

# Co-isolates of *Acinetobacter baumannii* complex in polymicrobial infections: a meta-analysis

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## Abstract

**Background.** *Acinetobacter baumannii* complex (ABC) infections are commonly polymicrobial. Examining which pathogens are most commonly co-isolated with ABC is an important first step for assessing disease potential due to pathogen-pathogen interactions.

**Methods.** Based on a systematic search of PubMed, Scopus and CENTRAL, we estimated percent proportions of co-isolates in polymicrobial pulmonary and bloodstream ABC infections using random-effects meta-analysis.

**Results.** Twenty-eight eligible studies were analysed reporting 575 polymicrobial bloodstream and 290 polymicrobial pulmonary infections. Common co-isolates in pulmonary infections were *P. aeruginosa* (36%, 95% CI 24–49%, I<sup>2</sup> 71%), *S. aureus* (28%, 95% CI 19–38%, I<sup>2</sup> 44%) and *Klebsiella* spp. (11%, 95% CI 6–20%, I<sup>2</sup> 56%), while the prevalence of other co-pathogens did not exceed 5%. Most common co-isolates in bloodstream infections were coagulase-negative *Staphylococci* (21%, 95% CI 12–34%, I<sup>2</sup> 84%), *Enterococci* (15%, 95% CI 9–26%, I<sup>2</sup> 73%), *P. aeruginosa* (12%, 95% CI 6–22%, I<sup>2</sup> 74%), *Klebsiella* spp. (10%, 95% CI 6–16%, I<sup>2</sup> 42%), *Enterobacter* spp. (10%, 95% CI 6–16%, I<sup>2</sup> 38%) and *S. aureus* (8%, 95% CI 4–15%, I<sup>2</sup> 58%).

**Conclusion.** The common co-isolation of certain pathogens (especially *P. aeruginosa*) with ABC suggests potential beneficial between-pathogen interactions, which may have treatment implications for polymicrobial infections and requires further study.

## INTRODUCTION

According to a recent systematic review of pulmonary and bloodstream infections by *Acinetobacter baumannii* complex (ABC), one out of every three to five such infections are polymicrobial [1]. The role of *Acinetobacter* in polymicrobial infection (pathogen vs bystander) is difficult to elucidate. Some studies [2, 3] and a meta-analysis [1] have found lower mortality in polymicrobial (vs monomicrobial) ABC infections. This has raised the hypothesis that *A. baumannii* may be an innocent bystander in some polymicrobial infections and some other co-isolate, which may be more susceptible to antibiotics, might represent the true infecting pathogen [1, 2, 4]. This is contrary to the findings of a recent study reporting higher mortality in polymicrobial (vs monomicrobial) *A. baumannii* bacteremia associated with Gram-negative co-pathogens but potentially lower mortality in polymicrobial (vs monomicrobial) bacteremia associated with Gram-positive co-pathogens [5]. The later study highlights that polymicrobial ABC infections are heterogeneous and different polymicrobial combinations may have a different impact on mortality.

To complicate matters further, *A. baumannii* has been shown to co-operate with other pathogens. For example, extracellularly released carbapenemases by *A. baumannii* may protect carbapenem-susceptible *Enterobacteriales* or *Pseudomonas aeruginosa* [6] and methicillin-susceptible *S. aureus* [7]. Other examples of beneficial interactions of *A. baumannii* with other pathogens include enhanced biofilm formation by quorum based communication with *P. aeruginosa* [8] and potential facilitation of *A. baumannii* colonization and subsequent infection by *Candida* colonization [9].

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**Keywords:** Acinetobacter; polymicrobial; *Pseudomonas*; pneumonia; bacteremia.

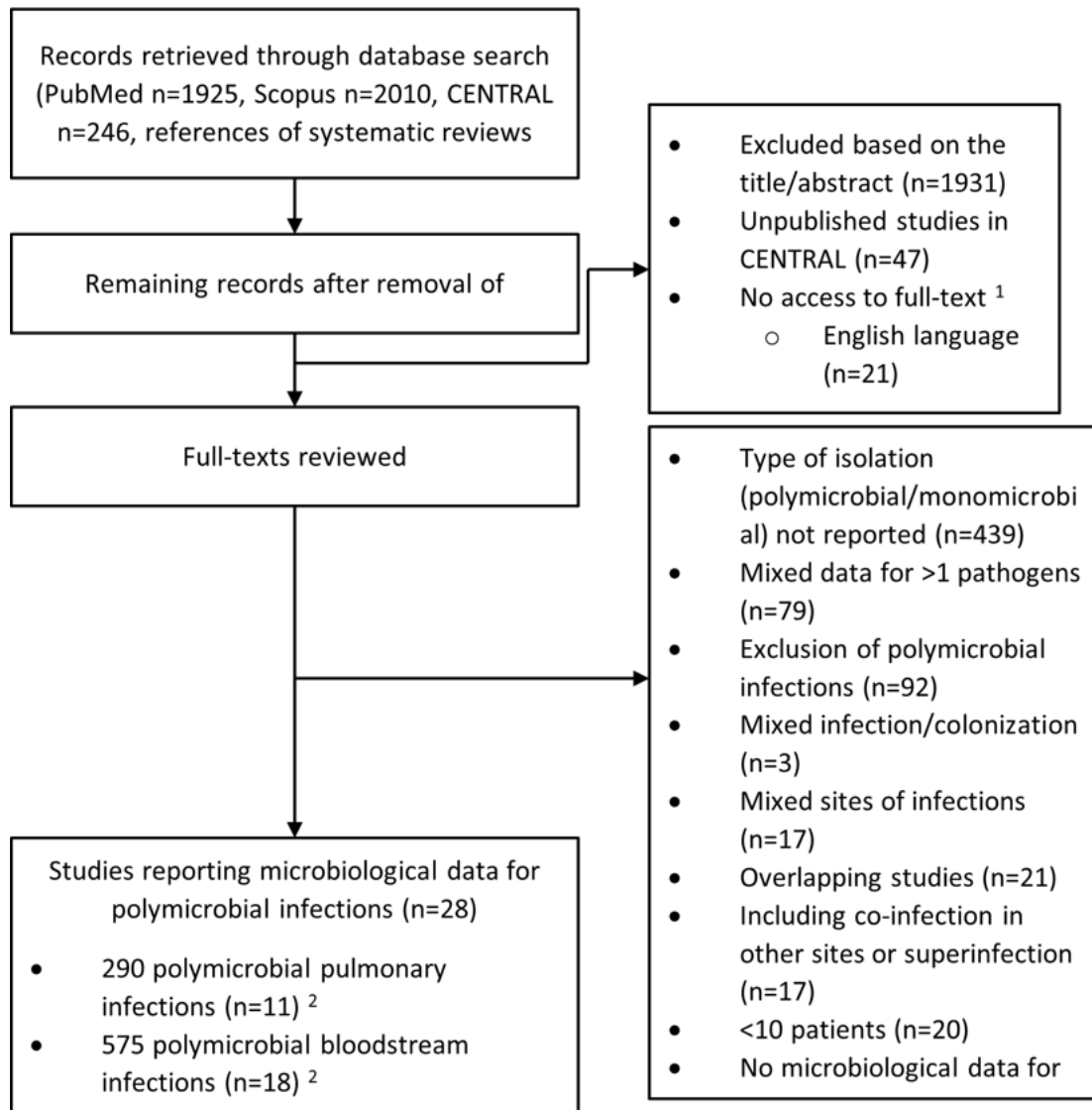
**Abbreviations:** AB, *Acinetobacter baumannii*; ABC, *Acinetobacter baumannii* complex; CENTRAL, cochrane central register of controlled trials; CoN-S, coagulase-negative *Staphylococci*.

Supplementary material is available with the online version of this article.

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**Fig. 1.** Flow-chart of the review <sup>1</sup> See Supplementary Material Section two for the list of studies without full-text access <sup>2</sup> One study reported data for both pulmonary and bloodstream infections.

Considering these interactions, it is of interest to evaluate which microorganisms are most frequently co-isolated from the same site of infection with ABC. We therefore estimated the percent distribution of co-isolates by meta-analysing microbiology data for the subgroup of polymicrobial ABC infections retrieved in our recent systematic review [1]. To the best of our knowledge this is the first systematic review and meta-analysis assessing co-isolates of *A. baumannii* infections.

## METHODS

### Search strategy, eligibility criteria and data extraction

The present study is based on additional data collected from a prior systematic review, which is described in full details elsewhere [1]. Briefly, a systematic search was conducted in PubMed, Scopus and the Cochrane Central Register of Controlled Trials (CENTRAL) for studies reporting ABC pulmonary and bloodstream infections, from inception to 06 January 2021. The search strategy is described in the Supplement (Section 1), available in the online version of this article. No language restriction was applied. Relevant full-text articles written in languages other than English were translated with Google Translate. Eligible for the current review was any study reporting the microorganisms associated with polymicrobial pulmonary or bloodstream infections involving ABC. Studies reporting exclusively infections by *Acinetobacter* spp. not belonging to the ABC complex were excluded. Studies that included co-infection or super-infection among polymicrobial infections were excluded from analysis. The literature

**Table 1.** Summary characteristics of reviewed studies

	No. of studies (%)	No. of polymicrobial infections (%)
Total reviewed	28 (100%)	853 (100%)
<b>Data collection</b>		
Retrospective	22 (79%)	728 (84%)
Prospective	6 (21%)	137 (16%)
<b>Design</b>		
Single centre	21 (75%)	665 (77%)
Multi-centre	7 (25%)	200 (23%)
<b>Publication period</b>		
2016–2020	5 (18%)	286 (33%)
2011–2015	6 (21%)	240 (28%)
2006–2010	3 (11%)	36 (4%)
2001–2005	3 (11%)	46 (5%)
1996–2000	5 (18%)	178 (21%)
<1996	6 (21%)	79 (9%)
<b>Polymicrobial definition- Site</b>		
Same site	26 (93%)	799 (92%)
Unspecified	2 (7%)	66 (8%)
<b>Polymicrobial definition- Timing</b>		
Same culture	7 (25%)	69 (8%)
Within 1–2 days	2 (7%)	36 (4%)
Same infection episode	2 (7%)	189 (22%)
Unspecified	17 (61%)	571 (66%)
<b>Non-etiologic co-isolates</b>		
Excluded	1 (3.5%)	89 (10%)
Included	1 (3.5%)	12 (1%)
Unspecified	26 (93%)	764 (88%)
<b>Species</b>		
AB	3 (11%)	146 (17%)
ABC	12 (43%)	492 (57%)
Unclear if AB or ABC	5 (18%)	110 (13%)
<i>Acinetobacter</i> spp.	8 (29%)	117 (14%)
<b>WHO region</b>		
Western pacific	11 (39%)	585 (68%)
Americas	9 (32%)	151 (18%)
Europe	6 (21%)	100 (12%)
Eastern Mediterranean	1 (3.5%)	20 (2%)
Southeast Asia	1 (3.5%)	9 (1%)
<b>Site of infection</b>		
Pulmonary	11	290
Bloodstream	18	575

AB, *Acinetobacter baumannii*; ABC, *Acinetobacter baumannii* complex.

**Table 2.** Co-isolates in polymicrobial pulmonary infections

	No. of studies*	Pooled proportion of co-isolate	95% confidence interval	I <sup>2</sup>
<b>Gram-positive</b>	7	32%	15–54%	60%
<i>Staphylococci</i>	8	27%	15–44%	49%
<i>S. aureus</i>	10	28%	19–38%	44%
CoN-S	8	0%	0–85%	86%
<i>Enterococci/Streptococci</i>	8	5%	2–15%	5%
<i>Enterococci</i>	8	0%	0–74%	78%
<i>Streptococci</i>	8	2%	1–8%	0%
Other Gram-positive	9	0%	0–100%	92%
<b>Gram-negative</b>	7	60%	31–83%	75%
<i>P. aeruginosa</i>	11	36%	24–49%	71%
<i>Klebsiella</i> spp.	11	11%	6–20%	56%
<i>S. maltophilia</i>	10	5%	2–10%	18%
<i>E. coli</i>	9	3%	1–6%	0%
<i>Enterobacter</i> spp.	8	4%	1–14%	37%
<i>Morganellaceae</i>	8	5%	2–12%	0%
<i>S. marcescens</i>	8	4%	1–18%	48%
Other Gram-negative	7	6%	1–27%	65%
<b>Candida spp.</b>	8	2%	1–8%	0%

\*Note that the set of studies available for meta-analysis for each co-isolate or group of co-isolates varied slightly because not all studies reported data for all pathogens (for example some studies provide data about *S. aureus* but not about Gram-positive co-isolates in total). Furthermore, more than one co-isolate was found in some polymicrobial infections but microbiological data about the co-isolate combinations was not reported in most studies. The respective forest plots are available in the Supplement (Section 3).  
CoN-S, coagulase-negative *Staphylococci*.

search, screening for relevant studies and data extraction were conducted by the first author. Accuracy of the extracted data was validated by a second author.

## Statistical analysis

The proportion of occurrence of ABC co-isolates in each study was defined as the ratio of the number of polymicrobial infections associated with the co-isolate over the total number of polymicrobial infections. Between-study heterogeneity was assessed with the I<sup>2</sup> statistic. As we anticipated considerable heterogeneity, we pooled the proportions of co-isolates across studies using a random-effects (random intercept) logistic regression model on logit-transformed proportions [10]. Between-study variance ( $\tau^2$ ) was estimated with the maximum-likelihood method. Confidence intervals (95% CI) for pooled proportions were adjusted with the Hartung-Knapp method [11]. The *metaprop* function of the *meta* package in R was used for these purposes [12].

## RESULTS

### Study selection and study characteristics

The flow chart of the review is depicted in Fig. 1. Co-isolates of ABC in polymicrobial infections were reported in 28 studies ( $n=865$  infections) [2, 5, 13–38], of which 11 provided data for polymicrobial pulmonary infections ( $n=290$ ) and 18 provided data for polymicrobial bloodstream infections ( $n=575$ ). Main characteristics of retrieved studies are summarized in Table 1.

### Microorganisms in polymicrobial pulmonary infections

Pooled proportions for ABC co-isolates found in polymicrobial pulmonary infections are reported in Table 2 and the respective forest plots are available in the Supplement (Section 3). Overall, 32% (95% CI 15–45%, I<sup>2</sup> 60%) of the infections were associated with Gram-positive bacteria and 60% (95% CI 31–83%, I<sup>2</sup> 75%) with Gram-negative bacteria. The most common co-isolates of

**Table 3.** Co-isolates in polymicrobial bloodstream infections

	No. of studies*	Pooled proportion of co-isolate	95% confidence interval	I <sup>2</sup>
<b>Gram-positive</b>	11	53%	39–66%	67%
<i>Staphylococci</i>	12	28%	14–48%	83%
CoN-S	16	21%	12–34%	84%
<i>S. aureus</i>	14	8%	4–15%	58%
<i>Enterococci/Streptococci</i>	15	16%	10–26%	67%
<i>Enterococci</i>	15	15%	9–26%	73%
<i>Streptococci</i>	13	0%	0–10%	70%
Other Gram-positive	14	1%	0–11%	70%
<b>Gram-negative</b>	11	56%	42–69%	71%
<i>P. aeruginosa</i>	15	12%	6–22%	74%
<i>Klebsiella</i> spp.	14	10%	6–16%	42%
<i>S. maltophilia</i>	14	3%	1–8%	52%
<i>E. coli</i>	14	6%	4–9%	0%
<i>Enterobacter</i> spp.	14	10%	6–16%	38%
Morganellaceae	13	1%	0–3%	0%
<i>S. marcescens</i>	13	0%	0–3%	0%
Other Gram-negative	13	5%	2–14%	64%
<b>Candida spp.</b>	14	5%	3–15%	23%

\*Note that the set of studies available for meta-analysis for each co-isolate or group of co-isolates varied slightly because not all studies reported data for all pathogens (for example some studies provide data about *S. aureus* but not about Gram-positive co-isolates in total). Furthermore, more than one co-isolate was found in some polymicrobial infections but microbiological data about the co-isolate combinations was not reported in most studies. The respective forest plots are available in the Supplement (Section 3).  
CoN-S, coagulase-negative *Staphylococci*.

ABC were *P. aeruginosa* (36%, 95% CI 24–49%, I<sup>2</sup> 71%), *S. aureus* (28%, 95% CI 19–38%, I<sup>2</sup> 44%) and *Klebsiella* spp. (11%, 95% CI 6–20%, I<sup>2</sup> 56%). The pooled proportion of *Candida* spp. co-isolation was 2% (1–8%, I<sup>2</sup> 0%). More than one co-isolate was found in some polymicrobial infections but microbiological data about the co-isolate combinations was not reported in most studies.

### Microorganisms in polymicrobial bloodstream infections

Co-isolates of ABC polymicrobial bloodstream infections are reported in Table 3 and the respective forest plots are available in the Supplement (Section 4). Overall, 53% (95% CI 39–66%, I<sup>2</sup> 67%) of the infections were associated with Gram-positive bacteria and 56% (95% CI 42–69%, I<sup>2</sup> 71%) with Gram-negative bacteria. The most common co-isolates included coagulase-negative *Staphylococci* (21%, 95% CI 12–34%, I<sup>2</sup> 84%), *Enterococci* (15%, 95% CI 9–26%, I<sup>2</sup> 73%), *P. aeruginosa* (12%, 95% CI 6–22%, I<sup>2</sup> 74%), *Klebsiella* spp. (10%, 95% CI 6–16%, I<sup>2</sup> 42%), *Enterobacter* spp. (10%, 95% CI 6–16%, I<sup>2</sup> 38%) and *S. aureus* (8%, 95% CI 4–15%, I<sup>2</sup> 58%). More than one co-isolate was found in some polymicrobial infections but microbiological data about the co-isolate combinations was not reported in most studies.

## DISCUSSION

A variety of pathogens have been co-isolated with ABC from the same site of infection. *P. aeruginosa* was the most common co-pathogen representing about a third of polymicrobial pulmonary ABC infections and about a tenth of polymicrobial bloodstream infections. Other common co-pathogens were *S. aureus*, *K. pneumoniae* and other *Enterobacterales*. Despite beneficial interactions between *Candida* and *Acinetobacter* spp. [9], *Candida* co-isolation in polymicrobial *Acinetobacter* infections was uncommon. However, it is unclear if the low percentage of *Candida* co-isolation is true or reflects a lack of reporting of *Candida* as a co-isolate.

Whether mortality differs in polymicrobial (vs monomicrobial) infections remains unclear due to limitations of the available evidence [1]. Mortality depending on the type of co-isolate was reported only in six studies [5, 13, 14, 17, 18, 20], and the data were too limited and too heterogeneous (e.g. different time-points for mortality) to allow a meaningful meta-analysis (Supplement, Sections 5–6). Furthermore, more than a single co-isolate were found in some polymicrobial infections, which produces a large number of microorganism combinations. Finally, studies providing both mortality data and the proportion of each co-isolate in polymicrobial infections were too few (<10) to allow meaningful meta-regression analyses [1].

Our review has several limitations. Firstly, detailed data about the subset of patients with polymicrobial infections were not available (a detailed description of polymicrobial infections was available in only one study [5]). Therefore, we could not retrieve data regarding the primary site infection or microbiological isolates from the primary site of infection in polymicrobial bloodstream infections. Furthermore, whether the frequent co-isolation of *A. baumannii* with certain pathogens reflects potential beneficial interactions with these pathogens or simply reflects the epidemiology of these pathogens and random co-isolation is unclear. Finally, the lack of a clear definition for polymicrobial infection in many studies is another important limitation of the available literature [1].

*A. baumannii* is now recognized as an important pathogen with high attributable mortality [13, 39], but differentiation of *Acinetobacter* infection from colonization remains problematic. However, the possibility of beneficial interactions between *A. baumannii* and other pathogens suggests that it may be prudent to cover *A. baumannii* with antimicrobial therapy even when other microorganisms are deemed to represent the true pathogen in polymicrobial infections. The best way to address this would be to compare the outcome of polymicrobial ABC infections of patients receiving antimicrobial therapy covering both ABC and co-pathogens compared to patients receiving antimicrobial therapy covering only the co-pathogens. To our knowledge such studies are lacking. Conducting such a study using randomization would be problematic because under-treatment of *A. baumannii* infection has been associated with higher mortality [40]. Nevertheless, it may be possible to address this question in observational studies of polymicrobial ABC infections.

## Conclusion

*Acinetobacter* infections are commonly polymicrobial. Certain pathogens, especially *P. aeruginosa*, are common in polymicrobial *Acinetobacter* infections. Whether this is explained by chance alone or reflects positive interactions between these pathogens remains unclear and requires further study because of potential treatment implications.

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## Author contributions

Conceptualization: S.K. Methodology: S.K., E.I.K. Screening of the literature; S.K. Data extraction: S.K., P.I. Statistical analysis: S.K., E.I.K. Writing - original draft: S.K., E.I.K. Writing - review and editing: S.K., E.I.K., P.I. All authors have approved the final version of the manuscript.

## Conflicts of interest

The authors declare that there are no conflicts of interest.

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