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Acinetobacter baumannii and Its Relationship to Carbapenem Resistance: A Meta-Analysis

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Abstract: Infections by antibiotic-resistant bacteria are a significant and complex global health issue. In this context, *Acinetobacter baumannii* is particularly important because of its ability to withstand treatments by β-lactams, such as carbapenem. The objective of this work was to investigate, through systematic analysis and meta-analysis, the chance of resistance to carbapenem in *A. baumannii* strains. For this, a search was conducted for the PubMed and Cochrane databases based on the keywords: "*Acinetobacter baumannii*" AND "beta-lactam" OR "penicillin" OR "cephalosporin" OR "cephamycin" OR "carbapenem" OR "monobactam". The initial search resulted in a total of 90,475 articles. It was filtered based on eligibility criteria, and eight articles were selected for analysis. An odds ratio value equivalent to 3.55 was obtained, indicating a high chance of resistance to the carbapenem of strains of the species. Therefore, it is supposed that *A. baumannii* infection cases have a high probability of not responding adequately to treatments based on carbapenem.

Keywords: CRAB; infection; resistome

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1. Introduction

Acinetobacter baumannii is a Gram-negative coccobacillus, which is catalase-positive and oxidase-negative [1]. According to the World Health Organization, it is one of the most important nosocomial pathogens and a great resistance model to antimicrobials [2]. This organism is related to several comorbidities such as pneumonia [3], bacteremia [4], cystitis [5], and meningitis [6], among others. As a pathogen, it also has increasing relevance to one health by being able to infect livestock and pets [7].

With the turn of the century, *A. baumannii* acquired fame for its exacerbated resistance to several classes of antimicrobials, among them, β-lactams. The origin of its resistance is still mysterious. Still, it is known that its mechanisms derive in part from elements derived from the horizontal gene transfer (HGT) from species belonging to the genera *Pseudomonas*, *Klebsiella*, and *Salmonella* [8]. Another justification for its resistance is the presence of elements related to the evolutionary origin of the species that remained in the genome and showed an adaptive advantage in a hospital environment [9–11]. Especially within the β-lactam class, the species has a higher degree of resistance to carbapenem. This fact culminated in creating the term CRAB (carbapenem-resistant *Acinetobacter baumannii*), widespread in academia and life sciences [2].

Recent studies suggest that the best treatment options for CRAB infections are based on colistin and tigecycline combination, or pharmacological associations with sulbactam

(beta-lactamase inhibitor antibiotic) [12–14]. However, there are case reports where these strategies have not been effective [15–17]. Nevertheless, due to the importance of the pathogen, there must be constant review and survey of scientific data to design the development of pathogenic factors and outline the best treatment strategies.

In this context, the meta-analysis is a statistical strategy that aims to combine the results of different studies in a single effect size with greater significance than individual studies [18]. In other words, it is a tool capable of treating several studies as single research and considers the result extracted from each population to produce a more significant effect size [19]. Thus, it composes an excellent statistical model to deal with data obtained from isolated studies and corroborate biological conclusions. For this reason, it is an adequate research strategy for the analysis of multiple case studies that deal with events of resistance and susceptibility of strains of the species.

Therefore, this study aimed to investigate the chance of resistance to carbapenem of the species *A. baumannii*, based on data prospected from clinical studies and summarized by a meta-analysis strategy.

2. Materials and Methods

2.1. Search Strategy

A bibliographic search was carried out based on the Cochrane Central Register of Controlled Trials database, which contains one of the largest repositories of clinical studies globally, and PubMed, one of the largest databases of articles and publications in the world. The search was limited to articles published from 2000 to 16 August 2020, with no language restrictions, for studies carried out on adult humans. In addition, all available comorbidities were considered. To frame articles related to the research point, the following keywords were used: "*Acinetobacter baumannii*" AND "beta-lactam" OR "penicillin" OR "cephalosporin" OR "cephamycin" OR "carbapenem" OR "monobactam".

2.2. Selection Criteria

The types of studies included in the analysis were clinical and laboratory reports in which there were reports of the presence of *A. baumannii* strains resistant to β-lactam classes. An in-house script was developed in Python 3 to perform specific filtering of abstracts. Studies that do not mention the species of interest in the abstract, title, or keywords were excluded. Studies that deal exclusively with *A. baumannii* strains have been banned, requiring data from other bacteria concurrently. This criterion was applied because the odds ratio statistics are based on the proportion and need at least two distinct groups with subgroups. Bacteria were considered resistant if the report presented (I) microbial susceptibility test indicating resistance; (II) isolates named as antimicrobial-resistant (i.e., carbapenem-resistant *A. baumannii*—CRAB; carbapenem-resistant *P. aeruginosa*—CRPA); (III) failure of clinical outcome defined by nonmicrobiological eradication of the pathogen or failure to resolve clinical signs and symptoms.

The articles obtained through the final screening were selected because they allow the statistical evaluation of the difference between the prevalence of *A. baumannii*-susceptible and -resistant isolates. Furthermore, as it applies a probabilistic method, different species were considered to generate comparative countable data capable of forming the primary basis. In addition, to address issues related to the prevalence of the species of interest, the phenotypes intrinsic to the species being compared were not considered, but only their epidemiological prevalence in the studies were surveyed. For the same reason, studies dealing only with *A. baumannii* were excluded, considering that they did not allow a comparative analysis of the increase or decrease in phenotypically resistant isolates compared with other species under the same conditions.

2.3. Data Extraction

The quantities required to carry out the study were previously selected through discussion between all authors. A standardized table was built to organize the selected data. The

first author extracted the following data from each study based on the standardized matrix: study title; number of resistant *A. baumannii* isolates; number of susceptible *A. baumannii* isolates; number of resistant isolates from bacteria other than *A. baumannii*; number of susceptible isolates from bacteria other than *A. baumannii*; dosage applied; class of antimicrobial used; author; year of study development; publication journal; the country where the study was developed.

2.4. Data Analysis

Statistical analysis was developed entirely in Rstudio using the *meta* package for calculations and plotting [20]. The meta-analysis compared the reasons for the chances of resistance to β-lactams if the pathogen was *A. baumannii* and if it was not *A. baumannii*. The heterogeneity of the effects of the studies was assessed using I^2 statistics. I^2 value > 75% accompanied by a significance value <0.05 was considered high heterogeneity. In addition, the outlier test was performed using the GOSH function based on the k-means, DBSCAN, and Gaussian mixture models algorithms.

To summarize the effects, the random-effects model was selected because it is considered the most suitable for analysis in life sciences. Publication bias was assessed using a funnel plot, and if ten or more studies were added to the research, the Egger's test would be used. For the correlation analysis, Pearson's statistics were used.

3. Results

3.1. Studies Selection and Characteristics

Prospecting started with 6019 articles derived from the Cochrane platform and 84,726 studies derived from the PubMed platform. After the first successive filtering, 2516 articles remained on the Cochrane platform, and 509 articles on the PubMed platform remained in the analysis. After removing redundancy, 2576 articles remained in the analysis. Subsequently, as a result of the specific abstract filtering, 86 papers were selected for study. Finally, eight articles were eligible, meeting the inclusion criteria [21–28] (Figure 1).

Among the reports excluded from the analysis: (I) 25 did not present precise data regarding the prevalence of resistant *A. baumannii* strains; (II) 15 did not harbor β-lactams; (III) 14 did not give published results; (IV) 9 did not address *A. baumannii* as at least 1 of the species raised; (V) 8 items were unavailable; (VI) 6 did not show conclusive results (see Figure 1); only (VII) 1 study addressed any β-lactam other than carbapenem, so the analysis was performed based on evidence of resistance only to carbapenem.

Data were extracted from the selected studies regarding the number of resistant and susceptible isolates in each case. The data distribution is shown in Table 1.

Table 1. Distribution of data extracted from each study, considered eligible for the development of the analysis and their respective values.

Author	Number of Susceptible Isolates/*N* (%)		Year	Country
	Acinetobacter baumannii	**Other Bacteria ***		
[27]	926/1870 (49.5)	477/4967 (9.6)	2007	Singapore
[24]	33/39 (84.6)	26/29 (89.6)	2010	USA
[21]	14/25 (56)	54/119 (45.4)	2012	Whole world
[26]	8/10 (80)	8/33 (24.2)	2012	India
[23]	2053/3350 (61.2)	641/3456 (18.5)	2014	South Korea
[25]	2/17 (11.8)	73/434 (16.8)	2014	Europe, USA, Canada, Latin America, Asia, India, Australia, and South Africa
[28]	12/16 (75)	18/90 (20)	2016	Belarus
[22]	131/137 (95.6)	36/40 (90)	2020	Italy, Greece, and Israel

* Other bacteria: *E. cloacae*, *E. faecalis*, *Escherichia coli*, *K. pneumoniae*, *P. aeruginosa*, *S. aureus*, *S. maltophilia*, *S. agalactiae*.

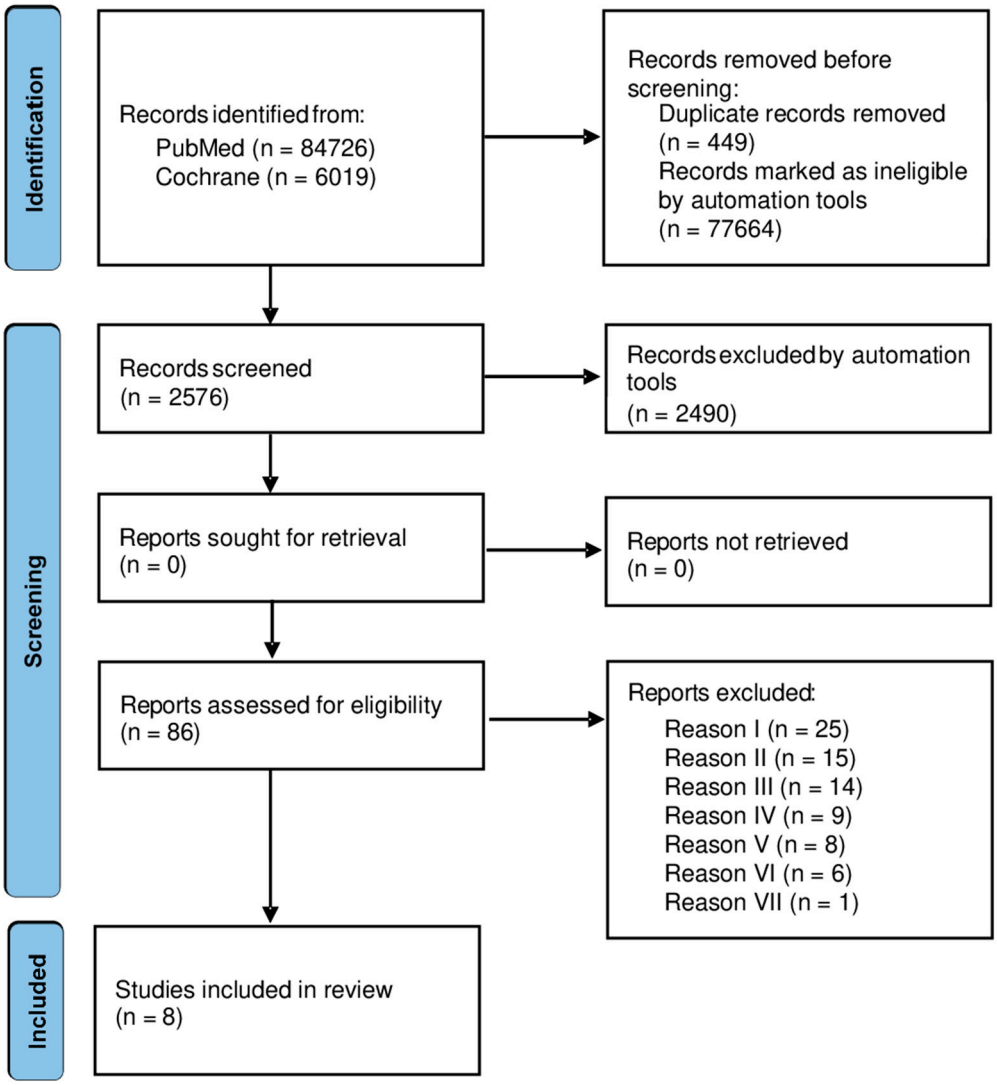

Figure 1. Systematic representation of selecting the studies according to the previously established filtering criteria.

3.2. Statistical Analysis and Synthesis

As a result of the statistical analysis, comparisons were made between the amounts of resistant and susceptible to carbapenem isolates in both raised groups, being categorized as group Ab (Acinetobacter baumannii) and group Ob (Other bacteria). In addition, comparisons were made due to the odds ratio of resistance if the isolate is *A. baumannii*. Figure 2 represents the individual results of each study, the values considered for the analysis of heterogeneity, and the final result of the summary of the results.

It was observed that four studies have a value of 1 within the confidence interval found considering p-value < 0.05 [21,22,24,25]. In contrast, two studies presented the most significant weight for the final prediction [23,27]. This fact is related to the size of the samples taken by the authors.

As a result of the analysis by the random-effects model, the carbapenem resistance index of *A. baumannii* strains was significantly higher than in other bacterial species (OR 3.55, 95% CI 1.29–9.75). This result points out that *A. baumannii* strains have about a 355% chance of resistance to carbapenem compared with other species resistance cases. These data suggest that carbapenem-based monotherapies have a lower success rate in *A. baumannii* strains.

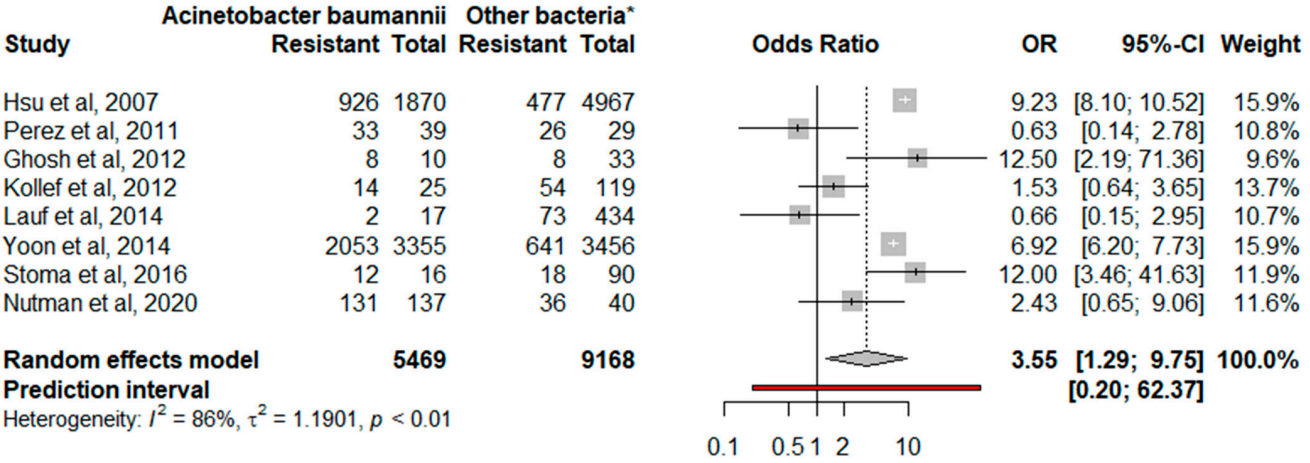

Figure 2. The forest plot summarizes the analysis results by an odds ratio of the selected studies [21–28]. * Other bacteria: *E. cloacae*, *E. faecalis*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *S. aureus*, *S. maltophilia*, *S. agalactiae*.

An I2 value equivalent to 86% was obtained in the heterogeneity analysis with a p-value < 0.01. This fact implies a high heterogeneity between studies. In contrast, τ^2 is equal to 1.1901, which corroborates the previous heterogeneity statement. However, it is worth noting that both I^2 and τ^2 statistics gain greater statistical power when ten or more studies are added to the analysis. However, even considering the high heterogeneity, the random removal of studies from the final analysis did not significantly reduce heterogeneity values (see Supplementary Figure S1).

As a result of the correlation analysis, an r value equivalent to 0.748 was obtained (p-value = 0.043) (see Supplementary Figure S2). It indicates a correlation between the advance of years and the increase in the percentage of carbapenem-resistant *A. baumannii* isolates. For this result, the alternative hypothesis considered was that the correlation is greater than 0. This fact indicates that the prevalence of resistant isolates of the species increased over the years.

3.3. Publication Bias Analysis

In the analysis of publication bias, Egger's test was performed, resulting in a p-value = 0.127, which would suggest the absence of asymmetry in the funnel plot. However, the number of studies added is less than 10 (k = 8). This fact significantly reduces the significance of Egger's test result, making its statistical support just illustrative.

Figure 3 represents the funnel plot built to analyze the symmetry of the data distribution. Through Duval and Tweedie's trim-and-fill procedure, it was possible to observe that by adding only two studies with high standard error and high effect size, it would be possible to recover the symmetry of the graph if the p-value of the Egger's test was inferior to 0.05.

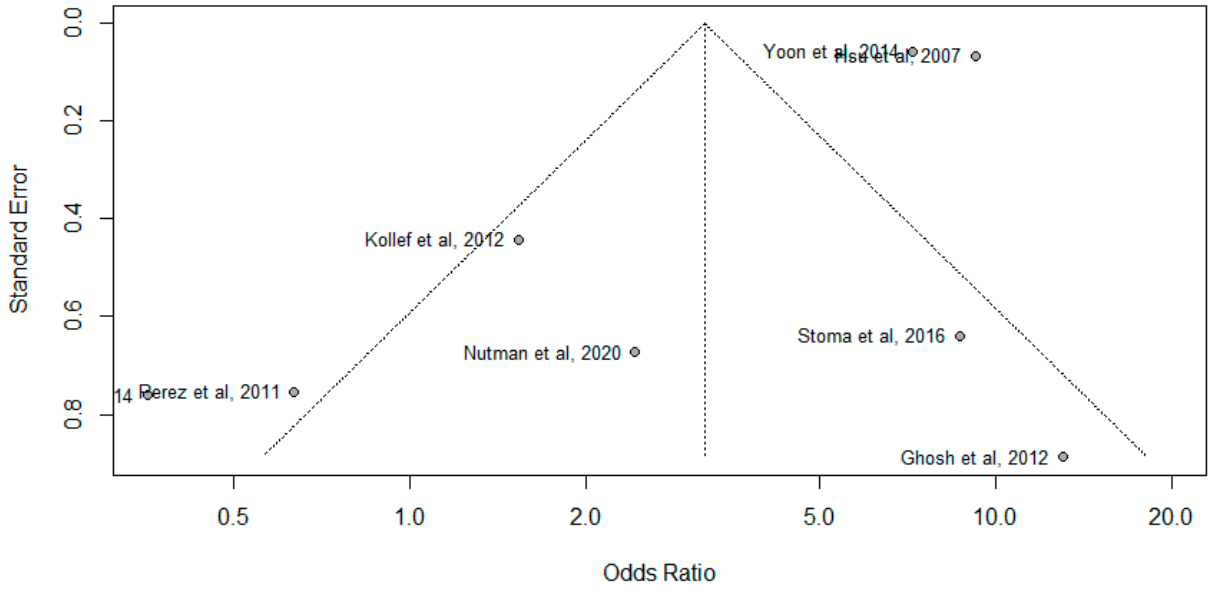

Figure 3. The funnel plot represents the distribution of data extracted from each study [21–28] and their spatial positions around the calculated standard error.

4. Discussion

An essential finding of the study is the value of summarizing the studies. This result shows that *A. baumannii* isolates are about three times more likely to resist carbapenem than other bacteria related to hospital infections.

The carbapenem resistance of *A. baumannii* comes mainly from carbapenemases and efflux pumps. Class D β-lactamases (oxacillinases) are part of the significant epidemiological problem of the species. This is because its expression implies a considerable increase in resistance to carbapenem and cephalosporins [29,30]. The most discussed and represented enzymes are OXA-23, OXA-24, and OXA-58 [31,32]. Thus, the OXA-23 enzyme is prevalent in 60.76% of the complete sequenced *A. baumannii* genomes available at NCBI [33]. However, studies have already pointed out a prevalence above 90% in certain regions [34]. In contrast, OXA-24 and OXA-58 have a prevalence of, respectively, 3.13% and 1.47% of the complete sequenced genomes of *A. baumannii* available at NCBI [33]. However, studies have also pointed out the presence of OXA-23 and OXA-24 in *P. aeruginosa*, another great resistance model, with a prevalence of 11.19% and 2.24%, respectively [35].

Among efflux pumps, it is known that their action against multiple classes of antimicrobials is one of the main factors of resistance to broad-spectrum drugs. For example, in the case of *A. baumannii*, the presence and expression of efflux systems such as AcrAB-TolC significantly reduce susceptibility to antimicrobials, including carbapenems [36,37].

In general, in previous studies, a prevalence of approximately 80% of *A. baumannii* strains resistant to meropenem was observed. At the same time, *P. aeruginosa*, another significant resistance model, showed about 20% of strains were resistant to the same drug [38]. Still dealing with strains of the genus *Acinetobacter*, resistant to carbapenem, there have been reports of prevalence above 90% [39]. All these data corroborate the result raised of high probability resistance of the species.

Finally, all studies removed from the analysis were excluded because they did not meet the criteria for automated filtering or did not present precise data regarding the exact proportion of resistant isolates of *A. baumannii* or other microbial species. However, it is worth mentioning that its scientific relevance was not questioned.

5. Conclusions

In conclusion, this study presents results corroborating the clinical and epidemiological data already presented by major global health agencies. In a general field, it was observed

that carbapenem treatments are more likely to be not efficient for infection cases associated with *A. baumannii*. Furthermore, the prerogative of detailed analysis of microbial sensitivity tests related to a meta-analysis data server as a guideline for preventive actions in the clinical scope and the improvement of antimicrobials management and consumption practices.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/bacteria1020010/s1, Figure S1: Graph representing the I^2 values obtained after the analysis's consecutive removal of random studies. Note that in no case was the value of I^2 lower than 0.80, Figure S2: Distribution graph of the percentage of resistant *A. baumannii* isolates over the years. The trend curve is based on Pearson correlation.

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References

1. Peleg, A.Y.; Seifert, H.; Paterson, D.L. *Acinetobacter baumannii*: Emergence of a successful pathogen. *Clin. Microbiol. Rev.* **2008**, *21*, 538–582. [CrossRef] [PubMed]
2. World Health Organization. *Guidelines for the Prevention and Control of Carbapenem-Resistant Enterobacteriaceae, Acinetobacter Baumannii and Pseudomonas Aeruginosa in Health Care Facilities*; World Health Organization: Geneve, Switzerland, 2017; ISBN 978-92-4-155017-8.
3. Jung, S.Y.; Lee, S.H.; Lee, S.Y.; Yang, S.; Noh, H.; Chung, E.K.; Lee, J.I. Antimicrobials for the treatment of drug-resistant acinetobacter baumannii pneumonia in critically Ill Patients: A systemic review and bayesian network meta-analysis. *Crit. Care* **2017**, *21*, 319. [CrossRef] [PubMed]
4. Eliopoulos, G.M.; Maragakis, L.L.; Perl, T.M. *Acinetobacter baumannii*: Epidemiology, antimicrobial resistance, and treatment options. *Clin. Infect. Dis.* **2008**, *46*, 1254–1263. [CrossRef]
5. Jiménez-Guerra, G.; Heras-Cañas, V.; Gutiérrez-Soto, M.; Del Pilar Aznarte-Padial, M.; Expósito-Ruiz, M.; Navarro-Marí, J.M.; Gutiérrez-Fernández, J. Urinary tract infection by *Acinetobacter baumannii* and *pseudomonas aeruginosa*: Evolution of antimicrobial resistance and therapeutic alternatives. *J. Med. Microbiol.* **2018**, *67*, 790–797. [CrossRef] [PubMed]
6. Siegman-Igra, Y.; Bar-Yosef, S.; Gorea, A.; Avram, J. Nosocomial *acinetobacter* meningitis secondary to invasive procedures: Report of 25 cases and review. *Clin. Infect. Dis.* **1993**, *17*, 843–849. [CrossRef]
7. Wareth, G.; Abdel-Glil, M.Y.; Schmoock, G.; Steinacker, U.; Kaspar, H.; Neubauer, H.; Sprague, L.D. Draft genome sequence of an *acinetobacter baumannii* isolate recovered from a horse with conjunctivitis in Germany. *Microbiol. Resour. Announc.* **2019**, *8*, e01128-19. [CrossRef]
8. Howard, A.; O'Donoghue, M.; Feeney, A.; Sleator, R.D. *Acinetobacter Baumannii*—An emerging opportunistic pathogen. *Virulence* **2012**, *3*, 243–250. [CrossRef]
9. Bergogne-Bérézin, E. Acinetobacter Spp., saprophytic organisms of increasing pathogenic importance. *Zentralblatt für Bakteriologie* **1994**, *281*, 389–405. [CrossRef]
10. Bergogne-Bérézin, E.; Towner, K.J. Acinetobacter Spp., as nosocomial pathogens: Microbiological, clinical, and epidemiological features. *Clin. Microbiol. Rev.* **1996**, *9*, 148–165. [CrossRef]
11. Kämpfer, P. Acinetobacter. In *Encyclopedia of Food Microbiology*, 2nd ed.; Batt, C.A., Tortorello, M.L., Eds.; Academic Press: Oxford, UK, 2014; pp. 11–17, ISBN 978-0-12-384733-1.
12. Huttner, B.; Jones, M.; Rubin, M.A.; Neuhauser, M.M.; Gundlapalli, A.; Samore, M. Drugs of last resort? The use of polymyxins and tigecycline at US veterans affairs medical centers, 2005–2010. *PLoS ONE* **2012**, *7*, e36649. [CrossRef]

13. Viehman, J.A.; Nguyen, M.H.; Doi, Y. Treatment options for carbapenem-resistant and extensively drug-resistant acinetobacter baumannii infections. *Drugs* **2014**, *74*, 1315–1333. [CrossRef] [PubMed]
14. Seok, H.; Choi, W.S.; Lee, S.; Moon, C.; Park, D.W.; Song, J.Y.; Cheong, H.J.; Kim, J.; Kim, J.Y.; Park, M.N.; et al. What is the optimal antibiotic treatment strategy for carbapenem-resistant *acinetobacter baumannii* (CRAB)? A multicentre study in Korea. *J. Glob. Antimicrob. Resist.* **2021**, *24*, 429–439. [CrossRef] [PubMed]
15. Moffatt, J.H.; Harper, M.; Harrison, P.; Hale, J.D.F.; Vinogradov, E.; Seemann, T.; Henry, R.; Crane, B.; Michael, F.S.; Cox, A.D.; et al. Colistin resistance in *acinetobacter baumannii* is mediated by complete loss of lipopolysaccharide production. *Antimicrob. Agents Chemother.* **2010**, *54*, 4971–4977. [CrossRef] [PubMed]
16. Navon-Venezia, S.; Leavitt, A.; Carmeli, Y. High tigecycline resistance in multidrug-resistant *acinetobacter baumannii*. *J. Antimicrob. Chemother.* **2007**, *59*, 772–774. [CrossRef] [PubMed]
17. Hornsey, M.; Wareham, D.W. Effects of in vivo emergent tigecycline resistance on the pathogenic potential of acinetobacter baumannii. *Sci. Rep.* **2018**, *8*, 4234. [CrossRef]
18. Sánchez-Meca, J.; Marín-Martínez, F. Meta Analysis. In *International Encyclopedia of Education*, 3rd ed.; Peterson, P., Baker, E., McGaw, B., Eds.; Elsevier: Oxford, UK, 2010; ISBN 978-0-08-044894-7.
19. Hoffman, J.I.E. Chapter 36—Meta-Analysis. In *Biostatistics for Medical and Biomedical Practitioners*; Hoffman, J.I.E., Ed.; Academic Press: Cambridge, MA, USA, 2015; pp. 645–653, ISBN 978-0-12-802387-7.
20. Balduzzi, S.; Rücker, G.; Schwarzer, G. How to perform a meta-analysis with R: A practical tutorial. *Evid. Based Ment. Health* **2019**, *22*, 153–160. [CrossRef]
21. Kollef, M.H.; Chastre, J.; Clavel, M.; Restrepo, M.I.; Michiels, B.; Kaniga, K.; Cirillo, I.; Kimko, H.; Redman, R. A Randomized trial of 7-day doripenem versus 10-day imipenem-cilastatin for ventilator-associated pneumonia. *Crit. Care* **2012**, *16*, R218. [CrossRef]
22. Nutman, A.; Lellouche, J.; Temkin, E.; Daikos, G.; Skiada, A.; Durante-Mangoni, E.; Dishon-Benattar, Y.; Bitterman, R.; Yahav, D.; Daitch, V.; et al. Colistin plus meropenem for carbapenem-resistant gram-negative infections: In vitro synergism is not associated with better clinical outcomes. *Clin. Microbiol. Infect.* **2020**, *26*, 1185–1191. [CrossRef]
23. Yoon, Y.K.; Yang, K.S.; Lee, S.E.; Kim, H.J.; Sohn, J.W.; Kim, M.J. Effects of Group 1 versus Group 2 carbapenems on the susceptibility of *Acinetobacter baumannii* to carbapenems: A before and after intervention study of carbapenem-use stewardship. *PLoS ONE* **2014**, *9*, e99101. [CrossRef]
24. Perez, F.; Endimiani, A.; Ray, A.J.; Decker, B.K.; Wallace, C.J.; Hujer, K.M.; Ecker, D.J.; Adams, M.D.; Toltzis, P.; Dul, M.J.; et al. Carbapenem-resistant *Acinetobacter baumannii* and *Klebsiella pneumoniae* across a hospital system: Impact of post-acute care facilities on dissemination. *J. Antimicrob. Chemother.* **2010**, *65*, 1807–1818. [CrossRef]
25. Lauf, L.; Ozsvár, Z.; Mitha, I.; Regöly-Mérei, J.; Embil, J.M.; Cooper, A.; Sabol, M.B.; Castaing, N.; Dartois, N.; Yan, J.; et al. phase 3 study comparing tigecycline and ertapenem in patients with diabetic foot infections with and without osteomyelitis. *Diagn. Microbiol. Infect. Dis.* **2014**, *78*, 469–480. [CrossRef] [PubMed]
26. Ghosh, I.; Raina, V.; Kumar, L.; Sharma, A.; Bakhshi, S.; Thulkar, S.; Kapil, A. Profile of infections and outcome in high-risk febrile neutropenia: Experience from a tertiary care cancer center in India. *Med. Oncol.* **2012**, *29*, 1354–1360. [CrossRef]
27. Hsu, L.-Y.; Tan, T.-Y.; Jureen, R.; Koh, T.-H.; Krishnan, P.; Lin, R.T.-P.; Tee, N.W.-S.; Tambyah, P.A. Antimicrobial drug resistance in Singapore hospitals. *Emerg. Infect. Dis.* **2007**, *13*, 1944. [CrossRef] [PubMed]
28. Stoma, I.; Karpov, I.; Milanovich, N.; Uss, A.; Iskrov, I. Risk factors for mortality in patients with bloodstream infections during the pre-engraftment period after hematopoietic stem cell transplantation. *Blood Res.* **2016**, *51*, 102–106. [CrossRef]
29. Kaitany, K.-C.J.; Klinger, N.V.; June, C.M.; Ramey, M.E.; Bonomo, R.A.; Powers, R.A.; Leonard, D.A. Structures of the class D carbapenemases OXA-23 and OXA-146: Mechanistic basis of activity against carbapenems, extended-spectrum cephalosporins, and aztreonam. *Antimicrob. Agents Chemother.* **2013**, *57*, 4848–4855. [CrossRef] [PubMed]
30. Tafreshi, N.; Babaeekhou, L.; Ghane, M. Antibiotic resistance pattern of *Acinetobacter baumannii* from burns patients: Increase in prevalence of BlaOXA-24-like and BlaOXA-58-like genes. *Iran. J. Microbiol.* **2019**, *11*, 502–509. [CrossRef]
31. Poirel, L.; Nordmann, P. Carbapenem resistance in Acinetobacter baumannii: Mechanisms and epidemiology. *Clin. Microbiol. Infect.* **2006**, *12*, 826–836. [CrossRef]
32. Walther-Rasmussen, J.; Høiby, N. OXA-Type carbapenemases. *J. Antimicrob. Chemother.* **2006**, *57*, 373–383. [CrossRef]
33. Alcock, B.P.; Raphenya, A.R.; Lau, T.T.Y.; Tsang, K.K.; Bouchard, M.; Edalatmand, A.; Huynh, W.; Nguyen, A.-L.V.; Cheng, A.A.; Liu, S.; et al. CARD 2020: Antibiotic resistome surveillance with the comprehensive antibiotic resistance database. *Nucleic Acids Res.* **2020**, *48*, D517–D525. [CrossRef]
34. Oliveira, E.A.D.; Paula, G.R.D.; Mondino, P.J.J.; Chagas, T.P.G.; Mondino, S.S.B.D.; Mendonça-Souza, C.R.V.D. High rate of detection of OXA-23-Producing acinetobacter from two general hospitals in Brazil. *Rev. Soc. Bras. Med. Trop.* **2019**, 52. [CrossRef]
35. Rouhi, S.; Ramazanzadeh, R. Prevalence of blaOxacillinase-23and blaOxacillinase-24/40-type carbapenemases in *Pseudomonas aeruginosa* species isolated from patients with nosocomial and non-nosocomial infections in the West of Iran Iran. *J. Pathol.* **2018**, *13*, 348–356.
36. Chetri, S.; Bhowmik, D.; Paul, D.; Pandey, P.; Chanda, D.D.; Chakravarty, A.; Bora, D.; Bhattacharjee, A. AcrAB-TolC efflux pump system plays a role in carbapenem non-susceptibility in *Escherichia coli*. *BMC Microbiol.* **2019**, *19*, 210. [CrossRef] [PubMed]
37. Yuhan, Y.; Ziyun, Y.; Yongbo, Z.; Fuqiang, L.; Qinghua, Z.; Yuhan, Y.; Ziyun, Y.; Yongbo, Z.; Fuqiang, L.; Qinghua, Z. Over expression of AdeABC and AcrAB-TolC efflux systems confers tigecycline resistance in clinical isolates of *Acinetobacter baumannii* and *Klebsiella pneumoniae*. *Rev. Soc. Bras. Med. Trop.* **2016**, *49*, 165–171. [CrossRef]

38. Baumgart, A.M.K.; Molinari, M.A.; Silveira, A.C.D.O. Prevalence of carbapenem resistant *Pseudomonas aeruginosa* and *acinetobacter baumannii* in high complexity hospital. *Braz. J. Infect. Dis.* **2010**, *14*, 433–436. [CrossRef] [PubMed]
39. Ramette, A.; Kronenberg, A. Prevalence of carbapenem-resistant *Acinetobacter baumannii* from 2005 to 2016 in Switzerland. *BMC Infect. Dis.* **2018**, *18*, 159. [CrossRef] [PubMed]