# Appropriateness of Broad Spectrum Antibiotics for Severe Sepsis and Septic Shock in the Emergency Department

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***Objective:*** *Determine the appropriateness of broad-spectrum antibiotics applied in severe sepsis and septic shock in an emergency room and its impact on the survival rate.*

***Material and Method:*** *This was a prospective observational study in an emergency room setting at a tertiary care facility where early goal-directed therapy (EGDT) was applied for resuscitation of severe septic and septic shock patients. The data recorded were the initial vital signs, SAP II score, time of EGDT goals achieved ($ScvO_2$ >70), time of antibiotics initiated, type of antibiotics used, organisms that were identified, source of infection, initial and final diagnosis, and outcome of treatment. The student's t-test and Mann Whitney U test were used to compare survival rates between appropriate and inappropriate antibiotics used.*

***Results:*** *Seventy-eight newly diagnosed severe septic and septic shock cases were treated per the EGDT protocol. There were 41 (52.6%) male and 37 (47.4) female patients. The organisms were identified by hemoculture in 28 cases, 18 (64.3%) cases were gram-negative, seven (25.0%) cases were gram-positive, and three (10.7%) were mixed organisms. The five most common sites of infection were 30 (38.5%) cases of lung infection, 18 (23.1%) cases of bacteremia, 16 (20.5%) of gastrointestinal tract infection, 15 (19.2%) cases were genito-urinary tract infection, and six (7.7%) were skin and soft tissue infection. The mean SAP II score was 44.2$\pm$15.4 and the mean time to initiate antibiotics was 59$\pm$50 minute. Fifty-five cases (70.5%) were classified as appropriate antibiotics group, 31 (56.4%) of the 55 cases survived, while only nine (39.1%) of the 23 cases in the inappropriate group survived. This was not statistically significant.*

***Conclusion:*** *The most common sources of infection of septic patients were lung infection, bacteremia, gastrointestinal tract infection, genito-urinary tract infection, and skin and soft tissue infection. The hemocultures were positive in 58.9% of the cases and the common organisms were E. coli, K. pneumonia, S. aureus, and S. pneumoniae. The immunocompromised, multiple co-morbid and prolonged intubated patients should receive antibiotics to cover ESBL-producing E. coli, P. aeruginosa, and A. baumannii.*

***Keywords:*** *Sepsis, Septic shock, Broad-spectrum antibiotics, Emergency department*

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Severe sepsis and septic shock is not only the common presentation in the emergency room but is also the cause of in-hospital death[1]. Early hemodynamic resuscitation and early administration of antibiotics are crucial steps for severe septis and septic shock patients. The benefits of early antibiotics are supported by many prospective studies[2-5]. Recently, the International Guidelines for Management of Severe Sepsis and Septic Shock 2012 recommends initiation of broad spectrum antibiotics within the first hour after recognition of severe sepsis or septic shock[6].

Songklanagarind Hospital is a tertiary care and referral center in southern Thailand. There are more than 42,000 cases in the emergency room each year. Early goal-directed therapy (EGDT) has been implemented in the emergency room of Songklanagarind Hospital in 2010.

The primary outcome of the present study was to determine the appropriateness of antibiotics

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initiated in severe septis and septic shock patients in the emergency room. An appropriate antibiotic was defined as an antibiotic that was effective against organisms identified or was in agreement with an infectious disease specialist. The secondary outcome was to determine the relationship of the appropriateness of the antibiotics on survival rates.

## Material and Method

This was a prospective observational study in the Emergency Department between April 1 and September 31, 2013. The study was conducted under the Research Quality and Safety Control Committee of Prince of Songkla University. The expenditures for the study were supported by the Faculty of Medicine of Prince of Songkla University and there were no conflicts of interest. Only newly diagnosed septic shock patients aged ≥16 years old were included. All of the severe sepsis and septic shock patients were resuscitated following the Surviving Sepsis Campaign Guideline 2008. The recorded data included the chief compliant, present history, initial vital signs, past medical history, laboratory tests, initial and final diagnoses, Simplified Acute Physiologic (SAP II) score, time and type of antibiotics initiated, organism identified in vitro, site of infection, and outcome of treatment were collected and analyzed. Only patients or authorized representatives who agreed to sign a written consent form and with complete medical research charts were enrolled into the present study. Sample size of the study is calculated with adding 10% drop out rate.

$$n = \frac{Z^2_{\alpha/2}\, P\,(1-P)}{d^2}$$

$Z_{\alpha/2}$ = confidence interval 95% ($\alpha = 0.05$) = 1.96

P = probability for appropriate antibiotic use = 0.80

d = precision = 0.09

N = 76

10% drop out = 85 cases

As soon as the patients were diagnosed as septic shock or severe sepsis and septic shock, all patients received initial resuscitation according to the Surviving Sepsis Campaign Guideline 2008, and broad-spectrum antibiotics were given as soon as possible. After initial standard resuscitation, the patients were divided into two groups, appropriate antibiotics and inappropriate antibiotics. The criteria are shown in Fig. 1.

The definition of appropriate antibiotics was defined by at least one of the antibiotics given could cover the pathogen (hemoculture positive group) or agree with the opinion of an infectious specialist (hemoculture negative group).

## Results

Between April 1 and September 31, 2013, there were 78 newly diagnosed severe sepsis and septic shock patients aged ≥16 years old. All of patients received initial resuscitation and broad-spectrum antibiotics were given as soon as possible according to the Surviving Sepsis Campaign Guideline 2008. There were 41 (52.6%) male and 37 (47.4%) female patients. The bacteria were identified by hemoculture in 28 cases, 18 (64.3%) cases were gram negative, seven (25.0%) cases were gram positive, and three (10.7%) were mixed organism. Among the 18 cases of gram negative pathogen, the identified organisms were *Escherichia coli* (6 cases), extended spectrum beta-lactamase (ESBL)-producing *E. coli* (2 cases), *Salmonella* spp. (2 cases), *Klebsiella pneumonia* (2 cases), *Vibrio vulnificus* (2 cases), *Aeromonas* spp. (2 cases), *Burkholderia pseudomallei* (1 case), and *Pseudomonas aeruginosa* (1 case). Among the seven cases of gram positive organisms were *Streptococcus* spp. (6 cases), and *Staphylococcus* spp. (1 case). The five most common sites of infection were lung with 30 (38.5%) cases, unknown with 18 (23.1%) cases, gastrointestinal tract with 16 (20.5) cases, genito-urinary tract with 15 (19.2%) cases, and skin and soft tissue with six (7.7%) cases. The mean SAP II score was 44.2±15.4 and the mean time to initiate antibiotics was 59±50 minute. The most common antibiotics initiated were ceftriaxone in 43 (55.1%) cases,

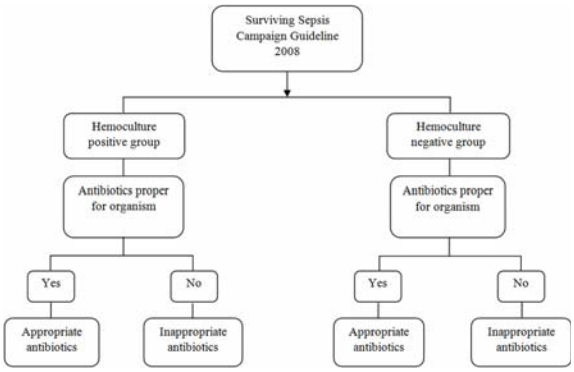


**Fig. 1** Grouping of appropriate and inappropriate antibiotics.

**Table 1.** Demographic data

| Factor | Appropriate antibiotics (n = 55) | Inappropriate antibiotics (n = 23) | Total (n = 78) | *p*-value |
|---|---|---|---|---|
| Gender | | | | |
| Male | 32 (58.2%) | 9 (39.1%) | 41 (52.6%) | 0.124 |
| Female | 23 (41.8%) | 14 (60.9%) | 37 (47.4%) | |
| Mean age (years) | 62.4±16.2 | 63.3±18.1 | 62.7±16.7 | 0.822 |
| Underlying disease | 54 (98.2%) | 21 (91.3%) | 75 (96.2%) | 0.206 |
| Diabetes mellitus | 12 (21.8%) | 3 (13.0%) | 15 (19.2%) | 0.370 |
| Hypertension | 15 (27.3%) | 7 (30.4%) | 22 (28.2%) | 0.777 |
| Cardiovascular | 7 (12.7%) | 2 (8.7%) | 9 (11.5%) | 0.611 |
| Stroke | 6 (10.9%) | 2 (8.7%) | 8 (10.3%) | 0.769 |
| Pulmonary disease | 6 (10.9%) | 1 (4.3%) | 7 (9.0%) | 0.438 |
| Other disease | 43 (78.2%) | 20 (87.0%) | 63 (80.8%) | 0.370 |
| Immunocompromised* | 38 (69.1%) | 18 (78.3%) | 56 (71.8%) | 0.412 |
| Name of antibiotics | | | | |
| Augmentin | 1 (1.8%) | 0 (0%) | 1 (1.3%) | 1.000 |
| Amikin | 1 (1.8%) | 2 (8.7%) | 3 (3.8%) | 0.206 |
| Ceftriaxone | 29 (52.7%) | 14 (60.9%) | 43 (55.1%) | 0.510 |
| Clindamycin | 9 (16.4%) | 2 (8.7%) | 11 (14.1%) | 0.375 |
| Ceftazidime | 9 (16.4%) | 3 (13.0%) | 12 (15.4%) | 0.711 |
| Metronidazole | 1 (1.8%) | 1 (4.3%) | 2 (2.6%) | 1.000 |
| Ciprofloxacin | 0 (0%) | 1 (4.3%) | 1 (1.3%) | 0.295 |
| Levofloxacin | 5 (9.1%) | 1 (4.3%) | 6 (7.7%) | 0.664 |
| Imipenem/meropenem | 11 (20.0%) | 1 (4.3%) | 12 (15.4%) | 0.081 |
| Piperacillin/tazobactam | 12 (21.8%) | 4 (17.4%) | 16 (20.5%) | 0.659 |
| Other | 11 (20.0%) | 2 (8.7%) | 13 (16.7%) | 0.222 |
| Final diagnosis | | | | |
| Lung infection | 22 (40.0%) | 8 (34.8%) | 30 (38.5%) | 0.666 |
| Bacteremia | 12 (21.8%) | 6 (26.1%) | 18 (23.1%) | 0.683 |
| Gastrointestinaltract infection | 14 (25.5%) | 2 (8.7%) | 16 (20.5%) | 0.128 |
| Genito-urinary infection | 6 (10.9%) | 9 (39.1%) | 15 (19.2%) | 0.006 |
| Skin and soft tissue | 6 (10.9%) | 0 (0%) | 6 (7.7%) | 0.172 |
| Other | 1 (1.8%) | 1 (4.3%) | 2 (2.6%) | 1.000 |
| Hemoculture result | | | | |
| Gram positive | 15 (68.2%) | 3 (50.0%) | 18 (64.3%) | 0.177 |
| Gram negative | 6 (27.3%) | 1 (16.7%) | 7 (25.0%) | |
| Mixed organism | 1 (4.5%) | 2 (33.3%) | 3 (10.7%) | |

* Immunocompromised host included end stage renal disease, on immune suppressant drugs, diabetes mellitus, leukemia, organ transplant, neutropenia.

ceftazidime in 15 (15.4%) cases, clindamycin in 11 (14.1%) cases, imipenem/meropenem in 12 (15.4%) cases, and piperacillin/tazobactam in 16 (20.5%) cases. The demographic data were shown in Table 1.

Among the 78 cases of severe sepsis and septic shock, microbes were identified by positive hemoculture in 28 (58.9%) cases. Twenty-two (78.6%) cases received at least one of the antibiotics that could cover the identified organisms and were classified as appropriate antibiotic group. Among 50 (64.1%) cases in the hemoculture negative group, 33 (66.0%) were in agreement among the emergency physicians who initiated the antibiotics and the infectious specialists who took care of the patients. These patients were classified as the appropriate antibiotics group (Fig. 2). The number of cases that were classified as appropriate antibiotics in both hemoculture positive and hemoculture negative group were 55 (70.5%) cases (95%

confidence interval 59.6-79.5) (Fig. 2).

The mean SAP II scores in the appropriate antibiotics group and the inappropriate antibiotics group were 43.1±14.1 and 46.8±18.1, respectively, which showed no statistically significant difference between the two groups ($p$ = 0.353). The mean times to receive antibiotics in the appropriate antibiotic group and the inappropriate antibiotic group were 58±56 minutes and 62±30 minutes, respectively, with no statistical significance between the two groups ($p$ = 0.133) (Table 2).

Among the 55 cases in the appropriate antibiotic group, 31 (56.4%) cases survived, while only nine (39.1%) cases survived from the 23 cases in the inappropriate antibiotics group. However, there were no statistically significant differences between the two groups ($p$ = 0.165) (Table 3).

Among the 13 death cases in the inappropriate antibiotics group, five cases were reported as positive hemoculture. Nearly all of them were in advanced age, had chronic illnesses, had ventilator/hospital associated pneumonia and the reported organisms were ESBL-producing *E. coli P. aeruginosa A. baumannii* and gram-negative septicemia.

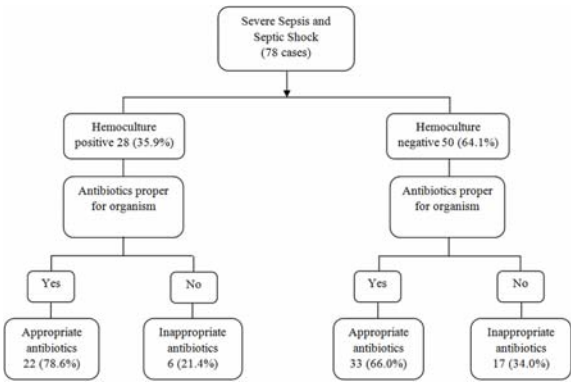


**Fig. 2** Numbers of patients in appropriate and inappropriate antibiotics group.

## Discussion

Songklanagarind Hospital has conducted Sepsis Fast Track in the emergency room since 2008. Early goal-directed therapy and antibiotics are given as soon as possible according to the Surviving Sepsis Campaign guideline 2008. In the present study, the mean time from diagnosis of severe sepsis and septic shock to initiate antibiotics was 59±50 minute. The mean SAP II score was 44.2±15.4, the overall mortality rate was 38 (48.7%) cases, and the mortality rate in the inappropriate antibiotics group was 60.9% ($p$ = 0.165), which were not statistically different between the two groups. The data were compatible with the prospective study in 261 cases of severe sepsis or septic shock by Gaieski et al[11]. The patients were age ≥16 years and the mean time from triage to antibiotics was 119 minute (interqualtile range, 76-192 minute). The mean APACHE II score was 17.9±6.4, the overall mortality rate was 31.0%, and the mortality rate of culture-positive patients who did not receive the appropriate initial antibiotics in the ED was 50.0% ($p$ = 0.15)[7]. The present study showed a 10% higher mortality rate in the inappropriate antibiotics group than the Gaieski et al[11] study because of higher severity index scores in the population.

The timing of initiating antibiotics is another factor that has an impact on the mortality rate in severe sepsis and septic shock in addition to the appropriate choice of antibiotics. A recent study in 162 ICUs in Europe and South America, which included 17,990 sepsis patients in a cohort study, reported that overall mortality was 29.7% and there was a statistically significant increase in the probability of death associated with the number of minutes delay for the first antibiotic administration[8]. A retrospective analysis in 100 ICU charts revealed the benefits of early antibiotics in severe sepsis and septic shock patients[9]. The data in Table 2 revealed there was no statistically significant difference in the time for initiating antibiotics between the appropriate (58±56 minute) and the

**Table 2.** Appropriateness of antibiotics

| Continuous variable data | Appropriate antibiotics (n = 55) | Inappropriate antibiotics (n = 23) | Total (n = 78) | $p$-value |
|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | | |
| Time to antibiotics | 58.0±56.0 | 62.0±30.0 | 59.0±50.0 | 0.133 |
| SAP II score | 43.1±14.1 | 46.8±18.1 | 44.2±15.4 | 0.353 |

**Table 3.** In-hospital mortality rates of the appropriate and inappropriate antibiotics groups

| Outcome | Appropriate antibiotics (n = 55) | Inappropriate antibiotics (n = 23) | *p*-value |
|---|---|---|---|
| Survived | 31 (56.4%) | 9 (39.1%) | 0.165 |
| Dead | 24 (43.6%) | 14 (60.9%) | |

inappropriate antibiotics group (62±30 minute) ($p = 0.133$).

The study revealed no statistically significant difference of mortality between the 24 (43.6%) death cases in the appropriate versus the inappropriate antibiotics group ($p = 0.165$).

**Conclusion**

The present study showed that the mortality rate in appropriate antibiotic group was lower than the inappropriate, but no statistically significant. Other factors such as underlying disease, organism, and instrumentation were important contributors to the prognosis of severe sepsis and septic shock. The high rate of inappropriate choice of antibiotic (29.5%) should be addressed and improved. High potency of board spectrum antibiotics should be consider in case of immunocompromised, multiple co-morbid, and prolonged intubated patients.

**What is already known in this topic?**

The benefits of early and appropriate antibiotics in severe sepsis and septic shock were supported by many prospective studies[2-5]. Recently, the International Guidelines for the Management of Severe Sepsis and Septic Shock 2012 recommended to initiate broad spectrum antibiotics within the first hour after recognition of severe sepsis or septic shock[6].

**What this study adds?**

The most common sites of infection of septic patients were lung infection, bacteremia, gastrointestinal tract infection, genito-urinary tract infection and skin and soft tissue infection. The common organisms were *E. coli K. pneumonia S. aureus and S. pneumococcus*. The immuno-compromised, multiple co-morbid, and prolonged intubated patients should receive antibiotics to cover ESBL-producing *E. coli P. aeruginosa* and *A. baumannii*. The inappropriate antibiotic were commom (29.5%). The mortality rate was lower in patients with appropriate antibiotic used, eventhough it was not statistically significant.

**Compliance with Ethical Requirements**

The present research was conducted and designed according to the ethical standards, which promote respect for the patients and protection of their rights. Approval was received by the Research Quality and Safety Control Committee of Prince of Songkla University. All patients in this study were well informed and consent forms were completed by the patients or an authorized person.

**Author contributions**

Panita Worapratya MD designed and performed the research, and wrote the paper. Jutharat Joraluck MD and Apisit Wanjaroenchaisuk MD gathered and analyzed the data. Prasit Wuthisuthimethawee MD, FRCST supervised the design and performed the research.

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**Potential conflicts of interest**

None.

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## ความเหมาะสมของการเลือกชนิดยาปฏิชีวนะที่มีฤทธิ์กว้างในผู้ป่วยที่มีภาวะช็อกจากการติดเชื้อรุนแรงในแผนกฉุกเฉิน

ปณิตา วรปรัชญา, จุฑารัตน์ จรลักษณ์, อภิสิทธิ์ วันเจริญชัยสุข, ประสิทธิ์ วุฒิสุทธิเมธาวี

**วัตถุประสงค์:** เพื่อศึกษาความเหมาะสมในการเลือกใช้ยาปฏิชีวนะในผู้ป่วย sepsis ที่รุนแรงและ septic shock ในห้องฉุกเฉินและผลกระทบต่ออัตราการเสียชีวิตของผู้ป่วย

**วัสดุและวิธีการ:** การศึกษาแบบไปข้างหน้าในผู้ป่วยที่มาที่ห้องฉุกเฉินและได้รับการวินิจฉัยเบื้องต้นเป็น severe sepsis ที่รุนแรง และ/หรือ septic shock ซึ่งได้รับการรักษาตามแนวทางของ early-goal directed therapy (EGDT) โดยเก็บข้อมูลพื้นฐานได้แก่ เพศ อายุ โรคประจำตัว อาการนำสัญญาณชีพ แรกรับ ผลตรวจทางห้องปฏิบัติการ การวินิจฉัยต้น การวินิจฉัยสุดท้าย คะแนนความรุนแรงของโรค (SAP II score) ผลการเพาะเชื้อจากเลือดและจากสิ่งส่งตรวจ ยาปฏิชีวนะที่ได้รับที่ห้องฉุกเฉิน และผลการรักษา

**ผลการศึกษา:** มีผู้ป่วยทั้งสิ้น 78 ราย ที่ได้รับการวินิจฉัยว่าเป็น severe sepsis และ septic shock ที่ได้รับการรักษาตามแนวทาง EGDT protocol, 41 ราย (ร้อยละ 52.6) เป็นชาย ผลการเพาะเชื้อจากเลือดที่สามารถระบุเชื้อได้จำนวน 28 ราย, 18 ราย (ร้อยละ 64.3) เป็นเชื้อกรัมลบ 7 ราย (ร้อยละ 25) เป็นเชื้อกรัมบวก และ 3 ราย (ร้อยละ 10.7) เป็นเชื้อหลายชนิด สาเหตุของการติดเชื้อที่พบบ่อย 5 อันดับแรกคือ ที่ปอด 30 ราย (ร้อยละ 38.5) ติดเชื้อในกระแสเลือด 18 ราย (ร้อยละ 23.1) ช่องท้องและระบบทางเดินอาหาร 15 ราย (ร้อยละ 19.2) และผิวหนังและชั้นใต้ผิวหนัง 6 ราย (ร้อยละ 7.7) ค่าเฉลี่ยของความรุนแรงโรค (SAP II score) 44.2±15.4 และระยะเวลาเฉลี่ยในการได้รับยาปฏิชีวนะคือ 59±50 นาที มีผู้ป่วย 55 ราย (ร้อยละ 70.5) ในกลุ่มที่ได้รับยาปฏิชีวนะเหมาะสมและ 31 ราย (ร้อยละ 56.4) รอดชีวิต ในขณะที่มีผู้ป่วย รอดชีวิตเพียง 9 ราย (ร้อยละ 39.1) จาก 23 ราย ในกลุ่มที่ได้รับยาปฏิชีวินะไม่เหมาะสม แต่ไม่มีความแตกต่างกันทางสถิติ

**สรุป:** สาเหตุของการติดเชื้อส่วนใหญ่ได้แก่ ในปอด ในกระแสเลือด ระบบทางเดินอาหารและทางเดินปัสสาวะ เชื้อสาเหตุที่พบบ่อยที่สุดคือ E. coli K. pneumonia S. aureus และ S. pneumococcus ผู้ป่วยที่มีโรคประจำตัว ผู้ป่วยที่มีภูมิคุ้มกับบกพร่อง สาเหตุของการติดเชื้อได้แก่ E. coli ESBL P. aeruginosa และ A. baumanii ผู้ป่วยที่ได้รับยาต้านจุลชีพไม่เหมาะสมสูงถึงร้อยละ 29.5 ซึ่งควรจะได้รับการแก้ไขต่อไป