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Systematic review and meta-analysis of the proportion and associated mortality of polymicrobial (versus monomicrobial) pulmonary and bloodstream infections by *Acinetobacter baumannii* complex.

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Abstract

Background: Differentiating *Acinetobacter baumannii* complex (ABC) infection from colonization remains difficult and further complicated in polymicrobial infections.

Purpose: To assess the frequency of polymicrobial ABC infections and associated mortality. We hypothesized a lower mortality in polymicrobial infections if ABC isolation reflects colonization in some polymicrobial infections.

Methods: A systematic review was conducted in PubMed, Scopus and CENTRAL for studies reporting ABC pulmonary and bloodstream infections. The proportion of infections that were polymicrobial and the magnitude of the association between polymicrobial (vs monomicrobial) infection and mortality were estimated with meta-analyses.

Results: Based on 80 studies (9759 infections) from 23 countries, the pooled proportion of polymicrobial infection was 27% (95% CI 22%-31%) and was similarly high for bloodstream and pulmonary infections. Polymicrobial infection was variably and insufficiently defined in most (95%) studies. Considerable heterogeneity (I^2=95%) was observed that persisted in subgroup analyses and meta-regressions. Based on 17 studies (2675 infections), polymicrobial infection was associated with lower 28-day mortality (OR=0.75, 95% CI 0.58-0.98, I^2=36%). However, polymicrobial infection was not associated with in-hospital mortality (OR=0.97, 95% CI 0.69-1.35, I2=0%) based on 14 studies (953 infections). The quality of evidence (GRADE) for the association of polymicrobial (vs monomicrobial) infection with mortality was low and at high risk of bias.

Conclusion: Polymicrobial ABC infections are common and may be associated with lower 28-day mortality. Considering the heterogeneity of polymicrobial infections and limitations of the available literature, more research is required to clarify the clinical impact of polymicrobial (vs monomicrobial) ABC infection.

Keywords: *Acinetobacter*, polymicrobial, mortality, infection, colonization

Introduction

Acinetobacter baumannii, once considered of low virulence, is now recognized as a pathogen associated with significant attributable mortality [1-4]. However, differentiating infection from colonization remains problematic, which may partly explain the similar mortality between infected and colonized patients in some studies [5, 6], and the approach taken by others to pool colonized and infected patients into a single group in order to assess mortality attributable to *A. baumannii* [1]. To further complicate matters, *A. baumannii* is often isolated in polymicrobial infections [3, 7, 8].

Differentiating infection from colonization has important antimicrobial stewardship implications. Overtreatment due to misclassification of colonization as infection can fuel the emergence of extensively-/pan-drug-resistant *A. baumannii* [9-12], for which treatment options are limited [13]. Reducing unnecessary use of last resort antibiotics may allow outcompeting of extensively-/pan-drug-resistant *A. baumannii* by more susceptible strains [9, 12].

Furthermore, clarifying the role of *A. baumannii* in polymicrobial infections (pathogen vs bystander) and whether polymicrobial infection is an independent predictor of patient outcome has implications for the design and analysis of studies assessing intervention or treatment effects. One approach is to exclude polymicrobial infections from such studies, but this might result in non-pragmatic and biased samples that exclude many eligible patients. Another approach is to ignore the type of isolation and examine infections as a single entity irrespective of polymicrobial vs monomicrobial status, but this would be inappropriate if polymicrobial infection independently predicts the outcome. In the latter case, polymicrobial isolation would need to be assessed as a confounding factor.

One way to assess the role of *A. baumannii* in polymicrobial infection is to compare clinical outcomes between polymicrobial and monomicrobial infections. *A. baumannii* infections are typically associated with higher mortality compared to other pathogens [14-16]. Therefore, mortality of polymicrobial ABC infections should at least be similar to that of monomicrobial ABC infections or higher [8]. However, according to one hypothesis [7, 17], *A. baumannii* is more likely the causative pathogen in monomicrobial infections, while in polymicrobial infections other organisms, that are usually more susceptible and more likely to be covered by empirical therapy [15, 18], probably represent the true infecting pathogen. This would result in higher clinical failure in monomicrobial infections caused by multidrug-resistant *A. baumannii* [7, 17].

This systematic review consolidates the available evidence to estimate the frequency of polymicrobial isolation in *Acinetobacter baumannii* complex (ABC)-implicated pulmonary and bloodstream infections and the associated mortality compared to monomicrobial infections. To our knowledge a similar review has not been previously conducted.

Methods

Search strategy

The search was conducted in PubMed, Scopus and the Cochrane Central Register of Controlled Trials from inception to January 6, 2021. The search terms are described in the Supplement (Section 1). The

references of recent systematic reviews of *Acinetobacter* infections (Supplement, Section 2) were screened to assess the adequacy of our search strategy.

Eligibility criteria

Any study reporting the proportion of polymicrobial infection among patients with ABC pulmonary or bloodstream infections was eligible. Studies including non-ABC together with ABC species were eligible but, where possible, only data for ABC infections were extracted. Retrieved articles were first evaluated based on their title and abstract, allowing exclusion of irrelevant articles, case reports and series with <10 patients. The full-text of potentially relevant articles was then evaluated applying the following exclusion criteria (in this order): (1) type of isolation (polymicrobial vs monomicrobial) not reported, (2) exclusion of polymicrobial infections without reporting the number of patients excluded, (3) mixed infection-colonization studies and extraction of data separately for infection not possible, (4) studies including infections by species other than *Acinetobacter* and extraction of data for *Acinetobacter* infections not possible, (5) mixed sites of infection and extraction of the data for pulmonary and bloodstream infections not possible, (6) studies having overlapping patient populations (overlapping affiliated institutions and time periods), in which case the largest study was selected for review. Non-English full-texts were translated with Google Translate.

Definition of polymicrobial infection

Studies including co-infection at other sites or superinfection (secondary infection during treatment of the primary infection) among polymicrobial infections were excluded. Other than that, we did not apply a specific definition as an inclusion criterion but recorded the definition used in each study. Specifically, we recorded the site of polymicrobial isolation (coded as 'same' or 'unspecified'), the timing of polymicrobial isolation (same culture, within a specific time-frame, or unspecified), and co-isolates recorded among polymicrobial infections (exclusion vs inclusion of colonizing/non-etiologic co-isolates, or unspecified).

Data extraction

The following data were extracted from each study: data collection method (retrospective/prospective), country, definition of polymicrobial infection, *Acinetobacter* species (categorized as *A. baumannii*, ABC or *Acinetobacter* spp), type of infection, percentage of ventilator-associated pneumonias and of secondary bacteraemia among patients with pulmonary infections, origin of infection (community-onset or hospital-acquired), percentage of carbapenem non-susceptibility among *Acinetobacter* isolates, number of polymicrobial cases, co-isolates in polymicrobial infections, and all-cause mortality (7-day, 14-day, 28/30-day, in-hospital mortality). Considering the problematic identification of ABC species by phenotypic-based systems [19-21] *Acinetobacter baumannii* was corrected to ABC (comprising of *A. calcoaceticus*, A. *baumannii*, *A. nosocomialis*, *A. pitti*, *A. seifertii* and *A. dijkshoorniae*) in studies not using molecular methods or MALDI-TOF-MS [21].

Risk of bias assessment

All studies were assessed as cohort studies comprising patients with *Acinetobacter*-implicated infection, with the exposure of interest being polymicrobial (vs monomicrobial) infection. Risk of bias was examined with the "Tool to Assess Risk of Bias in Cohort Studies", based on the following considerations [22]: (1) accuracy of measurement of the exposure; (2) similarity of the exposed (polymicrobial) and unexposed (monomicrobial) cohorts with regards to confounders and conduct of matched or adjusted analysis; (3) accuracy of outcome assessment; and (4) assessment for bias due to missing outcome data.

Grading of the evidence

Assessment of the quality of the evidence for the association between polymicrobial (vs monomicrobial) infection and mortality was based on the GRADE approach [23, 24].

Statistical analysis

Random-effects meta-analysis was conducted using the R packages "meta" [25], "metafor" [26] and "dmetar" [27]. The pooled proportion of polymicrobial infections was defined as the ratio of the number of polymicrobial infections over the total number of infections. This was meta-analyzed using the generalized linear mixed model [28, 29], where the observed number of polymicrobial infections was modelled using the binomial distribution and the random-effects were assumed to have a normal distribution following the logit transformation . The pooled association between mortality and polymicrobial (vs monomicrobial) infection was quantified as an odds ratio (OR) and was estimated with a random-effects model using the Mantel–Haenszel method. The 95% confidence intervals (95% CI) of the summary OR were adjusted with the Hartung-Knapp method [30]. Between study variance (τ^2) was estimated with the maximum-likelihood method in the analysis of single proportions and the restricted maximum-likelihood method in the analysis of ORs.

Heterogeneity between studies was assessed with the I^2 statistic and prediction intervals. The contribution of each study to the observed heterogeneity was assessed graphically with a Baujat plot [31]. Additionally, a GOSH plot (x-axis= summary log OR, y-axis= I^2) was generated by fitting the same meta-analysis model to 10^6 randomly sampled subsets of the studies to identify subclusters with different effect sizes [32]. Studies most contributing to subclusters were identified with clustering algorithms [27]. A leave-one-out sensitivity analysis was conducted to assess the influence of individual studies on the summary estimate. Finally, random-effects subgroup analysis (for categorical variables) and univariate meta-regression (for continuous variables, provided that ≥10 studies were eligible for analysis [30]) were conducted to explore heterogeneity. The moderator variables considered for these analyses are listed in the "Data extraction" sub-section.

Publication bias and small-study effects were assessed by visual inspection of contour-enhanced funnel plots [33] and the Peters test [34].

Results

Study characteristics

The flow chart of this review is depicted in Figure 1. Overall, 80 studies reporting 9759 *Acinetobacter* spp infections [3, 8, 17, 35-111] in 23 countries were reviewed (Supplement, Section 4). Most studies (n=59) were published in the last 15 years (Supplement, Section 4.1). Most studies (n = 29) were conducted in the Western Pacific Region (representing 58% of all infections), followed by Europe (21% of infections) and the Americas (14% of infections) (Supplement, Section 4.2). Of 56 studies reporting the origin of the infection, most included exclusively (n=37) or predominantly (n=16) patients with hospital-acquired infections. Seven-day, 14-day, 28/30-day and in-hospital mortality were reported in 2 (76 patients), 5 (704 patients), 17 (2675 patients) and 14 (953 patients) studies, respectively.

Definitions for polymicrobial infection

Polymicrobial infection was not sufficiently defined in most (95%) studies. The site of co-isolation of microorganisms other than ABC was specified as the same site (respiratory tract in pulmonary infections,

and blood in bloodstream infections) in 62 (78%) of the studies. The timing of isolation of other microorganisms in polymicrobial infections was variably specified in only 25 (31%) studies as: co-isolation from the same culture (n=14), during same infection episode (n=7), or within 1-2 days from the *Acinetobacter* culture (n=5). Only 6 (8%) studies specified which co-isolates were included in polymicrobial infections; 4 studies excluded possible contaminants/non-pathogenic co-isolates [8, 40, 82, 91], 1 included only polymicrobial infections with co-isolates that have been covered by antimicrobial therapy [50] and 1 included any co-isolate [3]. Therefore, the rest of the studies may or may not have reported non-etiological colonizing microorganisms as polymicrobial infections.

Proportion of polymicrobial infections

The pooled percentage of polymicrobial infections was 27% (95% CI 22%-31%) (Figure 2). This was similar in pulmonary (30%; 95% CI 21%-41%) and bloodstream (25%; 95% CI 21%-30%) infections, but ranged widely between studies from 0% [64, 66, 109] to >60% [53, 77, 79, 86, 104], resulting in a large heterogeneity index (I^2=95%) and a wide prediction interval (5%-71%).

In subgroup analyses and meta-regression, the observed heterogeneity was not sufficiently explained by any of the available variables, including publication year, data collection method (retrospective/prospective), definition of polymicrobial infection, *Acinetobacter* species, percentage of ventilator-associated pneumonia and secondary bacteraemia among patients with pulmonary infections, proportion of hospital-acquired infections, proportion of carbapenem non-susceptibility among *Acinetobacter* isolates, and proportion of Gram-positive or Gram-negative bacteria in polymicrobial infections (Supplement, Sections 5.1-5.4).

Nevertheless, the proportion of Gram-positive bacteria (GPB) in polymicrobial bloodstream infections correlated positively with the proportion of polymicrobial infections (OR = 1.033 for polymicrobial infection per 1% increase in GPB proportion; p=0.023; R2=47%) (Supplement, Section 5.4.8). Furthermore, the percentage of polymicrobial infection was lower (albeit with a test for subgroup differences p-value=0.32) in studies defining polymicrobial infection as isolation of >1 microorganism from the same culture (18%, 95% CI 7-39%, I^2=94%), compared to isolation of other organisms within 1-2 days from the ABC culture (35%, 95% CI 20-54%, I^2 =94%), or during the same infection episode (33%, 95% CI 20-49%, I^2=96%).

28/30-day mortality

Polymicrobial infection was associated with lower 28/30-day mortality (OR=0.75, 95% CI 0.58-0.98, I^2=36%, p=0.07) (Figure 3). Similar effect sizes were found for pulmonary (OR=0.70, 95% CI 0.48-1.03, I^2=0%) and bloodstream (OR=0.78, 95% CI 0.54-1.12, I^2=48%) infections.

Subgroup analyses and meta-regressions are presented in the Supplement (Sections 6.1-6.4). Notable is that the association of polymicrobial infection with lower 28/30-day mortality was stronger in studies with a higher proportion of carbapenem-resistant ABC (p=0.062) and the proportion of carbapenem resistance explained 60% of the observed heterogeneity (Figure 4). Considering only studies with >50% carbapenem-resistant ABC infections, mortality was lower in polymicrobial infections in both bloodstream (OR 0.61, 95% CI 0.46-0.82, I^2=0%) and pulmonary infections (OR 0.63, 95% CI 0.42-0.95, I^2=0%) (Supplement, Sections 6.2.7.4-6.2.7.7). Results were similar when studies with >80% carbapenem-resistant ABC infections were examined (Supplement, Sections 6.2.7.1-6.2.7.3). However, it should be acknowledged

that the subgroup analyses based on these cut-offs (50% and 80%) represent post-hoc analyses. The cut-offs were selected based on the distribution of studies as seen in the bubble plot in Figure 4.

In leave-one-out sensitivity analysis, the summary effect size was not altered appreciably (OR ranging from 0.71 to 0.80) (Supplement, Section 6.5). Four studies [8, 53, 70, 103] appeared to contribute most to the observed heterogeneity as evident in a Baujat plot, three of which [8, 53, 70] were also detected as influential by GOSH diagnostics. Excluding these influential studies, the summary measure for the association between polymicrobial infection and 28/30-day mortality was 0.69 (95% CI 0.55-0.88, I^2 0%).

Other mortality endpoints

The odds of 7-day and 14-day mortality were lower for polymicrobial compared to monomicrobial infection, but these associations were based on only 2 and 5 studies respectively and are highly uncertain (at 7 days: OR=0.56, 95% CI 0.00-95.83 I^2=0%; at 14 days: OR=0.94, 95% CI 0.51-1.74, I^2=29%) (Supplement, Sections 7 and 9). Furthermore, polymicrobial infection was not associated with in-hospital mortality (OR=0.97, 95% CI 0.69-1.35, I^2=0%) based on 14 studies (Supplement, Section 9). In contrast to 28/30-day mortality, the proportion of carbapenem resistance was not associated with the OR for in-hospital mortality (Supplement, Section 9.3). In a post-hoc meta-analysis combining all studies (irrespectively of the mortality endpoint used), polymicrobial infection was associated with lower odds of mortality (OR=0.81, 95% CI 0.67-0.97, I^2=19%)(Supplement, Section 10).

Mortality depending on the type of co-isolate

Mortality depending on the type of co-isolate was reported in only 6 studies [3, 8, 41, 53, 58, 68]. These data were too few and too heterogeneous (different time-points for mortality and >1 co-isolates in some polymicrobial infections) to allow meaningful meta-analysis. Furthermore, studies providing both mortality data and the proportion of co-isolates in polymicrobial infections were too few (<10) to allow meta-regression.

Risk of bias in individual studies

Regarding accuracy of measurement of the exposure (polymicrobial infection) the following are potential sources of bias; (1) Subjectivity in deciding whether a co-isolate is etiologic could affect whether an infection is classified as polymicrobial or monomicrobial. Most (n=74) studies did not clarify whether co-isolation of non-etiologic microorganisms was classified as monomicrobial or polymicrobial infection. (2) In the 11 studies not specifying the site of isolation of co-pathogens some cases of co-infection at other site may have been included among polymicrobial infections.

Considering the objectivity of ascertaining all-cause mortality and the fact that no study reported losses to follow-up, bias from outcome assessment or missing outcomes was considered low. Similarity of exposed (polymicrobial) and unexposed (monomicrobial) cohorts could not be assessed as no study (except [8]) reported a comparison of patient characteristics between polymicrobial and monomicrobial infections. Furthermore, no study did a matched analysis (case="polymicrobial" matched to control="monomicrobial"). Multivariable analysis regarding the association of polymicrobial infection with 28/30-day mortality was available in only 2 studies [3, 17]. The rest of the studies either excluded polymicrobial infection from multivariable analyses (due to lack of statistically significant association in univariate analysis) or did not report adjusted OR for polymicrobial infection (due to lack of statistical significance). Therefore, the risk of bias was judged to be high as our analysis was based on unadjusted OR.

Risk of bias across studies

Inspection of the funnel plot indicated some evidence of asymmetry, with bias towards a smaller proportion of polymicrobial infection (Supplement, Section 5.5). Regarding the meta-analyses of 28/30-day and in-hospital mortality, no asymmetry was observed in the funnel plots (Supplement, Sections 6.6 and 9.4).

GRADE of evidence

The overall quality of evidence for the association of polymicrobial infection with mortality was downgraded to very low considering high risk of bias due to confounding (as the meta-analysis was based on unadjusted OR), inconsistent results (between studies and comparing different mortality endpoints), imprecision (wide 95% CI and prediction intervals including null or with upper bound close to null) and indirectness (considering evaluation of all-cause mortality instead of infection-related mortality). A summary of findings table for each outcome assessed (7-, 14-, 28/30-day and in-hospital mortality) is available in the Supplement (Section 11).

Discussion

In this systematic review we showed that about 1 of every 3 to 5 ABC-implicated pulmonary and bloodstream infections are polymicrobial. Therefore, excluding polymicrobial infections, as commonly done in studies of *Acinetobacter* infections, may result in highly selective non-pragmatic studies. Additionally, we found that the type of isolation (polymicrobial vs monomicrobial) may be an important predictor of 28/30-day mortality. Therefore, ignoring the type of isolation when examining the clinical impact of ABC, which is common practice (Figure 1), may produce confounding bias.

The large heterogeneity observed in the proportion of polymicrobial infections is reasonable considering the multitude of potential moderators including variable definitions of polymicrobial infection, patients' characteristics, specimen type (sputum, endotracheal aspiration, bronchial washing, bronchoalveolar lavage, peripheral blood, culture from vascular catheter or catheter tip), source of infection in bacteraemia, receipt of antibiotics prior to culture (which may result in suppression of susceptible co-pathogens but not of resistant *A. baumannii* strains, resulting in a falsely monomicrobial culture). The positive correlation between the proportion of Gram-positive bacteria in polymicrobial bloodstream infections and the proportion of polymicrobial infections itself raises the hypothesis that the higher percentage of polymicrobial infections reported by some studies may be associated with higher blood culture contamination rates and/or inclusion of non-etiologic co-isolates in polymicrobial infections.

Considering a higher mortality of *A. baumannii* infections compared to other pathogens [14-16] mortality of polymicrobial ABC infections should be similar to that of monomicrobial ABC infections or higher. However, our meta-analysis showed a lower 28/30-day mortality in polymicrobial ABC infections. This supports the hypothesis that co-pathogens, which are usually more susceptible and more likely to be covered with effective antimicrobials [15, 18], may represent the true pathogen in some polymicrobial ABC infections, with ABC being a bystander [7]. This hypothesis is also supported by the negative correlation of the proportion of carbapenem resistance with the 28/30-day mortality OR in our meta-analysis. In other words, monomicrobial infections caused by carbapenem-resistant ABC are associated with higher mortality, while other (usually more susceptible) micro-organisms may represent the true pathogen in polymicrobial infections. Therefore, it is possible that a subset of patients with polymicrobial ABC infections may not require antimicrobial coverage of ABC. This has important antimicrobial

stewardship implications, especially considering the potential of ABC for in-vivo emergence of resistance during treatment with last resort agents [9, 10].

An alternative explanation for the lower mortality in polymicrobial infections, especially relevant to bloodstream infections, is that polymicrobial cultures may be more likely to represent colonization/contamination rather than infection, or may be associated with easier to treat sources of infection (e.g. central line-associated bacteraemia). Furthermore, polymicrobial infections are heterogenous and the type and antimicrobial susceptibility of co-isolates [8, 68] may be important predictors of outcomes in polymicrobial infections. This is exemplified by a study showing that monomicrobial *A. baumannii* bacteraemia is associated with lower mortality compared to polymicrobial bacteraemia with Gram-negative co-pathogens, but higher mortality compared to polymicrobial bacteraemia associated with Gram-positive co-pathogens [8]. This highlights that the summary OR in our meta-analysis indicating lower overall mortality in polymicrobial infections should be carefully interpreted, recognizing the possibility that different polymicrobial combinations may have conflicting effects on mortality.

A major limitation of the available literature is that it cannot answer whether polymicrobial infection is an independent predictor of mortality after adjusting for confounders. Notable is that, in contrast to 28/30-day mortality, polymicrobial infection was not associated with in-hospital mortality. The most appropriate time-point that best reflects mortality attributable to infection is debatable. Too early time-points (e.g. 7-day or 14-day mortality) may miss deaths due to slow-progressing infections, or delayed deaths attributable to infection-related complications [112]. On the other hand, too late time-points (such as in-hospital mortality of patients with prolonged hospitalizations) would inevitably include many deaths that would have occurred irrespectively of the infection and could therefore attenuate the observed measure of association between polymicrobial (vs monomicrobial) infection and mortality.

The lack of a clear definition for polymicrobial infection in many studies is another limitation. A clear definition would require: (1) defining the site and timing of isolation of co-pathogens as isolation from the same culture or from the same infection site within a specific time frame before/after ABC isolation, e.g. within 1-2 days, (2) specifying which co-isolates are included in polymicrobial infections (e.g. exclusion or inclusion of microorganisms considered as non-etiological in the infection), and (3) differentiating polymicrobial infection from co-infection at other sites or superinfection.

Another drawback is the problematic differentiation of *Acinetobacter* infection from colonization, which is a major reason for excluding polymicrobial infections in many studies. The best way to access the role of ABC (pathogen vs bystander) in polymicrobial infections would be to compare the outcome of polymicrobial ABC infections in patients receiving appropriate antimicrobial therapy covering ABC with patients who are not. However, to our knowledge such studies are lacking. Conducting such a study prospectively would be problematic as undertreatment of *A. baumannii* infections has been associated with higher mortality [113, 114]. Furthermore, the decision of whether to cover *A. baumannii* in polymicrobial infections is complicated by potential co-operative interactions with co-pathogens [115-117]. Additionally, identifying *Acinetobacter* to the species level is important to account for differential impact on mortality of different species [118, 119].

Based on the data of this review from studies with >50% carbapenem resistance in ABC infections, assuming a mortality OR of 0.62 (Supplement, Section 6.2.2.4), a polymicrobial proportion of 27% (Figure 2) and 28-day mortality of 53% in monomicrobial infections (Supplement, Section 11), a study would

require a sample size of 747 patients with ABC infection to achieve 80% power to detect a difference in overall mortality of this magnitude while retaining a 5% Type I error rate (Fleiss method with continuity correction [120]). This may explain the high p-values for the association between polymicrobial infection and 28/30-day mortality in most of the reviewed studies that had much smaller sample sizes. However, considering the possibility of differential effects of different polymicrobial combinations on mortality, smaller study samples may be sufficient for specific polymicrobial combinations.

Finally, a limitation of our study is the lack of a-priori registration of the review protocol. Nevertheless, we believe we provide an unbiased synthesis and interpretation of the available literature that highlights all the limitations and assesses the quality of the available evidence using the GRADE approach. Furthermore, necessary subgroup analyses and meta-regressions were conducted, several time-points for mortality were compared, and inconsistencies were reported. Lastly, the indirectness of our hypothesis that the lower mortality in polymicrobial infections may reflect a non-pathogenic role of *A. baumannii* in at least some polymicrobial infections is acknowledged.

Conclusion

Polymicrobial ABC infection is common in both pulmonary and bloodstream infections and associated with lower 30-day mortality that may reflect a non-pathogenic role of ABC in some polymicrobial infections. However, whether withholding antimicrobial coverage of ABC in selected polymicrobial infections is safe remains unknown. In light of the high risk of bias, low level of evidence and high heterogeneity identified in this review, more detailed comparisons between patients with polymicrobial and those with monomicrobial ABC infections are required, including stratified analysis by type of co-isolates and site of infection. Moreover, there is evident need for clear definition of polymicrobial infection in future studies, even when the study protocol requires exclusion of these infections.

Transparency declaration

Conflicts of interest: None

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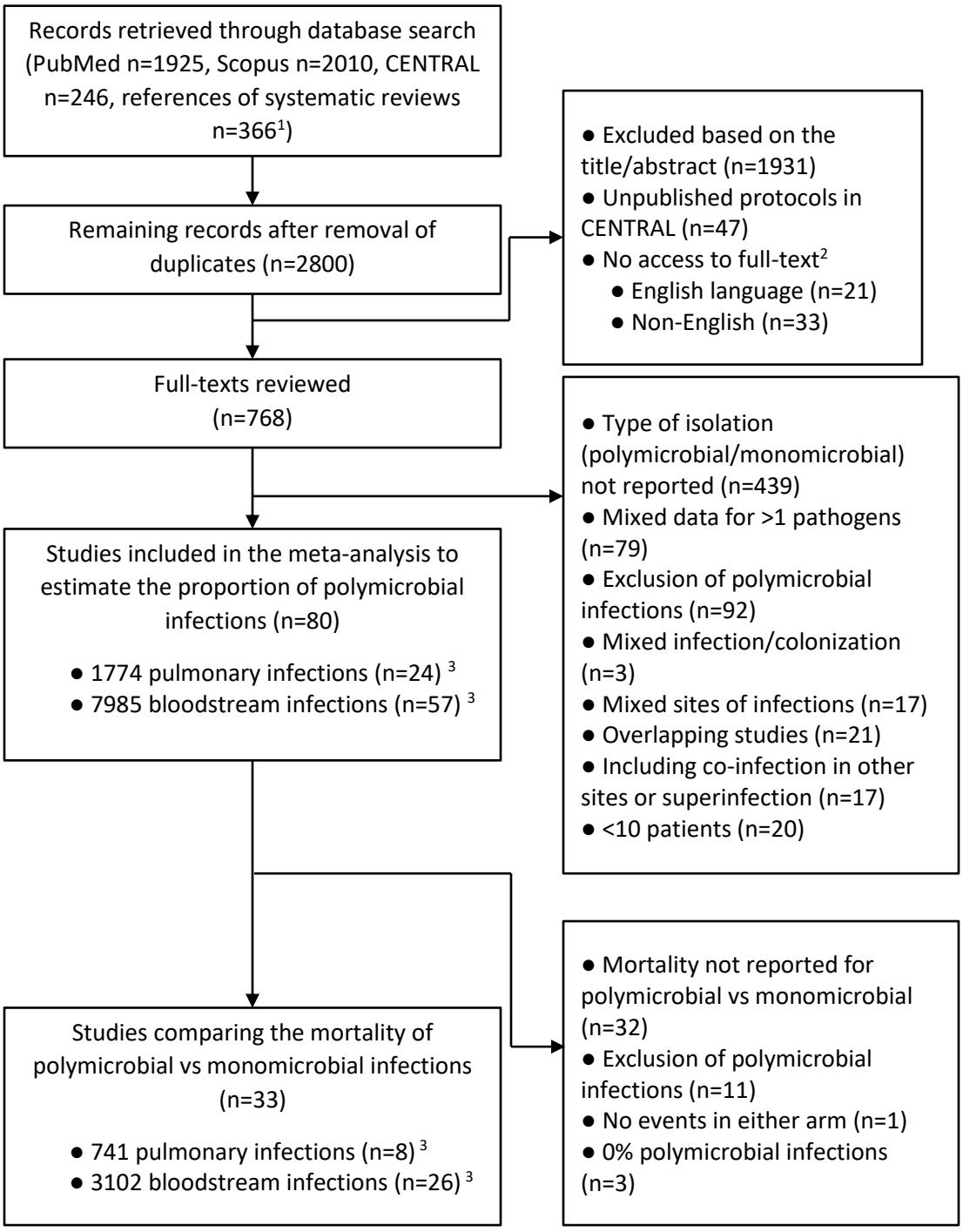
Figure 1: Flowchart of the review



[1] See Supplementary material Section 2.

[2] The list of articles without full-text access are available in the Supplementary Material (Section 3).

[3] In one study data were available for both bloodstream and pulmonary infections [3]

Figure 2; Forest plot for the proportion of polymicrobial isolations in *Acinetobacter baumannii* complex -implicated pulmonary and bloodstream infections

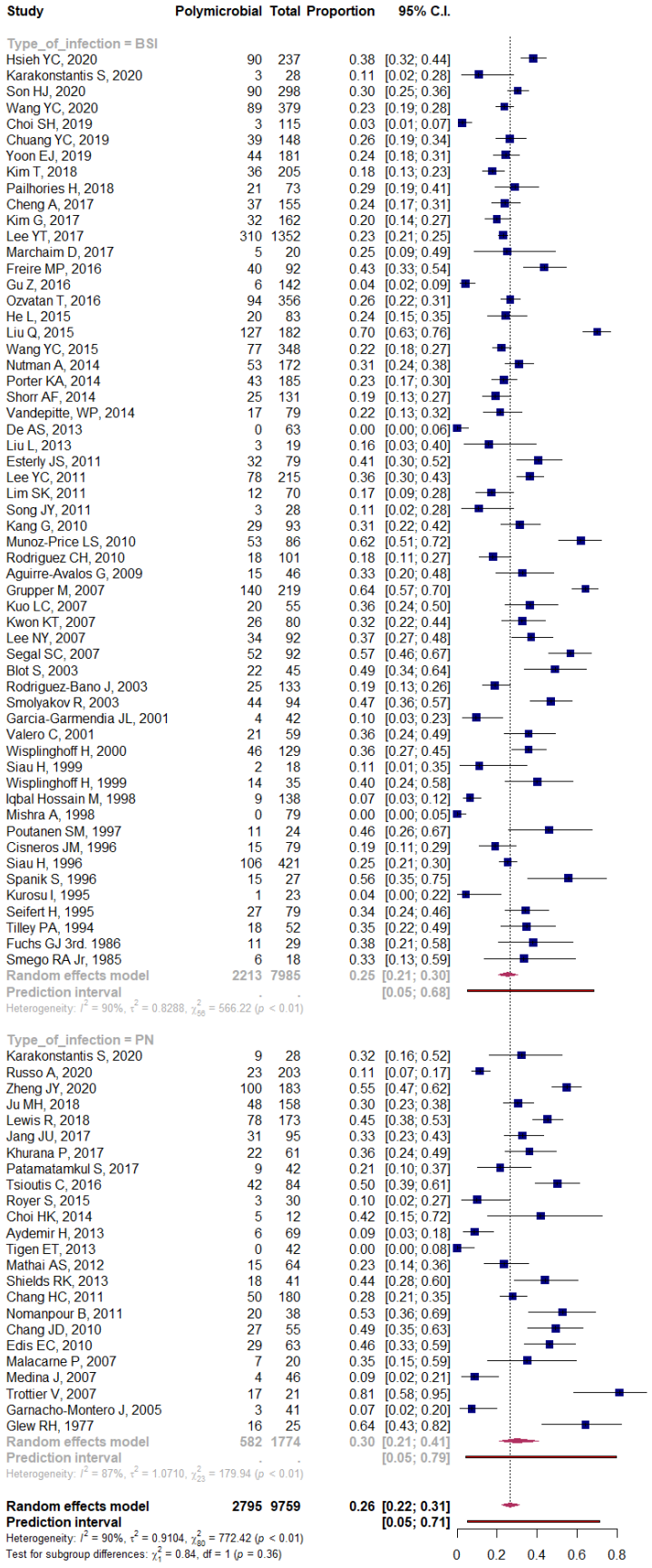


Figure 3: Forest plot for the meta-analysis of the 28/30-day mortality associated with polymicrobial (vs monomicrobial) infection by *Acinetobacter baumannii* complex

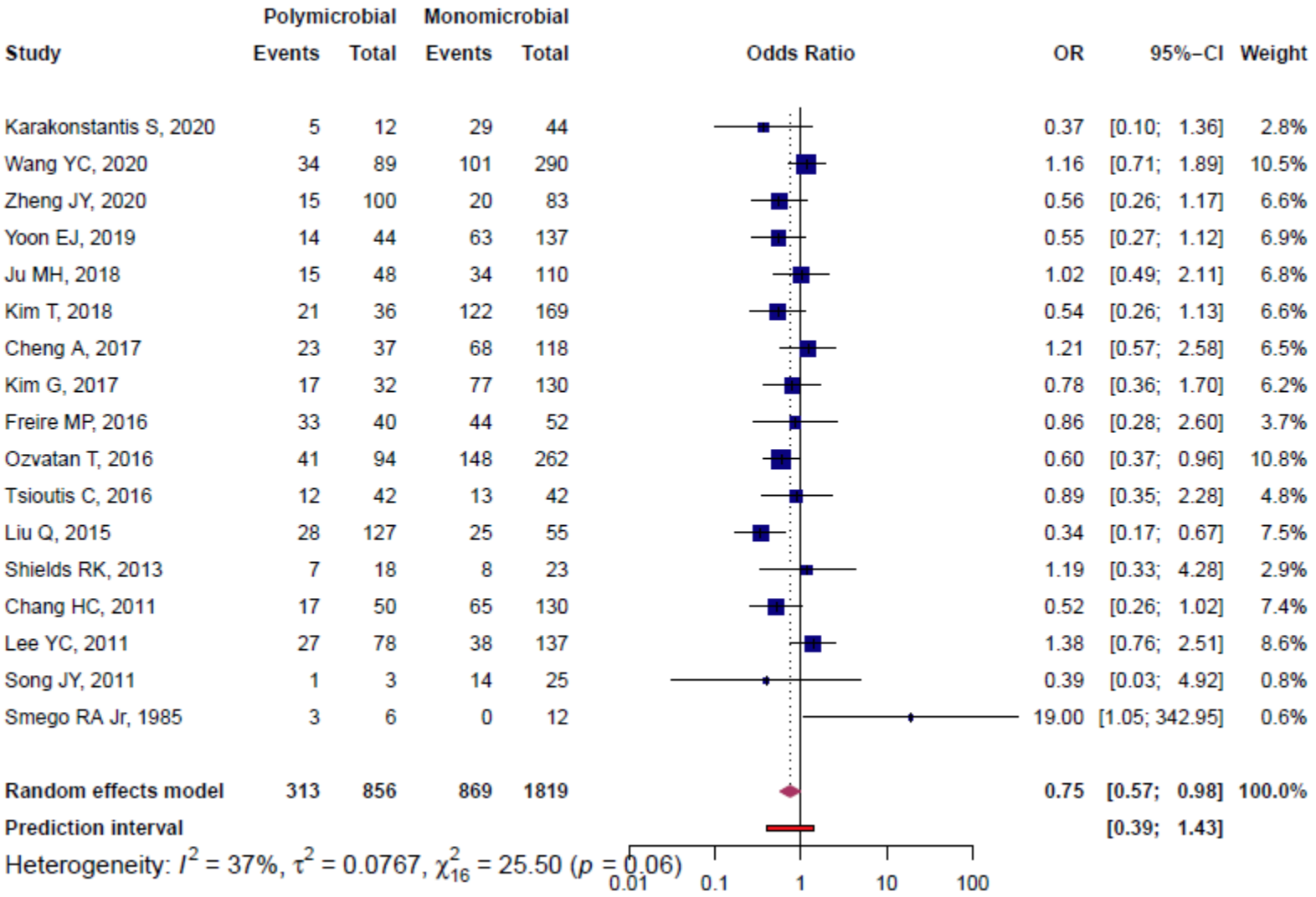
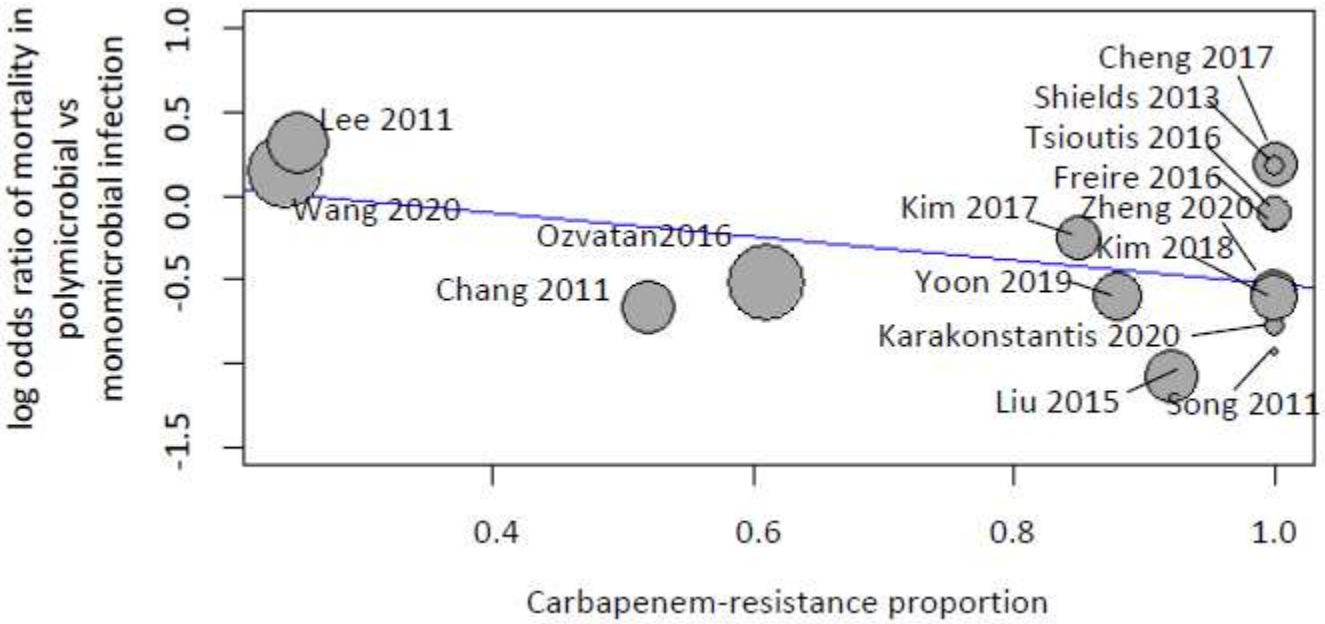


Figure 4: Bubble plot of the association between carbapenem resistance and the 28/30-day mortality odds ratio in *Acinetobacter baumannii* complex pulmonary and bloodstream infections



R2 (amount of heterogeneity accounted for): 60%

I2 (residual heterogeneity): 17%

Moderator test: p=0.062