



Addressing Carbapenem-Resistant Gram-Negative Infections Early | Part 1 of 4

Impact of Delayed Antibiotic Therapy for Severe Gram-Negative Infections

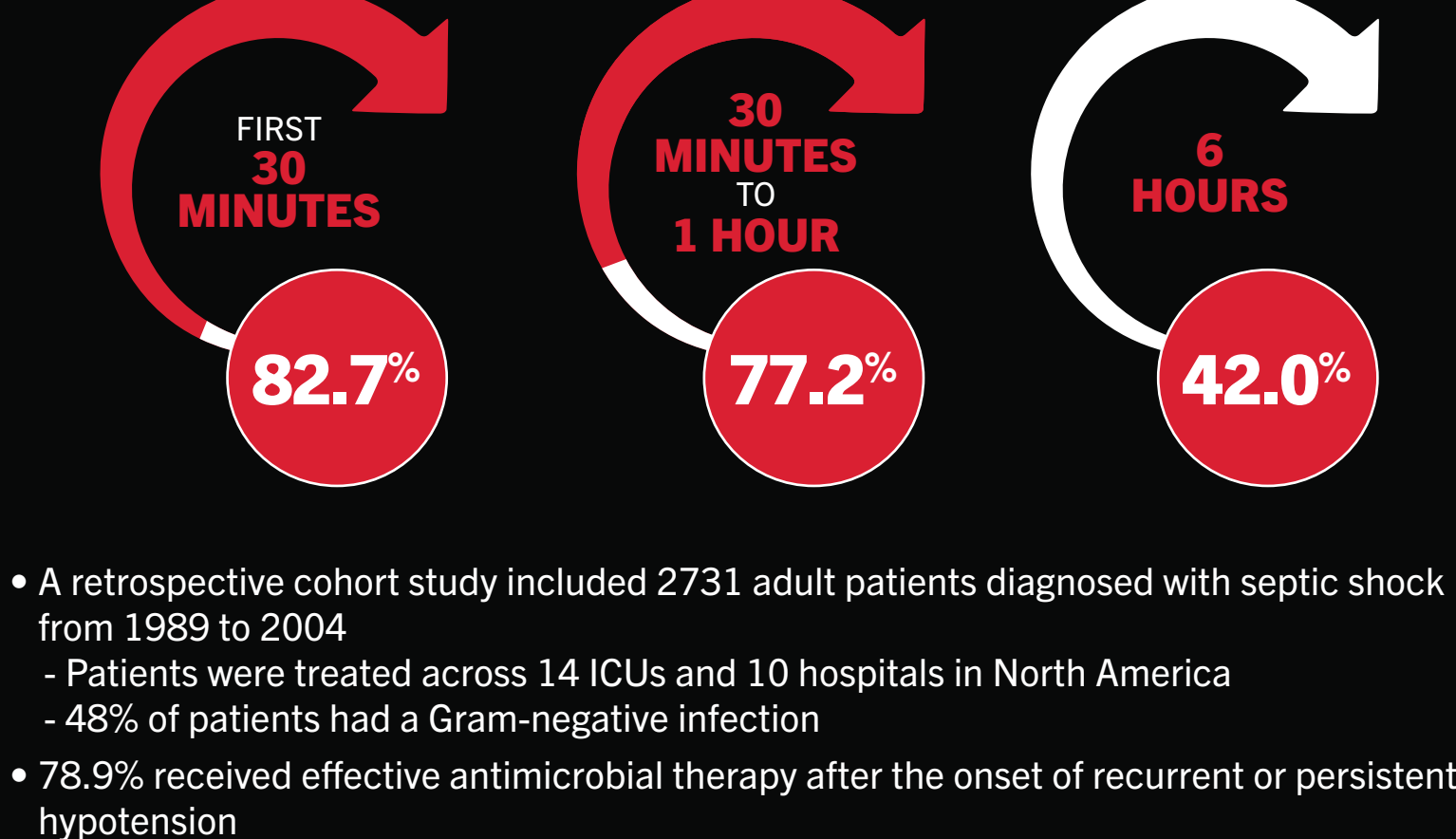
SUMMARY

- Delayed appropriate therapy for serious Gram-negative bacterial infections can lead to worse outcomes
- Carbapenem resistance is associated with increased mortality and longer hospital stays
- Newer antibiotics are underutilized

WITH GRAM-NEGATIVE INFECTIONS, EVERY HOUR COUNTS

Real-world evidence: Mortality rate is increased if appropriate antimicrobial therapy is delayed by even 1 hour¹

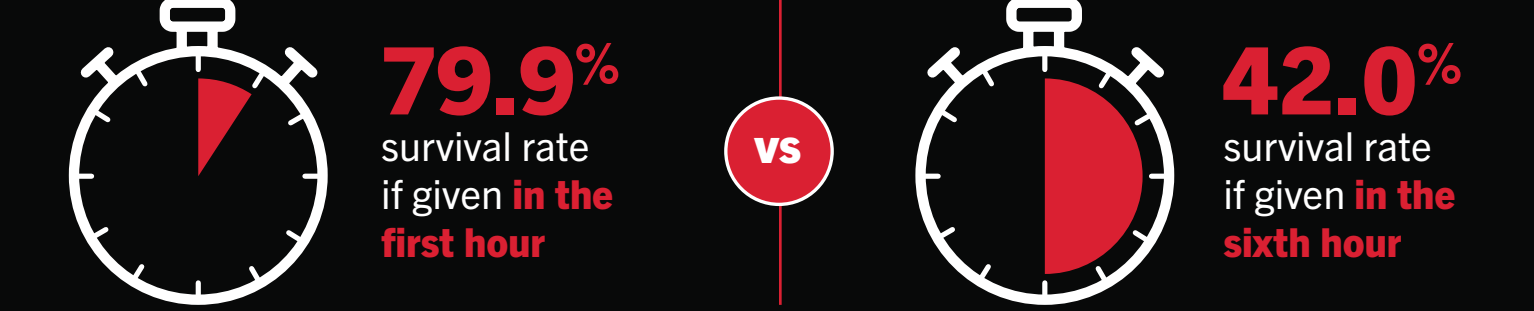
Survival based on timing of appropriate antimicrobial therapy following hypotension onset



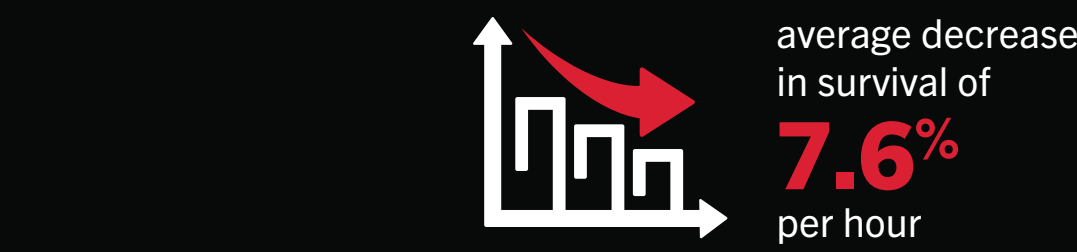
Study limitations:

- Retrospective study design
- Risk of confounding variable bias
- Potential selection bias
- Potential site heterogeneity

Administration of appropriate treatment following documented hypotension was associated with:



Each hour of delay in appropriate treatment administration over the first 6 hours was associated with:

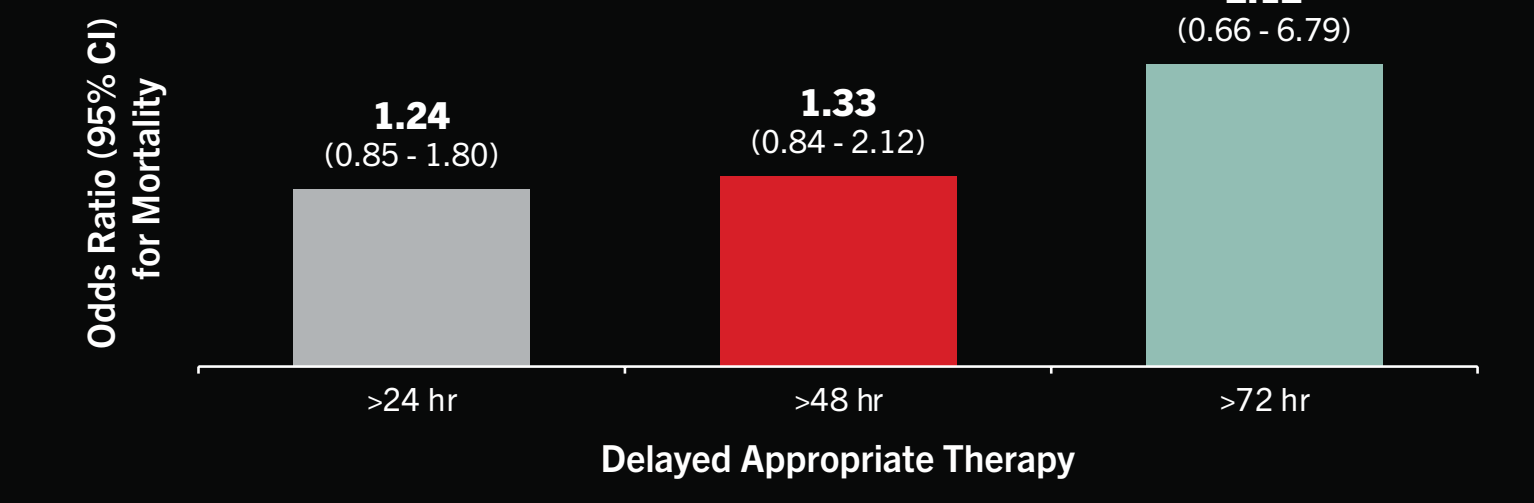


Meta-analysis: Delayed therapy can increase risk of death by up to 2-fold²

- A 2018 meta-analysis included 20 studies from 2004 to 2014 focused on hospitalized patients with *Klebsiella pneumoniae* or *Escherichia coli* infections
- Numeric trends suggesting an increase in mortality associated with delayed appropriate therapy >24 or >48 hours
- There was a statistically significant increase in the rate of mortality associated with combined results from patients for whom appropriate therapy was delayed >48 hours or after receiving culture and susceptibility results

Even a delay of 24 to 48 hours may negatively impact patient outcomes

Risk for Mortality Associated With Timing of Appropriate Therapy



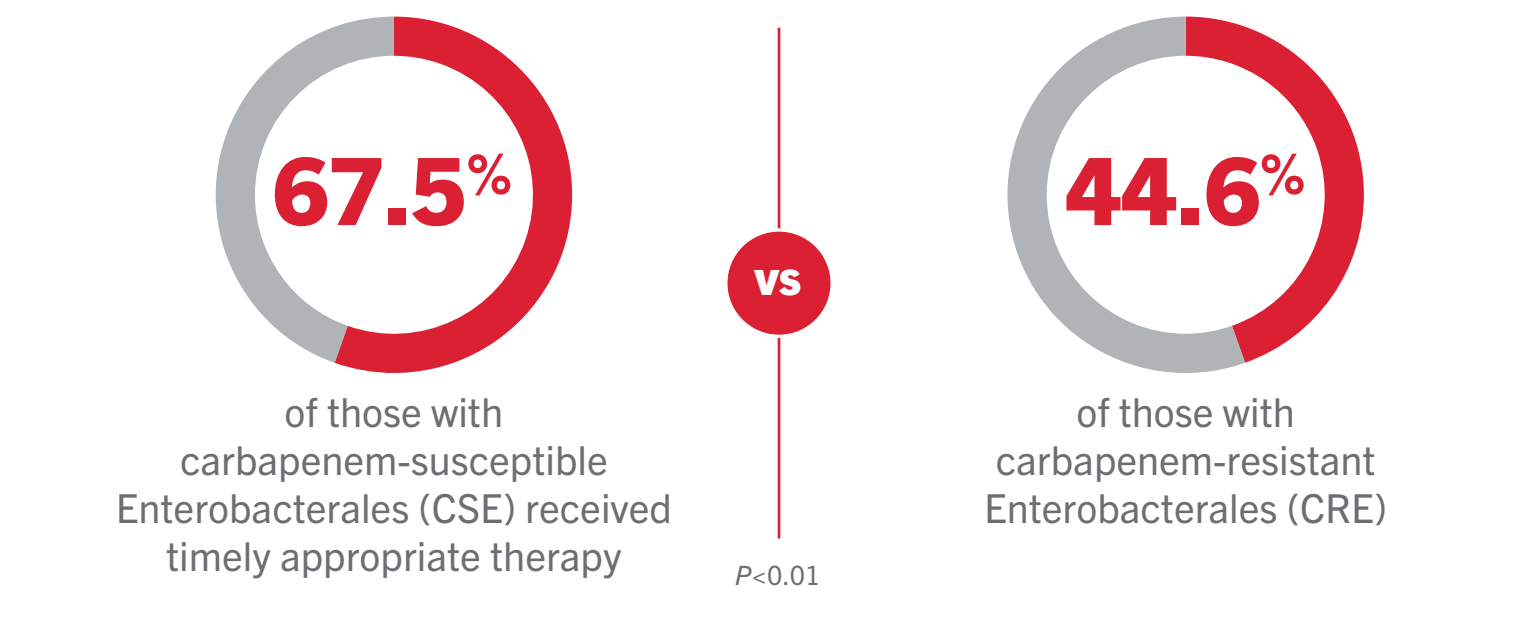
Study limitations:

- Limitations inherent to meta-analyses
- Definition of appropriate therapy varied across studies
- Most studies included in the analysis were retrospective
- Most studies focused on adults with bloodstream infections
- Other outcomes such as length of stay and cost were not evaluated

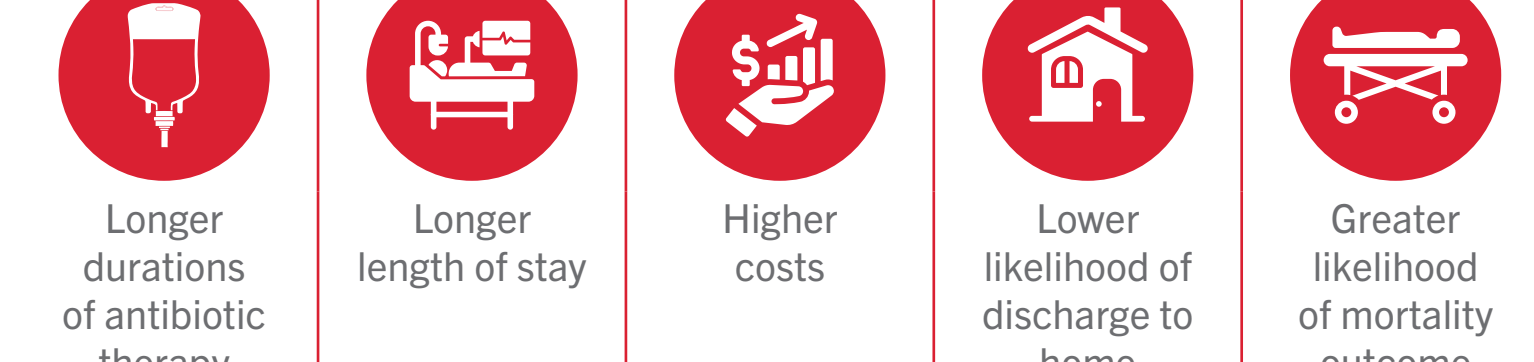
CARBAPENEM-RESISTANT INFECTIONS: GREATER IMPACT OF DELAYED THERAPY

Real-world evidence: Delays in appropriate therapy are more common and lead to worse outcomes in carbapenem-resistant infections³

- A retrospective study included 50,069 hospitalized patients with evidence of serious Enterobacterales infection:



Compared with those with CSE, patients with CRE who received delayed appropriate therapy had:



Study limitations:

- Retrospective database study
- Additional factors may be associated with the exposures and outcomes of interest
- Database lacks detailed clinical information and patient history
- Update to CLSI carbapenem susceptibility breakpoints during the study period
- Patients without in vitro susceptibility data were excluded
- Analysis focused on most common species

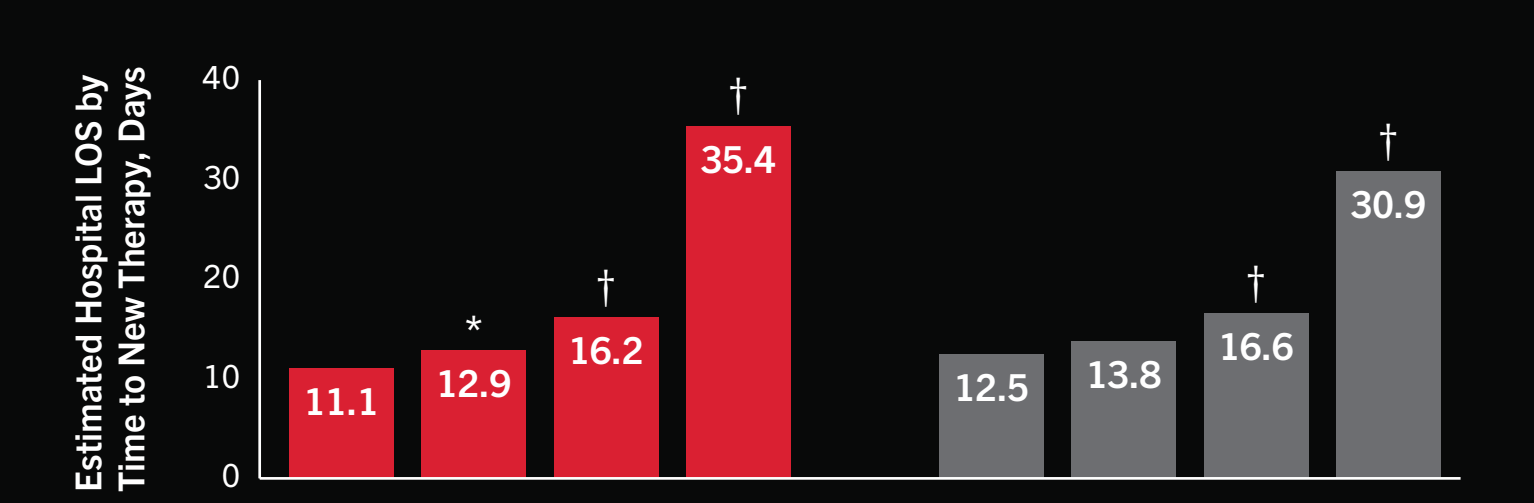
APPROPRIATE USE OF NEWER ANTIBACTERIALS: DELAYS HAVE IMPACT

Real-world evidence: Delayed use of newer antibacterials tied to significantly worse hospital outcomes⁴

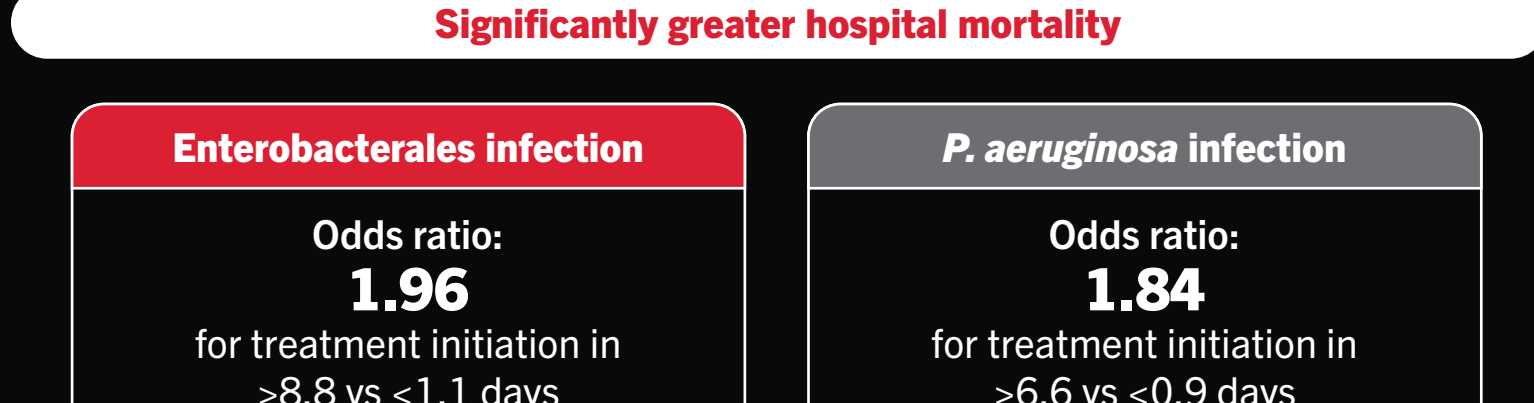
- A retrospective study included 265,347 patients with culture-positive Enterobacterales or *P. aeruginosa* infection
- Median time to start of new antibacterials was 87 hours for Enterobacterales and 84 hours for *P. aeruginosa*

Delayed use of newer antibacterials was associated with:

Significantly longer hospital length of stay



Significantly greater hospital mortality



Study limitations:

- AST performed locally
- Patients with positive bacterial cultures may not have had a confirmed bacterial infection
- Some bacteria may have been colonizers
- Information on outpatient antibacterial exposure was not available
- Antimicrobial therapy timing was based on time of the medication order
- Several US geographic regions were underrepresented in the database

**P* = 0.0022. †*P* < 0.0001.
AST=antimicrobial susceptibility testing; CI=confidence interval; CLSI=Clinical and Laboratory Standards Institute; CRE=carbapenem-resistant Enterobacterales; CSE=carbapenem-susceptible Enterobacterales; ICU=intensive care unit; OR=odds ratio.

References
1. Kumar A, et al. *Crit Care Med*. 2006;34(6):1589-1596. 2. Lodise TP, et al. *BMC Infect Dis*. 2018;18:625. 3. Lodise TP, et al. *Open Forum Infect Dis*. 2019;6(6):ofz194. 4. Riccobene T, et al. *BMC Infect Dis*. 2024;24(1):810.