Commentary

# Attributable mortality of *Acinetobacter baumannii*: no longer a controversial issue

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## Abstract

There has been controversy regarding the mortality directly attributed to *Acinetobacter baumannii* infections. Data from six case–control studies have been recently added to the literature regarding the attributable mortality of *A. baumannii* infections during the past months. The information from these studies, added to the previous knowledge on this issue, provides evidence that *A. baumannii* infections are indeed associated with increased mortality. In addition, there is relevant evidence from studies examining the effect of inappropriate treatment on mortality; specifically, inappropriate treatment of *A. baumannii* infections has been associated with excess mortality. We believe that the accumulated data suggest that attributable mortality due to *A. baumannii* infections should no longer be a controversial issue. The efforts of the scientific community interested in this pathogen should therefore be directed to the development and introduction of new antibiotics effective against multidrug-resistant and pandrug-resistant *A. baumannii* as well as the implementation of infection control measures that may help us in the control of the increasing problem of *A. baumannii* infections.

Infections due to *Acinetobacter baumannii* have been frequently considered by clinicians and researchers not to be associated with considerable mortality [1]. Indeed, *A. baumannii* has been placed in the list of low-virulence pathogens [2]. These beliefs have generated relative widespread beliefs among members of the medical community that this microorganism is not a cause of considerable mortality in hospitalized patients, and have generated controversy on the issue of attributable mortality of *A. baumannii* infections [1,3]. We recently performed a systematic review of the literature of cohort and case–control studies that focused on the issue [4]. The reviewed data suggest that infection with *A. baumannii* is associated with considerable mortality. In addition, we provided data regarding the impact of inappropriate empirical treatment of *A. baumannii* infections [5].

During the first 3 months of 2007, four new studies were added to the relevant literature. Specifically, investigators from the United States of America [6], Israel [7], Australia [8] and Korea [9] have provided their findings regarding the effect of *A. baumannii* infections in patients treated in the intensive care unit setting and also on medical and surgical wards. Another recent study from Israel compared *A. baumannii* bacteremia with *Klebsiella pneumoniae* bacteremia [10]. We summarize the findings of these five newer studies in Table 1.

The result of the main analysis of the latter study showed that *A. baumannii* remained significantly associated with mortality after adjustment for other important risk factors was performed [10]. Subgroup analyses in the same study again confirmed the association of *A. baumannii* with increased mortality in those patients not mechanically ventilated in the 30 days prior to bacteremia (multivariate analysis: odds ratio = 3.98, 95% confidence interval = 1.25–12.62) and in those patients not presenting with septic shock (odds ratio = 4.62, 95% confidence interval = 1.74–12.22).

In addition, in a recent letter to the editor, the summary findings of an older case–control study was reported that compared patients who were colonized or infected with multidrug-resistant *A. baumannii* with patients who were colonized or infected with multidrug-resistant *Pseudomonas aeruginosa*. Increased mortality was noted in the *A. baumannii* group (a statistically significantly result), even after adjusting for the stay in the intensive care unit [11].

Added to the findings of the previously available studies, we believe that these new data clearly show that infection of *A. baumannii* is associated with considerable mortality, even after adjustment for important potential confounders such as disease severity and the effect of the empirical antimicrobial treatment. While one could theoretically always argue that a specific risk factor may not have been included in the matching process of case–control and cohort studies (and thus differences in mortality may be attributed to this particular

**Table 1**

**Comparison of patients with *Acinetobacter baumannii* (AB) infections with matched controls**

| | | | | | Infection | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Mortality | | | | Length of ICU stay | | |
| Reference | Site of infection, patients and setting | Cases | Controls | Matching of controls to cases | Cases | Controls | Attributable mortality | *P* value/ odds ratio (95% CI) | Cases (days) | Controls | *P* value/ odds ratio (95% CI) |
| Sunenshine and colleagues, 2007 [6] | MDR *Acinetobacter* spp. infections in two tertiary care hospitals in Baltimore, USA | 96 patients with MDR *Acinetobacter* infection | 91 patients with susceptible *Acinetobacter* infection (control group 1) or 89 uninfected patients (control group 2) | For control group 1: (1) similar exposure time (preinfection length of stay within 5% of matched reference), (2) similar institution | 26% | 17.6% | 8.4% | 0.21*/2.6** (0.3–26.1) | 13.3 | 6.7 | 0.04*/2.1** (1.0–4.3) |
| | | | | For control group 2: (1) length of stay, (2) same ward (within 30 days) | 26% | 11.2% | 14.8% | <0.01*/6.6** (0.4–108.3) | | 7.3 | <0.01*/4.2** (1.5–11.6) |
| Grupper and colleagues, 2007 [7] | Nosocomial AB bacteremia in patients in ICU, medical and surgical wards in Israel | 52 patients with *Acinetobacter* spp. bacteremia | 52 matched controlled patients | (1) Age (±10 years), (2) sex (±3 years), (3) primary and secondary diagnosis of ICU admission, (4) operative procedures, (5) date of admission | 29/52 (55.7%) | 10/52 (19.2%) | 36.5% (95% CI: 27–46%) | <0.001*/4.41 (1.98–9.87)** <0.001** | Mean 11.5 | Mean 6.5 | 0.06 |
| Playford and colleagues, 2007 [8] | Nosocomial acquisition of carbapenem-resistant AB in general ICU in Australia | 66 patients (34 infected and 32 colonized) with AB | 131 patients without any AB isolation | (1) Sex, (2) age (±3 years), (3) APACHE II score, (4) period at risk (date of admission to carbapenem-resistant AB acquisition (for cases) or to discharge (controls)) | Inhospital: 15/34 (44%) | Inhospital: 16/68 (24%) | 20% | 0.03/ adjusted† odds ratio: 3.9 (1.4–10.7) | Median 24 (IQR: 12.5–36.5) | Median 9 (IQR: 5–13.5) | Adjusted odds ratio: 5.8 (3.3–10.4) |
| Kwon and colleagues, 2007 [9] | Nosocomial AB bacteremia in three tertiary care hospitals in Korea (ICU and wards) | 40 patients with imipenem nonsusceptible AB bacteremia | 40 patients with imipenem-susceptible AB bacteremia | 1) Age (± 5 years) | (Cumulative: 5 days, 37.5% | Cumulative: 5 days, 12.5% | 25% | <0.05 | NR | NR | NR |
| | | | | (2) Pitt bacteremia score (±1 point) | 10 days, 50% | 10 days, 17.5% | 32.5% | <0.05 | | | |
| | | | | (3) Date of admission | 30 days, 57.5% | 30 days, 27.5% | 30% | <0.05 | | | |
| Robenshtok and colleagues, 2006 [10] | Nosocomial AB bacteremia and nosocomial *K. pneumoniae* bacteremia in a single centre in Israel | 112 patients with AB bacteremia | 90 patients with *K. pneumoniae* bacteremia | Patients with underlying conditions (comparative cohort study) | 61.6% | 38.9% | 22.7% | 0.001*/3.6 (1.5–8.39)** | NR | NR | NR |

APACHE, Acute Physiology and Chronic Health Evaluation; 95% CI, 95% confidence interval; ICU, intensive care unit; IQR, interquartile range; *K. pneumoniae*, *Klebsiella pneumoniae*; MDR, multidrug resistant; NR, not reported. *Univariate analysis. **Multivariate analysis. †Adjusted for age and admission diagnosis.

nonexamined risk factor), one has simultaneously to acknowledge the hazards of adjusting to all possible factors [12].

Someone may rightfully ask why not all relevant studies showed increased mortality of patients with *A. baumannii* infections compared with controls without such infections. There are various explanations for these apparently controversial findings. These explanations may include differences in patient populations, methodological characteristics of the studies, proportions of patients who received appropriate empirical treatment, as well as factors associated with the pathogen itself, including genetic factors that lead to differences in virulence.

If *A. baumannii* infection was not an independent contributor to increased mortality, then inappropriate treatment should not have any major effect on the outcome of patients. In an older study, mortality due to *A. baumannii* bacteremia treated with inappropriate antibiotics was 7.6% in excess (although not a statistically significant difference) compared with that of patients treated with appropriate antibiotics [13]. The finding of this study has to be interpreted considering that no excess mortality was found for any other bacteremia (possibly due to the small number of patients) except for bacteremia due to coagulase-negative Staphylococci [13]. In a study by our group, inappropriate treatment of *A. baumannii* bacteremia was associated with considerably increased (25.8%) mortality compared with that of patients treated with appropriate antibiotics – significance reached a trend ($P = 0.1$) since the total study population was small (40 patients) [5].

In the recently published study by Kwon and colleagues, a 44.5% increased mortality was noted in the group of patients with imipenem nonsusceptible *A. baumannii* bacteremia treated with inappropriate antibiotics compared with those patients with imipenem nonsusceptible *A. baumannii* bacteremia who received appropriate treatment ($P = 0.007$) [9]. Moreover, when 30-day mortality was examined in the total study population of cases and controls, a 43.7% excess mortality was noted when *A. baumannii* bacteremia was treated with inappropriate versus appropriate antibiotic therapy ($P < 0.001$) [9]. Also, in a study regarding risk factors for mortality related to nosocomial pneumonia due to various Gram-negative, Gram-positive and fungal pathogens, *A. baumannii* was the second most commonly cultured pathogen of 132 patients. In this study *A. baumannii* was significantly more predominant in nonsurvivors than in survivors (13.6% versus 5.1%, $P = 0.04$). Of the nonsurvivors, 85.9% received inappropriate therapy – inappropriate antibiotic therapy was independently associated with mortality (odds ratio = 14.5, 95% confidence interval = 5.08–41.44) in the study [14].

We believe that a fair interpretation of the available evidence, especially in light of the recently published findings, suggests that attributable mortality due to *A. baumannii* is no longer a controversial issue. The attention of the scientific community with interest in this pathogen should therefore be directed to the development and introduction of new antimicrobial agents effective against multidrug-resistant and pandrug-resistant *A. baumannii*, as well as to the implementation of infection control measures that may help control the evolving problem of *A. baumannii* infections that have taken epidemic dimensions in several parts of the word, especially in critically ill patients.

## Authors' contributions

MEF had the idea for this commentary. PIR extracted the data for the relevant studies. Both authors contributed to writing the commentary and approved its final version.

## Competing interests

The authors declare that they have no competing interests.

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