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<tr><td>Critical Review Form
Prognosis</td><td>PGY-1</td></tr>
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Objectives: "to analyze the association between timing of antibiotic administration and mortality to evaluate whether an optical time window for empiric antibiotic administration could be found in the these patients with severe sepsis and septic shock." (p. 1750)

Methods: This international, multicenter retrospective analysis was conducted on data obtained prospectively from 165 ICUs in South America, Europe, and the United States. Patients admitted to an ICU between January 2005 and February 2010 with a suspected site of infection, two or more systemic inflammatory response (SIRS) criteria (https://www.mdcalc.com/sirs-sepsis-septic-shock-criteria), and one or more organ dysfunction criteria were eligible for inclusion. Patients who did not receive antibiotics, those who did not receive antibiotics in the first 6 hours, those missing time to antibiotic administration, and those receiving antibiotics prior to diagnosis of severe sepsis were excluded from the analysis.

Data was abstracted from the medical record, including time to antibiotic administration, and entered into the surviving sepsis campaign (SSC) database locally at each hospital. The duration of time until antibiotics were administered began at the time of triage for all patients admitted from the ED, and began at the diagnosis of severe sepsis (determined by chart review) for patients either already in the ICU or admitted to the ICU from medical or surgical wards. Logistic regression was used to control for confounders in order to determine the effect of timing on mortality.

Out of 28150 patients with severe sepsis or septic shock, 17990 received antibiotics and were eligible for inclusion. Overall mortality was 29.7%.

	Guide	Comments
I.	**Are the results valid?**	
A.	**Was the sample of patients representative?**	Yes. All patients meeting criteria for severe sepsis (an infectious source with 2 SIRS criteria and one

	In other words, how were subjects selected and did they pass through some sort of "filtering" system which could bias your results based on a non-representative sample. Also, were objective criteria used to diagnose the patients with the disorder?	or more organ dysfunction criteria) were eligible for enrollment. These criteria are fairly objective. The only filter was that only patients who ended up in the ICU were eligible for inclusion. While it is likely that most (if not all) patients meeting criteria would be admitted to the ICU, it is possible that some were admitted to the floor or expired before making it to the ICU.
B.	**Were the patients sufficiently homogeneous with respect to prognostic risk?** *In other words, did all patients share a similar risk from during the study period or was one group expected to begin with a higher morbidity or mortality risk?*	Yes. While there is certainly a spectrum of prognostic risk among patients with sepsis, this study specifically looked at patients meeting criteria for severe sepsis or septic shock. The authors could have further divided out those with and without shock, but it seems reasonable to evaluate the effect of timing of antimicrobial administration on both groups simultaneously.
C.	**Was follow-up sufficiently complete?** *In other words, were the investigators able to follow-up on subjects as planned or were a significant number lost to follow-up?*	Yes. Since the outcome being measured was in-hospital mortality, data was available for all patients in the cohort.
D.	**Were objective and unbiased outcome criteria used?** Investigators should clearly specify and define their target outcomes before the study and whenever possible they should base their criteria on objective measures.	Yes. The outcome was mortality, and it doesn't get much more objective than death. This was, presumably, an *a priori* outcome measure, though this is not specifically mentioned.
II.	**What are the results?**	
A.	**How likely are the outcomes over time?** *For the defined follow-up period, how likely were subjects to have the outcome of interest.*	• Unadjusted mortality among patients receiving antibiotics within one hour was 32.0%. This decreased to 28.1% for the 1-2 hour group, then steadily increased for each incremental timeframe thereafter. • Adjusted mortality was lowest in the 0-1 hour group, with incremental increases seen for each group thereafter (see Table 1 for adjusted odds ratios, using the 0-1 hour group as a baseline. Table 1. Adjusted in-hospital mortality <table><tr><td>Time to ABX (hrs)</td><td>OR</td><td>95% CI</td></tr><tr><td>0-1</td><td>1.00</td><td></td></tr><tr><td>1-2</td><td>1.07</td><td>0.97-1.18</td></tr><tr><td>2-3</td><td>1.14</td><td>1.02-1.26</td></tr></table>

		3-4	1.19	1.04-1.35
		4-5	1.24	1.06-1.45
		5-6	1.47	1.22-1.76
		> 6	1.52	1.36-1.70
B.	**How precise are the estimates of likelihood?** *In other words, what are the confidence intervals for the given outcome likelihoods?*	See above.		
III.	**How can I apply the results to patient care?**			
A.	**Were the study patients and their management similar to those in my practice?**	Uncertain. This was an international, multi-center trial consisting of patients in the US, South America, and Europe. The authors provide very little demographic information (age, gender, medical comorbidities) and provide no information regarding the proportion of patients from each location. It seems likely that management of patients with severe sepsis and septic shock would be similar to those in our practice, and, most importantly, the effect of timing of antibiotic administration on mortality would likely apply to our patients.		
B.	**Was the follow-up sufficiently long?**	Yes. The outcome of interest was mortality directly attributable to the patients' severe sepsis or septic shock. Therefore, using in-hospital mortality as the primary outcome measure seems reasonable. More long-term (30-day/90-day) mortality would have been less accurate and more costly to measure, and likely would not have been possible in this retrospective study.		
C.	**Can I use the results in the management of patients in my practice?**	Yes. Despite this being a retrospective study with several possible sources of bias, the ultimate premise that early administration of antibiotics to patients with severe sepsis or septic shock reduces mortality seems not only plausible, but likely. This study supports that premise, and given the lack of potential harm from early antibiotic administration, it is reasonable to strive to give antibiotics for such patients as early as possible.		

Limitations:

1. **Duration of time calculation unfair to ED patients.**

2. **Despite reporting that patients "who did not receive any antibiotics in the first 6 hours" were excluded, 2239 such patients were included in the analysis.**

3. **No baseline demographic data was provided for the cohort (median age, gender, medical comorbidities)**

<u>**Bottom Line:**</u>

In this retrospective study evaluating the association between timing of antibiotic administration and mortality in patients with severe sepsis or septic shock, an incremental increase in adjusted mortality was seen for every hour delay in antibiotic administration. This was, unfortunately, a retrospective analysis of previously collected data rife with potential sources of bias (despite the use of logistic regression to account for known confounders). Despite this limitation, it makes clinical sense to administer antibiotics in as timely a fashion as possible in septic patients, and there is likely to be some association with mortality as demonstrated in this study.