Journal of Hospital Infection 143 (2024) 123–139

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevier.com/locate/jhin

Review

Impact of antibiotic exposure on antibiotic-resistant *Acinetobacter baumannii* isolation in intensive care unit patients: a systematic review and meta-analysis

M.R. De Blasiis [a], A. Sciurti [a,*], V. Baccolini [a], C. Isonne [a], M. Ceparano [a], J. Iera [a,b], C. De Vito [a], C. Marzuillo [a], P. Villari [a], G. Migliara [a]

[a] *Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy*
[b] *Management and Health Laboratory, Institute of Management, Department EMbeDS, Sant'Anna School of Advanced Studies, Pisa, Italy*

ARTICLE INFO

Article history:
Received 1 September 2023
Accepted 2 November 2023
Available online 14 November 2023

Keywords:
Acinetobacter baumannii
Healthcare-associated infection
Antibacterial agents
Antibiotics
Multidrug resistance
Intensive care unit

SUMMARY

Background: *Acinetobacter baumannii* (AB) poses a significant threat to critically ill patients in intensive care units (ICUs). Although an association between antibiotic exposure and resistant AB is reported in the literature, a synthesis of evidence in ICU patients is still lacking.

Aim: To summarize the evidence on the association between prior antibiotic exposure and the occurrence of resistant AB in ICU patients.

Methods: Online databases were searched for cohort and case–control studies providing data on the association of interest. Carbapenem/multidrug-resistant AB isolation was compared with non-isolation; carbapenem/multidrug-resistant AB was compared with carbapenem/antibiotic-susceptible AB; and extensively drug-resistant AB isolation was compared with non-isolation. Each comparison was subjected to a restricted maximum likelihood random-effects meta-analysis per antibiotic class, estimating pooled ORs. Stratified meta-analyses were performed by study design, outcome type and association-measure adjustment.

Findings: Overall, 25 high-quality studies were retrieved. Meta-analyses showed that carbapenem/multidrug-resistant AB isolation was associated with previous exposure to aminoglycosides, carbapenems, third-generation cephalosporines, glycylcyclines, and nitroimidazoles. Increased risk of isolation of carbapenem/multidrug-resistant AB isolation vs carbapenem/antibiotic-susceptible AB was shown for prior exposure to aminoglycosides, antipseudomonal penicillins, carbapenems, fluoroquinolones, glycopeptides, and penicillins. Third-generation cephalosporin exposure increased the risk of extensively drug-resistant AB isolation vs non-isolation.

Conclusion: This systematic review clarifies the role of antibiotic use in antibiotic-resistant AB spread in ICUs, although for some antibiotic classes the evidence is still uncertain due to the small number of adjusted analyses, methodological and reporting

* Corresponding author. Address: Department of Public Health and Infectious Diseases, Sapienza University of Rome, Piazzale Aldo Moro 5, 00185 Rome, Italy. Tel.: +39 06 49914886; fax: +39 06 49914449.
E-mail address: antonio.sciurti@uniroma1.it (A. Sciurti).

https://doi.org/10.1016/j.jhin.2023.11.002

issues, and limited number of studies. Future studies need to be carried out with standardized methods and appropriate reporting of multivariable models.

Introduction

Healthcare-associated infections (HAIs) are the most common complications of hospital care and one of the leading causes of death in hospitalized patients [1]. Despite efforts to counteract their onset, HAIs remain a major threat for individual and public health worldwide [1—3]. Moreover, the challenges faced by healthcare systems during the COVID-19 pandemic have exacerbated the risk of HAI development, especially in intensive care units (ICUs), which already before the pandemic were among the wards with a higher HAI prevalence [4—9]. In effect, the poor clinical condition of patients who require intensive care, which may include the frequent use of invasive devices, makes it difficult to maintain a high degree of focus on infection prevention and control (IPC) practices [10]. In turn, this may lead to high rates of colonization and infection by micro-organisms with highly antibiotic-resistant profiles [11,12].

Acinetobacter baumannii (AB) is one of the major opportunistic pathogens responsible for HAIs in critically ill or debilitated ICU patients [13]. It can survive for long periods on surfaces, and it may colonize organs and systems, frequently causing HAIs such as ventilator-associated pneumonia, bloodstream infections, and urinary tract infections [14]. In addition, extensive antibiotic abuse and poor antimicrobial stewardship have led to a rapid escalation in antimicrobial resistance rates, such that more than 50% of AB isolates are multidrug resistant (MDR) [15]. The difficulty in treating these infections and the limited therapeutic options available lead to a high mortality rate among infected patients [16]. The extent of the problem is such that in 2017 the World Health Organization targeted several micro-organisms including AB by publishing guidelines to promote specific IPC practices and procedures that aim to prevent associated HAIs and to control their spread in acute healthcare facilities [17].

Over the years, a great deal of literature has been published identifying AB as an emerging cause of HAIs and emphasizing the spread of MDR strains as a consequence of high antibiotic consumption [15,18]. Indeed, epidemiological research has identified previous exposure to antibiotics as a risk factor for HAIs by MDR bacteria, including AB [18—25]. Furthermore, the widespread antibiotic usage in COVID-19 patients has led to an increase in antibiotic pressure and several outbreaks of MDR AB have been reported, especially in ICUs [18,26—28]. Although a direct relationship between antibiotic consumption and the emergence and dissemination of resistant strains of AB in ICUs has been reported, a synthesis of evidence in ICU patients is still lacking [29—31]. These patients represent a particular at-risk subgroup among hospitalized patients due to their critical condition, meaning that they may be particularly susceptible to HAIs and might suffer from specific risk factors [32]. In this systematic review and meta-analysis, we aimed to summarize the evidence on the association between prior antibiotic exposure and the occurrence of colonization or infection by antibiotic-resistant AB in ICU patients, providing a qualitative and quantitative synthesis of such evidence to support efforts to improve antibiotic use and antimicrobial stewardship.

Methods

This study was performed according to the Cochrane Handbook for systematic reviews and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [33,34]. The review protocol was registered at PROSPERO, identifier CRD42022328487. Because this study did not involve primary data collection, the protocol was not submitted for institutional review board approval.

Search strategy, study selection, and inclusion criteria

Three electronic bibliographic databases (PubMed, Scopus and Web of Science) were searched from inception to February 28th, 2023, using the following key terms, adapting the research string to fit the search criteria of each database (see Supplementary File 1): antibacterial; antimicrobial; antibiotic; carbapenem; aminoglycoside; fluoroquinolone; beta-lactam; cephalosporin; tigecycline; colistin; *Acinetobacter baumannii*.

The reference lists of retrieved articles were also searched to identify other potentially relevant studies. Duplicate articles were removed, and the title and abstract of all collected records were screened by two review authors to identify all articles that potentially met the inclusion criteria. Studies that clearly did not meet the inclusion criteria were excluded. Full texts of potentially relevant articles were retrieved and independently assessed for eligibility by two review-team members. Disagreements were resolved through discussion or by a third reviewer and the reasons for exclusion were recorded.

The review included any study that (i) included patients admitted in an ICU setting; (ii) included patients aged $\geq$18 years; (iii) had a cohort or case—control design; (iv) reported in English or Italian; (v) reported measures of association (i.e. odds ratios (ORs), risk ratios (RRs), or raw data) between antibiotic exposure and antibiotic-resistant AB infection, colonization or both, hereinafter indicated as acquisition; (vi) quantified the use of antibiotic agents and reported at least their antibiotic class.

The review excluded studies that (i) did not report a measure of association between antibiotic exposure and occurrence of antibiotic-resistant AB infection, colonization, or acquisition, or raw data; (ii) did not quantify the use of antibiotic agents; (iii) did not report at least the antibiotic class used; (iv) comprised letters, commentaries, or reviews.

Data collection and quality assessment

For each eligible study, two reviewers independently used a standardized data abstraction form to extract the following information: (i) study identification data (DOI, author, year,

country, language); (ii) study design; (iii) primary and secondary objectives of the study, (iv) target population; (v) type of ICU; (vi) outcome considered (infection, colonization, or acquisition); (vii) infection or colonization site (airways, bloodstream, urinary tract, rectum, etc.); (viii) reported antibiotic resistance pattern (carbapenem resistant, CR; imipenem resistant, IR; colistin resistant, CoR; at least multidrug resistant, MDR; at least extensively drug resistant, XDR; at least pan-drug resistant, PDR); (ix) case definition; (x) comparator/cohort definition; (xi) definition of previous exposure to antibiotic agents; (xii) antibiotic class or specific antibiotic agent, if available (data on the use of cephalosporins without specifying the generation were excluded); (xiii) measure of antibiotic exposure (dichotomous or continuous); (xiv) depending on data availability, absolute frequencies and/or association measures between antibiotic exposure and acquisition of outcome (unadjusted and/or adjusted RRs or ORs, and their 95% confidence interval); (xv) covariates included in the multivariable regression models, if available.

Two independent authors performed the quality assessment of the articles included in the systematic review using the Newcastle–Ottawa scale for case–control and cohort studies [35]. Discrepancies were resolved by consensus. Articles were considered of high quality when the total score was $\geq$7, of fair quality if the score was $\geq$5 and $<$7, and of poor quality if the score was $<$5.

Data synthesis

To account for the variety of outcome and comparator/cohort definitions used in the retrieved studies, data synthesis was performed separately for the following main comparisons: (i) studies investigating the risk of isolation of CR/MDR AB versus the non-isolation of CR/MDR AB; (ii) studies investigating the risk of isolation of CR/MDR AB versus the isolation of carbapenem-susceptible (CS) or antibiotic-susceptible (AS) AB; (iii) studies investigating the risk of isolation of XDR AB versus the non-isolation of AB. The few studies reporting other comparisons were described separately.

In the context of each comparison, a restricted maximum likelihood random-effects meta-analysis was conducted for each antibiotic class reported in at least two studies to estimate pooled ORs and their 95% confidence intervals (95% CIs) for the outcome of interest with respect to antibiotic exposure. Since the studies included were judged to have similar research questions and to be of high quality, case–control and cohort studies were analysed together [36]. When a study considered multiple outcomes in the same population, infection was considered as the outcome of interest. If a study investigated outcomes involving AB with antibiotic-specific resistance profiles (i.e. imipenem-resistant AB), it was categorized as resistant to the corresponding antibiotic class (i.e. carbapenem-resistant AB).

Moreover, if a study compared the same control group to outcomes involving AB with diverse antibiotic-resistance patterns (i.e. MDR, XDR, and PDR), these were combined into one group (i.e. as at least MDR). In addition, if a study evaluated antibiotic exposure based on different therapy duration criteria, the longest exposure was considered. Finally, when a study conducted separate comparisons in different periods, the study was divided into separate sub-analyses.

Adjusted ORs were preferentially included in the meta-analysis, if available. When they were not reported, unadjusted ORs (reported in studies or estimated from raw data) were used. The I^2 metric was used to quantify heterogeneity, which was considered statistically significant at $P<0.05$, and substantial heterogeneity was defined as $I^2 > 50\%$ [37]. For each meta-analysis including at least four analyses, stratified meta-analyses were carried out to explore the impact of relevant study characteristics, identified a priori, on the pooled OR estimates. Specifically, stratified meta-analyses were performed for (i) study design (cohort studies versus case–control studies); (ii) type of outcome (infection versus colonization versus acquisition); (iii) adjustment of association measures (adjusted versus unadjusted). For studies investigating the risk of isolation of CR/MDR AB versus the non-isolation of CR/MDR AB, a subgroup meta-analysis was performed for the inclusion or not of patients with CS/AS AB isolation in the control group.

Stratified meta-analyses were performed using the same methodology as for the primary analysis. The test for subgroup difference was used to reveal significant interactions of the stratification variable on the pooled ORs [38]. Moreover, for each meta-analysis including at least 10 analyses, the independent effect of these factors on the estimated association was investigated using multivariable meta-regression models [39]. Finally, potential publication bias was assessed by visually inspecting funnel plots and using Egger's test in

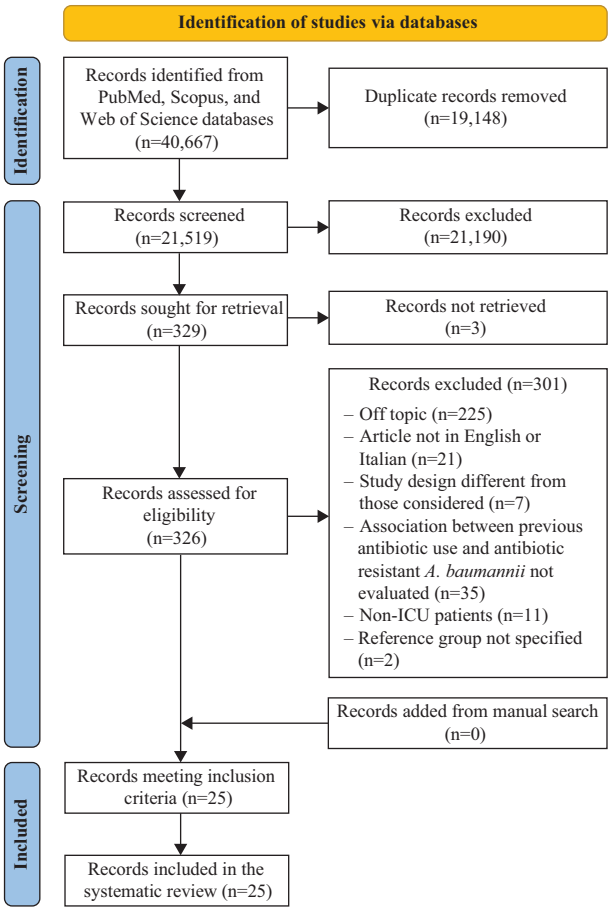


Figure 1. PRISMA flow diagram of the review process.

Table I
Characteristics of the studies included in the systemic review

First author, year	Country	Design	Setting and population	AB pattern	Definition of previous antibiotic exposure	Colonization site	Infection type	Quality assessment
Ceparano, 2022 [28]	Italy	Cohort	Mixed ICU, all patients (COVID-19 patients)	Endemic	Systemic administration for at least 48 h from admission to AB isolation or censoring, dichotomous	Any	Any	8
Munoz-Prince, 2016 [29]	USA	Cohort	Trauma ICU, all patients	Endemic	Systemic administration from admission to AB isolation or censoring, dichotomous and continuous	Rectal, respiratory tract	—	9
Zheng, 2020 [30]	China	Cohort	Unspecified ICU, ventilated patients	Endemic	Systemic administration from admission to AB isolation, dichotomous	—	VAP	8
Mantzarlis, 2020 [31]	Greece	Cohort	Mixed ICU, ventilated patients	Endemic	Systemic administration from admission to AB isolation, dichotomous and continuous	—	Any	9
Rosa, 2014 [41]	USA	Cohort	Mixed ICU, all patients	Endemic	Systemic administration from admission to environmental AB isolation, dichotomous	Rectal, respiratory tract	Any	9
Young, 2007 [42]	USA	Case—control, Matched	Surgical ICU, all patients	Outbreak	Not reported, dichotomous	—	Any	9
Gulati, 2010 [43]	USA	Case—control	Burns ICU, non-burns patients	Outbreak	Not reported, dichotomous	Any	Any	7
Husni, 1999 [44]	USA	Case—control	Medical ICU, ventilated patients	Outbreak	Not reported, dichotomous	Any	BSI/VAP	7
Katsaragakis, 2008 [45]	Greece	Cohort	Surgical ICU, all patients	Endemic	Systemic administration for at least 48 h within 14 days before AB isolation, dichotomous	—	Any	9
Apostolopoulou, 2014 [46]	Greece	Case—control, matched	Mixed ICU, ventilated patients	Endemic	Systemic administration for at least 48 h within 14 days before AB isolation or discharge, dichotomous	—	Any	9
Papakonstantinou, 2014 [47]	Greece	Cohort	Mixed ICU, ventilated patients	Endemic	Systemic administration from admission to AB isolation or censoring, dichotomous	Respiratory tract	VAP	8
Gulen, 2015 [48]	Turkey	Cohort	Medical ICU, neurology—neurosurgery ICU, all patients	Endemic	Systemic administration for at least 72 h within 30 days before AB isolation, dichotomous	—	BSI	8
Aksu Koca, 2018 [49]	Turkey	Cohort	Mixed ICU, all patients	Endemic	Not reported, dichotomous	Any	BSI/UTI/RTI	9
Mete, 2022 [50]	Turkey	Cohort	Unspecified ICU, all patients (COVID-19 patients)	Endemic	Not reported, dichotomous	—	BSI	8

Castelo Branco Fortaleza, 2013 [51]	Brazil	Cohort	Mixed ICU, all patients	Endemic	Systemic administration from admission to AB isolation or censoring, dichotomous	Any	Any	9
Romanelli, 2009 [52]	Brazil	Case—control, matched	Unspecified ICU, all patients	Outbreak	Not reported, dichotomous	Any	Any	9
Qiao, 2020 [53]	China	Case—control	Mixed ICU, all patients	Endemic	Not reported, dichotomous	Rectal	Any	9
Meschiari, 2021 [54]	Italy	Case—control, matched	Mixed ICU, all patients	Endemic	Systemic administration from admission to AB isolation or selection as control, dichotomous	Rectal	—	7
Playford, 2006 [55]	Australia	Case—control, matched	Mixed ICU, all patients	Endemic	Not reported, dichotomous and continuous	Any	Any	9
Kim, 2012 [56]	S. Korea	Case—control	Medical ICU, all patients	Endemic	Systemic administration for at least 48 h within 14 days before AB isolation or discharge, dichotomous	Any	BSI	9
Carbonne, 2005 [57]	France	Case—control	Unspecified ICU, all patients	Outbreak	Not reported, dichotomous	Any	Any	9
Moghnieh, 2016 [58]	Lebanon	Cohort	Mixed ICU, all patients	Outbreak	Systemic administration for at least four days before AB isolation or censoring, dichotomous	Any	—	9
Djordjevic, 2016 [59]	Serbia	Cohort	Mixed ICU, all patients	Endemic	Systemic administration for at least 24 h within 14 days before AB isolation, dichotomous	—	Any	9
Lee, 2014 [60]	Taiwan	Cohort	Mixed ICU, all patients	Endemic	Systemic administration for at least five days within 14 days before AB isolation, dichotomous	—	BSI	8
Inchai, 2015 [61]	Thailand	Cohort	Medical ICU, ventilated patients	Endemic	History of antibiotic uses within 90 days before AB isolation, dichotomous	—	VAP	8

AB, *Acinetobacter baumannii*; BSI, bloodstream infection; DDD, defined daily dose; ICU, intensive care unit; BSI, bloodstream infection; RTI, respiratory tract infection; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

meta-analyses including at least 10 analyses [40]. When a meta-analysis could not be performed, the results of individual studies were reported. All analyses were performed using Stata (StataCorp LLC, College Station, TX, USA), version 17.0. A two-sided value of $P<0.05$ was considered statistically significant.

Results

General characteristics of the studies

Overall, 40,667 records were identified by database searching. After removal of duplicates, 21,519 records resulted from the systematic search. Screening by title and abstract yielded 326 articles and a total of 25 studies were included after screening by full text (Figure 1). General characteristics of the studies are shown in Table I. The studies were published between 1999 and 2022, five in the USA, four in Greece, three in Turkey, and two each in Brazil, China, and Italy. One study each was conducted in Australia, South Korea, France, Lebanon, Serbia, Taiwan, and Thailand. More than half were cohort studies (N=15), and the remaining were case–control studies (N=5) or matched case–control studies (N=5). All articles were deemed to be of high quality using the Newcastle–Ottawa scale [35].

The setting consisted of mixed ICUs in more than half of the studies (N=13), while a smaller number of studies considered medical ICUs (N=3), surgical ICUs (N=2), a combined medical and neurology–neurosurgery ICU (N=1), a burns ICU (N=1), and a trauma ICU (N=1). In four studies the ICU setting was not specified. Most studies considered all patients on the ward (N=18), whereas six included only ventilated patients. The only study conducted in a burns ICU evaluated only non-burns patients.

In most cases the pattern of AB spread was endemic (N=19), whereas in the remaining cases the analyses were conducted during AB outbreaks (N=6).

Six studies defined previous exposure as the systemic use of antibiotics from ICU hospitalization to AB isolation, whereas others specified continuous use varying between two and five days, in some cases in a time window ranging from 14 to 30 days before the isolation of AB. Notably, Rosa *et al*. registered the use of antibiotics before the environmental isolation of AB, whereas Inchai *et al*. considered any systemic exposure in the 90 days before AB isolation [41,61]. Nine studies did not provide any explicit definition of previous use. Exposure was measured only dichotomously in almost all studies, with the exception of Mantzarlis *et al*. (as day of exposure, not used in association analyses), Munoz-Prince *et al*. (as cumulative grams and defined daily dose, used for the estimation of hazard ratios) and Playford *et al*. (defined daily dose, as overall antibiotic pressure) [29,31,55].

Considering the exposure of interest, all but two studies investigated the effect of multiple classes of antibiotics (N=22). Carbapenems (N=21) and fluoroquinolones (N=19) were the most frequently reported antibiotic classes, followed by third-generation cephalosporins (N=16), aminoglycosides (N=13), glycopeptides (N=12), antipseudomonal penicillins (N=11), and penicillins (N=9). Twelve analyses reported adjusted ORs for some of the antibiotic classes investigated, two analyses reported adjusted relative risks (not used in the meta-analyses) and one reported adjusted relative risk ratios. A complete overview of antibiotics analysed, together with adjustment of association measures, is reported in Table II.

Analyses and comparisons reported in the studies

The 25 studies included here reported the results of 29 analyses, 27 of which were included in the present review (see Table III). Overall, 17 analyses compared the isolation of CR/MDR AB versus its non-isolation, three the isolation of CR/MDR AB versus the isolation of CS/AS AB, two the isolation of XDR AB versus the non-isolation of AB, and one study each the isolation of XDR AB against the non-isolation of XDR AB, the acquisition of PDR AB versus the acquisition of non-PDR AB, the isolation of CoRAB versus the isolation of colistin-susceptible AB (CoSAB), the isolation of MDR AB versus the isolation of other non-AB Gram-negative micro-organisms, and the isolation of AB only susceptible to colistin versus the isolation of AB susceptible to colistin and at least one other antibiotic.

Analysis on isolation of CR or MDR AB versus non-isolation

General characteristics of the analyses

Fifteen studies investigated the impact of previous use of antibiotics on the isolation of CR/MDR AB versus its non-isolation, comprising 17 analyses involving 3953 patients. The median/average age ranged from 42.9 to 75.0 years for cases and from 45.4 to 76.0 for controls, while the prevalence of males ranged from 45.1% to 82.4% for cases and from 41.4% to 76.0% for controls.

Regarding case definition, five analyses considered infection only, four colonization only, and eight acquisition as a whole. Ten analyses defined the controls simply as patients without a demonstrated CR/MDR AB isolation, whereas the other seven explicitly excluded from the comparator/cohort patients with CS/AS AB isolation. The smallest comparison involved 27 patients and the largest 895 patients, with a median sample size of 144 patients (IQR: 89.5–310.5).

Evidence on the association between previous use of antimicrobial agents and CR or MDR AB isolation

Summary estimates of meta-analyses on the association between previous antimicrobial exposure and CR/MDR AB isolation are reported in Figure 2, together with OR for antibiotic classes reported only by single analyses.

Among the antibiotic classes not included in the meta-analyses, only diaminopyrimidines significantly increased the likelihood of CR/MDR AB isolation (OR: 7.20; 95% CI: 4.10–12.60), whereas use of anti-anaerobic antibiotics (not further specified by the authors) seemed to decrease the risk (0.50; 0.30–0.90) [56].

Meta-analyses showed a significant association with CR/MDR AB isolation for previous exposure to aminoglycosides (OR: 1.98; 95% CI: 1.45–2.71; I^2 = 0.00%), carbapenems (2.64; 1.86–3.76; 59.07%), third-generation cephalosporins (1.36; 1.04–1.76; 0.00%), glycylcyclines (2.42; 1.64–3.55; 2.91%), and nitroimidazoles (4.11; 1.91–8.81; 0.00%).

Stratified by outcome of interest (Figure 3A), adjustment of the measure of association (Figure 3B), and presence or

Table II

Antibiotic classes investigated in each analysis included in the systematic review

First author, year	Aminoglycosides	Anti-anaerobes	Beta-lactams	Carbapenems	1st gen. cephalosporins	2nd gen. cephalosporins	3rd gen. cephalosporins	4th gen. cephalosporins	Diamino-pyrimidines	Fluoroquinolones	Glycopeptides	Glycylcyclines	Lincosamides	Lipopeptides	Macrolides	Monobactams	Nitroimidazoles	Oxazolidinones	Penicillins	Antipseudomonal penicillins	Polymyxins	Adjustment variables
Ceparano, 2022 [28]				A			A[a]				A				A			A	A			Age; sex; comorbidities; SAPS II score; days of MV
Munoz-Prince, 2016[b] [29]	U			U	U	U	U	U		U	U								U	U		Reports adjusted RR for exposure to carbapenems and glycopeptides, not used in the meta-analysis
Zheng, 2020 [30]				A[c]			U[c]													U[c]		Tracheotomy; EN; no. of antibiotics used >3
Mantzarlis, 2020 [31]	U[c]			A[c]			U[c]	U[c]		U[c]		U[c]								U[c]	U[c]	Use of aminoglycosides, fluoroquinolones, 4th gen. cephalosporins, anti-pseudomonal penicillins, glycylcyclines[d]
Rosa, 2014[b] [41]	U			U						U	U											Reports adjusted RR for exposure to carbapenems, not used in the meta-analysis
Young, 2007 [42]				U			U			A			U		U[c]							APACHE II score; chronic lung disease; MV, bronchoscopy; use of fluconazole
Gulati, 2010 [43]																				U		NA
Husni, 1999 [44]							U				U[c]											NA
Katsaragakis, 2008 [45]	U[c]																					NA
Apostolopoulou, 2014 [46]	U			U			U			U	U		U				U		U	U		NA
Papakonstantinou, 2014 [47]	U			U			U			U	U	U		U		U		U	U	U	U	NA
Gulen, 2015 [48]	U[c]			A[c]	U[c]		U[c]			A[c]	U[c]						A[c]	U[c]	U[c]	U[c]		SAPS II score
Aksu Koca [C], 2018 [49]				A[c]						U										U[c]		CVC; MV; PEG; EN; previous ICU hospitalization; mean ICU LOS; ICU LOS >14 days; consciousness disorders
Aksu Koca [I], 2018 [49]				A																U		APACHE II score, CVC, MV, mean ICU LOS, ICU LOS >14 days; consciousness disorders; CRAB colonization
Mete, 2022 [50]			U[e]												U							NA
Castelo Branco Fortaleza, 2013 [51]				A						A							A					Tracheostomy
Romanelli [A], 2009 [52]				A			U			U												ASIS score; MV; CVC; UC; previous infection
Romanelli [B], 2009 [52]				A			A			U												ASIS score; CVC; liver transplantation
Qiao, 2020 [53]	U			A		U				U	U	U	U									APACHE II score; hematologic disease; pancreatitis; surgery; EN
Meschiari, 2021 [54]				U						U	U								U			NA
Playford, 2006 [55]	U			U						U												NA
Kim, 2012 [56]	U	U		U	U	U	U	U	U	U	U	U			U				U		U	NA
Carbonne, 2005 [57]	U[c]						A			U[c]											U[c]	Transferred from another ward; SAPS score >30; chronic ethanol abuse; AC; CVC; no. of invasive procedures >3
Moghnieh, 2016 [58]				U[c]			U[c]													U[a]		NA
Djordjevic, 2016 [59]	A			A		U[a]	U		U[c]	U	U						A[c]			U		Other department previous admission; LoS; ICU-LoS; hypertension; cancer; other hospital infection; CVC; MV; UC; use of 2nd and 3rd gen. cephalosporins, fluoroquinolones, antipseudomonal penicillins, glycopeptides, diaminopyrimidines[d]
Lee, 2014 [60]				U						U									U	U		NA
Inchai, 2015[f] [61]	U			U			U			U	U								U		U[c]	Reports adjusted RRR, not used in the meta-analysis

A, adjusted odds ratio; AC, arterial catheterization; APACHE, Acute Physiology and Chronic Health Evaluation; ASIS, Average Severity of Illness Score; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CVC, central venous catheterization; EN, enteral Nutrition; ICU, intensive care unit; LoS, length of stay; MV, mechanical ventilation; PEG, percutaneous endoscopic gastrostomy; PEN, parenteral nutrition; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; U, unadjusted odds ratio; UC, urinary catheterization.

[a]Includes cephalosporins classified as 3rd, 4th, and 5th generation.

[b]Odds ratio estimated from raw data.

[c]Not included in a meta-analysis.

[d]The study reported only a partial list of adjustment variables.

[e]Odds ratio not estimable.

[f]Odds ratios derived from the merge of the raw data of the three original comparisons.

Table III
Characteristics of the analyses included in the systematic review, by comparison

First author, year	Sample size	Comparison		Case age, years (mean ± SD)	Control age, years (mean ± SD)	Male cases (%)	Male controls (%)
		Case definition	Comparator/cohort definition				
CR/MDR AB isolation against non-isolation							
Ceparano, 2022 [28]	193	MDR[a] AB [A]	No AB [A]	63 (54–71)[b]	65 (57–74)[b]	67.6	72.1
Munoz-Prince, 2016 [29]	360	CRAB [C]	No CRAB [C]	NR	NR	60.0	76.0
Rosa, 2014 [41]	562	CRAB [A]	No AB [A]	NR	NR	68.9	64.7
Young, 2007 [42]	134	MDR[a] AB [I]	No AB [I]	42.9	45.4	80.6	67.2
Gulati, 2010 [43]	27	CRAB [A]	No AB [A]	51.6	46	81.8	75.0
Apostolopoulou, 2014 [46]	100	CRAB [I]	No AB [I]	67.5 ± 13.8	68.7 ± 14.5	62.0	64.0
Papakonstantinou, 2014 [47]	71	MDR[a] AB [A]	No MDR AB [A]	NR	NR	NR	NR
Aksu Koca, 2018 [49]	310	CRAB [C][c]	No CRAB [C]	69.1 ± 16.4	65.9 ± 18.4	52.4	46.8
		CRAB [I]	No CRAB [I]	71.6 ± 14.0	66.1 ± 18.2	52.1	48.1
Mete, 2022 [50]	79	CRAB [I]	No AB [I]	67.3 ± 14.8	67.0 ± 14.9	82.4	66.1
Castelo Branco Fortaleza, 2013 [51]	57	IRAB [A]	No IRAB [A]	NR	NR	NR	NR
Romanelli, 2009 [52]	153(a)	MDR[a]/CR AB [A]	No MDR/CR AB [A]	NR	NR	45.1	52.0
	105(b)	MDR[a]/CR AB [A]	No MDR/CR AB [A]	NR	NR	54.3	41.4
Qiao, 2020 [53]	895	CRAB [C]	No CRAB [C]	51 (40–70)[b]	56 (45–68)[b]	61.7	64.4
Meschiari, 2021 [54]	135	CRAB [C]	No CRAB [C]	75 ± 16	76 ± 15	57.8	65.6
Playford, 2007 [55]	197	CRAB [A]	No CRAB [A]	59[b]	59[b]	73.0	73.0
Kim, 2012 [56]	311	CRAB [I]	No AB [A]	61.8 ± 15.3	60.1 ± 16.2	58.5	64.9
CR/MDR AB isolation against CS/AS isolation							
Djordjevic, 2016 [59]	137	CRAB [I]	CSAB [I]	60.73 ± 15.86	57.21 ± 16.69	73.7	69.0
Lee, 2014 [60]	298	IRAB [I]	ISAB [I]	NR	NR	NR	NR
Inchai, 2015 [61]	105	MDR[a] AB [I][d]	ASAB [I]	64.6 ± 16.6	58.2 ± 18.4	54.2	51.5
	253	XDR[a] AB [I][d]	ASAB [I]	61.1 ± 18.1	58.2 ± 18.4	55.0	51.5
	45	PDR[a] AB [I][d]	ASAB [I]	58.9 ± 18.4	58.2 ± 18.4	50.0	51.5
XDR AB isolation against non-isolation of AB							
Husni, 1999 [44]	43	XDR[a] AB [I]	No AB [A]	50	60	79.0	41.0
Carbonne, 2005 [57]	45	XDR[a] AB [A]	No AB [A]	NR	NR	68.4	65.4
Other comparisons							
Zheng, 2020 [30]	105	PDR AB [I]	Non-PDR AB [I]	57.5 ± 7.5	57.3 ± 6.8	51.4	54.3
Mantzarlis, 2020 [31]	77	CoRAB [I]	CoSAB [I]	59.7	40.7	45.0	63.0
Katsaragakis, 2008 [45]	52	CS-XDR AB [I]	AB susceptible to colistin and at least another antibiotic [I]	63.9 ± 8.6	68.2 ± 12.1	52.1	51.7
Gulen, 2015 [48]	86	MDR[a] AB [I]	Non-AB Gram-negative micro-organism [I]	58.3 ± 21.9	60.6 ± 20.5	43.9	64.4
Moghnieh, 2016 [58]	257	XDR[a] AB [C]	No XDR AB [C]	NR	NR	62.5	60.4

AB, *Acinetobacter baumannii*; CR, carbapenem resistant; CS, carbapenem susceptible; CoR, colistin resistant; CoS, colistin susceptible; IR, imipenem resistant; IS, imipenem susceptible; NR, not reported; MDR, multidrug resistant, XDR, extensively drug resistant; PDR, pan-drug resistant; CS-XDR, carbapenem susceptible, extensively drug resistant.
Type of outcome: [A], acquisition; [C], colonization; [I], infection.
[a] Lowest degree of multi-resistance profile considered.
[b] Median (interquartile range).
[c] Analysis included only for antibiotic classes not reported in the infection outcome analysis.
[d] Combined in one single comparison.

absence of CS/AS AB among the comparator/cohort group (Figure 4A), no significant between-subgroup differences were found, although it should be noted that some stratifications were characterized by a relatively low number of subjects and high residual heterogeneity.

On the contrary, stratifying by study design (Figure 4B), cohort studies and case–control studies yielded pooled estimates that showed significant opposite trends in the case of fluoroquinolones.

Individual meta-analyses for each antibiotic class, with subsequent subgroup analyses, are reported in Supplementary File 2.

These results were confirmed by the meta-regression models for carbapenems, which did not show any study characteristic to be independently associated with the estimated ORs (Supplementary File 3) and fluoroquinolones (Supplementary Files 3 and 4), which confirmed the cohort design as independently associated with a decreased likelihood of the outcome ($a\beta = -0.725$; 95% CI: −1.361 to −0.090). A funnel plot for carbapenems and fluoroquinolones showed no evident signs of publication bias, as confirmed by Eggars' test (P=0.235 and P=0.956, respectively) (Supplementary Files 5 and 6).

Analyses on CR or MDR AB isolation versus CS or AS AB isolation

General characteristics of the analyses

Three studies investigated the impact of previous use of antibiotics on the acquisition of CR/MDR AB versus CS/AS AB acquisition, comprising five analyses involving 772 patients (472 cases and 300 controls) (Table III) [56,59,61]. The three analyses reported in Inchai *et al.* used the same control group (AS AB) to compare against MDR AB, XDR AB, and PDR AB groups and have thus been combined in a single analysis for the purpose of the meta-analyses. The median/average age ranged from 58.9 to 64.6 years for cases and from 57.2 to 58.2 for controls, while the prevalence of males ranged from 50.0% to 73.7% for cases and from 51.5% to 69.0% for controls. Regarding case definition, all three analyses defined cases as patients with an infection by CR/MDR AB and the controls as patients with an infection by CS/AS AB [59–61]. The smallest comparison involved 137 patients and the largest 403 patients [59,61].

Evidence on the association between previous use of antimicrobial agents and CR or MDR AB isolation versus CS or AS AB isolation

Summary estimates of meta-analyses on the association of previous antimicrobial exposure with CR/MDR AB isolation versus CS/AS AB isolation are reported in Figure 5, together with OR for antibiotic classes reported only by single analyses. Individual meta-analyses for each antibiotic class are reported in Supplementary File 2.

Among the antibiotic classes not subjected to meta-analysis, only nitroimidazoles (OR: 3.19; 95% CI: 1.28–7.93) were reported to significantly increase the likelihood of CR/MDR AB isolation compared to CS/AS AB isolation.

Meta-analyses showed an increased risk of acquiring CR/MDR AB for the previous use of aminoglycosides (OR: 4.86; 95% CI: 1.46–16.20; $I^2 = 0.00\%$), antipseudomonal penicillins (5.65; 1.98–16.43; 0.00%), carbapenems (23.16; 5.18–103.42; 64.81%), fluoroquinolones (5.44; 2.07–14.30; 47.16%), glycopeptides (7.43; 1.52–36.38; 40.35%), and penicillins (1.84; 1.01–3.35; 0.00%). Due to the limited number of analyses included in the meta-analyses (maximum three), no subgroup

Antibiotic class	No. of studies	No. of events	No. of subjects	95% CI	Tau²	Q test	I²
Aminoglycosides	7	475	2135	1.98 [1.45, 2.71]	0.000	0.607	0.00%
Anti-anaerobic	1	106	311	0.50 [0.30, 0.90]	NE	NE	NE
Carbapenems	14	820	3486	2.64 [1.86, 3.76]	0.243	0.004	59.07%
1st gen. cephalosporins	2	151	561	0.73 [0.35, 1.56]	0.000	0.476	0.00%
2nd gen. cephalosporins	2	266	1566	1.29 [0.18, 9.10]	2.630	0.000	89.79%
3rd gen. cephalosporins	8	457	1427	1.36 [1.04, 1.76]	0.000	0.41	0.00%
4th gen. cephalosporins	2	151	671	1.39 [0.80, 2.40]	0.000	0.476	0.00%
Diaminopyrimidines	1	106	311	7.20 [4.10, 12.60]	NE	NE	NE
Fluoroquinolones	13	804	3293	1.04 [0.83, 1.31]	0.031	0.064	18.63%
Glycylcyclines	3	253	1277	2.42 [1.64, 3.55]	0.004	0.413	2.91%
Glycopeptides	8	525	2266	1.55 [0.89, 2.72]	0.451	0.001	75.22%
Lincosamides	3	232	1129	0.95 [0.24, 3.72]	1.134	0.011	78.14%
Lipopeptides	1	32	71	5.43 [0.58, 51.25]	NE	NE	NE
Macrolides	3	194	583	1.73 [0.93, 3.10]	0.081	0.187	29.66%
Monobactams	1	32	71	0.60 [0.05, 6.90]	NE	NE	NE
Nitroimidazoles	2	78	421	4.11 [1.91, 8.81]	0.000	0.322	0.00%
Oxazolidinones	2	103	264	1.27 [0.56, 2.89]	0.000	0.403	0.00%
Penicillins	6	349	1170	0.88 [0.56, 1.38]	0.000	0.928	0.00%
Antipseudomonal penicillins	6	292	1179	1.31 [0.98, 1.76]	0.000	0.625	0.00%
Polymyxins	2	138	381	1.16 [0.26, 5.21]	0.911	0.034	77.70%

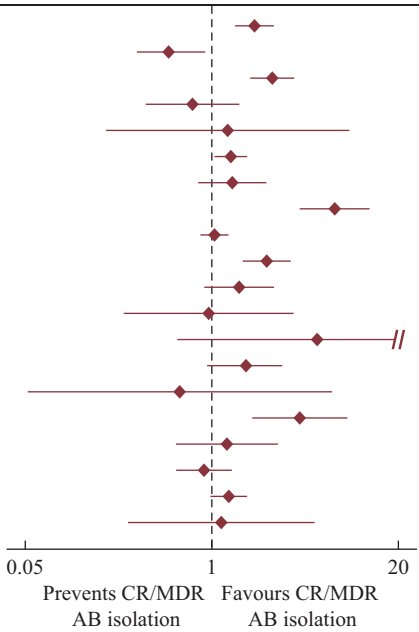
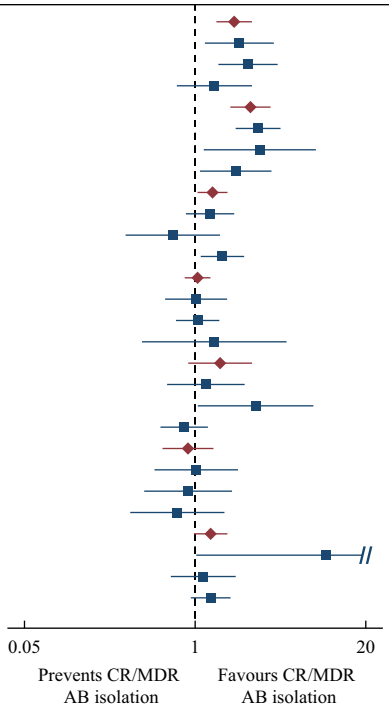


Figure 2. Pooled estimated odds ratios and reported odds ratios for carbapenem-/multidrug-resistant *Acinetobacter baumannii* (CR/MDR AB) isolation against non-isolation for previous use of each antibiotic class. REML, residual maximum likelihood; CI, confidence interval; NE, not estimable.

A

Antibiotic class	No. of studies	No. of events	No. of subjects	95% CI	Tau²	Q test	I²	Test of subgr. diff.
Aminoglycosides	7	475	2135	**1.98 [1.45, 2.71]**	0.000	0.607	0.00%	0.381
Acquisition	3	127	389	2.17 [1.19, 3.98]	0.000	0.449	0.00%	
Colonization	2	192	1362	2.53 [1.50, 4.26]	0.000	0.899	0.00%	
Infection	2	156	411	1.40 [0.73, 2.71]	0.083	0.221	33.35%	
Carbapenems	14	820	3486	**2.64 [1.86, 3.76]**	0.243	0.004	59.07%	0.053
Acquisition	6	312	1170	3.02 [2.04, 4.48]	0.036	0.158	14.52%	
Colonization	4	237	1461	3.11 [1.16, 8.33]	0.701	0.005	78.42%	
Infection	4	271	855	2.04 [1.09, 3.82]	0.246	0.054	61.58%	
3rd gen. cephalosporins	8	457	1427	**1.36 [1.04, 1.76]**	0.000	0.367	0.00%	0.169
Acquisition	3	157	451	1.30 [0.85, 1.99]	0.000	0.430	0.00%	
Colonization	2	77	431	0.68 [0.23, 1.60]	0.000	0.669	0.00%	
Infection	3	223	545	1.62 [1.10, 2.36]	0.006	0.417	4.07%	
Fluoroquinolones	13	804	3293	**1.04 [0.83, 1.31]**	0.031	0.064	18.63%	0.901
Acquisition	5	241	977	1.02 [0.59, 1.75]	0.227	0.039	62.66%	
Colonization	5	340	1771	1.05 [0.72, 1.53]	0.031	0.455	15.96%	
Infection	3	223	545	1.40 [0.39, 4.98]	0.950	0.054	84.14%	
Glycopeptides	8	525	2266	**1.55 [0.89, 2.72]**	0.451	0.001	75.22%	0.072
Acquisition	2	132	394	1.21 [0.61, 2.39]	0.128	0.147	52.47%	
Colonization	4	237	1461	2.89 [1.05, 7.97]	0.729	0.016	72.92%	
Infection	2	156	411	0.83 [0.54, 1.25]	0.000	0.796	0.00%	
Penicillins	6	349	1170	**0.88 [0.56, 1.38]**	0.000	0.928	0.00%	0.840
Acquisition	1	71	193	1.02 [0.49, 2.12]	NE	NE	NE	
Colonization	3	122	566	0.88 [0.41, 1.91]	0.000	0.733	0.00%	
Infection	2	156	411	0.73 [0.32, 1.67]	0.000	0.530	0.00%	
Antipseudomonal penicillins	6	292	1179	**1.31 [0.98, 1.76]**	0.000	0.625	0.00%	0.198
Acquisition	1	11	27	9.90 [1.02, 96.06]	NE	NE	NE	
Colonization	2	77	431	1.15 [0.65, 2.04]	0.000	0.779	0.00%	
Infection	3	204	721	1.31 [0.93, 1.86]	0.000	0.914	0.00%	



B

Antibiotic class	No. of studies	No. of events	No. of subjects	95% CI	Tau²	Q test	I²	Test of subgr. diff.
Aminoglycosides	7	475	2135	**1.98 [1.45, 2.71]**	0.000	0.607	0.00%	NE
Unadjusted	7	475	2135	1.98 [1.45, 2.71]	0.000	0.607	0.00%	
Adjusted	0			–	–	–	–	
Carbapenems	14	820	3486	**2.64 [1.86, 3.76]**	0.243	0.004	59.07%	0.606
Unadjusted	8	472	1509	2.38 [1.35, 4.20]	0.438	0.002	72.20%	
Adjusted	6	348	1977	2.86 [1.89, 4.34]	0.077	0.190	29.14%	
3rd gen. cephalosporins	8	457	1427	**1.36 [1.04, 1.76]**	0.000	0.41	0.00%	0.802
Unadjusted	6	351	1129	1.34 [1.01, 1.78]	0.000	0.343	0.00%	
Adjusted	2	106	298	1.50 [0.66, 3.38]	0.115	0.223	32.71%	
Fluoroquinolones	13	804	3293	**1.04 [0.83, 1.31]**	0.031	0.064	18.63%	0.859
Unadjusted	11	709	2838	1.07 [0.87, 1.32]	0.007	0.457	5.63%	
Adjusted	2	95	455	1.51 [0.03, 66.67]	6.708	0.002	89.60%	
Glycopeptides	8	525	2266	**1.55 [0.89, 2.72]**	0.451	0.001	75.22%	0.131
Unadjusted	7	454	2073	1.73 [0.92, 3.25]	0.506	0.001	76.96%	
Adjusted	1	71	193	0.89 [0.39, 1.72]	NE	NE	NE	
Penicillins	6	349	1170	**0.88 [0.56, 1.38]**	0.000	0.928	0.00%	0.623
Unadjusted	5	278	977	0.81 [0.46, 1.42]	0.00	0.890	0.00%	
Adjusted	1	71	193	1.02 [0.49, 2.12]	NE	NE	NE	
Antipseudomonal penicillins	6	292	1179	**1.31 [0.98, 1.76]**	0.000	0.625	0.00%	NE
Unadjusted	6	292	1179	1.31 [0.98, 1.76]	0.000	0.625	0.00%	
Adjusted	0			–	–	–	–	

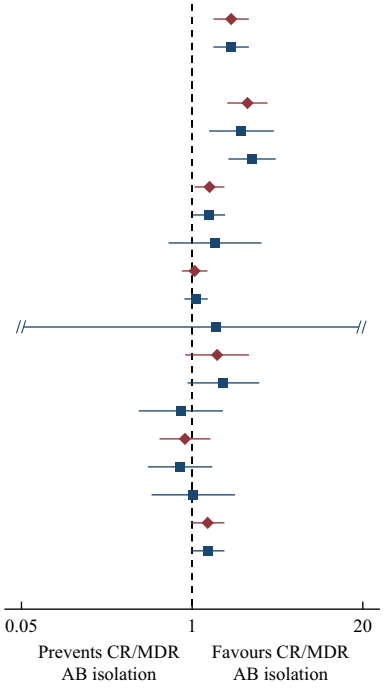
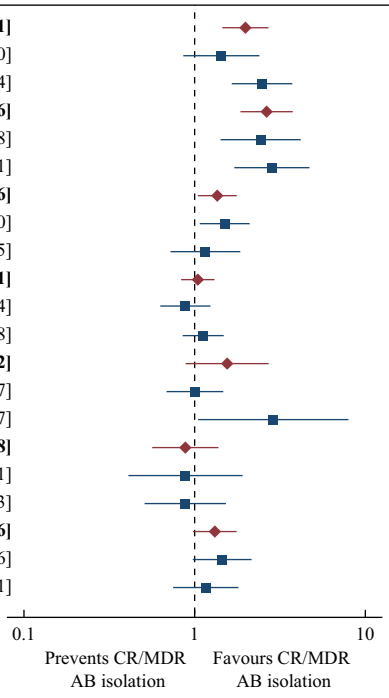


Figure 3. Subgroup meta-analyses for previous use of each antibiotic class for carbapenem-/multidrug-resistant *Acinetobacter baumannii* (CR/MDR AB) isolation against non-isolation. **(A)** Type of outcome. **(B)** Estimate adjustment. REML, residual maximum likelihood; CI, confidence interval; NE, not estimable.

A

Antibiotic class	No. of studies	No. of events	No. of subjects	95% CI	Tau²	Q test	I²	Test of subgr. diff.
Aminoglycosides	7	475	2135	**1.98 [1.45, 2.71]**	0.000	0.607	0.00%	0.101
No	3	217	612	1.43 [0.86, 2.40]	0.018	0.464	7.05%	
Yes	4	258	1523	2.48 [1.65, 3.74]	0.000	0.000	0.97%	
Carbapenems	14	820	3486	**2.64 [1.86, 3.76]**	0.243	0.004	59.07%	0.689
No	5	355	939	2.44 [1.42, 4.18]	0.234	0.039	64.37%	
Yes	9	468	2577	2.83 [1.71, 4.71]	0.333	0.010	60.73%	
3rd gen. cephalosporins	8	457	1427	**1.36 [1.04, 1.76]**	0.000	0.41	0.00%	0.378
No	4	294	738	1.50 [1.07, 2.10]	0.000	0.458	0.00%	
Yes	4	163	689	1.16 [0.72, 1.85]	0.032	0.295	12.32%	
Fluoroquinolones	13	804	3293	**1.04 [0.83, 1.31]**	0.031	0.064	18.63%	0.281
No	4	284	746	0.88 [0.63, 1.24]	0.000	0.101	0.00%	
Yes	9	520	2547	1.12 [0.85, 1.48]	0.034	0.139	19.27%	
Glycopeptides	8	525	2266	**1.55 [0.89, 2.72]**	0.451	0.001	75.22%	0.056
No	4	288	805	1.00 [0.69, 1.47]	0.047	0.267	30.51%	
Yes	4	237	1461	2.89 [1.05, 7.97]	0.729	0.016	72.92%	
Penicillins	6	349	1170	**0.88 [0.56, 1.38]**	0.000	0.928	0.00%	0.996
No	3	106	311	0.88 [0.41, 1.91]	0.000	0.733	0.00%	
Yes	3	122	566	0.88 [0.51, 1.53]	0.000	0.689	0.00%	
Antipseudomonal penicillins	6	292	1179	**1.31 [0.98, 1.76]**	0.000	0.625	0.00%	0.464
No	3	167	438	1.45 [0.98, 2.16]	0.000	0.237	0.00%	
Yes	3	125	741	1.16 [0.75, 1.81]	0.000	0.961	0.00%	



B

Antibiotic class	No. of studies	No. of events	No. of subjects	95% CI	Tau²	Q test	I²	Test of subgr. diff.
Aminoglycosides	7	475	2135	**1.98 [1.45, 2.71]**	0.000	0.607	0.00%	0.988
Cohort	3	138	632	1.97 [0.99, 3.95]	0.000	0.808	0.00%	
Case control	4	337	1503	1.99 [1.40, 2.81]	0.000	0.252	0.00%	
Carbapenems	14	820	3486	**2.64 [1.86, 3.76]**	0.243	0.004	59.07%	0.053
Cohort	6	285	1546	3.66 [2.15, 6.21]	0.251	0.037	59.62%	
Case control	8	535	2030	1.99 [1.36, 2.92]	0.098	0.113	35.18%	
3rd gen. cephalosporins	8	457	1427	**1.36 [1.04, 1.76]**	0.000	0.410	0.00%	0.068
Cohort	3	148	1427	0.83 [0.45, 1.51]	0.000	0.721	0.00%	
Case control	5	309	803	1.53 [1.14, 2.04]	0.000	0.513	0.00%	
Fluoroquinolones	13	804	3293	**1.04 [0.83, 1.31]**	0.031	0.064	18.63%	0.022
Cohort	5	269	1263	0.72 [0.49, 1.06]	0.009	0.283	4.74%	
Case control	8	535	2030	1.22 [0.97, 1.54]	0.005	0.205	4.08%	
Glycopeptides	8	525	2266	**1.55 [0.89, 2.72]**	0.451	0.001	75.22%	0.996
Cohort	4	209	825	1.57 [0.64, 3.84]	0.654	0.007	79.77%	
Case control	4	316	1441	1.57 [0.67, 3.68]	0.520	0.005	76.88%	
Penicillins	6	349	1170	**0.88 [0.56, 1.38]**	0.000	0.928	0.00%	0.665
Cohort	3	148	624	0.94 [0.55, 1.62]	0.000	0.718	0.00%	
Case control	3	201	546	0.76 [0.35, 1.68]	0.000	0.772	0.00%	
Antipseudomonal penicillins	6	292	1179	**1.31 [0.98, 1.76]**	0.000	0.625	0.00%	0.464
Cohort	3	125	741	1.16 [0.75, 1.81]	0.000	0.961	0.00%	
Case control	3	167	438	1.45 [0.98, 2.16]	0.000	0.237	0.00%	

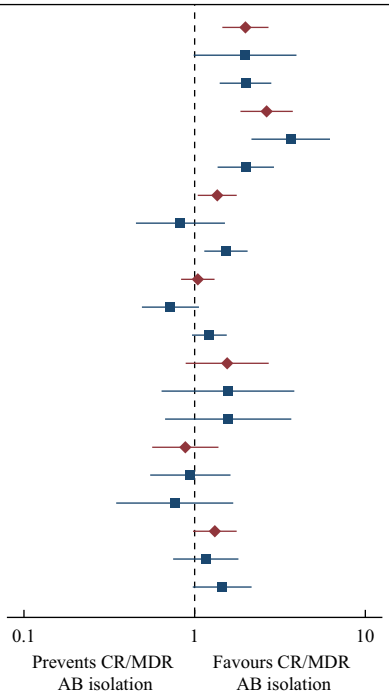


Figure 4. Subgroup meta-analyses for previous use of each antibiotic class for carbapenem-/multidrug-resistant *Acinetobacter baumannii* (CR/MDR AB) isolation against non-isolation. **(A)** Carbapenem-/antibiotic-susceptible *Acinetobacter baumannii* among controls. **(B)** Study design. REML, residual maximum likelihood; CI, confidence interval.

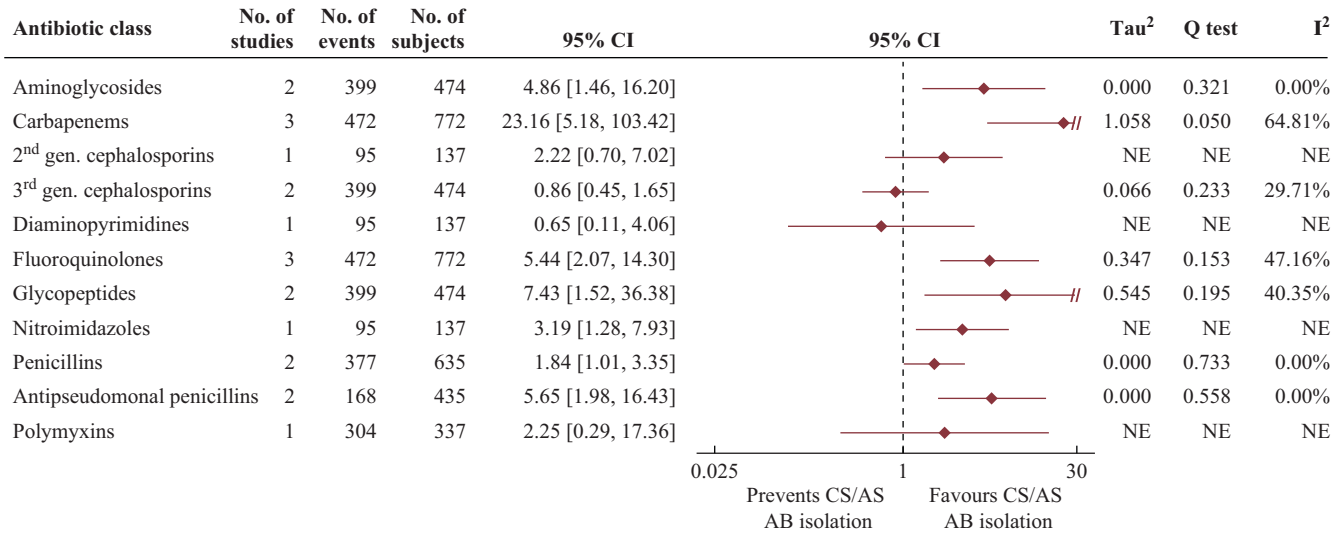


Figure 5. Pooled estimated odds ratios and reported odds ratios for carbapenem-/multidrug-resistant *Acinetobacter baumannii* (CR/MDR AB) isolation against carbapenem/antibiotic-susceptible (CS/AS). REML, residual maximum likelihood; CI, confidence interval; NE, not estimable.

analysis was performed. Individual meta-analyses for each antibiotic class are reported in Supplementary File 2.

Analyses on isolation of XDR AB versus non-isolation of AB

General characteristics of the analyses

Two studies investigated the impact of previous use of antibiotics on the acquisition of XDR AB versus the non-acquisition of AB, comprising one analysis each involving 88 patients (33 cases and 55 controls) [44,57]. The demographic characteristics of cases and controls are shown in Table III. The study by Carbonne *et al.* defined a case as an infection by XDR AB, whereas Husni *et al.* considered a case to be acquisition of XDR AB [44,57].

Evidence on the association between previous use of antimicrobial agents and isolation of XDR AB versus non-isolation of AB

Summary estimates of meta-analyses on the association of previous antimicrobial exposure with the acquisition of XDR AB versus the non-acquisition of AB are shown in Figure 6, together with OR for antibiotic classes reported only by single analyses. Of the antibiotic classes not subjected to meta-analysis, none showed an effect on acquisition risk. The meta-analysis of the effect of third-generation cephalosporins showed an increased risk of XDR AB acquisition among patients who used this antibiotic class (OR: 7.28; 95% CI: 1.86–28.46; $I^2 = 0.00$). Due to the limited number of analyses included in this meta-analysis, no subgroup analysis was performed.

Studies on other comparisons

Five studies investigated the impact of previous use of antibiotics on a variety of different outcomes of interest and comparator/cohort groups. In particular, Gulen *et al.* reported an effect on the risk of acquisition of MDR AB versus the acquisition of other non-AB Gram-negative micro-organisms for carbapenems (aOR: 11.96; 95% CI: 3.31–43.30), aminoglycosides (OR: 4.63; 1.78–12.03), glycopeptides (OR: 3.13; 1.12–8.74), fluoroquinolones (aOR: 6.71; 1.31–34.40) and nitroimidazoles (aOR: 331.85; 2.59–391.22) [48]. Katsaragakis *et al.* reported an increased risk of HAIs by XDR AB only susceptible to colistin versus those by an AB susceptible to colistin and at least one another antibiotic for the previous administration of aminoglycosides (OR: 3.51; 95% CI: 1.04–11.84) [45]. The risk of acquisition of colistin-resistant AB versus the acquisition of colistin-susceptible AB was investigated by

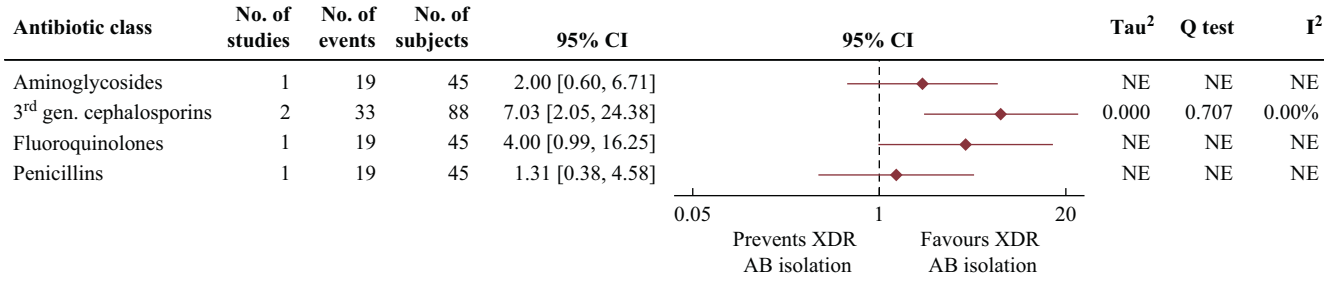


Figure 6. Pooled estimated odds ratios and reported odds ratios for extensively drug-resistant *Acinetobacter baumannii* (XDR AB) isolation against non-isolation for each antibiotic class. REML, residual maximum likelihood; CI, confidence interval; NE, not estimable.

Mantzarlis *et al.*, who found a significant association for aminoglycosides (OR: 14.00; 95% CI: 1.46—134.26), carbapenems (3.53; 1.22—10.18), fourth-generation cephalosporins (7.13; 1.81—28.08), fluoroquinolones (4.58; 1.55—13.59), and antipseudomonal penicillins (3.53; 1.22—10.18) [31]. Antibiotic exposure influencing the acquisition of XDR AB against non-XDR AB was investigated by Moghnieh *et al.*, who reported a significant association with carbapenems (OR: 3.45; 95% CI: 1.60—7.01), third-generation cephalosporins (4.36; 2.15—8.83), and antipseudomonal penicillins (4.36; 2.15—8.83) [58]. Finally, Zheng *et al.* reported a significant association with previous exposure to carbapenems (OR: 4.26; 95% CI: 1.64—10.97), comparing the acquisition of PDR AB with that of non-PDR AB [30]. The associations found in each study are reported in detail in Table IV.

Discussion

Epidemiological research on risk factors for the acquisition of antibiotic-resistant micro-organisms must deal with a variety of methodological challenges, among which one of the most prominent is the selection of the appropriate comparator and/or cohort [62—64]. Accordingly, this systematic review revealed great variety in the type of comparator/cohort involved. Two types of comparator are generally used in studies on antibiotic resistance: patients affected by the antibiotic-susceptible strain of the micro-organism or not affected by it at all, which ultimately determines the research question investigated [65]. Certainly, selecting patients affected by an antibiotic-susceptible strain of an organism as a comparator is appropriate when studying the risk factors associated with acquiring a resistant strain among the affected patients themselves, but it is not advisable for determining the risk factors related to acquiring a resistant pathogen among all hospitalized patients [62,63]. On the other hand, the latter option does not allow researchers to distinguish between risk factors associated with the organism in general or with the resistant phenotype [64]. Considering this, factors that are significant in both comparisons might be considered 'true' risk factors for acquisition of antibiotic resistance strains [66,67].

In this systematic review and meta-analysis, among the antibiotic classes investigated using both approaches, only aminoglycosides, carbapenems, second-generation cephalosporins, nitroimidazoles, and polymyxins seemed to exert similar effects on adult ICU patients regardless of the controls enrolled. Indeed, aminoglycosides and carbapenems have long been identified as risk factors for the acquisition of carbapenem- or multi-resistant strains of AB in many healthcare settings [68—75]. The same associations have been reported for

Table IV
Reported associations in analyses with other comparisons

First author, year	Antibiotic classes	No. of events	No. of subjects	OR	95% CI
Zheng, 2020 [30]		70	105		
	Carbapenems			4.33[a]	1.25—14.32
	3rd gen. cephalosporins			1.06	0.47—2.39
	Antipseudomonal penicillins			1.12	0.50—2.53
Mantzarlis, 2020 [31]		20	77		
	Aminoglycosides			14.00	1.46—134.26
	Carbapenems			1.21[a]	1.00—1.45
	3rd gen. cephalosporins			0.46	0.15—1.43
	4th gen. cephalosporins			7.13	1.81—28.08
	Fluoroquinolones			4.58	1.55—13.59
	Antipseudomonal penicillins			3.53	1.22—10.18
	Polymyxins			2.5	0.83—7.50
Katsaragakis, 2008 [45]		23	52		
	Aminoglycosides			3.51	1.04—11.84
Gulen, 2015 [48]		41	86		
	Aminoglycosides			4.63	1.78—12.03
	Carbapenems			11.96[a]	3.31—43.30
	1st gen. cephalosporins			0.69	0.26—1.85
	3rd gen. cephalosporins			1.58	0.68—3.72
	Fluoroquinolones			6.71[a]	1.31—34.40
	Glycopeptides			3.13	1.12—89.52
	Nitroimidazoles			31.85	2.59—391.22
	Oxazolidinones			0.81	0.17—3.85
	Antipseudomonal penicillins			1.81	0.70—4.71
	Penicillins			0.64	0.22—1.84
Moghnieh, 2016 [58]		40	257		
	Carbapenems			3.45	1.60—7.01
	3rd gen. cephalosporins			2.12	1.05—4.28
	Antipseudomonal penicillins			4.36	2.15—8.83

OR, odds ratio; CI, confidence interval.
[a] Adjusted OR.

infections and acquisitions of other antibiotic-resistant Gram-negative bacteria [19,21,22,24,25,75,76]. Our meta-analysis shows that carbapenems increase the risk of CR/MDR AB acquisition, although there was substantial heterogeneity in both comparisons. However, the consistency between subgroup estimates and between the two comparisons reinforces the importance of carbapenems. Our results on aminoglycosides, on the other hand, highlight the lack of any reported adjusted measures of association and a possible slight upward bias in studies that included CS/AS AB among comparators, which suggest caution in their interpretation, considering also that the only studies reporting this association in other settings use CS/AS AB as comparator [72,73,77]. As for nitroimidazoles, second-generation cephalosporins, and polymyxins, very few studies were included in both comparisons and findings from studies on AB and other Gram-negative bacteria are inconsistent [19,21,24,25,66,70,74—76,78]. Research on these antibiotic classes should be strengthened, particularly for colistin considering its importance in the treatment of XDR AB where it often represents the only therapeutic option available [79].

Conversely, previous use of third-generation cephalosporins and diaminopyrimidines was significantly associated with the isolation of CR/MDR AB only versus its non-isolation, but not versus CS/AS AB isolation, suggesting their role in the acquisition of AB as a whole [64]. Indeed, AB is intrinsically resistant to diaminopyrimidines [80], so that their use may reduce competition with other susceptible micro-organisms [81], while for third-generation cephalosporins, these results are in contrast with most of the literature, which generally reports a lack of effect [68,69,74,77]. For these reasons, further evidence should be gathered to better assess their possible impact.

Fluoroquinolones, glycopeptides, penicillins, and antipseudomonal penicillins all had an impact on the likelihood of being affected by a CR/MDR AB only versus CS/AS AB isolation. Several authors have reported fluoroquinolones, penicillins, and antipseudomonal penicillins as risk factors for antibiotic-resistant *K. pneumoniae* [21,25,82,83] and *P. aeruginosa* [20,22,76] acquisition, as well as for AB and *P. aeruginosa* together [24], while the data on glycopeptides are more conflicting [19,24,76,78,82]. Overall, these associations may not reflect a true excess of antibiotic use among cases, but rather decreased use among controls [62]. Especially in light of consistently non-significant estimates versus the non-isolation, the results suggest that these classes should not have an impact on AB isolation in adult ICU patients, accordingly with studies conducted in other settings [68—74,77].

Among the antibiotic classes investigated only in comparison versus the non-isolation of CR/MDR AB, only glycylcyclines increased the risk of acquisition, while anti-anaerobics decreased the risk. However, due to the limited number of studies on these antibiotic classes, caution is advisable in interpreting these findings. Indeed, to the best of our knowledge their effect on the risk of AB isolation has not been reported previously [68,77].

Interestingly, the two studies conducted during the COVID-19 pandemic and including SARS-CoV-2 patients only [28,50] showed results consistent with the other studies, suggesting that the increase in ICA observed in these patients should not be attributable to a higher or different susceptibility to these risk factors [18,26—28].

Finally, our systematic review identified some studies that compared the risk of isolation of various antibiotic-resistant AB strains against some more specific controls. As for the comparison between MDR AB and other non-AB Gram-negative micro-organism acquisition, carbapenems, aminoglycosides, glycopeptides, fluoroquinolones, and nitroimidazoles were all identified as risk factors, but these results may suffer from the same upward bias observed when using susceptible strains as controls [62]. Results of the other comparisons, which involved XDR and PDR AB as cases, were mainly in accordance with the risk factors found in other comparisons and may underline a role for some antibiotic classes in facilitating a cross-resistance mechanism and ultimately high grade of multi-resistance, possibly involving the AdeABC efflux pump [84].

This systematic review has some limitations. First, we included only studies published in English and Italian. Second, due to the nature of exposure, all studies were observational, and could have suffered from their typical bias and residual. However, the quality of all studies was deemed high and, when available, adjusted estimates were used in the analysis. Third, a high degree of heterogeneity was detected in some of the meta-analyses performed, as expected when dealing with observational studies, and subgroup meta-analyses were often unable to reduce this; in other cases, such subgroup meta-analyses were infeasible due to the few analyses included. Moreover, we retrieved very few analyses for some antibiotic classes and for comparisons other than CR/MDR AB isolation against non-isolation. Other limitations mostly result from the characteristics of the studies, such us the lack of standardization in defining previous antibiotic exposure and possibly the multidrug resistance pattern, poor adjustment analyses, and partial reporting of multivariable models. Nevertheless, this is the first review to quantify the risk of antibiotic-resistant AB strains occurring in adult ICU patients following exposure to a wide range of antibiotic classes, differentiating between various comparisons, and identifying well-founded associations for carbapenems, fluoroquinolones, glycopeptides, penicillins, and antipseudomonal penicillins, while highlighting some gaps in the evidence that might be addressed in future research.

In conclusion, the findings of this systematic review and of its meta-analyses show that there is convincing evidence of a role in the spread of antibiotic-resistant AB for numerous antibiotic classes, while for others ambiguities seem to persist. Whereas there are certainly many other factors that can influence resistant micro-organisms in ICU patients, use of antibiotics can be modified relatively easily, and it would therefore be beneficial to carry on studies on antibiotic resistance in a more standardized way, especially regarding the definition of 'previous antibiotic use' and of 'multi-resistance', and the construction and reporting of multivariable models.

Author contributions

M.R. De Blasiis: investigation, data curation, writing — original draft; A. Sciurti: software, investigation, data curation, visualization; writing — original draft; V. Baccolini: conceptualization, methodology, formal analysis, writing — review and editing; supervision; C. Isonne: data curation, writing — original draft; M. Ceparano: data curation, writing — original draft; J. Iera: data curation, writing — review and editing; C. De Vito: writing — review and editing, supervision; C. Marzuillo: writing — review and editing,

supervision; P. Villari: writing — review and editing, supervision G. Migliara: conceptualization, methodology, software, data curation, formal analysis, writing — original draft, review and editing, project administration.

Conflict of interest statement
None declared.

Funding sources
None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2023.11.002.

References

[1] Haque M, McKimm J, Sartelli M, Dhingra S, Labricciosa FM, Islam S, et al. Strategies to prevent healthcare-associated infections: a narrative overview. Risk Manag Healthc Policy 2020;13:1765—80.
[2] World Health Organization 2022. Global report on infection prevention and control. Geneva: WHO; 2022. p. 182.
[3] European Centre for Disease Prevention and Control. Point prevalence survey of healthcare associated infections and antimicrobial use in European acute care hospitals. Stockholm: ECDC; 2019.
[4] Stevens MP, Doll M, Pryor R, Godbout E, Cooper K, Bearman G. Impact of COVID-19 on traditional healthcare-associated infection prevention efforts. Infect Control Hosp Epidemiol 2020;41:946—7.
[5] Isonne C, Baccolini V, Migliara G, Ceparano M, Alessandri F, Ceccarelli G, et al. Comparing the occurrence of healthcare-associated infections in patients with and without COVID-19 hospitalized during the pandemic: a 16-month retrospective cohort study in a hospital intensive care unit. J Clin Med 2022;11:1446.
[6] Baccolini V, Migliara G, Isonne C, Dorelli B, Barone LC, Giannini D, et al. The impact of the COVID-19 pandemic on healthcare-associated infections in intensive care unit patients: a retrospective cohort study. Antimicrob Resist Infect Control 2021;10:1—9.
[7] Plachouras D, Kärki T, Hansen S, Hopkins S, Lyytikäinen O, Moro ML, et al. Antimicrobial use in European acute care hospitals: results from the second point prevalence survey (PPS) of healthcare-associated infections and antimicrobial use, 2016 to 2017. Eurosurveillance 2018;23:1800393.
[8] Barbato D, Castellani F, Angelozzi A, Isonne C, Baccolini V, Migliara G, et al. Prevalence survey of healthcare-associated infections in a large teaching hospital. Ann di Ig Med Prev e di Comunita 2019;31:423—35.
[9] Migliara G, Di Paolo C, Barbato D, Baccolini V, Salerno C, Nardi A, et al. Multimodal surveillance of healthcare associated infections in an intensive care unit of a large teaching hospital. Ann Ig 2019;31:399—413.
[10] Baccolini V, D'Egidio V, de Soccio P, Migliara G, Massimi A, Alessandri F, et al. Effectiveness over time of a multimodal intervention to improve compliance with standard hygiene precautions in an intensive care unit of a large teaching hospital. Antimicrob Resist Infect Control 2019;8:92.
[11] Alp E, Damani N. Healthcare-associated infections in intensive care units: epidemiology and infection control in low-to-middle income countries. J Infect Dev Ctries 2015;9:1040—5.
[12] European Centre for Disease Prevention and Control. Healthcare-associated infections in intensive care units — Annual Epidemiological Report for 2015. Annu Epidemiol Rep 2015;(December):1—10.
[13] Lynch JP, Zhanel GG, Clark NM. Infections due to *Acinetobacter baumannii* in the ICU: treatment options. Semin Respir Crit Care Med 2017;38:311—25.
[14] Weinberg SE, Villedieu A, Bagdasarian N, Karah N, Teare L, Elamin WF. Control and management of multidrug resistant *Acinetobacter baumannii*: a review of the evidence and proposal of novel approaches. Infect Prev Pract 2020;2:100077.
[15] Clark NM, Zhanel GG, Lynch JP. Emergence of antimicrobial resistance among *Acinetobacter* species: a global threat. Curr Opin Crit Care 2016;22:491—9.
[16] Xiao D, Wang L, Zhang D, Xiang D, Liu Q, Xing X. Prognosis of patients with *Acinetobacter baumannii* infection in the intensive care unit: a retrospective analysis. Exp Ther Med 2017;13:1630—3.
[17] World Health Organization. Guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in health care facilities4. Geneva: WHO; 2017. p. 88—100.
[18] Russo A, Gavaruzzi F, Ceccarelli G, Borrazzo C, Oliva A, Alessandri F, et al. Multidrug-resistant *Acinetobacter baumannii* infections in COVID-19 patients hospitalized in intensive care unit. Infection 2022;50:83—92.
[19] Migliara G, Baccolini V, Isonne C, Cianfanelli S, Di Paolo C, Mele A, et al. Prior antibiotic therapy and the onset of healthcare-associated infections sustained by multidrug-resistant *Klebsiella pneumoniae* in intensive care unit patients: a nested case—control study. Antibiotics 2021;10:302.
[20] Falagas ME, Kopterides P. Risk factors for the isolation of multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*: a systematic review of the literature. J Hosp Infect 2006;64:7—15.
[21] Li J, Li Y, Song N, Chen Y. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection: a meta-analysis. J Glob Antimicrob Resist 2020;21:306—13.
[22] Raman G, Avendano EE, Chan J, Merchant S, Puzniak L. Risk factors for hospitalized patients with resistant or multidrug-resistant *Pseudomonas aeruginosa* infections: a systematic review and meta-analysis. Antimicrob Resist Infect Control 2018;7:79.
[23] Li GL, Guo XW, Tang LL, Chen M, Luo XP, Peng LM, et al. Analysis of BRCA1/2 mutation spectrum and prevalence in unselected Chinese breast cancer patients by next-generation sequencing. J Cancer Res Clin Oncol 2017;143:2011—24.
[24] Lim CLL, Chua AQ, Teo JQM, Cai Y, Lee W, Kwa ALH. 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. Int J Infect Dis 2018;76:48—57.
[25] Liu P, Li X, Luo M, Xu X, Su K, Chen S, et al. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection: a meta-analysis. Microb Drug Resist 2018;24:190—8.
[26] Perez S, Innes GK, Walters MS, Mehr J, Arias J, Greeley R, et al. Increase in hospital-acquired carbapenem-resistant *Acinetobacter baumannii* infection and colonization in an acute care hospital during a surge in COVID-19 admissions — New Jersey, February—July 2020. Morb Mortal Wkly Rep 2020;69:1827—31.
[27] Pascale R, Bussini L, Gaibani P, Bovo F, Fornaro G, Lombardo D, et al. Carbapenem-resistant bacteria in an intensive care unit during the coronavirus disease 2019 (COVID-19) pandemic: a multicenter before-and-after cross-sectional study. Infect Control Hosp Epidemiol 2022;43:461—6.
[28] Ceparano M, Baccolini V, Migliara G, Isonne C, Renzi E, Tufi D, et al. *Acinetobacter baumannii* isolates from COVID-19 patients in a hospital intensive care unit: molecular typing and risk factors. Microorganisms 2022;10:1—13.

[29] Munoz-Price LS, Rosa R, Castro JG, Laowansiri P, Latibeaudiere R, Namias N, et al. Evaluating the impact of antibiotic exposures as time-dependent variables on the acquisition of carbapenem-resistant *Acinetobacter baumannii*. Crit Care Med 2016;44:e949—56.
[30] Zheng Y, Hong Z, Zhou D, Zhang A, Li J. Risk factor analysis of pan-drug resistant *Acinetobacter baumannii*-induced ventilator-associated pneumonia in ICU. Indian J Pharm Sci 2020;82:8—11.
[31] Mantzarlis K, Makris D, Zakynthinos E. Risk factors for the first episode of *Acinetobacter baumannii* resistant to colistin infection and outcome in critically ill patients. J Med Microbiol 2020;69:35—40.
[32] Blot S, Ruppé E, Harbarth S, Asehnoune K, Poulakou G, Luyt CE, et al. Healthcare-associated infections in adult intensive care unit patients: changes in epidemiology, diagnosis, prevention and contributions of new technologies. Intens Crit Care Nurs 2022;70:103227.
[33] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6:e1000100.
[34] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions. 2019. p. 694.
[35] Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. Ottawa Hospital Research Institute [cited 2023 Sep 6] The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses 2009. Available at: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
[36] Reeves BC, Deeks JJ, Higgins JPT, Shea B, Tugwell P, Wells GA. on behalf of the Cochrane Non-Randomized Studies of Interventions Methods Group. Including non-randomized studies on intervention effects. In: Cochrane handbook for systematic reviews of interventions. 2nd ed. 2019. p. 595—617. ch. 24.
[37] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557—60.
[38] Borenstein M, Higgins JPT. Meta-analysis and subgroups. Prev Sci 2013;14:134—43.
[39] Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. Stat Med 1999;18:2693—708.
[40] Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629—34.
[41] Rosa R, Arheart KL, Depascale D, Cleary T, Kett DH, Namias N, et al. Environmental exposure to carbapenem-resistant *Acinetobacter baumannii* as a risk factor for patient acquisition of *A. baumannii*. Infect Control Hosp Epidemiol 2014;35:430—3.
[42] Young LS, Sabel AL, Price CS, Young LS, Sabel AL, Price CS. Epidemiologic, clinical, and economic evaluation of an outbreak of clonal multidrug-resistant *Acinetobacter baumannii* infection in a surgical intensive care unit. Infect Control Hosp Epidemiol 2007;28:1247—54.
[43] Gulati RK, Choudhuri J, Fulton C, Chan JD, Evans HL, Lynch JB, et al. Outbreak of carbapenem-resistant *Acinetobacter baumannii* among non-burn patients in a burn intensive care unit. J Hosp Infect 2010;76:357—8.
[44] Husni RN, Goldstein LS, Arroliga AC, Hall GS, Fatica C, Stoller JK, et al. Risk factors for an outbreak of multi-drug-resistant acinetobacter nosocomial pneumonia among intubated patients. Chest 1999;115:1378—82.
[45] Katsaragakis S, Markogiannakis H, Toutouzas KG, Drimousis P, Larentzakis A, Theodoraki EM, et al. *Acinetobacter baumannii* infections in a surgical intensive care unit: predictors of multidrug resistance. World J Surg 2008;32:1194—202.
[46] Apostolopoulou E, Raftopoulos V, Zarkadas P, Toska A, Veldekis D, Tsilidis K. Risk factors and attributable mortality of carbapenem-resistant *Acinetobacter baumannii* infections. Heal Sci J 2014;8:126—36.
[47] Papakonstantinou I, Angelopoulos E, Baraboutis I, Perivolioti E, Parisi M, Psaroudaki Z, et al. Risk factors for tracheobronchial acquisition of resistant Gram-negative bacterial pathogens in mechanically ventilated ICU patients. J Chemother 2015;27:283—9.
[48] Gulen TA, Guner R, Celikbilek N, Keske S, Tasyaran M. Clinical importance and cost of bacteremia caused by nosocomial multi drug resistant *Acinetobacter baumannii*. Int J Infect Dis 2015;38:32—5.
[49] Aksu Koca N, Baran I, Yetkin MA, Kanyilmaz D, Mumcuoğlu I, Yağmurdur H, et al. Carbapenem-resistant *Acinetobacter baumannii* in adult intensive care units: risk factors for colonization and infection. Mediterr J Infect Microbes Antimicrob 2019;7 (August):25.
[50] Mete B, Kurt AF, Urkmez S, Demirkiran O, Can G, Dumanli GY, et al. The bad bug is back: *Acinetobacter baumannii* bacteremia outbreak during the COVID-19 pandemic in an intensive care unit. Niger J Clin Pract 2019;22:1070—7.
[51] Castelo Branco Fortaleza CM, Moreira De Freitas F, Da Paz Lauterbach G, Magno C, Branco C, Freitas FM De, et al. Colonization pressure and risk factors for acquisition of imipenem-resistant *Acinetobacter baumannii* in a medical surgical intensive care unit in Brazil. Am J Infect Control 2013;41:263—5.
[52] Romanelli RM de C, de Jesus LA, Clemente WT, Lima SSS, Rezende EM, Coutinho RL, et al. Outbreak of resistant *Acinetobacter baumannii* — measures and proposal for prevention and control. Braz J Infect Dis 2009;13:341—7.
[53] Qiao F, Huang W, Gao S, Cai L, Zhu S, Wei L, et al. Risk factor for intestinal carriage of carbapenem-resistant *Acinetobacter baumannii* and the impact on subsequent infection among patients in an intensive care unit: an observational study. BMJ Open 2020;10(9).
[54] Meschiari M, Kaleci S, Orlando G, Selmi S, Santoro A, Bacca E, et al. Risk factors for nosocomial rectal colonization with carbapenem-resistant *Acinetobacter baumannii* in hospital: a matched case—control study. Antimicrob Resist Infect Control 2021;10:1—11.
[55] Playford EG, Craig JC, Iredell JR. Carbapenem-resistant *Acinetobacter baumannii* in intensive care unit patients: risk factors for acquisition, infection and their consequences. J Hosp Infect 2007;65:204—11.
[56] Kim SY, Jung JY, Kang YA, Lim JE, Kim EY, Lee SK, et al. Risk factors for occurrence and 30-day mortality for carbapenem-resistant *Acinetobacter baumannii* bacteremia in an intensive care unit. J Korean Med Sci 2012;27:939—47.
[57] Carbonne A, Naas T, Blanckaert K, Couzigou C, Cattoen C, Chagnon JL, et al. Investigation of a nosocomial outbreak of extended-spectrum β-lactamase VEB-1-producing isolates of *Acinetobacter baumannii* in a hospital setting. J Hosp Infect 2005;60:14—8.
[58] Moghnieh R, Siblani L, Ghadban D, El Mchad H, Zeineddine R, Abdallah D, et al. Extensively drug-resistant *Acinetobacter baumannii* in a Lebanese intensive care unit: risk factors for acquisition and determination of a colonization score. J Hosp Infect 2016;92:47—53.
[59] Djordjevic ZM, Folic MM, Folic ND, Gajovic N, Gajovic O, Jankovic SM. Risk factors for hospital infections caused by carbapanem-resistant *Acinetobacter baumannii*. J Infect Dev Ctries 2016;10:1073—80.
[60] Lee HY, Chen CL, Wu SR, Huang CW, Chiu CH. Risk factors and outcome analysis of *Acinetobacter baumannii* complex bacteremia in critical patients. Crit Care Med 2014;42:1081—8.
[61] Inchai J, Liwsrisakun C, Theerakittikul T, Chaiwarith R, Khositsakulchai W, Pothirat C. Risk factors of multidrug-resistant, extensively drug-resistant and pandrug-resistant *Acinetobacter*

baumannii ventilator-associated pneumonia in a medical intensive care unit of university hospital in Thailand. J Infect Chemother 2015;21:570—4.
[62] Harris AD, Karchmer TB, Carmeli Y, Samore MH. Methodological principles of case—control studies that analyzed risk factors for antibiotic resistance: a systematic review. Clin Infect Dis 2001;32:1055—61.
[63] Harris AD, Samore MH, Lipsitch M, Kaye KS, Perencevich E, Carmeli Y. Control-group selection importance in studies of antimicrobial resistance: examples applied to *Pseudomonas aeruginosa*, enterococci, and *Escherichia coli*. Clin Infect Dis 2002;34:1558—63.
[64] Kaye KS, Harris AD, Samore M, Carmeli Y. The case—case control study design: addressing the limitations of risk factor studies for antimicrobial resistance, 26; 2015. p. 346—51.
[65] Schechner V, Temkin E, Harbarth S, Carmeli Y, Schwaber MJ. Epidemiological interpretation of studies examining the effect of antibiotic usage on resistance. Clin Microbiol Rev 2013;26:289—307.
[66] Zhu WM, Yuan Z, Zhou HY. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection relative to two types of control patients: a systematic review and meta-analysis. Antimicrob Resist Infect Control 2020;9:23.
[67] Rodríguez-Baño J, Ramírez E, Muniain MA, Santos J, Joyanes P, González F, et al. Colonization by high-level aminoglycoside-resistant enterococci in intensive care unit patients: epidemiology and clinical relevance. J Hosp Infect 2005;60:353—9.
[68] Chan MC, Chiu SK, Hsueh PR, Wang NC, Wang CC, Fang CT. Risk factors for healthcare-associated extensively drug-resistant *Acinetobacter baumannii* infections: a case—control study. PLoS One 2014;9:e85973.
[69] Baran G, Erbay A, Bodur H, Öngürü P, Akinci E, Balaban N, et al. Risk factors for nosocomial imipenem-resistant *Acinetobacter baumannii* infections. Int J Infect Dis 2008;12:16—21.
[70] Park YS, Lee H, Lee KS, Hwang SS, Cho YK, Kim HY, et al. Extensively drug-resistant *Acinetobacter baumannii*: risk factors for acquisition and prevalent OXA-type carbapenemases — a multicentre study. Int J Antimicrob Agents 2010;36:430—5.
[71] Sheng WH, Liao CH, Lauderdale TL, Ko WC, Chen YS, Liu JW, et al. A multicenter study of risk factors and outcome of hospitalized patients with infections due to carbapenem-resistant *Acinetobacter baumannii*. Int J Infect Dis 2010;14:764—9.
[72] Smolyakov R, Borer A, Riesenberg K, Schlaeffer F, Alkan M, Porath A, et al. Nosocomial multi-drug resistant *Acinetobacter baumannii* bloodstream infection: risk factors and outcome with ampicillin—sulbactam treatment. J Hosp Infect 2003;54:32—8.
[73] Sultan AM, Seliem WA. Identifying risk factors for healthcare-associated infections caused by carbapenem-resistant *Acinetobacter baumannii* in a neonatal intensive care unit. Sultan Qaboos Univ Med J 2018;18:e75—80.
[74] Tsai HT, Wang JT, Chen CJ, Chang SC. Association between antibiotic usage and subsequent colonization or infection of extensive drug-resistant *Acinetobacter baumannii*: a matched case—control study in intensive care units. Diagn Microbiol Infect Dis 2008;62:298—305.
[75] Palacios-Baena ZR, Giannella M, Manissero D, Rodríguez-Baño J, Viale P, Lopes S, et al. Risk factors for carbapenem-resistant Gram-negative bacterial infections: a systematic review. Clin Microbiol Infect 2021;27:228—35.
[76] Folic MM, Djordjevic Z, Folic N, Radojevic MZ, Jankovic SM. Epidemiology and risk factors for healthcare-associated infections caused by *Pseudomonas aeruginosa*. J Chemother 2021;33:294—301.
[77] Chen YH, Chiueh CC, Lee YJ. Risk factors of carbapenem-resistant *Acinetobacter baumannii* infection among hospitalized patients. J Exp Clin Med 2014;6:143—6.
[78] Gómez-Zorrilla S, Camoez M, Tubau F, Periche E, Cañizares R, Dominguez MA, et al. Antibiotic pressure is a major risk factor for rectal colonization by multidrug-resistant *Pseudomonas aeruginosa* in critically ill patients. Antimicrob Agents Chemother 2014;58:5863—70.
[79] Biswas S, Brunel JM, Dubus JC, Reynaud-Gaubert M, Rolain JM. Colistin: an update on the antibiotic of the 21st century. Expert Rev Anti Infect Ther 2012;10:917—34.
[80] EUCAST. Intrinsic resistance and Unusual phenotypes version 3.3 October 2021 EUCAST Expert Rules version 2.0 2021;3.3 (October 2011).
[81] Zhou HY, Yuan Z, Du YP. Prior use of four invasive procedures increases the risk of *Acinetobacter baumannii* nosocomial bacteremia among patients in intensive care units: a systematic review and meta-analysis. Int J Infect Dis 2014;22:25—30.
[82] Van Loon K, Voor In't Holt AF, Vos MC. A systematic review and meta-analyses of the clinical epidemiology of carbapenem-resistant Enterobacteriaceae. Antimicrob Agents Chemother 2018;62:1—18.
[83] Borer A, Saidel-Odes L, Eskira S, Nativ R, Riesenberg K, Livshiz-Riven I, et al. Risk factors for developing clinical infection with carbapenem-resistant *Klebsiella pneumoniae* in hospital patients initially only colonized with carbapenem-resistant *K. pneumoniae*. Am J Infect Control 2012;40:421—5.
[84] Xu C, Bilya SR, Xu W. adeABC efflux gene in *Acinetobacter baumannii*. New Microbes New Infect 2019;30:100549.