

*Delayed Appropriate Therapy (DAT)
in Serious Gram-Negative Infections:*

A Cause of Increased Morbidity,
Length of Stay (LOS), and
Hospital Costs

Evaluating DAT as an independent cause of poorer outcomes¹⁻³

- It is well documented that infections due to antibiotic-resistant Gram-negative pathogens are associated with poorer outcomes—including higher mortality rates, increased LOS, and higher in-hospital costs—vs infections caused by antibiotic-susceptible pathogens¹
- There is also an established link between DAT and worse outcomes among patients with Gram-negative infections; however, it is unclear whether the association is causal or confounded by antibiotic resistance¹⁻³
- What needs to be determined is whether DAT is an independent cause of poor outcomes or whether the driver of poor outcomes is severe disease associated with infections due to resistant Gram-negative pathogens¹

References: 1. Bonine NG, Berger A, Altincatal A, et al. Impact of delayed appropriate antibiotic therapy on patient outcomes by antibiotic resistance status from serious Gram-negative bacterial infections. *Am J Med Sci.* 2019;357(2):103-110. 2. Lodise T, Berger A, Altincatal A, et al. Antimicrobial resistance or delayed appropriate therapy—does one influence outcomes more than the other among patients with serious infections due to carbapenem-resistant versus carbapenem-susceptible Enterobacteriaceae? *Open Forum Infectious Diseases* (In press). 2019; <https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofz194/5477302>. 3. Lodise TP, Zhao Q, Fahrback K, Gillard PJ, Martin A. A systematic review of the association between delayed appropriate therapy and mortality among patients hospitalized with infections due to *Klebsiella pneumoniae* or *Escherichia coli*: how long is too long? *BMC Infect Dis.* 2018;18(1):625. 4. Zilberberg MD, Nathanson BH, Sulham K, Fan W, Shorr AF. Carbapenem resistance, inappropriate empiric treatment and outcomes among patients hospitalized with Enterobacteriaceae urinary tract infection, pneumonia and sepsis. *BMC Infect Dis.* 2017;17(1):279.



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In serious infections due to Enterobacteriaceae or *Pseudomonas aeruginosa*...

DAT resulted in worse clinical and economic outcomes¹

- Retrospective study of adult patients (N=56,357) with hospital admissions between July 1, 2011, and September 30, 2014,^a with evidence of a Gram-negative infection of interest and an LOS ≥ 1 day:
 - Hospital-acquired pneumonia (HAP)
 - Complicated urinary tract infections (cUTI)
 - Bloodstream infections
 - Complicated intra-abdominal infections (cIAI)
- Patients were stratified by antibiotic susceptibility of isolated pathogens (resistant or susceptible)
 - Those with evidence of ≥ 1 of the following resistant pathogens were deemed to have infection with a resistant organism: carbapenem-resistant Enterobacteriaceae (CRE), carbapenem-resistant *Pseudomonas* (CRP), multidrug-resistant *P. aeruginosa* (MDRP), and extended-spectrum β -lactamase-producing Enterobacteriaceae (ESBL)
- Receipt of appropriate therapy on the index date—the earliest date when a microbiologic culture positive for ≥ 1 Gram-negative bacteria was drawn—or within the subsequent 2 days was defined as “timely,” and all subsequent days were defined as “delayed”

Infection-related outcomes¹

- In a multivariate analysis of patients with infections due to resistant Gram-negative pathogens (CRE, CRP, MDRP, or ESBL), DAT resulted in worse clinical outcomes, including
 - 20% increase in the risk of in-hospital mortality or discharge to hospice
 - 30% decrease in the likelihood of being discharged to home
- In patients with infections due to susceptible Gram-negative pathogens, DAT resulted in similarly poor outcomes

^aThe Premier Hospital Database was used, which contains information from approximately 50 million discharges in the United States from approximately 500 acute-care hospitals, including teaching and nonteaching institutions as well as urban and rural facilities. Admission records from 150 hospitals that provided microbiologic data were included in this study.

Significant increases in duration of antibiotic therapy, LOS, and costs were also demonstrated in both groups receiving DAT, with a greater impact in patients with infections due to resistant pathogens, as shown below:

Outcome	Serious infections due to resistant pathogens (CRE, CRP, MDRP, or ESBL)		Serious infections due to susceptible pathogens	
	Timely appropriate therapy (n=3255)	DAT (n=2800)	Timely appropriate therapy (n=33,717)	DAT (n=16,585)
Mean duration of antibiotic therapy (days)	8.2	12.7 ^b	6.4	11.3 ^b
Mean LOS (days)	8.7	13.6 ^b	6.6	12.1 ^b
Mean total in-hospital costs (\$)	21,010	32,518 ^b	12,345	21,852 ^b

^bP<0.01.

These findings suggest the need to shift away from antibiotic escalation strategies that contribute to DAT and move toward early, aggressive, and comprehensive antibiotic therapy in patients at risk for serious Gram-negative infections.¹

Other studies have also demonstrated that DAT or failure of early antibiotic therapy is associated with greater mortality, LOS, and costs in patients with serious Gram-negative infections.^{3,4}

In another retrospective study of adult patients with serious infections due to Enterobacteriaceae...²

- DAT resulted in a greater risk of in-hospital death or being discharged to hospice
- Significant increases in duration of antibiotic therapy, LOS, and costs were also demonstrated in patients receiving DAT
- This study emphasizes the need for rapid diagnostics to shorten the lag time between clinical recognition of infection and downstream pathogen identification

These findings have important implications for clinical practice, as they suggest the worse outcomes associated with Enterobacteriaceae infection, regardless of carbapenem susceptibility status, can potentially be mitigated by timely appropriate antibiotic therapy.²