Accelerated Antibiotic Administration for Sepsis: Benefits Outweigh Risks, Even in Worst-Case Scenarios

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Donnelly JP, Seelye SM, Kipnis P, *et al.*
Impact of Reducing Time-to-Antibiotics on Sepsis Mortality, Antibiotic Use, and Adverse Events.
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Reducing the time-to-antibiotics is crucial in improving sepsis outcomes, but there are limited data on the impact of "spillover prescribing"* or antibiotic-associated harms. This simulation study aims to estimate the benefits and harms of shortening time-to-antibiotics for sepsis in the setting of spillover prescribing in a large cohort of over 1.5 million hospitalizations.

Methods

- Adult hospitalizations at 152 US VA** and KPNC*** hospitals from 2013-2018 admitted to the emergency department with ≥2 systemic inflammatory response syndrome (SIRS) criteria.
- Hospitalizations were categorized as septic shock, sepsis, infection, early cessation of antibiotics, or no treatment (no antibiotics within 48 hours).
- Effect of 50% reduction in time-to-antibiotics for sepsis in 12 hospital scenarios was simulated based on sepsis prevalence and spillover antibiotic prescribing to patients without infection.
- Outcomes assessed were mortality and adverse events possibly caused by antibiotics, including allergies, organ dysfunction, *C. difficile* infection (CDI), multi-drug resistant organism (MDRO) cultures.

Results

- 933,458 (59.9%) hospitalizations received antibiotic therapy within 48 hours of presentation.
- Adverse events potentially attributable to antibiotic therapy occurred in ~1 in 8 hospitalizations.
- **Most common adverse events:** acute liver injury (5.6%), new MDRO culture-positivity (3.5%), and CDI (1.7%).
- **Reducing time-to-antibiotics by 50%** resulted in a median of 9, 14, and 20 sepsis deaths averted among low, medium, and high-prevalence hospitals, or absolute risk reductions for 30-day mortality in sepsis hospitalizations of 0.38%, 0.39%, and 0.41%.
- **Low spillover prescribing:** a 50% reduction in time-to-antibiotics for sepsis resulted in only 1 to 4 additional antibiotic-treated patients per sepsis death averted, with no added adverse events.
- **High spillover prescribing:** a 50% reduction in time-to-antibiotics for sepsis led to treatment of 55 to 180 additional patients with antibiotics, and 2 to 7 new adverse events occurred for every sepsis death that was prevented, based on the prevalence of sepsis in the hospital.

In conclusion, the number of newly antibiotic-treated patients varied widely depending on the prevalence of sepsis and the magnitude of spillover prescribing. However, new antibiotic-associated adverse events were rare. This underlines the importance of monitoring antimicrobial stewardship concurrent with attempting to reduce time-to-antibiotics.

*Spillover prescribing: treating additional patient unnecessarily with antibiotics due to efforts to shorten the time-to-antibiotics for sepsis.
** VA: Veterans Affairs ***KPNC: Kaiser Permanente Northern California.

> *Even under the worst-case scenario […], the benefits of shortening time-to-antibiotics for sepsis outweighed the harms."*