxide synthase → decreased inflammation/endothelial damage

4) **Possible limitations of statin therapy in sepsis**
   i. Ubiquinone (aka coenzyme Q₁₀)
      1. HMG CoA reductase = rate-limiting enzyme in ubiquinone production
      2. Important roles in energy transduction and cell signaling, unknown importance in sepsis
   ii. Shock Liver
      1. Commonly seen in septic patients due to severely limited blood flow to liver
      2. Decreased metabolism of statins → increased risk of statin toxicity (myopathy, rhabdomyolysis, increased LFTs)
   iii. Hypoalbuminemia of sepsis
      1. Statins are highly protein bound
      2. Statin blood concentrations have been shown to be extremely elevated (20-fold increase) in septic patients → increased risk of statin toxicity
5) Data for Inhibition of inflammatory process in sepsis
   i. In vitro data
      1. Multiple statins exhibited reduction of IL-1, IL-6, and other inflammatory markers in human hepatocytes treated with inflammatory cytokines\textsuperscript{15}
      2. Atorvastatin strongly increased expression of thrombomodulin in human coronary artery\textsuperscript{16}, which is essential in formation of activated protein C
   ii. Animal Studies
      1. Pre-treatment of mouse with simvastatin prior to cecal ligation of polymicrobial sepsis showed significant increase in 3-day survival\textsuperscript{17}
      2. Pre-treatment of LPS-induced septic mouse with cerivastatin showed significantly improved 7-day survival along with decreased levels of TNF-α, IL-1 and nitric oxide\textsuperscript{18}
      3. Mice treated with rosuvastatin and atorvastatin six hours after inducing sepsis demonstrated prolonged survival compared to placebo\textsuperscript{19}

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**Major Questions to Answer**

VII. Does outpatient statin therapy provide a protective effect on patients admitted with sepsis, reducing the progression to severe sepsis or mortality?
   1) Almog Y et al. 2004\textsuperscript{20}
      i. Statin therapy ≥ 1 month before admission vs. statin-naïve patients
      ii. Primary Outcome: In-hospital mortality, ICU admit, development of severe sepsis at 28 days
   2) O’Neal H et al. 2011\textsuperscript{21}
      i. Prehospital statin use vs. statin-naïve patients
      ii. Primary Outcome: Severe Sepsis/ALI/ARDS @ day four of admit
   3) Yende S et al 2011\textsuperscript{22}
      i. Prehospital statin use vs. statin naïve patients, continuation vs. discontinuation of statin
      ii. Primary Outcome: 90-day mortality, rate of severe sepsis

VIII. Should statin therapy be discontinued in patients admitted to the hospital with sepsis?
   1) Yende S et al 2011\textsuperscript{22}
      i. Continued statin use vs. statin naïve, prior statin continued vs. prior statin discontinued
      ii. Primary Outcome: 90-day mortality, rate of severe sepsis
   2) Kruger P et al. 2011\textsuperscript{23}
      i. Atorvastatin 20mg vs. placebo in pre-existing statin users
      ii. Primary Outcome: Progression/regression of sepsis during hospital stay (28 days)

IX. Should statin therapy be initiated in patients admitted to the hospital with sepsis?
   1) Novack V et al. 2009\textsuperscript{24}
      i. Simvastatin 40mg x1 followed by 20mg QD vs. placebo in statin-naïve patients
      ii. Primary outcome: Development of severe sepsis

<table>
<thead>
<tr>
<th><strong>Purpose</strong></th>
<th>To evaluate whether patients treated with statins develop severe sepsis less frequently and to determine if this presumed protective effect decreases the rate of admission to the ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Prospective observational study</td>
</tr>
</tbody>
</table>
| **Patient Population** | **Inclusion**: pneumonia, UTI, or cellulitis, age > 40 y/o, in sepsis  
**Exclusion**: pregnancy, HIV, malignancy, statin therapy <1 month, non-sepsis related neutopenia |
| **Cohorts** | Statins ≥ 1 month before admit vs. statin naïve |
| **Outcomes** | Primary: in-hospital mortality, ICU admission, development of severe sepsis |
| **Methods** | Patients followed for 28 days or until death  
**Baseline measurements**: demographics, site of infection, APACHE II scores, pre-existing conditions, lab results, long-term drug therapy  
**Data collection points**: clinical, microbiological culture, laboratory, and organ failure indices |
| **Statistics** | t test for continuous data  
χ² for categorical data  
Logistic regression models used for multivariate analysis  
Two sided significance (α=0.05) |
| **Results** | n=361, age ≈ 70 y/o, APACHE II ≈ 11  
**Baseline characteristics**:  
- Statin group: significant higher rates of hypertension, coronary artery disease, diabetes mellitus, dyslipidemia, and chronic kidney disease  
- Lipid levels significantly higher in statin arm  
- Statin usage: 70% on simvastatin, 21% on pravastatin, 9% other statin  
| **Outcome** | **Statin (n=82)** | **Statin-naïve (n=279)** | **Difference** | **p value** |
| 28-day mortality (%) | 3.7 | 8.6 | 4.9 | 0.14 |
| ICU admission (%) | 3.7 | 12.2 | 8.5 | 0.03 |
| Development of severe sepsis (%) | 2.4 | 19 | 16.6 | <0.001 |
| **Authors’ Conclusions** | Therapy with statins for ≥ one month before onset of an acute bacterial infection was associated with a decreased rate of severe sepsis and ICU admission |
| **Strengths** | Assessed adherence to infectious disease guidelines  
Decision to admit to ICU was made by independent teams |
| **Weaknesses** | Didn’t design trial to test for mortality, but included it as a primary outcome  
Not randomized  
Patients were mildly ill (APACHE II ≈ 11)  
Investigator following patients was aware of statin treatment, possible bias |

**Purpose**
- To evaluate whether prehospital use of statins is associated with lower risk of severe sepsis and ALI/ARDS, as well as lower mortality, in critically ill patients

**Design**
- Prospective cross-sectional cohort study

**Patient Population**
- **Inclusion**: ≥18 y/o, admit to medical or surgical ICU for at least 2 days
- **Exclusion**: history of severe lung disease (COPD, asthma, fibrosis) in any other ICU for >3 days before admit, admit for any acute cardiac diagnosis, died/discharged from ICU <48 hrs from admit or transfer orders <4hrs. from screening, uncomplicated overdose or routine post-op admit

**Cohorts**
- Prehospital statin use vs. statin naïve patients

**Outcomes**
- **Primary**: inpatient mortality, rate of ALI/ARDS, rate of severe sepsis
- **Secondary**: ventilator days, ICU length of stay, hospital length of stay, mortality

**Methods**
- **Baseline measurements**: demographics, medical history, hemodynamics, ventilator variables, medications, laboratory data
- If given statin in-hospital, received simvastatin (exception of three patients)

**Statistics**
- Wilcoxon’s rank sum for continuous data
- Fisher’s exact for categorical variable
- Logistic regression for rates of severe sepsis, ALI/ARDS, and death
- Used a two-sided significance level (α=0.05)

**Results**
- n=575, age =61 y/o, APACHE II ≈ 25
- Baseline characteristics
  - Statin users: increased age, higher BMI, higher SCr, more likely to be diabetic, more Caucasian
  - Pre-hospital statin use: 51% simvastatin, 23% atorvastatin, 11% rosuvastatin, 10% lovastatin
  - 61% of statins not administered in first four ICU days
  - 3.1% of statin therapy initiated in-hospital

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Statin user (n=149)</th>
<th>Statin naïve (n=426)</th>
<th>Difference</th>
<th>p value</th>
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<tbody>
<tr>
<td>Severe sepsis @ day 4 (%)</td>
<td>43</td>
<td>54.9</td>
<td>11.9</td>
<td>0.01</td>
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<tr>
<td>Ventilator days</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>0.72</td>
</tr>
<tr>
<td>ICU Length of stay (days)</td>
<td>5</td>
<td>6</td>
<td>1</td>
<td>0.25</td>
</tr>
<tr>
<td>Hospital Length of stay (days)</td>
<td>10</td>
<td>12</td>
<td>2</td>
<td>0.24</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>18.1</td>
<td>20</td>
<td>1.9</td>
<td>0.72</td>
</tr>
</tbody>
</table>

- Logistic regression with prehospital statin use:
  - Severe sepsis: OR 0.62 (95% CI 0.40-0.96) (p=0.03)
  - ALI/ARDS: OR 0.60 (95% CI 0.36-0.99) (p=0.048)
- Lower trend in Type 2 statins vs. Type 1 (32% vs. 49%) (p=0.06)

**Authors’ Conclusions**
- Prehospital statin use was associated with fewer diagnoses of sepsis in patients admitted to the ICU

**Strengths**
- Patients with higher risk of mortality (APACHE II =25)
- Excluded pts. in cardiac/trauma ICU or w/ a primary cardiac diagnosis

**Weaknesses**
- Did not describe dosages of statins
- Possible “healthy-user” bias

**Purpose**
- To evaluate whether statin-treated patients are associated with decreased rates of severe sepsis and death, reduced dysregulation of plasma markers of inflammation and coagulation, and whether some of these differences are explained by patient characteristics, illness severity, indication bias, and healthy user effects

**Design**
- Prospective multicenter cohort study

**Patient Population**
- **Inclusion:** age > 18 y/o, diagnosis of CAP
- **Exclusion:** transfer from another hospital, D/C from hospital in past 10 days, pneumonia in past 30 days, chronic mechanical ventilation, cystic fibrosis, active TB, pregnancy, admit for palliative care

**Cohorts**
- **Cohort 1**
  - Prior statin use (n=426) vs. no prior statin use (n=1469)
- **Cohort 2**
  - Prior statin continued (n=354) vs. no prior statin use (n=1469)
- **Cohort 3**
  - Prior statin continued (n=354) vs. prior statin discontinued (n=72)

**Outcomes**
- **Primary outcomes:** 90-day mortality, rate of severe sepsis
- **Secondary Outcomes:** biomarker levels (IL-6, antithrombin, D-Dimer, factor IX, IL-10, TNF, plasminogen-activator inhibitor, thrombin-antithrombin complexes)

**Methods**
- **Baseline measurements:** demographics, illness severity, treatments administered, healthy user indicators (insured, lives at home, functional status, flu vaccine, quit smoking, aspirin use), lymphocyte cell surface proteins (CD3, CD4, CD5, CD8, CD14, CD19, CD64, CD120a, CD120b, HLA-DR, TLR2, TLR4)
- Patients followed for 90 days or until death
- Biomarkers for inflammation and coagulation were measured on days 1-7 days
  - TNF-α, IL-6, IL-10, D-dimer, antithrombin, factor IX, thrombin-antithrombin complex, plasminogen activator complex

**Statistics**
- Fisher’s exact or t test for categorical data
- χ² for continuous data
- Four confounding categories for adjustment were:
  - Demographics and co-morbidities (age, race, gender, Charlson comorbidity index)
  - Severity of illness (Pneumonia Severity Index, APACHE III)
  - Treatments received (pre-hospital antibiotic use, adequacy of inpatient antibiotics, inpatient steroids)
  - Healthy User indicators
- Two-sided significance level (α=0.05)

**Results**
- Age ≈ 69 y/o
- APACHE III acute physiology score ≈ 42, SOFA ≈ 2.4
- 14% in severe sepsis at baseline, 30.7% developed severe sepsis overall
- **Baseline characteristics Cohort 1 (Prior statin use vs. statin-naïve)**
  - Prior statin use arm: older, greater comorbidity, less likely to be admitted from a nursing home, higher Pneumonia Severity Index scores, greater likelihood of being a “healthy user”
  - No significant difference in APACHE III, SOFA, treatments administered, or admit to ICU
  - Prior statin usage: 47.7% atorvastatin, 39.4% simvastatin, 7.7% pravastatin, 3.5% lovastatin
Results

<table>
<thead>
<tr>
<th>COHORT 1</th>
<th>Outcome</th>
<th>Prior statin (n=426)</th>
<th>Statin naïve (n=1469)</th>
<th>Difference</th>
<th>p value</th>
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<tbody>
<tr>
<td>90-day unadjusted mortality (%)</td>
<td>9.2</td>
<td>12</td>
<td>2.8</td>
<td>0.11</td>
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<td>Severe Sepsis Rate (%)</td>
<td>30.8</td>
<td>30.7</td>
<td>0.1</td>
<td>0.98</td>
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</table>

*Remove those who had statin discontinued upon admission

<table>
<thead>
<tr>
<th>COHORT 2</th>
<th>Outcome</th>
<th>Prior statin continued (n=354)</th>
<th>Statin naïve (n=1469)</th>
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<th>p value</th>
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<tbody>
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<td>90-day unadjusted mortality (%)</td>
<td>7.9</td>
<td>12</td>
<td>4.1</td>
<td>0.02</td>
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<tr>
<td>Severe Sepsis Rate (%)</td>
<td>30.2</td>
<td>30.8</td>
<td>0.6</td>
<td>0.85</td>
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<table>
<thead>
<tr>
<th>COHORT 3</th>
<th>Outcome</th>
<th>Prior statin continued (n=354)</th>
<th>Prior statin discontinued (=72)</th>
<th>Difference</th>
<th>p value</th>
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<tbody>
<tr>
<td>90-day unadjusted mortality (%)</td>
<td>7.9</td>
<td>15.3</td>
<td>7.4</td>
<td>0.048</td>
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<tr>
<td>Severe Sepsis Rate (%)</td>
<td>30.2</td>
<td>33.3</td>
<td>3.1</td>
<td>0.60</td>
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</tr>
</tbody>
</table>

*Those that had prior statin discontinued twice as likely to be ventilated (11.1% vs. 5.4%) (p=0.07)

- 90 day mortality multivariable logistic regression
  - Cohort 1: prior statin use vs. statin naïve
    - Without propensity: OR 0.74 (0.48-1.24) p=0.19
    - With propensity: OR 0.90 (0.63-1.29) p=0.57
  - Cohort 2: Continued statin use vs. statin naïve
    - Without propensity: OR 0.60 (0.38-0.96) p=0.049
    - With propensity: OR 0.73 (0.47-1.13) p=0.15  ← lost significance
- Subset who developed severe sepsis showed no mortality benefit with statin use (data not given)
- Only biomarker to show significant decrease (<5% absolute difference) was antithrombin (p=0.001)

Authors’ Conclusions

- There was little to no evidence of a protective effect for statin use on clinical outcomes in CAP. “Healthy user” effects and indication bias may be important elements to consider in observational studies. Further, the near complete absence of differences in coagulation, and inflammatory markers calls into question the use of these measures as surrogate markers for any randomized controlled trial

Strengths

- Measured complete baseline labs and medical conditions

Weaknesses

- Adjusted for “healthy user” effects although baseline differences in comorbidity were present
- Mildly ill patients (mortality risk based on APACHE III =10%)
- 90-day mortality and development of severe sepsis did not correlate

**Purpose**
- To evaluate whether atorvastatin influences inflammation or organ dysfunction in patients admitted to the hospital with infection who were taking statins before hospital admission

**Design**
- Prospective randomized double-blind placebo-controlled trial

**Patient Population**
- **Inclusion:** on antibiotics for infection, ≥2 SIRS criteria, on pre-existing statin therapy
- **Exclusion:** pregnancy, liver disease, not expected to survive 24 hours, ACS or acute stroke, systemic manifestations of inflammation had abated for ≥36 hours, no PO intake possible

**Intervention**
- Atorvastatin 20mg once daily or placebo

**Outcomes**
- **Primary outcome:** Progression or regression of sepsis during hospital stay
- **Secondary Outcomes:** 28 day mortality, admit to the ICU, change in inflammatory cytokines (IL-6 or CRP) or lipid markers

**Methods**
- **Baseline measurements:** demographics, concurrent medications, antibiotic use, microbiologic data, oral intake, following laboratory data: CMP, LFT, CK, CRP, IL-6, lipid profile
- **Organ dysfunction** assessed by SOFA score (on days 1,3,5,10,14,28)
- **Study drug continued** daily up to a maximum of 28 days or when patient was discharged

**Statistics**
- Student t test or Mann-Whitney U test for continuous variables
- $\chi^2$ or Fisher exact test for categorical variables
- Anticipated 16% difference in rate of severe sepsis between groups
- Two sided significance level ($\alpha=0.05$)

**Results**
- n=150, age ≈ 68 y/o
- Baseline characteristics
  - Statin usage: 51% atorvastatin, 35% simvastatin, 10% pravastatin, 3% rosuvastatin
  - 32% in severe sepsis (24/75 patients in each arm)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Statin user (n=75)</th>
<th>Non-statin user (n=75)</th>
<th>Difference</th>
<th>p value</th>
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<tbody>
<tr>
<td>Severe Sepsis @ day 3 (# of patients in severe sepsis)</td>
<td>12</td>
<td>11</td>
<td>1</td>
<td>0.60</td>
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<tr>
<td>Severe Sepsis @ day 14 (# of patients in severe sepsis)</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0.70</td>
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<tr>
<td>Overall mortality (%)</td>
<td>8</td>
<td>5.3</td>
<td>2.7</td>
<td>0.75</td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
<td>7</td>
<td>6</td>
<td>1</td>
<td>0.73</td>
</tr>
</tbody>
</table>

- Organ dysfunction did not significantly differ between the two groups ($p=0.2$)
- ICU mortality (24 patients) of 20.8%
  - No difference between treatment groups
- Reduction of inflammatory markers (IL-6 and CRP) was not significantly different (overall $p=0.70$)
- Rate of bacteremia and use of IV antibiotics were similar
- Total cholesterol and LDL were significantly lower in study group (overall $p=0.002$ and $p=0.004$ respectively), no difference in HDL ($p=0.40$) or TG ($p=0.9$)

**Authors’ Conclusions**
- Continuation of prior statin therapy was not associated with an attenuation of inflammatory response or organ failure. Cessation of statin therapy was not associated with an inflammatory rebound or worsening of organ dysfunction

**Strengths**
- Measured cytokines as well as lipid markers
- Adequately powered to detect a difference

**Weaknesses**
- Only commented on rate of bacteremia and did not specify types of infection
- Mildly ill patients (overall mortality 6.6%)

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To determine if statin therapy reduces the incidence of severe sepsis and the levels of inflammatory cytokines in patients with acute bacterial infections.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Double-blind placebo controlled prospective trial</td>
</tr>
</tbody>
</table>
| Patient Population | **Inclusion:** > 18 y/o, no statin in 3 months preceding, within 12 hours of admit to a general medicine ward with a suspected or documented bacterial infection, on IV antibiotics  
**Exclusion:** previous statin-induced myopathy or hypersensitivity, any immunosuppressive therapy except steroids, pregnancy, HIV, neutropenic fever, LFTs 3x>ULN, CK ≤ 2.5x>ULN |
| Intervention | 40mg Simvastatin x1, followed by 20mg Simvastatin once daily vs. placebo                                                                                                                        |
| Outcomes | **Primary:** development of severe sepsis  
**Secondary:** change in cytokines from baseline to 72 hours  
**Tertiary:** death, length of stay, need for mechanical ventilation |
| Methods | Baseline measurements: demographics, admission diagnosis, preexisting conditions, chronic drug therapy, various laboratory tests, cytokine levels (IL-6, TNF-α) |
| Statistics | t test and Mann-Whitney test for continuous data  
χ² used for categorical data  
Two sided significance level (α=0.05) |
| Results | n=83, Age = 69 y/o, APACHE II = 10  
No significant baseline differences, progression to severe sepsis in only two patients  
Primary outcome was not assessed due to high level of refusal; trial stopped early  
No significant difference in decline of either IL-6 or TNF-α levels (p=0.17 and 0.97 respectively) |

![Graph of cytokines](image)

- Post-hoc analysis in pneumonia patients show a significant decrease in IL-6 (p=0.018) but not in TNF-α (p=0.12)

<table>
<thead>
<tr>
<th>Authors’ Conclusions</th>
<th>This study provides preliminary evidence that statins may affect the inflammatory response in patients with acute bacterial infections</th>
</tr>
</thead>
</table>
| Weaknesses           | Underpowered, stopped prematurely, did not assess primary or tertiary outcome  
Cytokine levels were much lower at baseline than previously studied in severe sepsis, only measured at baseline and 72 hours.  
Mildly ill patients (mean APACHE II = 10) |
X. Conclusion

1) **Does outpatient statin therapy provide a protective effect on patients admitted with sepsis?**
   
i. **Progression from Sepsis to Severe Sepsis**
   1. Almog: significant decrease, APACHE II ≈11
   2. O’Neal: significant decrease maintained after adjustment, APACHE II =25
   3. Yende: no decrease, low severity of illness
   4. **VERDICT:** Possibility of protective effect
   
ii. **Mortality**
   1. Almog: no significant difference
   2. O’Neal: no significant difference
   3. Yende: after adjustment for propensity, no significant difference
   4. **VERDICT:** no significant difference

2) **Should statin therapy be discontinued in patients admitted to the hospital with sepsis?**
   
i. **Progression from Sepsis to Severe Sepsis (when statin discontinued vs. continued)**
   1. Yende: no significant difference
   2. Kruger: no significant difference
   3. **VERDICT:** no significant difference
   
ii. **Mortality (when statin discontinued vs. continued)**
   1. Yende: significantly higher unadjusted 90-day mortality, not designed to assess this outcome
   2. Kruger: no significant difference, not designed to assess this outcome
   3. **VERDICT:** inconclusive/no significant difference

3) **Should statin therapy be initiated in patients admitted to the hospital with sepsis?**
   
i. **Progression from Sepsis to Severe Sepsis (when statin initiated in statin naïve patients)**
   1. Novack: inconclusive
   2. ASEPSIS abstract\textsuperscript{25}
      a. Randomized single center double-blind placebo-controlled trial
      b. 100 septic statin-naïve patients given atorvastatin 40mg once daily or placebo
      c. Significant decrease in progression to severe sepsis in statin group
   3. **VERDICT:** inconclusive
   
   ii. **Mortality**
   1. Novack: inconclusive
   2. ASEPSIS: no significant difference
   3. **VERDICT:** inconclusive
   
   iii. **Results of ongoing clinical trials may affect this answer soon**\textsuperscript{26,27,28}
XI. Sources

Appendix A: SIRS Criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever/Hypothermia</td>
<td>Temp. &gt;38°C (100.4 °F) or &lt;36°C (96.8°F)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Heart rate &gt;90 bpm</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>RR&gt; 20 resp/min. or PaCO₂&lt; 32 mm Hg</td>
</tr>
<tr>
<td>Leukocytosis/Leukopenia</td>
<td>WBC &gt;12k or &lt;4k/mm³ or &gt;10% bands</td>
</tr>
</tbody>
</table>

Appendix B: Early Goal Directed Therapy Algorithm

```
Supplemental oxygen ± endotracheal intubation and mechanical ventilation

Central venous and arterial catheterization

Sedation, paralysis (if intubated), or both

CVP
- <8 mm Hg: Crystalloid
- 8–12 mm Hg
- >90 mm Hg: Vasoactive agents

MAP
- <60 mm Hg: Colloid
- >90 mm Hg
- >65 and ≤90 mm Hg

ScvO₂
- <70%: Transfusion of red cells until hematocrit ≥30%
- ≥70%: Inotropic agents

Goals achieved

Yes: Hospital admission

No
```
<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>Setting/Interventions</th>
<th>Outcomes</th>
<th>Conclusion</th>
</tr>
</thead>
</table>
| Almog Y 2004<sup>20</sup> | Prospective observational | -n=361, APACHE II ≥11 -Non-statin users vs. statins >1 month                          | 28-day mortality: 8.6%(NS) vs. 3.7%(S) (p=0.14)  
ICU admit: 12.2%(NS) vs. 3.7%(S) (p=0.025)  
Severe sepsis: 19%(NS) vs. 2.4%(S) (p<0.001) | Statin use for >1 month before onset of bacterial infection is associated with lowered rates of severe sepsis and ICU admit |
| Hackam DG 2006<sup>29</sup> | Retrospective cohort    | -n=1,218, ≥65 y/o, ACS/stroke -Follow-up: 3.8 years -Non-statin users vs. statin users | Rate of sepsis per 10,000 person years: 88(NS) vs. 71.2(S) (p=0.0003)  
19% reduction of sepsis | Use of statins in patients with atherosclerosis is associated with reduced risk of subsequent sepsis |
| Schmidt H 2006<sup>30</sup> | Retrospective cohort    | -n=120, APACHE II ≥20, admit to ICU in MODS -Statin therapy continued vs. never on statin | Mortality: 35%(S) vs. 72%(NS) (p<0.0001)  
Overall mortality = 60% | Statin treatment with developing MODS may have better outcome than those without statin therapy |
| Mortensen E 2007<sup>31</sup> | Retrospective cohort    | -n=3,018, septic -Statins vs. no statin outpatient                                    | 30-day mortality: 16% (S) vs. 36%(NS) (p<0.0001) | Use of statins is associated with decreased mortality in hospitalized septic patients |
| Martin C 2007<sup>32</sup> | Retrospective cohort    | -n=180, >40 y/o, septic -Statin vs. non-statin users                                 | Rate of severe sepsis: 56%(S) vs. 86%(NS) (p<0.02)  
In-hospital mortality: 38%(S) vs. 49%(NS) (p=0.33) | Use of statins appear to prevent sepsis from progressing to severe sepsis |
| Dobesh PP 2009<sup>33</sup> | Retrospective cohort    | -n=188, >40y/o, ICU admit for severe sepsis, APACHE II ≥ 26 -Prehospital statin therapy vs. non-statin users | In-hospital mortality: 48.4%(NS) vs. 31.7%(S) (p=0.04)  
APACHE II >24 mortality: 57.5%(NS) vs. 32.3%(S) (p=0.03)  
APACHE II ≤24 mortality: 36.4%(NS) vs. 31%(S) (p=0.81) | There is an association between statin exposure in patients with severe sepsis and a decreased mortality compared to those not exposed to statins |
| Donnino M 2009<sup>34</sup> | Prospective observational cohort | -n=2,036, >18y/o presenting to ED with infection -Statin vs. no-statin during in-hospital course | In-hospital mortality: 1.9%(S) vs. 4.5%(NS) (p<0.01) | There is an association between statin therapy and reduced mortality in patients admitted with an infection |
| Novack V 2009<sup>24</sup> | Prospective double-blind placebo-controlled | -n=83, >18y/o, statin-naive, general medicine admit with infection on IV antibiotics -APACHE II=10 -40mg simvastatin x 1, then simvastatin 20mg QD vs. placebo | IL-6 levels: Not significant  
TNF-α levels: Not significant -0% mortality | Preliminary evidence shows that statins may affect the inflammatory response in patients with acute bacterial infections |
| Dessap A 2011<sup>14</sup> | Retrospective cohort Prospective atorvastatin concentrations | -n=76, ICU admit for severe sepsis, on statin outpatient -Continuation vs. discontinuation of outpatient statin -Atorvastatin concentration in 9 ICU septic patients continuing statin | Organ dysfunction-free days: 6(S) vs. 11(NS) (p=0.03)  
Inpatient mortality: 37%(NS) vs. 32%(S) (p=0.73)  
Pre-dose atorvastatin conc. = 66ng/mL  
Post-dose atorvastatin conc. = 144ng/mL | The apparent beneficial effects of continuation of chronic statin therapy in septic ICU pts. were driven by selection bias and confounders. Also, caution should be taken as statin levels were very high in these septic ICU patients |
| Kruger P 2011<sup>23</sup> | Prospective randomized double-blind placebo-controlled | -n=150, ≥2 SIRS, infection, on outpatient statin therapy -Atorvastatin 20mg vs. statin discontinued | Severe Sepsis @ Day 3: 16%(S) vs. 15%(NS) (p=0.60)  
Mortality: 8(S) vs. 5.3%(NS) (p=0.75)  
Biomarkers days 1-7: NS except for antithrombin | Continuation of prior statin therapy not associated with attenuation of inflammatory response. Discontinuation of statin not associated with inflammatory rebound |
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Study Population</th>
<th>Clinical Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yende S 2011&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Prospective observational cohort</td>
<td>n=1,895, &gt;18 y/o, CAP</td>
<td>Prior statin vs. statin-naïve 90-Day Mortality: OR 0.74 (0.48-1.24) (p=0.19)</td>
<td>Little to no evidence of a protective effect for statin use on clinical outcomes in CAP and “healthy user” effects and indication bias may be important elements to consider in observational studies</td>
</tr>
<tr>
<td>O’Neal H 2011&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Prospective cross-sectional cohort</td>
<td>n=575, ≥18 y/o, medical or surgical ICU, APACHE II =25</td>
<td>Prehospital statin vs. non-statin users</td>
<td>Prehospital statin use was associated with fewer diagnoses of sepsis in patients admitted to the ICU with critical illness</td>
</tr>
<tr>
<td>Williams J 2011&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Prospective observational</td>
<td>n=2,642, &gt;17 y/o, any infection, 38% sepsis overall</td>
<td>30-Day In-hospital mortality: OR 0.96 (0.55-1.69 95% CI)</td>
<td>There is no association between preadmission statin use and 30-day in-hospital mortality in ED patients admitted with an infection</td>
</tr>
</tbody>
</table>