

# Assessment of Racial, Ethnic, and Sex-Based Disparities in Time-to-Antibiotics and Sepsis Outcomes in a Large Multihospital Cohort

**OBJECTIVES:** To characterize associations between race/ethnicity/sex, time-to-antibiotics, and mortality in patients with suspected sepsis or septic shock.

**DESIGN:** Retrospective cohort study, with race/ethnicity/sex as the exposure, and time-to-antibiotics (relative to emergency department arrival) and in-hospital mortality as the outcome.

**SETTING:** Five Massachusetts hospitals.

**PATIENTS:** Forty-nine thousand six hundred nine adults admitted 2015–2022 with suspected sepsis or septic shock (blood cultures drawn and IV antibiotics administered within 24 hr of arrival, plus evidence of organ dysfunction for sepsis, and hypotension or lactate  $\geq$  4.0 mmol/L for septic shock).

**INTERVENTIONS:** None.

**MEASUREMENTS AND MAIN RESULTS:** Among included patients, 22,598 (46%) were women, 36,626 (75%) were White, and 4,483 (9.2%) were Black. Women had longer median time-to-antibiotics than men when presenting with either suspected sepsis (203 vs. 190 min) or septic shock (160 vs. 142 min). Differences in time-to-antibiotics for women vs. men persisted after adjusting for age, race, comorbidities, source of infection, and severity of illness (adjusted odds ratio [aOR] for 3–6 vs. < 3 hr; 1.16 [95% CI, 1.07–1.25] for sepsis and aOR, 1.09 [95% CI, 1.01–1.18] for septic shock). Median time-to-antibiotics was also longer for Black vs. White patients for both sepsis (215 vs. 194 min; aOR for 3–6 vs. < 3 hr; 1.24 [95% CI, 1.06–1.45]) and septic shock (median 159 vs. 148 min; aOR, 1.32 [95% CI, 1.12–1.55]). There was no association between race/ethnicity/sex and in-hospital mortality for sepsis without shock; however, women with septic shock had higher mortality (aOR, 1.16; 95% CI, 1.04–1.29) vs. men. Higher mortality for women with septic shock persisted when also adjusting for time-to-antibiotics (aOR, 1.16; 95% CI, 1.03–1.32).

**CONCLUSIONS:** In a large cohort of patients with sepsis, time-to-antibiotics was longer for both women and Black patients even after detailed risk-adjustment. Women with septic shock had higher adjusted in-hospital mortality than men, but this association was not moderated by time-to-antibiotics.

**KEYWORDS:** health inequities; racial health disparities; sepsis; sex health disparities; time-to-antibiotics

Theodore R. Pak , MD, PhD<sup>1,2</sup>

Sarimer M. Sánchez, MD, MPH<sup>2,3</sup>

Caroline S. McKenna, MPH<sup>1</sup>

Chanu Rhee, MD, MPH<sup>1,4</sup>

Michael Klompas, MD, MPH<sup>1,4</sup>

Sepsis is a leading cause of death among hospitalized patients (1). Clinical guidelines and quality measures emphasize rapid recognition and treatment, yet in-hospital mortality rates remain high with minimal evidence of improvement in recent years (1). Disparities in access to healthcare, care processes, and long-term outcomes of treatment are well-documented in U.S. populations and manifest in part from structural racism and sexism (2, 3). Recent studies have highlighted racial and ethnic disparities in emergency department

Copyright © 2024 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

DOI: 10.1097/CCM.0000000000006428



## KEY POINTS

**Question:** Are differences in race, ethnicity, and sex associated with differences in time-to-antibiotics or in-hospital mortality for patients with suspected sepsis or septic shock?

**Findings:** Among patients presenting to five hospitals with suspected sepsis, time-to-antibiotics was longer for women vs. men, and for Black vs. White patients. Women with septic shock had higher risk of death vs. men, but this was not mediated by time-to-antibiotics.

**Meanings:** Antibiotic timeliness differs by sex and by race/ethnicity among patients presenting with suspected sepsis; mortality rates are higher for women vs. men with septic shock. Further work is needed to identify reasons and solutions for these disparities.

(ED) triage procedures (4, 5). Observational studies suggest that American women and Black and Hispanic patients hospitalized with severe infections receive antibiotics later than White men and may have higher mortality, even after adjusting for individual and hospital characteristics (6–8). However, most analyses of disparities in sepsis management have been limited by small cohort sizes, lack of detailed risk-adjustment for comorbidities and severity of illness, and failure to report associations between differences in care and patient outcomes. We therefore evaluated a large multihospital cohort of patients with suspected sepsis or septic shock for differences in time-to-antibiotics and risk of in-hospital mortality, comparing 1) men vs. women of all races and ethnicities and 2) people of different races and ethnicities, using detailed clinical data for risk adjustment.

## METHODS

We retrospectively analyzed electronic health record (EHR) data for all adults 18 years old or older admitted via the ED to five Mass General Brigham (MGB) hospitals in Massachusetts from June 2015 to August 2022. The MGB Institutional Review Board approved this study on April 12, 2018 (2018P000602, title “Developing evidence-based sepsis time zero criteria

and quality metrics using electronic health record data”) with a waiver of informed consent. All procedures adhered to institutional ethics standards and the Helsinki Declaration of 1975.

All patients in this study had “suspected infection,” defined as collection of greater than or equal to 1 blood culture and administration of IV antibiotics within 24 hours of ED arrival. We created two mutually exclusive analytical cohorts of “suspected sepsis” (organ dysfunction) and “suspected septic shock” (hypotension or lactate  $\geq 4.0$  mmol/L) patients (inclusion/exclusion criteria summarized in **Supplement Fig. 1**, <http://links.lww.com/CCM/H590>) (9). The exposures of interest were: 1) sex assigned at birth and 2) pooled, mutually exclusive race/ethnicity categories (White, Black, Hispanic, Asian, Multiracial, and other) using data recorded during patient registration similarly to prior studies (5, 10). After excluding patients with missing data on sex or race/ethnicity, we calculated summary statistics and performed multivariable logistic regression in each cohort to evaluate the associations between these categories and: 1) the interval from ED arrival to first IV antibiotic administration (“time-to-antibiotics,” categorized into 0–3 vs. 3–6 hr windows from ED arrival) and 2) in-hospital mortality.

We adjusted for a comprehensive set of confounders (9), including: 1) demographics (age, insurance type, English vs. non-English language preference, median income of the patient’s home ZIP code categorized into quintiles, academic vs. community hospital, arrival from a healthcare facility, arrival by ambulance, hospital discharge within the past 90 d, and admission year); 2) selected Elixhauser comorbidities and the overall Elixhauser comorbidity index; 3) severity of illness (presenting laboratory data and vitals within 12 hr of arrival, pre-arrival intubation, highest respiratory support, and vasopressor administration); 4) suspected sources of infection derived from “present-on-admission” *International Classification of Diseases*, 10th Revision, Clinical Modification codes; and 5) history of penicillin or beta-lactam allergy.

Models of time-to-antibiotics and in-hospital mortality included interaction terms for each combination of sex and race/ethnicity categories to assess for intersectional effects. To test whether time-to-antibiotics mediates the association between demographics and mortality, we repeated the mortality analysis adding time-to-antibiotics and its interactions with race/

ethnicity/sex as covariates. We also performed subgroup analyses by hospital type, insurance status, and admission during the COVID-19 pandemic (2020–2022) vs. prior years (2015–2019). SES were used to calculate Wald 95% CIs for each odds ratio. Wilcoxon rank-sum and Kruskal-Wallis tests were used for unadjusted comparisons of time-to-antibiotics. Analyses were performed in R (Version 4.2.1; The R Foundation, Vienna, Austria).

## RESULTS

### Characteristics of Study Cohort

The cohort included 23,619 patients with suspected sepsis and 25,990 patients with suspected septic shock, of whom 23,259 (98%) and 25,524 (98%), respectively, had data recorded for sex and race/ethnicity (Table 1). Of these, 46% were female, 75% were White, 9.2% were Black, and 7.0% were Hispanic. Antibiotics were administered within 6 hours in 18,325 patients (78%) with suspected sepsis and 21,606 patients (83%) with suspected septic shock (Supplement Table 1, <http://links.lww.com/CCM/H590>).

### Differences in Time-to-Antibiotics

Median time-to-antibiotics for patients with suspected sepsis was 190 minutes (interquartile range [IQR], 114–328 min) for men vs. 203 minutes (IQR, 122–347 min) for women (Table 1). Among race/ethnicity categories, median time-to-antibiotics was 215 minutes (IQR, 123–373 min) for Black patients, 197 minutes (IQR, 117–338 min) for Hispanic patients, 194 minutes (IQR, 117–330 min) for White patients, and 180 minutes (IQR, 111–326 min) for Asian patients. Time-to-antibiotics was shorter among all patients with suspected septic shock, but differences between groups remained: 142 minutes (IQR, 79–157 min) for men vs. 160 minutes (IQR, 92–290 min) for women and 159 minutes (IQR, 88–289 min) for Black patients vs. 156 minutes (IQR, 87–293 min) for Hispanic patients vs. 148 minutes (IQR, 84–267 min) for White patients vs. 143 minutes (IQR, 76–255 min) for Asian patients. All differences were significant at  $p$  value of less than 0.05 (Table 1).

After adjusting for confounders, women were significantly more likely than men to receive antibiotics 3–6 hours after arrival instead of 0–3 hours for both suspected sepsis (adjusted odds ratio [aOR], 1.16; 95%

CI, 1.07–1.25) and septic shock (aOR, 1.09; 95% CI, 1.01–1.18) (Fig. 1A). Among race/ethnicity categories, when compared with White patients, Black patients were significantly more likely to receive antibiotics 3–6 hours after arrival instead of 0–3 hours for both suspected sepsis (aOR, 1.24; 95% CI, 1.06–1.45) and suspected septic shock (aOR, 1.32; 95% CI, 1.12–1.55). Hispanic patients were significantly more likely to receive antibiotics 3–6 hours after arrival for suspected sepsis (aOR, 1.21; 95% CI, 1.01–1.46) but not for suspected septic shock (aOR, 1.07; 95% CI, 0.88–1.29). Subgroup analyses by hospital type, insurance status, and the COVID-19 pandemic showed consistent directionality for these associations (Supplement Figs. 2A–4A, <http://links.lww.com/CCM/H590>). Significant differences in time-to-antibiotics were not observed among other categories of race/ethnicity nor any intersectional categories (Supplement Table 2, <http://links.lww.com/CCM/H590>).

### Differences in In-Hospital Mortality

There were no significant associations between sex or race/ethnicity and mortality among patients with suspected sepsis (Fig. 1B). However, among patients with suspected septic shock, women had significantly higher mortality than men (aOR, 1.16; 95% CI, 1.04–1.29). This difference persisted after adjusting for time-to-antibiotics (aOR, 1.16; 95% CI, 1.03–1.32). Subgroup analyses again showed consistent directionality for this association (Supplement Figs. 2B–4B, <http://links.lww.com/CCM/H590>). There were no significant associations between race/ethnicity categories and in-hospital mortality in patients with suspected septic shock (Supplement Tables 3 and 4, <http://links.lww.com/CCM/H590>).

## DISCUSSION

In this large multihospital cohort of patients presenting to EDs with suspected sepsis or septic shock, women were more likely to receive antibiotics later than men and Black patients later than White patients. These differences persisted after adjusting for detailed clinical data including demographics, socioeconomic indicators, comorbidities, site of infection, and severity of illness. We additionally found that Hispanic patients presenting with suspected sepsis without shock received antibiotics later than White patients,

**TABLE 1.**  
**Cohort Sizes and Median Time-to-Antibiotics by Race/Ethnicity and Sex**

Cohort	Count (%)	Median Time-to-Antibiotics, Min (25th–75th Percentiles, Min)	<i>p</i>
Suspected sepsis	23,619 (100)	196 (118–336)	
Excluding missing data <sup>a</sup>	23,259 (98)	196 (118–336)	
By sex <sup>b</sup>			<0.001
Male	13,344 (56)	190 (114–328)	
Female	10,275 (44)	203 (122–347)	
By race/ethnicity <sup>c</sup>			0.036
White	17,320 (73)	194 (117–330)	
Black	2,257 (9.6)	215 (123–373)	
Hispanic	1,616 (6.8)	197 (117–338)	
Asian	857 (3.6)	180 (111–326)	
Other	300 (1.3)	194 (120–384)	
Two or more	909 (3.8)	209 (125–356)	
Missing data	360 (1.5)	191 (114–341)	
Suspected septic shock	25,990 (100)	150 (84–273)	
Excluding missing data <sup>a</sup>	25,524 (98)	150 (84–272)	
By sex <sup>b</sup>			<0.001
Male	13,667 (53)	142 (79–257)	
Female	12,323 (47)	160 (92–290)	
By race/ethnicity <sup>c</sup>			0.020
White	19,306 (74)	148 (84–267)	
Black	2,226 (8.6)	159 (88–289)	
Hispanic	1,787 (6.9)	156 (87–293)	
Asian	976 (3.8)	143 (76–255)	
Other	314 (1.2)	143 (78–279)	
Two or more	915 (3.5)	161 (91–309)	
Missing data	466 (1.8)	162 (82–317)	

<sup>a</sup>Excluding patients with missing race/ethnicity. These patients were not included in the multivariable regression models.

<sup>b</sup>Sex was available for all patients in both cohorts. *p* values calculated using Wilcoxon rank-sum tests.

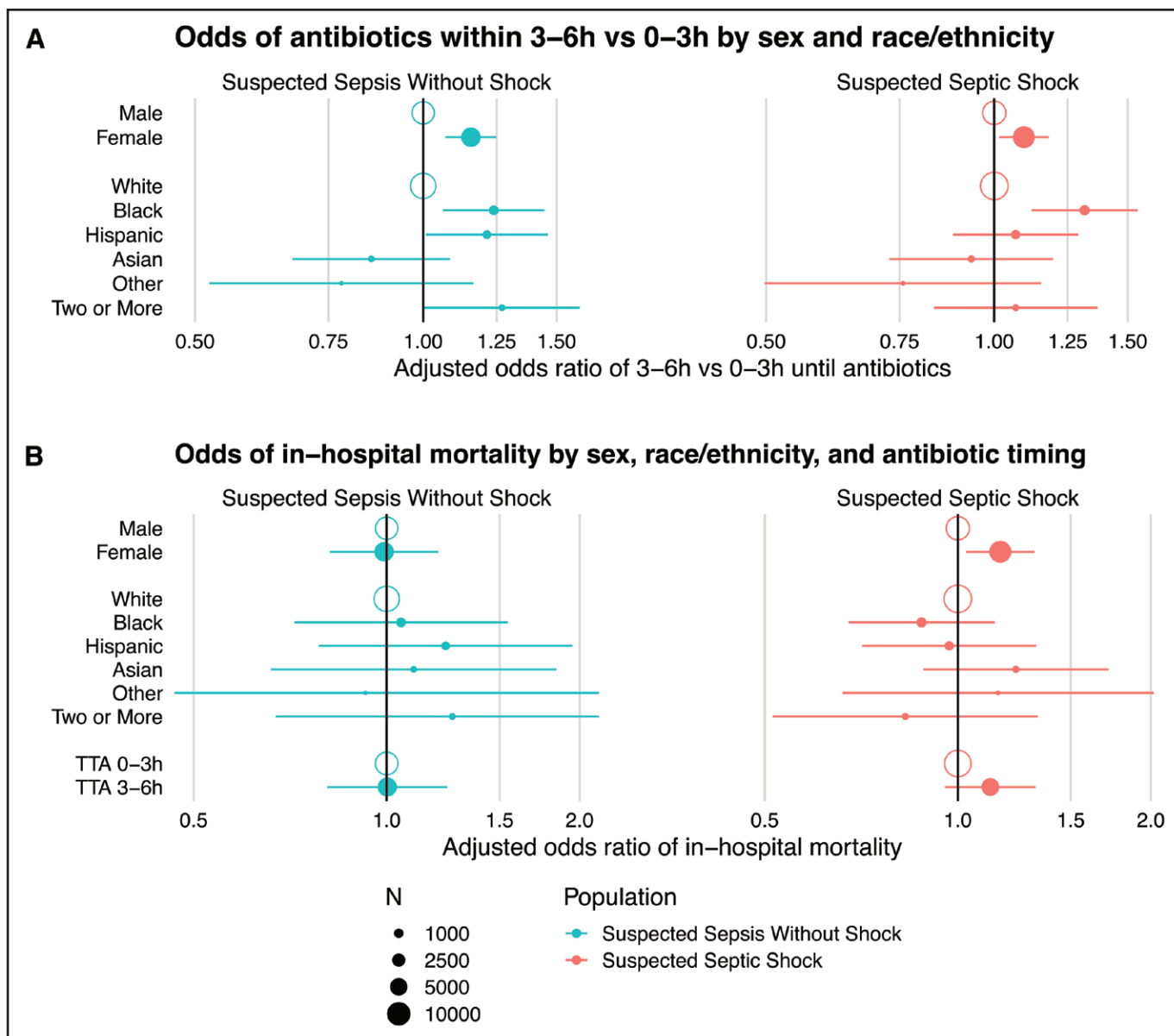
<sup>c</sup>Counts differ slightly from Table 1 in Pak et al (9) because additional ethnicity data fields were used to increase the accuracy of Hispanic categorization and reduce the number of patients with missing data. *p* values calculated using Kruskal-Wallis tests.

and women with suspected septic shock were more likely to die than men.

Our findings raise concern for inequities in care and outcomes for patients with severe infections, particularly those with septic shock. A previous single-center study in Rhode Island ( $n = 771$ ) found that time-to-antibiotics was 1.18 times longer in women of all races/ethnicities presenting with sepsis or septic shock (7). Another study of 16 million U.S. sepsis hospitalizations found that Black and Hispanic patients with sepsis

or septic shock were more likely to die than White patients (6). Our study did not support a moderating effect of time-to-antibiotics on differences in septic shock mortality between men and women. Their disparate outcomes might be influenced more strongly by other patient, provider, and institutional factors both at the time of admission and over the subsequent hospital course.

Our study is larger and includes more granular measures of severity of illness than prior studies of disparities



**Figure 1.** Disparities in time-to-antibiotics (TTA) and in-hospital mortality by sex and race/ethnicity for suspected sepsis with and without shock. Multivariable regression was used to model associations between race/ethnicity/sex and odds of receiving antibiotics within 3–6 vs. 0–3 hr (**A**) or in-hospital mortality (**B**), adjusting for potential confounders (see *Methods*). In-hospital mortality was additionally adjusted for TTA using the same categorization. Models included interaction terms between either race/ethnicity and sex (**A**) or all combinations of race/ethnicity, sex, and TTA (**B**), but none were significant at  $p < 0.05$ , and they are not depicted in this figure. Adjusted odds ratios are drawn with 95% CIs (*horizontal lines*). The *x*-axis is logarithmically scaled. *Point sizes* are scaled to the number of patients in each subcohort (*n*, legend).

in sepsis treatment. Nonetheless, residual confounding is possible, particularly since many potentially influential factors are not recorded as structured EHR data (e.g., education, income, health literacy, and cultural factors). We similarly could not include provider-specific factors, for example, provider demographics or assessment of provider-specific biases. Other limitations of our study include a focus on one regional healthcare system with

relatively few non-White patients, decreasing power to detect differences in all subgroups, particularly intersectional associations. We were limited to analyzing sex instead of gender identity due to small numbers of trans and gender diverse identities. Patient registration data can be incomplete and subject to unmeasured biases. Finally, we used proxies for socioeconomic status (e.g., linking patients' home ZIP codes to census data) in lieu of direct measures.

All told, we document disparities by race, ethnicity, and sex in antibiotic timeliness for patients with possible sepsis. We also document differences in outcomes for women vs. men with septic shock not clearly related to time-to-antibiotics. Further work, including study of provider-specific factors, is needed to characterize the specific processes contributing to these delays and the full spectrum of care factors that affect sepsis outcomes in different populations.

## ACKNOWLEDGMENTS

We thank Drs. Kathryn Himmelstein, Margaret Samuels-Kalow, Rama Salhi, and Claire Shappell and the Sepsis Time Zero team for helpful guidance.

- 1 Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Healthcare Institute, Boston, MA.
- 2 Division of Infectious Diseases, Department of Medicine, Massachusetts General Hospital, Boston, MA.
- 3 Division of Internal Medicine, Ponce Health Sciences University, Ponce, Puerto Rico.
- 4 Division of Infectious Diseases, Department of Medicine, Brigham and Women's Hospital, Boston, MA.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (<http://journals.lww.com/ccmjjournal>).

Dr. Pak had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Drs. Pak, Sánchez, Rhee, and Klompas conceptualized the study. Dr. Pak and Ms. McKenna performed data curation and wrote software. Dr. Pak performed the statistical analysis and visualization. Dr. Pak wrote the original draft of the article. All authors participated in review and editing of the article. Drs. Sánchez, Rhee, and Klompas were involved in supervision. All authors gave approval for the version to be published.

Dr. Pak's institution received funding from the National Institute of Allergy and Infectious Diseases (T32AI007061); he received funding from IDWeek. Dr. Rhee reports royalties from UpToDate for chapters related to procalcitonin use. Dr. Klompas reports royalties from UpToDate for chapters related to hospital-acquired pneumonia. Drs. Rhee and Klompas report grant funding from the Centers for Disease Control and Prevention (CDC) to conduct research related to sepsis and grant funding from the Agency for

Healthcare Research and Quality (AHRQ) (R01HS027170) to conduct research related to sepsis. Dr. Pak's and Ms. McKenna's institution received funding from the AHRQ. Drs. Pak and Rhee received support for article research from the National Institutes of Health. Ms. McKenna and Dr. Klompas received support for article research from the CDC and the AHRQ. Dr. Sánchez has disclosed that she does not have any potential conflicts of interest.

For information regarding this article, E-mail: [tpak@mgh.harvard.edu](mailto:tpak@mgh.harvard.edu)

## REFERENCES

1. Rhee C, Dantes R, Epstein L, et al; CDC Prevention Epicenter Program: Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014. *JAMA* 2017; 318:1241-1249
2. Williams DR, Mohammed SA: Discrimination and racial disparities in health: Evidence and needed research. *J Behav Med* 2009; 32:20-47
3. Boyd RW, Lindo EG, Weeks LD, et al: On Racism: A New Standard for Publishing on Racial Health Inequities. *Health Affairs Forefront*. 2020. Available at: <https://www.healthaffairs.org/content/forefront/racism-new-standard-publishing-racial-health-inequities>. Accessed June 27, 2023
4. Joseph JW, Kennedy M, Landry AM, et al: Race and ethnicity and primary language in emergency department triage. *JAMA Netw Open* 2023; 6:e2337557
5. Peitzman C, Carreras Tartak JA, Samuels-Kalow M, et al: Racial differences in triage for emergency department patients with subjective chief complaints. *West J Emerg Med* 2023; 24:888-893
6. Jones JM, Fingar KR, Miller MA, et al: Racial disparities in sepsis-related in-hospital mortality: Using a broad case capture method and multivariate controls for clinical and hospital variables, 2004-2013. *Crit Care Med* 2017; 45:e1209-e1217
7. Madsen TE, Napoli AM: Analysis of race and time to antibiotics among patients with severe sepsis or septic shock. *J Racial Ethn Health Disparities* 2017; 4:680-686
8. Mayr FB, Yende S, D'Angelo G, et al: Do hospitals provide lower quality of care to black patients for pneumonia? *Crit Care Med* 2010; 38:759-765
9. Pak TR, Young J, McKenna CS, et al: Risk of misleading conclusions in observational studies of time-to-antibiotics and mortality in suspected sepsis. *Clin Infect Dis* 2023; 77:1534-1543
10. Limaye NP, Matias WR, Rozansky H, et al: Limited English proficiency and sepsis mortality by race and ethnicity. *JAMA Netw Open* 2024; 7:e2350373