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Importance of control groups when delineating antibiotic use as a risk factor for carbapenem resistance, extreme-drug resistance, and pan-drug resistance in *Acinetobacter baumannii* and *Pseudomonas aeruginosa*: A systematic review and meta-analysis

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ABSTRACT

Background: Carbapenem-resistant (CR), extremely drug-resistant (XDR), and pan-drug-resistant (PDR) *Acinetobacter baumannii* and *Pseudomonas aeruginosa* pose a huge clinical threat. This study reviews the impact of control groups on the association of antecedent antibiotic use and the acquisition of CR/XDR/PDR *A. baumannii* and *P. aeruginosa*.

Methods: Studies investigating the role of antibiotics as a risk factor for CR/XDR/PDR *A. baumannii* and *P. aeruginosa* acquisition in adult hospitalized patients from 1950 to 2016 were identified in the databases. These were divided into two groups: antibiotic-resistant versus antibiotic-sensitive pathogens (group I); antibiotic-resistant versus no infection (group II). A random-effects model was performed.

Results: Eighty-five studies (46 *A. baumannii*, 38 *P. aeruginosa*, and one of both) involving 22 396 patients were included. CR was investigated in 60 studies, XDR in 20 studies, and PDR in two studies. Prior antibiotic exposure was associated with significant acquisition of CR/XDR/PDR *A. baumannii* and *P. aeruginosa* in both groups I and II ($p < 0.05$). Antibiotic classes implicated in both groups included aminoglycosides, carbapenems, glycopeptides, and penicillins. Cephalosporin use was not associated with resistance in either group. Fluoroquinolone exposure was only associated with resistance in group I but not group II.

Conclusions: Control groups play an important role in determining the magnitudes of risk estimates for risk factor studies, hence careful selection is necessary. Antibiotic exposure increases the acquisition of highly resistant *A. baumannii* and *P. aeruginosa*, thus appropriate antibiotic use is imperative.

Introduction

Pseudomonas aeruginosa and *Acinetobacter baumannii* are important pathogens frequently implicated in nosocomial infections, due to their ability to survive under a wide range of environmental conditions (Fournier and Richet, 2006). These pathogens develop mechanisms of antibiotic resistance easily. This results in limited therapeutic options available, which is then associated with increased hospitalization and significant morbidity and mortality (Garcia-Garmendia et al., 1999; Carmeli et al., 1999a; Obritsch et al., 2005).

There has been an increasing incidence of multidrug-resistant (MDR) *P. aeruginosa* and *A. baumannii* worldwide. In the most recent data published by the National Healthcare Safety Network in 2013 (Sievert et al., 2013), both multidrug resistance and carbapenem resistance were reported in more than 60% of *A. baumannii* among most hospital-acquired infections in the USA. With this rising emergence, many studies have been conducted to elucidate risk factors associated with the acquisition of MDR *P. aeruginosa* and *A. baumannii*, in the hope of devising strategies to minimize their spread. Common risk factors include mechanical ventilation, central venous catheterization, intensive care stay, and recent surgery or invasive procedures (Fournier and Richet, 2006;

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Manchanda et al., 2010; Trouillet et al., 1998), and prior antibiotic use was observed to be the most common risk factor for the acquisition of MDR *P. aeruginosa* and *A. baumannii* in a systematic review by Falagas and Kopterides (2006). Antibiotic exposure predisposes the patient to colonization with these pathogens, and may select for efflux pump cross-resistance, for instance with the use of fluoroquinolones and aminoglycosides (Aubert et al., 1992; Aires et al., 1999). Other resistance mechanisms in *P. aeruginosa* and *A. baumannii* include the production of extended-spectrum beta-lactamases and carbapenemases, and the presence of porins (Livermore, 2001; Quale et al., 2003).

The high prevalence of MDR *P. aeruginosa* and *A. baumannii* has led to the increased use of agents like carbapenems, tigecycline, and colistin. Studies by Furtado et al. and Baran et al. have reported the use of carbapenems to be a risk factor for imipenem-resistant *P. aeruginosa* and *A. baumannii* (Furtado et al., 2009; Baran et al., 2008). This results in the emergence of carbapenem-resistant (CR), extreme-drug resistant and not extremely-drug resistant (PDR) *P. aeruginosa* and *A. baumannii* (Peleg et al., 2007; Mentzelopoulos et al., 2007). These are of concern, as carbapenems are usually the first-line drugs of choice for the treatment of MDR *P. aeruginosa* and *A. baumannii*. With this increase in incidence of organisms like CR pathogens, the use of carbapenems will be futile.

Multiple small studies have been conducted to investigate the impact of prior exposure to other antibiotic classes on the acquisition of different MDR pathogens. For example, Lautenbach et al. and Paramythiotou et al. concluded that prior fluoroquinolone treatment is associated with the acquisition of MDR *P. aeruginosa* (Lautenbach et al., 2006; Paramythiotou et al., 2004). Previous aminoglycoside administration has also been associated significantly with XDR *A. baumannii* acquisition in another study (Katsaragakis et al., 2008). However, there have been few meta-analyses investigating the overall impact of exposure to more than two specific antibiotic classes on the acquisition of CR, XDR, and PDR *P. aeruginosa* and *A. baumannii*, in particular studies looking at PDR *P. aeruginosa* and *A. baumannii*.

Furthermore, the selection of control groups in the various studies has been shown to have an impact on the outcomes of risk factor studies on the acquisition of antimicrobial resistance; namely, the inclusion of a control group of patients with antibiotic-sensitive pathogens or patients with no infection, in comparison with the resistant pathogen of interest. In a systematic review, Harris et al. (2002a) concluded that risk estimates may portray stronger associations if control patients with antibiotic-susceptible target organisms are selected. However, Lepelletier et al. (2010) proved otherwise with their study results.

The primary objective of this meta-analysis was to determine the impact of different control groups on the risk association of prior antibiotic exposure for the isolation of CR/XDR/PDR *P. aeruginosa* and *A. baumannii*: one control group with pan-susceptible *P. aeruginosa* and *A. baumannii* and the other with no infection. The secondary objectives of this meta-analysis were to identify the specific antibiotic classes that have the highest risk of the possible induction of resistance and the mechanisms of resistance.

Methods

All studies investigating the role of antibiotic exposure as a risk factor for CR/XDR/PDR *P. aeruginosa* and *A. baumannii* acquisition, published up to December 2016, were retrieved from the PubMed, Ovid @ MEDLINE, and Embase databases. The search terms used included "risk factor", "*Pseudomonas aeruginosa*", "*Acinetobacter baumannii*", and "resistance" (refer to the **Supplementary Material**). The reference lists of relevant systematic reviews were also screened to include additional studies not retrieved from the database search. Studies in English that investigated the role of antibiotic exposure as a risk factor for CR/XDR/PDR *P. aeruginosa* and *A. baumannii* acquisition (colonization or infection) in adult hospitalized patients were used as inclusion criteria. The following were exclusion criteria: non-English studies; studies in pediatric patients; studies in community and outpatient settings; and studies that investigated the role of antibiotic exposure for non CR/XDR/PDR *P. aeruginosa* and *A. baumannii*, for example MDR *P. aeruginosa* and *A. baumannii*. The quality of the studies included was assessed using the Newcastle–Ottawa scale (NOS), with a focus on selection, comparability, and outcome assessment (Wells et al., 2013). The NOS assigns a maximum of 4 points for selection, 2 points for comparability, and 3 points for exposure or outcome. A NOS score of ≥ 7 was considered to indicate a high quality study (Appendix 1). Studies were assessed by two independent researchers; in cases of disagreement, the decision regarding inclusion was reached by consensus.

Studies included were divided into two major groups: those that compared the impact of antibiotic exposure between antibiotic-resistant and antibiotic-sensitive pathogens (group I) and those comparing the impact of antibiotic exposure between patients with antibiotic-resistant pathogens and those with no infection or colonization (group II). If individual studies included both types of control groups, they were counted as two different studies. Primary and secondary outcomes were evaluated in each group.

The primary outcome evaluated was the relative risk of CR/XDR/PDR *P. aeruginosa* and *A. baumannii* acquisition between the experimental arms with and without antibiotic exposure in groups I and II. Each group was further divided into three sub-groups based on the organism: *A. baumannii*, *P. aeruginosa*, or combined *A. baumannii*/*P. aeruginosa*. The difference in impact of antibiotic exposure on the incidence of CR/XDR/PDR resistance between the three sub-groups was further evaluated. For secondary outcomes, an investigation was performed to determine whether exposure to any specific antibiotic classes was a significant risk factor for the isolation of CR, XDR, and PDR *P. aeruginosa* and *A. baumannii* in groups I and II. Resistance mechanisms were also noted.

Definitions

Definitions were adapted from the paper published by Magiorakos et al. in 2012 (Magioakos et al., 2012). Carbapenem resistance was defined as resistance of a pathogen to any carbapenem. Pan-drug resistance was defined as resistance of a pathogen to all antimicrobial agents. Extreme-drug resistance was defined as resistance of a pathogen to all but one or two antimicrobial agents.

Statistical analysis

The likelihood of primary outcomes was calculated using the odds ratio (OR) with Review Manager 5.1 (Update Software Ltd, Oxford, UK). The results of these trials were pooled using a random-effects model because of the presumed heterogeneity of the trials included. Variance between studies was indicated by the Tau-squared (Tau^2) value: the lower the value, the lower the between-study variance. The I^2 statistic quantifies the amount of variation in results across studies beyond that of chance, and I^2 values of 30–60% represent moderate heterogeneity. Significance was taken at $p < 0.05$ with a two-tailed test. To check for publication bias, funnel plots were generated; symmetry was assessed by visual inspection of the funnel plots.

Results

A total of 2648 articles were retrieved from the databases. After removing duplicates and screening study titles, 704 studies were