Importance of Pharmacy Involvement in the Treatment of Sepsis

Joseph B. Cavanaugh Jr, PharmD^{}; Jesse B. Sullivan, PharmD, BCPS, BCCCP[†];
Nicole East, PharmD[‡]; and Jessica N. Nodzon, PharmD, BCPS, BCACP[‡]*

ABSTRACT

Purpose: A review of the impact of pharmacists on appropriate medication selection, timing of administration, and as members of a multidisciplinary sepsis response team.

Summary: Early goal-directed therapy (EGDT), currently recommended by the 2013 Surviving Sepsis Campaign guidelines for the management of patients with sepsis, includes the administration of appropriate antibiotics in patients with septic shock within the first hour. Multidisciplinary teams containing pharmacists have been shown to decrease time to antibiotic delivery, time to antibiotic administration, and patient mortality. The pharmacist can act as a drug information resource, expedite the medication verification and procurement process, and offer suggestions on how to better manage the patients. Pharmacists are often consulted for dosing and antibiotic selection recommendations for patients with sepsis, but they can also help increase the appropriateness of antibiotics selected. Additional recommendations and interventions made by pharmacists include fluid management and vasopressor facilitation for the more severe patients. A sepsis management team that included a pharmacist increased the number of patients receiving appropriate antibiotics within the first hour by as much as 22-fold. Another study has demonstrated that intensive care units with a pharmacist are associated with a 4% decrease in sepsis patient mortality compared to those without a pharmacist.

Conclusion: Multidisciplinary teams containing pharmacists have been shown to decrease time to administration of antibiotics, increase appropriate selection of medications, and decrease mortality; they may also decrease overall health care costs.

Key Words— early goal-directed therapy, multidisciplinary team, pharmacist, sepsis

Hosp Pharm 2017;52:191–197

Sepsis is the leading cause of death for patients in the intensive care unit (ICU) and its incidence continues to rise; it caused an estimated 19 million hospitalizations worldwide in 2014.^{1–3} Of those hospitalizations, more than 750,000 developed severe sepsis or septic shock, and 20% to 30% resulted in death.^{2,3} Sepsis is the leading cause of death for patients in the ICU.^{2,3} The diagnosis of sepsis, severe sepsis, and septic shock were a result of the definitions published in the 2013 Surviving Sepsis Campaign (SSC) guidelines. These definitions have since been updated with the 2016 publication of The Third International

Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).⁴ A comparison of these definitions can be seen in **Table 1**.

Early goal-directed therapy (EGDT) is currently recommended by the SSC guidelines.⁵ The guidelines recommend administration of antibiotics within 3 hours for patients with diagnosed or suspected sepsis and administration within 1 hour for patients with severe sepsis/septic shock.⁵ The Centers for Medicare & Medicaid Services (CMS) has adapted 3-hour and 6-hour bundles based on the SSC recommendations⁶ (**Table 2**). The CMS-based bundles are intended to

^{*}PGY1 Pharmacy Resident, Community Medical Center, Toms River, New Jersey; [†]Clinical Assistant Professor of Pharmacy Practice, Fairleigh Dickinson University, School of Pharmacy, Florham Park, New Jersey; [‡]Assistant Director of Clinical Pharmacy Services, Director – PGY1 Pharmacy Residency, Community Medical Center, Toms River, New Jersey. Corresponding author: Joseph B. Cavanaugh Jr, PharmD, PGY1 Pharmacy Resident, Community Medical Center, 99 Highway 37 West, Toms River, NJ 08755; phone: 732-557-8000 ext 10898; e-mail: joseph.cavanaugh@rwjbh.org

Table 1. Comparison of diagnostic criteria for sepsis

	Sepsis-3 ⁴	Surviving Sepsis Campaign ⁵
Sepsis	≥2 increase in SOFA or ≥2 qSOFA <u>plus</u> a known/suspected infection	Presence of ≥2 SIRS criteria <u>plus</u> a known/suspected infection
Severe sepsis	N/A	Sepsis <u>plus</u> evidence of end organ damage
Septic shock	Sepsis <u>plus</u> hypotension requiring vasopressors <u>plus</u> lactate ≥2mmol/L	Severe sepsis <u>plus</u> hypotension refractory to fluid boluses

Note: SOFA = Sepsis-Related Organ Failure Assessment score; qSOFA = Quick SOFA Score; SIRS = Systemic Inflammatory Response Syndrome.

Table 2. Centers for Medicare & Medicaid Services (CMS) 3-hour and 6-hour bundle requirements

	CMS core measure requirements ⁶
3-hour bundle	<ul style="list-style-type: none"> • Measure lactate • Obtain blood cultures prior to antibiotics • Administer broad-spectrum antibiotics • Administer a 30 mL/kg crystalloid fluid bolus for hypotension or lactate ≥2 mmol/L
6-hour bundle	<ul style="list-style-type: none"> • Vasopressors for persistent hypotension to maintain mean arterial pressure (MAP) ≥65 mm Hg • Reassess and document volume status if refractory hypotension is present or if initial lactate ≥4 mmol/L • Re-measure lactate if initial lactate ≥2 mmol/L

help promote earlier treatment of sepsis and are tied to hospital reimbursement. Studies have shown that having direct pharmacy involvement during those critical first 3 hours can decrease medication errors, help facilitate drug administration, decrease overall cost, and decrease mortality.⁷⁻¹⁰

Previous studies have examined the importance of the timing of antimicrobial administration in patients with sepsis.^{1,11-17} A pivotal retrospective study in 2006 by Kumar¹⁸ analyzed the effects of delayed antibiotic administration on mortality in patients with hypotension. The results revealed a 7.6% increase in mortality for each hour delay from recognition of hypotension to the time of antibiotic administration.¹⁸ Furthermore, the patients who received antibiotics within the first hour of hypotension had a survival rate of 79.9%.¹⁸ Timely antibiotic administration is of great importance, but appropriate antibiotics based on correct spectrum of activity and dose also play a role in treatment. In 2009, Kumar et al¹⁹ performed a retrospective review of 5,715 septic shock patients to evaluate the appropriateness of initial antibiotics after recognition of septic shock and its effect on outcomes. Of the patients studied, 80.1% received appropriate initial antibiotics, and those with appropriate empiric antibiotics were 5 times as likely to survive to hospital discharge compared to those who received inappropriate initial

antibiotics (52% vs 10.3%; odds ratio [OR], 9.45; 95% CI, 7.74-11.54; $p < 0.0001$).¹⁹

Several follow-up studies have been performed to further elucidate the effect of EGDT in septic patients. Puskas et al¹² studied the effect of early antibiotic administration on mortality in septic shock patients. The trial found no significant increase in mortality with each hour delay, however there was a significant decrease in mortality (OR, 2.4; 95% CI, 1.1-4.5) when septic patients received antibiotic prior to the development of septic shock compared to administration after shock recognition.¹²

A 2001 study performed by Rivers et al¹ looked at EGDT compared to standard care in septic shock patients. The patients in the EGDT group had an assigned treatment protocol to be completed within the first 6 hours of suspected onset, including placement of a central line catheter.¹ In-hospital mortality was higher in the standard group compared to the protocol group (relative risk [RR], 0.58; 95% CI, 0.38-0.87; $p = 0.009$) and remained consistently higher at 28 days (RR, 0.58; 95% CI, 0.39-0.87; $p = 0.01$) and at 60 days (RR, 0.67; 95% CI, 0.46-0.96; $p = 0.03$).¹ Similarly, another EGDT study was conducted in 2007 by Jones et al²⁰ using the goal of 33% relative risk reduction demonstrated by Rivers et al,¹ however the results failed to demonstrate any statistical difference during the period after the protocol was initiated.

Since the publication of Rivers et al in 2001, EGDT has continued to be studied. Over the past 2 years, there has been a trilogy of studies published that question the effectiveness of EGDT. The Protocolized Care for Early Septic Shock (ProCESS), Australian Resuscitation in Sepsis Evaluation (ARISE), and the Protocolized Management in Sepsis (ProMiSe) compared EGDT to usual care.²¹⁻²³ The first of the 3 to be published, the ProCESS trial, was conducted at 31 emergency departments across the United States. The trial compared the EGDT defined in Rivers et al, protocol-based standard therapy, and usual care in patients presenting with septic shock.²¹ The results showed that there was no difference in patient mortality at 60 or 90 days among the 3 groups.²¹

The second trial of the trilogy, the ARISE trial, took place at 51 hospitals across Australia.²² The groups in this trial were focused primarily on resuscitation, and patients in the EGDT arm were to have a central venous catheter capable of continuous ScvO₂ inserted within an hour after randomization.²² The primary outcome of patient mortality after 90 days was similar among the groups.²² The results of the trial brought into question the validity of continuous ScvO₂ as a goal for these patients.

The final and most recent trial of the 3, the ProMiSe trial, took place in 56 hospitals across the United Kingdom. The EGDT protocol was similar to that in the ARISE trial. After 90 days, the mortality rates among the groups were similar.²³ No difference was seen in cost effectiveness or mortality.²³ However, these results also showed that continuous ScvO₂ monitoring may not be a beneficial or cost-effective mode of treatment. Patients across all 3 studies received similar fluid boluses in mL/kg and received IV antibiotics prior to randomization. The results of these studies diverted future treatment strategies away from continuous ScvO₂ monitoring.

In addition to timing being crucial to the patients, it can also affect hospital costs. Judd et al²⁴ published a trial in 2014 that looked at the impact of EGDT on hospital costs relative to patient outcomes. The authors performed a retrospective observational analysis of septic patients. The study looked at patients who were treated as part of the STAT antibiotic treatment protocol and patients who were not.²⁴ The study results showed that there was a decrease in ICU length of stay (4.21 ± 3.64 days vs 5.85 ± 4.38 days; $p = 0.003$) as well as a decrease in overall patient costs (\$12,311 vs \$14,378; $p = 0.033$) for patients who were part of the STAT treatment protocol.²⁴

PHARMACIST INVOLVEMENT

Pharmacists offer a different perspective and are valuable members of the multidisciplinary team treating sepsis. Pharmacist involvement in the management of patients with sepsis has proven beneficial, as shown in Table 3. Beardsley and colleagues²⁵ worked as pharmacists on a multidisciplinary team to address antibiotic administration and sepsis-related mortality in a tertiary academic medical center as part of a descriptive study. As part of the protocol, a Code Sepsis process was initiated to identify possible septic patients by using an early warning screening tool.²⁵ If the screening tool was positive, the entire response team, including pharmacy, would be notified via page by the emergency response system, similar to a rapid response. These patients were then seen and evaluated by the multidisciplinary team. The role of the pharmacist was to assist in time to antibiotic ordering, antibiotic verification, and finally medication delivery.²⁵ In some instances based on the protocol that was implemented, if an antibiotic were not ordered within 15 minutes, then the pharmacist would contact the physician to obtain approval for entering an order. The pharmacist would evaluate the patient and enter an order for the antibiotic of his/her choice based on presentation, history, and suspected source of infection.²⁵ Of the 50 patients evaluated, 64% needed new or additional antibiotics; the pharmacy was responsible for ordering 18% of the new antibiotics compared to the physicians who ordered the remaining 46%. After the ordering process, the pharmacist would expedite the medication preparation and delivery process by his or her direct involvement in handling the order and by informing the rest of the pharmacy team of the urgency of the situation. Pharmacist participation resulted in the mean antibiotic delivery time of 14.1 ± 13.5 minutes and decreased antibiotic administration times from 396 minutes to 51 minutes in noncritical care areas and from 427 minutes to 31 minutes on the critical care units. After implementation of the Code Sepsis process, the sepsis-related mortality index was more than halved from 1.65 prior to implementation to 0.8 over 2 months post implementation.²⁵ Pharmacists acting as part of the multidisciplinary team resulted in the decrease in antibiotic administration time and sepsis-related mortality.

A similar study was performed by Flynn et al²⁶ in which pharmacists responded as part of a multidisciplinary team to a new sepsis treatment bundle initiated at their institution. The bundle included an order set, a physical response by the team including

Table 3. Studies with pharmacist involvement

Author	Study design	Endpoints	Pharmacist role	Results	Limitations
Beardsley et al ²⁵	Retrospective, descriptive	Identify reduction in turnaround time	<ul style="list-style-type: none"> – Ordered new abx for 18% of patients – Order verification – Expedite preparation and delivery process 	<ul style="list-style-type: none"> – Mean abx delivery time: 14.1 ± 13.5 minutes – Decreased administration time from 396 to 51 minutes in non-ICUs – Decreased administration time from 427 to 31 minutes in ICUs 	<ul style="list-style-type: none"> – No statistical analysis – Descriptive – Small sample size
Flynn et al ²⁶	Retrospective, case-control	% of patients with appropriate abx within 1 hour	<ul style="list-style-type: none"> – Order abx based on order set – Assess patient and abx appropriateness – Facilitate vasopressor preparation 	<ul style="list-style-type: none"> – 22-fold increase in appropriate abx within the first hour (OR, 22.4; 95% CI, 7.5-69) 	<ul style="list-style-type: none"> – Potential selection bias – Sample size (49 vs 59)
Weant et al ²⁷	Retrospective, descriptive	Identify number of consults for sepsis-related patients	<ul style="list-style-type: none"> – Dose recommendations – Appropriate empiric abx recommendations – Medication preparation – Drug information resource 	<ul style="list-style-type: none"> – 130 patients with 585 recommendations – 53% of consults: dosing recommendations – 22% of consults: addition of empiric abx – 19% of consults: medication preparation 	<ul style="list-style-type: none"> – No statistical analysis – Descriptive
Moussavi et al ²⁸	Retrospective, cohort	Time to abx (difference between order entry and time given)	<ul style="list-style-type: none"> – Appropriate empiric abx recommendations – Abx procurement and delivery from pharmacy 	<ul style="list-style-type: none"> – Decrease in median time to abx (0.61 hours [IQR 0.37-0.95] vs 0.88 hours [IQR 0.525-1.23]; $p=0.001$) – Increase in abx within 3 hours (100% vs 95%; $p=0.025$) – Increase in appropriate initial abx (97% vs 81%; $p=0.0008$) 	<ul style="list-style-type: none"> – Time of order vs time of sepsis identification – Sepsis diagnosis based on ED note
MacClaren et al ²⁹	Cross-sectional, survey	Mortality and economic effects of a pharmacist in the ICU	<ul style="list-style-type: none"> – ICU pharmacist on daily patient care rounds 	<ul style="list-style-type: none"> – No ICU pharmacist – Increased mortality from sepsis by 4.8% (OR, 1.06; $p=0.008$) – \$224,694,784 extra billing costs ($p<0.001$) – \$3,344,802 extra drug charges ($p=0.04$) – \$23,295,004 extra laboratory charges ($p<0.001$) 	<ul style="list-style-type: none"> – Reporting bias – Association not causality
Sarani et al ³⁰	Retrospective operational review	Median time in abx order to administration with a medical team redesign	<ul style="list-style-type: none"> – Pharmacist added to medical response team – Bedside response – Order verification and procurement from pharmacy 	<ul style="list-style-type: none"> – Pharmacy involvement reduced administration time by 103 minutes (157 min vs 54 min; $p<0.01$) 	<ul style="list-style-type: none"> – Sample size – Appropriateness not addressed – Lack of clinical outcomes

Note: abx = antibiotics; ED = emergency department; ICU = intensive care unit; IQR = interquartile range; OR = odds ratio.

the pharmacist, and a “sepsis cart” to help facilitate management of the patients. Patients being treated with the bundle were 22 times as likely as patients treated pre-bundle to receive appropriate antibiotics within the first hour (OR, 22.4, 95% CI, 7.5-69).²⁶ In addition, patients being treated with the bundle were more likely to reach a central venous pressure greater than 8 mm Hg within 6 hours (OR, 2.4; 95% CI 1.0-5.6), however no difference was seen in achieving a mean arterial pressure (MAP) greater than 65 mm Hg.²⁶ Pharmacists, as members of a multidisciplinary sepsis response team, were able to demonstrate improved time to antibiotic administration.

A retrospective review performed by Weant et al²⁷ demonstrated the number of times the emergency department clinical pharmacists were used in managing patient with sepsis, severe sepsis, or septic shock. Over 2 years, the pharmacists were consulted on 130 patients with sepsis and provided 585 recommendations. Dosing recommendations were the most common intervention (53%), followed by addition of empiric antibiotics (22%) and medication preparation (19%).²⁷ In a descriptive study, Weant et al identified roles that an ED pharmacist can have in the management of patients with sepsis.

Similarly, Moussavi et al²⁸ performed a 1-year retrospective analysis to study whether pharmacist presence in the ED decreased time to antibiotic administration. Patients were included if they were identified as having sepsis in the ED physician's note and if they were admitted to the ICU. Time to antibiotic administration was defined as the difference between the time that the order was originally entered and the time the antibiotic was recorded as given by a nurse. A total of 186 patients were included: 92 with a pharmacist present and 94 without a pharmacist present. Clinical ED pharmacist presence resulted in a decrease in median time to antibiotic given when compared to no pharmacist presence (0.61 hours [IQR, 0.37-0.95] vs 0.88 hours [IQR, 0.525-1.23]; $p = 0.001$).²⁸ Pharmacist presence also resulted in more patients receiving antibiotics within 3 hours (100% vs 95%; $p = 0.025$) and more patients receiving appropriate initial antibiotics (97% vs 81%; $p = 0.0008$).²⁸ However, no differences were seen in length of stay or patient mortality between the 2 groups.

To further elucidate the impact of a pharmacist, MacLaren et al²⁹ studied the clinical and economic effects of pharmacy presence in the ICU on

infections including sepsis. Pharmacist presence was assessed via national survey, and diagnosis of sepsis was obtained via ICD-9-CM codes. Clinical and economic outcomes data on ICU patients were obtained via the Expanded Modified Medicare Provider Analysis and Review from CMS. The investigators found that ICUs without a dedicated clinical pharmacist reported increased mortality from sepsis by 4.8% (OR, 1.06; $p = 0.008$). The economic impact was substantial with \$224,694,784 extra billing costs ($p < 0.001$), \$3,344,802 extra drug charges ($p = 0.04$), and \$23,295,004 extra laboratory charges ($p < 0.001$).²⁹

An operational study by Sarani et al³⁰ describes an improvement in operational efficiency when a pharmacist is present at the bedside to verify and procure antibiotics for septic patients. The median time from antibiotic order to administration was reduced by 103 minutes when a pharmacist was present versus not present (157 vs 54 minutes; $p < 0.01$). This time was saved between entering and verification (15 minutes), order verification to delivery of the drug (82 minutes), and time from delivery to administration (60 minutes).³⁰

Although no additional studies of pharmacist involvement in sepsis-related EGDT have been conducted to date, the following studies of similar scenarios may be applicable to the team-based sepsis response. One study demonstrated that the presence of a pharmacist on an intubation team can increase the appropriateness of the sedative and analgesic medications selected and also has a positive effect on time to appropriate sedation.⁷ The results showed that pharmacist presence decreased time to patient sedation by 19 minutes (9 vs 28 minutes; $p = 0.007$).⁷ Another study evaluated the effect of a pharmacist as part of a trauma response team on recorded intervention in the electronic medical records.⁸ The study recorded 304 interventions, and it was determined that the pharmacist made dosage recommendations 60% of the time and helped facilitate the medication administration 83% of the time.⁸ By helping facilitate medication administration, the patient received therapy sooner than if there were no pharmacist presence. These trials show the role a pharmacist can play on a health care team in helping decrease time to medication administration.

DISCUSSION

Many trials have been performed over the past decade to evaluate timing in sepsis patients. These trials show that it is important to initiate appropriate therapy early to decrease mortality and reduce health

care costs. Early administration and correct selection of antibiotics may be lifesaving. As discussed, recent trials, such as ProCESS, ARISE, and ProMISE, question the appropriateness of EGDT. Yet patients in all 3 trials received similar fluid boluses and antibiotics prior to randomization. The appropriateness called into question was the benefit of continuous ScvO₂ monitoring more so than the early fluids and antibiotic. These trials have caused the SSC to update their recommendations regarding EGDT. Although the guidelines no longer support using a central venous catheter or ScvO₂ monitoring for patients, it is still recommended that a fluid bolus and broad-spectrum antibiotics be given within 3 hours.⁵

EGDT in terms of prompt antibiotic and fluid administration should remain a priority for health care team members treating patients with sepsis. The timing and appropriateness of the antibiotics can decrease mortality and health care costs. The Beard-sley and Flynn^{25,26} studies demonstrated how pharmacists as members of a multidisciplinary team can decrease time to antibiotic administration while still appropriately treating those patients. The descriptive retrospective review by Weant also identified that pharmacists were often consulted for dosing and correct empiric therapy recommendations. By adding a pharmacist as a physical member of a medical team, Sarani et al were able to decrease time to antibiotics.

MacClaren et al remains the only study to show any mortality benefit. However, there are some limitations to that study. Since the study results were obtained via a national survey, the results are open to reporting bias and can only demonstrate association not causality. The study by Moussavi et al tried to show a mortality benefit but was unable to get a significant outcome. The authors were able to effectively show a decrease in time to antibiotic and number of patients getting antibiotics within the first 3 hours. A limitation and a possible reason the study was unable to demonstrate mortality benefit may be due to the small sample size of only 186 patients.

Based on the published data, if decreasing time to administration of appropriate antibiotics can decrease mortality and health care cost, and pharmacist teams have been shown to decrease timing, then pharmacists as part of a multidisciplinary team can help decrease mortality and health care costs. Yet studies showing direct outcomes rather than extrapolated data remain scarce. Pharmacists' effects on antibiotics and medication timing have been studied and proven multiple times. Future research should focus more on mortality and cost-benefit outcomes than

surrogate endpoints. With the CMS involvement and reimbursement being directly associated with bundle compliance, pharmacists' impact on cost per case and bundle compliance would also be of interest.

As the pharmacy profession continues to grow, pharmacists need to become more involved in health care teams and develop more clinical roles. While in these positions, it is the job of the pharmacist to advocate for their profession and expand their role further to optimize patient care. Pharmacists should be integrating themselves as members of sepsis response teams everywhere. As health care professionals, pharmacists are the drug experts and can optimize antibiotic selection, decrease timing, and even improve mortality. These are important functions of a pharmacist that have been effective and can and should be employed. Further research in an attempt to identify the specific interventions that provide the most clinical and financial results is necessary.

ACKNOWLEDGMENTS

The authors declare no conflicts of interest.

REFERENCES

1. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368-1377.
2. Angus DCM, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MRM. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29(7):1303-1310.
3. Vincent J-L, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: Results of the SOAP study. *Crit Care Med*. 2006;34(2):344-353.
4. Singer M, Deutschman CS, Seymour C, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA*. 2016;315(8):801-810.
5. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock, 2012. *Intens Care Med*. 2013;39(2):165-228.
6. National Quality Forum. NQF-endorsed voluntary consensus standards for hospital care: Sepsis. [http://www.nhfca.org/psf/resources/Updates1/SEP-1%20Measure%20Information%20Form%20\(MIF\).pdf](http://www.nhfca.org/psf/resources/Updates1/SEP-1%20Measure%20Information%20Form%20(MIF).pdf). Published October 2015. Accessed October 12, 2016.
7. Amini A, Faucett EA, Watt JM, et al. Effect of a pharmacist on timing of postintubation sedative and analgesic use in trauma resuscitations. *Am J Health Syst Pharm*. 2013;70(17):1513-1517.

8. Patanwala AE, Hays DP. Pharmacist's activities on a trauma response team in the emergency department. *Am J Health Syst Pharm.* 2010;67(18):1536-1538.
9. Pedersen CA, Schneider PJ, Scheckelhoff DJ. ASHP national survey of pharmacy practice in hospital settings: Dispensing and administration—2014. *Am J Health Syst Pharm.* 2015;72(13):1119-1137.
10. Wong JR, Bauer KA, Mangino JE, Goff DA. Antimicrobial stewardship pharmacist interventions for coagulase-negative staphylococci positive blood cultures using rapid polymerase chain reaction. *Ann Pharmacother.* 2012;46(11):1484-1490.
11. Cullen M, Fogg T, Delaney A. Timing of appropriate antibiotics in patients with septic shock: A retrospective cohort study. *Emerg Med Australas.* 2013;25(4):308-315.
12. Puskarich MA, Trzeciak S, Shapiro NI, et al. Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol. *Crit Care Med.* 2011;39(9):2066-2071.
13. Sterling SA, Miller WR, Pryor J, Puskarich MA, Jones AE. The impact of timing of antibiotics on outcomes in severe sepsis and septic shock: A systematic review and meta-analysis. *Crit Care Med.* 2015;43(9):1907-1915.
14. Vilella AL, Seifert CF. Timing and appropriateness of initial antibiotic therapy in newly presenting septic patients. *Am J Emerg Med.* 2014;32(1):7-13.
15. Gaieski DE, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. *Crit Care Med.* 2010;38(4):1045-1053.
16. Jalili M, Barzegari H, Pourtabatabaei N, et al. Effect of door-to-antibiotic time on mortality of patients with sepsis in emergency department: A prospective cohort study. *Acta Med Iran.* 2013;51(7):454-460.
17. Hanzelka KM, Yeung S-CJ, Chisholm G, et al. Implementation of modified early-goal directed therapy for sepsis in the emergency center of a comprehensive cancer center. *Support Care Cancer.* 2012;21(3):727-734.
18. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med.* 2006;34(6):1589-1596.
19. Kumar A, Ellis P, Arabi Y, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. *Chest.* 2009;136(5):1237-1248.
20. Jones AE, Focht A, Horton JM, Kline JA. Prospective external validation of the clinical effectiveness of an emergency department-based early goal-directed therapy protocol for severe sepsis and septic shock. *Chest.* 2007;132(2):425-432.
21. The ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. *N Engl J Med.* 2014;370(18):1683-1693.
22. The ARISE Investigators, ANZICS Clinical Trials Group. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med.* 2014;371(16):1496-1506.
23. Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med.* 2015;372(14):1301-1311.
24. Judd WR, Stephens DM, Kennedy CA. Clinical and economic impact of a quality improvement initiative to enhance early recognition and treatment of sepsis. *Ann Pharmacother.* 2014;48(10):1269-1275.
25. Beardsley JR, Jones CM, Williamson J, Chou J, Currie-Coyoy M, Jackson T. Pharmacist involvement in a multidisciplinary initiative to reduce sepsis-related mortality. *Am J Health Syst Pharm.* 2016;73(3):143-149.
26. Flynn JD, McConeghy KW, Flannery AH, Nestor M, Branson P, Hatton KW. Utilization of pharmacist responders as a component of a multidisciplinary sepsis bundle. *Ann Pharmacother.* 2014;48(9):1145-1151.
27. Weant KA, Baker SN. Emergency medicine pharmacists and sepsis management. *J Pharm Pract.* 2013;26(4):401-405.
28. Moussavi K, Nikitenko V. Pharmacist impact on time to antibiotic administration in patients with sepsis in an ED. *Am J Emerg Med.* 2016;34(11):2117-2121.
29. MacLaren R, Bond CA, Martin SJ, Fike D. Clinical and economic outcomes of involving pharmacists in the direct care of critically ill patients with infections. *Crit Care Med.* 2008;36(12):3184-3189.
30. Sarani B, Brenner SR, Gabel B, et al. Improving sepsis care through systems change: The impact of a medical emergency team. *Jt Comm J Qual Patient Saf.* 2008;34(3):179-182. ■