Block-A-Shock:
The Use of Beta-Blockers in Septic Shock

Molly Curran, Pharm.D.
PGY2 Critical Care Pharmacy Resident
Department of Pharmacy, University Health System, San Antonio, TX
Division of Pharmacotherapy, The University of Texas at Austin College of Pharmacy
Pharmacotherapy Education and Research Center,
University of Texas Health Science Center at San Antonio

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Learning Objectives

1. Discuss the pathophysiology of septic shock and sepsis-induced myocardial depression
2. Identify and recommend appropriate agents for hemodynamic management of septic shock
3. Describe the potential benefits and risks of using beta-blockers in septic shock
4. Devise an evidence-based recommendation for the appropriate use of beta-blockers in septic shock
I. Sepsis and septic shock

A. Definitions\textsuperscript{1-3}
   i. Systemic inflammatory response syndrome (SIRS) is the presence of more than one of following clinical manifestations:
      a. Body temperature \( > 38^\circ\text{C} \) or \( < 36^\circ\text{C} \)
      b. Heart rate (HR) \( > 90 \) beats per minute (BPM)
      c. Tachypnea with respiratory rate \( > 20 \) breaths per minute or hyperventilation with \( \text{PaCO}_2 < 32 \) mmHg
      d. White blood cell (WBC) count \( > 12,000 \) cu/mm or \( < 4,000 \) cu/mm or presence of \( > 10\% \) immature neutrophils (bands)
   ii. Sepsis: SIRS in response to infection
   iii. Severe sepsis: sepsis associated with organ dysfunction, hypoperfusion abnormality, or sepsis-induced hypotension
   iv. Septic shock: subset of severe sepsis defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation along with organ dysfunction and perfusion abnormalities

B. Incidence and epidemiology\textsuperscript{3-5}
   i. 750,000 cases annually in the US
   ii. Worldwide estimated 19 million cases per year
   iii. Significant health concern
      a. Severe sepsis represents 10\% of all intensive care unit (ICU) admissions
      b. Incidence of in-hospital mortality up to 50\%
      1. Influenced by patient factors: comorbidities, pathogens, infection source, organ dysfunction
      2. Introduction of guidelines is associated with decreased mortality during last 25 years
      3. Severity of illness measured by several classification scales (Appendix A)
   c. Annual US healthcare system cost of $24.3 billion

C. Pathophysiology\textsuperscript{2,3,7,8}
   i. Infection triggers pro-inflammatory and anti-inflammatory response
      a. Initial pro-inflammatory response cascade results in tissue injury

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Progression of SIRS to septic shock}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Relationship of SIRS, sepsis, and septic shock\textsuperscript{1}}
\end{figure}
b. Subsequent anti-inflammatory response cascade results in immunosuppression with enhanced susceptibility to secondary infections.

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**Figure 3:** Pro-inflammatory response to host-pathogen interaction in sepsis

- Leukocyte activation
  - Cytokines
  - Proteases
  - Reactive oxygen species
- Complement activation
  - Complement products
- Coagulation activation
  - Coagulation proteases
- Necrotic cell death
  - Damage and tissue injury

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**Figure 4:** Anti-inflammatory response host-pathogen interaction in sepsis

- Neuroendocrine regulation
  - Inhibit proinflammatory cytokine production via hypothalamic-pituitary-adrenal axis
- Impaired function of immune cells
  - Apoptosis of T, B, and dendritic cells
  - Expansion of regulatory T and myeloid suppressor cells
  - Impaired phagocytosis
- Inhibition of proinflammatory gene transcription
  - Anti-inflammatory cytokines
  - Soluble cytokine receptors
  - Epigenetic regulation

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ii. Factors influencing response
   a. Host: genetic characteristics and coexisting illnesses
   b. Causative pathogen: load and virulence

iii. Organ failure results from cumulative effect of decreased tissue oxygenation
   a. Tissue hypoperfusion
      1. Increased coagulation and decreased anticoagulation
      2. Vasodilation and hypotension
   b. Loss of barrier function
      1. Cell shrinkage and cell death
      2. Capillary leak and interstitial edema

iv. Leads to distributive shock
   a. Results from body’s attempts to compensate for vasodilation by increasing cardiac output (CO)
   b. Compounds intravascular volume deficits
   c. Induces myocardial depression

D. Treatment principles
   i. Initial resuscitation of patients with sepsis-induced hypoperfusion
      a. Initiate early, aggressive, quantitative resuscitation therapy when severe sepsis is identified
      b. During first three hours (hr), initiate aggressive fluid resuscitation (30 mL/kg minimum)
         1. Mean arterial pressure (MAP) ≥ 65 mm Hg
         2. Urine output ≥ 0.5 mL/kg/hr
      c. May consider other hemodynamic monitoring parameters (Appendix B)
      d. Normalize elevated lactate levels to < 4 mmol/L
      e. Fluid type
         1. Crystalloids are preferred fluid
            a) No benefit to use of colloids over crystalloids overall
            b) Financial advantage
         2. Colloids
            a) Equally efficacious as crystalloid approach
            b) Recommend when patients require substantial amounts of crystalloids for resuscitation
ii. Infection management and source control goals
   a. Obtain cultures as soon as possible and prior to antibiotic therapy
      1. At least two sets of blood cultures (in both aerobic and anaerobic bottles) with at least one culture from all vascular access sites and at least one percutaneous culture
      2. Culture other sites (urine, sputum, cerebrospinal fluid, etc.) as indicated
   b. Initiate empiric antibiotic therapy within one hr of identifying severe sepsis
      1. Association between each hr delay in antibiotic therapy and mortality in sepsis
      2. Empiric therapy should be selected to cover all likely pathogens (bacterial ± fungal ± viral)
      3. Reassess for de-escalation regularly to narrow coverage

![Figure 5: Relationship of antibiotic timing and mortality after identification of septic shock](image)

ię. Conduct imaging studies to assist with location of infection
d. Establish source control when feasible

II. Cardiovascular management of septic shock

A. Role of adrenergic receptors in cardiovascular system\textsuperscript{18-20}
   i. G-coupled protein receptors mediate effect via catecholamine release to exert excitatory/inhibitory effects on vasculature
   ii. Act as target of pharmacological agents (vasopressors) aimed at improving CO and vascular tone

<table>
<thead>
<tr>
<th>Type</th>
<th>Location</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$</td>
<td>Smooth muscle of arteries and veins</td>
<td>Contraction leading to vasoconstriction</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>Central nervous system</td>
<td>Inhibition of catecholamine release</td>
</tr>
<tr>
<td></td>
<td>Sympathetic nerve varicosities</td>
<td>Inhibition of sympathetic nervous system</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>Sinoatrial node</td>
<td>Increase HR</td>
</tr>
<tr>
<td></td>
<td>Atrial and ventricular muscle</td>
<td>Increase conduction velocity and contractility</td>
</tr>
<tr>
<td></td>
<td>Atrioventricular node and Purkinje fibers</td>
<td>Increase conduction velocity</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>Smooth muscle of arteries and veins</td>
<td>Relaxation and vasodilation</td>
</tr>
</tbody>
</table>

B. Vasopressor agents\textsuperscript{18,21-26}
   i. Activity at adrenergic receptors is variable by agent
   ii. Agent selection based on properties of agents and goals of therapy or type of shock
   iii. Have rapid onset and are administered via continuous infusion for hemodynamic management

<table>
<thead>
<tr>
<th>Type</th>
<th>$\alpha_1$</th>
<th>$\beta_1$</th>
<th>$\beta_2$</th>
<th>DA</th>
<th>$V_1/V_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine (NE)</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine (Epi)</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td></td>
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<tr>
<td>Phenylephrine (PE)</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoproterenol (Iso)</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td></td>
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<tr>
<td>Dobutamine (Dobut)</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine (Dopa)</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Vasopressin (VASO)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>
C. Role of vasopressors in septic shock\textsuperscript{2,18,22-27}
   i. Initiate vasopressor therapy for MAP $\leq 65$ mm Hg to maintain adequate tissue perfusion
      a. Below MAP goal, auto-regulation is lost and perfusion is dependent on pressure
         1. May result in ischemic injuries of heart, brain, and kidney
         2. Reduction in microcirculation
      b. MAP goals should be individualized for each patient
         1. Patients with chronic hypertension or atherosclerosis may require higher goals to maintain perfusion
            a) Higher goals associated with reduction in incidence of acute kidney injury
            b) Reduction in need for renal-replacement therapy
         2. Younger, normotensive patients may tolerate lower goals
   ii. Supplement MAP goals with other endpoints indicative of perfusion
      a. Global markers: blood lactate concentrations, mental status
      b. Local markers: urine output, skin perfusion
   iii. Agent selection
      a. NE
         1. Preferred vasopressor
         2. Increases MAP due to vasoconstrictive properties with little effect on HR or stroke volume (SV)
      b. Epi
         1. Alternative to NE in patients with refractory hypotension
         2. Effects at $\beta_2$-receptors may increase lactate production
      c. Dopa
         1. Not recommended for majority of patients
            a) Useful for absolute or relative bradycardia
            b) Associated with higher relative risk of arrhythmias and mortality
         2. Increases MAP and CO via increase in SV and HR
      d. VASO
         1. Endogenous vasopressin levels are lower in septic shock after 24-48 hr
         2. Initiate at low rate 0.04 units/min
         3. Higher doses of vasopressin are associated with cardiac, splanchnic, and digital ischemia
      e. PE
         1. Not recommended because decreases SV, CO, splanchnic, and renal perfusion
         2. Only recommended for certain patients
            a) Serious arrhythmias associated with NE use
            b) CO is known to be high
            c) Salvage therapy for patients who fail to achieve goal MAP with combination vasopressor, inotrope, and vasopressin therapy
         3. Unlikely to affect HR due to lack of $\beta$-activity
D. Alternative agents for additional hemodynamic support\textsuperscript{2,28-31}
   i. Addition of dobutamine
      a. Recommended for select patients
         1. Myocardial dysfunction (elevated cardiac filling pressure/low CO)
         2. Evidence of hypoperfusion despite adequate intravascular volume and MAP
      b. Clinical trials have failed to demonstrate benefit from increasing oxygen delivery with dobutamine

\textbf{Figure 6:} Effects of vasoactive agents on pressure and blood flow\textsuperscript{22}
ii. Addition of stress dose corticosteroids (CCS)
   a. Recommended for patients unable to maintain MAP goal despite adequate fluid resuscitation and vasopressor therapy
   b. Continue therapy until vasopressors no longer required and then initiate taper to withdraw CCS
iii. Cardiovascular agents not included in Surviving Sepsis Campaign guidelines
   a. Milrinone
      1. Inhibits cAMP phosphodiesterase III in cardiac and vascular muscle to improve contractility
      2. Increases CO, decreases PCWP and vascular resistance → improves left ventricular function without increasing myocardial oxygen consumption
   b. Levosimendan
      1. Binds to cardiac troponin C to enhance the calcium sensitivity of contractile proteins and opens ATP-sensitive potassium channels in vascular muscle to induce vasodilatation
      2. In vitro acts like a PDE III inhibitor
      3. Not available in the US

E. Complications from vasopressor use and ongoing septic shock\(^{8,32-34}\)
   i. Vasopressor supplementation of already elevated endogenous catecholamines increases adrenergic stress
      a. Excess catecholamines mediate injury over time
         1. Induce hyper-metabolism by mediating insulin resistance → stress-induced muscle catabolism
         2. Drives tachycardia and cardiac stress while preventing adequate cardiac perfusion

Figure 7: Deleterious effects of sustained catecholamine surge\(^{32}\)

ii. Myocardial depression may develop in septic shock
   a. Occurs in about 50% of patients with septic shock within first 48 hr
   b. Decreased left ventricular ejection fraction
   c. Confers poor prognosis
   d. Mechanism similar to process of chronic heart failure
   e. Autonomic system unable to adjust cardiovascular response to the intensity of inflammatory stress
      1. Complex process resulting from interaction between genetic, molecular, metabolic, structural, and hemodynamic alterations
      2. Occurs due to sustained reductions in preload, afterload, and the microcirculation
III. Potential role of beta-blockers in septic shock

A. Beta-blocker agents
   i. Block the action of endogenous catecholamines on adrenergic β receptors
   ii. Classified based on receptor activity
      a. Nonselective: work on all β-receptors
         1. Early studies evaluated propranolol, a nonselective agent in septic shock
         2. Some nonselective agents also have α-adrenergic antagonism
      b. Selective: preferentially block the action of one distinct subtype of β-receptor

B. Review of cardioselective β-blocker pharmacology
   i. Mechanism of action
      a. Selectively antagonize the β₁-receptor to counteract the catecholamine effect by competing for receptor sites

Table 3: Properties of cardioselective beta-blockers studied in septic shock

<table>
<thead>
<tr>
<th>Esmolol</th>
<th>Metoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulation:</strong> intravenous (IV)</td>
<td><strong>Formulations:</strong> IV, Oral</td>
</tr>
<tr>
<td><strong>Dosing:</strong> continuous infusion</td>
<td><strong>Dosing:</strong> intermittent dosing</td>
</tr>
<tr>
<td><strong>Pharmacokinetics</strong></td>
<td><strong>Pharmacokinetics</strong></td>
</tr>
<tr>
<td>• Achieves steady-state level within 10–20 minutes</td>
<td>• Achieves peak ~90 minutes after oral dose</td>
</tr>
<tr>
<td>• 55 % protein bound</td>
<td>• 10 % protein bound</td>
</tr>
<tr>
<td>• Elimination half-life: ~nine minutes</td>
<td>• Elimination half-life: three to four hr</td>
</tr>
<tr>
<td>• 73-88 % renally eliminated</td>
<td>• 95 % renally eliminated</td>
</tr>
<tr>
<td>• Undergoes esterase metabolism in blood</td>
<td>• Undergoes hepatic metabolism via CYP2D6</td>
</tr>
<tr>
<td><strong>Major adverse effects</strong></td>
<td><strong>Major adverse effects</strong></td>
</tr>
<tr>
<td>• Hypotension</td>
<td>• Hypotension</td>
</tr>
<tr>
<td>• Nausea</td>
<td>• Heart failure</td>
</tr>
<tr>
<td>• Injection site reaction</td>
<td>• Bradyarrhythmia</td>
</tr>
<tr>
<td></td>
<td>• Dizziness/fatigue</td>
</tr>
</tbody>
</table>

C. Beta-blocker theory
   i. External stimulation of β₁-receptors may further promote cell death via increased cardiac stimulation and demand
   ii. Blocking catecholamine effects may reduce exogenous stress on the heart and preserve cardiac myocytes
      a. Decrease HR
      b. Decrease contractility
   iii. The use of beta-blocker agents in other states associated with reduced left ventricular function (i.e., chronic heart failure) has resulted in decreased ventricular arrhythmias, cardiac hypertrophy, and mortality
   a. Record linkage analysis of an Italian administrative database reviewing sepsis hospitalizations between 2003 and 2008 to determine if there was a difference in mortality between patients who had been taking beta-blockers versus those who had not
   b. 1061 of 9465 patients reviewed were on beta-blocker therapy preadmission
   c. Patients with previous beta-blocker therapy found to have lower 28-day mortality (188/1061, 17.7 %) versus those previously untreated (1857/8404, 22.1 %), $P = 0.005$ for unadjusted analysis and $P = 0.025$ for adjusted analysis

D. Potential dangers of beta-blockade in septic shock$^{48,49}$
   i. Excessive beta-blocker dosages may cause negative inotropic effect and cardiac decompensation
      a. Generate pulmonary edema
      b. Excessively low CO
   ii. May result in higher rates of hemodynamic instability

E. Using beta-blockers in animal models (Appendix C for overview of all trials)$^{50,51}$
   i. Initial trials experimented in septic animal models in 1960s
   ii. Data explored effects of beta-blockade in rat, dog, and pig models

Table 4: Animal data for beta-blockade in septic shock$^{50,51}$

<table>
<thead>
<tr>
<th>Study design</th>
<th>Results</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berk, et al 1969</td>
<td>Purpose: effect of beta-adrenergic blockers on endotoxin-induced shock in a dog model</td>
<td>Survival significantly improved in propranolol treated group v. untreated or fluid resuscitation group (25/32 v. 7/36 v. 6/22, $P &lt; 0.001$)</td>
</tr>
<tr>
<td></td>
<td>Treatment groups:</td>
<td>Treated group required more fluid than propranolol group (80 mL/kg v 40 mL/kg)</td>
</tr>
<tr>
<td></td>
<td>1. Propranolol 2.5 mcg/kg infusion or doses ranging from 150 to 1500 mcg/kg over 3-minute period with fluid resuscitation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Fluid resuscitation treatment only</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Untreated</td>
<td></td>
</tr>
<tr>
<td>Aboab, et al 2011</td>
<td>Investigate cardiovascular tolerance of blockade of beta-adrenergic receptors in an endotoxin pig model</td>
<td>Esmolol infusion did not induce cardiovascular collapse in any of the septic animals</td>
</tr>
<tr>
<td></td>
<td>Treatment groups:</td>
<td>Esmolol improved stroke index from 31 mL/min/m² at 180 min to 47 mL/min/m² at 300 min</td>
</tr>
<tr>
<td></td>
<td>1. Esmolol titrated to reduce HR by 20%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Placebo group</td>
<td></td>
</tr>
</tbody>
</table>

F. Preliminary data exploring beta-blockade in septic human patients$^{52,53}$
      a. Purpose: to examine hemodynamic and metabolic effects of selective beta-blockade in patients
      b. Six septic subjects (three burn patients and three trauma patients) with pneumonia
         1. None required vasopressor therapy

### Overview

<table>
<thead>
<tr>
<th>Objective</th>
<th>To summarize clinical experience with combined use of milrinone and enteral metoprolol therapy in 40 patients with septic shock and cardiac depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial Design</td>
<td>Retrospective study design in Austria</td>
</tr>
</tbody>
</table>

### Patients

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary diagnosis of septic shock</td>
<td>&lt; 18 years old</td>
</tr>
<tr>
<td>Myocardial depression (ScvO₂ &lt; 65% despite adequate fluid resuscitation and/or cardiac index (CI) &lt; 2.5 L/min/m² requiring inotropic therapy)</td>
<td>Any cause of low CO other than sepsis</td>
</tr>
<tr>
<td>Treated with enteral metoprolol within 48 hr after onset of shock or admission to the ICU</td>
<td>Pre-existing decompensated heart failure</td>
</tr>
</tbody>
</table>

### Outcomes

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical course (ICU length of stay [LOS], 28-day mortality)</td>
<td>Vasopressor requirements (including NE, milrinone, vasopressin)</td>
</tr>
<tr>
<td>Reduction of HR to goal of 65–95 BPM</td>
<td>Surrogate markers: pH, arterial lactate, serum creatinine, C-reactive proteins</td>
</tr>
<tr>
<td>Hemodynamic effects measured by SVI, HR, central venous pressure (CVP)</td>
<td>Adverse events: decrease in BP (&gt; 20% reduction in MAP, MAP &lt; 65 mm Hg, decrease in CI, SVI, or ScvO₂, bradycardia &lt; 60 BPM)</td>
</tr>
</tbody>
</table>

### Interventions

- All patients monitored with an arterial, a central venous catheter, and a transpulmonary thermodilution device to assess CO
- Mechanical ventilation and sedation with midazolam/fentanyl initiated in all patients
- Continuous veno-venous hemofiltration (35 mL/min) was used for renal indications
- Parenteral nutrition was initiated on ICU day 2 and substituted with enteral nutrition on ICU day 3 or when CV function was established
- Hemodynamic protocol added NE plus hydrocortisone (HCT) for MAP < 65-70 (if persisted, added vasopressin) and milrinone for myocardial depression
- Metoprolol therapy with an extended release formulation was started as considered indicated by charge MD between 25 to 47.5 mg via enteral route and gradually increased to reach a targeted HR of 65-95 BPM
  - Initially, restricted to patients with chronic beta-blocker therapy to attenuate rebound tachycardia/decrease risk of perioperative myocardial ischemia
  - After 1/3 observation period, may use in patients without chronic beta-blocker therapy to treat tachycardia and economize cardiac function
  - All patients had stable cardiovascular function before initiating and held if HR < 60 BPM

### Statistics

- Descriptive statistics to report demographic and clinical data
- Linear mixed-effects model to assess changes in hemodynamic or laboratory parameters
- Bonferroni correction used to verify significant changes over time
- P-values < 0.05 indicate statistical significance
Results

Baseline Characteristics
- Of 174 patients reviewed, 40 received milrinone infusion plus metoprolol
- Age in years, mean (± standard deviation, SD): 71 ± 13
- Chronic beta-blocker therapy, n (%): 15 (38)
- Simplified Acute Physiology Score II (SAPS II), mean (± SD): 53 ± 16
- CVVH, n (%): 28 (70)
- Pre-morbidities, n (%):
  - Compensated heart failure: 12 (30)
  - Obstructive coronary artery disease: 10 (25)
- Baseline milrinone dose mcg/kg/min, mean: 0.31
- Baseline NE dose mcg/kg/min, mean: 0.17

Primary Outcomes
- 97.5% of patients achieved target HR 65–95 BPM (n = 39)

Table 5: Change in hemodynamic monitoring parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study initiation</th>
<th>Study conclusion</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVP, mean (± SD)</td>
<td>12 ± 3</td>
<td>9 ± 3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SVI, mean (± SD)</td>
<td>32 ± 12</td>
<td>44 ± 9</td>
<td>0.002</td>
</tr>
<tr>
<td>MAP, mean (± SD)</td>
<td>85 ± 23</td>
<td>90 ± 21</td>
<td>0.16</td>
</tr>
</tbody>
</table>

- 28-day mortality, n (%): 13 (33)
- Mean ICU LOS, days (± SD): 15 ± 11

Secondary Outcomes
- Lower mean NE, vasopressin, and milrinone requirements from initiation through conclusion; P < 0.001 for all values

Table 6: Change in surrogate markers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study initiation</th>
<th>Study conclusion</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH, mean (± SD)</td>
<td>7.36 ± 0.09</td>
<td>7.42 ± 0.07</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Arterial lactate (mg/dL), mean (± SD)</td>
<td>22 ± 15</td>
<td>10 ± 5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL), mean (± SD)</td>
<td>2.3 ± 1.3</td>
<td>1.6 ± 0.7</td>
<td>0.02</td>
</tr>
</tbody>
</table>

- Other organ function measurements remained unchanged
- Adverse events observed, n (%): asymptomatic bradycardia, 2 (5); increase in NE requirements, 9 (22.5); decrease in CI, 7 (17.5); increase in milrinone dose, 6 (15); decrease in SVI, 2 (5)

Conclusions

Author's Conclusions
- Enteral metoprolol has no major adverse effects on cardiovascular or organ function
- MAP increased despite decreasing NE, vasopressin, and milrinone dosages
- Cardiac function was economized, resulting in a maintained CI with a lower HR and higher SVI

Strengths
- Used cardioselective beta-blocker
- Assessed hemodynamic and markers of organ function to assess effect of beta-blockade
- Found mean increase in SVI and relatively unchanged CI demonstrating a potential economization of cardiac work and oxygen consumption

Limitations
- Retrospective study design
- Initial administration of beta-blockers aimed at reducing rebound tachycardia in chronic beta-blocker users
- Time to metoprolol initiation varied 17.7 ± 15.5 hr after onset of shock and initiation of standard therapy
- Management differed from guidelines because milrinone was used as inotropic agent in all patients
- Enrollment at MD discretion
- Used enteral route in patients on vasoactive agents
- Gave extended-release formulation metoprolol via enteral route
- Small population size

Take Home Points
- Lacks external validity due to institutional practice model versus current guidelines
- Beta-blocker use associated with decrease in cardiac work without affecting organ function
- Use of beta-blocker in resuscitated septic shock patients may allow decrease in vasopressor requirements

### Overview

<table>
<thead>
<tr>
<th>Trial Design</th>
<th>Single-center, observational, prospective study</th>
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<tr>
<td>Objectives</td>
<td>To investigate microcirculatory and macrocirculatory effects of reducing HR in septic shock below a predefined threshold using esmolol</td>
</tr>
<tr>
<td>Enrollment</td>
<td>25 ICU patients with septic shock diagnosis</td>
</tr>
</tbody>
</table>

### Exclusion criteria
- < 18 years old
- Need for inotropic agent
- Cardiac dysfunction (CI ≤ 2.2 L/min/m² with pulmonary capillary wedge pressure (PCWP) > 18 mm Hg)
- Valvular disease
- Pregnancy

### Patients

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<tbody>
<tr>
<td>Septic shock requiring NE to maintain MAP ≥ 65 mm Hg despite adequate fluid resuscitation after 24 hr</td>
<td>&lt; 18 years old</td>
</tr>
<tr>
<td>HR ≥ 95 BPM</td>
<td>Need for inotropic agent</td>
</tr>
</tbody>
</table>

### Outcomes

#### Primary
- Change in sublingual microvascular flow index (MFI) to measure microvascular circulation

#### Secondary
- Pulmonary artery monitoring (MAP, PCWP, right atrial pressure) to measure macrovascular circulation
- Differences in surrogate markers: arterial pH, lactate

### Interventions
- All treated with esmolol infusion to maintain HR between 80–94 BPM
  - Initiated at 25 mg/hr and increased by 50 mg/hr every 20 minutes or as needed to reach target HR
  - Continued for 24 hr with upper dose limit of 2000 mg/hr
- Standard therapy: IV fluids, red blood cell transfusion if hemoglobin < 7 g/dL, NE titrated to MAP ≥ 65 mm Hg, sedation with midazolam and sufentanil, IV HCT 200 mg/d
- Recorded hemodynamic variables, microcirculatory flow variables, blood gas, NE requirements at baseline and after 24 hr of esmolol

### Statistics
- Correlation of 0.99, standard deviation for MFI of 0.6
- 90% power to detect a minimum difference of 0.4 units before and after esmolol infusion
- Wilcoxon signed-rank test for continuous variables
- Expressed data as median (IQR)
- P-value < 0.05 was considered statistically significant

### Results

#### Baseline Characteristics
- Age in years, median (IQR): 62 (43–76)
- SAPS II score: median (IQR): 55 (48–62)
- HR of NE prior to esmolol infusion, median (IQR): 26 (24; 29)
- NE dose at baseline in mcg/kg/min, median (IQR): 0.53 (0.29; 0.96)
- Causes of septic shock (n): peritonitis (5), pneumonia (18), pyelonephritis (1), endocarditis (1)

#### Primary Outcome
- Sublingual MFI significantly increased after 24 hr of esmolol infusion from median 2.8 to 3.0 (P = 0.002)
- Heterogeneity index decreased from 0.06 to 0 (P = 0.002)

#### Secondary Outcomes
- HR decreased from 117 BPM to 86 BPM (P < 0.001)
- CI decreased after 24 hr esmolol therapy from 4 L/min/m² to 3.1 L/min/m² (P = < 0.001)
- NE requirements reduced from 0.53 mcg/kg/min to 0.41 mcg/kg/min (P = 0.03)
- Median esmolol dose used 250 mg/hr (IQR 100;1050)
- Oxygen delivery and consumption were decreased (P < 0.05)
- No significant change in median MAP from 71 mm Hg to 72 mm Hg (P = 0.67)

![Figure 10: Change in microcirculatory flow index of small vessels after 24 hr of esmolol administration](image)

<table>
<thead>
<tr>
<th>MFI</th>
<th>Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absent</td>
</tr>
<tr>
<td>1</td>
<td>Intermittent</td>
</tr>
<tr>
<td>2</td>
<td>Sluggish</td>
</tr>
<tr>
<td>3</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Overview

**Trial Design**
Single-center, open-label, randomized two-group phase II trial

**Objectives**
To determine whether esmolol could reduce HR to predefined threshold and measured subsequent effects on systemic hemodynamics, organ function, adverse events, 28-day mortality

**Enrollment**
154 ICU patients with severe septic shock were randomized to 2 study groups in 1:1 ratio

**Methods**

**Patients**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Septic shock requiring NE to maintain MAP ≥ 65 mm Hg after 24 hr</td>
<td>• &lt; 18 years old</td>
</tr>
<tr>
<td>• Appropriate volume resuscitation indicated by pulmonary arterial occlusion pressure (PCWP) ≥ 12 mm Hg and CVP ≥ 8 mm Hg</td>
<td>• Beta-blocker therapy prior to randomization</td>
</tr>
<tr>
<td>• HR ≥ 95 BPM</td>
<td>• Cardiac dysfunction (CI ≤ 2.2 L/min/m² with PCWP &gt; 18 mm Hg)</td>
</tr>
</tbody>
</table>

**Interventions**

Assigned in 1:1 ratio by computer-based random number generator to receive:

- Standard therapy: fluid resuscitation, red blood cell transfusion if hemoglobin < 7g/dL, NE titrated to MAP ≥ 65 mm Hg, 300 mg continuous infusion of IV HCT daily
- Standard therapy with esmolol infusion to maintain HR between 80-94 BPM
  - Initiated at 25 mg/hr and increased by 50 mg/hr every 20 min or as needed to reach target HR within 12 hr
  - Continued until ICU discharge or death with upper dose limit of 2000 mg/hr
- Adjunctive therapy: if mixed venous O₂ saturation < 65% with hemoglobin ≥ 8g/dL and increased lactate, patients also received levosimendan at 0.2 mcg/kg/min for 24 hr

**Outcomes**

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Reduction in HR below 95 BPM and maintenance of HR between 80–94 BPM for duration of ICU stay</td>
<td>• Mortality within 28 days after randomization and adverse events</td>
</tr>
<tr>
<td>• Mortality within 28 days after randomization and adverse events</td>
<td>• Hemodynamic and organ function measures</td>
</tr>
<tr>
<td>• Hemodynamic and organ function measures</td>
<td>• NE dosages at 24, 48, 72, and 96 hr</td>
</tr>
</tbody>
</table>

**Statistics**

- Pre-hoc sample size calculation found 64 patients per group were required to detect 20% change in HR with 80% power and α = 0.05 by using 2-sided t test; increased to 75 patients per group to account for nonparametric distribution of sample
- Intention-to-treat analyses were used for all statistics
- Wilcoxon-Mann-Whitney or χ² were used to compare baseline/demographic data and 28-day mortality
- Areas under the curve (AUC) were calculated for continuous variables with repeated measurements and analyzed with Wilcoxon-Mann-Whitney test
- Log-rank test using multivariable Cox regression model to compare 28-day overall survival → accounted for multi-drug resistant infection, sex, group assignment, levosimendan infusion, age, BMI, SAPS II score, NE dosage, lactate concentration, platelet counts
- Primary outcome was confirmatory tested at 2-sided significance level of α = 0.05

Curran | 12
Results

Baseline Characteristics
- 77 patients enrolled in esmolol group and 77 patients enrolled in control group
- No significant differences in age, gender, BMI, NE dosage, arterial lactate, platelet count, pathogens, or comorbidities between groups
- SAPS II score, median (IQR): 52 (47–60) in esmolol group v. 57 (49–62) in control group

Primary Outcome
- HR in the esmolol group was significantly lower than control group
- Median AUC for HR in esmolol group -28/min (IQR, -37 to -21) v. -6/min (IQR, -14 to 0) for control group ($P < 0.001$)

![](image1.png)

Figure 11: Change in HR over time

Secondary Outcomes
- Esmolol group required less NE over time during the study period
- AUC were reported for other hemodynamic parameters (MAP, SVI, and CI)

![](image2.png)

Figure 12: Esmolol infusion in study patients

![](image3.png)

Figure 13: NE infusion in study patients

![](image4.png)

Figure 14: Change in SVI

![](image5.png)

Figure 15: Change in CI

![](image6.png)

Figure 16: Change in MAP

Acid-base and metabolic
- AUC for pH were higher for esmolol (0.28 units) v. control (-0.02 units)
- Lower median AUC lactate concentration for esmolol (-0.1 mmol/L) v. control (0.1 mmol/L)

Organ function
- AUC of kidney function (based on MDRD) was better in esmolol group (14 mL/min/m$^2$) v. control group (2 mL/min/m$^2$)
- No difference in liver function, need for RRT
- CK-MB and troponin lower in esmolol group

28-day mortality
- 49.4% in esmolol group versus 80.5% in control group ($P < 0.001$)
- Overall survival higher in esmolol group
- Esmolol group allocation and SAPS II predicted survival
Conclusions

Author’s

- Open-label use of esmolol allowed patients to achieve target HR goals without an increase in adverse events
- The use of esmolol increased SV, maintained MAP, and reduced NE requirements without need for inotropic support or causing adverse effects on organ function
- Esmolol was also associated with improvement in 28-day survival

Strengths

- Accounted for worst-case scenario when conducting pre-hoc power analysis → recruited enough patients to meet power
- Use of AUC to evaluate continuous variables minimized outliers → limit confounder effect
- Achieved 80% power to detect 20% change in HR
- Assessed organ function via clinically meaningful surrogate markers → GFR

Limitations

- SAPS II score did not accurately predict observed mortality in control arm
- Numerous variables used in Cox proportion model for sample size of 154 patients
- Standard care differed from current US guidelines → levosimodan use, Swan-Ganz catheter to measure CVP, PCWP, duration of goal-directed therapy
- Large population of multi-drug resistant pathogens (*Klebsiella* and *Acinetobacter*) → may have influenced results, multivariate analysis attempted to account for differences
- No data on appropriateness of concurrent antibiotic therapy administered during study
- Potential investigator bias → two authors have conflicts of interest, investigators unblinded
- External validity questionable → larger patient population (*n* = 166) were excluded due to HR < 95 BPM
- Not designed to detect difference in secondary outcomes
- Excluded patients on chronic beta-blocker therapy
- Unable to assess weight-based esmolol dosing to determine range of therapy

Take Home Points

- Initial SAPS II score did not accurately predict observed mortality rate in control arm
- Esmolol was associated with significant mortality benefit in septic shock patients with poor prognosis with HR sustained > 95 BPM after initial 24 hr resuscitation period
- Unreported data would be important for determining the external validity of these results: anti-microbial therapy appropriateness, and MDR pathogen coverage
- Standard protocol differed from US approach to severe sepsis

V. Future directions

A. Esmolol to treat the hemodynamic effects of septic shock
   i. Randomized open label efficacy study sponsored by Beth Israel Deaconess Medical Center in collaboration with American Heart Association enrolling patients between March 2015 to January 2019
   ii. Primary outcome: determine if esmolol reduces need for vasopressor support six hr after initiation
   iii. Secondary outcomes: time to shock reversal, change in lactate levels, difference in HR, need for vasopressor support at 24 hrs
   iv. Clinicaltrials.gov identifier: NCT02369900

B. Esmolol effects on heart and inflammation in septic shock (ESMOSEPSIS)
   i. Open-label study sponsored by Central Hospital (Nancy, France) in collaboration with Baxter Healthcare Corporation enrolling patients between December 2013 and January 2016
   ii. Primary outcome: compare mean CI before and after esmolol administration
   iii. Secondary outcomes: effect of esmolol on vasopressor requirements, microcirculatory effects of esmolol, changes in cytokine patterns in esmolol patients, echocardiography assessment of ventricular function during esmolol administration
   iv. Clinicaltrials.gov identifier: NCT02068287

VI. Summary of evidence

A. Variety of studies examining role of beta-blockade in septic shock models
   i. Animal data using different beta-blocking agents in small and large mammals
   ii. Human data originally reported in retrospective, observational studies with metoprolol and esmolol
   iii. Prospective data has been published looking at hemodynamic effects of septic shock

B. Patients studied
   i. Mean SAPS II scores ranged from 50-60, indicating predicted mortality up to 50%
      a. Results do not match predicted mortality
      b. Morelli et al. had significantly sicker population than predicted by SAPS II score
   ii. Beta-blockade to be administered to patients who had persistent tachycardia > 95 BPM
a. Cardiac ICU patient threshold above which there were greater occurrences of major cardiac events including nonfatal MI, cardiac arrest, and cardiac death
b. Ensured underwent adequate volume resuscitation prior to enrollment to prevent deleterious effect on CO

iii. Treated with protocols that varied from Surviving Sepsis Campaign recommendations
   a. Concomitant inotrope therapy with milrinone in one study
   b. Italian studies included levosimendan use

iv. No data on appropriateness of antimicrobial therapy known to reduce mortality in septic shock

C. Efficacy outcomes
   i. Beta-blocker therapy resulted in majority of patients achieving desired HR goals
   ii. Mean vasopressor requirements (NE) were lowered across all studies for duration of esmolol therapy
   iii. Surrogate markers were also positively impacted by addition of esmolol in larger studies
      a. Lowering in arterial lactate levels
      b. pH increased to physiologic levels
      c. No evidence of developing organ dysfunction (MDRD, troponins, myoglobin)
   iv. Largest study associated esmolol with possible mortality benefit

D. Safety outcomes
   i. Concerns reducing CO due to use of beta-blocker not found to be clinically significant
   ii. Relatively few adverse events occurred resulting in the need to stop beta-blocker therapy

E. Limitations of current data
   i. No study designed to evaluate clinical outcome or mortality endpoint
   ii. Variable patient populations limit external validity of current studies

VII. Conclusions

A. Use of esmolol in persistently tachycardic, septic shock patients requiring vasopressors after adequate resuscitation mitigates development of myocardial depression
   i. Lowers HR to allow for better ventricular filling during diastole  improves SV
   ii. More efficient myocardial work and energy consumption via beta-adrenergic mitigation of catecholamine mediated pathways  reduce risk of arrhythmias and myocardial infarction
      a. Lower vasopressor requirements
      b. No changes in cardiac enzymes

B. Data lacking
   i. Optimal timing of esmolol administration from presentation
   ii. Esmolol dosing strategy: duration and weight-based dose
   iii. HR target (20% reduction versus goal of 80–94 BPM)
   iv. Safety and efficacy in a large patient population

VIII. Recommendations

A. Further studies are warranted before beta-blockers should be broadly introduced into the Surviving Sepsis Campaign guidelines
B. IV cardioselective beta-blockade with esmolol may be considered in septic shock patients with SAPS II score > 55
   i. Criteria for use:
      a. HR > 95 BPM
      b. MAP ≥ 65 mmHg
      c. Undergoing close cardiac monitoring
      d. Requiring vasopressor therapy with NE in combination with VASO/HCT
   ii. Titrate esmolol to target HR of 80–94 BPM
   iii. Continue until patient does not require vasopressors, ICU discharge, or death
   iv. Considerations for discontinuing esmolol
      a. HR < 80 BPM despite dose titration
      b. Sustained increase in NE requirements to maintain MAP > 65 mmHg
      c. Signs of progressive multi-organ failure
IX. References


36. Gorczyzny RJ. Basic pharmacology of esmolol. Am J Cardiol 1985;56:3F-13F.


Appendix A. ICU Severity Scores

<table>
<thead>
<tr>
<th>Scoring system</th>
<th>Mortality interpretation</th>
<th>Background</th>
</tr>
</thead>
</table>
| Simplified Acute Physiology Score (SAPS II) | Score range 0 to 163 points | Measure severity of disease for patients (> 15 years) admitted to ICU. Based on 12 measurements during first 24 hr including:  
- Age, HR, SBP, temperature, GCS, mechanical ventilation, \( \text{FiO}_2 \text{ PaO}_2 \), urine output, BUN, Na, K, bicarbonate, bilirubin, WBC, chronic diseases, type of admission | Predicts mortality of a patient. |
| Sequential Organ Failure Assessment Score (SOFA) | Score range 0 to 24 points | Determine extent of a person’s organ function or rate of failure. Every 24 hr assess:  
- Coagulation and respiratory, nervous, cardiovascular, hepatic, and renal function every 24 hr | |
| Acute Physiology and Chronic Health Evaluation II Score (APACHE) | Score range 0 to 71 points | Classifies severity of disease based on worst physiologic value during initial 24 hr after ICU admission. Based on age, chronic health conditions, and an acute physiological score (composite of):  
- Temperature, MAP, HR, RR, oxygenation, arterial pH, serum sodium, serum potassium, serum creatinine, hematocrit, WBC, GCS | |

Appendix B. Hemodynamic Monitoring Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Abbreviation</th>
<th>Normal</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Arterial Pressure</td>
<td>MAP</td>
<td>60–100 mm Hg</td>
<td>Average BP value derived from systolic and diastolic BP</td>
</tr>
<tr>
<td>Central Venous Pressure</td>
<td>CVP</td>
<td>2–6 mm Hg</td>
<td>Indicator of volume status and preload</td>
</tr>
<tr>
<td>Stroke Volume</td>
<td>SV</td>
<td>50–100 mL</td>
<td>Amount of blood ejected from left ventricle with each heart contraction</td>
</tr>
<tr>
<td>Stroke Volume Index</td>
<td>SVI</td>
<td>25–45 mL/m²</td>
<td>SV adjusted for body surface area (BSA)</td>
</tr>
<tr>
<td>Superior Vena Cava Oxygen Saturation</td>
<td>ScvO₂</td>
<td>≥ 60%</td>
<td>Represents oxygen delivery</td>
</tr>
<tr>
<td>Pulmonary Artery Occlusion Pressure (Wedge)</td>
<td>PAOP/PCWP</td>
<td>8–12 mm Hg</td>
<td>Elevations may indicated left ventricular failure or acute pulmonary edema</td>
</tr>
<tr>
<td>Systemic Vascular Resistance Index</td>
<td>SVRI</td>
<td>1600-2400 dynes·sec·cm</td>
<td>Vascular resistance across the whole systemic circulation</td>
</tr>
<tr>
<td>Cardiac Output</td>
<td>CO</td>
<td>4-7 L/min</td>
<td>Amount of blood the heart pumps through vasculature in one minute</td>
</tr>
<tr>
<td>Stroke Volume Variation</td>
<td>SVV</td>
<td>&lt; 13%</td>
<td>Variation in arterial pulsations during positive-pressure ventilation</td>
</tr>
</tbody>
</table>
### Appendix C. Evidence Table of Beta-Blockers in Septic Animal Models\textsuperscript{50, 51, 63-66}

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Model</th>
<th>Intervention</th>
<th>Results of beta-blocker treatment arms</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berk, et al.</td>
<td>1969</td>
<td>Dogs</td>
<td>Propranolol 0.15 to 1.5 mg/kg given 5 to 60 min after endotoxin injection</td>
<td>Survival increased from 27% to 72%</td>
<td>Only study using non-selective beta-blocker</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In vivo: Increased BP and PaO\textsubscript{2}; Decreased fluid requirements</td>
<td>Co-administered calcium chloride for contractility and atropine for bradycardia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Post-mortem: Decreased lung injury</td>
<td></td>
</tr>
<tr>
<td>Suzuki, et al.</td>
<td>2005</td>
<td>Rats</td>
<td>Esmolol infusion of 10 to 20 mg/kg/hr for 24 hr</td>
<td>In vivo: Decreased HR, BP, TNF-alpha</td>
<td>No outcome data</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ex vivo: Increased SV, CO, cardiac efficiency</td>
<td>Dosing of esmolol higher than typical human dosing</td>
</tr>
<tr>
<td>Hagiwara, et al.</td>
<td>2009</td>
<td>Rats</td>
<td>Landiolol infusion of 0.1 mg/kg/min for 24 hr</td>
<td>In vivo: Decreased HR, TNF\textsubscript{z}, IL-6</td>
<td>No outcome data</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ex vivo: Left ventricular end diastolic pressure decreased</td>
<td>Landiolol is an ultra-short acting, cardioselective beta-blocker not available in the US</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Post-mortem: Decreased lung injury</td>
<td></td>
</tr>
<tr>
<td>Ackland, et al.</td>
<td>2010</td>
<td>Rats</td>
<td>Metoprolol pre- and post-treatment (various doses)</td>
<td>In vivo: Increased survival in pre-treatment arm</td>
<td>Survival benefits were not conferred to post-treatment arm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Clinical endpoint improvements occurred in both arms</td>
</tr>
<tr>
<td>Aboab, et al.</td>
<td>2011</td>
<td>Pigs</td>
<td>Esmolol infusion titrated to reduce HR by 20%</td>
<td>In vivo: Decreased HR with increase in SVI</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No outcome data</td>
</tr>
<tr>
<td>Kimmoun, et al.</td>
<td>2015</td>
<td>Rats</td>
<td>Esmolol infusion of 300 mcg/kg/min</td>
<td>In vivo: Decreased HR, lactate, EF; No significant change in CO</td>
<td>Dosing was fixed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increased median time to death by 10 hr</td>
<td>All rats received 10 mg/kg imipenem for treatment of infection</td>
</tr>
</tbody>
</table>