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Introduction

- Antimicrobial resistance is associated with up to a two-fold increase in mortality and remains a major deciding factor for clinical outcomes (Friedman).
- It has been shown that patients with resistant bacterial strains are often given an ineffective empirical treatment before it is corrected into an appropriate regimen based on subsequent susceptibility data, which contributes to a significant delay in effective therapy (Eliopoulos).
- The detrimental impact of delayed therapy is well-accepted, but the majority of evidence focuses on gram-negative infections.
- A review and synthesis of the evidence evaluating the impact of delayed appropriate antibiotic therapy in serious gram-positive infections does not exist. Such data could help define the scope of the problem in this important patient population where antibiotic resistance is common.
- The purpose of this study is to assess the impact of delayed antibiotic treatment on mortality in patients with gram-positive bacteremia.

Methods

- All published literature up to March 30, 2020 relating to impact of delayed antibiotic therapy on mortality in were identified in Pubmed and Embase.
- Systematically constructed search was used: (Staphylococcus OR staphylococci OR enterococci OR enterococcus OR streptococci OR streptococcus OR gram-positive) AND (treatment delay OR delayed therapy OR early therapy OR timely therapy OR empiric antibiotic therapy OR empirical antibiotic therapy OR appropriate antibiotics) AND (bacteremia OR bloodstream infection).
- Three independent reviewers screened the search results for duplicates and applied a predefined exclusion criteria.
- Exclusion criteria were conference abstracts or poster, studies other than clinical trials, or observational cohort studies or case-control studies or observational clinical study, or case series, included pediatric patients, did not have culture-confirmed infection due to Staphylococci, streptococci, or enterococci, did not report the effect of delayed or early therapy on mortality, and published in languages other than English.
- Quality of included studies were assessed using Newcastle-Ottawa Scale by three independent reviewers.
- Delayed appropriate therapy and mortality were defined as they were defined in individual studies. 30-day mortality data were selected for analysis if available.
- Data reporting the association between delayed therapy and mortality were extracted by three independent reviewers.
- Meta-analysis was conducted in Review Manager 5.3 using random effect models via the Mantel Haenszel method for unadjusted analysis and generic inverse variance method for covariate-adjusted data
- I² statistic was used for heterogeneity & funnel plot for publication bias
- Prospero registration: CRD42020188930

References

- Eliopoulos, George M., Sara E. Cosgrove, and Yehuda Carmeli. 2003. "The Impact of Antimicrobial Resistance on Health and Economic Outcomes." *Clinical Infectious Diseases*. <https://doi.org/10.1086/375081>.
- Friedman, N. D., E. Tamkin, and Y. Carmeli. 2016. "The Negative Impact of Antibiotic Resistance." *Clinical Microbiology and Infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases* 22 (5): 416–22.

Results

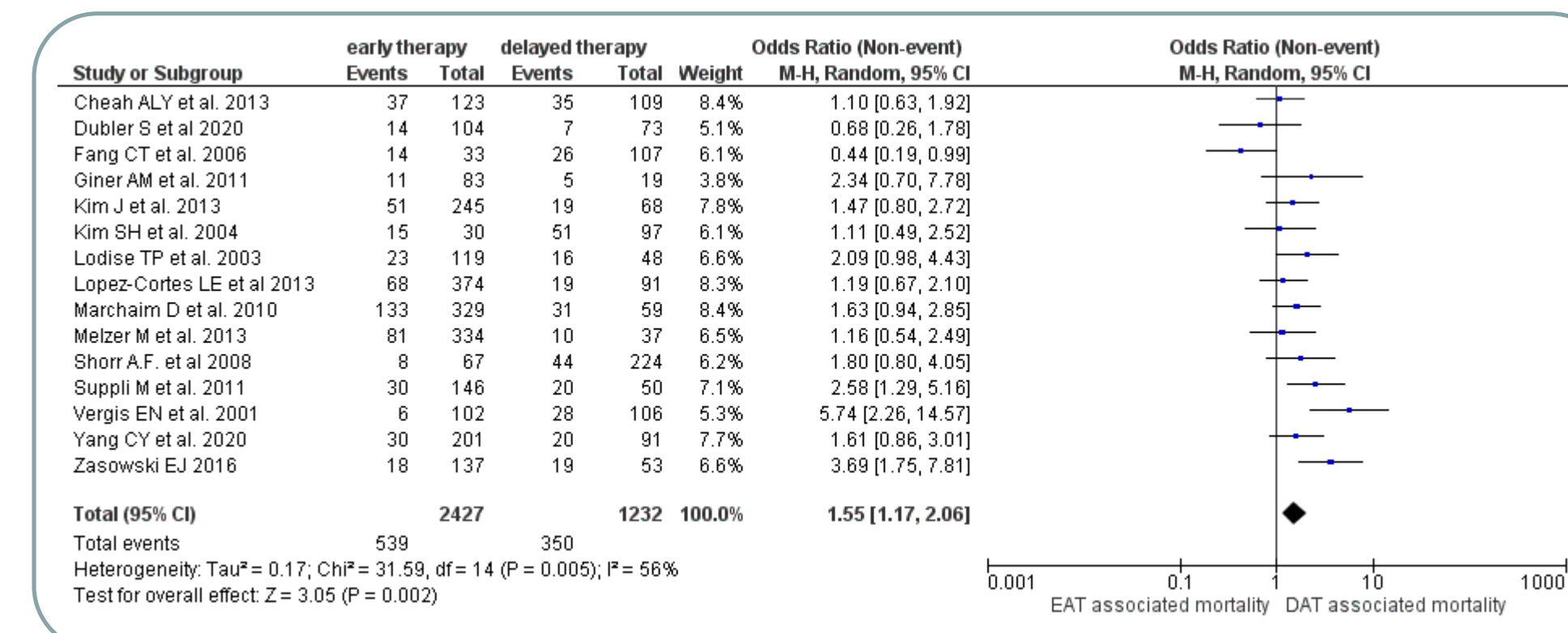


Figure 1. Forrest plot of meta-analysis of unadjusted association between delayed therapy and mortality

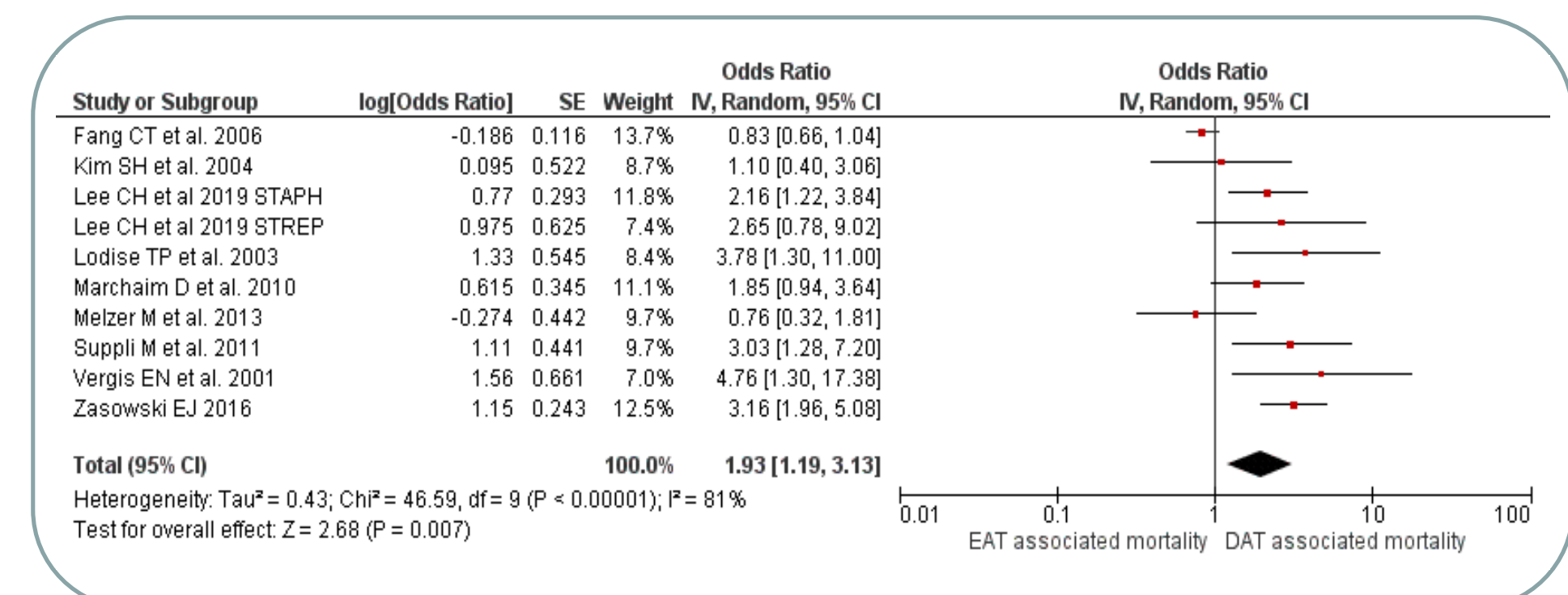


Figure 2. Forrest plot of meta-analysis of covariate adjusted association between delayed therapy and mortality

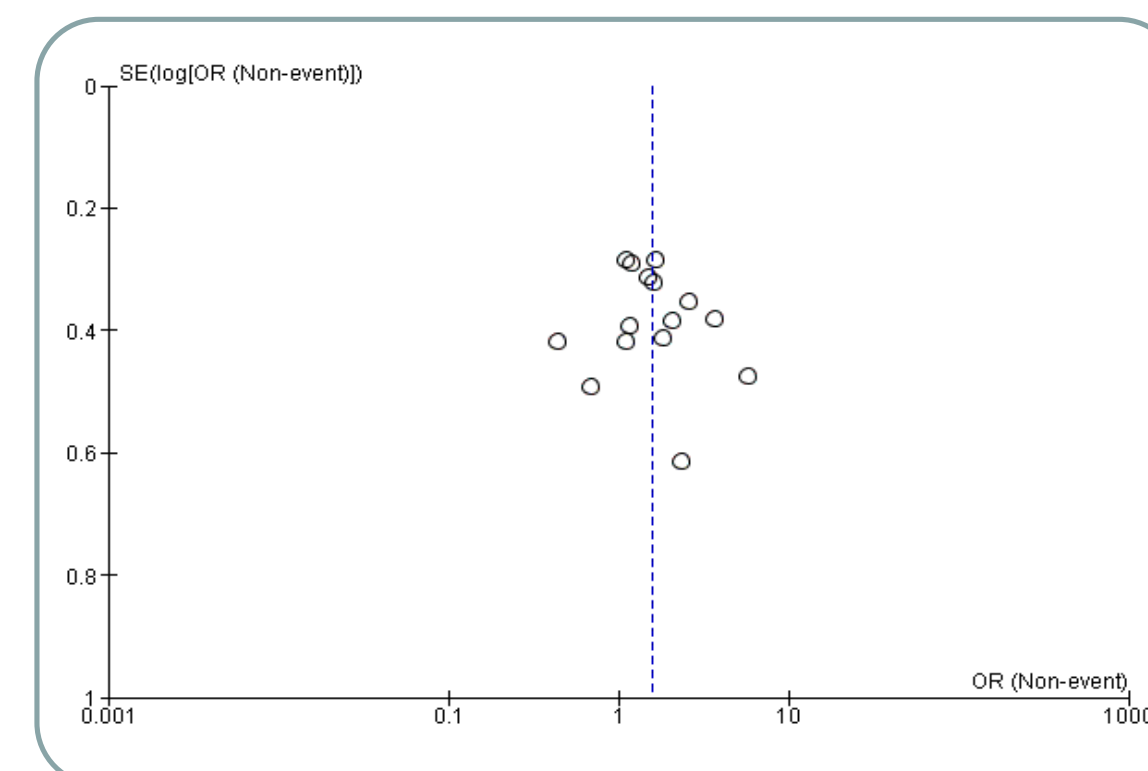


Figure 3. Funnel plot

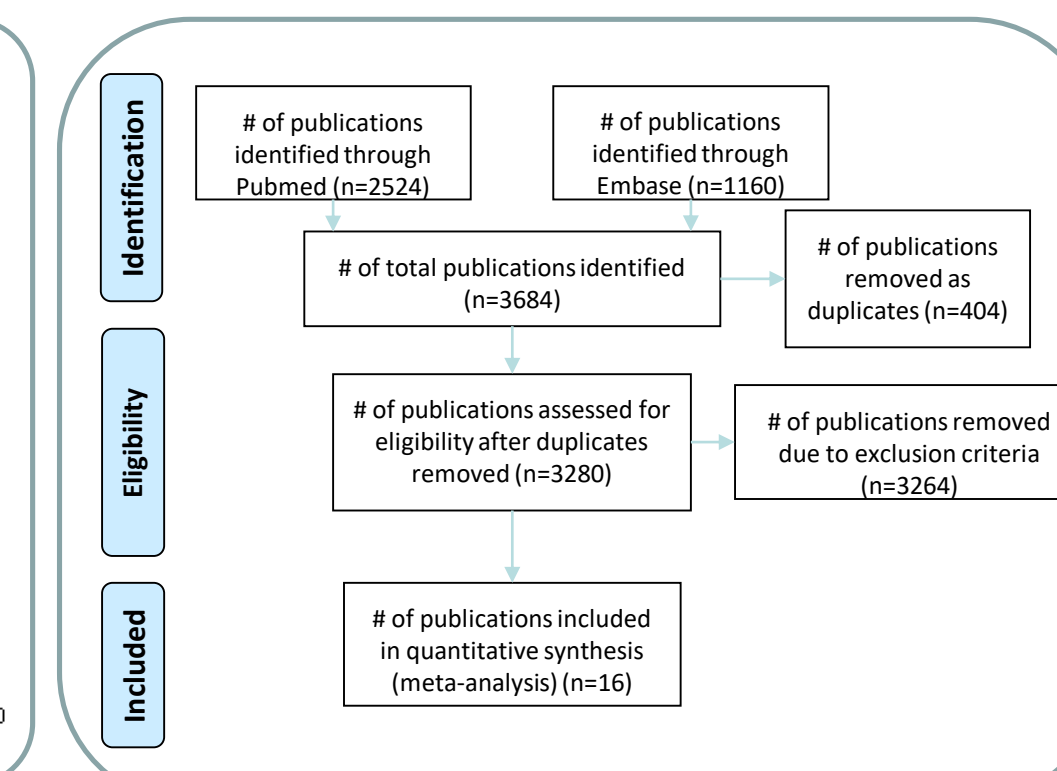


Figure 4. Study flow diagram.

Study	Newcastle-Ottawa Scale						Total score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	
Shorr, A.F., et al. 2008	*	*	*	*	*	*	7/9
Yang, C.Y., et al. 2020	*	*	*	*	**	*	8/9
Lee, C.H., et al. 2019	*	*	*	*	**	*	8/9
Lopez, L.E., et al. 2013	*	*	*	*	*	*	7/9
Dubler, S., et al. 2020	*	*	*	*	**	*	8/9
Zasowski, E.J., et al. 2016	*	*	*	*	**	*	9/9
Melzer, M., et al. 2013	*	*	*	*	**	*	8/9
Kasch, A.J., et al. 2013	*	*	*	*	**	*	8/9
Marchaim, D., et al. 2010	*	*	*	*	**	*	7/9
Han, S.H., et al. 2009	*	*	*	*	*	*	7/9
Fang, C.T., et al. 2006	*	*	*	*	**	*	8/9
Lodise, T.P., et al. 2003	*	*	*	*	**	*	8/9
Cho, S.Y., et al. 2013	*	*	*	*	*	*	7/9
Kim, L., et al. 2013	*	*	*	*	*	*	7/9
Cheah, A.L.V., et al. 2013	*	*	*	*	**	*	8/9
Giner, A., et al. 2011	*	*	*	*	*	*	6/9
Suppli, M., et al. 2011	*	*	*	*	**	*	8/9
Su, C., et al. 2011	*	*	*	*	*	*	7/9
Kim, S.H., et al. 2004	*	*	*	*	**	*	8/9
Vergis, E.N., et al. 2001	*	*	*	*	*	*	7/9

Table 1. Newcastle-Ottawa Scale Assessment

Conclusions

- Delayed appropriate therapy was associated with increased odds of mortality in patients with gram-positive bacteremia, predominantly from *S. aureus* and *Enterococcus* spp.
- The meta-analysis showed a significant association between delayed therapy and mortality using unadjusted data from ($P=0.02$) (Figure 1).
- This effect persisted in analysis using data that were adjusted for potential confounders in nine studies (Figure 2).
- Although adjusted analysis demonstrated a high level of heterogeneity in the effect estimate, with an I² statistic of 81%, the consistency of the direction and statistical significance of the findings suggests the observed association is not spurious.
- Assessment of the included studies using the Newcastle-Ottawa Scale showed that our included studies were mostly high quality with grades ranging from 6-8 out of 9 stars, though all studies failed to assess the follow-up of their cohorts (Table 1).
- Publication bias was assessed with a funnel plot which showed a mostly symmetrical distribution, indicating the absence of major bias (Figure 3).
- These findings support the need for antimicrobial stewardship efforts to ensure expeditious appropriate antibiotic therapy for patients with gram-positive bacteremia.