Literature Review on Antibiotic Delivery Time

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Objective: Is time from order to administration of antibiotics a valid target for process improvement?

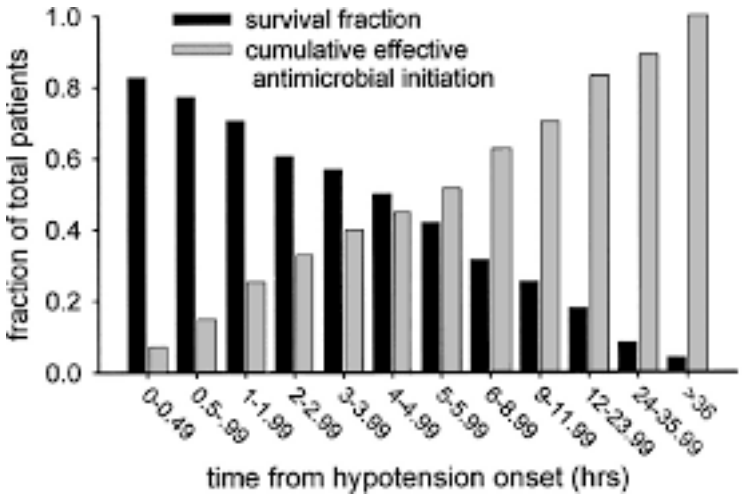
Conclusion:

1. *Antibiotic delivery time* (defined as time interval from when an antibiotic is first ordered and then delivered) is endorsed by the Society of Infectious Disease Pharmacists (**SIDP—Heil EL, et al. Pharmacotherapy 2020**)
2. A majority of current evidence supports early rather than delayed administration of antibiotics for patients with sepsis; data more strongly support time-to-antibiotic duration and mortality in septic shock
3. As a process measure, antibiotic delivery time is a reasonable metric; it is a metric that will allow opportunities for tangible process improvement
4. The IDSA supports the practice of appropriate antibiotic use; requiring clinicians to administer antibiotics immediately and empirically is probably the wrong metric. Allowing clinicians to take additional time to obtain laboratory and imaging results can be informative and improve prescribing practices. Hence, once an infection is diagnosed with some degree of higher probability, and a clinician decides that an antibiotic is required, time to administration may be a more reasonable metric. Reporting the time interval between the antibiotic order and delivery is a better metric (**Rhee C, et al. CID 2020**).
5. ACEP, NAEMSP, SCCM, and SHM recommend “prompt” administration of antibiotics, but reserve time thresholds for patients in septic shock (**Yealy DM, et al. Ann Emerg Med 2021**).

There are many confounding factors when examining time-to-antibiotic studies (Weinberger & Klompas, J Infect Dis 2020). Yet, prompt administration is unquestionably important. There is a strong relationship between each hour until antibiotics and mortality for septic shock but a less pronounced relationship for sepsis without shock.

Kumar A, et al. Crit Care Med 2006.

- Much of the literature and beliefs about the impact on mortality of delays in initiation of antimicrobial therapy is driven by this retrospective study of 2,154 septic shock patients in 14 ICUs
- Here is the classic figure from this study:



- A post on EMCRIT (https://emcrit.org/pulmcrit/the-fallacy-of-time-to-intervention-studies/) discusses the "fallacy of time to intervention studies," thereby casting doubt upon the concept that earlier antibiotics improve mortality in sepsis
- This study suggested a linear 8% (7.6% to be exact) increase in mortality for each hour antibiotics were delayed

Ferrer R, et al. Crit Care Med 2014.

- Retrospective study of 165 ICUs in Europe; N=17,990 patients
- This study suggested an 1% per hour reduction in mortality (much more conservative compared to the Kumar study); the increase was also found to be near-linear
- Results were similar in both sepsis and septic shock
- Mortality in the Kumar and Ferrer studies was quite high (30-47%)

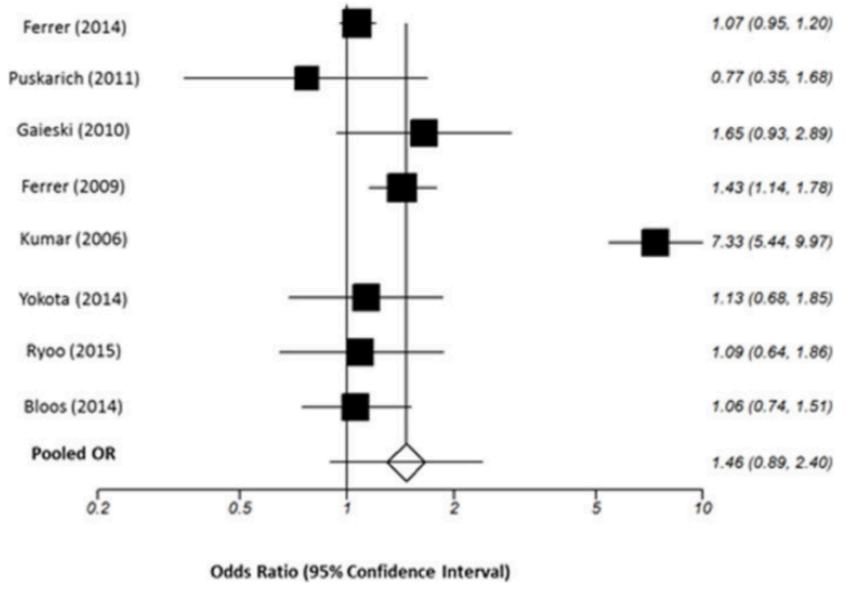
DeGroot B, et al. Critical Care 2015.

- Prospective, observational multicenter Dutch ED study
- Registration time at ED desk to antibiotic administration by nurse
- Appropriateness was assessed as secondary outcome

- No association found between shorter interval of antibiotic administration and survival
- Confounding effect of severity of illness—this study used the PIRO score to assess severity of illness; this score might not have discriminated very well, especially for lower severity patients
- The N was lower (<400) in the sickest patients; population was skewed towards a potentially healthier population
- Mortality was much, much lower in this study (10%), perhaps reflecting improvements in sepsis care over time (since Kumar study)

Sterling SA, et al. Crit Care Med 2015.

- Systematic review of 11 publications, 16,178 patients
- Search strategy suspect (search terms were very broad), analysis was missing some crucial statistics (i.e., I^2)
- No mortality benefit when antibiotics given <3 hrs of ED triage or within 1 hour of shock recognition
- Extremely wide confidence intervals (Table 5)
- Largest study by far in this review was Ferrer (17,990) which showed adjusted increased mortality for every hour delay in antibiotics (see above)
- Review limited by combining many different studies of varying quality and size
- Figure 2, < 1 hour from severe sepsis or septic shock, one study pulled odds ratio over, the rest were all with effect estimates > 1.0
- See the Seymour paper below



Lesiman D, et al. Crit Care Med 2017.

- Single tertiary care center, N=828 (Hofstra/Northwell)
- Adults with initial sepsis presentation in ED, Sep-1 definition used

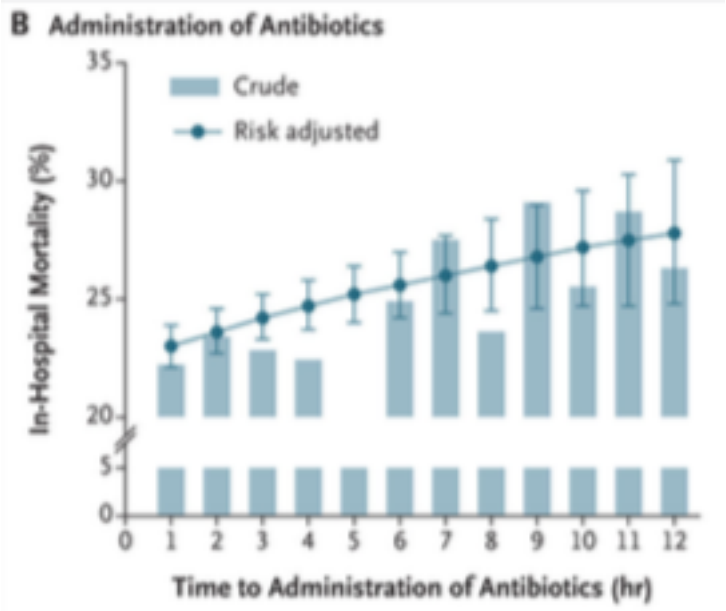
- Major second antibiotic dose delays were common; increased association with mortality and increased length of stay (and mechanical ventilation)
- OR 1.61 (1.01-2.57) increased risk of mortality associated with a first to second dose “major delay” (time > 25% of the recommended interval)

Liu VX. Am J Resp Crit Care Med 2017.

- Retrospective study of 35,000 patients with sepsis treated at 21 EDs in Northern California
- Overall mortality in this cohort: 9.4% (not as high as previous studies)
- Increased association with mortality observed for every elapsed hour of antibiotic delay; most pronounced in septic shock (OR 1.14; 95% CI, 1.06-1.23)

Seymour CW, et al. N Engl J Med 2017.

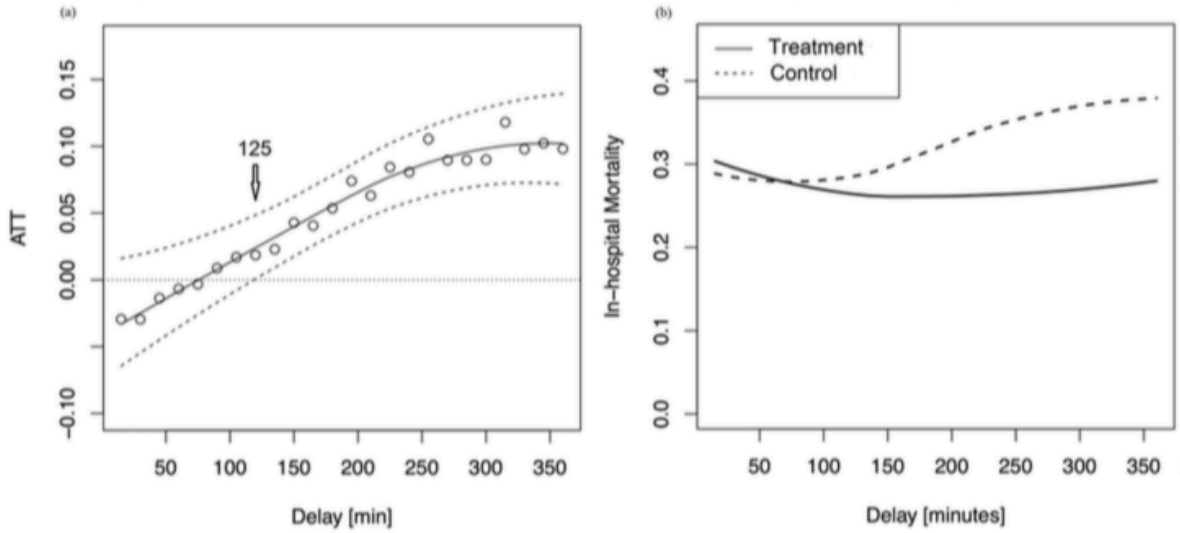
- 49,331 patients at 149 hospitals in a New York state database
- Primary outcome: mortality; primary exposure: time to completion of a 3-hour bundle (blood cultures, antibiotics given, lactate measured)
- Each hour of time to completion of the bundle was associated with higher mortality (1.04 odds increased per hour; 95% CI 1.02 to 1.05)
- Patients who received antibiotics in hours 3 to 12 had 14% higher mortality; this association was stronger for those in shock (requiring vasopressors)
- This study has a larger sample size and counters the Sterling systematic review as above



Pruinelli L, et al. Crit Care Med 2018.

- Retrospective study of a Midwest healthcare system, N=5,072 patients

- Purpose: to determine the effect of an average treatment effect in the treated (ATT); propensity score matching used
- Delays in performing guideline recommendations—including antibiotics—were associated with increased in-hospital mortality
- Modest delays may not be harmful; the longer the delay, he worse the harm (monotonic increase in mortality)
- Even very short delays can increase mortality
- Relatively high mortality in this study (27.8%)



Ko B, et al. Am J Med 2020.

- Prospective, observational study of multicenter septic shock registry (N=2250)
- No “every hour” delay observed, but mortality higher for patients with septic shock and an antibiotic delay

Rothrock SG, et al. Ann Emerg Med 2020.

- 13 studies, N=33,863
- 23% had a high risk of bias
- Immediate vs. early (1-3 hours) antibiotics and mortality
- No evidence that <1 hr is better than 1-3 hours
- Data supported immediate antibiotics for septic shock (not for sepsis)