A n increasing incidence of multidrug-resistant (MDR) infections has been noted in both human and veterinary ICU patient populations, stressing the importance of appropriate and effective antimicrobial treatment protocols.1,2 A recent prospective study2 showed that approximately 27% of patients with positive bacterial cultures admitted to the ICU of a tertiary referral veterinary teaching hospital were considered to be infected with an MDR pathogen. This percentage increased to 58% in patients that had cultures performed after 48 hours of hospitalization and treatment.2 Optimized dosing schedules, appropriate selection of antimicrobial spectrum, and timely antimicrobial administration are the primary actionable items in the optimization of antimicrobial therapy.3 There is a sparse pipeline of new antimicrobials available for use, emphasizing the need to develop more effective dosing schedules for the antimicrobials currently available to reduce the development of antimicrobial resistance, especially in the critically ill population.4

Critically ill patients exhibit a vast array of pathophysiologic changes that can complicate antimicrobial dosing.5 In fact, most antimicrobial dosing schedules have been derived from trials with patients who are not critically ill, and it is imperative that this is taken into consideration when developing a treatment plan for a critically ill patient.5-8

Comparison of the pharmacokinetics of continuous and intermittent infusions of ampicillin-sulbactam in dogs with septic peritonitis

Samuel D. Stewart, DVM, DACVECC1*; Sarah Allen, DVM, DACVECC1; Beth Eisenberg, DVM, DACVECC1; Katie Sakakeeny, DVM, DACVECC2; Tara N. Hammond, DVM, DACVECC2; Benjamin Schneider, PhD3; Jonathan Mochel, DVM, MS, PhD, DECVP3; Tianjian Zhou, PhD4

1Massachusetts Veterinary Referral Hospital, Ethos Veterinary Health, Woburn, MA
2Department of Emergency and Critical Care, Tufts Veterinary Emergency Treatment and Specialties, Walpole, MA
3SMART Pharmacology, Iowa State College of Veterinary Medicine, Ames, IA
4Department of Statistics, Colorado State University, Fort Collins, CO

*Corresponding author: Dr. Stewart (sstewart@ethosvet.com)
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OBJECTIVE
To evaluate the time-course of ampicillin-sulbactam and percentage of time that its concentration is above a given MIC (T% > MIC) in dogs with septic peritonitis when delivered as either a continuous infusion (CI) or intermittent infusion (II).

ANIMALS
11 dogs with septic peritonitis.

PROCEDURES
Dogs were randomized to receive ampicillin-sulbactam as either CI or II. Continuous infusions were delivered as a 50 mg/kg bolus IV followed by a rate of 0.1 mg/kg/min. Intermittent infusions were administered as 50 mg/kg IV q8h. Serum ampicillin-sulbactam concentrations were measured at hours 0, 1, 6, and every 12 hours after until patients were transitioned to an oral antimicrobial equivalent. All other care was at the discretion of the attending clinician. Statistical analysis was used to determine each patient’s percentage of time T% > MIC for 4 MIC breakpoints (0.25, 1.25, 8, and 16 µg/mL).

RESULTS
No dogs experienced adverse events related to ampicillin-sulbactam administration. Both CI and II maintained a T% > MIC of 100% of MIC 0.25 µg/mL and MIC 1.25 µg/mL. The CI group maintained a higher T% > MIC for MIC 8 µg/mL and MIC 16 µg/mL; however, these differences did not reach statistical significance (P = .15 and P = .12, respectively).

CLINICAL RELEVANCE
This study could not demonstrate that ampicillin-sulbactam CI maintains a greater T% > MIC in dogs with septic peritonitis than II; however, marginal differences were noted at higher antimicrobial breakpoints. While these data support the use of antimicrobial CI in septic and critically ill patients, additional prospective trials are needed to fully define the optimal doses and the associated clinical responses.

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Antimicrobial optimization strategies should account for specific patient characteristics by adjusting the dosing schedules, thereby potentially improving antimicrobial efficacy.9–14

Beta-lactam antimicrobials are commonly used for the treatment of life-threatening infections in critically ill patients with severe sepsis due to their general tolerability and broad spectrum of activity.15 Their bacterial killing properties are dependent on the amount of time that the concentration of the antimicrobial is greater than the minimum inhibitory concentration (MIC) of the infecting pathogen at the target site.16 Maintaining the percentage of time (T%) that the total serum concentration of the antimicrobial is above the MIC (T% > MIC) as close to 100% as possible has been associated with improved bacterial eradication and a greater cure rate in patients with severe infections.17–19

A 2012 study20 showed that only approximately 11% of human hospitals within the United States use CI of antimicrobials, the majority of these being medical schools, pharmacy schools, nursing schools, and allied health professions. In veterinary medicine, few studies have focused on the use of antimicrobials as CI. A recent study21 in canine septic shock reported the use of a CI for 22% of dogs receiving time-dependent antimicrobials.

The objective of this study was to obtain preliminary data that can be used to design larger prospective trials to investigate the clinical impact of delivering ampicillin-sulbactam as a CI or II to dogs with septic peritonitis. This will be accomplished by evaluating the time course of ampicillin-sulbactam and the respective T% > MIC for each group. The total serum concentration will be used to calculate the time course, which is defined as the summation of the ampicillin and sulbactam serum concentrations.

Methods

This prospective, multicenter, randomized, controlled study was conducted at 2 veterinary referral and emergency hospitals. The study received ethical approval through the Animal Clinical Investigation Animal Care and Use Committee (Chevy Chase, MD).

Patient population

Canine patients were eligible for enrollment if they were over the age of 6 months, weighed more than 5 kg, and were diagnosed with septic peritonitis, defined as the presence of intracellular bacteria on the cytology of abdominal effusion. All patients enrolled in the study had informed consent from their owners. Patients were excluded from the trial if they had a known hypersensitivity to beta-lactam antimicrobials, received prior antimicrobial therapy for more than 24 hours before study entry, had severe renal dysfunction (greater than International Renal Interest Society stage 2), or were pregnant.

Study design

The study was planned to enroll a total of 20 dogs. Patients were randomly assigned to 1 of 2 treatment arms (10 dogs in each arm): continuous infusion (CI; intervention arm) or intermittent infusions (II; control arm). Randomization was achieved by random selection of an envelope containing a trial identification number that correlated to one of the treatment arms.

Continuous infusion patients were administered an initial bolus of ampicillin-sulbactam (Unasyn; Auromedics) at a dose of 50 mg/kg IV and were then started on a constant rate infusion of ampicillin-sulbactam at 0.1 mg/kg/min IV (144 mg/kg/day for the infusion rate, 194 mg/kg total for the first day including the bolus dose). Intermittent infusion patients were administered an initial bolus of ampicillin-sulbactam at a dose of 50 mg/kg IV, which was then repeated every 8 hours (150 mg/kg/day). Initial bolus and intermittent infusion injections were given over a period of 15 minutes. All infusions (continuous and intermittent) were delivered using a medical grade syringe pump (Medfusion 2010; MedEx) or fluid-pump (Vet/IV Pump; Heska). All other treatments/interventions, including additional antimicrobials, were at the discretion of the attending clinician.

According to manufacturer recommendations, the powdered ampicillin-sulbactam was stored at room temperature and the reconstituted solution was refrigerated at 2 to 8 °C (35.6 to 46.4 °F) for up to 3 days. All infusions were prepared and administered by trained hospital staff according to the package insert. CI preparations were replaced every 8 hours, assuring that the ampicillin-sulbactam was never at room temperature for longer than this period of time. Interruptions in drug delivery in the CI patients were allowed for 10-minute blocks, no more than 4 times per day (for walks or other treatments that would require the patient to be removed from their cage). If a patient was outside of the cage for longer than 10 minutes, then the CI traveled with the patient to prevent lapses in antimicrobial administration.

Patients were monitored hourly for possible adverse events thought to be directly related to the study drug, including vomiting, diarrhea, urticaria, hives, facial swelling, fever, and hypotension (measured using SurgiVet; ICU Medical). All possible adverse events were documented in the patient’s medical record.

Blood collection

The time when each patient received the first bolus of ampicillin-sulbactam was labeled as hour 0. Blood samples to assess serum concentration of ampicillin-sulbactam were collected at hours 0, 1, 6, and every 12 hours after that until the patients were switched to an oral antimicrobial equivalent (e.g., amoxicillin-clavulanate; Clavamox; Pfizer). Samples were immediately transferred into blood tubes with no additives (Vacutette Tube 6 mL Z-No Additive; Grenier Bio-One) and were left to sit at room temperature for 20 minutes to clot. Once clotted, the tubes were centrifuged at 3,000 rpm for 10 minutes (Variable Speed Centrifuge MFR# 602; McKesson). The serum was then pipetted into new no additives tubes that were frozen in a standard freezer at −18°C (0 °F) and were shipped within 24 hours on wet ice to
a central laboratory (College of Pharmacy, University of New England). Once received by the lab, samples were stored at −80 °C (−112 °F) until analyzed.

**Bioanalytical methods**

Individual standards of ampicillin and sulbactam were used to spike purchased dog serum over a range of concentrations to create a calibration curve for liquid chromatography coupled to tandem mass spectrometry (LC/MS-MS). Sample preparation involved the addition of an internal standard of amoxicillin to an aliquot of serum followed by drying in SpeedVac and reconstitution in mobile phase. Calibration levels contained 2:1 ratio of ampicillin-sulbactam to correlate to commercial formulations. The calibration range was 0.16 to 120 µg/mL for a total amount of ampicillin-sulbactam, correlating to 0.8 to 600 µg/mL in dog serum samples. The limit of quantification was 0.8 µg/mL. The amoxicillin and ampicillin internal standards used were hydrate salts, which were taken into account for the final analysis and calculations were performed on a free base basis.

Study sample preparation involved the addition of an internal standard to an aliquot of serum followed by protein precipitation with an organic solvent. Following centrifugation, the supernatant was assayed by LC/MS-MS. A reverse phase column was used to chromatographically separate the drugs.

**Data analysis and statistical methods**

Distributions of continuous variables within each group were assessed by visualizing Q-Q plots and performing Shapiro-Wilk tests. Age and weight characteristics were assessed using 2-sample t tests with equal variances. Sex data were assessed using a Fisher’s exact test.

Visual data exploration and presentation was performed using the lattice and gridExtra package in R version 3.5.3. The T% > MIC was calculated using linear interpolation from the approx package in R 3.5.3. T% > MIC for each treatment group was determined at 4 MIC levels (0.25, 1.25, 8, and 16 µg/mL) using a time interval of 1/600 h (1/10th of a second) for interpolation. Serum concentration vs. time data that was below the limit of detection was right-censored for analysis (Figure 1). The following descriptive statistics were calculated for each T% > MIC within each study group: mean, standard deviation, median, minimum, and maximum. The assumption of equality of variances was tested using a Bartlett test. Based on these assessments, 2-sample t tests with a Welch approximation for unequal variances were performed to compare T% > MIC between study groups. Statistical significance between treatment groups was set for P values < 0.05.

**Results**

**Patient characteristics**

A total of 20 dogs were enrolled in the study, with 10 dogs being randomized to the CI group and 10 dogs to the II group. Unfortunately, the serum samples for 9 patients got lost following a change of ownership in the lab where the samples were being stored, leaving a total of 11 patients for the final analysis. The CI group included 1 each of Hound mix, Labrador Retriever, Pomeranian, Pug, and Yorkshire Terrier. The II group included 1 each of Fox Terrier, Labrador Retriever, Old English Bulldog, Pit Bull, Siberian Husky, and Swiss Mountain Dog. The age, weight, and sex data of the dogs in each group are summarized (Table 1). There were no significant differences between signalment characteristics of the 2 groups. All 11 dogs were diagnosed with septic peritonitis secondary to intestinal rupture caused by a mechanical obstruction.

**Table 1**—Signalment characteristics of CI and II groups: arithmetic mean ± standard deviation (SD).

<table>
<thead>
<tr>
<th></th>
<th>CI group</th>
<th>II group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Mean ± SD</td>
<td>8.0 ± 3.9</td>
<td>5.3 ± 3.8</td>
<td>.281</td>
</tr>
<tr>
<td>Range</td>
<td>3–14</td>
<td>2–11</td>
<td></td>
</tr>
<tr>
<td>Weight Mean ± SD</td>
<td>17.2 ± 14.4</td>
<td>30.3 ± 17.5</td>
<td>.21</td>
</tr>
<tr>
<td>Range</td>
<td>3.7–33.2</td>
<td>11.8–63</td>
<td></td>
</tr>
<tr>
<td>Sex Male [n (%)]</td>
<td>3 (60)</td>
<td>4 (67)</td>
<td></td>
</tr>
<tr>
<td>Female [n (%)]</td>
<td>2 (40)</td>
<td>2 (33)</td>
<td></td>
</tr>
</tbody>
</table>

1P value derived from 2-sample t test with equal variances. 2P value derived from Fisher’s exact test.
Patient outcomes

In the CI group, 3 dogs had pharmacokinetic (PK) samples collected out to 54 hours, 1 dog to 66 hours, and 1 dog to 78 hours. In the II group, 2 dogs had PK samples collected out to 18 hours, 1 dog to 54 hours, 1 dog to 66 hours, 1 dog to 78 hours, and 1 dog to 90 hours. Of the 2 dogs that only had 18 hours of samples collected, one dog died 24 hours postoperatively (2-year-old Fox Terrier) and the other responded exceptionally well to treatment and was discharged around 24 hours following surgery (1 year-old Pit Bull).

Adverse events

One dog in the intermittent infusion group died of cardiac arrest 24 hours postoperatively. This death was attributed to the patient’s disease state and not the antimicrobial administration. All remaining 10 dogs survived to discharge. None of the dogs in the study had any documented adverse events believed to be directly related to the administration of the ampicillin-sulbactam.

Antimicrobial time courses

Each dog’s serum ampicillin-sulbactam concentration over time and each dog’s individual T% > MIC for the 4 MIC levels reported are presented (Figure 2; Table 2). Both groups maintained a T% > MIC of 100% for MIC 0.25 µg/mL and MIC 1.25 µg/mL. The mean T% > MIC was greater in the CI group than in the II group for MIC 8 µg/mL and MIC 16 µg/mL (100% vs 95.4% and 100% vs 88.1% respectively); however, this difference did not reach the level of statistical significance (Figure 3).

Table 2—T% > MIC for individual patients for each MIC cutoff.

<table>
<thead>
<tr>
<th>Group/Patient Number</th>
<th>T% &gt; MIC (0.25 µg/mL)</th>
<th>T% &gt; MIC (1.25 µg/mL)</th>
<th>T% &gt; MIC (8 µg/mL)</th>
<th>T% &gt; MIC (16 µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>100</td>
<td>100</td>
<td>100</td>
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</tr>
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<td>2</td>
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<td>4</td>
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<tr>
<td>5</td>
<td>100</td>
<td>100</td>
<td>100</td>
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</tr>
<tr>
<td>Mean ± SD</td>
<td>100 ± 0</td>
<td>100 ± 0</td>
<td>100 ± 0</td>
<td>100 ± 0</td>
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<tr>
<td>Median (range)</td>
<td>100 (100–100)</td>
<td>100 (100–100)</td>
<td>100 (100–100)</td>
<td>100 (100–100)</td>
</tr>
<tr>
<td>II group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>100</td>
<td>100</td>
<td>96.3</td>
<td>96.3</td>
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<tr>
<td>2</td>
<td>100</td>
<td>100</td>
<td>60.0</td>
<td>60.0</td>
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</tr>
<tr>
<td>4</td>
<td>100</td>
<td>100</td>
<td>84.7</td>
<td>84.7</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>100</td>
<td>98.3</td>
<td>98.3</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>100 ± 0</td>
<td>100 ± 0</td>
<td>95.4 ± 6.7</td>
<td>88.1 ± 15.8</td>
</tr>
<tr>
<td>Median (range)</td>
<td>100 (100–100)</td>
<td>100 (100–100)</td>
<td>99.1 (84.7–100)</td>
<td>94.9 (60–100)</td>
</tr>
<tr>
<td>P value(^2)</td>
<td>1</td>
<td>1</td>
<td>.15</td>
<td>.12</td>
</tr>
</tbody>
</table>

\(^1\)All T% > MIC reported as a percentage of total hospitalization time. \(^2\)P value derived from 2-sample \(t\) test with unequal variances.
Discussion

In this study including a small cohort of dogs, it was demonstrated that in dogs with septic peritonitis, CI did achieve a greater T% > MIC than II; however, these differences were not statistically significant. The T% > MIC was marginally greater for MIC 8 µg/mL and MIC 16 µg/mL (P = .15 and =.12, respectively). This suggests that there could be a significant difference in T% > MIC at these MICs if investigated in a larger cohort of dogs.

A study comparing human ICU patients to non-ICU patients showed that the antimicrobial concentrations needed to kill 90% of gram-negative isolates in the ICU patients were 4 to 8 times higher than the MIC of those pathogens (i.e. 4 to 8 X MIC).22 Given this recommendation, the greater T% > MIC in the CI cohort at the higher MIC cutoff levels suggest possible benefits of using CI over II to meet PK and pharmacodynamic (PD) targets in dogs with septic peritonitis.

Antimicrobial susceptibility breakpoints are developed by the Clinical and Laboratory Standards Institute (CLSI). Reference laboratories use these breakpoints when reporting isolate susceptibility data. The 2020 CLSI veterinary performance standards do not contain a breakpoint for ampicillin-sulbactam. The CLSI susceptibility breakpoint reported for ampicillin as a sole agent against Enterobacterales was derived from a dog PK/PD study using amoxicillin at a dose of 11 mg/kg q12h and is set at ≤ 0.25 µg/mL.23 This breakpoint is the lowest MIC measured in most labs, resulting in almost all gram-negative bacteria being classified as resistant to ampicillin. In humans, the CLSI susceptibility breakpoint for ampicillin-sulbactam is 8 µg/mL.24 Studies to define the PK profile of ampicillin-sulbactam in veterinary patients are needed to allow for the development of antimicrobial optimization strategies, which would likely entail new breakpoint development (by bodies like CLSI) based on dose, dosing interval, and route of administration. This was supported by a recent PK trial conducted in healthy and critically ill dogs, which concluded that the use of a low breakpoint precludes the selection of antimicrobials for treatable bacteria with MICs from 1 to 8 µg/mL and results in the escalation to more critical antimicrobials.5

Beta-lactams are time-dependent antimicrobials, reaching an initial peak circulating concentration once administered, which then gradually decreases over time.25 Once the antimicrobial concentration falls below the MIC, bacterial multiplication has been shown to resume immediately and there is an increased risk for MDR to develop.26 As discussed above, it is recommended for serum antimicrobial concentrations to be maintained at 4 to 8 times the MIC of the infecting pathogen. With conventional bolus dosing regimens of beta-lactam antimicrobials it may be challenging and, in some cases impossible, to meet these PK targets, resulting in periods of time where the antimicrobial concentration falls below the MIC of the infecting pathogen.27

One of the most commonly used beta-lactam antimicrobials in veterinary intensive care units is ampicillin-sulbactam.21 Previous PK studies of ampicillin in healthy dog at doses of 20 to 22 mg/kg have demonstrated a short half-life (0.97 hours) and rapid clearance (655.03 mL/(kg h)).28 When given as a combination, the half-life for ampicillin and sulbactam were equally as short (0.98 hours and 0.76 hours respectively).29

The 2 primary factors in critically ill patients that can affect the PK, and therefore, the PD of the antimicrobials used, are changes in systemic clearance (CL) and volume of distribution (Vd).3 For instance, increased Vd caused by endothelial damage, increased capillary permeability, maldistribution of blood flow, or hypoalbuminemia will result in lower systemic concentrations of the antimicrobial at the target site (assuming CL remains unchanged).1

Drug elimination half-life (T1/2) is directly related to the drug Vd and CL (T1/2 = [0.693 X Vd]/CL).30 Increases in CL therefore will result in a reduced T1/2 when Vd remains unchanged. Critically ill patients frequently have an increased cardiac output, resulting in increased renal blood flow.31,32 This may lead to augmented renal clearance (ARC) of drugs from the circulation, thereby lowering the circulating concentration more rapidly than would occur in noncritically ill patients.32,33 Human studies have demonstrated ARC in approximately half of critically ill patients requiring antimicrobial therapy. Those patients with ARC also showed a greater rate of treatment failure.17

Previous human trials have demonstrated that continuous infusions (CI) of beta-lactam antimicrobials achieve a significantly greater T% > MIC than when they are delivered as intermittent infusions (II). For any MIC, CI has a higher likelihood of attaining PK/PD cut-off values than II, making it a safer choice when starting empirical therapy.6,25 In people with severe sepsis, the use of time-dependent antimicrobials as CI dosing was associated with decreased hospital mortality in a recent meta-analysis of individual patient data from randomized clinical trials.34

A future application of this data could be for the development of therapeutic drug monitoring protocols. Therapeutic drug monitoring involves measuring drug concentration in patients undergoing treatment and using the results to direct and adjust dosing schedules. In the setting of critically ill septic patients receiving antimicrobial therapy, serial serum antimicrobial concentration measurements can be obtained and used to adjust antimicrobial dosing to ensure that T% > MIC is maintained as close to 100% as possible. Although not currently available, a point-of-care device that allows for rapid assessment of serum drug concentrations would allow for real-time medication adjustments that may allow for improved patient outcomes.

There are several limitations to this study. While this PK study sought to be representative of a typical population of canine patients presenting with septic peritonitis and not an experimentally induced model, it is recognized that this can result in inherent variability in the data that can skew the final analysis. Additionally, this study derived total and not free drug concentrations, which could impact...
the final analysis. The syringe pumps used in the study were not calibrated before each use, which could introduce potential variability in the rates being delivered. While illness severity scoring was not performed in this study, its use in future trials is recommended to strengthen the ability to evaluate differences in the antimicrobial protocols using Monte Carlo simulations. This study was also constrained to a small number of dogs in each treatment group. Given the marginal differences in T% > MIC at the higher MIC cutoffs, it is reasonable to assume that a larger cohort of dogs may demonstrate a more significant difference.

Based on these preliminary results, sample size calculations were performed for a subsequent study to test the hypothesis that the T% > MIC for MIC 8 µg/mL will be higher with ampicillin-sulbactam CI compared to II. A target of 8 µg/mL was used because this is the susceptibility breakpoint reported for Enterobacteriales in humans. From the study results, it is expected that using an ampicillin-sulbactam dose of 144 mg/kg/day, the T% > MIC will be 100% for the CI group and 95.4% for the II group, resulting in an estimated difference of 4.6%. Furthermore, similar calculations suggest that the estimated standard deviations for the CI and II groups will be approximately 0% and 6.7%, respectively. A total sample size of 38 dogs (19 in each group) will provide 81% power to detect the estimated difference of 4.6% using a 2-sided t test with Welch’s approximation for unequal variances and a 5% level of significance (R statistical software, version 4.0.2).

In conclusion, this study could not demonstrate that ampicillin-sulbactam CI maintains a greater T% > MIC than II in dogs with septic peritonitis at any of the MIC levels; however, marginally greater T% > MIC were noted at MIC 8 µg/mL and MIC 16 µg/mL. While these data support the use of antimicrobial CI in septic and critically ill patients, additional prospective trials with larger sample sizes and the utilization of illness severity scoring are still needed to determine the optimal antimicrobial strategy. Additional studies are also needed to evaluate the clinical response (i.e., survival to discharge) between antimicrobial CI and II. These are active areas of research for the authors.

Acknowledgments

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