

References and Literature Grading

Does Early and Appropriate Antibiotic Administration Improve Mortality in Emergency Department Patients with Severe Sepsis or Septic Shock? (9/6/2015)

1. Dellinger, R.P., et al., *Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012*. Crit Care Med, 2013. **41**(2): p. 580-637.
2. Siddiqui, S. and J. Razzak, *Early versus late pre-intensive care unit admission broad spectrum antibiotics for severe sepsis in adults*. Cochrane Database Syst Rev, 2010(10): p. CD007081.
3. Parish, B., T. Cooksley, and P. Haji-Michael, *Effectiveness of early antibiotic administration in septic patients with cancer*. Acute Med, 2013. **12**(4): p. 196-200.
4. Jalili, M., 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): p. 454-60.
5. Lee, C.C., et al., *Impact of inappropriate empirical antibiotic therapy on outcome of bacteremic adults visiting the ED*. Am J Emerg Med, 2012. **30**(8): p. 1447-56.
6. Martin-Loeches, I., et al., *Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia*. Intensive Care Med, 2010. **36**(4): p. 612-20.
7. Nygard, S.T., et al., *Aetiology, antimicrobial therapy and outcome of patients with community acquired severe sepsis: a prospective study in a Norwegian university hospital*. BMC Infect Dis, 2014. **14**: p. 121.
8. Puskarich, M.A., 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): p. 2066-71.
9. Siddiqui, S., et al., *How early do antibiotics have to be to impact mortality in severe sepsis? A prospective, observational study from an emergency department*. J Ayub Med Coll Abbottabad, 2009. **21**(4): p. 106-10.
10. Vilella, A.L. and C.F. Seifert, *Timing and appropriateness of initial antibiotic therapy in newly presenting septic patients*. Am J Emerg Med, 2014. **32**(1): p. 7-13.
11. Gaieski, D.F., 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): p. 1045-53.
12. Vazquez-Guillamet, C., et al., *Using the number needed to treat to assess appropriate antimicrobial therapy as a determinant of outcome in severe sepsis and septic shock*. Crit Care Med, 2014. **42**(11): p. 2342-9.
13. Filbin, M.R., et al., *Sepsis visits and antibiotic utilization in U.S. emergency departments**. Crit Care Med, 2014. **42**(3): p. 528-35.
14. Kumar, A., et al., *Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*. Crit Care Med, 2006. **34**(6): p. 1589-96.
15. Labelle, A., et al., *The determinants of hospital mortality among patients with septic shock receiving appropriate initial antibiotic treatment**. Crit Care Med, 2012. **40**(7): p. 2016-21.
16. Kumar, A., et al., *Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis*. Crit Care Med, 2010. **38**(9): p. 1773-85.

Reference	Grade	Rank	Comment	Support for:
Parish B et al. Effectiveness of early antibiotic administration in septic patients with cancer. <i>Acute Medicine</i> . 12(4); 196-200, 2013	D	Poor	<ul style="list-style-type: none"> - Retrospective study Oncology hospital - Early antibiotics decreased LOS 	<u>Timing:</u> Supportive <u>Appropriateness:</u> Not addressed
Vilella AL et a. Timing and appropriateness of initial antibiotic therapy in newly presenting septic patients. <i>Am J of Emerg Med</i> . 32(1); 7-13, 2014 Jan.	D	Poor	<ul style="list-style-type: none"> - Retrospective case-control - Demonstrated decrease in median time to antibiotic therapy with CPOE - No difference in outcome with respect to antibiotic appropriateness or timing 	<u>Timing:</u> No association <u>Appropriateness:</u> No association
Jalili M et a. Effect of door-to antibiotic time on mortality of patients with sepsis in emergency department: a prospective cohort study. <i>Acta Medica Iranica</i> . 51(7); 454-60, 2013	C	Poor	<ul style="list-style-type: none"> - Prospective observational - Primary objective to assess association between timing and outcome. - Antibiotic timing and mortality were related in patients with APACHE scores of ≥ 21. - No overall association between timing and mortality 	<u>Timing:</u> Supportive : for patients w/ APACHE ≥ 21 ; No association for patients with APACHE < 21 <u>Appropriateness:</u> Not addressed
Lee CC et al . Impact of of inappropriate antibiotic therapy on outcome of bacteremic adults visiting the ED. <i>Am J of Emerg Med</i> . 30(8); 1447-56, 2012 Oct.	D	Good	<ul style="list-style-type: none"> - Retrospective study - Assessed patients with bacteremia only. - Appropriate antibiotics lowered mortality - Association stronger in critically ill patients 	<u>Timing:</u> Not addressed <u>Appropriateness:</u> Supportive
Martin-Loeches I et al. Combination	C	Good	- Prospective multi-	<u>Timing:</u>

therapy with macrolides improves survival in intubated patients with community acquired pneumonia. Intensive Care Med. 36 (4); 612-20, 2010 Apr.			center study - Intubated severe sepsis or septic shock patients w/ CAP - 27 European ICUs - Macrolide use associated with lower mortality versus fluoroquinolones	Not addressed <u>Appropriateness:</u> Supportive
Nygard ST et al. Aetiology, antimicrobial therapy and outcome of patients with community acquired severe sepsis: a prospective study in a Norwegian university hospital. BMC Infect Dis. 14: 121, 21014.	C	Adequate	- Prospective single center study in Norway - Community acquired severe sepsis - Antibiotic delay > 6 hour & inadequate antibiotic coverage both independent predictors of mortality.	<u>Timing:</u> Supportive <u>Appropriateness:</u> Supportive
Siddiqui S et al. How do early antibiotics have to be to impact mortality in severe sepsis? A prospective, observational study from an emergency department. J of Ayub Med Coll. 21 (4): 106-110, 2009 Oct-Dec.	C	Poor	- Prospective, 4 month single-center in Pakistan - <i>Salmonella typhi</i> was most frequent organism isolated - Antibiotic timing significantly associated with mortality. Mortality increased with every hour delay	<u>Timing:</u> Supportive <u>Appropriateness:</u> Not addressed
Siddiqui S. Early versus later pre-intensive care unit admission broad spectrum antibiotics for severe sepsis in adults. Cochrane Database of Syst Rev. (10) CD 007082, 2010.	A	Good	- Systemic literature review of early vs. late pre-ICU antibiotics. - Found no randomized controlled trials that met initial inclusion search criteria	<u>Timing:</u> N/A <u>Appropriateness:</u> N/A

<p>Puskarich 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; 2066-2071.</p>	<p>A</p>	<p>Outstanding</p>	<ul style="list-style-type: none"> - Multi-center randomized controlled trial - Adult septic shock patients receiving protocolized care - No mortality change with hourly antibiotic delays - Mortality increased if antibiotics given after shock recognition vs before (OR, 2.4; 95% CI, 1.1-4.5) 	<p><u>Timing:</u> Supportive: if given before shock develops</p> <p><u>Appropriateness:</u> Not addressed</p>
<p>Vazquez-Guillamet C et al. Using the Number needed to treat to Assess appropriate antimicrobial therapy as a determinant of outcome in severe sepsis and septic shock. Crit Care Med 42; 2342-2349, 2014.</p>	<p>D</p>	<p>Good</p>	<ul style="list-style-type: none"> - Retrospective 4 year, single center study in U.S. - 2,594 severe sepsis or septic shock patients - Inappropriate antimicrobial therapy (defined as a regimen that lacked in vitro activity against isolated pathogen) associated with increased in-hospital mortality (OR , 3.4; 95% CI, 2.8-4.1) - NNT with appropriate antimicrobial therapy to prevent one death was 4.0 (95% CI, 3.7-4.3) 	<p><u>Timing:</u> Not addressed</p> <p><u>Appropriateness:</u> Supportive</p>
<p>Gaieski D 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</p>	<p>C</p>	<p>Good</p>	<ul style="list-style-type: none"> - Retrospective single center cohort study in U.S. study of severe sepsis & septic shock patients receiving 	<p><u>Timing:</u> Supportive</p> <p><u>Appropriateness:</u> Not addressed</p>

<p>department. Crit Care Med 38; 1045-1053, 2010.</p>			<p>early goal directed therapy. - No mortality increase with hourly antibiotic delay - Mortality significantly associated with antibiotic timing; 19.5% v 33.2% mortality if administered < 1hr vs. ≥ 1hr, respectively</p>	
<p>Kumar A et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med; 34; 1589-1596, 2006.</p>	<p>C</p>	<p>Outstanding</p>	<p>- Retrospective cohort study of fourteen ICUs; 2,731 patients with septic shock - 15 year sample - Each hour delay of antibiotics associated with a decreased in survival of 7.6% - In multivariate analysis, time to initiation of effective antibiotic therapy was strongest predictor of patient outcome</p>	<p><u>Timing:</u> Supportive</p> <p><u>Appropriateness:</u> Not addressed</p>
<p>Labelle A et al. The determinants of hospital mortality among patients with septic shock receiving appropriate initial antibiotic treatment. Crit Care Med; 40: 2016-2016, 2012.</p>	<p>C</p>	<p>Good</p>	<p>- - Retrospective single center cohort study in U.S. study of 436 septic shock patients with a positive blood culture - All patients received appropriate antibiotics; no significant difference in time to antibiotics</p>	<p><u>Timing:</u> N/A; not specifically addressed</p> <p><u>Appropriateness:</u> Not addressed</p>

			<p>between survivors and non-survivors.</p> <ul style="list-style-type: none"> - Independent predictors of mortality were APACHE II & ICU acquired infection 	
<p>Kumar A et al. Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: A propensity-matched analysis. Crit Care Med 38: 1773-1783, 2010.</p>	C	Good	<ul style="list-style-type: none"> - Retrospective, propensity matched multi-center cohort study in 28 ICUs over 11 years - 4,662 cases of septic shock with positive blood cultures. - Combination antibiotic therapy associated with decreased 28-day mortality (HR 0.77; 95% CI, 0.67-0.88) - Combination therapy: treatment with B-lactams in combination with aminoglycoside, fluoroquinolone or macrolide/clindamycin 	<p><u>Timing:</u> Not addressed</p> <p><u>Appropriateness:</u> Supportive</p>